Reduced neural response to reward following 7 days treatment with the cannabinoid CB₁ antagonist rimonabant in healthy volunteers

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Abstract
Reduced subjective experience of reward (anhedonia) is a key symptom of major depression. The anti-obesity drug and cannabinoid type 1 receptor (CB₁) antagonist, rimonabant, is associated with significant rates of depression and anxiety in clinical use and was recently withdrawn from the market because of these adverse effects. Using a functional magnetic resonance imaging (fMRI) model of reward we hypothesized that rimonabant would impair reward processing. Twenty-two healthy participants were randomly allocated to receive rimonabant (20 mg), or placebo, for 7 d in a double-blind, parallel group design. We used fMRI to measure the neural response to rewarding (sight and/or flavour of chocolate) and aversive (sight of mouldy strawberries and/or an unpleasant strawberry taste) stimuli on the final day of drug treatment. Rimonabant reduced the neural response to chocolate stimuli in key reward areas such as the ventral striatum and the orbitofrontal cortex. Rimonabant also decreased neural responses to the aversive stimulus condition in the caudate nucleus and ventral striatum, but increased lateral orbitofrontal activations to the aversive sight and taste of strawberry condition. Our findings are the first to show that the anti-obesity drug rimonabant inhibits the neural processing of rewarding food stimuli in humans. This plausibly underlies its ability to promote weight loss, but may also indicate a mechanism for inducing anhedonia which could lead to the increased risk of depressive symptomatology seen in clinical use. fMRI may be a useful method of screening novel agents for unwanted effects on reward and associated clinical adverse reactions.

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Key words: CB₁ antagonist, depression, fMRI, obesity, reward, rimonabant.

Introduction
Rimonabant (SR141716) is an antagonist and possible inverse agonist (Pertwee, 2005) at the cannabinoid type 1 (CB₁) receptor in the brain. Rimonabant was licensed in Europe for the treatment of obesity in 2006. However, rimonabant treatment is associated with an increased risk of depression and anxiety and also suicidal behaviour (Le Foll et al. 2009; Moreira & Crippa, 2009). Due to concerns over these side-effects, rimonabant was withdrawn from use in Europe in October 2008 (during the course of the present study).

A meta-analysis of the first four randomized controlled trials of rimonabant in obesity found that ‘patients given rimonabant were 2.5 times more likely to discontinue the treatment because of depressive mood disorders than were those given placebo’ (Christensen et al. 2007). A US Food and Drug Administration analysis of the same trials noted that 26% of rimonabant (20 mg)-treated subjects vs. 14% of the placebo group reported psychiatric symptoms (US Food and Drug Administration Advisory Committee, 2007). Of particular concern was the significantly raised risk of suicidal ideation and behaviour (odds ratio vs. placebo = 2.0). Furthermore, these trials excluded patients with a history of psychiatric illness, including depression. Another recent investigation, the STRADIVARIUS trial, in which patients with a history of psychiatric illness were not specifically excluded, found the rate of reported psychiatric symptoms was 43% in the 20-mg rimonabant group vs. 28% in the placebo group (Nissen et al. 2008).

Early screening and detection of new compounds with these kinds of psychiatric side-effects is desirable...
to prevent widespread exposure of patients to the morbidity and risks of depression. However, animal experimental psychopharmacological models used to screen drugs such as rimonabant did not detect potential depression-inducing effects of rimonabant, and in fact some studies showed that CB₁ antagonists have a profile similar to antidepressant medications when tested (Griebel et al. 2005; Patel et al. 2005; Steiner et al. 2008; Takahashi et al. 2008). However, it is possible, that a human model of depression and reward may be better placed to predict possible induction of depression by new agents and also to investigate the possible neuropsychological mechanisms involved.

We developed a functional magnetic resonance imaging (fMRI) model that uses the sight and taste of chocolate to produce a robust activation of the primary reward system in the brain in healthy volunteers (Rolls & McCabe, 2007). Using this model, we have previously shown that those vulnerable to depression have deficits in their neural reward responses to chocolate compared to healthy controls, despite no differences in their subjective experiences of reward (McCabe et al. 2009). The clinical symptom of anhedonia (loss of pleasure) is linked to abnormal reward processing and is a key symptom of depression in all major diagnostic systems. Hence, assessment of the effect of drug treatments on neural reward mechanisms could provide some early indication of their propensity to produce depression in clinical use.

The current study therefore investigated the effects of rimonabant on reward processing in healthy volunteers. We hypothesized that this task would activate the key circuitry of ventral striatum, caudate, medial prefrontal and orbitofrontal cortices which we and others have shown to be sensitive to rewarding and aversive stimuli (McCabe & Rolls, 2007; McCabe et al. 2008; Rolls & McCabe, 2007). Notably, the CB₁ receptor is highly expressed in such reward areas including the basal ganglia (Herkenham et al. 1991). We used 7 d treatment with rimonabant, at a dose of 20 mg/d; this was the standard dose employed in the clinic for the treatment of obesity (Pi-Sunyer et al. 2006) and a dose at which psychiatric side-effects have been observed (Christensen et al. 2007).

Materials and methods

Participants

Ethical approval for the study was obtained from the Oxfordshire Research Ethics Committee. We recruited 25 participants (16 female), after a complete description of the study to the subjects, written informed consent was obtained. All subjects starting treatment completed the 7-d treatment period; however, MRI scanning was not performed for three subjects (one female) due to technical issues, leaving a final sample of 22 (15 female) with mean age 21.4 yr (s.d. = 1.8 yr, range 18–25 yr) which forms the basis for all subsequent analyses. In this study we aimed to recruit 30 participants but the study was terminated prematurely because of the withdrawal of rimonabant from clinical use by the European Medicines Agency in October 2008.

Participants were not currently using psychotrophic medication, were physically healthy as assessed by physical examination and reported medical history, had normal body mass index (BMI) (18–25), and were free from current or past Axis I psychiatric disorders on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders – IV (SCID-IV). Due to potential interactions between rimonabant and cannabinoids, such as those in marijuana, participants were required to provide a negative urine drug screen for marijuana (SureScreen Diagnostics, UK) on the day of the MRI scan. Female subjects were also required to provide a negative urine pregnancy test before starting treatment. MRI scanning was not carried out in the 7 d before the onset of menses for female subjects.

Participants were randomized to receive 20 mg/d rimonabant (Acomplia®, Sanofi-Aventis, UK) or lactose placebo. The randomization code was prepared by a researcher with no other involvement in this study. Treatments were presented in identical gelatine capsules in a double-blind manner. Participants were given a bottle containing seven capsules and instructed to take one capsule each morning immediately after breakfast. On the testing day subjects were instructed to take the capsule at a specified time, 2.5 h before the start of the MRI scan, in order to ensure comparable rimonabant plasma levels during scanning.

Subjective ratings

Baseline measurements. Participants’ height and weight was recorded at baseline. At baseline participants completed the Eysenck Personality Questionnaire (EPQ), Beck Depression Inventory (BDI; Beck et al. 1961), the Spielberger Trait Anxiety Inventory (STAI; Spielberger, 1983) (Table 1).

First and last treatment day. Participants completed a mood questionnaire, the Befindlichkeits Scale (BFS; von Zerssen et al. 1974) and also rated how much they
liked chocolate, craved chocolate on a scale of 1–10, and reported how often they ate chocolate in the past week (Rolls & McCabe, 2007) [Tables 1, S2 (available online)].

**Every treatment day.** Participants completed the following measures each morning before taking the capsule: STAI State (Spielberger, 1983), Positive and Negative Affect Scale (PANAS; Watson et al. 1988), and visual analogue scales (VAS) for the following words: hunger, thirst (Table S2). The VAS line was 140 mm long and the instructions were ‘Please place a vertical line at the point on the horizontal line which most represents how you have been feeling over the past 24 h. DON’T spend a long time thinking about each one. Please indicate how you have been feeling compared to how you typically feel. Each scale runs from –10 (Much LESS than normal) to 0 (How you normally feel) to +10 (Much MORE than normal).’ –10 was at 0 mm, 0 was at 70 mm, and +10 was at 140 mm.

Participants also completed a daily side-effects questionnaire, asking about the presence of nausea, dizziness, vomiting, insomnia, fatigue, cold/flu symptoms, and rating their severity (0 absent, 1 mild, 2 moderate, 3 severe) (Table S2).

**Overall design**

We compared brain responses to reward-related and aversive stimuli across the two groups. Each of the following conditions were applied nine times in a randomized order [see Table S1 (available online)]: chocolate in the mouth, chocolate picture, chocolate in the mouth with chocolate picture, strawberry in the mouth, strawberry picture, strawberry in the mouth with strawberry picture. Subjective effects of the stimuli were measured by psychophysical ratings of pleasantness, intensity, and wanting made on every trial by the subjects during the fMRI acquisition. The participants were instructed not to eat chocolate for 24 h before the scan, and to eat only a small lunch on the day of scanning.

**Stimuli**

Stimuli were delivered to the subject’s mouth through three Teflon tubes (one for the tasteless rinse control described below, one for chocolate taste, and one for strawberry taste) that were held between the lips. Each Teflon tube of ~3 m in length was connected to a separate reservoir via a syringe and a one-way syringe activated check valve (Model 14044-5, World Precision Instruments Inc., USA), which allowed 0.5 ml of any stimulus to be delivered manually at the time indicated by the computer. The chocolate was formulated to be liquid at room temperature, with a list of the six stimulus conditions described above in Table S1. A control tasteless solution 0.8 ml of water was used between trials (rinse in Table S1), and when subtracted from the effects of the other stimuli allowed somatosensory and any mouth movement effects to be subtracted from the effects produced by the other oral stimuli (de Araujo et al. 2003). The aversive stimulus was an artificial strawberry-flavoured drink (Rosemont Pharmaceuticals Ltd, UK), the taste of which has been previously shown to be rated as intense as the chocolate but unpleasant in valence (McCabe et al. 2009). Both the liquid chocolate and the strawberry had approximately the same sweetness and texture which enabled them to pass freely through the Teflon delivery tubes.

**Experimental procedure**

At the beginning of each trial, one of the six stimuli chosen by random permutation was presented. If the trial involved an oral stimulus, this was delivered in a 0.5-ml aliquot to the subject’s mouth. At the same time at the start of the trial a visual stimulus was presented, which was either the picture of chocolate, of mouldy strawberries or a grey control image of approximately the same intensity. The image was turned off after 7 s at which time a small green cross appeared on a visual display to indicate to the subject to swallow what was in the mouth. After a delay of 2 s, the subject was asked to rate each of the stimuli for pleasantness on

<table>
<thead>
<tr>
<th>Table 1. Group demographic and psychosocial measures</th>
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<tbody>
<tr>
<td>Measure</td>
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<tr>
<td>Mean (s.d.)</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Gender</td>
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<tr>
<td>BDI</td>
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<tr>
<td>EPQ-Neuroticism</td>
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<tr>
<td>EPQ-Psychoticism</td>
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<tr>
<td>EPQ-Lie Scale</td>
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<tr>
<td>EPQ-Extraversion</td>
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<tr>
<td>TRAIT</td>
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<tr>
<td>BMI</td>
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<tr>
<td>Choc Craving</td>
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<tr>
<td>Choc Liking</td>
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<td>Choc Freq Eat</td>
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</table>

BDI, Beck Depression Inventory; EPQ, Eysenck Personality Questionnaire; TRAIT, State-Trait Anxiety Inventory Trait score; BMI, body mass index [weight (kg)/height (m²)].
that trial (+2 very pleasant, −2 very unpleasant), for intensity on that trial (0 to +4), and for current wanting for chocolate (+2 wanting chocolate very much, 0 neutral, −2 very much not wanting chocolate). The ratings were made with a visual analogue rating scale in which the subject moved the bar to the appropriate point on the scale using a button box. Each rating period was 5 s long. After the last rating the grey visual stimulus indicated the delivery of the tasteless control solution that was also used as a rinse between stimuli, and this was administered in exactly the same way as a test stimulus and the subject was cued to swallow after 7 s by the green cross. The tasteless control was always accompanied by the grey visual stimulus. On trials on which only the picture of chocolate was shown, there was no rinse but the grey visual stimulus was shown, in order to allow an appropriate contrast as described below. There was then a 2-s delay period similar to other trials that allowed for swallowing followed by a 1-s gap until the start of the next trial. A trial was repeated for each of the six stimulus conditions (see Table S1), and the whole cycle was repeated nine times. The instruction given to the subject was (on oral delivery trials) to move the tongue once as soon as a stimulus or tasteless solution was delivered (at the time when the grey visual stimulus was turned on) in order to distribute the solution round the mouth to activate the receptors for taste and smell, and then to keep still for the remainder of the 7-s period until the green cross was shown, when the subject could swallow.

fMRI scan

The experimental protocol consisted of an event-related interleaved design using the six stimuli described above in random permuted sequence (see Table S1). Images were acquired with a 3.0-T Varian/Siemens whole-body scanner at the Oxford Centre for Magnetic Resonance (OCMR) where T2*-weighted EPI slices were acquired every 2 s (TR = 2). Imaging parameters were selected to minimize susceptibility and distortion artefact in the orbitofrontal cortex (Wilson et al. 2002). Coronal slices (n = 33) with in-plane resolution of 3 × 3 mm and between-plane spacing of 4 mm were obtained. The matrix size was 64 × 64 and the field of view was 192 × 192 mm. Acquisition was carried out during the task performance yielding 972 volumes in total. A whole-brain T2*-weighted EPI volume of the above dimensions, and an anatomical T1 volume with coronal plane slice thickness 3 mm and in-plane resolution of 1.0 × 1.0 mm was also acquired.

fMRI analysis

The imaging data were analysed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Pre-processing of the data used SPM5 realignment, reslicing with sinc interpolation, normalization to the Montreal Neurological Institute (MNI) coordinate system and spatial smoothing with a 6-mm full-width at half maximum isotropic Gaussian kernel and global scaling (Collins et al. 1994). The time-series at each voxel were low-pass filtered with a haemodynamic response kernel. Time-series non-sphericity at each voxel was estimated and corrected for (Friston et al. 2002), and a high-pass filter with a cut-off period of 128 s was applied. In the single event design, a general linear model was then applied to the time-course of activation where stimulus onsets were modelled as single impulse response functions and then convolved with the canonical haemodynamic response function (Friston et al. 1994). Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation (Worsley et al. 1996) linear contrasts of parameter estimates were defined to test the specific effects of each condition with each individual dataset. Voxel values for each contrast resulted in a statistical parametric map of the corresponding t statistic, which was then transformed into the unit normal distribution (SPM Z). The statistical parametric maps from each individual dataset were then entered into second-level, random-effects analyses accounting for both scan-to-scan and subject-to-subject variability. Further, to assess the between-group differences for each condition a repeated-measures factorial design was used with the between-group factor group (two levels, rimonabant and placebo) and the (within-subject) factor condition (six levels) (Glascher & Gitelman, 2008). SPM converts the t statistics to Z scores (Table 2). For the between-group analyses we report p values for each cluster within regions of a priori hypotheses (see Introduction), thresholded at p = 0.001 and fully corrected for the number of comparisons (resels) in the entire brain volume (multiple comparisons; Worsley et al. 1996) for which p < 0.05 family-wise error. We report small volume corrections for brain regions in which we had an a priori hypothesis (described in the Introduction) as follows (MNI coordinates): ventral striatum (x = −6, y = 10, z = −4) (McCabe et al. 2010; Rolls & McCabe, 2007) lateral orbitofrontal cortex (x = −16, y = 28, z = −18) (Rolls et al. 2003) and caudate nucleus (x = 10, y = 14, z = 0) (Fitzgerald et al. 2004; McCabe et al. 2009). Peaks within 15 mm of these which had a p value of at least <0.01
uncorrected in the whole-brain analysis and with a 
cluster threshold of 30 contiguous voxels \( k = 30 \) had 
applied small volume (false discovery rate) corrections 
for multiple comparisons (Worsley et al. 1996) with a 
radius corresponding to the full-width at half maxi-
mum of the spatial smoothing filter used. Plots of 
parameter estimates were extracted using the volume 
of interest eigenvariates tool in SPM5 with a sphere of 
6 mm around the peak voxel identified from the sig-
nificant contrast of interest in the key areas described 
in our a priori hypotheses. We also compared neural 
activations to a control visual condition (greypic) in 
subjects given rimonabant vs. placebo in the whole 
brain and also within a region of the occipital cortex. A 
structural mask of visual area 1 was created with WFU 
Pick Atlas (Maldjian et al. 2003) for the region-of-in-
terest analysis. For illustration purposes only WFU 
Pick Atlas (Maldjian et al. 2003) was used to display 
activations (www.fmri.wfubmc.edu/cms/software). 
Coordinates of the activations are listed in the stereo-
tactic space of the MNI’s ICBM152 brain [Tables 2, S3 
available online].

### Visual stimulation paradigm

A control visual stimulation paradigm was used to 
assess whether drug-related effects observed during 
reward processing might reflect global effects of 
rimonabant on baseline cerebral blood flow. A flashing 
checkerboard (frequency 8 Hz) was presented in 
blocks of 14 s alternating with 15 s of a fixation cross 
for a total of 10 on-off cycles. Subjects were instructed 
to lie with their eyes open during this control task.

### Results

**Demographic details and mood ratings**

The drug and the placebo groups were well-matched 
at baseline. There were no significant differences be-
tween the two groups as determined by independent-
samples \( t \) tests for: age, gender, BMI, self-reported 
chocolate consumption, chocolate liking and craving 
(all \( p > 0.2 \) (Table 1). There were also no significant 
differences on baseline (day 1) measures of personality 
(E PQ, TRAIT) or mood (BDI), all \( p > 0.07 \) (Table 1).

Seven days’ treatment with rimonabant vs. placebo 
produced no differences between the two groups in mood (STAI-State, PANAS, BFS, BDI) or on VAS of 
hunger and thirst or chocolate liking and craving as 
determined by repeated-measures ANOVAs with 
time (7 d) as a within-subjects factor (all time \( \times \) group 
interaction effects, \( p > 0.1 \) (Table S2). However, there 
was a significant difference in self-reported chocolate 
eating between the groups (repeated-measures ANOVA, 
time \( \times \) group interaction, \( p = 0.003 \). Subjects

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### Table 2. Regions showing significant treatment effect of rimonabant compared to placebo

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Montreal Neurological Institute (MNI) coordinates</th>
<th>Z score</th>
<th>Significance (( p ) value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo &gt; rimonabant Whole-brain correction (FWE) Sight of chocolate</td>
<td>OFC/amygdala transition area R 24 4 -16</td>
<td>4.31</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Ventral striatum/putamen R 16 18 -10</td>
<td>3.76</td>
<td>0.05</td>
</tr>
<tr>
<td>Strawberry in the mouth Caudate</td>
<td>R 8 10 12</td>
<td>3.24</td>
<td>0.03</td>
</tr>
<tr>
<td>Small volume correction (FDR) Sight of mouldy strawberries Caudate</td>
<td>R 6 4 6</td>
<td>3.89</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>L -8 0 10</td>
<td>3.36</td>
<td>0.007</td>
</tr>
<tr>
<td>Rimonabant &gt; placebo Small volume correction (FDR) Strawberry in mouth with the sight of mouldy strawberries L OFC</td>
<td>L -30 36 -8</td>
<td>2.25</td>
<td>0.05</td>
</tr>
</tbody>
</table>

FWE, Family-wise error; OFC, orbitofrontal cortex; FDR, false discovery rate, L OFC, lateral orbitofrontal cortex; R, right; L, left.
on rimonabant reported decreased chocolate eating in the treatment week, compared to the previous week, whereas the placebo group reported a small increase in chocolate eating.

**Adverse events**

No serious adverse events occurred, and no subjects dropped out. One subject in the rimonabant group reported moderate insomnia on days 5 and 6. There were no other reported psychiatric or behavioural effects. Subjects completed a daily side-effects questionnaire (nausea, dizziness, vomiting, insomnia, fatigue, cold/flu symptoms) which rated severity (0 absent, 1 mild, 2 moderate, 3 severe); total symptom score across 7 d did not differ between the two groups ($p = 0.65$) (Table S2).

**Ratings of stimuli**

Ratings of pleasantness, intensity and wanting for the stimuli were obtained during the scanning on each trial for every condition. All subjects rated the strawberry picture and taste as unpleasant and the chocolate stimuli as pleasant. Using repeated-measures ANOVA with ‘ratings’ as a first factor with three levels; pleasantness, intensity and wanting and ‘condition’ as a second factor with six levels (see Table S1 for the six condition levels) there was no significant main effect of group [$F(1,18) = 0.006$, $p = 0.93$] or condition × group interaction [$F(1,18) = 2.4$, $p = 0.14$] (see Fig. S1, available online).

**fMRI responses**

Table S3 provides a summary of the results for each contrast across all placebo subjects to indicate the main effect of task. Table 2 provides a summary of the results of the interaction with group.

**Main effect of task**

As expected, the taste stimuli of chocolate and strawberry activated a region of the anterior insula, i.e. the primary taste cortex, in all placebo-treated subjects (Table S3). The rewarding stimuli chocolate taste and chocolate picture activated reward-relevant circuitry including the ventral striatum and the orbitofrontal cortex. By contrast, the unpleasant stimuli of strawberry taste and sight of the mouldy strawberries activated areas involved in aversive processing including the lateral orbitofrontal cortex extending into the insula cortex and the caudate (Table S3).

**Chocolate reward**

The participants receiving rimonabant, compared to placebo, showed less blood oxygen level-dependent (BOLD) activation to the sight of chocolate in areas known to play a key role in reward, including the right ventral striatum/putamen (Fig. 1a, b) and the mid orbitofrontal cortex (Fig. 2a, b). There was also a non-significant trend ($p = 0.06$), towards reduced orbitofrontal activation to the taste of chocolate in the rimonabant group. There were no areas where the...
rimonabant group showed greater BOLD activation relative to placebo for any of the chocolate conditions (Table 2).

Aversive strawberry

The volunteers receiving rimonabant, compared to placebo showed less BOLD activation to the taste and sight of strawberry in the caudate, as illustrated in Fig. 3(a, b). The volunteers receiving rimonabant, also showed less BOLD activation to the sight of strawberry in the left ventral striatum, an area usually activated by pleasant stimuli. However, the volunteers receiving rimonabant, compared to placebo showed enhanced BOLD activation to the taste and sight of the strawberry condition in the lateral orbitofrontal cortex an area shown previously to respond to aversive stimuli.

Visual stimulation control experiment

A whole-brain analysis of visual stimulation on vs. visual stimulation off for the rimonabant compared to the placebo group revealed no significant differences \((n=15)\). A region of occipital (calcarine) cortex activated by photic stimulation across all subjects was identified as a region of interest. Analysis of mean % BOLD signal change in this region confirmed no differences between groups \((p=0.443)\) nor was there any difference in median % BOLD signal change \((p = 0.992)\) indicating that the observed effects of rimonabant did not result from non-specific haemodynamic changes.

Discussion

Our main finding is that 7 d treatment with rimonabant (20 mg), compared to placebo, reduces the neural processing of a rewarding stimulus in humans. Rimonabant reduced the neural response to the conditioned reinforcer, the sight of chocolate, in areas well characterized to play a key role in reward (the ventral striatum and the orbitofrontal cortex). While this finding is consistent with our hypothesis, the findings must be regarded as preliminary because withdrawal of the clinical license for rimonabant meant that we were unable to study the planned number of participants. Further using a between-group design in our study means that possible pre-existing differences between the groups cannot be ruled out; however, we did closely match the groups on baseline measures (Table 1) and used fMRI analysis designed for multiple-group designs.

We did not see any subjective changes in mood over the 7-d treatment period, or any between-group differences in subjective reports of ‘pleasantness’, ‘wanting’ or ‘intensity’ for each of the stimuli. However, such an effect was not anticipated given the short time-frame of the study with a small number of carefully screened participants and is consistent with our previous studies investigating the effects of 7-d pharmacological treatments on reward and emotional processing in healthy individuals (Harmer et al. 2009; McCabe et al. 2009). Despite this, we were able to detect an ability of rimonabant to lower neural responses to reward, a known neural accompaniment of
the symptom of anhedonia in clinical depression (Epstein et al. 2006; Keedwell et al. 2005). Interestingly, the drug group did report eating less chocolate over the treatment week compared to the placebo group.

Plausibly, inhibition of the neural basis of reward might precede any subjective changes in mood or anhedonia and thus lead to an increased risk of clinical lowering of mood during the course of extended treatment. This finding raises the possibility that early screening of psychotropic drugs in a human model of reward, designed to detect changes in neural biomarkers associated with risk of depression may one day have a part to play in avoiding the human and economic consequences of delivering poorly tolerated drugs to market.

Consistent with our results, studies in animals have shown that CB₁ antagonism can reduce the rewarding/reinforcing behaviours of several drugs of abuse including heroin (Navarro et al. 2001), cocaine (De Vries et al. 2001) nicotine (Cohen et al. 2002; Rigotti et al. 2009) and alcohol (Colombo et al. 2004). Further, there is evidence in rodents that CB₁ antagonism reduces food consumption (Carai et al. 2005; Di Marzo & Matias, 2005). Thus, in addition to lowered enjoyment (and consumption) of food, rimonabant may also decrease the motivation, seeking and experience of other sources of pleasure. Such behaviour is commonly seen in depressed patients where anhedonia has a pervasive quality which prevents any activities being regarded by the patient as pleasurable. It would be of interest to explore the generalization of the present action by studying, for example, the effect of CB₁ receptor antagonists on neural responses to monetary reward in healthy subjects.

Our study also revealed that rimonabant decreased activation in the caudate and ventral striatum to the unpleasant strawberry stimulus. Both of these striatal areas have been reported to respond to aversive (Jensen et al. 2003) and/or disgust-related (Fitzgerald et al. 2004; Phillips et al. 2004) stimuli in previous investigations. Indeed, the ventral striatum has been suggested to play a general role in motivational salience of aversive and positive cues alike (Horvitz, 2000). Such effects of rimonabant therefore suggest that this drug may also decrease the incentive salience of aversive cues and reduce motivation to avoid or escape their negative impact. Consistent with this possibility, rimonabant increased lateral orbitofrontal activity to the combination of the aversive strawberry taste and sight condition, an area of the brain that we have shown in previous studies to respond particularly to combinations of aversive stimuli (Rolls & McCabe, 2007) and which may be involved in higher-level valence evaluation (Kringelbach & Rolls, 2004).

Thus, it seems that in this model rimonabant can be seen to reduce activity in motivational areas to both pleasant and unpleasant stimuli but also increase activity specifically to the aversive combinations of stimuli in ‘punishment’ areas.

This effect of rimonabant on aversive processing shows an interesting contrast to that of the selective serotonin re-uptake inhibitor (SSRI) citalopram which had no effect on ventral striatal activity in response to an unpleasant strawberry stimulus but decreased activity to the sight and taste of strawberry in the lateral

Fig. 3. (a) Strawberry in the mouth condition (placebo > rimonabant). Axial, sagittal and coronal image of decreased caudate activation in the rimonabant group compared to the placebo group [(x=8, y=10, z=12), Z=3.24, p=0.03 family-wise error corrected]. (b) Parameter estimates from 6 mm sphere centred at (x=8, y=10, z=12) for rimonabant ( Continued) and placebo ( Continued).
orbitofrontal cortex (McCabe et al. 2009). Thus from these preliminary results it seems that rimonabant, as hypothesized, inhibits reward areas such as the ventral striatum but in terms of aversive processing, unlike citalopram, enhances the processing of aversive stimuli in lateral orbitofrontal cortex. This effect, in addition to the decreased neural response to reward may explain the reports of depressive-like symptoms in those treated with rimonabant. However, it would also be of interest to investigate the effects of rimonabant on the neural processing of negative emotional biases seen in depression. To do this, psychological probes, other than the one used in the current study, would need to be employed such as an emotional face perception task.

Our results are also consistent with evidence from animal studies showing that endocannabinoids play an important role in the modulation of the mesolimbic dopamine pathway, and are critically involved in reward processing. CB1 antagonists strongly reduce the reinforcing properties and consumption of highly palatable foods (Gessa et al. 2006; Maccioni et al. 2008; Mathes et al. 2008), but the effects on standard foods are less marked or absent entirely. For example, one study reported that rats offered a choice between standard chow and sugary desserts increased their calorie intake, which was reversed by rimonabant and another CB1 antagonist, but this was selective for the sweet foods while chow consumption was not reduced (Mathes et al. 2008). This implies that rimonabant may have an anhedonic effect in animal models and it is this that produces the reduced feeding and weight loss in rodents, rather than a primary anorectic effect. Our results support this interpretation and also provide the potential neural substrate in humans upon which rimonabant may exert its anti-obesity effects. However, it should be noted that CB1 receptors are expressed in other areas of the brain, such as the hypothalamus, and also in peripheral tissues (Despres et al. 2005). Antagonism of these receptors may also contribute to the ability of CB1 antagonists to produce weight loss and CB1 antagonists that do not enter the brain may avoid adverse psychiatric side-effects (Pavon et al. 2008; Verty et al. 2009). However, there is some evidence that central CB1 blockade is required for weight loss to occur (Son et al. 2010).

Whether the effects seen in our study are mediated by CB1 receptor antagonism or whether they are mediated by other effects of rimonabant is unclear; however, we believe that the former is more likely as rimonabant is highly selective for the CB1 receptor, with substantially less affinity for the other receptors known to be involved in endocannabinoid signalling, CB2 (Ka = 2–12 nM vs. 700–13 000 nM) (Pertwee, 2005) and TRPV1 (Ka = 1000 nM) receptors (De Petrocellis et al. 2001). Despite this, some animal studies have found that rimonabant has effects that cannot be explained by CB1 antagonism, e.g. in CB1 knockout mice (Haller et al. 2002). However, like rimonabant, other CB1 antagonists suppress preference for palatable foods (Mathes et al. 2008) and CB1 knockout mice show reduced body weight, increased anxiety and despair behaviours (Haller et al. 2002; Martin et al. 2002) all of which are consistent with the effects in this study being driven by CB1 antagonism.

Taken together, our data and previous animal evidence suggest that rimonabant has the ability to reduce the hedonic incentive value of stimuli such as food through inhibition of neural reward circuitry. This may be beneficial in reducing the ‘wanting’ and motivational drive for calorie-dense, palatable foods and aid weight loss. However, over time this inhibition of reward circuitry could lead to wider diminution of motivational behaviour to pleasurable activities which could in turn be associated with the development of anhedonia and thus depressive symptomatology.

As hypothesized, our results show that our model of reward can be sensitive to the neural effects of repeated treatment with a psychotropic drug, in the absence of a reported change in mood state. This could be of practical importance because it suggests that a neural model of reward may be a more sensitive measure of the early effects of pharmacological manipulations on the brain than subjective measures of reward and mood captured, for example, by self-rated questionnaires. Thus, this type of fMRI paradigm might be useful for the early screening of medications that could have adverse psychiatric side-effects in clinical use.

Note

Supplementary material accompanies this paper on the Journal’s website (http://journals.cambridge.org/ pnp).

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Statement of Interest

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