Reduced neural response to reward following 7 days treatment with the cannabinoid CB$_1$ antagonist rimonabant in healthy volunteers

CINP

Jamie Horder, Catherine J. Harmer, Philip J. Cowen and Ciara McCabe

University Department of Psychiatry, Warneford Hospital, Oxford, UK

Abstract

Reduced subjective experience of reward (anhedonia) is a key symptom of major depression. The anti-obesity drug and cannabinoid type 1 receptor (CB$_1$) antagonist, rimonabant, is associated with significant rates of depression and anxiety in clinical use and was recently withdrawn from the market because of these adverse effects.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.

*Received 5 February 2010; Reviewed 1 March 2010; Revised 15 March 2010; Accepted 22 March 2010;
First published online 29 April 2010*

Key words: CB$_1$ antagonist, depression, fMRI, obesity, reward, rimonabant.

Introduction

Rimonabant (SR141716) is an antagonist and possible inverse agonist (Pertwee, 2005) at the cannabinoid type 1 (CB$_1$) 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

Address for correspondence: Dr C. McCabe, Neuroscience Building, Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford OX3 7JX, UK.
Tel.: (01865)-223778   *Fax*: (01865)-251076
Email: ciara.mccabe@psych.ox.ac.uk

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 CB_1 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 CB_1 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 psychotropic 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

Table 1. Group demographic and psychosocial measures

Measure	Rimonabant ($n=12$) Mean (S.D.)	Placebo ($n=10$) Mean (S.D.)
Age, yr	21.4 (1.8)	21.4 (1.9)
Gender	5 male	2 male
BDI	2.6 (3.5)	0.5 (0.5)
EPQ-Neuroticism	8.2 (5.2)	5.4 (3.0)
EPQ-Psychoticism	4.3 (2.0)	3.4 (2.8)
EPQ-Lie Scale	6.2 (3.1)	7.5 (4.0)
EPQ-Extraversion	16.4 (4.0)	17.8 (1.9)
TRAIT	33.6 (9.4)	32.9 (8.1)
BMI	22.4 (2.0)	22.5 (0.7)
Choc Craving	5.4 (1.9)	5.5 (2.7)
Choc Liking	7.9 (1.2)	7.0 (2.5)
Choc Freq Eat	3.6 (2.2)	2.7 (2.0)

BDI, Beck Depression Inventory; EPQ, Eysenck Personality Questionnaire; TRAIT, State-Trait Anxiety Inventory Trait score; BMI, body mass index [weight (kg)/height (m²)].

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

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

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

Brain region		Montreal Neurological Institute (MNI) coordinates			Z score	Significance (*p* value)
		x	y	z		
Placebo > rimonabant						
Whole-brain correction (FWE)						
Sight of chocolate						
OFC/amygdala transition area	R	24	4	−16	4.31	0.05
Ventral striatum/putamen	R	16	18	−10	3.76	0.05
Strawberry in the mouth						
Caudate	R	8	10	12	3.24	0.03
Small volume correction (FDR)						
Sight of mouldy strawberries						
Caudate	R	6	4	6	3.89	0.002
	L	−8	0	10	3.36	0.007
Ventral striatum	L	−12	10	−8	3.24	0.01
Rimonabant > placebo						
Small volume correction (FDR)						
Strawberry in mouth with the sight of mouldy strawberries						
L OFC	L	−30	36	−8	2.25	0.05

FWE, Family-wise error; OFC, orbitofrontal cortex; FDR, false discovery rate, L OFC, lateral orbitofrontal cortex; R, right; L, left.

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 maximum 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 significant 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-interest 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 stereotactic 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 between 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 (EPQ, 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 × 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 × group interaction, $p=0.003$). Subjects
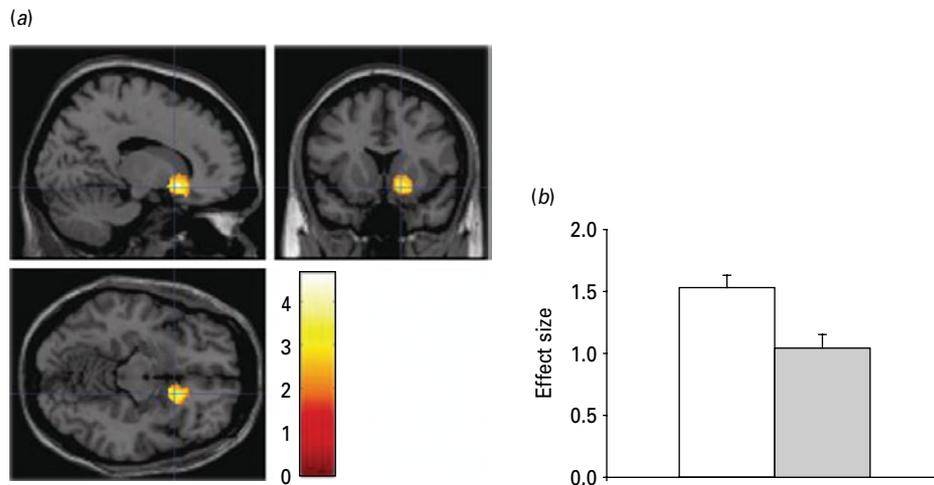
(*a*)

(*b*)

Fig. 1. (*a*) Sight of chocolate condition (placebo > rimonabant). Axial, saggital and coronal image of decreased ventral striatal activation in the rimonabant group compared to the placebo group [(x = 16, y = 18, z = −10], Z = 3.76, p < 0.05 family-wise error corrected]. (*b*) Parameter estimates from 6 mm sphere centred at (x = 16, y = 18, z = −10) for rimonabant (■) and placebo (□).

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. 1*a*, *b*) and the mid orbitofrontal cortex (Fig. 2*a*, *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
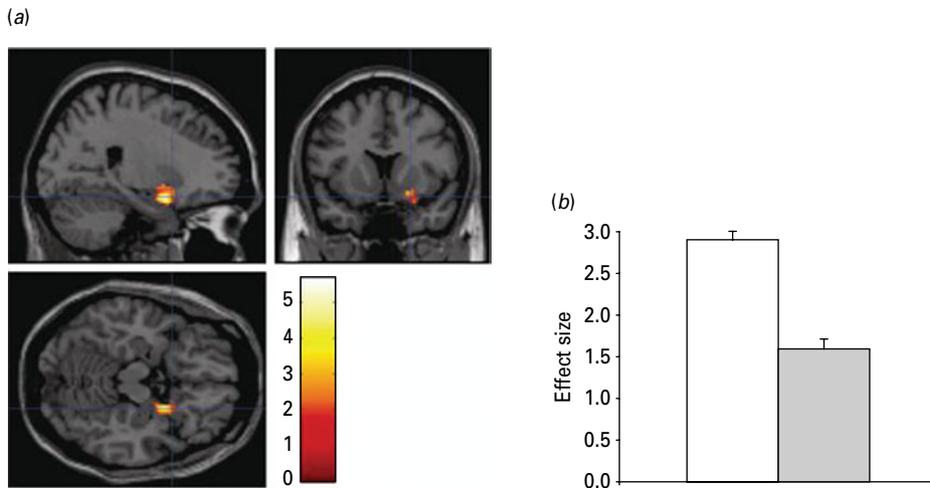
(*a*)

(*b*)

Fig. 2. (*a*) Sight of chocolate condition (placebo > rimonabant). Axial, saggital and coronal image of decreased mid orbitofrontal cortex activation in the rimonabant group compared to the placebo group [(x = 24, y = 4, z = −16], Z = 4.31, *p* = 0.05 family-wise error corrected]. (*b*) Parameter estimates from 6 mm sphere centred at (x = 24, y = 4, z = −16) for rimonabant (▢) and placebo (□).

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
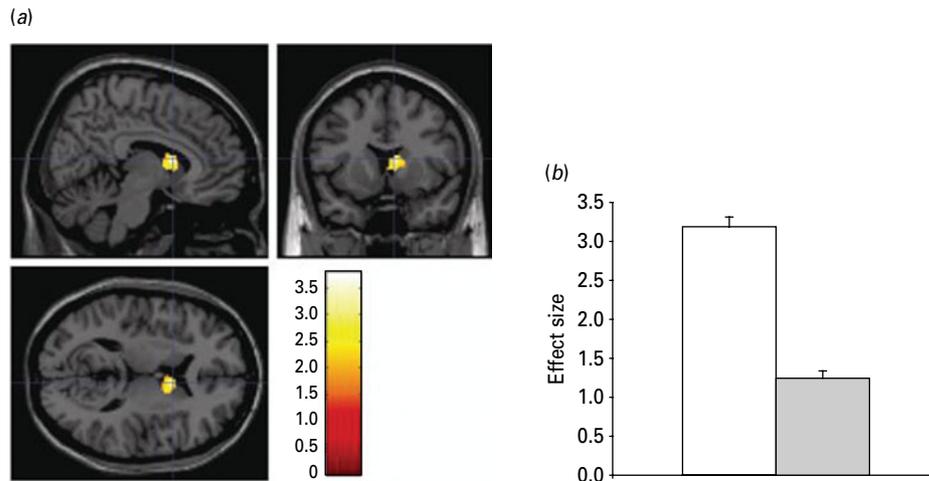
(*a*)

(*b*)

Fig. 3. (*a*) Strawberry in the mouth condition (placebo > rimonabant). Axial, saggital 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 (■) and placebo (□).

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 CB_1 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 CB_1 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 CB_1

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

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. CB_1 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 CB_1 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 CB_1 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 CB_1 antagonists to produce weight loss and CB_1 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 CB_1 blockade is required for weight loss to occur (Son *et al.* 2010).

Whether the effects seen in our study are mediated by CB_1 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 CB_1 receptor, with substantially less affinity for the other receptors known to be involved in endocannabinoid signalling, CB_2 ($K_i = 2$–12 nM *vs.* 700–13 000 nM) (Pertwee, 2005)

and TRPV1 ($K_i = 1000$ nM) receptors (De Petrocellis *et al.* 2001). Despite this, some animal studies have found that rimonabant has effects that cannot be explained by CB_1 antagonism, e.g. in CB_1 knockout mice (Haller *et al.* 2002). However, like rimonabant, other CB_1 antagonists suppress preference for palatable foods (Mathes *et al.* 2008) and CB_1 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 CB_1 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 sympomatology.

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).

Sharpe and Dohme. Professor Cowen has been a paid member of advisory boards of Eli Lilly, Servier, Wyeth and Xytis and has been a paid lecturer for Eli Lilly, Servier and GlaxoSmithKline.

References

Beck AT, Ward CH, Mendelson M, Mock J, *et al.* (1961). An inventory for measuring depression. *Archives of General Psychiatry* **4**, 561–571.

Carai MA, Colombo G, Gessa GL (2005). Rimonabant: the first therapeutically relevant cannabinoid antagonist. *Life Sciences* **77**, 2339–2350.

Christensen R, Kristensen PK, Bartels EM, Bliddal H, *et al.* (2007). Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* **370**, 1706–1713.

Cohen C, Perrault G, Voltz C, Steinberg R, *et al.* (2002). SR141716, a central cannabinoid (CB(1)) receptor antagonist, blocks the motivational and dopamine-releasing effects of nicotine in rats. *Behavioural Pharmacology* **13**, 451–463.

Collins DL, Neelin P, Peters TM, Evans AC (1994). Automatic 3D intersubject registration of MR volumetric data in standardized talairach space. *Journal of Computer Assisted Tomography* **18**, 192–205.

Colombo G, Vacca G, Serra S, Carai MA, *et al.* (2004). Suppressing effect of the cannabinoid CB1 receptor antagonist, SR 141716, on alcohol's motivational properties in alcohol-preferring rats. *European Journal of Pharmacology* **498**, 119–123.

de Araujo IE, Kringelbach ML, Rolls ET, McGlone F (2003). Human cortical responses to water in the mouth, and the effects of thirst. *Journal of Neurophysiology* **90**, 1865–1876.

De Petrocellis L, Bisogno T, Maccarrone M, Davis JB, *et al.* (2001). The activity of anandamide at vanilloid VR1 receptors requires facilitated transport across the cell membrane and is limited by intracellular metabolism. *Journal of Biological Chemistry* **276**, 12856–12863.

De Vries TJ, Shaham Y, Homberg JR, Crombag H, *et al.* (2001). A cannabinoid mechanism in relapse to cocaine seeking. *Nature Medicine* **7**, 1151–1154.

Despres JP, Golay A, Sjostrom L (2005). Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *New England Journal of Medicine* **353**, 2121–2134.

Di Marzo V, Matias I (2005). Endocannabinoid control of food intake and energy balance. *Nature Neuroscience* **8**, 585–589.

Epstein J, Pan H, Kocsis JH, Yang Y, *et al.* (2006). Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *American Journal of Psychiatry* **163**, 1784–1790.

Fitzgerald DA, Posse S, Moore GJ, Tancer ME, *et al.* (2004). Neural correlates of internally-generated disgust via autobiographical recall: a functional magnetic resonance imaging investigation. *Neuroscience Letters* **370**, 91–96.

Friston KJ, Glaser DE, Henson RN, Kiebel S, *et al.* (2002). Classical and Bayesian inference in neuroimaging: applications. *NeuroImage* **16**, 484–512.

Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, *et al.* (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping* **1**, 214–220.

Gessa GL, Orru A, Lai P, Maccioni P, *et al.* (2006). Lack of tolerance to the suppressing effect of rimonabant on chocolate intake in rats. *Psychopharmacology* (*Berlin*) **185**, 248–254.

Glascher J, Gitelman D (2008). Contrast weights in flexible factorial design with multiple groups of subjects (unpublished tutorial) (https://www.jiscmail.ac.uk/cgi-bin/webadmin?A2=ind0803&L=SPM&P=R16629).

Griebel G, Stemmelin J, Scatton B (2005). Effects of the cannabinoid CB1 receptor antagonist rimonabant in models of emotional reactivity in rodents. *Biological Psychiatry* **57**, 261–267.

Haller J, Bakos N, Szirmay M, Ledent C, *et al.* (2002). The effects of genetic and pharmacological blockade of the CB1 cannabinoid receptor on anxiety. *European Journal of Neuroscience* **16**, 1395–1398.

Harmer CJ, Goodwin GM, Cowen PJ (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *British Journal of Psychiatry* **195**, 102–108.

Herkenham M, Lynn AB, Johnson MR, Melvin LS, *et al.* (1991). Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *Journal of Neuroscience* **11**, 563–583.

Horvitz JC (2000). Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. *Neuroscience* **96**, 651–656.

Jensen J, McIntosh AR, Crawley AP, Mikulis DJ, *et al.* (2003). Direct activation of the ventral striatum in anticipation of aversive stimuli. *Neuron* **40**, 1251–1257.

Keedwell PA, Andrew C, Williams SC, Brammer MJ, *et al.* (2005). The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry* **58**, 843–853.

Kringelbach ML, Rolls ET (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in Neurobiology* **72**, 341–372.

Le Foll B, Gorelick DA, Goldberg SR (2009). The future of endocannabinoid-oriented clinical research after CB(1) antagonists. *Psychopharmacology* (*Berlin*) **205**, 171–174.

Maccioni P, Pes D, Carai MA, Gessa GL, *et al.* (2008). Suppression by the cannabinoid CB1 receptor antagonist, rimonabant, of the reinforcing and motivational properties of a chocolate-flavoured beverage in rats. *Behavioural Pharmacology* **19**, 197–209.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* **19**, 1233–1239.

Martin M, Ledent C, Parmentier M, Maldonado R, *et al.* (2002). Involvement of CB1 cannabinoid receptors in

emotional behaviour. *Psychopharmacology* (*Berlin*) **159**, 379–387.

Mathes CM, Ferrara M, Rowland NE (2008). Cannabinoid CB1 receptor antagonists reduce caloric intake by decreasing palatable diet selection in a novel dessert protocol in female rats. *American Journal of Physiology. Regulatory Integrative and Comparative Physiology* **295**, R67–75.

McCabe C, Cowen PJ, Harmer CJ (2009). Neural representation of reward in recovered depressed patients. *Psychopharmacology* (*Berlin*) **205**, 667–677.

McCabe C, Mishor Z, Cowen PJ, Harmer CJ (2010). Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biological Psychiatry* **67**, 439–445.

McCabe C, Rolls ET (2007). Umami: a delicious flavor formed by convergence of taste and olfactory pathways in the human brain. *European Journal of Neuroscience* **25**, 1855–1864.

McCabe C, Rolls ET, Bilderbeck A, McGlone F (2008). Cognitive influences on the affective representation of touch and the sight of touch in the human brain. *Social Cognitive and Affective Neuroscience* **3**, 97–108.

Moreira FA, Crippa JA (2009). The psychiatric side-effects of rimonabant. *Revista Brasileira de Psiquiatria* **31**, 145–153.

Navarro M, Carrera MR, Fratta W, Valverde O, *et al.* (2001). Functional interaction between opioid and cannabinoid receptors in drug self-administration. *Journal of Neuroscience* **21**, 5344–5350.

Nissen SE, Nicholls SJ, Wolski K, Rodes-Cabau J, *et al.* (2008). Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. *Journal of the American Medical Association* **299**, 1547–1560.

Patel S, Roelke CT, Rademacher DJ, Hillard CJ (2005). Inhibition of restraint stress-induced neural and behavioural activation by endogenous cannabinoid signalling. *European Journal of Neuroscience* **21**, 1057–1069.

Pavon FJ, Serrano A, Perez-Valero V, Jagerovic N, *et al.* (2008). Central versus peripheral antagonism of cannabinoid CB1 receptor in obesity: effects of LH-21, a peripherally acting neutral cannabinoid receptor antagonist, in zucker rats. *Journal of Neuroendocrinology* **20** Suppl 1, 116–123.

Pertwee RG (2005). Inverse agonism and neutral antagonism at cannabinoid CB1 receptors. *Life Sciences* **76**, 1307–1324.

Phillips ML, Williams LM, Heining M, Herba CM, *et al.* (2004). Differential neural responses to overt and covert presentations of facial expressions of fear and disgust. *NeuroImage* **21**, 1484–1496.

Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, *et al.* (2006). Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *Journal of the American Medical Association* **295**, 761–775.

Rigotti NA, Gonzales D, Dale LC, Lawrence D, *et al.* (2009). A randomized controlled trial of adding the nicotine patch to rimonabant for smoking cessation: efficacy, safety and weight gain. *Addiction* **104**, 266–276.

Rolls ET, Kringelbach ML, de Araujo IE (2003). Different representations of pleasant and unpleasant odours in the human brain. *European Journal of Neuroscience* **18**, 695–703.

Rolls ET, McCabe C (2007). Enhanced affective brain representations of chocolate in cravers *vs.* non-cravers. *European Journal of Neuroscience* **26**, 1067–1076.

Son MH, Kim HD, Chae YN, Kim MK, *et al.* (2010). Peripherally acting CB1-receptor antagonist: the relative importance of central and peripheral CB1 receptors in adiposity control. *International Journal of Obesity* (*London*) **34**, 547–556.

Spielberger CD (1983). *Manual for the State-trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Steiner MA, Marsicano G, Nestler EJ, Holsboer F, *et al.* (2008). Antidepressant-like behavioral effects of impaired cannabinoid receptor type 1 signaling coincide with exaggerated corticosterone secretion in mice. *Psychoneuroendocrinology* **33**, 54–67.

Takahashi E, Katayama M, Niimi K, Itakura C (2008). Additive subthreshold dose effects of cannabinoid CB(1) receptor antagonist and selective serotonin reuptake inhibitor in antidepressant behavioral tests. *European Journal of Pharmacology* **589**, 149–156.

US Food and Drug Administration Advisory Committee (2007). FDA briefing document: Zimulti (rimonabant) tablets, 20 mg (http://www.fda.gov/OHRMS/ DOCKETS/AC/07/briefing/2007-4306b1-00-index.htm). Accessed 6 August 2007.

Verty AN, Allen AM, Oldfield BJ (2009). The effects of rimonabant on brown adipose tissue in rat: implications for energy expenditure. *Obesity* (*Silver Spring*) **17**, 254–261.

von Zerssen D, Strian F, Schwarz D (1974). Evaluation of depressive states, especially in longitudinal studies. *Modern Problems of Pharmacopsychiatry* **7**, 189–202.

Watson D, Clark LA, Tellegen A (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology* **54**, 1063–1070.

Wilson JL, Jenkinson M, de Araujo I, Kringelbach ML, *et al.* (2002). Fast, fully automated global and local magnetic field optimization for fMRI of the human brain. *NeuroImage* **17**, 967–976.

Worsley KJ, Marrett P, Neelin AC, Friston KJ, *et al.* (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping* **4**, 58–73.