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# Effects of 7 days of treatment with the cannabinoid type 1 receptor antagonist, rimonabant, on emotional processing

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## Abstract

Rimonabant is a cannabinoid type 1 receptor (CB1) antagonist formerly used to treat obesity, but which was withdrawn from the market in late 2008 because of its association with psychiatric adverse effects such as depression and anxiety. Previously, we showed that a single dose of rimonabant produced a negative bias on an emotional word memory task, in the absence of subjective mood effects. The present study investigated whether a similar effect on emotional processing could be seen after 7 days' daily treatment with rimonabant 20 mg, using a randomized, placebo-controlled, between-subjects design in healthy volunteers (final  $n = 21$ ). In comparison with placebo, rimonabant induced a negative bias on a memory recognition task without producing a change in subjective mood. This raises the possibility that the depressogenic effects of rimonabant may be linked to emotional memory biases, and that such biases may be detectable in the absence of subjective mood changes. Investigating such effects could be useful in detecting adverse psychiatric effects of novel treatments.

## Keywords

Cannabinoids, CB1 antagonists, depression, endocannabinoids, facial expression recognition, healthy volunteers, memory, rimonabant

## Introduction

Negative biases in information processing are prominent in clinical depression. Patients with depression are more likely to retrieve negative self-relevant information in both explicit (i.e. free recall) and implicit (i.e. primed lexical decision) memory paradigms (Bradley et al., 1995). Also, depressed patients are more likely to perceive ambiguous facial expressions as negative compared with controls (Bouhuys et al., 1999; Gur et al., 1992). The increased accessibility of negative perceptions and memories is believed to maintain and exaggerate depressed mood, while itself being a product of the depressed mood state, leading to a self-perpetuating cycle (Beck, 2008). Recent studies suggest that these kinds of processing biases are affected by pharmacological manipulations which can treat or cause depression (see Harmer et al., 2009).

Rimonabant was the first cannabinoid receptor type 1 (CB1) antagonist to be licensed for clinical use. It was approved in Europe in 2006 for the treatment of obesity, but in early 2009 the licensing authorization was withdrawn due to the occurrence of psychiatric side effects, including depression, anxiety and suicidal ideation (Le Foll et al., 2009; Moreira and Crippa, 2009). A meta-analysis of four trials of rimonabant for obesity (total  $n = 4105$ ) reported 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 reported

that 26% of those taking rimonabant 20 mg/day experienced a psychiatric symptom reported as an adverse event versus 14% on placebo (US Food and Drug Administration Advisory Committee, 2007).

These side effects were not predicted from preclinical studies in rodents. Acute treatment with CB1 antagonists, including rimonabant, have repeatedly shown effects similar to those of antidepressants in commonly used models such as the rodent forced swim test (see for example Griebel et al., 2005), which led to suggestions that CB1 antagonists might even have clinical utility as antidepressants (Witkin et al., 2005). In rodent models of anxiety, conflicting results have been obtained with both increases (Navarro et al., 1997) and decreases (Griebel et al., 2005; Haller et al., 2002) in anxiety being observed in different studies. However, we have previously shown that a single dose of rimonabant impairs positive affective memory in healthy volunteers (Horder et al., 2009), an effect similar to that seen in depression and opposite to

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effects of antidepressant drug agents in this task (Harmer et al., 2009).

Adverse effects such as those reported with rimonabant are usually only identified after extensive use of these drugs by patients. The early detection of such effects in volunteer studies could therefore have significant implications for public health by helping to restrict the exposure of vulnerable patients to potentially harmful compounds. However, the effect of rimonabant on emotional memory was relatively specific, and there were no changes in facial expression recognition or attentional vigilance which have also been associated with depression and antidepressant drug action (Harmer et al., 2009). The current study therefore also examined whether subchronic (7 days') administration of rimonabant induces more extensive negative biases in emotional processing.

## Materials and methods

### Participants

We recruited 25 participants (16 female), who provided written informed consent for the study, which was approved by the local research ethics committee. There was no dropout, i.e. all subjects starting treatment completed the 7-day treatment period. However, behavioural data was not available for four participants due to technical issues, leaving a final sample of 21 (13 female) participants with mean age 21.6 years (SD 1.9, range 18–25 years), which forms the basis for all subsequent analyses. We had planned to recruit 30 participants, but this study was terminated prematurely because of the withdrawal of rimonabant from clinical use by the European Medicines Agency in early 2009.

Participants were not currently using psychotropic medication, were physically healthy as assessed by physical examination and reported medical history, had normal Body Mass Index (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) at the end of the 7-day treatment period. Female subjects were also required to provide a negative urine pregnancy test before starting treatment. Testing was not carried out in the 7 days before the onset of menses for female subjects.

Participants were randomized to receive rimonabant 20 mg/day (Acomplia, Sanofi-Aventis) or lactose placebo. The dose of 20 mg/day was that at which rimonabant was used clinically and was the dose associated with high rates of depression and anxiety in clinical trials, even though it has been suggested that this dose produces only partial blockade of CB1 receptors (Tallafuss et al., 2010).

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 for 7 days. On the psychological

testing day (generally the sixth day of the treatment period, or the seventh in some cases) subjects were instructed to take the capsule at a specified time, 2.5 h before the start of the testing, in order to ensure comparable rimonabant plasma levels during the tests.

The volunteers in this study also participated in a functional magnetic resonance imaging (fMRI) experiment investigating the effects of rimonabant on the neural response to food stimuli, the results of which have been published previously (Horder et al., 2010). The fMRI scanning took place on the day after the behavioural testing.

### Subjective ratings

Participants' height and weight was recorded at baseline. At baseline participants completed the Eysenck Personality Questionnaire (EPQ), Beck Depression Inventory (BDI), and the Spielberger Trait Anxiety Inventory (STAI), (Table 1).

On day 1 and 7 of treatment participants completed a mood questionnaire, the Befindlichkeits Scale (BFS). From day 1 (the first treatment day) to day 7 (the final treatment day), all participants completed the following measures each morning before taking the capsule: STAI State and Positive and Negative Affect Scale (PANAS).

### Psychological tasks

Psychological testing was conducted as described previously; for more details of the experimental tasks please refer to previous papers (Horder et al., 2009).

**Rey Auditory Verbal Learning Task.** Declarative verbal memory was measured with the Rey Auditory Verbal Learning Test (AVLT) (Rey, 1964), in which participants are read a list of 15 words and required to repeat them immediately afterwards, the list being read five times with responses required after each cycle.

**Word categorization and memory.** A total of 60 personality characteristic words selected to be extremely disagreeable (e.g. domineering, untidy, hostile) or agreeable (cheerful, honest, optimistic) (taken from Anderson, 1968) were presented on the computer screen for 500 ms. These words were matched in terms of word length, ratings of frequency, and meaningfulness. Participants were asked to categorize these personality traits as likable or dislikable, as quickly and as accurately as possible. Specifically, they were asked to imagine whether they would be pleased or upset if they overheard someone else referring to them as possessing this characteristic, so that the judgement was in part self-referring.

Approximately 15 min after completion of the categorization task, participants were asked to recall, and write down, as many of the personality trait words as possible, and they were given 2 min to do this. This task therefore allowed the assessment of incidental memory for positive and negative characteristics. Recognition memory was then assessed by asking volunteers to respond with a 'Yes' or 'No' to each

**Table 1.** Demographic Data. Group demographic measures, and baseline personality and mood scores. There were no significant between-group differences on any measure (*t*-tests) ( $p > 0.2$  in all cases)

*Group demographic and psychosocial measures.*

Measure	Placebo ( $n = 11$ ) Mean (SD)	Rimonabant ( $n = 10$ ) Mean (SD)
Age, years	21.4 (1.9)	21.6 (2.0)
Gender	4 male	4 male
BDI	2.5 (6.8)	2.4 (3.8)
EPQ-N	5.6 (3.6)	8.3 (5.7)
EPQ-P	4.6 (4.3)	4.0 (1.5)
EPQ-L	7.2 (4.3)	5.9 (2.5)
EPQ-E	17.9 (2.3)	16.5 (4.1)
TRAIT	33.6 (9.3)	34.0 (10.3)
BMI	22.7 (0.8)	22.2 (2.0)

BDI, Beck Depression Inventory; TRAIT, State-Trait Anxiety Inventory Trait score; EPQ, Eysenck Personality Questionnaire; N, Neuroticism; P, Psychoticism; L, Lie Scale; E, Extraversion. BMI, (Body Mass Index) = weight in kg/(height in meters \* height in meters).

item on a list containing the 60 targets plus 60 matched distractors (30 positive, 30 negative).

A similar categorization task was carried out as a control for non-specific effects on speed and incidental memory, in which participants were asked to indicate whether the characteristic would be an advantage (30 words, e.g. strong) or disadvantage (30 words, e.g. slow) for a predatory animal. Recall and recognition of these animal-related words were also assessed approximately 15 min after the categorization task, using the same parameters as the emotional categorization task.

The order of testing was: Emotional word categorization, Animal word categorization, Emotional Recall, Emotional Recognition, Animal Recall, Animal Recognition.

**Dot-probe task.** Two types of emotional words were used in this task: 60 social-threatening negative words and 60 positive words. Each emotional word was paired with a neutral word that began with the same letter and was matched for length. There were therefore 60 socially threatening-neutral pairs and 60 positive-neutral pairs. In addition there were 60 neutral-neutral pairs.

Each trial started with a fixation cross for 500 ms, followed by a word pair. On each trial, one of the words appeared above and the other below the central fixation position. The emotional words appeared in the top and bottom location with equal frequency. In the unmasked condition, the word pair was presented for 500 ms and then a probe appeared in the location of one of the preceding words. The probe was either one or two stars, and participants were asked to press one of two labelled buttons to indicate the number of stars present on the screen; their response terminated the probe display. Participants were asked to respond as quickly and as accurately as possible. The sequence of events was the same in the masked condition, except the duration of the word pair was 14 ms and the display of the word pair was immediately followed by a mask which was displayed for 186 ms.

Mean reaction time and accuracy scores were recorded. Reaction times which were at more than two standard deviations from individual means were considered as outliers and discarded. Vigilance scores were calculated for each participant by subtracting the reaction time from trials when probes appeared in the same position as the emotional word (congruent trials) from trials when probes appeared in the opposite position to the emotional word (incongruent trials).

**Facial emotion recognition task.** The facial expression recognition task featured six basic emotions (happiness, surprise, sadness, fear, anger and disgust) taken from the Pictures of Affect Series (Ekman and Friesen, 1976), which had been morphed between each prototype and neutral (Young et al., 1997). Briefly, this procedure involved taking a variable percentage of the shape and texture differences between the two standard images 0% (neutral) and 100% (full emotion) in 10% steps. Four examples of each emotion at each intensity were given (total of 10 individuals). Each face was also given in a neutral expression, giving a total of 250 stimuli presentations. The facial stimuli were presented on a computer screen (random order) for 500 ms and replaced by a blank screen. Participants were instructed to classify each face as being one of either angry, disgusted, fearful, happy, sad, surprised or neutral, as quickly and as accurately as possible.

**Statistical analysis**

The demographic characteristics of the two groups were compared using independent-samples *t*-tests. Subjective visual analogue scale scores were subjected to repeated-measures analysis of variance (ANOVA) with drug status as a between-subjects factor and time from baseline as a within-subject factor (four change values per item). BFS and STAI data were analysed in terms of change from baseline using independent values *t*-test. Data from the facial emotion recognition task, the dot-probe task, and the word

categorization and memory task were assessed using a repeated-measures ANOVA with drug as a between-subjects factor, and stimulus emotional valence as a within-subject factor. For the dot-probe, masking was also a within-subject factor. Statistically significant interactions were followed up with simple main effect analyses. Data from each task were analysed separately without correcting for multiple comparisons across tasks.

## Results

### Demographic and personality characteristics

The two treatment groups did not differ significantly in terms of gender, age, verbal IQ as estimated using scores on the National Adult Reading test (NART), baseline scores on the BDI, BFS, EPQ N-scale (Neuroticism), state measure of the STAI and trait measure of the STAI (all  $p > 0.2$ , two-tailed).

### Subjective state ratings

There were no between-group difference in the change in subjective state ratings following rimonabant versus placebo for the BDI, BFS, STAI State ( $p > 0.25$ ). There was no effect of group or group  $\times$  time interaction on PANAS Positive ( $p > 0.15$ ) or Negative ( $p > 0.6$ ) score. There was no difference in total side-effect burden ( $p = 0.59$ ). No treatment-emergent side effects were reported with the exception of moderate insomnia in one male in the rimonabant group. A full account of the data on the subjective state effects has been published previously (Horder et al., 2010).

### Emotional processing tasks

**Word categorization.** There were no significant between-group differences in the accuracy of classification of self-relevant emotional words: ANOVA group  $\times$  valence  $F(1,19) = 0.364$ ,  $p = 0.594$ ; main effect of group  $F(1,19) = 2.739$ ,  $p = 0.114$ . For non-self-relevant words, ANOVA group  $\times$  valence  $F(1,19) = 0.134$ ,  $p = 0.718$ ; main effect of group  $F(1,19) = 0.961$ ,  $p = 0.339$ .

There were likewise no significant between-group differences in the latency (RT) of classification of self-relevant emotional words: ANOVA group  $\times$  valence  $F(1,19) = 0.142$ ,  $p = 0.710$ ; main effect of group  $F(1,19) = 1.092$ ,  $p = 0.309$ . For non-self-relevant words, ANOVA group  $\times$  valence  $F(1,19) = 1.719$ ,  $p = 0.205$ ; main effect of group  $F(1,19) = 0.371$ ,  $p = 0.549$ .

**Word recall.** Rimonabant had no effect upon the correct recall of self-referent (emotional) words (ANOVA group  $\times$  valence  $F(1,19) = 0.141$ ,  $p = 0.711$ ; group main effect  $F(1,19) = 0.131$ ,  $p = 0.722$ ) or upon intrusion errors (ANOVA group  $\times$  valence  $F(1,19) = 0.772$ ,  $p = 0.391$ ; group main effect  $F(1,19) = 0.208$ ,  $p = 0.653$ ).

Likewise, rimonabant had no effect in the non-self-relevant (animal) words control task for correct recall

(ANOVA group  $\times$  valence  $F(1,19) = 2.246$ ,  $p = 0.150$ ; group main effect  $F(1,19) = 1.069$ ,  $p = 0.314$ ) or upon intrusion errors (ANOVA group  $\times$  valence  $F(1,19) = 0.304$ ,  $p = 0.588$ ; group main effect  $F(1,19) = 0.752$ ,  $p = 0.397$ ).

**Word recognition.** ANOVA revealed no emotion  $\times$  group ( $F(1,19) = 0.716$ ,  $p = 0.408$ ) or main effect of group ( $F(1,19) = 0.567$ ,  $p = 0.461$ ) on accuracy of recognition for previously seen self-relevant (emotional) words. Likewise, there was no emotion  $\times$  group ( $F(1,19) = 1.554$ ,  $p = 0.228$ ) or main effect of group ( $F(1,19) = 0.166$ ,  $p = 0.688$ ) on accuracy for previously seen non-self-relevant (animal) words.

There were likewise no significant between-group differences in the latency (RT) of recognition of self-relevant emotional words: ANOVA group  $\times$  valence  $F(1,19) = 0.745$ ,  $p = 0.399$ ; main effect of group  $F(1,19) = 1.549$ ,  $p = 0.228$ . For non-self-relevant words, ANOVA group  $\times$  valence  $F(1,19) = 0.197$ ,  $p = 0.662$ ; main effect of group  $F(1,19) = 2.048$ ,  $p = 0.169$ .

However, in the self-relevant (emotional) word task, rimonabant selectively reduced the number of positive versus negative word intrusion errors – the number of unseen words falsely reported as having been previously seen – (ANOVA group  $\times$  emotion  $F(1,19) = 5.262$ ,  $p = 0.033$ ) with no group main effect ( $F(1,19) = 2.382$ ,  $p = 0.139$ ).

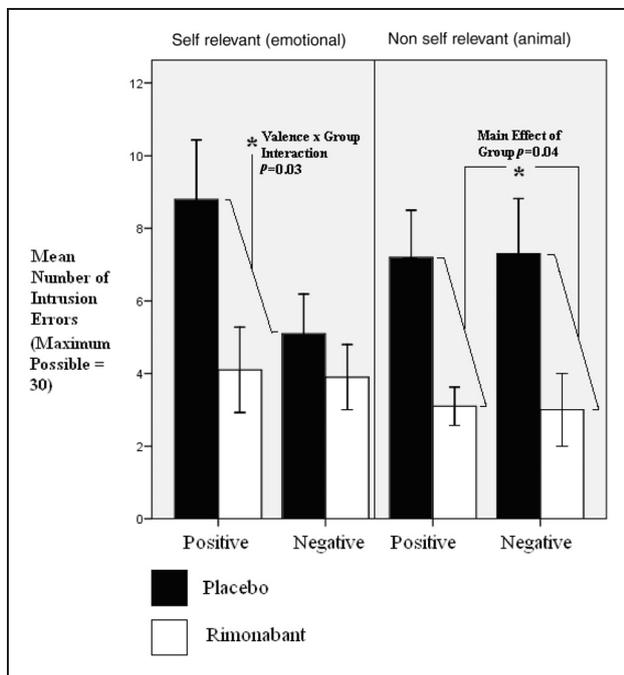
By contrast, in the non-self-relevant (animal) word variant of the task, there was no group  $\times$  valence effect on animal word intrusions ( $F(1,19) = 0.009$ ,  $p = 0.925$ ); however, there was a main effect of group ( $F(1,19) = 5.084$ ,  $p = 0.036$ ). The rimonabant group showed fewer intrusions overall (see Figure 1).

**Dot-probe.** ANOVA revealed no significant group effects or interactions with group (all  $p$  values  $> 0.4$ ) in performance on this task.

**Facial emotion recognition.** Considering accuracy to classify faces as each of the six basic emotions, ANOVA revealed a highly significant main effect of emotion ( $F(5,85) = 5.434$ ,  $p < 0.001$ ) but no emotion  $\times$  group interaction ( $F(5,85) = 0.626$ ,  $p = 0.680$ ) or group main effect ( $F(1,17) = 1.161$ ,  $p = 0.296$ ). No effect was seen after removing data from one subject with extremely poor accuracy scores and low reaction times ( $p > 0.6$ ). No effects were seen when accuracy to classify neutral was also considered ( $p > 0.3$ ).

For reaction time, ANOVA likewise revealed a main effect of emotion ( $F(5,85) = 10.798$ ,  $p < 0.001$ ), with no main effect of group ( $F(1,17) = 1.233$ ,  $p = 0.282$ ) and no emotion  $\times$  group interaction ( $F(5,85) = 1.245$ ,  $p = 0.295$ ).

**Rey AVLT.** A repeated-measures ANOVA on words correctly recalled over the five acquisition trials of the AVLT revealed a highly significant effect of time ( $F(4,76) = 76.858$ ,  $p < 0.001$ ), indicating successful learning, but no group  $\times$  time interaction ( $F(4,76) = 0.458$ ,  $p > 0.7$ ) nor a group main effect ( $F(1,19) = 0.082$ ,  $p > 0.7$ ), indicating that rimonabant had no



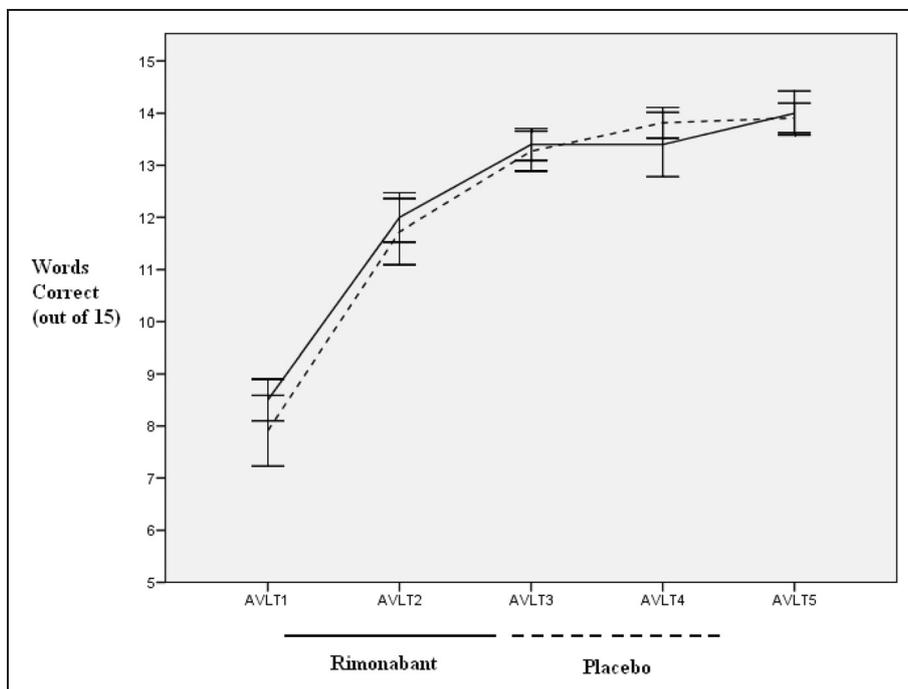
**Figure 1.** Mean number of intrusion errors (novel words falsely endorsed as previously seen) on Word Recognition memory task, for rimonabant 20 mg group and placebo group. Maximum possible intrusion errors = 30. Error bars represent  $\pm 1$  Standard Error of the Mean. Rimonabant selectively reduced intrusion errors for positive words in the Self Relevant condition ( $p = 0.03$ ) while in the Non Self Relevant condition, both positive and negative intrusion errors were reduced ( $p = 0.04$ ).

effect on this task (see Figure 2). Results from cognitive tasks are summarized in Table 2.

## Discussion

Seven days of treatment with rimonabant, 20 mg daily, selectively reduced the number of positive word intrusion errors on a recognition memory task. This effect is consistent with the idea that chronic treatment with rimonabant produces a negative bias in an aspect of emotional memory which is sensitive to depression (Mathews and MacLeod, 2005). Negative biases in the recall and recognition of self-relevant, emotional events are amongst the most consistent findings in the cognitive assessment of depression (Beck, 2008; Mathews and MacLeod, 2005). Interestingly, treatment of healthy volunteers with various antidepressants for 7 days reliably increases positive bias in emotional memory recall (Harmer et al., 2009), an effect, in *some* respects, opposite to that seen here.

Although this finding should be interpreted with caution as we did not apply statistical correction for the multiple tasks used in our battery, it is intriguing in the context of the known psychiatric adverse effects of rimonabant, and raises the possibility that performance in emotional memory tasks may have the potential to signal depressogenic potential of novel psychoactive drugs. This would be consistent with our hypothesis (Harmer, 2010) that the mood effects of certain psychotropic drugs are mediated through effects on the processing of emotional information in the absence of any changes in subjective state, and that these effects on emotional processing may be a key mechanism by which drugs lead to changes in mood over time. In particular, impaired positive



**Figure 2.** Mean number of words correctly recalled on Auditory Verbal Learning Test task measuring declarative memory, on each of five trials, for rimonabant 20 mg group and placebo group. Maximum score = 15. Error bars represent  $\pm 1$  Standard Error of the Mean. There were no significant between-group differences at any time point ( $t$ -tests) or overall (repeated measures ANOVA);  $p > 0.7$  in all cases.

**Table 2.** Results; data from all cognitive tasks

Results			
Measure	Placebo Mean (SD)	Rimonabant Mean (SD)	Significance (Test)
FERT: Happy	23.7 (4.2)	24.3 (4.1)	$p = 0.76$
FERT: Sad	17.0 (5.0)	19.6 (6.2)	$p = 0.32$
FERT: Disgust	19.9 (5.3)	20.6 (6.1)	$p = 0.80$
FERT: Surprise	24.0 (3.3)	23.4 (2.8)	$p = 0.64$
FERT: Anger	22.8 (2.9)	20.7 (2.8)	$p = 0.11$
FERT: Fear	19.8 (5.2)	20.8 (2.6)	$p = 0.58$
DOT PROBE: Positive Masked	+24.4 ms (50.7)	+8.4 ms (23.1)	$p = 0.37$
DOT PROBE: Negative Masked	+4.9 ms (34.5)	+2.5 ms (27.3)	$p = 0.86$
DOT PROBE: Positive Unmasked	-13.9 ms (31.8)	-6.2 ms (31.4)	$p = 0.58$
DOT PROBE: Negative Unmasked	-6.2 ms (32.5)	+5.3 ms (15.7)	$p = 0.32$
CAT: Emotional Positive	28.5 (1.9)	29.5 (0.8)	$p = 0.16$
CAT: Emotional Negative	28.7 (1.4)	29.3 (0.7)	$p = 0.25$
CAT: Animal Positive	27.2 (6.4)	29.1 (1.3)	$p = 0.35$
CAT: Animal Negative	27.6 (4.9)	29.2 (1.3)	$p = 0.31$
RECALL: Emotional Positive	4.1 (2.1)	4.6 (2.8)	$p = 0.65$
RECALL: Emotional Negative	3.0 (2.4)	3.2 (2.4)	$p = 0.85$
RECALL: Animal Positive	7.0 (2.7)	5.3 (2.5)	$p = 0.15$
RECALL: Animal Negative	4.3 (1.8)	4.3 (1.9)	$p = 0.97$
RECOG: Emotional Positive	26.6 (2.2)	25.0 (2.7)	$p = 0.15$
RECOG: Emotional Negative	20.5 (4.8)	20.1 (3.7)	$p = 0.85$
RECOG: Animal Positive	25.9 (4.1)	24.1 (4.5)	$p = 0.35$
RECOG: Animal Negative	20.8 (3.8)	21.5 (3.1)	$p = 0.66$
RECOG: Emotional Positive Intrusions	8.2 (5.3)	4.1 (3.7)	$p = 0.056$
RECOG: Emotional Negative Intrusions	4.7 (3.5)	3.9 (2.8)	$p = 0.56$
RECOG: Animal Positive Intrusions	6.6 (4.3)	3.1 (1.7)	$p = 0.026$
RECOG: Animal Negative Intrusions	7.3 (4.8)	3.0 (3.2)	$p = 0.030$
AVLT 1	7.9 (2.3)	8.5 (1.3)	$p = 0.47$
AVLT 2	11.7 (2.1)	12.0 (1.5)	$p = 0.73$
AVLT 3	13.3 (1.3)	13.4 (1.0)	$p = 0.80$
AVLT 4	13.8 (1.0)	13.4 (2.0)	$p = 0.53$
AVLT 5	13.9 (0.9)	14.0 (1.3)	$p = 0.86$
AVLT (Delay)	13.0 (1.6)	12.4 (1.4)	$p = 0.37$

FERT, Facial Emotion Recognition Task: Scores are out of 30 maximum.  $n = 20$ , 1 outlier removed (results unchanged if included). DOT PROBE: Results are vigilance scores, i.e. RT (word incongruent) - RT (word congruent). RECALL and RECOG: All scores are out of a maximum possible of 30. AVLT, Auditory Verbal Learning Test: All scores are out of a maximum of 15.

memory bias would be predicted to increase vulnerability to depression in combination with stressors or other negative environmental cues.

We observed no effect of rimonabant upon declarative verbal memory performance as assessed using the Rey AVLT task, nor upon recall for classified words. The effect seen here was therefore selective to words with a positive relevance, and not a general memory-impairing or enhancing effect, although interestingly, rimonabant also reduced the number of intrusion errors for non-self-relevant words.

These effects are similar, in some respects, to those seen in a previous study with a single dose of rimonabant 20 mg (Horder et al., 2009) in which rimonabant reduced the number of positive emotional words correctly recalled. In both studies, rimonabant affected memory for positive emotional words while not affecting negative ones.

However, there were differences in that in the first study rimonabant reduced true recall, while in this study it reduced false recognition, i.e. intrusion errors.

The effect of rimonabant in the current study was, also, selective; there was no effect upon other measures of emotional processing, such as facial expression recognition accuracy, which have been shown to be sensitive to both antidepressant drug administration and the state of depression. Thus the effect of rimonabant on these emotional tasks was relatively subtle. However, the fact that the study had to be terminated early, following the withdrawal of rimonabant from the European market, restricted the power of our investigation and it is possible that with the number of participants proposed originally, a broader range of effects on emotional processing might have been apparent. Also, administration of rimonabant to people at higher risk of depression through,

for example, a previous history of illness, might also have revealed more substantial effects on emotional bias.

We observed no effect of rimonabant treatment upon any subjective (self-report) measures of mood and anxiety. This stands in contrast to the data from numerous large randomized controlled trials finding that rimonabant 20 mg/day increases rates of depression, anxiety and other psychiatric symptoms, relative to placebo (see Introduction). There are several possible explanations for this difference. Firstly, we only used 1 week of treatment, while clinical trials of rimonabant for obesity were generally of several months duration (up to 24 months). Other short-term studies of rimonabant have likewise reported no mood changes with rimonabant 40 mg for 15 days (Huestis et al., 2007) or after rimonabant 20 mg for 14 days (George et al., 2009). Second, our volunteers were young, of healthy weight and carefully screened to exclude any possible psychiatric history; they may, therefore, have been less vulnerable to depression and anxiety than the overweight patients enrolled in rimonabant clinical trials.

The current results, and the previous single-dose results, stand in contrast to the data from preclinical animal studies in which both antidepressant-like effects in rodent models of depression (see Introduction) and enhanced memory processes in a number of species (Lichtman, 2000; Shiflett et al., 2004; Terranova et al., 1996) are seen following acute rimonabant administration. These differences may relate to differences in tasks. However, they do imply that current animal models may not be able to identify drugs that have a risk of causing depression in humans, and that human models may have an advantage in this respect. More recently, it has been reported that longer-term (21 days) daily treatment with rimonabant did, in fact, produce depression-like effects in a number of behavioural and neurochemical models in rats (Beyer et al., 2010). This implies that repeated administration of drugs might provide a better assessment of their antidepressant/depressogenic effect in animals, further underscoring the need for caution when interpreting results from acute administration.

In conclusion, our results suggest that subchronic treatment with rimonabant 20 mg has an effect upon an aspect of emotional processing that is opposite to that seen with acute antidepressant treatment and that is therefore consistent with its liability to cause depressive mood changes in some patients.

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## Conflict of interest

Catherine Harmer serves on the advisory panel for p1vital and has acted as a paid consultant for Lundbeck, Merck, Sharpe and Dohme and p1vital. Philip Cowen has acted as a paid consultant for Eli Lilly, Lundbeck and Servier.

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