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RESEARCH ARTICLE

Neural Effects of Cannabinoid CB1 Neutral Antagonist Tetrahydrocannabivarin on Food Reward and Aversion in Healthy Volunteers

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Abstract

Background: Disturbances in the regulation of reward and aversion in the brain may underlie disorders such as obesity and eating disorders. We previously showed that the cannabis receptor subtype (CB1) inverse agonist rimonabant, an antiobesity drug withdrawn due to depressogenic side effects, diminished neural reward responses yet increased aversive responses (Horder et al., 2010). Unlike rimonabant, tetrahydrocannabivarin is a neutral CB1 receptor antagonist (Pertwee, 2005) and may therefore produce different modulations of the neural reward system. We hypothesized that tetrahydrocannabivarin would, unlike rimonabant, leave intact neural reward responses but augment aversive responses.

Methods: We used a within-subject, double-blind design. Twenty healthy volunteers received a single dose of tetrahydrocannabivarin (10mg) and placebo in randomized order on 2 separate occasions. We measured the neural response to rewarding (sight and/or flavor of chocolate) and aversive stimuli (picture of moldy strawberries and/or a less pleasant strawberry taste) using functional magnetic resonance imaging. Volunteers rated pleasantness, intensity, and wanting for each stimulus.

Results: There were no significant differences between groups in subjective ratings. However, tetrahydrocannabivarin increased responses to chocolate stimuli in the midbrain, anterior cingulate cortex, caudate, and putamen. Tetrahydrocannabivarin also increased responses to aversive stimuli in the amygdala, insula, mid orbitofrontal cortex, caudate, and putamen.

Conclusions: Our findings are the first to show that treatment with the CB1 neutral antagonist tetrahydrocannabivarin increases neural responding to rewarding and aversive stimuli. This effect profile suggests therapeutic activity in obesity, perhaps with a lowered risk of depressive side effects.

Keywords: reward, THCv, obesity, fMRI, cannabinoid

Introduction

Obesity is among the most frequent preventable causes of mortality in the developed world and is associated with several

different causes of death, including heart disease, type 2 diabetes, and some forms of cancer (see Haslam and James, 2005,

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for an overview). As part of an effective treatment strategy for obesity, it may be useful to supplement behavioral control of food intake with the administration of drugs to modulate the processes by which the brain generates eating behavior.

The endocannabinoid system in the brain, involving cannabinoid type 1 (CB1) receptors, may regulate feeding behavior by modulating the reward signal associated with the consumption of food (Solinas et al., 2008). Rimonabant, a CB1 antagonist and inverse agonist (Pertwee, 2005), has been found to downregulate feeding and promote weight loss (Scheen et al., 2006), acting selectively on the consumption of sweet foods (Maccioni et al., 2008; Mathes et al., 2008). Furthermore, a reduced sensitivity to reward and to the effects of cannabinoid compounds has been demonstrated in animals with a lower expression of CB1 receptors in the striatum (Friemel et al., 2014).

Rimonabant was, however, withdrawn from clinical use in the EU in 2008 following mounting evidence of increased rates of depression following its use (Christensen et al., 2007). The rodent studies used in early screening of the drug largely failed to detect this potential for depressogenic side effects and in fact suggested antidepressant effects instead (Griebel et al., 2005). This highlights the importance of developing a human experimental medicine model for the development of weight-loss treatments, such that most adverse psychiatric effects of the drug can be detected before clinical use is approved.

Using a human experimental model of reward and aversion processing in the brain with functional magnetic resonance imaging (fMRI), we previously showed that 7 days' treatment with rimonabant reduced the neural response to rewarding chocolate stimuli in key reward areas such as the ventral striatum, putamen, and orbitofrontal cortex (OFC) (Horder et al., 2010). We have also demonstrated a similar pattern of reduced response using the same task with recovered depressed patients (McCabe et al., 2009). This similarity suggests a mechanism inducing anhedonia, which could lead to the increased risk of depressive symptomatology seen in clinical use of the drug. Rimonabant also increased lateral OFC activations to the sight and taste of an aversive food, and these effects might underlie its ability to promote weight loss.

Like rimonabant, tetrahydrocannabinol (THCv) acts on endocannabinoid CB1 receptors but does so as a neutral antagonist (Pertwee, 2005). Neutral antagonists have been suggested as a potentially safer alternative to rimonabant in the treatment of obesity (Meye et al., 2013) and appear to entail fewer side effects such as nausea, while still attenuating operant behavior in animals (Bergman et al., 2008). The increased safety and tolerability of neutral antagonists compared with rimonabant is not associated with an attenuation of the therapeutically valuable antagonistic action at CB1 receptors (Kangas et al., 2013). Most promisingly, recent animal studies have shown that neutral antagonists appear to reduce food intake and weight gain as rimonabant does, but unlike rimonabant do not suppress activity in emotion regulation areas such as the ventral tegmental area and basolateral amygdala (Meye et al., 2013). However, how THCv interacts with the reward and aversion systems in the human brain is as yet unknown.

Therefore, in this study we aim to examine the effects of THCv using our model of reward and aversion processing in the human brain. We hypothesize that as THCv is thought to be free from the depressogenic side effects seen with rimonabant, it will leave intact responses to rewarding stimuli in areas that our task (Rolls and McCabe, 2007; McCabe et al., 2009) and other studies (O'Doherty et al., 2001) have shown to be involved in reward processing, such as the anterior cingulate cortex (ACC), OFC, and striatum. To the extent that THCv nonetheless produces therapeutically valuable modulations of food aversion, we

hypothesize increased activations to aversive stimuli in areas that have been shown to be involved in the processing of food aversion, such as the amygdala, insula, and lateral OFC (Zald et al., 2002; McCabe et al., 2010, 2011, 2012).

Materials and Methods

Participants

Twenty participants (10 female), aged 20 to 36 years, completed a within-participants, double-blind, placebo-controlled, cross-over design. Participants were recruited from the university volunteer register and via internet advertisements. Participants were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders Schedule (First et al., 1997) to exclude a current or previous history of major depression or any other Axis 1 disorder. Participants also had no history of drug or alcohol misuse and did not smoke more than 5 cigarettes per day. Participants were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), had normal or corrected to normal vision, and were not taking medications apart from the contraceptive pill. Participants had no neurological disorders or contraindications for MRI. Ethical approval was obtained from the Oxford Research Ethics Committee. After receiving a complete description of the study, participants gave written informed consent.

Baseline ratings of mood and anhedonia were collected using the Beck Depression Inventory (Beck et al., 1961), the Fawcett-Clarke Pleasure Scale (Fawcett et al., 1983), the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995), and the Temporal Experience of Pleasure Scale (Gard et al., 2007). Participants reported liking and craving chocolate as measured by our previously designed questionnaire (Rolls and McCabe, 2007). Body mass index and an Eating Attitudes questionnaire were used to rule out eating disorders (Garner et al., 1982) (Table 1).

Experimental Design

Participants completed the task during fMRI, once with the drug (10mg THCv approximately 1 hour before scan to allow for peak blood plasma levels to occur) and then again 1 week later with the placebo, or vice versa. Both participant and experimenter were blind to the treatment condition. We compared brain responses with rewarding and aversive food tastes and images. Each of the following conditions was applied 9 times in randomized order (supplementary Table S1): chocolate taste, chocolate picture, chocolate taste and picture, medicinal strawberry

Table 1. Descriptive Statistics of Demographic Variables

	Mean	SD
Age (y)	25.4	4.5
BMI	22.1	1.80
SHAPS	17.8	4.7
FCPS	146	21.1
BDI	1.36	2.29
EAT	6.16	5.4
TEPS (state)	84.9	12.2
TEPS (trait)	83.7	10.4
Chocolate craving	6.6	2.0
Chocolate liking	8.7	1.4
Chocolate, frequency of consumption	2.0	1.3

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; EAT, Eating Attitudes questionnaire; FCPS, Fawcett Clarke Pleasure Scale; SHAPS, Snaith-Hamilton Pleasure Scale; TEPS Temporal Experience of Pleasure Scale.

taste, picture of moldy strawberries, strawberry taste and picture. Participants were instructed not to eat chocolate for 24 hours before the scan and to eat only a small breakfast on the day of scanning. Mood state and side effects were recorded on the study day with the Befindlichkeits scale of mood and energy (von Zerssen et al., 1974) and the visual analogue scale (VAS) for alertness, disgust, drowsiness, anxiety, happiness, nausea, sadness, withdrawal, and faintness (supplementary Table S4).

Rewarding and Aversive Stimuli

Stimuli were delivered to the participant's mouth through 3 Teflon tubes held between the lips. Each tube was connected to a separate reservoir via a syringe and a 1-way syringe-activated check valve (World Precision Instruments, Sarasota, FL), which allowed 0.5 mL of any liquid to be delivered manually at the time indicated by the computer. The chocolate was liquid at room temperature. The aversive stimulus was a medicinal-flavored strawberry solution (Rosemont Pharmaceuticals, Leeds, UK) rated equal in intensity to the chocolate but less pleasant in valence (McCabe et al., 2009). A control tasteless solution (25×10^{-3} mol/L KCl and 2.5×10^{-3} mol/L NaHCO_3 in distilled H_2O) was used after every trial that had a taste component, and a control gray image of approximately equal intensity to the food images was used after every trial that had a sight component. This allowed the subtraction on every trial of the appropriate control condition. This allows analysis of taste, texture, and olfactory effects independently of any somatosensory effects produced by introducing a fluid into the mouth. Both the chocolate and strawberry had approximately the same texture.

Experimental Procedure

At the beginning of each trial, 1 of the 6 conditions chosen by random permutation was presented. If the trial involved an oral stimulus, this was delivered in a 0.5-mL aliquot to the participant's mouth at the same time the image was presented. The image was turned off after 7 seconds. A small green cross then appeared, prompting the participant to swallow what was in the mouth. After a delay of 2 seconds, the participant was asked to rate each of the stimuli for pleasantness on that trial (+2 being very pleasant and -2 very unpleasant), intensity on that trial (0 to +4), and wanting (+2 for wanting very much, 0 for neutral, and -2 for very much not wanting). The ratings were made with a VAS in which the participant moved a bar to the appropriate point on the scale using a button box. After the last rating, the gray image indicated delivery of the control solution, which also served as a rinse. This was administered in the same way as the experimental tastes and the participant was cued to swallow after 7 seconds. After trials with an image but no taste, there was no rinse, but the gray visual stimulus was shown to allow an appropriate control as described above.

fMRI Data Acquisition

The experimental protocol was an event-related interleaved design with the 6 stimuli described above and in supplementary Table S1. Brain images were acquired with a 3.0-T VARIAN/SIEMENS whole-body scanner at the Oxford Centre for Functional Magnetic Resonance Imaging. $T2^*$ -weighted EPI slices were acquired every 2 seconds ($\text{TR}=2$). Imaging parameters were selected to minimize susceptibility and distortion artefacts in the OFC (Wilson et al., 2002). Coronal slices with in-plane resolution of 3×3 mm and between-plane spacing of 3 mm were obtained. The matrix size was 64×64 and the field of

view was 192×192 mm. Acquisition was carried out during 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 were also acquired.

fMRI Data Analysis

Imaging data were preprocessed and analyzed using statistical parametric mapping software SPM8. Data preprocessing included realignment, normalization to the Montreal Neurological Institute coordinate system, reslicing with sinc interpolation, and spatial smoothing with a full-width isotropic Gaussian kernel and global scaling. For each voxel, time-series nonsphericity was corrected for (Friston et al., 2002) and a low-pass filter was applied (with a hemodynamic response kernel), as was a high-pass filter, with a cutoff period of 128 seconds. In the single event design, where each trial contains a single event, a general linear model was then applied to the time course of activation where stimulus onsets were modeled as single impulse response functions and then convolved with the canonical hemodynamic response function (Friston et al., 1994). Time derivatives were included in the basis function set. Following smoothness estimation, 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). Movement parameters for each person were added as additional regressors in the first-level analyses. Second-level fMRI analyses first examined simple main effects of task with 1-sample t tests in the placebo test session only (supplementary Tables S3-4). To examine the effect of THCv, we used the 1-way ANOVA within-participants design implemented in SPM8 for each condition separately and reported all data thresholded at $P < .05$. Regions of interest (ROIs) in which we had a priori hypotheses, based on our previous studies using this task, were: OFC [26 32 -10] (McCabe et al., 2010), ACC [-2 26 20] [10 16 30] (McCabe et al., 2011, 2012), ventral striatum [-12 6 4] (Rolls and McCabe, 2007), insula [-34 16 0] [-32 18 6] [42 20 -10], and amygdala [20 -2 -22] (McCabe et al., 2009, 2011, 2012; Horder et al., 2010). Peaks within 15 mm of these locations and within the functional ROIs identified by our 1-sample main effects t tests (supplementary Tables S2-3) and which met a cluster threshold of 30 contiguous voxels ($k=30$) were small volume corrected (svc) for multiple comparisons (family wise error [FWE], $P < .05$). Exploratory whole brain analysis was also carried out, and clusters were corrected ($P < .05$ FWE) for multiple comparisons. Gender and order were also added as covariates of no interest in the SPM8 model. For the plots of peak, contrast estimates were extracted using the plots tool in SPM8, and WFU Pick Atlas was used to display neural activation (Maldjian et al., 2003). Activation coordinates are listed in the stereotactic space of the Montreal Neurological Institute ICBM 152 brain (Table 2).

Results

Demographic Data

Demographic data analysis (Table 1) revealed participants had low depression scores as well as normal scores on the Eating Attitudes questionnaire and were in the healthy weight range. Participants demonstrated a high level of chocolate craving and liking as demonstrated by their responses on the chocolate

Table 2. Blood Oxygen Level Dependent Responses to Rewarding (Chocolate) Stimuli and Aversive Strawberry THCv vs Placebo

Anatomical region	Coordinates (MNI)			Z-score	P
	X	Y	Z		
Chocolate sight					
Putamen	16	10	-6	2.74	.03 svc
ACC	-2	20	36	3.19	.03 svc
Caudate	-8	8	18	4.09	<.001
Mid brain	6	-6	-2	3.95	<.001
Cingulate gyrus	-18	-28	36	3.8	<.001
Chocolate sight and taste					
Mid cingulate gyrus	-14	-8	42	3.5	<.001
Strawberry sight					
Insula	38	10	10	3.46	<.001
Mid OFC	-16	36	-10	3.42	<.001
STG	54	10	-10	3.43	<.001
Putamen	-26	8	-12	3.3	<.001
Strawberry sight and taste					
Putamen	16	6	-2	2.74	.03 svc
Amygdala	24	6	-18	2.66	.03 svc
Insula	-38	14	-14	2.98	.005
Mid OFC	-18	32	-10	3.28	.005
STG	54	10	-10	3.81	.005
Thalamus	4	-6	6	3.23	.005
Caudate	-8	14	2	3.09	.005

Abbreviations: ACC, anterior cingulate cortex; FWE, family wise error; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; STG, superior temporal gyrus; svc, small volume corrected; tetrahydrocannabinol, THCv.

Threshold set at $P < .05$. P-values: svc ($P < .05$ FWE-corrected for multiple comparisons). P values: whole brain corrected ($P < .05$ FWE-corrected for multiple comparisons). Gender and order were added as covariates of no interest.

eating questionnaire. One-way ANOVAs revealed no significant effects ($P < .05$) of gender on any of the demographic measures.

Mood, Energy, and Affect Scores

Repeated-measures ANOVAs were employed to examine the effect of drug (placebo/THCv) and time (prescan/postscan) on scores of mood, energy, and affect, as measured by the Befindlichkeits scale of mood and energy and VAS (supplementary Table S4). Results revealed there was no main effect of drug on mood, energy, or affect ($P < .05$). To assess any potential confounding effects of gender or order (THCv first/placebo first) on mood, these factors were included in the analyses as independent variables. No main effects of gender or order and no gender \times drug or order \times drug interactions were revealed.

Subjective Ratings of Stimuli

Repeated-measures ANOVAs were used to examine the effect of drug (placebo/THCv) on subjective ratings of pleasantness, wanting, and intensity of the food stimuli (chocolate taste, chocolate picture, chocolate taste and picture, strawberry taste, strawberry picture, strawberry taste and picture). There was a main effect of condition; as expected, the pleasant chocolate stimuli and the less pleasant strawberry stimuli were rated differently, but there were no main effects of drug or drug \times condition interactions (supplementary Figure S1; supplementary Table S5).

Main Effects of Stimuli on BOLD Responses

Tables S2 and S3 provide a summary of the main effects for the rewarding chocolate stimuli vs control stimuli and the aversive strawberry stimuli vs control stimuli in the placebo group

only. As expected, the pleasant chocolate taste and picture stimuli activated reward-relevant circuitry, including the ventral striatum, OFC, ACC, and insula (supplementary Table S2). As expected, the less pleasant strawberry taste and picture stimuli activated circuitry including the amygdala, insula, and lateral OFC (supplementary Table S3).

Effect of THCv on BOLD Responses to Food Stimuli

Table 2 provides a summary of the results of the effects of THCv. ROI analyses revealed that THCv, compared with placebo, enhanced BOLD activations in response to the chocolate sight in the putamen (Figure 1) and ACC (Figure 2), and increased BOLD activations in response to the aversive strawberry taste and sight in the putamen and amygdala (Figure 3). Whole brain analysis revealed that, compared with placebo, THCv enhanced BOLD activations in response to the chocolate stimuli in the caudate, mid brain, and cingulate gyrus (Table 2). There was no effect of THCv on chocolate taste alone.

For the less pleasant conditions, we found that THCv enhanced activation to the strawberry sight in the insula (Figure 4), mid OFC, superior temporal gyrus, and putamen in the whole brain analysis. Similar regions such as the insula, mid OFC, superior temporal gyrus, thalamus, and caudate were also enhanced under the combination condition of strawberry taste and sight. The figures display the significant between-group differences.

A region of the occipital cortex activated by photic stimulation across all subjects was identified as a ROI. Repeated-measures ANOVA for drug/placebo in this region confirmed no suprathreshold clusters, FWE cluster corrected. Indicating that the observed effects of THCv did not result from global hemodynamic changes.

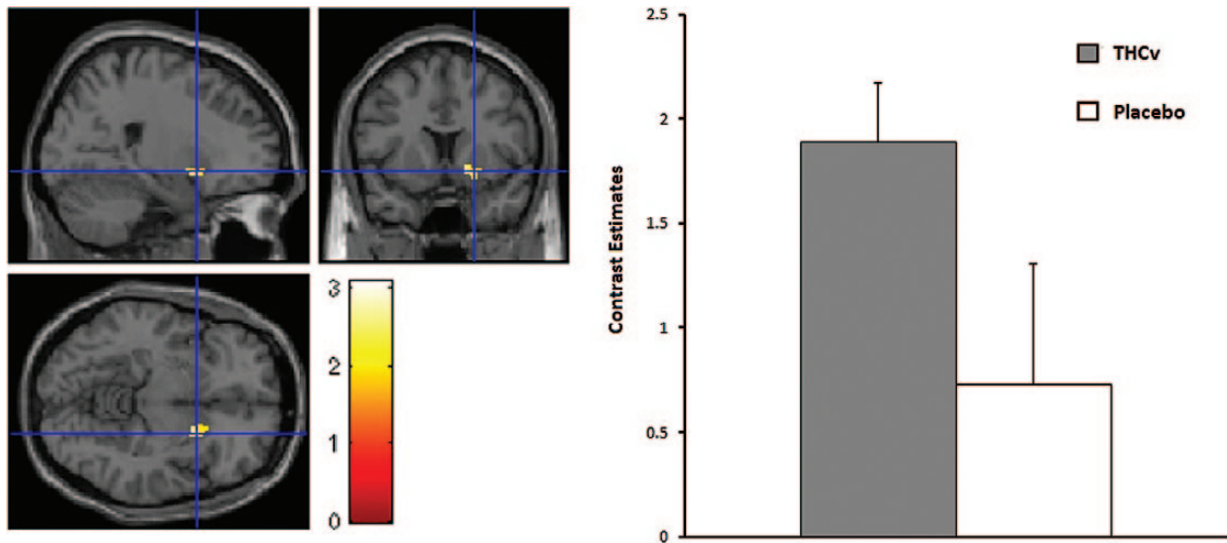


Figure 1. Left: Chocolate sight. Increase putamen activation under tetrahydrocannabivarin (THCv) compared with placebo, small volume corrected (svc) ($z=2.74$, $P=.03$ svc family wise error [FWE]-corrected for multiple comparisons). Right: Contrast estimates for putamen centered at 16 10 -6 for chocolate sight. Error bars show 1 SEM.

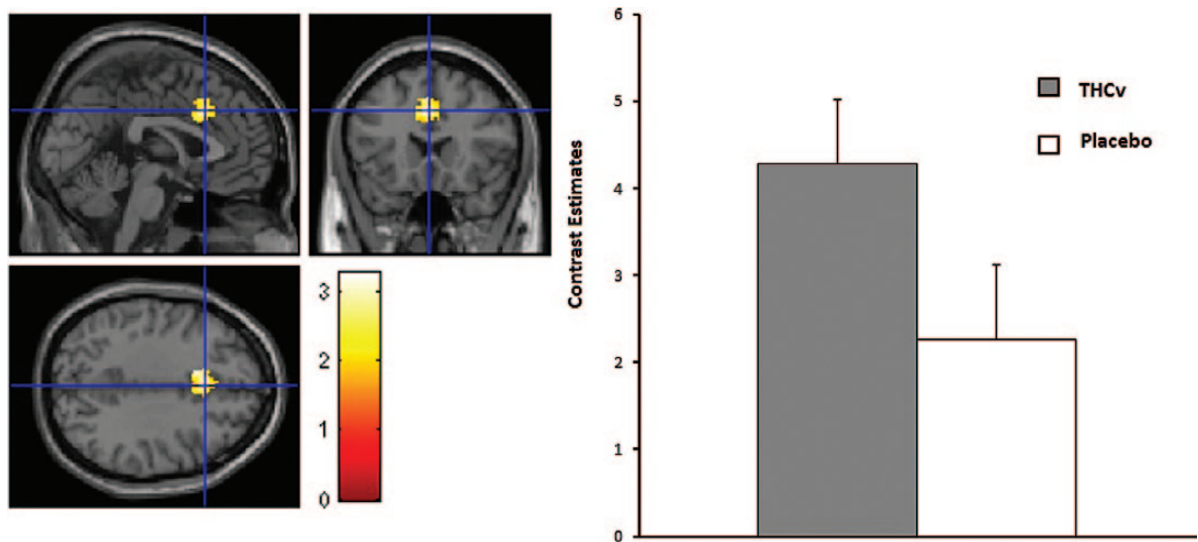


Figure 2. Left: Chocolate sight. Increased anterior cingulate activation under tetrahydrocannabivarin (THCv) compared with placebo, small volume corrected (svc) ($z=3.19$, $P=.03$ svc family wise error [FWE]-corrected for multiple comparisons). Right: Contrast estimates for anterior cingulate centered at -20 20 36 for chocolate sight. Error bars show 1 SEM.

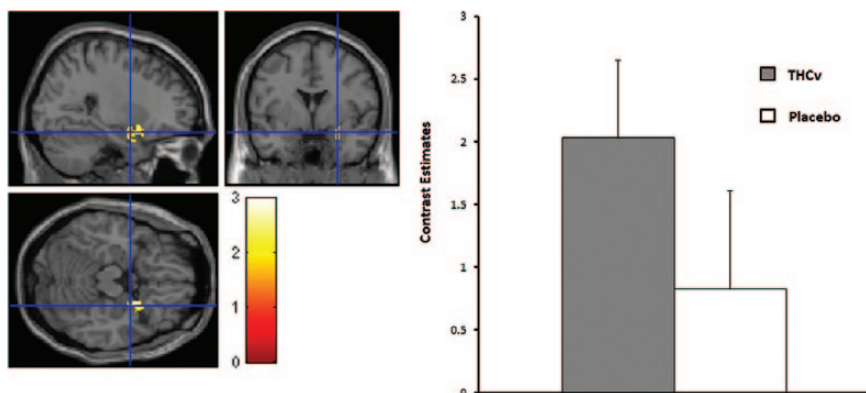


Figure 3. Left: Strawberry sight and taste. Increased amygdala activation under tetrahydrocannabivarin (THCv) compared with placebo, small volume corrected (svc) ($z=2.66$, $P=.03$ svc family wise error [FWE]-corrected for multiple comparisons). Right: Contrast estimates for amygdala centered at 24 6 -18 for strawberry sight and taste. Error bars show 1 SEM.

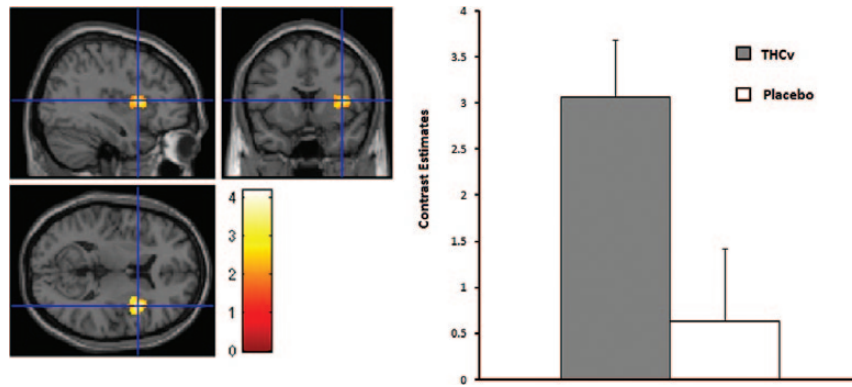


Figure 4. Left: Strawberry sight. Increased insula activation under tetrahydrocannabivarin (THCv) compared with placebo, small volume corrected (svc) ($z=3.46$, $P=.005$ svc family wise error [FWE]-corrected for multiple comparisons). Right: Contrast estimates for insula centered at 38 10 10 for strawberry sight. Error bars show 1 SEM.

Discussion

The aim of the current study was to examine the effects of a single dose (10mg) of the CB1 receptor neutral antagonist THCv on the neural processing of rewarding and aversive food stimuli in the healthy human brain. We found that there were no subjective effects of a single dose of THCv on ratings of pleasantness, wanting, and intensity of the stimuli made inside the scanner; however, we did detect significant neural differences. This study is thus further evidence that neuroimaging may be a more sensitive measure than a subjective report of the early effects of drug treatments and can provide an understanding of the neural mechanisms through which behavioral changes eventually emerge with repeated treatment (Harmer and Cowen, 2013).

In this study, we found enhancement of activation under the positive chocolate stimuli conditions in the ACC and striatum and in the striatum (caudate) mid cingulate and midbrain. Consistent with these findings, the striatal region has been shown to have a dense concentration of cannabinoid receptors located on striatal projection neurons (Herkenham et al., 1991a), and the cingulate cortex also has high levels of cannabinoid receptors (Sim-Selley et al., 2002). Both these regions have been previously highlighted in relation to reward processing and the endocannabinoid system (van Hell et al., 2012). This outcome is in direct contrast to our previous study, which found that the CB1 antagonist/inverse agonist rimonabant reduced activations to reward in key reward areas such as the OFC, ventral striatum, and putamen. We expected that, unlike rimonabant (with its depressogenic side effects), THCv would not reduce activations to the rewarding chocolate conditions in our study. In fact, we found that THCv increased activation to the sight of chocolate in a very similar region to that which was reduced under rimonabant, the ventral striatum/putamen region. These results are important in that reduced reward processing has been previously shown in patients with depression (Keedwell et al., 2005) and also in our own studies in recovered depressed patients (McCabe et al., 2009). Thus, the current results support the idea that THCv does not impair reward function, and this may be related to a potentially safer side effect profile.

Interestingly studies in obesity show a hypofunctioning striatal response to food taste, which can be further reduced by overeating (Stice et al., 2010). In our study, we examined healthy people and found effects on reward response to sight but less to taste. Given that obese individuals have a greatly reduced response to reward to begin with, THCv may produce a more pronounced enhancement of reward response to taste than observed in the present study for healthy individuals.

This enhancement could act to rebalance the reward system in response to food and help obese people reduce the overeating that may occur as an overcompensation for hypofunctioning striatal regions. Our results with healthy people are a first step towards understanding the action of THCv. The present study would need to be repeated in obese individuals to clarify whether THCv modulates reward activity to food stimuli in the same way and whether over time this leads to a reduction in eating.

We also found that THCv increased activations to the aversive conditions in a ventral striatum/putamen region similar to that in which aversion-related response was reduced under rimonabant. We discussed in our previous paper how this might suggest that rimonabant reduced activity in motivational areas to both pleasant and less pleasant stimuli (Horder et al., 2010). However, in the present study, regions such as the caudate and the putamen showed increased activity under THCv for both the positive and negative visual stimuli. This might indicate that THCv is not dampening down motivational processes, as these areas are involved in motivation and action in relation to both positive and negative events. Taken together, our results support the notion that THCv is less likely to cause depression-like side effects in humans, because it does not attenuate activations to either positively or negatively valenced stimuli in key motivational areas of the brain.

We also found enhancement in the mid brain to the chocolate condition and not the aversive condition under THCv compared with placebo. Studies have revealed that CB1 receptors are on axon terminals that impinge upon midbrain neurons (Melis et al., 2004; Riegel and Lupica, 2004; Matyas et al., 2008) and that this might be a mechanism by which cannabinoids can modify reward behavior through actions in the ventral tegmental area of the midbrain (Wang and Lupica, 2014). Interestingly, we only found modulation of this region in relation to the positive reward condition, which is consistent with the report that dopamine neurons preferentially report stimuli with appetitive rather than aversive motivational value (Mirenowicz and Schultz, 1996). This result again suggests that THCv does not inhibit the neural response to reward and may even enhance it. However, it is worth mentioning that we did not find any subjective effects of the drug, which most likely was due to the acute single dose. Thus, future studies would benefit from the examination of longer term treatments and higher doses to truly map the mechanism of action and how potential subjective effects might be related to the neural responses.

In the current study, we also found that for the combination of the taste and sight of the less pleasant stimuli there was

enhanced activation under THCv in the amygdala and insula. Aversive taste processing has been shown to involve the amygdala (Nitschke et al., 2006), and studies have identified distinct amygdala neuronal populations responsible for processing aversive information (Paton et al., 2006). The anterior insula is known to be part of the gustatory system (Faurion et al., 1998) but is also involved in the processing of aversive stimuli and disgust (Liu et al., 2011). Although no studies to date have directly examined the effect of THCv on the neural basis of aversive food processing in humans, it is interesting to note that one common feature between rimonabant and THCv is that both treatments increased activation to the aversive taste and sight condition in areas thought to be involved in negative information processing, such as the lateral OFC under rimonabant and the amygdala, insula, thalamus, and caudate under THCv. Although the amygdala and insula do indeed respond to positive information, in the present study we found that THCv increased amygdala and insula activity only to the aversive stimuli and in the case of the amygdala only when a taste was presented. This is likely to be a specific valence effect acting on the consummatory aspect of the unpleasant food and thus might be a mechanism by which THCv can make less pleasant food more salient and more unpleasant. By increasing the tendency on the part of appetitive regions to assess food as unpleasant, this effect may decrease time to satiety as food becomes unpleasant on repeated consumption, in turn reducing overall consumption. This is plausible in light of a study by Tallett et al. (2008), which found that the behavioral satiety sequence (time to stop feeding) was accelerated under a rimonabant and naloxone combination in rats. Because one aspect of satiety is the gradual change in the subjective experience of food from pleasant to unpleasant (Saker et al., 2014), it is possible that our finding of increased brain activity to less pleasant food stimuli under THCv might be a mechanism by which drugs that aid food reduction decrease time to satiety.

Analysis also revealed increased activity to the less pleasant food stimuli under THCv in the mid OFC. The OFC is a key player in the reward system and has been shown to be specifically related to the reward value of a stimulus and therefore to the decisions made based upon choices and preferences (Levy and Glimcher, 2012). It is also highly populated with cannabinoid receptors (Herkenham et al., 1991b). Our results indicate that THCv can modulate activity in OFC during the presentation of both the less pleasant taste and sight. This could be a mechanism by which choices and decisions made in relation to food preferences are modulated under cannabinoid antagonist treatment.

We also found that there was increased activity to the aversive stimuli under THCv in the superior temporal gyrus, an auditory and linguistic region of the human brain. A recent study examining the effects of THC on the human brain found that activity in this same region was decreased under THC in healthy volunteers and that the decrease was associated with an increase in psychotic symptoms (Winton-Brown et al., 2011). Right hemisphere activations play a role in resolving ambiguity in language (Harpaz et al., 2009), and as our results are only on the right hemisphere, perhaps THCv is having some effects on the clarity of decision making in the less pleasant conditions. This is, of course, speculative, as we did not have a task in this study that directly addressed the processing of auditory or linguistic cues.

In our recent study examining the effects of naltrexone (an opioid drug used to treat alcoholism) using the same task as described here, we found naltrexone also enhanced responses to aversive stimuli but had no effects on the striatum response

to reward (Murray et al., 2014). Naltrexone is by itself a weak antiobesity agent (Atkinson et al., 1985), and this may be because it has limited effects on the ventral striatal response to reward. THCv, on the other hand, enhanced striatal responses to the sight of chocolate in the present study. As it has been shown that people “at risk” of obesity have an increased neural response to reward (Stice et al., 2008) as do binge eaters (Filbey et al., 2012; Schienle et al., 2009), we suggested that drugs such as naltrexone that reduce reward are effective as preventative treatments in those “at risk” of obesity or binge eating but not for people who are currently overweight and already have reduced reward processing.

A recent study by Wang et al. (2014) tested the effects of a combined bupropion (dopamine reuptake inhibitor) and naltrexone treatment on brain responses to food cues in overweight females. Interestingly, they found no effects of the food pictures in the striatum, a finding that the authors attributed to the task's lack of sensitivity, but which could also indicate the hypofunctioning reward systems of the overweight volunteers. Similar to our results, they found enhancement in the anterior cingulate to food cues in drug vs placebo, which they describe as being a mechanism by which enhanced inhibitory control over food is induced due to the role of the ACC in cognitive control. Taken together, our results in healthy people show some enhancement in striatal and cognitive control areas that might make THCv a beneficial treatment in obese individuals with hypofunctioning reward systems and lack of control over food intake.

It should be noted that THCv also has a high affinity as a partial agonist for CB2 receptors, and studies have shown that CB2 receptors, although thought to be primarily involved in immune function (McPartland et al., 2014), can also be antagonized by THCv (Pertwee, 2005; Thomas et al., 2005). As CB2 receptor agonists act on the brain to induce food intake (Emadi et al., 2011), it is possible that CB2 antagonism by THCv could also reduce food intake. However, to date, how effects on CB2 receptors are related to neural responses to food in humans is as yet unknown, so effects of THCv on CB2 receptors in relation to food cannot be ruled out (Mechoulam et al., 2014).

In conclusion, our results are the first to examine the effects of THCv on the neural response to reward and aversion in the human brain. We found that THCv did not reduce reward processing but rather enhanced activations in key reward and aversion processing areas. There are contrasts between these effects and those we previously identified of rimonabant, indicating that there may be meaningful differences between the clinical effects of rimonabant and THCv. These data support functional neuroimaging as an important tool in drug development, one that allows the neural mechanisms underlying behavior to be studied in humans. It thereby may aid the detection of clinically relevant effects of treatments over shorter periods of time and speed the development of effective drugs and the rejection of unsuitable ones.

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Interest Statement

Dr. McCabe has acted as a consultant to P1Vital, Givaudan, GWpharma, the British Broadcasting Company, and Channel 4. Professor Cowen is a member of an advisory board for Lundbeck. Luke Tudge and Clare Williams report no biomedical financial interests or potential conflicts of interest.

References

- Atkinson RL, Berke LK, Drake CR, Bibbs ML, Williams FL, Kaiser DL (1985) Effects of long-term therapy with naltrexone on body weight in obesity. *Clin Pharmacol Ther* 38:419–422.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. *Arch Gen Psychiatry* 4:561–571.
- Bergman J, Delatte MS, Paronis CA, Vemuri K, Thakur GA, Makriyannis A (2008) Some effects of CB1 antagonists with inverse agonist and neutral biochemical properties. *Physiol Behav* 93:666–670.
- Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A (2007) Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 370:1706–1713.
- Emadi L, Jonaidi H, Hosseini Amir Abad E (2011) The role of central CB2 cannabinoid receptors on food intake in neonatal chicks. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 197:1143–1147.
- Faurion A, Cerf B, Le Bihan D, Pillias AM (1998) fMRI study of taste cortical areas in humans. *Ann NY Acad Sci* 855:535–545.
- Fawcett J, Clark DC, Scheftner WA, Gibbons RD (1983) Assessing anhedonia in psychiatric patients. *Arch Gen Psychiatry* 40:79–84.
- Filbey FM, Myers US, Dewitt S (2012) Reward circuit function in high BMI individuals with compulsive overeating: similarities with addiction. *NeuroImage* 63:1800–1806.
- First MB, Spitzer RL, Gibbon M, Williams JBW (1997) Structured clinical interview for DSM-IV Axis I disorders: clinical version. Washington DC: American Psychiatric Press.
- Friemel CM, Zimmer A, Schneider M (2014) The CB1 receptor as an important mediator of hedonic reward processing. *Neuropsychopharmacology* 39:2387–2396.
- Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC (1994) Assessing the significance of focal activations using their spatial extent. *Hum Brain Mapp* 1:214–220.
- Friston KJ, Glaser DE, Henson RN, Kiebel S, Phillips C, Ashburner J (2002) Classical and Bayesian inference in neuroimaging: applications. *Neuroimage* 16:484–512.
- Gard DE, Kring AM, Gard MG, Horan WP, Green MF (2007) Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. *Schizophr Res* 93:253–260.
- Garner DM, Olmsted MP, Bohr Y, Garfinkel PE (1982) The eating attitudes test: psychometric features and clinical correlates. *Psychol Med* 12:871–878.
- Griebel G, Stemmelin J, Scatton B (2005) Effects of the cannabinoid CB1 receptor antagonist rimonabant in models of emotional reactivity in rodents. *Biol Psychiatry* 57:261–267.
- Harmer CJ, Cowen PJ (2013) 'It's the way that you look at it' - a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc Lond B Biol Sci* 368:20120407.
- Harpaz Y, Levkovitz Y, Lavidor M (2009) Lexical ambiguity resolution in Wernicke's area and its right homologue. *Cortex* 45:1097–1103.
- Haslam DW, James WP (2005) Obesity. *Lancet* 366:1197–1209.
- Herkenham M, Lynn AB, de Costa BR, Richfield EK (1991a) Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. *Brain Res* 547:267–274.
- Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC (1991b) Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J Neurosci* 11:563–583.
- Holder J, Harmer CJ, Cowen PJ, McCabe C (2010) Reduced neural response to reward following 7 days treatment with the cannabinoid CB1 antagonist rimonabant in healthy volunteers. *Int J Neuropsychopharmacol* 13:1103–1113.
- Kangas BD, Delatte MS, Vemuri VK, Thakur GA, Nikas SP, Subramanian KV, Shukla VG, Makriyannis A, Bergman, J (2013) Cannabinoid discrimination and antagonism by CB(1) neutral and inverse agonist antagonists. *J Pharmacol Exp Ther* 344:561–567.
- Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML (2005) The neural correlates of anhedonia in major depressive disorder. *Biol Psychiatry* 58:843–853.
- Levy DJ, Glimcher PW (2012) The root of all value: a neural common currency for choice. *Curr Opin Neurobiol* 22:1027–1038.
- Liu X, Hairston J, Schrier M, Fan J (2011) Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev* 35:1219–1236.
- Maccioni P, Pes D, Carai MA, Gessa GL, Colombo G (2008) Suppression by the cannabinoid CB1 receptor antagonist, rimonabant, of the reinforcing and motivational properties of a chocolate-flavoured beverage in rats. *Behav Pharmacol* 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.
- Mathes CM, Ferrara M, Rowland NE (2008) Cannabinoid-1 receptor antagonists reduce caloric intake by decreasing palatable diet selection in a novel dessert protocol in female rats. *Am J Physiol Regul Integr Comp Physiol* 295:R67–75.
- Matyas F, Urban GM, Watanabe M, Mackie K, Zimmer A, Freund TF, Katona I (2008) Identification of the sites of 2-arachidonoylglycerol synthesis and action imply retrograde endocannabinoid signaling at both GABAergic and glutamatergic synapses in the ventral tegmental area. *Neuropharmacol* 54:95–107.
- McCabe C, Cowen PJ, Harmer CJ (2009) Neural representation of reward in recovered depressed patients. *Psychopharmacol (Berl)* 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. *Biol Psychiatry* 67:439–445.
- McCabe C, Huber A, Harmer CJ, Cowen PJ (2011) The D2 antagonist sulpiride modulates the neural processing of both rewarding and aversive stimuli in healthy volunteers. *Psychopharmacol (Berl)* 217:271–278.
- McCabe C, Woffindale C, Harmer CJ, Cowen PJ (2012) Neural processing of reward and punishment in young people at increased familial risk of depression. *Biol Psychiatry* 72:588–594.
- McPartland JM, Guy GW, Di Marzo V (2014) Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. *PLoS one* 9:e89566.
- Mechoulam R, Hanus LO, Pertwee R, Howlett AC (2014) Early phytocannabinoid chemistry to endocannabinoids and beyond. *Nat Rev Neurosci* 15:757–764.
- Melis M, Pistis M, Perra S, Muntoni AL, Pillolla G, Gessa GL (2004) Endocannabinoids mediate presynaptic inhibition of glutamatergic transmission in rat ventral tegmental area dopamine neurons through activation of CB1 receptors. *J Neurosci* 24:53–62.
- Meyer FJ, Trezza V, Vanderschuren LJ, Ramakers GM, Adan RA (2013) Neutral antagonism at the cannabinoid 1 receptor: a safer treatment for obesity. *Mol Psychiatry* 18:1294–1301.

- Mirenowicz J, Schultz W (1996) Preferential activation of mid-brain dopamine neurons by appetitive rather than aversive stimuli. *Nature* 379:449–451.
- Murray E, Brouwer S, McCutcheon R, Harmer CJ, Cowen PJ, McCabe C (2014) Opposing neural effects of naltrexone on food reward and aversion: implications for the treatment of obesity. *Psychopharmacol (Berl)* 231:4323–4335.
- Nitschke JB, Sarinopoulos I, Mackiewicz KL, Schaefer HS, Davidson RJ (2006) Functional neuroanatomy of aversion and its anticipation. *Neuroimage* 29:106–116.
- O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C (2001) Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci* 4:95–102.
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97–113.
- Paton JJ, Belova MA, Morrison SE, Salzman CD (2006) The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature* 439:865–870.
- Pertwee RG (2005) Inverse agonism and neutral antagonism at cannabinoid CB1 receptors. *Life Sci* 76:1307–1324.
- Riegel and Lupica (2004) Independent presynaptic and postsynaptic mechanisms regulate endocannabinoid signaling at multiple synapses in the ventral tegmental area. *J Neurosci* 24:11070–11078.
- Rolls ET, McCabe C (2007) Enhanced affective brain representations of chocolate in cravers vs. non-cravers. *Eur J Neurosci* 26:1067–1076.
- Saker P, Farrell MJ, Adib FR, Egan GF, McKinley MJ, Denton DA (2014) Regional brain responses associated with drinking water during thirst and after its satiation. *PNAS* 111:5379–5384.
- Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF (2006) Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* 368:1660–1672.
- Schienze A, Schafer A, Hermann A, Vaitl D (2009) Binge-eating disorder: reward sensitivity and brain activation to images of food. *Biol Psychiatry* 65:654–661.
- Sim-Selley LJ, Vogt LJ, Vogt BA, Childers SR (2002) Cellular localization of cannabinoid receptors and activated G-proteins in rat anterior cingulate cortex. *Life Sci* 71:2217–2226.
- Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P (1995) A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry* 167:99–103.
- Solinas M, Goldberg SR, Piomelli D (2008) The endocannabinoid system in brain reward processes. *Br J Pharmacol* 154:369–383.
- Stice E, Spoor S, Bohon C, Small DM (2008) Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. *Science* 322:449–452.
- Stice E, Yokum S, Blum K, Bohon C (2010) Weight gain is associated with reduced striatal response to palatable food. *J Neurosci* 30:13105–13109.
- Tallett AJ, Blundell JE, Rodgers RJ (2008) Endogenous opioids and cannabinoids: system interactions in the regulation of appetite, grooming and scratching. *Physiol Behav* 94:422–431.
- Thomas A, Stevenson LA, Wease KN, Price MR, Baillie G, Ross RA, Pertwee RG (2005) Evidence that the plant cannabinoid Delta9-tetrahydrocannabinol is a cannabinoid CB1 and CB2 receptor antagonist. *Br J Pharmacol* 146:917–926.
- van Hell HH, Jager G, Bossong MG, Brouwer A, Jansma JM, Zuurman L, van Gerven J, Kahn RS, Ramsey NF (2012) Involvement of the endocannabinoid system in reward processing in the human brain. *Psychopharmacol (Berl)* 219:981–990.
- von Zerssen D, Strian F, Schwarz D (1974) Evaluation of depressive states, especially in longitudinal studies. *Mod Probl Pharmacopsychiatry* 7:189–202.
- Wang GJ, Tomasi D, Volkow ND, Wang R, Telang F, Caparelli EC, Dunayevich E (2014) Effect of combined naltrexone and bupropion therapy on the brain's reactivity to food cues. *Int J Obes* 38:682–688.
- Wang H, Lupica CR (2014) Release of endogenous cannabinoids from ventral tegmental area dopamine neurons and the modulation of synaptic processes. *Prog Neuropsychopharmacol Biol Psychiatry* 52:24–27.
- Wilson JL, Jenkinson M, de Araujo I, Kringelbach ML, Rolls ET, Jezard P (2002) Fast, fully automated global and local magnetic field optimization for fMRI of the human brain. *Neuroimage* 17:967–976.
- Winton-Brown TT, Allen P, Bhattacharyya S, Borgwardt SJ, Fusar-Poli P, Crippa JA, Seal ML, Martin-Santos R, Ffytche D, Zuardi AW, Atakan, Z, McGuire, PK (2011) Modulation of auditory and visual processing by delta-9-tetrahydrocannabinol and cannabidiol: an fMRI study. *Neuropsychopharmacol* 36:1340–1348.
- Zald DH, Hagen MC, Pardo JV (2002) Neural correlates of tasting concentrated quinine and sugar solutions. *J Neurophysiol* 87:1068–1075.