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Resting-state functional connectivity following a single dose treatment with CB1 neutral antagonist tetrahydrocannabivarin (THCv) in healthy volunteers

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Research Article

RESEARCH ARTICLE

The CB1 Neutral Antagonist Tetrahydrocannabivarin Reduces Default Mode Network and Increases Executive Control Network Resting State Functional Connectivity in Healthy Volunteers

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Abstract

Background: The cannabinoid cannabinoid type 1 (CB1) neutral antagonist tetrahydrocannabivarin (THCv) has been suggested as a possible treatment for obesity, but without the depressogenic side-effects of inverse antagonists such as Rimonabant. However, how THCv might affect the resting state functional connectivity of the human brain is as yet unknown.
Method: We examined the effects of a single 10 mg oral dose of THCv and placebo in 20 healthy volunteers in a randomized, within-subject, double-blind design. Using resting state functional magnetic resonance imaging and seed-based connectivity analyses, we selected the amygdala, insula, orbitofrontal cortex, and dorsal medial prefrontal cortex (dmPFC) as regions of interest. Mood and subjective experience were also measured before and after drug administration using self-report scales.
Results: Our results revealed, as expected, no significant differences in the subjective experience with a single dose of THCv. However, we found reduced resting state functional connectivity between the amygdala seed region and the default mode network and increased resting state functional connectivity between the amygdala seed region and the dorsal anterior cingulate cortex and between the dmPFC seed region and the inferior frontal gyrus/medial frontal gyrus. We also found a positive correlation under placebo for the amygdala-precuneus connectivity with the body mass index, although this correlation was not apparent under THCv.
Conclusion: Our findings are the first to show that treatment with the CB1 neutral antagonist THCv decreases resting state functional connectivity in the default mode network and increases connectivity in the cognitive control network and dorsal visual stream network. This effect profile suggests possible therapeutic activity of THCv for obesity, where functional connectivity has been found to be altered in these regions.

Keywords: Cannabinoids, default mode, fMRI, obesity, resting state, reward

Introduction

Despite severe health and economic consequences of excess body weight (Andreyeva et al., 2004), the neurobiological mechanism of disordered eating in humans remains unclear. The endocannabinnoid system in the human brain, which involves cannabinoid type 1 (CB1) receptors, has been implicated in reward processing in animals and humans (Solinas et al., 2007)

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and in regulating feeding behavior by modulating brain reward signals related to appetite and the consumption of food (Solinas et al., 2008). For example, when tetrahydrocannabinol (THC), which is a psychoactive constituent of the cannabis plant and a partial agonist at the CB1 receptor, was administered in rats it led to an increase in the hedonic response to sucrose and a decrease in aversive reactions to bitter solutions (Jarrett et al., 2005). Moreover, Solinas and Goldberg reported that administration of THC, during food consumption, increased the motivation to respond for the food in rats (Solinas and Goldberg, 2005).

Rimonabant, an antagonist and possible inverse agonist (Pertwee, 2005) at the CB1 receptor, was licensed in Europe for the treatment of obesity in 2006 but was withdrawn from clinical use in 2008 due to depression-like side effects. Rimonabant was found to promote weight loss by decreasing food intake (Scheen et al., 2006); however, it also presented with depression- and anxiety-related side effects. In an attempt to try and understand how these treatments might be having their effects, we did a study in 2010 that examined the neural response to reward and aversion in humans after a 7-day treatment with rimonabant (Horder et al., 2010). We found that rimonabant reduced neural responses to a pleasant chocolate taste in reward areas of the brain such as the ventral striatum and orbitofrontal cortex (OFC), whilst increasing brain responses to aversive sights and tastes in regions such as the lateral OFC (Horder et al., 2010). We concluded that although reduced food intake might be due to a reduced neural response to reward, this may also have been a mechanism by which depression side-effects were induced, given that reduced neural responses to reward have been found in depressed patients (Keedwell et al., 2005; Wacker et al., 2009) and in those at risk of depression (McCabe et al., 2009, 2012) and are thought to be a possible biomarker for depression (Hasler and Northoff, 2011).

THCv, a neutral antagonist that acts on CB1 receptors, has been suggested as a potentially safer alternative with fewer side effects (Le Foll et al., 2009; Pacher and Kunos, 2013). Animal studies have shown that, like rimonabant, THCv reduces weight gain and food consumption but, unlike rimonabant, does not increase activity in the basolateral amygdala and ventral tagmental area: brain regions involved in emotion regulation (Meye et al., 2013). Moreover, our recent fMRI study, the first to investigate THCv effects on reward and aversion in the healthy human brain, found that relative to placebo, THCv increased activation to pleasant chocolate stimuli in the anterior cingulate cortex, caudate, putamen, and midbrain (Tudge et al., 2014), opposite to the profile of those at risk of depression (McCabe et al., 2009, 2012). Thus, our results supported the idea that THCv does not impair reward function, and this may be related to a potentially safer side-effect profile.

We also found that THCv increased activation to the aversive stimulus in the amygdala, insula, and OFC (Tudge et al., 2014). We suggested this might be a mechanism to reduce food intake, by increasing the salience of food and perhaps then decreasing the time to satiety. 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 (Tallett et al., 2008). However, how THCv might affect activity in these regions at rest in healthy individuals is as yet unknown.

Therefore, in this study we aimed to investigate the effects of a single oral 10 mg dose of THCv on resting state functional connectivity between the regions of interest (ROI)—the amygdala, insula, and the OFC—identified from our previous task findings (Tudge et al., 2014). Further, these regions have also been identified as altered in connectivity in studies of a resting state in obese individuals (Lips et al., 2014; Coveleskie et al., 2015; Zhang et al., 2015). We also selected the dorsal medial prefontal cortex (dmPFC) region, as we are interested in THCv's effects on the prefrontal regions, especially those known to be involved in resting state functional connectivity in depression (Sheline et al., 2010). We hypothesized that, relative to placebo, THCv would increase the region of interest functional connectivity, in line with our effects found during a task (Tudge et al., 2014).

Methods

Participants

Nineteen participants (nine female), aged 20–36 were included in a within-subjects, double-blind, placebo-controlled, crossover design and received a single dose of oral treatment with THCv (10 mg/day) or placebo. Participants completed the resting state scan once with the drug (10 mg 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. Ethical approval was provided by the Oxford Research Ethics Committee and written informed consent was obtained from all participants before screening and after a complete description of the study was given. Participants were recruited from the university volunteer register and via internet adverts. Volunteers 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 five cigarettes a day. Participants were right handed, had normal or corrected-to-normal vision, and were not on medications apart from the contraceptive pill. Participants had no neurological disorders or contraindications for MRI examination.

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). Body mass index (BMI) and an Eating Attitudes questionnaire were used to rule out eating disorders (EAT; Garner et al., 1982). Participants were scanned twice: once with THCv or placebo and then 1 week later with the other. To assess the effects of the treatment, the following questionnaires were taken before and after the treatment: Visual Analogue Scales (VAS) of happiness, sadness, anger, disgust, alertness, and anxiety; and the Befinldichkeit Scale of mood and energy (BFS; von Zerssen et al., 1974).

Experimental Design

MRI-derived measures of brain function, based on blood-oxygenation-level-dependent (BOLD) contrast, were used to compare brain responses at rest across the THCv and the placebo groups at approximately 1 hour after treatment. The resting state data were acquired before any other scans, including the structural scan. Subjects were instructed to keep their eyes open while lying in the dimmed light of the scanner, looking at a black screen.

fMRI Data Acquisition

Images were acquired with a 3.0-T VARIAN/SIEMENS whole-body scanner at the Oxford Centre for Functional Magnetic Resonance Imaging (FMRIB), where T2*-weighted echo planar

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imaging (EPI) slices were acquired every 2.41 seconds (TR = 2.41). Imaging parameters were selected to minimize susceptibility and distortion artifacts in the OFC (Wilson et al., 2002). Coronal slices with in-plane resolutions of 3.0 x 3.0 mm and between-plane spacings of 3 mm were obtained. The matrix size was 64 x 64 and the field of view was 192 x 192 mm. Acquisition was carried out during the resting scan, yielding 128 volumes in total. A whole-brain T2*-weighted EPI volume of the above dimensions, and an anatomical T1 volume with coronal plane slice thicknesses of 3 mm and in-plane resolutions of 1.0 x 1.0 mm were also acquired to improve the registration process.

Analysis Methods

Pre-Processing

Imaging data were pre-processed and analyzed using FSL tools (www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). fMRI data pre-processing was carried out using FEAT (FMRI Expert Analysis Tool, Version 6.0, a part of FSL software), and included the following steps: non-brain removal (Smith, 2002); motion correction using MCFLIRT (Jenkinson and Smith, 2001); spatial smoothing using a Gaussian kernel of full-width at half maximum of 5 mm; grand mean intensity normalization of the entire 4D dataset by a single multiplicative factor; and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 64.0 s). fMRI volumes were registered to the individual's structural scan and the MNI-152 standard space image (Montreal Neurological Institute) using FMRIB's Linear Image Registration Tool (Jenkinson et al., 2001).

Time Series Extraction and Higher Level Analysis

To study resting state functional connectivity, a seed-based correlation approach was used with the amygdala, OFC, and insula as selected seeds using the Harvard-Oxford subcortical structural atlas (Kennedy et al., 1998). To maximize the exact coverage, the masks of these seed regions were threshold by 20% to include voxels having at least 20% in these particular regions. We also created seeds for the dmPFC (18 34 29; -24 35 28; 8 mm radius) using coordinates from Sheline et al. (2010), as they showed this region to have increased connectivity within the default mode and affective network in depressed patients. The dmPFC seeds were created with the Wake Forest University Pickatlas tool in SPM8 (McCabe et al., 2010).

The mean time course within the left and right seeds of each ROI (except for the OFC, only comprising one medial seed) was calculated and used as a regressor in a general linear model for each of the networks. In addition, white matter and cerebrospinal fluid were segmented using FSL's FAST, and the six motion parameters (three translations and three rotations) and the global signal obtained from the pre-processing steps were all used as nuisance regressors. The resulting segmented white matter and cerebrospinal fluid images were then thresholded to ensure 80% tissue-type probability. For each individual, the general linear model was analyzed using the FMRI Expert Analysis Tool (version 5.4, part of FMRIB's Software Library; Smith et al., 2004). The resulting parameter estimate maps were then analyzed using higher level one-sample t-tests for group averages and paired-samples t-tests for treatment effects. Whole-brain z-statistical images were thresholded with an initial cluster-forming threshold of $z > 2.3$ and a corrected cluster significance threshold of $p < 0.008$ (i.e. $p < 0.05$ Bonferroni corrected for the six regions of interest: the right and left amygdala, right and left insula, OFC, and dmPFC (Worsley, 2001). The % BOLD signal change in the graphs is the PE/COPE values converted to mean % BOLD signal change via Featquery (FSL; www.fmrib.ox.ac.uk/fsl; Smith et al., 2004) for the regions that had significant correlations with the seeds (Table 2).

BMI Correlations

To examine the relationship with BMI, we took the % BOLD signal change from voxels identified as significantly different between the drug and placebo (Table 2) using Featquery in each individual subject and then correlated this with the BMI scores for each individual.

Results

Demographic Details and Mood Ratings

Demographic data analysis (Supplementary Table S1) revealed participants had low depression scores, as well as normal EAT scores. One-way ANOVAs revealed no significant effects of gender on any of the demographic measures ($p > 0.05$). Repeated-measures ANOVAs were employed to examine the effect of drug (placebo/THCv) and time (pre-scan/post-scan) on scores of mood, energy, and affect, as measured by the BFS and VAS. Results revealed there was no main effect of drug on mood, energy, or affect ($p > 0.05$; Supplementary Table S2). In order to assess any potential confounding effects of gender or order on mood, energy, and affect scores, gender and order were included in the analyses as independent variables. No main effects of gender or order and no gender x drug or order x drug interactions were revealed, suggesting that the order of drug condition and the gender of the participant did not have an effect on mood, energy, and affect ratings.

Functional Connectivity: Placebo

The functional connectivity for the seed regions is described in Supplementary Table S3 for the placebo group alone (baseline). Overall, the patterns of connectivity associated with each of the seed regions are consistent with resting state and functional connectivity experiments in healthy controls and obese patients or depressed patients (Anand et al., 2005; Greicius et al., 2007; Leh et al., 2007; Robinson et al., 2009; Sheline et al., 2010; Cauda et al., 2011; Kullmann et al., 2012).

Functional Connectivity of the A-priori Seeds

Left Amygdala Seed

Compared to the placebo group, there was reduced functional connectivity between the left amygdala seed and the left precuneus and the left posterior cingulate cortex (PCC), key areas constituting the default mode network (DMN) in the THCv group (Figure 1). There was also decreased connectivity with the lateral occipital cortex, but this did not meet the Bonferroni correction.

There was also increased functional connectivity between the left amygdala seed and the dorsal anterior cingulate gyrus/premotor area, which overlaps with the executive control network, in the THCv group (Table 1; Figure 2).

Functional Connectivity for the Exploratory Seeds

Right dmPFC Seed

Compared to the placebo group, there was an increased functional connectivity between the right dmPFC seed and the right inferior frontal gyrus/medial frontal gyrus (IFG/MFG), which overlaps with the right dorsal visual stream network in the THCv group (Table 1; Figure 3).

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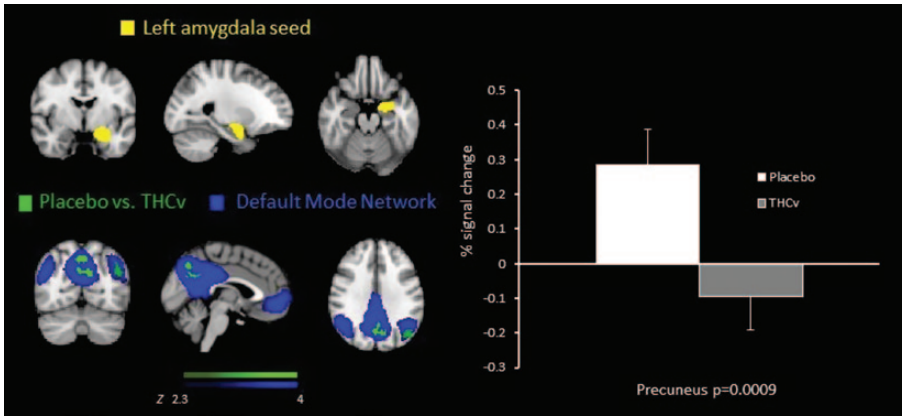

Figure 1. Coronal, sagittal, and axial slices showing the amygdala seed region and functional connectivity maps for the difference between placebo and tetrahydrocannabinol (THCv) groups, overlaid on the default mode network. The right graph displays the % blood-oxygenation-level-dependent signal change extracted from the region of significant treatment effect. Precuneus: – 8 -72 24 and $p = 0.0009$ for the placebo group and THCv group.

Table 1. Resting state functional connectivity for brain seed regions and the effects of THCv.

Brain region	MNI coordinates			z-score	Number of voxels	Significance (p-value)
	X	Y	Z			
Placebo > THCv						
L Amygdala seed						
Precuneus	-8	-72	24	3.41	333	0.0009
PCC	-2	-58	30	2.74	333	0.003
Lateral Occipital Cortex	-44	-70	30	4	283	0.034*
THCv > Placebo						
L Amygdala seed						
dACC/Supplementary motor cortex	6	4	52	3.89	501	0.00001
R dmPFC seed						
IFG/MFG	52	28	22	3.47	224	0.003

Gender was added as a covariate of no interest. All z values were cluster corrected for multiple comparisons ($z > 2.3$, $p < 0.008$) except *. dACC, dorsal anterior cingulate cortex; IFG/MFG, inferior frontal gyrus/medial frontal gyrus; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; THCv, tetrahydrocannabinol.

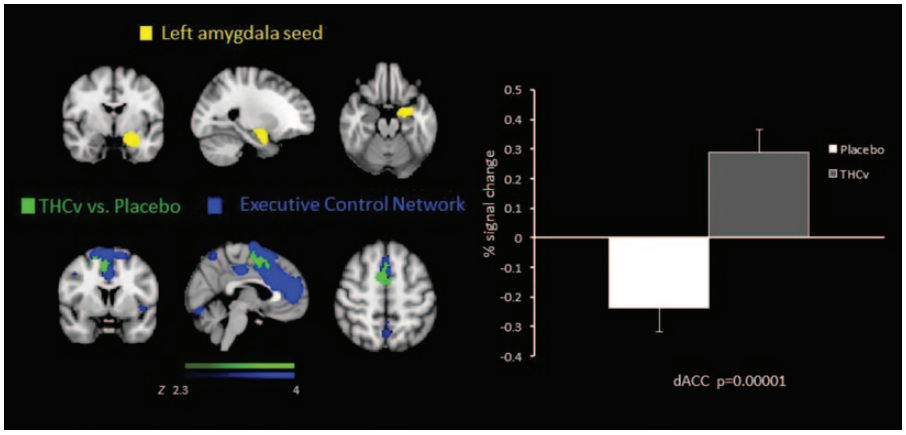

Figure 2. Coronal, sagittal, and axial slices showing the amygdala seed region and functional connectivity maps for the difference between placebo and tetrahydrocannabinol (THCv) groups, overlaid on the executive control network. The right graph displays the % blood-oxygenation-level-dependent signal change extracted from the region of significant treatment effect. Dorsal anterior cingulate cortex: 6 4 52 and $p = 0.00001$ for the placebo group and THCv group.

Correlation with BMI

We found a positive correlation between the % BOLD signal change extracted from the precuneus (the area that correlated with the amygdala seed region) and BMI ($r = 0.649$; $p = 0.003$) in the placebo group that was not present under THCv ($r = 0.38$; $p = 0.1$; Figure 4), with the difference scores between placebo and THCv plotted in Figure 4B. Further, when the outlier that was higher than two standard deviations from the mean (% BOLD change 1.5) was removed from the placebo group, the correlation with the BMI was still significant, at $r = 0.591$ and $p = 0.01$. We did not find a significant correlation between the BMI and brain connectivity for any of the other seed ROIs.

Discussion

Our study reveals that administration of a single THCv oral dose modulates resting state functional connectivity in a double-blind

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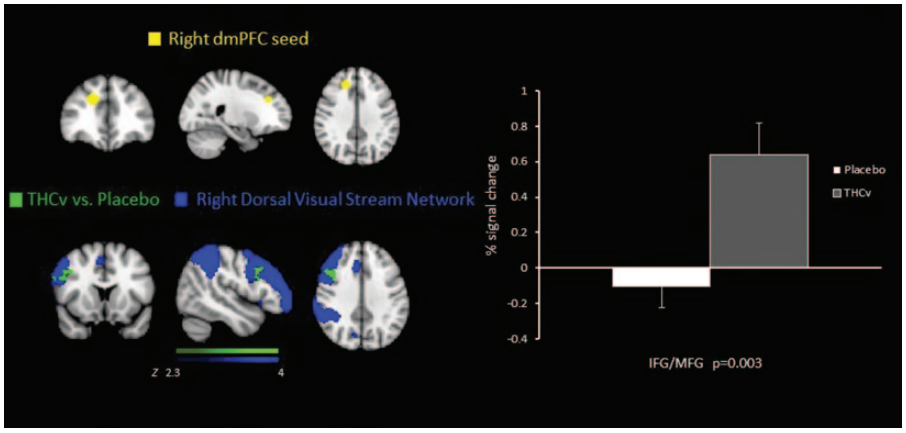

Figure 3. Coronal, sagittal, and axial slices showing the right dorsal medial prefrontal cortex seed region and functional connectivity maps for the difference between placebo and tetrahydrocannabinol (THCv) groups, overlaid on the right dorsal visual stream network. The right graph displays the % blood-oxygenation-level-dependent signal change extracted from the region of significant treatment effect. inferior frontal gyrus/medial frontal gyrus: 52 28 22 and $p = 0.003$ for the placebo group and THCv group.

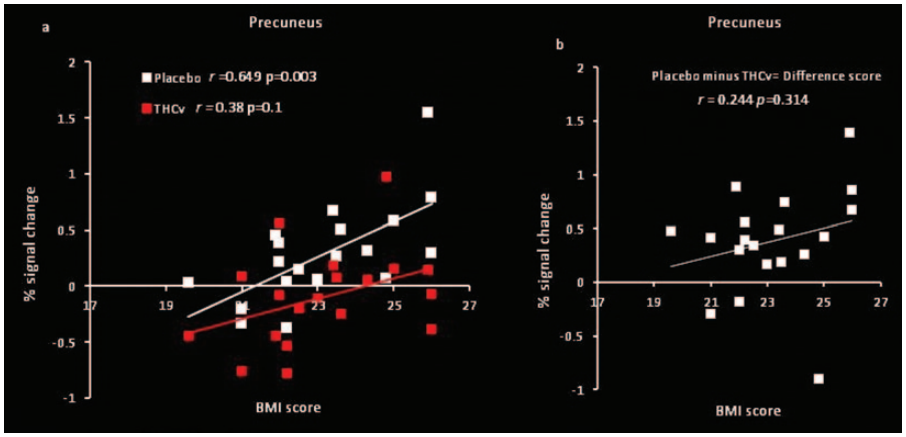

Figure 4. Graph of the % blood-oxygenation-level-dependent signal change extracted from the region of significant treatment effect: precuneus [– 8 -72 24 $p = 0.0009$] and correlated with body mass index (BMI) score for placebo and tetrahydrocannabinol (THCv).

placebo-controlled design in healthy volunteers, despite no significant effects on mood. Specifically, we found that resting state functional connectivity was reduced between the left amygdala and parts of the DMN (left precuneus and the PCC) for the THCv group when compared with the placebo group.

Previous studies in obese individuals have revealed increased activity in DMN regions, specifically in the precuneus and PCC, when compared with healthy subjects (Tregellas et al., 2011). Further, these brain areas have been highlighted in studies investigating obese versus lean individuals' visual responses to food cues and tastes (DelParigi et al., 2005; Cornier, 2009), suggesting an involvement in feeding behavior. Moreover, the posterior cingulate cortex has been found to play a crucial role in switching spatial attention to targets of salient and motivational value: i.e. directing attention to food stimuli in subjects experiencing hunger (Mohanty et al., 2008). Additionally, correlational analysis of the key nodes within the DMN revealed that the posterior cingulate cortex is involved in retrieving and integrating information from other subsystems implicated in self-referential thoughts and episodic memory (Hassabis et al., 2007; Buckner et al., 2008). Thus, increased activation of DMN in obese individuals has been suggested as a reflection of greater attention to internal states and memories influenced by past experience with food (Tregellas et al., 2011). Further, our reduced DMN connectivity under THCv might also be related to the reported safer side effect profile of THCv (less depression), as depressed patients have been found to have greater DMN connectivity (Sheline et al., 2010). Therefore it would be interesting to see if our result of decreased connectivity with the DMN under THCv could be replicated in obese patients and how this might relate to food intake and depression symptoms.

We also found increased connectivity between the left amygdala and the dorsal anterior cingulate cortex extending into the supplementary motor cortex, part of the executive control network, as well as an increased connectivity between the dmPFC and the IFG/MFG, part of the dorsal visual stream network. The executive control network is consistently recruited by cognitively demanding tasks of attention, working memory, and response selection (Seeley et al., 2007). Specifically, the dorsal regions of the PFC have been implicated in response activation and inhibition as investigated by GO/NOGO tasks (Garavan et al., 2002). Additionally, a study investigating neural activations during a food-specific GO/NOGO task in obese adolescents found reduced activation in the medial PFC when the participants were required to inhibit proponent responses to food, suggesting hypofunctioning of inhibitory control in obese individuals (Batterink et al., 2010). Thus our results of increased connectivity between the amygdala seed region and regions such as the anterior cingulate in the executive control network under THCv might help us understand

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how, at a mechanistic level, THCv could allow greater control over food intake.

Finding increased dmPFC connectivity with the IFG/MFG part of the dorsal visual stream resting state network under THCv is interesting, given that a recent study suggests that just thinking about eating food shown in images increases activation in the visual and prefrontal cortical regions in females with anorexia nervosa (Brooks et al., 2012). The authors concluded that such activations might underlie the biases toward controlling food intake commonly observed in individuals with anorexia nervosa (Brooks et al., 2012). Thus it is possible that increased connectivity between the dmPFC and visual networks under THCv might further enable THCv as a treatment to control food intake. Although there are as yet no other resting state studies on THCv in humans, there has been a study showing that the CB1 receptor agonist δ9-tetrahydrocannabinol, THC, increases functional connectivity between the dmPFC and the right dorsal visual stream network (Klumpers et al., 2012): this is directly opposite to our findings but consistent, as THCv is a neutral antagonist. Klumpers et al. discussed their findings with THC in relation to the known involvement of the dmPFC in decision making and cognitive control from previous behavioral studies also showing how THC can interfere with these processes.

Examining the relationship between BMI and brain results, we found a significant positive correlation between amygdala-precuneus connectivity under placebo but not under THCv. This seems to indicate that as BMI increases, functional connectivity between these regions increases, and that THCv removes this effect, especially at the top end of the BMI (see Figure 4). However, as our group did not contain obese individuals, a future study relating a greater range in BMI and resting state functional connectivity with pharmacological treatment effects would be very interesting.

Thus, in conclusion, our results show that THCv can modulate resting state functional connectivity in key networks such as the default mode network and the cognitive control network, and this might be relevant to the development of THCv as an anti-obesity medication. Future studies are needed to examine the relationship between resting state functional connectivity after repeated treatment with THCv in overweight individuals and how this relates to control over food intake.

Supplementary Material

For supplementary material accompanying this paper, visit http://www.ijnp.oxfordjournals.org/

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Statement of Interest

This work has been supported by GWPharma LtD. Drs Rzepa and Tudge report no biomedical financial interests or potential conflicts of interest. Dr McCabe has acted as a consultant to P1Vital, Givaudan, GWpharma, the British Broadcasting Company (BBC), and Channel 4.

References

Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, Mathews VP, Kalnin A, Lowe MJ (2005) Antidepressant effect on connectivity of the mood-regulating circuit: an FMRI study. Neuropsychopharmacology 30:1334–1344.

Andreyeva T, Sturm R, Ringel JS (2004) Moderate and severe obesity have large differences in health care costs. Obes Res 12:1936–1943.

Batterink L, Yokum S, Stice E (2010) Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study. Neuroimage 52:1696–1703.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571.

Brooks SJ, O'Daly O, Uher R, Friederich HC, Giampietro V, Brammer M, Williams SC, Schioth HB, Treasure J, Campbell IC (2012) Thinking about eating food activates visual cortex with reduced bilateral cerebellar activation in females with anorexia nervosa: an fMRI study. PLOS ONE 7:e34000.

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Ann NY Acad Sci 1124:1–38.

Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A (2011) Functional connectivity of the insula in the resting brain. Neuroimage 55:8–23.

Cornier MA (2009) The effects of overfeeding and propensity to weight gain on the neuronal responses to visual food cues. Physiol Behav 97:525–530.

Coveleskie K, Gupta A, Kilpatrick LA, Mayer ED, Ashe-McNalley C, Stains J, Labus JS, Mayer EA (2015) Altered functional connectivity within the central reward network in overweight and obese women. Nutr Diabetes 5:e148.

DelParigi A, Chen K, Salbe AD, Reiman EM, Tataranni PA (2005) Sensory experience of food and obesity: a positron emission tomography study of the brain regions affected by tasting a liquid meal after a prolonged fast. Neuroimage 24:436–443.

Fawcett J, Clark DC, Scheftner WA, Gibbons RD (1983) Assessing anhedonia in psychiatric patients. Arch Gen Psychiatry 40:79–84.

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.

Garavan H, Ross TJ, Murphy K, Roche RA, Stein EA (2002) Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. Neuroimage 17:1820–1829.

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.

Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, Reiss AL, Schatzberg AF (2007) Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry 62:429–437.

Hasler G, Northoff G (2011) Discovering imaging endophenotypes for major depression. Mol Psychiatry 16:604–619.

Hassabis D, Kumaran D, Maguire EA (2007) Using imagination to understand the neural basis of episodic memory. J Neurosci 27:14365–14374.

Horder 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 Neuropsychop 13:1103–1113.

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Jarrett MM, Limebeer CL, Parker LA (2005) Effect of Delta9-tetrahydrocannabinol on sucrose palatability as measured by the taste reactivity test. Physiol Behav 86:475–479.

Jenkinson M, Smith S (2001) A global optimisation method for robust affine registration of brain images. Med Image Anal 5:143–156.

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.

Kennedy DN, Lange N, Makris N, Bates J, Meyer J, Caviness VS, Jr. (1998) Gyri of the human neocortex: an MRI-based analysis of volume and variance. Cereb Cortex 8:372–384.

Klumpers LE, Cole DM, Khalili-Mahani N, Soeter RP, Te Beek ET, Rombouts SA, van Gerven JM (2012) Manipulating brain connectivity with delta(9)-tetrahydrocannabinol: a pharmacological resting state FMRI study. Neuroimage 63:1701–1711.

Kullmann S, Heni M, Veit R, Ketterer C, Schick F, Haring HU, Fritsche A, Preissl H (2012) The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum Brain Mapp 33:1052–1061.

Le Foll B, Gorelick DA, Goldberg SR (2009) The future of endocannabinoid-oriented clinical research after CB1 antagonists. Psychopharmacology (Berl) 205:171–174.

Leh SE, Ptito A, Chakravarty MM, Strafella AP (2007) Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study. Neurosci Lett 419:113–118.

Lips MA, Wijngaarden MA, van der Grond J, van Buchem MA, de Groot GH, Rombouts SA, Pijl H, Veer IM (2014) Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females. Am J Clin Nutr 100:524–531.

McCabe C, Cowen PJ, Harmer CJ (2009) Neural representation of reward in recovered depressed patients. Psychopharmacology (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, 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.

Meye 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.

Mohanty A, Gitelman DR, Small DM, Mesulam MM (2008) The spatial attention network interacts with limbic and monoaminergic systems to modulate motivation-induced attention shifts. Cereb Cortex 18:2604–2613.

Pacher P, Kunos G (2013) Modulating the endocannabinoid system in human health and disease--successes and failures. FEBS J 280:1918–1943.

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

Robinson S, Basso G, Soldati N, Sailer U, Jovicich J, Bruzzone L, Kryspin-Exner I, Bauer H, Moser E (2009) A resting state network in the motor control circuit of the basal ganglia. BMC Neurosci 10:137.

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.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356.

Sheline YI, Price JL, Yan Z, Mintun MA (2010) Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci USA 107:11020–11025.

Smith SM (2002) Fast robust automated brain extraction. Hum Brain Mapp 17:143–155.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23(Supp 1):S208–219.

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 (2005) Motivational effects of cannabinoids and opioids on food reinforcement depend on simultaneous activation of cannabinoid and opioid systems. Neuropsychopharmacology 30:2035–2045.

Solinas M, Yasar S, Goldberg SR (2007) Endocannabinoid system involvement in brain reward processes related to drug abuse. Pharm Res 56:393–405.

Solinas M, Goldberg SR, Piomelli D (2008) The endocannabinoid system in brain reward processes. Br J Pharmacol 154:369–383.

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.

Tregellas JR, Wylie KP, Rojas DC, Tanabe J, Martin J, Kronberg E, Cordes D, Cornier MA (2011) Altered default network activity in obesity. Obesity (Silver Spring) 19:2316–2321.

Tudge L, Williams C, Cowen P, McCabe C (2014) Neural effects of CB1 neutral antagonist tetrahydrocannabivarin (THCv) on food reward and aversion in healthy volunteers. Int J Neuropsychop 18. Advance online publication. Retrieved 25 Dec 2014. doi: 10.1093/ijnp/pyu094.

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

Wacker J, Dillon DG, Pizzagalli DA (2009) The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage 46:327–337.

Wilson JL, Jenkinson M, de Araujo I, Kringelbach ML, Rolls ET, Jezzard P (2002) Fast, fully automated global and local magnetic field optimization for fMRI of the human brain. Neuroimage 17:967–976.

Worsley KJ (2001) Statistical analysis of activation images. Chapter 14, In: Functional magnetic resonance imaging:an introduction to methods (Jezzard P, Matthews PM, Smith SM, ed), pp. 251–270. New York, NY: Oxford University Press.

Zhang B, Tian D, Yu C, Zhang J, Tian X, von Deneen KM, Zang Y, Walter M, Liu Y (2015) Altered baseline brain activities before food intake in obese men: a resting state fMRI study. Neurosci Lett 584:156–161.

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