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Title:

Modulation of auditory and visual processing by Delta-9-Tetrahydrocannabinol and Cannabidiol: an fMRI study.

Short title:

Δ -9-THC and CBD modulate sensory processing

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Abstract

Although the effects of cannabis on perception are well documented, little is known about their neural basis or how these may contribute to the formation of psychotic symptoms. We used fMRI to assess the effects of Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) during visual and auditory processing in healthy volunteers.

Fourteen healthy volunteers were scanned on 3 occasions. Identical 10mg THC, 600mg CBD and placebo capsules were allocated in a balanced double blinded pseudorandomised crossover design. Plasma levels of each substance, physiological parameters and measures of psychopathology were taken at baseline and at regular intervals following ingestion of substances. Volunteers listened passively to words read and viewed a radial visual chequerboard in alternating blocks during fMRI scanning.

Administration of THC was associated with increases in anxiety, intoxication and positive psychotic symptoms, whereas CBD had no significant symptomatic effects. THC decreased activation relative to placebo in bilateral temporal cortices during auditory processing, and increased and decreased activation in different visual areas during visual processing. CBD was associated with activation in right temporal cortex during auditory processing, and when contrasted, THC and CBD had opposite effects in the right posterior superior temporal gyrus, the right sided homologue to Wernicke's area. Moreover, the attenuation of activation in this area (maximum 61, -15, -2) by THC during auditory processing was correlated with its acute effect on psychotic symptoms.

Single doses of THC and CBD differently modulate brain function in areas that process auditory and visual stimuli and relate to induced psychotic symptoms.

Keywords: *Cannabis, Delta-9-Tetrahydrocannabinol, Cannabidiol, visual, auditory, sensory*

Introduction

Cannabis is the world's most commonly used illicit substance (Hall and Babor 2000). As well as effects on cognition and mood (Isbell, Gorodetzsky et al. 1967; D'Souza, Perry et al. 2004), it

has marked effects on sensory experiences, ranging from heightened subjective sensory awareness and appreciation, to vivid mental imagery, illusions and frank hallucinations (Tart 1971). In some individuals acute intoxication with cannabis can mimic sensory processing abnormalities associated with psychotic disorders (Koethe, Gerth et al. 2006) and cannabis use has been implicated in the onset of psychotic disorders (Murray et al 2007).

Both chronic cannabis use and the experimental administration of Delta-9-Tetrahydrocannabinol (THC- the main psychoactive constituent of cannabis) can affect regional brain activation during tasks that engage learning (Jager, Van Hell et al. 2007; Bhattacharyya, Fusar-Poli et al. 2009), motor response inhibition (Borgwardt, Allen et al. 2008), interference inhibition (Gruber and Yurgelun-Todd 2005), and emotional processing (Fusar-Poli, Crippa et al. 2009). However, there have been relatively few studies of the effects of cannabinoids on the neural correlates of sensory processing. O'Leary and colleagues, using ^{15}O H_2O Positron Emission Tomography to measure the effects of inhaled marijuana cigarettes on blood flow during an auditory attention task, reported that this was associated with increased perfusion in paralimbic regions, and reduced perfusion in the lateral temporal cortex bilaterally (O'Leary, Block et al. 2002). However, in addition to Δ -9-THC, marijuana cigarettes contain other cannabinoids, in particular Cannabidiol (CBD, (Mechoulam and Gaoni 1967)), the second most abundant constituent of *cannabis sativa*. Whilst administration of THC can induce psychotic symptoms, anxiety and cognitive impairments in healthy subjects (D'Souza, Perry et al. 2004), CBD has anxiolytic (Crippa, Zuardi et al. 2004) and possibly antipsychotic properties (Zuardi, Crippa et al. 2006), and does not impair cognitive performance (Zuardi 2008). The first aim of the present study was to assess and compare the respective effects of THC and CBD on neural activation during auditory and visual processing. A secondary aim was to examine the relationship between the

neural effects of THC and the induction of ‘psychotic like’ experiences. In schizophrenia, functional changes in the auditory and visual processing pathways have been implicated in the pathophysiology of auditory and visual hallucinations, respectively (Oertel, Rotarska-Jagiela et al. 2007; Allen, Laroi et al. 2008). As transient auditory and visual hallucinations are occasionally experienced under the influence of cannabis (Tart 1970; Hall and Solowij 1998), and appear to be mediated by THC (D'Souza, Perry et al. 2004), we investigated whether the acute induction of psychotic symptoms by THC was related to its effects on the areas involved in auditory and visual processing.

We used functional Magnetic Resonance Imaging (fMRI) in conjunction with a paradigm that engaged both auditory and visual processing to study the acute effects of THC and CBD on regional brain activation in healthy volunteers.

Our first hypothesis was that both THC and CBD would alter activation in the lateral temporal and occipital cortices during auditory and visual processing, respectively. The second hypothesis was the effects of THC (but not CBD) on activation during sensory processing would be related to the acute induction of psychotic symptoms.

Methods:

Design

A double-blind, placebo-controlled, pseudo-randomized, within subject study was conducted over three sessions, with each participant scanned three times (placebo, Δ -9-THC, CBD), and with a 1 month interval between sessions. The order of drug administration across sessions was pseudo-randomized across subjects, such that equal numbers followed each drug sequence.

Participants

Eighteen subjects initially took part in the study recruited from advertisements in local media. Three withdrew from the study because they experienced frank psychotic symptoms following THC administration, and could not tolerate the scanning procedure. Data from one further subject was corrupted, leaving a final sample of 14 subjects who completed all parts of the study.

These 14 subjects were healthy white right-handed males, aged 20 to 42 years (average 26.7 years, SD 5.7). Their mean total years of education was 16.5 (SD 3.9), and their mean estimated IQ (National Adult Reading Test (NART(Nelson 1991) was 98.67 (SD 7.0). All participants were native English speakers who had used cannabis at least once but fewer than 15 times in their lifetimes, with no cannabis use in the past month and minimal prior exposure to other illicit substances as assessed by the Structured Clinical Interview (SCID, (Spitzer, Williams et al. 1992) and the Addiction Severity Index (McLellan, Kushner et al. 1992). Participants were told to abstain from illicit drug use for the duration of the study and from alcohol and caffeine intake for 24 and 12 hours, respectively, before each study day. Following a light standardized breakfast a urine sample was collected for screening for amphetamines, benzodiazepines, cocaine, methamphetamine, opiates, and THC using immunometric assay kits. None of the participants tested positive on any of the sessions. Participants were carefully screened using a semistructured clinical interview to exclude psychiatric neurological or serious physical illness or a family history of psychiatric illness. The study had local ethics committee approval and all participants gave their informed consent after the study procedure had been explained to them in detail.

Procedure

One hour before each scanning session, participants were given a capsule of 10 mg Δ -9-THC, 600 mg CBD, or a placebo (flour). These doses of THC and CBD were selected on the basis of previous research (Agurell, Carlsson et al. 1981; Chesher, Bird et al. 1990; Leweke, Schneider et al. 1999; Koethe, Gerth et al. 2006) to produce an effect on regional brain function without provoking severe toxic, psychiatric, or physical symptoms. The capsules were identical in appearance and taste and neither the participants nor experimenters were aware of which drug was being administered. An intravenous line was inserted at the start of the testing session to monitor drug levels. All participants were physically examined before testing, and their heart rate and blood pressure were monitored at regular intervals (5 min/1 hour) throughout each session.

Symptom Ratings, Physiological and Biochemical Variables

Subjects were asked to rate their subjective experiences at baseline, immediately before scanning (1 hour), immediately after scanning (2 hours), and 1 hour postscanning (3 hours) using the Visual Analogue Mood Scale (VAMS, (Folstein and Luria 1973), the Spielberger State Trait Anxiety Inventory (STAI,(Spielberger 1983) and a visual analogue intoxication scale (AIS Mathew et al, 1992). The presence of psychotic phenomena was assessed using the Positive and Negative Syndrome Scale (PANSS, (Kay, Fiszbein et al. 1987) at the same time points along with measures of blood pressure, heart rate, and blood levels of THC and CBD. Concentrations of THC and CBD in whole blood were measured by immunoassay with positives confirmed by gas chromatography–mass spectrometry (Tricho-Tech Ltd, Cardiff, UK).

Functional MRI paradigm

Participants performed a number of cognitive tasks during each scanning session. For the current study we employed a sensory stimulation paradigm that has previously been shown to elicit

robust responses in the auditory and visual cortices (Williams et al 1996). During auditory stimulation blocks, each lasting 24 seconds, subjects listened passively through headphones to neutral words read at 30, 60 or 90 words per minute. During visual stimulation blocks, subjects viewed a radial checkerboard with flicker rates of 2, 4 or 8 Hz for a period of 16 seconds. In between blocks subjects viewed a fixation cross. The order of presentation of the auditory and visual blocks in each of 3 load conditions was pseudo-randomly varied between subjects, such that each subject was presented with a total of 4 repetitions of each load level of visual stimuli, and 3 repetitions of each load level of auditory stimuli.

Image Acquisition and Analysis

Images were acquired on a 1.5Tesla Signa scanner (General Electric Milwaukee Wisconsin) at the Maudsley Hospital, London and analysed using XBAM software developed at the Institute of Psychiatry (<http://brainmap.it>). Image acquisition parameters and preprocessing details are further described in supplementary material.

Following preprocessing we examined the main effect of each task condition (processing auditory and visual stimuli, separately) relative to viewing a fixation cross, independent of sensory load. We then examined the main effect of the drug (THC vs Placebo and CBD vs Placebo), independent of sensory load, in each task condition (auditory & visual processing), using nonparametric repeated measures analyses of variance (ANOVAs) and the interaction of drug and load using 2 (drug) x 3 (load) factorial ANOVAs. Results of load x drug interactions are reported in supplementary material.

All results are reported at a voxelwise threshold of $p < .05$ and, with the clusterwise threshold set such that the total number of false-positive clusters per brain volume was less than 1 (maximum $p < 0.01$).

To investigate the association between changes in activation following administration of THC and concurrently induced psychotic symptoms, Spearman's product-moment correlations were calculated between the mean change in PANSS positive and PANSS total ratings and the difference in the change in the median SSQ ratios in the voxel mean of each cluster between the placebo and THC scans. Two-tailed significance tests were employed. When a significant or trend level correlation was identified for a given cluster, sensitivity testing was performed using Cook's D calculations, and symptom specificity was tested post-hoc by analysing the correlation with the change in other symptom ratings (PANSS subscores, STAI, AIS, and VAMS scores).

Behavioural and Symptom Rating Analyses

Measures of self report data, symptom ratings, physiological data and drug levels were analyzed using repeated-measures ANOVAs to compare drug conditions in SPSS v15.0. When significant differences were found, the Tukey Test for pairwise comparisons was applied.

Results

Physiological parameters

Mean whole blood levels of THC at 1 and 2 hours after taking the drug were 3.9 (SD 7.3) ng/mL and 5.1 (SD 5.6) ng/mL, respectively; CBD levels at the same time points were 4.7 (SD 7.0) and

17.0 (SD 29.0) ng/mL, respectively. There was no significant drug effect on blood pressure; however, we did identify a (non-significant) trend for an increase in heart rate with THC + 1.93 beats/min (SD 5.74) and + 8.79 beats/min (SD 16.31) at 1 and 2 hours after baseline.

FIGURE1 HERE

Symptom Scores

No significant differences were observed between the drug conditions at baseline for any symptom variables. Pairwise comparisons between baseline and 2 hours post ingestion revealed significant increases in ratings over time for mental sedation (VAMS, $p < 0.01$), intoxication (AIS, $p < 0.01$), anxiety (STAI, $p < 0.01$) and positive psychotic symptoms (PANSS-P, $p < 0.01$) for THC vs. placebo. There were no significant changes in the corresponding ratings for the CBD condition and no significant effects of order of drug ($p > 0.1$).

Functional MRI Results

Effect of task

In the placebo condition, auditory processing was associated with bilateral activation in the superior temporal gyri (STG) and middle temporal gyri (MTG), insulae and supramarginal gyri, and in the left inferior frontal gyrus (IFG, Supplementary Table 1, Figure 2A). Visual stimulation was associated with bilateral activation in the fusiform, lingual, and middle occipital gyri, cuneus, and cerebellum (Supplementary Table 1, Figure 4A).

Main Effect of Drug during auditory processing

THC vs Placebo

During auditory stimulation, relative to placebo, THC reduced activation in the temporal cortex bilaterally in the anterior and posterior STG and MTG and insulae, the supramarginal gyri, and in the right IFG and left cerebellum (Table 1, Figure 2B). There were no regions where THC significantly increased activation relative to placebo.

The attenuation of activation in the right temporal cluster (cluster maximum $x=61$, $y=-15$ $z=-2$, STG) following THC was correlated with the concurrent increase in PANSS total ($r= -0.534$ $p=0.049$) score relative to placebo, although not with the change in PANSS positive score ($r= -0.437$, $p=0.118$). Following the removal of 2 outliers identified using Cook's D calculations with a threshold of $4/n$, these correlations were strengthened, and the PANSS positive correlation also became significant (PANSS total $r= -0.773$, $p=0.004$, PANSS positive $r= -0.754$ $p=0.004$, figure 3B). There were no significant correlations with changes in other PANSS subscores, or in any other symptom measures (STAI, AIS, VAMS).

FIGURE 2 HERE

CBD vs Placebo

During auditory processing, CBD increased activation relative to placebo in the temporal cortex bilaterally extending medially to the insulae and caudally to the parahippocampal gyri and hippocampi bilaterally (Table 1, Figure 2C). CBD reduced activation relative to placebo in a posterolateral region of the left STG incorporating parts of the insula, posterior middle temporal gyrus and supramarginal gyrus (Table 2; Figure 2C, 3B, 3D).

THC vs CBD

As THC and CBD appeared to have opposing effects on temporal activation during auditory processing, we directly compared activation during the THC and CBD conditions. There was a significant difference in the right superior and middle temporal gyri; in this region CBD increased activation relative to THC during auditory processing (Table 1 Figure 3A). There were no areas where CBD reduced activation relative to THC.

Main Effect of Drug during visual processing

THC vs Placebo

As found in the auditory task, THC reduced activation in areas that were activated under placebo conditions, predominantly in the extrastriate (secondary) visual cortex. (Table 2 Figure 4B). However, unlike during auditory processing, THC also increased activation relative to placebo in some regions. In the right hemisphere, THC increased activation in the lingual and middle occipital gyri (corresponding to the primary visual cortex); in the left hemisphere THC increased activation extending anteriorly into parts of the lingual and fusiform gyri that had not been activated under placebo (Table 2 Figure 4B). Drug-load interaction in this region is reported in supplementary material.

FIGURE 4 HERE

The increase in activation by THC relative to placebo across the visual cortex was correlated with the concomitant increase in PANSS positive score relative to the placebo condition ($r=0.536$ $p=0.048$, figure 5B), but not with the change in PANSS total score ($r=0.362$ $p=0.204$). Following removal of 2 significant outliers identified using Cook's D calculations with a threshold of $4/n$ this correlation was non-significant ($r=0.493$, $p=0.103$). There were no correlations with other PANSS subscales or symptom measures. There were no correlations between the attenuation of activation in the primary visual cortex following THC and the change in PANSS positive or total scores.

CBD vs Placebo

During visual processing, CBD increased activation relative to placebo in the right occipital lobe, with maxima in the middle and inferior occipital gyri, the lingual gyrus and cuneus (Table 4, figure 4C). There were no areas where CBD reduced activation relative to placebo.

THC vs CBD

Direct comparison of the effects of THC and CBD revealed that THC augmented activation relative to CBD in the left lingual and middle occipital gyri (corresponding to the primary visual cortex; Table 2 figure 5A). THC attenuated activation relative to CBD in widespread occipital regions bilaterally (Table 2 figure 5A). Mixed effects were seen within the cerebellum (Table 2).

FIGURE 5 HERE

Discussion

We used functional MRI to investigate how the two main psychoactive constituents of cannabis (THC and CBD) modulate brain function during auditory and visual processing. We employed a double blinded pseudo-randomised repeated measure crossover design measuring the BOLD response while subjects passively experienced auditory and visual stimulation of differing levels of intensity. Consistent with our hypotheses, we found that both THC and CBD modulated activation in the auditory and visual cortices, and that the effects of THC on temporal lobe activation during auditory processing, and on occipital cortical activation during visual processing were correlated with its acute induction of psychotic symptoms.

In our study 8 of the original 18 subjects (44.4%) experienced transient frank psychotic symptoms and of these 3 withdrew from the study. This rate is consistent with a growing literature on transient psychosis related to cannabis use. In a review article of self-reported cannabis effects to open ended questions, about 51% is reported to feel paranoid and 20% experienced hallucinations (Green, Kavanagh et al. 2003) whilst in a survey of adverse affects of cannabis, 15% reported to experience psychotic symptoms (Thomas 1996).

Auditory stimulation was associated with activation in primary auditory cortex (including Heschl's gyrus and planum temporale), the left posterior superior temporal gyrus (corresponding to Wernicke's area) and its right sided homologue, bilateral supramarginal and angular gyri, and a region of the left inferior frontal gyrus corresponding to Broca's area (Price, Wise et al. 1996). During visual processing we observed activation in primary visual cortex on the medial occipital

surface surrounding the calcarine fissure, and secondary extrastriate visual cortices medially and on the lateral occipital surface.

During auditory processing, THC attenuated activation in primary and secondary auditory regions bilaterally, relative to placebo. These findings are consistent with previous studies that used 15-Oxygen H₂O PET to measure the effect of marijuana cigarettes on rCBF during a dichotic auditory attention task (O'Leary, Block et al. 2000; O'Leary, Block et al. 2002; O'Leary, Block et al. 2007). In these studies, inhalation of marijuana cigarettes (which included THC and CBD) relative to placebo cigarettes (without THC, but including CBD) was associated with reduced blood flow in the temporal cortices bilaterally, and increased blood flow in the orbital frontal cortex, anterior cingulate, temporal pole, insula, and cerebellum. These increases in activation were not seen in the present study, which in contrast utilised pure cannabinoids and a different task and imaging technique.

The attenuation of temporal activation by THC was associated with an increase in psychotic symptoms in the same subjects, suggesting that the induction of psychotic symptoms by THC may be mediated by an effect on temporal cortical function. Altered temporal lobe structure and function are robust findings in patients with psychotic disorders, and there is evidence of a negative relationship between left STG activation and severity of auditory hallucinations in schizophrenia (reviewed in Allen et al, 2008). Woodruff et al (1997) report reduced activation of the left and right temporal cortex to external speech in patients experiencing auditory verbal hallucinations and suggest that internally-generated hallucinations and external speech compete for a common neurophysiological substrate.

In the left posterior STG (corresponding to Wernicke's area), both THC and CBD attenuated the response to auditory stimuli. In contrast, in the homologous right sided region, THC and CBD

had opposite effects, and the attenuation in activation in this area due to THC was correlated with its induction of psychotic symptoms; THC also attenuated activation in the right homologue to Broca's area. While left sided language areas are thought to process linguistic stimuli analytically in dealing with routine, dominant and frequent meanings, their right-sided homologues are thought to play a role in resolving ambiguity in language (Harpaz et al 2009), modulating affective components and prosody and perceiving infrequent subordinate meanings (reviewed in Jung-Beeman 2005). An effect of THC on these aspects of language processing could thus contribute to its psychotogenic properties and account for the correlation with psychotic symptoms in the right temporal cortex. Equally, the opposite effects of CBD on activation in this region may contribute to its reported antipsychotic properties (Zuardi et al 2006). CBD also increased activation in a smaller region corresponding to the left primary auditory cortex, and in the parahippocampal cortex bilaterally. Augmentation of activation in these areas by CBD has previously been reported in the same subjects when they were performing a verbal memory task (Bhattacharyya et al, 2009b).

THC and CBD have previously been found to have opposing effects on activation in a number of regions during tasks that engage verbal memory (Bhattacharyya et al, 2009b), response inhibition (Borgwardt, Allen et al. 2008), and emotional processing (Fusar-Poli, Crippa et al. 2009). The present data extend these findings by showing that while the two cannabinoids also have opposite effects on regional brain responses during auditory and visual processing in some regions, they have similar effects in others. The molecular basis of their similar and opposing effects is unclear: CBD may act as an inverse agonist/ antagonist at CB1 receptors even at low concentrations (Pertwee 2008). On the other hand, THC is known to be a partial agonist at CB1 receptors (Pertwee 2008). This may explain their opposite effects in some brain areas. However,

CBD may act through a number of other mechanisms as well, including hydrolysis of Anandamide, enhancement of adenosine signaling, as an agonist at 5HT1A and vanilloid receptors and through retrograde inhibition of a number of neurotransmitters predominately GABA and Glutamate, but also acetylcholine, dopamine and others (Bhattacharyya, Crippa et al. 2009).

During visual processing, THC attenuated bilateral regions of the occipital lobe compared to the placebo condition. Although less extensive than the auditory literature, studies of patients with visual hallucinations report reductions of activation in visual areas during visual stimulation (eg ffytche et al. 1998). This is thought to result from increased levels of spontaneous activity again consistent with the notion that hallucinations may develop through competition between internally and externally-generated visual stimuli for a common neural substrate.

However, in contrast to its effects during auditory stimulation, THC also augmented the response of some occipital regions during visual processing. In the left hemisphere, these effects included regions anterior to those activated under placebo conditions. The significance of this additional recruitment of visual cortical areas is unclear; however, this region is thought to mediate geometric hallucinations induced by flashing lights (Purkinje patterns ffytche 2008), and also corresponds to areas activated during the experience of spontaneous geometric hallucinations in subjects with Charles Bonnet syndrome (ffytche et al., 1998). The enhanced activation under THC in primary visual cortex correlated with the rise in concurrently induced psychotic symptoms, but this correlation did not survive sensitivity analysis.

The study has some limitations. The symptom rating scales we employed were not intended for use in healthy subjects, and provided limited information on the subjective nature of the sensory experiences induced by THC and CBD. This limited the amount of variance in the PANSS and

correlations with brain activation should be interpreted accordingly. As in previous functional neuroimaging studies, the sample size was modest, reflecting the logistical demands of these kind of studies, however greater drug effects may have been detected with a larger sample. We also administered THC and CBD orally, rather than via more rapid intravenous or inhaled routes, in order to provide a sustained level of drug throughout the scanning protocol.

Conclusions

Single acute doses of THC and CBD significantly modulate brain function in areas that process auditory and visual stimuli. These results are the first to demonstrate how the two major constituents of cannabis (THC and CBD) act on the sensory cortices, and how their effects are related to the induction of psychotic symptoms by cannabis. The data also provide further evidence that THC and CBD have distinct effects on regional brain activation, sometimes in opposite directions.

DISCLOSURE

The authors report no potential conflicts of interest.

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REFERENCES

- Ajurell, S., S. Carlsson, et al. (1981). "Interactions of delta 1-tetrahydrocannabinol with cannabiniol and cannabidiol following oral administration in man. Assay of cannabiniol and cannabidiol by mass fragmentography." *Experientia* **37**(10): 1090-1092.
- Allen, P., F. Laroij, et al. (2008). "The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations." *Neurosci Biobehav Rev* **32**(1): 175-191.
- Bhattacharyya, S., J. A. Crippa, et al. (2009). "Imaging the neural effects of cannabinoids: current status and future opportunities for psychopharmacology." *Curr Pharm Des* **15**(22): 2603-2614.
- Bhattacharyya, S., P. Fusar-Poli, et al. (2009). "Modulation of mediotemporal and ventrostriatal function in humans by Delta9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis." *Arch Gen Psychiatry* **66**(4): 442-451.
- Borgwardt, S. J., P. Allen, et al. (2008). "Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition." *Biol Psychiatry* **64**(11): 966-973.
- Chesher, G. B., K. D. Bird, et al. (1990). "The effects of orally administered delta 9-tetrahydrocannabinol in man on mood and performance measures: a dose-response study." *Pharmacol Biochem Behav* **35**(4): 861-864.
- Crippa, J. A., A. W. Zuardi, et al. (2004). "Effects of cannabidiol (CBD) on regional cerebral blood flow." *Neuropsychopharmacology* **29**(2): 417-426.
- D'Souza, D. C., E. Perry, et al. (2004). "The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis." *Neuropsychopharmacology* **29**(8): 1558-1572.
- Folstein, M. F. and R. Luria (1973). "Reliability, validity, and clinical application of the Visual Analogue Mood Scale." *Psychol Med* **3**(4): 479-486.
- Fusar-Poli, P., J. A. Crippa, et al. (2009). "Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing." *Arch Gen Psychiatry* **66**(1): 95-105.
- Green, B., D. Kavanagh, et al. (2003). "Being stoned: a review of self-reported cannabis effects." *Drug Alcohol Rev* **22**(4): 453-460.
- Gruber, S. A. and D. A. Yurgelun-Todd (2005). "Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation." *Brain Res Cogn Brain Res* **23**(1): 107-118.
- Hall, W. and T. F. Babor (2000). "Cannabis use and public health: assessing the burden." *Addiction* **95**(4): 485-490.
- Hall, W. and N. Solowij (1998). "Adverse effects of cannabis." *Lancet* **352**(9140): 1611-1616.
- Isbell, H., C. W. Gorodetzky, et al. (1967). "Effects of (--)delta-9-trans-tetrahydrocannabinol in man." *Psychopharmacologia* **11**(2): 184-188.
- Jager, G., H. H. Van Hell, et al. (2007). "Effects of frequent cannabis use on hippocampal activity during an associative memory task." *Eur Neuropsychopharmacol* **17**(4): 289-297.
- Kay, S. R., A. Fiszbein, et al. (1987). "The positive and negative syndrome scale (PANSS) for schizophrenia." *Schizophr Bull* **13**(2): 261-276.
- Koethe, D., C. W. Gerth, et al. (2006). "Disturbances of visual information processing in early states of psychosis and experimental delta-9-tetrahydrocannabinol altered states of consciousness." *Schizophr Res* **88**(1-3): 142-150.
- Leweke, F. M., U. Schneider, et al. (1999). "Effects of synthetic delta9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man." *Psychopharmacology (Berl)* **142**(3): 230-235.

- McLellan, A. T., H. Kushner, et al. (1992). "The Fifth Edition of the Addiction Severity Index." J Subst Abuse Treat **9**(3): 199-213.
- Mechoulam, R. and Y. Gaoni (1967). "Recent advances in the chemistry of hashish." Fortschr Chem Org Naturst **25**: 175-213.
- Nelson, H. E. W., J. (1991). "National Adult Reading Test (NART)." nFER-Nelson
- O'Leary, D. S., R. I. Block, et al. (2000). "Acute marijuana effects on rCBF and cognition: a PET study." Neuroreport **11**(17): 3835-3841.
- O'Leary, D. S., R. I. Block, et al. (2002). "Effects of smoking marijuana on brain perfusion and cognition." Neuropsychopharmacology **26**(6): 802-816.
- O'Leary, D. S., R. I. Block, et al. (2007). "Effects of smoking marijuana on focal attention and brain blood flow." Hum Psychopharmacol **22**(3): 135-148.
- Oertel, V., A. Rotarska-Jagiela, et al. (2007). "Visual hallucinations in schizophrenia investigated with functional magnetic resonance imaging." Psychiatry Res **156**(3): 269-273.
- Pertwee, R. G. (2008). "The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin." Br J Pharmacol **153**(2): 199-215.
- Price, C. J., R. J. Wise, et al. (1996). "Hearing and saying. The functional neuro-anatomy of auditory word processing." Brain **119 (Pt 3)**: 919-931.
- Spielberger, C. G., RL Lushene, R Vagg, PR (1983). State-trait anxiety inventory for adults. Palo Alto, CA, Consulting Psychologists Press.
- Spitzer, R. L., J. B. Williams, et al. (1992). "The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description." Arch Gen Psychiatry **49**(8): 624-629.
- Tart, C. T. (1970). "Marijuana intoxication common experiences." Nature **226**(5247): 701-704.
- Tart, C. T. (1971). On Being Stoned: A Psychological Study of Marijuana Intoxication.
- Thomas, H. (1996). "A community survey of adverse effects of cannabis use." Drug Alcohol Depend **42**(3): 201-207.
- Zuardi, A. W. (2008). "Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action." Rev Bras Psiquiatr **30**(3): 271-280.
- Zuardi, A. W., J. A. Crippa, et al. (2006). "Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug." Braz J Med Biol Res **39**(4): 421-429.

Table 1

Cerebral Region	Side	Size	Tal(x)	Tal(y)	Tal(z)	p
THC>Placebo						
Non-significant effect						
THC<Placebo						
Superior Temporal Gyrus	L	140	-58	-30	15	0.0006
Superior Temporal Gyrus	R	145	61	-19	-2	0.0006
Middle Temporal Gyrus	L	83	-58	-41	4	0.0006
Transverse Temporal Gyrus	R	47	61	-19	9	0.0006
Insula	L	37	-51	-37	20	0.0006
Supramarginal Gyrus	R	49	61	-19	15	0.0006
Supramarginal Gyrus	L	6	-58	-37	26	0.0006
Inferior Frontal Gyrus	R	18	47	26	-7	0.0006
Cerebellum	L	12	-43	-63	-18	0.0006
Angular Gyrus	L	7	-43	-70	20	0.0006
CBD> Placebo						
Superior Temporal Gyrus	R	80	51	-22	4	0.0009
Middle Temporal Gyrus	R	105	51	-22	-2	0.0009
Middle Temporal Gyrus	L	45	-51	-22	-2	0.007
Caudate	L	40	-22	-41	9	0.007
Caudate	L	21	-18	-37	15	0.007

Parahippocampal gyrus	L	16	-29	-56	-2	0.007
Parahippocampal gyrus	R	31	22	-44	9	0.0009
Insula/TTG	R	41	47	-22	9	0.0009
Insula/STG	L	28	-43	-22	4	0.007
Hippocampus	R	13	29	-44	4	0.0009
Insula	R	11	32	-26	15	0.0009

CBD < Placebo

Superior Temporal Gyrus	L	89	-54	-37	15	0.002
Insula	L	18	-51	-19	4	0.002
Supramarginal Gyrus	L	11	-47	-44	26	0.002
Middle Temporal Gyrus	L	49	-54	-48	4	0.002

THC > CBD

No significant regions

CBD > THC

Middle Temporal Gyrus	R	134	58	-19	-2	0.0003
Superior Temporal Gyrus	R	76	51	-22	4	0.0003
Supramarginal gyrus/Insula	R	10	51	-22	15	0.0003
Insula/TTG	R	53	47	-22	9	0.0003

Table 1 Talairach coordinates of illustrative peak areas of activation for the main effect of drug during auditory stimulation- areas with identical p values are drawn from contiguous clusters

Table 2

Cerebral Region	Side	Size	Tal(x)	Tal(y)	Tal(z)	BA	p
THC > Placebo							
Lingual Gyrus	R	38	14	-89	-7	17	0.0053
Middle Occipital Gyrus	R	19	25	-85	-2	18	0.0053
Lingual Gyrus	L	7	-18	-74	-7	18	0.0053
Cerebellum	L	81	-7	-78	-18	71	0.0053
Cerebellum	R	23	14	-81	-13	71	0.0053
THC < Placebo							
Middle Occipital Gyrus	R	20	22	-89	9	18	0.009
Lingual Gyrus	L	46	-4	-85	-2	18	0.009
Lingual Gyrus	R	20	14	-74	-7	18	0.009
Cuneus	R	3	18	-89	4	17	0.009
Cerebellum	R	25	14	-74	-13	71	0.009
Cerebellum	L	4	-22	-78	-18	71	0.009
CBD > Placebo							
Lingual Gyrus	R	81	11	-89	-2	18	0.0065
Inferior Occipital Gyrus	R	14	18	-89	-7	17	0.0065
Middle Occipital Gyrus	R	11	22	-85	15	19	0.0065
Cerebellum	R	10	18	-78	-18	71	0.0065
Middle Occipital Gyrus	R	6	29	-78	9	19	0.0065

Cuneus	R	10	25	-67	20	31	0.0065
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CBD < Placebo

No significant areas

THC>CBD

Lingual Gyrus	L	72	-4	-85	-13	18	0.007
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Cerebellum	L	85	-22	-67	-18	71	0.007
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CBD>THC

Lingual Gyrus	R	121	18	-89	-2		0.0045
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Lingual Gyrus	L	24	-11	-85	-13		0.0045
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Cerebellum	R	76	29	-78	-13		0.0045
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Cerebellum	L	114	-7	-56	-24		0.0045
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Table 2 Talairach coordinates of peak areas of activation for the main effect of drug during visual stimulation - areas with identical p values are drawn from contiguous clusters

Legend for Figures

Figure 1: Symptom measures across timepoints and drug conditions; VAMS Visual Analogue Mood Scale, STAI Speiberger State Trait Anxiety Scale, AIS Analogue Intoxication Scale, PANSS Positive and Negative Syndrome Scale

Figure 2: Brain Activation Maps during auditory stimulation: a) task effect (task > fixation cross under placebo conditions) b) THC< Placebo (Blue) c) CBD>Placebo (red); CBD < Placebo (Blue). L on figure = L side of brain

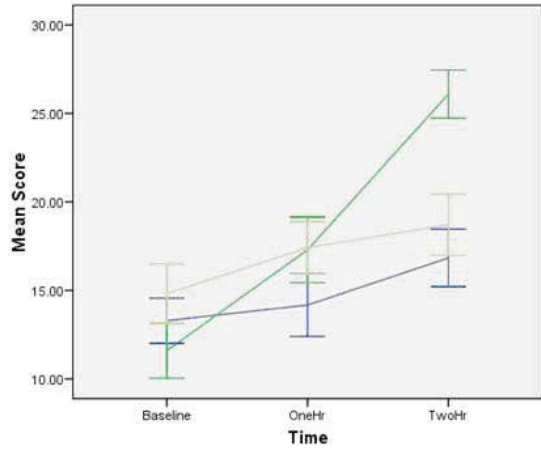
Figure 3: a) Brain Activation Map during auditory stimulation: CBD>THC b) Scatterplot showing change in activation of R temporal cluster (max 61, -15, -2) against change in PANSS-total due to THC relative to Placebo (THC - Placebo). L on figure = L side of brain

Figure 4: Brain Activation Map during visual stimulation: a)Task Effect (task > fixation cross under placebo conditions) b) THC> Placebo (Red) and THC < Placebo (Blue) c) CBD > Placebo (red). L on figure = L side of brain.

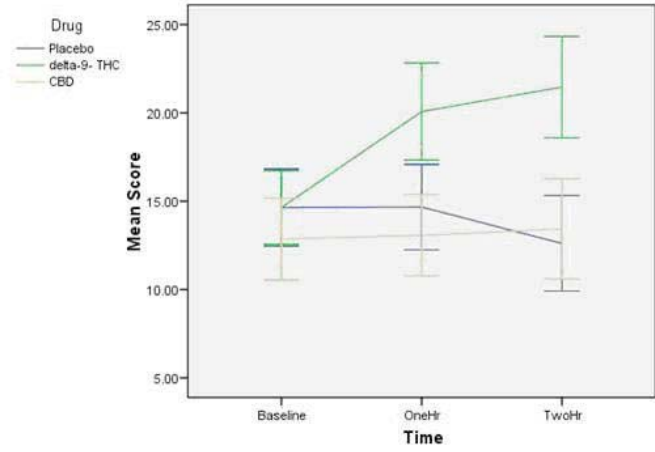
Figure 5: a) Brain Activation Map during visual stimulation: THC>CBD (red) and CBD>THC (blue) b) Scatterplot showing change in activation (THC - Placebo) in Primary Visual cortex Cluster against change in PANSS Pos (THC - Placebo). L on figure = L side of brain.

Supplementary Figure 1: Brain Activation Map showing area of interaction of drug and load under auditory stimulation, B) Activation from cluster mean from figure 1A; C) Change in PANSS positive induced by THC relative to placebo versus attenuation of activation in cluster maximum from Figure 5A $r = -0.508$, $p = 0.032$ D)Interaction of Drug and load under visual stimulation E)Activation in cluster mean from figure 1D

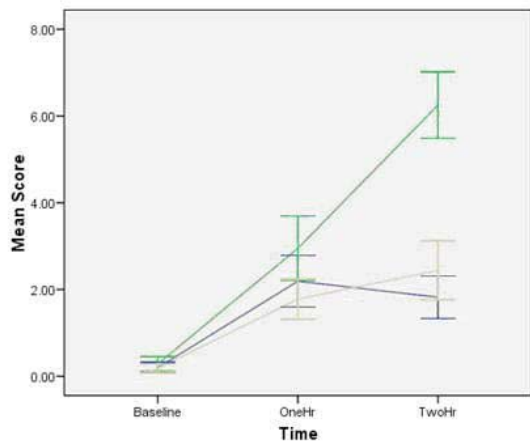
VAMS (mean, SEM)



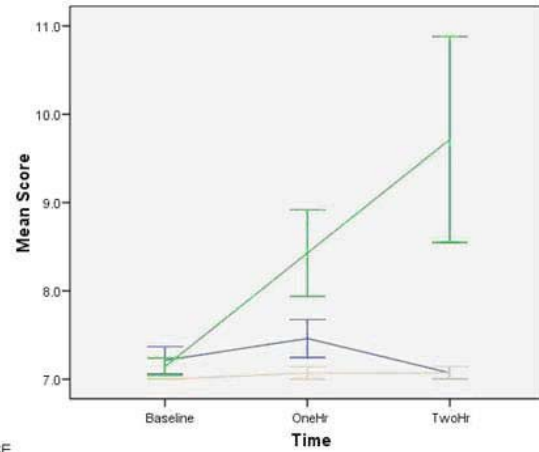
STAI (mean, SEM)



AIS (mean, SEM)



PANSS Positive (mean, SEM)



Error bars: +/- 1 SE

