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Neural Mechanisms for the Cannabinoid Modulation of Cognition and Affect in Man: A Critical Review of Neuroimaging Studies

Sagnik Bhattacharyya[1,*], Zerrin Atakan[1], Rocio Martin-Santos[2], Jose A. Crippa[1,3] and Philip K. McGuire[1]

[1]*Department of Psychosis Studies, King's College London, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF, UK;* [2]*Department of Psychiatry, Institute of Neuroscience, Hospital Clínic, IDIBAPS, CIBERSAM, Department of Psychiatry and Clinical Psychobiology, University of Barcelona; and Pharmacology Research Unit, IMIM-Hospital del Mar, Barcelona, Spain;* [3]*Department of Neuroscience and Behavior, Faculty of Medicine, University of São Paulo and National Institute for Translational Medicine (INCT-TM), Ribeirão Preto, SP – Brazil*

Abstract: Pharmacological challenge in conjunction with neuroimaging techniques has been employed for over two decades now to understand the neural basis of the cognitive, emotional and symptomatic effects of the main ingredients of cannabis, the most widely used illicit drug in the world. This selective critical review focuses on the human neuroimaging studies investigating the effects of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), the two main cannabinoids of interest present in the extract of the cannabis plant. These studies suggest that consistent with the polymorphic and heterogeneous nature of the effects of cannabis, THC and CBD have distinct and often opposing effects on widely distributed neural networks that include medial temporal and prefrontal cortex and striatum, brain regions that are rich in cannabinoid receptors and implicated in the pathophysiology of psychosis. They help elucidate the neurocognitive mechanisms underlying the acute induction of psychotic symptoms by cannabis and provide mechanistic understanding underlying the potential role of CBD as an anxiolytic and antipsychotic. Although there are ethical and methodological caveats, pharmacological neuroimaging studies such as those reviewed here may not only help model different aspects of the psychopathology of mental disorders such as schizophrenia and offer insights into their underlying mechanisms, but may suggest potentially new therapeutic targets for drug discovery.

Keywords: Cannabis, THC, CBD, neuroimaging, fMRI, PET, memory, salience, anxiety, psychotic symptoms.

INTRODUCTION

Pharmacological challenge studies involving the cannabinoids present in the extract of *Cannabis sativa* (*C sativa*) or their synthetic counterparts in combination with neuroimaging offer a way to model aspects of various psychiatric illnesses in man and understand their neural underpinnings [1]. These studies are also an invaluable tool to perturb the endocannabinoid system under controlled experimental conditions in order to understand its role in regulating human cognitive and emotional processes. Cannabis is the most commonly used illicit drug world-wide that is consumed by an estimated 4% of the adult population [2]. Modulation of cognitive and emotional processes in man by the extracts of *Cannabis sativa* has been known for a long time and extensively investigated in experimental and observational studies [3-7]. Evidence from human studies has complemented that from basic research on the role of the endocannabinoid system in the modulation of cognitive and emotional function [reviewed by [8]]. However, precise investigation of the neural basis of the acute effects of cannabinoids on cognitive and emotional processing as well as psychopathology in man was not possible *in vivo* until the availability of sophisticated neuroimaging techniques for human research over the past couple of decades. While the earliest studies [reviewed in [1, 9]] mainly investigated the effects of chronic use or of acute administration of cannabis on the resting cerebral blood flow (rCBF), more recent studies have employed neuroimaging technologies with better spatial resolution to investigate the modulation of the neural correlates of cognitive and emotional processes by cannabinoids. Renewed interest in the link between regular cannabis use and development of psychotic disorders coupled with interest in the therapeutic potential of certain cannabinoids has provided a strong impetus to this line of investigation. Interpretation of evidence emerging from studies that have examined the chronic effects of cannabis use is difficult, because it is confounded by i) diversity in dose, potency and composition of cannabis used, ii) inter-individual variation in the duration of cannabis use, iii) neuroadaptive processes related to tolerance, withdrawal and/ or sensitization and iv) the fact that cannabis use seldom occurs in isolation. Hence, the purpose of this article is to critically review current understanding of the neurocognitive basis of the acute effects of the different cannabinoids in man as evident from neuroimaging studies, with a particular emphasis on the distinctive and often opposite effects of the different cannabinoids that have been examined to date.

The extract of *C sativa* has over 60 different cannabinoids [10] and about 400 chemicals. However, the major psychoactive ingredient of the plant is delta-9-tetrahydrocanabinol (THC) which is thought to be responsible for most of its psychotropic effects [11]. Most of the available evidence regarding the acute effects of cannabis on human cognition, behaviour and the brain relates to evidence regarding the effect of either the crude extract, pure CBD or pure THC. Systematic experimental studies have generally shown that the main cognitive domains impaired by the acute administration of THC include learning and memory [6, 12, 13], psychomotor control [14-18] and attention [12, 19]. However, acute impairments in memory [6] and psychomotor control [20, 21] or an adverse effect on driving ability [22] have not been consistently reported by all studies. There is much less agreement regarding the persistence of the longer term effects of cannabis use [12, 23-27]. Nevertheless, these have been the main cognitive domains that have been investigated employing neuroimaging techniques in conjunction with challenge with THC or cannabis rich in THC. On the other hand, studies that have combined neuroimaging with administration of CBD have been mainly driven by the anxiolytic potential of CBD based on observations in laboratory animals [28-32] and healthy human volunteers [33, 34]. In this paper, neuroimaging studies investigating the effects of THC and CBD will be critically reviewed fol-

*Address correspondence to this author at the Department of Psychosis Studies & Psychosis Clinical Academic Group, King's College London, Institute of Psychiatry, 6th Floor, Main Building, PO Box 067, De Crespigny Park, SE5 8AF, London, UK; Tel: +44 20 78480955; Fax: +44 20 78480976; E-mail: sagnik.2.bhattacharyya@kcl.ac.uk

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lowed by a review of the literature comparing the effects of THC and CBD in man.

EFFECTS OF THC ON NEURAL SUBSTRATES OF COGNITIVE AND EMOTIONAL PROCESSES

Memory and Verbal Learning

Experimental administration of cannabis and its main psychoactive ingredient THC, has generally been shown to result in impairment in verbal learning and memory [3, 6, 35] and a previous meta-analysis suggested that learning and retrieval impairments were the only cognitive domains robustly affected in cannabis users [36]. Impaired memory also represents one of the most common neuropsychological impairments in patients with schizophrenia [37], which has been linked to regular, long-term use starting in adolescence [38, 39]. To date, three functional magnetic resonance imaging (fMRI) studies have examined the neural correlates of the effects of cannabinoids on memory processing in healthy volunteers. They employed different doses as well as different modes of administration of THC. Bhattacharyya *et al.*, [40] examined the effects of 10 mg of THC administered orally to healthy occasional cannabis users (not more than 15 times in lifetime) on neural activation while they performed a learning task that involved the repeated presentation of verbal stimuli. They demonstrated that a single modest dose of THC modulated the medial temporal cortex, which has a central role in relational memory binding [41]. Medial temporal activation has been shown previously to correlate with the quantity of novel and successful mnemonic processing [42-47]. Consistent with previous reports [47], under the placebo condition, most of the learning occurred during the first presentation of the encoding block and there was a linear decrement in the engagement of the parahippocampal cortex, which is involved in the encoding of contextual information about stimuli that may be reactivated later to aid in recollection [48]. THC administration disrupted this linear decrement in medial temporal engagement and its relationship with performance, consistent with evidence that THC impairs medial temporal function in animals [49-51] and memory performance in animals and man [13, 49-52]. These results may reflect increased demands on encoding under the influence of THC as a result of an impairment in the efficient encoding of contextual information in the parahippocampal cortex. During a subsequent recall condition of the task, THC augmented activation in the left medial prefrontal and dorsal anterior cingulate cortex (ACC), areas that have been related to retrieval monitoring and verification [53, 54]. THC also attenuated left rostral ACC and bilateral striatal activation, and its effect in the ventral striatum was directly correlated with the severity of psychotic symptoms induced by it concurrently. This study provided the first human evidence that impairments in learning and memory induced by cannabis are mediated through its effects on medial temporal and prefrontal function. Furthermore, this study demonstrated that the acute induction of psychotic symptoms by THC is related to its effects on striatal function.

Subsequently, Bossong *et al.*, [55] also employed a randomized, double-blind, placebo-controlled, cross-over design, but administered a total of 9 mg of THC through the inhalation route using a vaporizer, to investigate its effects on the neural correlates of associative memory using a task that employed pictorial stimuli. They reported an attenuation of activity under the influence of THC in the insula and inferior frontal gyrus on the right side and in the middle occipital gyrus on the left side during the encoding condition of the associative memory task. During the recall condition of the task, they noted an increase in activity in the cuneus and precuneus under the influence of THC. In both of these studies, there was no significant effect of THC on task performance, thus allowing an interpretation of the neural effects as being related to the pharmacological effects of the drug rather than being confounded by differential task performance.

In a more recent study, Bhattacharyya and colleagues [56] employed their previously established design [40] and examined the genetic moderation of the neural effects of orally administered THC during memory processing. Variations in genes modulating central dopaminergic neurotransmission, such as AKT1 and dopamine transporter (DAT1) were found to modulate the effects of THC on medial temporal, striatal and midbrain function during encoding and recall conditions. Furthermore, the effects of THC on striatal and midbrain activation during the encoding and recall conditions respectively of the verbal memory task were greater in those individuals who carried the risk variants of both the genes compared to the rest.

Attention and Response Inhibition

Attentional deficits have been reported both following acute administration and in chronic cannabis users [3, 12]. O'Leary and colleagues [57] employed a repeated measures, double-blind design that involved smoking marijuana cigarettes containing either about 20 mg THC or without THC in combination with positron emission tomography (PET) to investigate the modulation of resting cerebral blood flow (rCBF) during a focused attention task in regular cannabis users who were abstinent for at least 4 days. During a dichotic listening task, they observed an increase in rCBF in the temporal poles bilaterally, cerebellum, insula and putamen on the right side and the left ventral frontal cortex. They also reported a decrease in rCBF in the left superior temporal gyrus, right occipital lobe and bilateral frontal cortical regions. These areas form an integral component of the attentional network [58]. However, as both the active and placebo smoking sessions were carried out sequentially on the same day with approximately an hour between the two drug conditions, it is likely that carryover effects of THC from the sessions that involved smoking the active marijuana cigarette first would have influenced these results. In a subsequent study [59], the authors employed an improved design to compare the effects of smoked marijuana cigarettes with placebo cigarettes administered on separate sessions at least one week apart. The reported a significant increase in rCBF bilaterally in the anterior insula, anterior cingulate, orbital frontal lobe, temporal poles and cerebellum and decrease in rCBF in the mesial occipital lobes and precuneus under the influence of THC.

While impairments in psychomotor control in cannabis users have been well-documented [18, 60], recent neuroimaging studies have further explored modulation in regional activation that may underlie these impairments. Borgwardt *et al.*, [61] reported that administration of THC was associated with a decrease in the normal activation associated with response inhibition in the right inferior frontal gyrus as well as the ACC, key regions implicated in inhibitory control [62, 63]. This was also associated with a greater activation under the influence of THC in the right hippocampus, right superior and transverse temporal gyri, right fusiform gyrus, right caudate and thalamus and in the left posterior cingulate cortex and precuneus.

Acute effects of THC on the neural substrates for attention and inhibitory control presented here are consistent with attentional and inhibitory impairments and altered functioning of their neural substrates reported in schizophrenia [64-66], which is associated with regular long-term cannabis use.

Emotional and Sensory Processing

A number of studies have employed neuroimaging to study the effects of THC on the domains of emotional and sensory processing, respectively. Phan *et al.*, [67] employed a randomized, placebo-controlled, cross-over design and oral route of administration to investigate the modulatory effect of 7.5 mg THC during the processing of social signals of threat by using angry and fearful faces. They reported an attenuation of amygdalar activation related to the processing of threatening stimuli under the influence of THC.

This was not associated with either an increase or a decrease in anxiety ratings. However, attenuation of amygdala activation was interpreted by the authors as indicative of a potential anxiolytic role of THC. Fusar-Poli *et al*., [68] investigated the acute effects of a slightly higher dose (10 mg) of THC during the processing of fearful faces and reported an increase in engagement of the right inferior parietal lobule and attenuation of engagement of the left medial frontal gyrus while viewing mildly fearful faces. While viewing intensely fearful faces, THC was found to result in increased engagement of the left precuneus and primary sensorimotor corex bilaterally and decreased engagement of the middle frontal gyrus bilaterally and in the posterior cingulated gyrus. Although these effects were associated with an increase in anxiety levels and a concomitant increase in autonomic arousal (as indicated by increased fluctuations in electrodermal skin conductance response; SCR) under the influence of THC, there was no evidence of its effect on amygdala activity. However, in a subsequent 3-way comparison between the effects of THC and CBD relative to the placebo condition (please see below), the same group reported a modulatory effect of THC on amygdalar processing [69], which was directly correlated with the increase in anxiety induced by it. This may suggest that the lack of effect on amygdala activation in the former study [68] was possibly related to a modestly powered sample. Lack of effect on anxiety ratings in the Phan *et al*., [67] study and a significant anxiogenic effect reported by Fusar-Poli and colleagues [68] can be reconciled by the dose-dependent nature of the effect of THC on anxiety [1, 7].

As acute cannabis exposure can lead to abnormalities in sensory processing [70] similar to those experienced during psychotic episodes [71], neuroimaging studies have also focused on the effects of THC on these domains. Winton-Brown *et al*. [72] used fMRI to assess the modulation of activation during auditory and visual processing in healthy subjects. Relative to the placebo condition, THC attenuated activation bilaterally in the anterior and posterior superior temporal gyrus and middle temporal gyrus, the insulae and in the supramarginal gyri and in the right inferior frontal gyrus and left cerebellum during auditory processing. During the visual processing condition, relative to placebo, THC attenuated activation in the extrastriate visual cortex and enhanced activation in ligual and middle occipital gyri (corresponding to the primary visual cortex) on the right side and parts of the ligual and fusiform gyri extending anteriorly on the left side.

Reward and Salience Processing

Bhattacharyya and colleagues [73] examined the effect of THC on the processing of salience and its relationship with psychotic symptoms induced under its influence, as aberrant salience attribution has been related to the presence of psychotic symptoms such as delusions [74] and to abnormal salience attribution in patients with schizophrenia [75, 76] and as epidemiological evidence has linked regular cannabis use with increased risk of developing schizophrenia [38]. Employing a visual oddball detection task, they observed that relative to the placebo condition THC attenuated activation in the right caudate but augmented it in the right prefrontal cortex including the inferior frontal gyrus during the processing of 'salient' oddball stimuli relative to 'non-salient' standard stimuli. THC also reduced the response latency to standard relative to oddball stimuli, suggesting that THC may have made the non-salient stimuli to appear relatively more salient, consistent with evidence that insignificant sensory stimuli or commonplace conversations acquire new meanings and significance under the influence of cannabis [70]. The effect of THC in the right caudate was negatively correlated with the severity of the psychotic symptoms it induced, and its effect on response latency. Both the inferior prefrontal cortex [77-80] and the striatum [81, 82] are involved in the processing of stimulus salience, are strongly connected [83] and altered prefrontostriatal interactions are thought to be critical in the pathophysiology of psychosis [84]. These results are consistent with complementary evidence that striatal [75, 76, 85] and lateral prefrontal function [86, 87] are altered during salience processing in patients with psychosis [75, 76, 85], subjects at ultra high risk of psychosis [87], and subjects in a drug-induced psychotic state [86]. They provide experimental support for the salience model of psychosis [88] and provide the first evidence that the effects of cannabis on psychosis may be mediated by influencing the neural substrate of attentional salience processing.

In order to further explore the role of the endocannabinoid system in reward processing [89, 90] in man, van Hell and colleagues [91] examined the effect of THC during a monetary reward task that involved reward anticipation and feedback conditions. They reported a reduction in feedback-related activity under the influence of THC in the left inferior parietal cortex and the inferior temporal gyrus bilaterally during the rewarding trials. There was no effect of THC on feedback-related neural activity during the trials that were not rewarding. Overall, while subjects responded faster to the rewarding relative to the neutral trials, the neural effects of THC were associated with its trend-level slowing effect on the speed of task performance for both the rewarding and neutral trials, but this effect was more prominent for the reward trials. However, THC did not have any significant effect on neural activation during the anticipation of reward. One possible interpretation of the effects of THC during the monetary reward task [91] is that, under its influence salient, rewarding trials may appear as less attention-grabbing and salient. This is indicated by the greater slowing effect during the rewarding trials that normally elicit a faster response relative to the neutral trials as well as attenuation of activation under the influence of THC in the inferior parietal cortex, which functions as a 'behavioural integrator' that provides a 'salience representation' of the external world and signals attentional priority for behaviourally salient signals [92]. These results are consistent with the effects of THC on attentional salience processing [73], in that neural responses to behaviourally relevant, salient stimuli were attenuated under the influence of THC in both these studies. Furthermore, there was either a greater salience of normally non-salient stimuli [73] or a reduced salience of normally salient, rewarding stimuli [91] under the influence of THC. Lack of striatal activation in the study by van Hell and colleagues [91] may reflect the modest sample size and the fact that monetary reward associated with the rewarded trials in the task was an order of magnitude smaller than that offered to study participants to reimburse for their time. Furthermore, previous exposure to cannabis was greater in volunteers who participated in the van Hell study relative to the study by Bhattacharyya and colleagues [73].

Processing of Social stimuli

Although cannabis use is thought to make individuals more sociable [93], the effects of cannabinoids on the neural substrates for the different social cognitive processes have not been systematically studied in man. However, a previous study reported the effects of THC during the processing of neutral faces as part of a study that was interested in examining the neural correlates of these cannabinoids during the processing of fear [68]. Fusar-Poli *et al*. employed a task that involved viewing mildly and intensely fearful faces as well as neutral faces. Participants had to indicate the gender of the faces by pressing one of 2 buttons. THC did not have a significant effect on gender discrimination performance while viewing neutral faces, though gender discrimination accuracy was better irrespective of the drug condition while viewing fearful as opposed to neutral faces in these participants, all of whom were male. However, under the influence of THC there was increased engagement of the posterior-middle temporal gyrus and the left inferior parietal lobule while viewing neutral faces, consistent with the role of these regions in the processing of facial stimuli and emotional expression respectively [94-96].

EFFECTS OF CBD ON NEURAL SUBSTRATES OF COGNITIVE AND EMOTIONAL PROCESSES

Fewer studies have examined the neural basis of the effects of CBD on cognitive and emotional processes in man in comparison to those that have examined the effects of THC. The first report of the neural effects of CBD came from Crippa and colleagues [97] who employed SPECT imaging to demonstrate a reduction in rCBF in the amygdala and posterior cingulate cortex associated with a reduction in subjective ratings of anxiety under the influence of CBD. Following on from this, Fusar-Poli *et al*., [68] investigated the acute effects of 600 mg of orally administered CBD during the processing of fearful faces in healthy volunteers. They reported an attenuation of the activation in the amygdala and in the anterior and posterior cingulate cortex while processing intensely fearful faces. These effects were associated with a trend for a reduction of subjective anxiety ratings under the influence of CBD and a reduction in autonomic arousal (indicated by the number of fluctuations in SCR). Furthermore, the suppression of the amygdala and anterior cingulate activation by CBD was correlated with its effect on autonomic arousal. These two studies have provided the most robust evidence to date of the potential role of CBD as an anxiolytic and have led to studies in clinical populations. Although not the primary objective of their study, Fusar-Poli *et al.* [68] also reported the effect of CBD on gender discrimination performance and neural activation while viewing neutral faces. Relative to the placebo condition, CBD did not have a significant effect on gender discrimination accuracy or functional brain activation while viewing neutral faces.

Winton-Brown and colleagues [72] also examined the effect of CBD on visual and auditory processing. They reported that during auditory processing, CBD enhanced activation relative to placebo in the temporal cortex bilaterally extending medially to the insulae and caudally to the parahippocampal gyri and hippocampi bilaterally. CBD also 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. During the visual processing condition, CBD enhanced activation relative to placebo in the middle and inferior occipital gyri, the lingual gyrus, and cuneus on the right side.

More recently, Bhattacharyya and colleagues [73] investigated the effect of CBD on attentional salience processing during a visual oddball detection task in light of evidence of its role in incentive salience processing [98, 99]. Relative to the placebo condition, CBD attenuated activation in the left medial prefrontal cortex and enhanced it in the striatum, parahippocampal gyrus, insula and precentral gyrus on the right side as well as the thalamus.

OPPOSITE EFFECTS OF THC AND CBD ON NEURAL ACTIVATION

Evidence that CBD and THC may have opposing effects, particularly on symptoms emerged in the 1970s [33, 100, 101]. This was consistent with evidence that CBD and THC may have opposing effects on CB1 receptors [102]. Further evidence has been accumulating that while THC can induce acute psychotic and anxiety symptoms, CBD may have anxiolytic [97] and antipsychotic effects [103-105]. Recent evidence suggests that CBD can attenuate the incentive salience of drug and food cues under the influence of THC, by reducing the attentional bias to these stimuli in humans [106], complementing evidence from animal studies that while THC enhances the salience of drugs of abuse [107, 108], CBD may have the opposite effect [99].

Studies that have examined the opposite effects of THC and CBD on neural activity in man have been summarized in Table **1**. Bhattacharyya and colleagues [69] examined the neural correlates of the opposite symptomatic effects of THC and CBD by contrasting the effects of 10 mg of THC and 600 mg of CBD administered orally, relative to placebo, across a range of cognitive and emotional processing tasks in healthy occasional cannabis users. Volunteers performed a verbal memory task that involved viewing a pair of words and then recalling the associated word after being shown one word from each previously presented pair. During the retrieval condition, while volunteers recalled the associated word on presentation of the recall cue, THC and CBD had opposite effects on activation in the anterior cingulate/medial prefrontal and lateral prefrontal cortex and the striatum (Fig. **1A**). There was a direct and specific relationship between the symptomatic effects of THC and its neural effects. In the striatum, where THC and CBD had opposite effects, the effect of THC was inversely correlated with the severity of the psychotic symptoms it concurrently induced: the more it attenuated striatal activation, the more severe were the psychotic symptoms. Volunteers also performed an emotional processing task that involved viewing mild and intensely fearful faces that were contrasted against faces with a neutral expression. While viewing fearful faces, THC and CBD had opposite effects on activation in the left amygdala, fusiform, and lingual gyri, the lateral prefrontal cortex and the cerebellum (Fig. **1B**). THC augmented amygdala activation in response to fearful faces, and this effect was directly correlated with the associated level of anxiety; in contrast, CBD attenuated the amygdalar response. This effect of CBD in the amygdala was correlated with its trend level anxiolytic effect, as indexed by a visual analogue mood scale. THC and CBD also had opposite effects on autonomic arousal, indexed by the number of SCR fluctuations while viewing intensely fearful faces. While THC increased the number of SCR fluctuations, CBD resulted in a decrease in the number of SCR fluctuations relative to placebo. The effect of CBD on the number of SCR fluctuations was correlated with the attenuation of amygdala response it concurrently induced. During a response inhibition task that involved inhibiting a prepotent motor response when presented with a 'No-Go' arrow in the midst of a train of 'Go' arrows, the two drugs had opposite effects in the parahippocampal gyrus bilaterally, the left insula and caudate (Fig. **1C**). In these regions, THC attenuated activation, whereas CBD augmented activation relative to placebo. THC and CBD also had opposite effects on activation relative to placebo in the lateral temporal (Fig. **1D**) and occipital cortex (Fig. **1E**) bilaterally during auditory and visual processing tasks respectively.

Winton-Brown *et al*., [72] reported the results of a direct contrast between the effects of THC and CBD during a sensory stimulation paradigm that involved the presentation of auditory and visual stimuli. During the auditory processing condition, which involved passive listening to neutral words, THC and CBD had opposing effects on temporal activation, particularly in the right superior and middle temporal gyri as well as in the supramarginal gyrus and insula: in these regions, CBD increased activation relative to THC during auditory processing. There were no areas in which CBD reduced activation relative to THC. In a part of the superior temporal gyrus adjacent to where CBD increased activation relative to THC, the attenuating effect of THC relative to the placebo condition was correlated with the severity of psychotic symptoms induced by it concurrently. This was such that, the more THC attenuated superior temporal activation the more severe were the psychotic symptoms induced by it. During the visual stimulus condition, which involved viewing a radial checkerboard presented with varying flicker rates, THC augmented activation relative to CBD in the left lingual and middle occipital gyri (corresponding to the primary visual cortex). THC also attenuated activation relative to CBD in other occipital regions bilaterally. Direct contrast of the effects of THC and CBD during visual processing showed mixed effects in the cerebellum, with THC augmenting activation relative to CBD in some parts of the cerebellum and attenuating in others. Increased engagement of the primary visual cortex under the influence of THC was also correlated with the severity of psychotic symptoms induced under its influence.

More recently, Bhattacharyya and colleagues [73] directly contrasted the effects of THC and CBD relative to the placebo condi-

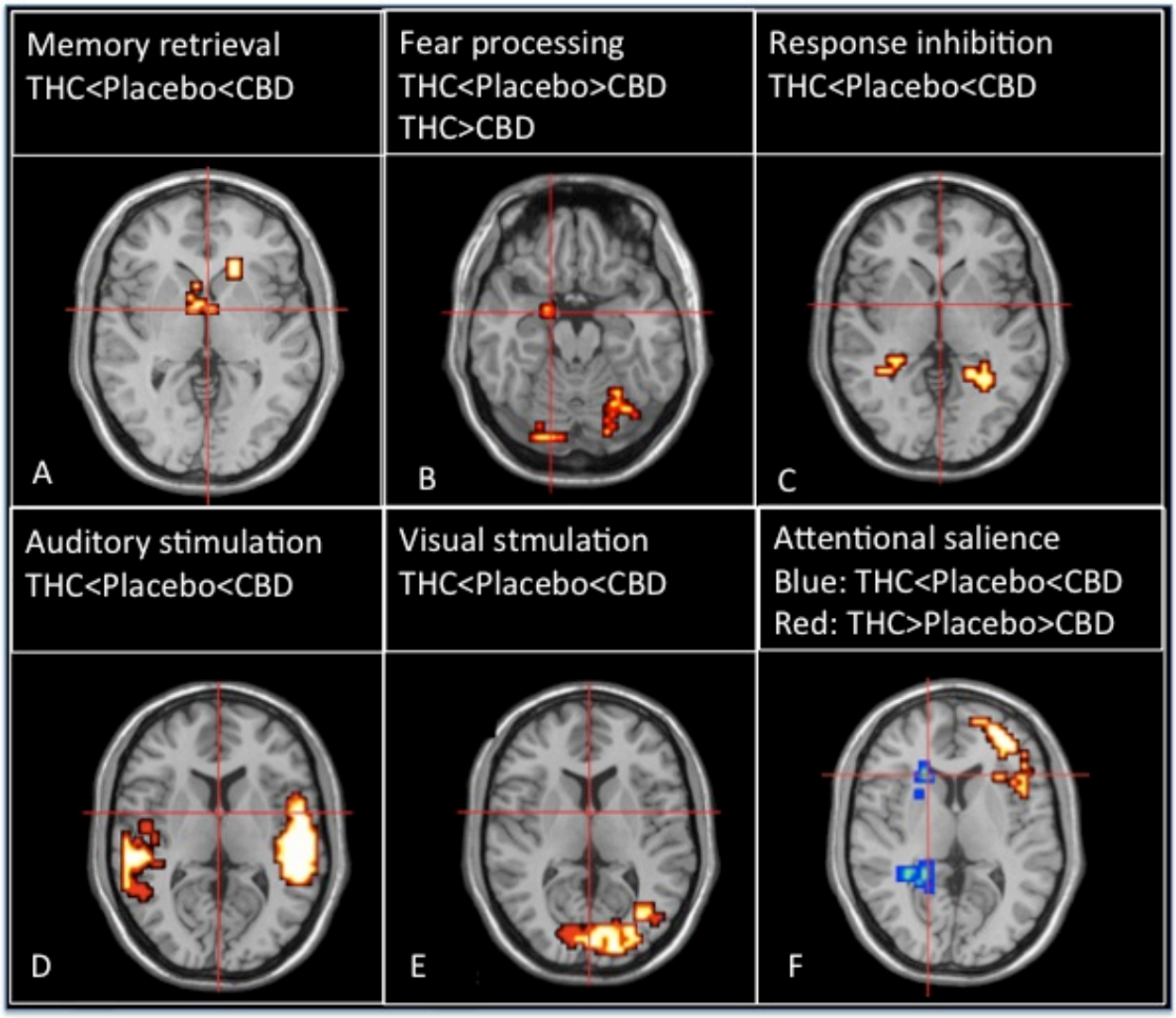

Fig. (1). Contrasting neural effects of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) relative to placebo across a range of cognitive and emotional paradigms. The left side of the brain is shown on the left side of the images (Based on references 69 and 73).

tion during attentional salience processing and reported opposite effect of the drugs on activation in several regions (Fig. **1F**). In the prefrontal cortex on the right side, THC augmented activation relative to placebo, whereas CBD attenuated activation. On the other hand, THC attenuated activation in the left caudate and putamen and in the left parahippocampal gyrus, lingual gyrus and thalamus, while it was augmented by CBD. There was a direct and spatially specific relationship between the symptomatic effects of THC and its neural effects. In the left caudate, where THC attenuated but CBD augmented activation relative to the placebo condition, the effect of THC on activation was inversely correlated with the severity of psychotic symptoms it induced: the more THC attenuated the striatal response to the 'salient' relative to the 'non-salient' stimuli, the more severe were the psychotic symptoms. The effect of THC in this part of the caudate was also inversely correlated with its effect on task performance: the greater the attenuation of left striatal activation by THC, the greater its effect on the response latency to 'non-salient' relative to 'salient' stimuli.

IMPLICATIONS

Neuroimaging studies summarized here suggest that, consistent with the polymorphic and heterogeneous nature of the cognitive and symptomatic effects of cannabis, the major cannabinoids such as THC and CBD present in *C sativa* have modulatory effects over widely distributed neural networks in man. These effects are consistent with and match the distribution of the main cannabinoid receptor (CB1), that is ubiquitous within the brain [109, 110] and are likely to be mediated through the modulation of different neurotransmitter systems [102, 111]. As is evident from these studies, the principal neural substrates for THC, the cannabinoid that is linked to psychotic symptoms and disorder, are the medial temporal and prefrontal cortex and the striatum, regions that map on to the known regions implicated in psychotic disorders such as schizophrenia [112]. These effects are consistent with complementary evidence of alterations of the endocannabinoid system in schizophrenia [summarized in [113]. Together, these studies provide converging evidence of the neural substrates for the symptomatic effects of cannabis and its ingredients.

The key finding of interest regarding the neurobiological basis of the link between cannabis use and psychosis, that has emerged from the neuroimaging studies reviewed here, relate to the acute effect of THC on striatal function across a number of cognitive paradigms [40, 56, 61, 73]. Furthermore, these effects on striatal activation were directly related to the severity of psychotic symp-

Table 1. Opposite Effects of THC and CBD on Functional Brain Activity

Author	No. of Participants/ Type	*Dose* THC/ CBD	Route	Condition	THC<Placebo<CBD	THC>Placebo>CBD
Bhattacharyya *et al.* 2010 (69)	15/ Occasional users	10 mg/ 600 mg	oral	Verbal memory-Recall	Striatum (L/R), L anterior cingulate/ medial prefrontal cortex, L Lateral prefrontal cortex	
Bhattacharyya *et al.* 2010 (69)	15/ Occasional users	10 mg/ 600 mg	oral	Emotional (Fearful faces) processing		L Amygdala*, Cerebellum (L/R), L Fusiform gyrus, L Lingual gyrus, L Lateral prefrontal cortex
Bhattacharyya *et al.* 2010 (69)	15/ Occasional users	10 mg/ 600 mg	oral	Response inhibition		Parahippocampal gyrus (L/R), L Insula, L Caudate
Bhattacharyya *et al.* 2010 (69)	15/ Occasional users	10 mg/ 600 mg	oral	Auditory processing	Temporal cortex (L/R), Insula (L/R)	
Bhattacharyya *et al.* 2010 (69)	15/ Occasional users	10 mg/ 600 mg	oral	Visual processing	Occipital cortex (L/R)	
Winton-Brown *et al.* 2011 (72)	14/ Occasional users	10 mg/ 600 mg	oral	Auditory processing	R superior and middle temporal gyrus, R supramarginal gyrus/ insula, R Insula/ transverse temporal gyrus **	
Winton-Brown *et al.* 2011 (72)	14/ Occasional users	10 mg/ 600 mg	oral	Visual processing	Lingual gyrus (L/R), Cerebellum (L, R) **	L Lingual gyrus, L Cerebellum ***
Bhattacharyya *et al.* 2012 (73)	15/ Occasional users	10 mg/ 600 mg	oral	Attentional salience processing	L Putamen and caudate (head, body and tail), L Hippocampus and parahippocampal gyrus, L Lingual gyrus and Thalamus	R Superior, middle, inferior frontal and orbitofrontal cortex

*THC<Placebo, Placebo>CBD; ** THC<CBD; *** THC>CBD

toms induced concurrently for two of the paradigms [40, 73]. While the precise neurochemical mechanisms underlying these effects of THC are unclear, THC is known to alter central dopamine transmission in humans [114, 115] and perturbed dopamine function may be a key factor in the inappropriate attribution of salience to environmental stimuli or events [116, 117]. It is thought that dopamine dysfunction leads to the development of psychotic symptoms through an effect on salience processing [88]. Hence, it is possible that THC present in cannabis results in perturbed salience processing and the induction of psychotic symptoms through its effects on central dopamine function. These studies have also demonstrated that CBD on the other hand, has an opposite effect to THC [69, 72, 73] and enhances the appropriate response to salient stimuli [73]. Complementing the evidence from behavioural studies, basic research and case series in patient populations [103-105], neuroimaging studies reviewed here provide proof of concept data for the potential of CBD as an antipsychotic. Similarly, results from the neuroimaging studies that have examined the effect of CBD during fear processing has led to the first studies exploring the potential of CBD as an anxiolytic [118, 119].

Over the years, studies investigating the neural basis of the acute effects of cannabinoids in humans *in vivo* have employed progressively more sophisticated designs. While the initial studies that combined neuroimaging techniques with pharmacological challenge examined the effects on the resting state, subsequent studies have employed cognitive paradigms to examine the effects of cannabinoids on specific cognitive processes and neural networks underlying those processes. Studies have also attempted to relate specific psychological phenomena such as symptomatic effects of cannabinoids to effects on brain networks. Combination of pharmacological challenge with cannabinoids and neuroimaging not only allows investigation of the neural mechanisms underlying the effects of cannabinoids on cognition and emotional processing but has also allowed the modeling of aspects of different psychiatric conditions such as anxiety and psychotic symptoms. Future studies combining these techniques with an appropriate experimental de-

sign can help test specific hypotheses related to the mechanistic role of different neurotransmitter systems in the generation of these symptoms.

ETHICAL AND METHODOLOGICAL ISSUES

Several caveats need to be considered while designing and interpreting the results of neuroimaging studies examining the effects of cannabinoids on cognition and affect. Firstly, there are the ethical issues. Cannabis is the most widely used illicit drug worldwide and its regular use has been linked to the development of serious mental illnesses such as psychosis [38]. Hence, appropriate consideration needs to be given to the ethical issues related to studies involving administration of cannabis or its psychotogenic ingredients. While assessment of the effects of cannabinoids in those that have never been exposed to cannabis before may be of great scientific interest, this needs to be carefully considered against any potential harm to the individual. Safeguards could however be embedded within the study design to limit recruitment of individuals that may be particularly at risk. Furthermore, appropriate access to rescue medications and medical and nursing support, well-defined stoppage criteria, adequate counselling of study participants regarding driving and use of heavy machinery whilst intoxicated, monitoring of mental state for return to baseline before allowing study participants to leave the research facility, follow-up assessments for carry–over effects and proper institutional research governance and oversight are some of the steps that may help mitigate the risks of potential harm to participants in such studies.

Another issue pertains to the accurate estimation of the history of previous cannabis use and selection of a homogeneous cohort based on history of previous cannabis use as appropriate to the specific hypothesis being examined. This will ensure that the presence or absence of effect of a specific cannabinoid on neural activation is not confounded by factors such as tolerance [35] or sensitization as a result of previous exposure.

One of the key methodological challenges in neuroimaging studies that involve pharmacological administration pertains to the effect of the drug administered on cerebral blood flow. It is often difficult to exclude the possibility that the drug effects reflect an influence on cerebral blood flow rather than neural activity. However, studies in rodents have shown that the administration of THC can reduce glucose metabolism in several brain regions including the striatum and medial temporal and prefrontal cortices [120], indicating that the drug has a direct effect on neural activity. Long-term cannabis use has not been shown to affect neurovascular coupling or the haemodynamic response measured with fMRI in man [121]. Acute challenge with other drugs that have known vascular effects also has not been shown to alter the shape of the haemodynamic response that is employed to estimate effects in fMRI studies. This is consistent with complementary evidence that fMRI can reliably estimate drug-induced changes in neural activity, even for drugs that affect the cerebral vasculture[122, 123]. Furthermore, previous studies have not found effects of THC on global cerebral blood flow[124], or on regional flow in the striatum during cognitive tasks [57, 125]. More recently, acute effect of THC on rCBF has been investigated using arterial spin labeling [126]. Results from this study suggest that while THC undeniably affects rCBF in several brain regions, the direction of these effects do not seem to be in the same direction as that measured using the blood oxygen level-dependent (BOLD) haemodynamic signal in the majority of the fMRI studies reviewed here, suggesting that the effects of THC on the BOLD signal are unlikely to be a result of changes in rCBF. Bhattacharyya and colleagues [73] have further attempted to address this issue in the context of the series of studies conducted by their group and observed that the same subjects who participated in different cognitive and emotional paradigms during their fMRI studies had opposite effects of the same drugs in identical brain regions within the context of the same scanning session. They noted these opposite direction of effects for both THC and CBD and observed that if these effects of THC and CBD had been due to their influence on the vascular supply to these regions, the same drugs would have to have had opposite effects on the blood flow to the same region in the same subjects, within the same scanning session. This seems very unlikely. Furthemore, some of the drug effects noted in their studies were in regions where similar effects have been reported in electrophysiological studies[127-129], which were independent of vascular effects.

CONCLUSION

Over the last couple of decades, functional neuroimaging research has produced extensive evidence in man for the modulation of cognitive functions and emotional processing by cannabinoids. The precise neural mechanisms underlying the distinct and often opposite acute effects of different cannabinoids in man are becoming increasingly clear through the combination of neuroimaging and pharmacological challenge studies involving cannabinoids. This may not only help in modeling different aspects of the psychopathology of mental disorders such as schizophrenia and offer insights into their underlying mechanisms, but may suggest potentially new therapeutic targets for drug discovery.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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