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REVIEW ARTICLE

Neuroimaging in cannabis use: a systematic review of the literature

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Background. We conducted a systematic review to assess the evidence for specific effects of cannabis on brain structure and function. The review focuses on the cognitive changes associated with acute and chronic use of the drug.

Method. We reviewed literature reporting neuroimaging studies of chronic or acute cannabis use published up until January 2009. The search was conducted using Medline, EMBASE, LILACS and PsycLIT indexing services using the following key words: cannabis, marijuana, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI, MRS and spectroscopy.

Results. Sixty-six studies were identified, of which 41 met the inclusion criteria. Thirty-three were functional (SPECT/PET/fMRI) and eight structural (volumetric/DTI) imaging studies. The high degree of heterogeneity across studies precluded a meta-analysis. The functional studies suggest that resting global and prefrontal blood flow are lower in cannabis users than in controls. The results from the activation studies using a cognitive task are inconsistent because of the heterogeneity of the methods used. Studies of acute administration of THC or marijuana report increased resting activity and activation of the frontal and anterior cingulate cortex during cognitive tasks. Only three of the structural imaging studies found differences between users and controls.

Conclusions. Functional neuroimaging studies suggest a modulation of global and prefrontal metabolism both during the resting state and after the administration of THC/marijuana cigarettes. Minimal evidence of major effects of cannabis on brain structure has been reported.

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Key words: Brain effect, cannabis, CBD, cognitive tasks, cognition, marijuana, neuroimaging, systematic review, THC.

Introduction

Marijuana (*Cannabis sativa*) is the world's most widely used illicit drug (Watson *et al*. 2000; Zuardi, 2006). The principal psychoactive constituent of cannabis is Δ^9-tetrahydrocannabinol (THC) (Hirst *et al*. 1998). Other important components of the plant are cannabidiol (CBD), cannabinol (CBN) and cannabigerol (CBG) (Williamson & Evans, 2000). Except for CBD, cannabinoids act as agonists at specific endogenous cannabinoid receptors, CB_1 and CB_2 (Pertwee & Ross, 2002). The CB_1 receptor is largely expressed in the central nervous system with the highest concentrations in the basal ganglia, prefrontal cortex, anterior cingulate cortex (ACC) and hippocampus (Pertwee & Ross, 2002). CB_2 receptors are mainly present in immune cells and peripheral tissues. CBD has weak partial antagonistic properties at the CB_1 receptor. It inhibits the reuptake and hydrolysis of anandamide, and exhibits neuroprotective antioxidant activity (Roser *et al*. 2008).

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Cannabis intoxication is associated with a large variety of physiological and cognitive alterations (Hollister, 1986; Hall & Solowij, 1998; Lundqvist, 2005). Moreover, use of the drug has been associated with an increased risk for the onset of schizophrenia, especially in adolescent users (Arsenault *et al*. 2004; DeLisi, 2008; Schneider, 2008). These effects may be related to the binding of cannabinoids to CB_1 receptors (Freund *et al*. 2003). CBD reverses some of the biochemical, physiological and behavioural effects of CB_1 receptor agonists, attenuating the anxiogenic effect of THC (Zuardi *et al*. 1982).

Neuroimaging has provided powerful tools to study the *in vivo* effects of cannabis on brain structure and function (Volkow *et al*. 2003; Crippa *et al*. 2005). These effects can be analysed in experimental settings following the administration of THC and CBD or indirectly by comparing subjects with and without a history of cannabis use. Recent reviews have examined this topic (Quickfall & Crockford, 2006; Chang & Chronicle, 2007; Gonzalez, 2007). However, these reviews only examined papers published up to 2005 (Quickfall & Crockford, 2006) or 2006 (Chang & Chronicle, 2007), and their selection criteria have not been clearly specified (Chang & Chronicle, 2007; Gonzalez, 2007) or have not been sufficiently restrictive (Quickfall & Crockford, 2006). In present study, we conducted a systematic review to assess the evidence for specific effects of cannabis on brain structure and function, focusing on the cognitive changes associated with chronic or acute cannabis use. Papers published up until January 2009 have been included. Given the large number of variables that might influence the results of neuroimaging studies, we established a comprehensive search strategy and restrictive set of criteria for selecting articles.

Method

Search strategy

Electronic searches were performed using EMBASE (1980–January 2009), Medline (1966–January 2009), PubMed (1966–January 2009), PsycLIT (1974–January 2009) and LILACS (1982–January 2009) databases, reference searching, and chapters in books on substance abuse neuroimaging. We used the following key words: marijuana; cannabis; delta-9-tetrahydrocannabinol, THC; cannabidiol, CBD; neuroimaging; brain imaging; computerized tomography, CT; magnetic resonance, MRI; single photon emission tomography, SPECT; functional magnetic resonance, fMRI; positron emission tomography, PET; diffusion tensor MRI, DTI-MRI; spectroscopy, MRS. We included all studies published up until January 2009 without any language restriction.

Selection criteria

Initially we performed a general review of all neuroimaging studies that investigated brain structure or function in relation to cannabis use. Studies were only included if they met the following criteria. (1) For studies with a case–control design: inclusion of a control group of healthy volunteers (participants of both groups had to be matched for age, sex and handedness; users had to be abstinent for at least 12 h before brain scanning). (2) For studies involving experimental administration of cannabinoids: use of a parallel design with healthy controls or cross-over design; subjects had to be abstinent for cannabinoids at least 1 week before the experiment, 24 h for alcohol, and no smoking of tobacco or drinking caffeine on the day of the experiment (Gorelick & Heishman, 2006).

The exclusion criteria were: (1) non-neuroimaging studies of cannabis use; and (2) neuroimaging studies that involved participants <18 years of age, or subjects who had other neurological or psychiatric disorders, or individuals with substance abuse disorders who were not abstinent or who tested positive for drugs other than cannabis on urine screening.

When the data from a single subject sample were reported in separate publications, these were treated as a single study with multiple independent variables. Conversely, a publication that reported two forms of different imaging data from the same subjects (e.g. MRI and PET) or a study examining the same subjects with two different cognitive tasks (e.g. auditory attention and verbal working memory) were considered as two studies.

Finally, we defined chronic cannabis users as persons who used cannabis several times a week and who had done so for at least 2 years. Recreational (or occasional) cannabis users were defined as persons who used cannabis sporadically (less than four times a month) whereas naïve cannabis users or healthy controls were persons who had used cannabis less than 15 times in their lifetime, according to standardized strict criteria (Crippa *et al*. 2004).

Recorded variables

Two of the authors extracted the data independently (A. F. and R. M. S.). When there was no agreement, a third author (J. A. C.) reviewed the paper independently. The recorded variables for each article were gender, age, number of joints (cannabis cigarettes)/week/years of use (to classify subjects as chronic, recreational or naïve cannabis users), handedness of

subjects, type of design, exclusion criteria (for neurological, psychiatric or drug history), interval of cannabis and other drugs abstinence (as checked by urine tests), rest/active condition (for functional imaging studies), type of task performed during functional imaging, blinded design, randomization, doses of cannabis (percentage of THC of cannabis cigarettes or mg/mi, of THC intravenous administered or oral THC (in mg), or oral CBD (in mg), plasma concentration levels, pulse rate, respiratory rate, blood pressure and degree of intoxication. We also recorded all psychopathological variables, such as ratings of depersonalization, temporal disintegration, paranoid symptoms, anxiety or depression. For structural and functional imaging data, the primary measures of interest were global and regional volume and global and regional activity [cerebral blood flow (CBF), regional CBF (rCBF) or blood oxygen level dependent (BOLD) signal].

Results

Of the 66 studies identified initially, three were published in the 1970s, four in the 1980s, 12 from 1991 to 1999, and 47 between 2000 and 2008. Twenty-five studies were eliminated because they did not meet *a priori* selection criteria (for excluded studies and reasons for exclusion, see Fig. 1). The remaining studies were grouped according to the neuroimaging technique used (structural/functional), effects of cannabis use (acute effects of THC/marijuana/CBD administration/chronic effects of cannabis use) and testing conditions (resting condition/cognitive task) (Fig. 1). The studies examined thus comprised: 15 studies involving experimental administration of THC/marijuana (nine in the resting state and six during a cognitive task), three studies involving experimental administration of CBD (one in the resting state and two during a cognitive task), eight structural imaging studies evaluating chronic effects of THC [five volumetric and three diffusion tensor imaging (DTI) studies] and 17 functional imaging studies on chronic THC effects (seven in the resting state and 10 during a cognitive task). The reviewed studies included a total number of 655 cannabis users and 402 healthy controls.

Because of the heterogeneity in the study design (case–control/parallel/cross-over) and the methods used (such as neuroimaging technique) we decided it would be impractical to perform a meta-analysis. Moreover, a systematic review without meta-analysis was chosen for several other reasons: (*a*) information needed to compute effect size was not always available, (*b*) the methods and extent of detailed information to define regions of interest vary widely in the studies, preventing accurate comparison, (*c*) there is a large difference in secondary variables across studies (i.e. gender), and (*d*) meta-analysis has intrinsic limitations in estimating negative findings that do not get published (the file drawer problem).

Acute effects (*see Table 1*)

Acute effects of cannabis on resting state activity

After smoking marijuana cigarettes. Three ^{133}Xe-SPECT studies examined resting state CBF in chronic or recreational cannabis users before and after smoking marijuana cigarette with controlled THC dose (Table 1).

The studies included in this category described increased regional activity at rest relative to baseline or marijuana cigarette without THC. An increase in resting global CBF relative to baseline at 30–60 min following the smoking of a marijuana cigarette with THC in a proportion of 1.75% or 3.55% was reported in cannabis users 2 weeks after cessation of use (Mathew *et al*. 1992*a*, Mathew & Wilson, 1993). Increased activity was also observed in the left temporal lobe after smoking a marijuana cigarette with 2.2% of THC (Mathew *et al*. 1989).

Subjective levels of intoxication (Mathew *et al*. 1992*a*, Mathew & Wilson, 1993), dissociative experiences [Temporal Disintegration Inventory (TDI)], measures of depersonalization [Depersonalization Inventory (DPI); Mathew & Wilson, 1993)] and measures of confusion (Mathew & Wilson, 1993) have been correlated with increased global CBF after marijuana smoking. Anxiety and confusion in chronic users following marijuana smoking have been inversely correlated with regional activity in several brain areas after controlling for multiple comparisons (Mathew *et al*. 1989). The heart rate correlated positively with changes in global CBF following the smoking of a marijuana cigarette (Mathew *et al*. 1992*a*) and inversely with rCBF in the right frontal, bilateral temporal, parietal and occipital cortices (Mathew *et al*. 1989). Increased global CBF has also been correlated with plasma THC levels (Mathew *et al*. 1992*a*).

After THC administration. Six studies examined resting state CBF and metabolism in chronic or recreational cannabis users before and after the experimental administration of THC. Four of these studies used $^{15}OH_2O$-PET (Mathew *et al*. 1997, 1998, 1999, 2002), one used ^{18}F-fludeoxyglucose (FDG)-PET (Volkow *et al*. 1996) and one used [^{11}C]raclopride-PET (Bossong *et al*. 2009). All but the Volkow *et al*. study (1996) were controlled with placebo (Table 1).

All of these studies described increased regional activity at rest relative to baseline or placebo following

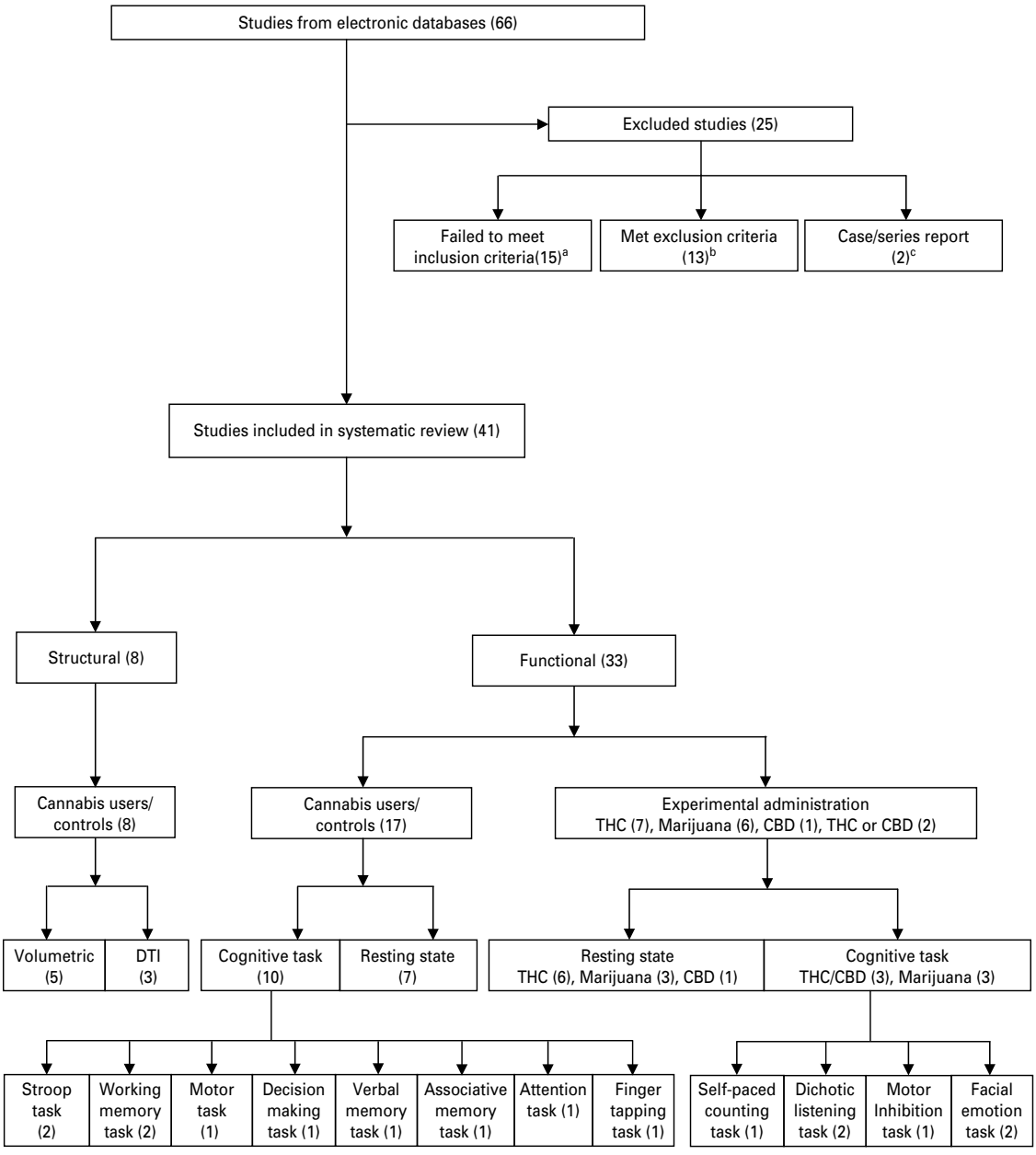

Fig. 1. Flow diagram (selection strategy) of included studies. [a] *No age, sex or handedness matched*: Campbell *et al*. 1971; Co *et al*. 1977; Kuehnle *et al*. 1977; Hannerz & Hinmarsh, 1983; Aasly *et al*. 1993; Amen & Waugh, 1998; Yurgelun-Todd *et al*. 1998; O'Leary *et al*. 2000; Ward *et al*. 2002; Jacobsen *et al*. 2004; Sneider *et al*. 2006. *No cannabis abstinence*: Wiesbeck & Taeschner, 1991; Aasly *et al*. 1993; O'Leary *et al*. 2000; Vorunganti *et al*. 2001; Hermann *et al*. 2007; Nestor *et al*. 2008; Weinstein *et al*. 2008. [b] *Psychiatric, other abuse or medical disorders*: Campbell *et al*. 1971; Wiesbeck & Taeschner, 1991; Yurgelun-Todd *et al*. 1998; Vorunganti *et al*. 2001; Ward *et al*. 2002; Li *et al*. 2005; Schweinsburg *et al*. 2005; Voytek *et al*. 2005; Jacobsen *et al*. 2007; Ashtari *et al*. 2009. *No healthy controls*: Wiesbeck & Taeschner, 1991; Wilson *et al*. 2000. *Others*: Volkow *et al*. 1991; Mathew *et al*. 1992*b*. [c] *Case/series report*: Kuehnle *et al*. 1977; Vorunganti *et al*. 2001.

administration of THC. An increase in resting global CBF relative to baseline at 30–60 min following THC administration was reported in cannabis users 2 weeks after cessation of use (Mathew *et al*. 1997). Increased activity was also described in the ACC (Mathew *et al*. 1997, 1998, 1999, 2002), the insula (Mathew *et al*. 1997, 1998, 1999, 2002), the prefrontal and orbitofrontal cortices (Volkow *et al*. 1996) and the cerebellum (Mathew *et al*. 1998, 2002). Findings in the basal ganglia, thalamus, amygdala and hippocampus have been inconsistent, with reports of both increased and reduced activity in these areas after administration of THC in

Table 1. *Acute effects of cannabis use: functional studies (resting state or with a cognitive task)*

Author	Method	Users/ controls	Mean age (S.D.) users/ controls	Users' type	THC dose[a]	THC route	Comparison placebo/ baseline	Image analysis	Condition	Greater volume/ resting blood flow/ BP_{ND}/activation in users	Reduced volume/ resting blood flow/ BP_{ND}/activation in users
Functional (resting state) after marijuana cigarette											
Mathew *et al.* (1989)	^{133}Xe-SPECT	17/14	28.3 (8.3)/ 26.9 (7.5)	C	2.2%	s	Baseline	Scintillation detector	Resting state	L/R frontal blood flow L temporal blood flow (chronic users)	Baseline global CBF (chronic users *versus* recreational users)
Mathew *et al.* (1992*a*)	^{133}Xe-SPECT	20/0	25.3 (6.4)	R	1.75%/3.55%	s	Placebo	Scintillation detector	Resting state	R frontal and temporal blood flow R hemisphere blood flow	
Mathew & Wilson (1993)	^{133}Xe-SPECT	35/0	21.7 (8)	R	1.75%/3.55%	s	Baseline	Scintillation detector	Resting state	Global CBF R frontal blood flow	
Functional (resting state) after THC administration											
Volkow *et al.* (1996)	^{18}F-FDG-PET	8/8	31 (6)/35 (7)	C	2 mg	i.v.	Baseline	ROI	Resting state	PFC blood flow OFC blood flow Basal ganglia blood flow	Cerebellar blood flow
Mathew *et al.* (1997)	$H_2{}^{15}O$-PET	32/0	32.5 (7.6)	R	0.15/0.25 mg/ min	i.v.	Placebo	ROI	Resting state	Global CBF R hemisphere blood flow L/R frontal, insula and ACC blood flow	
Mathew *et al.* (1998)	$H_2{}^{15}O$-PET	46/0	29.0 (6.1)	R	0.15/0.25 mg/ min	i.v.	Baseline	ROI	Resting state	L/R ACC blood flow L/R insula blood flow L/R cerebellum blood flow L/R frontal blood flow	Cerebellar blood flow
Mathew *et al.* (1999)	$H_2{}^{15}O$-PET	59/0	31.7 (7.5)	R	0.15/0.25 mg/ min	i.v.	Baseline	ROI[b]	Resting state	L/R ACC blood flow R frontal blood flow R insula blood flow	Basal ganglia, thalamus, hippocampus and amygdala blood flow
Mathew *et al.* (2002)	$H_2{}^{15}O$-PET	47/0	32.0 (8.3)	C	0.15/0.25 mg/ min	i.v.	Baseline	ROI[b]	Resting state	R ACC blood flow R insula blood flow Ratio of anterior: posterior blood flow L/R cerebellum blood flow	
Bossong *et al.* (2009)	[^{11}C]Raclopride-PET	7/0	21.9 (2.7)	R	8 mg	i	Placebo	ROI[b]	Resting state		BP_{ND} in: Ventral striatum Precommissural dorsal putamen

Table 1 (*cont.*)

Author	Method	Users/ controls	Mean age (S.D.) users/ controls	Users' type	THC dose[a]	THC route	Comparison placebo/ baseline	Image analysis	Condition	Greater volume/ resting blood flow/ BP_{ND}/activation in users	Reduced volume/ resting blood flow/ BP_{ND}/activation in users
Functional (resting state) after CBD administration											
Crippa *et al.* (2004)	^{99m}Tc-SPECT	0/10 cross-over	29.8 (5.1)	N	CBD: 400 mg	o	Placebo	Voxel-based	Resting state	L parahippocampal gyrus blood flow	L amygdala-hippocampal, hypothalamus L posterior cingulate gyrus blood flow
Functional (cognitive task) after marijuana cigarette											
O'Leary *et al.* (2002)	$H_2{}^{15}O$-PET	12/0	30.5 (8)	R	20 mg	s	Placebo	Voxel-based[b]	Dichotic listening task	L/R temporal activation L ventral frontal activation R insula and putamen activation L/R cerebellum activation	L/R frontal activation L STG activation R occipital activation
O'Leary *et al.* (2003)	$H_2{}^{15}O$-PET	12 heavy 12 moderate/0	21.7 (1.4)	R	20 mg	s	Baseline	Voxel-based[b]	Self-paced counting task	Both groups: ACC, R cerebellar and L OFC activation Moderate users: L/R ventral frontal lobe, R DLPFC, R mesial frontal, R middle temporal and R parietal activation Heavy users: L cerebellar, L thalamus, L hippocampal, R frontal and L STG activation	Both groups: R occipital, temporal and frontal activation
O'Leary *et al.* (2007)	$H_2{}^{15}O$-PET	12/0	23.5 (4.3)	R	20 mg	s	Placebo	Voxel-based	Dichotic listening task	OFC, ACC, temporal pole, insula and cerebellum activation	Visual and auditory cortices activation
Phan *et al.* (2008)	fMRI	0/16	20.8 (2.6)	R	7.5 mg	o	Placebo	Voxel-based[b]	Emotional face processing task		R amygdala

Functional (cognitive task) after THC and CBD administration											
Borgwardt *et al.* (2008)	fMRI	0/15 cross-over	26.7(5.7)	N	10 mg CBD: 600 mg	o	Placebo	Voxel-based[b]	Motor inhibition task	THC: R hippocampus, R parahippocampal gyrus, R superior, transverse temporal and L posterior cingulate cortex activation	THC: R inferior frontal, R ACC CBD: L temporal cortex and L insula activation
Fusar-Poli *et al.* (2009)	fMRI	0/15 cross-over	26.7(5.7)	N	10 mg CBD: 600 mg	o	Placebo	Voxel-based[b]	Facial expressions of emotion task	THC: L/R frontal cortex R parietal cortex	L amygdala L ACC and PCC R cerebellum

THC, Δ^9-Tetrahydrocannabinol; SPECT, single photon emission tomography; PET, positron emission tomography; FDG, fludeoxyglucose; fMRI, functional magnetic resonance imaging; CBD, cannabidiol; S.D., standard deviation; i.v., intravenous; s, smoking; i, inhaled; o, oral; ROI, region of interest; C, chronic; R, recreational; N, naïve; BP_{ND}, non-displaceable binding potential; L, left hemisphere; R, right hemisphere; CBF, global cerebral blood flow; PFC, prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; STG, superior temporal gyrus;

[a] %THC of cannabis cigarettes or mg/ml of THC i.v. administered.

[b] Multiple comparison correction.

cannabis users (Volkow *et al*. 1996; Mathew *et al*. 1997, 1999). Following administration of THC, the subjective level of intoxication was correlated positively with increases in the anterior/posterior ratio of brain activity (Mathew *et al*. 2002); and also activity in the ACC (Mathew *et al*. 1997), frontal (Mathew *et al*. 1997, 1999) and cerebellar cortices (Volkow *et al*. 1996). TDI scores have also been negatively correlated with cerebellar activity (Mathew *et al*. 1998). Moreover, the severity of paranoid symptoms following intravenous THC administration was correlated with the plasma level of THC (Volkow *et al*. 1996).

Finally, Bossong *et al*. 2009 studied the effects of THC inhalation on [^{11}C]raclopride specific binding (a dopamine D_2/D_3 receptor tracer) in seven healthy subjects, finding a reduction in the ventral striatum and dorsal putamen, which is consistent with an increase in dopamine levels in these regions.

After CBD administration. One study explored the acute effect of CBD relative to placebo in a sample of healthy subjects (Crippa *et al*. 2004). It showed reduced activity in medial temporal areas including the left amygdala–hippocampal complex, extending to the hypothalamus, and the left posterior cingulate gyrus and an increased activity in the left parahippocampal gyrus. No correlations were observed between subjective anxiety ratings (the Visual Analogue Mood Scale, VAMS) and the activity in the brain areas where the effects of CBD had been predicted *a priori*, or in the other unpredicted areas after correction for multiple comparisons.

Acute effects of cannabis on activation during cognitive tasks

After smoking marijuana cigarettes. Three PET studies have examined the acute effect of marijuana cigarettes with 20 mg of THC on rCBF while subjects were performing a cognitive task (Table 1).

(*a*) *Attention*. Two imaging studies used an attentional paradigm. O'Leary *et al*. (2002) evaluated the effects of marijuana cigarettes with THC on rCBF in regular cannabis users while performing a dichotic listening task after 4 days of abstinence. Marijuana with THC use was associated with increased rCBF (relative to a cigarette containing marijuana with the THC removed) in the left ventral frontal cortex, right insula, bilateral temporal pole, ACC, temporal and cerebellar cortices, whereas there was decreased activity in the left superior temporal gyrus (O'Leary *et al*. 2002). In a subsequent study by the same group, 12 recreational cannabis users were tested (O'Leary *et al*. 2007). rCBF was measured during a tasks requiring attention to left and right ears in different conditions, after smoking

marijuana cigarettes with or without THC, at least a week apart using a double-blind design. After smoking marijuana cigarettes with THC, there was an increase in rCBF increase in the orbitofrontal cortex, ACC, temporal pole, insula and cerebellum. On the contrary, smoking marijuana cigarettes with 20 mg of THC lowered rCBF in auditory cortices compared to marijuana cigarette without THC. However, THC did not alter the normal pattern of attention-related rCBF asymmetry (greater rCBF in the temporal lobe contralateral to the direction of attention) observed after subjects smoked marijuana cigarettes without THC. As attentional neuroanatomical networks are known to include prefrontal and posterior parietal regions (Berger & Posner, 2000), these results suggest alterations of the functional anatomical substrate of attentional processes as a consequence of acute cannabis use.

(*b*) *Motor performance*. The above group (O'Leary *et al*. 2003) has studied the acute effects of smoking marijuana cigarettes with 20 mg of THC in heavy and moderate cannabis users while they performed a self-paced counting task. In both groups, marijuana with THC was associated with increased activation in the cerebellum, the left orbitofrontal cortex and the ACC; and decreased activation in the right temporal, occipital and dorsolateral prefrontal cortices. The magnitude of this effect on right ventral and dorsolateral frontal activation was greater in the moderate than in the heavy users. Smoking marijuana cigarettes was also associated with faster response times, which was related to the change in cerebellar clock activity (O'Leary *et al*. 2003).

After THC administration. Three fMRI studies have examined the acute effect of THC on rCBF while subjects were performing a cognitive task (Table 1). Two of them (Borgwardt *et al*. 2008; Fusar-Poli *et al*. 2009) compared the two main compounds of cannabis, THC and CBD, controlled by placebo.

(*a*) *Motor response inhibition*. Fifteen healthy volunteers performed a motor inhibition task (Go/No-Go) following oral administration of either 10 mg of THC or 600 mg of CBD or a placebo (Borgwardt *et al*. 2008). Relative to the placebo, THC attenuated activation in the right inferior frontal cortex and the anterior cingulate gyrus. Conversely, THC was associated with greater activation in the right hippocampus/parahippocampal gyrus, right superior and transverse temporal gyri and the left posterior cingulated cortex. These THC-induced changes were not associated with behavioural effects. By contrast, CBD deactivated the left temporal cortex and insula. These results suggested that THC modulates brain function during response inhibition, whereas the effects of CBD are evident in other regions that do not mediate this cognitive process.

(*b*) *Emotional processing*. Two studies evaluated facial emotional processing after the administration of cannabinoids. Fusar-Poli *et al*. (2009) evaluated 15 healthy volunteers on three separate occasions while viewing faces that implicitly induced different emotional processing. Each scanning session was preceded by a single oral dose of 10 mg of THC, 600 mg of CBD or placebo. After CBD administration, reduced activation in the amygdala and the anterior and posterior cingulated cortices was observed while subjects processed intensely fearful faces. Conversely, THC administration modulated activation mainly in the frontal and parietal regions. Overall, the results suggested that both THC and CBD have effects on neural response to fearful faces. The second study (Phan *et al*. 2008) evaluated the effects of 7.5 mg of THC on amygdala reactivity to social signals of threat (fearful and angry faces) in 16 recreational cannabis users. The results suggest that THC significantly attenuated amygdala activation to threatening faces but had no effect on visual and motor cortex activation.

Non-acute effects (*see Table 2*)

Structural studies

Eight structural MRI studies have investigated grey matter volume in chronic cannabis users (Table 2). Although all of these studies were methodologically rigorous, three of them did not find any significant abnormalities in cannabis users relative to the controls (Block *et al*. 2000*a*; Tzilos *et al*. 2005; Jager *et al*. 2007). Two studies reported structural brain differences associated with chronic cannabis use (Matochik *et al*. 2005; Yücel *et al*. 2008). Matochik *et al*. (2005) found that cannabis users had a smaller grey matter volume than the controls in the right parahippocampal gyrus, and a larger white matter volume in the contralateral parahippocampal and fusiform regions. Differences in grey matter volume in the right lentiform nucleus, brain stem, precentral gyrus and right thalamus were also found. More recently, Yücel *et al*. (2008) report bilateral volumetric reductions in the hippocampal and amygdalar areas in a group of 15 chronic cannabis users compared with non-users. The volume of the left hippocampus was inversely associated with the severity of positive psychotic symptoms, as assessed by the Scale for the Assessment of Positive Symptoms (SAPS). Finally, three studies have used DTI to examine the integrity of white matter tracts in cannabis

users. Two of them found no differences between cannabis users and controls (Gruber & Yurgelun-Todd, 2005; DeLisi *et al*. 2006). The third study reported a significant reduction in mean diffusivity, but no decrease in fractional anisotropy associated with cannabis use, in the prefrontal section of the corpus callosum (Arnone *et al*. 2008). Taken together, these structural neuroimaging studies provide minimal evidence of major cannabis effects on brain structure, both in regional grey matter volumes and in the integrity of white matter fibres. Subtle alterations may be easier to detected using functional methods.

Non-acute effects on resting state activity

We included seven case–control studies that compared resting rCBF in cannabis users and healthy subjects. The imaging methods used were ^{133}Xe-SPECT (Mathew *et al*. 1986; Tunving *et al*. 1986; Lundqvist *et al*. 2001), $H_2{}^{15}O$-PET (Block *et al*. 2000*b*), [18F]-FDG-PET (Sevy *et al*. 2008), [^{11}C]raclopride-PET (Sevy *et al*. 2008) and dynamic susceptibility contrast (DSC)-MRI (DSMRI; Sneider *et al*. 2008). In a group of nine chronic cannabis users, assessed within 1 week of drug cessation, Tunving *et al*. (1986) found a reduction in global CBF relative to controls that did not correlate with the duration of cannabis consumption. When four of the cannabis users were rescanned following a further abstinence period, an increase in CBF relative to baseline was observed. Lundqvist *et al*. (2001) also report lower global CBF in cannabis users than controls after 5 days of abstinence, and described reduced rCBF in the right prefrontal and superior frontal cortex. Block *et al*. (2000*b*) report reduced bilateral cerebellar and ventral prefrontal activity but also greater right anterior cingulate rCBF in 17 young chronic marihuana users after 26 h of abstinence. Mathew *et al*. (1986) assessed 17 chronic cannabis users after 12 h of abstinence and found no differences in either global or rCBF between cannabis users and controls. Sneider *et al*. (2008) examined changes in regional blood volume (rCBV) in a group of 17 healthy controls and 15 cannabis users. Imaging data were collected between 6 and 36 h after the subjects' last cannabis use, and again after 7 and 28 days of supervised cannabis abstinence. Their findings demonstrated that, after 7 days of abstinence, cannabis users continued to display the same pattern of activation, characterized by increased rCBV in the right frontal, bilateral temporal lobes and the cerebellum. Nevertheless, after 28 days of abstinence only the temporal and cerebellar areas showed increased activity, suggesting that frontal regions begin to normalize with prolonged cannabis abstinence whereas other regions continue to show altered neural activity. Finally, a pattern of reduced metabolism in the right orbitofrontal region and striatum bilaterally was described in six subjects with cannabis dependence compared with six healthy controls. However, there were no differences between groups in striatal D_2/D_3 receptor availability. No correlations between striatal [^{11}C]raclopride binding potential and glucose metabolism were observed (Sevy *et al*. 2008).

Non-acute effects on activation during cognitive tasks

We included 10 studies that compared regional activation during performance of a cognitive task in cannabis users and healthy controls (Table 1).

Memory and attention. Cannabis is known to have robust effects on short-term episodic memory, which might be mediated by several mechanisms, including the inhibition of gamma-aminobutyric acid (GABA), glutamate and dopamine release (Ranganathan & D'Souza, 2006). Using $^{15}OH_2O$-PET, Block *et al*. (2002) report that 18 chronic cannabis users (after 26 h of abstinence) had worst performance with an associative memory task. This was associated with reduced activation in the right prefrontal cortex but greater activation in posterior cerebellum relative to 13 healthy controls. Similar activity in the right dorsolateral prefrontal cortex and attenuated bilateral parahippocampal activation were reported by Jager *et al*. (2007) in 20 chronic cannabis users after 7 days of abstinence compared with 20 healthy controls. There were no differences in task performance between groups.

Chang *et al*. (2006) used fMRI to examine visual attention in 24 chronic cannabis users, abstinent for 24 h, relative to 19 healthy controls. Cannabis users showed decreased activation in the right prefrontal, medial and dorsal parietal cortices and medial cerebellar regions. They also showed greater activation in left frontal subgyral, right parietal subgyral and left occipital regions. Early age of first cannabis use and greater estimated cumulative use of THC were both associated with reduced activation in the right prefrontal cortex and medial cerebellum, brain regions that have high concentrations of CB_1 receptors.

Working memory. Using fMRI, Kanayama *et al*. (2004) measured activation during a spatial working memory task in 12 heavy cannabis users, after 36 h of abstinence, and 10 healthy controls. There were no group differences in task performance but the cannabis users displayed greater activation than controls in the right superior, middle and inferior frontal gyri, the bilateral ACC, right precentral and superior temporal gyri, and in the basal ganglia. Jager *et al*. (2006) measured activation during a modified Sternberg item recognition

Table 2. *Non-acute effects of cannabis use: structural studies (volumetric or DTI) and functional studies (resting state or with a cognitive task)*

Author	Method	Users/ Controls	Mean age (S.D.) users/controls	Users' type	Image analysis	Condition	Greater volume/resting blood flow/MD/activation in users	Reduced volume/resting blood flow/activation in users
Structural (volumetric or DTI)								
Block *et al.* (2000*a*)	MRI	18/13	22.3 (0.5)/ 22.6 (0.5)	C	Voxel-based ROI	–		
Tzilos *et al.* (2005)	MRI	22/26	38.1 (6.2)/ 29.5 (8.5)	C	Voxel-based ROI	–		
Matochik *et al.* (2005)	MRI	11/8	25.4 (5)/ 29.7 (4.7)	C	Voxel-based ROI[a]	–	Precentral and R thalamic grey matter L parahippocampal and fusiform, R lentiform and brain stem white matter	R parahippocampal grey matter L parietal white matter
Jager *et al.* (2007)	MRI	20/20	24.5 (5.2)/ 23.6 (3.9)	C	Voxel-based ROI[a]	–		
Gruber *et al.* (2005)	DTI	9/9	26 (3.6)/ 26.2 (3.1)		Voxel-based[a] ROI			
DeLisi *et al.* (2006)	DTI	10/10	21.1 (2.9)/ 23 (4.4)	C	Voxel-based ROI	–		
Yücel *et al.* (2008)	MRI	15/16	38.8 (8.9)/ 36.4 (9.8)	C	Voxel-based ROI	–		L/R hippocampus L/R amygdala
Arnone *et al.* (2008)	DTI	11/11	25.0(2.9)/ 23.3 (2.9)	C	Voxel-based	–	Prefrontal regions of corpus callosum	
Functional (resting state)								
Tunving *et al.* (1986)	^{133}Xe-SPECT	9/9	25 (4.89)/ ND	C	Scintillation detector	Resting state		Global CBF
Mathew *et al.* (1986)	^{133}Xe-SPECT	17/17	25.5 (8)/ ND	C	Scintillation detector	Resting state		
Block *et al.* (2000*b*)	$H_2{}^{15}O$-PET	17/12	22.4 (0.5)/ 22.6 (0.5)	C	Voxel-based	Resting state	R anterior cingulate blood flow	L/R cerebellar and ventral prefrontal blood flow
Lundqvist *et al.* (2001)	^{133}Xe-SPECT	12/14	29.8 (5)/ 27.8 (5.2)	C	Voxel-based	Resting state		Global CBF R PFC blood flow R superior frontal blood flow
Sneider *et al.* (2008)	DSC-MRI	15/17	38.3 (5.6)/ 26.4 (3.8)	C	ROI	Resting state	7 days: R frontal L/R temporal cerebellum 28 days: L temporal cerebellum	
Sevy *et al.* (2008)	^{18}F-FDG-PET	6/6	20.0(1.0)/ 20.0 (1.0)	C	Voxel-based	Resting state		R OFC R posterior parietal cortex L/R putamen

Sevy *et al.* (2008)	[^{11}C]-raclopride-PET	6/6	20.0(1.0)/ 20.0 (1.0)	C	Voxel-based Volume of interest	Resting state		
Functional (cognitive task)								
Block *et al.* (2002)	$H_2{}^{15}O$-PET	18/13	22.3 (0.5)/ 22.6 (0.5)	C	Voxel-based ROI	Verbal memory		L/R PFC activation
Pillay *et al.* (2004)	fMRI	9/16	37 (6)/ 29 (10.3)	R	Voxel-based	Finger sequencing		L/R SMA activation L/R ACC activation
Kanayama *et al.* (2004)	fMRI	12/10	3 7 (7.4)/ 2 7.8 (7.9)	C	Voxel-based	Spatial working memory	R inferior and superior frontal gyrus activation, L/R middle frontal gyrus activation, R STG activation R precentral gyrus activation Bilateral ACC activation, L/R caudate activation	L/R middle frontal activation
Eldreth *et al.* (2004)	$H_2{}^{15}O$-PET	11/11	25/29	C	Voxel-based[a]	Stroop	L/R hippocampal activation R paracentral activation L occipital activation	L DLPFC and ACC activation R VMPFC and DLPFC activation
Bolla *et al.* (2005)	$H_2{}^{15}O$-PET	11/11	26 (21–35)/ 31	C	Voxel-based[a]	Iowa Gambling	L cerebellar activation L parietal activation	R OFC activation R DLPFC activation
Gruber *et al.* (2005)	fMRI	9/9	26 (3.6)/ 26.2 (3.1)	C	Voxel-based[a] ROI	Stroop	R DLPFC and L/R ACC activation	
Chang *et al.* (2006)	fMRI	24/19	27.9 (10.8)/ 30.6 (8.0)	C	Voxel-based[a] ROI	Visual attention task	Parietal cortex activation Occipital cortex activation	R PFC activation R parietal cortex activation Cerebellar activation
Jager *et al.* (2006)	fMRI	10/10	22.7 (4.2)/ 22.8 (2.9)	C	Voxel-based[a] ROI	Working memory	L superior parietal cortex activation (after practise)	
Murphy *et al.* (2006)	fMRI	20/25	23 (19–45)/ 25 (19–36)	C	Voxel-based[a] ROI	Finger-tapping task		
Jager *et al.* (2007)	fMRI	20/20	24.5 (5.2)/ 23.6 (3.9)	C	Voxel-based ROI[a]	Associative memory		L/R Parahippocampal regions R DLPFC

DTI, Diffusion tensor imaging; S.D., standard deviation; MRI, magnetic resonance imaging; SPECT, single photon emission tomography; PET, positron emission tomography; DSC, dynamic susceptibility contrast; FDG, fludeoxyglucose; fMRI, functional magnetic resonance imaging; L, Left hemisphere; R, right hemisphere; C, chronic; R, recreational; ROI, region of interest; CBF, global cerebral blood flow; MD, mean diffusivity; PFC, prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; STG, superior temporal gyrus; SMA, supplementary motor area.

[a] Multiple comparison correction.

task in 10 chronic cannabis users, after 1 week of cessation of use, and 10 controls. Again there were no task performance differences between groups but the controls shown decreased activation in the left superior parietal cortex over repeated trials, which did not occur with the cannabis users, suggesting a compensatory effect in cannabis users.

Inhibition. Eldreth *et al*. (2004), using $^{15}OH_2O$-PET, and Gruber & Yurgelun-Todd (2005), using fMRI, examined the degree of inhibitory control during a Stroop task in chronic cannabis users 25 and 14 days after cessation of use, respectively. In both studies cannabis users produced more errors of commission (failing to inhibit appropriately) than controls and also showed an altered pattern of brain activation. Eldreth *et al*. (2004) found that cannabis users showed relatively reduced left anterior cingulate, bilateral dorsolateral prefrontal cortex and right ventromedial prefrontal cortex activation but greater activation in the hippocampus bilaterally. Conversely, Gruber & Yurgelun-Todd (2005) report that nine users showed greater activation relative to nine controls in the midcingulate cortex and right dorsolateral prefrontal cortex. Consistent with the former study (Eldreth *et al*. 2004), cannabis users showed reduced anterior cingulated activation. These results suggest that alterations of cingulate and prefrontal circuits occur in chronic cannabis users, and leads to the hypothesis that they recruit alternative brain networks as a compensatory mechanism.

Decision making. Bolla *et al*. (2005) report dysfunction in decision making and associated decreased cortical activation in 11 cannabis users, after 25 days of cannabis abstinence, compared with 11 non-users. Using $^{15}OH_2O$-PET to study activation during the Iowa Gambling Task, they demonstrated that cannabis users not only had a poorer performance than controls but also showed less activation in the right orbitofrontal and dorsolateral prefrontal cortex and greater activation in the left parietal and cerebellar cortex. Within the cannabis user group, the number of joints smoked per week was also positively correlated with activation in the right parahippocampal gyrus but inversely correlated with activation in the right orbital gyrus and cerebellum (Bolla *et al*. 2005).

Motor performance. Pillay *et al*. (2004) reported decreased activation in the supplementary motor area and also in the ACC in nine cannabis users, 36 h after cessation of use, while they performed the finger sequencing task (a measure of fine motor function). No significant correlations between urinary cannabis level, verbal IQ, attention maintenance [the auditory Continuous Performance Test (CPT)], reaction time, memory [the Buschke selective reminding test (BSRT)] and brain activation were found. On the contrary, Murphy *et al*. (2006) found no activation differences between 20 chronic cannabis users, after 24 h of cessation of use, and 25 healthy controls during a finger-tapping task using fMRI. Both studies were methodologically well-designed and although the cannabis abstinence period was slightly shorter in the first study, these differences between them do not fully explain the divergent results.

Discussion

We found 41 studies suitable for inclusion. The results of this systematic review have indicated some of the methodological limitations of the work conducted to date and demonstrate the high level of heterogeneity in the findings of these studies. Some of the functional studies in the literature had groups that were smaller than what would be usually regarded as an acceptable minimum (for PET or SPECT studies 10 subjects and for fMRI studies 15 subjects). Therefore, studies involving larger samples and incorporating longitudinal designs may prove useful. The resting state studies conducted so far did not control spontaneous neural activity and modulation of the BOLD signal. The functional studies that used cognitive tasks explored different brain functions, making it difficult to confirm the results obtained. Thus there is a need for replication of these findings. Although the strict inclusion and exclusion criterion of the protocol is one of this review's strengths, it is possible that some of the excluded articles contain interesting pieces of cannabis research.

However, several relatively consistent findings emerged from this review. Functional neuroimaging studies suggest that resting global, prefrontal and ACC blood flow are lower in cannabis users than in controls (Mathew *et al*. 1986; Tunving *et al*. 1986; Block *et al*. 2000*b*; Lundqvist *et al*. 2001; Sevy *et al*. 2008; Sneider *et al*. 2008). The localization of resting state differences between users and controls to these regions is broadly consistent with data from neuropsychological studies. Impairments in time estimation, attention, working memory, cognitive flexibility (Solowij *et al*. 2002), decision making (Bechara *et al*. 2001), and psychomotor speed (Bolla *et al*. 2002) in chronic cannabis users are, at least partly, mediated by these cortical regions. Evidence of effects of THC on activity in these areas is also consistent with the relatively high concentration of CB_1 receptors in the prefrontal and cingulated cortex (Freund *et al*. 2003).

Functional imaging studies that compared activation in cannabis users and controls during cognitive

tasks indicate that cannabis users make use of similar brain areas to controls while performing some cognitive tasks, although to a lesser degree (Block *et al*. 2002; Eldreth *et al*. 2004; Pillay *et al*. 2004; Bolla *et al*. 2005; Gruber & Yurgelun-Todd, 2005; Jager *et al*. 2006, 2007). Moderately greater task-related activation in these areas may reflect impaired efficiency of processing following cannabis use, such that more activation is required to maintain normal performance. This is broadly consistent with the cognitive efficiency hypothesis (Vernon, 1983) that proposes that more direct connections between task-critical brain regions may correspond to decreases in task-related neural activity and improvements in performance (Rypma & D'Esposito, 2000). The recruitment of additional regions, such as the prefrontal cortex and hippocampus, also differentiates users from controls during cognitive performance (Block *et al*. 2002; Eldreth *et al*. 2004; Gruber & Yurgelun-Todd, 2005; Jager *et al*. 2007). This may indicate that increased neurocognitive resources are required to maintain memory and executive processes in this group. However, despite these differences in brain activity, the level of performance of the cannabis users was equivalent to that of controls (Kanayama *et al*. 2004; Jager *et al*. 2007). In this sense the brain seems to be capable of some degree of functional reorganization, activating brain regions not engaged in the non-users to achieve the cognitive demand. This interpretation implies that drug-related compensatory mechanisms may work, but the real impact of such alterations in daily users' life and its possibility to induce psychiatric disorders are still controversial.

With regard to structural neuroimaging studies, only two found significant differences between users and controls (Matochik *et al*. 2005; Yücel *et al*. 2008). It is likely that volumetric effects would only be observed in heavy long-term users whereas functional effects would be much easier to detect. Only one DTI study found differences in the mean diffusivity, suggesting that cannabis users have a small but significant effect on white matter structural integrity (Arnone *et al*. 2008).

Finally, more consistent results were evident in functional imaging studies that examined brain activity after the acute experimental administration of THC or marijuana cigarettes with THC. The most frequent finding was the increased resting prefrontal, insular and anterior cingulate activity (Volkow *et al*. 1996; Mathew *et al*. 1997, 1998, 1999, 2002). Studies that combined the administration of THC or marijuana with a cognitive task also described modulated activation in these regions (O'Leary *et al*. 2002, 2003, 2007; Borgwardt *et al*. 2008; Phan *et al*. 2008; Fusar-Poli *et al*. 2009). The acute administration of CBD has been associated with increased resting activity in the left parahippocampus gyrus and a reduction in medial temporal cortex activity while subjects were processing intensely fearful faces (Crippa *et al*. 2004). Of interest, two studies (Borgwardt *et al*. 2008; Fusar-Poli *et al*. 2009) showed, for the first time, different brain activation associated with THC and CBD in healthy volunteers, providing new insights into the pharmacodynamic effects.

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Declaration of Interest

None.

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