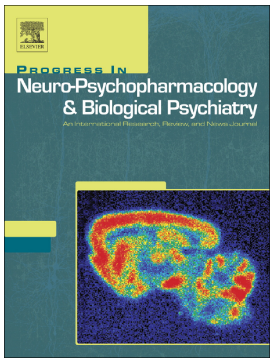

Acute and chronic effects of Δ9-tetrahydrocannabinol (THC) on cerebral blood flow: A systematic review

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Acute and chronic effects of Δ^9-tetrahydrocannabinol (THC) on cerebral blood flow: A systematic review

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Abstract

Acute and chronic exposure to cannabis and its main psychoactive component, △9-tetrahydrocannabinol (THC), is associated with changes in brain function and cerebral blood flow (CBF). We therefore sought to systematically review the literature on the effects of THC on CBF following PRISMA guidelines. Studies assessing the acute and chronic effects of THC on CBF perfusion and volume were searched in the PubMed database between January 1972 and June 2019. We included thirty-four studies, which altogether investigated 1,259 humans and 28 animals. Acute and chronic THC exposure have contrasting and regionally specific effects on CBF. While acute THC causes an overall increase in CBF in the anterior cingulate cortex, frontal cortex and insula, in a dose-dependent manner, chronic cannabis use results in an overall reduction in CBF, especially in the prefrontal cortex, which may be reversed upon prolonged abstinence from the drug. Future studies should focus on standardised methodology and longitudinal assessment to strengthen our understanding of the region-specific effects of THC on CBF and its clinical and functional significance.

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Keywords: cannabinoid, cannabis, CBF, cerebral blood flow, tetrahydrocannabinol, THC

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Declaration of interest

Dr Bloomfield has undertaken consultancy work at an advisory panel for Spectrum Therapeutics. Otherwise the authors have no conflicts of interest.

Introduction

Cannabis is one of the most widely used drugs with over 180 million of the world's population consuming it annually (UNODC, 2016) thus understanding its effects on the brain is paramount. As the decriminalisation and legalisation of cannabis spreads, it is important to understand the effects of cannabis and its main psychoactive ingredient ^{9}-tetrahydrocannabinol (THC). THC is a partial agonist at CB_1 and CB_2 receptors which are mainly expressed in the central nervous system (CNS) and immune cells respectively (Ashton, 2001; Pertwee, 2006). Acute intoxication and chronic heavy administration of cannabis have been associated with a range of effects, with potential long-term deleterious effects of particular concern in adolescence. Chronic heavy use of the drug is associated with increased risk of dependence, psychosis and affective disorder (Volkow *et al.*, 2014). Whilst there is some evidence of recovery following abstinence, it remains unknown if these effects can be completely reversed upon prolonged abstinence from the drug (Pope *et al.*, 2001). Positive subjective acute effects i.e. the '*high'*, include euphoria, relaxation and sensory intensification. Adverse acute effects include anxiety, paranoia, impaired psychomotor performance and cognitive function (Broyd *et al.*, 2016; Curran *et al.*, 2016). The acute psychoactive effects of the drug result from its effects on CB_1 receptors (Huestis *et al.*, 2007). Cannabinoid receptors are highly and widely distributed in the brain. The areas of the brain with the highest receptor expression include the cerebellum, amygdala, frontal lobes and basal ganglia (Herkenham *et al.*, 1990; Glass, Faull and Dragunow, 1997). Cannabinoid receptors are also located in and around the vasculature. When administered acutely, THC and several endocannabinoids consistently induce vasodilation (Ho and Kelly, 2017). Acute cannabis use also results in tachycardia with varied effects on blood pressure (Ho and Kelly, 2017).

As the brain requires ~20% of the body's oxygen for normal function, regulation of CBF is paramount for organism survival. It is widely known that cannabis induces effects on vasculature in a region-specific and dose-dependent manner, including for example, the conjunctival vasodilation observed during acute cannabis intoxication (Martin-Santos *et al.*, 2010). Yet, effects on cerebral vasculature are often overlooked in the literature. THC binds to type 1 endocannabinoid receptors (CB_1Rs) that are present in arterial tissue (Bilfinger *et al.*, 1998) and regulate the microvascular environment via dose-dependent dilation of cerebral arterioles (Ellis, Moore and Willoughby, 1995; Filbey *et al.*, 2017). For this reason, it is unclear whether THC-induced effects are due to direct effects on vasculature and/or indirect metabolic changes; and the relative contributions of these factors to cerebral and cognitive function. A series of processes, including autoregulation, maintain resting CBF (Cipolla, 2009). Region-specific changes in neural activity, and subsequent metabolic demand, are tightly coupled to changes in regional CBF (Heiss, 1981). This is in part due to the relationship between removal of metabolic waste and the supply and use of oxygen and glucose. During functional activation therefore, both CBF and neural activity increase (Paulson *et al.*, 2009). Changes in regional CBF have been associated with several neuropsychiatric disorders including anxiety, psychosis and schizophrenia (Hasler *et al.*, 2007; Kaczkurkin *et al.*, 2017; Kindler *et al.*, 2017). Given the associations between altered CBF and neuropsychiatric illness, together with a lack of a precise mechanistic understanding of how chronic cannabis exposure induces vulnerability to illness, it is therefore important to understand the acute and chronic effects of THC on CBF.

Previous reviews (Quickfall and David Crockford, 2006; Chang and Chronicle, 2007; Martin-Santos *et al.*, 2010; Batalla *et al.*, 2013; Lorenzetti, Solowij and Yücel, 2016) have not focused directly on the effects of THC and cannabis on CBF. Moreover, previous reviews have not included

neuroimaging and non-neuroimaging studies in both humans and animals and so it is timely for these studies to be systemically reviewed together.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. We performed an electronic search using PubMed and the following Boolean inputs "(THC OR MARIJUANA OR Cannabis OR tetrahydrocannabinol) AND "cerebral blood flow"" and included any items published before 27th June 2019. We then screened the abstracts of the reference list of systematic reviews identified in this initial search to identify any additional studies that met our inclusion criteria. Our inclusion criteria were as follows: (1) Studies measuring the effects of acute THC and/or cannabis exposure on cerebral blood flow, volume or perfusion in humans and other animals; (2) Studies measuring the effects of repeated THC and/or cannabis exposure on cerebral blood flow, volume or perfusion in humans and other animals; (3) Studies measuring the effects of repeated THC and/or cannabis exposure on cerebral activation in resting state in humans and other animals; (4) Studies measuring the effects of acute THC challenge on cerebral activation in resting state in humans and other animals. Our exclusion criteria were as follows: (1) single case reports; (2) Studies measuring the effects of chronic or acute THC challenge on cerebral activation during a cognitive task in humans and other animals; (3) Studies written in language other than English; (4) Studies measuring the effects of maternal THC consumption on foetal cerebral blood flow, volume or perfusion in humans and other animals; (5) Studies selecting participants from outpatient clinics

Results

Two-hundred and thirty total papers/records were identified for screening – 169 records identified through database searching and 61 additional records identified in reviews. After removing duplicates, 134 records remained. We then screened these 134 records and found that after initial screening, 90 either did not meet our inclusion criteria or met one of our exclusion criteria. Forty-four full-text articles were then assessed for eligibility and 10 records were excluded after full-text analysis. Therefore, 34 studies were included for data synthesis. These studies were grouped according to subject species (human/animal) and effect measured (acute/chronic) producing 4 subgroups (for more detailed information, see Fig. 1). Three studies measured the effects of acute THC challenge or cannabis on cerebral blood flow in animals. Thirteen studies measured the effects of acute THC/cannabis challenge on cerebral blood flow in humans. Only 1 study measured the effects of repeated THC challenge or cannabis on cerebral blood flow in animals. Finally, 19 studies measured the effects of repeated THC challenge or cannabis on cerebral blood flow in humans. In total, the effects of THC challenge or cannabis on cerebral blood flow was assessed in 28 animals and 1259 humans.

Acute THC challenge or acute cannabis effects on cerebral blood flow (CBF) in humans (Table 1)

13 studies using acute drug challenge in humans matched our inclusion criteria. Of these: 3 used ^{133}Xe inhalation, 2 used Transcranial Doppler flowmetry (TDF), 7 used ^{15}O-water positron emission tomography (PET) and 1 study used Arterial Spin Labelling (ASL) to measure CBF and perfusion. For ease of comparison, we will present the studies according to the method used.

Mathew *et al*. (1992a; 1992c) used TDF to demonstrate that inhalation of a '*joint'* (THC = 3.55%) with tobacco significantly increased middle cerebral artery (MCA) velocity, and therefore global cerebral blood flow, at rest. Both studies also measured heart rate (HR), blood pressure (BP) and partial pressure of mean expired CO_2 (P_ECO_2,) showing no association between these variables and MCA velocity. Despite methodological heterogeneity and small sample sizes, the evidence from both studies suggests that acute THC increases cerebral blood flow at rest in those with a previous, yet brief, history of exposure to cannabis.

In a series of experiments using ^{133}Xe inhalation, Mathew et al (1989; 1992b; 1993) demonstrated significant changes in global and regional CBF following THC administration in a crossover design. A joint-year is used in many studies as a measure of cumulative life exposure to THC. One joint-year is equivalent to smoking 365 joints i.e. 1 joint a day, every day for a year. Firstly, the CBF of "experienced" (i.e. >4 joint-years) and "inexperienced" (i.e. those that had not smoked cannabis for a minimum of 3 years) cannabis users were measured following smoking of a medium-potency (THC = 2.2%) joint. An hour after smoking the 'joint', a significant decrease in global as well as frontal, temporal, occipital, central and parietal CBF was observed within "inexperienced" cannabis users, when compared to their CBF following a placebo cigarette. However, "experienced users" had no significant change in CBF when compared to placebo (Mathew, Wilson and Tant, 1989). Mathew et al. (1992a;1993) measured changes in CBF following inhalation of a high-potency (THC=3.55%) and low-potency (THC = 1.75%) joint in a randomized, double-blind trial of 20 males with previous exposure (at least one use) to cannabis and 35 regular cannabis users (minimum of 4 joint years) respectively. In the analysis, both studies corrected for HR, respiratory rate (RR), BP, end-tidal CO and forehead skin perfusion and demonstrated THC-induced CBF increases particularly in the frontal cortex, right hemisphere and anterior regions of the brain, at both THC doses. Mathew et al., (1993) also used TDF to measure MCA velocity in 10 of the participants whereby MCA velocity was not

related to changes in global CBF in any of the participants. Seven studies used ^{15}O-water PET to measure CBF in specific areas of the brain. All of the 7 studies, except one, demonstrated an increase in global CBF after THC administration (Mathew *et al.*, 1997, 1998, 1999, 2002; O'Leary *et al.*, 2000, 2007). O'Leary et al. (O'Leary *et al.*, 2002) did not show this significant increase but did show increased rCBF in the frontal cortex, insula, cingulate gyrus, temporal poles and cerebellum. This change in CBF in temporal poles and cerebellum was also reported in 2 other studies belonging to this subgroup (O'Leary *et al.*, 2000; O'Leary *et al.*, 2007). Five of the studies also showed significant increased CBF in the frontal cortex, insula and cingulate gyrus (Mathew *et al.*, 1999, 2002, O'Leary *et al.*, 2000, 2002, 2007). Another common finding amongst most of the studies was a marked CBF increase in anterior regions of the brain. Three of these studies demonstrated THC-induced decreased CBF in both the visual and auditory cortices (O'Leary *et al.*, 2000, 2002; O'Leary *et al.*, 2007). Van Hell et al. (2011) used ASL to assess the effects of acute THC on both global and region-specific perfusion. They demonstrated that acute THC increased perfusion in the anterior cingulate, frontal and insula cortex (very similar to evidence found in the PET studies) and decreased perfusion in the right post-central gyrus and both occipital gyri. Despite varying doses, methodological heterogeneity and in some cases not matching subjects for handedness or sex, the consistency of the results across the studies suggests that acute THC challenge causes a region-specific change in CBF – most notably an increased CBF in the frontal cortex, insula and cingulate gyrus.

Acute THC and cannabis effects on cerebral blood flow (CBF) in animals (Table 2)

Three studies on the effects of acute THC or cannabis challenge on CBF in animals matched our inclusion criteria. Ellis, Moore and Willoughby (1995) assessed the effect of THC on cerebral circulation through topical application to young male New Zealand white rabbit cerebral arterioles in

vivo, measuring vessel diameter using microscopy. They demonstrated that flushing THC through the arteriole caused dose-dependent vasodilation (maximum dilation at 22% THC) with no alteration of mean cerebral arterial blood pressure. The effect of an intravenous (IV) THC (100µg/kg) injection on cerebral circulation of 4 adult male mongrel dogs was assessed by Beaconsfield et al. (1972), measuring CBF directly by the venous outflow technique. They demonstrated that THC led to a 5-12% increase in cerebral venous outflow. However, they did not correct for changes observed in heart rate (HR), systolic pressure and therefore pulse pressure which would influence venous outflow. Bloom et al. (1997) provided a more methodologically rigorous quantification of the effects of THC and its active metabolite, 11-OH-THC, on CBF. They injected groups of 4-6 rats with one of 6 IV drug treatments: 0.5, 1, 4, 16 mg/kg THC; 4 mg/kg 11-OH-THC; or vehicle, and used the freely diffusible tracer method (Sakurada *et al.*, 1978) to measure regional CBF (rCBF) autoradiographically. Significant THC-induced decreases in rCBF were observed in the hippocampus, entorhinal cortex, frontal and medial prefrontal cortex and basal ganglia. Significant increases in rCBF were seen mainly in the arcuate nucleus of the hypothalamus. However, the THC dose threshold for rCBF decreases ranged from 0.5mg/kg to 16mg/kg, the latter of which is an extremely large dose that far exceeds those of human use or experimental studies. They did not correct for the significant increase in pCO_2 which is a factor known to effect CBF as CO_2 causes vasodilation to increase glucose and oxygen reaching the metabolising tissue (Cipolla, 2009). However, as the majority of the areas saw a decrease in rCBF, it is unlikely that correcting for pCO_2 would have altered the results significantly. This is because increased CO_2 would increase CBF, however as a decrease in rCBF was reported, it would mean that the CO_2-mediated increase in CBF was overridden by the THC-induced decrease in rCBF. Despite the methodological heterogeneity, small sample size and limitations in addressing potential cardiovascular confounds, the evidence from these 3 studies suggests that acute THC increases global and alters rCBF in a region-specific, dose-dependent manner.

Repeated THC challenge and chronic cannabis effects on cerebral blood flow (CBF) in humans (Table 3)

Seventeen studies matched our inclusion criteria in this category. Of the 18 studies, 3 used ^{133}Xe inhalation, 3 used Doppler ultrasound, 7 used ^{15}O-water PET, 1 used single-photon emission computed tomography (SPECT), 2 used Magnetic Resonance Imaging (MRI) and 1 study used Arterial Spin Labelling (ASL) to measure CBF and perfusion. In 12 of the studies, CBF measurements were taken in resting state only. Whereas in the other 7 studies, participants performed a variety of tasks which would influence both regional and global CBF measured. Firstly, we will focus on the studies that measured CBF at rest only.

Three studies used ^{133}Xe inhalation to compare CBF in long-term cannabis users after cessation versus controls. Tunving et al. (1986) found that global CBF was significantly lower in cannabis users compared to controls but found no significant regional flow differences after correcting for partial pressure of CO_2 in arterial blood (P_aCO_2). Lundqvist et al. (2001) used the same method to measure CBF and demonstrated that chronic cannabis users (0.5-10g hash with 6-8% THC daily for 0.5-21 years) had hypofrontality when compared to controls after correcting for P_aCO_2 and P_ECO_2. However, Mathew et al. (1986) found no significant differences between chronic cannabis users (>0.4 joint-years) and age- and sex-matched controls. Jacobus et al. (2012) used ASL to compare CBF in chronic cannabis users (>0.5 joint-years) and demographically matched controls. After correcting for significant differences in alcohol, tobacco and other drug use, compared to controls cannabis users had reduced CBF in the left superior and middle temporal gyri, left insula, medial frontal gyri and left supramarginal gyrus. They also described increased CBF in the right precuneus in users compared to controls. However, after 4 weeks of cessation (confirmed by urinalysis and self-report) there were no significant differences in CBF between the two groups. Two studies used ^{15}O-water PET to measure

CBF at resting state in chronic cannabis users. Block et al. (2000) provided evidence to suggest that chronic cannabis users (>7 times weekly) had lower rCBF in the posterior cerebellum and ventral prefrontal cortex and higher rCBF in the right anterior cingulate gyrus when compared to controls. Wilson et al. (2000) measured global CBF and found evidence to suggest that males who had a younger age of first use had a significantly higher global CBF compared to those who started later. Three studies used Doppler ultrasound to analyse resting cerebral blood velocity in chronic cannabis users (Herning *et al.*, 2001, 2005; Herning, Better and Cadet, 2008). Each study used different criteria to define chronic cannabis use: aligned with DSM criteria for cannabis abuse, 2-350 joints per week, and used cannabis >14 times in the past 30 days respectively. All 3 studies provided evidence to suggest that pulsatility index, systolic velocity and therefore cerebrovascular resistance in the ACA and MCA are increased in chronic cannabis users after cessation compared to controls. This change in cerebrovascular circulation did not change after 30 days of abstinence or differ between severe and moderate cannabis users. Two studies used MRI to compare resting CBF between chronic cannabis users and healthy comparison controls. Sneider et al. (2008) described, using Dynamic susceptibility contrast MRI (DSC-MRI), chronic cannabis users (>13 joint-years) to have increased blood volume in the right frontal cortex, temporal cortex and cerebellum. However, similar to Herning et al's (2005) findings, after 28 days, all of the regions, except the left temporal and cerebellum which had an increase in blood volume, had no significant difference when comparing the two groups. Filbey et al. (2017) used Phase Contrast MRI (PC-MRI) to measure CBF in chronic cannabis users (>13 joint-years, daily use in previous 60 days) and unmatched controls (significantly greater females in control group). In this way, they provided evidence to suggest that cannabis users had higher rCBF in the right pallidum and putamen but overall no significant global difference in CBF when compared to controls. Reeves et al. (2007) used ^{99m}Tc-HMPAO SPECT at rest in long-term daily cannabis users (>5 joint-years). However, results differed among the 6 cases and there was no control group used which limits the ability to interpret these findings. In summary, the evidence suggests that while some

findings are mixed, chronic cannabis users typically have lower global CBF than nonusers. Additionally, chronic cannabis use is associated with region-specific effects on CBF, with the most consistent decrease occurring in the frontal region. There is some evidence to suggest that these effects may be reversible upon prolonged abstinence. However, this is based on a limited number of studies and these often used self-report methods.

Five studies used ^{15}O-water PET to compare chronic cannabis users with occasional/non-using controls when performing a task. Vaidya *et al.* (2011) showed chronic users (>1.7 joint-years) to have a greater increase rCBF in the ventral medial prefrontal cortex and cerebellum when performing the Iowa Gambling Task (IGT). Bolla *et al.* (2005) described chronic cannabis users (>1.4 joint-years) to have lower rCBF in the orbitofrontal cortex, prefrontal cortex, right cerebellum and right orbital gyrus but increased activation in the left cerebellum when performing the IGT. Both studies showed a dose/duration-related response, suggesting that increased cannabis use is associated with greater rCBF response to achieve the same result. Similarly, Block *et al.* (2002) and O'Leary *et al.* (2003) provided evidence to suggest that chronic cannabis users (>8 joint-years and unknown joint-years respectively) have lower rCBF in the frontal lobe (subdivisions were not investigated further) when performing a variety of tests (memory and self-paced counting tasks respectively). Block *et al.* (2002) also reported chronic (>6 joint-years) cannabis users to have a greater increase in rCBF in parts of the cerebellum during a memory task. O'Leary *et al.* (2003) also described chronic cannabis users (average of 10 joint-years) to have higher increases in rCBF in the left fusiform gyrus, pulvinar nucleus and left caudate nucleus and lower rCBF in the cerebellum. Eldreth *et al.* (2004) compared chronic cannabis users (>1.1 joint-years) after 25 days of inpatient abstinence to matched controls performing the Stroop task. The Stroop task typically increases rCBF in the anterior cingulate cortex and lateral prefrontal cortex. They demonstrated that the chronic cannabis group had decreased activation in the prefrontal

cortex and anterior cingulate cortex, and increased activation in the hippocampus, left occipital lobe and paracentral lobule when compared to the control group.

Although there is great variability between the results of the chronic cannabis studies, preliminary evidence suggests that there may be some reversibility towards the effects that cannabis has on CBF. Also, evidence suggests that chronic cannabis users either have to recruit the same neural network more strongly when performing the same task or increase activation in compensatory circuits to achieve the same result. However, standardized methodology is required to draw any region-specific conclusions on the effect of repeated THC on CBF.

Repeated THC challenge and chronic cannabis effects on cerebral blood flow (CBF) in animals

Only 1 study matched our inclusion criteria in this category. The study by Hayakawa et al. (2007) investigated whether tolerance developed to the vasodilatory effect of THC following repeated treatment. Two groups of male mice underwent THC treatment schedules followed by 4hr MCA occlusion. The first group were given intraperitoneal THC immediately before and 3h after MCA occlusion. The second group were given intraperitoneal THC immediately before, 3h after and once a day for 14 days after MCA occlusion. Laser-Doppler flowmetry was used to measure CBF both during and after the MCA occlusion. In this way, they demonstrated that THC increased CBF in the left cortex significantly during the occlusion. However, after 2 weeks of daily THC treatment the CBF decreased significantly below the initial recorded value. This suggests that tolerance develops to the THC-induced increase in CBF.

Discussion

To our knowledge, this is the first ever systematic review on the effects of THC on cerebral blood flow (CBF). The evidence reviewed suggests that acute THC challenge causes an overall increase in CBF – particularly in the anterior cingulate cortex, prefrontal cortex and insula – in a dose-dependent manner. However, the evidence assessing the chronic effects of THC suggests that it leads to an overall decrease in CBF, particularly in the prefrontal cortex, and that these effects have the potential to be reversed upon prolonged abstinence from the drug. These results are important because CBF and brain function are highly correlated, suggesting that observations found in BOLD fMRI may be skewed by residual THC effects on CBF. The effects observed in both humans and animals provide evidence to support three previously reported potential mechanisms of THC on CBF: (1) direct vasodilatory effect independent of neuronal activity thus increasing blood flow (elucidated by the topical application of THC on rabbit arterioles (Ellis, Moore and Willoughby, 1995; Wagner *et al.*, 2001; Ho and Kelly, 2017); (2) activation of CB_1 receptors leading to region-specific changes in CBF, including vasodilation and subsequent increase of blood flow (O'Sullivan *et al.*, 2005; O'Sullivan, Kendall and Randall, 2005) (3) downregulation of CB_1 receptors following their prolonged activation leading to the opposite effect seen with initial CB_1 receptor activation. Although this pattern of acute THC vasodilation is not reported in all studies (Kaymakcalan, Ercan and Turker, 1975; Duncan, Kendall and Ralevic, 2004).

Taken together, the results of acute THC administration in humans and animals provided consistent evidence for an increase in global CBF. Only one acute THC challenge did not measure an overall increase in global CBF (Mathew, Wilson and Tant, 1989). Mathew et al. (1989) found an overall reduction in CBF – particularly in the frontal lobes. This observation was found in "inexperienced" cannabis users only, defined as those with more than or equal to 3 years of abstinence from cannabis.

However, in this study, the participants were made to follow a strict smoking pattern which induced dysphoria in several participants and was described by several participants as a higher dose than they would usually smoke. Also, only the "inexperienced" cannabis users had increased anxiety following acute THC challenge whereas the chronic cannabis users did not experience adverse reactions, suggesting there is tolerance to the acute anxiogenic effects of the drug (D'Souza *et al.*, 2008). This is consistent with D'Souza et al.'s finding of tolerance to acute THC-induced anxiety. This may be important as tachycardia, which often occurs with both dysphoria and anxiety, could alter CBF (Craske *et al.*, 2017). This research is consistent with the cardiovascular effects of acute THC administration which showed THC reduce blood pressure and heart rate and increased blood flow in various animal models and in humans (Sultan *et al.*, 2018).

Regions with the highest neuronal CB_1-receptor density (Herkenham *et al.*, 1990; Glass, Faull and Dragunow, 1997) are those with most consistent effects following acute THC challenge (i.e. prefrontal cortex, insula and anterior cingulate cortex). These areas are involved in a range of functions including planning, decision making, short-term memory, attention, interoceptive awareness, reward processing, emotional processing and impulse control (Bush *et al.*, 2002; Critchley *et al.*, 2004; Rossi *et al.*, 2009; Xue *et al.*, 2010; Etkin, Egner and Kalisch, 2011; Stevens, Hurley and Taber, 2011; Preston and Eichenbaum, 2013; Beauchaine *et al.*, 2015; Domenech and Koechlin, 2015; Curran *et al.*, 2016). Deficits in all of these higher-order functions are associated with acute drug intoxication and cannabis use disorder (Campolongo and Fattore, 2015). While there is an association between elevated rCBF in the basal ganglia and salience and motivation processes linked to the compulsive use of cannabis (Volkow *et al.*, 1996), findings from animal studies indicate significant THC-induced reductions in basal ganglia rCBF.

Most studies assessing the chronic effects of THC on cerebral blood flow found regular users of cannabis to have a lower resting global CBF compared to controls. This observation provides evidence to support downregulation of globally distributed cannabis receptors following prolonged activation. There was great variability between the region-specific effects but the most consistent of these was reduced frontal blood flow and neural activity – particularly the ventral and dorsolateral prefrontal cortex. However, as most of these studies were cross-sectional it remains somewhat unclear whether the differences in CBF of these areas predated or even increased likelihood of cannabis misuse or were THC-induced.

In the chronic studies, the abstinence period before data acquisition in studies assessing the effects of THC on CBF in chronic cannabis users ranged from a few hours to years. It is important that the abstinence period is accurately ascertained and verified to it is clear at what stage of "recovery" participants are tested at. Similarly, in the acute challenge studies, the time from cessation of THC administration to data collection varied from unknown to several weeks. This adds heterogeneity and limits interpretation of acute versus chronic effects. Although there is a debate about the existence and time course of these effects, evidence suggests that cognitive function and cannabinoid receptor density may recover as quickly as 2-3 days (D'Souza *et al.*, 2016; Scott *et al.*, 2018). Future studies should use an extended period of abstinence confirmed with biological measures in addition to self-report, and continuous measures of CBF post-THC challenge.

The potential reversibility of the effects of chronic cannabis exposure on CBF upon prolonged abstinence from the drug has important implications (Tunving *et al.*, 1986; Chang and Chronicle, 2007; Sneider *et al.*, 2008; Jacobus *et al.*, 2012). It is widely known that CB_1 receptors undergo reversible downregulation upon prolonged activation (Hirvonen *et al.*, 2012; Ceccarini *et al.*, 2015; D'Souza *et*

al., 2016). This observation would explain why some regions showing increased CBF after acute THC challenge in controls have an overall lower resting CBF or show no change/decrease upon acute THC challenge in chronic cannabis users. Initially, THC may increase CBF in a region by activating CB_1 receptors, causing vasodilation. Gradually, after repeated exposure to THC, CB_1 receptors undergo region-specific, reversible, functional down-regulation and receptor density decreases so that upon cessation from the drug there is an overall lower CBF (Breivogel *et al.*, 1999; Hirvonen *et al.*, 2012). Then, during abstinence CB_1 receptor functionality may normalise (Hirvonen *et al.*, 2012; D'Souza *et al.*, 2016) resulting in recovery of resting CBF.

In several of the studies assessing the chronic effects of THC, the participants performed a cognitive task whilst CBF was measured. In the majority of these studies, chronic cannabis users showed similar behavioural performance to the controls (or at least achieved a 'normal' result) despite having a greater amount of non-specific increases in brain activity compared to controls (Block *et al.*, 2002; O'Leary *et al.*, 2003; Eldreth *et al.*, 2004; Bolla *et al.*, 2005; Vaidya *et al.*, 2012; Amen *et al.*, 2017). This supports a hypothesis proposed by Kanayama (2004) whereby chronic cannabis users recruit additional neural resources in order to complete the task at the same level of performance as controls.

A wide variety of techniques were used to assess CBF. Several of these are less sensitive to regional changes (e.g. venous outflow) and are therefore unable to demonstrate the findings seen with modalities such as PET and fMRI (Fantini *et al.*, 2016). Additionally, earlier studies focused on the CBF in predefined regions of interest as opposed to voxel-based morphometry which is more sensitive to changes in regional CBF. Also, several older studies used MCA velocity to infer changes in CBF which may not be a valid indicator of changes in CBF. Future studies should also aim to disentangle effects on CBF and BOLD signal (spontaneous neural activity and modulation) when interpreting

results. The differences in technique used likely contribute to contrasting results observed across studies.

In animal studies, THC concentration can be determined using intravenous THC, standardised dosing and pharmokinetic parameters. However, in human studies, the concentration of THC is more difficult to measure. The cannabis plant also contains over 400 chemical entities that could potentially modulate the effect of THC and clinical implications of a change in CBF (Atakan, 2012). There was also a high degree of variability in THC dose, both in acute and chronic studies (we have included data on THC dose where possible, although, not all studies have reported this). Also, the amount of THC consumed depends greatly on the preparation, pattern of use, dose, and route of administration. Similarly, there is wide geographical variation in THC content, and evidence that THC content in cannabis flowers and other preparations such as hash, resin and cannabis oil has been increasing over time (Chandra *et al.*, 2019; Freeman *et al.*, 2019). This may impact whether the doses used in the early studies are comparable to more recent studies. Leaving participants to smoke at will (i.e. self-titrate) leads to differences in inhaled volumes (Van der Pol *et al.*, 2014). However, attempts to standardise smoking timings and volume have led to dysphoria and anxiety which could ultimately influence CBF (Mathew, Wilson and Tant, 1989). Future studies should therefore investigate the effects of route of administration on THC-induced changes of CBF. However, given that the dose-specific effects are not yet fully established, the degree to which this may affect the results of these studies is unclear. From the acute challenge studies where dose was available, the reported dose ranged from 6mg to 20mg (inhaled) in humans and 100ug/kg to 16mg/kg (IV) in animals. These doses are within the range typically consumed by people who use cannabis; 5mg THC has been proposed as a ‘Standard THC Unit’ akin to a standard unit of alcohol (Freeman and Lorenzetti, in press). It was also not possible to calculate the dose in mg/kg received by the participants in the studies where THC was not administered intravenously. In future studies, a standardised set of doses (e.g. expressed in mg/kg) should be used in order to compare findings and

assess repeatability. Due to the high lipid solubility of THC and cannabis, the bioavailability of THC could also be calculated in each participant to overcome this limitation. There also needs to be a consensus on doses across species in order to generalize findings across species.

Furthermore, in the studies assessing both the acute and chronic effects of THC on CBF, it is difficult to accurately assess and compare cumulative THC exposure. A range of terms are used to describe cannabis users including "regular", "heavy", "occasional", "experienced", "inexperienced" and "chronic" – all with varying definitions. The studies rely on retrospective self-report and extrapolation which are not reliable methods. They also fail to capture information on dose per joint, which varies according to cannabis potency (Freeman *et al.*, 2014), level of intoxication (Hindocha, Freeman and Curran, 2017) and may increase over time as tolerance to the effects of cannabis develops (Ashton, 2001). Instead, current measures overemphasise frequency of use which is not equal to quantity of use. Many studies use 'joint-years' to measure the cumulative exposure to THC. This uses a self-reported average of weekly uses multiplied by the time passed since first exposure to cannabis, as well as patterns of cannabis consumption changing over time. However, this measure may not accurately capture dose due to variability in the strength and amount of cannabis used in each joint (Hindocha, Norberg and Tomko, 2018). A way to overcome this limitation would be to perform a longitudinal study following cannabis users over time and analysing sample joints at regular intervals and confirm abstinence by measuring urinary THC-COOH – the renal metabolite of THC. A more cost-effective method is the "roll a joint" paradigm, in which participants are required to roll a 'typical' joint and this is then analysed and used to estimate to the dose of THC consumed as well as tobacco co-administration which is an important confound as tobacco produces changes in CBF as well (Domino *et al.*, 2004; Hindocha, Freeman and Curran, 2017). In all of the human studies, participants were asked to abstain from any drugs, including nicotine and alcohol, on the day of THC administration or CBF measurement. However, it was not considered that long-term use of such drugs that alter CBF could influence the findings. In future studies, the long-term poly-consumption of CBF-altering drugs should be taken into account to understand the degree to which they might alter any conclusions. Overall, this review highlights a clear need for standardised cannabis use metrics in order to advance the field (Lorenzetti, Solowij and Yücel, 2016).

The sample population varied greatly between studies with differences in socio-economic status, substance and alcohol use, tobacco use, education level, sex, age, age of onset, psychiatric

abnormalities and handedness. These potential confounding factors were not adequately matched across all studies. Several studies used outpatient psychiatric databases or recruited regular users who wanted to quit smoking cannabis, complicating the interpretation of those findings. Future studies should match these confounding factors and also investigate whether the phase of brain development i.e. age at which cannabis exposure occurs effects THC-induced alterations in CBF and the reversibility of effects. Also, adolescence is a critical stage of brain development and cannabis is the most commonly consumed illicit drug at this age (Malone, Hill and Rubino, 2010). There is evidence that adolescents show a different response to adults when administered an acute, weight-adjusted dose of THC (Mokrysz *et al.*, 2016). Therefore, it is important to ascertain whether this group is at an increased (or decreased) risk of both acute and sustained THC-induced changes to CBF.

Conclusion

Chronic and acute cannabis use is associated with region-specific, dose-dependent alterations in cerebral blood flow. Acute cannabis use is associated with an overall increase in CBF whereas chronic cannabis use is associated with potentially reversible decreases in CBF. Common regions implicated include the anterior cingulate cortex, insula and prefrontal cortex in acute cannabis use and the frontal cortex in chronic cannabis use. These regions are involved in several higher-order functions compromised in acute THC intoxication and cannabis use disorder; and are implicated in the pathophysiology of several mental illnesses associated with long-term heavy cannabis use including schizophrenia.

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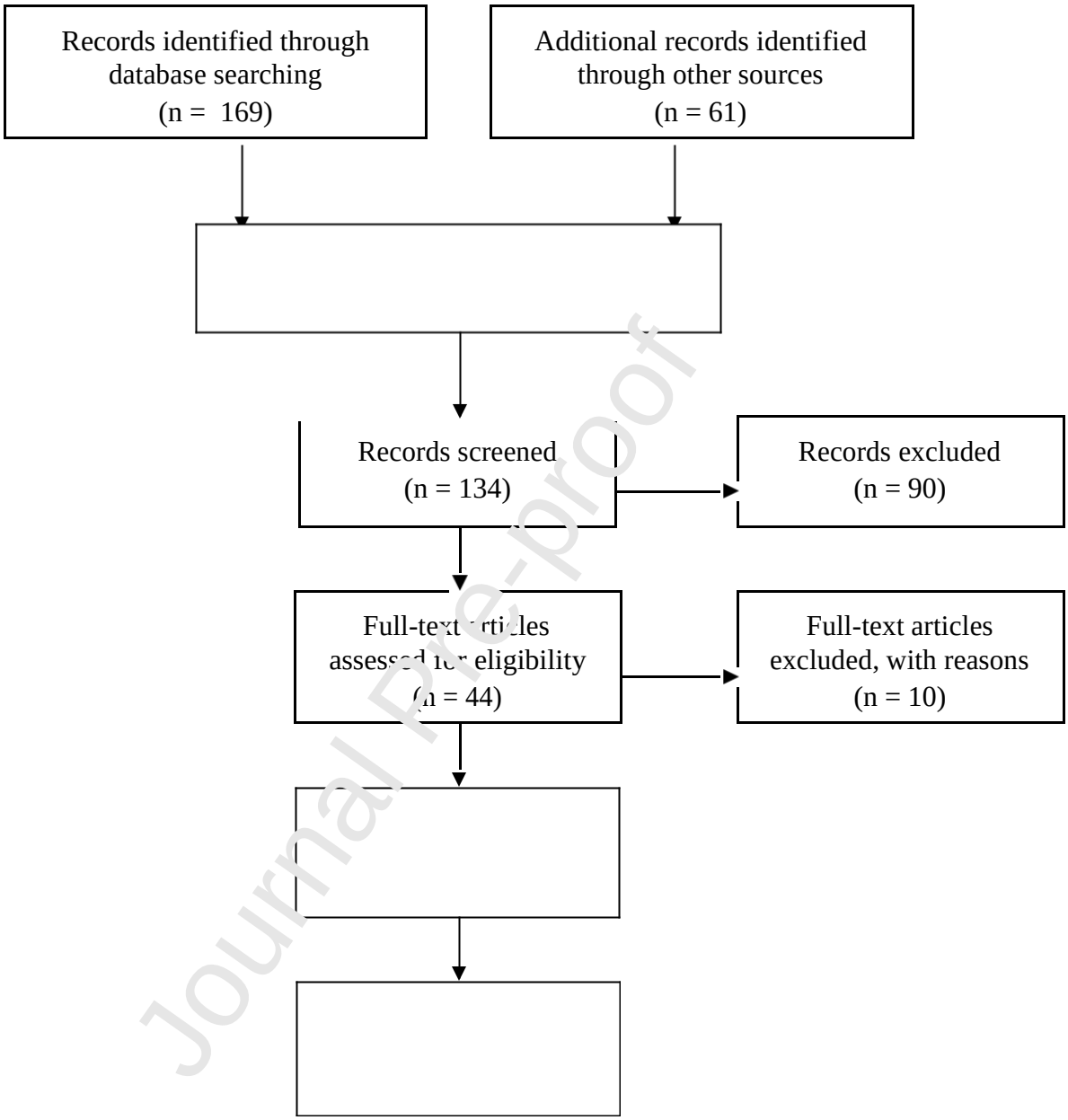

Figure 1. PRISMA flow diagram of the included studies

Table 1. Acute THC challenge or acute cannabis effects on cerebral blood flow (CBF) in humans

Author	Method	Users / Controls	Required minimum abstinence from cannabis prior to study	Cannabis use prior to study	THC dose	Route of administration	Comparison placebo / baseline	Condition	CBF measured X minutes after administration	Greater volume/flow velocity /perfusion	Reduced volume / blood flow / activation / perfusion
Mathew et al., 1989	^{133}Xe inhalation	9 experiences, 17 inexperienced/4	12h	"Experienced" - ≥10 joints/week for 3 years "Inexperienced" - ≥3 years abstinence Controls – unknown previous exposure	2.2%	S	Placebo	Resting	60m		"Inexperienced" Global, temporal, occipital, parietal, central
Mathew et al., 1992	Transcranial Doppler flowmeter	10/0	3 months	Previous exposure	3.55%	S	Placebo	Resting	0m, 60m	MCA velocity	
Mathew et al., 1992	^{133}Xe inhalation	20/0	2 weeks	Previous exposure	1.75% 3.55%	S	Placebo	Resting	30m, 60m, 120m	Both doses: R frontal blood flow High-dose: R temporal blood flow L parietal blood flow	
Mathew et al., 1992	Transcranial Doppler	10/0	2 weeks	Previous exposure	3.55%	S	Placebo	Resting	Continuous	MCA CBV – drop upon standing	
Mathew et al., 1993	133Xe inhalation	35/0	2 weeks		1.75% 3.55%	S	Baseline	Resting	30m, 60m, 120m	Global CBF R frontal blood flow	

Mathew et al., 1997	[15O] H_2O PET	21/11	2 weeks	Previous exposure	0.15mg /min 0.25mg /min	IV	Placebo	Resting	30m, 60m, 90m, 120m	High dose: Global CBF R/L frontal infusion R/T temporal infusion R/L parietal infusion Cingulate gyrus Insula Basal ganglia Thalamus R amygdala Hippocampus AP ratio Low dose: Global CBFR frontal infusion R cingulate gyrus L insula R/L frontal infusion R/L parietal infusion R/L temporal infusion AP ratio	
Mathew et al., 1998	[15O] H_2O PET MRI	46/0	2 weeks	147 ± 165.2 ‘joints’ per year	0.15mg /min – 20m 0.25mg /min – 20m	IV	Baseline	Resting	Rest, 30m, 60m, 120m		

Mathew et al., 1999	[15O] H_2O PET	38/21	2 weeks	Previous exposure	0.15mg /min 0.25mg /min	IV	Baseline	Resting	30m, 60m, 90m, 120m	Global CBF L/R ACC blood flow R frontal blood flow R insula blood flow	Basal ganglia, Hippocampus. Amygdala, Thalamus
Mathew et al., 2002	[15O] H_2O PET	47/0	2 weeks	228.3 ±416.75 'joints' per year	0.15mg /min – 20m 0.25mg /min – 20m	IV	Baseline	Resting	30m, 60m, 90m, 120m	High-dose: Global CBF R hemisphere blood flow L/R cerebellum Frontal blood flow Insula Low-dose: R cerebellum Both doses: Global CBF AP ratio L/R ACC	
O'Leary et al., 2000	[15O] H_2O PET	5/0	N/A	<10 uses/month for an average of 3.2 years	20mg	S	Baseline	Auditory attention task/Dichotic listening task	10m	R/L Anterior cingulate R/L Mesial frontal lobe L orbital frontal lobe Mesial orbital FL R straight gyrus R/L insula R/L temporal pole L cerebellum	L/L frontal lobe L/R Heschl's gyrus L superior temporal gyrus L Hesch'l gyrus R occipital L precuneus Cerebellar vemis

O'Leary et al., 2002 – no gap between cigarettes? !	[15O] H_2O PET	12/0	7 days	<10 uses/month for an average of 6 years	20mg	S	Placebo	Auditory attention task	10-15m	L ventral forebrain R insula R temporal pole L/R anterior cingulate L/R cerebellum	R/L superior temporal gyrus L./R motor strip R caudate L superior parietal lobe L/R precuneus L/R mesial parietal L/R mesial occipital R occipital (Auditory attention-related temporal lobe, visual cortex, attentional network)
O'Leary et al., 2007	[15O] H_2O PET	12/0	7 days	<10 uses (average 5.1)/month for an average of 3.1 years	20mg	S	Placebo	Auditory attention task	10-15m	L/R cerebellum L/R anterior cingulate L/R mesial frontal lobe L/R superior temporal gyrus L temporal pole L orbital frontal lobe	Precuneus L occipital L thalamus L parietal L inferior temporal
Van Hell et al., 2011	ASL	26/0	2 weeks	≥4 times/year ≤1/week Average: 19± 11.2 occasions/year	6mg (1mg every 30 min)	S (vaporiser)	Placebo	Resting	30m (only after first dose)	L/R anterior cingulate L superior frontal cortex L/R insula	R Post-central gyrus L/R occipital gyrus (somatosensory and visual cortex)

Table 2. Acute THC challenge or acute cannabis effects on cerebral blood flow (CBF) in animals

Author	Method	Test Animal / Controls	Animal	THC dose	Route of administration	Comparison placebo / baseline	Condition	Greater volume / blood flow / activation / perfusion	Reduced blood volume / flow / perfusion
Beaconsfield et al., 1972	Venous outflow	4/0	Mongrel dogs	100ug/kg	IV	Baseline	Resting	Cerebral venous outflow	
Bloom et al., 1997	Freely diffusible tracer	24/6	Sprague–Dawley derived rats	0.5, 1, 16 mg/kg	IV	Placebo	Resting	Arcuate nucleus	CA1 of hippocampus, frontal cortex, medial prefrontal cortex, nucleus accumbens, claustrum, dentate gyrus, entorhinal cortex, globus pallidus
Ellis et al., 1995	Light microscope	12/0	Rabbits	10^{-13}M to 10^{-3}M	Topical	Baseline	Resting	Vasodilation of arterioles	

Table 3. Repeated THC challenge and chronic cannabis effects on cerebral blood flow in humans

Author	Method	Users / Controls (Sex)	Duration of abstinence from cannabis	Definition of "chronic"	Control cannabis criteria	Condition	Greater volume/flow velocity /perfusion	Reduced volume/blood flow/activation/perfusion
Block et al., 2002	[15O] H_2O PET	18/13	26h+	18±2/week on average for the last 3.9±0.4	0-2 lifetime uses	Memory test	L/R cerebellum – posterior cerebellar hemisphere, vermis, dentate nucleus , BA 18,19,28,29,30, insula, putamen, tectum	Prefrontal cortex, BA 1,2,3,21,24,40,41, 42 and 45
Block et al., 2000	[15O] H_2O PET	17/12	26h	>7 times weekly	<3 lifetime occasions	Resting	R anterior cingulate	Posterior cerebellum, ventral prefrontal cortex
Bolla et al., 2005	[15O] H_2O PET	11/11	At admission, 25d	>4 times/week for at least 2 years	<3 days/month	IGT	L cerebellum activation, R orbital gyrus	R lateral orbitofrontal cortex activation, R dorsolateral prefrontal cortex activation, L medial orbitofrontal cortex activation, R cerebellum
Eldreth et al., 2004	[15O] H_2O PET	11/11	25d	>3 times/week for at past 2 years 24.7 (8-63) joints per week for 7.5 (2-22) years	No current or past use	Stroop task	L/R hippocampus R paracentral lobule L occipital lobe	L DLPFC L perigenual ACC R anterior ventromedial PFC R anterior DLPFC
Filbey et al., 2017	MRI	74/101	72h	>5000 lifetime occasions AND daily use in past 60 days	Absence of lifetime daily cannabis use	Resting	R pallidum	
Herning et al., 2001	Transcranial Doppler	16/19	Within 72h of admission, 28-30d after abstinence	DSM-IIIR criteria for cannabis dependence/abuse	Unknown	Resting	Pulsatility index and systolic velocity in ACA and MCA – no change after abstinence	

Herning et al., 2005	Transcranial Doppler	54/18	<72h; 28-30d abstinence	Severe: 78-350 joints per week Moderate: 17-70 joints per week Light: 2-25 joints per week	No previous exposure – unclear, blank table	Resting	Pulsatility index and systolic velocity in MCA and ACA – persisted after 1m	
Herning et al.,2008	Transcranial Doppler	75/33	<72h; 28-30d abstinence	Used cannabis >14 times in past 30 days Short duration group: smoked MJ <8 years (56) Long duration group: smoked MJ >8 years (19)	Unknown	Resting	Both groups: Pulsatility index in MCA – no change after abstinence	
Jacobus et al., 2012	ASL	23/23	1-17d; 4 weeks	>200 lifetime use days	<[illegible] lifetime use days	Resting	R precuneus – no difference at follow up	L superior temporal gyri, L middle temporal gyri, L insula, medial frontal gyri, L supramarginal gyrus – no difference at follow up
Lundqvist et al., 2001	^{133}Xe inhalation	12/14	<5d (2d mean)	0.5-10g (mean 2.4g) of 0.8% THC hash daily for 6m to 21 years	Unknown – non smokers	Resting		R prefrontal R superior frontal R/L central
Mathew et al., 1986	^{133}Xe inhalation	17/16	12h	>5 uses/week for 6 months or more	No previous exposure	Resting	No significant difference between groups	
O'Leary et al., 2003	[15O] H_2O PET	12 (chronic), 12 (occasional)/0			N/A	Self-paced counting	Chronic group: cerebellum increase in activation Chronic group: L fusiform gyrus, Pulvinar nucleus of thalamus, L caudate nucleus	Chronic group: ventral forebrain Frontal lobe activation Chronic group: Cerebellum Ventral forebrain increase, Frontal lobe activation, rCBF in cerebellum

Reeves et al., 2007	SPECT	6/0 (compared to 750 normals in neurometric database)	7-10d	Daily use >5 years	Unknown	Resting	Each subject had vastly different results	
Sneider et al., 2008	DSC-MRI	15/17	6-36h, 7d, 28d	>5000 lifetime occasions	No cannabis use within the last month and no history of cannabis abuse/dependence	Resting	Cerebral blood volume: Day 7 – R frontal cortex, R/L temporal cortex, cerebellum Day 28 – L temporal lobe, cerebellum	
Tunving et al., 1986	^{133}Xe inhalation	9/9	1-12 days 4 subjects only: 9d, 14d, 15d, 60d	Cannabis use disorder	Absence of history of cannabis use disorder	Resting		Global CBF – after 60d abstinence no significant difference when compared to controls
Valdya et al., 2012	[15O] H_2O PET	46/34	24h	>5 times/week for last 2 years	<7 lifetime occasions, no other psychoactive drugs except alcohol	IGT task	Ventromedial prefrontal cortex Cerebellar tonsil	Superior temporal gyrus
Wilson et al., 2000	MRI [15O] H_2O PET	57/0	2 weeks	Unknown (16.8 – average age of onset; mean age 31.3)	N/A	Resting	Global CBF – if cannabis use began before 17	

Table 4. Repeated THC challenge and chronic cannabis effects on cerebral blood flow in animals

Author	Method	Users/Controls	Animal	THC dose	Route of administration	Comparison placebo/baseline	Condition	CBF measured X minutes after administration	Greater volume/blood flow/activation/perfusion	Reduced blood volume/ flow /perfusion
Hayakawa et al., 2007	Laser Doppler flowmetry	Controls used – number unclear	Male ddY mice	1mg/kg 3mg/kg 10mg/kg	IP	Placebo	4h MCA occlusion	During occlusion, day 4	3mg/kg and 10mg/kg: Global CBF – during occlusion	10mg/kg: Global CBF – after repeated treatment

Highlights

Acute and chronic THC exposure have contrasting and regionally specific effects on

CBF

Acute THC dose-dependently increases CBF in anterior cingulate cortex, frontal cortex and insula

Chronic cannabis causes a reduction in CBF which may be reversed following abstinence from the drug

Further research is needed to elucidate the functional significance of THC-induced changes of CBF