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

M. Olabisi Ogunbiyi, Chandni Hindocha, Tom P. Freeman, Michael A.P. Bloomfield

PII: S0278-5846(19)30868-1
DOI: https://doi.org/10.1016/j.pnpbp.2020.109900
Reference: PNP 109900

To appear in: Progress in Neuropsychopharmacology & Biological Psychiatry

Received date: 15 October 2019
Revised date: 18 February 2020
Accepted date: 24 February 2020

Please cite this article as: M.O. Ogunbiyi, C. Hindocha, T.P. Freeman, et al., Acute and chronic effects of Δ9-tetrahydrocannabinol (THC) on cerebral blood flow: A systematic review, Progress in Neuropsychopharmacology & Biological Psychiatry(2020), https://doi.org/10.1016/j.pnpbp.2020.109900

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier.
Acute and chronic effects of $\Delta^9$-tetrahydrocannabinol (THC) on cerebral blood flow: A systematic review

M. Olabisi Ogunbiyi$^a$, Chandni Hindocha$^a$ b c, Tom P. Freeman$^a$ b d e, Michael A. P. Bloomfield$^a$ b c f g

$^a$ Translational Psychiatry Research Group, Research Department of Mental Health Neuroscience, Division of Psychiatry UCL, UK
$^b$ Clinical Psychopharmacology Unit, Research Department of Clinical and Health Psychology, Division of Psychology UCL, UK
$^c$ NIHR University College London Hospitals Biomedical Research Centre, University College Hospital, London UK.
$^d$ Addiction and Mental Health Group (AIM), Department of Psychology, University of Bath
$^e$ National Addiction Centre, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, UK
$^f$ The Traumatic Stress Clinic, St Pancras Hospital, Camden and Islington NHS Foundation Trust, London UK.
$^g$ The National Hospital for Neurology and Neurosurgery, London UK.

Abstract
Acute and chronic exposure to cannabis and its main psychoactive component, $\Delta^9$-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.
Acute and chronic effects of $^9$-tetrahydrocannabinol (THC) on cerebral blood flow: A systematic review

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.

Keywords: cannabinoid, cannabis, CBF, cerebral blood flow, tetrahydrocannabinol, THC
*Author to whom correspondence should be addressed:
Dr Michael A. P. Bloomfield
Translational Psychiatry Research Group
Research Department of Mental Health Neuroscience
Division of Psychiatry
UCL Institute of Mental Health
Maple House
149 Tottenham Court Road
London W1T 7NF
m.bloomfield@ucl.ac.uk

Acknowledgements

This research was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The funding source had no role in the study design or decision to submit the article for publication. We are grateful to Ting-Yun Chang for her assistance in preparing the manuscript for publication.

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 (CB₁Rs) 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 thresholds 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 ($P_a$CO$_2$). 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 $P_a$CO$_2$ and $P_E$CO$_2$. 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 CB₁ 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 CB₁ receptors following their prolonged activation leading to the opposite effect seen with initial CB₁ 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 CB₁-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; Friston 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 CB₁ receptors undergo reversible downregulation upon prolonged activation (Hirvonen et al., 2012; Ceccarini et al., 2015; D’Souza et
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 CB1 receptors, causing vasodilation. Gradually, after repeated exposure to THC, CB1 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 CB1 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 (Matthew, 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 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.
References


prostaglandin- like material from rabbit kidney and guinea-pig lung by (–)-trans-

Kindler, J. *et al.* (2017) ‘Increased Striatal and Reduced Prefrontal Cerebral Blood Flow in Clinical

alterations in cannabis users’, *Biological Psychiatry*, pp. e17–e31. doi:
10.1016/j.biopsych.2015.11.013.


Epidemiology and neurodevelopmental models’, *British Journal of Pharmacology*, pp. 511–522. doi:


Mathew, R. J. *et al.* (1999) ‘Regional cerebral blood flow and depersonalization after
tetrahydrocannabinol administration’, *Acta Psychiatrica Scandinavica*, 100(1), pp. 67–75. doi:

Mathew, R. J. *et al.* (2002) ‘Time course of tetrahydrocannabinol-induced changes in regional
cerebral blood flow measured with positron emission tomography’, *Psychiatry Research -


associated with marijuana smoking’, *Acta Psychiatrica Scandinavica*, 79(2), pp. 118–128. doi:

Mokrysz, C. *et al.* (2016) ‘Are adolescents more vulnerable to the harmful effects of cannabis than
adults? A placebo-controlled study in human males’, *Translational psychiatry*, 6(11), p. e961. doi:
10.1038/tp.2016.225.


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

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Users / Controls</th>
<th>Required minimum abstinence from cannabis prior to study</th>
<th>Cannabis use prior to study</th>
<th>THC dose</th>
<th>Route of administration</th>
<th>Comparison placebo / baseline</th>
<th>Condition</th>
<th>CBF measured X minutes after administration</th>
<th>Greater volume/flow velocity / perfusion</th>
<th>Reduced volume / blood flow / activation / perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathew et al., 1989</td>
<td>$^{133}$Xe inhalation</td>
<td>9 experiences, 17 inexperienced/4</td>
<td>12h, “Experienced” - ≥10 joints/week for 3 years, “Inexperienced” - ≥3 years abstinence, Controls – unknown previous exposure</td>
<td>2.2%</td>
<td>S</td>
<td>Resting</td>
<td>Placebo</td>
<td>60m</td>
<td>“Inexperienced” Global, temporal, occipital, parietal, central</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathew et al., 1992</td>
<td>Transcranial Doppler flowmeter</td>
<td>10/0</td>
<td>3 months, Previous exposure</td>
<td>3.55%</td>
<td>S</td>
<td>Placebo</td>
<td>Resting</td>
<td>0m, 60m</td>
<td>MCA velocity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathew et al., 1992</td>
<td>$^{133}$Xe inhalation</td>
<td>20/0</td>
<td>2 weeks, Previous exposure</td>
<td>1.75% 3.55%</td>
<td>S</td>
<td>Placebo</td>
<td>Resting</td>
<td>30m, 60m, 120m</td>
<td>Both doses: R frontal blood flow High-dose: R temporal blood flow L parietal blood flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathew et al., 1992</td>
<td>Transcranial Doppler flowmeter</td>
<td>10/0</td>
<td>2 weeks, Previous exposure</td>
<td>3.55%</td>
<td>S</td>
<td>Placebo</td>
<td>Resting</td>
<td>Continuous</td>
<td>MCA CBV – drop upon standing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathew et al., 1993</td>
<td>$^{133}$Xe inhalation</td>
<td>35/0</td>
<td>2 weeks, Previous exposure</td>
<td>1.75% 3.55%</td>
<td>S</td>
<td>Baseline</td>
<td>Resting</td>
<td>30m, 60m, 120m</td>
<td>Global CBF R frontal blood flow</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Mathew et al., 1997 | [15O] H₂O 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 |
|----------------------|-----------------|--------|----------|-------------------|------------|------------|----|---------|---------|-------------------|--------------------------------------------------|
| Mathew et al., 1998  | [15O] H₂O PET MRI | 46/0   | 2 weeks  | 14/7 ± 165.2 ‘joints’ per year | 0.15mg/min | 0.25mg/min | IV | Baseline | Resting | Rest, 30m, 60m, 120m | 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 |

| 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 |
|-----|---------|---------|-------------------|--------------------------------------------------|
| 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 |

| 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 |
|-----|---------|---------|-------------------|--------------------------------------------------|
| 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 |
<table>
<thead>
<tr>
<th>Study</th>
<th>[15O] H$_2$O PET</th>
<th>Duration</th>
<th>Previous exposure</th>
<th>Dose</th>
<th>Route</th>
<th>Baseline</th>
<th>Resting</th>
<th>Timepoints</th>
<th>CBF Measurements</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathew et al., 1999</td>
<td>[15O] H$_2$O PET</td>
<td>38/21</td>
<td>2 weeks</td>
<td>0.15mg/min – 20min, 0.25mg/min</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td>30m, 60m, 90m, 120m</td>
<td>Global CBF L/R ACC blood flow R frontal blood flow R insula blood flow L/R cerebellum Frontal blood flow Insula Low-dose: R cerebellum Both doses: Global CBF AP ratio L/R ACC</td>
</tr>
<tr>
<td>Mathew et al., 2002</td>
<td>[15O] H$_2$O PET</td>
<td>47/0</td>
<td>2 weeks</td>
<td>228.3 ±416.75 ‘joints’ per year</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td>30m, 60m, 90m, 120m</td>
<td>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</td>
</tr>
<tr>
<td>O’Leary et al., 2000</td>
<td>[15O] H$_2$O PET</td>
<td>5/0</td>
<td>N/A</td>
<td>&lt;10 uses/month for an average of 3.2 years</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td>10m</td>
<td>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 vermis</td>
</tr>
<tr>
<td>Study</td>
<td>Method</td>
<td>Time</td>
<td>Frequency</td>
<td>Dose</td>
<td>Treatment</td>
<td>Task</td>
<td>Duration</td>
<td>Hemispheres</td>
<td>Regions</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------</td>
<td>-------</td>
<td>-----------</td>
<td>---------------</td>
<td>-----------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>-------------</td>
<td>----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>O'Leary et al., 2002</td>
<td>[15O] H₂O PET</td>
<td>12/0</td>
<td>7 days</td>
<td>&lt;10 uses/month for an average of 6 years</td>
<td>20mg S</td>
<td>Placebo, Auditory attention task</td>
<td>10-15m</td>
<td>L/R cerebellum</td>
<td>L ventral forebrain, R insula, R temporal pole, L/R anterior cingulate, L/R cerebellum</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L/R motor strip</td>
<td>L/R superior parietal lobe, L/R precuneus, L/R mesial parietal, L/R mesial occipital, R occipital</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Auditory attention-related temporal lobe, visual cortex, attentional network)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L/R anterior cingulate</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Van Hell et al., 2011</td>
<td>ASL</td>
<td>26/0</td>
<td>2 weeks</td>
<td>≥4 times/year ≤1/week</td>
<td>6mg (vaporiser) S</td>
<td>Placebo, Resting</td>
<td>30m (only after first dose)</td>
<td>L/R anterior cingulate</td>
<td>L/R superior parietal lobe, L/R superior temporal gyrus, L temporal pole, L orbital frontal lobe</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L/R occipital gyrus</td>
<td>R Post-central gyrus, L/R occipital gyrus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(somatosensory and visual cortex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Method</td>
<td>Test Animal / Controls</td>
<td>Animal</td>
<td>THC dose</td>
<td>Route of administration</td>
<td>Comparison placebo / baseline</td>
<td>Condition</td>
<td>Greater volume / blood flow / activation / perfusion</td>
<td>Reduced blood volume / flow / perfusion</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------------</td>
<td>------------------------</td>
<td>-------------------</td>
<td>----------</td>
<td>-------------------------</td>
<td>-------------------------------</td>
<td>-----------</td>
<td>------------------------------------------------------</td>
<td>----------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Beaconsfield et al., 1972</td>
<td>Venous outflow</td>
<td>4/0</td>
<td>Mongrel dogs</td>
<td>100ug/kg</td>
<td>IV</td>
<td>Baseline</td>
<td>Resting</td>
<td>Cerebral venous outflow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloom et al., 1997</td>
<td>Freely diffusible tracer</td>
<td>24/6</td>
<td>Sprague–Dawley derived rats</td>
<td>0.5, 1, 16 mg/kg</td>
<td>IV</td>
<td>Placebo</td>
<td>Resting</td>
<td>Arcuate nucleus</td>
<td>CA1 of hippocampus, frontal cortex, medial prefrontal cortex, nucleus accumbens, claustrum, dentate gyrus, entorhinal cortex, globus pallidus</td>
<td></td>
</tr>
<tr>
<td>Ellis et al., 1995</td>
<td>Light microscope</td>
<td>12/0</td>
<td>Rabbits</td>
<td>10⁻¹⁷M to 10⁻¹⁵M</td>
<td>Topic</td>
<td>Baseline</td>
<td>Resting</td>
<td>Vasodilation of arterioles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Method</td>
<td>Users / Controls (Sex)</td>
<td>Duration of abstinence from cannabis</td>
<td>Definition of “chronic”</td>
<td>Control cannabis criteria</td>
<td>Condition</td>
<td>Greater volume/flow velocity/perfusion</td>
<td>Reduced volume/blood flow/activation/perfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>------------------------</td>
<td>-------------------------------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
<td>----------------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block et al., 2002</td>
<td>[15O] H2O PET</td>
<td>18/13</td>
<td>26h+</td>
<td>18±2/week on average for the last 3.9±0.4</td>
<td>0-2 lifetime uses</td>
<td>Memory test</td>
<td>L/R cerebellum – posterior cerebellar hemisphere, vermis, dentate nucleus, BA 18,19,28,29,30, insula, putamen, tectum</td>
<td>Prefrontal cortex, BA 1,2,3,21,24,40,41, 42 and 45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block et al., 2000</td>
<td>[15O] H2O PET</td>
<td>17/12</td>
<td>26h</td>
<td>&gt;7 times weekly/occasion</td>
<td>&lt;3 lifetime occasions</td>
<td>Resting</td>
<td>R anterior cingulate</td>
<td>Posterior cerebellum, ventral prefrontal cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolla et al., 2005</td>
<td>[15O] H2O PET</td>
<td>11/11</td>
<td>At admission, 25d</td>
<td>&gt;4 times/week for at least 2 years</td>
<td>&lt;7 days/month</td>
<td>IGT</td>
<td>L cerebellum activation, R orbital gyrus</td>
<td>R lateral orbitofrontal cortex activation, R dorsolateral prefrontal cortex activation, L medial orbitofrontal cortex activation, R cerebellum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eldreth et al., 2004</td>
<td>[15O] H2O PET</td>
<td>11/11</td>
<td>25d</td>
<td>&gt;3 times/week for at least 2 years</td>
<td>No current or past use</td>
<td>Stroop task</td>
<td>L/R hippocampus R paracentral lobule L occipital lobe</td>
<td>L DLPFC L perigenual ACC R anterior ventromedial PFC R anterior DLPFC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filbey et al., 2017</td>
<td>MRI</td>
<td>74/101</td>
<td>72h</td>
<td>&gt;5000 lifetime occasions AND daily use in past 60 days</td>
<td>Absence of lifetime daily cannabis use</td>
<td>Resting</td>
<td>R pallidum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herning et al., 2001</td>
<td>Transcranial Doppler</td>
<td>16/19</td>
<td>Within 72h of admission, 28-30d after abstinence</td>
<td>DSM-IIIIR criteria for cannabis dependence/abuse</td>
<td>Unknown</td>
<td>Resting</td>
<td>Pulsatility index and systolic velocity in ACA and MCA – no change after abstinence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Imaging Modality</td>
<td>n</td>
<td>Dose/Duration</td>
<td>Abstinence</td>
<td>Pulsatility Index</td>
<td>Resting</td>
<td>Group Details</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------</td>
<td>---</td>
<td>--------------</td>
<td>-----------</td>
<td>------------------</td>
<td>---------</td>
<td>---------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herning et al., 2005</td>
<td>Transcranial Doppler</td>
<td>54/18</td>
<td>&lt;72h; 28-30d abstinence</td>
<td>Severe: 78-350 joints per week Moderate: 17-70 joints per week Light: 2-25 joints per week</td>
<td>No previous exposure – unclear, blank table</td>
<td>Resting</td>
<td>Pulsatility index and systolic velocity in MCA and ACA – persisted after 1m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herning et al., 2008</td>
<td>Transcranial Doppler</td>
<td>75/33</td>
<td>&lt;72h; 28-30d abstinence</td>
<td>Used cannabis &gt;14 times in past 30 days Short duration group: smoked MJ &lt;8 years (56) Long duration group: smoked MJ &gt;8 years (19)</td>
<td>Unknown</td>
<td>Resting</td>
<td>Both groups: Pulsatility index in N.CA – no change after abstinence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobus et al., 2012</td>
<td>ASL</td>
<td>23/23</td>
<td>1-17d; 4 weeks</td>
<td>&lt;200 lifetime use days</td>
<td>&lt;= lifetime use day</td>
<td>Resting</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lundqvist et al., 2001</td>
<td>^133Xe inhalation</td>
<td>12/14</td>
<td>&lt;5d (2d mean) 0.5-10g (mean 3.4g) of 0.8% THC hash daily or 6m to 21 years</td>
<td>Unknown – non smokers</td>
<td>R/L central</td>
<td>R prefrontal R superior frontal R/L central</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathew et al., 1986</td>
<td>^133Xe inhalation</td>
<td>17/16</td>
<td>12h</td>
<td>5 uses/week for 6 months or more</td>
<td>No previous exposure</td>
<td>Resting</td>
<td>No significant difference between groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Leary et al., 2003</td>
<td>[15O] H2O PET</td>
<td>12 (chronic), 12 (occasional )/0</td>
<td>5 uses/week for 6 months or more</td>
<td>N/A</td>
<td>Self-paced counting</td>
<td>Chronic group: chronic group: cerebellum increase in activation Chronic group: L fusiform gyrus, Pulvinar nucleus of thalamus, L caudate nucleus</td>
<td>Chronic group: ventral forebrain Frontal lobe activation Chronic group: Cerebellum Ventral forebrain increase, Frontal lobe activation, rCBF in cerebellum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Imaging Technique</td>
<td>Duration</td>
<td>Frequency</td>
<td>Use Duration</td>
<td>History</td>
<td>Task</td>
<td>Findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------</td>
<td>----------</td>
<td>-----------</td>
<td>--------------</td>
<td>----------</td>
<td>------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reeves et al., 2007</td>
<td>SPECT</td>
<td>7-10d</td>
<td>Daily</td>
<td>&gt;5 years</td>
<td>Unknown</td>
<td>Resting</td>
<td>Each subject had vastly different results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sneider et al., 2008</td>
<td>DSC-MRI</td>
<td>6-36h, 7d, 28d</td>
<td>&gt;5000 lifetime occasions</td>
<td>No cannabis use within the last month and no history of cannabis abuse/dependence</td>
<td>Resting</td>
<td>Cerebral blood volume: Day 7 – R frontal cortex, R/L temporal cortex, cerebellum, Day 28 – L temporal lobe, cerebellum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tunving et al., 1986</td>
<td>^133Xe inhalation</td>
<td>1-12 days</td>
<td>4 subjects only: 9d, 14d, 15d, 60d</td>
<td>Cannabis use disorder</td>
<td>Absence of history of cannabis use</td>
<td>Resting</td>
<td>Global CBF – after 60d abstinence no significant difference when compared to controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valdya et al., 2012</td>
<td>[15O] H2O PET</td>
<td>24h</td>
<td>&gt;5 times weekly for last 2 years</td>
<td>&lt;7 lifetime occasions, no other psychoactive drugs except alcohol</td>
<td>IGT task</td>
<td>Ventromedial prefrontal cortex, Cerebellar tonsil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson et al., 2000</td>
<td>MRI [15O] H2O PET</td>
<td>2 weeks</td>
<td>Unknown (16.8 – average age of onset; mean age 31.3)</td>
<td>N/A</td>
<td>Resting</td>
<td>Global CBF – if cannabis use began before 17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Repeated THC challenge and chronic cannabis effects on cerebral blood flow in animals

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

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