The straight dope: A systematic review of neuroimaging and acute cannabis exposure in age-of-risk for psychosis

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Abstract

Acute exposure to cannabis has been associated with an array of cognitive alterations, increased risk for neuropsychiatric illness, and other neuropsychiatric sequelae including the emergence of acute psychotic symptoms. However, the mechanisms by which cannabis exposure induces these behavioral and clinical phenotypes remain disputed. To this end, neuroimaging can be a powerful technique to non-invasively study the impact of cannabis exposure on brain structure and function in both humans and animal models. The purpose of the present review is to: 1) provide an update on the findings of pharmacological neuroimaging studies examining the effects of cannabinoids and 2) focus the discussion on studies that examine the sensitive window for the emergence of psychosis. Curren literature indicates that cannabis exposure has varied effects on the brain, with the principal compounds in cannabis (delta-9-tetrahydrocannabinol and cannabidiol) both increasing and decreasing activity in various areas. There are gaps in the literature, especially regarding sex-dependent responses and long-term effects of chronic exposure.

1. Introduction

There has been a move towards decriminalization or legalization of recreational cannabis use worldwide (1,2). Despite rapid transitions, our understanding of the mental health consequences of cannabis exposure remain inconclusive. There is a gathering consensus on the positive (treatment for chronic pain and glaucoma (3,4)), and adverse (risk for major neuropsychiatric symptomatology (5)) effects of cannabis use. Cannabis use has been associated with increased risk for depressive (6) and anxiety disorders (7), and, central to this review, psychosis spectrum disorders (8). There is evidence associating dose-dependent cannabis use with increased likelihood of developing psychosis and schizophrenia (8). Short-term cannabis use has also been associated with increases in psychosis-related symptomatology (9).

In this review we synthesize cross-sectional and longitudinal neuroimaging studies in humans and animal models that examine the effects of cannabinoid administration in an age group coincident with the typical age-of-onset of psychosis. Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are ideal for detecting the acute effects of cannabis exposure on brain function. The translational neuroimaging focus of this review aims to demonstrate how whole-brain investigations of the effects of cannabis on brain function, the activity of specific receptor families, and neurochemistry can be contextualized across species.

2. Methods

2.1.1. Literature search

An Ovid search of Medline, Embase, and PsycINFO, was performed (1980-June Week 2, 2019) to identify articles that used neuroimaging to assay brain structure and function in populations within an age-range relevant to the development of psychosis-like symptoms (see below) and with acute exposure to cannabinoids (last search: June 10, 2019). Search terms included: (magnetic resonance imaging or MRI or functional magnetic

resonance imaging or fMRI or positron emission tomography or PET or diffusion tensor imaging or DTI or computed tomography or CT or magnetic resonance spectroscopy or MRS) and (cannab* or tetrahydrocannabinol or THC or marijuana) and (adolescen* or develop* or teenage* or matur* or youth or young). Additionally, reference sections of major relevant reviews (10), (11), (12) were reviewed for applicable articles that were potentially missed.

2.1.2. Inclusion criteria

Inclusion criteria were full-length, English-language articles that employed *in vivo* neuroimaging (using MRI, MRS, PET, CT, DTI) in humans aged 14-40 (>90% of the sample) or adolescent aged non-human animals (mouse: postnatal day [PND] ~23-50 (13), rat: PND ~28-60 (14)) as well as administration of synthetic or natural cannabinoids.

2.1.3. Exclusion criteria

Exclusion criteria included comorbid psychiatric disorders, administration of synthetic cannabinoid receptor agonists, or case-studies.

3. Results

After deduplication, the Ovid search yielded 2,810 results. All titles and abstracts were reviewed by L.C., and either E.G. or E.P. (each reviewed half). Forty-two articles (39 human and three preclinical studies) met the inclusion criteria and underwent full-text assessment for eligibility (Table 1).

3.1.1 Human studies

The majority of human studies reviewed (n=22) administered THC alone (15–36); methods of administration varied from vaporized (n=11) (17–20,24–26,31–33,35), to smoked (n=4) (28–30,37,38), and orally in gelatin capsules (n=7; Table 1) (15,16,21,22,27,34,36). The second most commonly administered cannabinoid was Dronabinol, a synthetic THC often prescribed medically and reported as Marinol (n=6) (administered orally [n=5] (39–43) and intravenously [n=1] (44)). Studies that compared THC and CBD used gelatin capsules (n=5) (45–49). Although not explicitly stated, these studies have a significant similarity in participant demographics and likely sample the same individuals. Remaining studies examined the THC homologue tetrahydrocannabivarin (n=2) (50,51), Bedrobinol (a strain of cannabis with 13.5% THC <1% CBD) (n=1) (37), CBD alone (n=1) (52), or smoked cannabis without reporting CBD and THC concentrations (n=1) (38).

3.1.2 Preclinical Models

All rodent studies administered the pharmacological intervention via intraperitoneal injection. These studies examined the effect of THC (1 mg/kg/day for 3 weeks) (53), or THC homologues (HU-210--single injection, 1 mL/kg--(54) or CP 55, 940--PND 28-38, 2 mL/kg (55)).

3.2 Imaging Modalities

The majority of human studies used fMRI to investigate the acute effects of cannabis exposure using resting-state fMRI (rs fMRI; n=5) (26,31,32,43,50) or event-related fMRI (e-r fMRI; n=27) (15–22,24,25,27,33,34,36,37,39–42,45–49,51,52,56), (see Table 1 for

classification by task-type). Arterial spin labeling (ASL; n=1) (33) and MRS (n=1) (23) were also used. Radioligand studies included positron emission tomography (PET) and single-photon emission tomography (SPET/SPECT) (n=6) (44) (see Table 1 for summary of tracers).

The three rat studies used PET to examine either glucose metabolism using [^{18}F]-FDG (n=2) (54,55,57) or dopamine receptor activity with [^{18}F]-Fallypride (53).

3.3. Behavioral Results

Twenty-two studies reported the impact of cannabis on behavioral and psychometric assays in humans.

THC studies. The Visual Analogue Mood Scale (VAMS) was commonly used to index experiences related to “highness”/”being high”, “alertness”, “external perception”, “internal perception”, “contentedness”, and “calmness” to verify the effects of THC administration (17–22,28,30,32,33,37,41,42,49). Rated with VAMS, THC exposure increased “drowsiness”, “nausea”, and “euphoria” (34,36), reduced “alertness” (17,18,33), "contentedness” (18,25), “tranquility” (15), and “calmness” (19,20).

THC administration also increased reports of anxiety (15,21–23,26,28,49), internal and external perception (18–20,25,26), tension and anger (29), sedation (21,23,49), and confusion (37). Assessments also revealed increased psychotic symptoms on the three Positive and Negative Syndrome Scale subscales (positive, negative, and general psychopathology) (15,21–23,47,49). *Comparison of THC and CBD administration.* There was evidence for increased intoxication, anxiety, sedation, and psychotic symptoms over time in response to THC, but not to CBD (48,56). Additionally, one study with a small sample (6 participants) reported that three of their participants experienced acute psychotic symptoms after THC, but these symptoms were ameliorated by pre-treatment with CBD (46).

THCv studies. Studies using THCv administration found no behavioral effects, as predicted, since THCv is intended to suppress appetite without inducing psychotomimetic effects (50,51).

Taken together, these studies provide evidence that THC increases psychotic symptoms, anxiety, confusion, and sedation, while simultaneously reducing alertness, calmness, and contentedness. By contrast, CBD may be protective against these behavioral features. Likewise, THCv may produce therapeutic effects for some conditions without psychoactive side-effects.

3.4. Biometric results

Studies examining biometric effects of acute cannabis exposure observed that THC exposure increased heart rate (17,18,23,26,30,32,33) and blood pressure (19,20). Further, reports of increased cortisol levels complement self-reports of increased levels of anxiety and tension (26). Meanwhile, prolactin levels were reduced, possibly related to increased dopamine activity (26,58).

3.5. Neuroimaging studies

First, we report rs and event-related and fMRI, ASL, and PET studies in humans; we further organize event-related fMRI studies by task type: emotional processing, memory, response inhibition, and sensory processing and examine those that do not cleanly fit into these categories. The final section investigates the three non-human animal studies together.

3.5.1 Resting-state fMRI

Five studies assessed rs fMRI with some convergent findings, despite differing analytical techniques.

Reward pathways. A study examining the effects of THC on impulse control in cocaine and cannabis users using bilateral nucleus accumbens seeds (31). They found that cannabis decreased resting state functional connectivity (rs-fc) between the accumbens and

left anterior cingulate cortex (ACC), frontal lobe, left thalamus, left temporal lobe, cerebellum, occipital lobe, and insula.

Fronto-Limbic pathways. The impact of THCv exposure was examined using a left amygdala (50). Decreased connectivity with important “hub” regions such as the left precuneus and left posterior cingulate (key-default mode network regions) was observed. THCv increased connectivity between a seed in the right dorsomedial PFC and the inferior frontal/medial frontal gyrus.

One Marinol study used specific regions of interest (ROIs: the amygdala, hippocampus [HC], and ventromedial PFC [vmPFC]) correlations to examine static and dynamic rs-fc (43). Their results indicated decreased static rs-fc between the amygdala and HC, but increased dynamic rs-fc between the amygdala and vmPFC.

Whole brain analysis. Using networks of interest (26) and a voxel-wise technique (26,32), rs-fc was most altered in the right dorsal visual stream network following administration of vaporized THC (26). Changes were localized in the bilateral frontal pole, and dorsomedial and left superior PFC. THC decreased rs-fc in the right hemisphere in the superior frontal pole, middle and inferior frontal gyri, and dorsolateral PFC. Finally, THC increased rs-fc between the cerebellum and sensorimotor network, left dorsal visual stream and an area comprising the occipital pole and lateral occipital cortex. The second study reported the results of THC on temporal signal-to-noise ratio (calculated by dividing mean blood-oxygen level dependent (BOLD) signal by its standard deviation over a time period) (32). THC reduced tSNR, a measure thought to reflect greater spontaneous fluctuations and brain activity, in the right insula, left cerebellum, and substantia nigra, as hypothesized by the authors (32). It is critical to note that results between the whole brain studies were markedly different, potentially due in part to the analytical techniques employed.

3.5.2. Event-related fMRI

Event-related fMRI experiments used emotional processing, memory, sensory perception, and response inhibition tasks (Table 1).

Emotional processing tasks. The amygdala is well-studied in the context of both THC exposure and emotional processing. A series of three studies assessed the effects of Marinol on emotional processing in sixteen participants (39–42) found that THC attenuated amygdala activation when viewing threatening faces (angry and fearful) (41). The second study investigated rs-fc between amygdala subfields and the cortex, revealing THC increased connectivity between both the left basal and superficial amygdala and rostral ACC/medial PFC (40), but was limited to the left basal amygdala and rostral ACC/medial PFC when viewing threatening faces. These findings suggest that the connection between these two regions may be especially integral to social threat processing and that THC exposure increases this connection. The final study examined limbic circuitry (amygdala and ACC) engagement in response to differing valence of stimuli and observed that THC exposure reduced activity in the subgenual ACC and did not impact amygdala activity (42). These results support the view that THC decreases activity in the limbic circuit; however, the lack of effect in the amygdala provides a point of contrast to the authors' previous findings.

The same group expanded their work to further examine the impact of THC on emotional regulation (n=78) (39). Participants were required to imagine positive contexts for negative images (e.g. reimagining a woman crying outside of a church as attending her wedding; a cognitive reappraisal task). An increase in left amygdala activity and decrease in bilateral amygdala-dorsolateral PFC coupling was observed during the reappraisal condition following THC administration compared with placebo. Another group examined the effects of THC when matching emotional faces (fearful, neutral, or happy), identifying twelve ROIs including the right, but not the left amygdala (20). The authors report decreased activity during the fearful face condition in the cerebellar vermis, left occipital cortex, right occipital cortex, left hippocampus, right prefrontal cortex (PFC), right superior parietal cortex, and right

supplementary motor area. While the decrease in activity during negative-expression-viewing is consistent with previous studies, the affected areas are inconsistent (40–42).

To examine the impact of long-term cannabis use on emotional processing, one study examined fear processing in cannabis-users and nonusers (< 5 exposures) (21). In-study administration of THC (10 mg) reduced activity in the right inferior frontal and middle frontal gyri, medial cerebellum, and fusiform gyrus. Cannabis users had greater activity in the right cingulate gyrus and left inferior parietal lobule. During THC exposure, cannabis users resembled nonusers in the placebo condition displaying activation in the left fusiform gyrus and deactivation in the left precuneus, cuneus, and left posterior cingulate cortex. These findings further support that THC reduces activity, though once again identifying novel areas of interest.

Finally, two publications from the same study population and experiment examined the differential effects of THC and CBD on emotional processing (46,49). When viewing intensely fearful faces compared with neutral faces, CBD reduced BOLD response in the left amygdala, left ACC, right posterior cingulate, and right cerebellum (49). THC exposure during fearful face viewing increased activation in the left precuneus, but decreased it in the right inferior frontal gyrus, right superior temporal gyrus, and left medial frontal gyrus. The second study reported opposite effects of THC and CBD during fearful face viewing, with THC and placebo increasing amygdalar activation while CBD decreased it (46). The authors also reported opposite effects in the fusiform and lingual gyri, lateral PFC, and cerebellum without specifying the directions of effects. While together the studies provide evidence for opposing effects of THC and CBD, more diverse samples are needed. Additionally, the reported results are not identical, necessitating further methodological clarification.

Memory tasks. Previous evidence suggests chronic cannabis use can impair memory (59). Six studies investigated the impact of THC on memory (17,18,22,45,46,52).

Verbal memory. One study demonstrated that cannabis users and nonuser controls both during THC and placebo, deactivated the right superior temporal gyrus during the task (22). Nonusers in the THC condition resembled the activity of cannabis users in the both the THC and placebo condition. Further, nonusers in the placebo condition activated the right inferior parietal lobule and the precuneus, as cannabis users did in the THC condition. However, in the THC condition, nonusers deactivated both of these areas. The authors attribute these findings to the development of tolerance, or alterations in endocannabinoid signalling

Another study found that following THC administration, recall was associated with increased activity in the left dorsal ACC and medial PFC and decreased activity in the bilateral striatum and left rostral anterior cingulate gyrus, but found no influence of the administration of CBD (45). Contradictory results are published in another study reporting on the same experiment in the same participant group, where the authors reported that THC and CBD had opposite effects in the striatum, ACC, and medial and lateral PFC during retrieval, with THC decreasing activity and CBD increasing it (46). The same group also studied individuals at clinical high risk (CHR) for psychosis and found that CBD decreased activation in the left parahippocampal gyrus during recall, but increased activation in the left cingulate gyrus, right precentral gyrus, and medial frontal gyrus (52). The authors reported a step-wise difference in activation across the 3 groups with the CHR group in the middle both during encoding and recall. These results provide intriguing evidence that CBD may normalize memory-task impairment for CHR populations.

Additional memory tasks. Two additional studies conducted with the same participants used the Sternberg item recognition paradigm (18) and a pictorial memory task (17). Difficulty of the Sternberg task can be scaled to allow for assessment of load-dependent increases in brain activity. THC reduced load-dependent activity in the left dorsolateral PFC, left inferior temporal gyrus, left inferior parietal gyrus, and cerebellum (18). In the pictorial memory task,

THC reduced activity in the right insula, right inferior frontal gyrus, left middle occipital gyrus during encoding of images and increased activity in the precuneus bilaterally during recall (17). While the results differed in areas impacted by THC, both studies indicate that during encoding, THC reduces activity. Differing areas of impact could be due to the respective brain-areas employed in the tasks.

Response Inhibition tasks:

Response inhibition was operationalized in a go/no-go test paradigm. In the no-go trials, THC administration attenuated activation in the left inferior frontal gyrus, adjacent insula, and precuneus, which were all activated following placebo administration (16) conversely THC increased engagement from the right hippocampus and caudate nucleus.

One study examined the impact of previous cannabis use on response to acute exposure during response inhibition (22). THC increased activation in the right ACC and, similar to the above study, reduced activation in the left insula. There was also an interaction between history of cannabis use and treatment, such that deactivation of the right middle frontal gyrus was observed in cannabis users in THC and nonusers in placebo conditions; activation was observed in cannabis users in the placebo condition and nonusers in the THC condition. The authors posit these results suggest moderate previous cannabis use results in long-term changes in cognition.

In a study examining the contrasting effects of THC and CBD, no-go trials following THC exposure were associated with greater activation in the right hippocampus, right postcentral gyrus, and bilateral lingual gyrus (48). No-go trials in the CBD condition were associated with greater activation in the superior and middle temporal gyri, bilateral insula, and right posterior cingulate gyrus. While the drugs had distinct effects, they did not exhibit the same oppositional pattern present in the emotional processing studies. The findings of the go/no-go task employed in the aforementioned THC and CBD experiment were reported again in a paper highlighting the different effects of THC and CBD (46). The authors reported

finding opposite effects during the go/no-go in the bilateral parahippocampal gyrus, left insula, and caudate, with THC reducing activation and CBD increasing it. While the methods are reported as the same, the results differ between papers. The latter (46) presents claims much more cleanly that CBD and THC have opposite effects, while activation was varied in the paper discussed above (48).

Sensory Processing:

Seven tasks examined the effects of cannabis on sensory perceptions, examining gustation ((51)), odor (27,34,36,46,51,56), visual and auditory stimuli ((46), (56)), and pain (27,34) .

Gustation. The sole study examined how THCv impacted appetite depending on pleasant or aversive flavor and visual stimuli (51). While THCv did not change subjective stimuli ratings, it increased activity in response to the chocolate stimuli (paired visual and taste) in the caudate, midbrain, and cingulate gyrus. In response to a picture of moldy strawberries, THCv increased activation in the insula, mid-orbital frontal cortex, superior temporal gyrus, and putamen.

Audition. A study involving listening to neutral words read aloud demonstrated that THC reduced activity primarily in the temporal cortex whereas CBD increased activity in the same region (56). CBD also increased activity in the right superior and middle temporal gyri relative to THC. These results were replicated in a paper discussing the opposing effects of THC and CBD, where authors observe opposite directions of activation in the bilateral lateral temporal cortex (46).

Vision. The same study investigating audition also examined the effects of cannabinoids on visual processing of checkerboard stimuli (46,56). Relative to placebo, THC reduced activity in the secondary visual cortex, and increased activity in the right lingual and middle occipital gyri, as well as the left lingual and fusiform gyri whereas CBD increased activation in the right occipital lobe. THC increased activity in the left lingual and middle occipital gyri, also decreasing it in scattered areas of the occipital cortex and cerebellum

relative to CBD. The opposite results in the occipital lobe are also reported in the larger study comparing THC and CBD activation (46).

Pain perception. Two studies examined the effect of THC on pain perception supporting the use of cannabis as an analgesic (27,34). One study demonstrated that THC reduced activation in the right anterior insula, hippocampus, and cerebellum after inducing pain by activating trigeminal nociceptors with CO_2 (34). An ROI analysis further revealed that THC decreased connectivity between the thalamus and secondary somatosensory cortex which agreed with lower ratings of pain perception following THC exposure.

THC decreased activity in the ACC in response to a topical application of capsaicin and lowered pain perception, but increased activity in the right amygdala in response to painful stimuli was correlated with the analgesic effects (27).THC also reduced functional connectivity between the right amygdala and the primary sensorimotor cortex during ongoing pain and decreased both subjective ratings of pain and limbic activity in response to painful stimuli.

Remaining tasks:

The remaining studies examined the effects of THC on monetary incentive delay (25,33), cannabis marketing (24), executive functioning (19), attention (21,47), and visuo-motor tracking (37).

Monetary Incentive Delay (reward processing (33)). THC reduced reward-related activity in the left inferior parietal cortex and bilateral inferior temporal gyrus (uncorrected for multiple comparisons). Another study used this task to assess the effects of THC in nicotine addicts (25). THC reduced activity in the nucleus accumbens and caudate putamen in response to reward anticipation in nicotine addicts compared to healthy controls. These results indicate THC reduces responsivity to reward anticipation and presentation.

Marketing. THC reduced BOLD signal in the right supplementary motor area in response to cannabis marketing (24). Additionally, THC treatment overall reduced BOLD in the bilateral pallidum, striatum, and right caudate.

Executive functioning. Task-induced deactivation in a continuous performance task with identical pairs was observed in a network comprising the posterior cingulate cortex, left inferior temporal gyrus, right cerebellum, and left angular gyrus, which was more sensitive to the effects of THC than other networks (19). These findings indicate THC may dysregulate the default mode network by increasing activity during tasks.

Visual Oddball detection. Two studies used the visual oddball detection task, where participants respond to presentation of visual stimuli, to assess attention (47). Relative to placebo, THC increased activity in the right inferior, middle, and superior frontal gyri and the right orbitofrontal cortex and frontal pole; THC also decreased activity in the right caudate, putamen, insula, and thalamus. CBD reduced activity in the left medial PFC and increased activity in the right caudate, parahippocampal gyrus, insula, precentral gyrus, and thalamus. The second study examined the impact of previous cannabis use and found that after THC exposure, nonusers activated the left medial frontal gyrus, as did cannabis users after placebo (21). Cannabis users in the THC condition deactivated the same area, as did nonusers in the placebo condition.

Motor Control. One study examined the impact of THC on psychomotor control with a visuo-motor tracking test to assess the impact of THC exposure on driving ability (37). THC increased BOLD response in the ACC and ventromedial PFC. They also found a decrease in activity in the anterior insula, dorsomedial thalamus, left middle frontal gyrus, left middle temporal gyrus, and right superior parietal lobule. Combined with results that indicate impaired tracking of the target in the task, these findings shed light on the urgent need for more research of the effects of cannabis on psychomotor activity in relation to safe driving.

3.5.3. Arterial Spin Labeling

Examining ASL, THC increased perfusion compared to placebo in the ACC, left superior frontal cortex and in the left and right insula, and decreased perfusion in the right postcentral gyrus as well as the bilateral occipital gyri (32). They also examined how heart rate and reports of “feeling high” impacted perfusion and observed that these factors explained a significant proportion of the variance between the THC and placebo conditions in the left superior frontal cortex and the ACC. Additionally, the authors found “feeling high” was primarily explained by perfusion in the left superior frontal cortex and to a lesser extent by the left insula, while “feeling high” was negatively correlated with perfusion in the superior frontal cortex and correlated with perfusion in the anterior insula. The increased perfusion associated with THC exposure may be explained by the vasodilative effects of cannabis.

3.5.4. Radioligand Studies

Three studies employed positron emission tomography (PET) to examine striatal dopamine receptor availability (35) and regional cerebral blood flow (30,38). Additionally, Single Photon Emission Tomography (SPET) was used to examine dopamine release in the striatum (44).

THC reduced the binding potential in the functionally limbic part of the ventral striatum (35). Furthermore, negative correlation between blood plasma THC concentration and percentage change of raclopride C11 binding in the striatum was reported, implying that increased levels of THC are associated with decreased dopamine receptor availability.

THC increased regional cerebral blood flow (rCBF) measured with H215O PET in the ACC, medial and orbital frontal lobes, insula, temporal poles, and cerebellum and decreased rCBF in auditory and visual cortices (30). In a follow-up study, this had similar findings, as well as decreased rCBF in the occipital lobe, precuneus, superior temporal gyrus, and posterior cingulate (38).

Barkus et al. administered a single dose of THC via intravenous injection and compared uptake of the tracer 123I-iodobenzamide in the basal ganglia (using the occipital

cortex as reference). To quantify DA release, the authors calculated the subtraction index [(ROI - background)/background x 100]. Following THC exposure, scores in the striatum ranged from a decrease by 16% to an increase by 34% and no results were significant, even though the dosages were large enough to elicit psychotic symptoms. (44).

3.5.5. Magnetic Resonance Spectroscopy

Colizzi et al. examined the effects of acute exposure to THC in participants with previous exposure to cannabis using MRS voxels in the left ACC, left hippocampus, and left head of the caudate using Proton Resolved Spectroscopy (PRESS) (23). They reported increased rates of Glx (a pseudo-concentration of glutamate and glutamine) in the left caudate head, with the highest rates of increase in those who had the lowest levels of Glx in the placebo condition. They also reported a positive correlation between the number of previous cannabis exposures and increase in Glx. There was no significant effect of acute THC administration on Glx in voxels in the ACC and hippocampus.

3.5.6. Animal Models

Only three animal studies (all using PET) met the inclusion criteria. Radioactive tracers and rat background strains are listed in Table 1.

Nguyen et al. performed [^{18}F]-FDG PET 15 minutes and 24 hours following the HU-210 (a THC homologue) injection in 10-11 week old rats. They observed that HU-210 increased global uptake of [^{18}F]-FDG only at the first timepoint, suggesting whole-brain hypermetabolism was acute and not persistent (54).

Ginovart et al. administered daily THC injections for three weeks to male rats. While age was not reported, the reported weights of rats suggest that they were between eight and nine weeks old (60). Results of the *in vivo* PET imaging revealed that THC increased D2 and D3 receptor availability in the dorsal striatum based on [^{18}F]fallypride binding. *Ex-vivo* autoradiography confirmed these findings, but also demonstrated increases in binding in the caudate, putamen, nucleus accumbens, and the ventral pallidum (53).

4. Discussion

4.1.1 Summary and Implications

A systematic review of the literature investigating cannabis administration and neuroimaging reveals the heterogeneity in both methodology and findings. Overall, in rs fMRI, certain findings converge, despite differing analytical approaches. After administration of both THC and THCv, there is increased connectivity between the dorsomedial PFC and the dorsal visual stream network across both in the seed-based and whole-brain approach (26,50). In order to facilitate interpretation and comparison with previous studies, future rs fMRI work should utilize multiple techniques for analysis, such as whole-brain voxel-wise analyses, seed-based approaches, and predefined ROIs, to examine in a single population which findings consistently appear across methodologies.

Event-related fMRI studies show disappointingly divergent results, for example THC both increases and decreases BOLD response in the amygdala during negatively valenced emotional stimuli (39,41). Experimental design may even change the effects of THC on pain sensitivity, with THC generally decreasing activity, but in different regions (27,34). The diversity of results renders it difficult to draw meaningful conclusions across studies, but ultimately highlights the need for more rigorous research into the effects of cannabinoids. Given the well publicized issues with underpowered task and rs fMRI studies (61,62), investigating the acute impact of cannabis exposure will require that studies be designed to be generalizable (large samples of diverse individuals, multiple-sites, harmonized whole-brain analyses), supporting robust conclusions.

4.1.2 THC and Psychosis

A major focus of this review is the potential relationship between THC exposure and psychotic symptoms/schizophrenia. Not only does chronic cannabis use increase the risk of developing psychosis (63), but reviewed studies also demonstrate acute cannabis exposure increases temporary psychotomimetic symptoms (15,21–23,47,49). There is also

convergence between fMRI studies in first episode psychosis and the effects of acute THC exposure, such as decreased activity in the dorsolateral PFC (26,64). Additionally, most alterations were focused in the PFC and limbic areas, similar to seven other studies in this review (17,26,31,37,39,40,46,64). Similar patterns of disrupted activity are seen between both pharmacological intervention with THC and in populations with first episode psychosis, complimenting symptomatic similarities such as PANSS scores.

4.1.3. Age of Risk

Given the epidemiological evidence linking cannabis use with the emergence of psychoses, this review focused on the age range commonly associated with psychosis onset: adolescence to early adulthood (65). It is well established that psychoses emerge earlier for men (mean age of first episode: 24.2, mean age of first negative symptom: 26.5) than for women (mean age of first episode: 27.4, mean age of first negative symptom: 41.6) (65). There is a higher incidence of schizophrenia among men (1.4:1); however, prevalence rates are similar, and women predominate at older onset (66). Although the cause of the discrepancy is unknown, it has been suggested that sex hormones, such as estrogen and testosterone, contribute to the differences sex differences schizophrenia (66). Given that females are typically more sensitive to the effects of cannabis use (67), it is important to examine the three-way relationship between, cannabis, psychosis, and sex.

4.1.4. Sex

Only 17 of the 39 reviewed human studies included female participants (23,24,26,30,31,34,36,38–43,46,50,52,55); similarly only one of three non-human animal experiments included female rodents (55). One of the groups that used the same sample for seven studies included in this review (17–20,25,32,33) attributed their choice of recruiting only males to the “expected interactions between hormonal cycle and brain activity patterns in women, which will flaw the design. In addition, there is evidence for sex differences in the effects of THC” (68), citing only a review of behavioral studies demonstrating sex-differences

in adult rodents (69). We hope that future researchers no longer cite the mysteries of having to deal with “female hormones” as an excuse for incomplete study design. Given the number of studies that adopt this philosophy, there is an urgent need for pharmacological studies involving females (70,71). To protect participants, future studies investigating sex-differences should administer a proportional dose based on weight to avoid attrition, as six of the studies did (24,31,53–55,57). Evidence regarding sex-effects are mixed, with some results indicating long-term behavioral changes may be greater for males than females, illustrating the need for more in-depth studies adequately powered to examine sex-differences (72).

In mice, cannabis has been found to differentially affect female and male rats, increasing female rats’ propensity to self-administer cocaine later in life, and reducing activity in the amygdala-entorhinal area while increasing activation in frontal cortex (55). These results further contribute to the understanding that results of cannabis exposure are likely amplified in females, compared to male counterparts, suggesting appropriately-powered, evenly-balanced studies may be sensitive enough to observe sex-differences consistent with the literature. Further investigation of the sex differences are necessary at many levels, from basic research examining differences in how THC is metabolized in males and females to population studies quantifying how cannabis differs as a risk factor for psychosis in females and males (73,74).

4.1.5. Chronic Use

While the current work investigated acute experimental exposure to cannabinoids, studies examining chronic exposure are important to learn how long-term cannabis use contributes to psychiatric disorders. Though chronic exposure falls outside of the bounds of this systematic review, here we provide context for how the reviewed findings relate to evidence from current reviews of chronic exposure to THC.

Neuroimaging studies in both adults and adolescents broadly suggest functional and structural changes associated with chronic cannabis use. Bidirectional cortical thickness and

volume alterations are demonstrated primarily in frontal and parietal regions responsible for higher-order cognitive functions, although the literature is far from conclusive, with some studies suggesting no significant differences (75). Recreationally, THC is most frequently either consumed in the form of edibles, smoked in cannabis-cigarettes (“joints”), or inhaled as a vapor, methods of exposure which have different mechanisms within the body (76). When THC is consumed orally, it is first metabolized by the liver, becoming 11-OH-THC, before the compounds enter the bloodstream. 11-OH-THC is a potent cannabinoid potentially contributing to psychoactive effects of cannabis and it is produced at higher rates following oral consumption of THC compared with inhalation (77). This must be considered when comparing results between studies that administered cannabinoids by various mechanisms.

4.1.6. Assessing Causality Between Cannabis Exposure and Psychiatric Disorders

While studies of chronic cannabis users are vital to understanding the effects of long-term cannabis exposure in humans, several limitations should be taken into consideration when interpreting the results of such studies. First confounding factors may play a role in both encouraging the onset of cannabis use and outcomes, such as psychotic symptomatology. Previous research suggests a shared genetic origin of both risk for psychosis and risk for cannabis use (78). As chronic exposure studies are retrospective, accuracy of estimates of dosage, THC content, and amount of use is limited. Longitudinal population studies can begin to address the second issue; however, preclinical work will continue to be an indispensable tool to understand causality with regards to cannabis exposure.

4.1.7. Overlapping studies

Several of the reviewed studies reported results from different tasks acquired from the same experiment, which is important to acknowledge as discussing them independently inflates sample of participants in the literature. Studies that reported on the same data set are indicated in Table 1 with matching asterisks. Additionally, ten of the studies did not indicate

that they drew from overlapping samples; however, the demographic summary statistics of participants indicate that they likely are (16,21,22,45–49,52,56). It is vital to weigh interpretations of these findings with knowledge that there may be limitations to generalizability and bias due to the subjects recruited possibly leading to inflated estimates of statistical significance (79). Judging purely by the number of papers published, the casual reader may obtain an inflated perspective on the number of neuroimaging cannabis studies. While they provide a strong foundation, the limited number of unique participants (733), and the homogeneity of the samples greatly compromises the generalizability of results.

Experiments are also limited by small sample sizes. Only three studies include more than sixty participants. Small sample sizes run the risk of being under-powered, leading to greater numbers of false negatives and overestimated effect sizes (80). Future research should include power analyses and adequate sample sizes to further verify early findings in the field.

5. Conclusion

While the effects of cannabis exposure have become a focal point for research in recent years, much remains unknown despite the rapid legalization of cannabis around the world. Studies of chronic users and acute pharmacological interventions provide a baseline for understanding. Future work should consider researching long-term cannabis exposure in rodents, characterizations of dose-response relationships, sex-differences in sensitivity, and differences across mechanisms of exposure, such as oral consumption versus inhalation. A deeper understanding of the potential harms and benefits of cannabis exposure in humans requires a multifaceted examination of the effects on neurodevelopment.

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Table 1: Study Information and Summary of Detailed Results

Terms: e-r fMRI = event-related fMRI, HC = hippocampus, In = Insula, MTG = medial temporal gyrus, STG = superior temporal gyrus, ACC = anterior cingulate cortex, vmPFC = ventromedial Prefrontal Cortex, dlPFC = dorsolateral Prefrontal Cortex, Thal = thalamus, Stri = striatum, PCBO = placebo, CT = control, sMA = supplementary Motor Area, ROI = Region of Interest, Glx = glutamate+glutamine, NAcc = nucleus accumbens, CPu = caudal putamen, BOLD = Blood Oxygen Level Dependent signal

Author (yr)	**Method**	**Species**	**Age: Mean(SD)**	***N(females)***	**Drug**	**Dose, Route**	**Multiple comparison corrections**	**Detailed Results**
Atakan (2013)	e-r fMRI Tasks: Response inhibition	Human	26.76(5) range = 20-42	21(0)	THC	10mg, Oral	NC	During no-go compared to oddball: THC increased activation in the HC, tail of the caudate nucleus, right In. Drug by group interaction: left parahippocampal gyrus, MTG, STG, right cerebellum. THC increased activation in the right MTG in the transiently psychotic group and attenuated activation in the non-psychotic group.
Barkus (2011)	123I-iodobenzamide SPET	Human	26.3 (4.2)	9(0)	Dronabinol	2.5mg, IV	NC	No difference in striatal dopamine release
Battistella (2013)	e-r fMRI Tasks: Tracking	Human	24 (3) range = 18 - 30	31(0)	Bedrobinol, 11% THC, <1% CBD.	0.7g CB, ~42mg THC, inhaled	MCC	THC increased BOLD in a cluster covering the ACC and vmPFC. THC decreased BOLD in anterior In, dorsomedial Thal, left middle frontal gyrus. THC induced relative decrease in activation in anterior In, dorsomedial Thal, Stri, right dlPFC, right superior parietal lobule and cerebellum.
Bhattachar-yya (2009)	e-r fMRI Tasks: verbal memory	Human	26.7	15(0)	THC and CBD	THC: 10mg; CBD: 600mg, Oral	NC	THC increased PANSS scores (negative and general subscales). Over the course of the task performance improved while associated activity in the parahippocampus, retrosplenial and dorsoanterior cingulate, medial PFC, and bilateral precuneus decreased. THC augmented parahippocampal, cingulate, and PFC activation, so this effect was no longer evident. THC decreased activation in the bilateral striatum and rostroanterior cingulate.

Bhattacharya (2010)	e-r fMRI: Tasks: Verbal memory, response inhibition, sensory processing, fearful face viewing	Human	26.7 (5.7)	MRI: 15(0) Behavior: 6(3)	THC and CBD	THC: 10mg; CBD: 600mg, Oral	MCC	Retrieval phase: THC and CBD had opposite effects in Stri, ACC, medial PFC and lateral PFC. Effects of THC inversely correlated with severity of psychotic symptoms: THC attenuated Stri. Fearful faces: THC and CBD had opposite effects on activation in left Amyg, fusiform and lingual gyri, lateral PFC. THC augmented amygdalar response to fearful faces, correlated with levels of anxiety. CBD attenuated amygdalar response. go/no-go task: opposite effects in parahippocampal gyrus bilaterally, left In and caudate: THC attenuated. Speech listening: opposite effects in lateral temporal cortex bilaterally. Checkerboard viewing: opposite effects in occipital cortex bilaterally.
Bhattacharya (2012)	e-r fMRI, Tasks: attention	Human	26.7 (5.7)	15(0)	THC and CBD	THC: 10mg; CBD: 600mg, Oral	MCC	THC increased activation in the right inferior, middle, and superior frontal gyri, right orbitofrontal cortex, frontal pole, attenuated activation in the head of the caudate, putamen, In, Thal on right side.
Bhattacharya (2014)	e-r fMRI, Tasks: Response inhibition	Human	26.5(5.8)	36(0)	THC	10mg, Oral	MCC	Response inhibition: THC attenuated activity in left inferior frontal gyrus and adjacent In, left precuneus. THC augmented right HC, caudate nucleus. THC attenuated inferior frontal activation correlated with greater frequency of response errors.
Bhattacharya (2018)	e-r fMRI Tasks: verbal memory	Human	25.35(5.24)	CBD: 16(6), Placebo: 17(10), HC: 19(8)	CBD or Vehicle	600mg, Oral	MCC	Relative to PCBO, during encoding: CBD increased activity in left parahippocampal gyrus and reduced activity in precentral gyri. Relative to PCBO, during recall: increased activation in left cingulate gyrus, right precentral gyrus, medial frontal gyrus. During encoding: clusters PCBO>CBD>CT: right inferior frontal and mid-frontal gyri and In, left In and putamen, precentral gyri, right fusiform gyrus, left cerebellum. PCBO<CBD<CT: left caudate head and putamen, ACC, right subcallosal gyrus, tail of right caudate, precuneus and right cuneus During recall: PCBO>CBD>CT: right inferior frontal gyrus, precuneus, right cerebellum. PCBO<CBD<CT: left parahippocampal gyrus, left Thal, left transverse temporal gyrus,

Borgwardt (2008)	e-r fMRI Tasks: verbal memory	Human	26.7(5.7), range = 20-42	15(0)	THC and CBD	THC: 10mg; CBD: 600mg, Oral	MCC	THC: no-go relative to oddball: activation in right HC, right postcentral gyrus, lingual gyrus bilaterally. CBD: activation in superior and middle temporal gyri and In bilaterally and in right posterior cingulate gyrus. Overall: THC reduced activation in right inferior frontal gyrus, ACC, bilateral precuneus. THC increased activation in right HC/parahippocampal gyrus, right superior and transverse temporal gyri, right fusiform gyrus, right caudate and Thal, left posterior cingulate and precuneus. CBD: reduced activation in left In and left superior and transverse temporal gyri.
Bossong (2009)	PET:[11C] Raclopride	Human	21.9(2.7) range = 20-27	7(0)	THC	8mg, vaporized	NC	THC reduced dopamine receptor availability in ventral Stri and precommissural dorsal putamen
Bossong (2012a)[a]	e-r fMRI Tasks: working memory	Human	21.4(2.1) range = 18-27	17(0)	THC	6mg, followed by 3 maintenance doses of 1 mg, vaporized	MCC	THC reduced load-dependent increase in activity associated with task. Linear interaction between drug and load. The harder the task, the more THC impacts activity. Significant linear difference in load between PCBO and THC in left dlPFC, left inferior temporal gyrus, left inferior parietal gyrus, and cerebellum.
Bossong (2012b)[a]	e-r fMRI Tasks: associative memory	Human	21.6(2.1), range = 18-27	14(0)	THC	6mg, followed by 3 maintenance doses of 1 mg, vaporized	MCC	During encoding: interaction between drug and condition and ROI: THC decreased activity in right In, right inferior frontal gyrus, left middle occipital gyrus. recall: THC increased activity in left and right precuneus.

Bossong (2013a)[a]	e-r fMRI Tasks: Continuous performance	Human	22.0(4.9), range = 18-40	23(0)	THC	6mg, followed by 3 maintenance doses of 1 mg, vaporized	NC	Task-induced deactivation (TID) in ROIs: activity increased after THC. TID regions were more sensitive to the effects of THC than task-induced activation networks. After THC, negative correlation with TID activity and task performance.
Bossong (2013b)[a]	e-r fMRI Tasks: emotional processing	Human	21.5(2.5) range = 18-26	11(0)	THC	6mg, followed by 3 maintenance doses of 1 mg, vaporized	NC	THC had a different effect on happy and fearful face (FF) viewing. THC decreased activity in FF condition. Interaction between drug and condition in vermis, left occipital cortex, right occipital cortex, left HC, right PFC, right superior parietal gyrus, right sMA
Colizzi (2018a)	e-r fMRI Tasks: verbal memory, response inhibition	Human	26.0(5.6)	24(0)	THC	10mg, Oral	MCC	Cannabis users (CUs) had greater activity in left middle and superior frontal gyrus, less activity in right parahippocampal gyrus, right posterior cingulate, right inferior parietal lobule and postcentral gyrus than Nonusers (NU). THC induces greater activity in the left medial frontal gyrus and left inferior frontal gyrus. Decreased activity in left cingulate gyrus and in the culmen and cerebellar lingual bilaterally. left medial frontal gyrus deactivated in NUs in PCBO condition, but activated by NUs in THC and CUs in PCBO. Parahippocampal gyrus deactivated in THC. Facial expressions: CU's greater activity in right cingulate gyrus and left inferior parietal lobule than NUs. THC reduced activity in right inferior frontal and middle frontal gyrus, declive, uvula, fusiform gyrus. Left brain areas found interaction between drug and lifetime use: NUs in placebo activated left fusiform gyrus and deactivated left precuneus, cuneus, left posterior cingulate.

Colizzi (2018b)	e-r fMRI, Tasks: attention, fearful face viewing	Human	26.0(5.6)	24(0)	THC	10mg, Oral	NC	No significant effect of THC during encoding for verbal memory, but there was an interaction between drug and previous cannabis exposure: encoding + PCBO, activation in right superior temporal gyrus in NU individuals, encoding + THC activation here decreased in Nonusers (NU). NU group: THC changed activation in left parahippocampal positively correlated with severity of psychotic symptoms. during response inhibition: THC increased activation in the right anterior cingulate and reduced it in left In. involvement of left inferior parietal lobule during inhibition control, THC had different effects for cannabis users (CU) and NU
Colizzi (2019)	MRS	Human	24.4(4.29)	16(9)	THC	1.19mg/2 ml, IV	NC	Increased Glutamate+Glutamine (Glx) in the left caudate head, positive correlation between previous cannabis exposure and increase in Glx, Glx levels were lower in subjects who were sensitive to THC-induced psychotomimetic effects.
de Sousa Fernandes Perna (2017)	e-r fMRI, Tasks: alcohol vs. cannabis marketing	Human	22.5(2.3)	62(26)	THC	300 microgram/ kg bodyweight in 2 doses	NC	Alcohol marketing increased BOLD response for all groups while sober in the parietal, temporal, and frontal brain regions. Main effect of group in left HC and right precuneus. After intoxication, there was a main effect of marketing on BOLD response in postcentral cluster, cingulum, temporal, parietal, frontal, and occipital cortices. Main effect of treatment on bold in right supplementary motor area (reduction)
Fusar-Poli (2009)	e-r fMRI, Tasks: Emotional processing	Human	26.67(5.7) range = 18-35	15(0)	THC and CBD	THC: 10mg; CBD: 600mg, Oral	NC	For 50% fearful faces, CBD decreased activation in a region in posterior lobe of cerebellum bilaterally. 100% fearful faces: CBD attenuated bold signal in left medial temporal region (Amyg) and anterior and posterior cingulate gyri, left middle occipital gyrus, right posterior lobe of cerebellum. Neutral faces: THC increases activation in posterior-middle temporal gyrus, left inferior parietal lobule. 50% fearful faces: THC increased activation in right inferior parietal lobule. decreased activation in left medial frontal gyrus. 100% fearful faces: THC increased activation in left precuneus and in primary sensorimotor cortex bilaterally. decreased activation in middle frontal gyrus bilaterally and in posterior cingulate gyrus.
Ginovart (2012)	PET: 18Ffallypride and 3H-(+)-PHNO	Rats(Sprague-Dawley)		4-15(0)	THC in saline/ethanol/cremophor	1 mg/kg/day, IP	NC	THC increased binding potential of 18Ffallypride in dorsolateral Stri.

Gorka (2014)[b]	e-r fMRI, Tasks: Emotional processing	Human	20.8(2.6) range = 18-28	16(8)	Marinol in Dextrose	7.5mg, Oral	MCC	Altered functional coupling between left basolateral Amyg and rostral ACC/medial PFC as well as left superficial Amyg and rACC/mPFC. THC increased left basolateral Amyg to range ACC/mPFC connectivity--more so in threatening faces than happy faces
Gorka (2016)[c]	e-r fMRI, Tasks: Emotional processing	Human	25.43(5.33)	78(44)	Marinol in Dextrose	7.5mg, Oral	NC	Group by instruction interaction in left Amyg. Within THC group, left Amyg activation increased during maintain compared with look. Group by condition interaction between both Amygdalae and dlPFC. Compared with PCBO, THC decreased Amyg-dlPFC coupling during reappraise and maintain, and during look, it increased left Amyg-dlPFC coupling
Higuera-Matas (2008)	PET: 18F FDG	Rats (Wistar)	P28-P38	Saline: 16(9), CP: 18(12)	CP 55, 940	0.4mg/kg/day, IP	NC	Reduced activation in amygdalo-enthorinal area. Increased activation in frontal cortex in CP 55 females. No changes in males
Jansma (2013)[a]	e-r fMRI: Monetary incentive delay	Human	21.2(0.8) range = 18-26	21(0)	THC	6mg + 1mg/30 min, Vaporized	NC (2 ROIs)	NAcc during anticipation: For controls (CT), reward increases brain activity, for nicotine addicts (NAD) it does not. After THC, lower response in NAD than CT. CPu during anticipation: CT increase in CPu brain activity with increased reward. THC, smaller effect of reward in NAD than in CT. CPu during feedback: CT increase in activity with increasing reward.
Klumpers (2012)	rs fMRI	Human	22.17(2.95) range = 18-45	12(3)	THC	3 doses, 2, 6, and 6 mg at 1.5 hour intervals, Vaporized	MCC	THC altered connectivity in sensorimotor, left and right dorsal visual stream networks. After THC, increases in right dorsal visual stream connection with left and bilateral frontal pole as well as dorsomedial PFC and left superior PFC. Connectivity decreased in right dorsal visual stream (superior frontal pole, middle and inferior frontal gyrus, dlPFC). Increase of connectivity found between cerebellum and sensorimotor network (occipital pole, lateral occipital cortex) and the dorsal visual stream network
Lee (2013)	e-r fMRI, Tasks: Pain response	Human	R = 24-34	12(0)	THC	15mg, Oral	MCC	Capsaicin increased activity in bilateral thal and ACC. Interaction between capsaicin and THC in ACC: THC decreased activity in response to capsaicin. THC increased activity in right Amyg in response to noxious stimulation. Significant correlation between effect of THC on right Amyg (increase) and analgesic effect of THC. During pain state, THC reduced connectivity between right Amyg and primary sensory cortex.

Mathew (1992)[d]	SPECT: 133Xenon inhalation	Human	25.3(6.4)	20(0)	THC	3.55%, 1.75%, 0%, smoked	MCC	Cerebral blood flow increase following both low and high-doses of cannabis, especially in anterior regions of hemispheres. Changes in right hemisphere persisted longer.
Mathew (1993)[d]	SPECT:133Xenon inhalation	Human	21.7(8)	35(0)	THC	3.55%, 1.75%, 0%, smoked	NC	Drug by time interaction: increase of global cerebral blood flow following low and high cannabis doses, especially in anterior parts of each hemisphere
Nguyen (2012)	PET: 18F-FDG	Rats(Wistar)	10-11 weeks of age	12(0)	HU-210(n=7) or vehicle (n=5)	100mg/kg, IP	NC	interaction between time and treatment: HU-210 increased 18F-FDG uptake on day 1.
O'Leary (2003)	PET: H215O	Human	21.6(1.6)	12(6)	THC	20mg, inhalation	MCC	Before smoking, chronic users had increased cerebral blood flow in left fusiform gyrus, pulvinar nucleus of Thal, left caudate nucleus. Chronic users had lower regional cerebral blood flow (rCBF) in left lateral cortical region of the inferior posterior lobe of cerebellum. In both groups, THC increased rCBF in anterior cingulate, mesial, and orbital frontal lobes, In, temporal poles, and cerebellum. THC reduced rCBF in auditory and visual cortices.
O'Leary (2007)	e-r fMRI, Tasks: Sensory Processing	Human	23.5(4.3)	12(6)	THC	20mg, inhalation	MCC	THC increased regional blood flow in ventral forebrain: bilateral, orbital frontal lobe, anterior temporal lobe, In, subgenual anterior cingulate. THC increased blood flow in superior ACC, mesial frontal lobe, right and left cerebellar regions. THC decreased rCBF in mesial occipital lobe and precuneus. Additional interaction results
Phan (2008)[b]	e-r fMRI, Tasks: Emotional processing	Human	20.8 (2.6) range = 18-28	16(8)	Marinol in Dextrose	7.5mg, Oral	MCC	THC attenuated Amyg activation to threatening faces. No effect on primary visual and motor activation. Right Amyg more activated in PCBO conditions than THC in threat conditions. THC increased Amyg activity in response to happy faces. Extent of attenuation of right Amyg activity related to extent of increase in "feel drug"(trend)
Rabinak (2011)[b]	e-r fMRI, Tasks: Emotional processing	Human	R = 18-28	16(8)	Marinol in Dextrose	7.5mg, Oral	MCC	THC reduced subgenual ACC activity

Rabinak (2018)[c]	rs fMRI	Human	25.43(5.05)	77(43)	Marinol in Dextrose	7.5mg, Oral	NC	THC associated with less static connectivity between Amyg and HC; greater dynamic connectivity between Amyg and vmPFC; low static connectivity between Amyg-HC after extinction learning associated with higher HC activation to conditioned stimulus during recall of extinction.
Ramaekers (2016)	rs fMRI	Human	22.8(3.7)	122(26)	THC	450micrograms/kg in two doses, 300 followed by 150, vaporized	MCC	Cannabis decreased functional connectivity between NAcc and left ACC, frontal lobe, left Thal,left Insula, temporal lobe, cerebellum, occipital lobe, In
Rzepa (2015)	rs fMRI	Human	R = 20-36	19(9)	THCv	10mg, Oral	MCC	Left Amyg seed: THC reduced connectivity with the left precuneus and left posterior cingulate area (default mode network). Right dmPFC: increased connectivity with inferior frontal gyrus/medial frontal gyrus (dorsal visual stream)
Tudge (2014)	e-r fMRI, Tasks: Sensory Processing	Human	25.4(4.5)	20(10)	THCv	10mg, Unreported	MCC	THCv effect on chocolate sight: increased activation in putamen, ACC, caudate, mid brain, cingulate gyrus. THCv effect on chocolate sight and taste: mid cingulate gyrus. Strawberry sight: In, mid orbital frontal cortex, superior temporal gyrus, putamen. Strawberry sight and taste: putamen, Amyg, In, mid orbital frontal cortex, superior temporal gyrus, Thal, caudate.
van Hell (2011)[a]	rs fMRI and ASL	Human	21.1(2.1) range = 18-27	26(0)	THC	6mg, followed by 3 maintenance doses of 1 mg, vaporized	NC	Arterial spin labelling: THC increased perfusion in ACC, left superior frontal cortex, left and right In. Decreased perfusion in right post-central gyrus, left and right occipital gyri. Feeling high was negatively correlated with activity in superior frontal cortex and moderately positive with left anterior In. rs fMRI: THC reduced temporal signal to noise ratio in right In, left cerebellum, left substantia nigra
van Hell (2012)[a]	e-r fMRI, Tasks: Reward Processing	Human	21.7(2.3) range:18-27	11(0)	THC	6mg, followed by 3 maintenance doses of 1 mg, vaporized	NC	THC during reward trials reduced reward-related brain activity. No ROI effects survived correction for multiple comparisons

Walter (2016)[e]	e-r fMRI, Tasks: Sensory Processing, Pain response	Human	28 (2.7)	15(7)	THC	10mg, Oral	MCC	Noxious stimuli increased activation in right secondary somatosensory cortex (S2). THC reduced activation in the right anterior In, HC, and cerebellum. THC decreased connectivity for ventral Thal and S2. THC influenced forward connections -- THC decreased strength between Thal and S2, S2 and anterior In or HC
Walter (2017)[e]	e-r fMRI, Tasks: Sensory Processing	Human	26.6 (2.9)	15(8)	THC	20mg, Oral	MCC	Loss of pleasantness of vanillin correlated with reduced activation in the left Amyg, HC, and superior temporal pole.
Winton-Brown (2011)	e-r fMRI, Tasks: Sensory Processing	Human	26.7 (5.7), range = 20-42	14(0)	THC and CBD	THC: 10mg; CBD: 600mg, Oral	MCC	Auditory stim: THC reduced activation in temporal cortex bilaterally in the anterior and posterior superior temporal gyrus and medial temporal gyrus and bilateral In, the supramarginal gyri, and in the right inferior frontal gyrus and left cerebellum. Correlation between reduction of activity in the right temporal cluster and increase in positive and negative symptom scale (PANSS) total. CBD increased activation in temporal cortex bilaterally, medially to the Insulae and caudally to the parahippocampal gyri and bilateral HC. CBD reduced activation relative to PCBO in a posterior-lateral region of the left superior temporal gyrus, incorporating parts of In, posterior middle temporal gyrus, and supramarginal gyrus. THC v CBD: CBD increased activation in right superior and middle temporal gyri. Visual stimuli: THC reduced activation in secondary visual cortex. Increased activation in right lingual and middle occipital gyri and in left hemisphere: increased activation anterior to lingual and fusiform gyri. Change correlated with increase in PANSS positive. CBD: increased activation relative to placebo in right occipital lobe. THC v CBD: THC augmented activation in left lingual and middle occipital gyri. THC attenuated activation in occipital regions bilaterally.

Note: superscript letters indicate papers with overlapping samples.

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