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Interactions between recreational cannabis use and cognitive function: lessons from functional magnetic resonance imaging

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Abstract

Cannabis use is becoming increasingly popular as a growing number of states pass legislation to legalize cannabis and cannabis-derived products for recreational and/or medical purposes. Given the widespread use of cannabis, it is critical to understand the neural consequences related to cannabis use. In this review, we focus on evidence from functional magnetic resonance imaging (fMRI) studies that document acute and residual alterations in brain function during tasks spanning a variety of cognitive domains: executive function, attention and working memory, memory, motor skills, error monitoring, and reward and affective processing. Although it is clear that cannabis affects brain function, the findings are somewhat inconsistent; variables that potentially affect study outcomes are outlined, including a discussion of the impact of chronological age and age of cannabis onset as well as length of abstinence at the time of assessment, which are important considerations when measuring cannabis use patterns. Inherent differences between recreational/adult cannabis use versus use for medical purposes are also discussed, given their importance to public policy decisions.

Keywords

cannabis; marijuana; neuroimaging; fMRI; cognition

Introduction

The earliest use of cannabis dates back thousands of years, with references to medical use found in numerous ancient cultures, as well as many modern civilizations. Known for its recreational use, cannabis remains the most widely used illicit substance within the United States. Comprising hundreds of chemical compounds, the plant *Cannabis sativa L*. contains over 100 phytocannabinoids, including Δ^9-tetrahydrocannabinol (THC), the primary psychoactive constituent of the plant, and cannabidiol (CBD), a primary non-intoxicating constituent[1]. Cannabinoids interact with the body's endocannabinoid system (ECS), which

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Competing Interests

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is responsible for maintaining homeostasis and is thought to play a role in neuroplasticity[2]. The ECS includes two receptor types, cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), and the endogenous cannabinoids N-arachidonoylethanolamine (anandamide) and 2- arachidonoylglycerol (2-AG), which bind to the G protein–coupled central and peripheral cannabinoid receptors CB1 and CB2, respectively[3]. THC is a CB1 agonist with strong binding affinity for CB1 receptors[4], and as a result, exposure to exogenous cannabinoids such as THC can directly impact the brain, particularly those areas with high CB1 receptor densities[5]. In contrast, CBD has low affinity for both CB1 and CB2 receptors,[6] but is speculated to have multiple mechanisms of action. As CBD has numerous positive effects (e.g., neuroprotective, anti-inflammatory, anti-oxidative),[7] it is thought to hold therapeutic potential for a range of conditions,[8–15] and in some cases has even been shown to mitigate the negative or less desirable effects commonly associated with THC.[16, 17] Notably, both THC and CBD have been formulated into approved medications in the United States and/or the United Kingdom, including Marinol (dronabinol/synthetic THC), Sativex (plant-derived formulation of THC and CBD in a 1:1 ratio), and Epidiolex (a purified, plant-derived CBD product).

Interestingly, although the use of most drugs has declined over the past decade, the use of cannabis has increased in recent years, perhaps not surprisingly given ongoing legalization efforts for medical and recreational purposes. According to the most recent National Survey on Drug Use and Health (NSDUH), an estimated 24 million Americans reported current cannabis use, or approximately 8.9% of the U.S. population, as compared to previous surveys suggesting lower levels of use[18]. For example, results from the 2014 survey indicated that approximately 22.2 million Americans (8.4%) used cannabis within the past month,[19] while the 2013 survey estimated 19.8 million past-month users (7.5%)[20]. This increase in cannabis use is primarily attributed to higher rates of use in adults over the age of 26 and, albeit to a lesser extent, those between the ages of 18–25. Although 1.6 million adolescents (6.7%) report current cannabis use, this number represents fewer adolescent cannabis users than in the years from 2009 to 2014. These statistics appear to reflect changing attitudes in cannabis use across the nation; as the medical benefits of cannabis are touted, more adults appear be initiating cannabis use. Currently, only three states completely prohibit cannabis and cannabinoids. Thirty states and the District of Columbia have fully legalized medical cannabis, with one additional state pending implementation, and of these, nine states plus the District of Columbia also allow recreational or adult cannabis use. In addition, 17 states have partial medical programs that allow only the use of CBD, often for specific indications. While many feared that legalization efforts would lead to increased use among adolescents, a particularly vulnerable population given ongoing neurodevelopmental changes, this trend has not been observed nationally to date[21]. It is important, however, to monitor the impact of legalization on rates of use within discrete age groups, as cannabis is likely to cause unique effects across the lifespan.

Over the past several decades, increasing research efforts have focused on clarifying the impact of cannabis on cognitive function in both adolescents and adults. Although there has been some variability in findings, the majority of studies have demonstrated that those who use cannabis regularly exhibit poorer cognitive performance across a range of domains relative to non-cannabis users, which is primarily attributed to THC. Recent reviews

documenting the cognitive effects of cannabis use suggest that executive functioning and memory are most strongly affected by regular cannabis use[22–24]. While processing speed is also adversely impacted[25–27], findings are more inconsistent with regard to IQ[28–30]. However, a recent meta-analysis[35] concluded that among studies citing negative effects of cannabis use on cognition, effect sizes are often small, raising the question of the clinical importance of these decrements, while others have not reported decrements among cannabis consumers[34]. Notably, findings are often inconsistent across studies due to a number of variables related to cannabis use or study methodologies, making it difficult to draw general conclusions about the effects of cannabis use on the brain without considering the impact of each of these unique factors. These factors include, but are not limited to, chronological age, age of onset, frequency/magnitude of use, length of abstinence, product choice, route of administration, and comorbidities (substance use, medical/psychiatric disorders).

Magnetic resonance imaging (MRI) has afforded researchers the opportunity to examine the underlying neural substrates associated with cannabis use, and a number of recent comprehensive reviews have been conducted on the impact of cannabis use on the brain, each focusing on various outcomes or aspects of cannabis use. For example, Volkow[31] reviewed the behavioral (cognitive, motivation, and psychosis) effects of cannabis use, while Lisdahl and colleages[24, 32] summarized the impact of cannabis use specifically in adolescent users, and Ganzer *et al.*[33] provided readers with a meta-analysis of studies utilizing an abstinence period of two or more weeks to examine the long-term effects of cannabis use on neurocognitive function. In this review, we will examine both the acute and residual impact of cannabis use on cognitive function across various domains, specifically through the lens of recent functional MRI (fMRI) investigations. As studies often utilize a variety of methodologies, Table 1 highlights important variables related to imaging analyses that may contribute to inconsistent findings observed across investigations, including sample size; Table 1 also provides information about the task(s) utilized in each study as well as a brief summary of task performance. In addition, Table 2 includes information about cannabis use/inclusion criteria; comorbid alcohol, nicotine, and other drug use; and duration of cannabis abstinence used in each study. These factors, as well as additional variables related to cannabis use, are explored, and areas in need of further investigation are highlighted.

Acute Impact of Cannabis

As previously noted, numerous studies examining the acute effects of cannabis on cognitive function have generally reported adverse effects across cognitive domains, including learning and memory, attention, executive function, decision making, abstract reasoning, and psychomotor control[23, 36, 37]. Fewer, however, have utilized fMRI techniques to examine the neural underpinnings of cognitive decrements associated with acute intoxication. While additional research is needed to fully understand the neural correlates associated with acute cannabis intoxication, several studies are highlighted below.

Acute administration: THC

Bossong and colleagues[38, 39] have specifically examined the acute effects of THC on memory/working memory function. Prior to completion of fMRI tasks, 6 mg of THC was

administered to occasional cannabis users via vaporizer, followed by three subsequent 1-mg THC doses to maintain stable THC levels throughout scanning. In the first study[38], participants completed a pictorial memory task, which contained both encoding and recall conditions in order to assess associative memory. Although THC administration did not affect task performance, imaging analyses demonstrated that it was correlated with attenuated activity in the right inferior frontal gyrus, right insula, and left middle occipital gyrus during encoding. In contrast, during recall trials, acute THC exposure appeared to result in a network-wide increase in activity, most notably in the bilateral cuneus and precuneus. Interestingly, during placebo recall conditions, functional activation was inversely correlated with performance, suggesting more efficient processing, but no association between activation and performance was detected during the THC recall condition. The second study[39] specifically assessed working memory function using a Sternberg Item Recognition task where participants are instructed to encode strings of 1, 3, 5, 7, or 9 letters; they are then are presented with individual letters and must identify each letter that appeared in the preceding string via a button press. In this study, the authors reported that THC negatively impacted task performance accuracy. Moreover, ROI analyses examining the working memory network revealed linear increases in activity as working memory load increased under placebo conditions, while THC exposure was associated with increased activity only for low working memory loads. THC also affected the relationship between working memory load and overall activity within the working memory neural network, specifically mediating activity in the left dorsolateral prefrontal cortex (DLPFC), inferior temporal gyrus, inferior parietal gyrus, and cerebellum. It is of note that these two studies revealed alterations across distinct, non-overlapping brain regions during the performance of memory tasks, likely due to the fact that (1) the tasks assess different aspects of memory (pictorial memory versus working memory), resulting in different patterns of activation, and (2) performance differences between placebo and THC conditions were only noted in the second study. Overall, these findings suggest that THC can impact various aspects of memory processing, even in the absence of performance decrements.

One of the most common public health policy concerns is the potential impact of cannabis on driving. In order to help understand specific functional changes that may affect driving, Battistella and colleagues[40] evaluated driving-related skills in occasional cannabis smokers using a visuomotor tracking task during fMRI. Specifically, participants tracked a square as it moved along pseudo-random trajectories during the active and passive conditions, but in the active condition, participants tracked the square by keeping it at the center of another square using a joystick, whereas in the passive condition, participants were simply asked to track the square visually. Results revealed that after smoking cannabis (an 11% THC joint), participants exhibited impaired psychomotor skills (i.e., difficulty with the active task condition) and decreased activity in several of the brain's primary cognitive networks (e.g., salience network, central executive network), perhaps reflective of less attention focused on the task. In contrast, ventromedial prefrontal cortex (vmPFC) and rostral anterior cingulate cortex (ACC), posited to be part of the default mode network, demonstrated increased activity. The authors note that the vmPFC and ACC have been shown to be related to spontaneous self-generated thoughts, and therefore concluded that cannabis users' performance may reflect an increase in self-oriented thoughts. If this is the case, individuals

who are intoxicated may be more likely to attend to stimuli related to themselves and subsequently fail to attend to the task, resulting in poorer task performance (as observed in the current study), which may ultimately correlate with poorer driving performance.

Acute administration: THC versus CBD

Given increased access to products containing CBD, particularly among medical consumers, researchers have begun to examine the effect of CBD in the presence of THC. Overall, several investigations focused on the effects of THC and CBD on cognition and clinical state have noted that CBD appears to have opposite effects from THC and may even mitigate some of the adverse consequences typically associated with THC exposure. For example, in one of the earliest studies to examine whether CBD modulates the effects of THC, Zuardi *et al.*[41] reported that acute administration of CBD blocked anxiety produced by administration of THC. More recently, Morgan and colleagues[42] reported that cannabis users who had CBD present in hair samples reported lower scores on a measure of psychosis-like symptoms. Although a later study conducted by Morgan and colleagues[43] study did not observe effects of CBD on psychomimetic symptoms in cannabis users who provided samples of their "real world" cannabis products, the authors posit this may be a related to a number of factors, including differing cannabis use patterns across studies and doses or ratios of cannabinoids. However, in this study the authors also assessed the potential mitigating effects of CBD on memory; results indicated that during intoxication, those using low CBD cannabis products (<0.14% CBD) exhibited significant declines in memory performance while those using high CBD cannabis products (>0.75% CBD) did not demonstrate significant performance decrements. These findings suggest that higher levels of CBD may be protective against memory impairment. In another more recent study, Morgan *et al.*[44] found that while higher THC levels (measured in hair) were associated with recall memory deficits and elevated levels of anxiety and depression, recognition memory was better in those with detectable levels of CBD. Similarly, Englund and colleagues[45] observed that THC-related psychotic symptoms, paranoia, and memory impairment were less common among those who received CBD as a pre-treatment relative to those who received placebo pre-treatment. In addition, Yucel and colleagues[46] examined hippocampal volumes in cannabis users and discovered that while those with no CBD exposure had smaller volumes relative to healthy controls, no differences were observed between cannabis users with CBD exposure and control participants. More recently, Beale *et al.*[47] extended these findings, reporting that regular cannabis users treated with 200 mg of CBD daily exhibited significant volume increases in specific hippocampal subfields. While a number of studies provide support for mitigation of the negative effects of THC, it is of note that some studies have not observed these effects. In a lab-based study that pretreated individuals with CBD and then administered whole plant cannabis, Haney and colleagues did not observe a mitigating effect of CBD on subjective ratings (e.g., ratings of the "high" produced, potency of the cannabis cigarette, liking of the cannabis cigarette), behavioral performance (digit symbol substitution task), or cardiovascular effects (heart rate and blood pressure).[48] Similarly, Ilan and colleagues[49] also failed to observe mitigating effects of CBD on heart rate or subjective reports of feeling high in a study in which participants smoked THC-containing cannabis which had either high or low CBD percentages. Furthermore, mitigating effects were not observed on behavioral (working memory and word recognition tasks) and neurological measures (EEG and ERP).

The unique effects of THC and/or CBD have been further explored with fMRI techniques. Using a go/no-go task to assess response inhibition, Borgwardt and colleagues[50] studied the acute impact of orally administered THC, CBD, and placebo in healthy control subjects. This task, which requires participants to execute a motor response for all stimuli except those displaying a specific target, has been shown to activate prefrontal regions, including the inferior frontal gyrus, middle frontal gyrus, and anterior cingulate, in healthy controls.[51–53] Although performance differences were not observed between the cannabinoid or placebo conditions, fMRI results demonstrated that administration of THC reduced activation in frontal regions, while CBD reduced activation in temporal and insular regions relative to placebo, areas not typically associated with response inhibition. In another study of healthy individuals with minimal previous exposure to cannabis, Bhattacharyya and colleagues[54] administered 10 mg of oral THC, 600 mg of CBD, or placebo to participants prior to completing a verbal paired associate learning task. During the encoding condition, participants viewed pairs of words, while during the recall condition they were shown one word and had to say the word previously paired with it. Although behavioral performance was not significantly affected by THC or CBD, fMRI results generated interesting findings. Under placebo conditions, completion of repeated encoding trials caused a linear reduction in cortical activation in the mediotemporal cortex, specifically the parahippocampal gyrus, a region implicated in verbal information encoding. Following THC exposure, however, completion of the task resulted in increased activation in the parahippocampal gyrus across learning trials. In addition, THC attenuated striatal and cingulate activation patterns, which are normally observed during retrieval conditions in non-intoxicated individuals. Interestingly, none of these effects were observed after acute CBD administration. In a series of studies, Bhattacharyya *et al.*[55] and Winton-Brown *et al.*[56] also administered THC and CBD to participants who completed a variety of tasks. Results revealed opposite effects of THC and CBD on brain activation patterns in regions typically associated with each task. Specifically, THC and CBD demonstrated opposite effects in the superior temporal cortex when participants were presented with auditory stimuli (spoken words), in the occipital cortex when viewing complex visual stimuli (radial checkerboard), and in the amygdala during affective processing (viewing fearful faces). Furthermore, THC exposure resulted in increased psychotic-like symptoms (higher Positive and Negative Syndrome Scale [PANNS] scores), elevated levels of anxiety, feelings of intoxication, and sedation; these effects were not observed after CBD administration. Fusar-Poli and colleagues[57] also examined functional correlates of THC versus CBD administration in healthy non-cannabis users. After ingesting either 10 mg THC, 600 mg CBD, or placebo, participants viewed fearful and neutral faces while undergoing fMRI. During placebo conditions, processing of fearful faces was related to activation in visual, limbic, and paralimbic regions typically implicated in the processing of facial affect. Interestingly, results revealed that administration of THC increased anxiety and modulated activation in frontal and parietal regions, whereas administration of CBD reduced anxiety and modulated activity in a separate group of brain regions, namely limbic (amygdala) and paralimbic (anterior and posterior cingulate cortex) regions.

Taken together, results suggest that THC and CBD appear to impact the brain quite differently, which is not surprising given their distinct mechanisms of action. Overall, CBD

has demonstrated the potential to mitigate the adverse consequences that have often been observed in recreational cannabis smokers. However, further research is needed to understand the mechanisms by which these effects occur and to clarify the factors that influence the ability of CBD to counteract or limit the effects of THC, including dose of THC and CBD, ratio of the two constituents to each other, timing of administration (i.e. pretreatment with CBD versus simultaneous administration with THC), presence of other cannabinoids/constituents, mode of administration, plant versus non-plant based products, and type of effect/symptom (i.e., psychological, behavioral, neurological), which may account for some of the mixed findings noted above in non-fMRI studies.

Residual impact of cannabis

A number of neuroimaging studies have also assessed the residual impact of cannabis by examining users who are not acutely intoxicated or high and who have had at least a brief period of abstinence from cannabis, typically 12–24 hours. The vast majority of fMRI studies of non-intoxicated cannabis users report altered brain activation patterns relative to non-users[32, 58, 59]. These alterations appear to be present across numerous brain regions and affect various cognitive domains. Although tasks involving executive function and memory are considered to be among the most affected in cannabis users, studies have also revealed alterations on tasks of attention, error monitoring/awareness, as well as reward and emotion paradigms.

Executive function

Executive function is considered a higher-order, multi-faceted cognitive construct that involves controlling and executing goal-directed behaviors. Executive functioning encompasses a myriad of important skills, including planning, reasoning, inhibitory processing, self-monitoring, and problem solving. Several studies, including our own, have utilized Stroop paradigms to study executive functioning and inhibitory processing in chronic cannabis smokers. During the traditional Stroop color word test, participants must complete three conditions in which they either name colors of blocks; read words printed in black ink; or, when presented with words printed in a different colored ink from what they spell, must name the color of the ink, thereby inhibiting the automatic tendency to read. Gruber and Yurgelun-Todd[60] observed altered patterns of activation in cannabis users relative to controls within the cingulate cortex and DLPFC, frontal regions typically activated during completion of the Stroop interference condition. Specifically, cannabis users demonstrated reduced anterior cingulate, but increased midcingulate, and a more diffuse bilateral pattern of DLPFC activity relative to non-cannabis users. Furthermore, although cannabis users and controls performed within normal limits on the task, the cannabis-using group exhibited higher rates of commission errors (incorrect responses) relative to controls, which were associated with activation in different brain regions. More recently, Sagar and colleagues[61] reported poorer performance on the Stroop task among cannabis users relative to control subjects, which was accompanied by reduced, but more diffuse, activation throughout the cingulate cortex. Furthermore, among the cannabis users, those with earlier onset of regular cannabis use (onset prior to age 16) demonstrated activation in anterior regions of the cingulate cortex while those with late onset exhibited activation in more

posterior cingulate regions, similar to the healthy control group. Kober et al.,[62] utilized a modified Stroop task containing a mix of congruent (e.g., “green” printed in green ink) or incongruent trials (e.g., “red” printed in blue ink) to assess functional activation patterns in treatment-seeking cannabis users. Despite similar activation patterns during congruent trials, relative to healthy controls, cannabis users exhibited poorer task performance coupled with reduced activity across multiple regions, including the prefrontal cortex (PFC), striatum, amygdala/parahippocampal gyrus, thalamus, and midbrain regions during incongruent trials.

The counting Stroop test has also been employed in young adult cannabis users (19–21 years old).[63] This variation of the traditional color word Stroop task presents individuals with sets of one, two, three or four words and then requires them to report the number of words presented; during congruent trails they are presented with names of animals, but during incongruent trials they are presented with number words (e.g., “one”, “two”, “three”, etc.) that are incongruent with the correct response. The counting Stroop has primarily been shown to increase activity in the ACC, but also activates a range of networks involved in attention, response selection, motor planning, and motor output.[64] Although Hatchard and colleagues[63] found that cannabis users demonstrated similar task performance as healthy controls, hyperactivation was observed during the completion of the task within the cingulate gyrus and additional regions, including the right rolandic operculum, postcentral gyrus, cerebellar tonsil, and right supplementary motor area, suggesting that recruitment of additional brain regions may have been necessary in order for cannabis users to achieve adequate performance.

Overall, studies using traditional Stroop paradigms primarily report reduced activation and poorer task performance in cannabis users relative to healthy control subjects while a study using an alternate version of the task (e.g. counting Stroop) revealed increased activation and similar task performance between cannabis users and controls. This may be due, at least in part, to the fact that the traditional Stroop interference condition requires verbally mediated responses that produce robust inhibitory effects, while the counting Stroop requires a button press, thereby utilizing different response outputs and related neural circuitry.

The multi-source interference task (MSIT) is a measure of cognitive control processing and response inhibition shown to reliably activate the cingulo-fronto-parietal (CFP) cognitive/attention network.[65] The MSIT uses aspects from the Stroop as well as other well-established measures of cognitive interference (e.g., Simon and Flanker tasks); subjects are presented with sets of three numbers and must indicate the identity of the number that is different regardless of its position within the set, which is consistent with its position on the button box in congruent trials, yet inconsistent with its button box position during interference trials. Using the MSIT, Gruber and colleagues[66] found that cannabis users exhibited more diffuse patterns of ACC activation compared to healthy controls despite similar task performance. Analyses examining age of onset of use revealed that while early onset users (those who initiated regular use prior to age 16) displayed more focal patterns of activation relative to later onset users (regular use after age 16), they tended to make more errors on the task, suggestive of possible neural adaptation in spite of difficulty with behavioral inhibition. Harding and colleagues[67] found similar behavioral performance and magnitude of brain activation during the MSIT among cannabis users and healthy controls;

however, the authors noted greater functional connectivity between the PFC and occipitoparietal cortex in cannabis users, and found that the magnitude of connectivity was positively correlated with age of onset of use.

A handful of investigations have also utilized go/no-go paradigms to examine response inhibition among cannabis-using adolescents.[68, 69] Tapert and colleagues found similar performance between abstinent cannabis users and healthy controls; however, brain activation patterns were notably different. The cannabis group demonstrated increased activity in frontal, parietal, and occipital areas during inhibition (no-go) trials. In contrast, Behan and colleagues[69] observed poorer task performance among cannabis users and healthy controls, but no differences were detected using ROI analyses. Connectivity analyses, however, indicated altered connectivity within the response inhibition circuit, which was correlated with cannabis use. As the cannabis groups had significantly different durations of abstinence across studies (ceasing use the night before the scan[69] versus 28 days of abstinence[68]), it is likely that recency of use affected neural response across these investigations. Nonetheless, the results suggest that cannabis use affects brain circuitry related to executive functioning and response inhibition.

Attention and working memory

A number of studies have specifically examined attention and working memory in cannabis users using task-related fMRI techniques. Abdullaev *et al.*[70] utilized various tasks to interrogate these networks in cannabis users. First, the attention network task (ANT) requires that participants indicate the direction of an arrow with a key press, but the task is able to parse the activity of three distinct aspects of attention: alertness, orienting to stimuli, and executive control. In a second, more difficult task, participants are rapidly presented with nouns and must provide a use for that noun (e.g., *pen – write*). The authors reported both behavioral and functional differences between adolescent chronic cannabis users and healthy controls, with cannabis users demonstrating poorer performance and increased activation within the right PFC while engaging in these tasks, both of which require executive attention. Although both groups activated the executive network, cannabis users demonstrated increased activation, suggesting that the executive network may be less efficient in those who use cannabis, given their decreased performance.

Chang and colleagues[71] investigated visual attention using a task in which participants were to mentally track multiple, digital targets (1–4 balls) among ten balls that moved randomly and collided with one another. Although abstinent (THC-negative) and active chronic cannabis users both demonstrated similar behavioral performance relative to healthy controls, the cannabis-using groups demonstrated different patterns of brain activation relative to non-using controls. Specifically, cannabis users exhibited decreased activity in several regions within the attentional network, but greater activation in several smaller clusters within additional regions, including the frontal, posterior parietal, occipital, and cerebellar areas; increased activation in these regions may reflect compensatory function necessary for cannabis users to achieve similar levels of task performance to control subjects. Interestingly, additional analyses revealed that frontal and cerebellar activation patterns appeared to normalize during abstinence. Jager and colleagues[72] examined attention

and working memory in a small sample of adolescent cannabis users. During the first task, individuals were required to memorize a string of five letters and then indicate when one of those letters was present in subsequent trails containing ten-letter stimuli. In the second task, a visuoauditory selective-attention task, participants either detected tones that had a higher or lower pitch than a baseline tone or detected dots that were larger or smaller than a baseline dot. Interestingly, the cannabis group and controls demonstrated similar performance across both tasks as well as similar patterns of overall brain activity in the attention executive system (ACC and DLPFC). However, a specific region of interest (ROI) analysis revealed increased left superior parietal activity in the cannabis users. As this region is also implicated in working memory, the authors posited that cannabis users may experience minor alterations in the attention network even though large disruptions may not always be evident.

Most other fMRI studies examining working memory in cannabis users have specifically examined spatial working memory (SWM). Kanayama *et al.*[73] utilized a short-delay response task that required participants to look at a series of three dots and then, after a 3-s delay, determine whether a target stimulus was placed in the same location as one of the dots. The authors found that adult long-term cannabis users exhibited similar task performance, but a greater expanse of activation, relative to controls. Specifically, relative to control subjects, cannabis users demonstrated increased activation in regions typically associated with the completion of SWM tasks (PFC and ACC) and also activated additional regions not typically associated with SWM (e.g., basal ganglia), suggestive of neural compensation. Smith *et al.*[74] also observed similar task performance among young adult cannabis users and controls and reported altered activation in cannabis users during the completion of a visuospatial 2-back task, which requires participants to indicate whether a target (letter “O”) was presented in the same position that it was in two presentation screens prior. Cannabis users demonstrated hyperactivation in regions typically associated with SWM (inferior and middle frontal gyri) as well as regions that are not typically associated with SWM (right superior temporal gyrus). As in the Kanayama *et al.* study, the authors hypothesized that since cannabis users exhibited similar task performance to controls, they may have altered neural functioning during visuospatial working memory tasks, which is subsequently compensated for by the recruitment of additional brain regions. Padula *et al.*[75] and Schweinsburg and colleagues[76] examined SWM in adolescent cannabis users after a 28-day abstinence period. Participants completed a task in which they had to indicate whether a figure appeared in the same location as a previous figure had been. As noted in previous studies, while the authors observed similar task performance among cannabis users and healthy controls, differential patterns of brain activation emerged. Cannabis users demonstrated hyperactivation in the right basal ganglia,[75] often associated with skill-learning, as well as increased activity in parietal areas[75, 76] which are related to a number of processes, including attention, spatial perception/encoding, organization, and working memory. These results provide additional evidence of potential neurocompensation in cannabis users in order to achieve the same level of performance as control subjects. In addition, Schweinsburg and colleagues[76] also noted decreased activation within the right DLPFC, a region implicated in the executive demands of SWM, which may suggest that cannabis users rely upon more basic strategies, including rehearsal and attention, rather than

employing more complex, executive processes. The authors subsequently conducted a follow-up study of adolescent cannabis users with a shorter duration of abstinence (2–7 days) and reported increased activity in frontal areas, highlighting the impact of recency of cannabis use on neural response.[77]

Becker and colleagues[78] examined cortical activation in adult cannabis smokers with high and low frequency of cannabis use (determined via median split) during the completion of a verbal n-back task. During n-back tasks, participants must indicate when a letter is identical to the one presented in the preceding 1, 2, or 3 trials, depending on the condition. Despite similar task performance, increased activation in the left parahippocampal gyrus was noted among the high frequency group relative to low frequency users, perhaps suggestive of reduced neural efficiency during working memory tasks. In contrast, Cousijn *et al.*[79] failed to detect any differences in verbal working memory network functional connectivity during completion of an n-back test among young adult cannabis users, even after assessing the relationship between network function and cannabis use patterns (e.g., onset, duration, lifetime use, weekly use, and problems). However, the authors suggest that null findings may be partially due either to the relatively late average age of onset of use (18.8 years old) within the sample or to ceiling effects in n-back performance, which may have obscured working memory network alterations related to cannabis use.

Taken together, findings from attention and working memory studies highlight the importance of utilizing neuroimaging techniques to supplement traditional neuropsychological assessments, as neurophysiologic differences appear common among cannabis users even when no differences in task performance are detected. Neural alterations may in fact be dependent on the type of task utilized, specific brain regions under investigation, or heterogeneity within samples of cannabis users (i.e., chronological age, age of onset, frequency or magnitude of use, length of abstinence, etc.). Although findings are somewhat mixed across investigations of attention and working memory in cannabis users, all but one fMRI study revealed altered patterns of activation[79], regardless of whether performance was similar or altered relative to non-cannabis users. More specifically, among cannabis users, hyperactivation during attention/working memory tasks is often noted in regions implicated in task performance.

Memory

Several investigations have explored functional correlates of memory, which is known to be significantly impacted by cannabis use. Using a virtual water maze task as a measure of spatial learning and memory (participants must virtually navigate to either visible or hidden platforms across trials), Sneider *et al.*[80] found that while chronic cannabis users demonstrated similar task performance on learning trials, a trend indicating subtle differences in memory retention was detected between cannabis users and healthy controls. Furthermore, imaging results indicated hypoactivation in the parahippocampal and cingulate gyri among cannabis users; the parahippocampal gyrus has been shown to be related to landmark-based memory, while the cingulate may be related to the attentional demands of this task. Accordingly, attenuated activation in the cingulate could reflect a poorer ability to meet the attentional demands of this task.

In addition, associative learning and memory are often studied in the context of abused drugs, as this type of memory process is thought to be influenced by repetitive drug use and may also influence subsequent drug use, as stimuli associated with rewards may eventually cue drug behavior. Ames and colleagues[81] examined implicit associative memory in heavy cannabis users and non-using controls between the ages of 18–25 using a cannabis-specific implicit associate task (IAT). Participants were asked to categorize items that fit a certain category and those that did not (e.g., “marijuana pictures,” “other pictures,” “relaxed words”, and “neutral words”). Trials were divided into compatible trials with implicit associations (e.g., “marijuana pictures + relaxed” versus “other pics + neutral”) and incompatible trails (e.g., “marijuana pictures + neutral” versus “other pictures + relaxed”). Results revealed that during compatible trials, cannabis users demonstrated greater bilateral activity in the caudate and putamen, regions typically associated with habit formation. In contrast, healthy controls only showed greater activation than cannabis users in the right inferior frontal gyrus, a region that is implicated in planned, purposeful behaviors. Results suggest that given users’ experience with cannabis, they may be able to complete trials comprising concepts associated with cannabis more easily than healthy controls, and as a result, cannabis users may not engage regions associated with more deliberative processes to the same extent as seen in non-users.

Jager and colleagues[82] examined associative learning in frequent cannabis users using a pictorial memory task designed to reliably activate the hippocampal formation. During this task, participants learn to associate pairs of pictures and must later identify these pairs. Despite similar performance between cannabis users and controls, cannabis users exhibited decreased activation compared to non-users in brain regions implicated in associative learning, particularly parahippocampal regions and the right DLPFC. However, as task performance was not related to neural response, the authors posited that hypoactivation may not have been related to cognition itself, but to other behavioral or physiological variables, such as vigilance or mental attitude during the task. In a similar study, Nestor and colleagues[83] examined cortical and parahippocampal activity in current cannabis users and healthy controls during a face–number associative learning paradigm. For this task, participants were presented with faces that were each paired with a unique number (encoding condition); they were later asked to recall the digits that matched the faces over a number of trials (recall condition). As with previous studies, no differences in behavioral performance were observed and decreased activation was noted in frontal regions: right superior temporal gyrus, right middle frontal gyri, and bilateral superior frontal gyrus. In contrast to previous studies, however, cannabis users exhibited increased activation within the right parahippocampal gyrus during learning trials. The authors hypothesized that the increased parahippocampal activity may represent neurocompensation that could account for the decreased frontal activity involvement during the encoding condition. Furthermore, the authors of this study also posited that variations in findings across associative learning studies may be related to differing task demands. For example, in the current study they required participants to recall digits associated with faces, whereas Jager and colleagues[82] required participants to recall pairs of faces.

Motor skills

Psychomotor speed and visuomotor processing are important skills, particularly when considering the potential impact of chronic cannabis use on driving. Several studies have directly assessed these underlying skills and their functional correlates in chronic cannabis users using finger-tapping tasks. King *et al.*[84] reported that male but not female chronic cannabis users exhibited slower psychomotor speed across several measures (e.g., Trails A; Rey–Osterrieth complex figure - copy; pegboard tasks), which was related to increased activation in the superior frontal gyrus and additional regions associated with attention and motor planning, as well as decreased activation in the lingual gyrus, which is typically associated with visual attention. During a bilateral finger-tapping task that did not formally assess performance, Pillay and colleagues[85] found that, compared to controls, cannabis users demonstrated reduced activation in the ACC (Broadmann areas 24 and 32) and supplementary motor cortex (BA6) after 4–36 hours of abstinence. In a more recent study using the same tapping task, Lopez-Larson[86] also reported hypoactivation of the cingulate in older adolescents with heavy cannabis use[86] compared to controls. In addition, the investigators also examined cerebellar activation, which was decreased in the cannabis-using group relative to controls, perhaps suggestive of disrupted cortico-cerebellar circuits. Furthermore, within the sample, decreased activation in the cerebellum and cingulate were associated with higher lifetime cannabis exposure. Overall, it is likely that relative to healthy controls, cannabis users demonstrate activation-related differences during tasks of motor control; future investigations should include clear measures of task performance in order to clarify any potential relationship between neural changes and performance patterns.

Error monitoring/awareness, reward processing, and affective processing

Error monitoring/awareness and a decreased ability to learn from errors (utilize feedback) has specifically been examined in cannabis users, as decrements in this domain are thought to be related to a combination of loss of insight and impaired cognitive control. Using various tasks, including paired associate learning[87] and go/no-go response inhibition tasks[88], researchers have examined cannabis users' ability to learn from errors. These studies report that cannabis users exhibit reduced learning from errors, and that this failure to utilize feedback is related to hypoactivity in regions related to cognitive control and error awareness, including the ACC[87, 88]. Some have also utilized monetary incentive delay tasks to examine reward processing in cannabis users. These tasks require individuals to respond to a target stimulus as quickly as possible to either win or avoid losing monetary rewards. Although frequent cannabis users perform similarly to controls across studies, functional differences have been observed. Two studies suggest that adolescent[89] and adult cannabis users[89, 90] demonstrate striatal hyperactivation, which may be indicative of an overly sensitive motivation circuitry; however, van Hell and colleagues reported attenuated activity in adult cannabis users within the caudate nucleus and nucleus accumbens, brain regions commonly associated with reward anticipation[91]. These inconsistent findings may be related to a number of factors, including age of participants (adolescents[89] versus adults[90, 91]) or length of abstinence (5 weeks[89] versus 1 week[91] versus 4 days[90]). In addition, van Hell and colleagues[91] posited that nicotine use may have impacted activity in the nucleus accumbens while cannabis use likely moderated activity in the caudate, but the effects of nicotine and cannabis use are currently difficult to disentangle in these studies.

In addition, several studies have assessed reward processing during the Iowa gambling task (IGT), a monetary decision-making task requiring participants to choose between small immediate gains with small long-term losses versus large immediate gains with larger long-term losses[92, 93]. Cousijn and colleagues[92] found that despite similar performance between heavy cannabis users and controls, the cannabis group demonstrated higher activation than controls during wins in the left superior temporal gyrus and right orbitofrontal cortex and insula, regions typically associated with decision making. Furthermore, magnitude of cannabis use (grams used) was positively correlated with neural activity related to win versus loss evaluation in the right insula as well as the caudate and ventrolateral prefrontal cortex. Wesley *et al.*[93] more closely examined task performance and activation during discrete stages of the task, and detected performance decrements in cannabis users relative to controls at the end of the IGT, despite no difference in task performance during the initial strategy development phase. Interestingly, although no functional differences were noted in response to losses, during the initial phase of the task (before performance differences emerged), cannabis users exhibited attenuated activity in response to losses in several regions, including the ACC, medial frontal cortex, precuneus, superior parietal lobe, occipital lobe and cerebellum. Furthermore, activation in response to losses was associated with task performance over time only within the control group. Results from this study therefore suggest that cannabis users are less sensitive to negative feedback while developing their initial strategy. De Bellis and colleagues[94] also measured risky decision making and reward response, but utilized a decision-reward uncertainty task, which contains three conditions: no risk (correct response rewarded 100% of the time), reward risk (correct response rewarded 50% of the time), and behavioral risk (correct response unknown and 50% chance of reward). No performance differences were noted between abstinent adolescents with cannabis use disorder (CUD) and controls; however, the CUD group demonstrated hyperactivation in brain regions related to decision making when making risky decisions, and attenuated OFC response to reward.

Altered responses to pleasant and negative stimuli have also been observed among cannabis users. Heitzeg and colleagues[95] detected differential activation patterns in adolescent cannabis users and non-users during an emotion-arousal word task in which participants were presented with positive, negative, and neutral words. In response to negative words, cannabis users demonstrated attenuated activity in regions linked to emotion processing and integration (insula, PFC, occipital cortex). Viewing positive words also resulted in hypoactivation, but in different regions, namely the right inferior parietal lobe, associated with attentional control. Moreover, cannabis users also demonstrated lower amygdala activation in response to both negative and positive words. The authors hypothesized that this altered emotional circuitry found in heavy cannabis-using adolescents may affect later emotional outcomes, as an association was also detected between greater frequency of cannabis use and higher negative emotionality. In fact, some studies have specifically examined affective processing, noting altered functional activation in cannabis users relative to non-users. In one fMRI study using masked affective faces presented below the level of conscious awareness, cannabis users exhibited attenuated activity within the ACC and amygdala compared to controls who demonstrated increased activity in these regions during the viewing of masked faces[96]. Recently, Zimmerman and colleagues[97] examined emotional

regulation in cannabis users when presented with neutral or negative pictures and had to either passively view the photos or try to regulate their emotions. During emotional regulation, cannabis users exhibited hyperactivity in a bilateral frontal network, which included the precentral gyrus, superior frontal gyrus, and midcingulate cortex, relative to healthy controls.

Overall, these findings suggest that chronic cannabis users appear to demonstrate altered reward circuitry and process affective information differently than those who do not use cannabis. Cannabis users appear to display a poorer ability to learn from errors and may be less sensitive to negative feedback, which is indicated by altered activation in reward circuitry. In addition, some evidence suggests that cannabis users demonstrate unique patterns of activation in response to affective stimuli and emotion regulation. Given that learning from mistakes, accurate and efficient appraisal of affective stimuli, and the ability to regulate one's emotions are all critical for successful social interactions, it is possible that these underlying neural changes could lead to negative consequences in recreational cannabis users.

Factors affecting the impact of cannabis use on the brain

Length of abstinence

Studies examining the chronic effects of cannabis have employed a wide range of abstinence thresholds, generally ranging from about 12 hours to 1 month. This variability in required abstinence across studies is likely to impact study findings, as heavy cannabis users may experience a range of withdrawal symptoms, each of which can occur during specific abstinence time periods. Withdrawal from cannabis has been characterized by mood-related symptoms including anxiety, aggression, anger, irritability, and restlessness, as well as physical symptoms such as sweating, decreased appetite, stomach pain, shakiness, and sleep problems (e.g., strange dreams, difficulty sleeping); symptoms can vary in their onset (1–6 days after cessation) and have been shown to peak in severity at different times over the course of the first 2 weeks of abstinence.[98] Variability in abstinence periods can impact findings within a single study, as subjects may choose to abstain for more than the minimum time required, and also makes cross-study comparisons complicated given the wide range of abstinence periods employed. While some studies choose to utilize specific periods of abstinence in an attempt to avoid withdrawal symptoms (e.g., less than 24 hours, more than 1 week),[67, 72] other studies may report and control for recency of use and/or cannabis withdrawal metrics (e.g., Refs. 66, 71, 73, and 87). It is of note, however, that this approach to controlling for abstinence periods is not standard and effects related to abstinence or withdrawal are often acknowledged as potential confounds or limitations in cannabis-related research studies.

In addition, few studies have investigated the effects of extended periods of abstinence in order to determine whether long-term abstinence results in recovery of function or normalization. Some preliminary evidence appears promising, as improvements have been observed longitudinally over the course of abstinence periods. For example, Hanson and colleagues[99], reported short-term memory improvements throughout three weeks of cannabis abstinence, and Fried and colleagues[27] found that cannabis users who abstained for

a minimum of three months demonstrated cognitive performance similar to that of healthy controls. These data suggest that altered cognitive performance observed in young cannabis users may begin to normalize after several weeks of abstinence; studies utilizing longer periods of abstinence combined with neuroimaging techniques are needed to more thoroughly examine the extent of recovery of function in cannabis users.

Chronological age and age of onset of cannabis use

Research efforts have largely focused on the effects of cannabis on adolescents, either by directly assessing adolescents or by examining individuals with onset of regular cannabis use during adolescence. Overall, although studies suggest that the neurobiological effects are similar in adult and adolescent cannabis users, those who use cannabis during adolescence are more likely to exhibit cognitive alterations, and deficits are more likely to persist in adolescent users and adults with adolescent onset[59]. This is perhaps not surprising, as the brain, once thought to be fully developed by puberty, actually undergoes critical neurodevelopment throughout adolescence and into at least the mid- to late-twenties[100], rendering youth more vulnerable to the negative neural effects associated with cannabis use. Accordingly, age of onset of cannabis use is a critical variable that must be included in cannabis-related research, as this factor may help to explain some of the inconsistency observed across investigations. In addition, some of our own research suggests that increased cannabis use (see below) may be a trait characteristic of early onset users, which could render these individuals even more vulnerable to the negative effects associated with cannabis use[61].

It is also important to recognize that much research to date has focused on adolescent users, given public health concerns regarding both expanded access to cannabis products and the increased vulnerability of the developing brain. Recently, however, with expanded legalization of medical and recreational cannabis, older adults are the fastest growing population of cannabis consumers in the United States[18]. Despite the increasing prevalence of cannabis use among older adults for medical purposes, the consequences of cannabis use are relatively unknown in this population, especially compared to literature focused on the impact of cannabis use among adolescent and emerging adult users. Although data indicates that recreational cannabis use during adolescence is related to cognitive decrements, recent data suggests improved cognitive function in older adults following three months of medical cannabis treatment[101], likely related to participants' age as well as a number of factors which differ between those using for medical versus recreational use (see below). Interestingly, a recent preclinical study reported a reversal of age-related cognitive decline in mature and old mice treated with low doses of THC[102]; these improvements may be the result of an upregulation of the aging endocannabinoid system via increased signaling secondary to low-dose THC exposure. Interestingly, the same cannabis exposure resulted in cognitive decrements in young mice. Despite these findings, virtually no studies have systematically assessed the specific impact of cannabis use among older adults. Accordingly, it is critical for future studies to assess the impact of cannabis in this growing population of cannabis consumers.

Frequency and magnitude of cannabis use

It is important to note that most investigations have examined the impact of heavy, chronic cannabis use, and although some have begun to examine the impact of light or more casual cannabis use, what is known about the effects of cannabis on the brain is typically reflective of more chronic users. Moreover, among studies of heavy users, there is no consensus in terms of the definition of "chronic," "regular," or "heavy" use. Criteria are often based on current days of use per week (regardless of amount of cannabis consumed), or estimated lifetime smoking or use episodes (see Table 2). Furthermore, unlike alcohol, there is no standardized measure of cannabis. Within the literature, the magnitude or amount of cannabis consumed is often measured in joints, smokes, or puffs taken, although some groups attempt to quantify the actual amount (grams, milligrams, etc.) of cannabis used. While these metrics related to cannabis use are informative, it is imperative to consider other factors that influence overall exposure, including routes of administration as well as cannabis potency (% THC) of products used. For example, in a study of individuals who vaporize cannabis, one of the main advantages cited was that subjects can achieve more effect from the same amount of cannabis relative to smoking[103]. Assessing exposure to cannabis is further complicated by rising levels of cannabis potency, which have increased exponentially over the last two decades. In fact, from 1995–2012 cannabis potency (% THC) rose from 4% to 12%[104]. Moreover, cannabis concentrates, also known as dabs, butane hash oil (BHO), shatter, wax, or budder, are novel products that contain significantly higher levels of THC that often reach or exceed 80%[105]. Although concentrates are growing in popularity, little formal research has been conducted regarding the impact of these products on the brain. However, use of these highly concentrated products is potentially concerning given that THC has been associated with adverse physiological and psychological effects[106]. Furthermore, although no studies have utilized fMRI techniques among concentrate users, one study assessed the impact of cannabis potency (determined via self report) on brain structure and noted alterations in corpus callosum white matter microstructure in high-potency compared to low-potency users and controls[107]. While more research is clearly indicated in this area, these findings suggest that the use of high potency cannabis products/concentrates may negatively affect the brain.

Medical versus recreational cannabis use

With at least some form of medical cannabis products legal in all but three states, many have begun to question whether results from studies of recreational cannabis users are applicable to medical cannabis patients. Research focused on the impact of cannabis for medical purposes, specifically with regard to potential cognitive alterations, is currently in its infancy. Interestingly, the only study to directly assess cognition in medical cannabis patients before and after initiating treatment reported improvements in cognitive function, specifically on measures of executive function, following three months of medical cannabis treatment[101]. These cognitive changes may have been due to a variety of reasons. First, medical cannabis patients tend to be adults who are beyond the critical stages of neurodevelopment, which may afford some protection from the neurocognitive decrements typically associated with cannabis use. In addition, medical cannabis patients and recreational cannabis users tend to differ in terms of the products they use and their constituent profiles. While recreational cannabis products are generally sought out for high

THC levels with the ultimate goal being to get high, medical cannabis patients seek symptom alleviation and often choose products with rich and varied cannabinoid profiles, including constituents other than THC. Although THC and CBD are generally the most abundant cannabinoids, many other cannabinoids, including cannabigerol, cannabinol, cannabichromene, and tetrahydrocannabivarin, are present in cannabis, and are often present in higher amounts in medical cannabis products. Each of these constituents is posited to have unique properties that may be beneficial. For example, cannabichromene is thought to have anti-inflammatory effects[6] and has been shown to increase the viability of adult neural stem progenitor cells (NSPCs), which are essential for brain plasticity and is suggestive of neurogenesis[108]. Cannabigerol has been shown to inhibit GABA uptake, has anti-inflammatory properties, and has also been hypothesized to be neurogenic[109, 110]. Research is clearly indicated for assessing the specific impact of these cannabinoids on the brain. Furthermore, while it is likely that each cannabinoid has a unique effect, it is also important to note that many have theorized an “entourage effect,” which refers to the synergistic action that occurs in the presence of multiple cannabinoids and terpenes, the essential oils contributing flavor and fragrance components to cannabis that share a common precursor with phytocannabinoids[111]. The combination of these constituents is thought to create a unique synergism, which supports anecdotal reports that whole plant-derived products may be more effective therapeutic agents than isolated or synthetic cannabinoids[111]. Functional MRI studies are needed to elucidate the effects of these constituents on the brain, especially as the number of recreational and medical consumers continues to grow. One recently published study is, to our knowledge, the first to utilize fMRI techniques to examine the impact of medical cannabis treatment on cognition and brain function using a pre/post model[112]. Results revealed that after three months of medical cannabis treatment, patients not only exhibited better task performance relative to baseline, but also exhibited apparent normalization of brain activation during completion of the MSIT, a robust measure of cognitive control. Additional research is needed to better understand the underlying mechanisms of this change, which could include the effects of various cannabinoid constituents, symptom relief, and/or the decreased use of conventional medications (e.g., opioids, benzodiazepines, antidepressants, and mood stabilizers), all of which can impact functional activation patterns.

Methodological approaches

In addition to numerous variables assessing cannabis use, different methodological approaches can limit the ability to draw conclusions across studies. First, fMRI studies are often limited by sample size, with most of the investigations reviewed enrolling approximately 12–20 cannabis users and a similarly sized group of healthy controls. While these samples appear to be large enough to detect between-group differences in brain activation patterns, they may not always be powered enough to detect subtle differences in cognitive performance that could be obscured by interindividual variability. This may explain, at least in part, why many studies report changes in functional activation patterns without detecting performance differences between groups. Additionally, across studies, fMRI investigations vary in analytic approaches and employ a range of statistical thresholds. As noted in Table 1, significance values typically range from $P < 0.05$ to $P < 0.001$, and may or may not be corrected for multiple comparisons. Furthermore, the minimum cluster extent

is often derived using a variety of methods and can vary widely across studies. Some investigations choose to utilize whole-brain analyses, while others use a region of interest (ROI) approach based on either *a priori* hypotheses or differences detected after first examining whole brain results, resulting in a combination whole brain/ROI analytic model.

It is also important to note that studies vary widely with regard to inclusion and exclusion criteria for other substance use. Although this review aimed to include only studies specifically focused on cannabis, several studies described did allow the regular use of nicotine, and study entry criteria for alcohol and other drug use varied across studies, as noted in Table 2. While investigators often include information regarding substance use-related inclusion/exclusion criteria, together these methodological factors pose limitations when attempting to summarize the overall effects of cannabis on brain function across studies. Despite this fact, most studies suggest that chronic, heavy cannabis users demonstrate altered patterns of brain activation relative to those who do not use cannabis.

Conclusions

A large body of evidence suggests that chronic, heavy cannabis use is associated with cognitive decrements across a range of domains. Through advanced neuroimaging techniques, fMRI studies have begun to elucidate the underlying neural mechanisms associated with the cognitive consequences commonly observed in cannabis users. In addition, fMRI studies have also revealed that functional alterations are often present even in the absence of notable performance deficits, suggesting that cannabis users may compensate for poorer performance through less efficient neural processing, including recruitment of additional brain regions or activation of regions not typically associated with a cognitive domain or task. Although findings may appear somewhat inconsistent across studies, they illustrate the range of tasks used to probe underlying neural processes both within and across cognitive domains. Moreover, cannabis products and cannabis use are also inherently variable. Given the difficulty in standardizing cannabis use patterns, studies are often impacted by differences in participants' exposure to cannabis or even specific cannabinoids, especially in the realm of medical use. Although it is clear that chronic recreational use impacts brain function, albeit subtly, future research exploring moderating factors, including age of onset, recovery of function after abstinence, frequency and magnitude of cannabis use, high- versus low-potency products, mode of use, and the unique effects of specific cannabinoids, are all needed to fully understand the impact of cannabis across the lifespan. Research efforts focused on the impact of cannabis have never been more important. As legalization efforts expand, overall rates of use continue to rise, and questions regarding cannabis and public policy measures remain at the forefront.

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Table 1.

Summary of sample size, study design, imaging thresholds and analytic approaches across studies

Acute administration studies	***n***	**fMRI Task**	**Performance differences**	**Between/within group?**	**Thresholds for imaging (as noted within each paper)**	**Analytic approach**
Battistella *et al*. (2013)[40]	31 (occasional CAN users)	Visuomotor pursuit tracking test	*Poorer performance* post-CAN smoking ↓	Within	$P < 0.005$, FWE-corrected, k > 40	Whole brain
Bhattacharyya *et al*. (2009)[54]	15 HC	Verbal paired associate learning task	*No performance changes* under any condition	Within (10mg THC, 600mg CBD, and placebo)	Voxelwise threshold of $P < 0.05$ and clusterwise threshold set such that the total number of false-positive clusters per brain volume was <1 per map; the P value at which this occurred is noted	Whole brain
Bhattacharyya *et al*. (2010)[55]; Borgwardt *et al*., (2008)[50]	15 HC	Verbal memory task, go/no-go, viewing a radial checkerboard, viewing fearful faces, listening to words	*No performance changes* during go/no-go, verbal memory, or for gender discrimination during viewing of fearful faces	Within (10mg THC, 600mg CBD, and placebo)	Group activation maps were compared using ANCOVAs; voxelwise threshold of $P < 0.05$; clusterwise threshold set so total false-positive clusters per brain volume were <1 per map	Whole brain
Bossong, Jager *et al*. (2012)[38]	14 CAN	Pictorial memory task	*No performance changes*	Within	$t = 4.5$, $P < 0.05$, corrected for multiple comparisons, k ≥ 10	ROI
Bossong, Jansma *et al*. (2012)[39]	17 CAN	Sternberg item-recognition paradigm	*Poorer performance* post-THC administration ↓	Within	$t = 4.5$, $P < 0.05$, corrected for multiple comparisons	ROI
Fusar-Poli *et al*. (2009)[57]	15 HC	Viewing of affective faces	*No performance changes* for gender discrimination of faces	Within (10mg THC, 600 mg CBD, placebo)	Whole-brain voxel-wise threshold was set at $P = 0.001$, uncorrected, k > 20. Regional activation was reported at a cluster threshold of $P < 0.05$, corrected.	Whole brain and ROI
Winton-Brown *et al*. (2011)[56]	14 HC	Viewing a radial checkerboard, listening to words	N/A	Within (10 mg THC, 600mg CBD, placebo)	Voxelwise threshold of $P < 0.05$; clusterwise threshold was set such that the total number of false-positive clusters per brain volume was <1 (maximum $P < 0.01$)	Whole brain
Chronic/residual use studies	***n***	**fMRI Task**	**Performance differences**	**Between/within group?**	**Thresholds for imaging (as noted within each paper)**	**Analytic approach**
Abdullaev *et al*. (2010)[70]	14 CAN, 14 HC	Attention network task (ANT), use generation task	*Poorer performance* in CAN users (ANT) ↓	Between-group	Cluster-level statistical threshold of $Z > 2.3$; $P < 0.05$, corrected for multiple comparisons	Whole brain
Ames *et al*. (2013)[81]	13 CAN, 25 HC	A cannabis implicit association test	N/A	Within-group and 2 × 2 (group × IAT blocks of trials) full-factor random effects model	Within-group: voxels were considered significant at $P < 0.005$ (uncorrected) with k > 30 (this cluster extent was considered equivalent to $P < 0.05$ corrected, based on Monte Carlo simulations). Between-group: the significance threshold was set at an exploratory, uncorrected $P < 0.005$, k > 30	Whole brain
Becker *et al*. (2010)[78]	42 CAN (low frequency versus high frequency)	Verbal n-back	*No performance differences*	Between-group (duration, frequency, onset)	$P < 0.05$, corrected for multiple comparisons (FWE). Minimum cluster size was set to 20 voxels.	Whole brain and ROI

Behan *et al.* (2014)[69]	17 CAN; 18 HC	Go/no-go	*Poorer performance* in CAN users ↓	Between-group	Whole brain: significant voxels passed a voxelwise statistical threshold ($t = 3.01$, $P < 0.005$) and >277-μl cluster of contiguous voxels; cluster-level threshold of $P < 0.05$, corrected. ROI: significant voxels passed a voxelwise statistical threshold ($t = 34.64048$, $P < 0.00005$) and >65-μl cluster of contiguous voxels; cluster-level threshold of $P < 0.01$, corrected.	Whole brain and ROI
Carey *et al.* (2015)[87]	15 CAN, 15 HC	Paired associate learning task	*Poorer performance* in CAN users ↓	Between-group	Voxelwise statistical threshold: $t = 4.31$, $P \leq 0.001$, >142-μl cluster of contiguous voxels	Whole brain and ROI
Chang *et al.* (2006)[71]	12 abstinent and 12 active CAN users, 19 HC	visual attention tasks	*No performance differences*	Between-group	At the cluster level, $P < 0.001$, $t \geq 3.21$, corrected; for group comparisons, only clusters >25 voxels and $P < 0.05$ (corrected for multiple comparisons) were considered significant	Whole brain and ROI
Cousijn *et al.* (2013)[92]	32 CAN, 41 HC	Iowa gambling task	*No performance differences*	Between-group	Activity was considered significant if $Z > 2.3$, with a whole-brain cluster correction at $P < 0.05$	Whole brain
Cousijn *et al.* (2014)[79]	22 current CAN, 4 abstinent CAN, 23 HC	n-back	*No performance differences*	Between-groups over time	$P < 0.05$ corrected for multiple comparisons	Whole brain and ROI
De Bellis *et al.* (2013)[94]	15 CUD remission, 23 psych. patients without SUD, 18 HC	Decision-reward uncertainty task	*No performance differences*	Between-group	Whole-brain voxelwise analyses were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$	Whole brain and ROI
Gruber and Yurgelun-Todd (2005)[60]	9 HC, 9 CAN	Stroop color word test	*Poorer performance* in CAN users ↓	Between-group	$P < 0.001$, uncorrected, $k \geq 10$ contiguous voxels	ROI
Gruber *et al.* (2009)[96]	15 HC, 15 CAN	Masked affect task	N/A	Between-group	$P < 0.005$ uncorrected, $k \geq 10$	ROI
Gruber *et al.* (2012)[66]	23 CAN; 16 HC	Multi-source interference task (MSIT)	*No performance differences*	Between-group	Voxel-wise comparisons were evaluated at $P < 0.005$ (uncorrected), $k \geq 15$ contiguous voxels, and only clusters that exceeded a false discovery rate (FDR) correction of $P < 0.05$ were included	ROI
Harding *et al.* (2012)[67]	21 CAN; 21 HC	Multi-source interference task (MSIT)	*No performance differences*	Between-group	Whole brain: $p < 0.04$, uncorrected ROI: $P < 0.001$, $k \geq 10$	Whole brain and ROI
Hatchard *et al.* (2014)[63]	10 CAN; 14 HC	Counting Stroop	*No performance differences*	Between-group	Multiple independent samples *t*-tests were conducted at a set threshold of $P = 0.001$ (uncorrected), with a cluster-wise correction at $P = 0.05$ (FWE-corrected)	Whole brain
Heitzeg *et al.* (2015)[95]	20 CAN; 20 HC	Emotion-arousal word task	*No performance differences (post-scan recognition task)*	Between-group	$P < 0.005$, uncorrected, $k \geq 77$	Whole brain and ROI
Hester *et al.* (2009)[88]	16 CAN, 16 HC	Go/no-go	*Poorer performance* in CAN users ↓	Between-group	Voxelwise statistical threshold: $t = 4.31$, $P \leq .001$, >142-μl cluster of contiguous voxels	Whole brain and ROI
Jager *et al.* (2006)[72]	10 CAN, 10 HC	Modified Sternberg item recognition task; visuoauditory selective attention task	*No performance differences*	Between-group	$Z = 4.5$ ($P < 0.05$, corrected), cluster size >10 voxels.	Whole brain and ROI

Jager *et al.* (2007)[82]	20 CAN, 20 HC	Associative (pictorial) memory task	*No performance differences*	Between-group	$P < 0.05$ corrected; $k \geq 10$ voxels; contrasts: $Z = 3.0$ or 5.0 (depending on contrast), $P < 0.05$, corrected)	Whole brain and ROI
Jager *et al.* (2013)[89]	21 CAN, 24 HC	Monetary incentive delay task	*No performance differences*	Between-group	$P < 0.05$, FWE corrected	Whole brain and ROI
Kanayama *et al.* (2004)[73]	12 CAN, 10 HC	Spatial working memory paradigm (perception task and short-delay response task)	*No performance differences*	Between-group	$P < 0.001$ (uncorrected), $k > 10$ contiguous voxels	Modified whole brain
King *et al.* (2011)[84]	30 CAN; 30 HC	Visually paced finger-sequencing task	N/A	Between-group	$P < 0.05$, uncorrected for single-subject analysis 2-way mixed-effect ANOVA for cannabis status and gender on BOLD signals: $Z > 2.3$ and cluster $P < 0.05$ (corrected)	ROI
Kober *et al.* (2014)[62]	20 CAN, 20 HC	Modified Stroop color-word task	*Poorer performance* in CAN users ↓	Between group	Results were FWE-corrected at $P < 0.05$	Whole brain
Lopez-Larson *et al.* (2012)[86]	24 CAN, 24 HC	Bilateral finger-tapping task	N/A	Between-group	$P < 0.05$, corrected, $k > 20$ voxels	ROI
Nestor *et al.* (2008)[83] Experiment 2	14 CAN, 14 HC	Face–number associative learning paradigm	*No performance differences*	Between-group	Voxelwise threshold of $t = 3.4$, $P < 0.005$ and >278-μl cluster of contiguous voxels (whole brain) or 114-μl cluster (hippocampal ROI)	Whole brain and ROI
Nestor *et al.* (2010)[90]	14 CAN, 14 HC	Monetary incentive delay task	*No performance differences*	Between-group	Voxelwise threshold ($t = 3.4$, $P \leq 0.005$) and cluster size of 276 μl; clusterwise threshold of $P \leq 0.05$ (corrected).	Whole brain and ROI
Padula *et al.* (2007)[75]	17 CAN, 17 HC	Spatial working memory task	*No performance differences*	Between-group	Clusters >50 contiguous voxels ($P < 0.05$; 1358 μl in volume) were considered significant, overall clusterwise $\alpha = 0.05$	Whole-brain
Pillay (2004)[85]	9 CAN, 16 HC	Sequential paced finger sequencing task	N/A	Between-group	$t = 2.0$ ($P < 0.03$), k ≥ 10 voxels	Whole brain and ROI
Sagar *et al.* (2015)[61]	50 CAN; 34 HC	Stroop color word test	*Poorer performance* in CAN users ↓	Between-group	$P < 0.0001$ uncorrected, k > 10	ROI
Schweinsburg *et al.* (2008)[76]	15 CAN, 17 HC	Spatial working memory task	*No performance differences*	Between-group	Significant group difference clusters consisted of contiguous significant voxels (p > 0.05) that exceeded 1328 μl	Whole brain
Schweinsburg *et al.* (2010)[77]	13 recent CAN, 13 abstinent CAN, 19 HC	2-back spatial working memory task	*No performance differences*	Between-group	49 contiguous voxels ($P < 0.05$) that exceeded 1328 μl in volume, yielding an overall cluster-wise $\alpha = 0.05$ for the whole brain	Whole brain
Smith *et al.* (2010)[74]	10 CAN, 14 HC	Visuospatial 2-back task	*No performance differences*	Between-group	Cluster level threshold $P < 0.05$	Whole brain
Sneider *et al.* (2013)[80]	10 CAN, 10 HC	Virtual water maze task	*No performance differences*	Between-group	p < 0.005, uncorrected, k ≥ 20	ROI
Tapert *et al.* (2007)[68]	16 CAN, 17 HC	Go/no-go	*No performance differences*	Between-group	Independent samples *t* tests in each voxel of the brain; k ≥ 22 at $\alpha = 0.05$ (≥943 μl)	Whole brain

Van Hell *et al.* (2010)[91]	14 CAN, 14 nicotine, 13 HC	Monetary reward task	*No performance differences*	Between-group	Group results were tested for significance ($P < 0.05$, corrected for multiple comparisons), resulting in a critical t-value of 4.5 for every voxel	Whole brain
Wesley *et al.* (2011)[93]	16 CAN, 16 HC	Modified Iowa gamling task	*Poorer performance* in CAN users ↓	Between-group	Between-group comparisons: a voxelwise P value of 0.01 was used with further adjustments at the cluster level ($P < 0.001$, corrected)	Whole brain
Zimmermann *et al.* (2017)[97]	23 CAN, 20 HC (18 HC for fMRI)	Modified cognitive reappraisal paradigm	*Poorer performance* in CAN users ↓	Between-group	The cluster-forming threshold was $t = 3.0902$, and significance was determined using cluster-level inference *at* $P < 0.05$, FWE-corrected	Whole brain and ROI

Note: CAN = cannabis users; HC = healthy controls; CUD = cannabis use disorder; SUD = substance use disorder; THC = Δ^9-tetrahydrocannabinol; CBD = cannabidiol; k = cluster extent; FWE = familywise error; BOLD = blood oxygenation level–dependent

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Table 2.

Cannabis and other substance use information

Acute administration studies	**Cannabis, nicotine, alcohol, and other drug use/criteria**	**Length of time since last cannabis use**
Battistella *et al.* (2013)[40]	**Cannabis**: Occasional cannabis smokers (1 joint/month to <1 per week) **Alcohol**: 1–10 drinks/week (mean = 5) **Nicotine**: Not exclusionary, participants estimated amount of tobacco in self-made joints using diagram (mean % of cannabis in mixture was 48%) **Other drugs**: Exclusionary	>12 h
Bhattacharyya *et al.* (2009)[54], (2010)[55]	**Cannabis**: 15 or fewer lifetime uses and no use in the past month **Alcohol**: No alcohol abuse or dependence history for subject or subject's family, no alcohol within 24 h of study **Nicotine**: 7 of 15 subjects current tobacco smokers (2.92 mean cig./day), participants requested to avoid smoking on morning of study **Other drugs**: <3 occasions of exposure to other illicit drugs	N/A
Bossong, Jager *et al.* (2012)[38]; Bossong, Jansma *et al.*, (2012)[39]	**Cannabis**: Incidental cannabis smokers (4–7 days/week in the past year) **Alcohol**: Average use of 16.7 units/week (range: 2–30) **Nicotine**: 5 cigarettes/day max (2.7 average) **Other drugs**: Lifetime use 5× (and not in past 6 months)	2 weeks
Borgwardt *et al.* (2008)[50]	**Cannabis**: 15 or fewer lifetime uses and no use in the past month **Alcohol**: < 21 units of alcohol/week **Nicotine**: Not reported **Other drugs**: No illicit, psychotropic drug use	N/A
Fusar-Poli *et al.* (2009)[57]	**Cannabis**: Used cannabis <15 times **Alcohol**: No alcohol within 24 h of study session **Nicotine**: Not reported **Other drugs**: Drug abuse exclusionary as evaluated by addiction severity index (ASI); no recreational or medical drugs for duration of study, exclusionary urine drug screen analyses	N/A
Winton-Brown *et al.* (2011)[56]	**Cannabis**: Used cannabis 1–15 times in their lives, but not use in past month **Alcohol**: No alcohol within 24 h of study session **Nicotine**: Not reported **Other drugs**: Minimal previous exposure to illicit substances	>1 month
Chronic/residual use studies	**Cannabis, nicotine, alcohol, and other drug use/criteria**	**Length of time since last use**
Abdullaev *et al.* (2010)[70]	**Cannabis**: Heavy cannabis users **Alcohol**: No significant alcohol use **Nicotine**: Not reported **Other drugs**: No significant drug use	>48 h
Ames *et al.* (2013)[81]	**Cannabis**: Heavy users who reported using cannabis >500 times in the past 3 years and current, daily use **Alcohol** Users and non-using controls were matched on past 3-year alcohol use (light alcohol or non-drinkers) **Nicotine**: Users and non-using controls were matched for tobacco use **Other drugs**: Minimal lifetime use of drugs other than cannabis (no significant differences in methamphetamine, tranquilizer, opiate or hallucinogen use, but slightly more cocaine use in cannabis group)	Assessed via a 12-item rating scale, ranging from "1= never used" to "12=within the last 24 h"; average rating was 11.46 ± 0.52

Becker *et al.* (2010)[78]	**Cannabis**: While most participants were current cannabis users, 8 (19.0%) reported no cannabis use in the month before the study. Average cannabis use: 14.2 days per month, 2.4 joints/day, 51.3-month duration, and 612.2 grams of cannabis in their lifetimes. **Alcohol**: Excluded participants with a history of alcohol abuse **Nicotine**: Authors acknowledge limitation that acute nicotine use may have been related to differences in parahippocampal blood oxygenation level–dependent response **Other drugs**: Excluded for >5 uses of any illicit substance aside from cannabis	Average self-reported time since last use was 86.52 days.
Behan *et al.* (2014)[69]	**Cannabis**: Tested positive for cannabis (average amount of use in past week = 42.9 joints) **Alcohol**: Groups matched for occasions of use in last week and month (cannabis-using group 1.4× in last week, 4.8× in last month; HC 1× in last week, 2.5× in last month) **Nicotine**: The cannabis-using group contained more smokers and these had smoked more cigarettes in the week and month prior to participation **Other drugs**: Cannabis-using group exhibited significantly greater use of nicotine and illicit drugs in general; all cannabis-using participants provided urine samples that tested positive for cannabinoid metabolites but not for any other drugs	The night before the scan
Carey *et al.* (2015)[87]	**Cannabis**: Regularly consumed cannabis (5–7 days/week) for the previous two years and to have smoked a minimum of 500 joints in their lifetime **Alcohol**: Excluded current or past alcohol dependence **Nicotine**: Nicotine smokers = 40% of HC, 47% of cannabis users; no reported current or past dependence on tobacco **Other drugs**: Excluded for positive drug test (except for cannabis in cannabis group); no reported concurrent or past dependence on other drugs	>12 h
Chang *et al.* (2006)[71]	**Cannabis**: Cannabis use at least 5 days per week for at least 2 years **Alcohol**: In the cannabis and control groups, most subjects used alcohol recreationally, but did not meet criteria for alcohol dependence **Nicotine**: 3/19 controls, 5/12 abstinent cannabis users and 5/12 active cannabis subjects smoked nicotine cigarettes daily; all were asked to abstain from nicotine use for at least 2 h before the fMRI **Other drugs**: Negative urine toxicology screen for other drugs (also other drugs used recreationally reported as <10 times in life)	4–24 h before scan
Cousijn *et al.* (2013)[92]	**Cannabis**: Heavy cannabis users who used cannabis >10 days/ month for at least 2 years (not seeking treatment or having a treatment history for cannabis use) **Alcohol**: Excluded participants with an AUDIT score >10 **Nicotine**: Excluded participants who smoked >20 cigarettes daily **Other drugs**: Excluded participants with a positive urine screen for other drugs	>24 h
Cousijn *et al.* (2014)[79]	**Cannabis**: Heavy cannabis users who used cannabis >10 days/ month for at least 1.5 at baseline **Alcohol**: Excluded participants with an AUDIT score >10 or positive urine screen for alcohol **Nicotine**: Excluded participants who smoked >20 cigarettes daily **Other drugs**: Excluded participants with more 100 lifetime uses of other drugs; positive urine screen for amphetamines, benzodiazepines, opioids, or cocaine	>24 h
De Bellis *et al.* (2013)[94]	**Cannabis**: Among the 15 adolescents receiving outpatient treatment for cannabis use disorder (full remission), 6 individuals met criteria for past cannabis abuse and 9 met criteria for past cannabis dependence **Alcohol and Nicotine**: 6 participants in the cannabis use disorder group met DSM-IV criteria for past history of alcohol abuse (without regular drinking) or for nicotine dependence (n = 2 alcohol and nicotine, n = 2 alcohol abuse, n = 2 nicotine dependence) **Other drugs**: Full remission of any substance use disorder prior to study enrollment.	Abstinent adolescents with cannabis use disorder
Gruber and Yurgelun-Todd (2005)[60]	**Cannabis**: Heavy cannabis users (smoked cannabis at least 4000 times in their lives, tested positive for urinary cannabinoids) **Alcohol**: Excluded for DSM-IV alcohol abuse/dependence **Nicotine**: Not reported **Other drugs**: Maximum of 10 lifetime episodes of illicit drug use in any category (including sedative-hypnotics, stimulants, cocaine, opioids, hallucinogens, and MDMA); excluded for any substance use disorders based on DSM-IV criteria (other than cannabis dependence for the cannabis smokers)	> 12 h
Gruber *et al.* (2009)[96]	**Cannabis**: >3000 joints in their lifetime, and smoked at least 4 of the last 7 days **Alcohol**: Did not meet criteria for current or previous alcohol abuse or dependence. Cannabis smokers reported more days of alcohol use per month (9.6 days) than control subjects (4.0 days), but no significant differences between groups for number of days intoxicated in the past month; **Nicotine**: Subjects did not meet criteria for tobacco abuse or dependence **Other drugs**: Excluded if >5 lifetime uses or tested positive for any category of illicit drugs	Night before (~ 12 h or more)

Gruber *et al.* (2012)[66]	**Cannabis**: Chronic, heavy cannabis users (minimum of 2500 times in their lives, used cannabis at least five out of the last seven days, tested positive for urinary cannabinoids, and met DSM-IV criteria for cannabis abuse or dependence; not regular cigarette smokers overall) **Alcohol**: Routinely <15 drinks per week; excluded for current or previous alcohol dependence based on SCID-P **Nicotine**: Not reported **Other drugs**: <15 lifetime uses of any category of illicit drug; Current or previous drug dependence based on SCID-P (with exception of cannabis for smokers)	> 12 h
Harding *et al.* (2012)[67]	**Cannabis**: Daily/near daily cannabis use **Alcohol**: Cannabis group consumed less alcohol than the HC group **Nicotine**: 5 on average in cannabis group, 0 in control group **Other drugs**: No regular consumption (>1×/month for any period of time) of any substance other than cannabis within the past 2 years; median lifetime episodes for amphetamines, benzodiazepines, cocaine, ecstasy, hallucinogens, inhalants, or opiates ranged from 0–6.5 uses	> 12 h
Hatchard 2014 (33)[63]	**Cannabis**: Heavy adolescent onset cannabis use (>1 joint/week for 3 years; average of 11.48 joints/week) **Alcohol**: Excluded individuals with substance abuse disorders as determined by DSM-IV criteria, **Nicotine**: 7/10 cannabis users reported regular use of nicotine (but controlled for in analyses) **Other drugs**: No regular illicit drug use, or within a month of fMRI testing (including amphetamines, crack, cocaine, heroin, mushrooms, hashish, lysergic acid, steroids, solvents, and tranquilizers); no substance abuse disorders as determined by DSM-IV criteria; no reported substance abuse disorders in parents	>2 h
Heitzeg *et al.* (2015)[95]	**Cannabis**: >100 lifetime occasions **Alcohol**: As all cannabis users reported >100 lifetime drinks, only healthy controls with >100 drinks were included in order to ensure subjects were matched **Nicotine:** Cannabis and healthy control groups were matched based on nicotine use **Other drugs**: All participants were required to abstain from other drug use for >48 h, excluded for positive drug screen (other than cannabis)	>48 h
Hester *et al.* (2009)[88]	**Cannabis**: Regularly consumed cannabis (5–7 days/week) for the previous 2 years and smoked a minimum of 500 joints in their lifetime **Alcohol**: Excluded if concurrent or past dependence on alcohol; no group differences **Nicotine:** Excluded if concurrent or past dependence on nicotine; no group differences **Other drugs**: Excluded if concurrent or past dependence on other drugs; no group differences	Average 38 h (+/− 47.7)
Jager *et al.* (2006)[72]	**Cannabis**: Median current use = 7 (range 2–17) joints per week; median past year use = 350 joints (range 75–900); median lifetime cannabis use = 1300 joints (range 675–5400) **Alcohol**: Cannabis users reported greater (but not statistically significant) alcohol consumption than the control subjects (median drinks per week: 17 versus 7); no alcohol within 1 week of testing **Nicotine**: Consumption of tobacco was significantly higher in cannabis users than in controls (8 versus 0 cigarettes per week) **Other drugs**: Limited other drug use, excluded for intravenous drug use and/or positive urine drug screen on day of testing	1 week prior to testing and negative urine screen
Jager *et al.* (2007)[82]	**Cannabis**: >500 lifetime joints (median lifetime use: 1900 joints; median past year use: 332.5 joints) **Alcohol**: Included as covariates in all analyses **Nicotine**: Included as covariates in all analyses **Other drugs**: <5 occasions of other substance use	>7 days
Jager *et al.* (2013)[89]	**Cannabis**: Abstinent, but frequent cannabis use; average lifetime joints in cannabis group = 4006 (range: 224–32,850), and control group = 1.8 (4.0, 0–15) **Alcohol**: 13.3 drinks/week in cannabis group versus 3.4 drinks/week in HC **Nicotine**: 63.8 cigarettes/week in the cannabis group versus 6.1 cigarettes/week in the control group; smoking cigarettes was allowed until 2 h before the scanning session (to avoid nicotine withdrawal). **Other drugs**: Regular use of illegal drugs other than cannabis (>10 episodes lifetime)	>1 week required; average abstinence was 5.1 weeks (range 1–16 weeks).
Kanayama *et al.* (2004)[73]	**Cannabis**: Smoked cannabis at least 5000 times and at least 7 times per week at the time of study entry **Alcohol**: No history of abuse or dependence **Nicotine**: Not indicated **Other drugs**: No history of abuse or dependence	6–36 h

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King *et al.* (2011)[84]	**Cannabis**: Using cannabis 6–7 days/week for at least one year, and tested positive for urinary cannabinoids on each day of testing (only 4 of 29 assessed subjects met DSM-IV criteria for cannabis dependence) **Alcohol**: Alcohol consumption (lifetime grams), duration and frequency of use, and amount per use showed no difference between groups **Nicotine**: No difference between groups in pack years of nicotine use. **Other drugs**: Negative urine toxicology screen for cocaine, amphetamine, methamphetamine, THC (except for cannabis users), opiates, and benzodiazepines	The night before (approximately 12 h*)*
Kober *et al.* (2014)[62]	**Cannabis**: Cannabis dependent (used cannabis in the previous 28 days; baseline days of cannabis use in in past 28 days = 17.55) **Alcohol**: Healthy controls excluded DSM alcohol abuse or dependence; exclusion criteria for cannabis group not reported **Nicotine**: 55% daily cigarette smokers **Other drugs**: Healthy controls excluded for DSM substance abuse or dependence (except nicotine); no mention of exclusion for cannabis group	Not reported
Lopez-Larson *et al.* (2012)[86]	**Cannabis**: Heavy cannabis use with >100 smokes in the previous year (average frequency of use: 10.3 times/week; average total lifetime use: 1500.6) **Alcohol**: Excluded for any alcohol dependence (during 2 months prior to scan or total past history of dependence ≥12 months); 4 cannabis participants met criteria for current alcohol abuse, and 2 cannabis participants for past alcohol dependence (over 1.5 years prior) **Nicotine**: 4 cannabis users reported current nicotine use (average duration: 1.31 ± 3.07 months) and 4 endorsed having a history of nicotine use (average duration: 1.47 ± 4.69 months). **Other drugs**: Use of any illicit substance <15 times	20/24 cannabis participants used cannabis <24 h prior to study; 3/24 reported using cannabis within 24–48 h of study; 1/24 reported using cannabis >48h prior to study
Nestor *et al.* (2008)[83] (Experiment 2)	**Cannabis**: Consumed cannabis 5–7 days/week for the past 2 years and >500 joints in their lifetime. **Alcohol**: No differences between control group and cannabis group; no participants reported concurrent or past alcohol misuse **Nicotine**: Not nicotine users **Other drugs**: 0 days of use in the past month for: nicotine, amphetamine, cocaine, MDMA, and hallucinogens; no participants reported concurrent or past misuse of any other substances	Average abstinence = 80.8 h
Nestor *et al.* (2010)[90]	**Cannabis**: Regularly consumed cannabis (5–7 days/week) for the previous 2 years and >500 lifetime joints. On average, 6.1 years (range = 2.5–17) of lifetime cannabis use, consumption of 7258 lifetime joints (range = 700–34,403), 20 days of use in the last 30 days (range = 6–30), and 64 joints in the last 30 days (range = 15–140) **Alcohol**: No past or concurrent abuse of alcohol; no significant difference in past month of alcohol use between groups, but significantly higher years of alcohol use in cannabis group (6.9 versus 5.2) **Nicotine**: No nicotine use **Other drugs**: No past or concurrent dependence of any substances (other than cannabis for the cannabis group)	Average abstinence period = 108 h (range=12–504).
Padula *et al.* (2007)[75]	**Cannabis**: Average of 477 episodes of lifetime cannabis use **Alcohol**: Cannabis users reported higher rates of alcohol than controls **Nicotine**: Both groups had low rates of tobacco use **Other drugs**: Although cannabis users reported more use of other drugs than controls, lifetime use of other drugs was <27 times across all substance types	After 28 days of monitored abstinence
Pillay *et al.* (2004)[85]	**Cannabis**: >5000 lifetime uses (mean = 16,711.5 ± 4695.35) **Alcohol**: Lifetime drinks (with one drink defined as a can of beer, a 4 oz glass of wine or 1.5 shots of spirits) = 4777.50 ± 3327.03; excluded for any history of alcohol abuse or dependence **Nicotine**: Lifetime packs of tobacco: 2138.5 ± 2249.78 (SD); no history of tobacco use disorder **Other drugs**: No current or past substance abuse or dependence (with exception of cannabis use for cannabis users); mean number of lifetime uses ± SD: stimulant = 5.25 ± 7.36; cocaine = 24.75 ± 32.48; hallucinogen = 19.63 ± 17.99; inhalant = 2.88 ± 3.69; opiate = 0.13 ± 0.33; PCP = 0.88 ± 1.05; sedative–hypnotic = 1.75 ± 1.92	4–36 h
Sagar *et al.* (2015)[61]	**Cannabis**: Heavy cannabis users (minimum of 2500 lifetime uses, used cannabis at least 5 of the last 7 days, tested positive for urinary cannabinoids, and met DSM-IV criteria for cannabis abuse/dependence) **Alcohol**: Excluded for alcohol use disorder based on DSM-IV criteria **Nicotine**: No significant differences between cannabis users and controls on the Fagerström test for nicotine dependence (FTND) **Other drugs**: No more than 15 lifetime uses of any illicit drugs (other than cannabis), no recreational use of Rx or OTC medications	> 12 h
Schweinsburg *et al.* (2008)[76]	**Cannabis**: While most cannabis teens were current users, five reported no use in the past month before abstinence	After 28 days of monitored abstinence

	Alcohol: Those in the cannabis group who met DSM-IV criteria for alcohol use disorder (abuse: $n = 2$, dependence: $n = 2$) were included due to high comorbidity with cannabis use disorder **Nicotine**: Average of 1.3 (cannabis group) and 0.8 (control group) cigarettes/day **Other drugs**: Excluded for drug use disorders based on youth or parent report	
Schweinsburg *et al.* (2010)[77]	**Cannabis**: Lifetime use episodes 342.31 ± 260.49 in recent cannabis users, 515.38 ± 275.67 in abstinent cannabis users, and 1.50±4.68 in healthy controls **Alcohol**: Cannabis groups had greater lifetime alcohol use than the healthy group (recent cannabis users: 140.92 ± 234.82; abstinent cannabis users: 184.85 ± 164.39; healthy controls: 7.11 ± 13.85); cannabis groups reported greater drinks/month than the healthy control group (recent cannabis users: 39.00 ± 47.34; abstinent cannabis users: 54.77 ± 50.96; healthy controls: 1.78 ± 4.68); alcohol use was controlled for in fMRI analyses **Nicotine**: No between-group differences on the Fagerström test for nicotine dependence (FTND) scores **Other drugs**: Abstinent users had significantly greater lifetime other drug user than healthy controls (recent cannabis users: 4.77 ± 7.90; abstinent cannabis users: 9.15 ± 12.24; healthy controls: 0.78 ± 3.30)	Recent cannabis (2–7 days of abstinence required, average: 3.33); abstinent cannabis (27–60 days of abstinence, average: 38.08)
Smith *et al.* (2010)[74]	**Cannabis**: >1 joint/week minimum; average of 11.48 cannabis joints/week (range of 2–37.5 joints/week), average duration of use of 4.55 years. **Alcohol**: Controlled for alcohol use in analyses **Nicotine**: 7/10 cannabis used nicotine (no healthy controls), but controlled for in analyses **Other drugs**: No use of illicit drugs on a regular basis or within the month prior to testing.	Not required to abstain
Sneider *et al.* (2013)[80]	**Cannabis**: Minimum of 2500 lifetime uses, used cannabis at least 5 of the last 7 days, tested positive for urinary cannabinoids, and met DSM-IV criteria for cannabis abuse on the day of scanning **Alcohol**: 4.4 ± 4.3 and 1.8 ± 2.5 alcoholic beverages per week in cannabis users and non-using comparison subjects, respectively; no alcohol use disorders based on DSM-IV criteria **Nicotine**: Four cannabis users reported recent nicotine use (1 pack per day; 1 pack every 2 weeks; 1 pack per month; occasional/social use) **Other drugs**: No substance use disorders based on DSM-IV criteria (except cannabis abuse in cannabis group)	>12 h
Tapert *et al.* (2007)[68]	**Cannabis**: >60 lifetime uses of cannabis (475 lifetime uses and 14 past month days on average) **Alcohol**: On average, cannabis users consumed 35 drinks per month and approximately 200 lifetime drinks; healthy controls consumed 2.7 drinks on average and 15 lifetime uses **Nicotine**: Cannabis users smoked of 1.4 cigarettes/day (FTND average score = 0.3; healthy controls smoked 0.2 cigarettes/day on average (FTND average score = 0.1) **Other drugs**: Limited histories of other drug use—average of about 7 uses in cannabis group and 0 in control group	28 days of abstinence
Van Hell *et al.* (2010)[91]	**Cannabis**: Average lifetime cannabis use: 3841 uses. Average past year cannabis use: 614 uses; 3 cannabis users tested positive via urinalysis—analyses were done with and without these subjects and no significant differences were found **Alcohol**: No alcohol use within one week of study, no history or alcohol use disorder, and all groups matched for alcohol use **Nicotine**: Cannabis group 6.9 cigarettes, nicotine group 13.2 cigarettes, control group = non-users/no nicotine use listed; no nicotine use within 2 h of testing (upon arrival at hospital) **Other drugs**: <7 lifetime uses of hard drugs and excluded for positive urine sample for any drug other than cannabis	1 week
Wesley *et al.* (2011)[93]	**Cannabis**: 4 of 16 cannabis users met criteria for dependence, all tested positive for THC the day of scanning; cannabis users reported using cannabis 2.1 ± 1.5 times/day, 29.4 ± 1.0 days/month; control group <50 lifetime uses occurring more than 2 years prior to study **Alcohol**: Excluded individuals with alcohol abuse **Nicotine**: Did not exclude individuals who met criteria for nicotine abuse **Other drugs**: Test negative for illicit drugs	Abstinent since the night before the scan
Zimmermann *et al.* (2017)[97]	**Cannabis**: >3 days per week during the previous 12 months, and use on >200 lifetime occasions **Alcohol**: No significant differences between healthy controls and cannabis users for number of drinks per week (13.09 versus 9.24) **Nicotine**: <20 cigarettes/day **Other drugs**: Cannabis users excluded for >50 lifetime uses of illicit substances or any use during the 28 days prior to the experiment; healthy controls excluded for illicit substance use >10 lifetime uses or any use within 28 days of experiment)	48 h