HHS Public Access

Author manuscript

J Pediatr Neuropsychol. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

J Pediatr Neuropsychol. 2020 March ; 6(1): 1–13. doi:10.1007/s40817-020-00076-5.

Neurocognitive Correlates of Adolescent Cannabis Use: An Overview of Neural Activation Patterns in Task-Based Functional MRI Studies

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Abstract

Adolescence is dynamic and comprises physiological, psychological, and neurocognitive changes. Notably, many developmentally associated neurobiological changes (e.g., synaptic pruning, myelination) coincide with peak substances use prevalence rates, particularly for cannabis use. Cannabis remains the most commonly used illicit drug among adolescents with 23.9% reporting cannabis use in the last year (Johnston et al., 2019). Adolescents who engage in cannabis use often show poorer neurocognitive performance and alterations in structural and functional brain development as compared to their non-using peers (Jacobus & Tapert, 2014). Over the past several decades, the cognitive domains most consistently associated with cannabis use among adolescents are learning and memory and several facets of executive functioning (e.g., inhibitory control, decision-making). Functional magnetic resonance imaging (fMRI) is a non-invasive method for probing the neural substrates underlying possible cannabis-related changes in cognition. This brief review aims to synthesize recent findings on the relationship between adolescent (≤25 years old) cannabis use and neural response during task-based functional magnetic resonance imaging (fMRI). Findings thus far suggest aberrant, often hyperactive, response to task-based stimuli in youth cannabis users. When considering the future directions of fMRI research with cannabis-using youth, review of existing studies also highlights the need for more prospective research with diverse samples.

Keywords

adolescent; cannabis use; decision making; working memory; inhibition; fMRI

1. Introduction

Cannabis has been one of the most commonly used substances among adolescents in the United States for decades (Johnston et al., 2019) and new evidence suggests cannabis is now

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more often the first drug used among adolescents, thereby displacing alcohol and tobacco as common first substances in the early stages of use (Keyes, Rutherford, & Miech, 2019). While past year prevalence rates have remained steady in recent years (35.9% of 12th graders, 27.5% of 8th graders in 2018), vaping high potency cannabis products have increased at an alarming rate (change of +2.6% from 2017-2018). Likewise, 2018 data suggest that only 1 in 3 adolescents aged 12 to 17 perceive smoking cannabis on a weekly basis of great risk. Decreased perception of risk coupled with changing cannabis trends and product variations may enhance vulnerability for any deleterious impact on youth neurodevelopment (McDonald, Roerecke, & Mann, 2019).

Cannabis elicits a central nervous system effect via activation of the endogenous cannabinoid system. For example, Δ-9-tetrahydrocannabinol (THC) is the psychoactive cannabis constituent that produces the desired effect in many youth users. THC binds to cannabinoid-1 receptors (CB1) in the brain which are found in high concentrations in regions that are being refined for optimal cognitive performance during adolescence (e.g., prefrontal cortex, basal ganglia, hippocampus) (Meyer, Lee, & Gee, 2018). The cannabinoid system is involved in many physiological processes and modulation of neurotransmitters systems (Hillard, 2015) therefore regular interference with this endogenous system likely has neurodevelopmental implications that impact behavioral outcomes (Sim-Selley, 2003; Schneider, 2008; Miller et al., 2019).

Brain development is a protracted process that includes changes in gray and white matter tissue compartments through adolescence and young adulthood. This includes increasing myelination and decreases in synaptic density in the cerebral cortex which has an impact on brain function through better neural integration (Luna & Sweeny, 2004) and more focal activation patterns in frontal circuits as compared to diffuse widespread neural activity (Uddin, Supekar, & Menon, 2010). Structural and functional neuroimaging modalities have expanded our knowledge of the developing brain and the varying trajectories of white and gray matter tissue change that underlie improving neural network integration and cognitive performance in typically developing children and adolescents (Stiles & Jernigan, 2010). The same imaging modalities can also elucidate the neural underpinnings of substance-related behavioral changes. Task-based functional magnetic resonance imaging (fMRI) paradigms have been increasingly utilized to identify patterns of brain activity that are associated with cannabis use in adolescence. In fMRI, a stimulus-related neural response during a cognitive task (e.g. stopping an already initiated motor action) is measured by a change in blood-oxygen-level-dependent (BOLD) signal response across brain regions in relation to rest or other stimulus conditions (i.e., control conditions) to remove non-task related activity. Therefore, both greater and less neural response can provide meaningful information on functional neural differences across cortical regions that underlie different cognitive processes (Buchbinder, 2016; Herting, Gautam, Chen, Mezher, & Vetter, 2018). Identification of brain regions and/or brain systems that are vulnerable to cannabis-related problems can ultimately guide prevention and intervention strategies as well as public health policy as cannabis products continue to proliferate and be more accessible (Wilson, Freeman, & Mackie, 2019).

Executive functioning (EF) has been theorized to contribute to substance use onset as it is involved in the planning, initiation, and regulation of goal-directed behaviors (Giancola & Moss, 1998; Kim-Spoon et al., 2017). EF is comprised of the ability to process, store and update information (working memory), ability to stop automatic responses (inhibition), set shifting, decision making, and verbal and design fluency (Robbins, 1998; Stuss & Alexander, 2000). Prior research has found an association between poorer executive function abilities and substance use problems (Brown, Tapert, Granholm, & Delis, 2000; Giancola & Mezzich, 2003). According to Kim-Spoon and colleagues (2017), substance use can be viewed as the inability to inhibit reward-seeking behaviors (approach) and punishment (avoidance). Approach sensitivity comprises of subcortical and cortical regions including the striatum and orbitofrontal cortex, while avoidance sensitivity comprises of the amygdala, hippocampus, and insula. EF modulates the approach and avoidance systems and involves the prefrontal cortex, basal ganglia, thalamus, and cerebellum (Rabinovici, Stephens, & Possin, 2015). EF evolves throughout adolescence and serves a critical role during development due to heightened reward sensitivity (Silverman, Jedd, & Luciana, 2015). Existing research examining the effects of EF on adolescent substance use largely focuses on working memory, inhibition, and decision making; thus for the purpose of this review, we focused on these three domains.

This brief narrative overview describes research on cannabis use and neural response among adolescents and young adults (defined as studies focused on individuals ≤25 years old) using task-based fMRI. We are particularly interested in this age group as it has been defined as a time of major physiological, psychological, and neurocognitive changes (Sussman & Arnett, 2014), consistent with the remarkable amount of neurodevelopment that occurs in this age group (J. Giedd, 2015). We also highlight the unique demographic and drug use factors that may contribute to group differences beyond cumulative cannabis use; namely, consideration of sex, age range, length of abstinence, sample size, and clarifying when a study includes individuals who are treatment seeking or meeting criteria for cannabis use disorder (CUD) (Volkow et al., 2016). Domains reviewed include those most often implicated in cannabis use (i.e., memory/working memory, inhibitory control, and decision making; see (Jacobus & Tapert, 2014; Gonzalez, Pacheco-Colón, Duperrouzel, & Hawes, 2017; Scott et al., 2018). Finally, we conclude by discussing limitations and common themes from the presented findings and future directions for the field.

2. Working Memory

Several of the first fMRI studies with adolescent cannabis users were conducted in our laboratory. In 2005, a spatial working memory task was administered to adolescent males and females with CUD + alcohol use disorder (AUD; n=15; 15-17 years-old). CUD+AUD showed less task-related activation (spatial working memory condition to vigilance contrast) in inferior frontal and temporal cortices and more activation in prefrontal regions as compared to controls (n=19) and adolescents with AUD alone (n=15) after a minimum of two days of abstinence from cannabis and alcohol (Schweinsburg et al., 2005). They further found recency of cannabis use associated with reduced right middle temporal activation. A follow-up study from Padula and colleagues (2007) using the same spatial working memory task with a slightly older sample of adolescents found increased task-related activation in the

basal ganglia, prefrontal, and parietal regions in 16-18 year-old cannabis users (n=17) relative to controls (n=17). This study included 28 days of monitored abstinence from cannabis and groups were matched for sex. Better performance on the spatial working memory task was also associated with more neural response in temporal, cingulate, thalamic, and hippocampal regions in cannabis users, with the opposite pattern in controls. Similarly, Schweinsburg et al., (2008) used the same task and found greater activation in dorsolateral prefrontal cortex (PFC), posterior parietal, and medial occipital regions in cannabis users (n=15) relative to controls (n=17) after 28 days of monitored abstinence from cannabis, with early age of onset and longer duration of use being associated with activation patterns.

Others have found similar results. Jacobsen and colleagues (2004) studied 7 cannabis users, 7 tobacco users, and 7 control male and female adolescents (exact age or abstinence requirements not reported). Cannabis users exhibited greater hippocampal activation during an auditory non-word 1- and 2-back task relative to controls, with cannabis users demonstrating worse behavioral performance than controls and no difference between cannabis users and tobacco users. Jager and colleagues (2010) performed a two-site (Dutch and US) cross-sectional study where they compared male adolescent cannabis users to male adolescent non-using controls aged 13-19 years using a verbal working memory task with a minimum of one week of abstinence (cannabis users n=21; controls n=24). There were three conditions for the task: a practice condition, where the participants were trained and tested on the same five letter memory set; a novel condition, where participants were presented with new and changing five letter memory sets; and a control task, where motor response time to a cue was assessed. During the novel-minus-control task, they found cannabis users increased activity in the inferior frontal gyrus, dorsolateral PFC, and anterior cingulate cortex (ACC), despite controls showing an overall deactivation. Further, in the cannabis users, number of joints in the past year and lifetime joints positively predicted left inferior frontal gyrus activation. Another study using a visuospatial N-back task with slightly older adolescents revealed greater activation in right inferior frontal gyrus, left middle frontal gyrus, and right superior temporal gyrus for cannabis users as compared to controls during the 2-back-minus-control contrast (Smith et al., 2011). Participants were 19-21-year-old males and females (10 cannabis users, 14 controls) who were asked not to use any substances on the day of imaging.

The more recent literature in this area is deploying longitudinal approaches to investigate how neural vulnerabilities (and thus neural activation differences) may predict changes in cannabis use patterns over time in youth. Heavy cannabis (n=32) and non-cannabis using (n=41) young adults (ages 18-25; males and females) completed an N-back task at an initial visit (Cousijn et al., 2014). Cannabis users were non-treatment seekers and had not received treatment for cannabis use in the past. With the exception of nicotine, all participants were asked to refrain from alcohol and other substances 24 hours prior to imaging. Six months after their initial visit, participants completed a follow-up phone interview on substance use. Despite no significant between-group differences at baseline, the bilateral frontal pole, ventrolateral PFC, dorsolateral PFC, premotor cortex, paracingulate cortex, and inferior parietal cortex were highlighted as a working memory network during the N-back task using independent component analysis. Working memory network connectivity response strength

was positively predictive of increased cannabis use within the cannabis group only. The authors suggest that increased neural effort during a working memory task may be a risk factor for increasing cannabis use.

In a second prospective task-based study, fMRI and cognitive performance were assessed before and after adolescents' first cannabis use (Tervo-Clemmens et al., 2018). Sixty-seven participants completed a visuospatial working memory task during fMRI at baseline (age 12) and follow up (age 15), as well as substance use assessments during annual visits. At baseline, no participant reported cannabis use; at three-year neuroimaging follow up, 21 participants were classified as cannabis users. Baseline results revealed increased activation in the inferior parietal lobe, middle frontal gyrus, and presupplementary motor area, with reduced precuneus and lateral occipital gyrus activation, in those who would later initiate cannabis use. By follow-up, longitudinal models suggest cannabis users show increased activation in the posterior parietal cortex as compared to controls. In addition, average weekly amount of cannabis use related positively to cuneus activation. These findings suggest while cannabis-related differences in neural response patterns can be observed, there are likely pre-existing brain activation differences prior to the initiation of cannabis which may be important biomarkers for identifying youth at risk of substance use onset.

Studies using working memory tasks have largely found greater activation across brain regions in cannabis users, particularly in prefrontal and parietal regions, despite a lack of difference in behavioral performance between groups. While these longitudinal studies utilizing neuroimaging are a welcome addition to the literature, a significant limitation remains that, other than Tervo-Clemmens and colleagues (2018), few studies to date have functional neuroimaging data prior to the initiation of cannabis use. Future longitudinal studies are needed with larger diverse samples and across more time points in order to understand preexisting neurocognitive differences to understand how cannabis use impacts working memory neural mechanisms.

2. Inhibition and Cognitive Control

Several studies to date have investigated functional activation during inhibitory or cognitive control tasks. Inhibition is commonly measured through Go/No-Go or Stop Signal Task (SST) behavioral paradigms (Aron, 2011). In a Go/No-Go Task, participants are taught to respond quickly to any "Go" stimuli and to withhold a response following any "No-Go" stimuli. During the more difficult SST, participants are instructed to respond quickly to each "Go" stimulus presented unless it is proceeded by a "Stop" stimulus presented on only a minority of trials. The delay between "Go" and "Stop" can be long or short, and longer delays increase the likelihood the participant will fail to execute a correct "Stop". Therefore, SST paradigms can be more demanding by requiring inhibition of an already initiated prepotent motor response. Using a Go/No-Go paradigm, Behan and colleagues (2014) examined differences in inhibitory processing between a group of current cannabis treatment seeking adolescents (n=17) and non-cannabis using controls (n=18). Groups were matched for sex and included adolescents aged 14-19 with CUD (minimum one day of abstinence) and healthy controls. Current cannabis using adolescents reported significantly higher stress and anxiety levels, more nicotine use in the month prior to participation, and fewer

successful inhibitions during the task. Groups did not differ in activation during inhibition trials (No-Go) in regions associated with response inhibition (i.e., frontal, parietal, and cerebral regions), but follow-up analyses revealed correlations, or connectivity, between these regions. Cannabis users had stronger correlations between frontal, parietal, and cerebellar regions during inhibition trials, and past week cannabis use correlated with network connectivity. Another study (Tapert et al., 2007) of adolescent (16-18 years-old, matched by sex) cannabis users (n=16) and non-users (n=17) used a Go/No-Go task after 28 days of monitored abstinence. Despite similar behavioral performance between groups, cannabis users demonstrated greater activation in parietal and dorsolateral prefrontal (PFC) cortices than healthy controls during the inhibition, or No-Go trials. Post-hoc analyses revealed a number of dose-dependent relationships, including age of onset, duration of cannabis use, cumulative lifetime use, and number of hits per month in relation to the observed activation patterns.

Smith and colleagues also used the Go/No-Go Task to investigate the effect of cannabis use on response inhibitions in young adults (2011). Participants included males and females ages 19-21 (n=10 current cannabis users, n=14 non-users). Abstinence varied within the cannabis-using group from 1 week to 3 hours prior to the testing session. There were no significant behavioral differences between groups, but the cannabis user group demonstrated greater fronto-cortical activity during inhibition trials relative to controls and greater self-reported cannabis use related to greater activation in the right thalamus, premotor cortex, middle frontal gyrus, inferior parietal lobe, and precuneus.

Antisaccade tasks are a means of studying executive control and share common features with inhibition tasks such as the Go/No-Go and Stop Signal tasks (Aron, 2011). Antisaccade tasks require the participant to inhibit prepotent eye movements and generate a new saccade in the opposite direction from a presented stimulus. Chung and colleagues (2015) studied cognitive and oculomotor control using antisaccade tasks in male and female adolescents (86% with CUD; n=14) scanned during or shortly after treatment and followed for 6-months (Chung et al., 2015). On reward trials, participants were offered small monetary rewards for quickly performing an antisaccade (i.e., look away from the target) following the presentation of a “$” stimulus. During neutral trials, participants were again instructed to perform an antisaccade when a “#” was presented, though no reward would be given. Increased activation in the amygdala, nucleus accumbens, left ventrolateral PFC, supplementary eye field, and putamen during the reward trials predicted decreased cannabis problem severity symptoms at 6-month follow-up, with similar results during reward-minus-neutral contrasts. In contrast, those who reported more symptoms at follow-up had lower activation during the reward condition at baseline, suggesting the importance of reward sensitivity as a means of facilitating cognitive control.

Taken together, studies on inhibitory and cognitive control in adolescent cannabis users suggest that cannabis use in adolescence is associated with greater neural activation and connectivity in frontal, parietal, and cerebellar regions (Tapert et al., 2007; Smith et al., 2011; Behan et al., 2014), despite mostly equivalent behavioral performance. Cannabis users may need to recruit greater cognitive resources to perform at comparable levels to non-users on cognitive control tasks. This is true even after long periods of sustained abstinence

(Tapert et al., 2007) and regardless of CUD status (Tapert et al., 2007; Behan et al., 2014). In addition, longitudinal findings on cognitive control during an antissaccade task (Chung et al., 2015) suggest a neural mechanism by which rewards may facilitate the use and development of cognitive control in adolescents with CUD. For example, Chung and colleagues propose either contingency management, which utilizes reward-based behavior change through giving patients small rewards for treatment adherence (Stanger & Budney, 2010), or motivational interviewing, which enhances internal motivation (Barnett et al., 2012), may tap into these neural systems underlying cognitive controls to aid in long-term treatment outcomes for adolescent cannabis users.

4. Decision-Making

To date, research on the neural mechanisms of decision-making and reward response in adolescent cannabis use remain understudied and research paradigms used to measure decision-making performance vary across studies. De Bellis and colleagues (2013) examined neural processing of decision-making and reward circuits using the Decision-Reward Uncertainty task in three groups of adolescent males: 1) adolescents who recently completed treatment for CUD (n=15); 2) adolescent controls with other psychopathology but no history of substance use disorder (n=23); and 3) healthy controls (n=18). Participants completed three decision conditions while undergoing fMRI: 1) Behavioral risk, where the correct response was unknown and only one response would result in a reward; 2) Reward risk, where correct button press would be rewarded with 50% probability; and 3) No risk, where correct bottom press would be rewarded 100% of the time. Less neural activity in the left superior parietal lobule, left lateral occipital cortex, and bilateral precuneus was observed in the CUD group for the reward risk and behavioral risk conditions compared to controls with psychopathology. However, in the reward condition, adolescents with CUD demonstrated decreased activity in the orbitofrontal cortex (OFC) relative to either control group. Finally, results suggested that less OFC neural response to reward was significantly correlated with more drug experimentation in the CUD group.

The Balloon Analogue Risk Task (BART;(Lejuez et al., 2002) was developed to assess risk taking in adolescents. In the BART, participants are instructed to pump air into a simulated balloon to earn points. They have the choice to cash-out and collect points earned on the balloon or continue to pump in order to receive a greater amount, while risking an explosion and no reward. In a recent study, the neural mechanisms of risky decision-making were examined using the BART among adolescent males reporting (1) frequent use cannabis, (2) frequent use of alcohol, (3) frequent use of both substances, and (4) minimal or no use of either substance (Claus et al., 2018). Participants were between the ages of 14 and 18 and were recruited through an alternative to incarceration program. They were asked not to use any substances within 24 hours of their appointment. Results indicated no behavioral differences on the BART across the four groups. However, adolescents who used both alcohol and cannabis demonstrated less insula, striatum, thalamus, supplementary motor area, and putamen neural activity compared to non-using controls during risky versus neutral conditions. Notably, when controlling for sex, activation differences during the risk taking were limited primarily to the nucleus accumbens, putamen, and thalamus. Furthermore, the

cannabis-only group demonstrated increased neural response in the superior parietal lobule relative to the co-use group.

The Iowa Gambling Task (IGT) has been used extensively in addictions research (Koffarnus & Kaplan, 2018) and requires participants to draw cards from any of four decks. Each card drawn indicates a gain or lose of some amount of pretend money. Participants select between these nondescript decks, two of which are advantageous (more likely to gain small pretend monetary amounts, with less money lost) and two of which are disadvantageous (more likely to have larger losses, though greater possibility of occasional large gains). Disadvantageous-minus-advantageous deck choices and total net money are commonly examined to capture deficits in decision making performance. Cousijn and colleagues (2013) administered the IGT in a prospective study of n=32 cannabis users and n=41 controls (males and females aged 18-25 years with 24 hours of abstinence at minimum). Participants completed a 6-month follow-up substance use interview after the initial study visit. Cannabis users at baseline had relatively greater neural activity when receiving win-versus-loss feedback in the right OFC, right insula, and left superior temporal gyrus than did controls. Greater weekly cannabis use was related to more activity in the right insula, right caudate, and right ventrolateral PFC for the win-versus-loss feedback contrasts. At 6-month follow-up, there was a significant decline in cannabis problem severity for all users. However, cannabis users who had greater activity in the lateral frontal pole and temporal gyrus during disadvantageous-versus-advantageous trials had increased weekly cannabis use by follow-up. Greater neural activity during win-versus-loss in the superior frontal gyrus was also associated with increased weekly cannabis use at 6-month follow-up. Thus, neural activation patterns were predictive of later cannabis use patterns.

In another reward-based study (Acheson et al., 2015) a block design win/loss task was used to study neural activity in adolescent cannabis users (n=14) compared to adolescent non-users (n=14). Participants included both males and females who were 15-19 years-old. Participants were asked not to use cannabis the night before testing. During the task, they were required to guess whether a simulated coin flip would be “heads” or “tails” and a subsequent message provided feedback on whether they made the correct guess. Results revealed enhanced neural response in frontal, subcortical, and cerebellar regions during both reward and loss conditions in adolescent cannabis users compared to controls. An effective connectivity analyses revealed minimal connectivity differences across groups.

Another common measurement of reward-based response is the monetary incentive delay (MID) task (Balodis & Potenza, 2015). During the MID, participants are presented with a chance to win a small amount of money, lose a small amount, or have no monetary change based on their response to a visual target following each cue. Nestor and colleagues (2010) examined BOLD responses to the MID in 14 adolescent cannabis users and 14 drug-naive adolescent controls. Cannabis users had a minimum of 12 hours of abstinence. Cannabis users demonstrated increased BOLD response in the right ventral striatum for reward (“win”) cues compared to healthy controls. There were no significant correlations between length of abstinence, neural activity, or behavioral performance in cannabis users. In a more recent study, Aloi and colleagues (2019) examined the relationship between Cannabis Use Disorder Test scores (CUDIT) in adolescents using a similar MID task. Participants included

150 male and female adolescents aged 14-18 years, of which 109 were current treatment seeking youth, 56 with responses suggestive of CUD, and 41 individuals without significant substance abuse histories (as measured by self-report screener measures, such as the CUDIT). Higher CUDIT scores were associated with decreased BOLD activation within the putamen when participants received feedback that they had made an error (inaccurate trials), as well as putamen, anterior cingulate, and dorsomedial PFC during feedback on trials where they lost money (inaccurate punishment trials). In contrast with these findings, Nestor and colleagues (2019) used the MID task with mostly male adolescents who were asked to not use cannabis the night before study completion. Participants included both cannabis users (n=18) and healthy controls (n=18). There were no group differences across trials. However, in general, the cannabis-dependent adolescents did demonstrate increased connectivity in regions associated with reward (OFC, medial PFC, lateral PFC, amygdala, hippocampus, nucleus accumbens, and temporal regions) compared to non-using adolescents.

Overall, results suggest cannabis users demonstrate different patterns of neural response based on the type of decision-making paradigm deployed and the extent to which reward processing is involved in the task (Cousijn et al., 2013; Acheson et al., 2015; Aloi et al., 2019). This is further complicated by patterns of substance co-use (De Bellis et al., 2013; Aloi et al., 2019) and sex [e.g., fewer group differences when controlling for sex (Claus et al., 2018); inclusion of male-only samples (De Bellis et al., 2013). Therefore, more prospective research is needed with larger and more diverse samples that replicate findings using similar decision-making tasks in order to delineate the neural substrates and of cannabis-related neurocognitive vulnerabilities in this domain (Casey et al., 2018; Jernigan & Brown, 2018).

5. Discussion

There is an emerging body of evidence to date that cannabis use and CUD are associated with aberrant functional activation in the adolescent brain. Our goal in this brief overview was to synthesize the literature while considering limitations and future directions for task-based functional imaging and cannabis research. We focused on three primary areas of cognitive functioning: working memory, inhibition, and decision-making. Results are largely consistent with the hypothesis that cannabis users may require recruitment of more neural resources to achieve the same performance on tasks across domains. While varying greatly by study and task, the frontal and parietal lobes were often key regions implicated (Schweinsburg et al., 2005; Padula et al., 2007; Tapert et al., 2007; Schweinsburg et al., 2008; Jager et al., 2010; Smith et al., 2011; Cousijn et al., 2013; Claus et al., 2018). Brain regions often found to be significantly different between groups are also fairly consistent with the neurobiology of addiction and circuit-specific pathways implicated in craving, impulsivity, executive dysfunction and substance misuse (e.g., frontal cortices, insula, anterior cingulate cortex, basal ganglia) (Koob & Volkow, 2016). For example, activation was revealed during reward (L. J. Nestor et al., 2019) and risky decision making tasks (Lejuez et al., 2002) in prefrontal and reward (nucleus accumbens) regions. The few preliminary longitudinal studies indicate that: (1) there may be pre-existing neural activation differences in teens who will initiate cannabis use, and (2) task-based activation patterns

may be useful biomarkers of later cannabis use, increases in cannabis use severity, and behavioral outcomes.

The current review also highlights a number of significant limitations for research in cannabis use and functional activation. First, we note that in many studies neural activation patterns are often consistent across brain regions (e.g., prefrontal, parietal regions) showing greater activation in youth who used cannabis *or* met criteria for a cannabis use disorder (e.g., (Tapert et al., 2007; De Bellis et al., 2013; Behan et al., 2014; Acheson et al., 2015). Given this, it will be important to determine whether this is due to pre-existing brain differences (as may be suggested by the recent study by (Tervo-Clemmens et al., 2018) or if there is a particular threshold of cannabis use that relates to such functional patterns. For example, externalizing symptomatology has been shown to be a neural and behavioral risk factor for atypical brain functioning and is frequently elevated in adolescent substance users (Griffith-Lendering, Huijbregts, Mooijaart, Vollebergh, & Swaab, 2011; Natalie Castellanos-Ryan et al., 2014; Scalco et al., 2014; Woltering, Lishak, Hodgson, Granic, & Zelazo, 2016; Loeber et al., 2018) . It is likely that dysfunction in common brain pathways underlying inhibitory control in particular (e.g., fronto-basal ganglia pathway) may contribute to the shared traits of externalizing behaviors (e.g., attention deficit/hyperactivity disorder) and probelmatic substance use patterns and thus vulnerability for poorer outcomes (Groman, James, & Jentsch, 2009).

In addition, as revealed in some analyses (Schweinsburg et al., 2005; Claus et al., 2018), use of multiple substances may uniquely impact neural outcomes and therefore, it is necessary to address co-use (e.g., alcohol, nicotine and tobacco-related products) and dynamic trajectories of drug use (vs. static group categorization, as done in the vast majority of studies to date). Studies were also limited to self-report metrics and mostly included assessment post-cannabis initiation. Additionally, control groups differed across studies, with some using healthy non-substance using controls and others using alcohol only controls. Finally, despite the advances made in fMRI studies, test-retest reliability remain a concern in longitudinal studies (Herting et al., 2018). It is important to note that there are numerous factors that can impact test-retest reliability of fMRI BOLD signal, including scanner device type and acquisition, head motion, task paradigm variation, and data processing. Choosing tasks with higher reliability estimates is encouraged in the fMRI field, and, moving forward, researchers are being encouraged to contribute to reference libraries for fMRI task reliabilities across different age groups (see Herting et al., 2018), however this remains a limitation in fMRI research.

Differences in imaging and substance use assessment methods across the studies may also contribute to some variability in the results. For example, some studies ran whole brain analyses while others focused on region of interest based analyses (as noted in Table 1). Studies also used a range of cannabis use definitions and measurement methods. Most also included relatively small sample sizes. While adolescence and young adulthood marks additional neurodevelopment and vulnerability to substance use and so is highlighted here, different age groups falling within different levels of neural maturation and neural integration. Finally, we note that aberrant patterns relate to cannabis misuse to some degree. Together, consistent patterns in brain networks observed are likely task-related and

reproducible, given the overlapping results in many findings, but differences in methods are likely also contributing to some “noise” variability and modest effect sizes.

Notably, there is an under-representation of females in studies of adolescent cannabis users. Two studies reviewed here included only males (Jager et al., 2010; De Bellis et al., 2013), while the remaining included participants who were majority male (see Table 1). Moreover, while there certainly is a gender disparity in this area of research, we also acknowledge that a more fundamental issue is a general lack of diversity within the field of neuroimaging and adolescent cannabis research (Falk et al., 2013; Bogdan et al., 2017). Along these same lines, while all but one study (Chung et al., 2015) controlled for or excluded psychiatric comorbidities, it is unclear how individuals with internalizing or externalizing symptomatology may be impacted by ongoing cannabis use. Cannabis studies are known to recruit non-representative samples of typical users (Rosen, Sodos, Hirst, Vaughn, & Lorkiewicz, 2018) such as through excluding psychiatric comorbidities or requiring periods of abstinence. In addition, all studies used in this review controlled for education level, which does not negate the concern that participants in these studies likely are not wholly representative of a typical random sample. Much greater effort needs to be made to include larger and more diverse samples over multiple time points both pre- and post-cannabis initiation, to aid in generalizability of findings and to better understand the full impact of cannabis use in youth.

Rich characterization of cannabis products, dose, and consumption methods are also essential for future study designs. A number of studies reviewed here found dose-dependent relationships. Age of onset (Tapert et al., 2007; Schweinsburg et al., 2008) duration of cannabis use (Tapert et al., 2007), recency of last use (Schweinsburg et al., 2005), weekly (Behan et al., 2014), past month (Tapert et al., 2007), past year (Jager et al., 2010), past several years (Tervo-Clemmens et al., 2018) and/or cumulative lifetime use (Tapert et al., 2007; Jager et al., 2010) all have been found to significantly relate to activation patterns, though not every metric is predictive in every case (e.g., Tapert et al. (2007). Furthermore, as there are 100+ cannabinoids contained within the cannabis plant (ElSohly, Radwan, Gul, Chandra, & Galal, 2017; Kinghorn, Falk, Gibbons, & Kobayashi, 2017) future research should aim to look at specific cannabinoid constituents. Therefore, greater understanding of the relationship between specific patterns of use (e.g., early substance debut, frequency and dosing) or the exact products used (e.g., concentrates, oils, THC potency) and observed neural patterns is needed. More preclinical studies and translational work would also assist in assessing the role and impact of specific cannabinoid constituents.

The Adolescent Brain and Cognitive Development (ABCD) study has recruited 11,875 9-10-year old’s nationwide and will follow them through adolescence (for 10 years) (Garavan et al., 2018). The ABCD study protocol comprehensively assesses brain development, substance use, and mental and physiological health. Imaging methods were selected, optimized, and harmonized across all 21 sites to for repeated structural and functional MRI scans (Hagler et al., 2019). Domains of function measured by ABCD overlap and expand on those reviewed here, including: decision making and reward processing (monetary incentive delay); impulsivity and cognitive control (stop signal task); and working memory (Emotional N-back) (Casey et al., 2018). The ABCD study will be able to address many

gaps in the current literature, particularly given that participants are almost exclusively substance naive at baseline. Yet, despite their strengths, large longitudinal observational studies will not be able to fully address all cannabis-related research questions. More broadly, there is a continued need to include quasi-experimental study designs that are better able to assess nuanced questions which cannot be answered through large, observational designs.

Our review focused on studies of adolescents and young adults ≤25 years old. There are other important and well-designed studies that cover additional points in the lifespan, including some studies which have a mean age closer to 25 years-old (e.g., (L. Nestor, Roberts, Garavan, & Hester, 2008; L. Nestor et al., 2010; Filbey & Yezhuvath, 2013)). Understanding patterns of activation in cannabis users across the lifespan is a promising avenue for diagnosis, prevention, and intervention efforts. While it is widely known that adolescence is a critical period of brain development (J. N. Giedd et al., 1999; Stiles & Jernigan, 2010; Jernigan & Brown, 2018) an influx of research in recent years underscores the importance of better understanding specific developmental changes and patterns that occur during this time, particularly amongst cannabis users. Research thus far suggests overall aberrant, often hyperactive, response to task-based stimuli. However, limitations such as homogeneity, cross-sectional studies, and small sample sizes preclude firm conclusions from being drawn.

Acknowledgements:

This work was supported by National Institute on Alcohol Abuse and Alcoholism (T32 AA13525), National Institute on Drug Abuse (U01 DA041089; R21 DA047953) and the California Tobacco-Related Disease Research Grants Program Office of the University of California (Grant 580264).

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Table 1.

Task-Based fMRI Studies in Adolescent Cannabis Users

Author (Year)	Cognitive Domain	Age Range	Sex	Cannabis Group Criteria	CUD	Task	Brain Analyses	Corrected	Abstinence Period	Primary Results
Cross-sectional Studies										
Jacobsen et al. (2004)	Working Memory	16-17	CU: 75%M; Tobacco: 75%M; CON: 40%M	24-1460 days		Auditory N-Back	ROI		1.5-24 months	2-Back Condition: CU>CON, hippocampal activation
Jager et al. (2010)	Working Memory	13-19	CU: 23M; CON: 24M	≥200 lifetime episodes		Verbal WM task	Both	+	24 hours	Novel-Task-minus-Control-Task: CU>Controls; left SPC, left IFG, left PCC/DLPFC, ACC
Padula et al. (2007)	Working Memory	16-18	CU: 14M, 3F; CON: 12M, 5F	477 lifetime episodes (average)		Spatial Working Memory Task	Whole	+	28 days	SWM-minus-Vigiliance: CU>Controls; right basal ganglia, right and left parietal lobes
Schweinsburg et al. (2005)	Working Memory	15-17	CUD+AUD: 10M, 1F; AUD: 10M, 1F; CON: 11M, 8F	≥100 lifetime episodes	+	Spatial Working Memory Task	Whole	+	≥2 days	SWM-minus-Rest: CUD+AUD<Controls; right inferior frontal gyrus, right superior temporal and supramarginal gyri activation CUD+AUD>Controls; right superior frontal and middle frontal gyri activation CUD+AUD>Controls; left inferior frontal gyrus, bilateral medial frontal cortex and anterior cingulate deactivation CUD+AUD <AUD; right inferior frontal gyrus, claustrum, and insula. Left precuneus, and right middle temporal and supramarginal gyri activation CUD+AUD <AUD; left superior temporal gyrus deactivation CUD+AUD >AUD; bilateral middle and superior frontal gyri, anterior cingulate deactivation
Schweinsburg et al. (2008)	Working Memory	16-18	CU: 11M, 4F; CON: 12M, 5F	480 lifetime episodes (average)		Spatial Working Memory Task	Whole	+	28 days	SWM-minus-Vigilance: CU>Controls; Right superior parietal lobule CU<Controls; Right middle frontal gyrus
Behan et al. (2014)	Inhibition and Cognitive Control	14-18	CU: 16M, 1F; CON: 17M, 1F	4168 lifetime joints (average)		Go/No-Go	Whole	+	>24 hours	No-Go Condition: CU>Controls, parietal and cerebellar regions increased correlations

Author (Year)	Cognitive Domain	Age Range	Sex	Cannabis Group Criteria	CUD	Task	Brain Analyses	Corrected	Abstinence Period	Primary Results
Cross-sectional Studies										
Claus et al. (2018)	Inhibition and Cognitive Control	14-18	CU+ALC:28M, 11F; ALC: 9M, 14F; CON: 20M, 17F	≥1 day use in the past month		BART	ROI	+	24 hours	Linear Risk Contrast: ↑CU+Alc frequent use, ↓response in ventral striatum and bilateral thalamus Risky Decision Making Contrast: CU+Alc<Controls, insula striatum and thalamus
Smith et al. (2011)	Inhibition and Cognitive Control	19-21	CU: 6M, 4F; CON: 9M, 5F	2697 lifetime joints		Go/No-Go Task	Whole	+	1-2 hours	No-Go-minus-Go: CU>Controls, precentral gyrus, superior, middle, orbital and inferior frontal gyri, lingual gyrus and supramarginal gyrus. ↑Canniabis use=↓Right thalamus, bilateral inferior parietal lobe
Tapert et al. (2007)	Inhibition and Cognitive Control	16-18	CU: 12M, 4F; CON: 12M, 5F	≥60 lifetime episodes		Go/No-go Task	Whole	+	28 days	No-Go-minus-Baseline: CU>Controls, right dorsolateral prefrontal cortex, bilateral inferior and superior parietal lobules, and right occipital gyri Go-minus-Baseline: CU>Controls, right prefrontal, insular, and parietal cortices
Acheson et al. (2015)	Decision Making & Reward Response	15-19	CU: 11M, 3F; CON: 11M, 3F	6.7 uses per week		Coin Flip Win/Loss Task	ROI		<24 hours	Reward-minus-Control: CU>Controls, middle and inferior frontal gyri, caudate, and claustrum Loss-minus-Control: CU>Controls, anterior and posterior cingulate, middle frontal gyrus, insula, claustrum, and declive
Aloi et al. (2019)	Decision Making & Reward Response	14-18	CU: 73M, 36F; CON: 19, 13F	CUDIT scores ranged from 0-32	+	MID	Whole	+	Not Reported	Feedback on Inaccurate Trials: ↑CUDIT score=↓Decreased activation in putamen Feedback on Inaccurate Punishment Trials: ↑CUDIT score=↓Decreased activation in putamen and ACC/ dmPFC during feedback
Cousijn et al. (2012)	Decision Making & Reward Response	18-25	CU: 21M, 11F; CON: 26M, 15F	1611 lifetime joints		IGT	Whole	+	24 hours	Win-minus-Loss: CU>Controls, right OFC, right insula, and left superior temporal gyrus

Author (Year)	Cognitive Domain	Age Range	Sex	Cannabis Group Criteria	CUD	Task	Brain Analyses	Corrected	Abstinence Period	Primary Results
Cross-sectional Studies										
De Bellis et al. (2013)	Decision Making & Reward Response	13-17	CU: 15M; Controls w/ psychopathology: 23M; CON: 18M	≤19 weekly use joints	+	Decision-Reward Uncertainty Task	Both	+	≥ 4 weeks	No Reward Condition: CUD>Controls, left OFC activation Behavioral Risk Condition: CUD>Controls, left superior parietal lobule Behavioral Risk Condition: CUD>Controls with psychopathology, left superior parietal lobule, left lateral occipital cortex, left and right precuneus
Nestor et al. (2010)	Decision Making & Reward Response	21-24	CU: 12M, 2F; CON: 11M, 3F	>500 lifetime joints		MID	Whole	+	12-504 hours	"Loss" Cues: CU>Controls right ventral putamen during "loss" "Win" Cues: CU>Controls right putamen and ventral putamen ↑ Right Putamen BOLD activity = ↑ Number of reported life-time cannabis joints smoked
Nestor et al. (2019)	Decision Making & Reward Response	16-19	CU: 17M, 1F; CON: 17M, 1F	Cannabis dependence diagnosis based on (DSM-IV)	+	MID	Both	+	<24 hours	CU>Controls, greater connectivity across reward regions
Author (Year)	**Cognitive Domain**	**Age Range**	**Sex**	**Follow-Up Length**	**Cannabis Group Criteria**	**CUD**	**Task**	**Brain Analyses**	**Corrected**	**Abstinence Period**	**Primary Results**
Longitudinal Studies											
Cousijn et al. (2014)	Working Memory	18-25	CU: 21M, 11F CON: 26M, 15F	6-month	1619.5 lifetime joints		N-Back	Whole	+	24 hours	↑ frontal pole, PFC, premotor cortex, paracingulate cortex, and inferior parietal cortex = ↑ Increased cannabis use within the cannabis groups at follow-up
Tervo Clemmens et al. (2018)	Working Memory	12-15	CU: 12M, 10F CON: 29M, 34 F	3 years, pre- and post-onset	.078 joints per day		Visuospatial Working Memory Task	ROI	+	Not Reported	SWM at Baseline: CU>Nonusers, inferior parietal, middle frontal, presupplementary motor area, CU<Nonusers, precuneus, lateral occipital SWM at Follow-Up: CU>Nonusers, posterior parietal Baseline>Follow-Up activation

Author (Year)	Cognitive Domain	Age Range	Sex		Cannabis Group Criteria	CUD	Task	Brain Analyses	Corrected	Abstinence Period	Primary Results
Cross-sectional Studies											
Chung et al. (2015)	Inhibition and Cognitive Control	14-18	10M, 4F	Baseline 6-month 1-year	≥1 lifetime DSM-IV cannabis use disorder symptom	+	Antissacade	Both	+	24 hours	↑amygdala, nucleus accumbens, left ventrolateral PFC, supplementary eye field and putamen = ↓ Cannabis problem severity symptoms at 6-month follow-up

ACC=anterior cingulate cortex; ALC=alcohol user; AUD=Alcohol Use Disorder; BOLD=blood-oxygen-level-dependent; Brain Analyses refers to whether studies included whole-brain, regions of interest (ROI), or both; CON=healthy control; Corrected=+ refers to analyses being corrected for multiple comparisons; CU=cannabis user; CUD + = cannabis using participants meet criteria for cannabis dependence or cannabis use disorder; F=Female; IFG=inferior frontal gyrus; M=male; OFC=orbitofrontal cortex; PCC/DLPFC=precentral and dorsolateral prefrontal cortex; ROI=region of interest; SPC=Superior Parietal Cortex; SWM=spatial working memory

Note: Primary results only include statistically significant differences