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Effects of Cannabis on the Adolescent Brain

Joanna Jacobus[1,2] and **Susan F. Tapert**[1,2]

[1]VA San Diego Healthcare System, Psychology Service (116B), 3350 La Jolla Village Drive, San Diego, CA 92161, USA

[2]University of California, San Diego, Department of Psychiatry, 9500 Gilman Drive (0603), La Jolla, CA 92093-0603, USA

Abstract

This article reviews neuroimaging, neurocognitive, and preclinical findings on the effects of cannabis on the adolescent brain. Marijuana is the second most widely used intoxicant in adolescence, and teens who engage in heavy marijuana use often show disadvantages in neurocognitive performance, macrostructural and microstructural brain development, and alterations in brain functioning. It remains unclear whether such disadvantages reflect pre-existing differences that lead to increased substances use and further changes in brain architecture and behavioral outcomes. Future work should focus on prospective investigations to help disentangle dose-dependent effects from pre-existing effects, and to better understand the interactive relationships with other commonly abused substances (e.g., alcohol) to better understand the role of regular cannabis use on neurodevelopmental trajectories.

Introduction

According to the 2011 Monitoring the Future Study, marijuana remains the most commonly used illicit drug in adolescence in the United States, one of few increasing in prevalence. In fact, marijuana has been the most commonly used illicit substance for almost 40 years, and presently 23% of 12th graders in the U.S. report using marijuana in the past month [1]. Marijuana use in adolescence could have implications for academic functioning, as well as social and occupational functioning extending into later life. Maturational brain changes, particularly myelination and synaptic pruning, are occurring throughout adolescence, well into early adulthood [2]. These remodeling processes are purportedly linked to efficient neural processing, and believed to underlie specialized cognitive processing necessary for optimal neurocognitive performance.

Cannabinoid receptors (CB1) are widely distributed throughout the brain (e.g., hippocampus, prefrontal cortex), and play a role in neurotransmitter release and concentrations across neural systems (excitatory and inhibitory). It has been suggested that these receptors increase during adolescence, have a role in genetic expression of neural development, and that alteration of the endocannabinoid system during adolescence may

*Corresponding author. Susan F. Tapert, Ph.D., VA San Diego Healthcare System, Psychology Service (116B), 3350 La Jolla Village Drive, San Diego, CA 92126, USA, 858-552-7563, stapert@ucsd.edu.

results in a cascade of neurochemical and neurostructural aberrations, thus leading to poorer cognitive and emotional outcomes in adulthood [3, 4].

Disruptions in brain development related to neurotoxic effects of regular marijuana use could significantly alter neurodevelopmental trajectories by not only changing neurochemical communication and genetic expression of neural development, but causing a toxic effect on brain tissue. Such a marijuana-related effect on white matter and gray matter structures (e.g., changes in myelin, axons, and synapses) could have widespread implications for healthy brain development from childhood to young adulthood on subtle cognitive functioning and success in daily functioning. Studies exploring the neurocognitive consequences and structural and functional neuroimaging changes related to marijuana use in adolescence will be discussed, along with recommendations for future work.

Cognition

Adult studies of marijuana use often find subtle decreases in performance compared to controls in cognitive domains such as attention, memory, and processing speed; such effects have been discussed as transient in the literature given limited group differences after prolonged abstinence from marijuana [5, 6]. It is unclear if findings translate to adolescent populations. Ongoing cognitive development in the domains of memory and executive functioning, and particularly in specialized functions like cognitive control, is not only tightly associated with adolescence and neocortical tissue maturation, but is likely to have implications for school performance and engagement in risk/reward behaviors [7]. One of the earliest studies on the effects of marijuana on adolescent neurocognitive development evaluated verbal and nonverbal memory performance in cannabis-dependent adolescents (ages 14 to 16) compared to matched controls [8]. Schwartz and colleagues found that short-term memory impairment persisted after six weeks of monitored abstinence. In contrast, Teichner and colleagues (2000) found no relationship between marijuana use severity and cognitive performance among cognitively impaired and unimpaired adolescents referred for drug treatment [9]. There have been considerable additions to the literature over the last decade, yet the degree of impairment related to marijuana use in adolescence remains inconclusive. A pattern of subtle yet potentially detrimental effects in cognitive domains related to attention, learning, and memory are most often described.

A prospective study conducted in 2005 examined neurocognitive performance among 17–21 year olds with history of soft drug exposure *in utero* compared to prior performance at 9–12 years old. Current heavy cannabis users performed significantly worse on measures of processing speed and memory, controlling for pre-drug performance. Notably, former heavy users (reporting 3 months without regular use) had similar scores to non-marijuana using controls [10]. In regard to higher-order cognitive functioning, Lane and colleagues (2007) found adolescents (ages 14–18) with histories of heavy marijuana use performed worse on perseverative responding and flexible thinking compared to controls with limited histories of use. This same research group also found evidence of reduced motivation among marijuana users compared to controls [11, 12]. In 2007, Harvey and colleagues found adolescent marijuana users (age 13–18; use greater than once per week) performed worse on tests of

attention, learning, and memory; furthermore, poorer performance on executive functioning in this sample was related to more days of cannabis use in the past month [13].

Studies from our laboratory have largely found differences in similar domains following four weeks of monitored abstinence. Our first prospective investigation found that cumulative marijuana use over the course of eight years (teens followed from ages 13–30) was related to poorer performance on measures of attentional functioning [14]. In a subsequent cross-sectional study of adolescent marijuana users ages 16–18, we found that marijuana users demonstrated slower processing speed, poorer verbal learning and memory, and sequencing abilities [15]. In order to better understand acute changes with abstinence, we examined neurocognitive performance over 3 weeks of monitored abstinence in marijuana users ages 15–19. Between-group differences in attention, learning, and memory were identified at baseline, however while learning and memory performance reached similar levels of performance to controls after 3 weeks of abstinence, attention differences persisted [16].

Group differences in our studies generally persist despite controlling for alcohol use present in both controls and marijuana users; but to further understand differential contributions of marijuana and alcohol to neurocognitive functioning in our sample, we examined unique associations between alcohol use severity and cognitive functioning in both marijuana users as well as controls. In a recent investigation, we found that more self-reported alcohol withdrawal symptoms predicted poorer performance on learning and memory in a sample of non-marijuana using teens with histories of episodic alcohol use, despite no relationship in our marijuana users with similar and/or heavier self-reported history of alcohol use [17]. This suggests differential relationships between marijuana, alcohol, and cognitive outcomes in our sample. We have observed similar relationships in magnetic resonance imaging (MRI) studies examining structural and functional brain alterations [18–20], which will be discussed in greater detail below.

In recent work, Tait and colleagues looked at young adult cannabis users (ages 20–24) and found memory deficits, however cessation of cannabis use was associated with improved performance with abstinence over the course of eight years [21]. Takagi and colleagues found that cannabis users (ages 13–24) performed worse on measures of immediate and delayed verbal memory compared to community controls. In a similar study by this team of investigators, no differences between cannabis users and community controls were found on measures of executive functioning [22, 23]. Similarly Gonzalez and colleagues (2012) found differences on immediate and delayed recall among young adult cannabis users (approximately age 20) compared to nonusing controls, however no differences were observed on measures of impulsivity. Despite no group differences on impulsivity, the authors found that worse performance on a decision making task was related to more cannabis use disorder symptoms [24]. Solowij and colleagues looked at 181 adolescents (ages 16–20) and found that cannabis users performed worse on learning and recall, and poorer performance was related to severity, frequency, and age of initiation of cannabis use [25]. A study on prospective memory evaluated undergraduates between the ages of 18 and 24 years old, while no differences in self-reported prospective memory was identified, cannabis users did recall fewer location-action combinations during the objective video-

based prospective memory task [26]. A large-scale (N = 1037) longitudinal investigation from New Zealand evaluating individuals from birth to age 38 recently found a decline in intelligence quotient, particularly executive functioning and processing speed, with persistent cannabis dependence. Notably, those individuals with weekly use before age 18 demonstrated greater decline in cognitive performance [27].

Early/Late Onset of Use—Studies evaluating early- and late-onset marijuana users have provided considerable insight into the effects of cannabis use on adolescent neurodevelopment. For example, Ehrenreich and colleagues (1999) found that initiation of marijuana use prior to age 16 predicted impaired reaction time on a task of sustained attentional processing [28]. In 2003, Pope and colleagues also found that early-onset (or initiation prior to age 17) was related to poorer performance on verbal memory and fluency tasks, as well as verbal IQ [29]. Focusing on executive functioning, Fontes and colleagues (2011) examined 104 chronic cannabis users ages 18–55. All participants met criteria for DSM-IV cannabis abuse or dependence. The authors found that adolescent cannabis users reporting initiation prior to age 15 demonstrated poorer performance on tasks of sustained attention, impulse control, and executive functioning [30]. Overall, the majority of data support poorer cognitive performance on measures of attention and learning, and memory in adolescent users of cannabis, however frequency and severity of use is likely to play a role, particularly in those reporting younger age of initiation. Further, some evidence suggests that many of the subtle cognitive effects are likely to resolve after longer-term abstinence.

Structural NeuroImaging

Gray Matter Macrostructure—A large body of literature has shown dynamic changes in gray matter structures that are ongoing over adolescent development (e.g., cortical volume decline after about 6 years of age). For instance, dendritic pruning and elimination of synapses likely results in cortical thinning and decreased cerebral volume (e.g., subtraction of overproduced or weaker synaptic connections) to some degree, whereas some subcortical structures such as the hippocampus and amygdala have been shown to increase with age [2, 31, 32]. Studies show a high density of CB1 cannabinoid receptors in neocortex, hippocampus, amygdala, hypothalamus, basal ganglia, and cerebellum [4]; therefore the degree to which cannabis use alters cortical and subcortical gray matter tissue development is being increasingly explored in the literature. While some alterations in gray matter macrostructure have been suggested, there has been inconsistent evidence of morphological changes as evaluated by structural MRI. For instance, Block and colleagues (1999) as well as DeLisi and colleagues (2006) found no differences in gray matter tissue volume between adolescent cannabis users and matched controls [33, 34].

In 2010, adolescent cannabis abusers (ages 16–19) were found to have decreased right medial orbital prefrontal cortex volume compared to non-using counterparts; volume was also found to be positively correlated with age of initiation of marijuana use in the sample (i.e., younger age of first use associated with reduced orbital prefrontal cortex volume) [35]. A second study published in 2010 found that while age was associated with changes in brain morphometry among non-users, there was no relationship between age and cortical gyrification in adolescent and young adult cannabis users. Cannabis users did show

decreased concavity of the sulci and sulci thinning in frontal, temporal, and parietal lobes compared to non-users, highlighting the potential for cannabis to disrupt normal brain developmental trajectories [36]. Ashtari and colleagues (2011) found that heavy adolescent cannabis users abstinent for a minimum of 30 days had smaller bilateral hippocampal volumes compared to controls, and smaller right hippocampal volume was correlated with more self-reported cannabis use among users; no between group differences were observed in amygdala volume [37].

Several studies from our laboratory evaluating abstinent adolescent cannabis users (approximately ages 16–19) have found similar outcomes in regard to gray matter macrostructural changes. Medina and colleagues (2007 and 2009) found no difference in hippocampal volumes or prefrontal cortex volume in adolescent cannabis users compared to matched controls, despite observed differences in both hippocampus and prefrontal cortex in adolescent alcohol users compared to matched controls [19, 38]. We did observe a subtle gender interaction, as female cannabis users had a slightly larger prefrontal cortex compared to non-using female controls; while this trend did not reach statistical significance, it may suggest that female marijuana users are more vulnerable to macrostructural alterations (given smaller prefrontal cortex volume was related to better executive functioning among users). Similarly, in 2011, amygdala volumes were compared between adolescent cannabis users and non-users. Findings suggest increased amygdala volume in female users compared to female non-users. Increased amygdala volume was associated with more self-reported depression and anxiety (internalizing) symptoms [39]. In a study investigating differences in cerebellum volumes, we found that adolescent marijuana users demonstrated larger inferior posterior vermis volume compared to controls; larger cerebellar volume was associated with poorer executive functioning [40].

In recent investigation of temporal lobe structures, Cousijn and colleagues (2012) found that amygdala and hippocampal volume in a sample of young adults ages 18–25 correlated negatively with amount of cannabis use. Specifically, more weekly cannabis use in grams was related to smaller hippocampus volume in heavy users and increased severity of cannabis use was associated with smaller amygdala volume. The authors also found that anterior cerebellum volume was larger in adolescent heavy cannabis users compared to non-users [41].

A prospective study looking at gray matter volume at 12 years of age, prior to initiation of marijuana, found that smaller orbitofrontal cortex volume predicted initiation of cannabis use by 16 years of age, suggesting pre-existing structural abnormalities may play a role in both behavioral differences that lead to cannabis use as well as continued differences in the course of development [42].

There have been limited studies evaluating cortical thickness exclusively, however, Lopez-Larson (2011) evaluated 18 adolescents (ages 16–19) with histories of heavy marijuana use (at least 100 marijuana use episodes in the past year) compared to non-using controls. Decreased cortical thickness was reported in the right caudal middle frontal and bilateral superior frontal cortices; decreased thickness was also found in the bilateral insula. Marijuana users demonstrated increased cortical thickness in the bilateral lingual, right

superior temporal, right parietal and left paracentral regions. Alterations of cortical thickness were related to severity of cannabis use and younger age of initiation of use in several brain regions. The authors suggest that marijuana may affect neurodevelopment (e.g., increased/decreased in cortical thickness) in two ways, 1) premature development and/or alterations in neurodevelopmental trajectories or 2) tissue loss or remodeling associated with marijuana-related toxicity [43].

Similar to findings by Lopez-Larson discussed above, the concept of deleterious effects related to early initiation of cannabis has been explored in the neuroimaging literature as well. According to Wilson and colleagues (2000), individuals reporting marijuana use prior to age 17 demonstrated decreased whole brain and cortical gray matter in addition to increased percent white matter volume. Findings also included higher cerebral blood flow in males reporting early initiation of marijuana use [44]. While findings do not necessarily support a clear and consistent pattern of changes in cortical/subcortical volume and thickness measurements, as emphasized by Lopez-Larson and colleagues, we can conclude that marijuana may influence the trajectories of appreciable gray matter changes in several ways. The compound may illicit premature tissue development, impose a marijuana-related effect on regressive changes (e.g., synaptic pruning, death of overproduced cells), and alter ongoing myelination of fiber tracts that are impacting gray matter estimates. Functional changes likely affect the mechanics that underlie structural brain changes, and interactions between these processes cannot be ruled out.

White Matter Microstructure—White matter tissue integrity (e.g., myelination, coherence of fiber tracts) is believed to be important for efficient cortical connectivity in the developing brain. The literature has shown linear increases in white matter over early development. As the brain becomes increasingly myelinated and fiber bundles mature from infancy to late adolescence, restriction of diffusing water molecules along the principal axis of an axon is commonly observed due to increasingly compact fibers and with more limited intracellular space [45, 46]. Diffusion tensor imaging (DTI) commonly utilizes two indices of white matter tract coherence to reflect water diffusion in white matter, fractional anisotropy (FA) and mean diffusivity (MD), which are thought to help to identify alterations in the health of white matter fibers. *Increases* in FA and *decreases* in MD are typically seen in healthy white matter development from young children to early adulthood [45]. In 2006, DeLisi and colleagues published one of the earlier studies to explore the potential for deleterious effects of cannabis on developing white matter.. The authors found higher FA and lower in MD in several tracts in MJ users compared to matched controls; they conclude no evidence of pathological white matter changes despite finding differences between groups [33]. Since this study, findings do suggest some evidence of alterations in white matter integrity in adolescent cannabis users. While DeLisi and colleagues suggest no evidence of pathology per se, subsequent studies have since shown changes in unanticipated directions [47]. While this may not represent a typical pathological process, group differences in either direction may still be reflective of a neural alterations.

For instance, increased MD in the prefrontal fiber bundles of the corpus callosum in heavy cannabis using adults (daily use for more than two years) who initiated use during adolescence suggest changes in white matter development associated with cannabis use [48].

Ashtari and colleagues (2009) found that adolescents with heavy cannabis use enrolled in residential drug treatment had reduced FA and increased MD in cortical association areas such as the temporal-parietal fiber tracts [49]. Recently, in a small sample of adolescents approximately 18 years of age, WM alterations were found in cannabis users compared to controls. Decreased FA in cortical and subcortical areas (e.g., hippocampal projections, superior longitudinal fasciculus) was found in cannabis users (weekly use for at least one year) compared to controls with no history of substance abuse [50].

In our laboratory, we have found white matter alterations in our abstinent teen marijuana users (ages 16–19) compared to controls. In two studies published in 2008 and 2009, we found poorer white matter integrity (e.g., decreased FA and increased MD) in several association and projection fiber tracts in adolescent cannabis users with concomitant alcohol use. Areas showing between group differences included tracts linked to fronto-parietal circuitry [51]. White matter integrity in several of these regions was linked to neurocognitive performance on measures of attention, working memory, and processing speed; we have also seen white matter linked to emotional functioning and prospective risk taking in our substance users [52, 53]. To better understand microstructural differences in tissue integrity among adolescent marijuana users as compared to binge drinkers, we looked at white matter differences between adolescent binge drinkers compared to binge drinkers with histories of heavy marijuana use (ages 16–19). While between group differences persisted between marijuana users and controls, surprisingly, teens engaging in binge drinking only looked significantly worse on indices of white matter integrity (i.e., decreased FA) in several areas (cortical and subcortical projection fibers) as compared to marijuana users, highlighting the need for further research to disentangle the effects of marijuana and alcohol on the developing brain [18].

In general, research points to poorer white matter integrity in adolescent marijuana users compared to non-substance using controls. While white matter findings are subtle in nature, we have observed poorer white matter integrity correlated with poorer neurocognitive functioning in our studies [47], which underscores the impact that slight alterations in white matter health during this time could have on optimal cognitive functioning. Interestingly, some preliminary evidence supports that marijuana-related toxicity on white matter integrity may be more modest compared to the impact adolescent alcohol use has on the developing brain, although more research in needed in this area.

Functional Imaging

fMRI Imaging—Changes in cognitive performance after acute and longer-term cannabis use are fairly well documented, even if residual effects are suspected to largely resolve. However, less is known on how brain functioning, or neural activation/signaling, may be changed by marijuana use and thereby reflected in declines in neuropsychological performance. Comparisons between blood oxygen dependent signal (BOLD) in adolescent marijuana users and controls in response to cognitive tasks have revealed subtle differences in brain activation patters in marijuana users. Jacobsen and colleagues (2004) were the first to pilot an auditory working memory (*n*-back) fMRI study comparing marijuana users (with tobacco use) compared to a tobacco using group and control group. The authors found

cannabis users performed the task less accurately and failed to deactivate the right hippocampus across conditions. In another study by the same authors, nicotine withdrawal elicited increased activation across brain regions in the marijuana group, including parietal cortex, superior temporal gyrus, posterior cingulate gyrus, and the right hippocampus. The same effect was not found in the tobacco-only control group suggesting marijuana use may lead to developmental changes masked by nicotine use [54, 55]

We have conducted several BOLD fMRI studies evaluating differences in activation patters between our sample of abstinent marijuana users and matched controls. In 2007, we found marijuana users to have substantially more activation than non-using peers in response to an inhibitory processing task, particularly in parietal and dorsolateral prefrontal cortices, suggesting additional neural resources required to maintain adequate executive control during response inhibition [56]. In evaluating response patterns to a spatial working memory task, adolescent marijuana users exhibited increased activation in the right parietal lobe along with diminished activation in the right dorsolateral prefrontal cortex to achieve good task performance, which was not observed in controls [57, 58]. In a follow-up investigation using the same spatial working memory task, we evaluated teens with more recent abstinence (2–7 days abstinent) compared to prolonged abstinence (27–60) from marijuana, as well as matched controls. Recent users showed greater brain activation in prefrontal cortices, regions needed for working memory processes, and bilateral insula [59]. In response to a third task assessing verbal encoding, marijuana users demonstrated increased encoding-related activation in anterior brain regions as compared to decreased activation in posterior regions, despite no differences in task performance [20]; findings may suggest increased recruitment of neural resources in brain areas subserving task-related processing in marijuana using teens.

Several recent studies outside of our laboratory have shown similar findings. For example, Jager and colleagues (2010) evaluated boys with frequent cannabis use (more than 200 lifetime cannabis use episodes) compared to matched controls (ages 13–19) and found that cannabis users showed excessive activity in prefrontal regions in response to a working memory task [60], studies from this same research group with young adults have yielded similar, although modest, aberrant findings of the working memory system [61]. In 2010, an investigation comprising chronic marijuana users and matched controls (approximately 19 years old), suggest increased activity in the prefrontal cortex in response to a task requiring executive aspects of attention [62]. Cousijn and colleauges recently found increased activation in heavy cannabis users (ages 18–25) in response to the Iowa Gambling task during win evaluations in brain areas such as the insula, caudate, and temporal gyrus, which was also positively related to weekly cannabis use; win-related increase in brain activity also predicted increased cannabis use six months later [63] Lopez-Larson and colleagues (2012) found differences in cortico-cerebellar activity in older adolescents with heavy marijuana use. The authors describe decreased activation in response to a bilateral finger-tapping task, and motor function activation was negatively correlated with total lifetime marijuana use [64]. Age of onset also continues to play an important role, as early-onset cannabis users (prior to age 16) demonstrated increased activation in the left superior parietal lobe in response to a verbal working memory challenge (verbal *n*-back task), and earlier initiation of

use was associated with increased BOLD activity [65]. The majority of findings suggest increased recruitment of neural resources (possibly reflecting compensation or changes in the efficiency of strategic neural processing) in brain areas subserving task-related processing in marijuana using teens.

Electroencephalogram (EEG)—There has been limited research on brain functioning using EEG among adolescent cannabis users. The strength in using EEG is the degree of temporal resolution that is not possible with BOLD imaging. Information on the degree of attentional bias to marijuana cues may provide some indication of brain-based differences in cue-reactivity resulting in heavier use of marijuana among certain teenagers. For instance, one lab based paradigm of cue reactivity found increased skin conductivity among teens diagnosed with cannabis use disorder [66]. Nickerson and colleagues (2011) found that among adolescents ages 14–17, P300 response (i.e., event-related potential response) was larger among cannabis users, and response increased (along with craving) in the user group after handling marijuana paraphernalia; findings suggest attentional bias, increased arousal, and possible neural differences (either pre-existing or altered by ongoing substance use engagement) that may elucidate discrepancies among teen substance use engagement [67].

Blood Perfusion—The neurovascular effect of marijuana use in adolescence has not been studied extensively. Understanding vascular changes in cerebral blood flow (CBF) can help us better understand neural signaling and vascular alterations that may be related to changes in neurocognitive functioning and/or changes in neural signaling related to the BOLD signal. Adult studies typically report increased CBF after acute exposure and lower or stabilized CBF after a period of abstinence in heavy users, although this has varied to some degree [68–70].

To our knowledge, there has only been one study in adolescent blood perfusion in heavy cannabis users. In a recent study in our laboratory utilizing arterial spin labeling (ASL), we found that heavy marijuana users (approximately 17 years old) assessed pre-and post 28 days of monitored abstinence showed reduced CBF in 4 cortical regions, including the left superior and middle temporal gyri, left insula, left and right medial frontal gyrus, and left supramarginal gyrus at baseline; users showed increased CBF in the right precuneus at baseline, as compared to controls. We did not observe group differences in neurovascular functioning after four weeks of abstinence, suggesting marijuana may influence cerebral blood flow acutely with a possible return to baseline with prolonged abstinence [71]. A study evaluating young adults (age range 21–27) found that acute THC administration increased blood perfusion in areas important for emotional and cognitive processing, such as the anterior cingulate, frontal cortex, and insula, and reduced perfusion in posterior brain regions. Resting state activity was also altered, as THC increased baseline activity [72].

Magnetic Resonance Spectroscopy—Very few studies have looked at neurochemical brain changes related to marijuana use in adolescence. Prescott and colleagues (2011) found decreases in metabolite concentrations (e.g., glutamate and N-acetyl aspartate) in the anterior cingulate, suggesting poorer underlying neuronal health in adolescent marijuana users [73], While the exact mechanisms by which cannabis would affect neuronal health is unclear, it is possible that modulation of neurotransmitters such as glutamate and GABA

have adverse consequences on cellular development and neuron integrity; changes in neuronal health is one suggested mechanism which may underlie neuroimaging and neurocognitive findings discussed above.

Preclinical Studies

A fairly large amount of work can be found on animal models of adolescent cannabis exposure. A detailed analysis of the preclinical studies is beyond the scope of this review, however briefly discussing the existing literature is important for translation to human models. Studies also focus on various cannabinoids beside Δ^9-tetrahydrocannabinol (Δ^9-THC), the principal psychoactive component of marijuana; for example increasing attention is being given to cannabidiol, a nonpsychoactive cannabinoid that may have promising therapeutic effects independent of THC [74]. However, this brief summary will focus on models of exposure to the natural compound or cannabinoid agonists, which mimic the structure Δ^9-THC. A great benefit of animal studies is lack of heterogeneity that corresponds with human consumption and substance use reporting.

In animals, postnatal days 28–49 correspond with human adolescent development (which can range from 21–59 for inclusion of early/late adolescent development) [75]. Studies during this postnatal time period in rats have evaluated both emotional behavior as well as cognitive/behavioral functioning. One of the first research groups to look at cannabinoid exposure found poorer performance on cognitive tasks, such as maze learning, in immature rats compared to mature rats treated with THC [76]. Schneider and Koch (2003, 2005) have reported alterations in pubertal rats treated with the receptor agonist WIN, discrepancies in performance range from sensorimotor functioning, object recognition memory, and social behavior [77, 78]. A more recent study by Schneider and colleagues (2008) found that chronic WIN treated pubertal rats demonstrated object/social recognition deficits, which the authors suggest is consistent with impairment in short-term information processing. Particularly, immature animals demonstrated more pronounced behavioral alterations as compared to mature animals after acute exposure to WIN, and more lasting deficits in social play and grooming behaviors [79]. Deficits in object recognition have also been reported in male and female pubertal rats treated with a cannabinoid receptor agonist as well as THC [80–82], and there is some support that findings are consistent across age groups.

Spatial functioning in adolescent rats has also shown affected by acute THC treatment [83]. In a recent investigation by Abush and colleagues (2012), chronic WIN treatment was found to result in both acute and longer term effects not only in spatial memory and object recognition, but interestingly, long term potentiation in areas such as nucleus accumbens pathways [84]. Studies are actively evaluating emotional functioning and neurochemical transmission in adolescent animals after exposure to cannabinoid agonists, as well as how cannabinoids moderate state-dependent learning based on brain regions [85, 86]. While this is not an exhaustive review of the preclinical findings, in general, the data suggest differential and often negative impact on adolescent animals compared to adult animals exposed to THC or other cannabinoid agonists in behavioral, emotional, and social outcomes. The animal work is particularly important to highlight, given the consistency in many adolescent neurocognitive and neuroimaging studies conducted with human subjects

reporting regular use of marijuana, as the findings often point to the deleterious effects on brain functioning compared to non-using controls.

Conclusions and Recommendations

Marijuana, second to alcohol, is the most widely used intoxicant. Approximately 25% of adolescents (8th, 10th, and 12th grade) report being drunk in the past month and close to the same (23%) report using marijuana in the past month [1]. As Gonzalez and Swanson point out in a recent commentary, annual prevalence rates of high school seniors have increased over the last decade (22% to 36%), while perceived risk of use has decreased from 80% of seniors reporting regular marijuana use as a “great risk” in 1992 to only 45% reporting marijuana use as risky in 2012 [1, 87]. The literature not only suggests neurocognitive disadvantages to using marijuana in the domains of attention and memory that persist beyond abstinence, but suggest possible macrostructural brain alterations (e.g., morphometry changes in gray matter tissue), changes in white matter tract integrity (e.g., poorer coherence in white matter fibers), and abnormalities of neural functioning (e.g., increased brain activation, changes in neurovascular functioning). Earlier initiation of marijuana use (e.g., before age 17) and more frequent use has also been associated with poorer outcome.

It is difficult to ascertain whether reported group differences reflect pre-existing brain architectural differences that lead to substance use and risk taking behaviors, and there is certainly some literature that suggests as such. Nevertheless, we have seen that differences in brain tissue integrity following heavier marijuana use does predict future risky behaviors such as increased marijuana use and aggressive and delinquent behaviors. This suggests imaging biomarkers may provide some clinical utility, despite the underlying pathological processes [53].

While the focus of this overview is on the existing adolescent literature, it is important to briefly touch on general findings in the adult literature. The amount of adult studies looking at the acute and non-acute effects of marijuana is large and investigations typically see changes in higher-order cognitive functioning and neural processes that are more pronounced immediately following THC administration and may persist after prolonged cessation of use; however current evidence suggests persisting differences are most likely subtle in nature [5, 6, 88–90]. In both the adult and adolescent literature abstinence periods and study designs vary widely (abstinence may vary from hours to years), and therefore making direct comparisons continues to be a challenge and the chronicity of cognitive alterations remains unclear. It is also unclear what defines acute versus longer-term effects (1 week compared to 6 months, etc). Findings from our laboratory discussed in this review reflect a “longer-term,” (residual) effect as adolescents are required to undergo a 28-day abstinence period confirmed by urine toxicology, yet in order to really understand the effects of this compound on the brain and cognition more rigorous study design needs to account for longer-term follow-up periods following monitored abstinence.

Early/late initiation of use as discussed in this review is also likely to interact with severity, frequency, and duration (and even administration) of use in both adolescent and adult studies. Similarly, there is emerging evidence on genetic vulnerability to cannabis, and more

information on consumed cannabis is needed as studies move sole focus from THC to other cannabinoids (e.g., cannabidiol) that are likely to influence neural changes and in both adolescents and adults [91, 92].

More adolescent longitudinal studies are still needed to understand both pre-existing differences as compared to discrepancies that develop post-initiation of use. Large longitudinal research would also help clarify the degree to which pre-existing differences and/or chronic marijuana use during adolescence contributes to the development of psychiatric disorders and cognitive impairment in adulthood. Furthermore, we need to better understand the interactive relationships between alcohol and marijuana use as these substance are commonly used together and may result in differing structural, functional, and cognitive brain changes when used alone or in combination.

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References

1. Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. Monitoring the future national results on adolescent drug use: Overview of key findings, 2011. Ann Arbor: Institute for Social Research, The University of Michigan; 2012.
2. Toga AW, Thompson PM, Sowell ER. Mapping brain maturation. Trends Neurosci. 2006; 29:148–159. [PubMed: 16472876]
3. Rubino T, Parolaro D. Long lasting consequences of cannabis exposure in adolescence. Mol Cell Endocrinol. 2008; 286:S108–S113. [PubMed: 18358595]
4. Iversen L. Cannabis and the brain. Brain. 2003; 126:1252–1270. [PubMed: 12764049]
5. Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. J Int Neuropsychol Soc. 2003; 9:679–689. [PubMed: 12901774]
6. Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry. 2001; 58:909–915. [PubMed: 11576028]
7. Casey BJ, Jones RM, Hare TA. The adolescent brain. Ann N Y Acad Sci. 2008; 1124:111–126. [PubMed: 18400927]
8. Schwartz RH, Gruenewald PJ, Klitzner M, Fedio P. Short-term memory impairment in cannabis-dependent adolescents. Am J Dis Child. 1989; 143:1214–1219. [PubMed: 2801665]
9. Teichner G, Donohue B, Crum TA, Azrin NH, Golden CJ. The relationship of neuropsychological functioning to measures of substance use in an adolescent drug abusing sample. Int J Neurosci. 2000; 104:113–124. [PubMed: 11011977]
10. Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marihuana--a comparison with pre-drug performance. Neurotoxicol Teratol. 2005; 27:231–239. [PubMed: 15734274]
11. Lane SD, Cherek DR, Pietras CJ, Steinberg JL. Performance of heavy marijuana-smoking adolescents on a laboratory measure of motivation. Addict Behav. 2005; 30:815–828. [PubMed: 15833584]
12. Lane SD, Cherek DR, Tcheremissine OV, Steinberg JL, Sharon JL. Response perseveration and adaptation in heavy marijuana-smoking adolescents. Addict Behav. 2007; 32:977–990. [PubMed: 16930850]
13. Harvey MA, Sellman JD, Porter RJ, Frampton CM. The relationship between non-acute adolescent cannabis use and cognition. Drug Alcohol Rev. 2007; 26:309–319. [PubMed: 17454021]

14. Tapert SF, Granholm E, Leedy NG, Brown SA. Substance use and withdrawal: neuropsychological functioning over 8 years in youth. J Int Neuropsychol Soc. 2002; 8:873–883. [PubMed: 12405538]
15. Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. J Int Neuropsychol Soc. 2007; 13:807–820. [PubMed: 17697412]
16. Hanson KL, Winward JL, Schweinsburg AD, Medina KL, Brown SA, Tapert SF. Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence. Addict Behav. 2010; 35:970–976. [PubMed: 20621421]
17. Mahmood OM, Jacobus J, Bava S, Scarlett A, Tapert SF. Learning and memory performances in adolescent users of alcohol and marijuana: interactive effects. J Stud Alcohol Drugs. 2010; 71:885–894. [PubMed: 20946746]
18. Jacobus J, McQueeny T, Bava S, Schweinsburg BC, Frank LR, Yang TT, Tapert SF. White matter integrity in adolescents with histories of marijuana use and binge drinking. Neurotoxicol Teratol. 2009; 31:349–355. [PubMed: 19631736]
19. Medina KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. Neurotoxicol Teratol. 2007; 29:141–152. [PubMed: 17169528]
20. Schweinsburg AD, Schweinsburg BC, Nagel BJ, Eyler LT, Tapert SF. Neural correlates of verbal learning in adolescent alcohol and marijuana users. Addiction. 2011; 106:564–573. [PubMed: 21134014]
21. Tait RJ, Mackinnon A, Christensen H. Cannabis use and cognitive function: 8-year trajectory in a young adult cohort. Addiction. 2011; 106:2195–2203. [PubMed: 21749524]
22. Takagi M, Yucel M, Cotton SM, Baliz Y, Tucker A, Elkins K, Lubman DI. Verbal memory, learning, and executive functioning among adolescent inhalant and cannabis users. J Stud Alcohol Drugs. 2011; 72:96–105. [PubMed: 21138716]
23. Takagi M, Lubman DI, Cotton S, Fornito A, Baliz Y, Tucker A, Yucel M. Executive control among adolescent inhalant and cannabis users. Drug Alcohol Rev. 2011; 30:629–637. [PubMed: 21355925]
24. Gonzalez R, Schuster RM, Mermelstein RJ, Vassileva J, Martin EM, Diviak KR. Performance of young adult cannabis users on neurocognitive measures of impulsive behavior and their relationship to symptoms of cannabis use disorders. J Clin Exp Neuropsychol. 2012
25. Solowij N, Jones KA, Rozman ME, Davis SM, Ciarrochi J, Heaven PC, Lubman DI, Yucel M. Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. Psychopharmacology (Berl). 2011; 216:131–144. [PubMed: 21328041]
26. Bartholomew J, Holroyd S, Heffernan TM. Does cannabis use affect prospective memory in young adults? J Psychopharmacol. 2010; 24:241–246. [PubMed: 19825904]
27. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, McDonald K, Ward A, Poulton R, Moffitt TE. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A. 2012
28. Ehrenreich H, Rinn T, Kunert HJ, Moeller MR, Poser W, Schilling L, Gigerenzer G, Hoehe MR. Specific attentional dysfunction in adults following early start of cannabis use. Psychopharmacology (Berl). 1999; 142:295–301. [PubMed: 10208322]
29. Pope HG Jr, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug Alcohol Depend. 2003; 69:303–310. [PubMed: 12633916]
30. Fontes MA, Bolla KI, Cunha PJ, Almeida PP, Jungerman F, Laranjeira RR, Bressan RA, Lacerda AL. Cannabis use before age 15 and subsequent executive functioning. Br J Psychiatry. 2011; 198:442–447. [PubMed: 21628706]
31. Ostby Y, Tamnes CK, Fjell AM, Westlye LT, Due-Tonnessen P, Walhovd KB. Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. J Neurosci. 2009; 29:11772–11782. [PubMed: 19776264]
32. Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev. 2010; 20:327–348. [PubMed: 21042938]

33. Delisi LE, Bertisch HC, Szulc KU, Majcher M, Brown K, Bappal A, Ardekani BA. A preliminary DTI study showing no brain structural change associated with adolescent cannabis use. Harm Reduct J. 2006; 3:17. [PubMed: 16684342]
34. Block RI, O'Leary DS, Ehrhardt JC, Augustinack JC, Ghoneim MM, Arndt S, Hall JA. Effects of frequent marijuana use on brain tissue volume and composition. Brain Imaging. 1999; 11:491–496.
35. Churchwell JC, Lopez-Larson M, Yurgelun-Todd DA. Altered frontal cortical volume and decision making in adolescent cannabis users. Front Psychol. 2010; 1:225. [PubMed: 21833280]
36. Mata I, Perez-Iglesias R, Roiz-Santianez R, Tordesillas-Gutierrez D, Pazos A, Gutierrez A, Vazquez-Barquero JL, Crespo-Facorro B. Gyrification brain abnormalities associated with adolescence and early-adulthood cannabis use. Brain Res. 2010; 1317:297–304. [PubMed: 20045399]
37. Ashtari M, Avants B, Cyckowski L, Cervellione KL, Roofeh D, Cook P, Gee J, Sevy S, Kumra S. Medial temporal structures and memory functions in adolescents with heavy cannabis use. J Psychiatr Res. 2011; 45:1055–1066. [PubMed: 21296361]
38. Medina KL, McQueeny T, Nagel BJ, Hanson KL, Yang TT, Tapert SF. Prefrontal cortex morphometry in abstinent adolescent marijuana users: subtle gender effects. Addict Biol. 2009; 14:457–468. [PubMed: 19650817]
39. McQueeny T, Padula CB, Price J, Medina KL, Logan P, Tapert SF. Gender effects on amygdala morphometry in adolescent marijuana users. Behav Brain Res. 2011; 224:128–134. [PubMed: 21664935]
40. Medina KL, Nagel BJ, Tapert SF. Abnormal cerebellar morphometry in abstinent adolescent marijuana users. Psychiatry Res. 2010; 182:152–159. [PubMed: 20413277]
41. Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Goudriaan AE. Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. Neuroimage. 2012; 59:3845–3851. [PubMed: 21982932]
42. Cheetham A, Allen NB, Whittle S, Simmons JG, Yucel M, Lubman DI. Orbitofrontal volumes in early adolescence predict initiation of cannabis use: a 4-year longitudinal and prospective study. Biol Psychiatry. 2012; 71:684–692. [PubMed: 22129756]
43. Lopez-Larson MP, Bogorodzki P, Rogowska J, McGlade E, King JB, Terry J, Yurgelun-Todd D. Altered prefrontal and insular cortical thickness in adolescent marijuana users. Behav Brain Res. 2011; 220:164–172. [PubMed: 21310189]
44. Wilson W, Mathew R, Turkington T, Hawk T, Coleman RE, Provenzale J. Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. J Addict Dis. 2000; 19:1–22. [PubMed: 10772599]
45. Lebel C, Beaulieu C. Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci. 2011; 31:10937–10947. [PubMed: 21795544]
46. Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C. Diffusion tensor imaging of white matter tract evolution over the lifespan. Neuroimage. 2012; 60:340–352. [PubMed: 22178809]
47. Bava S, Jacobus J, Mahmood O, Yang TT, Tapert SF. Neurocognitive correlates of white matter quality in adolescent substance users. Brain Cogn. 2010; 72:347–354. [PubMed: 19932550]
48. Arnone D, Barrick TR, Chengappa S, Mackay CE, Clark CA, Abou-Saleh MT. Corpus callosum damage in heavy marijuana use: preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. Neuroimage. 2008; 41:1067–1074. [PubMed: 18424082]
49. Ashtari M, Cervellione K, Cottone J, Ardekani BA, Sevy S, Kumra S. Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use. J Psychiatr Res. 2009; 43:189–204. [PubMed: 19111160]
50. Yucel M, Zalesky A, Takagi MJ, Bora E, Fornito A, Ditchfield M, Egan GF, Pantelis C, Lubman DI. White-matter abnormalities in adolescents with long-term inhalant and cannabis use: a diffusion magnetic resonance imaging study. J Psychiatry Neurosci. 2010; 35:409–412. [PubMed: 20731960]
51. Bava S, Frank LR, McQueeny T, Schweinsburg BC, Schweinsburg AD, Tapert SF. Altered white matter microstructure in adolescent substance users. Psychiatry Res. 2009; 173:228–237. [PubMed: 19699064]

52. Medina KL, Nagel BJ, Park A, McQueeny T, Tapert SF. Depressive symptoms in adolescents: associations with white matter volume and marijuana use. J Child Psychol Psychiatry. 2007; 48:592–600. [PubMed: 17537075]

53. Jacobus J, Thayer RE, Trim RS, Bava S, Frank LR, Tapert SF. White Matter Integrity, Substance Use, and Risk Taking in Adolescence. Psychol Addict Behav. 2012

54. Jacobsen LK, Pugh KR, Constable RT, Westerveld M, Mencl WE. Functional correlates of verbal memory deficits emerging during nicotine withdrawal in abstinent adolescent cannabis users. Biol Psychiatry. 2007; 61:31–40. [PubMed: 16631130]

55. Jacobsen LK, Mencl WE, Westerveld M, Pugh KR. Impact of cannabis use on brain function in adolescents. Ann N Y Acad Sci. 2004; 1021:384–390. [PubMed: 15251914]

56. Tapert SF, Schweinsburg AD, Drummond SP, Paulus MP, Brown SA, Yang TT, Frank LR. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. Psychopharmacology (Berl). 2007; 194:173–183. [PubMed: 17558500]

57. Schweinsburg AD, Nagel BJ, Schweinsburg BC, Park A, Theilmann RJ, Tapert SF. Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. Psychiatry Res. 2008; 163:40–51. [PubMed: 18356027]

58. Padula CB, Schweinsburg AD, Tapert SF. Spatial working memory performance and fMRI activation interaction in abstinent adolescent marijuana users. Psychol Addict Behav. 2007; 21:478–487. [PubMed: 18072830]

59. Schweinsburg AD, Schweinsburg BC, Medina KL, McQueeny T, Brown SA, Tapert SF. The influence of recency of use on fMRI response during spatial working memory in adolescent marijuana users. J Psychoactive Drugs. 2010; 42:401–412. [PubMed: 21053763]

60. Jager G, Block RI, Luijten M, Ramsey NF. Cannabis use and memory brain function in adolescent boys: a cross-sectional multicenter functional magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry. 2010; 49:561–572. 572 e1–572 e3. [PubMed: 20494266]

61. Jager G, Kahn RS, Van Den Brink W, Van Ree JM, Ramsey NF. Long-term effects of frequent cannabis use on working memory and attention: an fMRI study. Psychopharmacology (Berl). 2006; 185:358–368. [PubMed: 16521034]

62. Abdullaev Y, Posner MI, Nunnally R, Dishion TJ. Functional MRI evidence for inefficient attentional control in adolescent chronic cannabis abuse. Behav Brain Res. 2010; 215:45–57. [PubMed: 20600341]

63. Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Porrino LJ, Goudriaan AE. Individual differences in decision making and reward processing predict changes in cannabis use: a prospective functional magnetic resonance imaging study. Addict Biol. 2012

64. Lopez-Larson MP, Rogowska J, Bogorodzki P, Bueler CE, McGlade EC, Yurgelun-Todd DA. Cortico-cerebellar abnormalities in adolescents with heavy marijuana use. Psychiatry Res. 2012; 202:224–232. [PubMed: 22835865]

65. Becker B, Wagner D, Gouzoulis-Mayfrank E, Spuentrup E, Daumann J. The impact of early-onset cannabis use on functional brain correlates of working memory. Prog Neuropsychopharmacol Biol Psychiatry. 2010; 34:837–845. [PubMed: 20363277]

66. Gray KM, LaRowe SD, Watson NL, Carpenter MJ. Reactivity to in vivo marijuana cues among cannabis-dependent adolescents. Addict Behav. 2011; 36:140–143. [PubMed: 20851531]

67. Nickerson LD, Ravichandran C, Lundahl LH, Rodolico J, Dunlap S, Trksak GH, Lukas SE. Cue reactivity in cannabis-dependent adolescents. Psychol Addict Behav. 2011; 25:168–173. [PubMed: 21142334]

68. Lundqvist T, Jonsson S, Warkentin S. Frontal lobe dysfunction in long-term cannabis users. Neurotoxicol Teratol. 2001; 23:437–443. [PubMed: 11711246]

69. Tunving K, Thulin SO, Risberg J, Warkentin S. Regional cerebral blood flow in long-term heavy cannabis use. Psychiatry Res. 1986; 17:15–21. [PubMed: 3484830]

70. Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Valentine A, Hollister L. Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. Psychiatry Res. 1996; 67:29–38. [PubMed: 8797240]

71. Jacobus J, Goldenberg D, Wierenga CE, Tolentino NJ, Liu TT, Tapert SF. Altered cerebral blood flow and neurocognitive correlates in adolescent cannabis users. Psychopharmacology (Berl). 2012

72. van Hell HH, Bossong MG, Jager G, Kristo G, van Osch MJ, Zelaya F, Kahn RS, Ramsey NF. Evidence for involvement of the insula in the psychotropic effects of THC in humans: a double-blind, randomized pharmacological MRI study. Int J Neuropsychopharmacol. 2011; 14:1377–1388. [PubMed: 21489346]

73. Prescot AP, Locatelli AE, Renshaw PF, Yurgelun-Todd DA. Neurochemical alterations in adolescent chronic marijuana smokers: a proton MRS study. Neuroimage. 2011; 57:69–75. [PubMed: 21349338]

74. Kozela E, Pietr M, Juknat A, Rimmerman N, Levy R, Vogel Z. Cannabinoids Delta(9)-tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF-kappaB and interferon-beta/STAT proinflammatory pathways in BV-2 microglial cells. J Biol Chem. 2010; 285:1616–1626. [PubMed: 19910459]

75. Dinieri JA, Hurd YL. Rat models of prenatal and adolescent cannabis exposure. Methods Mol Biol. 2012; 829:231–242. [PubMed: 22231817]

76. Stiglick A, Kalant H. Residual effects of chronic cannabis treatment on behavior in mature rats. Psychopharmacology (Berl). 1985; 85:436–439. [PubMed: 3927340]

77. Schneider M, Koch M. Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. Neuropsychopharmacology. 2003; 28:1760–1769. [PubMed: 12888772]

78. Schneider M, Koch M. Deficient social and play behavior in juvenile and adult rats after neonatal cortical lesion: effects of chronic pubertal cannabinoid treatment. Neuropsychopharmacology. 2005; 30:944–957. [PubMed: 15592349]

79. Schneider M, Schomig E, Leweke FM. Acute and chronic cannabinoid treatment differentially affects recognition memory and social behavior in pubertal and adult rats. Addict Biol. 2008; 13:345–357. [PubMed: 18782382]

80. Quinn HR, Matsumoto I, Callaghan PD, Long LE, Arnold JC, Gunasekaran N, Thompson MR, Dawson B, Mallet PE, Kashem MA, Matsuda-Matsumoto H, Iwazaki T, McGregor IS. Adolescent rats find repeated Delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. Neuropsychopharmacology. 2008; 33:1113–1126. [PubMed: 17581536]

81. O'Shea M, McGregor IS, Mallet PE. Repeated cannabinoid exposure during perinatal, adolescent or early adult ages produces similar longlasting deficits in object recognition and reduced social interaction in rats. J Psychopharmacol. 2006; 20:611–621. [PubMed: 16714325]

82. O'Shea M, Singh ME, McGregor IS, Mallet PE. Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. J Psychopharmacol. 2004; 18:502–508. [PubMed: 15582916]

83. Cha YM, White AM, Kuhn CM, Wilson WA, Swartzwelder HS. Differential effects of delta9-THC on learning in adolescent and adult rats. Pharmacol Biochem Behav. 2006; 83:448–455. [PubMed: 16631921]

84. Abush H, Akirav I. Short- and long-term cognitive effects of chronic cannabinoids administration in late-adolescence rats. PLoS One. 2012; 7:e31731. [PubMed: 22348124]

85. Bambico FR, Nguyen NT, Katz N, Gobbi G. Chronic exposure to cannabinoids during adolescence but not during adulthood impairs emotional behaviour and monoaminergic neurotransmission. Neurobiol Dis. 2010; 37:641–655. [PubMed: 19969082]

86. Segev A, Akirav I. Differential effects of cannabinoid receptor agonist on social discrimination and contextual fear in amygdala and hippocampus. Learn Mem. 2011; 18:254–259. [PubMed: 21447623]

87. Gonzalez R, Swanson JM. Long-term effects of adolescent-onset and persistent use of cannabis. Proc Natl Acad Sci U S A. 2012; 109:15970–15971. [PubMed: 23012451]

88. Batalla A, Bhattacharyya S, Yucel M, Fusar-Poli P, Crippa JA, Nogue S, Torrens M, Pujol J, Farre M, Martin-Santos R. Structural and functional imaging studies in chronic cannabis users: a

systematic review of adolescent and adult findings. PLoS One. 2013; 8:e55821. [PubMed: 23390554]

89. Gonzalez R. Acute and non-acute effects of cannabis on brain functioning and neuropsychological performance. Neuropsychol Rev. 2007; 17:347–361. [PubMed: 17680367]
90. Crane NA, Schuster RM, Fusar-Poli P, Gonzalez R. Effects of cannabis on neurocognitive functioning: Recent advances, neurodevelopmental influences, and sex differences. Neuropsychology Review. 2012
91. Schoeler T, Bhattacharyya S. The effect of cannabis use on memory function. Substance Abuse and Rehabilitation. 2103; 4:11–27. [PubMed: 24648785]
92. van Winkel R. Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: sibling analysis and proband follow-up. Arch Gen Psychiatry. 2011; 68:148–157. [PubMed: 21041608]