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Mini-Review

Functional consequences of marijuana use in adolescents

J. Jacobus [d], S. Bava [b,c], M. Cohen-Zion [b,f], O. Mahmood [b,e], S.F. Tapert [a,b,*]

[a] VA San Diego Healthcare System, Psychology Service, San Diego, CA, USA
[b] University of California San Diego, Department of Psychiatry, San Diego, CA, USA
[c] University of California San Diego, Department of Radiology, San Diego, CA, USA
[d] SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA
[e] San Diego State University, Department of Psychology, San Diego, CA, USA
[f] Sleep Disorders Clinic, Assuta Medical Center, Tel-Aviv, Israel

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ABSTRACT

Nearly half of 12th graders have tried marijuana, and 6% use daily. This paper reviews studies on neuropsychological functioning, brain structure, brain function, and subjective and objective measures of sleep in relation to adolescent marijuana use. Adolescents who use marijuana heavily tend to show disadvantaged attention, learning, and processing speed; subtle abnormalities in brain structure; increased activation during cognitive tasks despite intact performance; and compromised objective indicators of sleep quality. Some abnormalities appear to persist beyond a month of abstinence, but may resolve within three months if cessation is maintained. Recommendations for future studies include characterizing these indices in youth prior to the onset of marijuana use then examining change after chronic use has started, and using large samples of youth with varying degrees of involvement with marijuana as well as alcohol, nicotine, and other drugs to characterize the interactive influences on neurocognition and neural health.

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Worldwide, recreational use of marijuana (including other cannabis products like hashish) is relatively common during adolescence, a period marked by important brain developments. In adults, chronic heavy marijuana use has been associated with alterations in brain structure, function, and behavior. Any cognitive deficits resulting from adolescent marijuana-related insults would have unfavorable implications for subsequent academic, occupational, and social functioning, extending into adulthood. Given the prevalence of marijuana use, elucidating the neurocognitive sequelae is vital.

U.S. school survey data (Johnston et al., 2008) show that 15% of 8th graders have tried marijuana at least once, and increasing to 43% by 12th grade. Of concern is that 6% of 8th graders and 19% of 12th graders report past-month marijuana use, and 6% of 12th graders report daily use. This represents a modest increase from the steady declines that followed the peak prevalence in 1999. Marijuana is implicated in nearly 120,000 emergency room visits per year, of which 15% are by adolescents (Substance Abuse and Mental Health Services Administration, 2003), and over a third of juvenile arrestees test

* Corresponding author. 9500 Gilman Drive (0603V), San Diego, CA 92093-0603, USA. Tel.: +1 858 552 8585; fax: +1 858 642 6474.
E-mail address: stapert@ucsd.edu (S.F. Tapert).

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positive for marijuana (National Institute of Justice, 2002). In contrast to the adult literature, adolescent marijuana use has been associated with an increased risk of future depressive and anxiety disorders (Rey et al., 2004; Substance Abuse and Mental Health Services Administration, 2007). During marijuana intoxication, teens may display impaired judgment, contributing to risky behaviors such as unprotected sex, driving under the influence, or riding with an intoxicated driver (Gruber and Pope, 2002). Teens who smoke marijuana are at greater risk of reduced educational performance and grades, truancy, dropout, and future unemployment (Lynskey and Hall, 2000).

Adolescence marks a period of rapid developments driving the transition from childhood to adulthood, involving complex biological, psychological, and social changes, and the progressions and interactions of these factors define adolescent outcomes. Exposure to marijuana during a critical period of neural development may interrupt maturational processes, yet on the other hand, the developing brain may be more resilient to neurotoxic effects. Brain changes that occur in adolescence relate to increased efficiency and specialization through synaptic pruning and myelination (Yakovlev and Lecours, 1967). Synaptic pruning involves reductions in cortical gray matter by eliminating neural connections that appear to be unnecessary (Sowell et al., 2004). During adolescence, this pruning occurs primarily in the prefrontal and temporal cortices (Giedd, 2004) and in subcortical structures such as the striatum, thalamus, and nucleus accumbens (Huttenlocher, 1990; Sowell et al., 1999). The adolescent brain also undergoes increased myelination, yielding improved integrity of white matter fiber tracts and efficient neural conductivity (Hüppi and Dubois, 2006; Jernigan and Gamst, 2005; Pfefferbaum et al., 1994; Sowell et al., 2001). Higher-order association areas develop after lower-order sensorimotor regions mature (Gogtay et al., 2004), providing faster communication between frontal–subcortical brain regions and better top–down cognitive control in adolescence (Luna and Sweeney, 2004). Sleep also plays a large role in development. The average teen needs approximately 8.50–9.25 h of sleep per night (Jenni and Carskadon, 2005) and a delay of intrinsic sleep phase occurs during adolescence, with teens often not feeling physiologically tired enough to fall asleep until later, compared to younger children (Herman, 2005). Marijuana use during adolescence may disrupt sleep architecture leaving teens highly vulnerable to sleep deprivation and alterations in neural development.

Neuromaturation during adolescence contributes to cognitive, emotional, and behavioral changes (Chambers and Potenza, 2003) that may convey an increased propensity for substance use in some adolescents (Casey et al., 2008; Spear, 2000). This review will present current research regarding subtle but significant abnormalities in neural function associated with marijuana use during adolescent neurodevelopment. Studies using neuropsychological assessment, structural and functional neuroimaging, and objective and subjective measures of sleep will be discussed, and recommendations for closing knowledge gaps in the field will be presented.

1. Cognitive consequences of marijuana use in adolescents

The neurocognitive effects of adult marijuana use following brief periods of abstinence have been well fairly well characterized. Studies report deficits in learning, memory, sustained attention, mental flexibility, and processing speed (Fletcher et al., 1996; Pope and Yurgelun-Todd, 1996; Solowij et al., 2002). Until 2001, few studies had evaluated the cognitive effects of marijuana use after more than a few days of abstinence, so it was unclear if observed deficits reflected transient or persisting effects. Pope et al. examined neurocognition in chronic heavy marijuana users, importantly, after 28 days of monitored abstinence (Pope et al., 2001). No differences were seen between users and controls on a comprehensive neuropsychological battery on testing day 28. Conversely, a study by Bolla et al. (2002) did find differences between heavy and light marijuana users after 28 days of abstinence, along with a dose-dependent relationship between joints smoked per week prior to enrollment and performance on measures of psychomotor speed, executive functioning, and manual dexterity (Bolla et al., 2002). A meta-analysis by Grant et al. (2003) attempted to identify the long-term effects of marijuana consumption on cognition, and reported small effects in the domains of learning, memory, and overall neurocognitive performance (Grant et al., 2003). Thus, subtle neurocognitive effects observed in heavy adult marijuana users may be attributable to “residual” sequelae present only in the first few hours or days of stopping marijuana use (Grant et al., 2003; Pope et al., 2001).

The neuropsychological effects of adolescent marijuana use are less well characterized. Lane et al. (2007) found that heavy adolescent marijuana users demonstrated more perseverative errors on a problem-solving task compared to youth with minimal use. In a longitudinal investigation examining adolescents with histories of substance use disorders (Tapert et al., 2002), greater cumulative marijuana use over an eight-year follow-up period predicted diminished performance over time on measures of attention (Tapert et al., 2002). Harvey et al. (2007) found that adolescent regular marijuana users performed worse on tests of attention, nonverbal memory, and learning, and more days of cannabis use in the past month predicted poorer performance on executive functioning and working memory tests, even after controlling for years of school completed and verbal intelligence (Harvey et al., 2007). However, no relationships between neuropsychological performance scores and marijuana use histories were observed in one sample of adolescents referred for drug treatment (Teichner et al., 2000).

Additional insights into the potentially deleterious effects of adolescent marijuana use on cognitive functioning come from studies of adult users that compared early- and late-onset marijuana users (Ehrenreich et al., 1999; Pope et al., 2003). Onset of marijuana use before age 17, (i.e., early-mid adolescent onset) predicted impaired reaction times on a task of visual scanning and attention (Ehrenreich et al., 1999) among young adult marijuana users. Pope et al. (2003) found that early-onset (before age 17) but not late-onset use was linked to performance decrements on verbal memory, IQ, and fluency.

We (Medina et al., 2007a) found that adolescent marijuana users demonstrated poorer performance on tests of attention, verbal learning/memory, sequencing, and psychomotor speed compared to non-using adolescents after approximately one month of abstinence. Those with greater lifetime marijuana use performed particularly poorly on these measures, above and beyond variability attributable to lifetime alcohol use. Marijuana dependent adolescents, ages 14 to 16, showed verbal and nonverbal short-term memory impairments as compared to control adolescents, and a trend for improved memory performance after six weeks of abstinence was observed (Schwartz, 1989). In another longitudinal study examining adolescents exposed to cannabis prenatally, current heavy marijuana users had lower scores on processing speed and immediate and delayed memory as compared to controls, even after accounting for performance prior to the onset of use. However, no differences were found between the users who had been abstinent at least three months and controls (Fried et al., 2005). Thus, it is possible that, in adolescents with heavy marijuana use, neurocognitive deficits in the areas of attention, verbal learning/memory, and processing speed persist beyond one month of abstinence, but largely remit after three months of sustained abstinence.

Overall, findings of neuropsychological impairments in adolescent marijuana users are fairly consistent with studies of adult users, suggesting significant but relatively subtle detrimental effects in the domains of attention, memory, processing speed, and some executive functions (planning, perseveration, and fluency). However, these cognitive disadvantages may be more likely to manifest, and to persist after a month of abstinence, with adolescent as opposed to adult marijuana use. Early-onset marijuana use, such as initiation during

mid-adolescence as compared to adulthood, may help explain some subtle persisting differences in neurocognitive performance over time. Those who start using at an earlier age may have greater susceptibility to the longer-term consequences of cannabis toxicity on the developing brain than those with a later onset of cannabis exposure. These findings have substantial implications in adolescent development. Adolescent marijuana users may be at increased risk for impairments in neurocognitive functioning, which may lead to negative consequences in school (e.g., trouble retaining information), impaired driving, and risky decision-making. Longitudinal studies are still necessary to identify which adolescent users will demonstrate cognitive impairments, ascertain critical junctures in adolescent neuromaturation when exposure to marijuana would result in worse neurocognitive outcomes, elucidate the time course of recovering neurocognitive impairments, and identify CNS alterations that may result from heavy adolescent marijuana use. Future studies are also needed to evaluate the premorbid cognitive status of adolescents prior to initiation of regular marijuana use, and to carefully examine the influence of other substance use (e.g., alcohol, tobacco, misused prescriptions, and other illicit drugs) in relation to marijuana use on cognitive functioning.

2. Brain structure and adolescent marijuana uses

Neuroimaging studies have recently begun to explore the volume, morphometry, and integrity of the brains of adolescent marijuana users, focusing on systems associated with vulnerability to mood and neurocognitive problems. Advanced magnetic resonance imaging (MRI) techniques have quantified tissue density, differentiated tissue composition, and evaluated tissue organization and integrity *in vivo*. Age at which exposure begins appears important. In an MRI/positron emission tomography study, male and female users who started marijuana before age 17 had smaller whole brain and cortical gray matter volumes and larger white matter volumes, and, among males, higher cerebral blood flow, compared to those who started later (Wilson et al., 2000).

The prevailing discussion in adolescent substance use research is whether observed abnormalities relate to risk factors associated with substance use disorders or to the neurotoxic effects of the substance. We (Medina et al., 2007c) controlled for preexisting differences that could affect brain morphometry in examining hippocampal volume and asymmetry in alcohol users ($n=16$), marijuana and alcohol users ($n=26$), and demographically similar controls ($n=21$), ages 15–18 and free from psychiatric disorders. Although groups did not differ on family history of substance use disorders, parent SES, verbal intellect, or reading ability, left hemisphere hippocampal volumes were smaller in alcohol users compared to marijuana and alcohol users, who showed the largest left hippocampal volume of all groups. More alcohol abuse/dependence symptoms was associated with greater right>left hippocampal asymmetry, whereas increased *marijuana* abuse/dependence symptoms was linked to more *left>right* hippocampal asymmetry. Although marijuana and alcohol users did not differ from controls in hippocampal volume or asymmetry, they demonstrated significantly weaker correlations between asymmetry and performance on the California Verbal Learning Test (Children's Version (CVLT-C) (Delis et al., 1994) or 2nd Edition (CVLT-II, Delis et al., 2000) than controls, among whom right>left hippocampal volume was associated with better first trial learning and recall performance. Compared to controls, the right>left asymmetry in alcohol users was due to smaller left hippocampal volumes that may be indicative of pathological processes, such as alcohol-related neuronal death or atrophy, and appears to have implications for verbal learning. Relative changes in tissue composition such as increased white matter density and reduced gray matter density, evident in adult users with chronic marijuana use histories (Matochik et al., 2005), may explain why hippocampal volumes were similar between marijuana and alcohol users and controls. That is, opposing processes may increase the white matter volume but decrease the gray matter volume, yielding an overall similar net volume that contains underlying pathology. Alternatively, early chronic activation of cannabinoid receptors may result in changed tissue integrity and organization that are not reflected in gross macrostructural measurements.

An examination of brain morphometry after a month of sustained abstinence quantified total brain white matter volume, bilateral hippocampal volume, and depressive symptoms among 16 heavy marijuana users and 16 controls (Medina et al., 2007b). Although users did not show white matter or hippocampal volume divergences from controls, users with smaller white matter volumes demonstrated an increased likelihood of depressive symptoms. This suggests that chronic marijuana use during adolescence may influence affect by disrupting mood regulating frontal–limbic–basal ganglia pathways. Indeed, brain regions that are rich in cannabinoid receptors, and therefore susceptible to effects of cannabis, include the frontal cortex, hippocampus, basal ganglia, cerebellum, amygdala, and striatum (Freedland et al., 2002; Iversen, 2003; Pontieri et al., 1999; Quickfall and Crockford, 2006). Selective mesocorticolimbic disturbance is also documented as a consequence of adolescent marijuana exposure in rats, where alterations in prefrontal cortex and nucleus accumbens are most prominent (Ellgren et al., 2008).

Gender may influence the effects of marijuana on the developing brain. In a study of 16 marijuana users (ages 16–18) and matched controls, prefrontal cortex volumes were larger in female and smaller in male marijuana users compared to same-gender controls, even after a month of sustained abstinence (Medina et al., submitted for publication). Smaller prefrontal cortex volumes were associated with better executive functioning for users, but poorer performance for controls. Among controls, larger volumes were associated with better executive functioning. Although preliminary, these data suggest that female adolescent marijuana users may be at greater risk for neurocognitive compromise than males. Gender differences in marijuana effects may relate to differences in hormone and receptor distributions that may interact with the cannabinoid system. Among young adults, increased age is associated with higher CB-1 density in the prefrontal cortex of females, but not males (Van Laere et al., 2008). Thus, increased CB-1 density in females could result in greater susceptibility to cannabis-induced neuromodulation effects. Together, these findings suggest possible perturbations in tissue integrity that may indicate underlying microstructural disruption in individuals with histories of heavy adolescent marijuana use.

To explore white matter microstructure in early-onset marijuana use, adolescents ages 16–19 with concurrent marijuana and alcohol use ($n=36$) and typically developing teens ($n=36$) were examined (Bava et al., submitted for publication) with diffusion tensor imaging (DTI), a non-invasive technique that enables quantification of microstructural changes in white matter. Two standard scalar measures derived from DTI data are the fractional anisotropy (FA), a measurement of the directional variance of diffusional motion, and mean diffusivity (MD), measuring the overall magnitude of diffusional motion within a given voxel (Moritani et al., 2004). These parameters were subjected to whole-brain voxelwise group comparisons using tract-based spatial statistics (Smith et al., 2006). Increased FA and decreased MD are typically thought to reflect ongoing myelination and increased organization and coherence in white matter fiber tracts.

Marijuana and alcohol users showed significantly lower FA than controls in 10 regions, suggesting poor fiber integrity. Results remained even after controlling for cigarette and other drug use, and family history. Lower FA was prominent in frontal–parietal circuitry comprising fibers of the inferior frontal region, splenium of the corpus callosum, postcentral gyrus, and left superior longitudinal fasciculus. Interestingly, users showed *increased* FA in three right hemisphere regions, including the occipital lobe, internal capsule, and arcuate portion of the superior

longitudinal fasciculus. MD was similar between groups in the regions of FA discrepancy, but higher among users in white matter adjacent the lingual gyrus, suggesting less tract coherence, and lower in the posterior aspect of the left inferior longitudinal fasciculus as compared to controls. Disruptions to white matter could indicate aberrant axonal and myelin maturation, while findings of increased anisotropic diffusion may suggest neuroadaptive processes. Higher FA in the rostral body of the corpus callosum and lower MD in the isthmus region were found in another study of adolescent substance users (De Bellis et al., 2008), highlighting the need for additional research to determine whether abnormalities in white matter microstructure might influence efficient cognitive processing.

Whether the reported changes in brain structure among marijuana using adolescents persist into adulthood remains tentative. Increased MD in the prefrontal fiber bundles of the corpus callosum in adults who initiated use during early adolescence suggests long-term changes to white matter quality as a result of adolescent marijuana use (Arnone et al., 2008). In addition, a voxel-based morphometry study of gray matter in young adults with first episode schizophrenia and history of adolescent marijuana use showed more prominent gray matter density and volume reduction in the right posterior cingulate cortex compared to their non-using counterparts (Bangalore et al., 2008). In conflict with these findings, a DTI study using whole-brain voxelwise analysis of 10 young adults who used moderately as adolescents suggests no loss of white matter integrity relative to non-users (Delisi et al., 2006). Although differences in power and sample characteristics likely contribute to the incongruity in findings, longitudinal studies are needed to ascertain the developmental relationship of macro- and micro-structural differences to marijuana use.

In summary, adolescent onset marijuana use has been linked to several brain structure abnormalities, including: reduced gray matter volume and density, increased white matter volume and density in non-depressed users, reduced white matter integrity in some areas, larger hippocampal volumes but which are not linked appropriately to learning performance, prefrontal cortex volumes that are smaller than expected in female users but larger in male users, and increased cerebral blood flow in male users. Longitudinal studies are required to determine which of these abnormalities are attributable to adolescent marijuana use, which predate the onset of cannabis exposure, and delineation of effects that persist despite abstinence.

3. Brain function and adolescent marijuana use

A number of studies have utilized functional magnetic resonance imaging (fMRI) methods to identify patterns of brain activity that are specific to cannabis use in adolescence. In general, researchers compared blood oxygen level dependent (BOLD) signal contrast between marijuana using adolescents and healthy age-matched control groups during the performance of identical cognitive tasks. To ensure that differences between users and non-users were likely attributable to chronic marijuana use and not simply to the acute effects of the substance, participants in these studies were required to maintain abstinence from marijuana and all other illicit substances for at least 28 days prior to the fMRI scan session.

The first fMRI study of adolescent marijuana use was a pilot (Jacobsen et al., 2004) in which marijuana users who also smoked tobacco were compared to a control group matched for tobacco use and a non-smoking control group. Both control groups showed deactivation of the hippocampus during an auditory working memory (*n*-back) task that was not seen in marijuana users. This failure to deactivate the hippocampus was interpreted as a deficiency in inhibiting mnemonic processing. The authors examined the interaction between marijuana use and nicotine withdrawal in a larger sample of adolescents (Jacobsen et al., 2007). Marijuana users who also smoked tobacco were compared to smokers with minimal marijuana use histories on a task of auditory working memory during periods of tobacco deprivation and ad-lib smoking. In marijuana users, nicotine withdrawal elicited increased activation across a network of brain regions involved in phonological processing and working memory function, 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. The authors posited that nicotine withdrawal may have unmasked some effects of heavy marijuana use during adolescence that lead to developmental changes in the neurocircuitry underlying verbal learning and memory. It is important to note that a potential confound in these studies is the neurocognitive effect of nicotine, which has been shown to activate a wide distribution of subcortical and cortical brain regions, particularly in systems underlying attention and arousal (Kumari et al., 2003; Stein et al., 1998).

Evidence for a reorganization of neural networks in adolescents with histories of heavy marijuana use has also been found in response to spatial working memory demands. In users and non-users, better spatial working memory performance correlated with activation in a network supporting spatial perception and working memory, including the prefrontal cortex and parietal regions (Schweinsburg et al., 2008b). However, adolescent marijuana users exhibited a differential pattern with increased activation in the right parietal lobe along with diminished activation in the right dorsolateral prefrontal cortex, compared to non-users. This suggests a weakened capacity among marijuana users to rely on executive functioning centers and a compensatory shift to networks subserving spatial rehearsal and attentional processes. The increased reliance on parietal regions during spatial working memory requirements was replicated (Padula et al., 2007), and a positive correlation between performance and left superior temporal gyrus activation in adolescent marijuana users suggested that the marijuana users employed verbal strategies to achieve good task performance scores, which was not seen in controls.

Inhibitory processing was studied in adolescent marijuana users using a go/no-go task (Tapert et al., 2007). Users had substantially more activation than non-using peers, particularly in parietal and dorsolateral prefrontal cortices, suggesting that marijuana users required additional neural resources to maintain adequate executive control during response inhibition. Interestingly, and as seen in Schweinsburg et al. (2008a,b), adolescents with more intense use histories (i.e., earlier onset, longer duration, more lifetime use times, and more hits per occasion) showed less activation than users with more moderate or recent-onset marijuana use patterns, suggesting that cannabis exposure may have different effects on the brain across adolescent development, or that compensatory mechanisms may falter after excessive use has occurred.

Although the literature is still growing, the aforementioned studies, have demonstrated that the effects of marijuana use on brain function are detectable after approximately 1 month of abstinence, so are not solely due to recent marijuana use. Adolescent marijuana use has been linked to increased activation in parietal, superior temporal, hippocampal, and posterior cingulate regions during working memory demands, and increased parietal and frontal activation during inhibition (Schweinsburg et al., 2008a). Future longitudinal studies will ascertain whether effects resolve with longer durations of abstinence and what, if any, marijuana-related deficits continue into adulthood, as well as to control for the possibility that altered cerebral blood flow could influence BOLD response.

4. Sleep-related consequences of marijuana use in adolescents

Sleep loss is exceedingly prevalent during adolescence. In a 2005 study conducted in the United States, 1602 6th to 12th graders and their primary caregivers were surveyed in order to better understand adolescent sleep. Findings suggest that 80% do not receive the necessary number of nightly sleep hours, with increasing adolescent age associated with more missed sleep (National Sleep Foundation, 2006).

Sleep debt accumulates over time, resulting in excessive daytime sleepiness for many adolescents. Sleep loss has been linked to mood, behavior, and substance use problems in adolescence (Institute of Medicine, 2006), but data on the effects of marijuana use on sleep in teens is limited. In adults, marijuana use has been associated with daytime sleepiness, particularly in the morning (Gillin and Drummond, 2000), which is of concern for teens, who typically have early morning classes. Chronic marijuana-using adolescents may not only receive insufficient sleep, but the sleep they receive may be less restorative, rendering them particularly vulnerability to the adverse consequences of restricted sleep. In support of this notion are data from a study of heavy marijuana using adults, who showed increased autonomic arousal, impaired physical equilibrium, and more reports of subjective impairment following one night of partial sleep deprivation (Solowij et al., 2002). Short-term low-dose marijuana use has been associated with altered sleep architecture, including reduced rapid eye movement (REM) sleep and mild increases in slow wave sleep (SWS) (Feinberg et al., 1975; Freemon, 1982; Tassinari et al., 1999). With higher marijuana doses, REM remained low while SWS was also reduced, in contrast to low dose and placebo conditions (Feinberg et al., 1975). Increasingly frequent marijuana use has been associated with similar REM sleep reductions, as well as gradual SWS suppression (Barratt et al., 1974; Bolla et al., 2008; Feinberg et al., 1976; Feinberg et al., 1975; Freemon, 1982; Karacan et al., 1976; Pranikoff et al., 1973).

Subjective sleep appears to be disrupted during marijuana abstinence. In double-blind inpatient studies (20–35 days) examining acute abstinence following low and high doses of marijuana, young adult participants reported reduced quality and quantity of sleep during placebo nights that were preceded by drug nights (Haney et al., 2004; Haney et al., 1999). Similarly, during a home study during two separate 3–5 day periods of abstaining from marijuana, participants reported increased difficulty with sleep initiation and maintenance, as well as "strange dreams" (Budney et al., 2001). Extending the abstinence period to >45 days resulted in parallel findings (Budney et al., 2003).

Objective indices of sleep during marijuana withdrawal are also altered, including reduced SWS coupled with a "REM rebound" indicating increasing REM sleep (Feinberg et al., 1975; Pranikoff et al., 1973; Tassinari et al., 1999), and shorter time to REM onset (Budney et al., 2003; Freemon, 1982; Karacan et al., 1976; Liguori et al., 2003). This REM increase may explain the common subjective reports of dreaming following withdrawal.

While very little data exist on adolescent marijuana use, data from our laboratory suggest that greater marijuana intake predicted lower percent SWS, and that past month alcohol use predicted increased percent REM sleep after 1–8 days of abstinence, in chronic heavy adolescent marijuana users. Specifically, 200 marijuana hits (the average rate in our sample of users) was associated with 3% less SWS time, and consuming 40 drinks in the past month was associated with 2% more REM times and 10-minute longer sleep latencies during this period of marijuana cessation (1–8 days) (Cohen-Zion et al., 2007). Following one month of abstinence, neither marijuana nor alcohol intake predicted objective measures of sleep. This suggests that, compared to adult users, teens may be more resilient to the long-term effects of these substances on sleep architecture, perhaps because teens usually have briefer and less frequent patterns of substance use, and may more rapidly rebound from physiological injury or insult, possibly leading to a shorter sleep recovery process.

Interestedly, we also found heavy marijuana use predicted the number of periodic limb movements during sleep, a condition characterized by repetitive limb movements associated with cortical arousals and sleep fragmentation. Such reports have been published in the alcohol literature (Aldrich and Shipley, 1993; Gann et al., 2002), but not much is known about the possible effects of marijuana use or cessation on sleep-related periodic limb movements. One recent study found a trend for more periodic limb movements in adult heavy marijuana users during acute withdrawal as compared to non-users (Bolla et al., 2008). Cessation of marijuana may bring about lowered dopamine levels, which may be a marker or contributor to periodic limb movements during sleep (Montplaisir et al., 2005).

In summary, adolescent marijuana use has been linked to reduced SWS after 1–8 days of abstinence that resolves after a month of abstinence, and an increased chance of periodic limb movements that may persist after 4 weeks of abstinence. Findings fit with those seen in young adult marijuana users: decreased SWS and REM, increased sleep latency, and increased vulnerability to partial sleep deprivation effects, but with less marked marijuana-related effects on REM and less clear persistence of abnormalities weeks after cessation. However, given that 80% of adolescents may be in a state of partial sleep deprivation, the compromised quality of sleep in adolescent marijuana users may render them particularly vulnerable to sleep loss effects. Adolescence is a critical developmental period of simultaneous biological, neurocognitive, and psychosocial changes marking the transition from childhood to adulthood. Sleep plays a critical role in this developmental process, and sleep loss, poor sleep quality, and a premature reduction in SWS and Slow Wave Activity during adolescence may lead to age-inappropriate alterations in essential cortical, metabolic, and physical maturational processes. Larger well-controlled studies are needed to examine the effects of active marijuana use, short-, and long-term abstinence on sleep architecture, periodic limb movements during sleep, and the possible involvement of dopaminergic deficiency in cannabis withdrawal. Given the consistently high rates of marijuana use among youth, the effects of adolescent cannabis exposure on sleep are important to characterize, as this may in turn have long-term effects on neurocognition, risky behaviors, and mood.

5. Conclusions and recommendations

Nearly half of 12th graders have tried marijuana, and 6% use daily. Adolescent marijuana use has been associated with risky behaviors, reduced educational performance, and increased probability of later psychiatric problems. Adolescents who use marijuana heavily tend to show some disadvantages in attention, verbal learning and memory, and processing speed that persist beyond one month of abstinence, but largely remit after three months of sustained abstinence. Adolescent onset marijuana use has been linked to abnormalities in brain structure, including reduced gray matter and increased white matter volume, reduced fronto–parietal white matter integrity, hippocampal volumes that are not appropriately linked to memory level, prefrontal cortex volumes that are larger than expected in female users but smaller in male users, and increased cerebral blood flow in male users. The effects of marijuana use on brain function are detectable after a month of abstinence, so are not solely due to recent marijuana use, and are characterized by increased activation in parietal, superior temporal, hippocampal, and posterior cingulate regions during working memory demands, and increased parietal and frontal activation during response inhibition. Earlier onset and more intense adolescent marijuana use has been linked to *less* activation, and users with late adolescent onset show notably *increased* activation, perhaps indicating early compensation. Adolescent marijuana use has also been linked to sleep problems, including reduced slow wave sleep within a few days of use, which resolves after a month of abstinence, and increased periodic limb movements that persist after a month of cessation.

Some abnormalities may predate the onset of adolescent substance use and relate to risk factors for early drug involvement (e.g., inhibitory dysfunction), while some abnormalities may relate to indirect effects of adolescent marijuana use (e.g., missing school or frequently being high, hence missing opportunities to stimulate brain development), and other aberrancies may relate to excessive stimulation of cannabinoid receptors during adolescent neuromaturation. The magnitude of the

abnormalities overall is relatively mild, with effect sizes appearing smaller than in similar studies focused on alcohol or other illicit drugs. Adolescents appear more vulnerable to persisting deleterious neurocognitive effects of chronic marijuana use, but the effects on sleep may resolve more quickly than in adults. In all, the majority of any marijuana-related abnormality appears to resolve within 3 months of abstinence. However, the degree to which neural consequences of marijuana use would emerge or resolve may depend on gender, genetic factors, premorbid cognitive reserves, psychiatric functioning, age of onset, intensity of THC exposure, and other substance use.

These findings have substantial implications for adolescent development. Teenage marijuana users may be at risk for neurocognitive decrements, which may lead to consequences in school (e.g., trouble retaining information, not meeting expectations) and risky decision-making. Given that 80% of adolescents appear partially sleep deprived, the compromised sleep quality of adolescent marijuana users may render them particularly vulnerable to sleep loss effects. Indicators of poorer white matter integrity and abnormal volume-performance relationships suggest that early and excessive CB-1 receptor antagonism may adversely affect oligodendroglial development, leading to reductions in myelin deposition and maintenance.

Longitudinal studies are necessary to determine which abnormalities are attributable to adolescent marijuana use, and which predate the onset of cannabis exposure, by evaluating adolescents prior to initiation of regular marijuana use and contrasting brain function indicators in those who develop frequent intake to pre-use levels. Prospective studies will identify which users will demonstrate cognitive impairments, ascertain junctures in neuromaturation when exposure to marijuana would result in worse neurocognitive outcomes, and elucidate the time course of neural recovery. The common concurrent use of marijuana and alcohol underscores the need for large samples with varying levels of involvement with each compound to examine potential interaction of these substances. Structural deviations linked to atypical neural networks in adolescent marijuana use will be elucidated by accurate separation of gray and white matter in areas of high cannabinoid receptor density, and incorporating fiber tractography with brain function data. Studies on brain functioning in marijuana users should control for the possibility that altered cerebral blood flow could influence BOLD response. The possible involvement of dopaminergic deficiency in cannabis withdrawal and sleep effects should also be explored. Given the consistently high rates of marijuana use among youth, its neural consequences are important to characterize, as they may have long-term effects on the neurocognition, risky behaviors, and mood of a sizable population.

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