

## Marijuana and Adolescence: What Can We Learn From Primates?

In an article published concurrently with this editorial, Verrico and colleagues (1) report that  $\Delta 9$ -tetrahydrocannabinol (THC), the active ingredient of marijuana, administered to monkeys for 6 months during their adolescence, impairs development of spatial working memory. Normal development of spatial working memory was observed in adolescent monkeys administered only saline. The spatial working memory task entailed monkeys 1) looking at a screen that had a square displayed at random in one of four corners, 2) touching the square, 3) looking at a “fixation” cross for an interval of 1, 4, 8, or 16 seconds, and 4) then pointing to the corner where the monkey remembered the square was before. The effect of chronic administration of THC was specific to spatial working memory in the monkeys, as the recall of a colored object independent of location was not affected by THC in terms of either accuracy or reaction time. The exposure to THC in adolescent monkeys was similar to that obtained by a human smoking one to two marijuana cigarettes, five times per week, for 6 months.

Verrico and colleagues earlier found that acute administration of THC similarly impaired spatial working memory (2). These prior data are consistent with an extensive literature showing that THC “challenge” leads to transient working and other memory impairment across species, including rodents, humans, and nonhuman primates (3). But while the transient cognitive effects of challenge or acute administration of THC can be studied in humans (specifically adults) to observe direct effects of marijuana, random assignment to chronic administration of marijuana cannot be done in human adolescents, perhaps the most vulnerable group. A model of chronic cannabis exposure in monkeys offers the opportunity to observe the direct biological effects of the active component of marijuana on the developing adolescent primate brain and its cognitive function, independent of the confounds that exist in observational studies of teens.

The effect of marijuana on the developing adolescent brain and its cognitive function is an especially salient public health issue in 2014. The prescription of marijuana for medical conditions is legal in nearly half of our 50 states. The sale of marijuana for recreational use is legal now in both Colorado and Washington, with other states weighing this option. The market for marijuana is large. For example, while in 2013 the state of Colorado collected \$9 million in tax revenue from “medical marijuana” dispensaries (4), the projected state tax revenue in 2014 in Colorado for retail marijuana is \$67 million, based on an estimated \$578 million in sales (5). A recent Gallup poll shows that more than half of all Americans support the legalization of marijuana (6); therefore, it is likely that more states will join the trend of legalization and marijuana will become even more widely available.

While marijuana can be sold legally only to adults in the United States, whether for medical or recreational purposes, it is nonetheless readily available to teens. The

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National Institute on Drug Abuse has reported that one in 10 eighth graders, and more than one-third of high school seniors, reported smoking marijuana in the past year (7). Among high school seniors, 6.5% smoke marijuana daily, and more than one-half do not believe that the regular use of marijuana is harmful (7). However, marijuana has increased in potency over the decades. The national mean concentration of THC in confiscated marijuana has increased from 3.4% in 1993 to 8.8% in 2008 (8), with a current concentration of about 13% in 2014.

Thus far, the evidence for an association of marijuana use with cognitive deficits in teens has primarily come from case-control studies (9). Strategies include evaluating the correlation of cognitive deficit with adolescent (versus adult) age at onset among adult heavy users, as well as comparing cognition in teens who use marijuana regularly with those who do not. Many but not all such cross-sectional studies have shown an association of teen onset of marijuana use with cognitive deficit. However, neuroimaging studies consistently show that individuals who begin using marijuana regularly as teens tend to have smaller cortical and subcortical volumes, disruption of white matter integrity, and changes in functional connectivity (9). They also have increased brain activation during cognitive testing, including spatial working memory (10), interpreted as compensatory effort, i.e., the user's brain must work harder to achieve comparable performance. Thus, even if performance of cognitive tasks does not seem to be affected in adolescent abusers, the brain's reserve may already be compromised.

Longitudinal studies provide further evidence for an association of marijuana abuse with cognitive deficits and brain changes in teens, although the relationship appears to be complex. Smaller orbitofrontal cortex volume in 12-year-olds predicts the initiation of marijuana use by age 16 (11), whereas disruption in white matter integrity is consequent to heavy marijuana use (12) and network function is predictive of sustained use (13). Antecedents of problematic marijuana use in teens include negative life events (i.e., parental divorce) and parental depressive symptoms and drug use (14), potential confounds that may have their own association with cognitive deficit and accompanying brain changes.

As yet, there are only two major prospective cohort studies of the effects of marijuana on cognition that have data available on cognition in children years before they abuse marijuana (15, 16). These studies adjusted for potential confounds such as other drug use, comorbid psychiatric disorder, socioeconomic status, and parental drug use. Both studies found a significant decline in IQ from childhood to adulthood among regular users, defined as four or five "joints" or occasions of marijuana use per week, a pattern of exposure similar to that of the monkeys in the current study by Verrico and colleagues (1). In the earlier study, only those teens (ages 17–20) who were current regular users of marijuana had a decline in IQ, while former regular users had a normal gain in IQ over the prior 8 years, despite greater lifetime exposure to marijuana (15). In the larger, more recent cohort study, a decline in IQ from childhood (ages 7 to 13) to middle adulthood (age 38) was found for persistent users, most of whom met criteria for cannabis dependence (16). Among these adult persistent users, cessation of marijuana use apparently did not reverse decline in IQ, particularly if the onset of use was in adolescence. Together, these studies suggest there is a window of recovery, such that teens who use marijuana regularly have the opportunity to restore cognition only if they can achieve abstinence soon thereafter.

While longitudinal studies provide much support for a causal association between teen marijuana use and cognitive deficits, only animal models can

demonstrate a direct biological effect of chronic exposure to marijuana and its active ingredient, THC, on cognition, independent of potential confounds. The report by Verrico et al. is significant in that it shows that chronic exposure to THC has a direct toxic effect on the adolescent brain and its cognitive function in nonhuman primates, such that it is highly likely that it does so in humans as well, even when comorbid substance use and risk factors for problematic use are accounted for. The work of Verrico et al. complements prior mechanistic studies of the effects of THC in rodents, which implicate effects on glutamatergic pathways in compromising neuroplasticity (17). A sobering thought is that this monkey biological model may be of utility in finding treatments to restore cognition, and in identifying related biomarkers of remediation, in young people who have developed cognitive impairment from heavy use of marijuana.

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