Commentary

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Cannabis Use in Adolescence: Vulnerability to Cognitive and Psychological Effects

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Worldwide, cannabis is more widely used than all other classes of illicit drugs combined (1). Despite the perception of cannabis as a low-risk drug, the proportion of treatment admissions for cannabis, relative to other drugs, is high. In addition, it is the most frequently used illicit drug among adolescents. Compared with a few decades ago, cannabis strains are increasingly potent, while at the same time, adolescents view it as being less harmful than they used to (1).

The high frequency of cannabis use seen in adolescents is important, as there is emerging evidence that the adolescent brain may be uniquely vulnerable to its effects. Adolescent cannabis use may have particularly long-term impacts on neural structure, neural function, cognition, and behavior. There are several reasons why the unique neurodevelopmental processes occurring during adolescence might impart a special vulnerability. Across the lifetime, in the prefrontal cortex there are changes in the density of cannabinoid CB_1 receptors, the type of cannabinoid receptors agonized by Δ^9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in cannabis. There are also changes in the distribution of CB_1 receptors among cortical layers (2). Interestingly, regions known to continue maturing during adolescence and that have been associated with both higher-level cognition and psychopathology, such as the hippocampus, amygdala, and dorsolateral prefrontal cortex, have high densities of CB_1 receptors. Exposure to THC may disrupt the typical patterns of prefrontal cortex maturation, and in particular the normal dendritic pruning process that occurs in adolescence. Consistent with these findings, cannabis use in adolescence has been associated with structural alterations in the prefrontal cortex. Therefore, it is critical to understand not only the acute impact of cannabis exposure on the adolescent brain but also the impact that cannabis use may have on the neurodevelopmental trajectory and on functional outcomes during this important period (3).

Several aspects of higher-level cognition, including executive function, are known to continue to mature across adolescence and even into early adulthood. Behaviorally, preclinical rodent data indicate that adolescent cannabis exposure may have a significant impact on cognition that may be more severe than the impact from adult usage (4). Likewise, human data indicate that initiation of use during adolescence is associated with more severe cognitive impairment, as well as functional disruptions during working memory tasks (3). Thus, the article by Ho *et al.* (5) in the current issue of *Biological Psychiatry: Global Open Science*, which focuses on cognitive impacts and particularly on executive function changes caused by cannabis use, is of particular importance.

In addition to cognitive changes, cannabis use has been associated with increased rates of psychopathology, including psychosis. Psychosis spectrum disorders typically have onset in late adolescence or early adulthood. Thus, use of cannabis during this particular period may have the potential to impact the developing brain in a way that increases risk for psychosis. This risk, however, is not uniform—it appears that risk increases with earlier use, and the use of high-THC cannabis may increase risk for both cognitive effects and psychosis (6). Furthermore, the interpretation of findings regarding cannabis risks can be complex and multidirectional. For example, the rates of cannabis use in patients with psychosis are often found to be higher than the rates in age-matched control subjects, and at the same time, the risk for psychosis is increased in individuals with high levels of cannabis use (3). Thus, while it is a topic of much interest, the degree to which cannabis use contributes causally to psychosis onset has been difficult to discern, and the relationship between cannabis use in adolescence and the risk for psychosis is not straightforward. This is in part because there are many strains of cannabis, each containing different cannabinoid profiles with unique effects, and in particular, different amounts of THC relative to other cannabinoids. Recent increases in access to higher-potency (higher-THC) cannabis as well as increased control over the relative proportions of cannabinoids in purchased cannabis, particularly in regions where cannabis is legal, further complicate future research in this area of work. These factors are important to consider when comparing recent and historical data. Finally, another complication in the existing literature is that many studies have focused on the development of full-blown psychiatric illnesses such as schizophrenia. However, there is evidence that in addition to risk of psychotic disorders, cannabis use might increase risk for experiencing low-level subclinical psychotic experiences that are below the threshold for diagnosis but can nonetheless impact functioning or set the stage for a further decline into illness (7). In sum, the complexity of the psychosis itself, in conjunction with the mixed state of the literature, makes the precise nature of the relationship between psychosis and cannabis difficult to disentangle.

To add an additional level of complexity to the understanding of cannabis and risk for decreased cognitive function or psychosis, it is likely that risk factors for psychosis may not only operate in isolation but also interact with each other. For example, while males have a higher incidence of psychosis overall, females may be more vulnerable to the deleterious effects of cannabis use than males (8). Further, as is addressed in the current paper by Ho *et al.* (5), cannabis use may also

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have different effects on those with preexisting factors such as a genetic risk for psychosis spectrum disorders. So, as with other risk factors, and consistent with a two-hit or multi-hit conceptualization of psychosis risk, adolescent cannabis use may interact with underlying genetic risk (9). Evidence for this interaction initially came from candidate genes that appeared to increase vulnerability to the effects of cannabis, although recent data are mixed. More recent evidence indicates that the relationship is even more complicated, and that there may be overlap in the genetic liability for cannabis use disorder and schizophrenia (3,10).

Ho *et al.* (5) used a unique design to address several central questions regarding cannabis use in adolescence. First, they focused not on those diagnosed with cannabis use disorders or clinically identified based on heavy use, but on the effects of a more typical adolescent pattern of low-level use. Second, assessing outcomes such as cognition or psychopathology can be complicated in retrospective studies, and it can be unclear whether the issue of interest preceded the use or was caused by it. Here, they leverage two longitudinal samples to use prospective analyses to help disentangle cause and effect. Finally, to assess whether genetic risk for schizophrenia increases one's risk for the adverse effects of cannabis use, they investigated not just healthy youth but individuals at genetic risk for schizophrenia. To accomplish this, Ho *et al.* analyzed one large longitudinal sample, the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, and a smaller longitudinal sample of individuals from Iowa that includes those at genetic risk for schizophrenia.

In the Iowa sample, using three measurements over the course of 3 years, the authors assessed neuropsychological function and emergent cannabis use in adolescents without genetic risk, those with first-degree relatives with schizophrenia, and those with second-degree relatives with schizophrenia. Individuals with emergent cannabis use showed less age-related improvement than expected on sustained attention, visuospatial working memory, and executive function. This failure to improve was compounded in individuals with first-degree relatives with schizophrenia but not in those with second-degree relatives with schizophrenia. This implies that the degree of genetic risk corresponds to the degree of cannabis effects, indicating that vulnerability to cannabis scales with genetic load, and again underscoring the complexity of the role of genetics. In the ALSPAC sample, using two measurements across 5 years, Ho *et al.* measured emergent cannabis use and intraindividual variability on a sustained reaction time task. In this sample, they were able to stratify the youth based on amount of use and found that increasing use was associated with increasing change in cognitive performance from baseline to follow up. This finding supports what was found in previous retrospective studies in the literature but uses the power of the longitudinal design to elucidate a potentially causal role for cannabis use.

Taken together, the data from these samples indicate that cognitive changes in those with adolescent cannabis follow, rather than precede, use, and that this may be amplified in those with a family history of schizophrenia. Moreover, despite the growing belief among adolescents that cannabis is a very low risk drug, changes were found not only for heavy users who met the criteria for cannabis use disorder, but also for those with a lower, more typical level of use. From a public health perspective, these findings can inform advice given to adolescents about the impact of even moderate cannabis use. Furthermore, for individuals with a family risk for schizophrenia, these findings may indicate that in addition to the potential influence on psychological symptoms there may also be an increased risk for cognitive changes.

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Article Information

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