Biological Psychiatry

Polysubstance Use Plays a Key Role in Midlife Structural Brain Alterations in Long-term Cannabis Users

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Approximately 147 million people across the world consume cannabis annually, making it the most commonly used illicit drug globally (1). Although the use of cannabis has generally become more accepted and perceptions of harm have been decreasing in recent years (2), negative effects of cannabis use on health and well-being have been identified. Cannabis use has been found to be associated with neurocognitive deficits in memory, learning, and attention and to contribute to alterations to both brain function and structure [see Volkow *et al.* (3) for review]. However, existing studies examining the neural correlates of cannabis use have produced mixed findings in relation to cannabis-specific effects. The question of whether—and to what extent—cannabis use produces unique neural detriments compared with other psychoactive substances remains largely unknown. A possible reason for this knowledge gap is that there are likely other variables at play, variables that are often unaccounted for, that confound direct associations between cannabis use and neural outcomes. Pulling from literature at the intersection of developmental science, addiction research, and neuroscience, two likely targets are age and polysubstance use.

In the current issue of *Biological Psychiatry,* Knodt *et al.* (4) incorporated these targets in their analyses examining the prospective influences of cannabis and other drugs on global and regional gray and white matter integrity measured at midlife. Analyses were conducted using data from the Dunedin Study, which is composed of a large-scale, population-representative sample with data on cannabis use and the use of other substances collected across 5 decades of development up to 45 years of age. Neuroimaging assessments were also conducted when participants were 45 years of age. One important finding from this work pertains to machine learning analyses used to create a brain age gap estimate. This estimate provided a measure of the difference between chronological age predicted from brain structure data and actual chronological age. Knodt *et al.* (4) reported that long-term cannabis users had older brain ages and thinner global and regional cortices compared with lifelong nonusers, and heavier cannabis use contributed to thinner global and regional cortices and smaller gray matter volume in the amygdala, hippocampus, thalamus, and ventral diencephalon. Interestingly, however, these results were no longer significant after adjusting for long-term use of other drugs. Knodt *et al.* (4) suggest that in midlife, long-term tobacco and alcohol use may lead to alterations in structural brain integrity to a greater extent than long-term cannabis use. Long-term alcohol users had older brain ages and greater detriments to both gray and white matter compared with long-term cannabis users; compared with both long-term cannabis and alcohol users, long-term tobacco users had even older brain ages and thinner cortices. Thus, cannabis use in itself may not be driving deficits in structural brain activity and accelerated brain age.

There are several key reasons why it is important for studies such as Knodt *et al.*'s (4) to account for the potential age-related impacts of substance use on neural indices, including brain structure. First, rates of substance use tend to vary by age, with initial experimentation beginning in adolescence, peak use occurring in young adulthood, and use then decreasing and leveling out through middle to older adulthood. According to the Monitoring the Future Survey, a national panel survey tracking substance use in the United States beginning in adolescence and continuing through older adulthood, nearly a quarter (24.5%) of adults 35 to 50 years of age used cannabis in the past year (2). Substances can also have differential effects on the brain at different phases of development. These impacts act in concert with normal developmental changes to the brain in middle to older adulthood. For example, in a healthy sample of adults 23 to 87 years of age in which structural brain integrity was measured approximately every 4 years, Storsve *et al.* (5) found increases in temporal and occipital cortices but decreases in prefrontal and anterior cingulate cortices as a function of age. Thus, age-related changes in the brain continue to occur throughout the lifespan.

In addition to developmental considerations, studies examining cannabis use in relation to neural outcomes, including impacts on structural brain integrity, often do not account for potential confounding effects of the use of other substances. On one hand, cannabis shares similarities with all drugs of abuse in that cannabis use elicits the release of dopamine in the mesocorticolimbic reward system. The highly rewarding properties of drugs of abuse then motivate continued use, which may lead to addiction. Indeed, about 9% of cannabis users meet the criteria for cannabis use disorder. Findings tend to be mixed, however, in terms of the unique effect of cannabis on neural indices (6). Advancing this existing body of research, Knodt *et al.* (4) leveraged substance use data across multiple data collection waves (ages 18, 21, 26, 32, 38, and 45 years) for cannabis, tobacco, and alcohol and 4 data collection waves (ages 26, 32, 38, and 45 years) for illicit drug use. Their sample was then categorized into long-term cannabis users and 3 other comparison groups—lifelong

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cannabis nonusers, long-term tobacco users, and long-term alcohol users. Regular cannabis use was exclusionary in long-term tobacco and alcohol user groups, but other substance use was allowed to vary for long-term cannabis users. In this way, regularity of use over time and use across substance types could be examined. Knodt *et al.* (4) also reported tests of dose-response associations to assess the effects of level of use on structural brain integrity. Indeed, more persistent use across substances and over time contributed to older brain age and a greater extent of impacts to structural gray and white matter.

The findings presented by Knodt *et al.* (4) are compelling, but future work is needed to expand upon their research and provide a more definitive answer regarding the unique role of specific psychoactive substances, including cannabis, on the aging brain. An important future direction is to examine associations between cannabis and other substance use on structural brain integrity beyond midlife and into older adulthood. The extent to which cannabis and other substances, especially when used chronically, impacts the aging brain is still relatively unknown, and findings are often mixed (7). Older adult substance users may be especially vulnerable to the neurotoxic effects of substances, considering that they metabolize substances more slowly and experience greater age-related impacts on brain plasticity and cognitive decline compared with younger adults (3). However, existing neuroimaging studies assessing cannabis use in older adults have often been limited by small sample sizes and the lack of adequate comparison groups (8).

Another avenue for future research to build upon findings presented by Knodt *et al.* (4) is to incorporate more nuanced measures of cannabis use. For example, additional research is needed that accounts for route of cannabis administration and Δ^9-tetrahydrocannabinol concentration. Methods to administer cannabis can affect how rapidly intoxication occurs. For instance, orally administered products (i.e., edibles) tend to take longer to metabolize. Not feeling an immediate high may lead to additional consumption and, later, more amplified psychotropic effects. Furthermore, an increasing array of products with highly concentrated Δ^9-tetrahydrocannabinol are available, especially in states and countries where cannabis has been legalized and dispensaries are easily accessible. Higher-potency cannabis is of particular concern, as it has been found to increase risk for the onset of first cannabis use disorder symptom (9). In addition, the extent to which concurrent use (i.e., the regular use of substances but not using more than one substance at a time) versus simultaneous use (i.e., the co-use of multiple substances at the same time, such as using alcohol and cannabis on the same occasion) may exert different influences on brain structure and function remains largely unknown. Simultaneous use of substances is relatively common, but its effects on the brain are complex and difficult to measure (10). Taken together, important future directions include using data from samples large enough to be able to account for comorbid substance use, leveraging longitudinal data that include imaging data as well as more nuanced information on quantity and frequency of use over time, and assessing developmental periods when cannabis use may be most detrimental to neuropsychological impairment (3).

In sum, Knodt *et al.* (4) advance the current literature in several important ways. Their work provides novel evidence that calls into question the unique role of long-term cannabis use on structural brain integrity in midlife and highlights the need to investigate the neural effects of other drug use, including alcohol and tobacco use. While it is likely that the cumulative effects of cannabis can include alterations to structural brain integrity, important questions remain. For instance, how expansive and long-lasting are the effects of Δ^9-tetrahydrocannabinol on the endocannabinoid system, and what is the relative harmfulness of cannabis compared with other drugs of abuse? The results reported by Knodt *et al.* (4) pave the way for future studies to begin answering these questions and to disentangle the complexities of cannabis-specific effects on the brain.

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