How does cannabis use affect brain health? Caution advised, more research needed

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Despite the perception that marijuana is harmless, there is some scientific evidence challenging that belief, and there are many unanswered questions about its impact on brain health, according to a

new American Heart Association scientific statement published today in the Association's journal *Stroke*. This scientific statement will be presented and discussed during a symposium at the Association's International Stroke Conference in New Orleans, today at 7 a.m. CT/ 8 a.m. ET. An American Heart Association scientific statement is an expert analysis of current research and may inform future clinical practice guidelines.

"There's a lot of uncertainty in the medical community about the health effects of marijuana. This scientific statement is intended to guide health care professionals in having a balanced and intentional discussion with patients about the potential known and unknown effects of marijuana on brain health," said writing group Chair Fernando D. Testai, M.D., Ph.D., FAHA, a professor of neurology and rehabilitation at the University of Illinois at Chicago.

This is the Association's first scientific statement on cannabis and brain health, following a statement on marijuana and cardiovascular health, published in August 2020. Both statements are important since marijuana use in the U.S. is increasing, particularly among adolescents and young adults, with about one-third of 12th graders and nearly half of college students reporting marijuana use in 2018. In addition, the use of marijuana medicinally and/or recreationally has been legalized or decriminalized in many states across the U.S. in the past 2 decades, and the concentration of tetrahydrocannabinol (THC, the psychoactive component in marijuana) in cannabis products has increased significantly, from about 4% in 1995 to 15% in 2018.

The most studied chemicals in cannabis are THC and CBD. THC is the compound in marijuana that gives the sensation of being high. CBD (cannabidiol) has antioxidant and anti-inflammatory properties but does not have psychoactive effects. The potential therapeutic benefits of CBD continue to be investigated in clinical trials.

The U.S. Drug Enforcement Agency (DEA) and the Food and Drug Administration (FDA) classify cannabis as a Schedule I controlled substance, on par with heroin and LSD, for having a "high potential for abuse and little to no medical benefit." In contrast, CBD is legal when derived from hemp, which is the same species of plant as cannabis and contains less than 0.3% THC.

To fully understand the potential impact of marijuana, it's important to know that the human body naturally produces compounds called endocannabinoids that are similar to those in marijuana. Endocannabinoids are involved in the regulation of many body processes throughout life (including learning, memory, pain control and sleep), and the action of endocannabinoids is essential to prenatal brain development and to brain maturation during adolescence.

Endocannabinoids, as well as THC, can attach to neurons in the brain through molecules called cannabinoid receptors. When THC activates cannabinoid receptors in the brain, it can disrupt the normal actions of endocannabinoids. "These receptors are highly concentrated in brain areas related to cognition," said Testai.

According to the statement, previous animal studies (in rodents) indicate that prolonged exposure to THC disrupts memory and learning, and impacts brain development and maturation in specific ways if exposed at certain stages of life:

- During prenatal life, an important time for brain development, THC disrupts the normal signaling pathways of the endocannabinoid system and may alter the offspring's thinking, emotional behavior and response to stress.
- During adolescence, an important time for brain maturation, THC changes the structure and function of brain circuits, particularly in areas involved in cognition, emotional regulation

and social behavior (such as the prefrontal cortex and hippocampus).

"Data obtained in these animal studies demonstrate that disruption of endocannabinoid pathways leads to behavioral and cognitive abnormalities, such as poorer memory and learning ability and a heightened sensitivity to stress. Also, there may be vital life periods—gestation and adolescence—when the brain may be particularly vulnerable to the impact of THC," Testai said.

While the exact timing and amount of marijuana exposure are more easily controlled in animal studies, as well as controlling the animals' social and environmental conditions, human research studies cannot replicate similar strict parameters. Thus, results from existing studies in humans have been mixed, yet raise similar concerns about the impact of marijuana exposure on brain health. Among the studies in humans summarized in the scientific statement, the findings included:

- While actively using marijuana, people demonstrated worse scores on driving road tests when using THC-dominant marijuana, compared to when they were using CBD-dominant marijuana or no marijuana.
- In young adults who were followed for 25 years as part of a heart disease research project, scores on verbal memory tests declined in correlation to more years of self-reported exposure to marijuana.
- There were more psychological problems and poorer cognitive function in children (average age 9) whose mothers reported using marijuana during pregnancy.
- Marijuana use during adolescence has been associated with thinning in an area of the brain involved in cognition (the prefrontal cortex), with greater exposure to marijuana associated with more thinning. However, other studies detected no

difference.

- Structural changes in the brain were visible in some studies comparing marijuana users and non-users. Specifically, there was thinning of brain areas important in orchestrating thoughts and actions, or decreased volume in an area of the brain important for memory. Other studies that compared cognitive testing and brain imaging found no differences between marijuana users and non-users.
- Cannabis users were found to have an increased risk of clot-caused stroke, with one study finding 17% more and another finding 24% more strokes among cannabis users.

The statement also highlights numerous open questions on the impact of cannabis on brain health, including:

- Does marijuana's impact on brain health differ depending on the person's age?
- How does marijuana interact with other substances such as prescription medications? This is a particular concern in elderly people who may be using multiple medications such as blood thinners, antiarrhythmia or anticonvulsant medications to treat other chronic health conditions.
- Do the effects of marijuana differ whether it is used recreationally or prescribed for the treatment of a specific medical condition?
- How much marijuana is too much? In older research studies conducted when marijuana was illegal in all U.S. states, there may have been significant under-reporting of how frequently marijuana was used.
- Do different types of marijuana (such as higher THC levels or synthetic cannabinoids) impact the brain differently?
- Are there differences in brain health depending on whether marijuana is smoked or consumed in an edible product?

"Our understanding of the effects of marijuana on the brain is imperfect, and human research in this area is a work in progress. Still, the results of recent animal studies challenge the widely accepted idea that cannabinoids are harmless and call for caution when using marijuana, particularly while pregnant or during adolescence," said Testai.

This scientific statement was prepared by the volunteer writing group on behalf of the American Heart Association's Stroke Brain Health Science Subcommittee of the Stroke Council; the Council on Arteriosclerosis, Thrombosis and Vascular Biology; the Council on Cardiovascular and Stroke Nursing; the Council on Lifestyle and Cardiometabolic Health; and the Council on Peripheral Vascular Disease. The American Academy of Neurology has affirmed this scientific statement as an educational tool for neurologists.

More information: *Stroke* (2022). www.ahajournals.org/doi/10.116 … STR.0000000000000396

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