Breaking memory circuits with marijuana

September 22 2017, by Emilie Reas

Credit: PLOS

Paranoia. Munchies. Giggles. Sleepiness. Memory loss. Although the effects of cannabinoids–the active components of marijuana–are familiar to many, their neurobiological substrates are poorly characterized. Perhaps the effect of greatest interest to both neuroscientists and to cannabis users hoping to preserve their cognitive function, is short-term memory impairment that often accompanies marijuana use. Our partial understanding of its physiological and behavioral effects is not for want of studies into its neural effects.

Ample research has shown a range of changes to neurotransmission, receptors, ion channels and mitochondria following cannabinoid exposure. However, knowledge of its cellular and molecular properties alone cannot offer a complete picture of its system-wide effects leading to cognitive and behavioral changes. A recent study published in *PLOS Computational Biology* took a novel approach to address this issue, combining computational modeling with electrophysiological brain recordings from rats performing a memory task, to unravel the dynamics of neural circuits under the influence of cannabinoids.

Cannabis impairs memory

To assess memory changes induced by cannabinoids, the scientists injected tetrahydrocannabinol (THC), the main psychoactive compound in marijuana, into rats before they performed a "delayed-nonmatch-to-sample" working memory task. In this task, rats are cued with one of two levers, and after a delay, are required to select the opposite lever. Compared to sober sessions, performance under THC was impaired by 12%, confirming the all-too-familiar memory impairment associated with cannabis use.

THC alters hippocampal activity

The researchers focused on the hippocampus, a brain region essential for forming new memories, to examine how THC alters neural function underlying these memory deficits. The hippocampus has a characteristic circuit through three main subregions, whereby signal projects from the dentate gyrus to CA3 (via mossy fibers), and from CA3 to CA1 (via Schaffer collaterals). Although THC did not alter the mean firing rate in either CA3 or CA1, the researchers discovered more nuanced drug effects within hippocampal subregions. Neurons in the hippocampus are known to demonstrate selectivity for particular stimuli, and in this task,

some neurons responded preferentially to lever presentations. After THC administration, this selectivity to lever presentation was reduced, suggesting that THC lowers information coding by the hippocampus. Further, theta power in CA1 was also reduced after THC administration.

THC breaks the memory circuit

While these preliminary results validate prior findings that cannabinoids disrupt traditional properties of neural activity, they do not speak to how THC modifies network-level signaling subserving memory. To probe functional circuitry, the researchers modeled intracellular and extracellular processes–such as refractory periods, potassium conductance or recurrent connections–contributing to CA3 to CA1 signaling. Memory deficits from THC correlated with both reduced feedforward excitation, and increased feedback excitation, along the CA3 to CA1 pathway. Modeling dynamic filters of this circuit, they further discovered that THC-induced memory impairments correlated with less feedforward theta and greater feedback theta-blocking from CA1. THC also reduced the number of CA3-CA1 connections, together suggesting that THC functionally isolates neurons from the hippocampal CA3 and CA1 subregions.

This study revealed a clear disruption by THC in the hippocampal circuitry supporting memory, though it didn't directly examine what causes this functional breakdown. The brain possesses its own endocannabinoid system, which includes several cannabinoid receptors and endogenous endocannabinoids, which act on these receptors. In the drug-free brain, this system is involved in regulating functions such as mood, sleep, appetite, and of course, memory. Follow-up research will be necessary to clarify exactly how exogenous cannabinoids like THC wreak havoc on this system, but the authors speculate that THC may reduce feedforward excitation by activating CA3 CB1 receptors and reducing glutamate release, and increase feedback excitation by reducing

CA1 interneuron output. Importantly, the authors emphasize, effects of cannabinoids on neural function aren't one-size-fits-all. It's likely that the brain's excitation/inhibition balance depends on THC dose, leading to unique functional and behavioral changes under distinct drug conditions. Such differences in neural signaling dynamics, determined by drug dose and the targeted brain circuitry, could explain inconsistent reports of cannabinoids on pro- and anti-convulsant activity.

This study helps to fill a critical gap in our understanding, between the microscopic cellular and macroscopic whole-brain levels, of the ways in which cannabis impairs memory. The authors stress that "in order to truly understand the effects of THC, one must study the systems level changes in circuit dynamics rather than taking a reductionist approach and studying the effects of THC on any particular receptor or cell type." By adopting the novel approach of modeling causal network dynamics, their research points to the breakdown of information flow along the hippocampal Schaffer collateral pathway as a major route of THC-induced memory disruption. As the researchers explain, their work "is the first which examines the effect of THC on neuronal systems dynamics, or the causal interactions between signals, rather than on neuronal signals themselves." More research examining causal brain circuitry will eventually lead to a more complete understanding of the diverse ways in which cannabinoids alter behavior and cognitive function, from causing memory loss and sleepiness to giggles and munchies.

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