Study links cannabis use in adolescence to schizophrenia

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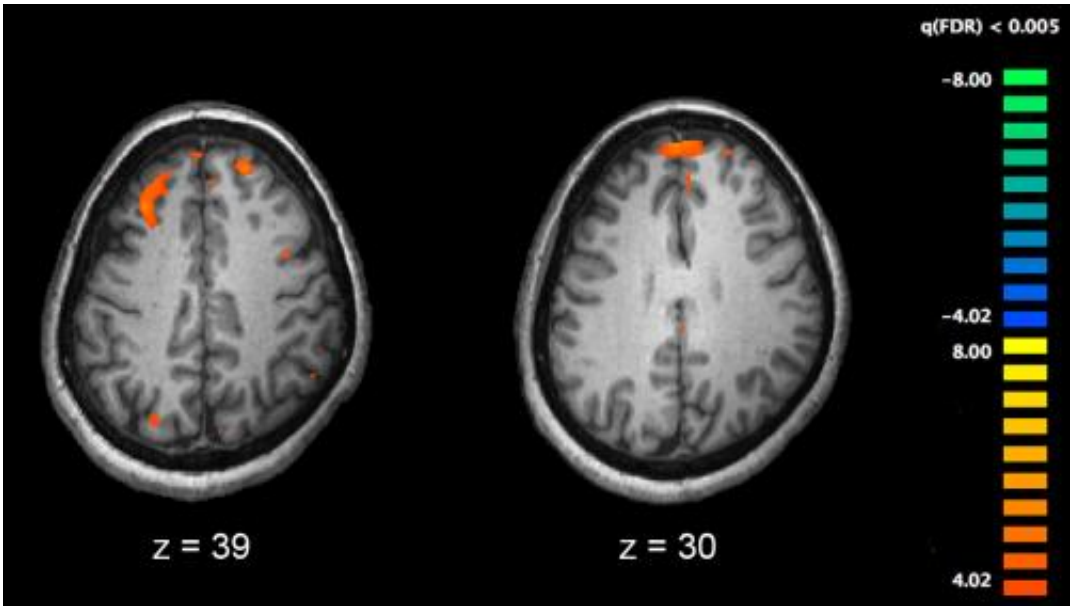

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

Scientists believe that schizophrenia, a disorder caused by an imbalance in the brain's chemical reactions, is triggered by a genetic interaction with environmental factors. A new Tel Aviv University study published in *Human Molecular Genetics* now points to cannabis as a trigger for

schizophrenia.

The research, conducted by Dr. Ran Barzilay and led by Prof. Dani Offen, both of TAU's Sackler School of Medicine, finds that smoking pot or using cannabis in other ways during adolescence may serve as a catalyst for schizophrenia in individuals already susceptible to the disorder.

"Our research demonstrates that cannabis has a differential risk on susceptible versus non-susceptible individuals," said Dr. Barzilay, principal investigator of the study. "In other words, young people with a genetic susceptibility to schizophrenia—those who have psychiatric disorders in their families—should bear in mind that they're playing with fire if they smoke pot during adolescence."

The research team included Prof. Inna Slutsky and Hadar Segal-Gavish, both of TAU's Sackler School of Medicine, and Prof. Abraham Weizman of Geha Medical Health Center and Prof. Akira Sawa of Johns Hopkins Medical Center.

Clinical picture of mouse models mimics human adolescence

Researchers exposed mouse models with a genetic susceptibility to schizophrenia—the mutant DISC-1 gene—to THC, the psychoactive compound in cannabis. During a time period similar to that of human adolescence, the susceptible mice were found to be at a far higher risk for lasting brain defects associated with the onset of schizophrenia.

Four categories of mice were used in the experiment: Genetically susceptible and exposed to cannabis; genetically susceptible and not exposed to cannabis; genetically intact and exposed to cannabis; and,

finally, genetically intact and not exposed to cannabis. Only the genetically susceptible mice developed behavioral and biochemical brain pathologies related to schizophrenia after being exposed to cannabis, behavioral tests and neurological biochemical analyses revealed.

"The study was conducted on mice but it mimics a clinical picture of 'first episode' schizophrenia, which presents during adolescence in proximity to robust cannabis use," said Dr. Barzilay, a child and adolescent psychiatrist.

The researchers also discovered the mechanism through which the cannabis and the specific gene interact.

"A protective mechanism was observed in the non-susceptible mice," said Prof. Offen. "This mechanism involves the upregulation of a protective neurotrophic factor, BDNF, in the hippocampus. We showed in the study that if we artificially deliver BDNF to the genetically susceptible mice, they could be protected from the deleterious effect of THC during adolescence.

"This research clearly has implications in terms of public health," Prof. Offen concluded. "The novel protective mechanism identified in the study may serve as a basis for the future development of compounds capable of attenuating the deleterious effect of cannabis on brain development. However, until that time, it is important that young people at risk for psychiatric disorders (i.e., have psychiatric disorders in their family or have reacted strongly to drugs in the past) should be particularly cautious with cannabis use during adolescence."

More information: Hadar Segal-Gavish et al, BDNF Overexpression Prevents Cognitive Deficit Elicited by Adolescent Cannabis Exposure and Host Susceptibility Interaction, *Human Molecular Genetics* (2017). DOI: 10.1093/hmg/ddx139

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