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Who dare-not smoke-pot – Can schizophrenia polygenic risk predict acute psychotic response to cannabis?

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Background: Cannabis exposure is a well-recognized environmental risk factor for schizophrenia (SCZ)/ Cannabis exposure has complex, possibly bidirectional relationship with the genetic risk of SCZ that is poorly understood. Genome Wide Association Studies have enabled estimation of a robust index of the genetic risk though polygenic risk scores (PRS). Several common variants, each conferring a small effect to the overall genetic risk of SCZ, can be summated to derive SCZ-PRS.

Significance: The rising rates of cannabis use calls for better understanding the relationship between cannabis exposure and individual's SCZ vulnerability.

Hypothesis: SCZ-PRS has a strong positive association with acute psychotomimetic response to intravenous delta-9-tetrahydrocannabinol (THC).

Methods: In a pilot study, subjects genotyped on an Illumina PGC array, participated in a double-blind, placebo-controlled study where they received intravenous THC or placebo. Positive subscale of the Positive and Negative Syndrome Scale (PANSS) scores and subjective effects were measured before and at several time points after the infusion. SCZ-PRS was calculated employing standard quality controls and methods using the summary statistics from Psychiatric Genomics Consortium.

Results: As hypothesized, individuals with higher SCZ-PRS manifested greater acute psychotic symptoms measured by THC induced changes on the positive symptoms. Further, there was a similar positive association between subjective high and SCZ-PRS. These relationships were statistically significant after controlling for age, gender and four principal ancestry components.

Conclusions: PRS influences the psychosis-like effects of cannabinoids. Future studies should validate these findings in larger sample and examine the moderating role of individual variability in the endocannabinoid function.