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Associations Between GABRA2 Genetic Variation, Subjective Response to Acute Alcohol Intoxication, and the Functional Connectivity of the Reward Circuitry

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Abstract

The GABRA2 gene encodes a subunit of a $GABA_A$ receptor found in the mesolimbic reward circuitry, and modulation of $GABA_A$ receptors by alcohol is hypothesized to contribute to the psychotropic properties of the drug. Linkage studies have found a significant correlation between a single nucleotide polymorphism (SNP, rs279858) in the GABRA2 gene and increased risk for alcohol use disorders (AUDs). Genetic variation in GABRA2 may impact risk for AUDs by modulating subjective responses to alcohol intoxication; however, it remains unclear whether risk-alleles are related to greater or lesser rewarding/stimulating effects of alcohol and how these subjective effects relate alcohol-induced changes in brain function. Therefore, this project used resting-state functional connectivity (rsFC) to examine the relationship between GABRA2 variation, subjective responses to alcohol intoxication, and reward circuit connectivity. During two separate laboratory sessions, participants (N=63) rated their subjective responses to alcohol or placebo beverages using the Biphasic Alcohol Effects Scale, which assesses mood, feelings, and physical state. During each session, participants also underwent functional magnetic resonance imaging to assess resting-state connectivity between the ventral tegmental area (VTA) and the nucleus accumbens (NAcc), key nodes in reward circuitry. Participants were then genotyped and grouped by GABRA2 AUD risk associated allele carrier status. The association between condition (alcohol vs placebo) and rsFC varied as a function of genotype, as individuals carrying the risk allele had greater VTA-NAcc rsFC after alcohol intoxication as opposed to placebo, while the opposite effect was seen in those without the risk allele (p=.044, N=21). Alcohol-induced differences in subjective stimulation and VTA-NAcc rsFC were positively correlated in participants carrying the risk allele (p=.028, N=19). These results suggest that the association between AUD and GABRA2 is linked to increased reward circuitry connectivity and that the increase in connectivity may mediate individual variation in subjective response to alcohol.