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Trace Amine Associated Receptor 1 (TAAR1) SNP rs8192620 is associated with increased craving and altered striatal functional connectivity in methamphetamine use disorder (MUD)

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Background: Methamphetamine (MA) is a potent agonist at TAAR1 expressed in dopaminergic brain regions, including ventral tegmental area, substantia nigra and striatum. Stimulation of TAAR1 blunts striatal dopamine signaling and mice with a non-functional TAAR1 have increased MA self-administration, implicating TAAR1 in MA use disorder (MUD).

Hypothesis: We hypothesized that a common variant (CV) allele would be associated with neural and behavioral manifestations of MUD.

Results: A human common variant (rs8192620) for TAAR1 is found with a 23% frequency that has a synonymous SNP in a valine codon (v288v). Cells transfected with cDNA for TAAR1 wild type (WT) or the TAAR1 CV showed a 30% increase in protein expression for TAAR1-CV above TAAR1-WT. The increase persisted for at least 48h, suggesting altered transcripton/translation efficacy. While individuals with MUD and controls show no differences in CV frequency, the CV is associated with greater craving ($p = .036$ in individuals with MUD (13 active users and 19 in early remission). In a second group of MUD individuals ($n=26$ abstinent < 3 months) those expressing the CV had increased resting-state functional connectivity between ventral striatum and dorsal striatum, midbrain and insula, while controls ($n=24$) showed opposite or no effects ($p=.018$; corrected for age and education).

Discussion: Collectively, the results suggest that chronic MA stimulation of over-expressed TAAR1 in CV individuals leads to neuroadaptations in striatal functional connectivity and an increase in craving after abstinence. The mechanism is plausibly related to blunted striatal dopamine release with MA use in the CV individuals.