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The association of *SNCA* with hazardous alcohol use is mediated by impulsivity

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To the Editor

The α -synuclein gene (*SNCA*) has been associated with alcohol consumption in rats and alcohol craving and use disorder in humans, and recent research has also associated *SNCA* with impulsive behavior (Guillot et al., 2015). Hence, impulsivity may account for the association between *SNCA* and alcohol-related variables, such that variations in *SNCA* may lead to impulsive tendencies, which in turn may increase the likelihood of problematic drinking; however, to the best of our knowledge, this possibility has not been investigated. Because the human single-nucleotide polymorphism *SNCA* rs356195 has been associated with both impulsivity and alcohol craving (Guillot et al., 2015), we examined if the association between *SNCA* rs356195 and hazardous alcohol use was statistically mediated by impulsivity in a cross-sectional analysis.

One hundred and thirty-nine healthy Caucasians (77 men; 62 women) aged 21 to 55 ($M = 25.95$, $SD = 7.45$) were recruited from the university and community and were genotyped for *SNCA* rs356195. The project was approved by The University of Southern Mississippi Human Subjects Protection Review Committee. Written informed consent was obtained prior to participation.

The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item self-report measure of hazardous drinking that inquires about alcohol use frequency, typical drinking amount,

binge drinking frequency, alcohol-related difficulties, and alcohol dependence symptoms, with higher scores (range: 0–40) indicating greater hazardous drinking levels (Babor et al., 2001). The Barratt Impulsiveness Scale Version 11 (BIS-11) is a 30-item self-report measure of trait impulsivity that inquires about motor impulsivity and (lack of) attention, cognitive stability, perseverance, forethought, and problem solving, with higher scores (range: 30–120) indicating greater impulsivity levels (Patton et al., 1995).

Alpha (two-tailed) was set at 0.05. The *SNCA* predictor variable for linear regression models consisted of C homozygotes and T-allele carriers (CC coded as 0; CT/TT coded as 1). Mediation analyses involved entering standardized regression coefficients (β s) and standard errors into RMediation from two linear regression models: The A path, which is the association between the predictor (*SNCA*) and the mediator (impulsivity), and the B path, which is the association between the mediator (impulsivity) and the criterion variable (hazardous alcohol use) controlling for the predictor (*SNCA*). To determine the effects of *SNCA* beyond what is accounted for by mediation (i.e., the remaining direct effect), additional linear regression models were run examining the relation of *SNCA* to hazardous alcohol use controlling for impulsivity.

The genotypic frequency distribution for *SNCA* rs356195 did not deviate significantly from expected Hardy-Weinberg equilibrium (78 CC, 50 CT, and 11 TT; $\chi^2 = 0.55$, $p = 0.46$). Fisher's exact tests and one-way ANOVAs revealed that C homozygotes and T-allele carriers did not differ significantly in respect to sex, age, years of education, or marital status (all $ps > 0.34$). On average, participants scored 6.4 ($SD = 3.5$) on the AUDIT and 64.1 ($SD = 11.2$) on the BIS-11. To put participant scores in perspective, 33% of participants had AUDIT scores of 8 or higher, which is indicative of hazardous drinker status (Babor et al., 2001), and 31% of participants had BIS-11 scores of at least 69, which was the average score for substance abuse patients in a prior study (Patton et al., 1995).

In individual regression models, *SNCA* was significantly associated with impulsivity ($\beta = 0.18$, $SE = 0.08$, $p = 0.031$) and hazardous alcohol use ($\beta = 0.19$, $SE = 0.08$, $p = 0.024$). The relation of *SNCA* to hazardous alcohol use was significantly mediated by impulsivity (β [95% CI] = 0.04 [0.002, 0.098]), and the remaining direct effect of *SNCA* on hazardous alcohol use was not significant, suggesting full mediation.

To examine alternatives regarding the directionality of mediational pathways, we then conducted reverse mediation analyses in which *SNCA* was either the mediator or the criterion variable instead of the predictor. However, *SNCA* did not significantly mediate the relation of impulsivity to hazardous alcohol use or the relation of hazardous alcohol use to impulsivity, and neither impulsivity nor hazardous alcohol use was significantly mediated by the other in relation to *SNCA*, which indirectly supports *SNCA* as the predictor (i.e., the potential causal variable), consistent with our proposed mediational pathway (*SNCA* → impulsivity → hazardous drinking).

These results support the notion that *SNCA* contributes to hazardous alcohol use through its influence on impulsivity. One potential explanation for these findings is that α -synuclein may modulate reward-related impulsive behaviors (e.g., addictive behaviors) by altering DA

neurotransmission (see Guillot et al., 2015). Another potential explanation for current findings is that α -synuclein aggregation and accompanying dopaminergic decline (such as in the prefrontal cortex) may lead to disinhibited behavior, as evidenced in transgenic rats (Nuber et al., 2013) and patients diagnosed with dementia with Lewy bodies (Kao et al., 2009), but perhaps extending to nonclinical participants to some extent.

This study is limited by the use of a cross-sectional design, which prevents us from determining the temporal and causal nature of the relations demonstrated herein, although reverse mediation analyses provided further support for our proposed directionality. Still, it is possible that hazardous alcohol use increases impulsivity via alcohol-induced biological dysregulation and psychosocial problems caused by drinking-related stressors rather than impulsivity leading to hazardous alcohol use. Also, impulsivity has been defined in a number of different ways, and no single measure (e.g., BIS-11) offers comprehensive coverage of the impulsivity construct. Other limitations are the inclusion of only European Americans, which limits our ability to generalize results to other racial groups, and the use of a non-representative sampling strategy and a small overall sample. Future work to replicate this risk pathway (ideally with multimodal assessments of impulsivity), extend its generalizability to the larger population, and explore its temporality with prospective designs is warranted.

Limitations notwithstanding, current findings expand the literature by highlighting impulsivity as a potential endophenotype in the relationship between *SNCA* and alcohol use.

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