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DISC1 Loci Not Associated with Anhedonia in Individuals with Genetic Liability for Schizophrenia

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Meta-analytic review has indicated that social symptoms are quite relevant to genetic liability for schizophrenia (Tarbox et al., 2011). Social anhedonia, in particular, consistently differentiates relatives of people with schizophrenia from controls, yet the biological mechanisms underlying anhedonia remain unclear. Recently, social anhedonia as a measure of psychosis-proneness has been linked to *DISC1* (Disrupted-in-schizophrenia 1), and eight other genes impacting the DISC1 pathway, in a large Finnish cohort (for details of two studies, see Tomppo et al., 2009 and Tomppo et al., 2012).

The current study examined whether anhedonia is associated with *DISC1* polymorphisms in a clinically-enriched sample of 346 schizophrenia probands, their first-degree relatives, and non-psychiatric controls from the Minneapolis Veterans Affairs (VA) Family Study of Schizophrenia.

Lifetime Axis I diagnoses for all participants were determined by doctoral-level psychologists through a consensus process, consistent with established guidelines, that involved review of structured diagnostic interviews, medical history, and family informant material when available. Relative and control participants were administered self-report anhedonia questionnaires identical to those used by Tomppo et al. The entire sample was additionally administered the *Schizotypal Personality Questionnaire* (*SPQ*; Raine, 1991), a measure with interpersonal and social withdrawal-related subscales. Scores across these measures were examined for association with 14 single nucleotide polymorphisms across *DISC1*.

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SNPS included, with minor allele frequency (MAF): rs3738401 (.26); rs1954175 (.26); rs2812393 (.48); rs1322784 (.20); rs1322783 (.08); rs2255340 (.26); rs2738864 (.22); rs6675281 (.13); rs1000731 (.26); rs1000730 (.42); rs7546310 (.48); rs821597 (.37); rs821616 (.32); rs3737597 (.03). The frequencies in patients, relatives, and controls for all markers were in Hardy–Weinberg equilibrium. The QFAM-TOTAL procedure in Plink for Linux performs family-based tests of between- and within-groups association with quantitative phenotypes, while accounting for dependence between related individuals.

Consistent with previous research, groups differed across all measures (relatives and controls, *Revised Social Anhedonia Scale* $Z_{(1,348)} = -2.31$, $p < .05$ and *Physical Anhedonia Scale* $Z_{(1,348)} = -2.12$, $p < .05$; probands, relatives and controls, *SPQ Interpersonal Factor* $X^2_{(2,518)} = 124.22$, $p < .001$; *SPQ No Close Friends* subscale $X^2_{(2,518)} = 118.92$, $p < .001$). Probands represented the most elevated scores, followed by relatives, followed by controls. Proband and control participants differed significantly with respect to one of the DISC1 SNPs, rs1000730 (*Wald* = 4.382, $p < .05$) but this did not remain significant after correcting for multiple testing. None of the SNPs were significantly associated with any anhedonia scores after Bonferroni correction for multiple testing. Inclusion of age, sex, and ethnicity covariates did not alter results.

Anhedonia was not associated with *DISC1* polymorphisms in this clinically-enriched sample, despite power being adequate to detect small-to-moderate effects ($f \geq .25$ with power $\geq .80$). Schizotypal anhedonia may be tied to dopaminergic innervations of prefrontal brain regions, while *DISC1* may be more related to manifestations of hippocampal dependent abnormalities reflective of genetic liability for schizophrenia. Future research examining DISC1 and anhedonia would benefit from inclusion of additional *DISC1* loci in biological relatives.

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