

## Dopamine-related Genetic Profile is Associated with Negative Symptom Severity, Reward Expectancy, and Behavioral Inhibition

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**BACKGROUND:** Anhedonia, reduced sensitivity to reward, and greater punishment-related behavioral inhibition are risk factors for substance use disorders. These behavioral phenotypes are present in several diseases that are often comorbid with substance use disorders including schizophrenia and obesity and are thought to be related to central dopamine function.

**OBJECTIVE:** Determine whether a dopamine-related genetic profile, constructed to reflect subcortical dopamine signaling, is associated with negative symptom severity and anhedonia in healthy controls, siblings of individuals with schizophrenia, and individuals with schizophrenia and with reward sensitivity and behavioral inhibition in normal-weight and obese individuals.

**METHODS:** Using the Brief Negative Symptom Scale (BNSS) and Scales for Physical and Social Anhedonia (SPSA), negative symptom severity and self-reported anhedonia were assessed in 34 healthy controls, 25 siblings of individuals with schizophrenia, and 65 individuals with schizophrenia or schizoaffective disorder. Several measures, including the Generalized Reward and Punishment Expectancy Scales, were used to assess self-reported reward sensitivity and behavioral inhibition in 13 normal-weight and 16 obese individuals. For each individual, an additive genetic profile of polymorphisms within dopamine-related genes previously associated with indices of dopamine signaling (*DRD2/ANKK1* rs1800497, *SLC6A3* DAT1, *DRD4* 48 bp exon 3, and *COMT* val158met (rs4680)) was formulated such that elevated scores are reflective of enhanced subcortical DA signaling capacity.

**RESULTS:** Higher dopamine-related genetic profile scores, reflecting greater subcortical dopamine signaling capacity, related to lower negative symptom severity and self-reported anhedonia across healthy controls, siblings of individuals with schizophrenia, and individuals with schizophrenia or schizoaffective disorder. Higher dopamine-related genetic profile scores were also associated with greater expectancy of reward and lower expectancy of punishment across normal-weight and obese individuals.

**CONCLUSION:** Greater dopamine signaling capacity, as reflected by dopamine-related genetic profiles, may protect against the development of anhedonia, even among those with a familial history of schizophrenia. Given evidence of compromised reward-related function among individuals with substance use disorders and offspring of substance dependent individuals, genetically-conferred elevations in subcortical DA signaling capacity may protect against the development of problematic substance use. Critically, however, in light of stage-based theories of addiction, it is possible that such genetic profiles may also be associated with an increased likelihood of substance use initiation.