Triangulating associations between genetic and neural risk for externalizing behaviors from early adolescence to adulthood

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Electrophysiology and genome-wide association studies (GWAS) are each powerful tools that have been used to improve our understanding of the etiology of externalizing disorders. The current study seeks to leverage information across these domains to improve our understanding of the biological bases of externalizing disorders and how these associations may change over development. The VP3 is an event related potential that occurs following a "significant" rare stimulus. Low VP3 amplitude has been identified as a candidate endophenotype for externalizing disorders (Porjesz et al., 2005). In the field of genetics, a recent GWAS of 1.5 million individuals found that genetic risk for several externalizing behaviors all load on a common externalizing (EXT) factor and includes loci enriched for genes expressed in the brain and related to development of the nervous system (Linnér et al., 2021). Using the single nucleotide polymorphisms identified in this study, polygenic risk scores (PRS) can be calculated in held-out samples to provide an index of genetic risk for externalizing psychopathology.

Method: Using data from the Collaborative Study on the Genetics of Alcoholism (COGA), the current study used P3 amplitude generated from the visual oddball task (VP3) and examined associations with the EXT PRS (Linnér et al., 2021) and a phenotypic externalizing factor derived from self-report of alcohol and cannabis use and antisocial behavior. Associations were stratified by ancestry and developmental period.

Results: Among participants of European Ancestry, bivariate analyses demonstrated that EXT PRS was significantly associated with VP3 and this significant association emerges in adulthood. In addition, both EXT PRS and VP3 are significantly associated with phenotypic externalizing, particularly in individuals aged 18 and older; however, only EXT PRS maintained significant association after controlling for its overlap with VP3 and covariates. Results from the participants of African Ancestry are largely similar.

Discussion: Genetic and neural (VP3) risk for externalizing were significantly associated although these analyses suggest that there is a developmental effect, with the two variables becoming more correlated as age increases. Both VP3 and EXT PRS were significantly associated with the phenotypic expression of externalizing; however, only the PRS maintained significant association when accounting for variance shared between PRS and VP3. Future work will utilize sibling structure of the dataset to determine individual and family-level effects. Also,

longitudinal modeling of these associations will be performed to determine the specific trajectories of these effects.

References: Linnér et al., Nat. Neurosci 24:1367-1376 (2021); Porjesz et al., Clin Neurophysiol 116(5) 993-1018 (2005)

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