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

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Examining Development, Genes, and Environment

Background

- 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).
- A recent GWAS of 1.5 million individuals found that genetic risk for several externalizing behaviors 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.

- **Purpose**: Determine the unique and shared associations between genetic and neural risk for externalizing psychopathology
    - Across developmental periods
    - Across European and African Ancestry participants

Methods

Sample: Data from the Collaborative Study of the Genetics of Alcoholism (COGA) participants ages 12-32 (*M age* = 20.81, SD = 4.93; 52.4% female)

- Racial/Ethnic Composition of the sample: 63.4% White, 26.1% Black, .8% Asian, 7.5% Other; 11.5% Hispanic

Measures:

- VP3 Amplitude: Target-evoked peak amplitude from the Visual Oddball Paradigm in the 250-600ms time window range at the Pz electrode (Porjesz et al., 2005)
- EXT PRS: A multivariate genome-wide association analysis of the latent genetic externalizing factor (EXT) was performed to identify SNPs. We adjusted GWAS effect sizes for the non-independence of nearby SNPs in the genome (referred to as linkage disequilibrium, or LD) using PRS-CS (Ge et al., 2019) for individuals of EA and PRS-CSx (Ruan et al., 2021) for individuals of AA.
- Externalizing Factor (EXT Pheno): Latent factor calculated in *lavaan* using indicators of alcohol (age of initiation, age of first intoxication, max drinks in 24 hrs, AUD sx count), cannabis (age of first use, CUD sx count), antisocial (ASPD sx count, CD sx count) behavior
- Covariates: age at date of VP3 collection; first 10 within-ancestry principal components

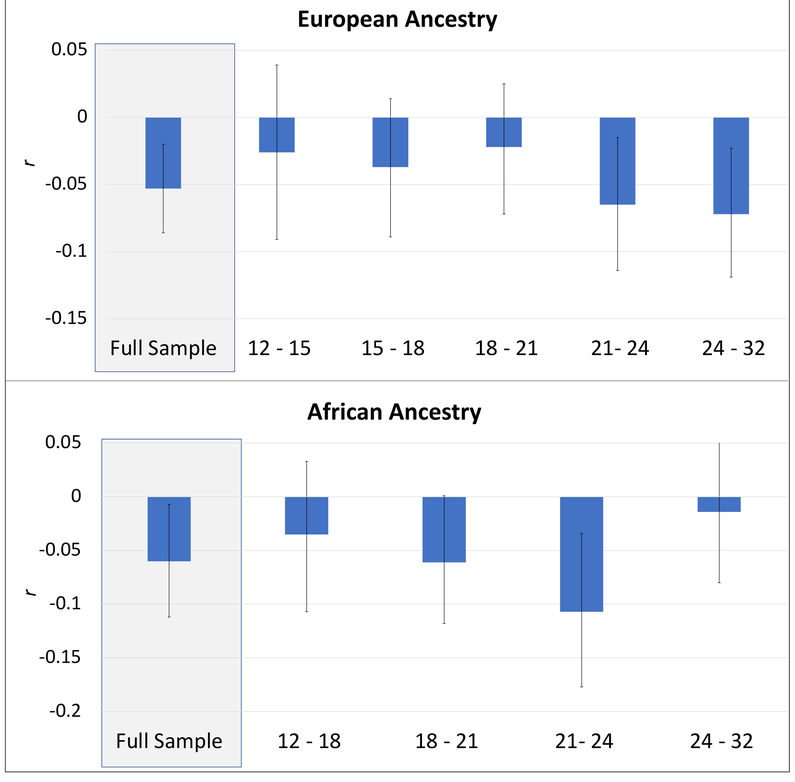
Analytic Strategy:

- All analyses stratified by ancestry (European/African)
- In full sample,
    - Partial correlations performed to determine the associations between VP3, EXT PRS, and EXT Pheno (controlling for age)
    - Multivariate regression analyses were used to determine the unique associations of VP3 and EXT PRS (IVs) with EXT Pheno (DV), controlling for age
- Parallel analyses were performed in developmentally stratified subsamples (*N*'s below)

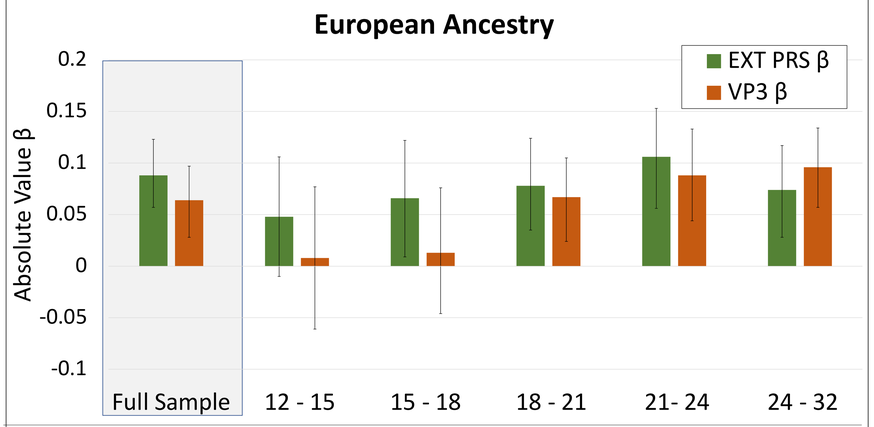
European Ancestry	*N*	African Ancestry	*N*
Full Sample	2685	Full Sample	1245
12-15	521	12-18	657
15-18	894	18-21	570
18-21	1078	21-24	475
21-24	957	24-32	511
24-32	1133		

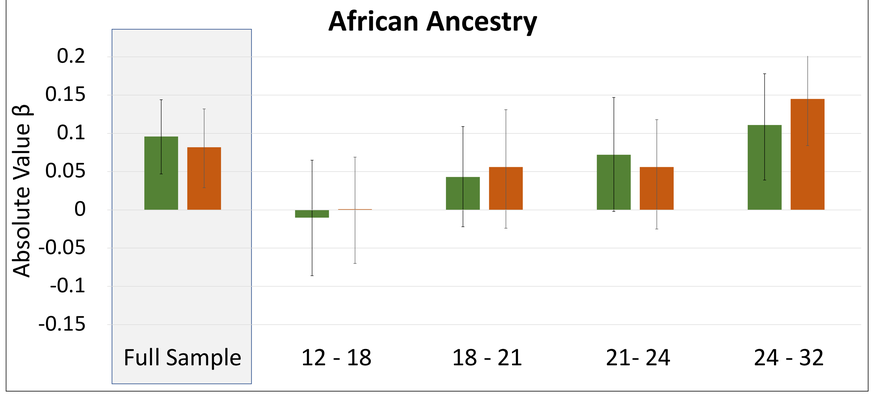
The association between VP3 and EXT PRS becomes significant in emerging adulthood; however, both maintain unique associations with externalizing behaviors even when accounting for shared variance.

Associations between VP3 and EXT PRS ($r_{partial}$)



EXT PRS, VP3 association with EXT Pheno (Absolute Value β)





Discussion

- Small but significant associations between genetic (EXT PRS) and neural risk (VP3 amplitude) for externalizing, with the magnitude of association increasing from emerging adulthood into adulthood
    - Individual differences in how people direct attention to important stimuli reflects, in part, the polygenic risk for externalizing disorders
- Consistent with previous studies, both EXT PRS and VP3 were associated with a latent externalizing factor.
- After accounting for shared variance between EXT PRS and VP3, both indicators significantly predicted general externalizing liability (EXT Pheno) in EA individuals 18+
    - EXT PRS may relate to other brain-based processes (e.g., response inhibition) beyond VP3. Additional work is needed to fully determine how EXT PRS impacts brain development and function
- Results in the EA sample were largely consistent in the AA sample although some subsets of analyses were underpowered.

Limitations: A more developmentally sensitive measure of externalizing may be needed to detect early associations between genetic, neural, and behavioral risk for externalizing.

Future Directions:

- Longitudinal modeling of the co-development of EXT PRS, VP3, and externalizing behavior to clarify developmental trajectories; Using additional neural indicators

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