E-Risk Study Concept Paper template

Provisional Paper Title: Using polygenic scores to study the gene-environment interplay of children's exposure to violence and their externalising symptoms.
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Today's Date: 29/04/2024
Please indicate if you will require an E-Risk independent reproducibility check: ☐

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Background & objective of the study:

Early exposure to violence is a common experience. In the United States, for example, up to 27% witness domestic violence and about 30% of children experience some form of sexual or physical abuse (Finkelhor et al., 2009, Gilbert et al., 2009). Prevalence rates for child maltreatment range from 5% to 13% in the UK and the US respectively (Radford et al., 2011, Wildelman, 2014) and from 5% to 30% for bullying worldwide (WHO, 2012).

Although no consensus definition of childhood exposure to violence (EtoV) has emerged (Evans, Davis et DiLillo, 2008; Mohr, Lutz, Fantuzzo, & Perry, 2000), EtoV can generally be defined as children being direct or indirect targets or witnesses of intentional acts to cause harm initiated by another person (Fowler et al., 2009, Evans, Davis et DiLillo, 2008).

Early exposure to violence across different contexts has consistently emerged as a strong predictor of later externalising behaviours (EXT; e.g., Evans, Davis et DiLillo, 2008). EXT are defined in the DSM-5 as disorders with prominent impulsive, disruptive conduct, and substance use symptoms including disorders exhibiting antisocial behaviours, conduct disturbances, addictions, and impulse-control disorders. They are generally characterized by difficulties with self-regulation (Tanksley et al., 2023) and lack of respect for social norms (Dhamija et al., 2015). They are behaviour problems that manifest in children's outward behaviour, resulting in conflicts with their external environment (Liu, 2004; Tanksley et al., 2023). Many dimensions of exposure to violence have been associated with development of externalising disorders including family violence (e.g., Chan & Yeung, 2009; Jaffee et al., 2002), harsh parenting (e.g., Huffman et al., 2020; Tabachnick et al., 2020), peer victimization (Reijntjes et al., 2010) and community violence (Fowler et al., 2009).

Some of the risk factors for the development of externalising behaviours are environmental factors (Tanksley et al., 2023) including the forms of exposure to violence cited above. Yet, socialization research has been criticized for ignoring potential influence of genes on behaviour (e.g., DiLalla and Gottesman, 1991; Rowe, 1994). Behavioural and quantitative genetic research has long suggested that genetic differences contribute to risk for externalising behaviours. Indeed, externalising disorders are highly heritable, about $h^2 = 0.80$ by late adolescence (Young et al.,

2000; Hicks et al., 2004) and a large proportion of variance (40–80%) in externalising traits during childhood is accounted for by genetic factors (Polderman et al., 2015; Nikolas & Burt, 2010).

Recently, the development of genome-wide association studies (GWAS) allowed the genotyping of hundreds of thousands of SNPs simultaneously and resulted in new discoveries and methodological developments (Friedman et al., 2021). In 2021, a GWAS by Karlsson Linnér et al. based on a large sample size (N= 1.5 million participants) identified over 500 genetic loci associated with differences in externalising behaviours. Adjusting for LD, they created a genome-wide polygenic score for EXT that explained about 10% of the variance (ΔR2 ~ 8.9-10.5%) of externalising outcomes in two independent cohorts. This EXT PGS was later used by Tanksley et al., 2023 who used two longitudinal cohorts from the UK: the Environmental Risk (E-Risk) and the Millennium Cohort Study to compute polygenic indices (PGI). They found that children with higher values on the EXT-PGI also exhibited more externalising behaviour problems.

One challenge of behavioural genetics is to disentangle genetic effects and environmental effects. Genes and environment constitute an interplay in which they are correlated (gene-environment correlation or rGE) and may interact with each other (genotype-environment interaction or GxE interactions).

Passive rGE emerges when children with genetic predispositions for externalising disorders are raised in family environments that are correlated with their genetic propensities (Plomin et al., 2012). Evocative rGE might occur when children evoke reactions and environmental effects that covary with their genetic propensities. For example, some studies suggested that externalising problems predicts significant increases in peer victimization (e.g., Reijntjes et al., 2010), a reaction which can further increase their behavioural disorders (Tanksley et al., 2023). Active rGE are apparent when children select or construct experiences that are correlated with their genetic propensities. For instance, children with predispositions for externalising disorders may develop peer affiliations and search for specific situations that increase their disorders (e.g., Denault, & Poulin, 2012).

GXE interactions occur when genetic effects vary according to different environments (or when environmental effects depend on genetic factors) (Plomin et al., 2012). Previous research provided various evidence of GxE interactions between genetic propensities for externalising disorders and exposure to violence (e.g., Dash et al., 2023, Derringer et al., 2010; Maglione et al., 2018, Weder et al., 2009), we will focus in this project on the use of polygenic scores (PGS).

Later studies have provided further evidence for potential interaction between violence exposure and genetic factors using polygenic risk scores (PRS). Musci et al. (2018) found a moderating role of a PRS for conduct disorders in teenagers between exposure to severe community violence and externalising disorders. In this study, participants who were lower than average on the PRS and exposed to violence were more likely to be in the moderately high aggressive and impulsive class in comparison with those who were not exposed to violence. Another study by Acland et al. (2024) derived two antisocial-linked polygenic risk scores (PRS) (N = 721) based on previous genome-wide association studies and assessed forms of antisocial behavior at age 13, 15, and 17. They concluded that by the age of 17 years old harsher parenting was associated with higher social aggression in the adolescents who scored higher antisocial PRS and lower social aggression in those with lower antisocial PRS.

Based on these previous studies, we expect to find interactions in the E-Risk cohort between exposure to violence and externalising behaviours. More specifically, we expect children

at high genetic risk (accounted by the EXT-PGI Karlsson Linnér et al., 2021) to display higher levels of externalising symptoms in environmental contexts of high exposure to violence.

Significance of the study (for theory, research methods or clinical practice):

1. General goal of the project

The goal of this project is to investigate the gene-environment interplay between children's genetic liability for externalising behaviour problems and early life exposure to violence in the E-Risk twin cohort. This study aims to study general early exposure to violence (EtoV) as a global predictor for externalising symptoms at age 12. Genetic data will be integrated with the EXT-PGI developed by Karlsson Linnér et al. (2021) and test for potential GxE interactions between EtoV, sex and EXT.

2. A focus on violence as a global risk factor

Previous studies on externalising disorders have focused on **limited and specific forms of violence**: harsh parenting (e.g., Huffman et al., 2020; Tabachnick et al., 2020), family violence (Chan & Yeung, 2009; Evans, Davis et DiLillo, 2008; Jaffee et al., 2002), community violence (e.g., Fowler, 2009; Gorman-Smith et al., 2004), peer victimization (Reijntjes et al., 2010), etc.

This study aims to **investigate general exposure to violence (EtoV) as a global risk factor for externalising symptoms**. This construct encompasses the direct and indirect measures of exposure to violence during childhood available in the E-Risk study: domestic violence, bullying by peers, physical violence and sexual harm.

3. A longitudinal perspective of risk factors

Despite all the research on risk factors for externalising behaviours, further cohort studies are required to provide a **better understanding of the developmental pathways leading to externalising disorders** (Wilson, Stover et Berkowitz, 2009). Developmental perspectives are necessary to design adapted treatments and interventions at the corresponding developmental epochs (Miller-Lewis et al., 2006).

This study aims to use the data of the E-Risk study to allow for this developmental perspective, integrating measures of exposure to diverse types of violence that were assessed at 5, 7, 10, and 12 years of age (Latham et al., 2019).

4. A developmental genetically-informed model of externalising behaviours

Previous environmental and socialization research on externalising disorders remained limited due to the lack of integration of research in behavioural genetics (Jaffee et al., 2002). As these disorders are largely influenced by genetic factors, integrating genetic data allows one to further understand the aetiology of the externalising spectrum (Kjeldsen et al., 2014).

The aim of this study is to investigate the gene-environment interplay between EtoV and EXT-PGI on externalising behaviours. The findings might contribute to build a developmental genetically-informed model of externalising behaviours.

Data analysis methods:

Hypothesis & questions:

Previous research has supported that various forms of childhood violence exposure is a risk factor for later externalizing behaviour (Kitzmann et al., 2003; Wolfe et al., 2003) and especially in early adolescence (Mrug & Windle, 2010). For example, family violence (Bozzay et al., 2020), community violence (Lambert et al., 2012) and domestic violence (Evans, Davis et DiLillo, 2008) are associated with externalising behaviours at the onset of adolescence.

Research also suggested that externalising disorders peak in adolescence (e.g., Loeber et al., 2012), which explains our focus on age 12 in the E-Risk study.

We hypothesize that:

- H1: general exposure to violence (EtoV) will be positively associated with higher rates of externalising behaviour (EXT) at age 12.

Based on recent research (e.g., Tanksley et al., 2023; Baselmans et al., 2022b) that used EXT-PGS (Karlsson Linnér et al., 2021) to study externalising disorders, we hypothesize that:

- H2: the association between EtoV and EXT is partly confounded by genetic risk (as indexed by PGS).

This study will investigate interactions between environmental factors (EtoV and sex) and EXT-PGS to detect GxE of externalising behaviours. Sex was integrated in our model due to the large evidence supporting sex differences in externalising disorders (e.g., Dhamija et al., 2015):

- H3: the effects of EtoV and sex on EXT will interact with genetic factors (Gene x Environment interaction) at age 12.

Variables and constructs:

1) Scores of externalising behaviour (EXT):

This index will be estimated using the Delinquent and Aggressive behaviour subscales from the Child behaviour Checklist (CBCL) (Achenbach, 1991a) reported by mothers and teachers at age 12. The subscales will be averaged across reporters for a specific observation and then summed together (see e.g. Tanksley et al., 2023).

2) Index of exposure to violence (EtoV):

This index will combine information about

- Domestic violence (between partners);

- Bullying by peers;
- Physical violence;
- Sexual harm by an adult;

3) SES:

Family socio-economic status (SES) will be defined based on a standardized composite of parental income, education and occupation.

Statistical models:

For all these models, we will use a clustering correction with the family ID to correct for the non-independence of the observations.

H1: general exposure to violence (EtoV) will be positively associated with higher rates of externalising behaviour (EXT) at age 12.

We will test the hypothesis H1 using the following models in a stepwise design.

- $EXT(12) = \beta_0 + \beta_1 SES + \epsilon$ (multiple linear regression)
- $EXT(12) = \beta_0 + \beta_1 SES + \beta_2 sex + \epsilon$
- $EXT(12) = \beta_0 + \beta_1 SES + \beta_2 sex + \beta_3 EtoV(12) + \epsilon$
- $EXT(12) = \beta_0 + \beta_1 EtoV(12) + \beta_2 sex + \beta_3 EtoV(12) * sex + \epsilon$

We will fit these models in lavaan, using both DZ pairs and one twin of MZ pairs and clustering the SE at the family level.

Where

- $EXT(12)$: refers to the externalising score of the child at age 12.
- SES: family socioeconomic status.
- sex: refers to the sex of the participant (male or female).
- $EtoV(12)$: refers to the general exposure to violence from birth to 12 years old.

Our model will include the sex of participants for several reasons:

- Sex differences in externalising and internalising behaviours have been established by past research (Dhamija et al., 2015). Boys generally display higher externalising trouble and girls more internalising difficulties. These sex differences emerge as early as about 4 years old (e.g., Chen, 2008) and remain stable across childhood until onset of adolescence. Furthermore, we are interested in whether EtoV effects differ between boys and girls, hence the interaction term.

H2: the association between EtoV and EXT is partly confounded by genetic risk (as indexed by PGS).

We will test hypothesis H2 with the following models:

- $EXT(12) = \beta_0 + \beta_1 SES + \beta_2 sex + \beta_4 PGS + \epsilon$
- $EXT(12) = \beta_0 + \beta_1 EtoV(12) + \beta_2 sex + \beta_3 EtoV(12) * sex + \beta_4 PGS + \epsilon$

Where PGS is a polygenic risk score for Externalising disorders. We will compare these three models and compare the differences in $\beta_1$weight and test for attenuation of β_1 when we integrate the PGS in our model.

H3: the effects of EtoV and sex on EXT will interact with genetic factors (Gene x Environment interaction) at age 12.

We will test hypothesis H3 with the following stepwise model:

$$EXT(12) = \beta_0 + \beta_1 EtoV(12) + \beta_2 sex + \beta_3 EtoV(12) * sex + \beta_4 PGS + \beta_5 PGS * sex + \epsilon$$

$$EXT(12) = \beta_0 + \beta_1 EtoV(12) + \beta_2 sex + \beta_3 EtoV(12) * sex + \beta_4 PGS + \beta_5 PGS * sex + \beta_6 EtoV(12) * PGS + \epsilon$$

$$EXT(12) = \beta_0 + \beta_1 EtoV(12) + \beta_2 sex + \beta_3 EtoV(12) * sex + \beta_4 PGS + \beta_5 PGS * sex + \beta_6 EtoV(12) * PGS + \beta_7 EtoV(12) * PGS * sex + \epsilon$$

- These hypotheses will be tested by testing the statistical significance of β_4, β_5, β_6 and β_7 .

Variables needed and at which ages:

Phenotypic data:

Age 5:

Variable name	Description
familyid	Family ID
atwinid	Twin1 ID
btwinid	Twin2 ID
rorderp5	Random order
sampsex	Sex
zygosity	Zygosity
SESWQ35	Social Class Composite

Age: 10

Variable name	Description
EXPV_DV510	Exposure to domestic violence up to age 10, Elder twin

Age: 12

Variable name	Description
SASEVTYE12	Sexual abuse by 12, severity, Elder twin
PABSEVTYE12	Physical abuse by 12, severity, Elder twin
BULLSEVE12	Bullying victim to Age 12, Elder twin
TOTEXTE12	Total Mum & Teacher Externalising Scale - Elder twin
EXT-PGS	PGI for externalising disorders as used in Tanksley et al., 2023

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