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Original article

Parental support moderates the interaction of COMT and BDNF genotypes with early life adversity on problem gambling severity index scores among young adults

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ABSTRACT

The development of gambling-related harm and gambling disorder involves several genetic and environmental factors. However, how these factors interact to influence the development and whether such interactions confer to diathesis-stress or differential susceptibility models remains largely unexplored. To address this gap, data from the Survey of Adolescent Life in Västmanland (SALVe cohort) were utilized, Participants provided a saliva sample for genotyping, completed early life adversity (ELA) and Parents as Social Construct (PASCQ) surveys at age 17, and the Problem Gambling Severity Index (PGSI) at age 23. A total of 391 participants (54% females) with complete data were included for analysis. Negative binomial models were utilized to examine the interaction between candidate genes (COMT, BDNF, and DRD2), ELA, and parental support in PGSI scores. Interactions between COMT and BDNF, ELA, and parental support were found but not for DRD2, ($\beta = -0.01$ and -0.009, 95% CI [-0.02, -0.006 and -0.01, -0.005], $p = 2.2 \times 10^{-5}$ and 1.2×10^{-5} respectively). The interactions remained significant after accounting for sex interactions, $p = 0.005$. Notably, evidence for a differential susceptibility framework was found in gambling-related harm scores. Participants with the major allele for both COMT and BDNF displayed plasticity by exhibiting higher PGSI scores when exposed to weak parental support but lower PGSI scores in strong parental support despite higher ELA scores. Positive parental support acted as a protective factor against the genetic sensitivity of gambling-related harm. Studies pursuing the interplay between genetic and environmental factors would benefit from including positive environments that may mitigate the risk associated with adverse environments.

1. Introduction

Gambling disorder (GD), the first behavioral addiction to be included in the Diagnostic and Statistical Manual (DSM-5), is characterized as "persistent recurring maladaptive gambling behavior that leads to clinically significant distress or impairment" (American Psychiatric Association, 2013). Gambling-related harm describe a continuum of recurrent patterns of gambling that ranges in severity and may lead to negative gambling-related consequences including gambling disorder (Raisamo et al., 2015; Calado and Griffiths, 2016; Hellström et al., 2017; Potenza et al., 2019; Bastiani et al., 2025). The development of gambling-related harm and GD is complex and likely to involve a multitude of genetic, environmental, neurobiological, and psychiatric factors (Allami et al., 2021; Davis et al., 2019; Dowling et al., 2017, 2015; Gyollai et al., 2014; Potenza et al., 2019; Shaffer and Martin, 2011; Slutske et al., 2010). There has been an increasing body of

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research focusing on the genetic underpinnings of gambling-related harm (Black et al., 2006; Davis et al., 2019; Gyollai et al., 2014; Lobo and Kennedy, 2009; Potenza et al., 2019; Slutske et al., 2009). Twin studies have shown an overlap of genetic factors in disordered gambling and alcohol use disorder (Slutske et al., 2013b), antisocial behaviors (Slutske et al., 2001), and personality subtypes ((Slutske et al., 2013a). Likewise, Genome-wide association studies (GWAS) are scarce but recent studies have linked gambling-related harm to polygenic scores of schizophrenias (Piasecki et al., 2019) and personality traits subtypes (Spychala et al., 2022). Candidate gene studies are also limited with contradictory results (Gyollai et al., 2014; Pettorruso et al., 2020; Potenza et al., 2019).

On the other hand, research on how environmental factors interact and influence the genetic sensitivity to gambling-related harm remains largely unexplored. Contrary to a diathesis-stress framework which assumes that specific genotypes confer an increased risk for behavioral or psychiatric disorders in a stressful environment (Manuck and McCaffery, 2014; Szyf, 2012), the differential susceptibility model hypothesizes that candidate genes do not confer the risk of psychiatric disorders but may instead alter the sensitivity to both negative and positive environmental factors (Åslund and Nilsson, 2018; Belsky and Beaver, 2011; Belsky and Pluess, 2013; Ellis et al., 2011; Hankin et al., 2011). Accordingly, failure to account for positive environments may contribute to poor replication rates in genetic and gene-environment studies. For instance, negative environments during sensitive periods in early life are a common risk factor for psychiatric symptomatology (Hanson et al., 2015). Individuals with psychiatric phenotypes exhibit a greater prevalence of negative environmental events and a reduced prevalence of positive ones when compared to unaffected groups (Hodgins et al., 2009; Larm et al., 2010). In regard to gambling-related harm, data on its interplay with early life adversity (ELA) is limited. However, existing literature suggests an association with child maltreatment (Felsher et al., 2010; Lane et al., 2016). Nonetheless, the majority of studies focused on risk factors with limited research on positive or protective factors (Dowling et al., 2017).

The present study included both positive and negative environments with a focus on three candidate genes of interest to the development of gambling-related harm (COMT, DRD2, and BDNF). Dysregulation in the dopamine system has been linked to impulsive behavior and poor decision-making (Dalley and Roiser, 2012; Peters et al., 2020), factors associated to gambling pathology (Clark et al., 2013; Grant et al., 2006; Pettorruso et al., 2020). COMT Val158Met (COMT rs4680), a common variant at codon 158, modifies the structure of the COMT enzyme and alters dopaminergic signaling and was previously linked to gambling-related harm, albeit with contradictory results (Farrell et al., 2012; Grant et al., 2015, 2013; Guillot et al., 2015). Similarly, DRD2, which encodes the dopamine receptor D2 (DRD2) regulates dopamine receptors and is of particular interest to gambling behavior (Pettorruso et al., 2020). The DRD2 Taq1A (rs1800497) single nucleotide polymorphism (SNP) is associated with a decrease in dopamine binding and has been linked with psychiatric comorbidities and addictive behaviors (Munafò et al., 2007; Nisoli et al., 2007; Rivera-Iñiguez et al., 2019). Changes in DNA methylation of DRD2 are suggested to have an association with gambling-related harm (Hillemacher et al., 2015). Finally, the Brain-derived neurotrophic factor (BDNF), plays a vital role in regulating synaptic transmission. A frequent SNP in the gene, BDNF rs6265, occurs at codon 66 substituting a Val to Met amino acid and is associated with psychiatric diseases and impaired cognitive functions (Correa et al., 2016; Notaras et al., 2015). Additionally, neurotrophin genes have been linked recently to the development of gambling-related harm (Solé-Morata et al., 2022). However, the exact relationship between these three genes and gambling-related harm remains elusive, with prior research yielding inconclusive results.

In this study, we aim to assess the effect of candidate genes (COMT rs4680, DRD2 Taq1A, and BDNF rs6265) in the presence of ELA and trajectories of parental support on subsequent gambling-related harm among young adults. Specifically, if candidate genes display differential susceptibility for gambling-related harm scores in the presence of a negative and/or positive environment. This analysis aims to investigate risk and resilience factors related to gambling behaviour with the intention of offering insights for future research and early intervention and prevention strategies.

2. Study design

Data from the "Survey of Adolescent Life in Västmanland Cohort" (SALVe cohort) were used for the present study. The SALVE project started in 2012 with data at four-time points collected in the cohort represented by wave 1 to wave 4 (w1-w4, Fig. 1). Adolescents born in 1997 or 1999 were invited by regular mail to participate in the study and followed through adolescence into young adulthood. The present study utilizes data from three-time points (w1, w2, w4) to investigate risk and resilience factors for gambling-related harm (Fig. 1). Participants provided saliva samples for genotyping at the first wave (mean age: 14 years old), completed measurements of early life adversity at the second wave (2015, mean age; 17), and measurements of gambling behavior at the fourth wave (mean age:23 years old). The total population was 993 participants. Of which, 447 (45%) participants reported gambling in the last 12 months and completed PGSI measurements. The final study sample included a total of 391 participants (179 males and 212 females) who provided a saliva sample and had available data on all the variables of interest.

2.1. Measurements

2.1.1. Gambling behavior

Participants reported whether they had gambled in the last 12 months on a list of gambling activities (poker, online casino, offline slot machines, betting, lotteries, Esports, loot boxes). Those who reported gambling were then evaluated for gambling-related harm using the Problem Gambling Severity Index (PGSI) scale. PGSI consists of 9 items with a possible maximum score of 27 points to measure gambling-related harm in the general population. The PGSI has a response scale ranging from "0 = Never" to "3 = almost always". The scale showed high internal consistency in the SALVe cohort (Mohamed et al., 2023).

2.1.2. Control variables

Sex was recorded based on the personal identity number, which discloses the individual's biological sex. Coding was done as 1 = male, 2 = female. To account for sex interactions, both the main and interaction effects between sex and the three independent variables were added.

2.1.3. Environmental factors

During the second wave (2015, mean age; 17), participants completed surveys on their perceived home and school environments and parental support. The present study pursued to examine the differential susceptibility of candidate genes in the presence of a negative or positive environment. Cumulative early life adversity (ELA), constituted the negative environment in this study and was comprised of both negative home (family and non-family maltreatment), and negative school environments. On the other hand, parental support (Warmth, Structure, and Autonomy support) constituted the positive environment in this study.

Family maltreatment was measured using the following four questions as previously described (Torres Soler et al., 2023); 1) Have there been difficult and/or upsetting arguments between your parents? 2) Has it happened that one of your parents pushed, hit, or used other violence against the other? 3) Have you ever been psychologically ill-treated/abused (e.g. mocked, violated) by one of your parents? 4) Has it happened that one of your parents pushed, hit, or used other violence against you? The questions had a response scale of 0–5 as follows;

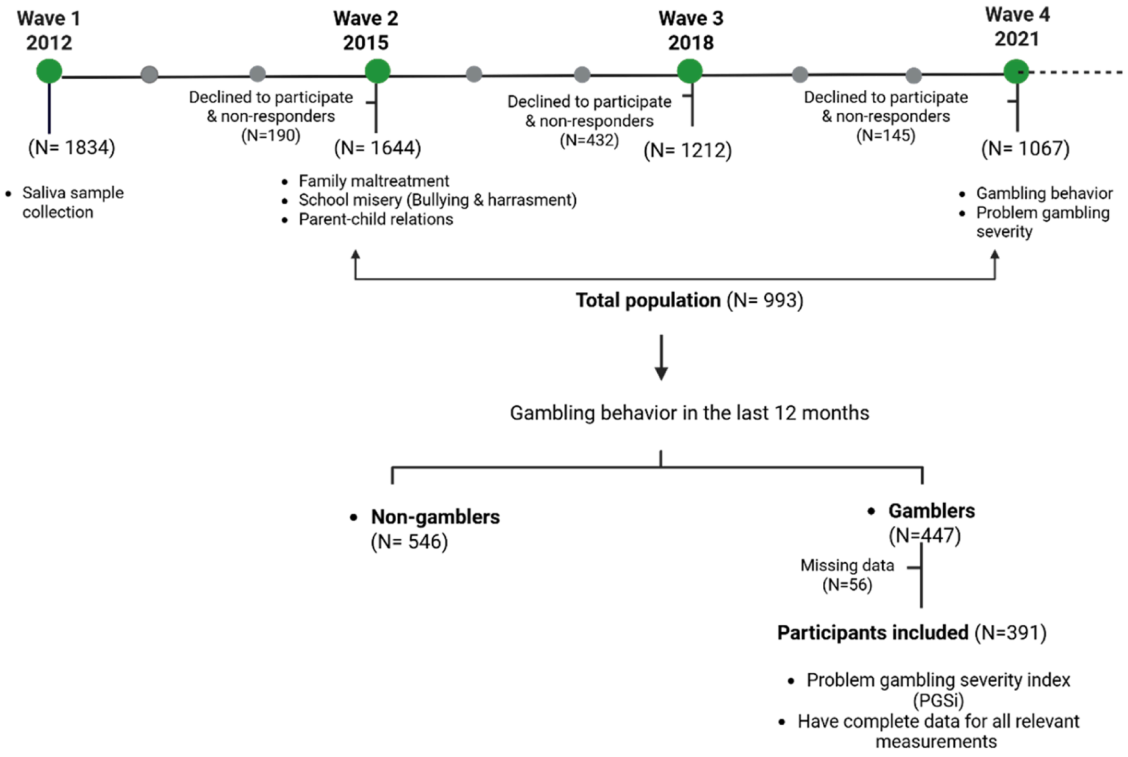

Fig. 1. Study design: 993 participants completed included measurements in both waves. 54.9% reported no gambling activity in the last 12 months. Among gamblers, 56 had missing data and were omitted from this study. The final sample size was 391 young adults with complete data on all measurements of interest.

0= No, 1= Yes, less than once a year, 2= Yes, once a year, 3= Yes, sometime a month, 4= Yes, sometime a week, 5= Yes, every or almost every day. Non-family maltreatment was measured using two questions; 1) Have you ever been mentally ill-treated (e.g. mocked, offended) by an adult who is not part of the family? And 2) Have you ever been physically abused (e.g. beaten, kicked) by an adult who does not belong to the family? with a response scale 0–3 (0= No, 1= Yes, once, 2= Yes, a few (2–4 times, 3= Yes, many (more than 5) times).

Participants were also asked about their school environment using the following questions; 1) During the past year, have you felt uncomfortable with the thought of going to school because of fear of getting into a fight during the school day? 2) During the past year, have you been beaten, kicked, or subjected to other violence by one/some of your schoolmates? 3) Have you been seriously teased, eg accused of things you didn't do, threatened, or called ugly things by one/some of your schoolmates in the last year? 4) In the past year, has it happened that one/some of your schoolmates lied about you, talked crap about you behind your back, didn't pretend to be you, or excluded you from the group? 5) In the past year, have you been subjected to bullying, threats, or harassment via mobile phone and/or the internet (Snapchat, SMS, Messenger, email, or the like)? The questions had a response scale from zero to three as follows; 0=Never, 1= Some/a few times, 2 = 1–3 times per month, 3= At least once a week. Finally, a cumulative ELA variable was computed by summing the two home and school measurements. The ELA scale ranged from 0–35 and showed good internal consistency as measured by Cronbach's alpha, α= 0.69.

Perception of parenting was measured using the Parents as Social Context Questionnaire (PASCQ) (Skinner et al., 2005) which was translated into Swedish (Keijser et al., 2020). This questionnaire measures six distinct dimensions: Warmth, Rejection, Structure, Chaos, Autonomy Support, and Coercion. Each dimension comprises four questions with a response scale for each item ranging from 0= not at all true to 3= very true. A positive parental support (PASCQpos) index was created for three dimensions (Warmth, Structure, and Autonomy support) as previously described (Keijser et al., 2020). The PASCQpos index had good internal consistency as measured by Cronbach's alpha, $\alpha = 0.85$.

2.1.4. Genotyping

Genomic DNA were extracted from the saliva collected through a self-collection kit (Oragene® DNA, DNA Genotek, Ottawa, Ontario, Canada). DNA extraction was performed from 200 µL of saliva using KleargeneTM (LGC, Biosearch Technologies, UK). Genotyping was performed using a fluorescence-based competitive allele specific PCR (KASPar) assay (KBioscience®). Allele discrimination was done using SNPviewer®. The genotype calling was carried out blind to phenotype data. Three candidate genes (*COMT rs4680, DRD2 Taq1A, and BDNF rs6265*) of interest were examined in this study. For analysis, genotype data were categorized into two groups as follows: COMT rs4680 and BDNF rs6265: major allele (GG or GA) =1, AA = zero, DRD2 rs1800497: major allele (CC or CT) = 1, TT = zero. The allele frequencies of the candidate genes aligned with the Hardy-Weinberg equilibrium.

2.2. Statistical analysis

Mean, median, standard deviations, and percentages were calculated for descriptives. The main objective of this study was to examine the differential susceptibility in candidate genes in the presence of a negative or positive environment and (Åslund and Nilsson, 2018). Due to the skewness and overdispersion of the PGSI count with a large proportion of participants scoring zero, a negative binomial (NBN) model with a log link was used.

Two models were used with Model I adjusting solely for sex main effects and Model II adjusting for sex interactions. In Model II, interaction terms between sex and the two environmental factors, genotypes, and the genotypes × environment interaction were included. The beta coefficient was exponentiated to calculate incidence rate ratios (IRR). To account for multiple testing, a Bonferroni correction was applied to adjust the significance threshold. The standard significance level was divided by the number of tests; two models per gene of interest

($p = 0.05/6 = 0.008$). P-values below this threshold were considered statistically significant. To visualize the interaction, we computed a dichotomous parental support variable for weak or strong parental support (greater or lesser than the mean). Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS, Software version 28.0; IBM Corporation, NY: USA).

2.3. Ethical considerations

The research received approval from the Ethical Review Board in Uppsala, under reference number 2012/187, and adhered to the principles outlined in the Declaration of Helsinki. Every participant provided their written informed consent to take part in the study. For measurements when participants were less than 15 years of age, written informed consent was provided by the participants' legal guardians/next of kin.

3. Results

3.1. Descriptives

Descriptive statistics of the participants are presented in Table 1. At wave 4, The mean age of participants was 23 years old. The mean PGSI score for males, 0.80, was roughly five folds more than in females' score of 0.15. The median score of parental support was similar for both sexes but females showed two-fold increase in the median score for ELA compared to males. The distribution of the G major allele (GG/GA) in *COMT rs4680* was 70.5% in males and 66.4% in females. For *BDNF rs6265*, 97.8% of males and 97.6% of females had the G allele (GG/GA) while 96.6% of males and 95.8% of females had the major C allele (CC/CT) in *DRD2 Taq1A*. Table 1 summarizes the sample descriptive in the SALVe cohort.

3.2. Parental support moderates the interaction between COMTrs4680 and BDNFrs6265 genotype and early life adversity in gambling-related harm scores

For COMT *rs4680*, the main effects of the genotype and the two environmental factors, ELA and parental support, were not significant in both models. In Model I, nominally significant two-way interaction effects were observed between ELA and COMT ($\beta = 0.30$, SE = 0.08, 95% CI [0.13, 0.45], $p = 2.9 \times 10^{-4}$) in PGSI scores. The interaction was not significant in Model II after adjusting for sex interactions. Finally, parental support moderated the interaction between the COMT genotype and ELA for PGSI scores (Table 2), ($\beta = -0.01$, SE = 0.003, 95% CI [−0.02, −0.006], $p = 2.9 = 2 \times 10^{-5}$) . Moreover, the moderation interaction effect size decreased but remained statistically significant when adjusted for sex interactions, ($\beta = -0.005$, SE = 0.002, 95% CI [−0.009, −0.002], p = 0.005).

To visualize the moderation interaction effects, linear graphs with fitted models are presented for males and females with COMTrs4680 G allele divided by weak and strong parental support (Fig. 2). Sex-stratified analysis was done for COMTrs4680, ELA, and parental support. A significant four-way interaction in males, COMTrs4680 major (G) allele, ELA, and parental support was found (NBN: $\beta = -0.03$, IRR= 0.97 SE = 0.007, 95% CI [−0.05, −0.02], $p = 1 \times 10^{-6}$).

Similarly, the main effects of the BDNF rs6265 genotype and the two environmental factors were not significant in both models (Table 3). The interaction between BDNF and ELA was significant in Model I ($\beta = 0.36$, SE = 0.11, 95% CI [0.14, 0.58], $p = 0001$). Moderation analysis showed a significant interaction between parental support, BDNF genotype, and ELA, ($\beta = -0.009$, SE = 0.002, 95% CI [−0.013,−0.005], $p = 1.3 \times 10^{-5}$). This interaction remained significant after adjusting for sex interactions, ($\beta = -0.004$, SE = 0.001, 95% CI [−0.007,−0.001], $p = 0.005$).

Linear graphs with fitted models for the moderation effect are presented in Fig. 3 divided by weak or strong parental support. Sex stratified analysis revealed a weak effect size and nominally significant interaction between male sex, ELA, BDNF major (G) allele, and parental support, ($\beta = -0.028$, IRR= 0.97 SE = 0.006, 95% CI [−0.04, −0.02], $p = 5 \times 10^{-6}$). On the other hand, no significant interactions were found for DRD2Taq1A polymorphism in the final model (Table 4).

4. Discussion

The present study explored if candidate genes (COMT rs4680, BDNF rs6265, and DRD2 rs1800497) displayed plasticity in the presence of a negative or positive environment. Results indicated a significant moderation effect of parental support on the interaction between COMT rs4680 and BDNF rs6265 genotypes and early life adversity. This moderation remained significant when controlling for sex interactions but had a decrease in effect size. Notably, gambling-related harm scores in young adults conferred to a differential susceptibility framework which may explain some of the previous contradictory results. The nine-year follow-up period in the SALVe cohort allowed for the timely combination of genotype data and early adolescence events to decipher associated factors in gambling-related harm development in adulthood. The present analysis is particularly relevant as Sweden continues to report increased levels of gambling-related harm among adolescents (Thor S, 2023) and the increased prevalence of gambling-like features in gaming such as loot boxes (Newzoo, 2023). Parental support acted as a protective factor against the genetic sensitivity of gambling-related harm in COMT rs4680 and BDNF rs6265 major allele carriers in the presence of ELA.

The inclusion of environmental factors is essential for a robust understanding of gambling-related harm development. Large twin cohorts indicate a strong association between genetic and individual-specific environmental factors for the development of disordered gambling

Table 1
Sample Descriptives of the SALVe cohort measurements for participants included in the present analysis.

Scales		Males N = 179		Females N = 212	
		Mean (Median)	Std Deviation	Mean (Median)	Std Deviation
Age (wave 4)		22.9	1.04	23	1.04
PGSI (wave 4)		0.80 (0.00)	2.7	0.15 (0.00)	0.75
Early Life Adversity (wave 2)		2.07 (1.0)	2.7	3.1 (2.00)	3.84
Parental support (wave 2)		27.7 (29.0)	5.5	28.2 (29.00)	6.02
cG Distribution (wave 1) **%**					
COMT *rs4680*	Major allele (G)	70.5%		66.4%	
	A: A	29.5%		33.6%	
BDNF *rs6265*	Major allele (G)	97.8%		97.6%	
	A: A	2.2%		2.4%	
DRD2 *rs1800497*	Major allele (C)	96.6%		95.8%	
	T: T	3.4%		4.2%	

Table 2
Moderation models on the main effect and interactions of Early Life Adversity, COMT rs4680 genotype, and parental support.

Model	Negative binomial model with log-link				
	β	SE	95% CI		*P*
			LL	UL	
Model I					
ELA [a]	0.02	0.08	−0.13	0.17	0.8
COMT rs4680 genotype [a]	−1.40	1.00	−3.3	0.60	0.17
Parental Support [a]	−0.04	0.036	−0.11	0.04	0.33
ELA × COMT	0.30	0.08	0.13	0.43	$\mathbf{2.9 \times 10^{-4}}$
Parental support × COMT	0.08	0.03	0.01	0.14	0.02
ELA × COMT × Parental support	−0.01	0.003	−0.02	−0.006	$\mathbf{2.2 \times 10^{-5}}$
Model II					
ELA [a]	0.003	0.13	−0.25	0.26	0.98
COMT rs4680 genotype [a]	0.19	0.50	−0.80	1.18	0.70
Parental Support [a]	0.09	0.06	−0.04	0.22	0.18
Sex [a]	−0.31	1.94	−3.97	3.36	0.87
Sex × COMT	−0.20	0.81	−1.78	1.38	0.81
Sex × ELA	−0.02	0.11	−0.19	0.25	0.83
Sex × Parental support	−0.08	0.06	−0.20	0.03	0.15
Sex × ELA × COMT	0.11	0.05	0.001	0.21	0.03
Sex × Parental support × COMT	0.03	0.02	−0.02	0.07	0.14
Sex × ELA × COMT × Parental support	−0.005	0.002	−0.009	−0.002	**0.005**

B; regression coefficients, SE; standard error, CI; Confidence intervals, LL; Lower limit, UL; Upper limit, Model I; adjusted for sex main effects, ELA; Early life adversity, Model II; adjusted for sex main effects and sex interaction terms. Significant p-values and final interaction models are in bold.
[a] Main effects.

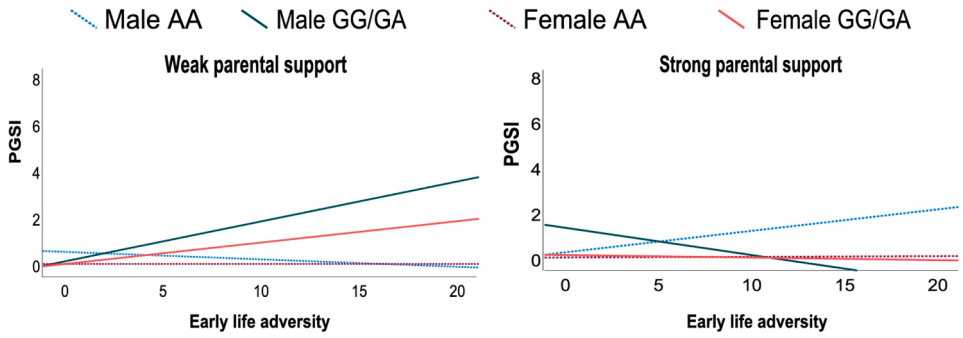

Fig. 2. Three-way interaction effects of ELA, parental support, and COMT in gambling-related harm: In weak parental support, PGSI scores in males carrying the major allele (G) increased with the increase of ELA. However, strong parental support reduced the risk of gambling-related harm in G allele carriers irrespective of ELA scores, NBN model, $p \leq 0.001$.

(Davis et al., 2019). However, the majority of previous studies on gambling-related harm did not explore the association in the presence of negative and/or positive environments and lacked a longitudinal design. Meta analysis of the genetic and environmental Influences on gambling in twin studies highlight moderate non-shared environmental factors and genetic risks (Xuan et al., 2017). Studies that included such factors yielded differential results such as the role of local area disadvantages in disordered gambling genetic risk (Slutske et al., 2015). Early adverse life events are considered risk factors for relevant psychiatric comorbidities and traits (Birnie et al., 2020; Gaffrey et al., 2018; Lovallo et al., 2013). Similarly, our analysis showed that early life adversity contributed to the subsequent sensitivity to gambling-related harm among major allele carriers.

There are limited studies to compare with the present analysis. Our results are partially consistent with an early study in China that found parental warmth acted as a protective factor among COMT Val/Val homozygotes to influence decision-making in gambling tasks (He et al., 2012). The study however was of cross-sectional design and found that Met carriers interacted with stressful events leading to poorer decision-making in contrast to the present study, Likewise, a longitudinal cohort in the U.S investigating several parental trajectories found that stable parental supervision throughout adolescence was associated with lower gambling-related harm among young adults (Lee et al., 2014). As for the BDNF Val66Met polymorphism, the variation has been linked to cognitive function modification and a multitude of psychiatric comorbidities (Notaras et al., 2015). Moreover, the polymorphism may lead to alterations in decision-making in gambling tasks (Kang et al., 2010). Notably, both genotypes have been previously associated to a differential susceptibility framework for other psychiatric traits (Sulik et al., 2015; L. Zhang et al., 2016; W. Zhang et al., 2016). Likewise, genetic overlap with substance-related addictions has also been reported (Guillot et al., 2015; Lang et al., 2016).

The final model remained significant but with a very low effect size. This is not surprising given that our model did not account for psychiatric comorbidities, for example, or scales of impulsivity. Such factors contribute significantly to disordered gambling (Browne et al., 2019; Dowling et al., 2015; Dussault et al., 2011; Ioannidis et al., 2019; Lorains et al., 2011). However, the model used here would be overly complex when adding psychiatric traits and may lead to overfitting and obscure the effects of the primary variables of interest. This finding first highlights the vital role of strong parental support during adolescence irrespective of sex and secondly, demonstrates that genetic vulnerability to gambling-related harm is subject to plasticity in the presence of protective or adverse environments.

The present study has several limitations that should be noted when analyzing the results. Notably, the SALVe cohort high attrition rate

Table 3
Moderation models on the main effect and interactions of Early Life Adversity, BDNF rs6265 genotype, and parental support.

Model	Negative binomial model with log-link				
	β	SE	95% CI		*P*
			LL	UL	
Model I					
ELA [a]	−0.05	0.15	−0.34	0.24	0.73
BDNF rs6265 genotype [a]	−0.43	1.37	−3.12	2.27	0.75
Parental Support [a]	0.04	0.08	−0.12	0.19	0.65
ELA × BDNF	0.36	0.11	0.14	0.58	**0.001**
Parental support × BDNF	0.03	0.045	−0.06	0.01	0.63
ELA × BDNF × Parental support	−0.009	0.002	−0.013	−0.005	**1.3×10^{-5}**
Model II					
ELA [a]	0.08	0.13	−0.16	0.33	0.52
BDNF rs6265 genotype [a]	−2.00	1.17	−4.30	0.30	0.09
Parental Support [a]	0.10	0.06	−0.03	0.22	0.14
Sex [a]	−5.2	3.96	−12.98	1.57	0.20
Sex × BDNF	2.32	1.78	−1.16	5.80	0.19
Sex × ELA	0.01	0.17	−0.33	0.35	0.94
Sex × Parental support	−0.03	0.10	−0.23	0.18	0.79
Sex × ELA × BDNF	0.076	0.07	−0.07	0.22	0.31
Sex × Parental support × BDNF	−0.006	0.04	−0.09	0.08	0.89
Sex × ELA × BDNF × Parental support	−0.004	0.001	−0.007	−0.001	**0.005**

B; regression coefficients, SE; standard error, CI; Confidence intervals, LL; Lower limit, UL; Upper limit, Model I; adjusted for sex main effects, ELA; Early life adversity, Model II; adjusted for sex main effects and sex interaction terms. Significant p-values and final interaction models are in bold.
[a] Main effects.

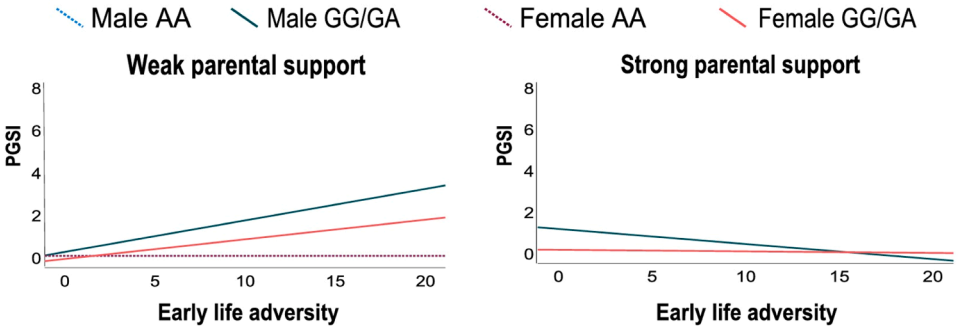

Fig. 3. Three-way interaction effects of ELA, parental support, and BDNF genotype in gambling-related harm stratified by sex:. In weak parental support, male major allele (G) carriers had higher PGSI scores as ELA scores increase. However, in presence of strong parental support, the risk of gambling-related harm in G allele carriers decreases irrespective of higher ELA scores, G allele NBN, $p \leq 0.001$. The lines for AA carriers (both male and female) overlap with each other in weak support and with Females G allele carriers in Strong parental support.

combined with relatively low mean PGSI scores led to a small sample size and restricted the study's power to detect the relationships between the variables of interest. Secondly, the use of a candidate gene approach in contrast to a genome-wide approach is often associated with a low replication rate. However, the study approach at the start of the SALVE cohort was hypothesis-driven to investigate candidate genes plasticity in the presence of a negative and/or positive environment. Future genome-wide association studies that account for adverse and protective environmental factors would be vital in aiding in identifying risk and protective factors. The study also relied on self-reported measurements which are at risk of memory or recall bias. Using objective measures such as official bank records in combination is a novel method to overcome this drawback in future studies. Nonetheless, the study also has several strengths worth highlighting. The strength of the present study lies in the unique longitudinal design with timely measurements throughout adolescence and transition to young adulthood. Moreover, early life adversity measurements included both home and school environments to provide a more realistic view of negative events. The present study also accounted for positive factors that may counterbalance adverse environments which has been a frequent limitation in previous genetic and gene-environment studies in gambling behavior. The inclusion of sex interactions with both the genetic and the two environmental factors in the second model yielded results that can be better interpreted as parental support emerged as a protective independent of sex interactions and adverse life events. Future research studying the genetic factors of gambling-related harm may benefit from considering how positive and/or negative factors interact to influence the genetic sensitivity to gambling related harm.

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Ethics declaration

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

This study included organ or tissue donors. This study includes human biological material and consent was obtained by donors, or their

Table 4
Moderation models on the main effect and interactions of Early Life Adversity, DRD2 rs1800497 genotype, and parental support.

Model	Negative binomial model with log-link				
	β	**SE**	**95% CI**		***P***
			LL	UL	
Model I					
ELA [a]	0.10	0.03	0.04	0.17	0.002
DRD2 rs1800497 genotype [a]	−6.75	1.73	−10.12	−3.37	**8.8×10^{-5}**
Parental Support [a]	−0.05	0.023	−0.10	−0.007	0.02
ELA × DRD2	0.46	0.24	−0.003	0.93	0.05
Parental support × DRD2	0.24	0.05	0.13	0.35	**1.1×10^{-5}**
ELA × DRD2 × Parental support	−0.02	0.01	−0.04	−0.003	0.02
Model II					
ELA [a]	0.05	0.11	−0.177	0.27	0.65
DRD2 rs1800497 genotype [a]	2.62	0.87	0.92	4.32	**0.003**
Parental Support [a]	0.02	0.06	−0.11	0.14	0.77
Sex [a]	−0.12	1.32	−2.71	2.47	0.93
Sex × DRD2	−9.16	2.24	−13.56	−4.76	**4.4×10^{-5}**
Sex × ELA	−0.01	0.07	−0.12	0.15	0.84
Sex × Parental support	−0.05	0.04	−0.14	0.03	0.23
Sex × ELA × DRD2	0.45	0.21	−0.05	0.85	0.03
Sex × Parental support × DRD2	0.24	0.06	0.13	0.35	**3.7×10^{-5}**
Sex × ELA × DRD2 × Parental support	−0.02	0.01	−0.03	−0.002	0.03

B; regression coefficients, SE; standard error, CI; Confidence intervals, LL; Lower limit, UL; Upper limit, Model I; adjusted for sex main effects, ELA; Early life adversity, Model II; adjusted for sex main effects and sex interaction terms. Significant p-values and final interaction models are in bold.
[a] Main effects.

next of kin or legal representatives, for use in this study and for publication of the article. The samples used in this research were not sourced from executed prisoners or prisoners of conscience.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was approved by the Ethical Review Board in Uppsala. (Approval No 2012/187)

Declaration of competing interest

The authors declare that the research was conducted in the absence of any potential conflict of interest

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