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COMT Val/Met, stressful life events and externalizing behaviors in youth: A longitudinal study from the ABCD sample☆

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ABSTRACT

Early adolescence is a crucial time for understanding and detecting the risk factors that may influence youth externalizing/disruptive behaviors and disorders. Previous literature reported evidence that risk factors for disruptive behaviors include *catechol-O-methyltransferase* (*COMT*) Val158Met (rs4680) polymorphism and environmental influences. An unanswered question is whether there is a change in these risk factors over stages of youth development. This longitudinal study examines the interaction effect of Val158Met and stressful life events (SLE) on youth externalizing behaviors from ages 9–11. Participants were 2363 children of European ancestry recruited as part of the Adolescent Brain Cognitive Development study. Repeated measures linear mixed models were used to examine the effect of the interaction between Val158Met and SLE (G × E) on disruptive behaviors over development. Externalizing behaviors were analyzed at both baseline and two-year follow-up. Both Val158Met genotype and SLE scores demonstrated significant main effects on disruptive behaviors in youth, and those effects were consistent at both time points. G × E was not associated with externalizing behaviors. Youth who carried the Val allele and/or were exposed to higher SLE consistently had increased externalizing behavior scores. To our knowledge, this is the first study to longitudinally examine the interaction effects of Val158Met and SLE on externalizing behaviors in youth. The results highlight the importance of understanding the genetic and environmental factors underlying externalizing behaviors for better detection of at-risk youth, helping further with early prevention efforts. The findings

☆ Baseline data were collected between September 2016 and October 2018, and the two-year follow-up data were collected between August 2018 and January 2020. The current study uses data from the ABCD 4.0 data release. The ABCD data were accessed from the National Institutes of Mental Health Data Archive.

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propose that *COMT* Val158Met genotype may act as a biomarker for development of novel treatment strategies for disruptive behaviors.

1. Introduction

Youth externalizing behaviors are serious public health concerns, with significant negative outcomes. Forty-two percent of the homicides globally, up to 200,000 homicides, are committed by youth every year [1]. Externalizing behaviors, also known as disruptive behaviors [2], start early during childhood, may be characterized by socially deviant, hyperactive, delinquent, non-compliant and hard-to-manage behaviors [2], and increase the risk for persistent antisocial behaviors, adjustment problems and crime into adulthood [3]. Early adolescence marks an important developmental period for both brain development and biopsychosocial changes thus may point to a crucial time to detect and understand the risk factors that may influence youth psychopathology [4–6].

Risk for disruptive behaviors include genetic, hormonal, neurobiological, environmental, and social factors [7]. Catechol-*o*-methyltransferase (COMT) is an enzyme that is coded by the dopaminergic *COMT* gene on chromosome 22 9, and has been implicated in youth externalizing behaviors [8]. COMT metabolizes active catecholamines such as dopamine, epinephrine and norepinephrine to their inactive forms [9]. Dopamine, epinephrine and norepinephrine levels all exhibit substantial role in regulating stress response and impulsive behaviors [10–13]. Meanwhile, increased stress can in turn influence dopaminergic function [14], contributing to a change in disruptive behaviors. Therefore, genetic polymorphisms that modify the enzymatic activity of COMT, thus the levels of active catecholamines, can provide promising variants to study in relation to an increased risk for maladaptive disruptive behaviors. One of the most commonly studied functional single-nucleotide polymorphisms (SNP) of *COMT* is Val158Met (rs4680). The non-synonymous change of the nucleotides of G (Val) to A (Met) leads to a reduced COMT enzyme activity for Met/Met carriers, possibly leading to higher dopamine and norepinephrine levels mainly in the prefrontal cortex (PFC) [15]. Although this change in catecholamine levels can impact the risk for exhibiting disruptive behaviors [12], there have been mixed results in the literature for the association between Val158Met and externalizing behaviors in youth [8]. A study with Russian male adolescent inmates demonstrated that youth with the Val allele showed increased conduct problems than Met carriers [16]. Similarly, Park and Waldman [17] reported that compared to Met carriers, Val/Val carriers had higher commission error variability in the A-X Continuous Performance Task, representing impulsivity. On the other hand, many studies did not show a significant main effect of Val158Met polymorphism on youth aggressive and externalizing behaviors [18,19,20].

A factor that may affect the inconsistency of the effects of Val158Met on externalizing behaviors is stressful life events (SLE) in early childhood. While increased childhood stress alone is reported to increase externalizing behaviors and the risk for disruptive behavior disorders [21,22,23,24,25], literature points to a gene-environment interaction where youth with certain genotypes are at a higher risk for exhibiting disruptive behaviors after being exposed to childhood stress and maltreatment [26]. Similar to childhood stress, Abraham and colleagues (2020) reported that while neither Val158Met genotype nor socioeconomic status (SES) alone had a main effect on the levels of aggressive behaviors, their interaction increased externalizing behaviors in youth, further suggesting that environmental stressors may modify the effects of Val158Met polymorphism on behavior.

Development is another factor that may influence the association between Val158Met and externalizing behavior, leading to inconsistent results. Previous literature with Val158Met demonstrated a differential effect of the polymorphism on delay discounting behavior and executive functioning over development [27]. Similarly, the interaction between Val158Met and negative caregiving on attention deficit/hyperactivity disorder (ADHD) hyperactivity and impulsivity symptoms was significant only in middle childhood between ages 7 and 10, and not in early childhood. In middle childhood, children with one copy of the Met allele had a higher risk of exhibiting ADHD symptoms than Val/Val carriers [28]. Moreover, studies report a change in the influence of genes on behavior through development [8,29–32]. This supports the importance of understanding development in genetic studies, as the major biological changes that happen throughout the body during development may significantly impact the genetic effects on behavior [33].

To elucidate the possible effects of development on the association between Val158Met-childhood stress and externalizing behaviors on males and females, we analyzed the longitudinal data from the Adolescent Brain Cognitive Development (ABCD) study [34]. ABCD is the largest longitudinal study of brain development and child health in the U.S. where over 11,000 socioeconomically diverse children (5561 M) (and their parents/guardians) are recruited from 21 collection sites. Children will be followed over ten years from preadolescence (9–11 years old) into early adulthood. For further details on ABCD, please see Garavan and colleagues (2018).

Previous literature with the ABCD sample report that youth diagnosed with conduct disorder or oppositional defiant disorder had a higher externalizing factor score [4]. Furthermore [35], demonstrated that in the ABCD sample, disruptive behaviors, including aggression and rule breaking, increase as early life adversities increase; further elucidating the possible role of environment as a risk factor for disruptive behaviors. While previous literature used the ABCD sample to study the social and neurological factors associated with externalizing behaviors and disruptive behavior disorders [36–42], as well as genetic factors in association with other behavioral phenotypes [43], there is limited research on genetic factors underlying externalizing behaviors.

Although previous literature points to the importance of understanding the effects of gene-environment interaction on youth behavior through development, the effects of Val158Met and childhood stress on externalizing behaviors over time in late childhood and early adolescence is still unknown. To our knowledge, there has been limited, if any, longitudinal research on the effects of this interaction on disruptive behaviors through development. Moreover, there has also been limited research studying the sex-specific effects in female youth. The aim of this study was to longitudinally analyze the effects of the interaction between *COMT* Val158-Met and childhood stressful events on youth externalizing behaviors in a large sample of male and female youth, and examine the risk

factors over stages of youth development.

2. Methods

2.1. Participants

A subset of the participants from the ABCD study (initial 11,872 youth) were analyzed. Participants with European ancestry (n = 4098) who had genotype information, were unrelated to each other, had questionnaire data from both baseline (9–10 years old at the time) and two-year follow up (11–13 years old at the time), and passed quality control and remained after the principal component analysis for population stratification (n = 2363, 1279 male, 1084 female) were included in the analyses. Further details on the participants, study design, inclusion/exclusion criteria, and data collection methods have been described previously [44–46]; and [47].

The ABCD study was approved by the institutional review board (IRB) at University of California, San Diego for central IRB and additionally at each participating site [48]. Before participation in the study, procedures were fully explained, and guardians were provided with written informed consent. Our study was approved by the Research Ethics Board at the Centre for Addiction and Mental Health. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

2.2. Measures

2.2.1. Child behavior checklist (CBCL)

Consistent with the literature, previous studies with the ABCD sample defined externalizing behaviors from the sub-scales for attention deficit/hyperactivity (ADH), conduct problems (CP), oppositional defiant problems (ODP) and externalizing behaviors from the DSM-oriented and summary scale scores of the CBCL [41,42,49].

Based on the previous literature, for the current study, the continuous age and sex standardized t-scores for ADH, CP and ADP were obtained from DSM-oriented scales of CBCL, from the "ABCD Parent Child Behavior Checklist Scores Aseba (CBCL)" questionnaire [50]. Moreover, the syndrome scale score of externalizing problems that includes rule-breaking and aggressive behaviors in the last six months were also collected from the parent-reported CBCL. The raw checklist items were used to calculate the t-scores [51] and were used in our analyses.

2.2.2. Stressful life events

To analyze the effects of the environment, we followed the methods by Ref. [52] to code for the stressful life events (SLE) (see Supplementary Material for more details). The data were calculated from the baseline, one-year follow-up or the two-year follow-up when available. Participants with missing SLE values were removed from the analyses. A cumulative risk score was created by summing the scores as explained in Supplementary Table 1, from the questionnaires by parent and/or youth. Each "yes" to the following questions, representing an endorsement of experiencing the event in question, were coded as one additional point to the cumulative score. The cumulative stressful life events score could range from 0 to 15, and ranged from 0 to 11 in our sub-sample.

2.2.3. DNA collection, genotyping and data quality control

Genomic DNA was extracted from saliva and blood for each participant by the ABCD Study Group at the Rutgers University Cell and DNA Repository. Quality control (QC) were conducted by ABCD Study Group, Krembil Centre for Neuroinformatics (KCNI) at CAMH and our group. For more details on DNA collection, genotyping and QC, please see the Supplementary Material.

The final QC was performed using PLINK GWAS analysis toolkit version 1.9 [53] and R [54] to generate the final file for the analyses. The QC included identification of individuals of divergent ancestry via 1000 Genomes reference population data set, excluding individuals with call rate <95 %, with an excessive heterozygosity of more than three standard deviations, related individuals and excluding SNPs with variants with <99 % call rate, markers with a minor allele frequency <1 %, and SNPs with HWE $p < 10^{-6}$.

Val158Met (rs4680) genotypes were extracted from the quality controlled full genome-wide data. Genotype frequencies of Val158Met did not deviate significantly from HWE (p = 0.20).

2.2.4. Ancestry information

Individuals of European ancestry were identified with the principal component analysis (PCA). From the data that were subsetted to 4447 non-Hispanic white participants based on self-report from the Parent Demographics Survey [55], we performed principal component analysis using the 1000 Genome Project CEU population [56] as reference population data to identify the participants of European ancestry (n = 4098). The analyses were repeated 76 times to create the final sample size until all outliers, who were beyond the ± six standard deviations from the means, were removed.

2.2.5. Statistical analyses

Association between *COMT* Val158Met polymorphism and externalizing behaviors was examined by linear regression mixed effects models with repeated measures using the *lmer* function from the *lme4* and *lmerTest* R packages [57]. Data analysis was performed using PLINK [53,54] Biostatistics Softwares. Males and females were analyzed separately and three separate models were analyzed, where each model included CBCL externalizing behavior and problem scores as dependent variable, study site and subject ID as random effects (subject ID nested within the study site), and top three ancestral principal components (PCs) as covariates. As females and males

Table 1
Summary statistics of CBCL subscale scores. For males and females based on *COMT* Val158Met genotype, at baseline and two-year follow-up assessment time points.

	MALES																			
	Baseline										**Two-Year Follow-Up**									
	Val					**Met/Met**					**Val**					**Met/Met**				
	N	**Mean**	**St. Dev.**	**Min**	**Max**	**N**	**Mean**	**St. Dev.**	**Min**	**Max**	**N**	**Mean**	**St. Dev.**	**Min**	**Max**	**N**	**Mean**	**St. Dev.**	**Min**	**Max**
Age	951	9.98	0.62	8.92	11.00	323	10.00	0.64	8.92	11.00	951	11.97	0.63	10.58	13.33	323	11.98	0.66	10.83	13.17
Externalizing Score		46.15	10.37	33	83		44.83	9.61	33	76		45.31	9.81	33	82		44.01	9.11	33	69
Attention Deficit/ Hyperactivity		53.50	5.99	50	80		52.91	5.34	50	80		53.62	5.80	50	77		52.83	5.26	50	80
Conduct Problems		52.84	5.39	50	86		52.24	4.30	50	81		52.36	4.67	50	84		52.03	3.99	50	71
Oppositional Defiant Problems		54.00	5.81	50	80		53.13	4.74	50	77		53.73	5.47	50	80		52.89	4.39	50	75
	FEMALES																			
	Baseline										**Two-Year Follow-Up**									
	Val					**Met/Met**					**Val**					**Met/Met**				
	N	**Mean**	**St. Dev.**	**Min**	**Max**	**N**	**Mean**	**St. Dev.**	**Min**	**Max**	**N**	**Mean**	**St. Dev.**	**Min**	**Max**	**N**	**Mean**	**St. Dev.**	**Min**	**Max**
Age	808	9.92	0.60	8.92	11.00	272	9.92	0.61	8.92	11.00	808	11.92	0.63	10.75	13.42	272	11.92	0.64	10.83	13.25
Externalizing Score		44.38	9.42	34	73		44.07	8.76	34	67		43.18	8.99	34	77		42.71	8.86	34	71
Attention Deficit/ Hyperactivity		52.22	4.50	50	78		52.41	4.38	50	73		52.38	4.51	50	80		52.70	5.02	50	75
Conduct Problems		52.14	4.63	50	74		52.03	4.09	50	70		51.69	4.08	50	80		51.85	3.88	50	70
Oppositional Defiant Problems		52.93	4.64	50	77		52.66	4.04	50	73		52.45	4.20	50	80		52.37	4.16	50	71

Note: St. Dev.: Standard Deviation.

Table 2
Regression table for Model 3 - males. Linear regression mixed effects models with repeated measures predicting CBCL subscale scores in males.

	Externalizing Behaviours score			Attention Deficit/Hyperactivity score			Conduct Problems Score			Oppositional Defiant Problems Score		
Predictors	Estimates	std. Error	p	Estimates	std. Error	p	Estimates	std. Error	p	Estimates	std. Error	p
(Intercept)	45.00 (44.17–45.83)	0.43	<**0.001**	53.15 (52.71–53.59)	0.23	<**0.001**	52.24 (51.86–52.61)	0.19	<**0.001**	53.52 (53.10–53.94)	0.21	<**0.001**
Genotype (Val vs MetMet)	−1.48 (−3.03–0.07)	0.79	0.061	−0.84 (−1.74–0.05)	0.46	0.064	−0.49 (−1.24–0.26)	0.38	0.198	−0.91 (−1.75 to −0.06)	0.43	**0.036**
Assessment Time	−0.63 (−1.20 to −0.06)	0.29	**0.031**	0.15 (−0.19–0.49)	0.17	0.388	−0.32 (−0.63 to −0.01)	0.16	**0.040**	−0.15 (−0.49–0.19)	0.18	0.395
Stressful Life Events	1.13 (0.60–1.65)	0.27	<**0.001**	0.39 (0.08–0.69)	0.15	**0.012**	0.58 (0.33–0.83)	0.13	<**0.001**	0.45 (0.16–0.74)	0.15	**0.002**
PC1	1.08 (−30.03–32.19)	15.87	0.946	2.57 (−14.94–20.08)	8.93	0.774	−0.62 (−15.08–13.84)	7.37	0.933	1.13 (−15.28–17.54)	8.37	0.893
PC2	11.55 (−21.11–44.21)	16.66	0.488	−3.61 (−22.02–14.80)	9.39	0.700	9.03 (−6.17–24.23)	7.75	0.244	−1.56 (−18.81–15.69)	8.80	0.859
PC3	20.87 (−9.66–51.40)	15.57	0.180	7.84 (−9.58–25.27)	8.89	0.378	8.15 (−6.24–22.54)	7.34	0.267	7.45 (−8.88–23.78)	8.33	0.371
Genotype × Assessment Time	−0.09 (−1.24–1.07)	0.59	0.883	0.09 (−0.60–0.79)	0.35	0.789	0.10 (−0.52–0.73)	0.32	0.748	−0.06 (−0.75–0.64)	0.35	0.875
Genotype × SLE	0.37 (−0.84–1.59)	0.62	0.544	0.08 (−0.62–0.78)	0.36	0.824	−0.04 (−0.62–0.55)	0.30	0.906	0.21 (−0.46–0.87)	0.34	0.540
SLE × Assessment Time	−0.14 (−0.54–0.25)	0.20	0.474	−0.07 (−0.30–0.16)	0.12	0.561	−0.04 (−0.26–0.17)	0.11	0.681	−0.07 (−0.31–0.16)	0.12	0.557
Genotype × SLE × Assessment Time	0.06 (−0.85–0.96)	0.46	0.903	−0.19 (−0.73–0.35)	0.28	0.493	0.23 (−0.26–0.72)	0.25	0.360	0.01 (−0.54–0.55)	0.28	0.978
Observations	2338			2338			2338			2338		
Marginal R^2/Conditional R^2	0.025/0.727			0.034/NA			0.067/NA			0.046/NA		

Table 3
Regression table for Model 3 - females. Linear regression mixed effects models with repeated measures predicting CBCL subscale scores in females.

	Externalizing Behaviours score			Attention Deficit/Hyperactivity score			Conduct Problems Score			Oppositional Defiant Problems Score		
Predictors	Estimates	std. Error	p	Estimates	std. Error	p	Estimates	std. Error	p	Estimates	std. Error	p
(Intercept)	42.28 (41.46–43.10)	0.42	<**0.001**	51.50 (51.08–51.92)	0.21	<**0.001**	51.36 (51.00–51.72)	0.19	<**0.001**	52.09 (51.72–52.46)	0.19	<**0.001**
Genotype (Val vs MetMet)	0.64 (−0.87–2.15)	0.77	0.406	0.32 (−0.45–1.09)	0.39	0.420	0.14 (−0.57–0.85)	0.36	0.702	0.13 (−0.60–0.85)	0.37	0.731
Assessment Time	−1.10 (−1.74 to −0.47)	0.32	**0.001**	0.22 (−0.12–0.56)	0.17	0.204	−0.37 (−0.71 to −0.03)	0.17	**0.031**	−0.41 (−0.73 to −0.10)	0.16	**0.010**
Stressful Life Events	2.36 (1.76–2.95)	0.30	<**0.001**	1.09 (0.79–1.39)	0.15	<**0.001**	0.89 (0.61–1.17)	0.14	<**0.001**	0.97 (0.68–1.25)	0.14	<**0.001**
PC1	−3.90 (−35.36–27.57)	16.05	0.808	−1.93 (−17.80–13.94)	8.09	0.812	−6.18 (−20.44–8.08)	7.27	0.396	−2.51 (−17.32–12.30)	7.55	0.740
PC2	10.51 (−21.48–42.49)	16.31	0.520	1.43 (−14.71–17.56)	8.23	0.863	−1.09 (−15.56–13.38)	7.38	0.882	8.53 (−6.49–23.56)	7.66	0.265
PC3	31.47 (0.19–62.75)	15.95	**0.049**	4.26 (−11.51–20.03)	8.04	0.596	9.14 (−5.14–23.41)	7.28	0.209	16.00 (1.18–30.82)	7.56	**0.034**
Genotype × Assessment Time	−0.07 (−1.32–1.17)	0.64	0.909	−0.15 (−0.82–0.52)	0.34	0.662	−0.17 (−0.83–0.50)	0.34	0.625	−0.06 (−0.68–0.56)	0.32	0.839
Genotype × SLE	0.08 (−1.17–1.34)	0.64	0.896	−0.49 (−1.13–0.15)	0.33	0.134	0.15 (−0.44–0.75)	0.30	0.618	0.02 (−0.59–0.62)	0.31	0.959
SLE × Assessment Time	−0.04 (−0.52–0.45)	0.25	0.883	0.00 (−0.26–0.26)	0.13	0.978	0.11 (−0.15–0.37)	0.13	0.390	0.04 (−0.20–0.28)	0.12	0.758
Genotype × SLE × Assessment Time	−0.38 (−1.42–0.66)	0.53	0.472	0.15 (−0.40–0.71)	0.28	0.591	−0.29 (−0.85–0.26)	0.28	0.297	−0.02 (−0.54–0.49)	0.26	0.930
Observations	2033			2033			2033			2033		
Marginal R^2/Conditional R^2	0.079/0.686			0.054/0.644			0.127/NA			0.155/NA		

were analyzed separately, and the age of participants did not have high variability, age and sex were not included as covariates. Based on the previous results on the differential effects of Val and Met alleles with development [8,58], statistical tests based on the Val dominance model were conducted where youth with at least one Val allele were coded as "0" and youth with the genotype Met/Met were coded as "1". To analyze the effects of genotype on behavior over time, the first model included only the Val158Met genotype and assessment time, and their interaction, as the fixed effects. To analyze the effects of stressful life events (SLE) on behavior over time, the second model included the SLE and assessment time, and their interaction, as the fixed effects. To analyze the effects of both Val158Met genotype and SLE over time, a third model included Val158Met genotype, SLE assessment time, and their interactions, as the fixed effects, while controlling for the three PCs previously described.

To calculate the percentages of variance explained, *r.squaredGLMM* function from the *MuMIn* R package was used, reporting the conditional R^2_{GLMM} metric [59], that includes variance explained by both fixed and random effects. Tables were created using the *tab_model* function from the *sjPlot* R package [60]. To accurately report the main effect p-values of the variables in the interaction models, the p-values were reported from the Type III analysis of ANOVA tables, created by the *anova* function from the *stats* R package [61], and not from tables created through *tab_model*.

2.2.5.1. Multiple testing correction. As the CBCL subscales were highly correlated, multiple testing correction for non-independent tests, Meff [62], was used. Based on the correlations among the four outcome variables being tested, the effective number of tests was predicted to be 2.56. Thus, the corrected alpha level was calculated to be 0.05/Meff, or 0.019.

3. Results

3.1. Model 1: COMT Val158Met × assessment time

Our results indicate that neither male nor female youth showed a significant genotype x assessment time interaction on CBCL scores (Table 1, Supplementary Tables 2 and 3). Both groups showed an overall decrease in their behavior scores over time from baseline to two-year follow-up (Supplementary Fig. 1), except the ADH scores. Both males and females demonstrated a statistically significant decrease in externalizing behaviors score ($p \leq 0.001$) and CP ($p \leq 0.01$), whereas only females demonstrated a decrease in ODP ($p = 0.001$). While females did not show any significant association between externalizing behavior and Val158Met, males Val-allele carriers scored higher on CBCL at both time points (externalizing behavior ($p = 0.024$), ADH ($p = 0.042$) and ODP ($p = 0.006$)). When the interaction term was removed from the model, the significance of the main effects did not change. After multiple testing correction, the main effect of assessment time on all CBCL outcomes, as well as genotype on ODP scores remained significant. All significant outcomes had small effect sizes ($\eta^2 = 0.004$).

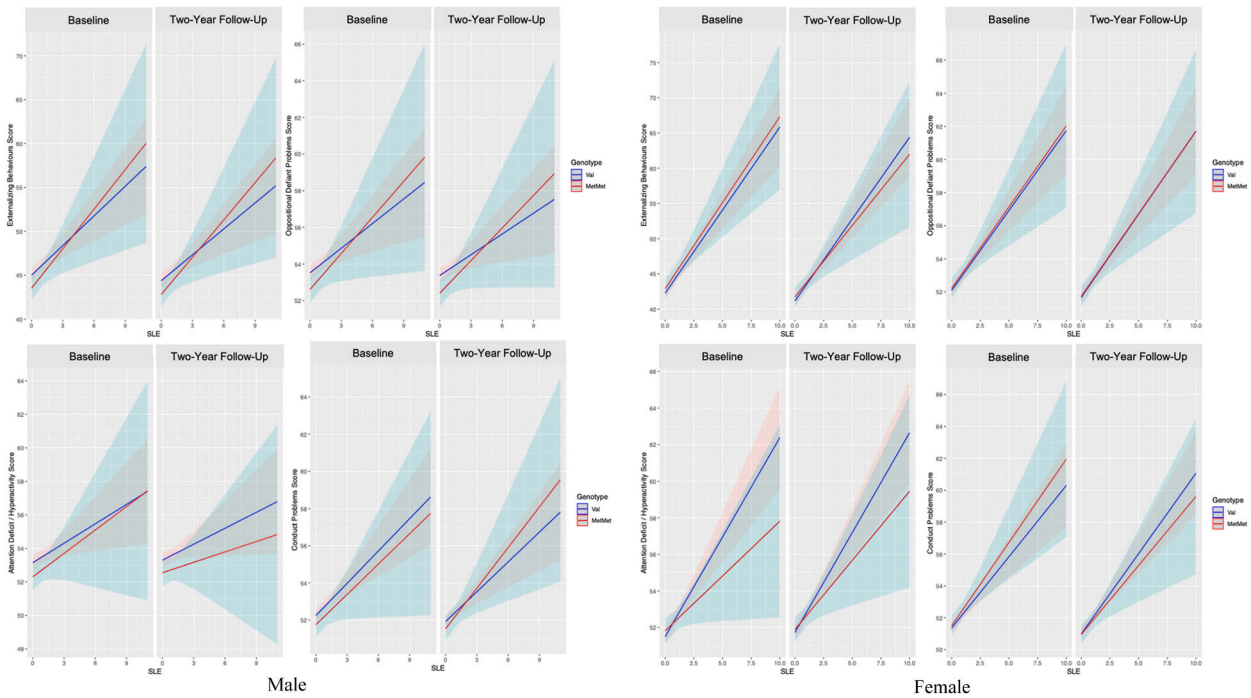

Fig. 1. Plots of Model 3 (full sample). CBCL subscale scores based on SLE scores, at baseline and two-year follow-up assessment time points for males (left) and females (right).
Note: Error bars (shaded areas) indicate 95 % confidence intervals.

3.2. Model 2: SLE × assessment time

For model 2, we tested if SLE scores were associated with CBCL scores at both time points. Both male and female youth exhibited significantly increased externalizing behaviors, ADH, CP and ODP scores as SLE scores increased at both baseline and two-year follow up, indicating a significant SLE main effect on behavior scores ($p \leq 005$) (Supplementary Tables 4, 5, 6, Supplementary Fig. 2). Moreover, externalizing behavior and CP scores were higher at baseline time collection for all SLE scores, indicating a non-significant SLE × assessment time effect (Supplementary Tables 5 and 6). The sample size decreased as SLE scores increased, with only 2 participants at SLE 11 and no participants at some cells (ex: males at SLE score 9 and females at SLE score 11) (Supplementary Table 4). All of the results, except the association between assessment time and CP scores in males, survived multiple testing correction.

3.3. Model 3: COMT Val158Met × SLE × assessment time

Model 3 tested if the interaction between Val158Met genotype and SLE scores affected the CBCL behavior scores over time at two time points using repeated measures linear mixed model. The genotype × SLE × assessment time interaction was not significant for any CBCL outcome, for either in males or females (Tables 2 and 3). There was no significant genotype × SLE interaction, indicating that the Val158Met genotype did not have a significant differential effect in behavioral scores in youth for different levels of SLE scores (Tables 2 and 3, Fig. 1). However, a trend for a gene × environment interaction (G × E) was observed in male youth, where youth Val-carriers exhibited higher CBCL scores when SLE scores were low, while Met/Met carriers reported higher scores when SLE scores increased. The main effects of SLE on all CBCL scores remained significant ($p < 0.05$), whereas the main effects of genotype for males were still significant for externalizing behavior scores and ODP scores ($p < 0.04$), but the genotype effect for males was only at trend level for ADH scores ($p = 0.058$). In males, the association between genotype and externalizing behavior scores, the association between assessment time and externalizing behavior scores, and the association between SLE and ADH scores did not survive the multiple testing correction. In female youth, all results survived multiple testing correction.

4. Discussion

To our knowledge, this is the first study to examine the interaction effects of *COMT* Val158Met and stressful life events (SLE) on externalizing behaviors in a large sample of youth, longitudinally through development and into puberty. Our results were consistent with previous studies that reported youth who carried the Val high-activity allele showing increased impulsivity and externalizing behaviors compared to Met/Met carriers [16,17], though we only observed this genotypic main effect in males. It is also important to note that the effect sizes were small, thus these results should be interpreted with caution.

Moreover, our findings of SLE scores being positively correlated to externalizing behavior, ADH, CP and ODP scores at both time points in both males and females were consistent with previous reports on the main effects of environment on externalizing behaviors [21,22,23,24,25]. Although there was an observed trend of G × E for some CBCL outcomes, the G × E was not significant, consistent with studies reporting no significant effect of Val158Met × environment interaction on externalizing behaviors [20,63]. However, this was in disagreement with numerous studies reporting that the effects of Val158Met on youth externalizing behaviors may change depending on the presence of different environmental stressors [19,64–66]. Our results may have been limited by narrow range of age of the ABCD sample, however there could also be advantages to having a narrower age range to reduce the heterogeneity.

While the majority of CBCL subscale scores decreased over time from baseline to two-year follow-up, we did not observe significant interactions between genotype and assessment time as well as between G × E and assessment time. In the current sample, the influence of Val158Met polymorphism on behaviors did not change over development, thus was inconsistent with the results of some previous studies [8,28]. There are several interpretations regarding the mixed findings. First, the current ABCD sample has data only from ages 9–11 to ages 11–13, while our previous study was based on children and adolescents from ages 6 to 18 [8]. Therefore, the current limited ABCD age range might have limited our ability to capture the effects of development in the genotype-behavior and genotype-environment-behavior associations. Moreover, different demographics, such as country of origin, participant recruitment, and behavioral data collection methods of the ABCD sample may have also led to the mixed findings.

The current study has several strengths, one of the biggest being the large sample size, which provides increased power to detect small effects that Val158Met may have on behaviors. Moreover, the ABCD study also has a wide range of available behavioral data, including scores on SLE, SES, and various phenotypes, which allows for in-depth behavioral analyses while controlling for confounding variables. As the study follows the same sample over time, within-sample variability can also be controlled. Thus, any changes in the association between Val158Met and disruptive behaviors through development may be observable, while minimizing random effects.

Despite the significant results that were observed, there are a number of limitations to the current study that warrant caution while interpreting results, and require future research. First the preliminary nature of the study and the results must be emphasized. As mentioned above, currently available longitudinal data are limited with narrow age range, as the ABCD study is in the beginning of its longitudinal data collection plan. As previous studies have demonstrated that the effects of Val158Met on behaviors may change over development [8,28], the current narrow age range may have limited the results and the ability to capture significant time/-developmental effects. Therefore, analyses on the future follow-up data from children as they grow into early adulthood are necessary to allow meaningful conclusions to be formulated regarding the effects of development on the interaction of Val158Met with childhood stress and disruptive behaviors. The results from longer study designs with the ABCD sample may emphasize the importance of considering development in psychiatric genetic studies and that results from adult samples should not be generalized to children.

Moreover, the lack of variability in SLE with the smaller sample size of those with higher SLE scores may impede the ability to

detect the potential gene-environment effects while being less representative of the true population. To address this limitation, follow-up analyses were conducted. The results of these analyses, where participants with higher SLE scores (equal/above score 3) treated as one group, remained largely unchanged: demonstrating significant effects of SLE and non-significant effects of gene-environment interaction (Supplementary Tables 7 and 8). An additional limitation regarding the SLE scores is the method for calculation. The initial method by Ref. [52] include abuse, disasters, and other negative high impact events in one main score. To address the potential limitation of including different stressor types as one main score, we have further analyzed the separate effects of an interaction between Val158Met and abuse, disasters, neglect, financial adversities and parental divorce/separation on behavior using our model 3 (Supplementary Tables 9, 10, 11, 12, 13). The results remained largely similar to the main SLE score analyses, no significant gene-environment interaction was detected. However, when analyzed separately, abuse and parental divorce/separation were not significantly associated with externalizing behaviors.

Furthermore, the current study focused on the European subsample, which limits the generalizability of the results to other ancestries. Therefore, future research is required to examine the potential effects in populations with diverse ancestries. Moreover, although a general population sample, a minority of the participants may have been treated by drugs or psychological intervention during the two years of follow-up, which may lead to a change in the CBCL scores over time, and potentially confound the results. Last, future studies can consider epistatic interactions and polygenic risk scores (PRS). As disruptive behaviors are known to be polygenic, focusing on a single genetic polymorphism has limited the scope and applicability of our study. Although single genetic polymorphisms may point to a highly relevant gene in certain pathways [67], such as *COMT* in the dopaminergic system, it is susceptible to the overestimation of effect sizes, also known as the statistical winner's curse [68]. Thus, future studies with multigene risk panels to compute multigenic risk scores [69], GWAS and PRS of externalizing behaviors through development are necessary.

Results from this study may have important clinical significance. COMT enzyme is expressed mainly in PFC and is a key enzyme that regulates the levels of dopamine, epinephrine and norepinephrine in this region [13,70,71]. The results suggest that the high activity Val genotype may increase externalizing behaviors in youth, pointing to an increased risk with lower dopamine levels. As PFC is a critical region for executive control, cognition, and the inhibition of impulsive behaviors [72], lower dopamine and norepinephrine levels, regulated by the COMT enzyme, may indicate reduced inhibition from the PFC to the limbic system, thus may explain the increased risk for disruptive behaviors [12,70,73]. Dopamine levels are hypothesized to lie on an inverted U-shape; critical dopamine levels can lead to the optimal levels of cognitive functions and impulse control [74], whereas below or above this critical level can increase the risk for disruptive behaviors. The effects of *COMT* Val158Met on behavior and cognition is potentially explained by this inverted U-shape [58,75,76]. Moreover, an inverse relationship between brain norepinephrine levels and aggressive behaviors have been first demonstrated by rats [77], and later confirmed in human studies [78]. Thus the potential lower norepinephrine levels of Val carrier youth may explain the increased risk for exhibiting disruptive behaviors in this study. The results of this study emphasize the potential influence of *COMT* Val158Met genotype on behavior, proposing that Val158Met genotype may act as a biomarker for novel drug discovery and for the prescription of existing drugs. Developing novel stimulant drugs and/or drugs that focus specifically on inhibiting COMT may help in increasing dopamine and norepinephrine levels, thus may be a useful treatment method for disruptive behaviors in youth who are Val carriers and who were at a higher risk for disruptive behaviors in the current study [79–81]. On the other hand, increasing dopamine levels for Met carriers, who have less COMT activity thus higher dopamine levels, may lead to above optimal levels of dopamine, thus may not be a useful treatment method. This is also in line with the majority of previous literature where increasing dopamine levels through drugs was shown to consistently be effective in reducing the symptoms of ADHD in youth with Val allele, but not with Met/Met genotype [79–81]; please see Ref. [82] for review of the effects of dopaminergic drugs on behaviors based on Val158Met genotype). Therefore, it is crucial not only to conduct research on drug development based on *COMT* as a biomarker, but to consider the genotype of youth before prescribing medication to them. Overall, results from this study and the previous literature suggest that *COMT* Val158Met may be a crucial factor in novel drug development, treatment choice and dosage for externalizing behaviors.

The results of *COMT* underlying externalizing behaviors may also be used as an additional factor to incorporate into risk models for disruptive behaviors, which are currently lacking genetic risk as part of their makeup [82,83]. Currently, there are various treatment methods that are designed to target symptoms for externalizing behaviours after they occur, however not the underlying mechanisms or risk factors before the behaviors are exhibited. These strategies include workshops on life-style changes, child-rearing practices, supportive practices, and parental close monitoring [84,85]. These current psychosocial intervention strategies can be personalized and applied as early prevention methods for youth and their families by identifying and predicting at-risk youth with the use of the newly developed risk models.

5. Conclusion

In conclusion, the results of the current study demonstrate that Val allele of the *COMT* Val158Met polymorphism and exposure to stressful life events can both significantly increase the risk for exhibiting externalizing behaviors, attention-deficit hyperactivity problems and oppositional defiant problems in male youth. More importantly, their effects are consistent over time longitudinally through development and into puberty. Detecting genetically and environmentally at-risk youth during development may lead to personalized preventative strategies to promote resilience against stressful life events and may decrease the risk of maladaptive externalizing behaviors into adulthood.

Author contributions

Tuana Kant: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Emiko Koyama, Clement C. Zai: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Marcos Sanches: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Joseph H. Beitchman, James L. Kennedy: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data associated with this study has been deposited at ABCD Dataset Data Release 4.0 at https://nda.nih.gov/abcd.

ABCD NDA study acknowledgment

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Ethical statement

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Research Ethics Board at Centre for Addiction and Mental Health (#014/2021).

Informed Consent Statement: Informed consent forms were collected from all subjects and/or their guardians involved in this study.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:J.L.K. is an unpaid member of the Scientific Advisory Board of Myriad Neurosciences Inc. J.L.K. and C.C.Z. are authors on patents for pharmacogenetic interventions and suicide markers.

Appendix A. Supplementary data

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