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Short communication

Effects of the interaction between genetic factors and maltreatment on child and adolescent psychiatric disorders

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ABSTRACT

We evaluated the effects of the interaction between child maltreatment (CM) and single nucleotide polymorphisms (SNPs) on development of mental disorders (MD) and psychopathology. We genotyped 720 individuals from a Brazilian community school-based prospective study, focusing on SNPs in 21 genes known to be associated with mental disorders. CM was assessed via a multi-informant-measure, which was previously validated. To test *G* × CM, we used linear or logistic models depending on variable evaluated (MD or dimensional psychopathology). After Bonferroni multiple comparison correction, we did not find any statistically significant association of *G* × CM with either MD or psychopathology.

1. Introduction

The gene-environment-interactions (*G* × *E*) model suggests that the association between genotypes and traumatic events may increase the likelihood of developing a mental disorder (MD) (Cicchetti and Rogosch, 2012). It suggests that variations in vulnerability and resilience to environmental hazards may explain the onset of MD in some individuals and not others (Fritz et al., 2018).

Epidemiological studies showed that the prevalence of MD in childhood/adolescence is around 10–15%, being more frequents diagnoses of behavioral (7%) and anxiety (5.2%) disorders (Scivoletto et al., 2012). In addition, MD is the leading cause of health-related disability in this age group with lifelong effects (Kieling et al., 2011).

Childhood maltreatment (CM) is a traumatic event that has been associated with MD, one study showed that in adults with severe MD, the rate of childhood trauma is high (Aas et al., 2016). World Health Organization estimates that almost a quarter of adults experienced CM (Kessler et al., 2010). These traumas may change the brain development, leading to a higher risk of developing MD (Bick et al., 2017; Brietzke et al., 2012; Daruy-Filho et al., 2011; Heim and Nemeroff, 2001). However, not all children exposed to maltreatment develop MD. One of the reasons might be individual differences in the children's resilience, a feature associated with genetic factors as well as individual life experiences (Cicchetti and Rogosch, 2012).

Given that, we investigated whether *G* × *E* interactions between single nucleotide polymorphisms (SNPs) and CM may predict the development of MD in childhood and adolescence. In addition, since there is evidence of low stability and high co-morbidity of psychiatric categories in youth, we explored whether these *G* × *E* interactions were associated with dimensional psychopathology.

2. Methods

We evaluate 720 children aged 6–14 years from a large community school-based-prospective-study, the Brazilian High Risk Cohort (HRC), hailing from two Brazilian cities, São Paulo and Porto Alegre. For more information about the design of the HRC study, see Salum et al. (2015). Research Ethics Committee approved the study protocol. The

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Table 1
Main results of the $G \times$ CM analysis.

Dependent variable	$G \times$ CM model adjusted for site and PCs	Statistical method	p Value	Adjusted p-value	Beta or odds ratio
Externalizing CBCL	*DRD3* gene (rs9288993)	Linear Model	0.020	**1**	−5.83
	TCF4 gene (rs17594301)	Linear Model	0.026	**1**	5.11
	NR3C1 gene (rs6196)	Linear Model	0.051	**1**	4.49
Internalizing CBCL	*TCF4* gene (rs2060888)	Linear Model	0.108	**1**	4.07
	NPY gene (rs16131)	Linear Model	0.13	**1**	−3.62
	NRG1 gene (rs13282123)	Linear Model	0.13	**1**	2.44
Total CBCL	*DRD3* gene (rs9288993)	Linear Model	0.071	**1**	−13.83
	SLC1A4 gene (rs2075209)	Linear Model	0.088	**1**	8.84
	TCF4 gene (rs2060888)	Linear Model	0.113	**1**	12.54
Presence of any mental disorder	*NRG1* gene (rs6986789)	Logistic Model	0.0016	**0.32**	3.82
	NRG1 gene (rs1503499)	Logistic Model	0.0064	**1**	3.96
	NRG1 gene (rs1381871)	Logistic Model	0.0162	**1**	0.26

Notes: $G \times$ CM model: interaction; PCs: principal components.

participants' parents provided written informed consent, and the children provided written and verbal assent.

2.1. Clinical assessments

Psychiatric disorders were assessed using the Development and Well-Being Behavior Assessment (DAWBA) according to DSM-IV criteria. Dimensional psychopathology was assessed using the Child Behavior Checklist (CBCL) which is a parent-report questionnaire assessing the child's emotional, behavioral, and social problems. CBCL score may divided in internalizing-score (e.g. emotional, somatic and isolation problems), externalizing-score (e.g. behavioral problems) and total-score (included all items).

The CM variable used in this study combines self-and-parent-rated information regarding physical abuse, neglect, and emotional maltreatment. Parents provided information on sexual abuse. Through hierarchical confirmatory factorial analysis, we created a composite CM score (factor score) for each participant using self and parent reports. For more information about how this CM latent trait was constructed, see Salum et al. (2016).

1.2. Genetic analysis

DNA samples were obtained from blood or saliva samples and were genotyped using the Infinium®HumanCore Array BeadChip (Illumina, USA) with approximately 300,000 markers.

Based on a literature review, we selected 21 genes found to be associated with neurodevelopment, neurotransmission, and pathogenesis of MD from studies that used the candidate genes and genome wide association study approaches (Table S1).

All SNPs falling 1 kb upstream or downstream of the candidate genes that met quality control (QC) criteria were included in the analysis. QC procedures excluded samples with missingness at more than 1%, markers with genotype missingness in at least 1% of the samples, minor allele frequency less than 5%, and no violation of the Hardy-Weinberg equilibrium ($p < 0.001$), as well as indels markers were excluded. For the candidate genes, 201 SNPs met inclusion criteria (Table S2).

1.3. Statistics

All genetic association analyses were performed in PLINK1.9 (Purcell et al., 2007), adopting a significance level of $p < 0.05$ and we used the Bonferroni correction for multiple comparisons.

We initially tested each SNP for associations with MD or dimensional psychopathology (CBCL scores). We used the Versatile Gene-based Association Study web platform (VEGAS) to verify if the selected genes being associated with specific MD. VEGAS performed gene-based association tests using results from genetic association studies; it produces a gene-based test statistic and then uses simulation to calculate an empirical gene-based p-value (Liu et al., 2010).

Finally, we evaluated the association of the $G \times$ CM interaction with any MD using logistic regression models (model based on the study of Caspi et al., 2003). We tested whether $G \times$ CM interaction could be associated with dimensional psychopathology (CBCL scores) using linear models. In both models, we used the following predictor variables: CM score, genotype (one for each of the 201 SNPs), and the interaction between these two. All models were adjusted for the subjects' city of origin and the top five principal components for ancestry.

3. Results

We genotyped 201 candidate SNPs in 720 individuals and due to genotyping failure one sample was excluded after QC. Based on the DAWBA interviews, 220 subjects (30.60%) met the criteria for at least one MD (cases group). The remaining 499 subjects (69.40%) were considered controls. While the groups did not differ regarding sex and age, they showed the expected significant differences in CBCL (total-CBCL $p = 3.68 \times 10^{-33}$, internalizing-CBCL $p = 4.9 \times 10^{-28}$, externalizing-CBCL $p = 3.04 \times 10^{-24}$) and CM scores ($p = 7.86 \times 10^{-12}$). Subjects in the cases group were also more likely to be from Porto Alegre than from São Paulo ($p = 2.13 \times 10^{-9}$) (Table S3).

We did not find any association between any of the 201 SNPs and the presence of MD or any measure of dimensional psychopathology. The candidate genes ($n = 21$) were also not associated with a general category encompassing all MD (Table S4).

$G \times$ CM interaction models between CM score and SNP-based genotype did not yield any significant finding for either case vs. control or dimensional psychopathology approaches after multiple comparison correction ($N = 201$). Table 1 shows the main $G \times$ CM findings.

Discussion

The main goal of this study was to test the moderation effect of CM on the genetic risk for MD and dimensional psychopathology in children and adolescents from a community-based sample. We used a set of 201 candidate SNPs as genetic risk factors, and a latent CM composite score as environmental risk factor. No $G \times$ CM interaction was able to explain the risk of MD or dimensional psychopathology.

Previous research suggests that children exposed to maltreatment are at a higher risk of developing MD (Cicchetti and Rogosch, 2012; Heim and Nemeroff, 2001; Maglione et al., 2018; Salum et al., 2016). Our findings corroborate these studies by confirming that children exposed to abuse were at a higher risk of presenting with a psychiatric diagnosis and had higher CBCL scores.

To date, there are a few studies assessing $G \times E$ effects on child psychopathology, and their results remain controversial (Barkley et al.,

2006). The heterogeneity of $G \times E$ studies suggests that the potential of specific alleles to contribute to the development of MD might be dependent on the specific study population, adversity and outcome measures used (Maglione et al., 2018; Weeland et al., 2015). Previous studies have provided initial evidence for genes interacting with childhood trauma to influence the risk of developing depression, bipolar disorder, or psychosis (Kim and Lee, 2016; Uher, 2014). In contrast, in this study the $G \times E$ between CM and the various SNPs tested were not significant for MD outcomes. one possible explanation is the influence of other genetic and environmental factors not assessed in the present analysis, such as resilience, stressful life events, copy number variations, and epigenetic mechanisms (Brown et al., 2013).

Our study has some limitations. First, the psychiatry evaluation was based only on report of parents. Second, although we could recruit a significant number of participants, the sample size might not be sufficiently large for an association study. Third, it remains unclear whether the participants may develop MD in the future, since our findings are based on a single evaluation of a cohort of children/adolescents.

However, it is important to evaluate the risk of developing MD in individuals with major genetic vulnerabilities (as the children's); in these individuals, early trauma exposure may have especially adverse effects on brain development.

In conclusion, we found no effect of $G \times E$ interactions on the potential of CM and SNP to cause psychiatric diagnoses and dimensional psychopathological measures. Further studies examining more genes, other CM measures, and larger samples are needed to further explore these findings.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.01.078.

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