


Genome-wide gene-environment interaction in depression: A systematic evaluation of candidate genes

The childhood trauma working-group of PGC-MDD

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Funding information

GlaxoSmithKline Australia, Grant number: G0701420; European Science Council, Grant number: 230374; Netherlands Organization for Health Research and Development, Grant number: 10-000-1002; Australian National Health and Medical Research Council, Grant numbers: 1078901, 1087889; NBIC/BioAssist/RK, Grant number: 2008.024; MQ Fellows Award, Grant number: MQ14F40; BBMRI-NL, Grant number: 184.021.007; Marie Curie Industry-Academia Partnership and Pathways, Grant number: 286213; Center for Medical Systems Biology, Grant number: 912-10-020; German Research Foundation, Grant number: DFG: GR 1912/5-1; Netherlands Organization for Scientific Research, Grant numbers: 911-09-032, 56-464-14192; Bundesministerium für Bildung und Forschung, Grant numbers: 01ZZ9603, 01ZZ0103, 01ZZ0403, 03ZIK012, 01ZX13; Netherlands Scientific Organization, Grant number: 480-05-003; GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation, Grant numbers: 3200B0-105993, 3200B0-118308, 33CSO-122661, 33C; Rutgers University Cell and DNA Repository, Grant number: NIMH U24 MH068457-06; National Institutes of Health, Grant numbers: NIH R01 HD042157-01A1, MH081802, Grand Opportunity

Gene by environment (GxE) interaction studies have investigated the influence of a number of candidate genes and variants for major depressive disorder (MDD) on the association between childhood trauma and MDD. Most of these studies are hypothesis driven and investigate only a limited number of SNPs in relevant pathways using differing methodological approaches. Here (1) we identified 27 genes and 268 SNPs previously associated with MDD or with GxE interaction in MDD and (2) analyzed their impact on GxE in MDD using a common approach in 3944 subjects of European ancestry from the Psychiatric Genomics Consortium who had completed the Childhood Trauma Questionnaire. (3) We subsequently used the genome-wide SNP data for a genome-wide case-control GxE model and GxE case-only analyses testing for an enrichment of associated SNPs. No genome-wide significant hits and no consistency among the signals of the different analytic approaches could be observed. This is the largest study for systematic GxE interaction analysis in MDD in subjects of European ancestry to date. Most of the known candidate genes/variants could not be supported. Thus, their impact on GxE interaction in MDD may be questionable. Our results underscore the need for larger samples, more extensive assessment of environmental exposures, and greater efforts to investigate new methodological approaches in GxE models for MDD.

KEYWORDS

candidate genes, depression, GWAS, Psychiatric Genomics Consortium

1 | INTRODUCTION

Major depressive disorder (MDD) is known to be substantially heritable but also has a huge number of well-established environmental and lifestyle factors that contribute to the disease risk (Cerdá, Sagdeo, Johnson, & Galea, 2010). Although the proportion of variance attributable to genome-wide SNPs (SNP heritability) for MDD has been estimated to be about 21–32% (Lee et al., 2013; Lubke et al., 2012), there are only a few genome-wide significant hits for MDD or depressive symptoms that have been detected to date (CONVERGE consortium, 2015; Hek et al., 2012; Hyde et al., 2016; Okbay et al., 2016) and their biological impact on depression is largely unknown. Many factors could explain the lack of success so far including limited sample size, the high symptom heterogeneity for MDD as well as the strong contribution of environmental and, lifestyle factors and life events (Flint & Kendler, 2014), and it has been hypothesized that genetic factors need the presence of environmental triggers to exhibit an effect on the individual (Caspi et al., 2003; Dunn et al., 2015).

Early childhood trauma (CT) is the most frequently investigated environmental factor, which shows a high impact on major depression

and many other psychiatric disorders (Mandelli, Petrelli, & Serretti, 2015). Previous studies have suggested interaction effects between CT and individual variants from several genes including the highly studied serotonin-transporter-linked polymorphic region (*5-HTTLPR*) (Caspi et al., 2003; Karg, Burmeister, Shedden, & Sen, 2011; Van der Auwera et al., 2014), but also for *BDNF*, *TPH2*, *FKBP5*, *DRD2* and many other genes from candidate pathways (Appel et al., 2011; Grabe et al., 2012; Mandelli & Serretti, 2013). These candidate gene approaches in gene-environment (GxE) interaction analyses select single variants in specific genes belonging to plausible disease-related pathways. Although this approach seems sensible, there are many challenges in this work. Many factors impact on their interpretation, not least non-significant results are less likely to be taken forward for publication generating a reporting bias (Duncan & Keller, 2011). Comparisons between studies are difficult because of the different environmental exposures considered such as stressful life events, abuse and neglect subtypes, social support or living in rural/urban areas, different methods of assessment (questionnaires vs. interviews), and the different quantification of exposures (binary, categorical or continuous) (Dunn et al., 2011; Mandelli & Serretti, 2013). Likewise, the

phenotype definition varies between a binary lifetime major depression variable to a dimensional score of current depression. Moreover, there are no common guidelines regarding how to perform GxE analyses in MDD (type of regression model (linear or logistic model), mode of action (multiplicative or additive), or assumed genetic effect (additive, allelic, dominant or recessive model)). Until now, only two GxE interaction analyses for depressive symptoms have been performed on a genome-wide level. One was published by Dunn et al. (2016) in a sample of African American and Hispanic women. In $N = 7179$ African American women one genome-wide significant hit was found near *CEP350*, a centrosomal protein which has never been associated with a psychiatric phenotype before. Another study in a Japanese population ($N = 320$) reported the genome-wide hit rs10510057 near *RGS10* (Otowa et al., 2016), but given the small sample size this result should be regarded with caution. Both studies performed a linear regression GxE analysis assessing the p -value of the interaction term with a dimensional depression score as the outcome, and stressful life events during the past 12 months as the environmental exposure. Whether these findings can be replicated in a population of European ancestry, although the environmental exposure is different, needs to be elucidated.

Here, we focus on the most important known risk exposure for MDD, early CT, and combine all cohorts from the Psychiatric Genomics Consortium (PGC) with available CT and MDD data to perform gene-environment (GxE) interaction. At the outset, despite being the largest European ancestry study to date, we recognized that our study was likely under-powered to detect GxE effects on a genome-wide level, so we sought to reduce the multiple testing burden by screening the literature and identified genes and SNPs previously implicated in MDD or GxE in MDD. Our aims were 1) to analyze candidate variants, 2) to compare different methodological approaches, and 3) to analyze the genome-wide summary statistics of the GxE analyses for an enrichment of significant findings. We hypothesize that candidate genes/SNPs for a GxE interaction in MDD that have been proposed in the past should at least show a nominally significant association ($p < 0.05$) in our analyses.

2 | MATERIALS AND METHODS

2.1 | Participants

The PGC collates genome-wide genotypic and phenotypic data for MDD (Psychiatric Genomics Consortium Steering Committee, 2009). Subjects were recruited from the PGC wave two for MDD, with phenotypic and genetic data of 16823 MDD cases and 25632 controls from 24 different cohorts with individuals from European ancestry. All cases were diagnosed according to DSM-IV lifetime MDD using structured diagnostic instruments from direct interviews by trained interviewers or clinician-administered DSM-IV checklists. Controls were screened for absence of MDD. Nine of these cohorts also provide phenotyping of exposure to environmental factors as risk for psychiatric disorders including CT. Five cohorts used the most widely applied Childhood Trauma Questionnaire (CTQ) that

distinguishes between different dimensions of childhood abuse and neglect (Bernstein et al., 2003) (Table S1): Cognition and Function in Mood Disorders Study (COFAMS) from Australia (Baune & Air, 2016), the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008), Radiant-UK from the United Kingdom (Lewis et al., 2010), and two independent samples from the Study of Health in Pomerania (SHIP) from Germany (Völzke et al., 2011). Six cohorts used study-specific versions of CT assessment that do not capture all five dimensions of abuse and neglect from the CTQ or used different types of questions (Table S1): Depression Gene Network (DGN) from the USA (Mostafavi et al., 2014), the Genetics of Recurrent Early-Onset Depression (GenRED) from the USA (Holmans et al., 2007), two independent samples from the Queensland Institute of Medical Research (QIMR) from Australia (Nelson et al., 2002; Wray et al., 2012), the psychiatric arm of the population-based CoLaus study (PsyCoLaus) from Switzerland (Preisig et al., 2009) and the Bonn/Mannheim study from Germany (BOMA) (Cichon et al., 2011). To reduce the heterogeneity in our samples, we only included the five studies that measured CT with the same standardized instrument (CTQ). In addition, COFAMS was excluded from the analysis due to the low number ($N = 56$) of MDD cases with available CTQ data.

2.2 | Childhood trauma questionnaire

The CTQ assesses CT, defined as trauma before the age of 16 (CTQ, Table S1) (Bernstein et al., 2003), which covers three sub-scales of abuse, sexual abuse, physical abuse and emotional abuse, as well as two sub-scales of neglect, emotional neglect, and physical neglect, all covered by five questions (range 1–5). This results in a score per domain ranging from 5 to 25, and an overall CTQ continuous score ranging from 25 to 125. Per domain, cutoffs from the CTQ manual (Bernstein et al., 2003) were applied to get a broad definition of CT separating no trauma from mild, moderate, or severe trauma. CT was transformed to a dichotomous abuse variable separating childhood abuse in any of the three domains (1 = Yes) from no abuse in all domains (0 = No) to address the skewness of the CTQ score.

2.3 | Genotyping, quality control, and imputation

The cohorts were genotyped following their local protocols, after which quality control and imputation to the 1000 genomes reference panel (Abecasis et al., 2010) was conducted through the standardized PGC pipeline (see Schizophrenia Working Group of the PGC, 2014) per cohort (PGC MDD: wave two GWAS results, In preparation). For details see supplemental material.

2.4 | Statistical analysis

We performed these analyses in three steps: 1) Power calculation and selection of candidate SNPs/genes for GxE analyses, 2) Analysis of the candidate variants and genes in GxE, and 3) Analysis of the genome-wide GxE GWAS results.

2.4.1 | Different methodological approaches

Our main analytic models assuming additive genetic effects include (i) a standard GxE analysis with a multiplicative interaction term and a dichotomous environmental exposure (abuse 0/1) and (ii) case-only analyses, recommended by VanderWeele (*Explanation in Causal Inference*, 2015; VanderWeele, Hernández-Díaz, & Hernán, 2010), with the dichotomous abuse 0/1 variable as well as the continuous CTQ score as outcome (for overview see Figure 1). Case-only analyses have a higher statistical power to detect GxE effects (Gauderman, Zhang, Morrison, & Lewinger, 2013) than case-control GxE models with a multiplicative interaction term and circumvent the statistical difficulties of the low robustness of interaction terms. But these models require that no gene-environment ($G \sim E$) correlation is present (VanderWeele, 2015; VanderWeele et al., 2010). For all case-only models $G \sim E$ correlation in MDD negative controls was analyzed. We used MDD negative controls because these constitute of roughly 85% of the population and can thus be used as an approximation for the full population.

(1) GxE case-control (CC) interaction analyses included a multiplicative interaction term between the SNPs and abuse 0/1 assessing the p -value for the interaction term. Analyses were controlled for sex, the first three genetic principal components as well as all SNPxCov and ABUSExCov interaction terms as recommended by Keller (2014).

$\text{logit}(\text{MDD}) \sim \text{SNP} + \text{ABUSE} + \text{SNP} \times \text{ABUSE} + \text{sex} + \text{PC1} + \text{PC2} + \text{PC3} + \text{SNP} \times \text{SEX} + \text{SNP} \times \text{PC1} + \text{SNP} \times \text{PC2} + \text{SNP} \times \text{PC3} + \text{ABUSE} \times \text{SEX} + \text{ABUSE} \times \text{PC1} + \text{ABUSE} \times \text{PC2} + \text{ABUSE} \times \text{PC3}$

(2) MDD case-only (CO) analyses with abuse 0/1 as dependent variable assessed the SNP p -value:

$\text{logit}(\text{abuse}) \sim \text{SNP} + \text{sex} + \text{PC1} + \text{PC2} + \text{PC3}$ if MDD = 1

(3) MDD CO analyses with CTQ score as dependent variable assessed the SNP p -value:

$\text{CTQ} \sim \text{SNP} + \text{sex} + \text{PC1} + \text{PC2} + \text{PC3}$ if MDD = 1

These three approaches enable the comparisons between CC GxE and COy analysis as well as between dichotomous and continuous measurement of CT (abuse 0/1 vs. CTQ-score).

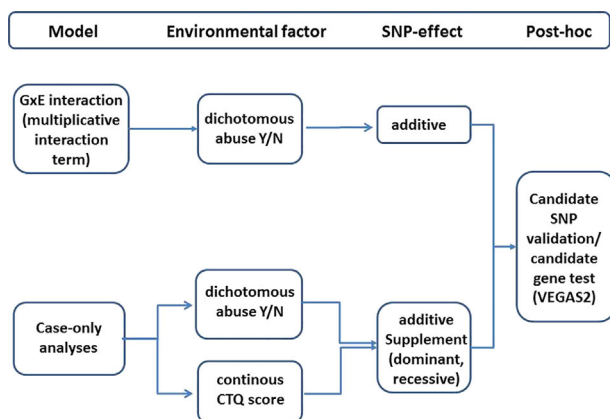


FIGURE 1 Overview of the seven different models and approaches for GxE. [Color figure can be viewed at wileyonlinelibrary.com]

As a sensitivity analysis, the CO analyses were also performed assuming a dominant and recessive SNP effect (see supplement). This analysis was empirically driven by the fact that in many candidate studies for GxE in MDD dominant or recessive effects were found (Mandelli & Serretti, 2013).

2.4.2 | GWAS and meta-analyses

For each of the four cohorts (SHIP-0, SHIP-TREND, NESDA, Radiant-UK) GWAS have been performed as described above. A logistic regression model was used for a binary outcome and a linear regression model for a continuous outcome using PLINK (Chang et al., 2015). Quantile-quantile (QQ) and Manhattan (MH) plots were generated using R (<https://cran.r-project.org/>). The final meta-analysis comprised $N = 3944$ individuals ($N = 1891$ MDD cases and $N = 2053$ controls). The results were combined using an inverse variance-weighted fixed effects meta-analysis in METAL (Willer, Li, & Abecasis, 2010) with the following QC parameters; $\text{MAF} > 0.05$, info score > 0.6 , $\text{HWE} > 0.001$ and including only SNP present in at least three of the four cohorts. The genomic inflation factor λ for each study was calculated, and genomic control (GC) correction was applied when $\lambda > 1$. The I^2 statistic was used to evaluate between-study heterogeneity.

3 | RESULTS

The number of MDD cases and controls with and without CT are summarized in Table 1. In each of the four cohorts the CTQ total score as well as the abuse 0/1 variable were highly associated with MDD, adjusted for sex and age.

3.1 | Power calculation and selection of candidate genes/SNPs

The software Quanto (vs. 1.2.4) was used to determine the interaction effect size we would be able to detect as genome-wide significant given our sample (see Table S2). In the case-control GxE model with $N \approx 1900$ MDD cases, we would only be able to detect large effects ($\text{OR} \geq 2.5$) with a power of 80% for SNPs with high MAF ($\text{MAF} \geq 0.2$). In the case-only model with $N \approx 2000$ MDD cases, we would be able to detect large effects ($\text{OR} \geq 2.4$) for SNPs with low MAF (5%), and medium effects ($\text{OR} > 1.5$) with SNPs with large MAF (50%). Because in GWAS small effects ($\text{OR} < 1.5$) are observed, we assumed that with our current sample size we were underpowered to detect genome-wide interaction signals. Thus, we will focus on candidate SNPs and genes for GxE in MDD.

Since the literature on candidate genes for MDD and GxE interaction in MDD is very broad, we focused on papers that reviewed the previous work in the field. The candidate list comprises SNPs/genes that were taken from two major reviews (Mandelli & Serretti, 2013 for GxE interaction in MDD; Luo et al., 2016 for candidate genes/SNPs in MDD). These candidates cover genes from central monoaminergic systems such as serotonin, dopamine or noradrenalin, from the

TABLE 1 Sample description and descriptive statistic of the four samples included in the meta-analysis

	N	MDD cases		Controls		MDD ~ abuse		Abuse prevalence (%)
		No abuse	Abuse	No abuse	Abuse	Odds ratio	p-value	
SHIP-0	1505	239	117	921	171	2.55	7.6E-11	19
SHIP-TREND-0	665	114	46	428	59	3.06	1.5E-6	16
NESDA/NTR	1396	500	627	208	61	4.19	1.1E-19	49
Radiant UK	525	85	175	199	66	6.09	2.6E-20	46
Total	4091	938	965	1756	357	-	-	-

glutamatergic system, corticotrophin system, neurotropic system or from inflammatory processes (e.g., *SLC6A4*, *DRD2*, *COMT*, *NR1*, *CRHR1*, *BDNF*, *FKBP5*, *NR3C1*). We also included SNPs from recent GWAS results for MDD or GxE interaction (Dunn et al., 2016; Hyde et al., 2016; Otowa et al., 2016). The final list included 268 different candidate SNPs (supplemental Table S4) and 27 candidate genes (supplemental Table S6). From the candidate SNP list, 184 SNPs were available in the meta-analyses after QC (most of these candidate SNPs were excluded based on $MAF < 0.05$).

3.2 | Analysis of candidate SNPs/genes

The candidate genes/variants were analyzed using different methodological approaches. In the CO analyses the candidate SNPs revealed no excess of G~E correlation (supplemental material, Table S7), justifying continuation into case-only analyses. A full list of the results from the candidate SNPs in all models is provided in supplemental Table S4.

3.2.1 | Case-control GxE analysis with a multiplicative interaction term

In the fully adjusted GxE model no candidate SNP reached statistical significance after correcting for multiple testing ($p_{corrected}$ set to $0.05/184 \approx 0.0003$) and five SNPs showed nominal significance ($p < 0.05$), which was fewer than expected by chance (expected $N = 9$): rs2433320 (*PDLIM5*), rs1656369 (*RSRC1*), rs1539243 (*IKBKE*), rs900144 (*ARNTL*), and rs6582078 (*TPH2*).

3.2.2 | Case-only approach on abuse 0/1 and CTQ score

Abuse 0/1: From the candidate list, eight SNPs were at least nominally significant in the additive SNP model: rs1656369 (*RSRC1*), rs41423247/rs6191/rs33388 (*NR3C1*), rs1801262 (*NEUROD1*), rs4763327 (*EMP1*), rs2433320 (*PDLIM5*). **CTQ-score:** Seven SNPs from the candidate list were nominally significant in the additive SNP model: rs909486 (*CSF2RB*), rs3754674 (*NPAS2*), rs9450282 (*NT5E*), rs4244813/rs2279861 (*SLC29A2*), rs6191 (*NR3C1*), rs737865 (*COMT*). Results for the dominant/recessive case-only models can be found in supplementary Table S4.

3.2.3 | Exploratory comparison of all three approaches

Taking the CC GxE and CO GxE approaches, only 16 (=9%) of the 184 SNPs showed nominal significance in at least one of the approaches (Table S4), 13 of them with consistent directions of effects in all three approaches. Some of them showed consistently significant associations across approaches. Two SNPs (rs33388 and rs6191) of *NR3C1* (glucocorticoid receptor) which acts as a transcription factor and player in the hypothalamic-pituitary-adrenal (HPA) axis could be supported (Keller et al., 2016) in both case-only models but not in the direct GxE interaction. Rs2433320 in *PDLIM5* (PDZ and LIM domain containing 5) and rs16566369 in *RSRC1* (arginine and serine rich coiled-coil 1) showed nominal significant results in at least two different approaches.

3.3 | GWAS to identify GxE interaction loci

Meta-analysis of all four cohorts included nearly 4.3 million variants. An overview of the top loci in all three models, assuming an additive SNP-effect, is given in Table 2. In all three meta-analysis no SNP achieved genome-wide significance (all $p > 5E-8$). The top SNPs from the genome-wide CO approaches revealed no excess of gene-environment correlation (supplemental material, Table S7).

Manhattan-plots for all three models are given in supplemental Figure S1. The quantile-quantile plots showed a deflation of the observed results to those expected by chance (supplemental Figure S2) and the λ s were between 0.96 and 0.99. A full list of SNPs with $p < 1E-5$ in all different approaches is given in supplemental Table S3.

The top-hit in the case-control GxE approach on abuse 0/1 assuming an additive SNP effect was the variant rs7128637 near the *ARHGAP20* gene, a Rho GTPase activating protein, with $p = 4.4E-6$. The top hit in the case-only analysis on abuse 0/1 was rs17578476 ($p = 3.3E-6$) harboring at *LRR1Q3* Locus, a locus previously implicated as one of the 108 Loci associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In the case-only analysis for CTQ score the minimum p -value was achieved for rs3214187 ($p = 7.4E-7$) near the *NPY* (neuropeptide Y) gene. Another top variant from this analysis was rs75184661 ($p = 4.1E-6$), intronic of *CACNA1C* (subunit of calcium voltage-gated channel). Results for the dominant/recessive case-only models can be found in supplementary Table S3.

3.3.1 | Exploratory comparison of all three approaches

The correlation between effect estimates (betas and log(OR)) of all three genome-wide approaches assuming an additive SNP effect was highest between both CO approaches on abuse 0/1 and CTQ-score ($r = 0.58$), medium between both analyses on abuse 0/1 (CC and CO) ($r = 0.54$) and lowest between the dimensional CO approach using CTQ score and the GxE interaction approach using abuse 0/1 ($r = 0.33$). The overlap between SNPs with a notable p -value < 0.001 is given in the

Venn diagram (supplemental Figure S3). Although in theory all approaches were applied to measure GxE interaction for CT in MDD, the overlap between all three analyses with $p < 0.001$ was only one SNP (rs10504767) on chromosome eight with no known gene nearby.

3.3.2 | Lookup of candidate genes

We performed a gene-based test using VEGAS2 (Mishra & Macgregor, 2015) on the genome-wide summary statistics of the three main

TABLE 2 List of top independent signals from the three meta-analyses (case-control GxE, case-only with abuse 0/1 and case-only with CTQ-score) assuming an additive SNP effect ($p < E-5$); * log(OR); **beta

RSID	MAF	p-value	Effect	Genes nearby	Alleles	CHR	I^2	Sirection	Gene information from NCBI resource
Case-only analysis (dichotomous childhood abuse 0/1)*									
rs17578476	0.27	3.3E-6	-0.368	LRR1Q3	AC	chr1	0.0	- - - -	A SNP at the LRR1Q3 Locus has been associated with SCZ
rs6553019	0.40	5.1E-6	0.321	FAT1	AG	chr4	46	+ + + +	Probable function as an adhesion molecule or signaling receptor, and is likely to be important in developmental processes and cell communication; cadherine gene
rs10846719	0.49	5.6E-6	0.335	SCARB1, NCOR2	TC	chr12	0.0	+ + + ?	plasma membrane receptor for high density lipoprotein cholesterol (HDL)
rs10504765	0.39	9.5E-6	-0.547	-	AG	chr8	0.0	- - ? -	
Case-only analysis (dimensional CTQ score)**									
rs3214187	0.13	7.4E-7	-3.443	NPY	D_I3	chr7	48	- - - -	Widely expressed in the central nervous system and influences many physiological processes, including cortical excitability, stress response, food intake, circadian rhythms, and cardiovascular function
rs199719135	0.09	1.5E-6	6.044	SH3BP4	D_I11	chr2	62	+ + ? +	Involved in cargo-specific control of clathrin-mediated endocytosis
rs75184661	0.06	4.1E-6	5.479	CACNA1C (intronic)	TC	chr12	0.0	? + + +	Mediate the influx of calcium ions into the cell upon membrane polarization
rs6822352	0.34	6.8E-6	2.291	KDR	AG	chr4	16	+ + + ?	VEGF receptor
rs6997589	0.26	7.7E-6	-3.575	SH2D4A (intronic)	AG	chr8	0.0	- - ? -	
rs200510841	0.23	9.9E-6	3.787	SEMA6D	D_I2	chr15	0.0	+ + ? +	Mediates transport to and from the nucleus
GxE analysis (dichotomous childhood abuse 0/1)*									
rs7128637	0.26	4.4E-6	-0.880	ARHGAP20	CG	chr11	0.0	- - ? -	
rs10772578	0.06	6.0E-6	1.268	CREBL2	TC	chr12	45	+ + + +	Suggestions that CREBL2 encodes a protein with DNA binding capabilities and has tumor-suppressor properties
rs10808504	0.44	7.9E-6	0.755	ENPP2	TC	chr8	0.0	+ + ? +	Regulating myelin formation

I^2 as measurement of heterogeneity between studies. Direction reporting the direction of effects in SHIP-0, TREND, NESDA, Radiant-UK.

analyses assuming additive SNP-effects. The gene definition was set to ± 10 kb and all SNPs per gene were used for analysis. No gene was significant after correction for multiple testing and the top results contained no gene previously associated with a psychiatric phenotype (supplemental Table S5). Also our list of candidate genes revealed not even a nominally significant ($p < 0.05$) hit in the VEGAS2 results (supplemental Tables S6).

4 | DISCUSSION

This is the first genome-wide GxE interaction GWAS for depression and CT in subjects of European ancestry. The aims of this study were to validate candidate SNPs and genes for GxE in MDD while applying different model assumptions to acknowledge the variety of GxE models in previous candidate gene studies. Our methods included standard case-control GxE analysis with a multiplicative interaction term as well as case-only analyses with two different parametrizations of CT (dichotomous childhood abuse 0/1 and a continuous CT score) assuming an additive SNP-effect.

Two published GxE studies on depressive symptoms reported genome-wide significant SNPs in African American women (rs4652467) (Dunn et al., 2016) and in a Japanese population (rs1051057) (Otowa et al., 2016). We were not able to replicate these findings as rs4652467 only has a MAF < 0.001 in populations of European ancestry and was therefore excluded from our analyses. The association between rs1051057 and MDD in this sample was non-significant, even at a nominal level. One explanation for our failure to replicate this finding could be due to the different phenotype definition, as we used lifetime MDD and not current depressive symptoms. As expected, due to the limited number of subjects, we were underpowered to identify robust genome-wide significant interaction effects in 3944 individuals. None of the genome-wide approaches suggested an inflation of the p -values in the QQ-plots (supplemental Figure S2).

Overall, the candidate variants could not sufficiently be supported by our analyses; only 9% of the SNPs revealed a nominally significant effect in at least one of the three main approaches. Also the introduction of dominant and recessive SNP models led to no association with $p < 0.0003$. Subsequent gene-based analyses on the summary statistics using VEGAS2 allowed for no biologically meaningful interpretation. These findings are also consistent with recent large-scale efforts to validate candidate genes, especially the 5-HTTLPR variant (Culverhouse et al., 2017). With such limited validation of candidate variants it seems questionable if the current approaches of candidate gene studies are the right tool to gain insights into the biology of gene-environment interactions in MDD. Our results suggest that published studies on candidate variants in GxE for MDD are in part likely subject to publication bias.

4.0.3 | Methodological limitations and challenges

GxE studies face even larger methodological challenges than genetic association studies looking for main effects of SNPs.

1. Power: Our main limitation was the lack of power due to the limited sample size in our analysis which only allows for the robust identification of huge genetic effects which are not expected when analyzing common variants. We tried to circumvent this limitation by focusing on previously reported candidate variants.
2. Assumptions behind GxE models: The methodological approaches that have been performed are based on different assumptions. In case-only analysis, independence between the genetic signal and the environmental factor is required. This might be a problem as studies suggest a significant heritability of childhood adversity through inherited ways of behavior. Nevertheless, as previously shown for the MDD PGC wave2 data, SNP heritability for CT was estimated to be not significantly different from 0.00 in GRM based analyses (Peyrot et al., 2017). Because of limited sample size, estimating the proportion of variance attributable to the interaction between CT and genome-wide genetic effects was not possible. But we also found no evidence for a gene-environment correlation for the top hits of our meta-analyses.
3. Heterogeneity across samples: The samples used in these analyses were taken from different settings, general population and clinical patients. Although this might have biased the results, all subjects were of European ancestry, all subjects were screened for MDD with the same instrument, all controls were also screened for absence of MDD and CT was assessed using the same instrument (CTQ).
4. Childhood trauma measurement: As with many other measures for CT, the CTQ is a retrospective self-report measure and thus reports are likely to be influenced by recall bias and particularly depressive state. One solution would be to control for mood at the time of reporting in the analyses (Fisher et al., 2013). But other groups have found that depressive symptoms do not result in exaggeration of retrospectively recalled stressful events (Brewin, Andrews, & Gotlib, 1993; Fisher et al., 2011) and thus the use of retrospective self-reports is likely to have had only a minimal impact on these results. Nevertheless, this could be a source of bias leading to false positive results in our analyses.
5. GxE models: Although a number of different model assumptions were tested in this study, there are other models that need further investigation like the distinction between additive and multiplicative interaction models which is circumvented in the case-only approach as this method is assuming a multiplicative interaction. Also environmental factors different from CT such as social status or BMI could exhibit a GxE interaction as these are also risk factors for depression (Mansur, Brietzke, & McIntyre, 2015; Schlossberg, Massler, & Zalsman, 2010).
6. Lack of replication samples: We had no independent replication samples but we used different models to assess the robustness of the results. Unfortunately, no consistency between models was found.
7. Coverage of genetic variants: A GWAS approach does not cover all possible genetic variants that could contribute to depression, for example, insertions, deletions or rare genetic variants. One of the most prominent examples is the serotonin-transporter polymorphism (Caspi et al., 2003).

Nevertheless, our analyses may provide some insights into GxE analyses and the genetic underpinning of gene-environment interactions in MDD as some of the top signals in the three main analyses involved genes previously implicated in psychiatric phenotypes (Table 2) like *ENPP2* (Aston, Jiang, & Sokolov, 2007) the *LRR1Q3* Locus identified in the latest GWAS for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), *FAT1* (Abou Jamra et al., 2008; Light et al., 2005), *NPY* (Nakhate, Yedke, Bharme, Subhedar, Kokare, 2016; Soleimani et al., 2014) and *CACNA1C*, a candidate gene in depression that also shows pleiotropic effects on other major psychiatric disorders (Cross-Disorder Group of the PGC, 2013; Rao et al., 2016). Although some of these genes are well known in psychiatric research, the significant SNPs from the analyses showed no overlap with previously identified candidate SNPs of these genes.

Finally, we can say that with the current sample size we were not able to detect a robust genome-wide significant interaction with childhood trauma and depression and most of the candidate variants and genes could not be supported when utilizing different methodological approaches. An important point of this analysis is the lack of replication, even if only nominal *p*-values are considered. Moreover, the analyses showed a lack of stability of findings in the different methodological approaches.

It will be necessary to collect more data on CT in MDD samples to validate our top hits and achieve a higher power to detect robust genome-wide significant findings. Also it might be prudent to at least partially question some of the former candidate SNP results for MDD as these could be attributed to publication bias and inconsistent models. One approach could be to harmonize the different CT measures throughout all of the PGC cohorts and perform the analyses with a much larger sample size. We also recommend reconsideration of the different models currently performed in GxE analyses for MDD and to perform consistent analyses in samples large enough to identify robust GxE interaction signals. Our next steps will be to perform the GxE analyses on single sub-dimensions of abuse where we have more data within the PGC as well as performing the analysis under the assumption of an additive interaction effect.

4.1 | ROLE OF FUNDING SOURCES

The Netherlands Study of Depression and Anxiety (NESDA) and the Netherlands Twin Register (NTR): funding was obtained from the Netherlands Organization for Scientific Research (NWO) and MagW/ZonMW grants Middelgroot-911- 09-032, Spinozapremie 56-464-14192, Center for Medical Systems Biology (CSMB, NWO Genomics), Genetic influences on stability and change in psychopathology from childhood to young adulthood (ZonMW 912-10-020), NBIC/BioAssist/RK (2008.024), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL, 184.021.007), VU University's Institute for Health and Care Research (EMGO +) and Neuroscience Campus Amsterdam (NCA); the European Science Council (ERC Advanced, 230374). The infrastructure for the NESDA

study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Centre, GGZ inGeest, Arkin, Leiden University Medical Centre, GGZ Rivierduinen, University Medical Centre Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Institute for Quality of Health Care (IQ Healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos)). Part of the genotyping of NESDA and NTR was funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health, Rutgers University Cell and DNA Repository (NIMH U24 MH068457-06), the Avera Institute, Sioux Falls, South Dakota (USA) and the National Institutes of Health (NIH R01 HD042157-01A1, MH081802, Grand Opportunity grants 1RC2 MH089951 and 1RC2 MH089995). Computing was supported by BiG Grid, the Dutch e-Science Grid, which is financially supported by NWO.

SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research Grant Nos. 01ZZ9603, 01ZZ0103, and 01ZZ0403; the Ministry of Cultural Affairs; and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Genome-wide data were supported by the Federal Ministry of Education and Research Grant No. 03ZIK012 and a joint grant from Siemens Healthcare, Erlangen, Germany, and the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the "Center of Knowledge Interchange" program of the Siemens AG. SHIP-LEGEND is funded by the German Research Foundation (DFG: GR 1912/5-1). S. V. was supported by the German Federal Ministry of Education and Research within the framework of the e:Med research and funding concept (IntegraMent) Grant No. 01ZX1314E.

This report represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. The RADIANT studies were funded by a joint grant from the UK Medical Research Council, GlaxoSmithKline (G0701420) and by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, King's College London. N.M. and C.M.L. have received funding from the European Community's Seventh Framework Programme under the Marie Curie Industry-Academia Partnership and Pathways (grant 286213). H.L.F. is supported by an MQ Fellows Award (MQ14F40). We thank all individuals who participated in the RADIANT study and all involved with data collection and management.

NRW acknowledges funding from the Australian National Health and Medical Research Council 1078901, 1087889.

The CoLauS|PsyCoLauS study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of

Lausanne, and the Swiss National Science Foundation (grants 3200B0-105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468 and 33CS30-148401).

Statistical analyses were carried out on the Genetic Cluster Computer (<http://www.geneticcluster.org>) hosted by SURFsara and financially supported by the Netherlands Scientific Organization (NWO 480-05-003 PI: Posthuma) along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam.

ACKNOWLEDGMENTS

We thank all people participating in the studies.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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SUPPORTING INFORMATION

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How to cite this article: Van der Auwera S, Peyrot WJ, Milaneshi Y, et al. Genome-wide gene-environment interaction in depression: A systematic evaluation of candidate genes. *Am J Med Genet Part B*. 2018;177B:40–49. <https://doi.org/10.1002/ajmg.b.32593>