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Gene–environment interactions between HPA-axis genes and childhood maltreatment in depression: a systematic review

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Review Article

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Abstract

Objective: Gene–environment (GxE) interactions may comprise an important part of the aetiology of depression, and childhood maltreatment (CM), a significant stressor, has consistently been linked to depression. Hence, in this systematic review, we aimed to investigate the interaction between hypothalamus–pituitary–adrenal axis (HPA-axis) genes and CM in depression. *Methods*: We conducted a literature search using the Pubmed, Embase, and PsychINFO databases in adherence with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. We included studies investigating GxE interactions between HPA-axis genes [*Angiotensin Converting Enzyme* (*ACE*), *Arginine Vasopressin* (*AVP*), *Corticotrophin Releasing Hormone* (*CRH*), *Corticotrophin Releasing Hormone Receptor 1* (*CRHR1*), *Corticotrophin Releasing Hormone Receptor 2* (*CRHR2*), *FK506 binding protein* (*FKBP5*), *Nuclear Receptor subfamily 3 group C member 1* (*NR3C1*), *Nuclear Receptor subfamily 3 group C member 2* (*NR3C2*)] and CM in depression. *Results*: The literature search identified 159 potentially relevant studies. Following screening, 138 of these were excluded. Thus, 21 studies, investigating a total of 51 single nucleotide polymorphisms, were included in the final study. The most prevalent genes in the current study were *CRHR1* and *FKBP5*. Significant GxE interactions were reported in seven of eight studies for *CRHR1*:rs110402 and CM, and in five of eight studies for *FKBP5*:rs1360780 and CM. In summary, our results suggest possible GxE interactions between *CRHR1, FKBP5, NR3C1*, and *NR3C2* and CM, respectively. For the remaining genes, no relevant literature emerged. *Conclusions*: We find that genetic variation in four HPA-axis genes may influence the effects of CM in depression.

Significant outcomes

- A systematic literature search was conducted using the search databases Pubmed, Embase, and PsychINFO. Twenty-one original studies were singled out, in which the main objective was addressed: interaction between variation in eight HPA-axis genes and CM in depression.
- We found that genetic variation in four HPA-axis genes (*CRHR1, FKBP5, NR3C1,* and *NR3C2)* is likely to influence the effects of CM in depression. The best studied genes and polymorphisms were *CRHR1*:rs110402 and *FKBP5*:rs1360780.
- No relevant literature was identified for *AVP, ACE, CRH,* and *CRHR2.*

Limitations

- In spite of strictly following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, we cannot exclude potential exclusion of relevant literature.
- The majority of the identified studies lacked control for confounders, and it is worth considering whether some of the gene–environment (GxE) interactions were in fact gene–environment correlations (rGE) or combinations of GxE and rGE.
- The majority of GxE studies currently consist of candidate gene studies. Future research is highly probable to shift towards genome wide environment interaction studies (GWEISs).

Introduction

Stressful life events have consistently been linked with the development of depression (Kendler *et al.*, 1998, 1999; Paykel, 2003; Stroud *et al.*, 2008; Normann & Buttenschon, 2019). Especially, childhood maltreatment (CM) has drawn attention in previous research

(Heim & Nemeroff, 2001; Heim *et al.*, 2004; Harkness *et al.*, 2006; Pariante & Lightman, 2008; Ehlert, 2013; Peyrot *et al.*, 2014; Mazurka *et al.*, 2015): CM is a behaviour towards a child that is outside the norms of conduct, and entails substantial risk of causing physical or emotional harm. Within the research literature, there is a general consensus of four subtypes of CM: neglect, emotional, sexual, and physical abuse (Pekarsky, 2015). A multitude of clinical and epidemiologic studies have provided evidence of an association between CM and depressive symptoms (Chapman *et al.*, 2004; Nanni *et al.*, 2012; Kim & Lee, 2016). This finding has also been supported in twin studies (Thapar & McGuffin, 1996; Thapar *et al.*, 1998). The fact that some individuals exposed to severe stress like CM never develop depression, while others do, has led to the diathesis–stress theory, suggesting that the interaction between stress and an individual's vulnerability (diathesis) is key in the development of depression (Arnau-Soler *et al.*, 2019). GxE interactions may comprise a significant contribution to the aetiology of depression (Sullivan *et al.*, 2000; Saveanu & Nemeroff, 2012; Binder, 2017), and continued research in this field is of great importance, as it might be key to a better understanding of the psychopathology and is likely to ease diagnosis and treatment of depression in the future. The neuroendocrine stress response system (Heim *et al.*, 2008) is represented by the hypothalamus–pituitary–adrenal (HPA) axis, and in depression this system is reported to be hyperactive (Aborelius *et al.*, 1999; Bremmer *et al.*, 2007; Starr & Huang, 2018). The association between HPA-axis genes and stressful conditions (such as CM) has also been supported by a large amount of non-clinical data (Sanchez, 2006; Rogers *et al.*, 2013; Matosin *et al.*, 2018). The brain reacts to stress by hypothalamic secretion of arginine vasopressin (AVP) and corticotrophin-releasing hormone (CRH). The anterior pituitary is activated by these hormones and responds by secreting adrenocorticotropic hormone (ACTH). In the adrenal cortex, ACTH stimulates the release of corticosteroids (van Bodegom *et al.*, 2017). The effects of corticosteroids are mediated through binding to two types of receptors – glucocorticoid receptors (GR, NR3C1) and mineralocorticoid receptors (MR, NR3C2), and the whole system is based on negative feedback. FK506-binding protein (FKBP5) regulates the sensitivity of the GR (van Bodegom *et al.*, 2017) and ultimately decreases the GRs affinity for corticosteroids (Binder, 2009).

Another important system is the renin–angiotensinogen–angiotensin system (RAAS), which upregulates blood pressure, and includes conversion of angiotensin 1 into active angiotensin 2 by the angiotensin converting enzyme (ACE). The relationship between the stress response and the RAAS system has been established by a multitude of studies, and angiotensin 2 has been thought to have an impact on the HPA-axis (Aguilera *et al.*, 1995; Armando *et al.*, 2007; Dempster *et al.*, 2009), for which reasons the *ACE* gene is also included in our review.

Several studies have investigated whether variants in HPA-axis genes increase the risk for stress-related disorders, in the event of adverse life events (Assary *et al.*, 2017; Maglione *et al.*, 2018; Wang *et al.*, 2018). The results have generally shown that GxE interactions between HPA-axis genes and stressful life events such as CM influence the risk of depression (Maglione *et al.*, 2018; Wang *et al.*, 2018). However, to the best of our knowledge, no systematic review has been published, focusing on GxE interactions between HPA-axis genes and CM in depression. Thus, the present study aimed to utilise the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Welch *et al.*, 2012) in order to identify all relevant original studies investigating the interaction between genetic variation in eight genes involved in the HPA-axis and CM in depression.

Methods

A systematic literature search was performed, following the recommended PRISMA guidelines (Welch *et al.*, 2012). The searches were conducted using the Pubmed, Embase, and PsychINFO databases on 17 October 2018. Keywords were combined covering the eight selected genes involved in the HPA-axis, CM, and depression: ((((((*'Gene-Environment Interaction'* [*MeSH*]) *OR* (*'Genetic predisposition to disease'* [*MeSH*]) *OR* (*HPA-axis*) *OR* (*'Polymorphism, Single Nucleotide'* [*MeSH*])) *AND* (*AVP OR ACE OR CRH OR CHRH1 OR CRHR2 OR NR3C2 OR NR3C1 OR FKBP5*)) *AND* (((((*childhood maltreatment) OR childhood adversement*) *OR early life stress*) *OR adult survivors of child adverse events* [*MeSH*]) *OR life change events* [*MeSH*]))) *AND* ((((*mood disorders* [*MeSH*]) *OR* (*affect* [*MeSH*]) *OR depression*) *OR depressive disorder*).* Filters: Publication date from 01 January 2000 to 31 December 2018. Moreover, an individual search for each gene was performed, using the gene name in abbreviation as well as fully spelled. Firstly, screening of titles and abstracts were made, and secondly evaluation of full-text versions of relevant records followed. Finally, reference lists from the included papers were scanned. Main inclusion criteria were articles with the involvement of at least one of the eight selected genes involved in the HPA-axis and consideration of GxE interactions with CM in depression. Furthermore, the included studies had to be original human research and published in a peer-reviewed journal in English. The following information were extracted from each included study: author, publication year, gene, single nucleotide polymorphism (SNP) identification numbers, number of study participants, study design, type of exposure, assessment of exposure, outcome assessment, assessment of depression severity, *p*-values, and major findings. After applying the aforementioned criteria, 21 studies remained to be included in the review (Fig. 1). Of these, three were identified by scanning reference lists from the included studies. The eligibility was performed independently by both authors, and any differences were addressed by discussion.

Results

The 21 included studies examined a total of 51 SNPs in 4 different genes. Table 1 depicts the population characteristics from each included study, and the main findings are displayed in Table 2.

The interaction between genetic variants in *CRHR1* and CM in depression was investigated in eight studies. These studies included 34 SNPs in total (Bradley *et al.*, 2008; Heim *et al.*, 2009; Polanczyk *et al.*, 2009; Ressler *et al.*, 2009; Grabe *et al.*, 2010; Kranzler *et al.*, 2011; Laucht *et al.*, 2012; Starr *et al.*, 2014). *CRHR1*:rs110402 was investigated in all studies, and the interaction was furthermore significant in seven of eight studies (Bradley *et al.*, 2008; Heim *et al.*, 2009; Polanczyk *et al.*, 2009; Ressler *et al.*, 2009; Grabe *et al.*, 2010; Kranzler *et al.*, 2011; Starr *et al.*, 2014). Five studies (Bradley *et al.*, 2008; Polanczyk *et al.*, 2009; Grabe *et al.*, 2010; Kranzler *et al.*, 2011; Laucht *et al.*, 2012) found significant interactions between *CRHR1*:rs242924 × CM and *CRHR1:* rs7209436 × CM. *CRHR1*:rs17689882 (Grabe *et al.*, 2010; Laucht *et al.*, 2012) and *CRHR1*:rs4792887 (Bradley *et al.*, 2008; Grabe *et al.*, 2010) were investigated in two studies. The

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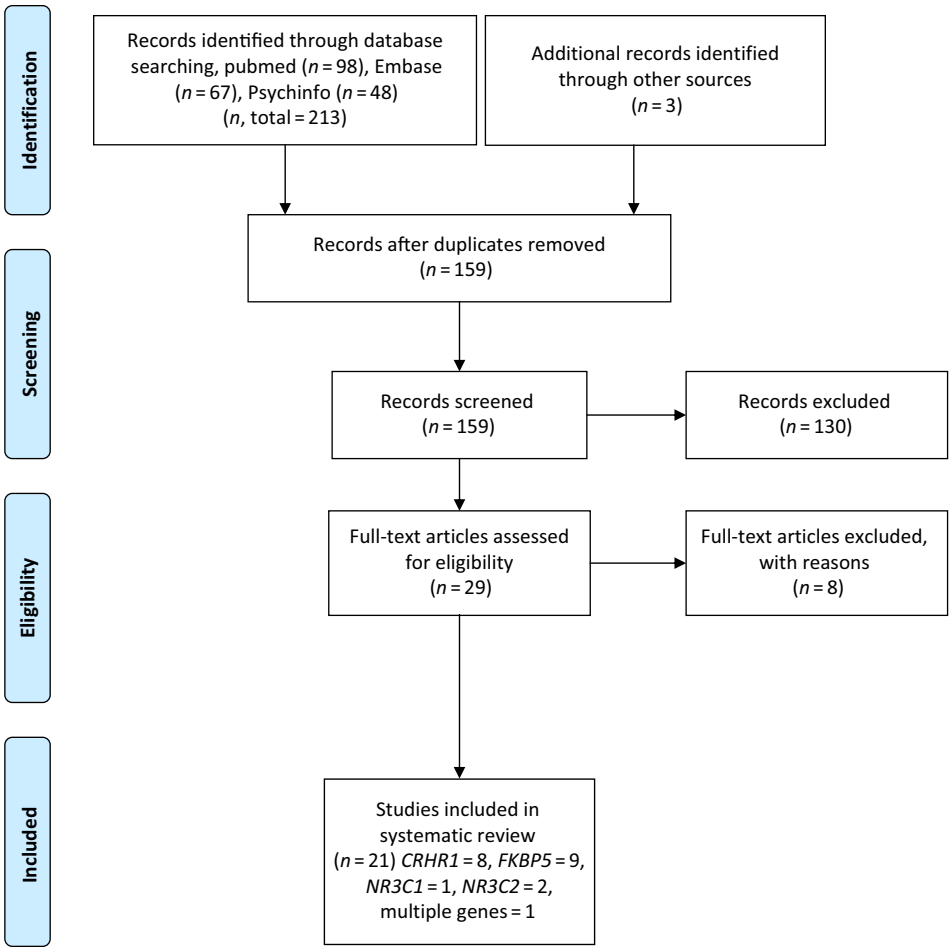

Fig. 1. PRISMA flowchart illustrating the literature search with identification, screening, eligibility, and inclusion of final papers.
Source: Moher et al. (2009). www.prisma-statement.org

remaining 29 SNPs were investigated in a single study by either Grabe *et al.* (2010) or Bradley *et al.* (2008). The study by Bradley *et al.* (2008) found two significant interactions after correction for multiple testing (*CRHR1*:rs110402 and *CRHR1*:rs7209436), and the study by Grabe *et al.* (2010) found significant interactions in 23 of 28 SNPs.

The interaction between genetic variants in *FKBP5* and CM was investigated in nine studies. These studies examined six SNPs in total (Lavebratt *et al.*, 2010; Appel *et al.*, 2011; Zimmermann *et al.*, 2011; Dackis *et al.*, 2012; Comasco *et al.*, 2015; Kohrt *et al.*, 2015; Lahti *et al.*, 2015; Scheuer *et al.*, 2015; de Castro-Catala *et al.*, 2017). The best studied SNP was *FKBP5*:rs1360780, as it was investigated in eight (Lavebratt *et al.*, 2010; Appel *et al.*, 2011; Zimmermann *et al.*, 2011; Dackis *et al.*, 2012; Comasco *et al.*, 2015; Lahti *et al.*, 2015; Scheuer *et al.*, 2015; de Castro-Catala *et al.*, 2017) of nine studies. All but three studies (Lavebratt *et al.*, 2010; Dackis *et al.*, 2012; de Castro-Catala *et al.*, 2017) reported significant interactions between *FKBP5:* rs1360780 × CM: One study did not find a significant interaction (Lavebratt *et al.*, 2010), and two studies investigated the SNP as part of two different haplotypes both containing rs3800373, rs9296158, and rs1360780 (Dackis *et al.*, 2012; de Castro-Catala *et al.*, 2017). Additional five SNPs in *FKBP5* (rs3800373, rs4713916, rs9296158, rs9394309, and rs9470080) were included in significant GxE (Appel *et al.*, 2011; Zimmermann *et al.*, 2011; Comasco *et al.*, 2015; Lahti *et al.*, 2015; Scheuer *et al.*, 2015). Eight SNPs in *NR3C1* were investigated in two studies (Bet *et al.*, 2008; Hardeveld *et al.*, 2015), of which one found significant GxE (Bet *et al.*, 2008). Three SNPs in *NR3C2* were investigated in three studies totally (Hardeveld *et al.*, 2015; Vinkers *et al.*, 2015; Gerritsen *et al.*, 2017) of which two studies found significant interactions (Vinkers *et al.*, 2015; Gerritsen *et al.*, 2017), whereas one did not (Hardeveld *et al.*, 2015). As regards the *ACE, AVP, CRH*, and *CRHR2* genes, no relevant literature was identified.

The 21 included studies counted analyses of a pooled total of 27 886 participants. Fifteen studies investigated 22 635 participants of Caucasian origin, and six studies investigated 5251 subjects of Asian (Kohrt *et al.*, 2015), African American (Bradley *et al.*, 2008; Heim *et al.*, 2009; Ressler *et al.*, 2009; Kranzler *et al.*, 2011; Dackis *et al.*, 2012), Hispanic (Dackis *et al.*, 2012), or other (Dackis *et al.*, 2012) origins. The mean age of the included populations in the 21 studies varied considerably from 5.2 to 77 years (Table 1). Furthermore, the sample sizes in each study varied considerably, with inclusion from 186 to 3080 participants. Three different study types were represented; hence, 14 831 participants were analysed in cohort studies (Heim *et al.*, 2009; Polanczyk *et al.*, 2009; Grabe *et al.*, 2010; Appel *et al.*, 2011; Kranzler *et al.*, 2011; Zimmermann *et al.*, 2011; Laucht *et al.*, 2012; Starr *et al.*, 2014; Vinkers *et al.*, 2015; de Castro-Catala *et al.*, 2017), 10 830 in case–control studies (Bet *et al.*, 2008;

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Table 1. Population characteristics

Gene(s)	Total sample size, ethnicity	Design	Males (%)	Cases (males, %)	Controls (males, %)	Mean age	References
CRHR1	444, Caucasian	Cohort study with follow-up	41	–	–	20	Starr *et al.* (2014)
CRHR1	300, Caucasian	Cohort study with follow-up	46	–	–	19	Laucht *et al.* (2012)
CRHR1	3080 (1211 European-Americans, 1869 African American)	Cohort study	57.1	–	–	39.7	Kranzler *et al.* (2011)
CRHR1	1638, Caucasian	Cohort study with follow-up	47.4	–	–	53.6	Grabe *et al.* (2010)
CRHR1	1059, African American	Case–control	56.8	–	–		Ressler *et al.* (2009)
CRHR1	1063, African American	Cohort study	39.9	–	–	41.8	Heim *et al.* (2009)
CRHR1	621 (422 African Americans, 199 Caucasians)	Case–control (part of an extended study by Ressler *et al.*, 2009)	39.0 and 0	–	–	38.4 (sample 1) and 31.9 (sample 2)	Bradley *et al.* (2008)
CRHR1	2153 (1116 + 1037), Caucasian	Two cohort studies	100 and 46.6	–	–	39.6 and 32	Polanczyk *et al.* (2009)
FKBP5	808, Caucasian	Cohort study	23	–	–	20.8	de Castro-Catala *et al.* (2017)
FKBP5	236 (127 African American, 80 Caucasian, 20 Hispanic, 9 other)	Cross-sectional	0	–	–	33.8	Dackis *et al.* (2012)
FKBP5	682, Asian	Cross-sectional	50.9	–	–	37.0	Kohrt *et al.* (2015)
FKBP5	1307 (909 + 398), Caucasian	Cross-sectional study and follow-up study	50.1 and 54.3	–	–	12.0 and 17.2	Comasco *et al.* (2015)
FKBP5	1431, Caucasian	Case–control	39.2	346 (40.8)	1085 (37.6)	61.8 (cases), 64.5 (controls)	Lahti *et al.* (2015)
FKBP5	186, Caucasian	Case–control	41.9	141 (48.2)	45 (35.6)	5.2	Scheuer *et al.* (2015)
FKBP5	2157, Caucasian	Cohort study with follow-up	47.3	–	–	55.8	Appel *et al.* (2011)
FKBP5	2743, Caucasian	Case–control with follow-up	35.0	457 (24.6)	2286 (45.5)		Lavebratt *et al.* (2010)
FKBP5	884, Caucasian	Cohort study with follow-up	47.7	–	–	26	Zimmermann *et al.* (2011)
NR3C1, NR3C2	1870, Caucasian	Case–control	27.4	951 (30.7)	919 (24)	42.6 (cases), 44.4 (controls)	Hardeveld *et al.* (2015)
NR3C1	906, Caucasian	Case–control	43	68 (31)	377 (55)	76	Bet *et al.* (2008)
NR3C2	2304 (665 + 1639), Caucasian	Two cohort studies	44 and 34	–	–	21 and 42	Vinkers *et al.* (2015)
NR3C2	2014, Caucasian	Case–control	34	1615 (34)	399 (34)	42.5	Gerritsen *et al.* (2017)

Table 2. Studies of GxE interactions involving childhood maltreatment and depression

Gene(s)	Genetic variant(s)	Exposure	Assessment of exposure	Assessment of depression severity	Main findings, *p*-value	References
CRHR1	rs110402	Early adversement	Parent interview	BDI	CRHR1:rs110402 × CM, $p = 0.011$	Starr *et al.* (2014)
CRHR1	rs110402	Childhood adversity	CTQ + standardised parent interview	None	CRHR1:rs17689882 × CM, $p = 0.048$	Laucht *et al.* (2012)
	rs17689882					
	rs242924					
	rs7209436					
CRHR1	rs110402	Adverse childhood experiences	SSADDA	None	CRHR1:TAT-haplotype (rs110402, rs242924, rs7209436) × CM, $p = 0.005$	Kranzler *et al.* (2011)
	rs242924					
	rs7209436					
CRHR1	rs110402	CM	CTQ	BDI	23 of 28 SNPs (including rs110402, rs17689882, rs242924, rs4792887, and rs7209436) in CRHR1 showed significant interactions with physical neglect, $p < 0.05$	Grabe *et al.* (2010)
	rs17689882					
	rs242924					
	rs4792887					
	rs7209436					
	23 other SNPs					
CRHR1	rs110402	Childhood and lifetime trauma	CTQ	BDI	CRHR1:rs110402 × CM, $p = 0.0095$	Ressler *et al.* (2009)
CRHR1	rs110402	Childhood trauma	CTQ	BDI	CRHR1:rs110402 × CM, $p = 0.018$	Heim *et al.* (2009)
CRHR1	rs110402	Child abuse	CTQ	BDI	CRHR1:rs7209436 × CM, $p = 0.009$; CRHR1:rs110402 × CM, $p = 0.008$	Bradley *et al.* (2008)
	rs12942300					
	rs1360780					
	rs173365					
	rs242924					
	rs242940					
	rs242948					
	rs242950					
	rs4076452					
	rs4792887					
	rs7209436					
CRHR1	rs110402	CM	CTQ	None	CRHR1: TAT-haplotype (rs110402, rs242924, rs7209436) × CM, $p = 0.04$ (sample 1)	Polanczyk *et al.* (2009)
	rs242924					
	rs7209436					
FKBP5	rs1360780	Childhood trauma	CTQ	SCL-90-R	*FKBP5*:rs4713916 × CM, $p < 0.05$	de Castro-Catala *et al.* (2017)
	rs3800373					
	rs4713916					
	rs9296158					
	rs9470080					
FKBP5	rs1360780	CM	CTQ	None	$p > 0.05$	Dackis *et al.* (2012)
	rs3800373					
	rs9296158					
	rs9470080					

(*Continued*)

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Table 2. (*Continued*)

Gene(s)	Genetic variant(s)	Exposure	Assessment of exposure	Assessment of depression severity	Main findings, *p*-value	References
FKBP5	rs3800373 rs9296158 rs9470080	Childhood trauma	CTQ	BDI	*FKBP5*:rs9296158 × CM, $p = 0.022$	Kohrt *et al.* (2015)
FKBP5	rs1360780 rs3800373	Early life adversity	Life Incidence of Traumatic Events scale, Juvenile Victimisation Scale	None	FKBP5:rs3800373 × CM, $p = 0.019$ (cohort 1) *FKBP5*:rs3800373 × CM, $p = 0.001$ (cohort 2) *FKBP5*:rs1360780 × CM, $p = 0.007$ (cohort 2)	Comasco *et al.* (2015)
FKBP5	rs1360780 rs9394309 rs9470080	Early life stress	Finnish national archives, self-reported separation of families	BDI	*FKBP5*: all three investigated SNPs × CM, *p*-values < 0.05	Lahti *et al.* (2015)
FKBP5	rs926158 rs3800373 rs1360780 rs9470080 rs4713916	Adverse life events in childhood	PAPA	None	*FKBP5*: all five investigated SNPs × CM, *p*-values < 0.05	Scheuer *et al.* (2015)
FKBP5	rs1360780	Childhood physical abuse	CTQ	BDI	*FKBP5*:rs1360780 × CM, $p = 0.006$	Appel *et al.* (2011)
FKBP5	rs1360780	Childhood problems and negative life events	List of 23 negative life events	None	$p > 0.05$	Lavebratt *et al.* (2010)
FKBP5	rs1360780 rs3800373 rs4713916 rs9296158 rs9470080	Childhood maltreatment	CTQ	None	*FKBP5*: all five investigated SNPs × CM, *p*-values < 0.001	Zimmermann *et al.* (2011)
NR3C1, NR3C2	9beta ER22/23EK, BclI TthIIII NR3C1-1 NR63S −2C/G I180V	Childhood trauma	4 questions in a clinical interview	None	$p > 0.05$	Hardeveld *et al.* (2015)
NR3C1	9beta 22/23EK N363S	Childhood adversity	Interview with questions about childhood	None	NR3C1:22/23 EK × CM, $p = 0.02$ NR3C1:9beta × CM, $p = 0.04$	Bet *et al.* (2008)
NR3C2	rs5522 rs2070951	CM	CTQ	None	NR3C2: all haplotypes from the two SNPs × CM, *p*-values < 0.001	Vinkers *et al.* (2015)
NR3C2	rs17581262	CM	Nemesis trauma interview	None	NR3C2:rs17581262 × CM, $p = 0.036$	Gerritsen *et al.* (2017)

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Bradley *et al.*, 2008; Ressler *et al.*, 2009; Lavebratt *et al.*, 2010; Hardeveld *et al.*, 2015; Lahti *et al.*, 2015; Scheuer *et al.*, 2015; Gerritsen *et al.*, 2017), and 2225 in cross-sectional studies (Dackis *et al.*, 2012; Comasco *et al.*, 2015; Kohrt *et al.*, 2015).

Nine studies in total adjusted for multiple testing using a Bonferroni correction (Bradley *et al.*, 2008; Ressler *et al.*, 2009; Zimmermann *et al.*, 2011; Comasco *et al.*, 2015; Hardeveld *et al.*, 2015; Scheuer *et al.*, 2015) or other ways (Bet *et al.*, 2008; de Castro-Catala *et al.*, 2017; Gerritsen *et al.*, 2017) in order to counteract the problem of multiple comparisons; however, 12 studies (Heim *et al.*, 2009; Polanczyk *et al.*, 2009; Grabe *et al.*, 2010; Lavebratt *et al.*, 2010; Appel *et al.*, 2011; Kranzler *et al.*, 2011; Dackis *et al.*, 2012; Laucht *et al.*, 2012; Starr *et al.*, 2014; Kohrt *et al.*, 2015; Lahti *et al.*, 2015; Vinkers *et al.*, 2015) did not apply any corrections.

Different questionnaires were used to assess the exposure to CM. The child trauma questionnaire (CTQ) was used in 11 studies (Bradley *et al.*, 2008; Heim *et al.*, 2009; Polanczyk *et al.*, 2009; Ressler *et al.*, 2009; Grabe *et al.*, 2010; Appel *et al.*, 2011; Dackis *et al.*, 2012; Laucht *et al.*, 2012; Kohrt *et al.*, 2015; Vinkers *et al.*, 2015; de Castro-Catala *et al.*, 2017), other lists of adverse events were also utilised (Lavebratt *et al.*, 2010; Comasco *et al.*, 2015). Eight studies (Bet *et al.*, 2008; Kranzler *et al.*, 2011; Zimmermann *et al.*, 2011; Starr *et al.*, 2014; Hardeveld *et al.*, 2015; Lahti *et al.*, 2015; Scheuer *et al.*, 2015; Gerritsen *et al.*, 2017) applied various types of interviews, and one study utilised the national archives in addition to self-reports (Lahti *et al.*, 2015).

Depression was assessed by either diagnostic interviews such as Composite International Diagnostic Inventory (Reed *et al.*, 1998; Zimmermann *et al.*, 2011; Hardeveld *et al.*, 2015; Gerritsen *et al.*, 2017), Structured Clinical Interview according to DSM-IV (First *et al.*, 1995), other types of interviews (Bet *et al.*, 2008; Polanczyk *et al.*, 2009; Kranzler *et al.*, 2011; Scheuer *et al.*, 2015), self-rating questionnaires on depression [Major Depression Inventory (Lavebratt *et al.*, 2010), Beck Depressive Inventory (BDI) (Bradley *et al.*, 2008; Heim *et al.*, 2009; Grabe *et al.*, 2010; Appel *et al.*, 2011; Dackis *et al.*, 2012; Laucht *et al.*, 2012; Starr *et al.*, 2014; Kohrt *et al.*, 2015; Lahti *et al.*, 2015)], or other self-rating questionnaires (Lavebratt *et al.*, 2010; Comasco *et al.*, 2015; Vinkers *et al.*, 2015; de Castro-Catala *et al.*, 2017). Depression severity was assessed by BDI-scores in 8 (Bradley *et al.*, 2008; Heim *et al.*, 2009; Ressler *et al.*, 2009; Grabe *et al.*, 2010; Appel *et al.*, 2011; Starr *et al.*, 2014; Kohrt *et al.*, 2015; Lahti *et al.*, 2015) of 21 studies. One study (de Castro-Catala *et al.*, 2017) used another term for depression severity.

Four studies performed gender-specific GxE interaction analyses (Heim *et al.*, 2009; Lavebratt *et al.*, 2010; Kranzler *et al.*, 2011; Vinkers *et al.*, 2015), and significant differences between gender were reported in *CRHR1* (Heim *et al.*, 2009; Kranzler *et al.*, 2011) and *NR3C2* (Vinkers *et al.*, 2015).

Discussion

The present study is a comprehensive review of publications investigating the interactions between eight HPA-axis genes and CM in depression in strict adherence to the PRISMA guidelines (Welch *et al.*, 2012). However, despite our profound search strategy, relevant literature may have been missed. Our search period was confined to studies published in the period between 01 January 2000 and 17 October 2018, which implies that potentially relevant studies conducted before or after these dates were not included in this paper.

In summary, the 21 included studies examined a total of 51 SNPs in four different genes – of these, 34 SNPs were located in the gene region of *CRHR1,* 6 SNPs in *FKBP5*, 8 SNPs in *NR3C1*, and 3 SNPs in *NR3C2*. The most prevalent polymorphisms were *CRHR1:* rs110402 and *FKBP5*:rs1360780. No relevant literature was identified as regards the *ACE, AVP, CRH,* and *CRHR2* genes.

Two recent systematic reviews are similar to the present study (Maglione *et al.*, 2018; Wang *et al.*, 2018). In spite of overlap between the studies, they differ substantially in important parameters such as search periods, the use of PRISMA guidelines, outcome, and the included genes. Firstly, our study is most recent, with search periods until the end of 2018 compared to 2017. Secondly, our study was the only one to use the search database Embase. Furthermore, the study by Maglione *et al.* (2018) did not follow the PRISMA guidelines. We chose to focus on depression, whereas Maglione *et al.* (2018) also investigated other outcomes such as internalising symptoms and anxiety. Wang *et al.* (2018) studied post-traumatic stress disorder (PTSD) and depression. In contrast to the studies by Wang and Maglione, the focus of present review was GxE interactions between genes in the HPA-axis and CM. More specifically, the current review focused on eight genes in the HPA-axis, whereas Wang *et al.* (2018) only focused on the *FKBP5* gene, and Maglione *et al.* (2018) included *FKBP5* and *CRHR1* from the HPA-axis in addition to other genes. The studies included in the present review investigated six SNPs in *FKBP5* (Lavebratt *et al.*, 2010; Appel *et al.*, 2011; Zimmermann *et al.*, 2011; Dackis *et al.*, 2012; Comasco *et al.*, 2015; Kohrt *et al.*, 2015; Lahti *et al.*, 2015; Scheuer *et al.*, 2015; de Castro-Catala *et al.*, 2017), whereas the review by Wang *et al.* (2018) merely studied three SNPs in *FKBP5* (rs1360780, rs3800373, and rs9470080). The review by Maglione *et al.* (2018) only identified one study investigating *FKBP5* (Scheuer *et al.*, 2015). In contrast, our study included nine studies (Lavebratt *et al.*, 2010; Appel *et al.*, 2011; Zimmermann *et al.*, 2011; Dackis *et al.*, 2012; Comasco *et al.*, 2015; Kohrt *et al.*, 2015; Lahti *et al.*, 2015; Scheuer *et al.*, 2015; de Castro-Catala *et al.*, 2017). Both studies included the study by Scheuer *et al.* (2015).

Interestingly, interactions between HPA-axis genes and CM have likewise been identified in other psychiatric disorders and conditions. Thus, the following SNPs in *FKBP5* have been shown to interact with CM as a predictor of adult PTSD symptoms: rs9296158, rs3800373, and rs1360780 (Binder *et al.*, 2008). These SNPs also showed significant GxE interactions in the studies included in the present review (Appel *et al.*, 2011; Zimmermann *et al.*, 2011; Comasco *et al.*, 2015; Kohrt *et al.*, 2015; Lahti *et al.*, 2015; Scheuer *et al.*, 2015). Likewise, in *CRHR1*, the haplotype consisting of rs7209436, rs110402, and rs242924 (also referred to as the TAT-haplotype) has been shown to moderate the association between CM and neuroticism (DeYoung *et al.*, 2011). The highly prevalent SNP in our study, *FKBP5*: rs1360780, has shown to interact with CM in the cortisol response to stress (Tyrka *et al.* 2009; Buchmann *et al.*, 2014) – these findings suggest a functional involvement of *FKBP5* in long-term alteration of the neuroendocrine stress regulation related to CM. This has been proposed to represent a premorbid risk or resilience factor in the context of stress-related disorders.

HPA-axis gene variation and environmental stress-related factors may be important in individual differences in responsivity

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to negative emotional stimuli (Pagliaccio *et al.*, 2015) or negative memory bias (Vogel *et al.*, 2013; Vrijsen *et al.*, 2015). Finally, epigenetic modifications of the *NR3C1* gene in response to CM have been proposed to alter the HPA-axis function and ultimately lead to psychopathology (Perroud *et al.*, 2011; Zannas & Binder 2014). Thus, both molecular and system-wide mechanisms have been suggested as explanatory models. An establishment of the responsible processes (or combinations of processes) for a given phenotype, among a large amount of potential models, continues to constitute a challenge for the empirical investigation of the interactions between genes and environment. However, the importance of continued research in this field must be emphasised, as it is still lacking behind other research fields, and an understanding of the biological effects of GxE interactions is clinically highly relevant, as it may lead to novel therapeutic approaches.

The findings of this study must be interpreted in the context of its limitations. The studies were based on various study designs, which implied a greater flexibility and concurrently decreasing specificity of our study. Furthermore, exposure to CM was assessed differently, for example, some studies used broad definitions such as adverse childhood experiences, whereas others applied abuse as the chosen exposure. Future research may profit from utilising narrower definitions of exposure, as this would entail greater external validity – yet, we chose a broad definition of adversity in order to include all feasibly relevant studies. Moreover, as the vast majority of the studies succeeded in identifying GxE interactions, possible publication bias must also be considered. Another potential issue is the heterogenic nature of psychiatric disease, and it has been argued that different subtypes of depression exist depending on whether one has experienced CM or not (Thapar *et al.*, 1998). In the current study, we did not distinguish between different types of depression.

The level of detail in the assessment and interpretation of the statistics in the studies varied greatly. Accordingly, it cannot be excluded that some of the GxE interactions investigated in this review were in fact GxE correlations (rGE) or combinations of rGE and GxE (Briley *et al.*, 2018a,b). A combination of the two types of interplay may have been a benefit in our analysis.

Controlling for confounders is another potentially problematic aspect in the interpretation of our results, as the majority of the studies did not control for the possible confounding influence each confounding variable could have on the interaction term in the statistical models used to test GxE interactions (Keller, 2013). Merely one (Lahti *et al.*, 2015) of the studies included in this review used this method to ensure proper control for confounders.

The vast majority of current GxE research is based on candidate gene studies, where a limited number of polymorphisms are chosen for investigation (Uher, 2013). This is a hypothesis-driven approach, which will induce selection bias. Furthermore, this method is criticised for the limited ability to include all possible causative genes and polymorphisms, and for the lack of replication of results (Ioannidis *et al.*, 2001; Tabor *et al.*, 2002). Moreover, the statistical power is a general challenge in GxE research. Another problem which have proven itself difficult, is the assessment of environmental variables (Uher, 2013) – that is, it is difficult to gather information about CM in very large samples. Finally, a large number of genes influence the phenotype in psychiatric disorders, and the polygenic character of depression makes it more complex to study (Videbech & Rosenberg, 2013). To the best of our knowledge, only a handful of genome wide gene–environment interaction studies (GWEISs) exist with stressful life events as exposure (Dunn *et al.*, 2016; Ikeda *et al.*, 2016; Otowa *et al.*, 2016; Coleman *et al.*, 2018) and none to date with CM as exposure. However, a large ($n = 5765$) recent meta-analysis by Peyrot *et al.* (2018) was not able to find evidence for interactions between polygenic risk and CM in depression.

The important next step in GxE research will imply a GWEIS approach with a systematic characterisation of multiple environmental factors in ample sample sizes (Ioannidis, 2005; Uher 2013). Moreover, employment of a uniform definition of CM will improve the possibility of performing future meta-analyses and ease interpretation and comparisons of GxE papers. Collaborative work between countries and research departments is prerequisite in order to obtain these goals (Peyrot *et al.*, 2014).

Conclusion

In conclusion, the present literature search suggests that genetic variation in four HPA-axis genes interacts with CM in depression. More specifically, our results support GxE interactions between genetic variation in *FKBP5, CRHR1, NR3C1,* and *NR3C2*, respectively, and CM in depression. *FKBP5* and *CRHR1* were particularly well investigated, and studies of these genes generally support GxE interactions with CM in depression. Future research will be strengthened by making use of uniform assessments of environmental factors, larger sample sizes, and conduction of GWEIS.

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Conflicts of interest. The authors have no conflicts of interest.

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