What DNA methylation modifications and/or genetic variations interact with childhood maltreatment in the development of depression: A systematic review

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ABSTRACT

Background: Child maltreatment predicts a significant risk factor for depression. The relationship between child maltreatment and depression has been shown to vary as a function of genetic factors. There have been very few systematic reviews conducted to date to synthesize what DNA methylations and/ or genetic variations interact with childhood maltreatment in the course of depression. This systematic review aimed to provide an overview of DNA methylation modifications with/without genetic variations associated with childhood maltreatment in depression.

Methods: Computerized and manual search on six databases (EMBASE, HealthStar, PsychoInfo, Medline, PubMed and Cochrane Library) and grey literature up to June 30th 2018 were conducted. Studies were critically evaluated for their eligibility and study quality.

Results: The initial search resulted in 196 articles. Five articles met the eligibility criteria being included in this review. All the selected studies were from the United States and published within the last five years. Changes in ID3, TPPP, GRIN1, and OXTR DNA methylation sites were found to be involved in the childhood maltreatment-depression relationship.

Limitations: The number of eligible articles included in this review was small. Selected articles had small sample sizes. A high degree of heterogeneity was found. It is difficult to conclude what the roles of DNA methylation modifications are in the relationship between maltreatment and depression. Population stratification has not been extensively studied so far and should be considered in the further research.

Conclusions: This review synthesizes an overview of the interaction between childhood maltreatment, DNA methylation modifications and genetic variations in depression. Findings of this review highlight an urgent need for genetic and epigenetic research in the area of childhood maltreatment and depression. Future etiological explorations should target on the above identified sites.

Keywords: Childhood maltreatment; Depression; DNA methylation; Genetic variations

1. Introduction

Childhood maltreatment, including physical abuse, sexual abuse, emotional abuse and neglect, has a wide range of negative consequences on individual's physical and mental health (Corso et al., 2008; Draper et al., 2008; Gould et al., 2012). WHO estimated that 1 in 5 women and 1 in 13 men worldwide have been sexually abused during childhood, and up to 50% of adults having the exposure of physical abuse during early life (WHO, 2014). Childhood maltreatment not only relates to negative consequences accompanying its exposure during childhood, but also initiates a negative developmental trajectory that potentially disrupts optimal development and normal functioning. For instance, childhood maltreatment can lead to altered neurocognitive functioning, that is associated with higher vulnerability to psychiatric diseases (McCrory et al., 2017).

Childhood maltreatment is a major causal factor for major depression (Li et al., 2016). Major depression contributes most to the burden of mental illness, followed by anxiety disorders (Ferrari et al., 2013; Whiteford et al., 2013). Both retrospective and prospective studies have consistently found that early life exposure of maltreatment: 1) alters neural reactivity of challenge and/or threat, even in resilient children and adolescents who are not presenting with depression, and the degree of reactivity appears to be associated with the severity of childhood adversity (Mueller et al., 2010). McLaughlin et al. (2014) found that child maltreatment was associated with a dysregulated pattern of physiological reativity; 2) reduces activity in subcortical reward-related areas, such as the striatum, which links to neuroanatomical and neurochemical brain reward systems, and triggers the onset of depression (Forbes and Dahl, 2012; Ubl et al., 2015a; Ubl et al., 2015b); and, 3) indicates functional alterations in a group of brain regions and networks associated with emotional regulation and executive functioning, which are closely connected to the risk of depression (Heleniak et al., 2016; McLaughlin et al., 2015; Snyder et al., 2015). People with the history of child maltreatment, often are associated with alternations in neurocognitive functioning, such as emotional regulation, executive functioning, etc., and have latent vulnerability to later on psychiatric problems (McCrory et al., 2017). Over one-half of global depression and anxiety cases are estimated to potentially attributable to self-reported childhood maltreatment (Li et al., 2016). The neurobiological processes underlying this heightened vulnerability remain to be understood (Lutz et al., 2017).

A recent systematic evaluation of genome-wide gene-environment interaction in depression using a total of 3944 subjects of European ancestry from the Psychiatric Genomics Consortium with the complete information on childhood maltreatment did not find the known candidate genes/variants involved in the relationship between child maltreatment and depression (Van der Auwera et al., 2018). Another recent study selected candidate genes based on previous animal and human studies, possible functional polymorphisms, and influences on the main putative pathways of depression (serotonin, hypothalamic pituitary adrenal (HPA), neuropeptide, neurotrophin, endocannabinoid, and neuroinflammatory mechanisms), and found that no main effects of such genes in depression (e.g. serotonin transporter, 5-Hydroxytryptamine Receptor 1A (HTR1A), 5-Hydroxytryptamine Receptor 2A (HTR2A), Brain-derived neurotrophic factor (BDNF), cannabinoid type 1 receptor (CB1), Galanin receptor 2 (GALR2), Purinergic receptor P2X7 (P2RX7)), but rather found a modulatory effect as a result of high exposure to negative life events, which induced the occurrence of depression (Gonda et al., 2018). Findings on the interaction between candidate genes and childhood maltreatment in depression have been inconsistent. A collaborative meta-analysis concluded no interaction between stress and serotonin-transporter-linked polymorphic region (5-HTTLPR) in the development of depression (Culverhouse et al., 2018).

With the advancement in high-throughput sequencing approaches, progress in epigenetics, more and more studies have been focused on interaction between child maltreatment and epigenetics and a combination of genetic and epigenetic variations associated with depression (Ousley et al., 2017). There is an increasing need to have a

clear understanding of the interaction between genetic variations and DNA methylation changes in the childhood maltreatment- depression relationship (Hoppen and Chalder, 2018). Compared to a number of reviews and meta-analyses on genetic variants and major depression (Rao et al., 2016) and gene-environment interactions in major depression (Saraceno et al., 2009; Wang et al., 2018), there have been very few systematic reviews conducted to investigate what DNA methylation sites are involved in the child maltreatment-depression relationship, nor their interactions with genetic variants.

This systematic review aimed to critically summarize the literature on the role of DNA methylation modifications in the relationship between childhood maltreatment and depression and to explore whether or not genetic variations were also involved in this relationship. The current review can lay the groundwork for the rising interest in the area of childhood maltreatment and depression by exploring both genetic variations and DNA methylation modifications. The review provides answers on the following questions: 1) what DNA methylation modifications have been studied in the relationship between childhood maltreatment-depression? 2) did genetic variations potentially mediate or moderate the interaction between childhood maltreatment and DNA methylations in depression? and, 3) what were underlying biological mechanisms of identified DNA methylations and/or genetic variations involved in the relationship between childhood maltreatment and depression?

2. Methods

This systematic review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 2009 revision (Moher et al., 2009).

2.1. Search strategy

We used both computerized and manual search to ensure all potentially relevant literature being evaluated. Six databases including EMBASE, HealthStar, PsychoInfo, Medline, PubMed and Cochrane Library were considered. Appendix 1 provides the detailed searching strategies for each database. The literature search comprised articles up to June 30th, 2018.

2.2. Eligibility criteria

Only original studies met all the following selection criteria were selected for this systematic review: 1) used an observational study design (case-control, cohort or cross-sectional); 2) examined the relationship between child maltreatment and adult depression; 3) used well-accepted measurements for child maltreatment and psychiatric diagnoses for depression; 4) used control groups (including abuse exposed and abuse not exposed groups); 5) either explored DNA methylation modifications or a combination of genetic and DNA methylation variations in bio-specimens, respectively in both analysis), and, 6) provided statistical indicators to examine the impact of maltreatment during childhood on adult depression. Studies were excluded if they: 1) did not provide information on child maltreatment, depression, or DNA methylation variations; 2) were not written in English; 3) did not provide comparative data between those with the history of childhood maltreatment and those without such a history; or 4) did not use a quantitative approach to summarize research findings.

2.3. Data extraction and synthesis

PM and SL independently evaluated the eligibility of titles, abstracts and full texts. At each stage all the eligible entries were kept for further evaluation. Group discussions with XM were used to solve those records with uncertainties. RefWorks and Endnote were used to manage literature retrieval. Figure 1 provides the details of searching procedure.

Data on author(s), year of publication, sample size, study designs, measurements of child maltreatment, locations of genes, DNA methylation sites, experimental approaches for epigenetic arrays, diagnoses of depression, covariates (if any), and major results were extracted. Inconsistencies were solved by group discussions. We also evaluated study quality of selected studies by the Newcastle-Ottawa-Scale (NOS), which was designed to assess the quality of observational studies. The score of NOS scale ranges between 0 and 9, with higher scores indicating better study quality.

2.4. Data synthesis

Heterogeneity of included studies was assessed to take into account of the following study characteristics: study cohorts, study designs, measurements of childhood maltreatment, subtypes of childhood maltreatment, measurements of depression, bio-specimens used for methylation arrays, genetic locations, methylation sites, and statistical analyses used in these studies. We identified a high degree of heterogeneity in these study characteristics across the selected studies. Meta-analyses assume that studies are from a normal distribution of overall target population, therefore it has requirement for the maximum heterogeneity that could be tolerated, even for random-effects models. The articles in this review did not meet this assumption as they have a high degree of heterogeneity. Thus, as suggested by Cochrane review, a qualitative approach was adopted to synthesize findings on the interaction between childhood maltreatment and DNA methylation modifications (with or without consideration of genetic variations) in depression.

3. Results

3.1. A summary of the selected studies

This systematic review is in two parts: Part I reviews articles on the interaction between childhood maltreatment and DNA methylation modifications in depression; and Part II reviews articles on the interaction between childhood maltreatment and DNA methylation modifications and genetic variations in depression. Table 1 presents an overview of characteristics of selected articles for both Part I and Part II reviews.

3.2. Part I: Childhood maltreatment and DNA methylation modifications in depression

The initial search resulted in 196 articles and 5 articles met the eligibility criteria were included in this review on the interaction between childhood maltreatment and DNA methylation modifications in depression. Generally, these included studies suggested that DNA methylations (either hyper- or hypo-methylations) combined with childhood maltreatment predicted the risk of depression. All the selected studies were from the United States and were published with the last five years. Compared to saliva, blood samples were the more frequently used biological samples, including both whole blood and lymphoblast cells. No study commented on the purification of DNA extraction or methylation validation in the experimental process. Age and sex were commonly considered in the analyses. According to the NOS scale, these selected articles had average quality. All studies had small sample sizes (N<500), and were case-control or short-term cohort studies. Representativeness and generalizability of

research findings were not mentioned in original studies. We summarized the research findings based on genetic coverage.

Whole-methylome study. We included *one methylome study* (Weder et al., 2014), which included a total of 485548 CpG sites. This study identified three genes: DNA-Binding Protein Inhibitor (ID3) (Konishi et al., 2010), Glutamate Receptor, Ionotropic NMDA 1 (GRIN1) (Tordera et al., 2011), and Tubulin Polymerization Promoting Protein (TPPP) (Lehotzky et al., 2010) as genome-wide significant predicators of depression. These genes have important neurobiological functions, for example, ID3 is involved in the stress response, GRIN1 in neural plasticity and TPPP in neural circuitry development. Compared to control children, maltreated children had significantly different methylation levels at multiple methylation sites in the gene body regions of these three genes. Combined epigenetic changes in ID2, GRIN1 and TPPP with childhood maltreatment predict the risk of depression in children.

FK506 binding protein 5, *FKBP5.* Two studies focused on FKBP5 DNA methylation modifications and genetic variations were included in this review (Bustamante et al., 2018; Tozzi et al., 2018). Tozzi et al. (2018) that for those genetically predisposed individuals carrying a high-risk variant of FKBP5, childhood maltreatment might induce demethylation of FKBP5. This was in turn associated with structural and functional changes in the inferior frontal orbital gyrus, a relevant area for the clinical symptoms of MDD. One the other hand Bustamante et al. (2018) did not replicate this significant finding and suggested that DNA methylation in FKBP5 did not mediate the childhood maltreatment-depression relationship.

Serotonin transporter-5-HTT. A study of a cohort female adoptees found that changes in CpG methylation sites on the Exon 1 of 5-HTT gene did not mediate the relationship between children sexual abuse and depression, even after taking into account of genetic loading (biological parents' psychopathology) (Beach et al., 2013).

Oxytocin Receptor, OXTR. A study that explored roles of OXTR DNA methylations in the relationship between childhood maltreatment and depression among adult African American, found that abuse interacted with methylation of multiple OXTR CpG sites to predict depressive symptoms (Smearman et al., 2016a). This study did not find that hypermethylations of OXTR served as a mediator of the relationship between maltreatment-psychopathology.

3.3. Part II: Childhood maltreatment and DNA methylation modifications and genetic variations in depression

Three eligible studies examined the roles of DNA methylation modifications and genetic variations in the relationship between childhood maltreatment and depression. These studies selected of what genetic variations and DNA methylations sites to analyze were based on previous more consistent findings and were designed to explore potential biological mechanisms to explain the maltreatment-depression relationship. Table 1 summarizes the detailed information on study characteristics. Table 2 provides detailed genetic and epigenetic information for each selected study. Part II identified two genes (OXTR and FKBP5) being tested to explore their DNA methylation modifications and genetic variations in maltreatment-depression relationships. There are inconsistent findings as to whether FKBP5 DNA methylation modifications and genetic variations interacted with childhood maltreatment in the etiology of depression (Bustamante et al., 2018; Tozzi et al., 2018). The study on OXTR suggested that abuse interacted with multiple OXTR DNA methylation sites to predict depressive symptoms (Smearman et al., 2016a).

4. Discussion

To the knowledge of the authors, this systematic review first critically synthesizes research findings on DNA methylation modifications and genetic variants in the childhood maltreatment-depression relationship. Our syntheses indicate several DNA methylation modifications and genetic variants significantly interacted with childhood maltreatment to predict the risk of subsequent depression. Although replications of these study findings still need to be validated by different populations and large-scale cohort studies, in line with the previous literature, identified DNA methylation modifications and genetic variants have important biological function in the development of depression. For instance, FKBP5, 5-HTT and OXTR play important roles in the hormone response system (Rao et al., 2016), serotonin and serotonergic energy process (Saraceno et al., 2009), and hormone and neurotransmitter (Kimura et al., 1992). Similarly, one whole-methylome study also suggested several DNA methylation sites on ID3, GRIN1 and TPPP were also involved in the relationship of maltreatment-depression. These identified genes are known for their biological links with the risk of depression.

Articles selected in this review were mostly based on candidate gene approaches. These chosen genes (FKBP5, 5-HTT, OXTR) are all biologically relevant to the development of depression. They are involved in the stress response, aggression, neural plasticity, neural circuitry and social behavior (Rao et al., 2016; Saraceno et al., 2009). Oxytocin is a neurohormone, which influences an individual's sensitivity to social environment (Bartz et al., 2011). Interaction between OXTR and adverse environments can result in both positive and negative health outcomes (McQuaid et al., 2013). Previous studies also suggested that OXTR CpG methylation might moderate the relationship between abuse and psychiatric symptoms (Smearman et al., 2016b). However, study findings have been very inconsistent as to whether or not FKBP5 and 5-HTT methylation sites are involved in the relationship between childhood maltreatment and depression. In this review, only one study on OXTR suggested that abuse interacted with multiple OXTR methylation sites to predict psychiatric symptoms (Smearman et al., 2016a).

The inconsistency in study findings can be explained by: 1) the high degree of heterogeneity in measurements of childhood maltreatment and phenotypes (depression). One study used a community-based setting, which had different prevalence of disease (and its severity) and exposure of maltreatment (and its severity). 2) the effect size of DNA methylation modifications in the maltreatment-depression relationship may be small. The Bustamante et al., (2018) study which had non-significant findings, had a total of 106 sample subjects and tested more gene regions, which required statistical corrections for multiple comparisons. Larger sample size would improve the reliability and consistency of results.

This review included one study applied whole-methylome approach using saliva samples, and identified three genes (ID3, GRIN1, and TPPP) that interact with maltreatment to predict the risk of depression. ID3 has several important functions that are closely linked with depression, for example it is upregulated in the pituitary during chronic stress (Konishi et al., 2010). Simulations with the pituitary adenylate cyclase-activating polypeptide (PACAP) encoding gene, that has been found to predict the risk of post-traumatic stress disorder (Ghzili et al., 2006; Ressler et al., 2011). It is also responsible for neurogenesis and attaining neural plasticity (Farioli-Vecchioli et al., 2009). TPPP can develop and maintain white matter tracts in brain (Vincze et al., 2011). TPPP and has a critical role in oligodendrocyte differentiation (Lehotzky et al., 2010). Animal studies of depression have found that GRIN1 is downregulated in frontal cortex (Tordera et al., 2011). Glutamate is involved in pathophysiology of depression and anxiety disorders (Krystal et al., 2010; Sanacora et al., 2012) and its receptors are one of the key regulators of synaptic plasticity, fear conditioning and memory (Blair et al., 2001). Together with childhood maltreatment, multiple DNA methylations modifications on these three genes predicted the risk of depression

among children. Notably, these findings emerge from a single study that was the only study to date to explore the role of DNA methylations in the maltreatment-depression relationship by using a whole-methylome approach with saliva samples.

This systematic review provides a critically synthesized overview of the research on DNA methylations and genetic variations in the relationship between childhood maltreatment and depression. Clearly, this is a new area that has had only a 5-year period to accumulate relevant evidence to identify potential DNA methylation sites actively involved in this relationship. Findings of this review point to possible biological targets for in-depth exploration in terms of underlying biological mechanisms of these genes. This review also identifies an important research gaps in this area that warrant much greater research attention.

There are several limitations to be noted. First, the number of eligible articles included in this review was small. Cautions are needed to interpret the findings of this review. Second, selected studies had small sample sizes (N<500). For studies that took approaches involving whole-methylome approach or multiple methylation sites, special attention is necessary to develop any future research based on these potential targets. Third, it is difficult to make conclusion about the roles of DNA methylation modifications in the maltreatment-depression relationship as some studies reviewed were case-control studies, which by their nature cannot provide the temporal order between the presence of DNA methylation modifications and onset of depression. Fourth, the set of covariates analyzed in these selected studies varied from study to study. They could have influenced the consistency of research findings. Lastly, population stratification should be considered in the further research, as it has not been extensively studied so far.

Multiple DNA methylation modifications and genetic variations significantly interacted with childhood maltreatment to predict the risk of subsequent depression. This review highlights that research is urgently needed to take DNA methylations and genetic variations into account in understanding the maltreatment-depression relationship. More large-scale prospective cohort studies are needed. It is of neurobiological and clinical importance to have in-depth understanding what genetic makeup and DNA methylations modifications interaction with exposure to childhood maltreatment contributed to the risk of depression.

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Author contributions

PM and SL conducted the search, together with XM reviewed the articles returned by the search for eligibility and reviewed all data extraction. XM and PM prepared the draft of this manuscript. XM oversaw the project, provided feedback on all steps of the search and data extraction and interpretation. All authors contributed to the writing and editing of the manuscript.

Ethical standards

The manuscript does not contain patients or population data.

Conflict of interest

The authors declare no conflict of interest.

References

Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. Trends Cogn Sci 15, 301-309.

Beach, S.R., Brody, G.H., Lei, M.K., Gibbons, F.X., Gerrard, M., Simons, R.L., Cutrona, C.E., Philibert, R.A., 2013. Impact of child sex abuse on adult psychopathology: a genetically and epigenetically informed investigation. J Fam Psychol 27, 3-11.

Blair, H.T., Schafe, G.E., Bauer, E.P., Rodrigues, S.M., LeDoux, J.E., 2001. Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. Learn Mem 8, 229-242.

Bustamante, A.C., Aiello, A.E., Guffanti, G., Galea, S., Wildman, D.E., Uddin, M., 2018. FKBP5 DNA methylation does not mediate the association between childhood maltreatment and depression symptom severity in the Detroit Neighborhood Health Study. J Psychiatr Res 96, 39-48.

Corso, P.S., Edwards, V.J., Fang, X., Mercy, J.A., 2008. Health-related quality of life among adults who experienced maltreatment during childhood. Am J Public Health 98, 1094-1100.

Culverhouse, R.C., Saccone, N.L., Horton, A.C., Ma, Y., Anstey, K.J., Banaschewski, T., Burmeister, M., Cohen-Woods, S., Etain, B., Fisher, H.L., Goldman, N., Guillaume, S., Horwood, J., Juhasz, G., Lester, K.J., Mandelli, L., Middeldorp, C.M., Olie, E., Villafuerte, S., Air, T.M., Araya, R., Bowes, L., Burns, R., Byrne, E.M., Coffey, C., Coventry, W.L., Gawronski, K.A.B., Glei, D., Hatzimanolis, A., Hottenga, J.J., Jaussent, I., Jawahar, C., Jennen-Steinmetz, C., Kramer, J.R., Lajnef, M., Little, K., Zu Schwabedissen, H.M., Nauck, M., Nederhof, E., Petschner, P., Peyrot, W.J., Schwahn, C., Sinnamon, G., Stacey, D., Tian, Y., Toben, C., Van der Auwera, S., Wainwright, N., Wang, J.C., Willemsen, G., Anderson, I.M., Arolt, V., Aslund, C., Bagdy, G., Baune, B.T., Bellivier, F., Boomsma, D.I., Courtet, P., Dannlowski, U., de Geus, E.J.C., Deakin, J.F.W., Easteal, S., Eley, T., Fergusson, D.M., Goate, A.M., Gonda, X., Grabe, H.J., Holzman, C., Johnson, E.O., Kennedy, M., Laucht, M., Martin, N.G., Munafo, M.R., Nilsson, K.W., Oldehinkel, A.J., Olsson, C.A., Ormel, J., Otte, C., Patton, G.C., Penninx, B., Ritchie, K., Sarchiapone, M., Scheid, J.M., Serretti, A., Smit, J.H., Stefanis, N.C., Surtees, P.G., Volzke, H., Weinstein, M., Whooley, M., Nurnberger, J.I., Jr., Breslau, N., Bierut, L.J., 2018. Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. Mol Psychiatry 23, 133-142.

Draper, B., Pfaff, J.J., Pirkis, J., Snowdon, J., Lautenschlager, N.T., Wilson, I., Almeida, O.P., Depression, Early Prevention of Suicide in General Practice Study, G., 2008. Long-term effects of childhood abuse on the quality of life and health of older people: results from the Depression and Early Prevention of Suicide in General Practice Project. J Am Geriatr Soc 56, 262-271.

Farioli-Vecchioli, S., Saraulli, D., Costanzi, M., Leonardi, L., Cinà, I., Micheli, L., Nutini, M., Longone, P., Oh, S.P., Cestari, V.J.P.o., 2009. Impaired terminal differentiation of hippocampal granule neurons and defective contextual memory in PC3/Tis21 knockout mice. PLoS One 4, e8339.

Ferrari, A.J., Charlson, F.J., Norman, R.E., Flaxman, A.D., Patten, S.B., Vos, T., Whiteford, H.A., 2013. The epidemiological modelling of major depressive disorder: application for the Global Burden of Disease Study 2010. PLoS One 8, e69637.

Forbes, E.E., Dahl, R.E., 2012. Research Review: altered reward function in adolescent depression: what, when and how? J Child Psychol Psychiatry 53, 3-15.

Ghzili, H., Grumolato, L., Thouënnon, E., Vaudry, H., Anouar, Y.J.R.p., 2006. Possible implication of the transcriptional regulator Id3 in PACAP-induced pro-survival signaling during PC12 cell differentiation. Regul Pept 137, 89-94.

Gonda, X., Hullam, G., Antal, P., Eszlari, N., Petschner, P., Hokfelt, T.G., Anderson, I.M., Deakin, J.F.W., Juhasz, G., Bagdy, G., 2018. Significance of risk polymorphisms for depression depends on stress exposure. Sci Rep 8, 3946.

Gould, F., Clarke, J., Heim, C., Harvey, P.D., Majer, M., Nemeroff, C.B., 2012. The effects of child abuse and neglect on cognitive functioning in adulthood. J Psychiatr Res 46, 500-506.

Heleniak, C., Jenness, J.L., Stoep, A.V., McCauley, E., McLaughlin, K.A., 2016. Childhood Maltreatment Exposure and Disruptions in Emotion Regulation: A Transdiagnostic Pathway to Adolescent Internalizing and Externalizing Psychopathology. Cognit Ther Res 40, 394-415.

Hoppen, T.H., Chalder, T., 2018. Childhood adversity as a transdiagnostic risk factor for affective disorders in adulthood: A systematic review focusing on biopsychosocial moderating and mediating variables. Clin Psychol Rev 65, 81-151.

Kimura, T., Tanizawa, O., Mori, K., Brownstein, M.J., Okayama, H., 1992. Structure and expression of a human oxytocin receptor. Nature 356, 526-529.

Konishi, H., Ogawa, T., Nakagomi, S., Inoue, K., Tohyama, M., Kiyama, H.J.N., 2010. Id1, Id2 and Id3 are induced in rat melanotrophs of the pituitary gland by dopamine suppression under continuous stress. Neuroscience 169, 1527-1534.

Krystal, J.H., Mathew, S.J., D'Souza, D.C., Garakani, A., Gunduz-Bruce, H., Charney, D.S., 2010. Potential psychiatric applications of metabotropic glutamate receptor agonists and antagonists. CNS Drugs 24, 669-693.

Lehotzky, A., Lau, P., Tőkési, N., Muja, N., Hudson, L.D., Ovádi, J., 2010. Tubulin polymerization-promoting protein (TPPP/p25) is critical for oligodendrocyte differentiation. Glia 58, 157-168.

Li, M., D'Arcy, C., Meng, X., 2016. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. Psychol Med 46, 717-730.

Lutz, P.E., Tanti, A., Gasecka, A., Barnett-Burns, S., Kim, J.J., Zhou, Y., Chen, G.G., Wakid, M., Shaw, M., Almeida, D., Chay, M.A., Yang, J., Lariviere, V., M'Boutchou, M.N., van Kempen, L.C., Yerko, V., Prud'homme, J., Davoli, M.A., Vaillancourt, K., Theroux, J.F., Bramoulle, A., Zhang, T.Y., Meaney, M.J., Ernst, C., Cote, D., Mechawar, N., Turecki, G., 2017. Association of a History of Child Abuse With Impaired Myelination in the Anterior Cingulate Cortex: Convergent Epigenetic, Transcriptional, and Morphological Evidence. Am J Psychiatry 174, 1185-1194.

McCrory, E.J., Gerin, M.I., Viding, E., 2017. Annual Research Review: Childhood maltreatment, latent vulnerability and the shift to preventative psychiatry - the contribution of functional brain imaging. J Child Psychol Psychiatry 58, 338-357.

McLaughlin, K.A., Sheridan, M.A., Alves, S., Mendes, W.B. 2014. Child Maltreatment and Autonomic Nervous System Reactivity: Identifying Dysregulated Stress Reactivity Patterns using the Biopsychosocial Model of Challenge and Threat. Psychosom Med 76, 538-546.

McLaughlin, K.A., Peverill, M., Gold, A.L., Alves, S., Sheridan, M.A., 2015. Child Maltreatment and Neural Systems Underlying Emotion Regulation. J Am Acad Child Adolesc Psychiatry 54, 753-762.

McQuaid, R.J., McInnis, O.A., Stead, J.D., Matheson, K., Anisman, H.J.F.i.n., 2013. A paradoxical association of an oxytocin receptor gene polymorphism: early-life adversity and vulnerability to depression. Front Neurosci 7, 128.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339, b2535.

Mueller, S.C., Maheu, F.S., Dozier, M., Peloso, E., Mandell, D., Leibenluft, E., Pine, D.S., Ernst, M., 2010. Early-life stress is associated with impairment in cognitive control in adolescence: an fMRI study. Neuropsychologia 48, 3037-3044.

Ousley, O., Evans, A.N., Fernandez-Carriba, S., Smearman, E.L., Rockers, K., Morrier, M.J., Evans, D.W., Coleman, K., Cubells, J., 2017. Examining the Overlap between Autism Spectrum Disorder and 22q11.2 Deletion Syndrome. Int J Mol Sci 18.

Rao, S., Yao, Y., Ryan, J., Li, T., Wang, D., Zheng, C., Xu, Y., Xu, Q., 2016. Common variants in FKBP5 gene and major depressive disorder (MDD) susceptibility: a comprehensive meta-analysis. Sci Rep 6, 32687.

Ressler, K.J., Mercer, K.B., Bradley, B., Jovanovic, T., Mahan, A., Kerley, K., Norrholm, S.D., Kilaru, V., Smith, A.K., Myers, A.J.J.N., 2011. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. 470, 492.

Sanacora, G., Treccani, G., Popoli, M.J.N., 2012. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neurophamacology 62, 63-77.

Saraceno, L., Munafo, M., Heron, J., Craddock, N., van den Bree, M.B., 2009. Genetic and non-genetic influences on the development of co-occurring alcohol problem use and internalizing symptomatology in adolescence: a review. Addiction 104, 1100-1121.

Smearman, E.L., Almli, L.M., Conneely, K.N., Brody, G.H., Sales, J.M., Bradley, B., Ressler, K.J., Smith, A.K., 2016a. Oxytocin Receptor Genetic and Epigenetic Variations: Association With Child Abuse and Adult Psychiatric Symptoms. Child Dev 87, 122-134.

Smearman, E.L., Almli, L.M., Conneely, K.N., Brody, G.H., Sales, J.M., Bradley, B., Ressler, K.J., Smith, A.K.J.C.d., 2016b. Oxytocin receptor genetic and epigenetic variations: association with child abuse and adult psychiatric symptoms. Child Dev 87, 122-134.

Snyder, H.R., Miyake, A., Hankin, B.L., 2015. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. Front Psychol 6, 328.

Tordera, R.M., Garcia-Garcia, A., Elizalde, N., Segura, V., Aso, E., Venzala, E., Ramirez, M.J., Del Rio, J.J.E.N., 2011. Chronic stress and impaired glutamate function elicit a depressive-like phenotype and common changes in gene expression in the mouse frontal cortex. Eur Neuropsychopharmacol. 21, 23-32.

Tozzi, L., Farrell, C., Booij, L., Doolin, K., Nemoda, Z., Szyf, M., Pomares, F.B., Chiarella, J., O'Keane, V., Frodl, T., 2018. Epigenetic Changes of FKBP5 as a Link Connecting Genetic and Environmental Risk Factors with Structural and Functional Brain Changes in Major Depression. Neuropsychopharmacology 43, 1138-1145.

Ubl, B., Kuehner, C., Kirsch, P., Ruttorf, M., Diener, C., Flor, H., 2015a. Altered neural reward and loss processing and prediction error signalling in depression. Soc Cogn Affect Neurosci 10, 1102-1112.

Ubl, B., Kuehner, C., Kirsch, P., Ruttorf, M., Flor, H., Diener, C., 2015b. Neural reward processing in individuals remitted from major depression. Psychol Med 45, 3549-3558.

Van der Auwera, S., Peyrot, W.J., Milaneschi, Y., Hertel, J., Baune, B., Breen, G., Byrne, E., Dunn, E.C., Fisher, H., Homuth, G., Levinson, D., Lewis, C., Mills, N., Mullins, N., Nauck, M., Pistis, G., Preisig, M., Rietschel, M., Ripke, S., Sullivan, P., Teumer, A., Volzke, H., Major Depressive Disorder Working Group of the Psychiatric Genomics, C., Boomsma, D.I., Wray, N.R., Penninx, B., Grabe, H., 2018. Genome-wide gene-environment interaction in depression: A systematic evaluation of candidate genes: The childhood trauma working-group of PGC-MDD. Am J Med Genet B Neuropsychiatr Genet 177, 40-49.

Vincze, O., Oláh, J., Zádori, D., Klivényi, P., Vécsei, L., Ovádi, J., 2011. A new myelin protein, TPPP/p25, reduced in demyelinated lesions is enriched in cerebrospinal fluid of multiple sclerosis. Biochem Biophys Res Commun 409, 137-141.

Wang, Q., Shelton, R.C., Dwivedi, Y., 2018. Interaction between early-life stress and FKBP5 gene variants in major depressive disorder and post-traumatic stress disorder: A systematic review and meta-analysis. J Affect Disord 225, 422-428.

Weder, N., Zhang, H., Jensen, K., Yang, B.Z., Simen, A., Jackowski, A., Lipschitz, D., Douglas-Palumberi, H., Ge, M., Perepletchikova, F., O'Loughlin, K., Hudziak, J.J., Gelernter, J., Kaufman, J., 2014. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. J Am Acad Child Adolesc Psychiatry 53, 417-424 e415.

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 13 July 2018).

Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., Burstein, R., Murray, C.J., Vos, T., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382, 1575-1586.

World Health Organization, 2014. Media Centre: Child Maltreatment. Geneva: WHO; 2014. http://www.who.int/news-room/fact-sheets/detail/child-maltreatment (assessed 1 March 2018)

Table 1

A summary of selected articles in this systematic review

ID	Authors	Year	Country	Sample size	Sample characteristics	Measurements of childhood maltreatment	Diagnoses of depression and its scales	Biological samples	DNA methylation methods/kits	Targeted genetic locations and/or genetic variations	Covariates	Major findings
1	Tozzi et al.*	2018	USA	106	Aged 15~65 yrs, MDD +healthy controls	CTQ	MDD, Hamilton Depression Scale, Beck's Depression Inventory	Whole blood	PyroMark Q96 platform, PyroMark CpG Software	Intron 7 region of FKBP5, rs1360780	Age, sex, T allele distribution	Those genetically predisposed individuals carrying a high-risk variant of the gene, childhood maltreatment might induce demethylation of FKBP5. This was in turn associated with structural and functional changes in the inferior frontal orbital gyrus, a relevant area for the clinical symptoms of MDD.
2	Bustamante et al.*	2018	USA	112	A community-based, population-representative cohort	CTQ	MDD, Patient Health Questionnaire (PHQ-9)	Whole blood	Qiagen's Epitect Bisulfite Kit, pyrosequencing	Intron 2, 7 and promoter regions of FKBP5, rs1360780	Age, sex, race, use of antidepressants, PBMC count	DNA methylation in FKBP 5 did not mediate the childhood maltreatment-depression relationship.
3	Smearman et al.*	2016	USA	393	African American adults	CTQ, Traumatic Events Inventory	MDD, Beck's Depression Inventory	Whole blood	EZ DNA Methylation-Gold kit; HumanMethylation 450 BeadChip (Illumina)	18 OXTR CpG sites, 44 SNPs	Age, sex, race, cellular heterogeneity positional effects	Abuse interacted with methylation of multiple OXTR CpG sites to predict psychiatric symptoms.

4	Weder et al.	2014	USA	190	Children	CTQ, Child Behavior Checklist	Depression, Mood and Feelings Questionnaire	Saliva	EZ DNA Methylation-Gold kit; HumanMethylation 450 BeadChip (Illumina)	Whole methylome, >485, 000 CpG sites	Age, sex, and race	Epigenetic changes in ID3, GRIN1, and TPPP genes, in combination with experiences of maltreatment, may confer risk for depression in children.
5	Beach et al.	2013	USA	155	Women adoptee samples	Clinical record of child sexual abuse	MDD, the Structured Assessment for Genetic Studies of Alcoholism	Lumphoblast cells	Bisulfite converted DNA, touchdown PCR procedures	CpG island surrounding exon 1 of 5-HTT	Age, sex, age of mother at birth, biological parent's psychopathol-ogy	Methylation changes didn't mediate the relationship between sexual abuse and depression, with the consideration of biological parents' psychopathology.

Note: MDD=Major Depressive Disorder; * indicates those studies were included both by Part I and II. CTQ= Childhood Trauma Questionnaire. FKBP5= FK506 binding protein 5. PBMC= Peripheral blood mononuclear cell. OXTR= Oxytocin Receptor. 5-HTT=Serotonin transporter. ID3=DNA-Binding Protein Inhibitor. GRIN1= Glutamate Receptor, Ionotropic NMDA 1. TPPP=Tubulin Polymerization Promoting Protein. SNP= Single Nucleotide Polymorphisms.

Table 2

Studied DNA methylation modifications for depression

Studied genes	**Targeted genetic locations and/or genetic variations**	**Markers found in genome-wide studies/** **CpG sites for candidate genes studies**	**Function of gene**	**Results**	**Reference**
FKBP5	Intron 7 region of FKBP5, rs1360780	Intron 7 region of FKBP5	FK506 binding protein 5: immunoregulation and basic cellular processes involving protein folding and trafficking	Those genetically predisposed individuals carrying a high-risk variant of the gene, childhood maltreatment might induce demethylation of FKBP5.	Tozzi et al., 2018
FKBP5	Intron 2, 7 and promoter regions of FKBP5, rs1360780	None	FK506 binding protein 5: immunoregulation and basic cellular processes involving protein folding and trafficking	DNA methylation in FKBP 5 did not mediate the childhood maltreatment-depression relationship.	Bustamante et al., 2018
OXTR	18 OXTR CpG sites, 44 SNPs	Promoter, intron regions of OXTR	Oxytocin Receptor: receptor for oxytocin, mediated by G proteins which activate a phosphatidylinositol-calcium second messenger system	Abuse interacted with methylation of multiple OXTR CpG sites to predict psychiatric symptoms.	Smearman et al., 2016
Whole methylome	Whole methylome, >485,000 CpG sites	Gene body of ID3, GRIN1 and TPPP	DNA-Binding Protein Inhibitor 3: Glutamate Receptor: DNA binding transcription factor activity and protein domain specific binding; Glutamate Ionotropic Receptor NMDA Type Subunit 1: plasticity of synapses, which is believed	Epigenetic changes in ID3, GRIN1, and TPPP genes, in combination with experiences of maltreatment, may confer risk for depression in children.	Weder et al., 2014

			to underlie memory and learning; Tubulin Polymerization Promoting Protein: integrity of the microtubule network		
5-HTT	CpG island surrounding exon 1 of 5-HTT	None	Serotonin transporters: transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons	Methylation changes didn't mediate the relationship between sexual abuse and depression, with the consideration of biological parents' psychopathology.	Beach et al., 2013

Note: FKBP5= FK506 binding protein 5. OXTR= Oxytocin Receptor. 5-HTT=Serotonin transporter. ID3=DNA-Binding Protein Inhibitor. GRIN1= Glutamate Receptor, Ionotropic NMDA 1. TPPP=Tubulin Polymerization Promoting Protein. SNP= Single Nucleotide Polymorphisms.

Appendix 1 Search strategies for each database

Part I: Searching strategy for epigenetic studies

PubMed

((((((((depressive disorder[MeSH Terms]) OR major depressive disorder[Text Word]) OR major depression[Text Word]) OR unipolar depression[Text Word]) OR depression[Text Word]) OR depressed[Text Word]) OR depressive[Text Word])) AND ((((DNA methylation*[MeSH Terms]) OR methylation*[Text Word]) OR epigenetic*[Text Word])) AND (child* AND (abus* OR maltreat* OR neglect OR abandon* OR illtreat* OR ill-treat* OR mal-treat* OR advers* OR trauma* OR ACE*)) Filters: Humans

EMBASE, Medline, PsychoInfo, HealthStar

#1 ("DNA methylation" OR "methylation*" OR epigenetic*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

#2 limit 1 to human

#3 1 and 2

#4 ("depressive disorder" OR"major depressive disorder" OR"major depression" OR"unipolar depression" OR"depression"OR"depressed"OR"depressive").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

#5 limit 4 to human, humans

#6 4 and 5

#7 3 and 6

#8 ("child*" AND ("abus*" OR "maltreat*" OR "neglect" OR "abandon*" OR "illtreat*" OR "ill-treat*" OR "mal-treat*" OR "advers*" OR "trauma*" OR "ACE*")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

#9 7 and 8

Cochrane Library

#1 MeSH descriptor: [Depressive Disorder] explode all trees

#2 "major depressive disorder" or "major depression" or "unipolar depression" or "depressed" or "depression" (Word variations have been searched)

#3 #2 or #1 or "depressive" (Word variations have been searched)

#4 MeSH descriptor: [DNA Methylation] explode all trees

#5 methylation* or epigenetic* (Word variations have been searched)

#6 #4 or #5

#7 #3 and #6

#8 MeSH descriptor: [child maltreatment] explode all trees

#9 child* AND (abus* OR maltreat* OR neglect OR abandon* OR illtreat* OR ill-treat* OR mal-treat* OR advers* OR trauma* OR ACE*)

#10 #8 or #9

#11 #7 and #10

Part II: Searching strategy for studies on both genetic and epigenetic variations

PubMed

(((((((depressive disorder[MeSH Terms]) OR major depressive disorder[Text Word]) OR major depression[Text Word]) OR unipolar depression[Text Word]) OR depression[Text Word]) OR depressed[Text Word]) OR depressive[Text Word])) AND ((((DNA methylation*[MeSH Terms]) OR methylation*[Text Word]) OR epigenetic*[Text Word])) AND (child* AND (abus* OR maltreat* OR neglect OR abandon* OR illtreat* OR ill-treat* OR mal-treat* OR advers* OR trauma* OR ACE*))AND (GWA* OR genetic* OR SNP* OR genome* OR WGA* OR gene*)
Filters: Humans

EMBASE, Medline, PsychoInfor, HealthStar

1 ("DNA methylation" OR "methylation*" OR epigenetic*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

2 limit 1 to human

3 1 and 2

4 ("depressive disorder" OR"major depressive disorder" OR"major depression" OR"unipolar depression" OR"depression"OR"depressed"OR"depressive").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

5 limit 4 to human, humans

6 4 and 5

7 3 and 6

8 ("genome-wide" OR "GWA*" OR "genetic*" OR "SNP*" OR "genome*" OR "WGA*" OR "gene*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

9 ("child*" AND ("abus*" OR "maltreat*" OR "neglect" OR "abandon*" OR "illtreat*" OR "ill-treat*" OR "mal-treat*" OR "advers*" OR "trauma*" OR "ACE*")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

10 7 and 8 and 9

Cochrane Library

#1 MeSH descriptor: [Depressive Disorder] explode all trees

#2 "major depressive disorder" or "major depression" or "unipolar depression" or "depressed" or "depression" (Word variations have been searched)

#3 #2 or #1 or "depressive" (Word variations have been searched)

#4 MeSH descriptor: [DNA Methylation] explode all trees

#5 methylation* or epigenetic* (Word variations have been searched)

#6 #4 or #5

#7 #3 and #6

#8 MeSH descriptor: [Genome-Wide Association Study] explode all trees

#9 GWA* OR genetic* OR SNP* OR genome* OR WGA* OR gene* (Word variations have been searched)

#10 #8 or #9

#11 MeSH descriptor: [child maltreatment] explode all trees

#12 child* AND (abus* OR maltreat* OR neglect OR abandon* OR illtreat* OR ill-treat* OR mal-treat* OR advers* OR trauma* OR ACE*)

#13 #11 or #12

#14 #7 and #10 and #13