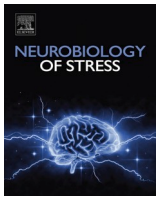
Neurobiology of Stress 23 (2023) 100525

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr



Genetics and epigenetics of stress: New avenues for an old concept

Marina Soliva-Estruch [a,b,c], Kellie L. Tamashiro [d], Nikolaos P. Daskalakis [a,b,*]

[a] Department of Psychiatry, McLean Hospital and Harvard Medical School, Belmont, MA, United States
[b] Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, United States
[c] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, Limburg, The Netherlands
[d] Department of Psychiatry & Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

ARTICLE INFO

Handling Editor: Rita Valentino

Genetics and epigenetics of stress involves the genetic and genetic-by-environmental factors that influence the effects of stress on mental health and disease. The study of the *genetics and epigenetics of stress* is of fundamental importance as stress is widespread among the global population, with over 70% of the population reporting exposure to traumatic events at some point over their lifetime (Benjet et al., 2016). Importantly, trauma exposure is an environmental factor that increases the risk for the development of different psychopathologies, such as post-traumatic stress disorder (PTSD), major depressive disorders (MDD) and anxiety disorders (ANX), collectively referred to as "stress-related disorders" (Smoller, 2016). These disorders are complex and heterogeneous in symptom presentation and biomarker profiles (Jovanovic and Ressler, 2010). They have a polygenic etiology with the genetic risk interacting with diverse environmental exposures across the lifetime to influence disorder liability (Daskalakis et al., 2013). On top of this, these disorders are highly comorbid and, at the molecular level, are characterized by presenting shared and unique dysregulation of biological pathways (Bulik-Sullivan et al., 2015; Gandal et al., 2018). This Special Issue aims to aggregate reviews and original basic, animal, translational and clinical research on the domain. Here, we provide an overview of the 16 papers with the goal of providing context and linking their content.

1. Molecular effects of stress

Stress was defined by Hans Selye as the "non-specific response of the body to any demand for challenge" (Selye, 1936). From a physiological point of view, this means that exposure to stress activates the autonomic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis. The latter is the major neuroendocrine stress-response system, and its activation results in the synthesis and release of glucocorticoids (GC), which bind to glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) (de Kloet et al., 2005). GC-binding to the receptors results in acute and persistent changes in gene expression in central and peripheral tissues (Daskalakis et al., 2022, 2022de Kloet et al., 2005; Johnson et al., 2018). The goal of the initial changes is to orchestrate physiological and behavioral responses, while the persistent changes help the organism to overcome the challenge and better adapt to ongoing and future environmental demands.

One of the processes that is responsible for the persistent stress-induced alterations is the establishment of epigenetic modifications (Meaney and Szyf, 2005). Epigenetic changes encompass a wide variety of chemical processes (e.g., in DNA methylation and post-transcriptional modifications on histone proteins) that dynamically regulate expression of many genes in diverse tissues (Bowman and Poirier, 2015; Kuehner et al., 2019). The reviews of Dick and Chen (2021) and Dion et al. (2022) compiled evidence on changes in the expression of DNA methyltransferases, histone deacetylases (HDACs) and the ten-eleven translocation (TET) family of dioxygenase enzymes after stress exposure and the molecular impact of these changes on behavioral adaptation in response to stress and on the unexposed offspring. Bartlett et al. (2021) studied histone alterations due to acute glucocorticoid elevation in the mouse hippocampus and in a cell culture system. They show that ligand-bound GR induces depletion of histone H3K9me3 at the B2 SINE retrotransposon regions leading to its transcription. The impact of stress on non-coding gene regions is of particular interest as there have been few protein-coding DNA regions that have been associated with etiology of stress-related disorders (Daskalakis et al., 2018).

* Corresponding author. Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, USA.
E-mail address: ndaskalakis@mclean.harvard.edu (N.P. Daskalakis).

https://doi.org/10.1016/j.ynstr.2023.100525
Received 16 January 2023; Received in revised form 6 February 2023; Accepted 6 February 2023
Available online 8 February 2023
2352-2895/© 2023 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

2. Etiology and genetic stress-related disorders

Vulnerability to stress-related mental disorders is traditionally conceptualized under the "diathesis-stress" hypothesis, which states that genetic risk, environmental adversity, and their interaction are the main contributors to disorder liability. In this case, the genetic component helps to explain why some people are more likely than others to develop a pathogenic phenotype after being exposed to stress. However, while it addresses vulnerability, it does not address a path to resilience. The outcome of the myriad of stress-induced molecular alterations can impact both vulnerability and resilience; depending on context they could also help the individual to adapt to new environments and their challenges (Belsky et al., 2009). The more recent "Three-hit concept for vulnerability and resilience", posits that the interaction of genetic predisposition (hit-1) and early-life environment (hit-2) will program the individual's epigenetic and hormonal machinery to adapt in the future environment (hit-3) (Daskalakis et al., 2013). Because this model accounts for the role of the stress response in adaptation, it explains why stress-induced molecular alterations can be expressed as vulnerability in one context and resilience in another.

Over the last two decades, major efforts have been put on international collaborations to study the genetics of stress-related disorders. In this issue, Dalvie et al. (2021) reviewed SNP-based heritability (h^2) of stress related disorders based on recent gene-wide association studies (GWAS) and their genetic correlation, which confirmed their suspected genetic overlap. GWAS also revealed a polygenic architecture, meaning that genetic risk results from the interaction of multiple common variants, spread across the genome, with small effect sizes (Smoller, 2016). Each of the mentioned disorders show different, yet sometimes overlapping risk loci. Current efforts aim to functionally characterize these loci using a variety of post-GWAS approaches and to identify the causal variants and genes. The shared genetic effects are possibly key to understand their high comorbidity.

Among others, HLA-B was found as a risk locus in the largest multicohort PTSD GWAS. The human leukocyte antigen (*HLA*) region is one of the most genetically diverse regions of the genome, it regulates immune and inflammatory processes by presenting antigens to T cells (Trowsdale and Knight, 2013). Katrinli and Smith (2021) reviewed the relationship between HLA and PTSD. At the genetic level, PGC-PTSD GWAS found a significant hit located in the *HLA-B* gene (rs142174523) in a subpopulation of male patients with African American ancestry across 12 cohorts (Nievergelt et al., 2019). Expression quantitative trait locus (eQTL) analysis found rs142174523 to be significantly associated with changes in expression of 16 genes, several of which are involved in inflammatory and immune processes. Moreover, PTSD *HLA* associated alleles cause changes in gene expression networks involved in neural activity (Katrinli et al., 2019). At the epigenetic and transcriptomic levels, multiple associations have been reported and direction is influenced by the nature of trauma (military trauma, childhood abuse) and genetic ancestry.

Finally, GWAS can be used to calculate the polygenic risk scores (PRS) in an independent target population (Fullerton and Nurnberger, 2019; Lewis and Vassos, 2020). These scores may eventually be used as a proxy to predict intra-individual differences emerging after stress exposure. Dalvie et al. (2021) reviewed the accuracy PRSs of stress-related disorders in recent studies of diverse populations. First results have been promising, but Dalvie et al. also emphasized the importance of studying multiple ancestral backgrounds to increase the power and generalizability of the findings.

3. Interaction of genetic risk, trauma and (endo)phenotypes

Although the PRS targets the differences in genetic liability to develop a stress-related phenotype, the PRS often explains a small portion of the phenotypic variance of a stress-related disorder. Therefore, recent risk models have included the effect of exposure to specific traumatic experiences together with PRS to improve predictive ability. In this issue, Daskalakis et al. (2021) studied the association between genetic risk to stress –modeled by PRS-PTSD– and the exposure to environmental stressors to explain variability of preadolescent suicidality in a mixed cohort of European and African ancestry subjects. PRS-PTSD could significantly explain a small proportion of suicidality risk, while 3 environmental stressors (negative life events, family conflict and sexual-orientation discrimination) showed moderate to large effect sizes. In addition, stressors interacted with genetic risk to explain suicidality outcomes. Interestingly, variance on suicidality explained by PRS on the subpopulation exposed to sexual-orientation discrimination was low and did not reach significance, possibly suggesting that genetic effects being less penetrant when the environmental risk is high.

Other research groups in this Special Issue have studied genetic risk of PTSD account by a psychiatric endophenotype [i.e., empathy (Wendt et al., 2022)], and shared genetics between two endophenotypes, resilience and well-being (de Vries et al., 2021). Wendt et al. (2022), using a multivariate generalized linear model showed that polygenic scores (PGS) for empathy explained variability of PTSD symptom severity after accounting for multiple psychiatric PRSs. Importantly, this relationship was the strongest in the patients who experienced childhood maltreatment. de Vries et al. (2021) investigated the causal relationship between resilience and well-being traits. Such traits show high levels of genetic and environmental correlations. Causation was analyzed using an approach based on Mendelian Randomization (Smith and Ebrahim, 2003). Their model used the heritability based on twin studies and the PGS from GWAS from both endophenotypes to determine the causal direction. Results showed significant causal effect from well-being to resilience, whereas causal effect on the other direction could not be fully studied. Overall, these PRS/PGS based investigations contribute to our understanding of the contributions of genetic and environmental risk, and the mediation by endophenotypes.

4. Brain molecular studies of stress-related disorders

Childhood is a sensitive period of heightened brain plasticity, during which external stimuli can lead to changes in the development and refinement of neural circuitry to allow adaptation to the environment (Nelson and Gabard-Durnam, 2020). Thus, environmental stressors during childhood can leave a long-lasting mark that persists into adulthood (Heim et al., 2008). Ibrahim et al. (2021) review brain epigenetic and gene expression changes induced by childhood abuse that alter HPA axis function, myelination and neuron-based signaling.

Most recent studies of postmortem brains tissues from subjects with a history of stress-related disorders focused on the prefrontal cortex (PFC). The PFC is of particular interest since changes in connectivity have been related with stress-related phenotypes (Holmes et al., 2018), and expression of PFC genes have been shown to be altered by genetic risk for PTSD (Huckins et al., 2020; Stein et al., 2021), among others. In this issue, Logue et al. (2021) found differentially expressed genes (DEGs) in the dorsolateral (dl) and ventromedial (vm) PFC of subjects with PTSD. These genes play a role in learning and memory, immune regulation, and myelination with the immune system gene *IL1B* identified as an upstream regulator of PTSD associated genes. Results showed a partial overlap in their transcriptomic signatures of PTSD and MDD. Both showed enrichment of immune-related genes, reflecting the complex relationship between PTSD and central immune function. The study was concordant with Girgenti et al. who performed a transcriptome-wide analysis on 4 dorsal PFC subregions (including the dlPFC) of individuals with PTSD (Girgenti et al., 2021). Zhang et al. (2021) emphasized in their review, both PTSD and MDD have a GABAergic interneuron transcriptional dysregulation; however, PTSD and MDD share few DEGs, suggesting that the dysregulation occurs in different subpopulations of GABAergic interneurons. These results reflect the heterogeneity in cell population and cell function in the brain and suggest that future transcriptomic wide studies using droplet-based

single cell genomics to study RNA expression at the single cell and/or single nucleus level would be beneficial.

Psychiatric disorders, including stress-related disorders, show accelerated epigenetic age, meaning that their cellular age in blood and brain tissue exceeds their chronological age. Wolf et al. (2021) studied epigenetic age, based on DNA methylation (Horvath, 2013), and gene expression in human postmortem cortical tissue from PTSD and alcohol-use disorder (AUD) subjects. Results yielded 11 genes which differentially correlated with epigenetic age in cases compared to controls. Genes were enriched for inflammation and immune related processes. Glucocorticoid, circadian, and oxidative stress-related genes networks were also overrepresented. The authors propose anti-inflammatory innervations to mitigate the pace of cellular aging and increase resilience to aging as a consequence of stress.

Meijer et al. (2021) identified the stress-reactive brain regions in healthy siblings of patients with schizophrenia (considered as the high stress-sensitivity group) and healthy controls that were assessed in an fMRI study. Gene expression from the Allen Human Brain Atlas was compared in the stress-reactive and stress non-reactive regions. The 201 DEGs were functionally enriched for neurodevelopment, neurogenesis, synaptic signal transmission and glutamate receptor signaling. Interestingly, many of these DEGs overlapped with risk loci for schizophrenia found by GWAS, and others are GC targets.

Finally, Ponomareva and Ressler (2021) showed how sexual dimorphism at the genetic, transcriptomic, and gonadal hormone levels interact with the severity of environmental exposure to determine the impact of stress exposure. Regarding trauma exposure, males and females have differences on the prevalence of exposure to certain trauma types, however these differences have not been directly linked with the difference in PTSD prevalence. While some studies have shown sex differences in PTSD prevalence after controlling for type of trauma, pointing to sex as the driver of differences in PTSD prevalence, others point out that environmental exposure (such as history of sexual victimization), rather than sex, as the driving factor. At the genetic level, females show higher heritability of PTSD in initial PTSD GWAS studies (Duncan et al., 2018), and GWAS stratified by sex show differences on the discovered significant loci. At the transcription and epigenetic levels, stress-induced changes are modulated by sex steroid hormone levels (Maddox et al., 2018). One of the genes described is *FKBP5* that encodes an immunophilin protein that interacts with GR/MR and both the androgen and progesterone receptors and might influence estrogen receptor activity, while at the same time, it has been found to be upregulated only in females with PTSD in PFC subregions (Girgenti et al., 2021).

5. Integrative models to improve treatment efficiency

The presented findings reflect the complexity of the underlying molecular etiology of stress-related disorders. However, the complex molecular targets of interventions used to treat stress-related disorders is less studied. In a study by Cordner et al. (2021), mice were exposed to chronic defeat paradigm to induce depressive-like and anxiety-like symptoms. Disease phenotypes were rescued after treatment with fluoxetine or environmental enrichment. To determine the molecular mechanisms that accounted for the stress phenotype and their treatment, gene expression of 168 genes associated with synaptic plasticity and oxidative stress in the amygdala of these animals was studied. Twenty-four genes were differentially expressed due to stress, with 20 of them showing normalization of expression after fluoxetine treatment while just 3 were normalized in the enriched environment group. These results highlight divergent effects of type of treatment intervention on the molecular profiles of brain regions leading to similar behavioral outcomes. Thus, there may be multiple pathways to the same endpoint and studies, such as this one, suggest that different interventions may be considered when developing individualized treatment plans for each patient.

Nasca et al. (2021) sought to identify multidimensional predictors of antidepressant treatment response, in pursuit of personalized medicine strategies. They studied how the mitochondrial mediator of epigenetic function, acetyl-L-carnitine (*LAC*), which influences epigenetic regulation of histone acetylation (Nasca et al., 2013), predicted treatment response of insulin-sensitizing agent pioglitazone together with emotional abuse, BMI, sex, and leucocytes telomere length. The authors interpret the results as indicating that mitochondrial metabolism of LAC acts as a rate limiting substrate on the therapeutic effect of pioglitazone.

6. Conclusion

This Special Issue brings together a series of cutting-edge data papers and reviews that reflect how the studies of the genetics and epigenetics of stress have begun to reveal the complex ways that stress may influence the physiology and behavior of an individual. The body of literature included here underscores the need for determining the causal mechanisms between (traumatic or chronic) stress and mental health, as well as the methodologies needed to untangle this intricate relationship between the genome and environmental stress exposure. Meanwhile, available treatments are limited, and each patient's therapeutic approach is determined empirically and with little consideration of biological criteria, which may account for the alarmingly low treatment efficacy. Incorporation and analysis of multi-dimensional data is necessary to characterize stress-related disorders at the integrated biological systems level (Dalvie et al., 2021). Large multi-omic-wide human studies are expected to facilitate the identification of mechanistic pathways that drive inter-individual differences in mental health outcomes after stress exposure. Together, these types of studies will facilitate attainment of the final goal of this field: to improve and broaden the arsenal of effective treatments for complex and heterogeneous mental illnesses.

CRediT authorship contribution statement

Marina Soliva-Estruch: Writing - original draft, Writing - review & editing. **Kellie L. Tamashiro:** Writing – review & editing. **Nikolaos P. Daskalakis:** Conceptualization, Writing – review & editing.

Declaration of competing interest

In the past 3 years, NP Daskalakis has been a consultant for Sunovion Pharmaceuticals and is on the scientific advisory board for Sentio Solutions and Circular Genomics for unrelated work.

Acknowledgements

This work was supported by NIMH (R01-MH117292, R01-MH10659 and R21-MH121909), Stichting Universitas and the Bontius Foundation.

References

Bartlett, A.A., DeRosa, H., Clark, M., Lapp, H.E., Guffanti, G., Hunter, R.G., 2021. Corticosterone dynamically regulates retrotransposable element expression in the rat hippocampus and C6 cells. Neurobiol Stress 15, 100397.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., Williams, R., 2009. Vulnerability genes or plasticity genes? Mol. Psychiatr. 14, 746–754.

Benjet, C., Bromet, E., Karam, E.G., Kessler, R.C., McLaughlin, K.A., Ruscio, A.M., Shahly, V., Stein, D.J., Petukhova, M., Hill, E., Alonso, J., Atwoli, L., Bunting, B., Bruffaerts, R., Caldas-de-Almeida, J.M., de Girolamo, G., Florescu, S., Gureje, O., Huang, Y., Lepine, J.P., Kawakami, N., Kovess-Masfety, V., Medina-Mora, M.E., Navarro-Mateu, F., Piazza, M., Posada-Villa, J., Scott, K.M., Shalev, A., Slade, T., ten Have, M., Torres, Y., Viana, M.C., Zarkov, Z., Koenen, K.C., 2016. The epidemiology of traumatic event exposure worldwide: results from the World Mental Health Survey Consortium. Psychol. Med. 46, 327–343.

Bowman, G.D., Poirier, M.G., 2015. Post-translational modifications of histones that influence nucleosome dynamics. Chem. Rev. 115, 2274–2295.

Bulik-Sullivan, B., Finucane, H.K., Anttila, V., Gusev, A., Day, F.R., Loh, P.R., ReproGen, C., , Psychiatric Genomics, C., Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control, C., Duncan, L., Perry, J.R., Patterson, N.,

Robinson, E.B., Daly, M.J., Price, A.L., Neale, B.M., 2015. An atlas of genetic correlations across human diseases and traits. Nat. Genet. 47, 1236–1241.
Cordner, Z.A., Marshall-Thomas, I., Boersma, G.J., Lee, R.S., Potash, J.B., Tamashiro, K.L. K., 2021. Fluoxetine and environmental enrichment similarly reverse chronic social stress-related depression- and anxiety-like behavior, but have differential effects on amygdala gene expression. Neurobiol Stress 15, 100392.
Dalvie, S., Chatzinakos, C., Al Zoubi, O., Georgiadis, F., workgroup, P.-P.S.B., Lancashire, L., Daskalakis, N.P., 2021. From genetics to systems biology of stress-related mental disorders. Neurobiol Stress 15, 100393.
Daskalakis, N.P., Bagot, R.C., Parker, K.J., Vinkers, C.H., de Kloet, E.R., 2013. The three-hit concept of vulnerability and resilience: toward understanding adaptation to early-life adversity outcome. Psychoneuroendocrinology 38, 1858–1873.
Daskalakis, N.P., Meijer, O.C., de Kloet, E.R., 2022. Mineralocorticoid receptor and glucocorticoid receptor work alone and together in cell-type-specific manner: implications for resilience prediction and targeted therapy. Neurobiol Stress 18, 100455.
Daskalakis, N.P., Provost, A.C., Hunter, R.G., Guffanti, G., 2018. Noncoding RNAs: stress, glucocorticoids, and posttraumatic stress disorder. Biol. Psychiatr. 83, 849–865.
Daskalakis, N.P., Schultz, L.M., Visoki, E., Moore, T.M., Argabright, S.T., Harnett, N.G., DiDomenico, G.E., Warrier, V., Almasy, L., Barzilay, R., 2021. Contributions of PTSD polygenic risk and environmental stress to suicidality in preadolescents. Neurobiol Stress 15, 100411.
de Kloet, E.R., Joels, M., Holsboer, F., 2005. Stress and the brain: from adaptation to disease. Nat. Rev. Neurosci. 6, 463–475.
de Vries, L.P., Baselmans, B.M.L., Luykx, J.J., de Zeeuw, E.L., Minica, C.C., de Geus, E.J. C., Vinkers, C.H., Bartels, M., 2021. Genetic evidence for a large overlap and potential bidirectional causal effects between resilience and well-being. Neurobiol Stress 14, 100315.
Dick, A., Chen, A., 2021. The role of TET proteins in stress-induced neuroepigenetic and behavioural adaptations. Neurobiol Stress 15, 100352.
Dion, A., Munoz, P.T., Franklin, T.B., 2022. Epigenetic mechanisms impacted by chronic stress across the rodent lifespan. Neurobiol. Stress 17, 100434. https://doi.org/10.1016/j.ynstr.2022.100434.
Duncan, L.E., Ratanatharathorn, A., Aiello, A.E., Almli, L.M., Amstadter, A.B., Ashley-Koch, A.E., Baker, D.G., Beckham, J.C., Bierut, L.J., Bisson, J., Bradley, B., Chen, C. Y., Dalvie, S., Farrer, L.A., Galea, S., Garrett, M.E., Gelernter, J.E., Guffanti, G., Hauser, M.A., Johnson, E.O., Kessler, R.C., Kimbrel, N.A., King, A., Koen, N., Kranzler, H.R., Logue, M.W., Maihofer, A.X., Martin, A.R., Miller, M.W., Morey, R.A., Nugent, N.R., Rice, J.P., Ripke, S., Roberts, A.L., Saccone, N.L., Smoller, J.W., Stein, D.J., Stein, M.B., Sumner, J.A., Uddin, M., Ursano, R.J., Wildman, D.E., Yehuda, R., Zhao, H., Daly, M.J., Liberzon, I., Ressler, K.J., Nievergelt, C.M., Koenen, K.C., 2018. Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. Mol. Psychiatr. 23, 666–673.
Fullerton, J.M., Nurnberger, J.I., 2019. Polygenic risk scores in psychiatry: will they be useful for clinicians? F1000Res 8.
Gandal, M.J., Haney, J.R., Parikshak, N.N., Leppa, V., Ramaswami, G., Hartl, C., Schork, A.J., Appadurai, V., Buil, A., Werge, T.M., Liu, C., White, K.P., CommonMind, C., Psych, E.C., i, P.-B.W.G., Horvath, S., Geschwind, D.H., 2018. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. Science 359, 693–697.
Girgenti, M.J., Wang, J., Ji, D., Cruz, D.A., , Traumatic Stress Brain Research, G, Stein, M. B., Gelernter, J., Young, K.A., Huber, B.R., Williamson, D.E., Friedman, M.J., Krystal, J.H., Zhao, H., Duman, R.S., 2021. Transcriptomic organization of the human brain in post-traumatic stress disorder. Nat. Neurosci. 24, 24–33.
Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology 33, 693–710.
Holmes, S.E., Scheinost, D., DellaGioia, N., Davis, M.T., Matuskey, D., Pietrzak, R.H., Hampson, M., Krystal, J.H., Esterlis, I., 2018. Cerebellar and prefrontal cortical alterations in PTSD: structural and functional evidence. Chronic Stress 2, 1–11 (Thousand Oaks).
Horvath, S., 2013. DNA methylation age of human tissues and cell types. Genome Biol. 14, R115.
Huckins, L.M., Chatzinakos, C., Breen, M.S., Hartmann, J., Klengel, T., da Silva Almeida, A.C., Dobbyn, A., Girdhar, K., Hoffman, G.E., Klengel, C., Logue, M.W., Lori, A., Maihofer, A.X., Morrison, F.G., Nguyen, H.T., Park, Y., Ruderfer, D., Sloofman, L.G., van Rooij, S.J.H., , Consortium, P.W.G.o.P.G., Baker, D.G., Chen, C. Y., Cox, N., Duncan, L.E., Geyer, M.A., Glatt, S.J., Im, H.K., Risbrough, V.B., Smoller, J.W., Stein, D.J., Yehuda, R., Liberzon, I., Koenen, K.C., Jovanovic, T., Kellis, M., Miller, M.W., Bacanu, S.A., Nievergelt, C.M., Buxbaum, J.D., Sklar, P., Ressler, K.J., Stahl, E.A., Daskalakis, N.P., 2020. Analysis of genetically regulated gene expression identifies a prefrontal PTSD gene, SNRNP35, specific to military cohorts. Cell Rep. 31, 107716.
Ibrahim, P., Almeida, D., Nagy, C., Turecki, G., 2021. Molecular impacts of childhood abuse on the human brain. Neurobiol Stress 15, 100343.
Johnson, T.A., Chereji, R.V., Stavreva, D.A., Morris, S.A., Hager, G.L., Clark, D.J., 2018. Conventional and pioneer modes of glucocorticoid receptor interaction with enhancer chromatin in vivo. Nucleic Acids Res. 46, 203–214.
Jovanovic, T., Ressler, K.J., 2010. How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. Am. J. Psychiatr. 167, 648–662.
Katrinli, S., Lori, A., Kilaru, V., Carter, S., Powers, A., Gillespie, C.F., Wingo, A.P., Michopoulos, V., Jovanovic, T., Ressler, K.J., Smith, A.K., 2019. Association of HLA locus alleles with posttraumatic stress disorder. Brain Behav. Immun. 81, 655–658.
Katrinli, S., Smith, A.K., 2021. Immune system regulation and role of the human leukocyte antigen in posttraumatic stress disorder. Neurobiol Stress 15, 100366.
Kuehner, J.N., Bruggeman, E.C., Wen, Z., Yao, B., 2019. Epigenetic regulations in neuropsychiatric disorders. Front. Genet. 10, 268.
Lewis, C.M., Vassos, E., 2020. Polygenic risk scores: from research tools to clinical instruments. Genome Med. 12, 44.
Logue, M.W., Zhou, Z., Morrison, F.G., Wolf, E.J., Daskalakis, N.P., Chatzinakos, C., Georgiadis, F., Labadorf, A.T., Girgenti, M.J., Young, K.A., Williamson, D.E., Zhao, X., Grenier, J.G., , Traumatic Stress Brain Research, G., Huber, B.R., Miller, M. W., 2021. Gene expression in the dorsolateral and ventromedial prefrontal cortices implicates immune-related gene networks in PTSD. Neurobiol Stress 15, 100398.
Maddox, S.A., Kilaru, V., Shin, J., Jovanovic, T., Almli, L.M., Dias, B.G., Norrholm, S.D., Fani, N., Michopoulos, V., Ding, Z., Conneely, K.N., Binder, E.B., Ressler, K.J., Smith, A.K., 2018. Estrogen-dependent association of HDAC4 with fear in female mice and women with PTSD. Mol. Psychiatr. 23, 658–665.
Meaney, M.J., Szyf, M., 2005. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. Dialogues Clin. Neurosci. 7, 103–123.
Meijer, M., Keo, A., van Leeuwen, J.M.C., Dzyubachyk, O., Meijer, O.C., Vinkers, C.H., Mahfouz, A., 2021. Molecular characterization of the stress network in individuals at risk for schizophrenia. Neurobiol Stress 14, 100307.
Nasca, C., Barnhill, O., DeAngelis, P., Watson, K., Lin, J., Beasley, J., Young, S.P., Myoraku, A., Dobbin, J., Bigio, B., McEwen, B., Rasgon, N., 2021. Multidimensional predictors of antidepressant responses: integrating mitochondrial, genetic, metabolic and environmental factors with clinical outcomes. Neurobiol Stress 15, 100407.
Nasca, C., Xenos, D., Barone, Y., Caruso, A., Scaccianoce, S., Matrisciano, F., Battaglia, G., Mathe, A.A., Pittaluga, A., Lionetto, L., Simmaco, M., Nicoletti, F., 2013. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc. Natl. Acad. Sci. U. S. A. 110, 4804–4809.
Nelson 3rd, C.A., Gabard-Durnam, L.J., 2020. Early adversity and critical periods: neurodevelopmental consequences of violating the expectable environment. Trends Neurosci. 43, 133–143.
Nievergelt, C.M., Maihofer, A.X., Klengel, T., Atkinson, E.G., Chen, C.Y., Choi, K.W., Coleman, J.R.I., Dalvie, S., Duncan, L.E., Gelernter, J., Levey, D.F., Logue, M.W., Polimanti, R., Provost, A.C., Ratanatharathorn, A., Stein, M.B., Torres, K., Aiello, A. E., Almli, L.M., Amstadter, A.B., Andersen, S.B., Andreassen, O.A., Arbisi, P.A., Ashley-Koch, A.E., Austin, S.B., Avdibegovic, E., Babic, D., Baekvad-Hansen, M., Baker, D.G., Beckham, J.C., Bierut, L.J., Bisson, J.I., Boks, M.P., Bolger, E.A., Borglum, A.D., Bradley, B., Brashear, M., Breen, G., Bryant, R.A., Bustamante, A.C., Bybjerg-Grauholm, J., Calabrese, J.R., Caldas-de-Almeida, J.M., Dale, A.M., Daly, M. J., Daskalakis, N.P., Deckert, J., Delahanty, D.L., Dennis, M.F., Disner, S.G., Domschke, K., Dzubur-Kulenovic, A., Erbes, C.R., Evans, A., Farrer, L.A., Feeny, N.C., Flory, J.D., Forbes, D., Franz, C.E., Galea, S., Garrett, M.E., Gelaye, B., Geuze, E., Gillespie, C., Uka, A.G., Gordon, S.D., Guffanti, G., Hammamieh, R., Harnal, S., Hauser, M.A., Heath, A.C., Hemmings, S.M.J., Hougaard, D.M., Jakovljevic, M., Jett, M., Johnson, E.O., Jones, I., Jovanovic, T., Qin, X.J., Junglen, A.G., Karstoft, K. I., Kaufman, M.L., Kessler, R.C., Khan, A., Kimbrel, N.A., King, A.P., Koen, N., Kranzler, H.R., Kremen, W.S., Lawford, B.R., Lebois, L.A.M., Lewis, C.E., Linnstaedt, S.D., Lori, A., Lugonja, B., Luykx, J.J., Lyons, M.J., Maples-Keller, J., Marmar, C., Martin, A.R., Martin, N.G., Maurer, D., Mavissakalian, M.R., McFarlane, A., McGlinchey, R.E., McLaughlin, K.A., McLean, S.A., McLeay, S., Mehta, D., Milberg, W.P., Miller, M.W., Morey, R.A., Morris, C.P., Mors, O., Mortensen, P.B., Neale, B.M., Nelson, E.C., Nordentoft, M., Norman, S.B., O'Donnell, M., Orcutt, H.K., Panizzon, M.S., Peters, E.S., Peterson, A.L., Peverill, M., Pietrzak, R.H., Polusny, M.A., Rice, J.P., Ripke, S., Risbrough, V.B., Roberts, A.L., Rothbaum, A.O., Rothbaum, B.O., Roy-Byrne, P., Ruggiero, K., Rung, A., Rutten, B.P. F., Saccone, N.L., Sanchez, S.E., Schijven, D., Seedat, S., Seligowski, A.V., Seng, J.S., Sheerin, C.M., Silove, D., Smith, A.K., Smoller, J.W., Sponheim, S.R., Stein, D.J., Stevens, J.S., Sumner, J.A., Teicher, M.H., Thompson, W.K., Trapido, E., Uddin, M., Ursano, R.J., van den Heuvel, L.L., Van Hooff, M., Vermetten, E., Vinkers, C.H., Voisey, J., Wang, Y., Wang, Z., Werge, T., Williams, M.A., Williamson, D.E., Winternitz, S., Wolf, C., Wolf, E.J., Wolff, J.D., Yehuda, R., Young, R.M., Young, K. A., Zhao, H., Zoellner, L.A., Liberzon, I., Ressler, K.J., Haas, M., Koenen, K.C., 2019. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nat. Commun. 10, 4558.
Ponomareva, O.Y., Ressler, K.J., 2021. Genomic factors underlying sex differences in trauma-related disorders. Neurobiol Stress 14, 100330.
Selye, H., 1936. A syndrome produced by diverse nocuous agents. Nature 138, 32-32.
Smith, G.D., Ebrahim, S., 2003. Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int. J. Epidemiol. 32, 1–22.
Smoller, J.W., 2016. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology 41, 297–319.
Stein, M.B., Levey, D.F., Cheng, Z., Wendt, F.R., Harrington, K., Pathak, G.A., Cho, K., Quaden, R., Radhakrishnan, K., Girgenti, M.J., Ho, Y.A., Posner, D., Aslan, M., Duman, R.S., Zhao, H., , Department of Veterans Affairs Cooperative Studies, P, Program, V.A.M.V., Polimanti, R., Concato, J., Gelernter, J., 2021. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. Nat. Genet. 53, 174–184.
Trowsdale, J., Knight, J.C., 2013. Major histocompatibility complex genomics and human disease. Annu. Rev. Genom. Hum. Genet. 14, 301–323.
Wendt, F.R., Warrier, V., Pathak, G.A., Koenen, K.C., Stein, M.B., Krystal, J.H., Pietrzak, R.H., Gelernter, J., Goldfarb, E.V., Baron-Cohen, S., Polimanti, R., 2022.

Polygenic scores for empathy associate with posttraumatic stress severity in response to certain traumatic events. Neurobiol Stress 17, 100439.
Wolf, E.J., Zhao, X., Hawn, S.E., Morrison, F.G., Zhou, Z., Fein-Schaffer, D., Huber, B., , Traumatic Stress Brain Research, G., Miller, M.W., Logue, M.W., 2021. Gene expression correlates of advanced epigenetic age and psychopathology in postmortem cortical tissue. Neurobiol Stress 15, 100371.
Zhang, J., Kaye, A.P., Wang, J., Girgenti, M.J., 2021. Transcriptomics of the depressed and PTSD brain. Neurobiol Stress 15, 100408.