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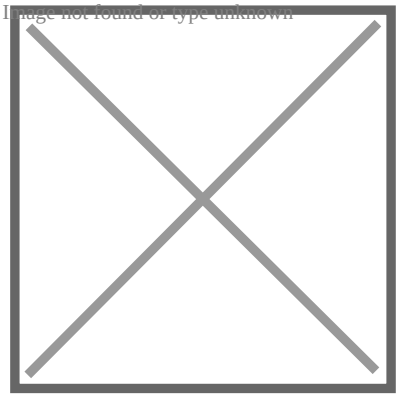

Effects of trauma on personality and genetics

Description

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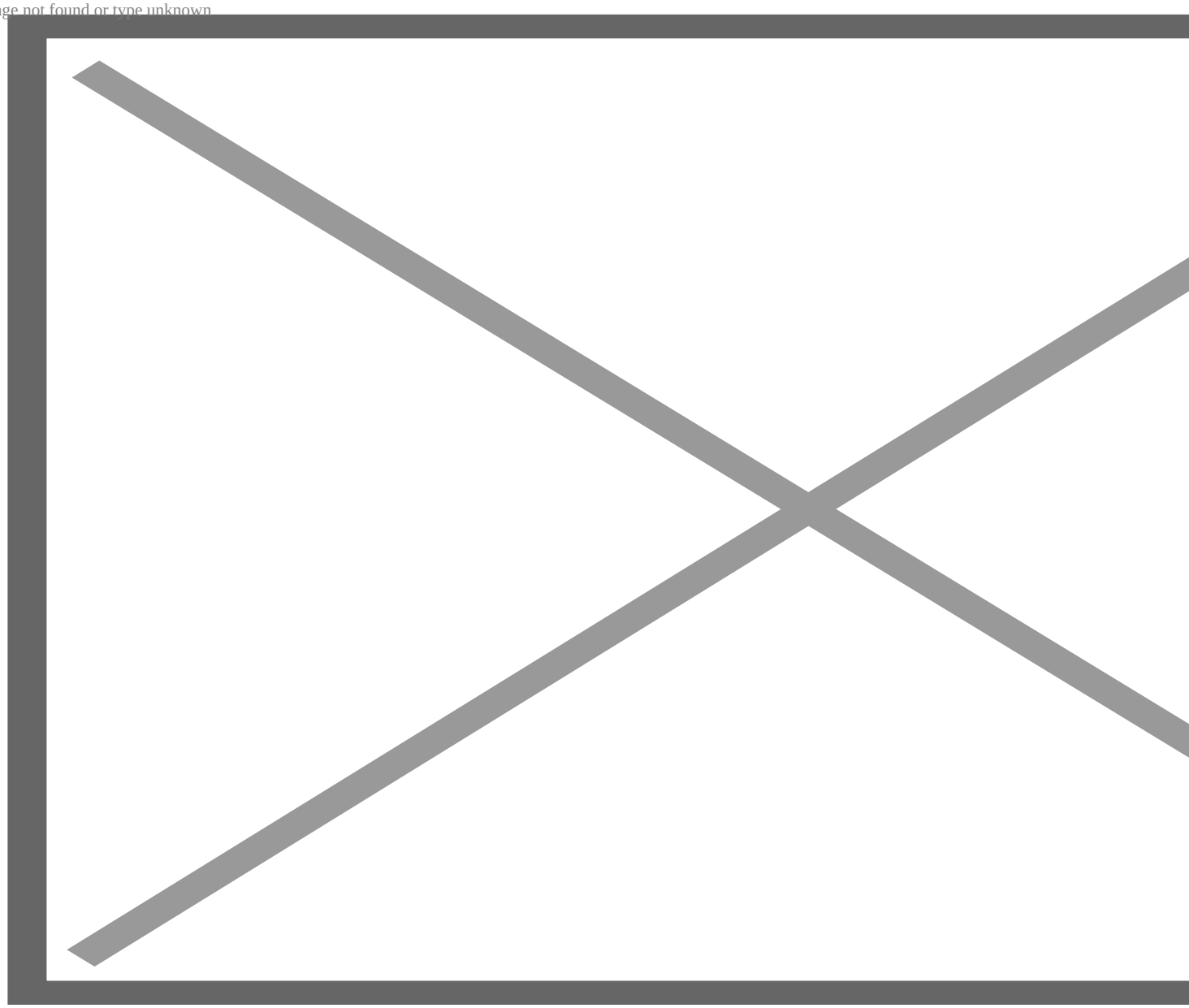

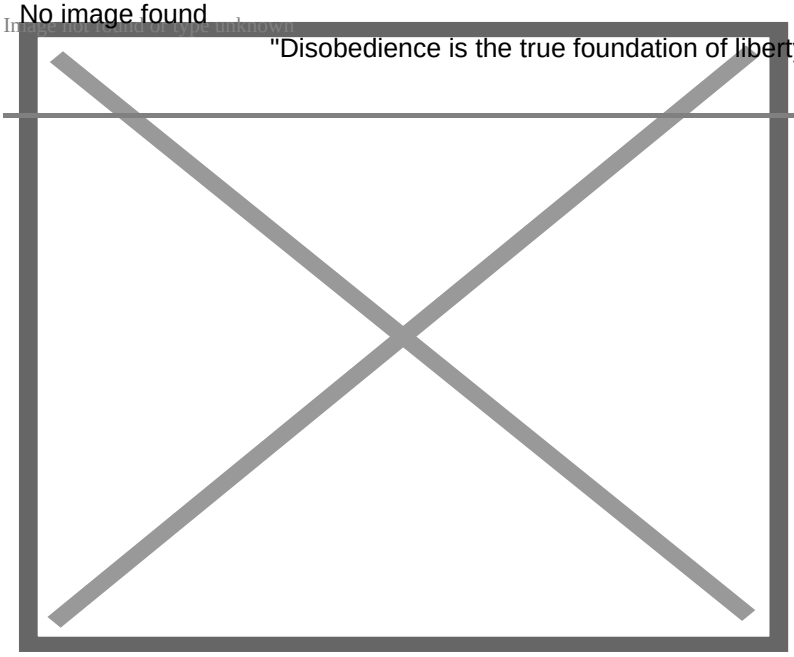

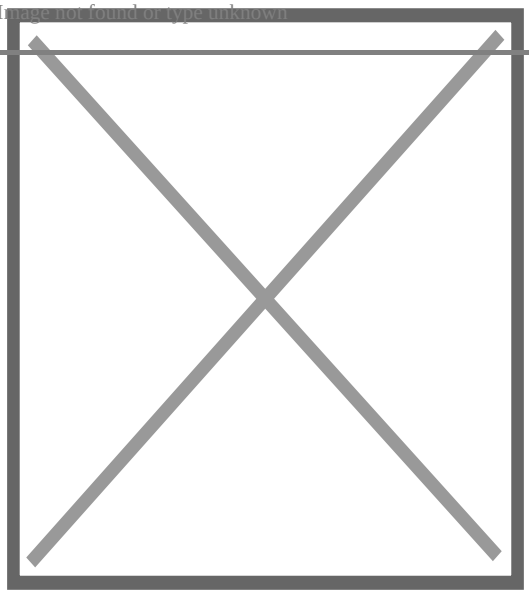

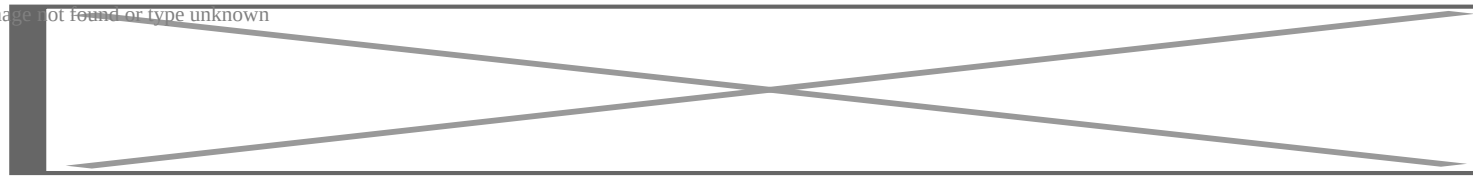

Further References

Pfefferbaum, B., Nitiéma, P., & Newman, E.. (2019). A Meta-analysis of Intervention Effects on Depression and/or Anxiety in Youth Exposed to Political Violence or Natural Disasters. Child and Youth Care Forum

Plain numerical DOI: 10.1007/s10566-019-09494-9
DOI URL
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“Background: meta-analyses of youth mass trauma intervention studies have focused primarily on posttraumatic stress even though depression and anxiety are common maladaptive outcomes that require intervention. objective: this meta-analysis examined youth mass trauma intervention effects on depression and anxiety relative to natural recovery and characteristics of the event, context, population, intervention, and intervention delivery that may have moderated these effects. method: a literature search identified 21 studies investigating the effectiveness of 24 randomized controlled trials with inactive controls (21 trials examined depression and 8 examined anxiety; 5 examined both). intervention effects were computed as hedge’s g estimates and combined using random effects models. moderator analysis computed intervention effect sizes across selected covariates. results: the summary intervention effect was not significant for either depression or anxiety. there were statistically significant effects for depression with interventions delivered following a natural disaster (g = 0.40; p = 0.0192) or in a high income country (g = 0.30; p = 0.0253) and with non-trauma-focused interventions

(g = 0.29; p = 0.0155) and those delivered in more than eight sessions (g = 0.23; p = 0.0416). the effect for anxiety symptoms was significant only with non-trauma-focused interventions (g = 0.83; p = 0.0428). conclusions: given the prevalence of depression and anxiety post event, greater attention is warranted to develop and maximize the benefit of interventions for these outcomes. the findings suggest that trauma-focused interventions may need to be augmented with specific components directed at depression and/or anxiety."
Pfefferbaum, B., Noffsinger, M. A., & Wind, L. H.. (2012). Issues in the assessment of Children's coping in the context of mass trauma. Prehospital and Disaster Medicine

Plain numerical DOI: 10.1017/S1049023X12000702
DOI URL
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"Exposure to mass trauma has contributed to increasing concern about the well-being of children, families, and communities. in spite of global awareness of the dramatic impact of mass trauma on youth, little is known about how children and adolescents cope with and adapt to disasters and terrorism. while coping has yet to be fully conceptualized as a unified construct, the process of responding to stress includes recognized cognitive, emotional, and behavioral components. unfortunately, research on the complex process of adaptation in the aftermath of mass trauma is a relatively recent focus. further study is needed to build consensus in terminology, theory, methods:, and assessment techniques to assist researchers and clinicians in measuring children's coping, both generally and within the context of mass trauma. advancements are needed in the area of coping assessment to identify internal and external factors affecting children's stress responses. additionally, enhanced understanding of children's disaster coping can inform the development of prevention and intervention programs to promote resilience in the aftermath of traumatic events. this article examines the theoretical and practical issues in assessing coping in children exposed to mass trauma, and includes recommendations to guide assessment and research of children's coping within this specialized context. © 2012 copyright world association for disaster and emergency medicine."
Pfefferbaum, B., Nitiéma, P., & Newman, E.. (2021). A critical review of effective child mass trauma interventions: What we know and do not know from the evidence. Behavioral Sciences

Plain numerical DOI: 10.3390/bs11020025
DOI URL
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"Over the last 20 years, numerous interventions have been developed and evaluated for use with children exposed to mass trauma with six publications reporting meta-analyses of randomized controlled trials of child mass trauma interventions using inactive controls to examine intervention effects on posttraumatic stress, depression, anxiety, and functional impairment. the current report reviews the results of these meta-analytic studies to examine the status of the evidence for child mass trauma mental health interventions and to evaluate potential moderators of intervention effect and implications for practice. the meta-analyses reviewed for the current report revealed a small to medium overall effect of interventions on posttraumatic stress, a non-statistically significant to small overall

effect on depression, a non-statistically significant overall effect on anxiety, and a small overall effect on functional impairment. the subgroup analyses suggest that interventions should be matched to the populations being served and to the context. additional research is needed to tailor future interventions to further address outcomes other than posttraumatic stress including depression, anxiety, and functional impairment."
Pfefferbaum, B., Nitiéma, P., & Newman, E.. (2020). The Effect of Interventions on Functional Impairment in Youth Exposed to Mass Trauma: a Meta-Analysis. Journal of Child and Adolescent Trauma

Plain numerical DOI: 10.1007/s40653-019-00266-0
DOI URL
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"This study examined the benefit of psychosocial interventions on functional impairment in youth exposed to mass trauma. a random effects meta-analysis was used to estimate the overall effect in 15 intervention trials identified through a literature review. the moderator analysis examined how the effect of intervention differed across types of populations receiving the intervention (targeted or non-targeted samples), characteristics of intervention delivery (individual or group application and number of sessions), and the context of intervention administration (country income level). the results revealed a significant small effect on functional impairment (hedges' g = 0.33; 95%ci = (0.16; 0.50); p = 0.0011). none of the moderators explained the heterogeneity in intervention effect, perhaps due to the small number of trials. the effect of the interventions on functional impairment and on posttraumatic stress were positively correlated. the current analysis provides preliminary evidence that interventions can improve functioning in youth exposed to mass trauma, but the mechanisms, moderators, and duration of benefit are yet unknown."
Pfefferbaum, B., Nitiéma, P., Newman, E., & Patel, A.. (2019). The Benefit of Interventions to Reduce Posttraumatic Stress in Youth Exposed to Mass Trauma: A Review and Meta-Analysis. Prehospital and Disaster Medicine

Plain numerical DOI: 10.1017/S1049023X19004771
DOI URL
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"Numerous interventions to address posttraumatic stress (pts) in youth exposed to mass trauma have been delivered and evaluated. it remains unclear, however, which interventions work for whom and under what conditions. this report describes a meta-analysis of the effect of youth mass-trauma interventions on pts to determine if interventions were superior to inactive controls and describes a moderator analysis to examine whether the type of event, population characteristics, or income level of the country where the intervention was delivered may have affected the observed effect sizes. a comprehensive literature search identified randomized controlled trials (rcts) of youth mass-trauma interventions relative to inactive controls. the search identified 2,232 references, of which 25 rcts examining 27 trials (n = 4,662 participants) were included in this meta-analysis. intervention effects were computed as hedge's g estimates and combined using a random effects model. moderator

analyses were conducted to explain the observed heterogeneity among effect sizes using the following independent variables: disaster type (political violence versus natural disaster); sample type (targeted versus non-targeted); and income level of the country where the intervention was delivered (high- versus middle-versus low-income). the correlation between the estimates of the intervention effects on pts and on functional impairment was estimated. the overall treatment effect size was converted into a number needed to treat (nnt) for a practical interpretation. the overall intervention effect was statistically significant (g = 0.57; p <.0001), indicating that interventions had a medium beneficial effect on pts. none of the hypothesized moderators explained the heterogeneity among the intervention effects. estimates of the intervention effects on pts and on functional impairment were positively correlated (spearman's r = 0.90; p <.0001), indicating a concomitant improvement in both outcomes. these findings confirm that interventions can alleviate pts and enhance functioning in children exposed to mass trauma. this study extends prior research by demonstrating improvement in pts with interventions delivered to targeted and non-targeted populations, regardless of the country income level. intervention populations and available resources should be considered when interpreting the results of intervention studies to inform recommendations for practice."
Tarvydas, V. M., Levers, L. L., & Teahen, P. R.. (2017). Ethical Guidelines for Mass Trauma and Complex Humanitarian Emergencies. Journal of Counseling and Development

Plain numerical DOI: 10.1002/jcad.12140
DOI URL
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"Issues pertaining to trauma, especially mass trauma and complex humanitarian emergencies, are explored through the lens of ethical counseling guidelines. in mass trauma, particular attention must be paid to the experiences of both survivors and counselors to enhance understanding of ethical best practices and to emphasize the importance of contextual factors in framing effective responses to trauma and humanitarian crises. recommendations regarding ethical guidelines for counseling practice, clinical involvement, and training are offered."
Pfefferbaum, B., Tucker, P., Nitiéma, P., Van Horn, R. L., Varma, V., Varma, Y., … Newman, E.. (2022). Inconclusive Findings in Studies of the Link Between Media Coverage of Mass Trauma and Depression in Children. Current Psychiatry Reports

Plain numerical DOI: 10.1007/s11920-022-01328-1
DOI URL
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"Purpose of review: this paper reports a review of the empirical research examining the association between mass trauma media contact and depression in children, the factors that may influence the association, and the difficulties encountered in the study of media effects on depression. recent findings: all of the included studies assessed general population samples. pre-covid-19 research focused primarily on television coverage alone or on multiple media forms including television, while covid-19 media studies examined various media forms including social media. most studies used cross-sectional design and non-probability sampling. the review revealed inconclusive findings across

studies. summary: the study of mass trauma media effects on depression in children is complicated by a number of potential confounding factors and by the relatively high prevalence of depression in the general population. media contact was a relatively minor consideration among other interests in the extant studies which failed to explore numerous issues that warrant attention in future research." Meffert, S., & Ekblad, S.. (2013). Global mental health intervention research and mass trauma. Open Access Journal of Clinical Trials

Plain numerical DOI: 10.2147/OAJCT.S37037
DOI URL
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"The impact of mass trauma on mental health and the treatment of resulting disorders has been a major focus of global mental health work since the inauguration of the field. descriptive studies in the 1990s provided convincing evidence of the importance of addressing global mental health needs in the aftermath of mass trauma. nonetheless, despite calls to move ahead with interventional research, few studies have tested the effectiveness of the treatments for survivors of mass trauma. in this study, we use a translational science model to review the status of intervention research for adult survivors of mass trauma with the goal of identifying promising treatments, and presenting a logic model for using available data in a manner that is sensitive to community needs, and integrating with existing systems for capacity building. © 2013 meffert and ekblad, publisher and licensee dove medical press ltd." Hobfoll, S. E., Watson, P., Bell, C. C., Bryant, R. A., Brymer, M. J., Friedman, M. J., … Ursano, R. J.. (2007). Five essential elements of immediate and mid-term mass trauma intervention: Empirical evidence. Psychiatry

Plain numerical DOI: 10.1521/psyc.2007.70.4.283
DOI URL
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"Given the devastation caused by disasters and mass violence, it is critical that intervention policy be based on the most updated research findings. however, to date, no evidence-based consensus has been reached supporting a clear set of recommendations for intervention during the immediate and the mid-term post mass trauma phases. because it is unlikely that there will be evidence in the near or mid-term future from clinical trials that cover the diversity of disaster and mass violence circumstances, we assembled a worldwide panel of experts on the study and treatment of those exposed to disaster and mass violence to extrapolate from related fields of research, and to gain consensus on intervention principles. we identified five empirically supported intervention principles that should be used to guide and inform intervention and prevention efforts at the early to mid-term stages. these are promoting: 1) a sense of safety, 2) calming, 3) a sense of self- and community efficacy, 4) connectedness, and 5) hope."

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Husain, M. I., Umer, M., Chaudhry, I. B., Husain, M. O., Rahman, R., Shakoor, S., … Husain, N.. (2021). Relationship between childhood trauma, personality, social support and depression in women attending general medical clinics in a low and middle-income country. Journal of Affective Disorders

Plain numerical DOI: 10.1016/j.jad.2021.06.010
DOI URL
directSciHub download

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“Background: associations between childhood trauma, personality, and major depressive disorder (mdd) have been well established in studies conducted in high-income countries. however, there are limited studies on these associations in low and middle-income countries (lmics), where mdd is highly prevalent. we assessed the relationships between childhood trauma, personality, and mdd in women in karachi, pakistan. method: in this cross-sectional study of 455 female patients attending general medical outpatient clinics, a diagnosis of mdd was confirmed using the structured clinical interview for dsm-iv (scid); retrospective reports of childhood trauma were collected using the childhood trauma questionnaire (ctq); and big five personality traits were assessed using the neo personality inventory revised (neo pi-r). other measures included the life events questionnaire (leq) and the multidimensional scale of perceived social support (mspss). factors independently associated with mdd were determined using logistic regression analyses. results: of the 455 women recruited between august 1, 2011 and july 31, 2013, 242 (53%) had a diagnosis of mdd. women with mdd were significantly more likely to be separated, had more stressful life events and higher ctq scores. higher perceived social support, conscientiousness and extraversion were independently associated with significantly reduced odds of mdd. there were no significant associations between ctq scores and any of the neo pi-r subscales. limitations: ratings of childhood trauma were based on retrospective recall. conclusion: mdd and a history of childhood trauma were highly prevalent in pakistani women attending general medical clinics. interventions to prevent childhood trauma and promote social support in women may improve public mental health in lmics like pakistan.”
Fuchshuber, J., & Unterrainer, H. F.. (2020). Childhood Trauma, Personality, and Substance Use Disorder: The Development of a Neuropsychoanalytic Addiction Model. Frontiers in Psychiatry

Plain numerical DOI: 10.3389/fpsyt.2020.00531
DOI URL
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“Background: while traditional psychoanalysis has been criticized as insufficient for the treatment of substance use disorder (sud), recent progress in the field of neuropsychoanalysis has generated new and promising hypotheses regarding its etiology. however, empirical research applying this framework has been sparse. aim and scope: the present overview aims at developing and empirically validating a neuroscientifically informed psychodynamic framework regarding the etiology of sud. for this purpose, this review provides a concise overview of the most relevant historical and contemporary psychoanalytic theories on sud etiology. furthermore, the original research summarized in this paper consists of three studies investigating connections between childhood trauma, primary emotions,

personality structure and attachment, as well as their relation to sud development and treatment. conclusions: the results highlight the empirical validity of the neuropsychoanalytic approach towards sud etiology. in particular, the findings underscore the conceptualization of sud as a disorder related to dysfunctional attachment and affect regulation abilities especially linked to increased sadness and anger dispositions, which mediated the relationship between sud and traumatic childhood relationships. based on these findings, a refined model of sud etiology is proposed, which should be tested in future studies."
Stevanovi?, A., Fran?iškovi?, T., & Vermetten, E.. (2016). Relationship of early-life trauma, war-related trauma, personality traits, and PTSD symptom severity: A retrospective study on female civilian victims of war. European Journal of Psychotraumatology

Plain numerical DOI: 10.3402/ejpt.v7.30964
DOI URL
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"Background: consequences of war-related traumatisation have mostly been investigated in military and predominant male populations, while research on female civilian victims of war has been neglected. furthermore, research of post-war posttraumatic stress disorder (ptsd) inwomen has rarely included early-life trauma in their prediction models, so the contribution of trauma in childhood and early youth is still unexplored. objective: to examine the relationship of early-life trauma, war-related trauma, personality traits, and symptoms of posttraumatic stress among female civilian victims of the recent war in croatia. method: the cross-sectional study included 394 participants, 293 war-traumatised adult women civilians, and 101 women without war-related trauma. participants were recruited using the snowball sampling method. the applied instruments included the clinician-administrated ptsd scale (caps), the neo personality inventory-revised (neo-pi-r), thewar stressors assessment questionnaire (wsaq), and the early trauma inventory self report-short form (etisr-sf). a hierarchical multiple regression analysis was performed to assess the prediction model of ptsd symptom severity measured by caps score for current ptsd. results: the prevalence of current ptsd (caps cut-off score[1]65) in this cohort was 20.7%. the regression model that included age, early-life trauma, war-related trauma, neuroticism, and extraversion as statistically significant predictors explained 45.8% of variance in ptsd symptoms. conclusions: older age, exposure to early-life trauma, exposure to war-related traumatic events, high neuroticism, and low extraversion are independent factors associated with higher level of ptsd symptoms among women civilian victims of war."
Yalch, M. M., Stewart, A. M., & Dehart, R. M.. (2021). Influence of Betrayal Trauma on Antisocial Personality Disorder Traits. Journal of Trauma and Dissociation

Plain numerical DOI: 10.1080/15299732.2020.1792025
DOI URL
directSciHub download

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"Antisocial personality disorder (aspd) is linked to a number of social problems and accordingly is the focus of intensive empirical study. there is reason to believe that aspd is influenced at least in part by exposure to trauma, but there has been minimal research on the association between trauma and aspd

traits. specifically, research has not examined how traumatic experiences with different degrees of interpersonal betrayal differentially influence aspd traits. this is notable in light of recent studies indicating that exposure to traumatic experiences high in betrayal (i.e., high betrayal trauma) is the primary predictor of borderline and narcissistic personality pathology. in this study, we examined the relative associations between high, medium, and low betrayal trauma and aspd traits in a sample recruited from amazon's mechanical turk (n = 363) using structural equation modeling. results confirmed a strong association between trauma and aspd traits in general, although the influence of specific forms of trauma differed depending on both sex and how trauma was calculated (i.e., in terms of severity vs. exposure). in general, high betrayal trauma was the most consistent predictor of aspd traits for men, whereas medium and low betrayal traumas were more consistently associated with aspd traits for women. study findings extend research on betrayal trauma to more malevolent forms of personality pathology. sex differences in the influence of trauma across aspd traits suggest the possibility of sex-specific personality responses to trauma high in betrayal, a topic that can be addressed in the future research."
Paris, J.. (1998). Does childhood trauma cause personality disorders in adults?. Canadian Journal of Psychiatry

Plain numerical DOI: 10.1177/070674379804300203
DOI URL
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"Objective: to examine the relationship between trauma in childhood and personality disorders in adulthood. method: a review of the literature was conducted. results: the reported associations between trauma and personality pathology are illuminated by the following research findings: 1) personality is heritable; 2) only a minority of patients with severe personality disorders report childhood trauma; and 3) children are generally resilient, and traumatic experiences do not consistently lead to psychopathology. conclusions: the role of trauma in the personality disorders is best understood in the context of gene-environment interactions."
Bahari, A., Hasani, J., & Mashhadi Akbar Boojar, M.. (2021). Childhood trauma and type D personality: The endocrine and cardiovascular effects on stress reactivity. Journal of Health Psychology

Plain numerical DOI: 10.1177/1359105320934181
DOI URL
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"Both exaggerated and blunted cardiovascular stress reactions are associated with health problems. moreover, early life experiences and personality traits affect stress responses. regarding the childhood traumas and type d personality, this study aimed to compare the endocrine and cardiovascular reactions against acute laboratory stress. results showed that the simultaneous existence of childhood traumatic experiences and type d personality leads to exaggerated stress reactivity, while each factor results in a blunted cardiovascular response. although the cardiovascular responses are dampened in type d personality people, their endocrine reactions are exaggerated. the underlying mechanisms of

blunted cardiovascular reactivity differ between childhood trauma and type d personality groups." Rutkowski, K., Dembi?ska, E., & Walczewska, J.. (2016). Effect of trauma onset on personality traits of politically persecuted victims. BMC Psychiatry

Plain numerical DOI: 10.1186/s12888-016-0853-2
DOI URL
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"Background: the hypothesis that traumatic experiences in early childhood impact personality formation and psychopathology is well known in psychology and psychiatry, but this is difficult to verify statistically in methodological terms. the aim of this study, conducted with politically persecuted poles, was to establish the influence of the time when trauma is experienced on the development of psychopathological symptoms. methods: the subjects were divided into two groups: those who had experienced trauma before age five (group 1) and those who experienced trauma at an older age (group 2). subjects in both groups suffered from chronic untreated post-traumatic stress disorder. in order to test the research hypothesis, the minnesota multiphasic personality inventory-2 profiles of both groups were compared using student's t-test, and the mann-whitney u-test. results: statistically significant between-group differences were found for the f validity scale and the following clinical scales: hypochondriasis, depression, psychopathic deviate, psychasthenia, schizophrenia, and social introversion. all the significantly different scores were higher in the group traumatized in early childhood. people exposed to trauma under age five had profiles similar to those traumatized after age five, but they experienced their symptoms more intensely. conclusions: of clinical significance, higher scores on the psychasthenia, schizophrenia, and social introversion scales, especially on the psychopathic deviate scale, indicated pathology only in the early childhood trauma group. taken together, these symptoms lead to withdrawal and hindrance of social functioning. this outcome confirms the hypothesis of the influence of various early childhood factors (such as trauma) on personality formation and personality traits in adulthood."
Sansone, R. A., & Sansone, L. A.. (2007). Childhood trauma, borderline personality, and eating disorders: A development cascade. Eating Disorders

Plain numerical DOI: 10.1080/10640260701454345
DOI URL
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"In this article, we discuss the nature and role of trauma in relationship to borderline personality disorder and eating disorders. as is clinically evident, trauma can result in a variety of psychological consequences. these consequences include both axis i and ii disorders. among the axis ii disorders, trauma appears to heighten the risk for the development of borderline, antisocial, avoidant, paranoid, and even schizotypal personality disorders. likewise, trauma may heighten the risk for developing an eating disorder. there appear to be complex inter-relationships among trauma, borderline personality disorder, and eating disorders. in this article, we attempt to summarize these inter-relationships."
Green, K., & Browne, K.. (2020). Personality Disorder Traits, Trauma, and Risk in Perpetrators of Domestic Violence

. International Journal of Offender Therapy and Comparative Criminology

Plain numerical DOI: 10.1177/0306624X19826516
DOI URL
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“Crimes committed against partners and family members have devastating effects on victims. unfortunately, recidivism rates for offenders are high, and there is a need to establish risk factors that may be potential treatment targets. this study aimed to investigate childhood maltreatment, symptoms of trauma, and personality disorder (pd) traits in males convicted of domestic violence (dv) offences. data were extracted from the files of 40 males under the supervision of the probation service in the united kingdom. actual return to custody was recorded after a minimum follow-up of 6 months. self-reported childhood maltreatment was associated with increases in pd traits, posttraumatic symptoms, and assessed risk. however, maltreatment did not predict return to custody. tension-reducing behaviours and depressive symptoms predicted return to custody as did antisocial pd. these preliminary findings highlight important areas of future research, in particular, factors which may be relevant treatment targets in reducing the risk of recidivism.”
Li, Y., Lv, Q., Li, B., Luo, D., Sun, X., & Xu, J.. (2020). The role of trauma experiences, personality traits, and genotype in maintaining posttraumatic stress disorder symptoms among child survivors of the Wenchuan earthquake. BMC Psychiatry

Plain numerical DOI: 10.1186/s12888-020-02844-1
DOI URL
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“Background: posttraumatic stress disorder (ptsd) is the most prevalent type of psychiatric disorder among children after an earthquake. this study investigated the role of trauma experiences, personality traits, and genotype in the maintenance of ptsd symptoms. methods: in a previous large-scale epidemiological investigation 1 year after the wenchuan earthquake, 215 children with ptsd symptoms were selected at random with their blood samples collected. all of them were followed up, and their ptsd symptoms were assessed 3 years later. the adolescent version of the ucla ptsd reaction index, the earthquake exposure scale, and the junior eysenck personality questionnaire were used to determine ptsd symptoms, trauma experiences, and personality traits, respectively. we sequenced candidate genes involved in the regulation of long-term potentiation via nmda-type receptors to identify the related snp variations. results: being trapped for a longer period of time, feeling one’s own or a family member’s life to be in danger, losing a close family member or friend, extraversion, neuroticism, trkb, g72 and cntf were found to be associated with the maintenance of ptsd symptoms. conclusions: experiences, personality traits, and genotype influenced the maintenance of ptsd in child survivors who were considered to be followed up without medicine. this result could help to identify potential targets for treatment and promote the rational allocation of medical resources.”
Back, S. N., Flechsenhar, A., Bertsch, K., & Zettl, M.. (2021). Childhood Traumatic Experiences and Dimensional Models of Personality Disorder in DSM-5 and ICD-11: Opportunities and Challenges.

Current Psychiatry Reports

Plain numerical DOI: 10.1007/s11920-021-01265-5
DOI URL
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“Purpose of review: childhood trauma is an important risk factor for the development of personality disorders (pds), yet most research has been devoted to categorical models of personality pathology. considering the introduction of a dimensional pd model with icd-11, we review current findings related to various forms of childhood trauma, and pds, operationalized in the form of personality functioning and maladaptive traits. we focus on the magnitude of associations and examine specific relationships between emotional and physical trauma with areas of personality functioning and single traits. recent findings: two studies showed a strong association between childhood trauma and personality dysfunction. seven studies, including clinical and forensic samples, demonstrated heterogeneous associations between various forms of childhood trauma and maladaptive traits. overall, four studies indicated a slightly stronger association between personality dysfunction, maladaptive trait expression, and higher levels of emotional trauma than for physical or sexual trauma. regarding specific trait domains and childhood trauma, most studies yielded the strongest associations for either psychoticism or detachment. summary: research on childhood trauma and dimensional pd models (i.e., personality functioning and traits) has the potential to contribute to a better understanding of their complex relationship. however, high intercorrelations among different types of childhood trauma, areas of personality functioning, and trait domains increase the difficulty of disentangling single effects. more research is needed including clinical and non-western samples, especially considering the upcoming icd-11 classification.”
Sheehan, A. E., Bounoua, N., Miglin, R., Spielberg, J. M., & Sadeh, N.. (2021). A multilevel examination of lifetime aggression: Integrating cortical thickness, personality pathology and trauma exposure. Social Cognitive and Affective Neuroscience

Plain numerical DOI: 10.1093/scan/nsab042
DOI URL
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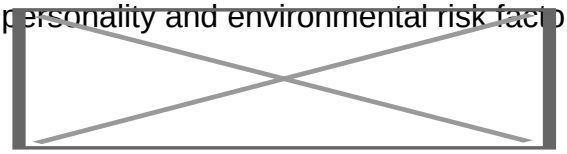
“Aggression represents a significant public health concern, causing serious physical and psychological harm. although many studies have sought to characterize the etiology of aggression, research on the contributions of risk factors that span multiple levels of analysis for explaining aggressive behavior is lacking. to address this gap, we investigated the direct and unique contributions of cortical thickness (level 1), pathological personality traits (level 2) and trauma exposure (level 3) for explaining lifetime physical aggression in a high-risk sample of community adults (n = 129, 47.3% men). first, the frequency of lifetime aggression was inversely associated with cortical thickness in regions of prefrontal and temporal cortices that have been implicated in executive functioning, inhibitory mechanisms and socio-emotional processing. further, aggression was positively associated with pathological personality traits (antagonism and disinhibition) and exposure to assaultive trauma. notably, all three levels of analysis (cortical thickness, pathological personality traits and assaultive

trauma exposure) explained non-overlapping variance in aggressive behavior when examined simultaneously in integrative models. together, the findings provide a multilevel assessment of the biopsychosocial factors associated with the frequency of aggression. they also indicate that cortical thickness explains novel variance in these harmful behaviors not captured by well-established personality and environmental risk factors for aggression."



Watkeys, O. J., Kremerskothen, K., Quidé, Y., Fullerton, J. M., & Green, M. J.. (2018). Glucocorticoid receptor gene (NR3C1) DNA methylation in association with trauma, psychopathology, transcript expression, or genotypic variation: A systematic review. Neuroscience and Biobehavioral Reviews

Plain numerical DOI: 10.1016/j.neubiorev.2018.08.017
DOI URL
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"The glucocorticoid receptor gene (nr3c1) is a critical component of the stress response system. cytosine methylation of nr3c1 has been repeatedly associated with trauma and mental disorders, including major depression, post-traumatic stress disorder, anxiety, and personality disorders, suggesting that nr3c1 methylation may play a role in stress-related psychopathology. we systematically reviewed 55 studies examining nr3c1 dna methylation in association with trauma exposure, psychopathology, gene expression, and/or common genetic variants. overall, a number of nr3c1 cpg sites were significantly associated with trauma or psychopathology, but significant findings were often inconsistent across studies. this lack of consistency is likely influenced by significant methodological variability – experimentally and analytically – across studies. selected common genetic variants show no significant effect on nr3c1 cpg methylation. in contrast, there was ample evidence linking increased methylation of nr3c1 to reduced expression of this gene. the inverse association between methylation and gene expression shown across eight out of ten studies supports the notion that methylation in the promoter region of nr3c1 is associated with transcriptional silencing."
Light, A. E., Holt-Lunstad, J., Porter, C. L., & Light, K. C.. (2019). Early life trauma: An exploratory study of effects on OXTR and NR3C1 gene expression and nurturing self-efficacy in mothers of infants. International Journal of Psychophysiology

Plain numerical DOI: 10.1016/j.ijpsycho.2018.03.018
DOI URL
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"Background: in animals, adverse early experience alters oxytocinergic and glucocorticoid activity and maternal behavior in adulthood. this preliminary study explored associations among childhood trauma (loss of a parent or sexual abuse in childhood), maternal self-efficacy, and leukocyte gene expression (mrna) of oxytocin and glucocorticoid receptors (oxtr and nr3c1) in mothers of infants. methods: 62

mothers (20 with early life trauma) with healthy 3-month old infants reported maternal self-efficacy, depression, infant temperament, and overall social support; the effects of early trauma on these measures were assessed. of these, 35 mothers (14 with early trauma) underwent blood draws after 2 infant feeding times; their oxtr and nr3c1 mrna was compared to a control group of 25 no-infant women without early trauma, and also was examined for associations with self-efficacy. results: oxtr mrna was increased in mothers of infants versus no-infant controls ($p < 0.0003$), and mothers with greatest prior maternal experience had higher oxtr than those with less experience (0–2 vs. 3+ older children, $p < 0.033$). mothers with early trauma and less maternal experience had lower oxtr mrna than no-trauma mothers ($p < 0.029$) and lower nr3c1 mrna than controls ($p < 0.004$). mothers with depression also had lower nr3c1 than other mothers ($p < 0.003$) but did not differ in oxtr. mothers with early trauma also reported their support network to be less helpful and more upsetting and unpredictable than other mothers ($p < 0.035$–$p < 0.005$). regarding maternal behavior, in mothers with early trauma, helpful support networks increased self-reported nurturing self-efficacy when babies were not fussy but decreased it with fussy babies ($p < 0.05$). support was unrelated to self-efficacy in no-trauma mothers. similarly, among mothers with low oxtr or nr3c1 (?1sd, most having early trauma and lower maternal experience), greater support was associated with lower self-efficacy ($p < 0.05$), while mothers with high oxtr or nr3c1 (+1sd) tended to have higher self-efficacy with greater support. conclusions: these preliminary findings need confirmation in a larger sample but suggest that childhood trauma influences maternal behavior and both oxtr and nr3c1 pathways in mothers of infants, and that both depression and prior maternal experience may be other important factors. effects on maternal behavior appear to require more complex modeling."
de Assis Pinheiro, J., Freitas, F. V., Borçoi, A. R., Mendes, S. O., Conti, C. L., Arpini, J. K., … Alvares-da-Silva, A. M.. (2021). Alcohol consumption, depression, overweight and cortisol levels as determining factors for NR3C1 gene methylation. Scientific Reports

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"The nr3c1 glucocorticoid receptor (gr) gene is a component of the stress response system, which can be regulated by epigenetic mechanisms. nr3c1 methylation has been associated with trauma and mental issues, including depression, post-traumatic stress, anxiety, and personality disorders. previous studies have reported that stressful events are involved in nr3c1 gene methylation, suggesting that its regulation under environmental effects is complex. the present study aimed to analyze associations involving stressors such as socioeconomic status, health conditions, and lifestyle in relation to nr3c1 methylation in adults. this study included 386 individual users of the brazilian public unified health system (sus), and evaluated socioeconomic and health conditions, body mass index, cortisol levels, and lifestyle. data were correlated with nr3c1 methylation, determined using dna pyrosequencing. the results showed that alcohol consumption, overweight, and high cortisol levels were related to nr3c1 demethylation, while depression was related to its methylation. habits, lifestyle, and health status may influence nr3c1 gene regulation via methylation, revealing the complexity of environmental impacts on nr3c1 methylation."
Çetin, ?., Sözeri-Varma, G., Çetin, G. O., Türel, S., U?urlu, T. T., & Özdel, O.. (2022). The Relationship Between Methylation of the Glucocorticoid Receptor Gene (NR3C1) and Childhood Trauma and Alexithymia.

Israel Journal of Psychiatry

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“Background: childhood traumas affect the hypothalamo-pituitary-adrenal (hpa) axis functions, and therefore emotional regulation response to stress. glucocorticoid receptor (gr) gene nr3c1 plays a key role in hpa axis. the aim of the study was to investigate the relationship between methylation of nr3c1 gene with childhood trauma and alexithymia in somatic symptom disorder (ssd) and major depressive disorder (mdd). methods: a total of 48 patients with ssd, 50 patients with mdd and 50 healthy controls were included in the study. mongomery-asberg depression rating scale (madrs), toronto alexithymia scale (tas-20), and the childhood trauma questionnaire (ctq) were applied to the participants. methylation levels of the nr3c1 gene were determined quantitatively in dna blood samples. results: tas-20 and ctq total scores were found to be the highest in patients with ssd. ctq scores were observed to be higher in ssd and mdd compared with the control group. nr3c1 gene methylation levels were found to be lowest in ssd and highest in mdd. there was no correlation between scores of tas-20 and nr3c1 methylation. high alexithymia level was predictive for ssd (or: 1.237, 95% ci: 1.018-1.504). high methylation levels increase the risk of mdd (or: 7.449, 95% ci: 3.702-14.986), decrease the risk of ssd (or: 0.00006 95% ci: 0.000-0.038). conclusion: our results show that emotion processing processes and gr methylation are different in both disorders. childhood trauma may be related to epigenetic changes in the gr gene. the type of epigenetic changes may result in vulnerability to different psychiatric disorders.”
Alexander, N., Kirschbaum, C., Wankerl, M., Stauch, B. J., Stalder, T., Steudte-Schmiedgen, S., … Miller, R.. (2018). Glucocorticoid receptor gene methylation moderates the association of childhood trauma and cortisol stress reactivity. Psychoneuroendocrinology

Plain numerical DOI: 10.1016/j.psyneuen.2018.01.020
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“Exposure to childhood trauma (ct) has been linked to sustained dysregulations of major stress response systems, including findings of both exaggerated and attenuated hypothalamus–pituitary–adrenal (hpa) axis activity. likewise, ct constitutes a common risk factor for a broad range of psychiatric conditions that involve distinct neuroendocrine profiles. in this study, we investigated the role of epigenetic variability in a stress-related gene as a potential mediator or moderator of such differential trajectories in ct survivors. for this, we screened adult volunteers for ct and recruited a healthy sample of 98 exposed (67 with mild-moderate, 31 with moderate-severe exposure) and 102 control individuals, with an equal number of males and females in each group. dna methylation (dnam) levels of the glucocorticoid receptor exon 1f promoter (nr3c1-1f) at functionally relevant sites were analyzed via bisulfite pyrosequencing from whole blood samples. participants were exposed to a laboratory stressor (trier social stress test) to assess salivary cortisol stress responses. the major finding of this study indicates that dnam in a biologically relevant region of nr3c1-1f moderates the specific direction of hpa-axis dysregulation (hypo- vs. hyperreactivity) in adults exposed to moderate-severe ct. those trauma survivors with increased nr3c1-1f dnam displayed, on average, 10.4 nmol/l (62.3%) higher peak cortisol levels in response to the tsst compared to those with low dnam. in contrast, unexposed and mildly-moderately exposed individuals displayed moderately sized

cortisol stress responses irrespective of nr3c1-1f dnam. contrary to some prior work, however, our data provides no evidence for a direct association of ct and nr3c1-1f dnam status. according to this study, epigenetic changes of nr3c1-1f may provide a more in-depth understanding of the highly variable neuroendocrine and pathological sequelae of ct."
Vangeel, E. B., Kempke, S., Bakusic, J., Godderis, L., Luyten, P., Van Heddegem, L., … Claes, S.. (2018). Glucocorticoid receptor DNA methylation and childhood trauma in chronic fatigue syndrome patients. Journal of Psychosomatic Research

Plain numerical DOI: 10.1016/j.jpsychores.2017.11.011
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"Objective although the precise mechanisms are not yet understood, previous studies have suggested that chronic fatigue syndrome (cfs) is associated with hypothalamic-pituitary-adrenal (hpa) axis dysregulation and trauma in early childhood. consistent with findings suggesting that early life stress-induced dna methylation changes may underlie dysregulation of the hpa axis, we previously found evidence for the involvement of glucocorticoid receptor (gr) gene (nr3c1) methylation in whole blood of cfs patients. methods in the current study, we assessed nr3c1-1f region dna methylation status in peripheral blood from a new and independent sample of 80 female cfs patients and 91 female controls. in cfs patients, history of childhood trauma subtypes was evaluated using the childhood trauma questionnaire short form (ctq-sf). results although absolute methylation differences were small, the present study confirms our previous findings of nr3c1-1f dna hypomethylation at several cpg sites in cfs patients as compared to controls. following multiple testing correction, only cpg_8 remained significant (dna methylation difference: 1.3% versus 1.5%, $p < 0.001$). in addition, we found associations between dna methylation and severity of fatigue as well as with childhood emotional abuse in cfs patients, although these findings were not significant after correction for multiple testing. conclusions in conclusion, we replicated findings of nr3c1-1f dna hypomethylation in cfs patients versus controls. our results support the hypothesis of hpa axis dysregulation and enhanced gr sensitivity in cfs."
Martín-Blanco, A., Ferrer, M., Soler, J., Salazar, J., Vega, D., Andión, O., … Pascual, J. C.. (2014). Association between methylation of the glucocorticoid receptor gene, childhood maltreatment, and clinical severity in borderline personality disorder. Journal of Psychiatric Research

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"The hypothalamus-pituitary-adrenal axis (hpa) is essential in the regulation of stress responses. increased methylation of the promoter region of the glucocorticoid receptor gene (nr3c1) has been described both in subjects with history of childhood trauma and in patients with borderline personality disorder (bpd). however, no data on the possible association between a higher methylation of this gene and clinical severity is available. the aim of this study was to evaluate the association between nr3c1 methylation status, the history of childhood trauma, and current clinical severity in subjects with bpd. a sample of 281 subjects with bpd (diagnosed by scid-ii and dib-r semi-structured diagnostic interviews)

was recruited. clinical variables included previous hospitalizations, self-injurious behavior, and self-reported history of childhood trauma. dna was extracted from peripheral blood. the results indicated a significant positive correlation between nr3c1 methylation status and childhood maltreatment (specifically physical abuse). in addition, a positive correlation between methylation status and clinical severity (dib-r total score and hospitalizations) was observed. these findings suggest that nr3c1 methylation in subjects with bpd may be associated not only with childhood trauma but also with clinical severity, adding new evidence to the involvement of gene-environment interactions in this disorder. © 2014 elsevier ltd."
Perroud, N., Dayer, A., Piguet, C., Nallet, A., Favre, S., Malafosse, A., & Aubry, J. M.. (2014). Childhood maltreatment and methylation of the glucocorticoid receptor gene NR3C1 in bipolar disorder . British Journal of Psychiatry

Plain numerical DOI: 10.1192/bjp.bp.112.120055
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"Background early-life adversities represent risk factors for the development of bipolar affective disorder and are associated with higher severity of the disorder. this may be the consequence of a sustained alteration of the hypothalamic-pituitary-adrenal (hpa) axis resulting from epigenetic modifications of the gene coding for the glucocorticoid receptor (nr3c1). aims to investigate whether severity of childhood maltreatment isassociated with increased methylation of the exon 1f nr3c1 promoter in bipolar disorder. method a sample of people with bipolar disorder (n = 99) were assessed for childhood traumatic experiences. the percentage of nr3c1 methylation was measured for each participant.results the higher the number of trauma events, the higher was the percentage of nr3c1 methylation (? = 0.52, 95% ci 0.46-0.59, p"0.0001). the severity of each type of maltreatment (sexual, physical and emotional) was also associated with nr3c1 methylation status. conclusionsearly-life adversities have a sustained effect on the hpa axis through epigenetic processes and this effect may be measured in peripheral blood. this enduring biological impact of early trauma may alter the development of the brain and lead to adult psychopathological disorder. declaration of interest none."
Straight, B., Fisher, G., Needham, B. L., Naugle, A., Olungah, C., Wanitjirattikal, P., … Lalancette, C.. (2021). Lifetime stress and war exposure timing may predict methylation changes at NR3C1 based on a pilot study in a warrior cohort in a small-scale society in Kenya. American Journal of Human Biology

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"Objectives: candidate gene methylation studies of nr3c1 have identified associations with psychosocial adversity, including war trauma. this pilot study (sample sizes from 22 to 45 for primary analyses) examined nr3c1 methylation in a group of kenyan pastoralist young men in relation to culturally relevant traumatic experiences, including participation in coalitional lethal gun violence. methods: adolescent and young adult samburu men ('warriors') were recruited for participation. dna was obtained from whole saliva and methylation analyses performed using mass spectrometry. we

performed a data reduction of variables from a standardized instrument of lifetime stress using a factor analysis and we assessed the association between the extracted factors with culturally relevant and cross-culturally comparative experiences. results: cumulative lifetime trauma exposure and forms of violence to which warriors are particularly susceptible were associated with dna methylation changes in the nr3c1 1f promoter region but not in the nr3c1 1d promoter region. however, sensitivity analyses revealed significant associations between individual cpg sites in both regions and cumulative stress exposures, war exposure timing, and war fatalities. conclusions: this study supports the importance of nr3c1 methylation changes in response to challenging life circumstances, including in a global south cultural context that contrasts in notable ways from global north contexts and from the starkly tragic examples of the rwandan genocide and war-associated rape explored in recent studies. timing of traumatic exposure and culturally salient means to measure enduring symptoms of trauma remain important considerations for dna methylation studies."
Malhi, G. S., Das, P., Outhred, T., Dobson-Stone, C., Irwin, L., Gessler, D., … Mannie, Z.. (2019). Effect of stress gene-by-environment interactions on hippocampal volumes and cortisol secretion in adolescent girls. Australian and New Zealand Journal of Psychiatry

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"Objective: adolescence is a time of increased susceptibility to environmental stress and mood disorders, and girls are particularly at risk. genes interacting with the environment (g × e) are implicated in hypothalamic-pituitary-adrenal axis dysregulation, hippocampal volume changes and risk or resilience to mood disorders. in this study, we assessed the effects of stress system g × e interactions on hippocampal volumes and cortisol secretion in adolescent girls. methods: we recruited 229 girls aged 12–18 years, and scans were obtained from 202 girls. of these, 76 had been exposed to higher emotional trauma (abuse or neglect). hippocampal volumes were measured using freesurfer and high-resolution structural magnetic resonance imaging scans. saliva samples were collected for measurement of cortisol levels and genotyping of stress system genes: fkbp5, nr3c1 (both n = 194) and nr3c2 (n = 193). results: among girls with the 'g' allelic variant of the nr3c1 gene, those who had been exposed to higher emotional trauma had significantly smaller left hippocampal volumes (n = 44; mean = 4069.58 mm 3 , standard deviation = 376.99) than girls who had been exposed to minimal emotional trauma with the same allelic variant (n = 69; mean = 4222.34 mm 3 , standard deviation = 366.74). conclusion: in healthy adolescents, interactions between emotional trauma and the 'protective' nr3c1 'gg' variant seem to induce reductions in left hippocampal volumes. these g × e interactions suggest that vulnerability to mood disorders is perhaps driven by reduced 'protection' that may be specific to emotional trauma. this novel but preliminary evidence has implications for targeted prevention of mood disorders and prospective multimodal neuroimaging and longitudinal studies are now needed to investigate this possibility."
Smart, C., Strathdee, G., Watson, S., Murgatroyd, C., & McAllister-Williams, R. H.. (2015). Early life trauma, depression and the glucocorticoid receptor gene-an epigenetic perspective. Psychological Medicine

Plain numerical DOI: 10.1017/S0033291715001555

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“Hopes to identify genetic susceptibility loci accounting for the heritability seen in unipolar depression have not been fully realized. family history remains the ‘gold standard’ for both risk stratification and prognosis in complex phenotypes such as depression. meanwhile, the physiological mechanisms underlying life-event triggers for depression remain opaque. epigenetics, comprising heritable changes in gene expression other than alterations of the nucleotide sequence, may offer a way to deepen our understanding of the aetiology and pathophysiology of unipolar depression and optimize treatments. a heuristic target for exploring the relevance of epigenetic changes in unipolar depression is the hypothalamic-pituitary-adrenal (hpa) axis. the glucocorticoid receptor (gr) gene (nr3c1) has been found to be susceptible to epigenetic modification, specifically dna methylation, in the context of environmental stress such as early life trauma, which is an established risk for depression later in life. method. in this paper we discuss the progress that has been made by studies that have investigated the relationship between depression, early trauma, the hpa axis and the nr3c1 gene. difficulties with the design of these studies are also explored. results. future efforts will need to comprehensively address epigenetic natural histories at the population, tissue, cell and gene levels. the complex interactions between the epigenome, genome and environment, as well as ongoing nosological difficulties, also pose significant challenges. conclusions. the work that has been done so far is nevertheless encouraging and suggests potential mechanistic and biomarker roles for differential dna methylation patterns in nr3c1 as well as novel therapeutic targets.”
Qi, R., Luo, Y., Zhang, L., Weng, Y., Surento, W., Xu, Q., … Thompson, P. M.. (2021). Decreased functional connectivity of hippocampal subregions and methylation of the NR3C1 gene in Han Chinese adults who lost their only child. Psychological Medicine

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“Background losing one’s only child is a major traumatic life event that may lead to post-traumatic stress disorder (ptsd); however, the underlying mechanisms of its psychological consequences remain poorly understood. here, we investigated subregional hippocampal functional connectivity (fc) networks based on resting-state functional magnetic resonance imaging and the deoxyribonucleic acid methylation of the human glucocorticoid receptor gene (nr3c1) in adults who had lost their only child. methods a total of 144 han chinese adults who had lost their only child (51 adults with ptsd and 93 non-ptsd adults [trauma-exposed controls]) and 50 controls without trauma exposure were included in this fmri study (age: 40-67 years). fcs between hippocampal subdivisions (four regions in each hemisphere: cornu ammonis1 [ca1], ca2, ca3, and dentate gyrus [dg]) and methylation levels of the nr3c1 gene were compared among the three groups. results trauma-exposed adults, regardless of ptsd diagnosis, had weaker positive fc between the left hippocampal ca1, left dg, and the posterior cingulate cortex, and weaker negative fc between the right ca1, right dg, and several frontal gyri, relative to healthy controls. compared to non-ptsd adults, ptsd adults showed decreased negative fc between the right

ca1 region and the right middle/inferior frontal gyri (mfg/ifg), and decreased negative fc between the right dg and the right superior frontal gyrus and left mfg. both trauma-exposed groups showed lower methylation levels of the nr3c1 gene. conclusions adults who had lost their only child may experience disrupted hippocampal network connectivity and nr3c1 methylation status, regardless of whether they have developed ptsd."
Schür, R. R., van Leeuwen, J. M. C., Houtepen, L. C., Joëls, M., Kahn, R. S., Boks, M. P., & Vinkers, C. H.. (2018). Glucocorticoid receptor exon 1 F methylation and the cortisol stress response in health and disease. Psychoneuroendocrinology

Plain numerical DOI: 10.1016/j.psyneuen.2018.07.018
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"Childhood trauma has been proposed to increase vulnerability to develop psychopathology in part through an altered cortisol stress response. research in rats has suggested that this effect is mediated by methylation in the glucocorticoid receptor 1 7 region (gr-1 7 or gr-1 f in humans), with higher methylation after poor maternal care leading to an increased cortisol stress response in adulthood. in humans, the associations between childhood trauma and gr-1 f methylation or the cortisol stress response are equivocal. remarkably, evidence for the relation between gr-1 f methylation and the cortisol stress response has been conflicting as well. to further explore this, we investigated the associations of peripheral gr-1 f methylation (52 cpgs) with the cortisol stress response (trier social stress test) and with childhood trauma in three independent studies (total n = 241) including healthy controls, patients with schizophrenia and bipolar disorder and unaffected siblings of patients with one of these disorders. we did not find any significant association between gr-1 f methylation and the cortisol stress response (areas under the curve) or childhood trauma, nor did we observe any group differences between patients, siblings and healthy controls. our findings do not support gr-1 f methylation as a proxy for the cortisol stress response, nor its link with childhood trauma or psychopathology. these results suggest that multifactorial models for stress-related psychopathology are needed. alternatively, future longitudinal studies may reveal gr-1 f methylation to be a useful parameter at an individual level."
Yehuda, R., Flory, J. D., Bierer, L. M., Henn-Haase, C., Lehrner, A., Desarnaud, F., … Meaney, M. J.. (2015). Lower Methylation of Glucocorticoid Receptor Gene Promoter 1F in Peripheral Blood of Veterans with Posttraumatic Stress Disorder. Biological Psychiatry

Plain numerical DOI: 10.1016/j.biopsych.2014.02.006
DOI URL
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"BACKGROUND: enhanced glucocorticoid receptor (gr) sensitivity is present in people with posttraumatic stress disorder (ptsd), but the molecular mechanisms of gr sensitivity are not understood. epigenetic factors have emerged as one potential mechanism that account for how trauma exposure leads to sustained ptsd symptoms given that ptsd develops in only a subset of trauma survivors. methods: cytosine methylation of a relevant promoter of the gr gene (nr3c1-1f promoter) and

three functional neuroendocrine markers of hypothalamic-pituitary-adrenal axis function were examined in a sample of 122 combat veterans. results: lower nr3c1-1f promoter methylation in peripheral blood mononuclear cells (pbmcs) was observed in combat veterans with ptsd compared with combat-exposed veterans who did not develop ptsd. nr3c1-1f promoter methylation was also associated with three functional measures of glucocorticoid activity that have been associated with ptsd in combat veterans: pbmcs' lysozyme inhibition on the lysozyme suppression test, plasma cortisol decline on the low-dose (.50 mg) dexamethasone suppression test, and 24-hour urinary cortisol excretion. finally, nr3c1-1f promoter methylation was inversely correlated with clinical markers and symptoms associated with ptsd. conclusions: alterations in nr3c1-1f promoter methylation may reflect enduring changes resulting from combat exposure that lead to functional neuroendocrine alterations. because epigenetic measures are thought to reflect enduring effects of environmental exposures, they may be useful in distinguishing combat-exposed veterans who do or do not develop ptsd."
Vangeel, E., Van Den Eede, F., Hompes, T., Izzi, B., Del Favero, J., Moorkens, G., … Claes, S.. (2015). Chronic fatigue syndrome and DNA hypomethylation of the glucocorticoid receptor gene promoter 1F Region: Associations with HPA Axis Hypofunction and childhood trauma. Psychosomatic Medicine

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"Objectives: chronic fatigue syndrome (cfs) has been associated with hypothalamic-pituitary-adrenal axis hypofunction and enhanced glucocorticoid receptor (gr) sensitivity. in addition, childhood trauma is considered a major risk factor for the syndrome. this study examinesdna methylation of the gr gene (nr3c1) in cfs and associations with childhood sexual and physical trauma. methods: quantification of dna methylation within the 1f promoter region of nr3c1 was performed in 76 female patients (46 with no/mild and 30 with moderate/severe childhood trauma) and 19 healthy controls by using sequenom epityper. further, we examined the association of nr3c1-1f promoter methylation with the outcomes of the low-dose (0.5 mg) dexamethasone/corticotropin-releasing factor test in a subset of the study population. mann-whitney u tests and spearman correlations were used for statistical analyses. results: overall nr3c1-1f dna methylation was lower in patients with cfs than in controls. after cytosine guanine dinucleotide (cpg)-specific analysis, cpg-1.5 remained significant after bonferroni correction (adjusted p = .0014).within the cfs group, overall methylation (p = 0.477, p = .016) and selective cpg units (cpg-1.5: p = 0.538, p = .007; cpg-12.13: p = 0.448, p = .025) were positively correlated with salivary cortisol after dexamethasone administration. there was no significant difference in nr3c1-1f methylation between traumatized and nontraumatized patients. conclusions:we found evidence of nr3c1 promoter hypomethylation in female patients with cfs and the functional relevance of these differences was consistent with the hypothalamic-pituitary-adrenalaxis hypofunction hypothesis (gr hypersuppression). however, we found no evidence of an additional effect of childhood trauma on cfs via alterations in nr3c1 methylation."
Fiacco, S., Gardini, E. S., Mernone, L., Schick, L., & Ehlert, U.. (2019). DNA Methylation in Healthy Older Adults With a History of Childhood Adversity—Findings From the Women 40+ Healthy Aging Study. Frontiers in Psychiatry

Plain numerical DOI: 10.3389/fpsyt.2019.00777

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“Background: adversity in early development seems to increase the risk of stress-related somatic disorders later in life. physiologically, functioning of the hypothalamic–pituitary–adrenal and hypothalamic–pituitary–gonadal axes is often discussed as long-term mediators of risk. in particular, dna methylation in the glucocorticoid receptor gene promoter (nr3c1) has been associated with type and strength of early life adversity and subsequent effects on hpa axis signaling in humans. animal studies, moreover, suggest changes in dna methylation in the estrogen receptor gene (er?) upon early life adversity. we investigated the association of type and severity of childhood adversity with methylation in nr3c1 and er? and additionally considered associations between methylation and steroid hormone secretion. methods: the percentage of methylation within the nr3c1 promoter and the er? shore was investigated using dried blood spot samples of 103 healthy women aged 40–73 years. childhood adversity was examined with the childhood trauma questionnaire. linear regression analyses were performed with methylation as dependent variable and the experience of emotional abuse and neglect, physical abuse and neglect, and sexual abuse (compared to non-experience) as independent variables. all analyses were controlled for age, bmi, annual household income, and smoking status and were adjusted for multiple testing. results: overall, over 70% of the sample reported having experienced any kind of abuse or neglect of at least low intensity. there were no significant associations between childhood adversity and methylation in the nr3c1 promoter (all p >.10). participants reporting emotional abuse showed significantly higher methylation in the er? shore than those who did not (p =.001). additionally, higher levels of adversity were associated with higher levels of er? shore methylation (p =.001). conclusion: in healthy women, early life adversity does not seem to result in nr3c1 promoter hypermethylation in midlife and older age. this is the first study in humans to suggest that childhood adversity might, however, epigenetically modify the er? shore. further studies are needed to gain a better understanding of why some individuals remain healthy and others develop psychopathologies in the face of childhood adversity.”
Perroud, N., Paoloni-Giacobino, A., Prada, P., Olié, E., Salzmann, A., Nicastro, R., … Malafosse, A.. (2011). Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: A link with the severity and type of trauma. Translational Psychiatry

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“Childhood maltreatment, through epigenetic modification of the glucocorticoid receptor gene (nr3c1), influences the hypothalamic-pituitary- adrenal axis (hpa axis). we investigated whether childhood maltreatment and its severity were associated with increased methylation of the exon 1 f nr3c1 promoter, in 101 borderline personality disorder (bpd) and 99 major depressive disorder (mdd) subjects with, respectively, a high and low rate of childhood maltreatment, and 15 mdd subjects with comorbid post-traumatic stress disorder (ptsd). childhood sexual abuse, its severity and the number of type of maltreatments positively correlated with nr3c1 methylation (p=6.16 × 10-8, 5.18 × 10-7 and 1.25 × 10-

9, respectively). in bpd, repetition of abuses and sexual abuse with penetration correlated with a higher methylation percentage. peripheral blood might therefore serve as a proxy for environmental effects on epigenetic processes. these findings suggest that early life events may permanently impact on the hpa axis though epigenetic modifications of the nr3c1. this is a mechanism by which childhood maltreatment may lead to adulthood psychopathology. © 2011 macmillan publishers limited all rights reserved."
Womersley, J. S., Martin, L. I., van der Merwe, L., Seedat, S., & Hemmings, S. M. J.. (2018). Hypothalamic-pituitary-adrenal axis variants and childhood trauma influence anxiety sensitivity in South African adolescents. Metabolic Brain Disease

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"Anxiety sensitivity (as) is characterised by the fear of anxiety-related symptoms and is a risk factor for the development of anxiety-related disorders. we examined whether genetic variation in three stress response genes, crhr1, nr3c1, and fkbp5, interact with childhood trauma (ct) to predict as in south african adolescents. xhosa (n = 634) and coloured (n = 317) students completed self-report measures of as and ct, and a total of eighteen polymorphisms within crhr1, nr3c1, and fkbp5 were genotyped. differences in as based on genetic variation and ct were analysed within population and gender groups using multiple linear regression. associations were found between as and fkbp5 rs9296158 (p = 0.025) and rs737054 (p = 0.045) in coloured males. analysis of gene x ct interactions indicated that nr3c1 rs190488 cc-genotype, nr3c1 rs10482605 g-allele addition, and fkbp5 rs3800373 c-allele addition protect against as with increasing ct in xhosa females (p = 0.009), xhosa males (p = 0.036) and coloured males (p = 0.049), respectively. we identified two different protective single nucleotide polymorphism (snp) combinations in a four-snp crhr1 haplotype in coloured males. an analysis of the interaction between ct and a six-snp fkbp5 haplotype in coloured males revealed both protective and risk allelic combinations. our results provide evidence for the influence of both genetic variation in crhr1, nr3c1 and fkbp5, as well as ct x snp interactions, on as in south african adolescents. this study reinforces the importance of examining the influence of gene-environment (g x e) interactions within gender and population groups."
Rovaris, D. L., Mota, N. R., Bertuzzi, G. P., Aroche, A. P., Callegari-Jacques, S. M., Guimarães, L. S. P., … Grassi-Oliveira, R.. (2015). Corticosteroid receptor genes and childhood neglect influence susceptibility to crack/cocaine addiction and response to detoxification treatment. Journal of Psychiatric Research

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"The aim of this study was to analyze hypotheses-driven gene-environment and gene-gene interactions in smoked (crack) cocaine addiction by evaluating childhood neglect and polymorphisms in mineralocorticoid and glucocorticoid receptor genes (nr3c2 and nr3c1, respectively). one hundred thirty-

nine crack/cocaine-addicted women who completed 3 weeks of follow-up during early abstinence composed our sample. childhood adversities were assessed using the childhood trauma questionnaire (ctq), and withdrawal symptoms were assessed using the cocaine selective severity assessment (cssa) scale. conditional logistic regression with counterfactuals and generalized estimating equation modeling were used to test gene-environment and gene-gene interactions. we found an interaction between the rs5522-val allele and childhood physical neglect, which altered the risk of crack/cocaine addiction (odds ratio=4.0, p=0.001). moreover, a nr3c2-nr3c1 interaction (p = 0.002) was found modulating the severity of crack/cocaine withdrawal symptoms. in the post hoc analysis, concomitant carriers of the nr3c2 rs5522-val and nr3c1 rs6198-g alleles showed lower overall severity scores when compared to other genotype groups (p-values ? 0.035). this gene-environment interaction is consistent with epidemiological and human experimental findings demonstrating a strong relationship between early life stress and the hypothalamic-pituitary-adrenal (hpa) axis dysregulation in cocaine addiction. additionally, this study extended in crack/cocaine addiction the findings previously reported for tobacco smoking involving an interaction between nr3c2 and nr3c1 genes."
Holmes, L., Shutman, E., Chinaka, C., Deepika, K., Pelaez, L., & Dabney, K. W.. (2019). Aberrant epigenomic modulation of glucocorticoid receptor gene (NR3C1) in early life stress and major depressive disorder correlation: Systematic review and quantitative evidence synthesis. International Journal of Environmental Research and Public Health

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"Early life stress (els) induced by psychological trauma, child maltreatment, maternal separation, and domestic violence predisposes to psycho-behavioral pathologies during adulthood, namely major depressive disorder (mdd), anxiety, and bipolar affective disorder. while environmental data are available in illustrating this association, data remain to be established on the epigenomic underpinning of the nexus between els and mdd predisposition. specifically, despite the observed aberrant epigenomic modulation of the nr3c1, a glucocorticoid receptor gene, in early social adversity and social threats in animal and human models, reliable scientific data for intervention mapping in reducing social adversity and improving human health is required. we sought to synthesize the findings of studies evaluating (a) epigenomic modulations, mainly dna methylation resulting in mdd following els, (b) epigenomic modifications associated with els, and (c) epigenomic alterations associated with mdd. a systematic review and quantitative evidence synthesis (qes) were utilized with the random effect meta-analytic procedure. the search strategy involved both the pubmed and hand search of relevant references. of the 1534 studies identified through electronic search, 592 studies were screened, 11 met the eligibility criteria for inclusion in the qes, and 5 examined els and mdd; 4 studies assessed epigenomic modulation and els, while 2 studies examined epigenomic modulations and mdd. the dense dna methylation of the 1f exon of the nr3c1, implying the hypermethylated region of the glucocorticoid receptor gene, was observed in the nexus between els and mdd, common effect size (ces) = 14.96, 95%ci, 10.06–19.85. with respect to epigenomic modulation associated with child els, hypermethylation was observed, ces = 23.2%, 95%ci, 8.00–38.48. in addition, marginal epigenomic alteration was indicated in mdd, where hypermethylation was associated with increased risk of mdd, ces = 2.12%, 95%ci, ?0.63–4.86. substantial evidence supports the implication of nr3c1 and environmental interaction, mainly dna methylation, in the predisposition to mdd following els. this qes

further supports aberrant epigenomic modulation identified in els as well as major depressive episodes involving dysfunctional glucocorticoid-mediated negative feedback as a result of allostatic overload. these findings recommend prospective investigation of social adversity and its predisposition to the mdd epidemic via aberrant…"
Grillault Laroche, D., Curis, E., Bellivier, F., Nepost, C., Courtin, C., Etain, B., & Marie-Claire, C.. (2020). Childhood maltreatment and HPA axis gene expression in bipolar disorders: A gene network analysis. Psychoneuroendocrinology

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"Introduction: bipolar disorder (bd) is highly associated with childhood maltreatment (cm), the exposure to such early adversity being suggested to disrupt the expression of several biological pathways. this study aims at exploring associations between the mrna levels of 9 hpa axis genes in lymphoblastoid cell lines from patients with bd according to their self-reported exposure to cm. methods: the sample consisted of 33 caucasian patients with a diagnosis of bd type 1, assessed for the exposure to cm with the childhood trauma questionnaire (ctq). quantitative rt-pcr was performed on 9 transcripts of the hpa axis genes: dgkh, fkbp5, nr3c1, sgk1, sgk2, sgk3, ska2, stat5a and ucn. rt-qpcr data were analyzed using the method of disjoint gene networks with sarp.compo package for r. results: we found no associations between ctq total score and the amount of hpa axis transcripts neither in univariate analyses, nor with network analyses. emotional abuse (ea) was associated with a significant decreased expression of two transcripts, dgkh ($p = 0.009$) and nr3c1 ($p = 0.04$). this was confirmed by the disjoint network analysis, which showed that nr3c1 and dgkh were expressed differently from the rest of the hpa axis network in presence of emotional abuse. discussion: this study described the expression levels of a comprehensive set of hpa axis genes according to childhood maltreatment in a sample of patients with bd type 1 and suggested that emotional abuse decreased the expression of nr3c1 and dgkh. our results require further replication in independent larger samples."
Sheerin, C. M., Lind, M. J., Bountress, K. E., Marraccini, M. E., Amstadter, A. B., Bacanu, S. A., & Nugent, N. R.. (2020). Meta-Analysis of Associations Between Hypothalamic-Pituitary-Adrenal Axis Genes and Risk of Posttraumatic Stress Disorder. Journal of Traumatic Stress

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"The hypothalamic-pituitary-adrenal (hpa) axis has been of interest in attempts to identify genetic vulnerability for posttraumatic stress disorder (ptsd). although numerous hpa-axis genes have been implicated in candidate gene studies, the findings are mixed and interpretation is limited by study design and methodological inconsistencies. to address these inconsistencies in the ptsd candidate gene literature, we conducted meta-analyses of hpa-related genes from both a traditional single nucleotide polymorphism (snp)–level analysis and a gene-level analysis, using novel methods aggregating markers in the same gene. database searches (pubmed and psycinfo) identified 24 unique

articles examining six hpa-axis genes in ptsd; analyses were conducted on four genes (adcyap1r1, crhr1, fkbp5, nr3c1) that met study eligibility criteria (original research, human subjects, main effect association study of selected genes, ptsd as an outcome, trauma-exposed control group) and had sufficient data and number of studies for use in meta-analysis, within 20 unique articles. findings from snp-level analyses indicated that two variants (rs9296158 in fkbp5 and rs258747 in nr3c1) were nominally associated with ptsd, ps =.001 and.001, respectively, following multiple testing correction. at the gene level, significant relations between ptsd and both nr3c1 and fkbp5 were detected and robust to sensitivity analyses. although study limitations exist (e.g., varied outcomes, inability to test moderators), taken together, these results provide support for fkbp5 and nr3c1 in risk for ptsd. overall, this work highlights the utility of meta-analyses in resolving discrepancies in the literature and the value of adopting gene-level approaches to investigate the etiology of ptsd."
Peng, H., Zhu, Y., Strachan, E., Fowler, E., Bacus, T., Roy-Byrne, P., … Zhao, J.. (2018). Childhood Trauma, DNA Methylation of Stress-Related Genes, and Depression: Findings from Two Monozygotic Twin Studies. Psychosomatic Medicine

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"Objective dna methylation has been associated with both early life stress and depression. this study examined the combined association of dna methylation at multiple cpg probes in five stress-related genes with depressive symptoms and tested whether these genes methylation mediated the association between childhood trauma and depression in two monozygotic (mz) twin studies. methods the current analysis comprised 119 mz twin pairs (84 male pairs [mean = 55 years] and 35 female pairs [mean = 36 years]). peripheral blood dna methylation of five stress-related genes (bdnf, nr3c1, slc6a4, maoa, and maob) was quantified by bisulfite pyrosequencing or 450k beadchip. we applied generalized poisson linear-mixed models to examine the association between each single cpg methylation and depressive symptoms. the joint associations of multiple cpgs in a single gene or all five stress-related genes as a pathway were tested by weighted truncated product method. mediation analysis was conducted to test the potential mediating effect of stress gene methylation on the relationship between childhood trauma and depressive symptoms. results multiple cpg probes showed nominal individual associations, but very few survived multiple testing. gene-based or gene-set approach, however, revealed significant joint associations of dna methylation in all five stress-related genes with depressive symptoms in both studies. moreover, two cpg probes in the bdnf and nr3c1 mediated approximately 20% of the association between childhood trauma and depressive symptoms. conclusions dna methylation at multiple cpg sites are jointly associated with depressive symptoms and partly mediates the association between childhood trauma and depression. our results highlight the importance of testing the combined effects of multiple cpg loci on complex traits and may unravel a molecular mechanism through which adverse early life experiences are biologically embedded."
Nöthling, J., Malan-Müller, S., Abrahams, N., Hemmings, S. M. J., & Seedat, S.. (2020). Epigenetic alterations associated with childhood trauma and adult mental health outcomes: A systematic review. World Journal of Biological Psychiatry

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“Objectives: multiple, chronic and repeated trauma exposure in childhood is associated with adverse mental health outcomes in adulthood. in this paper we synthesise the literature on epigenetic modifications in childhood trauma (ct) and the mediating effects of differential epigenetic mechanisms on the association between ct and the later onset of psychiatric disorders. methods: we reviewed the literature up to march 2018 in four databases: pubmed, web of science, ebscohost and scopus. non-human studies were excluded. all studies investigating ct exposure both in healthy adults (18years and older) and adults with psychiatric disorders were included. results: thirty-six publications were included. for mood disorders, methylation of the glucocorticoid receptor nr3c1 gene, specifically at the ngfi-a binding site in exon 1f, and correlation with ct was a robust finding. several studies documented differential methylation of slc6a4, bdnf, oxtr and fkbp5 in association with ct. common pathways identified include neuronal functioning and maintenance, immune and inflammatory processes, chromatin and histone modification, and transcription factor binding. conclusions: a variety of epigenetic mediators that lie on a common pathway between ct and psychiatric disorders have been identified, although longitudinal studies and consistency in methodological approach are needed to disentangle cause and effect associations.”
Brown, V.. (2021). Methylation of the glucocorticoid receptor gene NR3C1: a summary for clinicians working with children and families. BJPsych Open

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“Aims it has been shown that the glucocorticoid receptor nr3c1 gene can be methylated (‘switched off’) in response to early adversity. methylation has also been linked to physiological changes in the body’s response to stress by changing the sensitivity of the hypothalamic-pituitary-adrenal (hpa) axis. in adults, associations have been made between nr3c1 methylation and borderline personality disorder, depression and post-traumatic stress disorder. environmental and social co-variates increase with lifespan so establishing cause and effect is difficult. studies in children, then, may illuminate patterns to inform current hypotheses. this paper reviews the literature on children and adolescents linking glucocorticoid gene receptor nr3c1 to the psychopathology of mental illness. findings are presented in an accessible manner to engage people less familiar with genetics and to inform frontline clinicians of this quickly growing area of research. method medline and psychinfo were searched for relevant peer-reviewed original research using the following keywords and associated mesh terms: nrc31, glucocorticoid receptor gene, methylation, epigenetics, child, adolescent, trauma, psychopathology, gene expression. result 14 studies were identified involving 5475 young people. degree of nr3c1 methylation was associated with severity of early life adversity. methylation was linked with psychopathology including borderline personality disorder, internalising symptoms and externalising symptoms with sex differences. the most consistent association was with depression. methylation seems to modulate the interaction between environment and genetics with the suggestion that the

effect may be protective in some cases. however, longitudinal genetic sampling was only conducted in one study. conclusion heterogeneity of studies in the epigenetics field are discussed but should not detract from future possibilities. the hope is to identify therapeutic targets or monitor response to treatment as we work to better understand the biology of developmental psychology, mental illness and resilience. there is a growing understanding that epigenetic modifications likely change over time and clinical significance is most likely dictated by changes at multiple gene locations. thus future research may need to move away from single gene research typically employed in favour of longitudinal whole genome studies in larger population studies. it is time that clinician…"

Category

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1. Childhood trauma
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