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Neurobiological Effects of Child Maltreatment

A Bibliography

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Scope

This bibliography lists publications pertaining to the effects of child maltreatment and trauma upon brain and neurobiological development.

Organization

Publications include articles, book chapters, reports, and research briefs and are listed in date descending order. Links are provided to full text publications when possible. However, this collection may not be complete. More information can be obtained in the Child Abuse Library Online.

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Neurobiological Effects of Child Maltreatment

A Bibliography

Samson, J. A., Newkirk, T. R. & Teicher, M. H. (2024). Practitioner review: Neurobiological consequences of childhood maltreatment – clinical and therapeutic implications for practitioners. *Journal of Child Psychology and Psychiatry*, *65*(3), 369-380. DOI:10.1111/jcpp.13883

Background: Childhood maltreatment is one of the most important preventable risk factors for a wide variety of psychiatric disorders. Further, when psychiatric disorders emerge in maltreated individuals they typically do so at younger ages, with greater severity, more psychiatric comorbid conditions, and poorer response to established treatments, resulting in a more pernicious course with an increased risk for suicide. Practitioners treating children, adolescents, and young adults with psychiatric disorders will likely encounter the highest prevalence of clients with early-onset maltreatment-associated psychiatric disorders. These may be some of their most challenging cases. Method: In this report, we explore key validated alterations in brain structure, function, and connectivity associated with exposure to childhood maltreatment as potential mechanisms behind their patients' clinical presentations. Results: We then summarize key behavioral presentations likely associated with neurobiological alterations and propose a toolkit of established trauma and skills-based strategies that may help diminish symptoms and foster recovery. We also discuss how some of these alterations may serve as latent vulnerability factors for the possible development of future psychopathology. Conclusions: Research on the neurobiological consequences of childhood adversity provides a vastly enriched biopsychosocial understanding of the developmental origins of health and pathology that will hopefully lead to fundamental advances in clinical psychology and psychiatry.

Uy, J. P., Tan, A. P., Broeckman, B. B. F. P., Gluckman, P. D., Chong, Y. S., Chen, H., Fortier,M. V., Meaney, M. J., & Callaghan, B. L. (2023). Effects of maternal childhood trauma on child emotional health: maternal mental health and frontoamygdala pathways. *Journal of Child Psychology and Psychiatry*, *64*(3), 426–436. DOI:10.1111/jcpp.13721

Background: Experiences of early life adversity pose significant psychological and physical health risks to exposed individuals. Emerging evidence suggests that these health risks can

be transmitted across generations; however, the mechanisms underlying the intergenerational impacts of maternal early-life trauma on child health remain unknown. Methods: The current study used a prospective longitudinal design to determine the unique and joint contributions of maternal childhood trauma (neglect and abuse) and maternal prenatal and postnatal mental health (anxiety and depressive symptoms) (N = 541) to children's resting frontoamygdala functional connectivity at 6 years (N = 89) and emotional health at 7–8 years, as indexed by parent-reported internalizing problems and child self-reported anxiety and depressive symptoms (N = 268–418). Results: Greater maternal childhood neglect was indirectly associated with greater internalizing problems serially through a pathway of worse maternal prenatal and postnatal mental health (greater maternal anxiety and depressive symptoms). Worse maternal postnatal mental health was also uniquely associated with more negative child frontoamygdala resting-state functional connectivity, over and above maternal childhood trauma (both neglect and abuse) and prenatal mental health. More negative frontoamygdala functional connectivity was, in turn, associated with poorer child emotional health outcomes. Conclusions: Findings from the current study provide support for the existence of intergenerational influences of parental exposure to childhood trauma on childhood risk for psychopathology in the next generation and point to the importance of maternal factors proximal to the second generation (maternal prenatal and postnatal mental health) in determining the intergenerational impact of maternal early experiences.

Bendezú, J. J., Handley, E. D., Manly, J. T., Toth, S. L., & Cicchetti, D. (2022). Psychobiological foundations of coping and emotion regulation: Links to maltreatment and depression in a racially diverse, economically disadvantaged sample of adolescent girls. *Psychoneuroendocrinology*, *143*, 105826. DOI:10.1016/j.psyneuen.2022.105826

Adolescent risk for depression and passive or active suicidal ideation (PASI) involves disturbance across multiple systems (e.g., arousal regulatory, affective valence, neurocognitive). Exposure to maltreatment while growing up as a child or teenager may potentiate this risk by noxiously impacting these systems. However, research exploring how coordinated disturbance across these systems (i.e., profiles) might be uniquely linked to depressogenic function, and how past maltreatment contributes to such disturbance, is

lacking. Utilizing a racially diverse, economically disadvantaged sample of adolescent girls, this person-centered study identified psychobiological profiles and linked them to maltreatment histories, as well as current depressive symptoms and PASI. Girls (N=237, Mage=13.98, SD=0.85) who were non-depressed/non-maltreated (15.1%), depressed/non-maltreated (40.5%), or depressed/maltreated (44.4%) provided morning saliva samples, completed questionnaires, a clinical interview, and a neurocognitive battery. Latent profile analysis of girls' morning cortisol:C-reactive protein ratio, positive and negative affect levels, and attentional set-shifting ability revealed four profiles. Relative to Normative (66.6%), girls exhibiting a Pro-inflammatory Affective Disturbance (13.1 %) , Severe Affective Disturbance (10.1%), or Hypercortisol Affective Neurocognitive Disturbance (n=24, 10.1%) profile reported exposure to a greater number of maltreatment subtypes while growing up. Girls exhibiting these dysregulated profiles were also more likely (relative to Normative) to report current depressive symptoms (all three profiles) and PASI (only Pro-inflammatory Affective Disturbance and Hypercortisol Affective Neurocognitive Disturbance). Of note, girls' cognitive reappraisal utilization moderated profile membership–depression linkages (depressive symptoms, but not PASI). A synthesis of the findings is presented alongside implications for person-centered tailoring of intervention efforts.

Campbell K. A. (2022). The neurobiology of childhood trauma, from early physical pain onwards: As relevant as ever in today's fractured world. *European Journal of Psychotraumatology*, *13*(2), 2131969. DOI:10.1080/20008066.2022.2131969

Background: The situation in the world today, encompassing multiple armed conflicts, notably in Ukraine, the Coronavirus pandemic and the effects of climate change, increases the likelihood of childhood exposure to physical injury and pain. Other effects of these worldwide hardships include poverty, malnutrition and starvation, also bringing with them other forms of trauma, including emotional harm, neglect and deliberate maltreatment. Objective: To review the neurobiology of the systems in the developing brain that are most affected by physical and emotional trauma and neglect. Method: The review begins with those that mature first, such as the somatosensory system, progressing to structures that have a more protracted development, including those involved in cognition and emotional

regulation. Explored next are developing stress response systems, especially the hypothalamic–pituitary–adrenal axis and its central regulator, corticotropin-releasing hormone. Also examined are reward and anti-reward systems and genetic versus environmental influences. The behavioural consequences of interpersonal childhood trauma, focusing on self-harm and suicide, are also surveyed briefly. Finally, pointers to effective treatment are proffered. Results: The low-threshold nature of circuitry in the developing brain and lack of inhibitory connections therein result in heightened excitability, making the consequences of both physical and emotional trauma more intense. Sensitive and critical periods in the development of structures such as the amygdala render the nervous system more vulnerable to insults occurring at those points, increasing the likelihood of psychiatric disorders, culminating in self-harm and even suicide. Conclusion: In view of the greater excitability of the developing nervous system, and its vulnerability to physical and psychological injuries, the review ends with an exhortation to consider the long-term consequences of childhood trauma, often underestimated or missed altogether when faced with adults suffering mental health problems.

Cortes Hidalgo, A. P., Thijssen, S., Delaney, S. W., Vernooij, M. W., Jansen, P. W., Bakermans-Kranenburg, M. J., van IJzendoorn, M. H., White, T., & Tiemeier, H. (2022). Harsh parenting and child brain morphology: A population-based study. *Child Maltreatment*, *27*(2), 163–173. DOI:10.1177/1077559520986856

Evidence suggests that maltreatment shapes the child's brain. Little is known, however, about how normal variation in parenting influences the child neurodevelopment. We examined whether harsh parenting is associated with the brain morphology in 2,410 children from a population-based cohort. Mothers and fathers independently reported harsh parenting at child age 3 years. Structural and diffusion-weighted brain morphological measures were acquired with MRI scans at age 10 years. We explored whether associations between parenting and brain morphology were explained by co-occurring adversities, and whether there was a joint effect of both parents' harsh parenting. Maternal harsh parenting was associated with smaller total gray (β = -0.05 (95%CI = -0.08; -0.01)), cerebral white matter and amygdala volumes (β = -0.04 (95%CI = -0.07; 0)). These associations were also observed with the combined harsh parenting measure and were robust to the adjustment for multiple

confounding factors. Similar associations, although non-significant, were found between paternal parenting and these brain outcomes. Maternal and paternal harsh parenting were not associated with the hippocampus or the white matter microstructural metrics. We found a long-term association between harsh parenting and the global brain and amygdala volumes in preadolescents, suggesting that adverse rearing environments common in the general population are related to child brain morphology.

Hakamata, Y., Suzuki, Y., Kobashikawa, H., & Hori, H. (2022). Neurobiology of early life adversity: A systematic review of meta-analyses towards an integrative account of its neurobiological trajectories to mental disorders. *Frontiers in Neuroendocrinology*, *65*, 100994. DOI:10.1016/j.yfrne.2022.100994

Adverse childhood experiences (ACEs) may leave long-lasting neurobiological scars, increasing the risk of developing mental disorders in later life. However, no review has comprehensively integrated existing evidence across the fields: hypothalamic–pituitary–adrenal axis, immune/inflammatory system, neuroimaging, and genetics/epigenetics. We thus systematically reviewed previous meta-analyses towards an integrative account of ACE-related neurobiological alterations. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, a total of 27 meta-analyses until October 2021 were identified. This review found that individuals with ACEs possess blunted cortisol response to psychosocial stressors, low-grade inflammation evinced by increased C-reactive protein levels, exaggerated amygdalar response to emotionally negative information, and diminished hippocampal gray matter volume. Importantly, these alterations were consistently observed in those with and without psychiatric diagnosis. These findings were integrated and discussed in a schematic model of ACE-related neurobiological alterations. Future longitudinal research based on multidisciplinary approach is imperative for ACE-related mental disorders' prevention and treatment.

Kim-Spoon, J., Herd, T., Brieant, A., Peviani, K., Deater-Deckard, K., Lauharatanahirun, N., Lee, J., & King-Casas, B. (2021). Maltreatment and brain development: The effects of abuse and neglect on longitudinal trajectories of neural activation during risk processing and cognitive control. *Developmental Cognitive Neuroscience*, *48*, 100939. DOI:10.1016/j.dcn.2021.100939

The profound effects of child maltreatment on brain functioning have been documented. Yet, little is known about whether distinct maltreatment experiences are differentially related to underlying neural processes of risky decision making: valuation and control. Using conditional growth curve modeling, we compared a cumulative approach versus a dimensional approach (relative effects of abuse and neglect) to examine the link between child maltreatment and brain development. The sample included 167 adolescents (13–14 years at Time 1, 53 % male), assessed annually four times. Risk processing was assessed by blood-oxygen-level-dependent responses (BOLD) during a lottery choice task, and cognitive control by BOLD responses during the Multi-Source Interference Task. Cumulative maltreatment effects on insula and dorsolateral anterior cingulate cortex (dACC) activation during risk processing were not significant. However, neglect (but not abuse) was associated with slower developmental increases in insula and dACC activation. In contrast, cumulative maltreatment effects on fronto-parietal activation during cognitive control were significant, and abuse (but not neglect) was associated with steeper developmental decreases in fronto-parietal activation. The results suggest neglect effects on detrimental neurodevelopment of the valuation system and abuse effects on accelerated neurodevelopment of the control system, highlighting differential effects of distinct neglect versus abuse adverse experiences on neurodevelopment.

Lo Iacono, L., Trentini, C., & Carola, V. (2021). Psychobiological consequences of childhood sexual abuse: Current knowledge and clinical implications. *Frontiers in Neuroscience, 15*, 771511. DOI:10.3389/fnins.2021.771511

A large body of research has documented the long-term harms of childhood sexual abuse (CSA) on an individual's emotional-adaptive function and mental health. Recent studies have also provided evidence of the biological impact of CSA, implicating specific alterations in many systems, including the endocrine and immune systems, and in DNA and chromatin, in

the pathogenesis of medical disorders. Although the effects of CSA are often examined with regard to the general impact of early-life traumatic experiences, the study of CSA per sè, as a trigger of specific pathogenic pathways, would be more appropriate to understand their long-term implications and develop tailored diagnostic and therapeutic strategies. Based on these premises, this narrative minireview summarizes the research on the short-term and long-term sequelae of CSA, focusing on dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, the effects on the immune system, and the changes to DNA through altered methylation. Also, we discuss the literature that examines dysfunctional DNA telomere erosion and oxidative stress markers as a sign of CSA. Finally, recent evidence of the intergenerational transmission of the effects of CSA is reported. The impact of CSA on brain connectivity and functions is out of the scope of this review, thus brain imaging studies are not included. The results of this minireview are discussed, considering their implications for prevention and clinical practice.

Parish-Plass, N. (2021). Animal-assisted psychotherapy for developmental trauma through the lens of interpersonal neurobiology of trauma: Creating connection with self and others. *Journal of Psychotherapy Integration*, *31*(3), 302-325. DOI:10.1037/int0000253

Chronic maltreatment in childhood has been found to have serious deleterious effects on the child's present and future medical and psychological health, self-regulation, and ability to function in interpersonal relationships, resulting in developmental trauma (DT). In recent years, researchers in the field of neurobiology have discovered pervasive neurological implications of maltreatment, negatively affecting the functioning of the neurological system, bringing further understanding of the emotional and behavioral issues in those suffering from DT. Integration of knowledge of the psychological effects of chronic maltreatment with knowledge of the interpersonal neurobiology of trauma has proved useful for psychotherapists in their treatment of survivors of maltreatment. However, the symptoms of DT form barriers to some of the very principles of psychotherapy that are meant to treat sufferers of DT. This article presents the background for trauma- and neurobiology-informed psychotherapy, focusing on some symptoms of DT that might form barriers to psychotherapy, specifically distrust in others (leading to difficulty in

establishing the therapeutic alliance), emotional numbness and loss of touch with self (leading to lack emotional expression, implicit memories without the context of explicit memories, lack of recognition of the trauma and its implications), and shame and the subsequent presentation of false self to others (preventing the ability to work through the trauma with the therapist). Experts in the field of DT state that therapy must take place in the context of relationships. Animal-assisted psychotherapy, conducted in a highly relational environment, is discussed as an approach which might lower these barriers.

Price, M., Albaugh, M., Hahn, S., Juliano, A. C., Fani, N., Brier, Z. M. F., Legrand, A. C., van Stolk-Cooke, K., Chaarani, B., Potter, A., Peck, K., Allgaier, N., Banaschewski, T., Bokde, A. L. W., Quinlan, E. B., Desrivières, S., Flor, H., Grigis, A., Gowland, P.... & Garavan, H. (2021). Examination of the association between exposure to childhood maltreatment and brain structure in young adults: A machine learning analysis. *Neuropsychopharmacology*, *46*(11), 1888-1894. DOI:10.1038/s41386-021-00987-7

Exposure to maltreatment during childhood is associated with structural changes throughout the brain. However, the structural differences that are most strongly associated with maltreatment remain unclear given the limited number of whole-brain studies. The present study used machine learning to identify if and how brain structure distinguished young adults with and without a history of maltreatment. Young adults (ages 18–21, n = 384) completed an assessment of childhood trauma exposure and a structural MRI as part of the IMAGEN study. Elastic net regularized regression was used to identify the structural features that identified those with a history of maltreatment. A generalizable model that included 7 cortical thicknesses, 15 surface areas, and 5 subcortical volumes was identified (area under the receiver operating characteristic curve = 0.71, $p < 0.001$). Those with a maltreatment history had reduced surface areas and cortical thicknesses primarily in fronto-temporal regions. This group also had larger cortical thicknesses in occipital regions and surface areas in frontal regions. The results suggest childhood maltreatment is associated with multiple measures of structure throughout the brain. The use of a large sample without exposure to adulthood trauma provides further evidence for the unique contribution of childhood trauma to brain structure. The identified regions overlapped with regions associated with psychopathology

in adults with maltreatment histories, which offers insights as to how these disorders manifest.

Ashy, M., Yu, B., Gutowski, E., Samkavitz, A., & Malley-Morrison, K. (2020). Childhood maltreatment, limbic dysfunction, resilience, and psychiatric symptoms. *Journal of Interpersonal Violence*, *35*(1-2), 426–452. DOI:10.1177/0886260516683174

Previous research has indicated that childhood maltreatment is predictive of psychiatric symptoms in adulthood. Among the potential intervening factors in this relationship are affective reactions in the victims, neurodevelopmental problems, and resilience. The purpose of this study was to test, in a nonclinical low-risk sample, an integrative developmentally based psychoneurological model of the roles of limbic system dysfunction, shame and guilt, and resiliency as potential intervening variables between childhood maltreatment and adult psychiatric symptoms. Also of interest was whether there were gender-specific pathways from maltreatment to symptoms. Based on the results of preliminary analyses, several regressions were conducted separately by gender, entering the different forms of parental aggression at Step 1, resilience at Step 2, the resilience by parental aggression interaction term at Step 3, shame and guilt at Step 4, and limbic dysfunction at Step 5, as predictors of psychiatric symptoms. Analyses indicated that both maternal psychological maltreatment and paternal physical maltreatment were predictive of total psychiatric symptomatology in adulthood, with shame mediating the relationship in women and guilt mediating it in men, limbic system symptoms mediating the relationship in both genders, and trait resilience moderating the relationship in both genders.

Young-Southward, G., Svelnys, C., Gajwani, R., Bosquet Enlow, M., & Minnis, H. (2020). Child maltreatment, autonomic nervous system responsivity, and psychopathology: Current state of the literature and future directions. *Child Maltreatment*, *25*(1), 3= 19. DOI:10.1177/1077559519848497

Child maltreatment may affect autonomic nervous system (ANS) responsivity, and ANS responsivity may influence the impact of child maltreatment on later outcomes including long-term mental/physical health. This review systematically evaluated the evidence

regarding effects of maltreatment on ANS responsivity in children and examined how ANS responsivity may influence the association between maltreatment and psychopathology, with attention to relevant developmental issues. We searched the literature for relevant studies using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched five electronic databases, performed key word searches in relevant journals, hand searched reference sections of relevant articles, and contacted experts in the field. Articles were extracted according to inclusion criteria and their quality assessed. The search produced 1,388 articles; 22 met inclusion criteria. Most of the studies suggested blunted cardiovascular responsivity generally and sympathetic activation specifically in response to stress in maltreated children compared to nonmaltreated children. Findings around vagal responsivity and skin conductance were mixed. Limited evidence was found for ANS responsivity as a moderator or mediator of psychopathology risk among maltreated children. Maltreatment may be associated with blunted sympathetic activation in stressful situations. Differences in ANS responsivity may influence psychopathology risk among maltreated children. Further research is needed to confirm the nature and magnitude of such effects.

Demers, L. A., Handley, E. D., Hunt, R. H., Rogosch, F. A., Toth, S. L., Thomas, K. M., & Cicchetti, D. (2019). Childhood maltreatment disrupts brain-mediated pathways between adolescent maternal relationship quality and positive adult outcomes. *Child Maltreatment*, *24*(4), 424–434. DOI:10.1177/1077559519847770

The quality of early caregiving may partially shape brain structure and circuits involved in regulating emotions, including the frontal cortex, affecting vulnerability to the development of psychopathology and maladaptation. Given the profound impact of child maltreatment (CM) on psychological and neural development, we tested whether CM alters the pathways linking mother–adolescent relationship, frontal cortex, and adult outcomes. We used structural equation modeling to investigate whether CM history affected the association between mother–child relationship quality during early adolescence, frontal lobe volume in adulthood, and adult internalizing and externalizing symptomatology and competence. Participants from a longitudinal high-risk, low-income sample included 48 adults with a history of CM and 40 adults without such history (M = 30.0 years). Results showed that greater frontal lobe volume predicted higher levels of adult adaptive functioning and fewer

adult internalizing symptoms but showed no relation to adult externalizing symptoms. Frontal lobe volume significantly mediated the effect of adolescent maternal relationship quality on both adult internalizing symptoms and adult adaptive functioning, but only for individuals with no maltreatment history. Given the observed relationship between frontal lobe volume and healthy adult functioning across the full sample, it will be important to identify protective factors in maltreated individuals that foster frontal lobe development.

Cassiers, L. L., Sabbe, B. G., Schmaal, L., Veltman, D. J., Penninx, B. W., & Van Den Eede, F. (2018). Structural and functional brain abnormalities associated with exposure to different childhood trauma subtypes: A systematic review of neuroimaging findings. *Frontiers in Psychiatry*, *9*, 329. DOI:10.3389/fpsyt.2018.00329

Background: Childhood trauma subtypes sexual abuse, physical abuse, emotional maltreatment, and neglect may have differential effects on the brain that persist into adulthood. A systematic review of neuroimaging findings supporting these differential effects is as yet lacking. Objectives: The present systematic review aims to summarize the findings of controlled neuroimaging trials regarding long-term differential effects of trauma subtypes on the human brain. Methods: A systematic literature search was performed using the PubMed and PsycINFO databases from January 2017 up to and including January 2018. Additional papers were identified by a manual search in the reference lists of selected papers and of relevant review articles retrieved by the initial database search. Studies were then assessed for eligibility by the first author. Only original human studies directly comparing neuroimaging findings of exposed and unexposed individuals to well-defined emotional, physical or sexual childhood maltreatment while controlling for the effects of other subtypes were included. A visual summary of extracted data was made for neuroimaging modalities for which comparison between trauma subtypes was feasible, taking the studies' numbers and sample sizes into account. Results: The systematic literature search yielded 25 publications. Sexual abuse was associated with structural deficits in the reward circuit and genitosensory cortex and amygdalar hyperreactivity during sad autobiographic memory recall. Emotional maltreatment correlated with abnormalities in fronto-limbic socioemotional networks. In neglected individuals, white matter integrity and connectivity

were disturbed in several brain networks involved in a variety of functions. Other abnormalities, such as reduced frontal cortical volume, were common to all maltreatment types. Conclusions: There is some evidence for long-term differential effects of trauma subtypes on the human brain. The observed alterations may result from both protective adaptation of and damage to the brain following exposure to threatening life events. Though promising, the current evidence is incomplete, with few brain regions and neuroimaging modalities having been investigated in all subtypes. The comparability of the available evidence is further limited by the heterogeneity of study populations regarding gender, age and comorbid psychopathology. Future neuroimaging studies should take this potentially differential role of childhood trauma subtypes into account.

Hoffmann, F., Puetz, V. B., Viding, E., Sethi, A., Palmer, A., & McCrory, E. J. (2018). Risk taking, peer-influence and child maltreatment: A neurocognitive investigation. *Social Cognitive and Affective Neuroscience*, *13*(1), 124–134. DOI:10.1093/scan/nsx124

Maltreatment is associated with increased risk of a range of psychiatric disorders, many of which are characterized by altered risk-taking propensity. Currently, little is known about the neural correlates of risk-taking in children exposed to maltreatment, nor whether their risk-taking is atypically modulated by peer influence. Seventy-five 10- to 14-year-old children [maltreated (MT) group: N = 41; non-maltreated Group (NMT): N = 34] performed a Balloon Analogue Risk Task (BART), under three different peer influence conditions: while alone, while being observed by a peer and while being encouraged by a peer to take risks. The MT group engaged in less risk-taking irrespective of peer influence. There was no differential effect of peer influence on risk-taking behaviour across groups. At the neural level, the right anterior insula (rAI) exhibited altered risk sensitivity across conditions in the MT group. Across groups and conditions, rAI risk sensitivity was negatively associated with risk-taking and within the MT group greater rAI risk sensitivity was related to more anxiety symptoms. These findings suggest that children with a history of maltreatment show reduced risk-taking but typical responses to peer influence. Abnormal rAI functioning contributes to the pattern of reduced risk-taking and may predispose children exposed to maltreatment to develop future psychopathology.

Nooner, K. B., Hooper, S. R., & De Bellis, M. D. (2018). An examination of sex differences on neurocognitive functioning and behavior problems in maltreated youth. *Psychological Trauma: Theory, Research, Practice, and Policy*, *10*(4), 435-443. DOI:10.1037/tra0000356

Objective: In the developmental traumatology model, the biological construct of sex is considered a moderator that may negatively influence child maltreatment sequelae including those pertaining to neurocognitive function. Method: This study examined sex-differences in neurocognitive function and behavior problems in maltreated boys (n = 42), maltreated girls (n = 56) versus nonmaltreated boys (n = 45) and girls (n = 59). Maltreated boys were hypothesized to have poorer neurocognitive functioning than maltreated girls, and nonmaltreated boys and girls, in all neurocognitive domains, particularly pertaining to executive function and attention. We also examined correlations between cognitive function and parent report of child behavior problems for maltreated and nonmaltreated children. Results: Maltreated boys performed more poorly on measures of intelligence, attention, language, memory, executive function, and academic achievement in both reading and math than nonmaltreated boys. Maltreated boys did not perform more poorly on these cognitive measures or behavioral measures than maltreated girls, except for one memory measure. Maltreated girls performed more poorly on measures of intelligence, language, memory, executive function, and academic achievement than nonmaltreated girls. Maltreated girls with better visual-spatial skills had more internalizing and externalizing problems. Effect sizes for these sex differences ranged from small to large. Conclusions: Both maltreated boys and girls showed poorer cognitive function than their nonmaltreated sex-matched controls. Maltreated girls had subtle sparing of attention and short-term memory (STM). Understanding sex differences in neurocognitive functioning may have implications for designing large population studies of maltreated youth.

Teicher, M. H., Anderson, C. M., Ohashi, K., Khan, A., McGreenery, C. E., Bolger, E. A., Rohan, M. L., & Vitaliano, G. D. (2018). Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus. *NeuroImage*, *169*, 443-452. DOI:10.1016/j.neuroimage.2017.12.055

The hippocampus is a highly stress susceptible structure and hippocampal abnormalities have been reported in a host of psychiatric disorders including major depression and post-traumatic stress disorder (PTSD). The hippocampus appears to be particularly susceptible to early life stress with a graded reduction in volume based on number of types (multiplicity) or severity of maltreatment. We assessed whether the most important predictors of adult hippocampal volume were multiplicity, severity or duration of exposure or timing of maltreatment during developmental sensitive periods. 3T MRIs were collected on 336 unmedicated, right-handed subjects (132M/204F, 18–25 years). Exposure to broad categories of abuse and neglect during each year of childhood were assessed using the Maltreatment and Abuse Chronology of Exposure scale and evaluated using artificial intelligence and predictive analytics. Male hippocampal volume was predicted by neglect, but not abuse, up through 7 years of age. Female hippocampal volume was predicted by abuse, but not neglect, at 10, 11, 15 and 16 years. Exposure at peak age had greater predictive importance than multiplicity, severity or duration. There were also marked gender differences in subfields and portions (head, body or tail) affected by exposure. History and symptoms of major depression, PTSD or anxiety disorders were not predictive of hippocampal volume once maltreatment was accounted for. Neglect appears to foster inadequate hippocampal development in males while abuse appears to produce a stress-related deficit in females. Studies assessing hippocampal volume in psychiatric disorders need to control for the gender-specific effects of abuse and neglect.

Cross, D., Fani, N., Powers, A., & Bradley, B. (2017). Neurobiological development in the context of childhood trauma. *Clinical Psychology*, *24*(2), 111–124. DOI:10.1111/cpsp.12198

Neurobiological systems may be particularly susceptible to deleterious impact of childhood trauma, and the impact of childhood trauma on development and subsequent functional outcomes across the lifespan has been well-documented. The current review addresses the

neurobiological impact of exposure to interpersonal trauma in childhood in the context of executive function, emotion regulation, and dissociation/interoceptive awareness. Subsequent risk for PTSD and depression is also discussed. The pathway of risk from childhood trauma to these cognitive, emotional, and psychiatric outcomes is addressed in terms of potential structural and functional alterations within the hippocampus, prefrontal cortex, and amygdala resulting from chronic or repeated activation of the hypothalamic-pituitary-adrenal (HPA) axis and its interaction with and influence on genetic and epigenetic processes during sensitive periods of development. Implications for practice are discussed.

Danese, A., & Lewis, S. J. (2017). Psychoneuroimmunology of early-life stress: The hidden wounds of childhood trauma?. *Neuropsychopharmacology*, *42*, 99–114. DOI:10.1038/npp.2016.198

The brain and the immune system are not fully formed at birth, but rather continue to mature in response to the postnatal environment. The two-way interaction between the brain and the immune system makes it possible for childhood psychosocial stressors to affect immune system development, which in turn can affect brain development and its long-term functioning. Drawing from experimental animal models and observational human studies, we propose that the psychoneuroimmunology of early-life stress can offer an innovative framework to understand and treat psychopathology linked to childhood trauma. Early-life stress predicts later inflammation, and there are striking analogies between the neurobiological correlates of early-life stress and of inflammation. Furthermore, there are overlapping trans-diagnostic patterns of association of childhood trauma and inflammation with clinical outcomes. These findings suggest new strategies to remediate the effect of childhood trauma before the onset of clinical symptoms, such as anti-inflammatory interventions and potentiation of adaptive immunity. Similar strategies might be used to ameliorate the unfavorable treatment response described in psychiatric patients with a history of childhood trauma.

Lawson, G. M., Camins, J. S., Wisse, L., Wu, J., Duda, J. T., Cook, P. A., Gee, J. C., & Farah, M. J. (2017). Childhood socioeconomic status and childhood maltreatment: Distinct associations with brain structure. *PloS One*, *12*(4), e0175690. DOI:10.1371/journal.pone.0175690

The present study examined the relationship between childhood socioeconomic status (SES), childhood maltreatment, and the volumes of the hippocampus and amygdala between the ages of 25 and 36 years. Previous work has linked both low SES and maltreatment with reduced hippocampal volume in childhood, an effect attributed to childhood stress. In 46 adult subjects, only childhood maltreatment, and not childhood SES, predicted hippocampal volume in regression analyses, with greater maltreatment associated with lower volume. Neither factor was related to amygdala volume. When current SES and recent interpersonal stressful events were also considered, recent interpersonal stressful events predicted smaller hippocampal volumes over and above childhood maltreatment. Finally, exploratory analyses revealed a significant sex by childhood SES interaction, with women's childhood SES showing a significantly more positive relation (less negative) with hippocampus volume than men's. The overall effect of childhood maltreatment but not SES, and the sex-specific effect of childhood SES, indicate that different forms of stressful childhood adversity affect brain development differently.

Nemeroff, C. B. (2016). Paradise lost: The neurobiological and clinical consequences of child abuse and neglect. *Neuron*, *89*(5), 892-909. DOI:10.1016/j.neuron.2016.01.019

In the past two decades, much evidence has accumulated unequivocally demonstrating that child abuse and neglect is associated with a marked increase in risk for major psychiatric disorders (major depression, bipolar disorder, post-traumatic stress disorder [PTSD], substance and alcohol abuse, and others) and medical disorders (cardiovascular disease, diabetes, irritable bowel syndrome, asthma, and others). Moreover, the course of psychiatric disorders in individuals exposed to childhood maltreatment is more severe. Recently, the biological substrates underlying this diathesis to medical and psychiatric morbidity have been studied. This Review summarizes many of the persistent biological alterations associated with childhood maltreatment including changes in neuroendocrine and

neurotransmitter systems and pro-inflammatory cytokines in addition to specific alterations in brain areas associated with mood regulation. Finally, I discuss several candidate gene polymorphisms that interact with childhood maltreatment to modulate vulnerability to major depression and PTSD and epigenetic mechanisms thought to transduce environmental stressors into disease vulnerability.

Teicher, M. H., & Samson, J. A. (2016). Annual research review: Enduring neurobiological effects of childhood abuse and neglect. *Journal of Child Psychology & Psychiatry*, *57*(3), 241-266. DOI:10.1111/jcpp.12507

Childhood maltreatment is the most important preventable cause of psychopathology accounting for about 45% of the population attributable risk for childhood onset psychiatric disorders. A key breakthrough has been the discovery that maltreatment alters trajectories of brain development. This review aims to synthesize neuroimaging findings in children who experienced caregiver neglect as well as from studies in children, adolescents and adults who experienced physical, sexual and emotional abuse. In doing so, we provide preliminary answers to questions regarding the importance of type and timing of exposure, gender differences, reversibility and the relationship between brain changes and psychopathology. We also discuss whether these changes represent adaptive modifications or stress-induced damage. Parental verbal abuse, witnessing domestic violence and sexual abuse appear to specifically target brain regions (auditory, visual and somatosensory cortex) and pathways that process and convey the aversive experience. Maltreatment is associated with reliable morphological alterations in anterior cingulate, dorsal lateral prefrontal and orbitofrontal cortex, corpus callosum and adult hippocampus, and with enhanced amygdala response to emotional faces and diminished striatal response to anticipated rewards. Evidence is emerging that these regions and interconnecting pathways have sensitive exposure periods when they are most vulnerable. Early deprivation and later abuse may have opposite effects on amygdala volume. Structural and functional abnormalities initially attributed to psychiatric illness may be a more direct consequence of abuse. Childhood maltreatment exerts a prepotent influence on brain development and has been an unrecognized confound in almost all psychiatric neuroimaging studies. These brain changes may be best understood

as adaptive responses to facilitate survival and reproduction in the face of adversity. Their relationship to psychopathology is complex as they are discernible in both susceptible and resilient individuals with maltreatment histories. Mechanisms fostering resilience will need to be a primary focus of future studies.

Glaser, D. (2014). The effects of child maltreatment on the developing brain. *Medico-Legal Journal*, *82*(3), 97-111. DOI:10.1177/0025817214540395

Lasting effects of child abuse and neglect are well recognised. Apart from physical effects resulting from injuries and neglect, the effects are on behaviour, emotional well-being, interpersonal relationships and cognitive functioning. These psychological aspects are now known to have their counterparts in brain structure, chemistry and function. The growing knowledge of brain development has shed new light on our understanding of the processes by which especially early abuse and neglect may have a profound effect on the child's later adjustment. The brain undergoes its greatest growth and development in the first years of life, (with a second phase in adolescence). While the sequence of development within the brain is genetically determined, the nature of this development is determined to a considerable extent on the young child's experiences. The absence of some experiences, such as extreme deprivation during sensitive periods of development may mean that certain functions will not develop. For most functions, the nature of experience will shape brain development. Negative experiences and certain ways of interaction will be incorporated into the brain's connectivity. While learning and new experiences continue throughout life, and their effects continue to be incorporated into brain structure and functioning, previous patterns cannot be erased, only added on to and more slowly. As we know from our adult experiences, learning is far faster in childhood. A further aspect of child maltreatment which has a profound effect on brain development is the significant neurobiological stress which the young, maltreated, child experiences. It is interesting to learn that secure attachment organisation protects the developing brain from the worst effects of the stress response. The effects of the experiences interact with the child's genetic resilience or vulnerability.

Munro, E., & Musholt, K. (2014). Neuroscience and the risks of maltreatment. *Children and Youth Services Review*, *47*, 18-26. DOI:10.1016/j.childyouth.2013.11.002

Findings from neuroimaging are increasingly being cited in policy debates to strengthen the case for early identification of, and intervention with, children at risk of maltreatment and poor outcomes. While agreeing that neuroscientific research into the risks of maltreatment is a very valuable and exciting area of study, this article challenges the confidence with which these findings are used in policy discussions. It critically discusses the reliability and validity of the relevant findings and the contribution they can currently make to our understanding of the causes and consequences of maltreatment. In addition, it is argued that this type of evidence, which is new in policy debates, is often being used in ways that are problematic. Many participants in the relevant policy debates seem to subscribe either to an implicit version of dualism about the relationship between the mind and the body, or to reductionism — the view that the mental can be reduced to the physical. Such assumptions threaten the way we think about human agency and moral responsibility but it is argued that they are misguided for conceptual reasons. It is concluded that neuroscience has the potential to contribute to our understanding of the causes and effects of maltreatment but cannot do so in isolation from the social sciences.

Barrera, M., Calderón, L., & Bell, V. (2013). The cognitive impact of sexual abuse and PTSD in children: A neuropsychological study. *Journal of Child Sexual Abuse*, *22*(6), 625-638. DOI:10.1080/10538712.2013.811141

Sexual abuse is known to have an impact on both child and adult mental health, but the neuropsychological basis of this effect is still largely unknown. This study compared neuropsychological test results from a group of 76 children, 13 of them sexual abuse victims with symptoms of post-traumatic stress disorder, 26 victims of sexual abuse who showed no symptoms post-traumatic stress disorder, and 37 controls. The groups were matched by age, sex, socioeconomic status, and educational level. Child sexual abuse was associated with reduced ability to inhibit automatic responses measured by the Stroop test regardless of post-traumatic stress disorder status. These findings indicate possible attentional inhibition difficulties in child victims of sexual abuse, which may help explain.

Painter, K., & Scannapieco, M. (2013). Child maltreatment: The neurobiological aspects of posttraumatic stress disorder. *Journal of Evidence-Based Social Work*, *10*(4), 276-284. DOI:10.1080/10911359.2011.566468

Childhood trauma due to physical abuse, neglect, or sexual abuse is a serious problem in the United States. Trauma can result in disruption or injury to the developing brain and lead to neurodevelopmental deficits that affect a child's functioning and can result in lifelong problems. Research has provided insight into how early childhood maltreatment affects brain development. This article examines the research on trauma, its effects on the brain, and evidence-based interventions. An overview of normal brain functioning and posttraumatic stress disorder is presented. Implications for social work practice with children who have experienced child maltreatment are discussed.

Hart, H., & Rubia, K. (2012). Neuroimaging of child abuse: A critical review. *Frontiers in Human Neuroscience*, *6*, 1-24. DOI:10.3389/fnhum.2012.00052

Childhood maltreatment is a stressor that can lead to the development of behavior problems and affect brain structure and function. This review summarizes the current evidence for the effects of childhood maltreatment on behavior, cognition and the brain in adults and children. Neuropsychological studies suggest an association between child abuse and deficits in IQ, memory, working memory, attention, response inhibition and emotion discrimination. Structural neuroimaging studies provide evidence for deficits in brain volume, gray and white matter of several regions, most prominently the dorsolateral and ventromedial prefrontal cortex but also hippocampus, amygdala, and corpus callosum (CC). Diffusion tensor imaging (DTI) studies show evidence for deficits in structural interregional connectivity between these areas, suggesting neural network abnormalities. Functional imaging studies support this evidence by reporting atypical activation in the same brain regions during response inhibition, working memory, and emotion processing. There are, however, several limitations of the abuse research literature which are discussed, most prominently the lack of control for co-morbid psychiatric disorders, which make it difficult to disentangle which of the above effects are due to maltreatment, the associated psychiatric conditions or a combination or interaction between both. Overall, the better controlled studies

that show a direct correlation between childhood abuse and brain measures suggest that the most prominent deficits associated with early childhood abuse are in the function and structure of lateral and ventromedial fronto-limbic brain areas and networks that mediate behavioral and affect control. Future, large scale multimodal neuroimaging studies in medication-naïve subjects, however, are needed that control for psychiatric co-morbidities in order to elucidate the structural and functional brain sequelae that are associated with early environmental adversity, independently of secondary co-morbid conditions.

De Bellis, M. D., Spratt, E. G., & Hooper, S. R. (2011). Neurodevelopmental biology associated with childhood sexual abuse. *Journal of Child Sexual Abuse*, *20*(5), 548-587. DOI:10.1080/10538712.2011.607753

Child maltreatment appears to be the single most preventable cause of mental illness and behavioral dysfunction in the US. There are few published studies examining the developmental and the psychobiological consequences of sexual abuse. There are multiple mechanisms through which sexual abuse can cause PTSD, activate biological stress response systems, and contribute to adverse brain development. This article will critically review the psychiatric problems associated with maltreatment and the emerging biologic stress system research with a special emphasis on what is known about victimization by sexual abuse.

Delima, J., & Vimpani, G. (2011). The neurobiological effects of childhood maltreatment: An often overlooked narrative related to the long-term effects of early childhood trauma? *Family Matters*, (89), 42-52.

This paper aims to discuss the concept that some current societal dysfunction may well be an overlooked significant consequence of childhood maltreatment, with its associated trauma effect upon the developing brain. These changes prevent and impair the ability to remediate disadvantage and its effects through purely social policy and justice measures.

Heim, C., Shugart, M., Craighead, W. E., & Nemeroff, C. B. (2010). Neurobiological and psychiatric consequences of child abuse and neglect. *Developmental Psychobiology*, *52*(7), 671-690. DOI:10.1002/dev.20494

The effects of early-life trauma and its consequences for the treatment of depression are reviewed. The prevalence and clinical sequelae of early sexual and physical abuse, neglect and parental loss are described. An overview of preclinical studies that help guide clinical research and practice is presented. Human clinical studies on the neurobiological consequences of early trauma are summarized. Moderating factors, such as genetic variation and sex differences, are discussed. The few current treatment outcome studies relevant to this research area are described. Guidance for the management of patients with depression and a history of child abuse and neglect are provided. Most patients who have experienced early traumatic experiences are likely best treated with a combination of psychotherapy and pharmacotherapy. This review is dedicated to the memory of Seymour Levine who pioneered the field of early experience research and to a considerable extent inspired the clinical studies described in this review. © 2010 Wiley Periodicals, Inc.

McCrory, E., De Brito, S. A., & Viding, E. (2010). Research Review: The neurobiology and genetics of maltreatment and adversity. *Journal of Child Psychology & Psychiatry, 51*(10), 1079-1095. DOI:10.1111/j.1469-7610.2010.02271.x

The neurobiological mechanisms by which childhood maltreatment heightens vulnerability to psychopathology remain poorly understood. It is likely that a complex interaction between environmental experiences (including poor caregiving) and an individual's genetic make-up influence neurobiological development across infancy and childhood, which in turn sets the stage for a child's psychological and emotional development. This review provides a concise synopsis of those studies investigating the neurobiological and genetic factors associated with childhood maltreatment and adversity. We first provide an overview of the neuroendocrine findings, drawing from animal and human studies. These studies indicate an association between early adversity and atypical development of the hypothalamicpituitary-adrenal (HPA) axis stress response, which can predispose to psychiatric vulnerability in adulthood. We then review the neuroimaging findings of structural and functional brain differences in children and adults who have experienced childhood maltreatment. These

studies offer evidence of several structural differences associated with early stress, most notably in the corpus callosum in children and the hippocampus in adults; functional studies have reported atypical activation of several brain regions, including decreased activity of the prefrontal cortex. Next, we consider studies that suggest that the effect of environmental adversity may be conditional on an individual's genotype. We also briefly consider the possible role that epigenetic mechanisms might play in mediating the impact of early adversity. Finally, we consider several ways in which the neurobiological and genetic research may be relevant to clinical practice and intervention.

Twardosz, S., & Lutzker, J. R. (2010). Child maltreatment and the developing brain: A review of neuroscience perspectives. *Aggression and Violent Behavior*, *15*(1), 59-68. DOI:10.1016/j.avb.2009.08.003

In this article we review neuroscience perspectives on child maltreatment to facilitate understanding of the rapid integration of neuroscience knowledge into the academic, clinical, and lay literature on this topic. Seminal articles from developmental psychology and psychiatry, a discussion of brain plasticity, and a summary of recent reviews of research on stress system dysregulation are presented with some attention to methodological issues. A common theme is that maltreatment during childhood is an experience that may affect the course of brain development, potentially leading to differences in brain anatomy and functioning with lifelong consequences for mental health. The design of prevention and intervention strategies for child maltreatment may benefit from considering neuroscience perspectives along with those of other disciplines.

Tyrka, A. R., Price, L. H., Kao, H. T., Porton, B., Marsella, S. A., & Carpenter, L. L. (2010). Childhood maltreatment and telomere shortening: Preliminary support for an effect of early stress on cellular aging. *Biological Psychiatry*, *67*(6), 531-534. DOI:10.1016/j.biopsych.2009.08.014

Psychological stress and trauma are risk factors for several medical and psychiatric illnesses. Recent studies have implicated advanced cellular aging as a potential mechanism of this association. Telomeres, DNA repeats that cap the ends of chromosomes and promote

stability, shorten progressively with each cell division; their length is a marker of biological aging. Based on previous evidence linking psychosocial stress to shorter telomere length, this study was designed to evaluate the effect of childhood adversity on telomere length. Thirty-one adults with no current or past major Axis I psychiatric disorder participated. Subjects reported on their history of childhood maltreatment and telomere length was measured from DNA extracted from frozen whole blood using quantitative PCR. Participants reporting a history of childhood maltreatment had significantly shorter telomeres than those who did not report a history of maltreatment. This finding was not due to effects of age, sex, smoking, BMI, or other demographic factors. Analysis of subscales showed that both physical neglect and emotional neglect were significantly linked to telomere length. These results extend previous reports linking shortened leukocyte telomere length and caregiver stress to more remote stressful experiences in childhood, and suggest that childhood maltreatment could influence cellular aging.

Neigh, G. N., Gillespie, C. F., & Nemeroff, C. B. (2009). The neurobiological toll of child abuse and neglect. *Trauma, Violence, & Abuse*, *10*(4), 389-410. DOI:10.1177/1524838009339758

Exposure to interpersonal violence or abuse affects the physical and emotional well-being of affected individuals. In particular, exposure to trauma during development increases the risk of psychiatric and other medical disorders beyond the risks associated with adult violence exposure. Alterations in the hypothalamic-pituitary-adrenal (HPA) axis, a major mediating pathway of the stress response, contribute to the long-standing effects of early life trauma. Although early life trauma elevates the risk of psychiatric and medical disease, not all exposed individuals demonstrate altered HPA axis physiology, suggesting that genetic variation influences the consequences of trauma exposure. In addition, the effects of abuse may extend beyond the immediate victim into subsequent generations as a consequence of epigenetic effects transmitted directly to offspring and/or behavioral changes in affected individuals. Recognition of the biological consequences and transgenerational impact of violence and abuse has critical importance for both disease research and public health policy.

Perry, B. D. (2009). Examining child maltreatment through a neurodevelopmental lens: Clinical applications of the neurosequential model of therapeutics. *Journal of Loss and Trauma*, *14*(4), 240-255. DOI:10.1080/15325020903004350

This article provides the theoretical rationale and overview of a neurodevelopmentally-informed approach to therapeutic work with maltreated and traumatized children and youth. Rather than focusing on any specific therapeutic technique, the Neurosequential Model of Therapeutics (NMT) allows identification of the key systems and areas in the brain which have been impacted by adverse developmental experiences and helps target the selection and sequence of therapeutic, enrichment, and educational activities. In the preliminary applications of this approach in a variety of clinical settings, the outcomes have been positive. More in-depth evaluation of this approach is warranted, and is underway.

Andersen, S. L., Tomada, A., Vincow, E. S., Valente, E., Polcari, A., & Teicher, M. H. (2008). Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *The Journal of Neuropsychiatry and Clinical Neurosciences, 20*(3), 292-301. DOI:10.1176/jnp.2008.20.3.292

Volumetric MRI scans from 26 women with repeated episodes of childhood sexual abuse (CSA), and 17 healthy women (18–22 years) were analyzed for sensitive periods effects on hippocampal and amydgala volume, frontal cortex gray matter volume and corpus callosum area. Hipppocampal volume was reduced in association with CSA at 3–5 years ($\beta=-0.69$, $p<0.0001$) and 11–13 years ($\beta=-0.25$, $p<0.05$). Corpus callosum was reduced with CSA at 9–10 years ($\beta=-0.44$, $p<0.005$), and frontal cortex was attenuated in subjects with CSA at ages 14–16 ($\beta=-0.48$, $p<0.005$). Brain regions have unique windows of vulnerability to the effects of traumatic stress.

Niehoff, D. (2007). Invisible scars: The neurobiological consequences of child abuse. *DePaul Law Review*, *56*(3), 847-877.

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C. H., Perry, B. D., Dube, S.R., & Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. *European Archives of Psychiatry and Clinical Neuroscience*, *256*(3), 174-186. DOI:10.1007/s00406-005-0624-4

Childhood maltreatment has been linked to a variety of changes in brain structure and function and stress-responsive neurobiological systems. Epidemiological studies have documented the impact of childhood maltreatment on health and emotional well-being. After a brief review of the neurobiology of childhood trauma, we use the Adverse Childhood Experiences (ACE) Study as an epidemiological "case example" of the convergence between epidemiologic and neurobiological evidence of the effects of childhood trauma. The ACE Study included 17,337 adult HMO members and assessed 8 adverse childhood experiences (ACEs) including abuse, witnessing domestic violence, and serious household dysfunction. We used the number of ACEs (ACE score) as a measure of cumulative childhood stress and hypothesized a "dose-response" relationship of the ACE score to 18 selected outcomes and to the total number of these outcomes (comorbidity). Based upon logistic regression analysis, the risk of every outcome in the affective, somatic, substance abuse, memory, sexual, and aggression-related domains increased in a graded fashion as the ACE score increased ($P < 0.001$). The mean number of comorbid outcomes tripled across the range of the ACE score. The graded relationship of the ACE score to 18 different outcomes in multiple domains theoretically parallels the cumulative exposure of the developing brain to the stress response with resulting impairment in multiple brain structures and functions.

Gunnar, M. R., & Fisher, P. A. (2006). Bringing basic research on early experience and stress neurobiology to bear on preventive interventions for neglected and maltreated children. *Development and Psychopathology*, *18*(3), 651-677. DOI:10.1017/S0954579406060330

A major focus in developmental psychopathology is on understanding developmental mechanisms and, armed with this information, intervening to improve children's outcomes. Translational research attempts to bridge the distance between understanding and intervention. In the collaborations that have formed the core of our research network on early experience, stress, and prevention science, we have focused on translating basic research on

early experiences and stress neurobiology into preventive interventions for neglected and abused children. Our experiences in attempting to move from bench to bedside have led us to recognize the many challenges that face translational researchers. This review provides a brief synopsis of the animal model literature on early experience and stress neurobiology from which we glean several key bridging issues. We then review what is currently known about the impact of childhood neglect and abuse on stress neurobiology in human adults and children. Next, we describe how this work has informed the evaluation of our preventive interventions with maltreated children. Finally, we discuss several considerations that should facilitate a more complete integration of basic research on early experience and stress neurobiology into preventive intervention strategies.

Wasserman, E. (2005). *Understanding the effects of childhood trauma on brain development in Native children*. Tribal Law and Policy Institute.

The information in this article was compiled to assist victim advocates who work with children and their caretakers to understand how the trauma affects the child's development when abuse has occurred – especially when it occurs early in the child's life. This article should also be helpful to Tribes and Tribal agencies seeking to develop programs and services that will promote healing and wellness for Tribal children. This article also provides basic information that will help extended family members, foster parents, teachers and others who are involved with a child that has suffered trauma early in life.

Cellini, H. R. (2004). Child abuse, neglect, and delinquency: The neurological link. *Juvenile and Family Court Journal*, *55*(4), 1-14. DOI:10.1111/j.1755-6988.2004.tb00169.x

Recent research has demonstrated a clear connection between physical, emotional, and sexual abuse and neglect during childhood, and negative changes in a child's neurological development. Abnormal growth and developmental patterns in a child's brain as a result of abuse and neglect can lead to life-long problems with self-control, memory, emotion, judgment, consequential thinking, and moral reasoning, resulting in an increased likelihood

of substance abuse, juvenile delinquency, and adult criminal behaviors. This article provides information on the abused child, neurological implications, and recommendations.

Nemeroff, C. B. (2004). Neurobiological consequences of childhood trauma. *The Journal of Clinical Psychiatry*, *65*(Suppl1), 18-28.

There is considerable evidence to suggest that adverse early-life experiences have a profound effect on the developing brain. Neurobiological changes that occur in response to untoward early-life stress can lead to lifelong psychiatric sequelae. Children who are exposed to sexual or physical abuse or the death of a parent are at higher risk for development of depressive and anxiety disorders later in life. Preclinical and clinical studies have shown that repeated early-life stress leads to alterations in central neurobiological systems, particularly in the corticotropin-releasing factor system, leading to increased responsiveness to stress. Clearly, exposure to early-life stressors leads to neurobiological changes that increase the risk of psychopathology in both children and adults. Identification of the neurobiological substrates that are affected by adverse experiences in early life should lead to the development of more effective treatments for these disorders. The preclinical and clinical studies evaluating the consequences of early-life stress are reviewed.

van der Kolk, B. A. (2003). The neurobiology of childhood trauma and abuse. *Child and Adolescent Psychiatric Clinics of North America*, *12*(2), 293-317. DOI:10.1016/S1056-4993(03)00003-8

During the past decade there has been rapid progress in the understanding of the effects of exposure to traumatic life experiences on subsequent psychopathology in children. Trauma exposure affects what children anticipate and focus on and how they organize the way they appraise and process information. Trauma-induced alterations in threat perception are expressed in how they think, feel, behave, and regulate their biologic systems. The task of therapy is to help these children develop a sense of physical mastery and awareness of who they are and what has happened to them to learn to observe what is happening in present time

and physically respond to current demands instead of recreating the traumatic past behaviorally, emotionally, and biologically.

De Bellis, M. D. (2001). Developmental traumatology: The psychobiological development of maltreated children and its implications for research, treatment, and policy. *Development and Psychopathology*, *13*(3), 539-564. DOI:10.1017/S0954579401003078

In this review, a developmental traumatology model of child maltreatment and the risk for the intergenerational cycle of abuse and neglect using a mental health or posttraumatic stress model was described. Published data were reviewed that support the hypothesis that the psychobiological sequelae of child maltreatment may be regarded as an environmentally induced complex developmental disorder. Data to support this view, including the descriptions of both psychobiological and brain maturation studies in maltreatment research, emphasizing the similarities and differences between children, adolescents, and adults, were reviewed. Many suggestions for important future psychobiological and brain maturation research investigations as well as public policy ideas were offered.

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry*, *49*(12), 1023-1039. DOI:10.1016/S0006-3223(01)01157-X

Epidemiologic studies indicate that children exposed to early adverse experiences are at increased risk for the development of depression, anxiety disorders, or both. Persistent sensitization of central nervous system (CNS) circuits as a consequence of early life stress, which are integrally involved in the regulation of stress and emotion, may represent the underlying biological substrate of an increased vulnerability to subsequent stress as well as to the development of depression and anxiety. A number of preclinical studies suggest that early life stress induces long-lived hyper(re)activity of corticotropin-releasing factor (CRF) systems as well as alterations in other neurotransmitter systems, resulting in increased stress responsiveness. Many of the findings from these preclinical studies are comparable to findings in adult patients with mood and anxiety disorders. Emerging evidence from clinical

studies suggests that exposure to early life stress is associated with neurobiological changes in children and adults, which may underlie the increased risk of psychopathology. Current research is focused on strategies to prevent or reverse the detrimental effects of early life stress on the CNS. The identification of the neurobiological substrates of early adverse experience is of paramount importance for the development of novel treatments for children, adolescents, and adults.

Kaufman, J., & Charney, D. (2001). Effects of early stress on brain structure and function: Implications for understanding the relationship between child maltreatment and depression. *Development and Psychopathology*, *13*(3), 451-471. DOI:10.1017/s0954579401003030

Child abuse is associated with markedly elevated rates of major depression (MDD) in child, adolescent, and adult cohorts. This article reviews preclinical (e.g., animal) studies of the effects of early stress and studies of the neurobiological correlates of MDD in adults and children, and it highlights differences in the neurobiological correlates of MDD and stress at various developmental stages. The preclinical studies demonstrate that stress early in life can alter the development multiple neurotransmitter systems and promote structural and functional alterations in brain regions similar to those seen in adults with depression. Preclinical and clinical studies suggest, however, that long-term neurobiological changes associated with early stress can be modified by familial/genetic factors, the quality of the subsequent caregiving environment, and pharmacological interventions. Little is known about how developmental factors interact with experiences of early stress and these other modifying factors. Moreover, in cases of child maltreatment, the effects of early abuse are often exacerbated by failures in the child protection system and repeat out-of-home placements. Given the number of factors that impact on the long-term outcome of maltreated children, multidisciplinary research efforts are recommended to address this problem—with foci that span from neurobiology to social policy.

Kaufman, J., Plotsky, P. M., Nemeroff, C. B., & Charney, D. S. (2000). Effects of early adverse experiences on brain structure and function: Clinical implications. *Biological Psychiatry*, *48*(8), 778-790. DOI:10.1016/S0006-3223(00)00998-7

Child abuse is associated with markedly elevated rates of major depression and other psychiatric disorders in adulthood. This article reviews preclinical studies examining the effects of early stress, factors that modify the impact of these experiences, and neurobiological changes associated with major depression. Preclinical studies demonstrate that early stress can alter the development of the hypothalamic-pituitary-adrenal axis, hypothalamic and extrahypothalamic corticotropin releasing hormone, monoaminergic, and g-aminobutyric acid/benzodiazepine systems. Stress has also been shown to promote structural and functional alterations in brain regions similar to those seen in adults with depression. Emerging data suggest, however, that the long-term effects of early stress can be moderated by genetic factors and the quality of the subsequent caregiving environment. These effects also can be prevented or reversed with various pharmacologic interventions. Preclinical studies of early stress can provide valuable insights in understanding the pathophysiology and treatment of major depression. They also can provide an important tool to use to investigate interactions between genes and environments in determining an individual's sensitivity to stress. More research is needed to understand how inherent factors interact with experiences of abuse and other psychosocial factors to confer vulnerability to develop depression.

Glaser, D. (2000). Child abuse and neglect and the brain—A review. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, *41*(1), 97-116. DOI:10.1111/1469-7610.00551

Developmental psychology and the study of behaviour and emotion have tended to be considered in parallel to the study of neurobiological processes. This review explores the effects of child abuse and neglect on the brain, excluding nonaccidental injury that causes gross physical trauma to the brain. It commences with a background summary of the nature, context, and some deleterious effects of omission and commission within child maltreatment. There is no post-maltreatment syndrome, outcomes varying with many factors including nature, duration, and interpersonal context of the maltreatment as well as the nature of later

intervention. There then follows a section on environmental influences on brain development, demonstrating the dependence of the orderly process of neurodevelopment on the child's environment. Ontogenesis, or the development of the self through self-determination, proceeds in the context of the nature–nurture interaction. As a prelude to reviewing the neurobiology of child abuse and neglect, the next section is concerned with bridging the mind and the brain. Here, neurobiological processes, including cellular, biochemical, and neurophysiological processes, are examined alongside their behavioural, cognitive, and emotional equivalents and vice versa. Child maltreatment is a potent source of stress and the stress response is therefore discussed in some detail. Evidence is outlined for the buffering effects of a secure attachment on the stress response. The section dealing with actual effects on the brain of child abuse and neglect discusses manifestations of the stress response including dysregulation of the hypothalamic-pituitary-adrenal axis, and parasympathetic and catecholamine responses. Recent evidence about reduction in brain volume following child abuse and neglect is also outlined. Some biochemical, functional, and structural changes in the brain that are not reflections of the stress response are observed following child maltreatment. The mechanisms bringing about these changes are less clearly understood and may well be related to early and more chronic abuse and neglect affecting the process of brain development. The behavioural and emotional concomitants of their neurobiological manifestations are discussed. The importance of early intervention and attention to the chronicity of environmental adversity may indicate the need for permanent alternative caregivers, in order to preserve the development of the most vulnerable children.