



Early life trauma – review of clinical and neurobiological studies

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Abstract

Purpose: Psychological trauma is a significant risk factor for physical and mental health development distortion. This paper presents the results of longitudinal epidemiological surveys and naturalistic observations. It also reviews the results of the most important neurobiological findings in the field of impact of early life trauma on cognitive and emotional development, and the structure and functions of the brain.

Views: Trauma is defined as subjective experiences that overwhelm a person's ability to maintain psychophysical integrity. During the stage of neurodevelopment, various life adversities, such as emotional and sensory deprivation, abandonment and neglect by caregivers as well as physical or emotional violence and sexual abuse overwhelm the physiological and mental capacity of a child and impact their cognitive, emotional and social development, adversely influencing adulthood functioning. Symptoms of abused children can evolve and change with time, from moderate signs of distress to more complex symptoms and organized disorders. The most important longitudinal studies, such as the Lives Across Time Study, Minnesota Study, Adverse Childhood Experiences Study, The Great Smoky Mountains Study, and the English and Romanian Adoptee Study are discussed in the paper. The lifelong influences of early adversities on brain structures like the corpus callosum, hippocampus, the amygdaloid nuclei, ventral striatum and cerebral cortex has been described. The variability of the sensitivity of specific brain regions, based on different rates of maturation, has also been discussed.

Conclusions: This review integrates and summarizes the basic knowledge about the impact and neurobiological consequences of early traumatic adversities.

Key words: trauma, neurobiology, development, longitudinal studies, emotional deprivation.

INTRODUCTION

In clinical practice of psychiatry, it is becoming evident that traumatic life experiences during childhood and adolescence are more common than usually recognized. In recent years, a rapidly increasing number of studies concern the mutual interplay of the cumulative impact of negative incidents and the quality of attachment, which correlates with severity of psychopathology [1]. The author provides evidence that traumatic events in the earliest years do not disappear but, like a footprints in wet cement, are often preserved lifelong. Memories of them are embodied and hidden by time, shame and social taboos. Time does not heal these wounds, it conceals them. That is why the biomedical model and service practice for most psychiatric disor-

ders, but also common diseases like obesity, diabetes, and heart disease, need revision in order for us to obtain a proper comprehension of early adversity and manage the dedicated treatment of it.

The aim of this review is to describe some clinically significant studies concerning the neurodevelopment and functioning of people who experienced trauma or adverse events during their infancy and childhood. Major naturalistic studies and neurobiological research that provide proof of and explain this phenomenon are presented. The article first presents historically significant longitudinal observations conducted in groups of problematic families and orphans, as well as in the general population; the neurobiological underpinnings of the problems under review are discussed in the second part.

VIEWS

The Greek word trauma means wound, damage and defeat. In medicine, trauma refers to a body injury that overwhelms the capacity for defense and requires medical assistance to heal. In psychology, trauma means circumstances overwhelming or exceeding a person's capacity to protect their own mental well-being and integrity. According to DSM-5 trauma is defined as an organism's reaction in face of "actual or threatened death, serious injury or sexual violence". Stressful events not involving threat to life or physical injury such as psychosocial stressors (e.g., divorce or job loss) are not considered to be trauma according to this definition [2]. Nevertheless, in the context of relations John Bowlby defined the trauma as "any events that seriously threatened the attachment relationship, like parental death, divorce, psychotic outbreak" [3]. In 1963, M. Masud Khan, in his paper titled "The concept of cumulative trauma" introduced the idea of "cumulative trauma" with reference to the chronic, day-to-day demeaning of a child and parental conflict, differentiating such experiences from discrete episodes of trauma [4].

One of the first studies in the field conducted longitudinally – from birth to age 30 – was the *Lives Across Time* study. This survey was based on Bowlby's definition of trauma as concerning significant threats to attachment relations. Full-term healthy infants were recruited among married couples between 1964 and 1965. Mother-infant interactions including play, feeding and the quality of mothering care were classified according to criteria of empathy, organization and efficiency. Moreover, the mothers underwent attachment assessment, a global psychiatric check-up and life history interviewing [5, 6]. The course of the children's development was followed until the age of 6 years; the children were next checked at the age of 18 years, and some of them were followed until they were 35. The *Lives Across Time* study revealed that physical and emotional abuse or neglect during childhood results in lower social and psychological functioning and a higher number of psychiatric diagnoses in adulthood in comparison to non-abused group. It was shown that symptoms evolved and changed with time, starting from moderate signs of distress and then developing into more complex symptoms and organized disorders like hyperactivity, anxiety disorder or eating disorders. In the group of the 76 interviewees observed for the longest time, adult functioning was inversely related to the number of traumatic relational experiences. Episodic trauma seems to influence adverse functioning in adulthood, though not to the same extent as chronic or multiple traumatic experiences. Not only overt abuse and severe neglect, but also psychological adversities related to parents' death, illness, addiction or divorce, may have enduring effects. For example, children frequently

experience their parents' divorce as equivalent to the loss of them through death.

The *Minnesota Study* was the next prospective analysis confirming findings of the *Lives Across Time* study. A group of 180 children born of primiparous mothers from low socioeconomic families [7, 8] were included in the study. The children were followed for 20 years, since 1974. The mothers were divided into two groups, according to the characterization of "unsafe" (abused in their childhood) and "safe" (having had supportive and loving parental care). It was found out that 40% of "unsafe" mothers maltreated their children, a further 30% provided borderline childcare and the rest provided adequate care. Further analysis revealed that maltreated children showed decreased levels of persistence and goal-oriented activity, increased inattention, higher anger expression, frustration and non-compliance in comparison to those children who received adequate care. In adulthood 90% of the maltreated children had at least one psychiatric diagnosis; the severity of neglect and abuse correlated highly with psychopathology. The authors also characterized some protective factors counteracting the effect of early adversities, which are: experiences of support and competence, an alternative available caregiver, a good school and an organized home environment. Interestingly, child temperament did not account for differences. Strouffe, in his final publication, concluded that the most powerful predictor of child outcome was a cumulative history of care rather than quality of attachment alone [8].

Another American epidemiological survey to provide significant data on the lifelong consequences of trauma was the *Adverse Childhood Experiences (ACE) Study* [9]. This grew out of the nationwide weight loss programs, which had a high dropout rate, surprisingly restricted only to patients successfully losing weight. The patients were middle class Americans with high-quality health insurance; they were 80% white, 10% black and 10% Asian. 74% of them graduated from college, and their average age was 57. Seeking to explain this unexpected patients' behavior was the basic purpose of the retrospective and prospective analyses of the incidence of traumatic experiences in a larger group of individuals from birth into adulthood (18 years). The history of medical and psychiatric disease, sexual behavior and healthcare costs were also analyzed. For the purpose of this study, a simple scoring system was established, ranging from 0-10. The occurrence of any category of adverse experiences during childhood or adolescence was scored as 1 point, whereas there were no additional points for multiple incidents within the same category. Observations led to the conclusions that 30% of the middle-class population had a null ACE score, but if only one category of adversity was experienced there was an 87% likelihood that an additional category of traumatic experiences would also be revealed. Twenty eight percent of the studied population had

a high ACE Score (more than 4). The authors described in this group a high prevalence of experiences, such as emotional abuse (11%), physical maltreatment (28%), contact sexual abuse (28% women, 16% men), household dysfunction like mother treated violently (13%), an alcohol or drug abuse problem (27%), family member imprisonment (6%), household member chronically depressed, suicidal, mentally ill or psychiatrically hospitalized (17%), and not raised by both biological parents (23%) [10]. The probability of more than four categories of adversity was 50% higher in the group of women than in that of men. The analysis revealed that ACE categories did not occur randomly as the number of individuals with high scores was distinctly higher than might result from separate and independent occurrence of categories. These results confirmed the relationship between ACE score and psychopathology. The other significant finding was the fact that 12% of participants recalled a period of amnesia, particularly some time before the onset of their weight gain. The ACE study also revealed a distinct relationship between impaired memory of childhood and level of scoring, which might well indicate dissociated responses to emotional trauma [11, 12]. In the context of health risk behaviors there was a strong relationship between ACE scores and psychoactive substance abuse, particularly intravenous drug administration, and sexual behavior such as teenage pregnancy and promiscuity [13]. Moreover, the findings concerning the condition of population health revealed a correlation between biomedical parameters and early experience of adversities. This correlation was described for liver disease, chronic obstructive pulmonary disease, coronary artery disease, and autoimmune disease as well as for healthcare costs and life expectancy. The analysis of adult death rates showed that individuals with ACE scores higher than 6 had a lifespan almost two decades shorter than those with null ACE scoring but with similar socioeconomic characteristics. Moreover, among this group of the patients the rate of prescription of antidepressants, antipsychotics or anxiolytics was significantly higher than in average population [14]. The results of the Adverse Childhood Experiences Study, then, showed a life-long impact of early life adversities underlying many somatic and mental health problems.

The *Great Smoky Mountains Study (GSMS)* was a longitudinal one exploring child psychiatric epidemiology and mental health service needs. It was conducted on a population living in the southern Appalachian region of North Carolina. The children recruited for the study, aged 9-13, were from the general American population and from Cherokee Indians of the Eastern Band living on the federal Qualla Boundary reservation. The aim of this study was: (1) to understand the developmental pathways of a large sample of children with the highest need for mental healthcare (2) to estimate the prevalence of dis-

orders and risk factors in the population, and (3) to map the identified cases onto the general population (generalizability). Over 20 years, the GSM Study also expended its range to include the developmental epidemiology of psychiatric problems and their socioeconomic-biological predictors. All children were assessed for symptoms of psychopathology with the use of brief screening questionnaires. Among the many correlations analyzed were the prevalence and characteristics of anxiety disorders. The analysis revealed a U-shaped age prevalence curve of all anxiety disorders, due to high levels of childhood separation anxiety and panic attacks, agoraphobia, and generalized anxiety in adulthood. An overlap between anxiety disorders and depression or behavioral disorders was also shown. It was found that the occurrence of anxiety disorders during childhood was associated with impaired functioning in at least one life domain in adulthood, with the poorest outcome for generalized anxiety disorder correlated with adult depression [15]. Separation anxiety was associated with poor health outcomes and social phobia was associated with interpersonal problems. Moreover, every anxiety disorder during childhood was associated with poor health functioning in early adulthood.

The next significant correlation was found between the prevalence and intensity of irritability in childhood and disrupted functioning [16]. Irritability overlapped with depressive disorders, particularly in a group of girls with externalizing problems [17]. The GSM study showed correlation between bullying, aggression at school and the incidence of eating disorders [18].

In conclusion, the most significant findings of this study was the assumption that mental problems in childhood, even those not fulfilling the diagnostic criteria of DSM-5, are strong predictive factors in impaired functioning in adult life. The cumulative number of psychiatric disorders during childhood was the strongest predictor of a negative life outcome [19]. Thus, prevention and prophylaxis from the earliest years of human life should be the main goal of mental healthcare [20].

Finally, the *English and Romanian Adoptee Study* was a naturalistic and prospective study that confirmed the impact of early adversities on human emotional and cognitive development. Romanian orphans, raised in institutions but later adopted by families from the United Kingdom, were examined, and their development followed. The aim of this naturalistic observation was to reveal what deprivation-related features in childhood would be presented into adulthood. The adoptees were divided into two groups according to the duration of their institutional care (shorter or longer than 6 months). The control group was recruited from English orphans living and adopted in Great Britain. Analysis revealed that English and Romanian adoptees with shorter periods of institutional care/deprivation were presenting

similar functional problems, in contrast to children with a longer history of institutionalization. The latter presented a higher incidence of problems like autism spectrum symptoms (called quasi-autistic, characterized by specific communication problems, obsessions and compulsions), conduct disorders (like inappropriate social openness and sociability), attention – hyperactivity disorders and cognitive dysfunctions lasting from childhood into adulthood. In adolescence the emotional problems were frequently enhanced, while cognitive dysfunction tailed off. Only a fifth of the children with a longer duration of institutional deprivation revealed no symptomatology. Further observation showed the persistence of disinhibited social disorder until adulthood, understood as the main outcome of protracted emotional deprivation. The autistic symptoms associated with early deprivation were enhanced at the beginning of the study but later remitted with time, while social communication impairments and compulsions were most pronounced in later years [21].

The neurobiology of the impact of early life adversities on the developing brain is still an open discussion. There is an increasing amount of preclinical and clinical research proving the lifelong influences of early adversities on neurohormones, neurotransmission, and the development and structure of many brain regions. It is worth remembering that the majority of the results described are correlational and do not provide casualty between a history of abuse and neurobiological differences.

The studies mentioned above, conducted by Professor M. Rutter among Romanian orphans, proved that persistent changes in the reactivity of the HPA axis in children exposed to long-term emotional deprivation, in spite of successful adoption and a supportive family [22]. Prospective observations revealed a decreased or flattened level of morning serum peak of cortisol until adulthood, directly proving the lifelong consequences of institutional deprivation. Similarly dysregulated cortisol levels and HPA reactivity in response to stress were described in institutionalized children [23].

The research on the influence of maltreatment on neurohormones has shown different correlations. Higher levels of noradrenaline, dopamine and cortisol have been detected in the urea of maltreated children in comparison to a control group, whereas women with a history of depression and maltreatment had higher levels of cortisol [24]. The results shown by Yechuda, revealed decreased production of cortisol in patients suffering from PTSD (post-traumatic stress disorder), which in consequence insufficiently inhibited the stress reaction in the organism [25].

Besides HPA (hypothalamic-pituitary-adrenal axis) activation, there is a functional network called “an emotional brain”, consisting of the amygdala, hippocampus and striatum. It plays significant role in reactions to everyday experiences and stressful situations. In response

to danger, the activation of the amygdala, locus coeruleus and then the sympathetic nervous system takes place, leading to the “fight or flight” reaction. This response is modulated by increase in noradrenaline and is expressed as accelerated heart beat, higher blood pressure, increased metabolism, enhanced concentration and defense-readiness [26]. In the light of intense and overwhelming danger, another defense reaction like “freezing” is observed, characterized by immobilization, metabolic slowdown, and reduced heart and respiratory rate, to survive in the circumstances in which there are minimal chances for fight or escape. The parasympathetic autonomic nervous system underlies this reaction to stress. Regions particularly vulnerable to the effects of early trauma are myelinated areas like the corpus callosum. Excessive amounts of stress hormones suppress the glial cell division critical for myelination. Studies conducted by Denenberg showed decreased volumes of corpus callosum, which correlated with early life adversities in a gender-dependent manner [27]. Teicher confirmed these findings, showing particular sensitivity of this brain region to neglect in boys and to sexual abuse in girls [28]. A reduced size of the corpus callosum is associated with increased hemispheric laterality, decreased hemispheric integration and attenuated integration of memory processes connected to trauma [29].

The hippocampus is the next brain structure influenced by stress. This region is characterized by protracted ontogeny, persistent postnatal neurogenesis and a high density of glucocorticoid receptors. Exposure to stress hormones can markedly alter pyramidal cell morphology, induce pyramidal cell death and suppress the production of new granule cells [30]. Bremner [31] and Stein [32] first reported reduced hippocampus volume in individuals with history of childhood trauma or current PTSD diagnosis. The reduced hippocampal volume is probably due to the attenuated postnatal neurogenesis of pyramidal cells and arrested peripubertal overproduction of synapses without prevention of pruning, which in consequence leads to enduring deficits in synaptic density [33]. Hippocampal reduction was described in women with borderline personality disorder (BPD), depression or dissociative identity disorder [34, 35].

The structure particularly sensitive to stimulation by repeated stressful experiences is the amygdaloid nuclei [36], where the phenomenon of kindling takes place. Kindling is a process of repeated intermittent stimulation that induces a growing alteration of neuronal excitability and results in increased neuronal reactivity to stimuli and seizures. The above changes have significant impacts on behavior. Some studies have revealed that early stress alters the structure and reduces the density of GABA-A receptors in the amygdala and hippocampi, which impairs the inhibition of neuronal excitability. These abnormalities may lead to temporal and limbic seizure-like

activity associated with anxiety, irritability and seizure susceptibility. Other studies on the impact of childhood trauma revealed a seizure-like psychomotor phenomenon in the absence of seizures, described as “limbic irritability symptoms”, including perceptual distortions, brief hallucinatory events, motor automatism, dissociative phenomena [37] with increased incidence of clinically significant electroencephalograph (EEG) abnormalities (in 78% patients), characterized by fronto-temporal origin spikes, sharp waves and paroxysmal slowing [38]. The other limbic structure – the ventral striatum (*nucleus accumbens and nucleus caudatus*) – has been also proved to be influenced by adverse experiences. Japanese studies revealed significantly decreased activity in this region in children with reactive attachment disorder. Structural changes were related to the avoidant attachment style and correlated with the stage of development. The first four years of life turned out to be the sensitive period in the development of the striatum, differently for each hemisphere; this is longer for the right and shorter for the left hemisphere [39].

The last, but most important, brain structure impacted by negative and traumatic life events is the cerebral cortex, particularly the prefrontal area. The neocortex as a whole matures slowly through cyclic reorganization until adulthood. The prefrontal cortex has the most delayed functional ontogeny of any brain region. Major projections to the prefrontal cortex scarcely begin to myelinate until adolescence and continue into the third decade of life. Delayed myelination is responsible for functional specialization and independent development of both hemispheres until maturation. For example, language and motor lateralization are largely established before 5 years of age, whereas right hemisphere specialization for perception of human faces emerges between 8 and 13 years of age. Early stress exerts debilitating effects on lateralization and myelination in humans [40]. Adversities in childhood activate and enhance prefrontal development, producing precocious maturation, at the same time arresting the development of this region to its full adult capacity. Significant reductions in total brain and cerebral gray matter volume (GMV) and loss of normal left-right asymmetry of the frontal lobes were revealed in children exposed to traumas. Children with PTSD symptoms had significant decrease in GMV in the dorsal regions of the prefrontal cortex [41]. The prospective studies conducted in the project “English Romanian Adoptee Young Adult Follow-up” showed an 8.57% reduction of total brain volume in adults adopted before 4 years of age [42]. The magnitude of the cortical regions correlated with the duration of institutional emotional deprivation, after the exclusion of such factors as malnutrition and parental preference of children with bigger heads. However, there were no relations between deprivation and volume of sub-cortical regions like the amygdala, hippocampus, thalamus,

nucleus accumbens, nucleus caudates, putamen and globus pallidus [43]. On the other hand, the area and volume of the right ventral temporal cortex were increased in emotionally deprived group, which is presumed to be compensatory to symptoms of hyperactivity [42]. Findings from many research studies suggest that exposure to various forms of maltreatment affect the sensory systems or pathways through which the aversive stimuli is processed or interpreted, which is consistent with the idea that sensory systems are strongly influenced by early experiences. It has been proven that there are white matter tract abnormalities in young adults exposed to parental verbal abuse who witnessed domestic violence, and those exposed to verbal peer bullying [44].

Finally, it is worth considering differences in the sensitivity of specific brain regions to stress, due to differential rates of maturation. Andersen analyzed the effect of sexual abuse occurring during different developmental stages on brain region volumetrics [45]. Hippocampal volume was reduced in association with SA at 3-5 and 11-13 years of age. The corpus callosum was reduced with SA at 9-10 years and frontal cortex GMV was attenuated in women sexually abused at ages 14-16 years of age. Studies conducted by Tomoda also showed a particularly sensitive period in left visual cortex development, mainly between the fifth and sixth years of life [46].

CONCLUSIONS

This review presents and summarizes longitudinal studies that revealed the impact of early trauma throughout the life course. These findings provide preliminary evidence that brain regions in humans have different windows of vulnerability, which leads to variability in morphological, functional and clinical outcomes in patients traumatized in childhood.

One of the most important conclusions that needs to be remembered is that maltreated children showed decreased levels of persistence and goal-oriented activity, increased inattention, higher anger expression, frustration and non-compliance in comparison to those children who received adequate care. The severity of neglect and abuse correlated highly with psychopathology. The cumulative number of psychiatric disorders during childhood is the strongest predictor of a negative life outcome. In adulthood 90% of maltreated children had at least one psychiatric diagnosis. Thus, prevention and prophylaxis from the earliest years of human life should be the main goal of mental healthcare. On the other hand, some protective factors counteracting the effects of early adversities were also characterized. These are experiences of support and competence, an alternative available caregiver, good school or organized home environment. The authors of the research surveyed concluded that the most powerful predictor of outcomes for children was

the cumulative history of care. The second important observation was that episodic trauma seemed to adversely influence functioning in adulthood, but not to the same extent as chronic or multiple traumatic experiences. Not only overt abuse and severe neglect, but also psychological adversities related to parents' death, illness, addiction or divorce may have enduring effects. The naturalistic observation of Romanian adoptees revealed also that protracted emotional deprivation has a negative impact on human development. In children deprived for more than 6 months in institutions, further observation showed enhanced autistic symptoms at the beginning, whereas persistent disinhibited social disorder, social communication impairments and compulsions lasted until adulthood. Finally, the results of the Adverse Childhood Experience Study showed a life-long impact of early life adversities underlying not only mental health but many somatic problems.

One could conclude that the development of the human brain and related emotional, cognitive and social functioning are not only genetically directed, but need particular preliminary conditions and a social environment (quite structured and complex) to gain its full potential and capacity. It seems that stable and non-violent

relations with caregivers ensuring emotional and material safety is the first prerequisite for the human growth to maturity. The second prerequisite seems to be an enriched and socially complex environment, in which a child can obtain the necessary skills to regulate emotions and build satisfactory social interactions. All forms of cultural, traditional or social customs which provide such conditions can enhance human brain development to its full capacities and potential.

Consequently, the successful treatment of the psychological effects of early life trauma requires attention not only to what happened to the survivor but also to what failed to happen. Prolonged, recurring abuse is generally coupled with neglect. The survivor must try to cope with the impact of abuse, while lacking the emotional support or developmental skills coming from a secure attachment figure. In planning treatment, it is so important to deal with traumatic recalled or embodied memories but also to learn and enhance the necessary social and emotional skills. It is also worth remembering that the fundamental prerequisite for good recovery, as well as for good life and health, is safety. It is only in safe and violence-free environments that any changes or recovery are possible. Safety assurance should be the first step in trauma treatment.

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