

Early stress and dissociation: psychopathological pathways

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SUMMARY

Objectives

In the last two centuries, researchers tried to investigate the complex effects of early life stress on developing brain as well as the mechanisms underlying dissociation that may be frequently linked to traumatic experiences. Clinically, dissociation may be found in many psychiatric disorders and may be defined as the disruption of important human functions such as memory, identity, consciousness, thinking, emotions, body representation, motor control as well as behavior. The aim of the present review was to selectively review data about the link between traumatic experiences, dissociation and psychopathological pathways.

Methods

A detailed search regarding the association between traumatic experiences, dissociation, and psychopathological pathways has been carried out.

Results

Based on the most relevant included studies (n = 16), a chronic hypothalamic pituitary adrenal (HPA) axis dysregulation (that may include both hyperactivity and hypoactivity) has been found in subjects with childhood traumatic experiences. The dysregulated stress system in subjects who have suffered from early traumatic conditions is able to promote important neuroendocrine and immune impairments together with inducing inflammatory-related conditions. Exposure to early-life traumatic experiences may be also linked to relevant psychopathological and neurocognitive consequences with multiple psychopathological conditions that may be developed in individuals with a positive history of traumatic experiences. Importantly, early adversities are closely related to enhanced chronicity, suicidal behavior, and poorer treatment response.

Conclusions

Although dissociation may be diagnosed both in acute and chronic conditions, many clinicians are, unfortunately, not able to correctly detect these conditions. The main implications related to the link between trauma, dissociation, and most relevant psychopathological conditions are discussed.

Key words: early stress exposure, traumatic experiences, dissociation, psychopathological pathways, emotional-behavioral disturbances

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Conflict of interest

The Authors declare no conflict of interest

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The impact of early stressful experiences on developing human brain

Approximately in 400 BC, Plato was the first to recognize the fragility of the developing human brain stressing the impact of early experiences and the importance of trauma on the development of human brain functions. In the last two centuries, researchers tried to investigate the complex effects related to early life stress on developing brain as well as the mechanisms underlying dissociation and dissociative disorders (which are frequently linked to early stressful experiences), especially by a neurobiological

point of view. Seminal studies clearly demonstrated in 1970 the negative behavioral effects and the complex consequences related to early maternal separation in baby rhesus monkeys¹. These studies are based on the assumption that trauma and adverse early experiences such as abuse or maltreatment may induce the presence of “scars” leading to significantly impaired wellbeing and psychosocial disability^{2,3}. Currently, research tried to analyze the nature of these “scars” in the effort to identify the exact nature of the biological vulnerability underlying early stress and recognize the illness trajectories together with the multiple psychopathological pathways associated to early stress.

Exposure to early-life traumatic experiences may be linked to relevant psychopathological and neurocognitive consequences. Importantly, child abuse and maltreatment may be considered as leading causes of disability and are significantly associated with the emergence and maintenance of psychiatric conditions according to the Centers for Disease Control (CDC)⁴. Furthermore, there are studies in the current literature supporting the notion that early adversities are closely related to enhanced chronicity⁵, suicidal behavior⁶, and poorer treatment response⁷. Adverse childhood experiences are also linked to learning and behavioral problems, impairments in school performance⁸, enhanced school absence⁹, and significantly reduced verbal Intelligence quotient (IQ)¹⁰ exerting important effects on the individual functioning. Overall, traumatic experiences have been documented in 15% to 60% of children and adolescents¹¹ with early adversities representing a public health priority worldwide.

From chronic developmental stress to dissociation

Dissociation may be considered one of the possible adaptive responses to early-life stress perceived as a traumatic experience or chronic developmental stress exerting important consequences for the individual functioning. Some researchers¹² suggested that trauma and dissociation need to be addressed at the crossroad of neurobiology and psychopathology. Interestingly, dissociation may be found in many psychiatric disorders and may affect both the phenomenology as well as treatment response in psychiatric conditions¹³. The recent history of psychiatry is closely linked with the history of dissociation and dissociative disorders (related to the existence of trauma).

Dissociation is associated with as the disruption of important human functions such as memory, identity, consciousness, thinking, emotions, body representation, motor control as well as behavior¹⁴. Dissociative conditions represent acute and transient reactions to stressful

life events or interpersonal problems and may manifest in the form of stupor (usually considered a mild transient state of dissociation) but even as acute psychotic conditions. The emergence of dissociative conditions may be with the following symptoms: palpitations, fainting, shaking, depersonalization, and non-epileptic seizure. Overall, it has been hypothesized that dissociative conditions are aimed to self-protection in response to specific or aspecific threats¹⁵.

According to recent diagnostic manuals, amnesia with fugue, depersonalization, derealization, identity confusion/alteration are the five primary dissociative disorders but dissociative identity disorder is the most pervasive form covering all the entire spectrum of dissociative symptoms^{12,14}. In DSM-5, dissociative fugue has been considered as a specific subtype of dissociative amnesia as it is not confirmed as a separate condition (similarly to previous editions). Interestingly, the DSM-5 diagnostic criteria for post-traumatic stress disorder (PTSD) now include the existence of a dissociative subtype (PTSD-DS)¹⁴. By a clinical point of view, dissociative disorders are not recognized as a unitary phenomenon in the community and some individuals may claim only some symptoms which appear prevalent in their current symptomatology.

Although dissociation may be diagnosed both in acute and chronic conditions, many clinicians are, unfortunately, not able to correctly detect dissociative conditions. Existing studies exploring the link between early life trauma and dissociative identity disorder documented significant rates of childhood adversities in the histories of individuals with dissociative identity disorder relative to other diagnostic groups¹⁶ Spiegel et al.¹⁶ also suggested that childhood sexual abuse is very common, childhood physical abuse often present and both sexual and physical abuse/maltreatment (performed by multiple perpetrators) present in a percentage variable between 77% to 100% in patients with dissociative identity disorder. Overall, 5-12 years are needed for patients with dissociative disorders in order to reach the correct diagnosis while during this period at least 3-4 incorrect diagnoses were usually carried out by clinicians with important negative consequences in terms of clinical management and treatment.

Psychobiological and neurobiological theories in the field of trauma and dissociation

Abnormally prolonged stress reactions may exceed the individual adaptive ability to fight stressful situations and enhance the likelihood of psychopathological responses. According to Trauma Model, dissociation is considered as a psychobiological state/trait having a protective role against traumatic or pervasive early experiences¹⁷. It has been suggested that dissociation modulates the impact of trauma by psychobiologically

attenuating the negative implications of trauma directly through the activation of different states of consciousness. Dissociation has been described in humans as the equivalent of the animal “freeze” in the context of a life-threatening danger when the “fight or flight response” has generally failed¹⁸. Based on Porges’ theory¹⁹, given the failure of fight-flight sympathetic stress responses, the dominance of the primitive vagal parasympathetic system is directly linked with the freeze response. Many evidence (e.g., genetic, developmental, neurobiological, and psychophysiological) supported the existence of a model in which the exposure to chronic repeated traumatic experiences is associated with the emergence of a freezing behavior¹⁶. Hypothalamic pituitary adrenal (HPA) axis hyperactivity as well as higher circulating cortisol levels, enhanced cortisol awakening response, increased adrenocorticotrophic (ACTH) hormone and enhanced cortisol responses to psychosocial stress or endocrine challenges have been all documented in adult patients with childhood traumatic experiences representing one of the most specific form of early life stress²⁰⁻²³. In particular, it is well-known that the pathophysiology of stress-related disorders is closely related to a chronic dysregulation of the HPA²⁴ with the hyperactivation of the stress system that is related to the hypersecretion of ACTH and arginine-vasopressin (AVP) by the hypothalamus and ACTH hypersecretion by the pituitary²⁵. These events determine abnormally higher cortisol levels due to the “insensitive” negative glucocorticoid feedback of the HPA axis loop. However, there are also reports regarding the

existence of HPA axis hypo-activity (e.g., lower circulating cortisol levels, blunted cortisol stress responses) in similar populations and study designs²⁶⁻²⁸. This abnormally reduced activity might represent a compensatory adaptation related to a negative feedback hypersensitivity of glucocorticoids, downregulated secretion of corticotropin releasing hormone (CRH)/AVP to the pituitary²³ or a long-lasting glucocorticoid catabolism drop associated with higher active cortisol persistence in liver and kidney²⁹ (Fig. 1). The dysregulated stress system in subjects who have suffered from early traumatic conditions is able to promote important neuroendocrine and immune impairments, and induce inflammatory-related or immunosuppressed conditions³⁰. In particular, childhood traumatic experiences may activate an abnormal inflammatory response through the secretion of pro-inflammatory cytokines, and the stimulation of systemic acute-phase proteins such as C-reactive protein³¹. A positive history of childhood traumatic experiences has been reported as an independent risk factor for peripheral immune dysregulation and long-term, low-grade inflammatory excess in adulthood³². Stress-related alterations in pro-inflammatory pathway have been supposed as one of the most relevant biological links through which the environment may influence the general health³³. It has been reported that neuroendocrine responses to stress may enhance the transcription of pro-inflammatory genes encoding for the production of interleukin-1 beta, interleukin-6, interleukin-8, cyclooxygenase 2 and tumor necrosis factor alpha³⁴. However, several non-

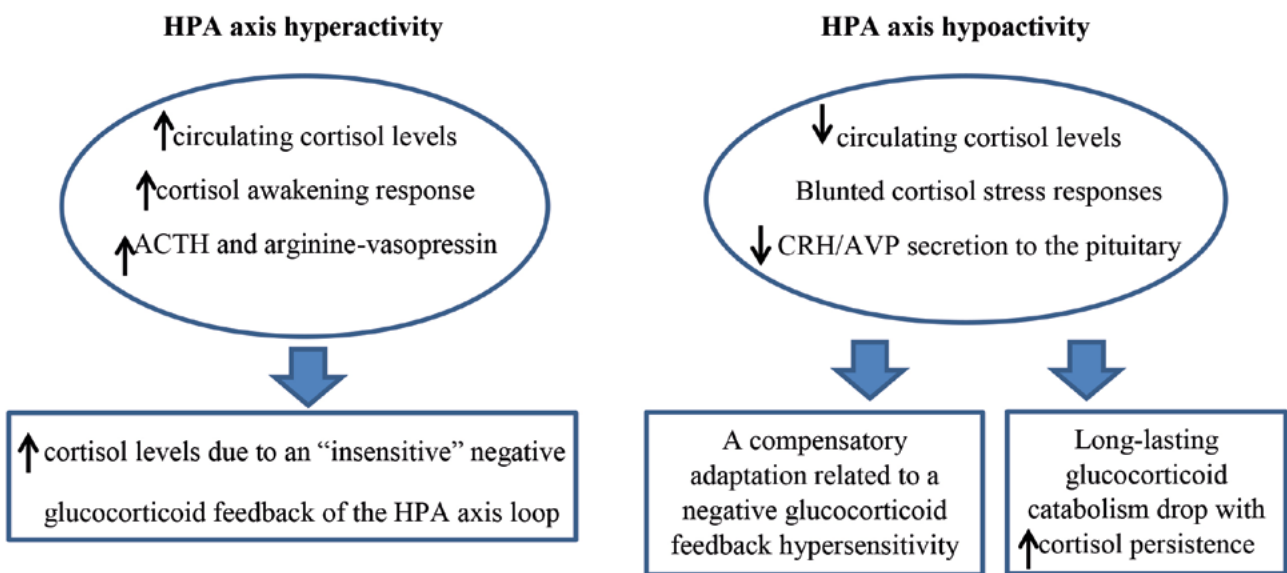


FIGURE 1. Chronic HPA axis dysregulation in subjects with childhood traumatic experiences.

stress pathways that might contribute to differential gene expression are associated with increased drinking and smoking as well as higher rates of obesity enhancing the risk of mortality³⁵.

In addition, existing evidence suggested that the abnormally impaired human microbiome could be another pathway linking childhood traumatic experiences with altered neuroimmune reactions and might abnormally impair neurodevelopment with long-lasting effects on general health and behaviors³⁶. According to a very recent study from Taft et al. (2019), more than 30% of patients with inflammatory bowel disease reported significant PTSD symptoms and 25% manifested a clinical PTSD diagnosis since disease onset, with the majority of patients stating that their PTSD was mainly related to their inflammatory bowel disease experiences. Based on the recent growing understanding about the brain-gut-microbiome axis^{37,38}, the negative impact of stress on disease course may help clinicians to recognize psychological distress as a component of inflammatory bowel disease patient care and treatment³⁹.

Evidence also reported a correlation between childhood adversities, endothelial dysfunction, and increased superoxide production⁴⁰ with reduced endothelial nitrous oxide system and dysfunctional endothelial Angiotensin II-mediated signaling as well as sensitization to Angiotensin II-induced vasoconstriction⁴¹. Evidence demonstrated that a history of traumatic experiences may be associated with an increased risk of endothelial injury and dysfunctions (reported as on the initiating event in atherosclerosis⁴² and consequently cardiovascular diseases)⁴³⁻⁴⁵. Thurston et al.⁴⁶ stressed the importance of considering trauma exposure as an important psychosocial factor in midlife women's cardiovascular health based on the findings of their study on 272 nonsmoking peri- and post-menopausal women in which over 60% of the sample reported at least one traumatic exposure, 18% had three or more exposures and a greater number of traumatic exposures was linked to poorer endothelial function.

The stress system is even interconnected with alterations in metabolism with evidence reporting that chronic stress is associated, during critical periods of growth and development, with a significant disruption of circadian and metabolic system having permanent adverse effects on body size and composition as well as associated physical inactivity, emotional eating disorders, and disrupted sleep pathway. Sleep disturbances have been reported very frequently after traumatic experiences with insomnia and trauma-related nightmares as the most common symptoms closely linked to stress-traumatic events⁴⁷. In addition, severe sleep disorders with sympathetic activation and disruptive nocturnal behaviors (that may be defined as extreme nocturnal

manifestations of traumatic experiences encompassing nightmares, disruptive nocturnal behaviors, and comorbid insomnia) are frequently reported in the context of traumatic experiences⁴⁸.

Relevantly, the response to early developmental cues may be facilitated by persistent changes in the transcriptome playing a very relevant role in long-term biological trajectories of stress-related diseases^{49,50}. This is mainly related to the assumption that early development represents a particularly sensitive period for epigenetic modification of the genome⁵¹ with one of the most investigated epigenetic marks being DNA methylation, proposed as an important epigenetic mechanism through which childhood maltreatment may exert long lasting effects on gene expression and human behavior⁵². Importantly, the timing of childhood maltreatment/abuse has been suggested as crucial in determining the severity of epigenetic alterations⁵¹. To this specific regard, some researchers⁵³ suggested that exposure to trauma occurring earlier in the course of development could lead to enhanced damage, supposing the existence of a critical temporal window in which childhood abuse/maltreatment seems able to more significantly affect and modify the human epigenome. It is presumable that DNA methylation together with alternative epigenetic marks and mechanisms may act at the interface of genes in association with life experiences, behavioral regulation, and mental health⁵².

Trauma and dissociation: possible psychopathological pathways

Severe impairments in child development, disruption of attachment security and self-regulatory processes, poorer physical/mental health outcomes have been described after the exposure to childhood traumatic experiences in both childhood and adulthood⁵⁴. From childhood to adulthood, it has been suggested that approximately 70% of individuals may experience at least one lifetime traumatic event⁵⁵. The area of stress is clinically a condition of great complexity, with many studies that have been conducted on this topic and many controversies regarding different psychopathological pathways related to the exposure to early traumatic experiences. Table I summarizes the most relevant studies about the association between early stress, dissociation, and multiple psychopathological pathways related to early traumatic experiences. Overall, 13 cross-sectional and 2 longitudinal follow-up studies investigated the relation between early stress, dissociation, and multiple psychopathological pathways. Among cross-sectional studies, there are contributions⁵⁶⁻⁵⁸ stressing the link between child sexual abuse, behavioural problems, attachment insecurity, and psychological difficulties while

TABLE I. Most relevant studies about the association between early stress, dissociation, and multiple psychopathological pathways related to traumatic experiences.

Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
van Duin et al. ⁵⁶	41 parents; 44 children (30 boys, 14 girls)	Cross-sectional study	1) Diagnostic Infant and Preschool Assessment; 2) Anxiety Disorders Interview Schedule for DSM-IV Child Version, parent Interview Schedule; 3) Children's Revised Impact of Event Scale, (PV); 4) Child Dissociative Checklist; 5) Child Sexual Behavior Inventory; 6) Child Behavior Checklists 1-5 and 6-18; 7) Attachment Insecurity Screening Inventories 2-5 and 6-12 years; 8) Impact of Event Scale – Revised; 9) Parent Emotional Reaction Questionnaire; 10) Experiences in Close Relationships	Overall, 3% of child victims reported PTSD, 30% sexual behavior problems, 24% internalizing problems, 27% attachment insecurity, and 18% any psychiatric disorder but 39% were asymptomatic. In parents, feelings of guilt, shame, and anger about the abuse of their child were found. 19% showed PTSD symptoms, 3% avoidant, and 8% anxious attachment problems in their intimate relationship. Finally, 25% of child victims and 45% of parents received psychological treatment	1) The children's ages restricted to a single informant source; 2) The study represents a biased subgroup of families; 3) The study participation itself may have mitigated possible negative outcomes; 4) The small sample size; 5) The lack of a control group	Child sexual abuse in very young children was linked to both sexual and non-sexual behavior problems and attachment insecurity, but rarely with PTSD or dissociation
Schalinski et al. ⁶¹	49 females; 16 healthy controls	Cross-sectional study	1) Life Event Checklist; 2) Clinician Administered PTSD Scale; 3) Shutdown Dissociation Scale; 4) Resting state magnetoencephalography	Increased delta and reduced beta power were found linked to dissociative symptoms. Theta and alpha oscillatory power (in particular childhood sexual abuse) were modulated by adversity-related measures	1) Results are based on women with comorbid depressive symptoms; 2) No reliable source for the early infancy are available about childhood adversities	TRA in neural organization vary with exposure to adversities but even with the potential to evoke ongoing shutdown responses.
Karatzias et al. ⁵⁹	82 subjects with a history of interpersonal trauma and 78 non-clinical controls	Cross-sectional study	1) Young Schema Questionnaire-Short Form; 2) PTSD Checklist-Civilian Version; 3) The Symptom Checklist-90; 4) Dissociative Experiences Scale; 5) Rosenberg self-esteem scale	Survivors of interpersonal trauma showed higher maladaptive schemas than controls. Schemas in the domains of Disconnection and Impaired Autonomy were associated with all psychopathological characteristics	1) The sample consisted only of subjects with interpersonal trauma; 2) Different schema profiles may be active in different trauma groups; 3) limited information are available concerning the severity/duration of trauma	Findings stressed the importance of interventions targeting schemas in the domains of Disconnection and Impaired Autonomy

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Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Thomson and Jaque ⁶²	209 dancers who were exposed to traumatic events	Cross-sectional study	1) Adverse Childhood Experiences; 2) Beck Depression Inventory II; 3) Coping Inventory for Stressful Situations; 4) Dissociative Experience Scale-II; 5) Internalized Shame Scale; 6) Inventory of Childhood Memories and Imaginings; 7) Posttraumatic Stress Diagnostic Scale; 8) State-Trait Anxiety Inventory; 9) Traumatic Events Questionnaire	A higher distribution of PTSD (20.2%) in dancers relative to normal population (7.8%) was found. Dancers showed a higher frequency of family members with PC, more difficulties to deal with trauma, and more suicidal thoughts. PTSD group of dancers showed more childhood adversities and adult trauma, higher levels of anxiety, depression, dissociation, and shame. Relative to no-PTSD group, PTSD group reported higher fantasy proneness and emotion-oriented coping strategies (linked to psychological instability)	1) The evaluation of traumatic events and dissociative symptoms were based on self-administered questionnaire; 2) The lack of a control group; 3) The study results are not generalizable to more homogeneous groups of dancers; 4) The study included only dancers who met PTSD Criteria A	Dancers should be helped to early address abuse/maltreatment. By understanding PTSD in dancers, medical and mental health treatment protocols may be carried out to manage the impact of disabling PTSD symptoms
Jepsen et al. ⁶³	55 early traumatized inpatients	Cross-sectional study	1) Somatoform Dissociation Questionnaire-20; 2) 28-item Dissociative Experiences Scale-II; 3) Impact of Event Scale; 4) Symptom Checklist 90 Revised; 5) Beck Depression Inventory-II; 6) Structured Clinical Interview for Dissociative Disorders-Revised	Overall, 32.7% reported psychoform and SDS; 40% SD symptoms; 27.3 non-dissociative symptoms. The highly dissociative group showed younger age, more frequency of living alone, higher levels of post-traumatic and general distress, more frequent reports of suicidality, self-mutilation, eating problems, and less favorable treatment response	1) The small sample size reducing power to detect a medium effect size to 0.40; 2) Retrospective self-report may be vulnerable to recall or bias. 3) The assessment of childhood abuse did not include a validated measure	The present findings suggest the importance of using dissociation measures to identify subgroups of patients with severe psychopathology who may be more treatment resistant



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Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Price et al. ⁶⁰	1676 youth aged 4-18	Prospective longitudinal study	1) My exposure to violence; 2) Revised-child behavior checklist 6-18 years; 3) Emotionality, activity, sociability, and impulsivity temperament survey; 4) Family socioeconomic status	Interpersonal traumas including significant interpersonal proximity were associated with oppositional defiant and conduct problems. Nearly all the symptom domains were positively linked to direct trauma experiences and emotionality	1) Lack of information regarding subjective experiences of social betrayal; 2) Examination of TE carried out only in the year prior to assessments at the second and third waves 3) relevant information about past TE might have been missed; 4) Data was collected every two to three years; 5) Anxiety subscale derived from the Revised-child behavior checklist-R had poor-moderate reliability	Each symptom domain was predicted by at least one type of trauma experience. The present findings underlined the important role of traumatic experiences in the etiology of childhood psychopathological pathways
Gaon et al. ⁵⁷	505 outpatients	Cross-sectional study	1) Dissociative Experience Scale; 2) Trauma History Questionnaire; 3) Impact Of Event Scale; 4) Post-traumatic Diagnostic Scale	Overall, 97% reported nearly one lifetime traumatic event. At the time of occurrence, TE were experienced as meaningful and severe. Victims reported that the effects of sexual and childhood emotional abuse remained very intense lifetime and were perceived as powerful experiences. However, TE such as natural disasters and battle trauma were linked to long-term effects of low intensity	1) The evaluation of traumatic events and dissociative symptoms were based on self-administered questionnaire; 2) The use of a clinical interview in a randomized sample of participants was not carried out; 3) The Post-traumatic Diagnostic Scale was not available in Russian/Spanish; 4) Only 90.3% of participants completed all the questionnaires	The screening and procedures to diagnose PTSD should be more accurate. Among all traumatic experiences, sexual abuse exerted the most relevant effects on later life

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Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Etter et al. ⁵⁸	173 adult psychiatric inpatients	Cross-sectional study	1) Symptom Checklist-90-Revised; 2) Dissociative Experiences Scale; 3) Structured Interview of Self-Destructive Behaviors; 4) Structured Interview for PTSD; 5) Structured Interview for Social Support as a Child; 6) Jacobson's structured interviews interpersonal violence and sexual experiences	Depression, dissociation, self-destructive behavior, PTSD, and global psychopathology were negatively associated with positive affect. Significantly less positive affect were found in subjects who experienced both physical and sexual abuse relative to those with only physical or no abuse experiences. Lower childhood social support and greater severity of sexual abuse predicted lower positive affect	1) The potential for error in subjects' recollection of childhood experiences and reports of low positive affect; 2) The reliability/validity of the positive affect items were not performed; 3) Findings are limited to psychiatric inpatients population	Subjects experiencing multiple types of early adversity, more severe sexual abuse experiences, and less social support are at higher risk of psychological difficulties
Kleim et al. ⁶⁴	222 assault survivors	Prospective longitudinal study	1) Trauma History Interview; 2) Depressive Attributions Questionnaire; 3) Beck Hopelessness Scale – short form; 4) Cognitive Processing Questionnaire; 5) Posttraumatic Cognitions Inventory; 6) Response to Intrusions Questionnaire; 7) State Dissociation Questionnaire	MDD and PTSD models predicted both MDD and PTSD symptom severity, but disorder-specific models predicted the respective outcome best (43% for MDD, 59% for PTSD). Maintaining cognitive variables (hopelessness and self-devaluative thoughts in MDD; cognitive responses to intrusive memories and persistent dissociation in PTSD) showed the clearest specific relations with outcome. Model-derived variables predicted MDD and PTSD at 6 months over and above the initial diagnoses	1) The number of variables in the structural equation models was limited due to restrictions in sample size; 2) The numbers of trauma survivors within the disorder categories were too small in order to investigate subgroups of "pure" disorders; 3) Results were limited as they have been derived only by a sample of assault survivors	The study stressed the importance of cognitive factors in the development of depression and PTSD after trauma



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Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Matos et al. ⁶⁵	90 participants from the general population	Cross-sectional study	1) Shame Experiences Interview; 2) Impact of Event Scale – Revised; 3) Rumination Responses Questionnaire; 4) White Bear Suppression Inventory; 5) The Dissociative Experiences Scale – Revised; 6) Depression, Anxiety and Stress Scale	Emotion regulation processes (e.g., brooding, thought suppression and dissociation), were found to mediate the association between shame traumatic memory with others and MDD. Shame traumatic memory with attachment figures had a direct effect on MDD but only brooding partially mediated this relation	1) The transversal study design; 2) Findings may not be generalized to clinical populations; 3) The use of self-report instruments to evaluate traumatic events and dissociation	These results stressed the importance of addressing shame memories, especially those involving attachment figures, particularly when working with patients with depressive symptoms and/or that find compassion difficult or scary
Matos and Pinto-Gouveia ⁶⁶	11 subjects from the general population	Cross-sectional study	1) Experience of Shame Scale; 2) Depression, Anxiety and Stress Scales; 3) Impact of Event Scale-Revised	ESE revealed TM characteristics. Importantly, TME were linked to current feelings of internal and external shame in adulthood. Current shame and MDD were found associated. More depressive symptoms were showed by subjects with more TSM. An effect of shame traumatic memory on the relation between shame and MDD was finally reported	1) The transversal nature of the study design, the use of self-reports questionnaires, the possibility of selective memories in participants' retrospective reports and the use of a general community sample, are some methodological limitations that should be considered	Shame memories have TM characteristics, able to affect shame but also moderate the impact of shame on MDD. Interventions need to address shame memories
Simeon et al. ⁶⁷	46 participants with depersonalization disorder, 21 with PTSD and 35 healthy controls	Cross-sectional study	1) Dissociative Experiences Scale; 2) Cambridge Depersonalization Scale; 3) Toronto Alexithymia Scale; 4) Tellegen Absorption Scale; 5) Cognitive Failures Questionnaire; 6) Childhood Trauma Questionnaire	Higher absorption and cognitive failures scores were found in the DD and PTSD groups. Elevated alexithymia (DIF) were reported only in the DD group. Alexithymia-DIF was the only predictor of both DD and depersonalization scores. Finally, CTE and absorption predicted amnesia scores	1) The cross-sectional design that did not allow causal relations between constructs; 2) The self-report nature of measures (although they are well-validated instruments)	The link between depersonalization and alexithymia appeared to be specific rather than broadly related to early CTE or to trauma-spectrum psychopathology

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Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Semiz et al. ⁶⁹	579 male patients diagnosed with APD	Cross-sectional study	1) Structured Trauma Interview; 2) Turkish version of the Dissociative Experiences Scale	CSA, physical abuse, neglect, and early separation from parents were more common among APD subjects than controls. APD group reported more dissociative symptoms and 50.4% reported pathological dissociation. Overwhelming childhood experiences of all four types were significant predictor of APD. CTE and comorbid features relevant to APD were linked to dissociation	1) It remains unclear whether these findings are specific to antisocial personality disorder; 2) It was not possible to control for the presence of comorbid Axis II and some Axis I diagnoses; 3) The use of retrospective reporting of childhood traumatic events further limits the generalization of the main findings	CTE are important components in the etiology of APD. Dissociative symptoms in patients with APD appear as a defense against significant childhood trauma and persist into adulthood
Riggs et al. ⁷⁰	80 inpatients	Cross-sectional study	1) Adult Attachment Interview; 2) Experiences in Close Relationships Scale; 3) Milion Clinical Multiaxial Inventory III; 4) Dissociative Experiences Scale; 5) Dissociative Disorders Interview Schedule – Self-Report Version	Personality dimensions were closely linked to self-reported romantic attachment style; fearful adults showed the most maladaptive personality profiles. Self-report dimensions of self and other contribute to different psychological dysfunctions. Adult Attachment Interview unresolved trauma was linked to dissociation and PTSD; unresolved trauma and loss contributed to schizotypal and borderline personality disorder scores as well	1) The comorbidity/prevalence of MDD should be taken into account when interpreting results; 2) The sample size did not allow to generalize findings; 3) Retrospective reports of childhood trauma and parent-child relationships may have introduced subjective biases; 4) Data collection did not permit the examination of temporal/causal relation between attachment/personality and psychopathology	Results partially supported theoretical predictions concerning distinct measures of adult attachment in the analyzed sample



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Mellman et al. ⁶⁸	83 inpatients	Prospective follow-up study	1) Clinician Administered PTSD Scale; 2) Initial Subjective Reactions Scale; 3) The Peri-traumatic Dissociation Scale; 4) COPE	At follow-up, 24% of the available 50 subjects met criteria for PTSD and an additional 22% met criteria for two of three symptom clusters. At follow-up, PTSD severity was independently predicted by early symptoms of elevated arousal and coping with disengagement	1) It is possible that the variation of these findings is related to the nature of the traumas; 2) It is possible that the impact of prior mood and anxiety disorders and prior trauma has been attenuated; 3) The sample was predominantly composed by Hispanic subjects	In the setting of severe injury, early manifestations of enhanced arousal and use of certain coping styles were associated with the risk of developing PTSD
Ogawa et al. ⁷¹	168 young adults	Cross-sectional study	1) Pre-school Behavior Questionnaire; 2) Teacher Report Form; 3) The Youth self-Report; 4) Child Dissociative Checklist; 5) Dissociative Experiences Scale; 6) Life Events Inventory; 7) Adolescent Perceived Events Scale; 8) The Adolescent Life Stress scale; 9) The Adolescent Health Survey; 10) The Carey Infant Temperament Scale; 11) The Projected Self-Esteem scale; 12) Ainsworth Strange Situation; 13) Wechsler Adult Intelligence Scale	First, age of onset, chronicity and severity of trauma predicted dissociative symptoms. In addition, both the avoidant and disorganized patterns of attachment predicted dissociation. Childhood dissociation may be a more normative response to disruption and stress while dissociation in adolescence and young adulthood may be more indicative of psychopathology	1) The checklist measures of dissociation were not designed to detect dissociation; 2) The relatively small number of participants with clinical dissociation; 3) The preliminary nature of the present study findings; 4) Sexual abuse has been underreported as information to this regard was extremely limited	Dissociative behaviors is usually more frequent early in life and may gradually become more indicative of psychopathology with age

Note: Antisocial personality disorder (APD); childhood sexual abuse (CSA); childhood traumatic events (CTE); depersonalization disorder (DD); difficulty identifying feelings (DIF); early shame experiences (ESE); major depressive disorder (MDD); Parent Version (PV); post-traumatic stress disorder (PTSD); psychiatric conditions (PC); somatoform dissociative symptoms (SDS); Trauma-related alterations (TRA); traumatic memory (TM); traumatic events (TE); traumatic memory experiences (TME).

others⁵⁹ suggested the relevance of interpersonal traumatic experiences in determining higher maladaptive schemas (especially, in the domains of Disconnection and Impaired Autonomy) and subsequent higher psychopathological characteristics. The importance of interpersonal proximity as associated with specific neuropsychiatric conditions such as oppositional defiant and conduct problems was also stressed by longitudinal studies⁶⁰. In addition, existing reports⁶¹ suggested the variation with exposure to adversities of trauma-related alterations in neural organization. While

some studies⁶² focused on specific populations (e.g., dancers), other reports contributions⁶³ supported the importance of using dissociation measures to identify subgroups of patients with severe psychopathology or the relevance of specific factors such as cognitive profile⁶⁴, shame memories^{65,66}, alexithymia-difficulty identifying feelings⁶⁷, and early enhanced arousal or specific coping styles (based on a longitudinal follow-up study⁶⁸ in the development of psychopathological pathways related to traumatic experiences). Childhood experiences may be also considered as important com-

ponents of specific psychopathological conditions such as antisocial personality disorder⁶⁹, while unresolved trauma and loss may be frequently found in the history of individuals with schizotypal and borderline personality disorders⁷⁰. Finally, there are studies reporting that dissociation gradually become more indicative of psychopathology with age⁷¹.

Here, as follows we list different psychopathological conditions that are clinically associated with traumatic experiences.

First, *dissociative disorders* are, no doubt, the most important response to traumatic or overwhelming experiences during childhood and they have been carried out by individuals in order to attenuate psychological distress and promote coping and survival¹⁶. The dissociative psychopathology which is closely related to chronic developmental stress and traumatic experiences may be historically articulated in dissociative disorders which may have a fluctuating chronic course over years. Dissociative disorders have been first introduced by Janet and Freud when they initially described traumatic hysteria that included dissociative and amnesic phenomena⁷². Dissociation is the first human psychological process against trauma-related threats while maltreatment and complex traumatic experiences such as sexual or physical abuse, emotional maltreatment or unpredictable parenting are usually linked to the development of long-term dissociative reactions during childhood such as PTSD responses⁷³. Importantly, alterations in self-regulatory processes, poorer impulse control, impairments in interpersonal relations, impulse and self-perception abnormalities may be all linked with trauma-related dissociation. The fundamental characteristic of dissociative disorders (dissociative amnesia, depersonalization, derealization, identity confusion, and identity alterations) is the disruption of one or more mental functions. Dissociative disorders are fundamental phenomena of dissociative psychopathology that may vary in terms of spectrum of severity¹³.

In addition, evidence⁷⁴ reported that a traumatic reactive disorder related to trauma occurs with a prevalence above 20%. Although *PTSD* is usually considered a construct which is still under construction conceptually, it may be considered a trasversal diagnosis through the different contexts of the human activities⁷². PTSD has been separated in DSM-5 by the group of Anxiety Disorders and included in a new group named Trauma- and Stressor-Related Disorders¹⁴.

One of the most relevant recognized pathways related to PTSD is the dissociative subtype of PTSD defined by symptoms of depersonalization and derealization together with other PTSD symptoms⁷⁵. There are authors⁷⁶⁻⁷⁸ suggesting that the dissociative subtype of PTSD ranges from 12% to 50% of PTSD cases. Sub-

jects with the dissociative subtype of PTSD may develop overwhelming depersonalization and derealization and may endorse significantly childhood trauma and adult sexual trauma^{79,80}. Kerig et al.⁸¹ reported a higher prevalence rate (83%) of dissociative subtype for PTSD in young adolescents having troubles with the juvenile justice, and they also identified a three-factor dimension of post-traumatic dissociation including depersonalization/ derealization, amnesia, and loss of conscious control. In addition, these individuals may exert higher levels of avoidant and borderline personality disorder behaviors^{79,80}. Beyond the classical definition of PTSD by DSM-5, ICD-11 describes two diagnostic entities with different symptom profiles defined as PTSD and complex PTSD. Interestingly, disturbances in Self-Organization, which affect emotional regulation, interpersonal relationships, and identity arising soon, repeatedly, and prolonged in time may be usually found in complex PTSD.

Chronic dissociative depression may be identified as a specific psychopathological construct that tends to have a earlier age of onset when compared to major depressive disorder representing a distinct psychopathological pathway related to traumatic experiences and dissociation^{13,82-83}. Sar et al.⁸² reported that relative to those with a major depression, individuals with dissociative depression were more likely to suffer from pervasive worthlessness and guilt, abnormally reduced concentration, suicidal behavior, loss of appetite, and weight alterations. Thus, chronic dissociative depression may be recognized as a more severe illness subtype relative to major depression without dissociative aspects.

Affect dysregulation may be considered another crucial psychopathological pathway related to the occurrence of traumatic experiences. Subjects suffering from affect dysregulation may be distinguished from those with bipolar disorder by the abrupt nature of affective changes occurring many times daily and having a very brief duration, with these patients that usually perceive the abnormal nature of their mood changes¹³. Patients with affect dysregulation are often misdiagnosed with a bipolar mood disorder or cyclothymic disorder according to the multiple fluctuations related to post-traumatic affect dysregulation. Importantly, there are also individuals with dissociative disorders that meet criteria for borderline personality disorder⁸⁴. Evidence^{13,85} suggested that among subjects with borderline personality disorder, over 70% suffer from a *dissociative disorder with borderline personality disorder* criteria usually reporting interpersonal aspects of dissociation. Symptoms of somatization and conversion may be also common among those with dissociative disorders with more than 25% of individuals with dissociation⁸⁶ and at least 50% of psychiatric inpatients⁸⁷ who reported having experienced

at least one conversion symptom lifetime. Patients with *dissociation and comorbid conversion symptoms* usually suffer from predominant somatic symptoms such as non-epileptic seizure, have more psychiatric comorbidity, childhood traumatic experiences, suicide attempts, and non-suicidal self-injury. However, dissociative disorders may even reach the severity of acute psychosis (*dissociative disorder with psychotic features*)⁸⁸ with the acute dissociative disorder that may clinically resemble a clinical condition of delirium, mania, or schizophrenic disorder given the existence of psychotic characteristics. Generally, palpitations, fainting, shaking, and depersonalization are very common during these episodes with patients that are very worried about the clinical manifestations of their dissociative episode. Another psychopathological pathway related to dissociative disorders is even *amnesia with fugue*. However, only a minority of fugue cases get a solitary diagnosis of dissociative fugue with the majority of cases involving dissociative fugue in the context of a chronic dissociative disorder⁸⁸. Some authors^{89,90} also proposed the existence of a *dissociative subtype of schizophrenia* with those having a positive history of

childhood emotional abuse/maltreatment who tended to have more dissociative symptoms and more positive symptoms of schizophrenia and the subgroup with highest childhood sexual/physical abuse and physical neglect who tended to have more general psychiatric comorbidity, enhanced borderline personality characteristics, and more frequent somatic complaints⁹⁰. Relevantly, dissociative disorders may also suffer from substance abuse (*the dissociative disorder subtype with substance abuse*) with dissociative conditions that may be observed in over 15% of individuals who suffer from substance abuse⁹⁰. Most patients with dissociative symptoms initiate early to use substances, very frequently in early adolescence. A dissociative disorder may be predicted by suicide attempts, childhood emotional abuse, and female gender. Moreover, the comorbidity with migraine, attention deficit hyperactivity disorder, comorbid obsessive compulsive disorder may be also clinically observed⁸⁸ (Fig. 2). Finally, according to a novel classification system initiated by National Institute of Mental Health with the aim to integrate diagnostic elements derived by neuroscience, cognitive sciences and other research areas con-

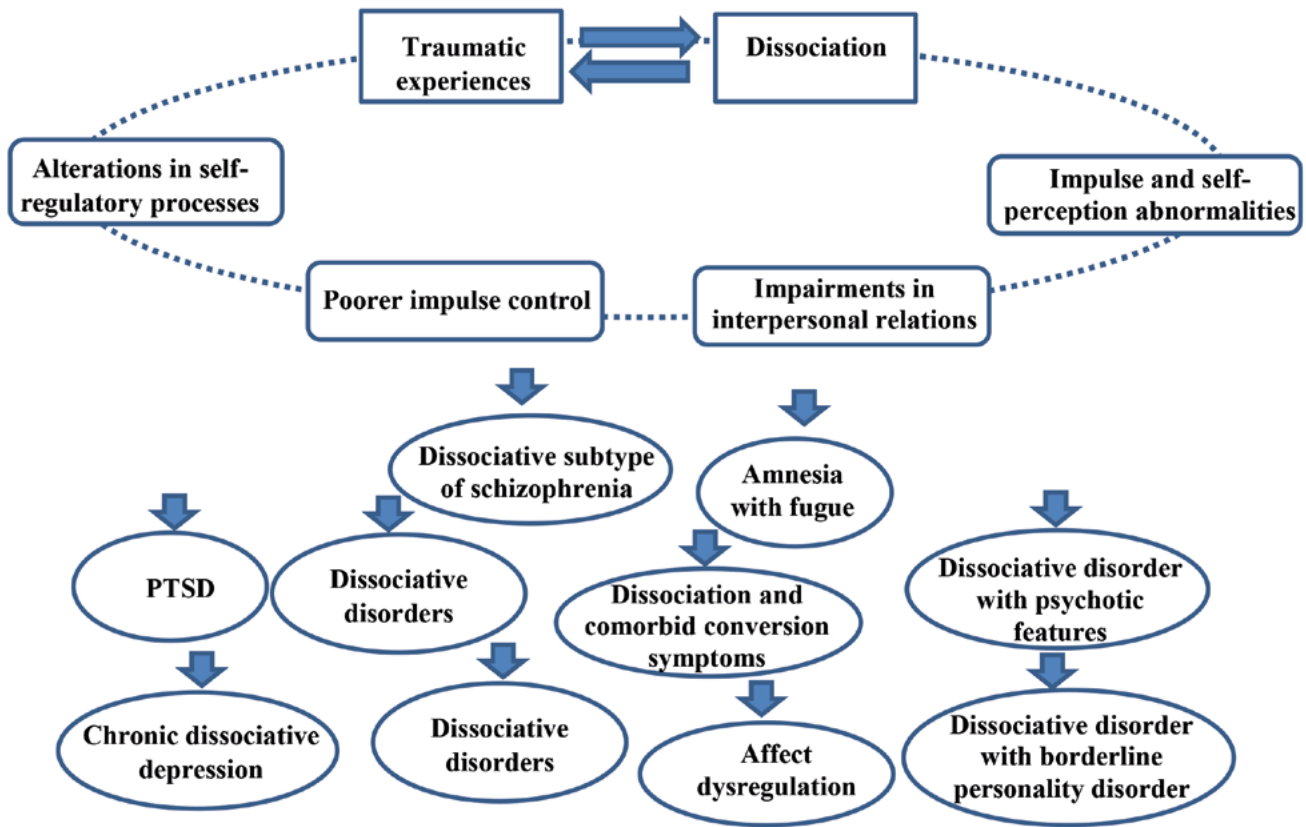


FIGURE 2. Psychopathological pathways related to the exposure to traumatic experiences.

tributing to new nosological information and promote a more personalized medicine for mental disorders, the Research Domain Criteria (RDoC) project proposed the following five domains for the area of trauma and dissociation: the systems with negative value, systems of positive valence, cognitive systems, social processes, and alert/regulatory systems^{91,92}. According to RDoC criteria, new diagnostic groups might be identified based on emerging novel neurobiological correlates that will probably help clinicians to explore novel therapeutic and preventive strategies. To this specific regard, Weston⁹³ clearly proposed a new theoretical model of PTSD identifying the hyperarousal subtype based on the complementation of the symptoms with the neurobiological basis sustaining them according to RDoC criteria.

Conclusive remarks

As suggested by Cuijpers et al.⁹⁴, the careful identification of all the factors related to risk and resilience

after exposure to childhood traumatic experiences is of critical importance for public health interventions. Future studies are required in order to understand the molecular pathways related to neural circuits disruption after early trauma exposure as well as the complex effects of psychopathological dysregulation related to traumatic experiences. These studies may shed light into the complex illness trajectories linking early stress in childhood to psychopathology in adulthood. Further evidence also need to investigate the impact of possible confounders as well as the combined effects at the epidemiological, biological, and epigenetic level on adult psychopathology including conditions associated with suicidal behavior and negative outcome in subjects with stress-related disorders⁹⁵⁻⁹⁷. Finally, screening strategies are needed in order to detect specific at-risk conditions, and given the early exposure to trauma help to better predict individual treatment response for patients population⁹⁸.

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