THE IMPACT OF EARLY-LIFE STRESS IN THE DEVELOPMENT AND COURSE OF BIPOLAR DISORDER: MECHANISMS AND IMPLICATIONS

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Abstract

Traumatic events experienced throughout the different stages of childhood and adolescence are frequent circumstances with a detrimental impact on the physical and psychological health of the individual. A growing body of evidence shows the trauma-related effects on the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, the serotonin system, the immune system, on brain development, structure, and connectivity. Interestingly, a relation was found between early life stress and Bipolar Disorder: the patients who were exposed to childhood trauma showed a worsened course of the disorder with poor clinical and psychopathological factors. According to the kindling hypothesis, early environmental stressors interact with the genetic susceptibility through epigenetic mechanisms, making the subject more vulnerable to milder stressors, and lowering the threshold for the occurrence of subsequent mood episodes. Understanding these processes is crucial to the discovery of new targets of treatment to reduce or, possibly, revert the effect of early life stress on bipolar disorder.

Key words: Bipolar Disorder, Early Life Stress, Trauma, Adverse Childhood Experiences (ACEs), Epigenetics, Kindling Hypothesis, Environmental Stressors.

Introduction

Since Kraepelin, the relevance of environmental stressors in influencing the natural history of bipolar disorder (BD) has been considered[1]. A history of childhood maltreatment is highly prevalent in patients with bipolar disorder: according to Garno et al.[2], 37% of bipolar patients report emotional abuse, 24% report physical abuse, 24% emotional neglect, 21% sexual abuse and 12% physical neglect. Early life stress (ELS) has been associated with earlier onset of bipolar disorder, worse clinical course, psychotic symptoms and higher lifetime suicidal ideation and suicide attempts, reduced response to treatment and comorbid substance misuse [3,4,5,6,7,8]. If early life stress alone is unlikely to be a causal agent specifically in BD, such interaction might have an influence in two different ways, both by increasing the probability of developing the disorder and by worsening the clinical features associated with it. When exposed to early life stress, patients with BD have been found to show an unfavourable course in a recent meta-analysis[7]. Indeed, those patients exhibited a greater number and more severe illness episodes, both manic and depressive, increased severity of psychotic symptoms, earlier age of onset, higher risk of rapid cycling, suicide attempts and comorbid conditions, as substance misuse, anxiety disorders and Post-Traumatic Stress Disorder (PTSD). However, a clear causal relation between early traumatic events and these factors is far to be confirmed; rather, early life stress should only be interpreted as a risk indicator. In fact, these results generally depend on the use of retrospective self-reports as evaluation scales, frequently Childhood Trauma Questionnaire (CTQ), an evaluation scale aimed at retrospectively assessing traumatic events during childhood. This self-report includes 28 items that can measure childhood trauma in general, but it also distinguishes five different subtypes - emotional, physical, and sexual abuse, emotional and physical neglect[9]. Despite the high consistency of this questionnaire in Bipolar Disorder (BD) [10], it might still be subjected to errors or misperceptions in the recollection of the traumatic event, leading to a possible bias.

Early-life stress

Stressful events can be generally defined as experiences or situations individually perceived as threatening, for which the subject does not show adequate coping resources. When such events occur during any developmental stage, they can be considered as early life stresses[11]. The most extreme forms of early life stresses can be classified as abuse, neglect and parental loss, but milder forms can be considered as well, including accidents, illnesses, natural disasters, dysfunctional relationships with the caregiver, war and poverty, whose traumatic impact is strictly related to coping mechanisms and subjective experiences. The World Health Organization (WHO) has addressed the different kinds of childhood abuse and neglect[12]. Physical abuse is defined as those acts perpetrated by a caregiver causing or having the potential for physical harm, while sexual abuse as those acts where a caregiver uses a child for sexual gratification. Emotional abuse includes the failure of a caregiver to provide an appropriate and supportive environment, and includes acts that have an adverse effect on the emotional health and development of a child.

On the other hand, neglect refers to the failure of the caregiver to provide for the development of the child in one or more areas among health, education, emotional development, nutrition, shelter and safe living conditions, despite the availability of adequate resources.

Given the high variability of traumatic experiences and the different subjective response to trauma, a more comprehensive term to indicate the broad range of early distressing events can be used, that is "Adverse Childhood Experiences" (ACEs), an extended definition of all types of abuse, neglect, and other potentially traumatic experiences that occur to people under the age of 18[13].

Beginning in 1994, the ACE Study, a partnership between the Centers for Disease Control (CDC) and Kaiser Permanente, assessed the relationship between adult health risk behaviours and childhood abuse. The results showed that a history of childhood maltreatment was not only associated with a higher prevalence of mental disorders in adulthood but also with a higher prevalence of physical diseases, including heart, lung, liver diseases, cancer[14] and a 20-year reduction in lifespan[15]. The results of the ACE study have shed light on the pathogenic importance of the adverse experiences occurring in early life and helped to reduce the gap between physical and mental diseases.

Unfortunately, traumatic events experienced throughout the different stages of childhood and adolescence are frequent circumstances with a detrimental impact on the physical and psychological health of the individual. The prevalence estimates are quite various across the globe, not only due to social or cultural issues, but also to the lack of consistent and comprehensive data. In fact, most of the available information is based on self-report studies, in which the global estimated prevalence was 127/1000 for sexual abuse, 226/1000 for physical abuse, 363/1000 for emotional abuse, 163/1000 for physical neglect and 184/1000 for emotional neglect, with considerable differences between males and females[16]. The World Health Organization (WHO) estimates that a quarter of all adults has been physically abused as a child, with childhood sexual abuse reported by one in five women and one in thirteen men[17]. In western countries, about 30-40% of the adult population has experienced some form of maltreatment during childhood, including emotional or physical abuse and neglect[18].

Interestingly, it has been found that subjects affected by a mental disorder are more frequently exposed to early life stresses. In fact, several studies highlight that patients affected by psychiatric disorders have a highly prevalent history of childhood maltreatment[19, 20, 21]. Nearly 80% of patients seen in community mental health clinics has experienced at least one incident of trauma during their lifetime[22] and a large US national study has showed how 84% of the patients who reported a history of physical abuse developed at least one major psychiatric disorder in their lifetime[23].

Neurobiological mechanisms

Experiencing some forms of distressing experiences is common and learning how to face them since childhood is fundamental. Resilience, a psychological construct that defines the ability of a person to cope positively with stressors, starts to take shape in the childhood, when the presence of moderate, brief-lasting, stressors are overcome successfully with the help of supportive parents. These sorts of traumas are considered positive for the psycho-/physiological development, educating the stress systems of the individual without disrupting them. On the other hand, excessive and chronic stress leads to the dysregulation of the biological stress systems and can stamp a long-lasting scar on the developing brain[24].

Early adversities can affect several interacting and reciprocally influential neurobiological pathways and organs; the next paragraphs will concern the effects of ELS on the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system (SNS), serotonin system, oxytocin system, immune system, brain development, structure and connectivity.

_ Hypothalamic-pituitary-adrenal axis[25]

The HPA axis is an ancestral neuroendocrine pathway involved in the stress-response[26]. A huge amount of research has outlined the hyperactivity of the HPA axis as a prominent biological feature of major depression[27]. Whether this stress system plays a vital role in dealing with positive stressors in early life, his persistent and poorly controlled activation induced by toxic stress may lead to the dysregulation of the stress-response physiology. The main feature of the HPA axis in abused people, as shown in several studies, is its sensitization, or priming, occurring as a reflection of chronic compensatory adaptation of the HPA axis after repeated traumas exposure[28]. A "primed system" will "hyper"-respond when a new emotional stressor or traumatic event is experienced[25]. Studies have helped shedding light on the HPA sensitization associated with ACEs at various levels of the stress system axis. The hyper-responsiveness to stress involves the Adreno Cortico Tropic- Hormone (ACTH), as shown in a study by Heim et al.[29], where women with a history of childhood abuse exhibited increased (ACTH) response to stress compared with controls. Interestingly, the Authors also evidenced that the presence of depression determined 6-fold grater ACTH response and increased cortisol response to psychosocial stress, while the presence of previous abuses without depression was associated with normal cortisol response despite the ACTH increase, perhaps suggesting adrenal adaptation to central sensitization as a marker of resilience[30]. In addition to the response to external stimuli, the ACTH hyper-responsiveness in abused people has also been assessed through pharmacological provocation tests, as highlighted in another study of Heim and colleagues, where stimulations with CRF determined increased ACTH responses in women with a history of childhood abuses[31]. Even Cortisol, the final element of the HPA axis stress system, shows increased responsiveness to stimulation tests in abused subjects when compared with non-abused men[32]. According to other evidences, the link between traumas and the hyper-activation of the HPA system is strengthen by the discovery that victims of abuses had significantly higher CRF concentration in cerebrospinal fluid[33] and that the CRF concentrations were positively related to the abuses severity[25]. Taken these data together, it seems clear that ACEs determine HPA hyper-activation. What do we know about the CRH, ACTH and cortisol concentrations variations over time in people with early life stress? As far as cortisol concentrations are concerned, studies have shown higher cortisol levels in maltreated children, compared to individuals with no maltreatment history[34] but, while central CRF elevation persists into adulthood, initial elevations of ACTH and cortisol levels become attenuated with the chronic exposure to elevated Corticotropin-Releasing-Hormone (CRH). In fact, high CRH causes adaptive down-regulation of pituitary CRH and neural CRF receptors after trauma onset[27]. Studies on animal models have shown that early life stress is associated with altered methylation of the glucocorticoid receptor gene, this resulting in insufficient glucocorticoid signaling[33]. This phenomenon, the glucocorticoid resistance, reflects a compensatory adaptive mechanism aimed to prevent the cortisol related detrimental effects. To conclude, the different inter-individual subjective response to traumatic experiences finds a biological confirmation in genetic studies, elucidating the resilience genetic component; in fact, specific polymorphisms of the genes involved in the HPA axis seem to modulate the trauma effects on the child[34].

_Sympathetic Nervous System

The SNS, together with the HPA axis, represents a relevant biological mediator of the stress response. Research has detected higher catecholamine levels in abused children with dystimia[35] and PTSD[36, 37]. In

line with the evidences about the HPA axis, even the SNS exhibits a higher responsiveness in people with early trauma exposure[38, 39] and specific polymorphisms of genes involved in the SNS, seem to modulate the psychological consequences of early trauma as well[40].

_Serotonin System

Serotonin plays a crucial role in regulating emotions, behaviours, cognitive function, motor function, appetite and sleep[27]. Traumas seem to impact on the brain serotonin system in humans as evidenced in research studies. Murrogh and colleagues revealed the association between early trauma and lower serotonin type 1B receptor expression in caudate, amygdala and anterior cingulate cortex[41], suggesting a traumas serotonin mediated pathogenicity. In fact, the circuit involving anterior cingulate cortex (ACC), striatum, amygdala that receives serotonin projections from the brain stem is thought to be relevant in the neurobiology of stress-related disorders[41]. The interplay between traumas, serotonin system and risk of mental illnesses seems to have a genetic basis, in particular concerning specific serotonin-transporter-gene-promoter-polymorphisms (5-HTTLPR). Carriers of the short-allele of the serotonin transporter have a higher risk of developing depressive symptoms when exposed to stressful life events and childhood maltreatment[42, 43].

_Oxytocin System

Oxytocin is a hormone involved in milk production and interpersonal relationships[44]. Apparently, ACEs hinder the oxytocin production, although the implications of this finding are yet to clarify[45].

_Immune System[46]

Inflammation, both peripheral and in the central nervous system, has been suggested as a potential player in the pathophysiology of mood disorders[47]. Several evidences disclose the link between childhood trauma and elevated inflammation markers (C-reactive protein) [48, 49]. Trauma has been associated with hyper-activation of B cells, as indicated by the higher levels of antinuclear antibodies found in abused girls[50] and hyper-activation of T-cells, as well[51]. In addition to that, studies show that maltreated subjects exhibit heightened inflammatory responses, secondary to psychological stressors in adulthood[52, 53]. Once again, as observed in the HPA and serotonin systems, the hyper-responsiveness concept seems to be applicable even for the trauma associated immune system alterations. On one hand, the dysregulation of the immune system could be a consequence of the neuroendocrine abnormalities, representing the immune hyper-activation a compensatory mechanism secondary to the insufficient glucocorticoid signaling[54]. On the other hand, inflammation could determine secondary neuroendocrine abnormalities, by activating the HPA axis[55] and inducing glucocorticoid resistance[56].

_Brain Development, Structure and Connectivity[27, 57, 58]

A huge amount of literature has highlighted the cortisol related detrimental effects, causing both medical illness and neuro-toxicity; actually, either suppressed or elevated glucocorticoid levels can impair brain

development and function[27, 59, 60]. For this reason, during brain maturation, the dysregulation of the HPA axis may lead to abnormal brain development. The steroids related neurotoxic mechanisms include apoptosis[61], delays in myelination[62], pruning abnormalities[63], loss of dendritic spines[27] and inhibition of neurogenesis[64, 65]. Although the whole brain is susceptible, hippocampal neurons, particularly the CA3 region, seem to be more vulnerable to stress and glucocorticoids. The impact of ACEs on the brain has been object of interest and clinical studies have tried to identify the long-term consequences of childhood trauma with regard to brain structure, function and connectivity. The Anterior Cingulate Cortex (ACC) is the cortical region most frequently identified as abnormal in maltreated individuals, with reports of reduced volume[66] and connectivity[67]. As far as grey matter is concerned, decreased hippocampal[68, 69], amygdala[70], dorsolateral prefrontal cortices[71] and caudate[72] volumes have been associated with early life stress. Interestingly, chronic exposure to a specific type of adversity primarily affects the development of sensory systems that process or convey the adverse sensory input. Subjects witnessing domestic violence during childhood report reduced grey matter volume in right lingual gyrus, left occipital pole and bilateral secondary visual cortex (V2)[73] and decreased integrity of the left inferior longitudinal fasciculus (ILF), which serves as a visual-limbic pathway[74]. Similarly, an increase in grey matter volume in left superior temporal gyrus (auditory cortex) and decreased integrity of the left arcuate fasciculus have been observed in a sample of young adults exposed to high levels of parental verbal abuse[75]. Adults with a history of sexual abuses tend to have reduced grey matter volume in right and left primary visual cortex (V1) and visual association cortices, as well as reduced thickness in right lingual, left fusiform and left middle occipital gyri[76] and reduced cortical representation of genital somatosensory field[77]. By contrast, exposure to multiple forms of adversity has been associated with corticostriatal-limbic morphology abnormalities[78], smaller brain volume, corpus callosum atrophy[79, 80] and smaller hippocampal volume[81, 82]. These differences could be explained as an attempt to attenuate the trauma effects, by hindering the transmission to consciousness of specific traumatic experiences[58]. As regards functional imaging studies, the most reliable finding in individuals with maltreatment histories is an increased amygdala response to threatening faces[58, 83]. As suggested by Teicher et al.[58], the enhanced threat detection and response to fearful stimuli, might be the expression of an adaptive plastic mechanism of the maltreated individual to better handle future adversities. Another consistent functional imaging finding in maltreated individuals is the disrupted reward processing, implicating hypo-responsiveness during reward anticipation and hyper-responsiveness when receiving a reward[84]. Even this functional datum could be a protective mechanism, facilitating avoidance towards external stressors[58]. Finally, childhood trauma seems to hamper brain microstructure and connectivity. Specifically, early adversities are associated with corpus callosum[85, 86], left anterior cingulate, right occipital, left temporal lobes and right medial frontal gyrus[72] abnormalities. These areas are respectively involved in intelligence[86], emotion regulation[87], social cognition[88] and mentalizing[89]. The trauma-related brain microstructure effects could explain the cognitive impairment in executive functioning[90], working memory[91] and verbal Intelligence Quotient (IQ) [75] observed in people exposed to ACEs.

Early-life stress and Bipolar Disorder: clinical and psychopathological dimensions

Maternal stress, prenatal medical illnesses and obstetric complications

The role of early life stresses in the development of mental disorders, including Bipolar Disorder (BD), should be addressed in a broader sense. Indeed, brain maturation is a dynamic process, both morphologically and functionally[92]. Alongside with a structural brain growth from new-borns to adultness, a continuous remodelling of functional connectivity of networks and domains has been described throughout this period, with different systems being at different levels of maturation according to age. It is, therefore, important to reconsider the pathophysiology of psychiatric disorders in light of a neurodevelopmental hypothesis, assuming that the susceptibility to specific traumatic events is mediated by the different developmental stages. This dynamic interaction between stress and brain maturation might be traced back to early age, possibly to the prenatal period. Prenatal exposure to maternal stress, pregnancy-related anxiety and general stressful events can affect several biological systems, including functional and structural brain connectivity involving amygdalae and (pre)frontal cortex, changes in hypothalamo-pituitary-adrenal (HPA)-axis, autonomous nervous system[93] and epigenetic mechanisms through microRNA[94]. Many factors have been analysed to ascertain the impact of prenatal events in the development of BD, mostly retrospectively, including infections, exposure to substances, maternal stress, obstetric complications and foetal morphological and developmental features[95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109]. Taken together, the results are quite controversial[110, 111] often failing in replication, due to heterogeneity in methods and assessments and lack in disease specificity. However, it is not possible to exclude their role in the pathophysiology of BD, as it should be re-evaluated in light of the specific genetic predisposition: again, stress should not be considered a factor per se, but in its interaction with the characteristics of the subject.

Different types of trauma on BD

Even though early life stress in general plays a role in the development and course of BD, it is necessary to mention that not all subtypes of trauma may have equivalent clinical consequences[15]. The use of CTQ sub-scores allows for a differential investigation of various forms of abuse and neglect; unfortunately, these maltreatments frequently co-occur, making difficult to determine a specific relation for each of them. Despite conflicting results, there is evidence of a specific effect of emotional and sexual abuse on the clinical severity of BD, while physical abuse was related more strongly to the presence of psychotic features[112, 113]; however, this effect might be mediated by concomitant emotional and sexual abuse[110]. In a systematic review specifically assessing sexual abuse in BD[114], it was found to be strongly associated with comorbid PTSD, while less strongly with suicide attempts, substance abuse, psychotic features and early age of onset. In summary, different types of traumatic experiences were postulated to have a direct effect not only on the severity of the clinical features of BD but also on specific dimensions of BD, indirectly mediating the effect on the worse clinical outcome.

Childhood trauma and dimensions of psychopathology

If the presence of early life stress can partly explain the severity of BD, such effect was argued to lack disease specificity. In this way, it was postulated that traumatic experiences can affect clinical indicators of BD severity indirectly through the impact on various psychopathological dimensions. In fact, childhood trauma correlated with higher emotional dysregulation[115, 116], hostility and impulsivity[117]. These dimensions, in turn, were positively related to the clinical outcomes of BD: affect intensity and affective lability with lifetime comorbidities, earlier age of onset and suicide attempts, impulsivity with substance abuse, rapid cycling and mixed episodes, and hostility/aggression with suicide attempts[118, 119, 120, 121, 122, 123]. However, a correlation between psychopathological dimensions and clinical features does not automatically imply a causal link with BD, as early life stress may just have an impact on psychopathology irrespective of the diagnosis. Therefore, a subject who has experienced traumatic events might show specific symptoms that act as comorbidities with, rather than causative agents of BD. In this regard, Etain et al[124], examined these factors with a comprehensive approach using path analysis. Interestingly, emotional abuse and sexual abuse resulted to be correlated with specific psychopathological dimensions, confirming the differential role of trauma sub-types, with a significant effect of those stressors on clinical features both directly and indirectly, mediated by the same psychopathological dimensions. However, given the retrospective nature of the study, it is not possible to assume a causative relation of psychopathology on clinical features, as the reverse is also possible.

Genetic × Environment

If a role of early life stress on different psychopathological dimensions can be postulated, the development of BD relies on its interaction with the genetic susceptibility. In this way, the occurrence of early life stress can increase specifically the risk of BD only in presence of specific genetic backgrounds, which, in turn, mediate the onset of the psychiatric disorder in susceptible individuals. However, the evidence regarding the role of genetics is still fragmented although promising. Many allelic variants have been investigated, with conflicting results.

_Ankyrin-3 (ANK-3):

ANK-3 is a gene coding for Ankyrin-G, a scaffolding protein with many neuronal isoforms involved in action potential, neuronal excitability and neurotransmission[125, 126, 127, 128, 129]. Despite conflicting results, single nucleotide polymorphisms (SNPs) located at ANK-3 were found to be significantly associated with BD using genome-wide association studies (GWAS), particularly rs10994336 and rs1938526, as recently reviewed[130, 131, 132, 133, 134, 135]. Such findings were even replicated in samples with different ethnicity. Interestingly, multiple studies linked the disruptions of Ank-G expression in the brain with stress-related response in animal models[136, 137]: when the levels of brain-specific isoforms are decreased, a heightened reactivity to external stressors was showed in mice. In the attempt to explain the complex interplay between exposure to early life stress and genetic susceptibility, a key role can be attributed to epigenetics. Actually, a recent study[136] observed an altered methylation pattern in rats who suffered from prenatal stress with a specific temporal profile, showing consequently a variation in mRNA levels and

protein synthesis. More importantly, the reduction of ANK-3 expression seemed to be expressed only in later stages of life, indicating a sort of "epigenetic imprinting" persisting far beyond the occurrence of the stressor. The identification of epigenetics mechanisms mediating the impact of early life stress comes with the possibility to use pharmacological treatments to revert, even partly, this process. Consistently with that, long-term administration of lithium was found to increase the Ank-G levels in the hippocampus in rodents[138].

_5-HTTLPR:

A polymorphic region has been described in the promoter of the serotonin transporter (5-HTT) gene, namely the 5-HTT-linked polymorphic region (5-HTTLPR). Two particular alleles were linked with many neuropsychiatric disorders, including affective disorders and BD and response to stress, based on a 44-base pair insertion/deletion: long (*l) and short (*s) variant. Those subjects carrying the l/l genotype were found to have higher 5-HTT mRNA levels in post-mortem brain tissues and platelets[139, 140], a higher density of 5-HTT in the raphe nucleus[141], and higher amounts of circulating serotonin[142]. Being 5-HTT also one of the major pharmacological targets in depression, either unipolar and bipolar, a correlation emerged between the allele combination and response to selective serotonin reuptake inhibitors (SSRI), with a better outcome for the *l carriers[143, 144]. Interestingly, 5-HTTLPR seems to mediate the response to stress and emotional regulation[145, 146]. In particular, *s carriers showed more vulnerability to stress exposure, both early in life and during adultness, being more liable to the development of affective disorders with worsened clinical features, including suicidal attempts and earlier age of onset[43, 147, 148]. There is evidence that such predisposition can interact specifically with trauma subtypes, as previously observed: in a recent study evaluating BD patients, the s/s genotype was significantly related to age of onset when the individual reported being a victim of emotional neglect, but not of other subtypes[149]. 5-HTTLPR seems to regulate the interplay between early life stress and BD by impairing the neurobiology of cognitive-emotional regulation. The *s allele was found to negatively affect the functional cortico-limbic connectivity when exposed to negative stimuli[150], resulting in psychopathological and autonomic reactions, which include behavioural anxiety, harm avoidance[151], HPA reactivity to stress[145], and higher brain activation when reflecting on one's own negative characteristics[152]. However, despite the great enthusiasm surrounding 5-HTTLPR, its role is still controversial and requires to be considered in a broader context. A recent meta-analysis concluded that the effect size of the *s allele is modest and its influence might be limited to specific cases[153].

_BDNF:

Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in neuronal growth and differentiation during brain development and in synaptic plasticity during adultness[154]. Its relation to affective disorders has been known for a long time, given that cerebrospinal fluid and peripheral levels were found to vary both during illness episodes with normalization in euthymic conditions and according to the presence of treatment resistance[155, 156]. More recently, the functional polymorphism val66met was identified in the BDNF gene, causing a reduced transcription and a diminished secretion of BDNF[157], which was supposed to have an impact on the BD pathophysiology[158]. When exposed to early life stress, met allele carriers affected by BD showed an earlier age of onset, a worse severity/chronicity of the

disorder[159] and lower BDNF mRNA circulating levels, with a peculiar dose-dependent relationship between total childhood trauma experiences and lower BDNF levels[160, 161]. Interestingly, in all these studies the effect was specific for sexual abuse while not confirmed for the other trauma subtypes investigated.

_HPA-related genes:

Consistently with the role of the HPA axis in reaction and adaptation to stressful events, multiple genes involved in this network were found to mediate the effect of early life stress on the onset and severity of affective disorders, mainly depression. First, a polymorphism in the corticotropin-releasing hormone type 1 receptor (CRHR1) gene, namely rs110402, was reported to have a protective role against depression in adulthood after experiencing childhood trauma[162]. Interestingly, the A-allele showed opposite effects on men and women: if males had a decreased likelihood to develop depression and a reduced cortisol response to the dexamethasone/CRH test, females displayed a higher cortisol response. However, such differences were confirmed only in the presence of trauma occurrence. Later findings confirmed the involvement of CRHR1: a 3-SNPs haplotype (T-A-T) increased the risk of depression in African-American females exposed to early life stress[163]. Similarly, a marked gender effect was found on two polymorphisms of the mineralocorticoid receptor (MR), rs5522 and rs2070951. While the CA haplotype appeared to be protective against depression in women who have experienced childhood trauma, the GA and CG haplotypes were found advantageous for men[164]. Noteworthy, a direct effect of gender still needs to be ascertained, as it might be indirectly explained by the differential exposition to different trauma subtypes in men and women. Another gene involved in the activation of the glucocorticoid pathway in response to stress is the one coding for FK506 binding protein 5 (FKBP5), a co-chaperone that influences the glucocorticoid receptor (GR) sensitivity[165]. Hyper-expression of FKBP5 can induce GR resistance and diminish the central negative feedback, thus enhancing cortisol response[166]. Among various polymorphisms of this region, those who are carriers of the rare CATT haplotype are more prone to develop neuropsychiatric disorders, including affecting disorders, after experiencing childhood trauma[165]. Despite promising results, none of the mentioned findings specifically addressed BD. Though, a recent trial found an FKBP5 polymorphism (rs2766533-GG genotype) that was related to suicidality in BD with early life stress, after multiple test correction[167]. However, no genetic-environment interaction was found, demanding further analysis on larger samples.

_Neuro-inflammation:

Neuro-inflammation has been widely investigated as one of the major factors in the aetiology of BD in the latest years, as an increase in the serum level of pro-inflammatory cytokines and a reduction in the anti-inflammatory cytokines were observed in the acute phases of BD[168, 169]. The genesis of a pro-inflammatory environment in BD and other affective disorders is a complex phenomenon that arises from the interplay of multiple factors: on one side the microglia responds to injuries or stress by producing a large number of cytokines and, consequently, reactive species of oxygen (ROS) [170]. On the other hand, a defect in the antioxidant defences was described in affective disorders, both directly through the reduction of albumin, zinc and –SH groups on proteins[171], and indirectly, with increased lipid peroxidation[172], oxidative damage to lipids, protein oxidation, and reactive nitrogen species[173]. In this

context, childhood trauma might create an imbalance favouring a persistent pro-inflammatory environment in the brain, promoting the development of affective disorders. Preliminary evidence linked childhood trauma, especially sexual abuse, to increased oxidative stress in the general population[174, 175]; few studies replicated these results on BD. Interestingly, a recent study[173] measured the levels of various enzymes and metabolites involved in neuro-oxidative and neuro-nitrosative stress pathways together with CTQ scores; the results showed a differential association of trauma subtypes with distinctive combinations of inflammatory-related molecules, categorical diagnosis (BD or Major Depressive Disorder) and clinical features. Nevertheless, further research is necessary to replicate these findings and to elucidate the neurobiological mechanisms underlying the association between neuro-inflammatory processes, BD and early life stress.

Kindling Hypothesis

The existence of a relationship between ACEs and mood disorders has long been hypothesised. As part of the generally accepted aetiological model of complex disorders, life stress acts as a strong environmental factor interacting with an underlying genetic predisposition. Ultimately, this dynamic process can lead to the development of psychopathological symptoms and, eventually, to the onset of mental disorders with negative prognostic indicators. In recent years, new evidence which points to a specific role for ACEs in BD has been accumulating. However, it is hard to determine if a causal connection exists between them, considering that most of the findings are derived from retrospective analyses. Given the technical limitation with longitudinal assessments, different models tried to fill this gap. In the early '90s, Post formulated the kindling hypothesis[176], according to which the first mood episodes are more influenced by major traumatic events than the subsequent ones. In this way, early life stress might operate as an imprinting factor, leaving the subject vulnerable to minor or subthreshold stressors that account for the recurrence of later episodes. Interestingly, the quality of life events – negative or positive - was even supposed to differentially anticipate depressive and (hypo) manic episodes respectively[177, 178, 179]. However, such results are still preliminary and lack adequate replication. Within the context of the kindling model, further research led to the development of two plausible mechanisms, namely stress sensitization and stress autonomy[180, 181]. The stress sensitization hypothesis posits that individuals experiencing significant trauma become sensitized to stressors in general, making them considerably more susceptible to minor events. Therefore, in BD, if severe stressors precede earlier episodes, the following ones might be anticipated also by less substantial stressors, progressively lowering the threshold for new episodes. On the other hand, the stress autonomy hypothesis focuses on early life stress as the primary factor: if it plays an important role in triggering the initial episodes, the occurrence of the following ones appears to develop independently of any kind of stressor, both major and minor. To date, no definitive data clearly support either of the two models[182, 183]. Indeed, the results from trials are inconclusive, and do not completely fit any of the hypotheses: for example, Shapero et al[181] found evidence in line with stress sensitization only for depressive episodes, but not for (hypo) manic episodes. Despite that, the sensitization model is accumulating more support over stress autonomy from newer neurobiological evidence. In this context, epigenetics is gaining growing attention: the occurrence of multiple traumatic events can affect genetic expression in a maladaptive way, by enhancing stress-related responses (i.e. CRH and cortisol) and downregulating adaptive and neuroprotective factors

(i.e. BDNF). As the mood episodes keep taking place, such memory-like epigenetic-based mechanisms are then worsened by other nonspecific ones, including inflammation, oxidative stress, mitochondrial dysfunction, and shortening of the average length of telomeres[184, 185, 186, 187, 188, 189]. This contributes to the creation of a vicious cycle, making the subject oversensitive to milder or scarcely traumatic events, triggering new episodes. Despite the appeal of the kindling hypothesis, it lacks definitive proof[183], opening up to alternative theoretical models, such as the Behavioural Approach System (BAS) dysregulation theory[190] and the Social rhythm disruption theory[191]. The former postulates that BD arises from an imbalance between reward-driven positive behaviours (BAS) and punishment-driven inhibitory behaviours (BIS): according to the relevance of different situations, susceptible individuals can manifest an over-activated BAS, leading to (hypo) manic symptoms, or hypo-activated BAS, leading to depressive symptoms, possibly with a sensitization to those situations. Instead, the latter theorises that mood episodes are triggered by disruptions in the social and biological rhythms of the individual, leading to either depressive or (hypo) manic episodes. Nevertheless, indisputable data in support of either of these models are currently lacking[183].

Treatment and future developments: conclusion

Understanding the role of childhood trauma in BD and its psychopathological and biological dimensions is necessary to develop newer diagnostic tools and therapeutic approaches. Indeed, the evaluation of childhood trauma, especially abuse, can be inadequate or completely lacking during the psychiatric evaluation[192], with the risk of underestimating the severity of the disorder and its negative impact. Recognizing childhood trauma is, therefore, the first step in the management of BD: beside CTQ, more than 20 different interviews have been published, none of which is superior to the others[193]. Once assessed, childhood trauma should be taken into consideration when defining the intervention strategies. Many psychological approaches have been investigated in the context of traumatic events, including both trauma-focused and non-trauma-focused cognitive-behavioural therapy (CBT), mindfulness techniques, interpersonal therapy and Eye Movement Desensitization and Reprocessing (EMDR) [194, 195], but trials specifically assessing these interventions in BD are lacking. A CBT approach focused on victims of traumatic events affected by PTSD and other mental disorders, including BD, was found to be more effective than the usual treatment, both for PTSD severity and other symptoms severity[196]. If confirmed specifically in the management of BD, these results might suggest a dual beneficial effect of psychological interventions. In fact, CBT approaches might improve the course of the disease, potentially reducing the susceptibility to new episodes, episode severity and the global quality of life of the patients. On the other hand, identifying those subjects who have experienced a traumatic event and are at risk of developing BD (based on their premorbid symptoms and familial history) can lead to the development of primary prevention strategies, with the theoretical chance to reduce the impact of the disorder or ultimately prevent its onset[15]. Though promising, such strategies are merely speculative and further research is necessary to determine the most effective interventions and how to differentially target trauma subtypes. The disentanglement of the complexity between BD, childhood trauma and their biological consequences opens up the possibility for developing new pharmacological treatments. Epigenetics is crucial to this extent, as some of the medications available alter the epigenetic cellular profile beyond their known pharmacodynamics. Besides lithium, described above, other medications were found to act

on epigenetic targets. The anticonvulsant and mood stabilizer valproate has shown an inhibitory action on histone deacetylase (HDAC), with effects on extinction and reconsolidation of conditioned fear[197], while clozapine exerts a potentiation in reversing the hyper-methylation of the promoters of GABAergic genes (down-regulated in BD) when combined to valproate in mice[198]. These findings are preliminary but promising in the identification of new targets among epigenetic regulators. Unfortunately, epigenetic manipulations require further research. In fact, methylation and acetylation of the histones are dynamic processes; accessibility to the genetic information is highly variable not only in space but also in time, and depends on different environmental, psychological and familiar factors[125]. The key to producing a therapeutic effect through epigenetic mechanisms is, therefore, to target specific cellular groups at specific times, thus opening new perspectives in the combination of pharmacological and psychological approaches aimed at addressing those specific traumatic memories that might play a role in the aetiology and pathophysiology of BD[184].

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