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Potential Interactions Between Environmental and Psychoneurobiological Factors in the Interface Between Stress and Depression: A Road Map to Resilience

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Introduction

The role of stress in the origin and development of depression and anxiety disorders has long been demonstrated, including the long-lasting effect of early life stress and the impact of chronic stress, later in life [1–5]. In this regard, sustained and prolonged exposure to environmental stressors may stimulate a repertoire of adaptive responses, mediated by different neural structures involved in emotional and cognitive processing in the central nervous system (CNS), and the subsequent activation of the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal axis (HPA) [6, 7]. Environmental stressors may be bio-ecological, when associated to the natural environment, and psychosocial, when associated to the interaction between individuals in a social environment. Chronic stress has been mostly studied in social conditions, where it has been possible to describe different disorders produced by the prolonged and sustained impact of psychosocial stressors. It has been demonstrated that exposure to chronically stressful conditions may lead to the origin and development of different symptoms of anxiety and depression, with different characteristics according to specific features associated with stressors, diverse aspects associated with each individual, and the resulting interactions between them. Stressors may be acute or chronic, mild or severe, positive or negative, predictable or unexpected, controllable or not. Each individual may perceive environmental stressors in a different manner, according to cognitive and emotional features involved in their subjective appraisal, their personal resources, and the resulting coping strategies. In this regard, according to their personal characteristics, each individual may be affected in a different manner, which in turn may differ according to their potential vulnerability or resilience. Therefore, different interactions between stressors and individuals may be translated into different conditions, which in turn may depend on individual factors of vulnerability or resilience.

Stress: From the Environment to the Brain

Stressors are perceived as environmental stimuli, which are transmitted through sensory pathways to different structures in the CNS, including the

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thalamus, the amygdala, the hippocampus, and cortical areas, including sensory and associative cortices, which in turn convey information to the prefrontal cortex (PFC) [5, 7]. Direct projections from the thalamus may reach the amygdala, to stimulate arousal and early alarm reactions, which in turn may lead to the activation of the ANS, more specifically its sympathetic branch, and the HPA system. The amygdala may also receive indirect projections from sensory, associative and transitional cortices, which in turn are known to send projections to the hippocampus, where sensory input is integrated with contextual information to be subsequently conveyed from the hippocampus to the lateral nucleus of the amygdala (LNA) [8]. Projections from the hippocampus may also reach the para-ventricular nucleus (PVN) of the hypothalamus, where it plays an inhibitory role [9, 10]. The LNA is also the source of multiple projections to other ports of the amygdala, such as the basal, accessory basal, and central nucleus of the amygdala (CNA) [8, 11]. The CNA sends projections to the lateral nucleus of the hypothalamus (LNH), which activates the sympathetic branch of the ANS [12], the dorsal motor nucleus of the vagus, which activates the para-sympathetic branch, and the PVN, with the consequent activation of the HPA axis [12, 13], as part of the adaptive response to stress. The amygdala also shares connections with different areas of the PFC, including the orbito-frontal cortex (OFC) and the medial PFC (MPFC) [14]. The OFC participates in the integration and evaluation of sensory stimuli, including the primary appraisal of their positive or negative value and, subsequently, in the integration of their emotional and cognitive appraisal [14]. The MPFC, together with the anterior cingulated cortex (ACC), participates in the regulation of emotional responses, particularly those related to the amygdala [15]. All these cortices are also connected with the dorso-lateral PFC (DLPFC), which is involved in cognitive control and voluntary regulation of emotional responses. The DLPFC is known to be critically involved in executive aspects of cognitive processing [16], such as conscious processing and working memory. It receives projections from the amygdala through the OFC and ACC, and projects back to limbic structures through indirect connections to specific areas of the MPFC, namely, the ventromedial PFC (VMPFC), which projects to specific areas of the ACC, such as the subgenual ACC (sgACC) [16]. Projections from the VMPFC and the sgACC may reach the amygdala to exert a modulatory effect [16, 17], which in turn is also connected with the hypothalamic PVN. Therefore, the HPA axis may be regulated by stimulatory projections from the amygdala and inhibitory projections from the hippocampus, which in turn may be reflected in the adaptive response to stress.

The Role of the HPA Axis

It has been shown that the HPA axis is modulated by limbic components, such as the amygdala and the hippocampus, and cortical areas also involved in the regulation of these neural structures. Therefore, the amygdala sends stimulatory projections to the PVN [6], where the corticotropin releasing hormone (CRH) is synthesized and released to the hypophyseal portal blood to reach the anterior pituitary. There, CRH stimulates the transcription of the pro-opio-melanocortin (POMC) gene, a precursor for the adrenocorticotropic hormone (ACTH), which in turn is released into the bloodstream to reach the adrenal cortex, where it stimulates the biosynthesis and release of cortisol (see Fig. 28.1). At the molecular level, cortisol binds to mineralocorticoid receptors (MRs or type I) and glucocorticoid receptors (GRs or type II), constituting a hormone–receptor complex, which in turn may be ready to interact with a glucocorticoid response element (GRE), in the promoter region of target genes [18], to participate in transcription regulation. This molecular mechanism may explain the down-regulation of the POMC [19] and the CRH genes [20], where cortisol regulates its own synthesis and release through negative feedback circuits involved in the regulation of the HPA axis. In addition, cortisol may also bind to hippocampal GRs, which in turn may inhibit the PVN [21, 22]. It has been shown that chronic stress may abolish these negative-

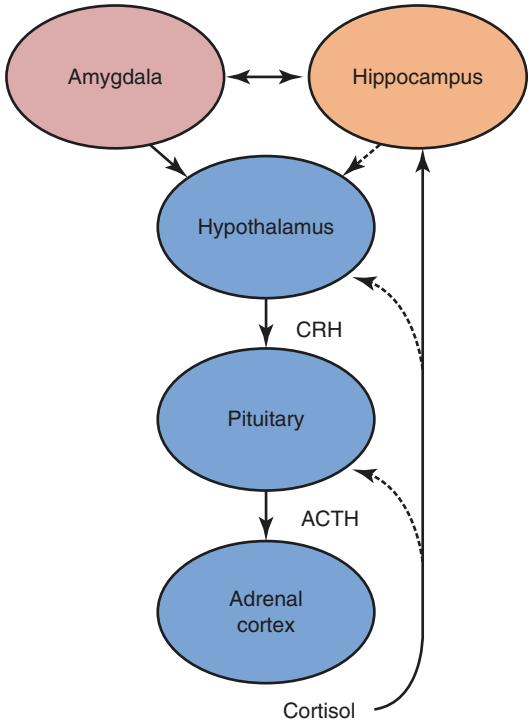

Fig. 28.1 A schematic representation of the hypothalamic–pituitary–adrenal axis, with excitatory projections from the amygdala, inhibitory projections from the hippocampus, and ther negative feedback circuits mediated by cortisol. (Modified from Tafet and Nemeroff [5])

feedback circuits, therefore resulting in sustained activation of the HPA axis [18]. Chronic stress may also reduce the expression of brain derived neurotrophic factor (BDNF) in the hippocampus, therefore decreasing its capability to inhibit the HPA axis [23, 24]. These alterations in the regulation of the HPA axis, associated with chronic stress, have been involved in the origin and development of depression and anxiety disorders, where hyperactivity of the HPA axis, with the consequent increase in CRH and cortisol levels, are commonly observed [25, 26]. In addition to the PVN, CRH neurons have been also described in the amygdala [27, 28], particularly in the CNA, which activates the HPA axis through projections to the PVN. Reciprocal connections have been also described between these and aminergic nuclei, such as the locus coeruleus (LC) and the raphe nuclei (RN) [3], which may be involved in reciprocal interaction between the noradrenergic and the serotonergic systems with the HPA axis [3, 29], probably involved in the pathophysiology of mood and anxiety disorders [30].

It has been shown that a history of traumatic events during childhood represents a critical factor of vulnerability in the origin and development of depression later in life [3, 31]. These stressful conditions have been associated with enduring alterations in different neural structures, reflected in hyperreactivity of neural and neuroendocrine responses to stress, with the consequent increase in CRH concentrations, glucocorticoid resistance, and reduced volume of the hippocampus [31, 32].

The Role of the Serotonergic System

Among the aminergic systems involved in the stress response, it has been long demonstrated that alteration in the serotonergic system plays a critical role in the origin and development of anxiety and depressive symptoms [29]. This system has its main sources in the RN, which project to different neural structures, including projections to the forebrain from the dorsal (DRN) and medial raphe nuclei (MRN) [33] (Azmitia 1987). Projections from the DRN may reach different neural structures involved in adaptive responses to stress, and the origin of anxiety-related symptoms [34–36], including the amygdala, particularly the CAN [37], the bed nucleus of the stria terminalis (BNST) [38], the PVN and different areas of the PFC [39]. Projections from the DRN may also reach other neural structures related to regulation of fight-or-flight responses, such as the periaqueductal grey (PAG) [40, 41] and the striatum, which have been shown to be involved in passive coping behavior [42], and the state of anticipatory anxiety that plays a critical adaptive role in threatening situations, informing the amygdala about current negative stimuli and emotional reactions associated with them [10]. On the other hand, projections from the MRN may reach other neural structures, including the hippocampus and the hypothalamus [43, 44], which have been associated with tolerance to per-

sistent aversive stimuli [45], such as those perceived during chronic stress, and adaptive control on negative emotional experiences [10]. Hence, alteration of the MRN-hippocampal projections has been associated with decreased tolerance to aversive stimuli, learned helplessness, and subsequent depression [43].

At the molecular level, serotonin (5-hydroxitryptamine, 5HT) is normally released to the synaptic cleft, where it binds to specific 5HT receptors. Serotonergic neurotransmission is regulated by the serotonin transporter (5HTT), which is responsible for reuptaking 5HT from the synaptic cleft, therefore regulating the concentrations of the neurotransmitter. This represents the target of different antidepressants, including the tricyclics (TCs) and the selective serotonin reuptake inhibitors (SSRIs), which have been shown to block the 5HTT, therefore leading to increased concentrations of 5HT in the synaptic cleft, hence allowing the activation of 5HT receptors [46]. These molecules may also induce adaptive changes, including desensitization or down-regulation of somato-dendritic $5HT_{1A}$ auto-receptors in the RN and up-regulation of postsynaptic $5HT_{1A}$ and desensitization of $5HT_{2A}$ receptors [47], particularly in the MRN-hippocampal tract. Postsynaptic $5HT_{1A}$ receptors may be down-regulated or desensitized in different limbic structures by cortisol or exposure to chronic stress [48–50]. Alteration of 5HT neurotransmission by cortisol may be exerted tonically through binding to MRs, while sustained and prolonged increased levels of cortisol, such as the observed during chronic stress, bind predominantly to GRs, which in turn may interact with GREs in the promoter region of target genes, therefore inhibiting the expression of the 5HT1A gene [48]. Interestingly, it has been shown that cortisol may stimulate 5HT uptake in vitro, due to increased expression of the 5HTT gene [51], providing additional evidence about the reciprocal regulation between the HPA axis and the serotonergic system, and their potential interactions in the interface between stress and depression.

The Role of Cognitive Vulnerability

The influence of stress in the origin and development of depression and anxiety disorders has long been observed at the clinical level, where cognitive processing has been shown to play a critical role. In this regard, the harmful effect of environmental stressors may depend on various aspects associated to stressful events, including their length and strength, and the availability of cognitive resources to cope with them. The availability of these resources may also depend on subjective cognitive processing, aimed at assessing the potential efficacy of these resources, and the resulting balance between them and environmental stressors, which is part of the cognitive appraisal, and the resulting coping strategies [52]. This adaptive cognitive processing is necessary to assess diverse characteristics of environmental stimuli, which may lead to the assumption that many of them may be noxious or negative, while many others may be perceived as positive stressors. In this regard, certain environmental stimuli, assessed and perceived as desirable, predictable, and controllable situations, may constitute positive conditions, hence distinguished as pleasant or exciting challenges, known as "eustress," or positive stress. On the other hand, "distress," which is commonly known and identified as negative stress, is characterized by undesirable, unpredictable, and uncontrollable conditions, generally provoked by more intense and persistent stimuli, which may be perceived as dangerous or threatening, and consequently may lead to maladaptive responses, which in turn may be associated with the origin and development of various disorders [53]. In this regard, distress may engender an array of adaptive responses, including a defense reaction, which represents the active mode of adaptive responses, or a defeat reaction, which represents the passive mode. Active responses may result as a consequence of perceived threat, when subjective feelings of control are threatened by environmental stimuli, and are usually associated with effortful coping strategies. On the other hand, passivity is associated with per-

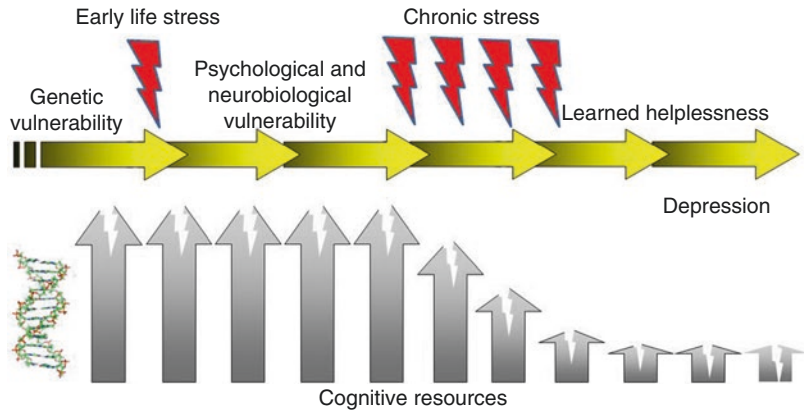

Fig. 28.2 A schematic representation of the effect of stress in the origin and development of depression, including factors of vulnerability

ceived loss, when subjective feelings of control are considered null and void, which in turn may lead to inability to cope. Accordingly, sustained and prolonged impact of undesirable, unpredictable, and uncontrollable stimuli may lead to the subjective feeling of loss, associated with the belief that the available resources are not effective or not enough, with the consequent impossibility to cope with the situation, which in turn may lead to subjective feelings of helplessness [54]. In this regard, chronic distressful conditions may lead to learned helplessness, which in turn has been associated with increased vulnerability to develop depression or anxiety disorders [54], and this is more evident when chronic stressful conditions occur during childhood [3, 31] (illustrated in Fig. 28.2).

The Role of Early Adverse Experiences

It has been shown that, in addition to chronic stress, the harmful impact of adverse conditions, a hostile environment, and traumatic events suffered during early periods of life represent a significant factor of vulnerability in the origin and development of depression [3, 31]. In this regard, the impact of adverse experiences, such as abuse, neglect, or loss, has long been associated with increased vulnerability to stressful conditions later in life, and the consequent development of depression [30, 31]. An increasing body of research has demonstrated the association between early adverse conditions and diverse alterations in different neural structures, including cortical and limbic areas, and the HPA axis. In this regard, CRH neurotransmission may be particularly affected [25], which may lead to increased reactivity to stress [3, 31]. Increased levels of CRH have been associated with hyperactivity of the HPA axis and the consequent increase in cortisol levels, which in turn may lead to functional and structural changes in the hippocampus [55]. It has been shown that increased levels of cortisol, in a sustained and prolonged manner, may affect GRs availability in the hippocampus [56]. It has been shown that early adverse experiences may lead to decreased availability and reduced efficacy of hippocampal GRs [31, 57], which in turn has been associated with glucocorticoid resistance and increased reactivity of the HPA axis in response to further stressful situations. In addition, it has been shown that decreased GRs induced by early adverse experiences, along with increased levels of cortisol, may lead to decreased hippocampal function and volume in adulthood [58]. In this regard, decreased function and volume of the hippocampus, along with hyperreactivity of the amygdala, have been associated with a history of early life stress [31, 59]. Changes in cortical thickness have been also described in patients exposed to specific stressors during childhood [60]. Therefore, early life stress

may lead to functional and structural changes, including hyperreactivity of neural and neuroendocrine responses to stress, which may affect potential responses to upcoming stressful situations later in life (illustrated in Fig. 28.2).

The Role of Genetic Polymorphisms

The role of stressors has been extensively elaborated; however, some individuals may be more vulnerable to stress, while some others may be more resistant or even resilient [61]. The influence of stressors may depend not only on their attributes, but also on the interactions between them and the characteristics of each individual, including psychological conditions, including their cognitive resources, and biological conditions, including their genetic background [31]. The relationship between different genetic polymorphisms and possible alterations, either functional or structural, in the CNS is an important aspect to better understand the molecular mechanisms underlying potential gene–environment interactions. Various polymorphisms have been studied in different candidate genes, critically involved in diverse molecular pathways closely involved in the origin and development of depression. These genetic variations may participate in the development of depression, either in response to adverse experiences during childhood or environmental stressors during adulthood, therefore representing important factors of vulnerability [31, 61–63]. Among these genetic variations, a polymorphism was identified in the promoter region of the 5-HTT gene [64]. Activity in the promoter region may be regulated by sequence elements located in the upstream regulatory region, termed the 5-HTT gene-linked-polymorphic-region (5-HTTLPR), where a short (5-HTTLPR-S) and a long (5-HTTLPR-L) variant have been described [63]. The short allele was associated with decreased transcriptional efficiency, compared to that observed in the long one, resulting in down-regulation of the 5-HTT gene [64] with a resulting decrease in the 5-HTT availability. It has been shown that the potential effect of various antidepressants, including the serotonin reuptake inhibitors, may depend mostly on 5-HTT blockade, therefore increasing 5-HT concentrations in the synaptic cleft, and also on down-regulation of presynaptic 5-HT_{1A} auto-receptors [47, 65]. Hence, it has been proposed that down-regulation of the 5-HTT gene, with the resulting effect on 5-HT concentrations in the synaptic cleft, may be different between the expressed by congenital conditions, and the triggered by environmental stressors. Congenital alterations, such as that observed in the short allele carriers, may result in increased concentration of 5-HT, which in turn may lead to down-regulation of postsynaptic 5-HT receptors, with the resulting desensitization of the serotonergic system [65], which may provide a mechanism to explain the vulnerability expressed by carriers of the 5-HTTLPR-S allele. It has been demonstrated that alterations in the regulation of the 5-HTT gene may be involved in the modulation of serotonergic activity in response to stress, and this was further supported by clinical and preclinical studies [66]. In addition, it has been observed in functional brain imaging studies that 5-HTTLPR-S carriers expressed an increased reactivity in the amygdala, in the presence of fearful and threatening stimuli, comparing to that observed in 5-HTTLPR-L carriers [67], strongly suggesting that these genetic variations may be involved in psychological responses to stress [61]. It has been shown that the amygdala participates in the regulation of emotional reactions, including anxiety and mood regulation, and also participates in the activation of the HPA axis, with the resulting hyper-cortisolism, therefore explaining the role of this polymorphism as a potential factor of vulnerability. Another important polymorphism has been investigated in the brain-derived neurotrophic factor (BDNF) gene, particularly in its coding region at nucleotide position 196, where a guanine base is replaced by an adenine, which in turn is translated into the substitution of valine (Val) by methionine (Met) at codon 66, therefore termed "Val66Met." This substitution has been associated with altered intracellular trafficking and decreased availability of BDNF [68–70] (Duman and Monteggia 2006; Egan et al. 2003; Gatt et al. 2009). It has

been shown that BDNF plays a critical role in the stimulation of neuroplasticity and neurogenesis in the hippocampus, which may be critical in the treatment of mood disorders [70], while decreased concentrations of BDNF have been associated with depressive symptoms [71]. In this regard, it has been observed that carriers of the Met-BDNF allele exhibited reduced hippocampal volumes, compared with carriers of the Val-BDNF allele [70], and decreased hippocampal activation [69], with the consequent deficient cognitive performance [70], which in turn have been associated with emotional instability and vulnerabilitsy to develop depressive symptoms. Many other polymorphisms have been also studied, and are currently investigated, therefore representing additional factors of vulnerability (illustrated in Fig. 28.2).

Neurobiological Circuits of Vulnerability and Resilience

It has been shown that serotonergic projections from the RN may reach different targets in the CNS. Projections from the MRN may reach the hippocampus to stimulate 5HT1A receptors involved in adaptation to chronic aversive stimuli, with the consequent tolerance to adverse events, such as that experienced during chronic stress. Therefore, impairment of this serotonergic pathway has been associated with learned helplessness and subsequent depressive symptoms [35]. Projections from the DRN may reach the extended amygdala, including the BNST and certain nuclei of the amygdala itself [36, 43] to stimulate 5HT2A receptors. Activation of these serotonergic pathways has been shown to be sufficient and necessary to produce increased fear and anxiety [72, 73]. In acute stress conditions, fear represents an adaptive emotion, necessary to implement and sustain active behavioral responses, such as the activation of fight or flight. During chronic stress, excessive fear and anxiety become more intense and less adaptive, as it is usually described in anxiety disorders and depression. In addition, serotonergic projections from the DRN may also reach additional neural structures, such as the striatum and the periaqueductal gray (PAG), which are known to be involved in active coping behavior [74]. Serotonergic input from the DRN to these areas has been shown to exert inhibitory effect, which may lead to inhibition of active responses, such as fight or flight, which in turn may be replaced by passive responses [72, 73]. The lack of active responses, also known as passivity, combined with increased fear and anxiety, represent core symptoms of learned helplessness [75], and therefore are usually observed in anxiety disorders and depression. The DRN may be modulated by multiple inputs, including excitatory projections from the noradrenergic LC, which participate in adaptive responses to stress, and inhibitory projections from cortical sources, particularly from the prelimbic region of the ventromedial prefrontal cortex (VMPFC) [76]. Input from the VMPFC is mediated by glutamatergic neurons, which synapse to GABAergic interneurons in the DRN, therefore inhibiting serotonergic neurons. It has been shown that neurons in the VMPFC participate, with the dorsal medial striatum, in a circuit involved in detection of control, which in turn may lead to inhibit the DRN [42, 77]. Therefore, passivity, associated with chronic stress and learned helplessness, may be overcome by learned control, which may be understood as a result of VMPFC inhibition of the DRN. In addition, prelimbic and infra-limbic neurons in the VMPFC have been shown to extend glutamatergic projections to synapse GABAergic interneurons in the amygdala, therefore exerting inhibitory effect on this neural structure. Therefore, increased fear and anxiety, associated with hyperactivation of the amygdala, may be also overcome by learned control, which has been associated with activity in the VMPFC. Learned control also requires the concerted activity of other PFC areas, such as the DLPFC, which is involved in working memory and cognitive processing, and therefore participates in cognitive aspects of inhibitory control, the OFC, which participates in emotional aspects of inhibitory control, and the ACC, which is involved in emotion regulation [78]. Hence, cognitive processing may exert control on limbic structures, such as the amygdala, by means of inhibitory projections

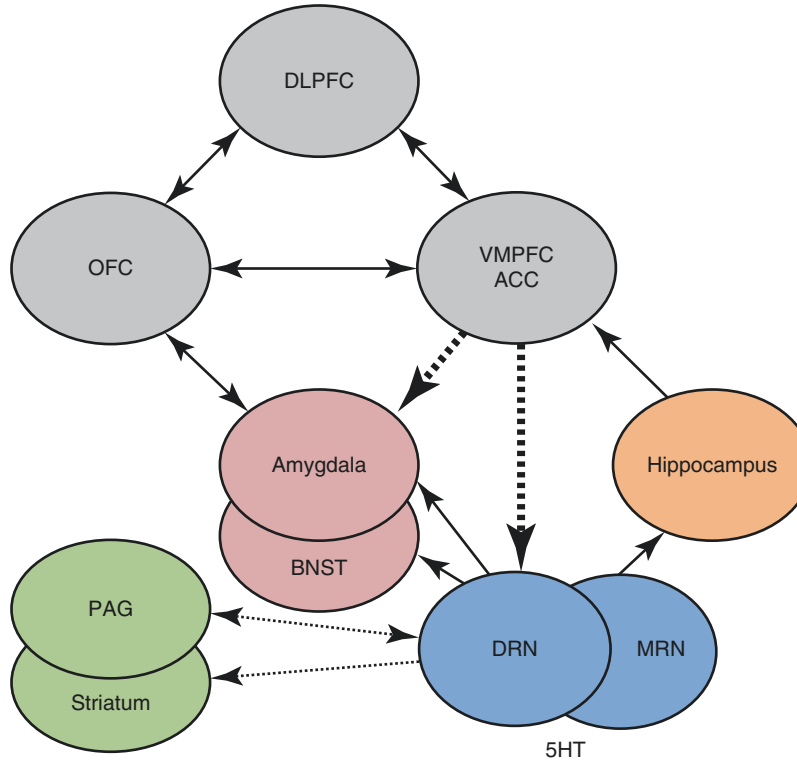

Fig. 28.3 A schematic representation of stimulatory serotonergic pathways from the DRN to the amygdala and BNST, involved in increased anxiety, inhibitory pathways to the striatum and PAG, involved in passivity, and projections from the MRN to the hippocampus, involved in increased tolerance to stressors. Reciprocal connections between the DLPFC, the OFC, and the VMPFC, together with the ACC, which in turn send inhibitory projections to the DRN and the amygdala. (Modified from Tafet and Nemeroff [5])

from the VMPFC to the amygdala. In addition, increased controllability, exerted by inhibitory projections from the VMPFC to the DRN, may be followed by synthesis of new proteins, therefore reinforcing these adaptive connections involved in controllability and predictability, both aspects of resilience (illustrated in Fig. 28.3).

From Distress to Eustress: The Road Map to Resilience

The role of stress in the origin and development of anxiety and depressive symptoms has long been investigated, demonstrating to be a multifactorial relationship. Among these, it is possible to identify an array of features corresponding to the impact of different environmental stressors, where it is also possible to differentiate between the characteristics of stressors themselves and their environment, either bio-ecological or psychosocial. To successfully cope with these stressors, it is important to know the characteristics of each individual, which in turn may explain their potential vulnerability or resilience. In this regard, it is possible to identify biological factors, including genetic and epigenetic mechanisms, and psychological aspects, including those related to the biography, where a history of traumatic events in early periods of life has been shown to represent an important factor of vulnerability. Traumatic events during adulthood may also predispose to increased vulnerability, although it has been shown that many subjects with such a traumatic history exhibit certain ability to develop an extraordinary strength and additional skills to cope with stressful events, therefore becoming less vulnerable and more resilient. This has been shown to depend on different factors, mostly related to their ability to perceive stressful events in a different manner and appraise them according to their potential resources. Cognitive appraisal may provide cognitive resources to increase predictability and controllability, which in turn may lead to more effective coping strategies. The feeling of controllability may be suf-

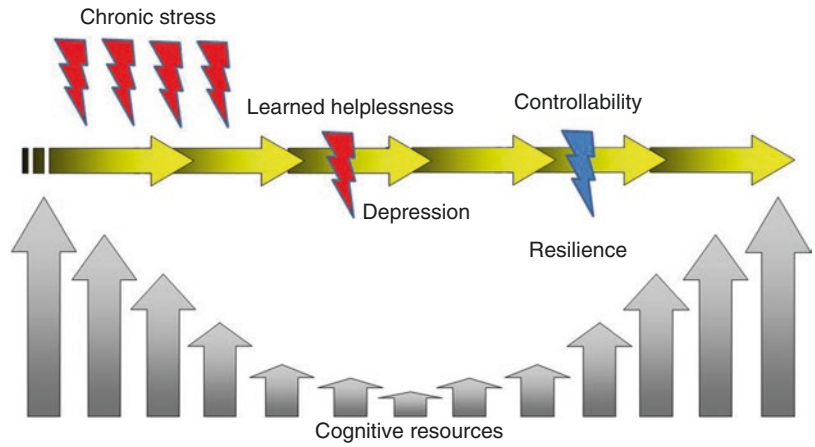

Fig. 28.4 A schematic representation of the effect of stress, learned helplessness, and controllability

ficient and necessary to transform distress into eustress. Therefore, cognitive strategies aimed at improving appraisal and related information processing may be highly effective to improve subjective feelings of controllability (illustrated in Fig. 28.4). More effective approaches to improve controllability, therefore avoiding learned helplessness, are currently investigated, which in turn may provide effective strategies for the treatment of depression and anxiety disorders, but also to promote resilience, providing novel approaches for the prevention of anxiety and depression in vulnerable individuals, including those exposed to chronic stress and those with a history of traumatic events in early periods of life.

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