Gustavo E. Tafet

Neuroscience of Stress

From Neurobiology to Cognitive, Emotional and Behavioral Sciences

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Chapter 1
Introduction to the Study of Stress

Stress constitutes one of the most studied concepts in health sciences and neurosciences. It has been associated with the origin and development of different clinical conditions, including depression and diverse anxiety disorders. Therefore, an increasing body of research has investigated the psychological and neurobiological processes involved in the effects of stress, including the consequences of early adverse experiences and the impact of chronic stressful conditions. Stress may be provoked by the impact of different environmental stressors, which in turn may lead to an array of adaptive responses, aimed at protecting or recovering the optimal functioning of the organism, associated with the homeostatic equilibrium. Different neurobiological processes in the central nervous system (CNS), involving diverse neural structures, are involved in the shaping of these responses, which are mainly mediated by the activation of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) system. Cognitive and emotional processes also participate in the shaping of behavioural responses, which in turn play a critical role in the development of coping strategies, which may lead to more effective adaptive responses. In response to certain stressful events, limited in time and extent to the exposure of specific stressors, acute responses may be sufficient and necessary for adaptation. If the impact of stressful events continues in a sustained and prolonged manner, chronic activation of stress responses may lead to exhaustion of the ANS and dysregulation of the HPA system. In addition, chronic stress may lead to less effective cognitive strategies, with the consequent feeling that available resources are not enough to successfully cope with the ongoing situation, which in turn has been associated with the origin and development of learned helplessness and subsequent depression. Effective cognitive and emotional processing has been associated with resilience, which represents the ability and capacity to cope with adversity and adapt successfully to stressful situations.

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Stress: Historical Perspective and Evolution of the Concept

Stress constitutes one of the most studied concepts in health sciences, including different chapters of medicine in its full extent, particularly the classical psychosomatic medicine, psychology, psychiatry and more recently also psychoneuroimmunoendocrinology. In this regard, stress has been closely associated with the origin and development of different disorders, from mild clinical conditions, which are usually referred as minor symptoms associated with brief or moderate stressful situations, to severe health alterations, including depression and different anxiety disorders. Therefore, stress has been studied at different levels of complexity, including all kind of signs and symptoms associated with potential clinical expressions, as well as the molecular and neurobiological processes involved in the origin and development of different disorders produced by the effects of stressful conditions (Tafet & Bernardini, 2003; Tafet & Nemeroff, 2016).

There is no doubt that stress is a common condition in human life. Naturally it was present since the origins of humankind and throughout its historical development, although it has not been always recognized and called this way. Most probably, our remote ancestors recognized the role of stress, mostly as a trigger of different affective states and certain cognitive conditions, but it was also an inherent part of their daily life, including their inner world, represented by their cognitive and emotional experiences, and their surrounding environment, including all kind of stimuli and the potential threats and challenges associated with these experiences.

Regarding the recognition and development of the concept of stress, during the classical era, in ancient Greece, Heraclitus described the changing nature of things with the flow of time and observed the importance of harmony through adaptation to change. Empedocles proposed the idea that nature consisted of elements in a constant and dynamic balance and also focused on the concept of harmony, as a necessary condition for the survival of living organisms. Hippocrates associated health to a harmonious balance of the elements of life while associated disharmony to disease, suggesting that the disturbing forces that provoked disharmony derived from natural sources, as well as the adaptive forces necessary to recover the threatened balance. Epicurus introduced the notion that the mind would be involved in these adaptive forces, necessary to recover a healthy equilibrium, therefore representing an important precedent. Moreover, he also proposed certain association between this harmonious and balanced state and the "imperturbability of mind", which he called "ataraxia". This concept is closely associated with equilibrium and mental health, therefore suggesting that the opposite would be associated with mental perturbation, with the resulting physiological and mental disorders.

During the second half of nineteenth century, Claude Bernard extended the classical concept of harmony and developed the principle of a dynamic physiological internal equilibrium, which resulted from the interactions between the impact of the external world and the sustained compensations, aimed at protecting and recovering the constancy and stability of the internal environment (Bernard, 1865). In the 1920s, Walter Cannon proposed the term "equilibrium" to designate relatively

simple physical and chemical processes, where forces may keep balanced, although the condition characterized by more complex physiological reactions, aimed at maintaining the steady state of the organism, should be called "homeostasis". This new term was composed from the Ancient Greek words "*homoios*", meaning "similar", and "*stasis*", meaning "standing", therefore implying the homeostatic notion of "standing the same" (Cannon, 1932). This dynamic equilibrium may be maintained through a complex repertoire of physiological mechanisms involved in adaptive responses to internal or external threatening forces. Cannon extended the concept to integrate emotional and physiological parameters and also introduced the notion of a "fight or flight" reaction, which is usually observed in acute stress responses. This is characterized by a rapid activation of the autonomic nervous system (ANS), more specifically by a general and non-specific discharge of the sympathetic nervous system (SNS), followed by compensating activation of the parasympathetic nervous system (PNS), rapidly preparing the organism for fighting or flying in response to threatening environmental stimuli. In the 1930s, Hans Selye observed that prolonged implementation of adaptive responses may lead to serious clinical conditions, which he described as the "general adaptation syndrome" (GAS), which was associated with chronic activation of the pituitary and the adrenal glands, later included as critical components of the hypothalamic-pituitary-adrenal (HPA) axis (Selye, 1936). The described syndrome was characterized by an initial alarm reaction, which would be similar to the acute stress reaction described by Cannon, followed by an adaptive stage, which is characterized by physiological processes associated with resistance to chronic stress. If stressful conditions continue, then adaptation may lead to maladaptation, with the consequent clinical effects, which in turn may lead to the last stage, termed exhaustion, characterized by the inability of the organism to elicit any adaptive response (Selye, 1946).

Regarding the original definition of "stress" by Selye, it would be a non-specific response of the body to any demand (Selye, 1936), provoked by different environmental stimuli, recognized as "stressors". Therefore, environmental stressors may provoke an array of adaptive responses, either physiological or psychological, which in turn may be associated to the pathophysiology of the stress syndrome. Selye proposed that prolonged and sustained exposure to stress, what is currently known as chronic stress, resulted in "diseases of adaptation" (Selye, 1946).

Regarding the origins of the term "stress", and its introduction in health sciences, it is interesting to know that it was not always related to the concept we are currently familiar with. According to different sources, the term "stress" is first introduced in Middle English around the beginning of the fourteenth century to mean "hardship", "adversity" or "pressure", which probably derived from the term "estresse" in the Old French, used to refer to "narrowness" and "oppression", which in turn derived from the Latin term "strictus", which means "tight", "compressed" or "drawn tight". It was first used to describe the impact of a physical force on a material object around the mid-fifteenth century and later introduced in mechanics to describe an "abstract force" around the mid-nineteenth century, where Selye referred to have taken from. In this regard, he borrowed the term "stress" from physics to describe the effects produced by environmental stimuli, or external forces, to which an

organism reacts with adaptive responses, or internal forces, characterized by a repertoire of psychological and physiological events. Although the term "stress" has been used previously by Cannon, in the context of his work about homeostasis in 1935 (Cannon, 1935), Selye might be credited for introducing and expanding the term "stress" in the generous lexicon of medicine, pathophysiology, psychology, psychiatry, particularly in psychosomatic medicine, and more recently in PNIE (Selye, 1976, 1978).

Stress in Daily Life: Stressors and Adaptive Responses

Stress is present in our daily life; it may stay longer in our past memory and return to our present, suddenly appearing at every moment, in every interaction with our environment. In order to survive, and continue developing, every living organism should maintain and preserve an internal equilibrium, which may be constantly challenged or threatened by environmental changing conditions. Any environmental stimulus, capable of triggering adaptive, or maladaptive, responses to stress, constitutes a stressor. Hence, the impact of environmental stressors may trigger an array of adaptive responses, aimed at protecting or recovering the optimal functioning of the organism, associated with the homeostatic equilibrium (Fig. 1.1). According to different authors and researchers, stressors may be classified into different, mainly overlapping, categories, including bio-ecological and psychosocial, physical and psychological, environmental and internal, objective and subjective, acute and chronic and positive or negative. These classifications may depend on certain characteristics of stressful stimuli, the cognitive and emotional processing of the perceived impact, the available resources to cope with them and the resulting adaptive responses and their potential efficacy.

Certain features may be critical to understand the potential threat posed by different stressors and the possible effects produced by their impact, which may provoke more or less effective reactions. Adaptive responses may be followed by the protection or recovery of healthy conditions or, depending on their potential success or failure, may lead to the development of maladaptive responses with the consequent diseases. Among these aspects, the magnitude and the intensity may be critical to assess the potential consequences of diverse environmental stimuli. Therefore, stressors may be also classified according to their severity, ranging from mild or moderate environmental stimuli to severe and extreme stressful situations. The extent of the impact, and its persistence during certain periods, represent another critical feature. In this regard, stressors may impact in a limited manner, during a short period of time, therefore associated with acute stress, or may persist during longer periods, characterized by the sustained and prolonged impact of environmental stimuli, as it is usually observed during chronic stress.

Among the mainly accepted classifications, bio-ecological stressors are those environmental factors originated from natural sources or physical forces, while psychosocial stressors are those associated with the effects produced by the interactions

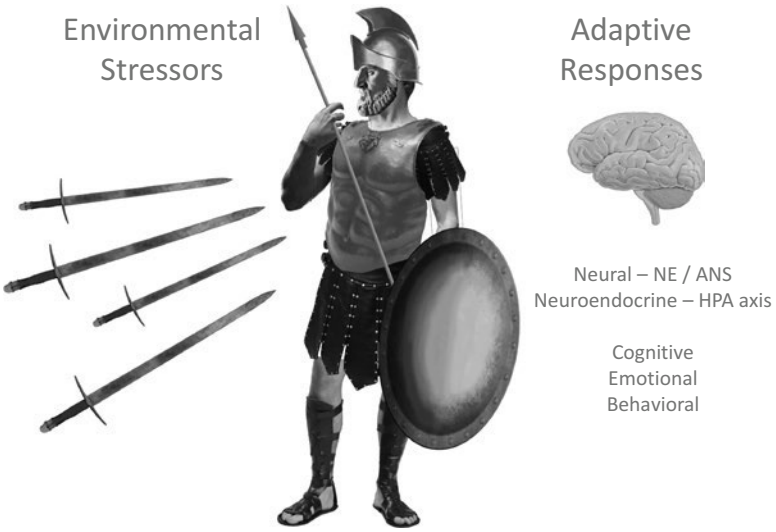

Fig. 1.1 Stressors and adaptive responses. Stress is provoked by the impact of environmental stressors. In order to protect or recover homeostatic equilibrium, the organism reacts with an array of adaptive responses. Physiological responses are mainly accomplished through neural and neuroendocrine mechanisms. Neural mechanisms are mediated by the activation of the autonomic nervous system (ANS) and the noradrenergic (NE) system. Neuroendocrine mechanisms are mediated by the activation of the hypothalamic-pituitary-adrenal (HPA) axis. In addition, more complex adaptive responses are mediated by cognitive, emotional and behavioural mechanisms, aimed at improving efficacy to successfully cope with stress

within the social environment and its psychological consequences. Bio-ecological stressors include natural disasters, also referred as cataclysmic events, such as earthquakes, seaquakes, tsunamis, floods, big storms, big fires, hurricanes and volcanic eruptions. These extremely stressful events may occur abruptly and unexpectedly, with few chances to predict their onset or their progress, and therefore less prone to be controlled with available resources. Although they are intense and may be considered acute stressors, their consequences may continue much longer, therefore representing an important source of chronic stress. Other disasters, not related to natural forces but associated with catastrophic events produced by human activities, including all kind of accidents, such as car and plane crashes, shipwrecks or big industrial accidents, may also be considered cataclysmic, according to their magnitude, although their origin is not associated with the effects produced by natural forces. In addition, other stressors related to the natural environment, but much less harmful and destructive than cataclysmic events, such as climatic changes, including heavy rains, snow storms, intense and extreme temperature changes, may be also considered mild or moderate bio-ecological stressors, which are usually associated with chronic stress conditions.

Psychosocial stressors constitute an extensive group of factors associated with different personal circumstances and all the potential interactions with the social

and cultural environment. These stressors may be also shaped, and critically influenced, by subjective cognitive and emotional processing, and their behavioural consequences. Among these, it is important to distinguish a series of major personal experiences, which are usually referred as stressful life events, that provoke more intense cognitive, emotional and behavioural efforts, as part of the adaptive responses. Stressful life events constitute all these imaginable and sometimes unimaginable situations associated with relevant personal circumstances, usually experienced as major changes in life. These include critical changes in the affective life, either positive or negative, including marriage, major crisis and divorce, changes in the occupational or professional environment, such as job loss, unemployment and the search for a new job, challenges related to the residential environment, including moving to another house or migration to a different city or another country, and of course disease and dead of a loved person. Although the critical event itself may occur during a short period, the pathophysiological and psychological consequences may continue much longer, therefore representing a source of chronic stress and long lasting traumas.

Psychosocial stressors may also include an array of chronic conditions, such as those represented by daily hassles, including a hostile environment at work, usually recognized as "mobbing", psychophysiological exhaustion due to excessively adverse occupational conditions, constituting a "burnout" syndrome, psychological harassment at school, also known as "bullying", and persistent conflicts at home, including violence, abuse and neglect, all of them constituting a continuous source of severe chronic stressful conditions. In this wide category, it is also necessary to include extremely stressful conditions, such as those provoked by the continuous threat posed by social conflicts, such as terrorism and war, which may also represent an extreme source of chronic stress, whose consequences may last much longer than the direct impact of stressful conditions, which in turn may be perceived and referred as traumatic experiences.

In addition, there is no doubt that stressors may be also originated through mental processes, representing a subjective internal source of stress, sometimes stronger than any objective environmental event. In this regard, stressful life events are known to impact through different periods of life, including early adverse experiences, such as domestic violence, abuse and neglect, which may be experienced during childhood but whose consequences may be also suffered during adulthood. These traumatic experiences, with the resulting consequences stored in the long-term memory, may represent potential sources of stress throughout life, usually associated with the origin and development of depression and diverse chronic anxiety disorders (Fig. 1.4). Certain stressful life events experienced during adulthood, usually recalled as chronic overwhelming situations, may also represent a critical source of chronic stress, which in turn may be also associated with the origin and development of mood and anxiety disorders, including depression, post-traumatic stress disorder (PTSD), panic attacks and generalized anxiety disorder (GAD).

These internal sources of chronic stress are strongly associated with our subjective interpretation of symptoms provoked by stress responses elicited by traumatic memories, sometimes experienced as automatic intrusive memories. In this regard,

we are able to evoke stressful life events, traumatic experiences stored in our long-term memory, which may lead us to re-experience some of the psychological burden and physiological responses we previously experienced during the original event, as if it was occurring at the present moment, which may lead to feelings of anxiety, fear and alarm, that may occur in a chronic manner, representing another source of internal chronic stress. Hence, cognitive and emotional processing of traumatic memories may also lead to chronic stress, in a vicious cycle characterized by anxiety, irritability, fatigue, excessive worrying and re-experiencing of traumatic events, usually followed by physiopathological changes, which may be perceived as diverse autonomic symptoms.

In order to cope with stressors, the organism reacts with an array of adaptive responses, aimed at protecting or recovering the threatened equilibrium. Adaptive responses are mainly coordinated by the central nervous system (CNS), in a complex and dynamic process, which involves different neural structures implicated in the processing of perceived sensory input. Therefore, cognitive and emotional processing may lead to the rapid activation of neural and neuro-endocrine responses, aimed at preparing the whole organism to activate basic adaptive reactions, such as the classical "fight or flight" adaptive response, and the slower activation of more sophisticated resources, mediated by cognitive strategies, which may lead, in the long term, to more effective adaptive responses.

Neural and neuro-endocrine responses are mediated by the activation of the ANS, more specifically the SNS, and the HPA axis, respectively. Activation of the HPA axis is closely regulated by cortical and limbic structures, constituting a cortico-limbic-HPA system (C-L-HPA). Therefore, activation of the SNS, with the consequent biosynthesis and release of adrenaline, also known as epinephrine, contributes to improve the availability of natural resources to cope with ongoing demands, including increased heart rate and blood pressure to provide oxygen and glucose to different organs and tissues, such as the muscles involved in fighting or flying. Systemic activation of the ANS is associated with increased release of noradrenaline (NA), also known as norepinephrine (NE), mainly by the locus coeruleus (LC), the main noradrenergic nucleus in the CNS. Increased NE release in the CNS participates in improving focused attention and arousal, also contributing to more effective cognitive appraisal and coping. Neuroendocrine responses are mediated by the activation of the HPA axis, with the consequent biosynthesis and release of corticotropin-releasing hormone (CRH, also known as corticotropin-releasing factor or CRF), by the paraventricular nucleus (PVN) of the hypothalamus, with the subsequent release of adrenocorticotropic hormone (ACTH), by the pituitary gland, and glucocorticoids, mainly cortisol, by the adrenal cortex (Fig. 1.2). Increased release of glucocorticoids is necessary to keep adequate concentrations of glucose in blood, therefore providing a necessary source of circulating energy for successfully coping with environmental demands. Regarding the HPA axis, it is regulated by limbic structures, such as the amygdala and the hippocampus, which in turn are closely associated and mutually regulated by certain cortical structures, mainly located in the prefrontal cortex (PFC). In addition, neural structures involved in the regulation of the ANS and the HPA axis are reciprocally regulated and mutually

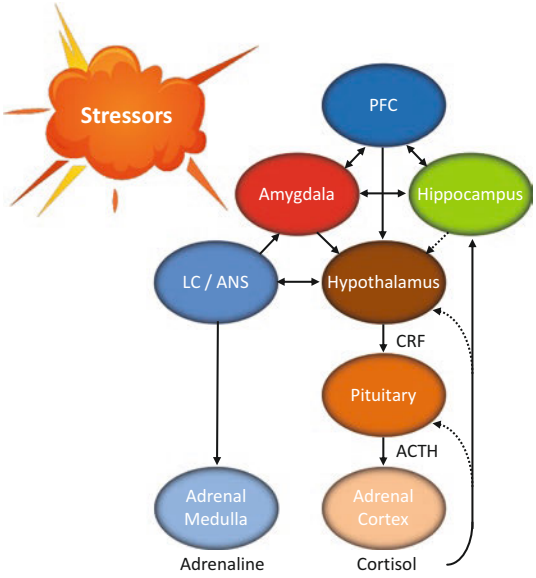

Fig. 1.2 Neural and neuroendocrine systems are activated in response to stress. In response to environmental stressors, neural and neuroendocrine responses are mediated by the activation of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the HPA axis is regulated by cortical structures, mainly located in the prefrontal cortex (PFC), and limbic structures, including the amygdala and the hippocampus. Activation of the ANS is associated with increased release of norepinephrine (NE), mainly by the locus coeruleus (LC), and adrenaline by the adrenal medulla. Neuroendocrine responses are mediated by the activation of the HPA axis, with the consequent biosynthesis and release of corticotropin-releasing factor (CRF) by the paraventricular nucleus (PVN) of the hypothalamus, with the subsequent release of adrenocorticotropic hormone (ACTH), by the pituitary gland, and cortisol by the adrenal cortex. Neural structures involved in the regulation of the ANS and the HPA axis are reciprocally regulated and mutually enhanced in response to stress

enhanced in response to stress, hence potentiating each other to prepare the organism for a rapid fight or flight response (Fig. 1.2). Therefore, physiological adaptive responses are coordinated by cortical and limbic structures in the CNS and thus are also strongly affected by cognitive and emotional processes, which in turn represent the basis for more complex and sophisticated adaptive responses. In this regard, cognitive and emotional processing may lead to more efficacious assessment of stressful events, which in turn may lead to more effective coping strategies, which represent the highest level of complexity of adaptive responses.

Stress responses may be also classified in acute and chronic, active and passive and of course adaptive and maladaptive. Acute responses are known to be limited to the restricted impact of limited stressful events. In this regard, this kind of responses is meant to be promptly adaptive, in the sense that may allow us to successfully defend or recover our previous equilibrium during stressful situations, which are limited in time and extent. Therefore, if the impact of stressful events is not limited,

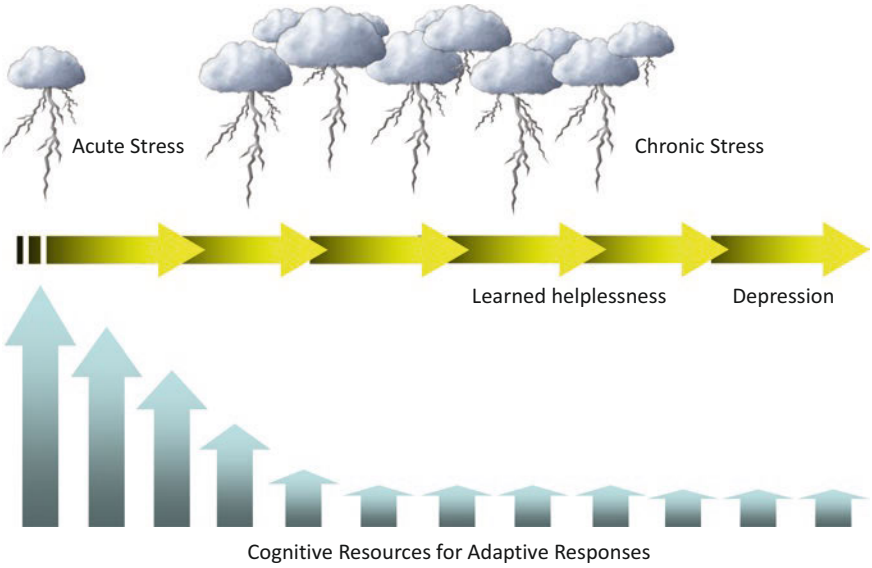

Fig. 1.3 From the impact of stress to the development of depression. Acute stress has been associated with activation of adaptive responses, mediated by available resources. Chronic stress has been associated with decreasing resources, with the consequent maladaptive responses, which may lead to learned helplessness, which in turn has been associated with the origin and development of depression

but continues in a sustained and prolonged manner, we are experiencing a chronic stress situation (Fig. 1.3). Hence, during chronic stress, previously successful responses may result less effective, and therefore less adaptive. Chronic activation of the ANS may result less efficacious and may lead to exhaustion of the system. Chronic activation of the HPA axis may also result in excessive demand, which in turn may lead to increased and sustained levels of cortisol, aimed at maintaining adequate resources for longer. Sustained challenging of cognitive strategies may put in jeopardy the efficacy of cognitive resources, or the subjective feeling that available resources are not enough to successfully cope with the ongoing situation, which in turn has been associated with the origin and development of learned helplessness (Fig. 1.3).

Acute responses are usually associated with active ways of coping, which are frequently provoked by subjective feelings of threat, or controlled danger. This may lead to defensive reactions, which are associated with increased activation of the ANS and the implementation of coping strategies. In contrast, chronic stress is usually associated with passive ways of response, which are commonly characterized by subjective feelings of defeat, provoked by uncontrollable stressful situations. Passive responses are usually associated with chronic activation of the HPA axis, with the resulting hypercortisolism. At the cognitive level, passive responses represent the failure to implement coping strategies, the subjective feeling that available resources are not enough to cope with ongoing stressful situations, with the

resulting feelings of hopelessness and helplessness, associated with the origin and development of depression.

The Good and the Bad: Eustress, Distress and Learned Helplessness

The study of stress and its consequences on health have always emphasized its most negative aspects, those related to poor quality of life and the origin of different disorders, mostly associated with anxiety and depression. According to the original sequence proposed by Selye and other authors, characterized by the impact produced by different stressors, from simple environmental stimuli to the most complex life experiences, we can identify certain stressful situations, which according to their characteristics, constitute positive experiences. In this regard, positive stress is called "eustress" (from the Greek prefix "*eu*", to denote that something is good or true). These are experiences that can be objectively valued as positive, although it is mainly their subjective perception and interpretation what confer them a positive character. They are characterized by various aspects related to perceived stimuli themselves, which can be observed and understood objectively, and with the subjective cognitive evaluation, which is characteristic and idiosyncratic for each subject. Positive experiences are usually characterized by the presence of relatively brief stimuli, limited in time, whose intensity can be perceived within a wide range of values. Although they can be moderately motivating or highly stimulating experiences, mainly from the affective point of view, eustress represents a desirable experience. In this regard, a positive experience may be represented by certain situations that we expect to happen, which may fulfil our motivations and expectancies, and hence we choose to cope with them while doing our best efforts to achieve desired and expected challenges. Another important aspect is represented by predictability, which is translated into our ability and capacity to predict their effects and future consequences. For stress to be considered positive, we have to be able to predict its effects within a certain range of options, beyond which it could generate a level of uncertainty, incompatible with the positive nature of the experience. Finally, the main aspect that defines positive stress is represented by controllability, which may be explained by our subjective feeling and compelling belief that we have the ability and capacity to exert certain effect on a stressful situation. The perception of the effects we may provoke, with the consequent changes produced by our own efforts, may reinforce our feelings of control.

Controllability may be achieved through a complex cognitive processing, which in turn may be experienced primarily as a positive emotion. It is the result of a complex cognitive and emotional evaluation, where is required the processing of multiple aspects related to each experienced event, to each perceived stimulus, and the available resources to cope with them. Psychological resources include all the knowledge and skills we developed from past experiences, our cognitive aptitudes

and expertise for problem-solving, our emotional self-regulation and our self-esteem. More specific cognitive resources include attentional control, which may allow us to maintain focused attention on specific stimuli for longer periods, and shift our attention between our different thoughts, and working memory, which may allow us to keep certain content in mind and changing relevant information related to specific goals. Working memory is also necessary to integrate past information and future projects, which in turn is necessary to develop plans and take decisions. In addition, we can consider also the access to social resources, represented by all the significant people who may be supportive in the face of a challenge, as well as material resources, necessary to exert certain effect on our environment, successfully achieving our goals and reaching positive outcomes. The subjective perception of controllability, or the belief in such possibility, is critical for the development of a positively stressful experience. This can make the difference between a threat and a challenge, and how an event can be faced, experienced and remembered in our long-term memory.

At the opposite extreme is negative stress, technically defined as "distress", which means all the opposite we mentioned about "eustress". Negative stress constitutes an undesirable experience. It is something that may happen against our will, it has never been our choice, and we have to face it because it is imposed on us from the external environment. These are usually experiences where it is very difficult to predict any possible result. Although there is a certain possibility that the results may be within certain known options, which may represent certain margin of predictability, there are certain options that escape this safety margin, which may lead to feelings of uncertainty. Obviously, under these circumstances, the perception of controllability is significantly low. Although there is the possibility of evaluating the controllability according to certain objective parameters, in which it is evident that the stressful situation is clearly overwhelming, usually it is the subjective perception, and the resulting appraisal, what determines that an event may be more or less controllable. The lack of controllability may be usually the result of biased or distorted cognitive evaluation, according to which the person learned to believe that their resources are never enough and all their efforts will be in vain. In this sense, the lack of controllability is an important factor, often determining in situations of chronic stress, which may lead to the development of learned helplessness (Fig. 1.3).

The concept of learned helplessness was originally introduced in the 1960s by Martin Seligman and Steven Maier (Seligman & Maier, 1967). This concept was developed based on the observations that animals exposed to adverse experimental conditions learned to believe that outcomes were independent of their behaviour, hence undermining their possibility to escape from adversity. Hence, the concept was also widely studied in human behaviour, where, according to the authors, the subject learned to believe that nothing they did mattered, which in turn was translated into passive responses, associated with feelings of defeat, and the avoidance of active responses, associated with the possibilities to fight or flight. The concept of learned helplessness was coined to express the belief that outcomes are uncontrollable. Hence, if we start to believe that we have no control over what happens to us, this may critically affect our cognitive, affective and behavioural responses,

therefore, thinking, feeling and behaving in a helpless way. It is a condition learned through personal events, where we truly experienced the feeling of lack of control, which may be an objective fact, or just the subjective perception that we have no control over certain stressful situation.

The feeling of controllability may turn a threat into a challenge, which is usually possible through different psychotherapeutic strategies, where we are able to transform certain distress into eustress. On the contrary, chronic stress, which may be perceived as unpredictable, unavoidable, inescapable and, more specially, uncontrollable, may lead to learned helplessness, which may be considered as the gateway to depression.

Homeostasis, Allostasis and Allostatic Load

The concept of stress involves the effects produced by the impact of different stressors, with the consequent activation of adaptive responses, mediated by an array of physiological and psychological reactions. Adaptive responses have been originally described as those physiological reactions aimed at protecting or recovering the homeostasis, which has been threatened by environmental forces. In this regard, homeostasis represents a dynamic process aimed at maintaining the steady state of the organism, threatened by external forces. In other words, it is the process through which an organism has the capability to protect its own stability, through maintaining constant conditions in the internal environment (Bernard, 1865; Cannon, 1932). More recently, it has been proposed that the concept of homeostasis would refer to certain vital parameters, including blood oxygen, fluid balance, body temperature and blood pH, which should be maintained within narrow ranges. Upon exposure to environmental challenges, potential variations in these critical systems, even within narrow ranges, should return to a set point, which in turn is necessary for survival. In addition, adequate nutrition plays also a critical role to provide the necessary energy to protect and maintain homeostasis. In contrast, it has been proposed the term "allostasis" to define a dynamic process, characterized by the activation of adaptive functions, aimed at achieving and maintaining stability through changing conditions (Sterling & Eyer, 1988). Hence, upon exposure to environmental stressors, activation of allostatic systems, such as the ANS and the HPA axis, with the consequent release of catecholamines and glucocorticoids, may operate within much broader boundaries, allowing an efficacious implementation of adaptive responses, aimed at protecting and recovering stability, and their effective termination when the stressful situation would be finished. Allostatic mediators include different molecular pathways, which may be reciprocally regulated, such as pro-inflammatory and anti-inflammatory cytokines, cortisol and dehydroepiandrosterone (DHEA) and sympathetic and parasympathetic mediators. Excessive stressful events, such as the sustained and prolonged impact observed during chronic stress, or inefficient implementation of allostatic responses, such as the sustained and prolonged activation of an adaptive system when it is no longer necessary, may lead to

maladaptive responses. The terms “allostatic load” and “overload” were introduced to define these situations, with the consequent maladaptive responses, which in turn have been involved in the origin and development of various diseases associated with chronic or excessive stress (McEwen, 1998). Hence, the concept of allostatic load implies the chronic impact of stressors, with the consequent overactivation of allostatic responses, which in turn may lead to cumulative pathophysiological changes (McEwen & Seeman, 1999). Therefore, chronic or excessive stress may lead to certain imbalance in the regulatory systems involved in allostasis, which in turn may lead to excessive or inadequate production of certain mediators, which may be translated into different clinical conditions, each one constituting an allostatic state. These clinical conditions include hypertension, sustained increased concentrations of pro-inflammatory cytokines, such as the observed in inflammatory disorders, and altered cortisol rhythm and increased concentrations, such as the observed in chronic stress and depression. Allostatic load may lead to cumulative pathophysiological changes, which in turn may be involved in the origin and development of various clinical conditions, including higher levels of cholesterol, with low levels of high-density lipoprotein (HDL) and high levels of low-density lipoproteins (LDL), such as the observed in the metabolic syndrome, and neuronal atrophy in the hippocampus, such as the observed in chronic stress and depression.

Acute and Chronic Stress: The Road Map to Trauma or Resilience

Stressful events are often experienced in normal life, including eustress and distress, with their consequent adaptive responses, although it has been demonstrated that certain distressful life events, which may be characterized by their unusual intensity or excessive extent, may lead to cognitive and emotional alterations, which in turn may be associated with an array of maladaptive responses. Extreme stressful events are frequently referred as overwhelming or devastating experiences, which may occur at a certain moment, as an acute traumatic event, or may happen during an extended period, as a chronic stressful situation. In any case, these acute or chronic life events represent the core of a traumatic experience. In order to define these extreme experiences, *trauma* is an ancient Greek word that means “wound”. Therefore, we refer to a psychological trauma as a cognitive and emotional wound, which is not specifically located in the brain, but it may be stored in the long-term memory. Traumatic memories may remain silent for a long time but may be also evoked and reactivated by subtle cognitive processes or environmental stimuli, arousing the signs and symptoms of traumatic experiences.

Traumatic events may be experienced during different periods of life, although it has been shown that severe stressful life experiences during childhood, including psychosocial conditions such as domestic violence, abandonment, abuse and neglect, may represent an important source of vulnerability in the origin and

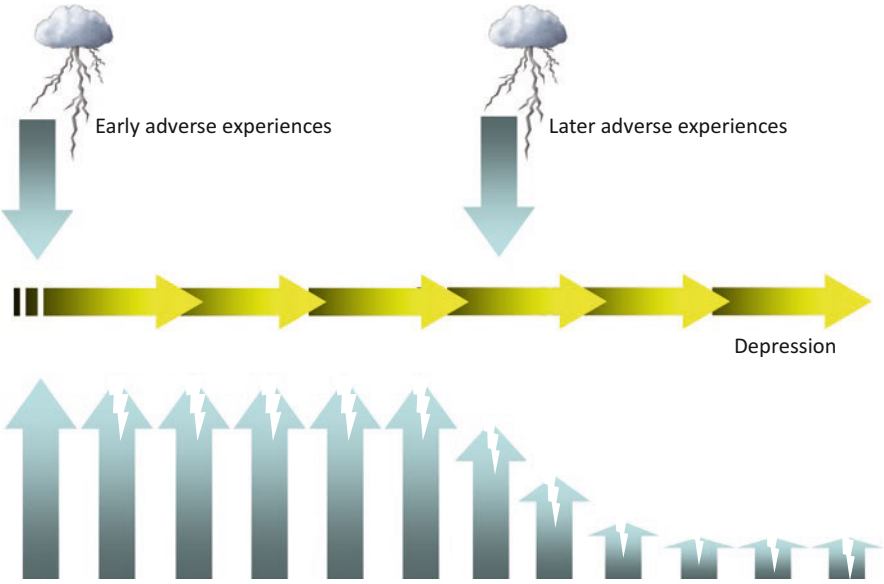

Fig. 1.4 From early adverse experiences to the development of depression. Early adverse experiences, constituted by traumatic events during childhood, may lead to pathophysiological and psychological changes, which in turn represent an important factor of vulnerability. Upon exposure to stressful events later in life, vulnerable individuals may be at higher risk to develop depression or anxiety disorders

development of depression and anxiety disorders (Fig. 1.4). Traumatic events may be also associated with catastrophic bio-ecological conditions, including all kind of natural disasters, and the extreme traumatogenic conditions referred by victims of war and terrorism, which in turn may develop particular vulnerability for the development of depression and PTSD.

It has been shown that stressful life events may lead to the origin and development of long-lasting traumatic experiences, with the resulting pathophysiological consequences, depending on the dynamic balance of cognitive appraisal. In this regard, environmental stressors are perceived and may provoke a primary response, mostly mediated by the activation of the ANS, as part of any adaptive response. Perceived environmental information is also processed through a primary appraisal, which is a basic information process to allow us to assess the potential value of stimuli, either positive or negative, appetitive or aversive, which in turn may also contribute to increase or decrease the autonomic activation of the primary response. Primary appraisal is also the gateway to a secondary appraisal, which is a more complex cognitive process, which may allow us to assess the characteristics of perceived stimuli, such as the potential stressful impact of stressful events, and the attributes of our available resources to successfully cope with them. The secondary appraisal allows us to evaluate if stressful events may be desirable or not, predictable or not, controllable or not, which in turn may allow us to distinguish between

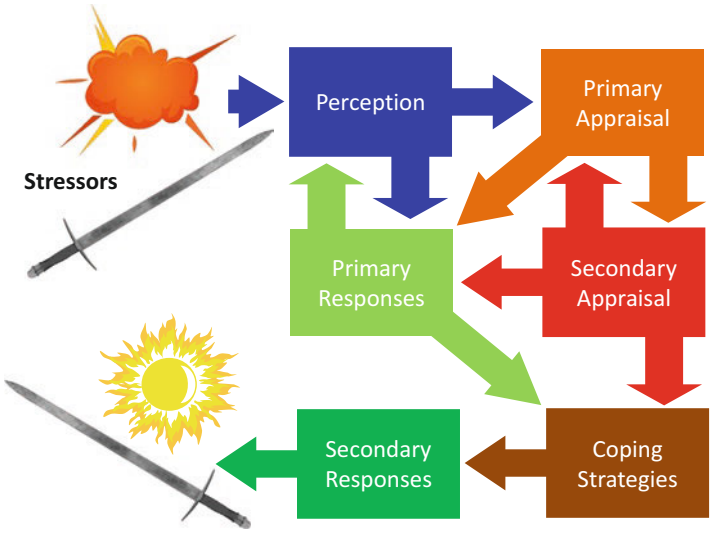

Fig. 1.5 Cognitive processing of perceived stressors. Environmental stressors are perceived and processed through a primary appraisal, which allows a basic distinction between positive and negative stimuli, which in turn activates a primary response, mainly mediated by activation of the ANS, and a secondary appraisal. The secondary appraisal allows assessing different characteristics of stressors and the available resources to cope with them. According to this cognitive appraisal, coping strategies are developed to produce an array of adaptive responses, represented by secondary responses

distress and eustress (Fig. 1.5). This cognitive processing integrates current information, which is held in our short-term memory, as well as previously learned information, either based on our own experience or the knowledge we learned from different sources, which is stored in our long-term memory. If the cognitive balance results positive, and we consider that the quality of our personal resources are effective enough to cope with the challenge, we are in condition to develop coping strategies to improve the efficacy of our adaptive responses, which in turn may be expressed as a secondary response (Fig. 1.5). On the contrary, if the cognitive balance results negative, so we believe that perceived stressors are stronger and the quality of our available resources are less effective, or are not available at all, to cope with the potential threat, we are more vulnerable to suffer a traumatic experience. Therefore, cognitive appraisal, with the adequate emotional assessment, may lead us to the negative feelings of trauma or the positive experience represented by resilience (Fig. 1.6).

Resilience represents the ability and capacity to adapt successfully to stress, overcoming stressful situations and adversity, maintaining a normal psychophysiological functioning. In this regard, a resilient person has not been free from stressful experiences but has been affected by adversity and continues developing successful adaptive responses. Resilience is a dynamic process that implies molecular, biological, cognitive, emotional and behavioural changes, all of them integrated in an array

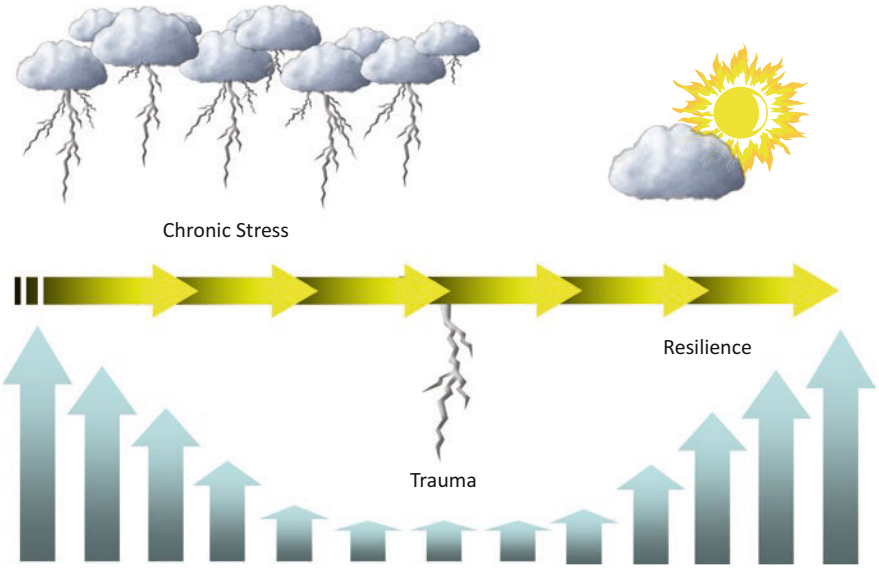

Fig. 1.6 Stress, trauma and resilience. Chronic stress may lead to decreased availability of cognitive resources and emotional exhaustion, which in turn may lead to learned helplessness and trauma. Improving the availability of cognitive resources and recovering the emotional equilibrium may allow increased feelings of predictability and controllability, which in turn may be reflected in the development of resilience

of active and adaptive physiological and psychological responses. In this regard, resilience has been associated with the ability to perceive stressful situations in a less threatening way, therefore promoting more adaptive and effective coping strategies. Moreover, resilience has been associated with the ability and capacity to successfully cope with adverse situations and emerge stronger from adversity, implying an opportunity for personal growth and development.

Although there are certain characteristics of stressors, especially observed during chronic stressful situations, or overwhelming acute stressful experiences, which cannot be changed, it is still possible to modify certain aspects, which still make possible to transform a negative experience into a positive challenge. In this regard, resilience is also characterized by the possibility to find cognitive strategies aimed at improving the margins of predictability, considerably reducing the degree of uncertainty. Moreover, resilience is also characterized by the ability and capacity to develop cognitive strategies aimed at increasing the subjective perception of controllability, which may lead to successfully cope with adversity, avoiding the long-lasting effects of traumas, while transforming distressful events into positive eustressful experiences.

References

Bernard, C. (1865). *An introduction to the study of experimental medicine*. Dover Publications. (Published 1957).

Cannon, W. B. (1932). *The wisdom of the body* (p. 1932). Norton.

Cannon, W. B. (1935). Stresses and strains of homeostasis. *The American Journal of the Medical Sciences, 189*(1), 13–14.

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840*, 33–44.

McEwen, B. S., & Seeman, T. (1999). Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Annals of the New York Academy of Sciences, 896*, 30–47.

Seligman, M. E. P., & Maier, S. F. (1967). Failure to escape traumatic shock. *Journal of Experimental Psychology, 74*, 1–9.

Selye, H. (1936). A syndrome produced by diverse nocuous agents. *Nature, 138*, 32.

Selye, H. (1946). The general adaptation syndrome and diseases of adaptation. *The Journal of Clinical Endocrinology, 6*, 117–230.

Selye, H. (1976). *Stress in health and disease*. Butterworths.

Selye, H. (1978). *The stress of life*. McGraw-Hill.

Sterling, P., & Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology. In S. Fisher & J. Reason (Eds.), *Handbook of life stress, cognition and health* (pp. 629–649). John Wiley & Sons.

Tafet, G. E., & Bernardini, R. (2003). Psychoneuroendocrinological links between chronic stress and depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 27*(6), 893–903.

Tafet, G. E., & Nemeroff, C. B. (2016). The links between stress and depression: Psychoneuroendocrinological, genetic, and environmental interactions. *The Journal of Neuropsychiatry and Clinical Neurosciences, 28*(2), 77–88.

Chapter 2
Neurobiological Approach to Stress

Stress may be provoked by environmental stressors, which are perceived and transmitted through sensory pathways to different neural structures in the brain, while internal stressors may be perceived as symptoms, provoked by external stimuli or evoked memories. Sensory information is processed through the thalamus and different cortical areas to reach limbic structures, such as the hippocampus and the amygdala, which in turn activates responses mediated by the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. Cognitive and emotional processing involves certain areas of the prefrontal cortex (PFC), which in turn are interconnected with the hippocampus and the amygdala, therefore contributing to improve adaptive responses to stress. Different neurotransmitter systems are also involved in cognitive and emotional processing, therefore contributing to shape stress responses. Serotonin is mainly produced in the dorsal raphe nuclei (DRN), which participate in fear and anxiety in response to stressful situations, and the medial raphe nuclei (MRN), which participate in conferring tolerance to unpleasant, unavoidable and persistent aversive stimuli, such as those associated with chronic stressful situations. Dopamine is mainly produced in the substantia nigra (SN) and the ventral tegmental area (VTA), which project to different structures, such as the nucleus accumbens (NAc), which in turn have been associated with salience and valence, therefore participating in reward detection and anticipation. Norepinephrine is mainly produced in the locus coeruleus (LC), which projects to cortical and limbic structures, which participates in enhanced arousal and vigilance, which contribute to improve adaptive responses to stress. These monoaminergic systems are interconnected, therefore contributing to their reciprocal regulation, as well as different cortical and subcortical structures involved in the regulation of the ANS and the HPA axis. In response to stressful events, the HPA axis is activated by excitatory projections, targeting the paraventricular nucleus (PVN) of the hypothalamus, to produce and release CRF, which stimulates the synthesis of ACTH, which in turn stimulates the biosynthesis and release of glucocorticoids. Chronic stress may lead to persistent activation of the HPA system with the consequent increase in cortisol levels,

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which in turn participates in the interface between chronic stress and the origin and development of depression. Therefore, successful adaptive responses to stress may lead to the development of resilience and the acquisition of resources aimed at improving health conditions.

Stress from the Environment to the Brain

Stressors are normally perceived as environmental stimuli, which are transmitted through sensory pathways to different neural structures in the brain. In order to be considered as a stressor, every stressful event should be perceived in some way, either as environmental stimuli from the external world or as internal stimuli, perceived as symptoms or signals that arise from different parts of the body. In this regard, perceived symptoms from the inner world may be provoked by activation, or altered functioning, of different systems, in response to the impact of real external stimuli, or associated with consciously or unconsciously evoked memories. These cognitive events are usually combined in our daily experience, where external environmental stimuli, from a simple breeze that touches our skin, to the complexity of spoken language, expressed in words impacting our ears, and probably also our soul, provoke a cognitive-emotional process. The effective integration of cognitive and emotional factors constitutes the most evolved component of adaptive responses, where internal stimuli, represented by different pieces of information stored in our long-term memory, are evoked and therefore translated into bodily reactions, which in turn may be perceived as symptoms, and again subjected to a subsequent cognitive-emotional processing, all of which are involved in the experience of stress, including the positive effect of eustress and the negative impact of distress (Fig. 2.1).

Regarding the external world, all information perceived from our surrounding environment is perceived and transformed into signals capable of being transmitted through sensory pathways from the environment to the CNS. If we are facing a storm, the image of dense and dark clouds covering the sky, the sound of a thunder, a sudden lightning and the impact of falling raindrops on our skin may be perceived as visual, auditory and tactile uni-modal stimuli, to be integrated into more complex poli-modal representations, allowing the construction of the complete experience of what a storm represents. Hence, the perception of the storm may generate various adaptive responses, starting with the activation of the ANS, which contributes to a quick defensive reaction. A rapid response by the ANS may provoke activation of different organs and systems, which are necessary to implement defensive reactions, such as the classic fight or flight response, which in turn may lead to the typical autonomic symptoms associated with stress responses. These typical sympathetic symptoms are usually associated with increased heart rate, increased breath rate, digestive problems, excessive sweating and diverse pains, which in turn may be also perceived as internal stressful stimuli. The simultaneous perception of external and internal stimuli, organized in our short-term memory, together with the activation of

Fig. 2.1 Environmental and internal stressors. Stressors may be represented by different external stimuli, which may be perceived from the surrounding environment, or internal stimuli, which may be evoked from the long-term memory storage. External and internal stimuli may provoke bodily reactions, which in turn are also perceived and interpreted through cognitive and emotional processing. External and internal stressors may lead to subjective stressful experiences

learned information associated with previous experiences, stored in our long-term memory, may lead to the implementation of behavioural responses. Hence, these behavioural responses may be shaped by the rapid activation of the ANS, with the resulting perception of sympathetic symptoms, the simultaneous processing of previous and current information, the integration of emotional and cognitive resources in our working memory and the resulting strategies and behavioural responses, aimed at successfully coping with perceived stressors (Fig. 2.2).

Therefore, environmental stressors are perceived and transmitted through sensory pathways, from the peripheral nervous system (PNS) to the CNS, where sensory information reaches the thalamus, which in turn sends information simultaneously to the amygdala, and to sensory and associative cortices, which in turn also convey projections to different areas of the prefrontal cortex (PFC), including well-differentiated parts of the medial PFC (MPFC), such as the orbitofrontal cortex (OFC) and parts of the anterior cingulate cortex (ACC) (Fig. 2.3). Direct projections from the thalamus to the amygdala contribute to activate arousal and early alarm reactions, with the subsequent activation of the ANS and the HPA axis (Chrousos & Gold, 1992; López et al., 1999), while indirect projections may reach the amygdala from other sources, including uni-modal input from sensory cortices and poli-modal input from associative cortices (LeDoux, 1998) (Fig. 2.4). Sensory cortices continue processing the information corresponding to each modality, identifying the perceived stimuli, and then sending more elaborated information to the

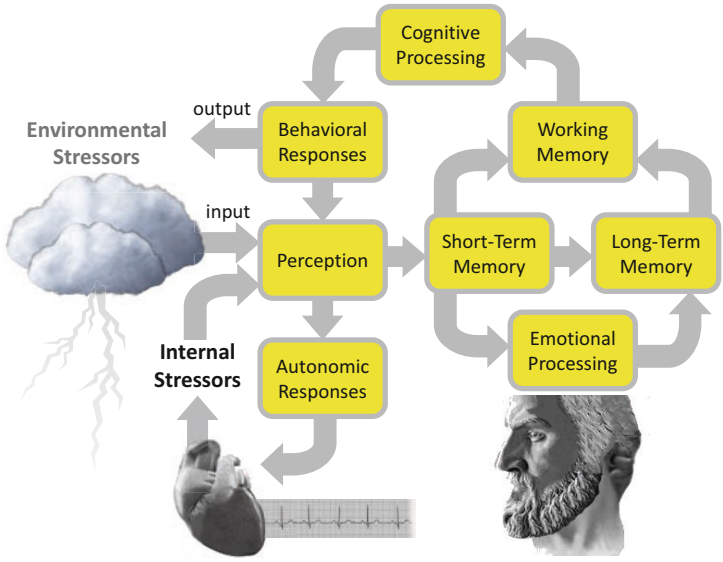

Fig. 2.2 Cognitive and emotional processing of stressors. Environmental and internal stressors are perceived and decoded, constituting signals to be held in our short-term memory. According to our emotional processing, information held in our short-term memory may be considered emotionally relevant and accordingly stored in our long-term memory. According to our cognitive processing, perceived information may be integrated with learned information, stored in our long-term memory, to be consciously represented in our working memory. Therefore, cognitive and emotional processing may lead to behavioural responses

associative cortices, where the information corresponding to each sensory modality is integrated into more complex poli-modal information. Hence, visual, auditory and tactile information, processed by the respective cortices located in the occipital, temporal and parietal lobes, converges in associative cortices, such as the parieto-temporo-occipital cortex (PTOC), located in the intersection of these lobes. Sensory cortices, alongside the PTOC, send information to different areas of the PFC, including the OFC, which represents an important associative area, the MPFC, and more specifically the ACC, which contribute to cognitive and emotional information processing (Fig. 2.4).

Sensory and associative cortices also send information to a group of cortices located in the medial temporal lobe (MTL), known as transitional cortices, which are neural structures involved in the processing of previously acquired information, stored in long-term memory. These neural structures, including the entorhinal, perirhinal and parahippocampal cortices (LeDoux, 1992), continue processing perceived sensory information, finally projecting to sub-cortical structures located in the limbic system, deep in the MTL (Fig. 2.5). The perirhinal cortex participates fundamentally in the identification of stimuli, while the parahippocampal cortex participates in the identification of their context. Both cortices converge in the entorhinal cortex, which sends information to the hippocampal formation, where stimuli

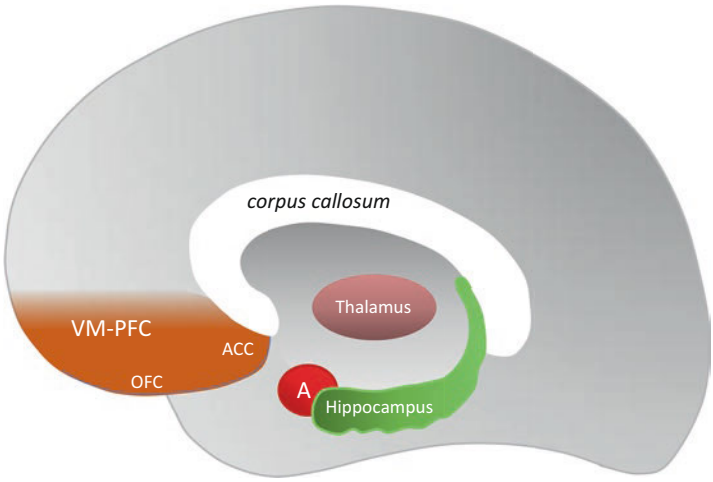

Fig. 2.3 Schematic representation of a medial view of a brain hemisphere. In the middle of the figure is represented the corpus callosum and different neural structures, such as the thalamus, the amygdala (A) and the hippocampus around it. On the left, in the rostral part of the figure, is represented the prefrontal cortex (PFC), where it is possible to identify the ventro-medial PFC (VM-PFC), and overlapping areas, such as the orbitofrontal cortex (OFC) and the anterior cingulated cortex (ACC)

can be identified and processed based on their own characteristics, as well as on various contextual variables. In this way, the system formed by the hippocampus and the transitional cortices participates in the integration of perceived information, kept in the short-term memory, with previous information, stored in the long-term memory, and with current contextual variables. This information is transmitted from the hippocampus to the amygdala, which plays a fundamental role in emotional processing and in activating adaptive responses to stressful stimuli (Fig. 2.4).

The amygdala plays a critical role in emotional processing, including the assessment of the emotional relevance of perceived environmental stimuli, as well as the internal symptoms. It plays a key role in the regulation of autonomic and neuroendocrine responses, through projections to the lateral hypothalamus, which participate in the activation of the SNS, and projections to the paraventricular nucleus (PVN) of the hypothalamus, mostly through the bed nucleus of the stria terminalis (BNST), which are involved in activation of the HPA axis. In addition, the amygdala shares important connections with the MPFC, particularly with the OFC and certain area of the ACC, specifically the rostral and ventral area adjacent to the genu of the corpus callosum, also known as the subgenual ACC (sgACC) (Price & Drevets, 2010). The OFC has been associated with integration of multi-modal sensory stimuli and primary appraisal of their positive or negative value, therefore participating in their affective assessment. The MPFC overlaps with the ACC, particularly in the sgACC, which regulates emotional responses generated by the amygdala (Fig. 2.6). These neural structures are connected with the dorso-lateral PFC (DL-PFC) and the ventro-lateral PFC (VL-PFC), which participates in cognitive control and voluntary

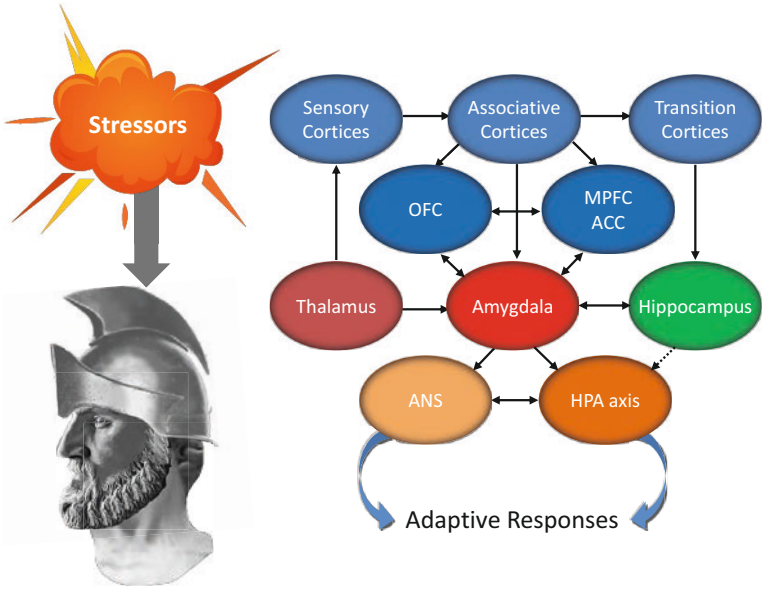

Fig. 2.4 Neurobiological processing of perceived environmental stressors. Environmental stressors are perceived and transmitted through sensory pathways to the thalamus, which in turn sends direct projections to the amygdala. Simultaneously, the thalamus sends information to sensory and associative cortices, which in turn also projects to the amygdala and different parts of the PFC, including the OFC and the ACC. Associative cortices send projections to transition cortices, which in turn project to the hippocampus. The hippocampus provides more elaborated information, including contextual cues, and project to the amygdala, which confers emotional tone to the processed information. Activation of the amygdala contributes to activate the ANS and the HPA axis, which participate in the implementation of rapid adaptive responses

regulation of emotions. The DL-PFC, which has been associated with executive aspects of cognitive processing, most notably with conscious processing and working memory, receives input from the amygdala through the OFC and ACC, and reciprocally the DL-PFC projects back to limbic structures mostly through indirect connections to the ventro-medial PFC (VM-PFC), which overlaps with the sgACC (Fig. 2.6). It has been proposed that projections from the VM-PFC, particularly from the sgACC, exert a modulatory effect on the amygdala, which in turn sends excitatory output to the BNST and the hypothalamus, therefore regulating the activity of the HPA axis. Moreover, a decreased volume of the sgACC has been described, together with hyperactivity of the amygdala, in subjects with mood disorders, which has been associated with the role of the sgACC in the interaction between the cognitive influences of the DL-PFC on the emotional processing of the amygdala. The amygdala also shares direct connections with the hippocampus and its associated cortices, located in the MTL. In this regard, decreased hippocampal volume has been also observed, along with increased activity of the amygdala and reduced activity of the DL-PFC, in subjects with mood disorders.

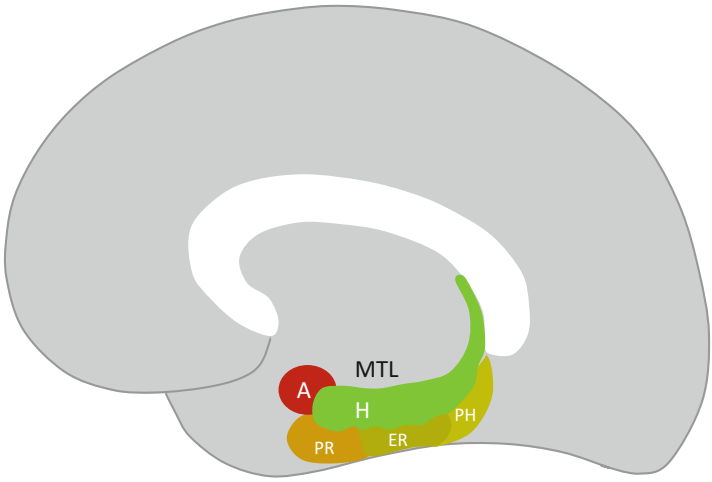

Fig. 2.5 Schematic representation of a medial view of the brain. The medial temporal lobe (MTL) contains different limbic structures, including the amygdala (A), the hippocampus (H) and transition cortices, such as the entorhinal (ERC), perirhinal (PRC) and parahippocampal (PHC) cortices

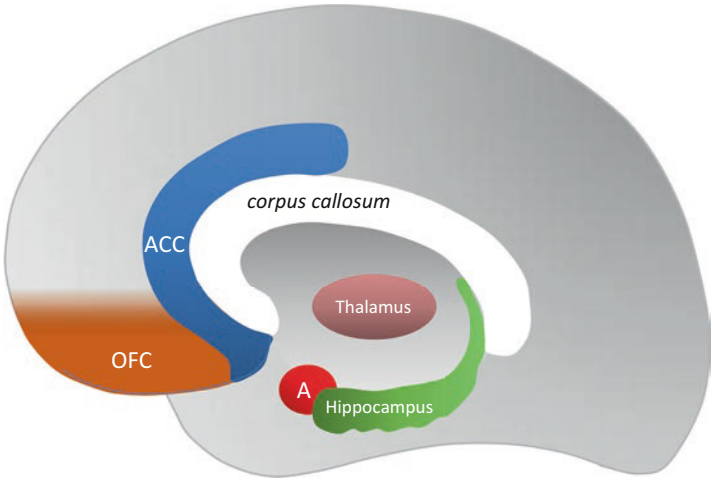

Fig. 2.6 Schematic representation of different components of the limbic system. The limbic system contains different neural structures, including the amygdala (A), the hippocampus (H), the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC)

The information transmitted directly from the thalamus to the amygdala constitutes a shorter and more direct pathway (Fig. 2.4), which in turn allows the implementation of faster adaptive responses, the efficacy of which consists in preparing the body for a rapid activation of alarm reactions, characterized by the subsequent activation of the ANS and the HPA axis. In this way, the opportune activation of

the ANS, starting with the immediate reaction of the SNS, generates a rapid activation of the organs and systems involved in adaptive responses. This rapid activation is necessary to prepare the organism to face potentially dangerous or threatening situations, fundamentally through fight or flight responses, even before having any conscious idea of the perceived information. Activation of the ANS is necessary to mobilize the essential resources to cope with stress, providing increased concentrations of oxygen and circulating glucose to the tissues involved in adaptive responses, through increasing heart rate, blood pressure and respiratory rate, which in turn may be perceived as symptoms associated with stress. The impact produced by the perception of these symptoms may lead to feelings of fear and anxiety, even before having a more precise elaboration about potential threats and the resources available to cope with them. Upon exposure to stressful situations, certain amount of fear, or anticipatory anxiety, may be necessary to stimulate arousal and focused attention, which in turn may be critical for survival in the face of stressful situations.

The information transmitted indirectly from the thalamus to the amygdala constitutes a longer circuit, which involves various structures and different pathways, which in turn allows more complex information processing (Fig. 2.4). This longer circuit involves sensory and associative cortices, transition cortices and hippocampal formation processing, which convey more elaborated information to the amygdala, which in turn plays a critical role in the integration of emotional and cognitive processing of adaptive responses to stress.

Neural Structures and Neurotransmitters Involved in Adaptive Responses to Stress

As we mentioned previously, adaptive responses to stress are mediated by different neural structures, including cortical and subcortical areas, and their respective interconnections, mediated by an array of neural pathways. Cortical areas involved in this process include sensory and associative cortices, which are associated with the processing of sensory input received through the thalamus and output to limbic structures, transition cortices, associated with the processing of input from associative cortices and output to the hippocampal formation, and different areas of the PFC. Subcortical structures involved in this process include different parts of the limbic system, most prominently the amygdala, the hippocampus, the hypothalamus and various associated structures, constituting neural circuits. In addition, various nuclei located in the brainstem, including the main nuclei of the principal aminergic systems, are also involved, therefore providing the neural bases for stress processing and the consequent adaptive responses.

Psychoneurobiology of the Limbic System: Amygdala and Hippocampus

The limbic system constitutes an important group of neural structures, principally located on both sides of the thalamus, around the *corpus callosum* (Fig. 2.6). This group of functional and anatomically interconnected structures includes the amygdala and the hippocampal formation, which are integrated in the MTL, the hypothalamus and parts of the thalamus, transition cortices, such as the parahippocampal gyrus, the OFC, the insular cortex, the septum and the cingulate gyrus, including the ACC. This group of structures was first described by Paul Broca in 1878, who utilized the word "limbic" (originally termed "*le grand lobe limbique*" in French, meaning "the great limbic lobe") to refer to a group of cortical areas, including the cingulate and parahippocampal gyri, located bilaterally, at the margins of each hemisphere. Precisely, the name "limbic" derives from the Latin word *limbus*, which means "border". The role of some of these structures in the processing of emotions was later described by James Papez in 1937, who proposed a circuit composed by the hippocampus, the parahippocampal gyrus, the cingulate gyrus, the fornix, the mammillary bodies and the anterior nucleus of the thalamus. The term "limbic system" was coined by Paul MacLean in 1952, who proposed the "triune brain theory", according to which the brain would be composed by the most primitive area, termed the "reptilian brain"; the visceral area, termed the "limbic system"; and the most evolved area, represented by the neocortex. According to MacLean, the limbic system was involved in the processing of emotional experiences, which resulted from the integration between external perceptions and internal bodily sensations, including also autonomic and somatic information. The role of the limbic system in the processing of emotions was later expanded by Walle Nauta in 1958 and many other researchers in the 1960s. The multiple functions of the limbic system were later investigated by Joseph LeDoux in the 1980s, who described the critical role of certain structures, such as the amygdala and the hippocampus, and their reciprocal connections with other cortical and sub-cortical structures, in the interface between emotional and cognitive functions.

Neurobiology of the Hippocampus and Associated Structures

The hippocampus is an important limbic structure, which represents a critical hub for cognitive and emotional information processing, where various inputs from different neural structures may converge to be integrated within a spatiotemporal framework (Fig. 2.7). This allows the hippocampus to play a critical role in the formation and storage of long-term memory, organizing and combining sensory, emotional and cognitive information related to these experiences, which in turn may be retrieved as a conscious recall of these memories (Knierim, 2015). The name "hippocampus" means "sea horse" in Greek, to denote the elongated shape of this neural structure, resembling a sea creature. The hippocampal formation, located in

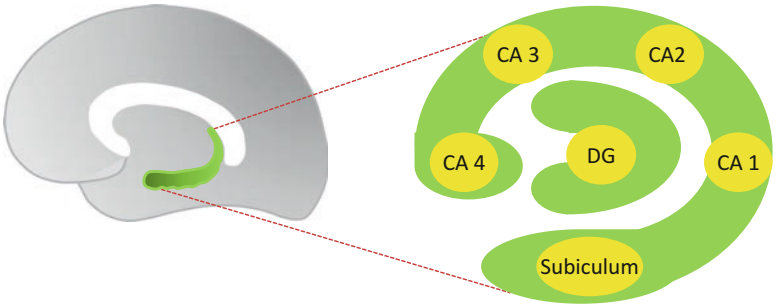

Fig. 2.7 Schematic representation of the hippocampus. The hippocampal formation includes the hippocampus and the subiculum, located in the limbic system. Within the hippocampal formation are represented the dentate gyrus (DG) in the middle, the CA1, CA2, CA3 and CA4 fields, around it, and the subiculum

the upper area of the MTL and posterior to the amygdala, includes the hippocampus, which in turn constitutes a heterogeneous neural structure consisting of the dentate gyrus (DG) and the Ammon horn (*Cornus Ammonis*, CA), where it is possible to identify CA1, CA2, CA3 and CA4, and the subiculum (Fig. 2.7). In addition, the hippocampus may be functionally subdivided into dorsal, intermediate and ventral regions (Fanselow & Dong, 2010). It has been shown that the dorsal or septal pole of the hippocampus, originally described in rodents, corresponds to the posterior hippocampus in the human brain, while the ventral or temporal pole corresponds to the human anterior hippocampus. The dorsal/posterior hippocampus has been associated with cognitive functions, more specifically involved in contextual memory, while the ventral/anterior hippocampus has been associated with emotional processing, such as in fear memory (Maren & Fanselow, 1995). Moreover, the ventral/anterior hippocampus sends projections to the BNST, which in turn sends projections to CRF neuroendocrine neurons in the PVN (Dong & Swanson, 2006). Therefore, upon the impact of psychological stressful events, the hippocampus may regulate the HPA axis through the BNST, which in turn also plays a critical role in anxiety (Walker et al., 2009).

The DG represents the main gateway to the hippocampus, receiving the major cortical input from the entorhinal cortex (ERC), through the perforant path (Fig. 2.8). At the same time, the ERC receives and integrates input from the perirhinal cortex (PRC) and the parahippocampal cortex (PHC). The DG sends projection to the CA3 region, through the mossy fibre pathway, which sends projection to the CA1 region, through the Schaffer collateral pathway, which in turn sends projections back to the ERC. Direct projections from the ERC may also reach the CA1 and CA3 regions, and direct projections from the CA3 region may also reach the DG, providing a feedback circuit (Fig. 2.9). In addition, the hippocampus also receives noradrenergic input from the LC, serotonergic input from the RN and input from the amygdala (Tafet & Bernardini, 2003). The CA1 region represents the main output source from

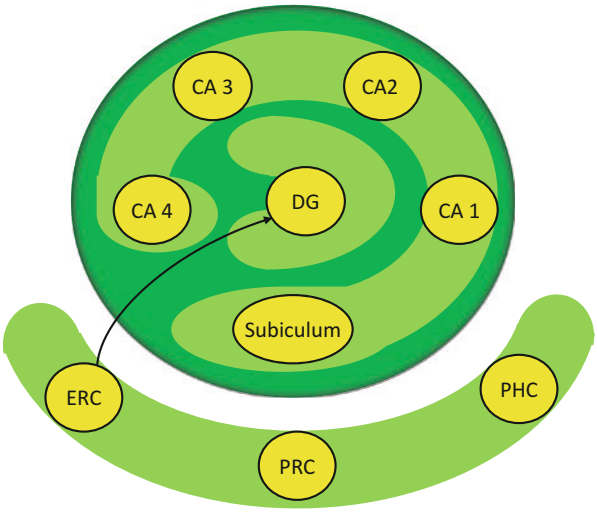

Fig. 2.8 The hippocampal formation and transition cortices. The hippocampal formation includes the dentate gyrus (DG) in the middle, the CA1, CA2, CA3 and CA4 fields, around it, and the subiculum. Closely associated are transition cortices, including the entorhinal (ERC), perirhinal (PRC) and parahippocampal (PHC) cortices

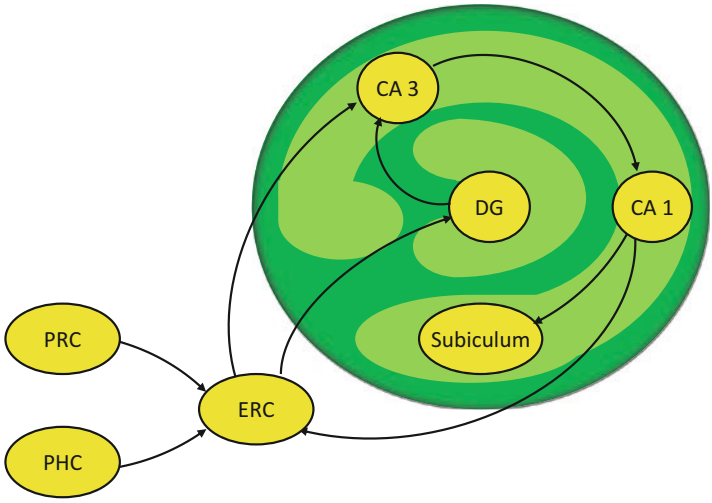

Fig. 2.9 Projections from transition cortices to the hippocampal formation. The perirhinal (PRC) and parahippocampal (PHC) cortices send projections to the entorhinal cortex (ERC), which in turn sends projections to different areas of the hippocampus, including the dentate gyrus (DG) and the CA3 area. The CA3 projects to the CA1 field, which in turn sends projections to the subiculum and the ERC

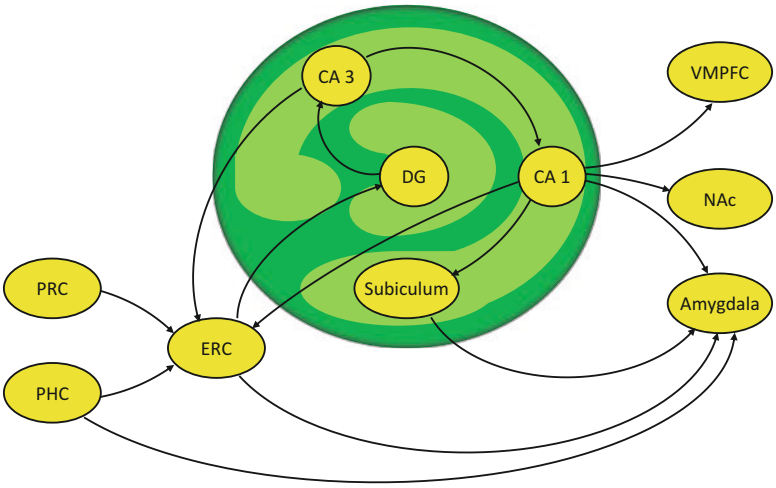

Fig. 2.10 Projections from the hippocampal formation to different neural structures. The hippocampal formation sends projections from the CA1 area to different neural structures, including the amygdala, the nucleus accumbens (NAc) and the ventro-medial prefrontal cortex (VMPFC). The amygdala also receives projections from the subiculum and from transition cortices, including the entorhinal cortex (ERC) and the parahippocampal cortex (PHC)

the hippocampus. In this regard, it has been shown that the dorsal CA1 region (D-CA1) sends projections to the subiculum and ERC, and the ventral CA1 region (V-CA1) sends projections to the MPFC, the NAc and the amygdala (Yang & Wang, 2017) (Fig. 2.10).

Different areas of the MTL have been associated with distinct functions. Upon a stressful event, information processing includes the identification of specific stimuli, including all kind of objects, and the spatial context where they are perceived (Eichenbaum & Lipton, 2008). In this regard, the perirhinal cortex receives input from sensory and associative cortices and has been involved in the identification and processing of "what" is perceived. The parahippocampal cortex also receives input from sensory and associative cortices and has been involved in the identification of the context "where" stimuli have been perceived. The perirhinal cortex conveys information to the entorhinal cortex, more specifically to the lateral area. Both structures participate in the processing of information about specific sensory stimuli (Suzuki & Eichenbaum, 2000). Moreover, these cortices may also participate in the recognition of stimuli and their potential familiarity. The parahippocampal cortex also conveys information to the entorhinal cortex, more specifically to the medial area, and both cortices participate in the processing of spatial information, associated with perceived stimuli (Eichenbaum & Lipton, 2008), which project to the hippocampus, where sensory input is integrated with contextual cues, to convey more elaborated information to the amygdala (Fig. 2.10) (LeDoux, 1992).

Neurobiology of the Amygdala and Associated Structures

The amygdala constitutes a complex neural structure, located at the most anterior area of the MTL. The name "amygdala" means "almond" in Greek, to denote its almond-like shape. The amygdala is composed of 13 nuclei, which may be further subdivided into sub-nuclei (Fig. 2.11). The main nuclei are distributed in two regions: the centro-medial region (CM), which includes the medial (MNA) and the central nucleus of the amygdala (CNA), and the baso-lateral region, or baso-lateral complex (BLA), which includes the lateral (LNA), the basal (BNA) and the accessory basal nucleus of the amygdala (ABA) (Fig. 2.12) (LeDoux, 2007). The BNA may be also identified as BLA (Yang & Wang, 2017), and the ABA may be also identified as baso-medial nucleus (Šimić et al., 2021). A third region has been considered as a separated group, the cortical-like group, which includes the cortical nucleus and the nucleus of the lateral olfactory tract (Yang & Wang, 2017; Sah et al., 2003). Some of these nuclei can be subdivided into sub-nuclei, which in turn, according to their cytological constitution and their respective connections, may be involved in different functions. For example, the LNA may be subdivided into the dorsal (D-LNA), medial (M-LNA) and ventro-lateral (VL-LNA) sub-nuclei, and the CNA may be subdivided into the medial (M-CNA), the lateral (L-CNA) and the capsular (C-CNA) sub-nuclei (LeDoux, 2007).

Regarding their connectivity, each nucleus of the amygdala, with their respective sub-nuclei, has their specific inputs and outputs, which in turn may be associated with different functions (Fig. 2.13). The LNA, located in the dorso-lateral region of the amygdala, receives projections from sensory systems, including visual, auditory, somatosensory, taste and olfactory information from the thalamus. In addition, the LNA also receives cortical sensory information, including projections from associative cortices and uni-modal sensory cortices (Fig. 2.13). It has been shown that the PFC, which integrates information from all sensory modalities, sends projections mainly to the BNA, but additional projections to the LNA, ABA, CNA and MNA have been also described. The amygdala also shares important reciprocal

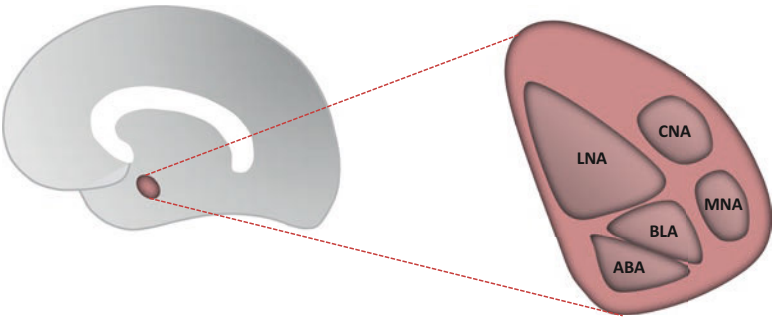

Fig. 2.11 Schematic representation of the amygdala in the brain. The amygdala is located in the limbic system. Within the amygdala are represented the lateral (LNA), the baso-lateral (BLA), the accessory basal (ABA), the medial (MNA) and the central (CNA) nuclei

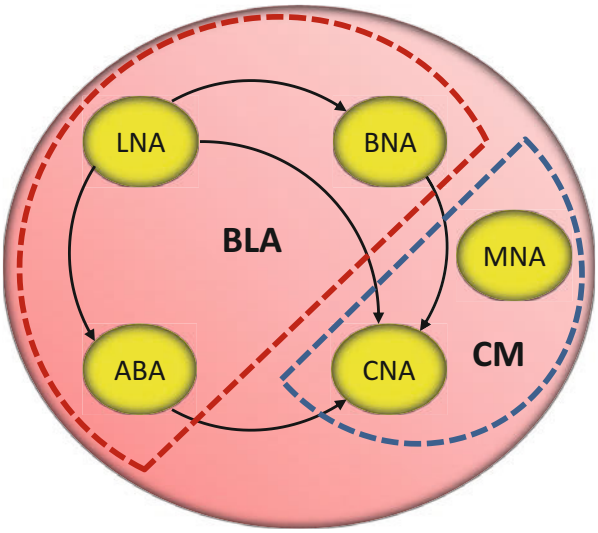

Fig. 2.12 Schematic representation of the amygdala and its components. The amygdala contains different nuclei, which in turn may be part of different groups, including the baso-lateral group (BLA) and the centro-medial group (CM). The BLA includes the lateral (LNA), the basal (BNA) and the accessory basal (ABA) nuclei. The CM includes the medial (MNA) and the central (CNA) nuclei. The CNA receives direct projections from the LNA, and indirectly through the BNA and the ABA

projections with areas involved in long-term memory, such as the entorhinal, perirhinal and parahippocampal cortices, as well as from the hippocampus. Projections from the hippocampal formation originate mainly in the CA1 region and the subiculum. Reciprocal connections between the hippocampal formation and the amygdala have been shown to play a critical role in emotional and cognitive responses to stress (Richter-Levin & Akirav, 2000). In this regard, CA1 is the main hippocampal region that shares substantial reciprocal connections with the amygdala, mainly with the BNA (Fig. 2.13). The subiculum projects to different amygdaloid nuclei, including the LNA, the BNA, the ABA and the CNA and receives substantial projections from the BNA and ABA. The amygdala also shares reciprocal connections with the entorhinal cortex, particularly the LNA, the BNA and the ABA. The LNA also shares reciprocal connections with the perirhinal cortex, and the CNA receives projections from the entorhinal cortex but does not send reciprocal projections (Pitkänen et al., 2000).

The LNA, which represents the main gateway into the amygdala, has direct projections to the CNA, which in turn represents the main source of output projections from the amygdala to other neural structures (LeDoux, 1998). The LNA also sends indirect projections through the BNA and the ABA, which in turn also project to the CNA (Fig. 2.14). Therefore, the CNA projects to different nuclei in the brainstem, which participate in emotional reactions and associated physiological responses. It has been shown that output from the CNA to certain nuclei in the brainstem, such as

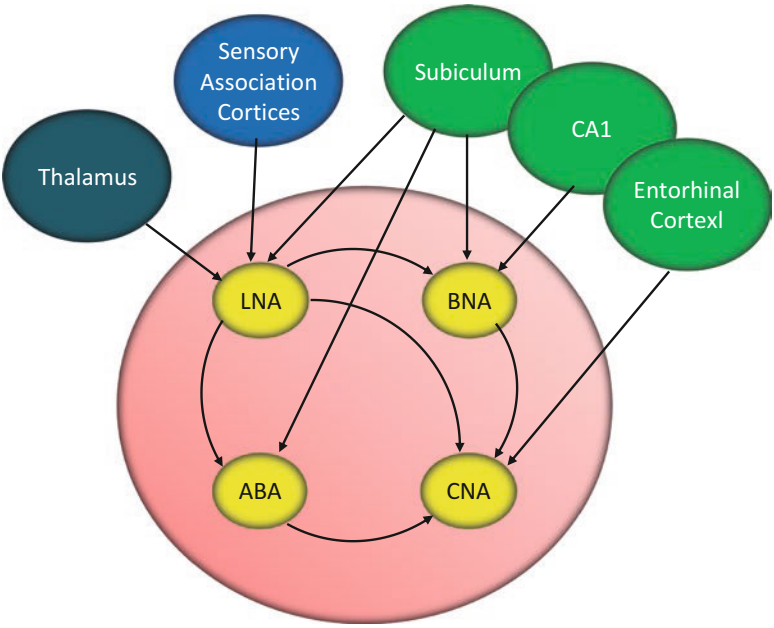

Fig. 2.13 Projections from different neural structures to the amygdala. The amygdala receives information through projections from the thalamus, sensory and association cortices to the lateral nucleus (LNA). The hippocampal formation conveys more elaborated information through projections from the subiculum to the LNA, as well as the basal (BNA) and accessory basal (ABA) nuclei. The BNA also receives direct projections from the AC1 area of the hippocampus. The CNA may also receive projections from the entorhinal cortex (ERC)

the periaqueductal grey (PAG), may be associated with freezing reactions in response to threatening stimuli, and output from the BNA to the striatum participate in active behavioural responses, such as fight or flight (LeDoux, 2007) (Fig. 2.15). The BNA is also involved in anxiety responses, where activation of glutamatergic neurons may elicit anxiogenic effects. In addition, activation of the connections between the BNA and the NAc may elicit reward seeking.

The CNA contains different sub-populations of neurons, around 90% of which are GABAergic (Šimić et al., 2021). The CNA may also synthesize and release different neuropeptides. In this regard, the CNA represents the main source of CRF, out of the hypothalamic PVN (McCall et al., 2015). It has been demonstrated that under basal conditions, these neurons may release mostly GABA, which plays a critical role in the regulation of baseline anxiety, while under stressful conditions, with the impact of more salient events, CNA neurons may produce and release CRF, which induces sustained modulatory effects, associated with anxiety-like behaviour (McCall et al., 2015; Šimić et al., 2021) (Fig. 2.15).

Based on the projections from the CNA to the BNST, the centro-medial region of the amygdala and the BNST constitutes a functional unit, therefore termed the "extended amygdala" (Alheid & Heimer, 1988) (Fig. 2.16). Within the CNA, the

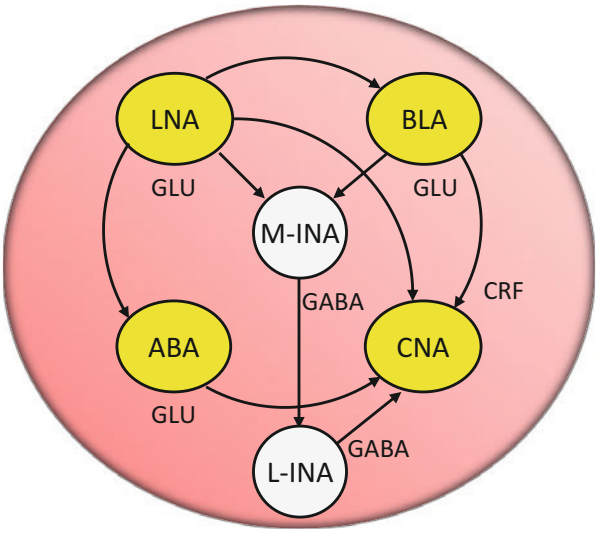

Fig. 2.14 Projections between different nuclei within the amygdala. Within the amygdala, the LNA communicates with the CNA through direct excitatory projections, or indirectly through projections from the LNA to the BNA and the ABA, which in turn also send excitatory projections to the CNA. The LNA and the BNA also project to intercalated neurons (INA), more specifically to the medial group (M-INA), which sends inhibitory GABAergic projections to the CNA. The M-INA also sends inhibitory GABAergic projections to the lateral group of intercalated neurons (L-INA), which in turn also sends inhibitory GABAergic projections to the CNA. Therefore, excitatory glutamatergic projections from the LNA to the M-INA may lead to subsequent inhibition of the L-INA, which in turn may neutralize the inhibitory GABAergic tone of these intercalated neurons on the CNA

M-CNA and the L-CNA have been shown to send CRF projections to the BNST, involved in anxiety responses, and different brainstem nuclei, involved in autonomic responses (Paul & Chen, 2017). The M-CNA receives excitatory glutamatergic projections from the ABA, and the L-CNA receives inhibitory GABAergic projections from the MNA.

The amygdala is regulated by an important inhibitory GABAergic system that prevents neurons from reacting to irrelevant stimuli (LeDoux, 2007). Therefore, novel stimuli may stimulate increased activity in the amygdala, but this may lead to habituation if similar stimuli are repeated. Since novel stimuli may be associated with a significant event, the responses may be potentiated. The amygdala receives mostly excitatory input through glutamatergic pathways from different neural structures. These glutamatergic input may stimulate excitatory neurons in different nuclei of the amygdala, as well as inhibitory GABAergic interneurons, which in turn may provide inhibitory feedback to excitatory and inhibitory neurons.

The thalamus conveys excitatory glutamatergic projections to the LNA, which also contains excitatory glutamatergic neurons. Then, the LNA communicates with the CNA through direct excitatory projections, or indirectly through projections from the LNA to the BNA and the ABA, which in turn also send excitatory

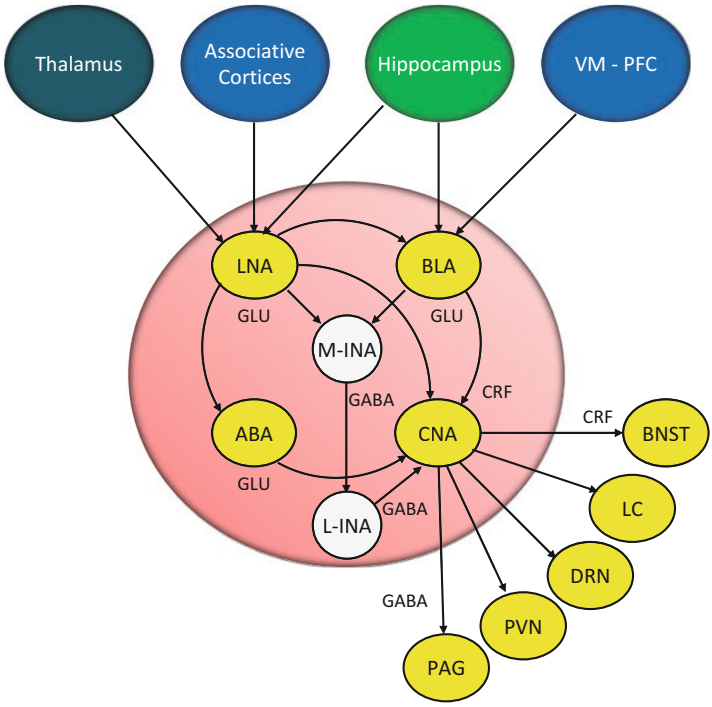

Fig. 2.15 Projections from the amygdala to different neural structures. The CNA represents the main source of projections from the amygdala to different neural structures. The CNA sends projections to the bed nucleus of the stria terminalis (BNST), to different aminergic nuclei in the brainstem, including the locus coeruleus (LC) and the dorsal raphe nucleus (DRN), to the periaqueductal grey (PAG) and to the hypothalamic paraventricular nucleus (PVN)

projections to the CNA (Fig. 2.14). In this regard, the LNA and the BNA also project to a group of intercalated neurons (INA), located in the interface between both nuclei and the CNA, more specifically to the medial group (M-INA), which sends inhibitory GABAergic projections to the CNA (Fig. 2.14). The M-INA also sends inhibitory GABAergic projections to the lateral group of intercalated neurons (L-INA), which in turn also sends inhibitory GABAergic projections to the CNA. Therefore, excitatory glutamatergic projections from the LNA to the M-INA may lead to subsequent inhibition of the L-INA, which in turn may neutralize the inhibitory GABAergic tone of these intercalated neurons on the CNA (Fig. 2.14), with the resulting increased output from the CNA with the resulting fear response (Pare et al., 2004, Pare & Duvarci, 2012).

In addition, various neurotransmitter systems, including the serotonergic, dopaminergic and noradrenergic systems, send projections to different nuclei in the amygdala, therefore exerting modulatory effects on inhibitory and excitatory neurons, and reciprocally, the amygdala, particularly through the CNA, sends projections to the main nuclei of these neurotransmitter pathways, located in the brainstem.

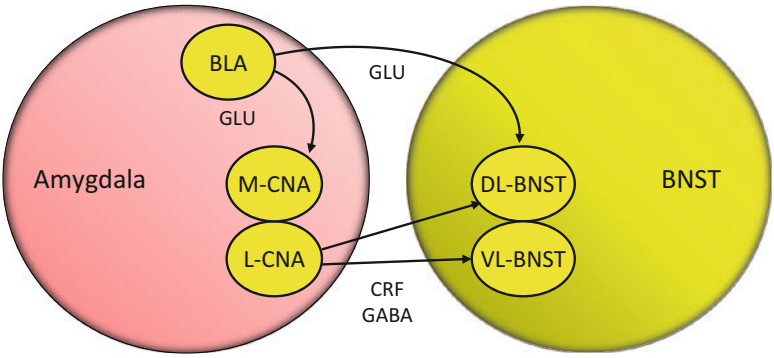

Fig. 2.16 Projections within the extended amygdala. Within the extended amygdala, excitatory projections from the BLA may reach the medial CNA (M-CNA), which in turn allows the lateral CNA (L-CNA) to send projections to de ventro-lateral (VL-BNST) and ventro-medial nuclei of the bed nucleus of the stria terminalis (VM-BNST). The BLA also sends excitatory projections to the BNST

In this regard, neurons in the different nuclei of the amygdala are known to express receptors for these neurotransmitters, as well as for different hormones, such as glucocorticoids, and peptides, such as CRF.

It has been shown that the amygdala plays a critical role in emotional processing, including the assessment of the emotional relevance of environmental stimuli, as well as the emotional appraisal of internal stressors (LeDoux, 1992). In addition, the amygdala plays a key role in the regulation of autonomic and neuroendocrine responses, through projections to the PVN and the lateral hypothalamus, which mediate the activation of the ANS, and direct projections to the hypothalamic PVN, or indirectly through the BNST, which are involved in adaptive responses to stressful stimuli, through the activation of the HPA axis (LeDoux et al., 1988). The effects of the amygdala on the regulation of the HPA axis have been attributed to direct projections from the CNA to the PVN or indirect projections from the CNA to the BNST (Davis, 1992). In this regard, it has been shown that the stimulatory effect of the amygdala may be better understood as the result of projections from the CNA to different nuclei in the BNST, which in turn send projections to the PVN (Choi et al., 2007), therefore stimulating the neuro-endocrine response to stress, mediated by the HPA axis (Fig. 2.17).

The amygdala also shares important connections with certain cortices located in the frontal lobe (FL), such as the OFC and the ACC (Price & Drevets, 2010), which are known to be part of the PFC and functionally integrated in the limbic system, participating in the interface of cognitive and emotional functions. In addition, the hypothalamus constitutes also an important component of the limbic system, which participates in the regulation of autonomic and neuroendocrine functions.

The amygdala projects substantial connections to the OFC (Price & Drevets, 2010, 2012), and to the MPFC, including Brodmann areas (BAs) 10 and 32 (Phillips

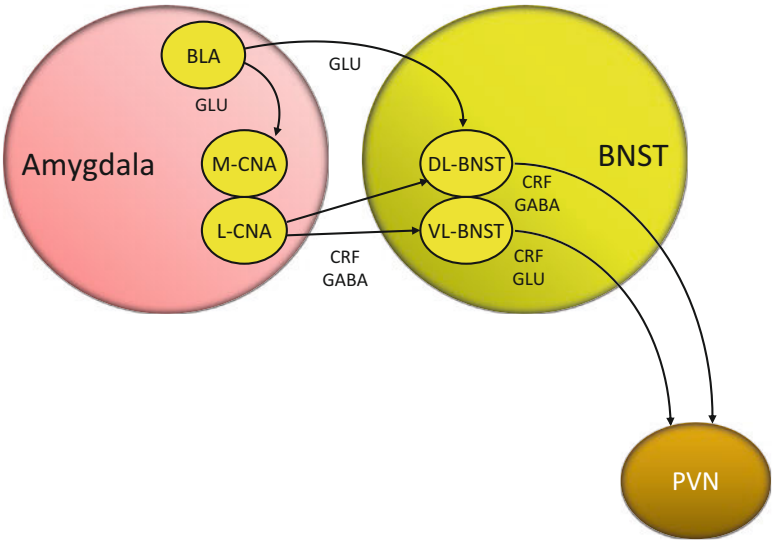

Fig. 2.17 Projections from the extended amygdala to the hypothalamus. The amygdala exerts stimulatory effect on the hypothalamic paraventricular nucleus (PVN) mainly through projections to the BNST, which in turn sends excitatory projections to the PVN

et al., 2008), and the rostral and ventral area adjacent to the genu of the corpus callosum, in BA 25 (also referred as the subgenual ACC, sgACC or Cg25) (Mayberg et al., 1999, Drevets et al., 2008). The OFC has been associated with integration of multi-modal sensory stimuli and primary appraisal of their positive or negative value (Rolls, 2004), and the sgACC has been shown to play a regulatory role on emotional responses generated by the amygdala (Etkin et al., 2011). These structures are in turn connected with the dorso-lateral PFC (DLPFC) (BAs 9 and 46) and the ventro-lateral PFC (VLPFC) (BAs 45 and 47), which participate in cognitive control and voluntary regulation of emotion (Phillips et al., 2008). The DLPFC, which has been associated with executive aspects of cognitive processing (Ray & Zald, 2012), most notably with conscious processing and working memory, receives minimal connections from the amygdala, but it is mostly connected through the OFC (BAs 11, 12, 13 and 14) and ACC (Price & Drevets, 2010). Subsequently, the DLPFC projects back to limbic structures mostly through indirect connections to the ventro-medial PFC (BA 32), which projects to the sgACC (BA 25). Therefore, the strongest connections from the PFC to the amygdala arise from the sgACC and the dorsal ACC, comprising BAs 25 and 24, respectively (Ray & Zald, 2012) (Fig. 2.18). It has been proposed that projections from the sgACC exert strong influence on the amygdala, which in turn allows the activation of the PVN of the hypothalamus (Ray & Zald, 2012), therefore stimulating the HPA axis.

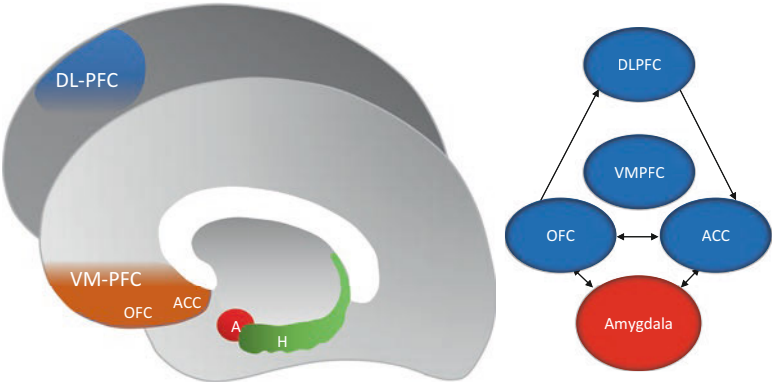

Fig. 2.18 Projections between the amygdala and the prefrontal cortex. The amygdala sends projections to the orbitofrontal cortex (OFC) and to the anterior cingulate cortex (ACC), in the ventro-medial PFC (VM-PFC), which in turn are also connected with the dorso-lateral PFC (DL-PFC)

Neurocircuitry and Psychoneurobiology of the Prefrontal Cortex

The PFC constitutes the anterior area of the frontal lobe. It includes the cortices located just beside the motor and premotor areas and represents the most rostral area of the frontal lobe. The PFC may be subdivided into different areas, which may be identified on the basis of anatomical, topographical and functional criteria, including a lateral region, located on the external surface of each hemisphere, a medial region, located on the internal surface, and dorsal and ventral areas, located on both lateral and medial regions (Fig. 2.19). Therefore, it is possible to describe diverse neural structures in the PFC, which have been associated with different cognitive and emotional processes. Hence, the PFC constitutes a well-defined region that includes an array of sub-regions, which in turn may be identified on the basis of different functional and neuro-anatomical criteria. In this regard, the different subdivisions of the PFC cover different Brodmann Areas (BA), including BA 8, 9, 10, 11, 12, 13, 14, 24, 25, 32, 44, 45, 46 and 47, which in turn are also organized in different sub-regions (Dixon et al., 2017; Barbas, 2000; Carmichael & Price, 1996; Mackey & Petrides, 2010; Ongür et al., 2003; Vogt, 2009). Therefore, the PFC may be subdivided into different, some of them partially overlapping, subdivisions, including the dorso-lateral PFC (DL-PFC), the ventro-medial PFC (VM-PFC), the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC), which in turn are associated with an array of emotional and cognitive processes, or in the integration between them (Figs. 2.20 and 2.21).

The DL-PFC represents an important subdivision of the PFC, mostly involved in executive functions and higher cognitive processing, including working memory, selective attention and planning of goal-directed behavioural responses (Barbey et al., 2013; Baddeley, 1998; Baddeley & Petrides, 1996). The topographical location of the DL-PFC includes the lateral part of BA 9, the dorsal part of BA 46 and certain parts of BA 8 in the surface of the PFC (Fig. 2.20).

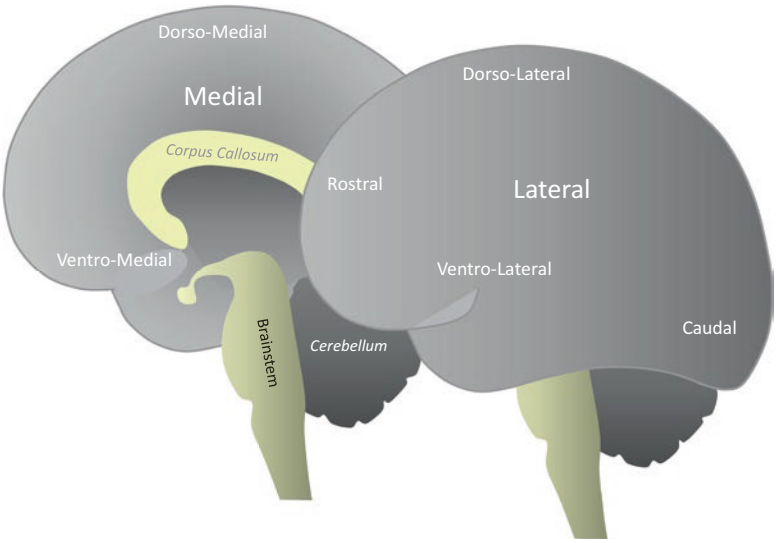

Fig. 2.19 Schematic representation of medial/lateral and dorsal/ventral areas of the brain. The figure depicts the medial and lateral surfaces of the brain, with the dorso-lateral, dorso-medial, ventro-lateral and ventro-medial areas

Among the executive functions associated with the DL-PFC, working memory represents an important concept, closely associated with that of conscious information processing, which represents our capability to consciously thinking and planning. Therefore, working memory constitutes the ability to keep in mind certain information, transiently and consciously, for its cognitive processing, including thinking, comprehending, abstract reasoning and planning potential responses (Goldman-Rakic, 1995). In this regard, working memory constitutes a complex process that integrates current or just perceived information with just retrieved long-term stored information, and the consequent cognitive and affective processing, which in turn may lead to behavioural responses, new experiences and the resulting storage of new information.

In order to better understand the role of working memory, it is very illustrative to imagine our mind as a computer, with different cognitive and affective processes occurring simultaneously, as it usually happens with the different programmes involved in the normal functioning of a system. Working memory constitutes the "screen" where conscious experience may be represented, integrating the presence of currently perceived stimuli, the different aspects of perceived objects and contextual information kept in the short-term memory, and additional information related to previous experiences, stored in the long-term memory. In addition, cognitive and affective aspects may also shape the whole picture by modulating the intensity and extent of the emotional charge, such as the colours, contrasts, brightness, lights and shadows of images in a screen. Therefore, working memory represents the dynamic background to develop an array of integrated cognitive and affective functions, from

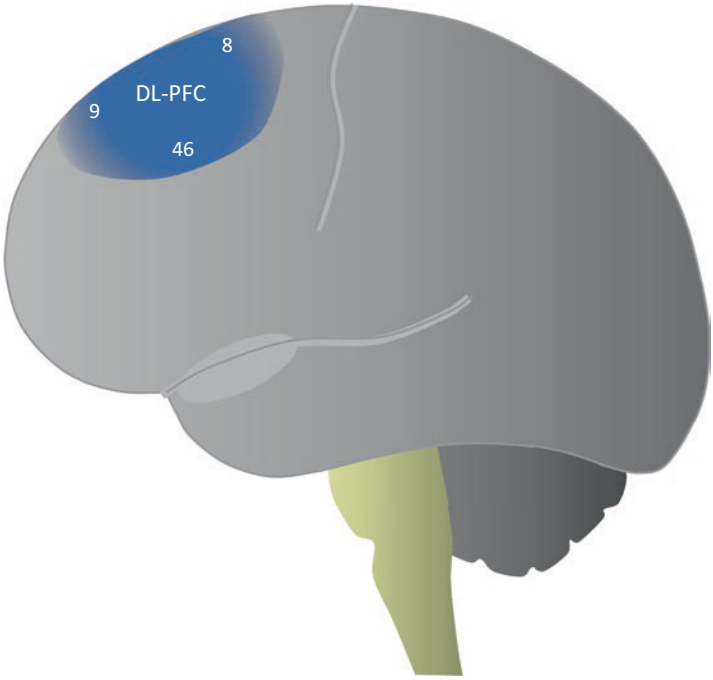

Fig. 2.20 Schematic representation of the dorso-lateral prefrontal cortex (DL-PFC). The figure depicts the location of the DL-PFC, comprising BAs 8, 9 and 46

the simplest to the more sophisticated, such as solving an arithmetic challenge, creating a sentence, composing a musical piece, or developing a hypothesis, as usually happens in our daily life. Hence, working memory may provide the psychoneurobiological basis of mental representations and a valuable concept to better understand the mechanisms of human mind (Goldman-Rakic, 1995) (Fig. 2.22).

During stressful situations, just perceived environmental stimuli are processed together with evoked information stored in the long-term memory. These elements are processed together to assess the current situation and potential future consequences, the cost-benefit ratio of potential responses and the development of coping strategies to restore control and equilibrium. In order to perform these computational mechanisms, the DL-PFC receives input from sensory cortices, which provide the ongoing information about current events, and is interconnected with the hippocampus, which provides the neural bases for the retrieval, storage and consolidation of long-term memories. The DL-PFC is also involved in cognitive functions associated with the capacity for problem-solving and the resulting decision-making, which requires a balanced integration of cognitive and affective information processing. In this regard, the DL-PFC is also critically involved in the effects of cognitive processing on emotional regulation, particularly in the development of cognitive strategies to control emotional reactions (Koenigs & Grafman, 2009; Ochsner et al., 2002, 2004), which is supported by the extensive connections between the DL-PFC

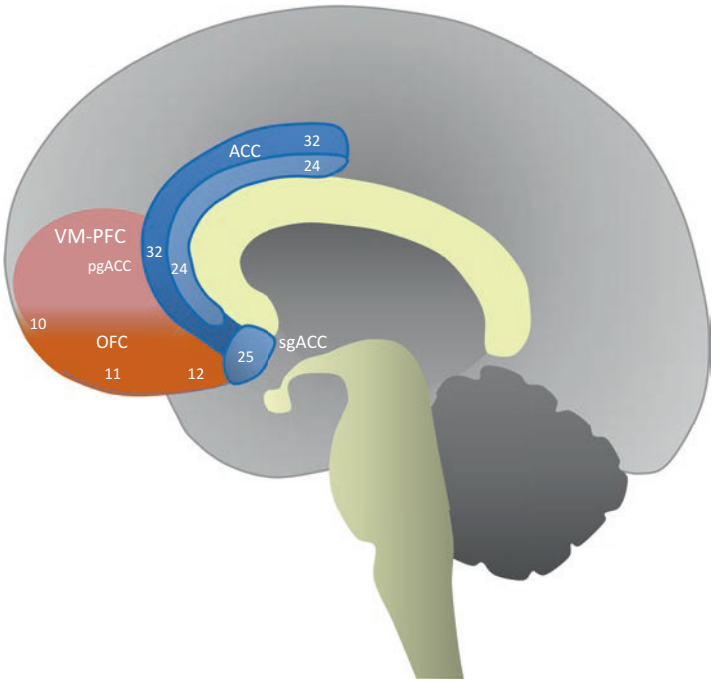

Fig. 2.21 Schematic representation of the ventro-medial prefrontal cortex (VM-PFC). The figure depicts the location of the orbitofrontal cortex (OFC), comprising BAs 10, 11 and 12, the anterior cingulated cortex (ACC), comprising BAs 24, 25 and 32, and overlapping areas with the VM-PFC

and the VM-PFC. Despite the fact that direct projections from the DL-PFC to limbic structures, such as the amygdala, are rather modest, its effects are met through indirect projections. The links between the VM-PFC and the amygdala have been shown to be much stronger and significant than those between the amygdala and the DL-PFC. In this regard, it has been shown that the OFC and the VM-PFC are significantly interconnected with different nuclei of the amygdalar complex (Carmichael & Price, 1995; Ray & Zald, 2012) (Fig. 2.23).

As we mentioned previously, the VM-PFC is another important subdivision of the PFC, mostly involved in emotional processes, particularly in emotion regulation (Fig. 2.21). As it was previously described for the DL-PFC, the VM-PFC is also a highly interconnected area, which receives and integrates diverse input associated with sensory, memory, social and self-related information (Roy et al., 2012). Integration of this information is critical for emotional processing, social and self-perception, memory consolidation and decision-making.

The VM-PFC has strong connections with the amygdala (Amaral & Price, 1984; Ghashghaei et al., 2007) and receives an important input from the hippocampal formation, particularly from the CA1 and the subiculum (Cenquizca & Swanson, 2007; Hoover & Vertes, 2007). The topographical location of the VM-PFC shares an important overlap with certain areas of the ACC. These include a region on the

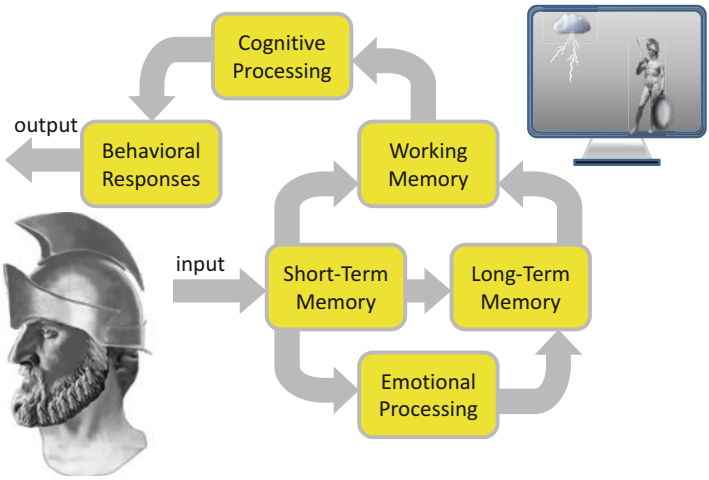

Fig. 2.22 Cognitive and emotional processing of environmental stimuli. Environmental stressors are perceived and may be held in the short-term memory. According to the emotional processing, information held in the short-term memory may be labelled relevant and therefore stored in the long-term memory. According to the cognitive processing, perceived information may be integrated with learned information, stored in the long-term memory, to be consciously represented in the "screen" of working memory. Therefore, cognitive and emotional processing may lead to behavioural responses

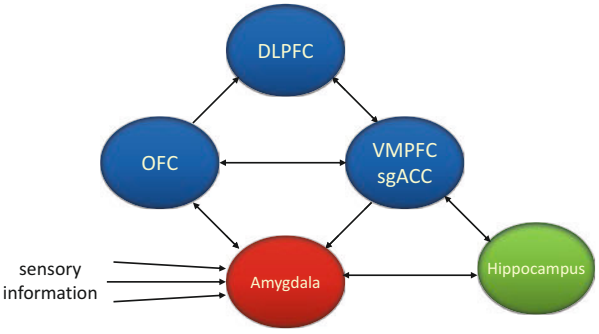

Fig. 2.23 Neural processing of perceived stimuli. Perceived environmental stimuli are processed together with evoked information stored in the long-term memory. The DL-PFC receives input from sensory cortices, which provide the ongoing information about current events, and is interconnected with the hippocampus, which allows the retrieval, storage and consolidation of long-term memories. The DL-PFC is also involved in the effects of cognitive processing on emotional regulation, which is supported by the connections between the DL-PFC and the VM-PFC, which in turn is connected with the amygdala through reciprocal connections with the OFC and the ACC

medial surface of the PFC, broadly identified as BA 32, the rostral surface of the ACC, anterior to the genu of the corpus callosum, also known as pregenual ACC or pgACC, identified as BA 24, and the most ventral surface of the ACC, around the genu of the corpus callosum, also known as subgenual ACC or sgACC, identified as

BA 25 (Myers-Schulz & Koenigs, 2012). It is interesting to remark that in certain studies, mostly performed in rats, BA 25 is referred as infra-limbic (IL), while the BA32 is referred as prelimbic (PL). In addition, the VM-PFC also shares certain overlapping with the OFC, particularly the medial surfaces of BA 10 and 14 (Ray & Zald, 2012) (Fig. 2.21).

It has been shown that projections from certain areas of the VM-PFC, particularly from the sgACC (BA 25), to certain nuclei of the amygdala may exert a modulatory effect. These inhibitory projections from the VM-PFC to the amygdala, which in turn sends excitatory projections to the hypothalamus, may be translated into a regulatory effect of the VM-PFC on the HPA axis. Moreover, projections from the DL-PFC to the VM-PFC, with the subsequent regulatory effects of the VM-PFC on the amygdala, may explain the role of the sgACC in the regulatory pathway between the DL-PFC and the amygdala. This may provide the neurobiological bases for therapeutic cognitive interventions, which may allow conscious processing, with the resulting down-regulation of negative emotions (Motzkin et al., 2015) (Fig. 2.23).

The VM-PFC has been also associated with the subjective experience of reward and the encoding of emotional value (Winecoff et al., 2011; Hiser & Koenigs, 2018). In this regard, it has been shown that the VM-PFC plays a critical role in processing of positive and appetitive stimuli. Moreover, activation of the VM-PFC has been also associated with the presence of positive emotional stimuli and motivationally attractive stimuli (Goel & Dolan, 2001; Schoenbaum et al., 2009), which can be altered by emotion regulation processes. The VM-PFC participates in the encoding of rewarding properties of perceived stimuli, and therefore it has been also associated with value-based decision-making (Hiser & Koenigs, 2018). The role of the VM-PFC in reward processing and value-based decision-making has been shown to depend on interactions with the amygdala and the nucleus accumbens, in the ventral striatum. In this regard, it has been shown that the VM-PFC sends stimulatory glutamatergic projections to the ventral striatum, therefore enhancing reward processing in this area. The VM-PFC also sends glutamatergic projections to inhibitory GABAergic neurons in the amygdala, therefore allowing its role in the regulation of negative emotions (Hiser & Koenigs, 2018). The VM-PFC also plays a critical role in the subjective perception of controllability. In this regard, activation of serotonergic neurons in the dorsal raphe nuclei (DRN), which project mainly to the amygdala, has been associated with the presence of aversive stimuli, with the resulting perception of threat and increased feelings of anxiety, while activation of serotonergic neurons in the medial raphe nuclei (MRN), which project mainly to the hippocampus, has been associated with increased tolerance to aversive events. The VM-PFC also sends glutamatergic projections to GABAergic interneurons in the DRN, therefore inhibiting its anxiogenic activity (Fig. 2.24). Inhibition of the amygdala and the DRN by projections from the VM-PFC may lead to increased feelings of controllability, which is critical in the successful treatment of depression and anxiety disorders, and for the development of resilience.

The OFC plays a critical role in the processing of emotional information. Moreover, it participates in the positive and negative valence of perceived stimuli associated with emotional arousal, including the representation of the potential

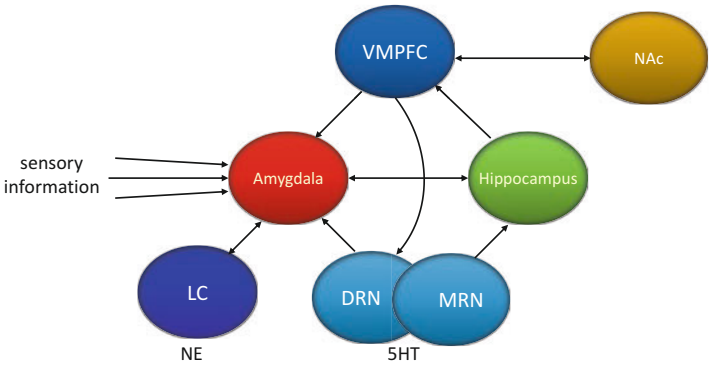

Fig. 2.24 Processing in the ventro-medial prefrontal cortex (VM-PFC). The VM-PFC participates in rewarding experiences and the encoding of emotional value. This reward processing depends on interactions between the VM-PFC and the amygdala (A) and the nucleus accumbens (NAc). The VM-PFC sends stimulatory glutamatergic projections to the NAc, therefore enhancing reward processing, and glutamatergic projections to inhibitory GABAergic neurons in the amygdala, therefore allowing its role in the regulation of negative emotions. The VM-PFC plays a critical role in the perception of controllability. Activation of 5HT neurons in the dorsal raphe nuclei (DRN), which project mainly to the amygdala, has been associated with the presence of aversive stimuli, while activation of 5HT neurons in the medial raphe nuclei (MRN), which project mainly to the hippocampus, has been associated with increased tolerance to aversive events. The VM-PFC also sends glutamatergic projections to GABAergic interneurons in the DRN, therefore inhibiting its anxiogenic activity

rewarding value of certain stimuli, as well as the failure to obtain an expected reward. In this regard, the OFC receives information from various sensory and associative cortices, to confer a positive or negative emotional valence. More specifically, two important subdivisions have been identified in the OFC, each one of them associated with different and opposite processes. Hence, the medial OFC (MOFC) is involved in the rewarding value of stimuli, whereas the lateral OFC (LOFC) participates in the opposite, including the non-rewarding value and punishment, which has been shown to be relevant in the neurobiological processes underlying chronic stress and depression (Rolls et al., 2020) (Fig. 2.25). It has been observed increased activity and over-responsiveness in the LOFC and the opposite in the MOFC in patients with depression (Rolls et al., 2020). Activation of the LOFC has been associated with the processing of aversive stimuli, usually referred as subjectively unpleasant stimuli, and with the absence of expected rewards, while activation of the MOFC has been associated with the processing of rewarding stimuli, identified and referred as subjectively pleasant stimuli. The MOFC is connected with the pgACC (BA 25), an area associated with reward-related processing, whereas the LOFC is connected with the supracallosal area of the ACC (BA 32), which is associated with lack of reward and punishment (Fig. 2.25).

The OFC cortex also participates in the processing of sensory information. It includes the processing of taste, more specifically the representation of its rewarding value, and olfactory areas, where the identity of odours and its rewarding value

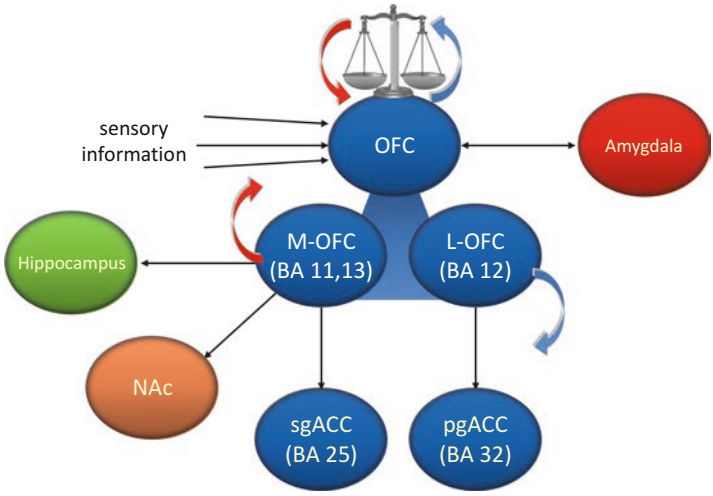

Fig. 2.25 Processing in the orbitofrontal cortex (OFC). The OFC participates in the positive and negative valence of perceived stimuli associated with emotional arousal. The OFC receives information from sensory and associative cortices to confer a positive or negative emotional valence. Two subdivisions have been identified in the OFC: the medial OFC (MOFC) is involved in the rewarding value of stimuli, whereas the lateral OFC (LOFC) participates in the opposite, including the non-rewarding value and punishment. Activation of the LOFC has been associated with the processing of aversive stimuli, while activation of the MOFC has been associated with the processing of rewarding stimuli. The MOFC is connected with the pgACC (BA 25), an area associated with reward-related processing, whereas the LOFC is connected with the supracallosal area of the ACC (BA 32), which is associated with lack of reward and punishment

are also represented. It also receives visual information, through projections from the temporal lobe, which in turn received information about visual input from the occipital lobe, hence participating in the association learning between visual stimuli with other sensory information. It also receives somatosensory information, and it has been demonstrated that certain areas of the OFC may be activated by pleasant or painful tactile stimuli. Therefore, the OFC participates in the decodification and representation of olfactory, gustatory and tactile information; in the association between these stimuli with visual information; in the control and monitoring of behavioural responses related to reward and punishment; and in the processing of emotional valence of different stimuli and more complex experiences. Therefore, the OFC participates in motivational behaviour, in emotional behaviour and in social behaviour (Rolls et al., 2020).

The topographical location of the OFC includes BA 11, 12 and 13 (Rolls, 2019). Some researchers have also described certain overlap with the VM-PFC, including BA 14 and parts of BA 10. The LOFC has been identified in the BA 12, which is also referred as 12/47 in various human studies, and the MOFC includes BA 11 and 13 (Ongür et al., 2003; Rudebeck et al., 2013) (Figs. 2.21 and 2.25).

Projections from the OFC to the ACC provide reward value information, which may be used for action-outcome learning (Rushworth et al., 2012; Rolls, 2019a, b).

Projections from the OFC to the ventral striatum provide reward-related information, which in turn may reach dopaminergic neurons involved in the reward circuit (Rolls, 2017). In this regard, projections from the OFC may also reach dopaminergic neurons in the VTA (Namboodiri et al., 2019). The OFC plays a critical role in the subjective experience of emotion and affective value. Moreover, it is considered the first stage of cortical processing representing rewarding value (Rolls, 2019b). In this regard, the OFC has strong connections with the amygdala (Rolls & Grabenhorst, 2008). It receives projections from the amygdala and projects back to temporal lobe structures, including the amygdala (Barbas, 2007). Parts of the MOFC also project to the ACC (Price, 2006), the ventral striatum, particularly the nucleus accumbens (Ferry et al., 2000), the BA 10, in the MPFC (Price 2007), transition cortices, such as the entorhinal and perirhinal (Barbas, 2007), providing rewarding information to the hippocampus (Rolls & Xiang, 2005). In humans, the MOFC is activated in the presence of different rewarding stimuli and reflects their subjective pleasantness (Grabenhorst and Rolls, 2011).

The cingulate cortex (CC) is located in the medial surface of each hemisphere, adjacent and on the upper border of the *corpus callosum*. The rostral subdivision constitutes the anterior cingulate cortex (ACC), which includes BA 24, 25, 32 and 33, whereas the caudal area represents the posterior cingulate cortex (PCC), which includes BA 23, 29, 30 and 31. It is interesting to remark that, according to certain researchers, the ACC is topographically located in the PFC, although it is functionally considered part of the limbic system. This particularity allows the ACC to constitute a neurobiological bridge for the integration between higher-order cognitive functions, associated with the PFC, and emotional processing, associated with the limbic system. In this regard, the ACC has been also subdivided in different areas, associated with more specific functions, such as the rostral or ventral ACC (vACC), which is located surrounding the *genu* of the *corpus callosum*, and the dorsal/caudal ACC, which is located adjacent to the PCC, also referred as the medial anterior cingulate cortex (mACC). The rostral/ventral ACC also includes the area located just in front and adjacent to the *genu* of the *corpus callosum*, also known as the pregenual ACC (pgACC), which encompasses the BA 24 and part of BA 32, and the area located below the *genu* of the *corpus callosum*, also known as the subgenual ACC (sgACC), more specifically located in the BA 25 (Stevens et al., 2011) (Fig. 2.26). These further subdivisions allowed identifying the vACC as the "affective" component of the ACC, while the mACC has been identified as the more "cognitive" component (Bush et al., 2000). In this regard, it has been shown that the mACC has broad connections with cognitive-related areas, such as the DL-PFC, while the vACC has extensive connections with emotion-related areas, such as the amygdala, OFC and ventral striatum (Fig. 2.26). In addition, it has been shown that the vACC has also important connections with the hippocampus, the lateral hypothalamus and brainstem centres. More specifically, the sgACC has strong connections with the amygdala, hippocampus, ventral striatum and autonomic centres in the hypothalamus and brainstem nuclei.

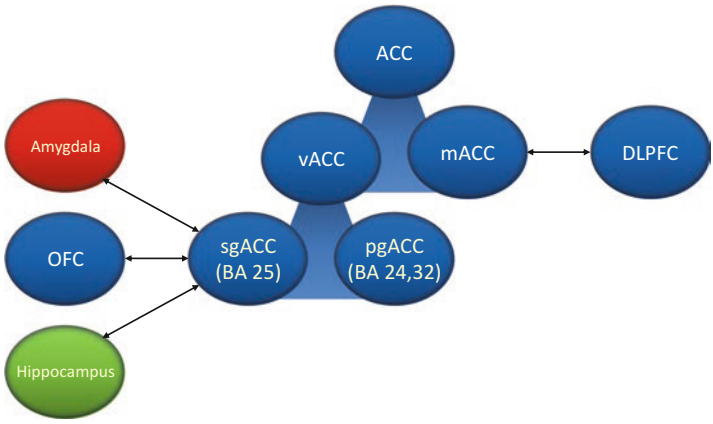

Fig. 2.26 Processing in the anterior cingulate cortex (ACC). The cingulate cortex (CC) is located in the medial surface of each hemisphere, adjacent and on the upper border of the *corpus callosum*. The rostral subdivision constitutes the anterior cingulate cortex (ACC). The ACC has been subdivided in the rostral or ventral ACC (vACC), which is located surrounding the *genu* of the *corpus callosum*, and the dorsal/caudal ACC, which is located adjacent to the PCC, also referred as the medial anterior cingulate cortex (mACC). The rostral/ventral ACC also includes the pregenual ACC (pgACC), which encompasses the BA 24 and part of BA 32, and the subgenual ACC (sgACC), more specifically located in the BA 25. The mACC has connections with cognitive-related areas, such as the DL-PFC, while the vACC has connections with emotion-related areas, such as the amygdala, OFC and ventral striatum. The vACC has also connections with the hippocampus, the lateral hypothalamus and brainstem centres. The role of the ACC in emotion regulation is associated with connections with the amygdala and the PFC, constituting a "top-down" process. Activation of the pgACC by emotional conflict resolution may lead to reduced amygdala activity, therefore regulating potentially excessive emotional responses

The ACC is activated during emotional experiences. Activation of the pgACC has been associated with positive emotions, such as happiness, whereas activation of the sgACC has been associated with negative emotions, such as sadness. In addition, activation of the sgACC has been also associated with the expected value of options. Activation of the mACC, and to a lesser extent pgACC, has been associated with activities requiring cognitive control, including conflict-monitoring, error-detection or emotion-related appraisal. Activation of the mACC and sgACC has been associated with reappraisal, where mACC represents the cognitive component involved in conflict-monitoring and approach-avoidance decisions, and the vACC, including pgACC and sgACC, represents the affective component involved in emotional assessment and autonomic regulation. More specifically, the pgACC participates in emotional regulation and the sgACC in autonomic control and visceral integration. The role of the ACC in emotion regulation is closely associated with various connections with the amygdala and the PFC, constituting a "top-down" process, which involves several cortical and limbic areas. In this regard, activation of the pgACC by emotional conflict resolution may lead to reduced amygdala activity, therefore regulating potentially excessive emotional responses (Bush et al., 2000).

The Raphe Nuclei and the Serotonergic System: The Role of Serotonin (5HT)

Serotonergic neurons in the CNS are mainly found in the raphe nuclei (RN), a group of aminergic neurons located in the brainstem, where an array of ascending projections arises from two main subdivisions: the dorsal RN (DRN, also identified as B6 and B7) and the medial RN (MRN, also identified as B5 and B8) (Fig. 2.27). The DRN-forebrain tract sends its projections mainly to certain nuclei of the amygdala; to different parts of the PFC; to the striatum, including the nucleus accumbens; and to the ventral region of the hippocampus, among other forebrain structures (Hensler, 2006). Activation of the DRN has been associated with anticipatory anxiety, therefore playing a significant adaptive role during stressful situations (Deakin & Graeff, 1991). Activation of the DRN has been associated with an important stimulatory effect on limbic structures, such as the amygdala, in the presence of environmental stressors associated with negative or unpleasant experiences, and also participates in the regulation of potential emotional reactions (Fig. 2.28). Alterations of this serotonergic tract, particularly involving DRN-amygdala projections, may be associated with anxiety (Deakin & Graeff, 1991).

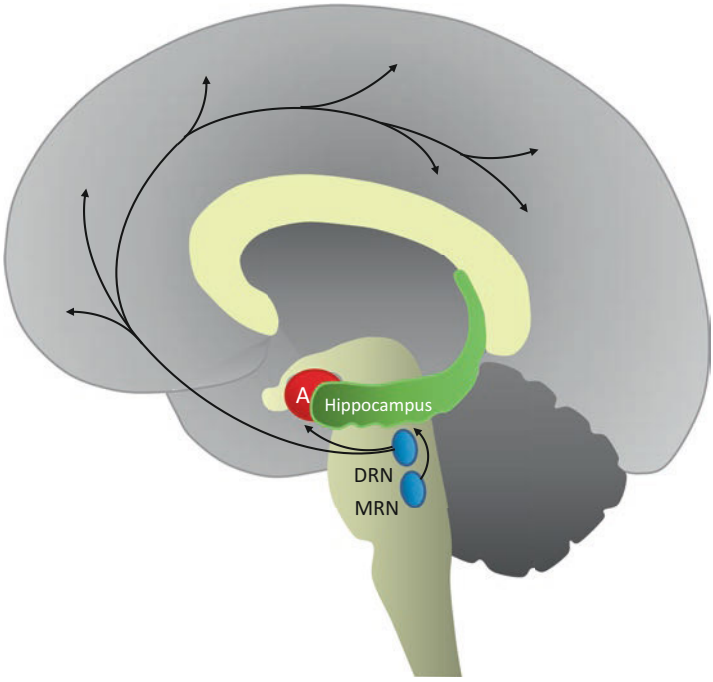

Fig. 2.27 Schematic representation of the serotonergic system. Serotonergic neurons in the CNS are located in the raphe nuclei (RN), where ascending projections arise from two main subdivisions: the dorsal RN (DRN, also identified as B6 and B7) and the medial RN (MRN, also identified as B5 and B8)

The MRN-forebrain tract projects to the dorsal region of the hippocampus and certain nuclei of the hypothalamus, among other neural structures. The MRN plays a critical role in conferring tolerance to unpleasant, unavoidable and persistent aversive stimuli, such as those associated with the impact of chronic stressful situations (Deakin & Graeff, 1991) (Fig. 2.28). This serotonergic tract also participates in the

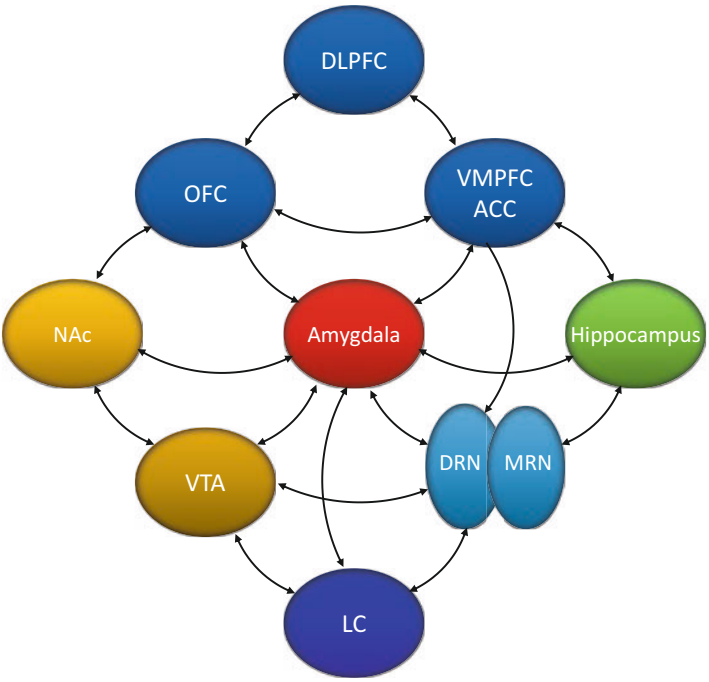

Fig. 2.28 Schematic representation of different aminergic system, their reciprocal connections and their projection to different cortical and limbic structures. The DRN-forebrain tract sends projections to the amygdala, different parts of the PFC and the striatum. Activation of the DRN has been associated with anticipatory anxiety, therefore playing a significant adaptive role during stressful situations. The MRN-forebrain tract projects to the hippocampus and certain nuclei of the hypothalamus, among other neural structures. The MRN plays a critical role in conferring tolerance to unpleasant, unavoidable and persistent aversive stimuli, such as those associated with the impact of chronic stressful situations. This serotonergic tract also participates in the adaptive control of negative emotional experiences. Hence, alterations of this tract, particularly involving MRN-hippocampal projections, may be associated with decreased tolerance to aversive stimuli, learned helplessness and the subsequent development of depression. Serotonergic neurons in the RN are interconnected with other monoaminergic systems in the brainstem, including dopaminergic and noradrenergic circuits. The DRN and the MRN receive noradrenergic projections, which appear to play an excitatory effect, and, reciprocally, the LC also receives serotonergic projections from the RN, which play a modulatory effect by inhibiting glutamatergic activation of the LC. Serotonergic projections from the DRN may exert excitatory effect on the LC by stimulation of $5HT_{1A}$ receptors. The DRN also regulates dopaminergic activity through projections to the ventral tegmental area (VTA), which appear to be excitatory, and reciprocally dopaminergic projections to the DRN exert an indirect inhibitory effect, by increasing the activity of somato-dendritic 5HT autoreceptors

adaptive control of negative emotional experiences. Hence, alterations of this tract, particularly involving MRN-hippocampal projections, may be associated with decreased tolerance to aversive stimuli, learned helplessness and the subsequent development of depression (Deakin & Graeff, 1991, reviewed in Tafet & Bernardini, 2003). It is noteworthy that serotonergic neurons in the RN are interconnected and physiologically integrated with other monoaminergic systems in the brainstem, including dopaminergic and noradrenergic circuits (Hamon & Blier, 2013) (Fig. 2.28). In this regard, it has been shown that both the DRN and MRN receive noradrenergic projections, which appear to play an excitatory effect, and, reciprocally, the LC also receives serotonergic projections from the RN (Ressler & Nemeroff, 1999), which appear to play an indirect modulatory effect by inhibiting glutamatergic activation of the LC. More recently, it has been shown that serotonergic projections from the DRN may exert excitatory effect on the LC by stimulation of $5HT_{1A}$ receptors. The DRN also regulates dopaminergic activity through projections to the ventral tegmental area (VTA), which appear to be excitatory, and reciprocally dopaminergic projections to the DRN exert an indirect inhibitory effect, by increasing the activity of somato-dendritic 5HT autoreceptors (Kranz et al., 2010).

Fig. 2.28 illustrates the network of functional connections between different aminergic neurotransmitters in the CNS and their reciprocal connections with different cortical and limbic structures involved in the stress response (modified from Tafet & Nemeroff, 2016).

At the molecular level, 5HT stored in synaptic vesicles is released from the presynaptic terminal into the synaptic cleft, where it may bind to both pre- and postsynaptic specific receptors (Fig. 2.29). Numerous 5HT receptors have been identified, including 14 different types, classified in 7 families with various subtypes each (Fig. 2.30). Most of these are metabotropic receptors, therefore constituting a big family of G-protein-coupled receptors (GPCR), characterized by a high sequence similarity throughout their 7 transmembrane domains, with the sole exception of the $5HT_3$, which represents the only ionotropic 5HT receptor (Marin et al., 2020). Among the 5HT GPCRs family, the $5HT_1$ class is known to be coupled to specific G proteins, termed G_i or G_o, that exert inhibitory effect on adenylyl cyclase (AC), an enzyme involved in the synthesis of cAMP, therefore reducing the intracellular concentrations of this second messenger, which in turn may lead to the inhibition of the molecular cascade of events mediated by protein kinase A (PKA). The $5HT_1$ class includes the $5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$ and $5HT_{1F}$ receptors, all of which are known to be coupled to G_i proteins. Regarding the $5HT_{1C}$ receptor, it was originally believed to belong to this family, although it was later demonstrated to be coupled to a different G protein, and therefore it was termed $5HT_{1C}/5HT_{2C}$, to be included in the $5HT_2$ class, where it was finally known as the $5HT_{2C}$ receptor. The $5HT_{1A}$ receptor has been extensively studied, due to its role in the pathophysiology of mood and anxiety disorders. Hence, $5HT_{1A}$ receptors are known to play different roles, depending on their specific cellular location. In this regard, $5HT_{1A}$ receptors have been identified in the soma and dendrites of serotonergic neurons, therefore termed somato-dendritic autoreceptors, which play an inhibitory role in

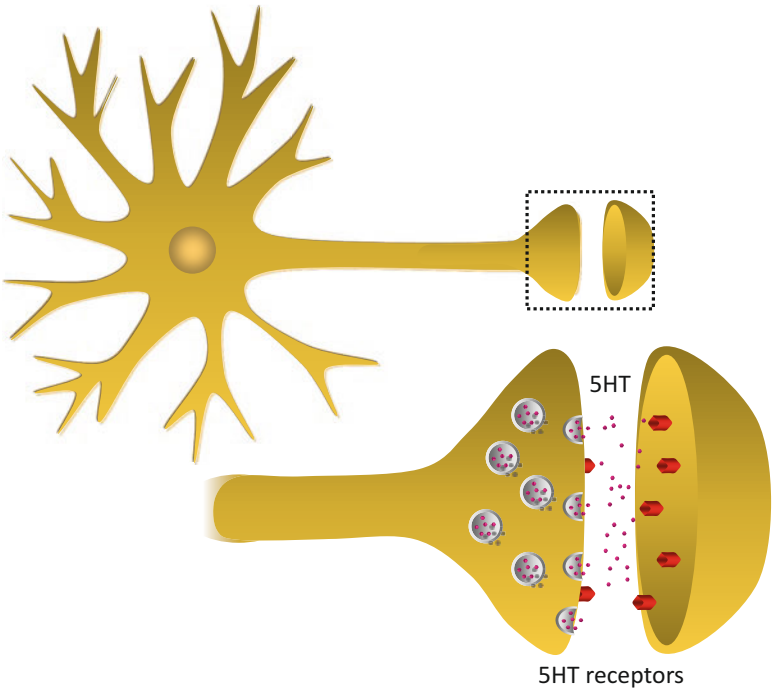

Fig. 2.29 Schematic representation of synaptic neurotransmission. At the molecular level, 5HT is stored in synaptic vesicles to be released from the pre-synaptic terminal into the synaptic cleft, where it may bind to both pre- and post-synaptic specific receptors

serotonergic neurotransmission. Hence, binding of 5HT to somato-dendritic $5HT_{1A}$ receptors may lead to activation of G_o-mediated opening of hyperpolarizing K^+ channels, which in turn may induce a transient decrease in the firing rate of 5HT neurons. Post-synaptic $5HT_{1A}$ receptors, also termed heteroreceptors, are usually expressed in target neurons receiving serotonergic innervations, including pyramidal neurons and GABAergic interneurons. These post-synaptic heteroreceptors are highly expressed in neural structures involved in cognitive and emotional processes, including the hippocampus, the amygdala and certain areas in the PFC. Upon release of 5HT to the synaptic cleft, activation of these $5HT_{1A}$ heteroreceptors may lead to decreased concentrations of intracellular cAMP and opening of G protein-gated inward rectifying K^+ channels, which may lead to inhibition of voltage-gated Ca^{++} channels (Garcia-Garcia et al., 2014), with the resulting hyperpolarization, and the consequent inhibition, of target neurons. Although hyperpolarization induced by activation of $5HT_{1A}$ receptors may be the same in pre- and post-synaptic terminals, it has been shown that sustained administration of a $5HT_{1A}$ agonist agent, or a selective serotonin reuptake inhibitor, may lead to internalization of autoreceptors in serotonergic neurons, hence allowing an increased release of 5HT, and up-regulation of heteroreceptors in target neurons, for example, in the hippocampus. The $5HT_2$

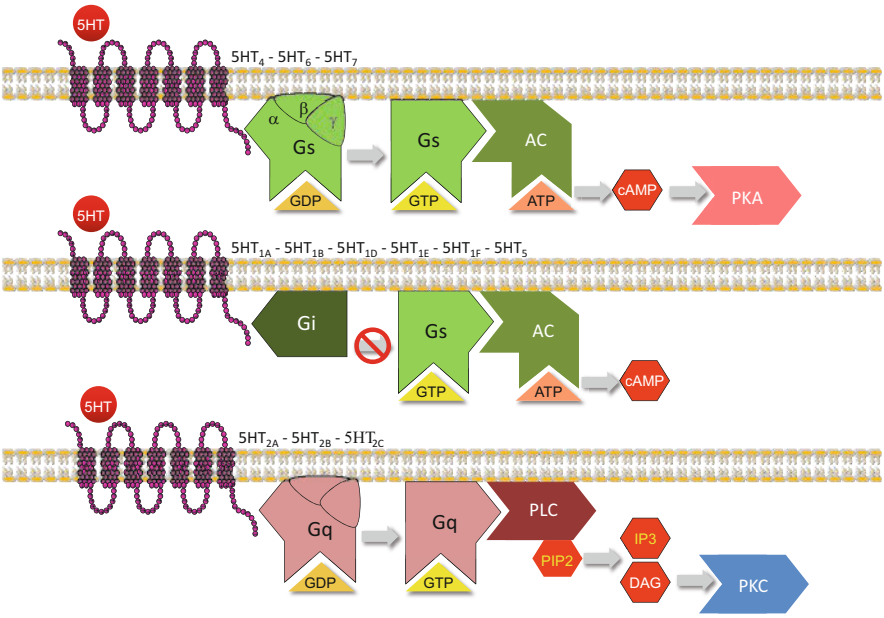

Fig. 2.30 Serotonergic receptors and their molecular cascades. Numerous 5HT receptors have been identified, including 14 different types, classified in 7 families with various subtypes each. Most of these are metabotropic receptors, therefore constituting a big family of G-protein-coupled receptors (GPCRs), with the exception of the $5HT_3$, which represents the only ionotropic 5HT receptor. Among the 5HT GPCRs family, the $5HT_1$ class is coupled to G_i or G_o that exert inhibitory effect on adenylyl cyclase (AC), and which is involved in the synthesis of cAMP. The $5HT_1$ class includes the $5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$ and $5HT_{1F}$ receptors. The $5HT_{1A}$ receptor plays different roles, depending on their specific cellular location. Somato-dendritic $5HT_{1A}$ autoreceptors play an inhibitory role in serotonergic neurotransmission. Post-synaptic $5HT_{1A}$ receptors are expressed in target neurons receiving serotonergic innervations. Upon release of 5HT to the synaptic cleft, activation of these $5HT_{1A}$ heteroreceptors may lead to hyperpolarization and the inhibition of target neurons. The $5HT_2$ class includes the $5HT_{2A}$, $_{2B}$ and $_{2C}$ receptors, which are coupled to a G_q that exerts stimulatory effect on phospholypase C (PLC), which is involved in the synthesis of di-acyl-glycerol (DAG) and inositol-3-phosphate (IP3), therefore increasing the intracellular concentrations of these second messengers. The $5HT_3$ receptor is coupled to a ligand-gated ion channel. The $5HT_4$, $5HT_6$ and $5HT_7$ receptors are coupled to a G_s protein, which exerts stimulatory effect on AC, therefore increasing the intracellular concentrations of cAMP, which in turn may lead to the activation of the molecular cascade of events mediated by PKA. The $5HT_5$ receptor is known to be also coupled to a G_i protein, therefore decreasing the intracellular concentrations of cAMP. The 5HT/G_s/cAMP/PKA pathway is involved in the phosphorylation and activation of different proteins, which in turn may lead to transcriptional regulation of various genes

class includes the $5HT_{2A}$, $_{2B}$ and $_{2C}$ receptors, which are known to be coupled to a different G protein, termed G_q, that exerts stimulatory effect on phospholypase C (PLC), an enzyme involved in the synthesis of di-acyl-glycerol (DAG) and inositol-3-phosphate (IP3), therefore increasing the intracellular concentrations of these second messengers, which in turn may lead to the activation of the molecular cascade of events mediated by protein kinase C (PKC). The $5HT_3$ receptor is

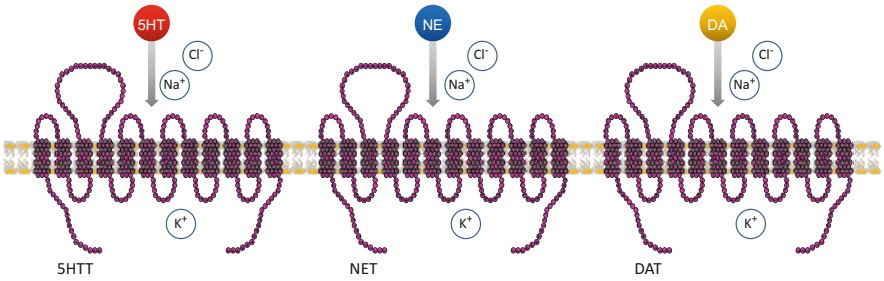

Fig. 2.31 Monoaminergic transporters. Available concentration of 5HT in the synaptic cleft is regulated by the pre-synaptic serotonin transporter (5HTT, also known as SERT), which is responsible for its reuptake from the synaptic cleft into the pre-synaptic terminal. The 5HTT is a 12-transmembrane domain protein, which accomplishes the co-transport process of 5HT, along with Na^+ and Cl^-, with the simultaneous counter-transport of K^+, utilizing the energy of the Na^+ gradient provided by the plasma membrane Na/K ATPase. Upon being uptaken from the synaptic cleft, 5HT may be reuptaken back into synaptic vesicles by a non-specific monoamine transporter, known as the vesicle monoamine transporter. In a similar way, available concentrations of NE in the synaptic cleft are regulated by a norepinephrine transporter (NET), and concentrations of DA in the synaptic cleft are regulated by a dopamine transporter (DAT)

coupled to a ligand-gated ion channel, composed by five subunits, of four transmembrane domains each. Activation of this receptor, upon binding of 5HT, results in the opening of the ion channel, which is permeable to Na^+, K^+ and Ca^{++}, which in turn may lead to increased concentrations of Ca^{++}, with the consequent depolarization of target neurons. The $5HT_4$, $5HT_6$, and $5HT_7$ receptors are known to be coupled to a different G protein, known as the G_s protein, which exerts stimulatory effect on AC, therefore increasing the intracellular concentrations of cAMP, which in turn may lead to the activation of the molecular cascade of events mediated by PKA. The $5HT_5$ receptor is known to be also coupled to a G_i protein, therefore decreasing the intracellular concentrations of cAMP. The 5HT/G_s/cAMP/PKA pathway is involved in the phosphorylation and activation of different proteins, which in turn may lead to transcriptional regulation of various genes.

All these variety of serotonin receptor subtypes display a distinctive regional neuro-anatomical distribution, conferring certain specificity on the effects of activation of this widespread and diffuse serotonergic network. Available concentration of 5HT in the synaptic cleft is regulated by the pre-synaptic serotonin transporter (5HTT, also known as SERT), which is responsible for its reuptake from the synaptic cleft into the pre-synaptic terminal (Fig. 2.31). The 5HTT is a 12 transmembrane domain protein, which accomplishes the co-transport process of 5HT, along with Na^+ and Cl^-, with the simultaneous counter-transport of K^+, utilizing the energy of the Na^+ gradient provided by the plasma membrane Na/K ATPase (Rudnick & Clark, 1993). Upon being uptaken from the synaptic cleft, 5HT may be reuptaken back into synaptic vesicles by a non-specific monoamine transporter, known as the vesicle monoamine transporter (VMAT). Therefore the availability of 5HT in the synaptic cleft, to bind and activate specific 5HT receptors, is regulated by the 5HTT

(Hamon & Blier, 2013). In addition, the concentrations of synaptic 5HT may be also down-regulated by enzymatic degradation by the monoamine oxidase (MAO), which is not specific for 5HT but is responsible for the degradation of different monoamines. The 5HTT represents the primary molecular target of different antidepressant agents, including the tricyclic antidepressants (TCA) and the selective serotonin reuptake inhibitors (SSRIs) antidepressants (Schloss & Williams, 1998). Hence, 5HTT blockade by SSRIs is translated into higher 5HT concentrations in the synaptic cleft, allowing increased activation of specific post-synaptic 5HT receptors. Pre-synaptic $5HT_{1A}$ receptors are known to exert a modulatory effect on 5HT release. Therefore, the clinical efficacy of antidepressants is associated with adaptive changes produced by continuous administration of SSRIs, after several days, which may lead to desensitization or down-regulation of somato-dendritic $5HT_{1A}$ auto-receptors in the RN, which are known to moderate the release of 5HT into the synaptic cleft, and up-regulation of post-synaptic $5HT_{1A}$ and desensitization of $5HT_{2A}$ receptors (Gray et al., 2013).

In addition to serotonergic projections to different neural structures, directly involved in cognitive and emotional functions, serotonergic projections from the RN have been shown to innervate CRF-containing neurons in the hypothalamic PVN (Lesch & Gutknecht, 2004). It has been shown that these projections stimulate the HPA axis and the ANS, and reciprocally, glucocorticoids and catecholamines may impact upon the serotonergic system during stressful situations. In this regard, various studies have shown that post-synaptic $5HT_{1A}$ receptors in different limbic structures may be down-regulated or desensitized by glucocorticoids or exposure to chronic stress (López et al., 1998; van Riel et al., 2004). In addition, it has been shown that cortisol may increase 5HT uptake in vitro, an effect attributed to increased expression of the 5HTT gene through transcriptional regulation exerted by the hormone-receptor complex constituted by cortisol bound to the glucocorticoid receptor (Tafet et al., 2001), therefore providing further support to the reciprocal regulation of the HPA and 5HT systems, and their potential interplay in the interface between stress and depression (Tafet & Bernardini, 2003; Tafet & Nemeroff, 2016).

The role of the serotonergic system in health and disease has been extensively studied. In this regard, it has been shown that good mood, technically known as "euthimia", is closely associated with adequate concentrations of 5HT, particularly active in the projections from the MRN to the hippocampus, which have been associated with adequate tolerance to adversity (Deakin & Graeff, 1991). Reduced concentrations of 5HT in this pathway have been associated with low tolerance to adverse events and bad mood, technically known as "disthymia". Moreover, decreased concentrations of 5HT have been also associated with the development of learned helplessness, which in turn has been closely associated with the origin and development of depression (Ressler & Nemeroff, 2000). This notion has been further supported by numerous studies and an increasing body of clinical evidence, where it has been shown that various antidepressants may exert their therapeutic effects through normalization and stimulation of the serotonergic system (Nemeroff, 1998).

Moreover, various studies focused on the study of different genes involved in the regulation of the serotonergic system. Among these, numerous studies have focused on the 5HTT gene, where a polymorphism was identified in its promoter region, which has been associated with increased vulnerability to depression and anxiety disorders (Lesch et al., 1996).

The Reward System and Dopaminergic Pathways: The Role of Dopamine (DA)

The role of DA in emotional processing, particularly in the neurobiology of reward and positive emotions, has been demonstrated. In addition, DA also participates in the neural mechanisms of stress responses, including a role in the regulation of the HPA axis, and also in the mechanisms involved in the pathophysiology of depression (Dunlop & Nemeroff, 2007; Nestler & Carlezon Jr, 2006). Dopaminergic neurons in the CNS are mainly found in certain nuclei of aminergic neurons located in the brainstem, including the retro-rubro field (also identified as A8), the substantia nigra pars compacta (also identified as A9) and the ventral tegmental area (VTA, also identified as A10) (Fig. 2.32).

At the molecular level, DA stored in synaptic vesicles of dopaminergic neurons is released from the pre-synaptic terminal into the synaptic cleft, where it may bind to specific receptors. Different DA receptors have been identified and classified as "D1-like", including the D_1 and D_5 receptors, and "D2-like", including the D_2, D_3 and D_4 receptors. All of these receptors are known to be metabotropic and therefore are coupled to G proteins, hence constituting the DA GPCRs family. The "D1-like" receptors are primarily coupled to G_s proteins, which participate in the activation of AC and the formation of cAMP, and the "D2-like" receptors are primarily coupled to G_i or G_o proteins, which may induce the opposite effect (Fig. 2.33). As it was previously described for serotonergic neurotransmission, termination of dopaminergic neurotransmission is also regulated by a specific transmembrane protein, known as the DA transporter (DAT), which is responsible for the reuptake of DA from the synaptic cleft (Fig. 2.31).

The main projections involved in cognitive and emotional processes are those originated in the VTA, which is the main source of the mesolimbic (M-L) and the mesocortical (M-C) dopaminergic pathways (Fig. 2.32). The M-L pathway sends dopaminergic projections from the VTA to the nucleus accumbens (NAc), as well as other limbic structures, including the amygdala, hippocampus, BNST and septum. The NAc, in the ventral striatum (VS), receives cue-related environmental information through excitatory glutamatergic projections from the PFC; through the OFC and the AAC, from the hippocampal formation; through the ventral subiculum, from the amygdala; and through the BLA, from the dorso-medial nucleus of the thalamus.

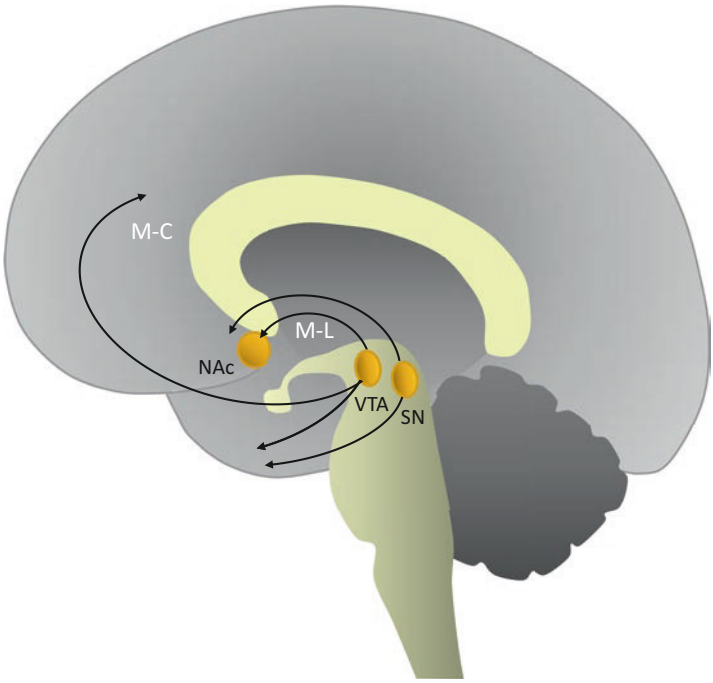

Fig. 2.32 Schematic representation of the dopaminergic system. Dopaminergic neurons in the CNS are mainly found in certain nuclei of aminergic neurons located in the brainstem, including the retro-rubro field (also identified as A8), the substantia nigra pars compacta (SNc, also identified as A9) and the ventral tegmental area (VTA, also identified as A10). The main projections involved in cognitive and emotional processes are those originated in the VTA, which is the main source of the mesolimbic (M-L) and the mesocortical (M-C) dopaminergic pathways. The M-L pathway sends dopaminergic projections from the VTA to the nucleus accumbens (NAc)

Therefore, the NAc participates in the integration of environmental information with stored information related to past experiences. After receiving excitatory glutamatergic projections, neurons in the NAc receive dopaminergic projections from the VTA, which has been associated with salience and valence, associated with reward information, therefore participating in reward detection and anticipation. Therefore, the M-L is known as the "reward pathway" because it plays a critical role in the processing and reinforcement of rewarding stimuli, motivation and the subjective experience of pleasure (Dunlop & Nemeroff, 2007). The M-C pathway sends dopaminergic projections to different parts of the PFC, mainly to the ACC, as well as projections to the MTL, particularly to the entorhinal cortex, and participates in cognitive functions such as working memory and concentration. In this regard, the impact of environmental stressors may provoke increased activity in the amygdala, which in turn may provoke increased concentrations of DA in the M-C pathway, particularly in the PFC, therefore assigning excessive salience to negative stimuli,

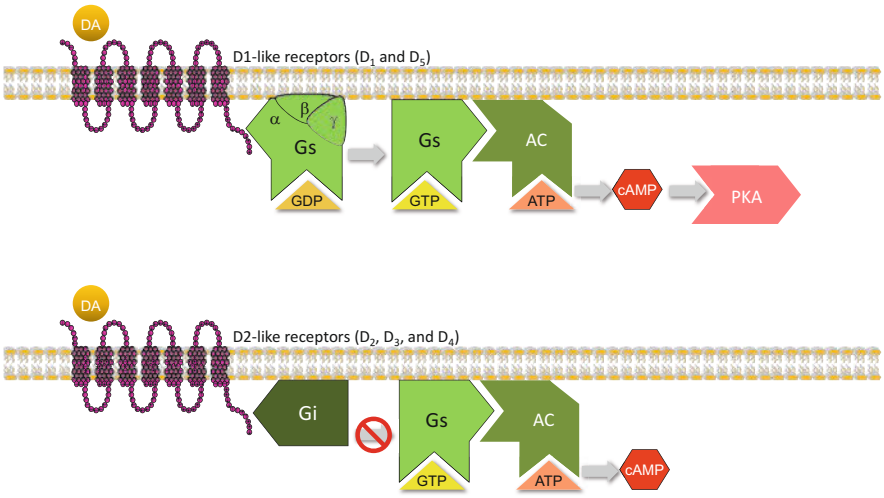

Fig. 2.33 Dopaminergic receptors and their molecular cascades. At the molecular level, DA stored in synaptic vesicles is released from the pre-synaptic terminal into the synaptic cleft, where it may bind to specific receptors. Different DA receptors have been identified and classified as "D1-like", including the D_1 and D_5 receptors, and "D2-like", including the D_2, D_3 and D_4 receptors. All of these receptors are known to be metabotropic and therefore are coupled to G proteins, hence constituting the DA GPCRs family. The "D1-like" receptors are coupled to G_s proteins, which participate in the activation of AC and the formation of cAMP, and the "D2-like" receptors are primarily coupled to G_i or G_o proteins, which may induce the opposite effect

otherwise perceived as relatively mild events, hence contributing to the consequent negative bias in cognitive processing (Dunlop & Nemeroff, 2007).

Regarding the M-L pathway, environmental stressors may provoke opposite responses, which may depend on the potential controllability of perceived stressful events (Suridjan et al., 2012), and the associated subjective appraisal. Therefore, exposure to acute and controllable stressors has been associated with increased DA release in the ventral striatum, particularly in the NAc, whereas exposure to chronic and uncontrollable stressors has been associated with decreased dopaminergic activity in the M-L pathway (Suridjan et al., 2012). Moreover, the impact of unavoidable or uncontrollable stressors has been associated with decreased DA release in the NAc and impaired response to environmental stimuli, which may result in the expression and exacerbation of certain depressive symptoms, which have been associated with chronic stress (Cabib & Puglisi-Allegra, 2012). In this regard, the difficulty or inability to experience pleasure, associated with loss of interest and motivation in usual activities, constitutes the typical anhedonia exhibited by depressed subjects (Nestler & Carlezon Jr, 2006), and it has been demonstrated that impaired dopaminergic function is critically involved in altered reward processing underlying anhedonia (Krishnan & Nestler, 2010; Bogdan et al., 2013). Moreover, the M-L dopaminergic pathway, and more specifically the NAc, is critically involved in the processing of rewarding and hedonic experiences in association with the

OFC, which in turn is involved in the subjective assessments of hedonic and rewarding value (Der-Avakian & Markou, 2012). The OFC shares important connections with other areas of the PFC, such as the ACC and the DLPFC, where the emotional input participates in the cognitive processing. In addition to dopaminergic projections from the VTA, the NAc also receives glutamatergic stimulation from the amygdala, which may enhance the dopaminergic input, therefore increasing motivation (Der-Avakian & Markou, 2012).

The dopaminergic VTA and the serotonergic RN also share an important interaction, which may be involved in emotional processing (Fig. 2.28). Interestingly, it has been shown that increased DA release in the M-L pathway has been associated with the impact of rewarding stimuli, as well as in response to certain aversive situations, particularly when these are perceived as controllable and escapable. The subjective perception of controllability is highly relieving, which in turn is also rewarding. Therefore, it has been proposed that DA plays an adaptive role associated with motivation, increased arousal and behavioural control in response to appetitive and aversive stressful conditions (Pruessner et al., 2004).

The Locus Coeruleus and the Noradrenergic System: The Role of Norepinephrine (NE)

Norepinephrine (NE, also known as noradrenaline, NA) has long been involved in the pathophysiology of stress, particularly in the origin and development of depression and anxiety disorders. Noradrenergic neurons in the CNS are mainly located within the LC (also identified as the catecholaminergic cell group A6), which represents the source of various noradrenergic projections to widely innervate cortical and subcortical areas (Ressler & Nemeroff, 1999), such as the amygdala, the hippocampus and the PVN of the hypothalamus (Valentino et al., 1993) (Fig. 2.34). Projections from the noradrenergic LC to the dopaminergic VTA have been also described, where NE has been shown to potentiate DA release, and projections from the LC to the serotonergic RN have been also described, where NE exerts regulatory effects on 5HT release (Ressler & Nemeroff, 1999). Reciprocal regulation between NE and 5HT has been also demonstrated, not only through connections between both aminergic systems but also through limbic structures, such as the hippocampus (Mongeau et al., 1997) (Fig. 2.28). Moreover, reciprocal connections between NE and CRF containing neurons reveal the critical role played by the noradrenergic system in the regulation of neural and neuroendocrine responses to stress (Valentino et al., 1993).

At the molecular level, upon the impact of an action potential into a pre-synaptic terminal, voltage-gated Ca^{++} channels are activated, with the resulting influx of Ca^{++}, which in turn causes synaptic vesicles to bind cell membranes, therefore releasing stored NE into the synaptic cleft. Hence, released NE may bind to specific receptors, all of them coupled to G proteins, hence constituting the NE GPCRs

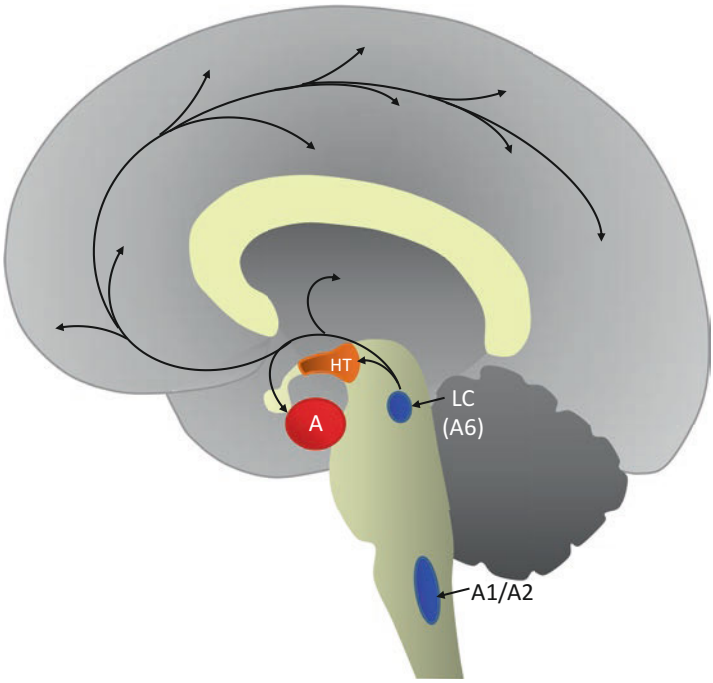

Fig. 2.34 Schematic representation of the noradrenergic system. The noradrenergic system: Noradrenergic neurons in the CNS are mainly located within the LC (also identified as the catecholaminergic cell group A6), which represents the source of noradrenergic projections to innervate cortical and subcortical areas, such as the amygdala, the hippocampus and the PVN of the hypothalamus

family (Fig. 2.35). Alpha-1 (α_1) receptors, which may be further subdivided into α_{1a}, α_{1b} and α_{1d} receptors, are known to be coupled to a G_q protein, which activates PLC with the resulting increase in IP3 and DAG concentrations. These NE receptors are mainly located in the LC, PFC, amygdala, thalamus and DG of the hippocampus. Alpha-2 (α_2) receptors, which may be further subdivided into α_{2a}, α_{2b} and α_{2c} receptors, are known to be coupled to a $G_{i/o}$ protein, which inhibits AC, with the resulting decrease in cAMP concentrations. These NE receptors are pre-synaptic and post-synaptic and may be mainly located in the LC, amygdala and hypothalamus. Beta (β) receptors may be further subdivided into β_1, and β_2 receptors, and are known to be coupled to a G_s protein, which stimulates AC, with the resulting increase in cAMP concentrations, with the consequent activation of the NE/AC/cAMP/PKA signalling pathway. The β_2 receptors may also couple to a G_i protein. As it was previously described for 5HT and DA, termination of noradrenergic neurotransmission is also regulated by a specific transmembrane protein, known as the NE transporter (NET), which is also responsible for the reuptake of NE from the synaptic cleft (Fig. 2.31).

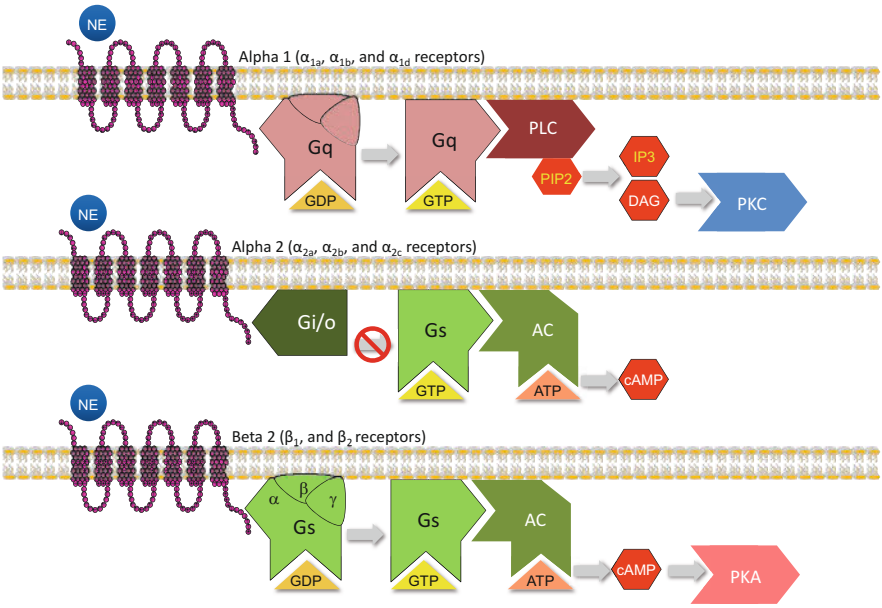

Fig. 2.35 Noradrenergic receptors and their molecular cascades. At the molecular level, voltage-gated Ca^{++} channels are activated, with the resulting influx of Ca^{++}, which in turn causes synaptic vesicles to bind cell membranes, therefore releasing stored NE into the synaptic cleft. Released NE may bind to specific receptors, all of them coupled to G proteins, hence constituting the NE GPCRs family. Alpha-1 (α_1) receptors, which may be further subdivided into α_{1a}, α_{1b} and α_{1d} receptors, are coupled to a G_q protein, which activates PLC with the resulting increase in IP3 and DAG. These NE receptors are mainly located in the LC, PFC, amygdala, thalamus and DG of the hippocampus. Alpha-2 (α_2) receptors, which may be further subdivided into α_{2a}, α_{2b} and α_{2c} receptors, are coupled to a $G_{i/o}$ protein, which inhibits AC, with the resulting decrease in cAMP. These NE receptors are pre-synaptic and post-synaptic and may be mainly located in the LC, amygdala and hypothalamus. Beta (β) receptors may be further subdivided into β_1 and β_2 receptors and are coupled to G_s protein, which stimulates AC, with the resulting increase in cAMP, with the consequent activation of the NE/AC/cAMP/PKA signalling pathway

It has been shown that in response to acute stressful events, NE is widely released throughout different neural structures in the CNS, resulting in enhanced arousal and vigilance, which represent an important component of adaptive responses to stress (Valentino et al., 1993). Furthermore, activation of the LC has been also associated with subsequent stimulation of the lateral hypothalamus, which in turn is critically involved in the activation of the ANS, particularly the SNS, therefore sustaining and strengthening adaptive responses to stress. In response to chronic stressful situations, certain dysfunction of the LC has been observed, particularly upon exposure to unavoidable or uncontrollable stressors, leading to altered NE release, which in turn has been associated with some aspects of learned helplessness (Robbins & Everitt, 1995). This potential dysfunction of the noradrenergic system has been also associated with altered cognitive functions, such as attention and memory, frequently observed in chronic stress and depression. Moreover, dysfunction of the

noradrenergic system has been also associated with altered states of arousal, usually observed in depression and anxiety disorders.

Activation of the LC system is usually complemented by activation of the ANS (Valentino et al., 1993). In association with the LC, the lateral hypothalamus mediates the activation of the sympathetic branch of the ANS, which is critically involved in adaptive responses through the activation of sympathetic nerves and the adrenal medulla, with the consequent release of adrenaline. The integration of both, the central and the peripheral components of the sympatho-adrenergic system, is the explanation for the ample spectrum of central and autonomic symptoms observed in response to different stressful situations.

The Role of Neurotrophic Factors: Neuroplasticity and Neurogenesis

The critical role of neurotrophic factors has been widely studied in various neural processes, with particular attention on the neurotrophin (NT) family, including the nerve growth factor (NGF), the brain-derived neurotrophic factor (BDNF), the NT3 and the NT4. Neurotrophins exert their effects on target cells mainly through binding to tropomyosin receptor tyrosine kinases (Trk). In this regard, NGF binds to TrkA, BDNF binds to TrkB, NT3 binds to TrkC, and NT4/NT5 also binds to NtrkB (Waterhouse & Xu, 2009). Among these neurotrophins, various studies focused on the role of BDNF in the regulation of brain development, neurogenesis and neuroplasticity (Mitchelmore & Gede, 2014). Moreover, BDNF has been associated with neuronal proliferation and development at early ages, as well as neuronal survival and functioning later in life (Wu et al., 2013), particularly in the hippocampus, where it has been shown that BDNF plays a critical role in the development of resilient adaptation to chronic stress (Taliaz et al., 2011).

In this regard, it has been demonstrated the association of decreased levels of BDNF with depressive symptoms, whereas its normalization was associated with clinical improvement (Duman & Monteggia, 2006). Chronic stress, with the consequent hyperactivity of the HPA axis, with the resulting increased levels of cortisol, may induce damage to neurons located in various neural structures, particularly in the hippocampus, where high levels of GRs have been found, and these changes have been also associated with decreased levels of BDNF (Ota & Duman, 2013). In this regard, interactions between BDNF and glucocorticoids have been observed at the level of their respective receptors, TrkB and GRs (Franklin et al., 2012). Furthermore, it has been shown that increased levels of glucocorticoids may be involved in down-regulation of BDNF (Suri & Vaidya, 2013). The role of BDNF on the functioning of the serotonergic system has been also demonstrated through in vivo studies, where it has been shown that infusion of BDNF in the CNS stimulates functional and structural changes in 5HT neurons. In addition, it has been also shown that different antidepressants increase the expression of BDNF in the

hippocampus, in a dose- and time-dependent manner, therefore suggesting an additional role for BDNF in their mechanism of action (Duman, 2004). The association between clinical recovery after successful pharmacotherapy and the observed up-regulation of BDNF in the hippocampus suggested that BDNF may be involved in long-lasting neuroplastic changes in various neural structures, such as the hippocampus, amygdala and PFC, associated with the effects produced by antidepressants (Duman and Monteggia, 2006). It is well known that most neurons are generated during early periods of development, though more recently it has been demonstrated that some neural structures, such as the dentate gyrus of the hippocampus, may continue generating neurons later in life (Jacobs et al., 2000). Adult neurogenesis may be stimulated by certain conditions, particularly those related to enhanced hippocampal activity and increased concentrations of 5HT (Mahar et al., 2014; Malberg et al., 2000; Alenina & Klempin, 2015), while it may be inhibited during stressful conditions, with increased activation of the HPA axis and the resulting increased concentrations of glucocorticoids. Under chronic stress conditions, with hyperactivation of the HPA system, the inhibition of neurogenesis in the hippocampus may interfere with the generation of new cognitions, therefore contributing to generate and sustain depressogenic conditions. Therefore, successful therapeutic interventions may involve recovery of hippocampal neurogenesis, which in turn has been also associated with the effect of antidepressants, through normalization of 5HT levels, or indirectly, through down-regulation of the HPA axis, and up-regulation of BDNF levels, which was associated with its stimulatory effect on hippocampal neuroplasticity and neurogenesis.

Brief Introduction to Molecular Genetics and Transcriptional Regulation

It has been shown that neuroplasticity and neurogenesis depend on the synthesis of new proteins, which requires the activation of molecular cascades involved in transcriptional regulation. Adaptive responses to stress depend on the concerted activation of various molecular pathways, mediated by an array of factors involved in cell signalling, allowing fluent and effective communication between cells, and their corresponding systems. Cell signalling includes the synaptic communication between neurons, the neural structures involved in different cognitive, emotional and behavioural processes, as well as the crosstalk between neurotransmitters, hormones and different peptides, including cytokines and neurotrophins. In this regard, peptidic neurotransmitters and their receptors, the enzymes involved in their production, as well as the enzymes involved in the synthesis of monoaminergic and amino acidic neurotransmitters, their receptors and transporters, the enzymes involved in the synthesis of steroid hormones and their receptors, as well as the enzymes involved in different polypeptides, are encoded in our genes. Therefore, the effects produced by internal and environmental stimuli, and the consequent

adaptive responses, may be mediated by the activation of different signal transduction pathways, which in turn may be translated into molecular processes involved in the regulation of gene expression.

A gene represents a basic unit of biological information, encoded in a specific discrete sequence of deoxyribonucleic acid (DNA), constituted by the combination of four different nucleotides: adenine (A), thymine (T), cytosine (C) and guanine (G). These nucleotides represent the building blocks of DNA, which are arranged in long sequences, according to specific genetic programming, constituting two complementary polynucleotide chains of DNA, which are held together by hydrogen bonding between the corresponding nucleotides, along both chains. In this regard, each nucleotide is paired with its corresponding partner between the complementary strands, where each A is always paired with a T, each T with an A, each C with a G and each G with a C (Fig. 2.36).

Genetic information for the synthesis of a protein is encoded in certain areas of each gene, known as "coding region", where the basic information is arranged in a sequence of small units of three nucleotides each, constituting a "codon". Each codon corresponds to a specific amino acid; therefore, the location of each codon along the genetic sequence may determine the location of each amino acid in the corresponding peptidic sequence, according to the genetic programming. Gene expression depends on the presence of specific molecular signals, known as "transcription factors", which play a critical role in the transcription of genetic messages, from specific DNA sequence into a complementary sequence of ribonucleic acid (RNA). This newly synthesized RNA sequence is constituted by a complementary sequence of nucleotides, where each C, originally encoded in the DNA sequence,

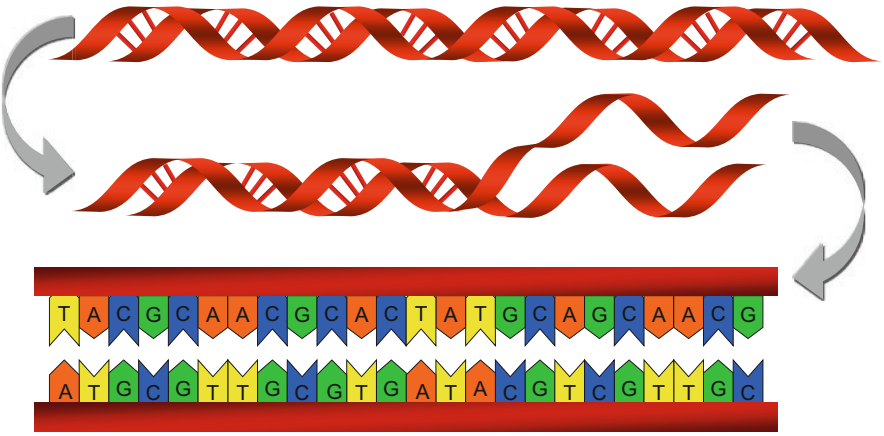

Fig. 2.36 Genetic encoding. Genes represent basic units of biological information, encoded in a specific discrete sequence of deoxyribonucleic acid (DNA), constituted by the combination of four different nucleotides: adenine (A), thymine (T), cytosine (C) and guanine (G), which are arranged in long sequences, constituting two complementary polynucleotide chains of DNA, which in turn are bound by hydrogen bonding between the corresponding nucleotides, along both chains. Each A is always paired with a T, each T with an A, each C with a G and each G with a C

will be replaced with a complementary G, each G with a C, each T with an A and each A, instead of a T, will be replaced with an uracil (U). In addition, the extent of the RNA chain will be determined by an initiation codon, identified as AUG, which codes for methionine in the peptidic sequence, and a termination codon, which may be UAG, UGA or UAA, which represent non-coding codons. This RNA sequence, known as "messenger RNA" (mRNA), is necessary for carrying genetic information from the nucleus to the cytoplasm, where assembled units, constituted by "ribosomal RNA" (rRNA) and "transcription RNA" (tRNA), contribute to translate the genetic message from mRNA into the synthesis of a peptidic product, including shorter oligopeptides and longer proteins, according to the genetic programming. In order to regulate gene expression, transcription factors should interact with specific, discrete DNA sequences, in certain area of each gene, known as "promoter region", located upstream of the "coding region". Therefore, specific transcription factors may interact with specific DNA sequences, known as "consensus sites", in the promoter region of target genes. Binding of transcription factors to their specific consensus sites may lead to transcriptional regulation, which may be translated into the activation or the inhibition of gene expression. Hence, up-regulation or down-regulation of gene expression may depend on the activation of transcription factors, the presence of specific consensus sites in the promoter region, their specific location and the potential interactions between different transcription factors, which constitute a transcription complex. Therefore, environmental stimuli may lead to activation of different molecular pathways, mediated by signalling molecules, such as hormones, neurotransmitters and neurotrophins. Interactions between signalling molecules and their receptors may lead to activation of specific transcription factors, which may bind to their specific sites in the promoter region of target genes, which may lead to the assembly of a transcription initiation complex, which in turn may lead to the binding of RNA polymerase to certain DNA sequence, therefore leading to gene expression (Alberts et al., 2002) (Fig. 2.37).

Transcriptional regulation may be altered by different pathophysiological processes, including the presence of subtle modifications in the structure of genes, known as polymorphisms. Various genetic polymorphisms have been identified, where a single nucleotide may be replaced by a different one, which in turn may be translated into the synthesis of an altered protein. Various of these polymorphisms have been associated with increased vulnerability for the development of certain pathophysiological conditions, such as depression and anxiety disorders.

Regulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis is known to be regulated by direct or indirect effects of different limbic structures, such as the amygdala and the hippocampus, which in turn are also regulated by projections from cortical structures, including different areas of the PFC, such as the DLPFC, VMPFC, OFC and ACC, therefore constituting a complex cortico-limbic-HPA (C-L-HPA) system (Fig. 2.38). It has been shown that the

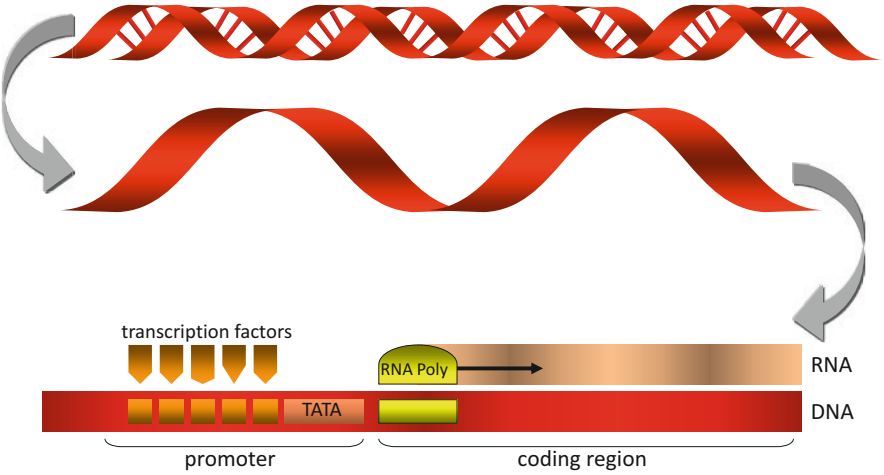

Fig. 2.37 Transcriptional regulation. Genetic information is encoded in the coding region of each gene, where the information is arranged in small sequence of three nucleotides each, constituting a codon. Each codon corresponds to a specific amino acid; therefore, the location of each codon along the genetic sequence may determine the location of each amino acid in the corresponding peptidic sequence. Gene expression depends on the presence of transcription factors, which play a critical role in the transcription of genetic messages, from specific DNA sequence into a complementary sequence of ribonucleic acid (RNA). This synthesized RNA sequence is constituted by a complementary sequence of nucleotides. This RNA sequence is necessary for carrying genetic information from the nucleus to the cytoplasm, where the genetic message may be translated from RNA into the synthesis of a peptidic product, including shorter oligopeptides and longer proteins. Transcription factors interact with specific DNA sequences, known as consensus sites, in the promoter region, located upstream of the coding region. Binding of transcription factors to their specific consensus sites may lead to transcriptional regulation, which may be translated into the activation or the inhibition of gene expression

amygdala provokes stimulatory effects on the HPA axis, through input from the CNA to the hypothalamic PVN, or indirectly through projections from the BNST (Davis, 1992; LeDoux et al., 1988), while the hippocampus exerts inhibitory effects on the HPA axis (Herman et al., 1989; McEwen & Brinton, 1987).

The hypothalamus is a neural structure, located under the thalamus and around the third ventricle, which contributes to control basic life functions (Fig. 2.39). It is a complex structure composed by more than ten different nuclei (Fig. 2.40), involved in the control of different functions, including metabolism, reproduction, thermoregulation, arousal, wake-sleep cycles, circadian rhythms, and the regulation of autonomic, neuroendocrine, and behavioural responses to stress (Saper & Lowell, 2014). The hypothalamus may be divided in three parts. The rostral hypothalamus includes the suprachiasmatic (SXN) and the preoptic (PON) nuclei, which participate in thermoregulation, wake-sleep cycles and circadian rhythms. The middle part of the hypothalamus, also known as the tuberal hypothalamus, includes the anterior and lateral areas and the ventro-medial (VMN), dorso-medial (DMN), supraoptic (SON), paraventricular (PVN) and arcuate nuclei, which participate in the

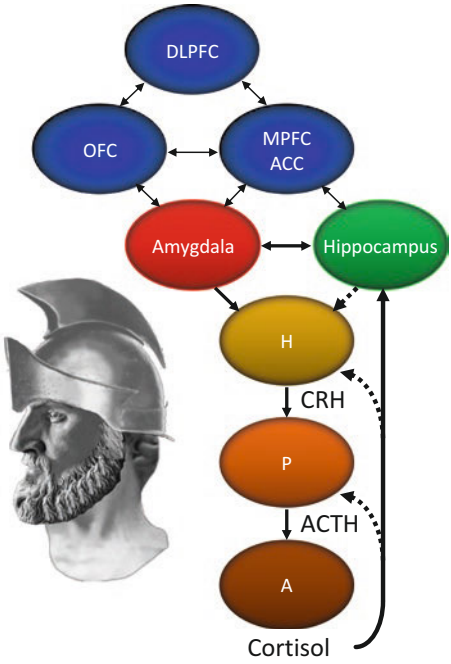

Fig. 2.38 Regulation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is regulated by limbic structures, such as the amygdala and the hippocampus, which in turn are also regulated by projections from cortical structures, including different areas of the PFC, such as the DLPFC, VMPFC, OFC and ACC, therefore constituting a complex cortico-limbic-HPA (C-L-HPA) system. The amygdala provokes stimulatory effects on the HPA axis, through input from the CNA to the hypothalamic PVN, or indirectly through projections from the BNST, while the hippocampus exerts inhibitory effects. Activation of the hypothalamic PVN may lead to the synthesis of CRF, which is released into the portal blood to reach the anterior pituitary, where it may stimulate the synthesis of ACTH, which in turn is released into the systemic blood, to reach the adrenal cortex, where it may stimulate the synthesis and release of cortisol

integration and regulation of autonomic and neuroendocrine functions. The posterior part includes the mammillary bodies and the supramammillary, tuberomammillary and posterior nuclei, which participate in arousal and wakefulness (Saper & Lowell, 2014).

The PVN contains a magnocellular group of neurosecretory neurons, which produce and release oxytocin and vasopressin, a parvocellular group of neuroendocrine neurons, which produce different peptides, such as CRF, to be released through the median eminence in the hypophyseal portal vessels to reach the anterior pituitary, where in turn they stimulate the release of different hormones, and a group of parvocellular pre-autonomic neurons, involved in the regulation of the ANS (Ferguson et al., 2008). In addition, the PVN also contains glutamatergic and GABAergic interneurons, which participate in the regulation of the main neuronal groups.

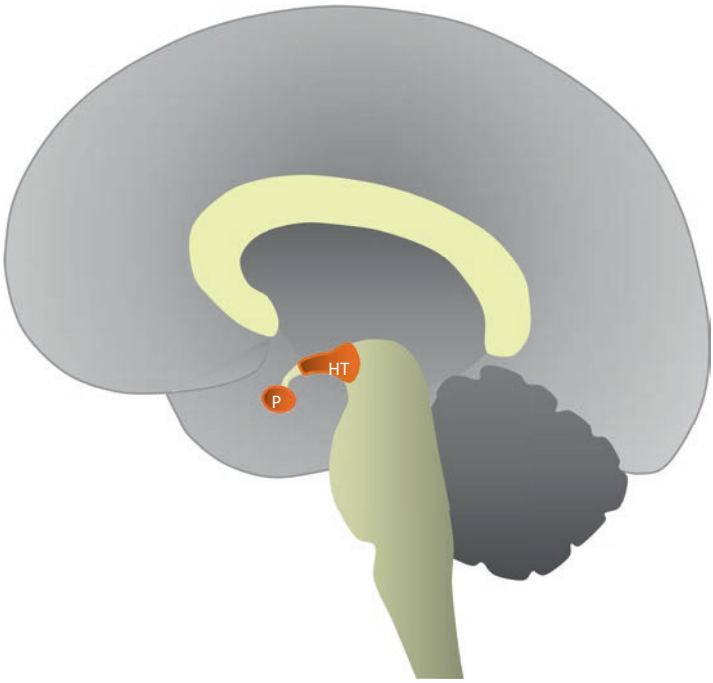

Fig. 2.39 Schematic representation of the hypothalamus in the brain. The hypothalamus (H) is located under the thalamus and around the third ventricle and connected with the pituitary (P) gland

Activating input may reach the hypothalamic PVN, where corticotropin-releasing factor (CRF, also known as corticotropin-releasing hormone, CRH) is produced by parvocellular neurons and released to the portal blood, to reach the anterior pituitary. In addition, among other hypothalamic nuclei, it has been shown that the suprachiasmatic nucleus (SCN) stimulates the PVN, to release CRF and arginine-vasopressin (AVP). These hormones may reach the anterior pituitary, also known as adenohypophysis, where they stimulate corticotroph cells. It has been shown that CRF up-regulates the transcription of the proopiomelanocortin (POMC) gene, which is a common precursor for the synthesis of the adrenocorticotropic hormone (ACTH, also known as adrenocorticotropin), β-endorphin, which is an endogenous opioid, and three similar peptides called alpha-, beta- and gamma-melanocyte-stimulating hormones. In order to stimulate POMC synthesis, CRH binds to specific receptors, which activate an AC/cAMP/PKA molecular cascade, which in turn activates transcription factors, such as the cAMP-response-element-binding-protein (CREB) (Boutillier et al., 1998). Newly synthesized ACTH may be released into the systemic blood circulation. Once ACTH reaches the adrenal cortex, it stimulates the biosynthesis and release of glucocorticoids (Arborelius et al., 1999). Cortisol is expected to exert widespread metabolic effects, necessary for the mobilization of energetic resources and maintenance of homeostasis, therefore contributing to cope with the stressful situation, more effectively and for longer.

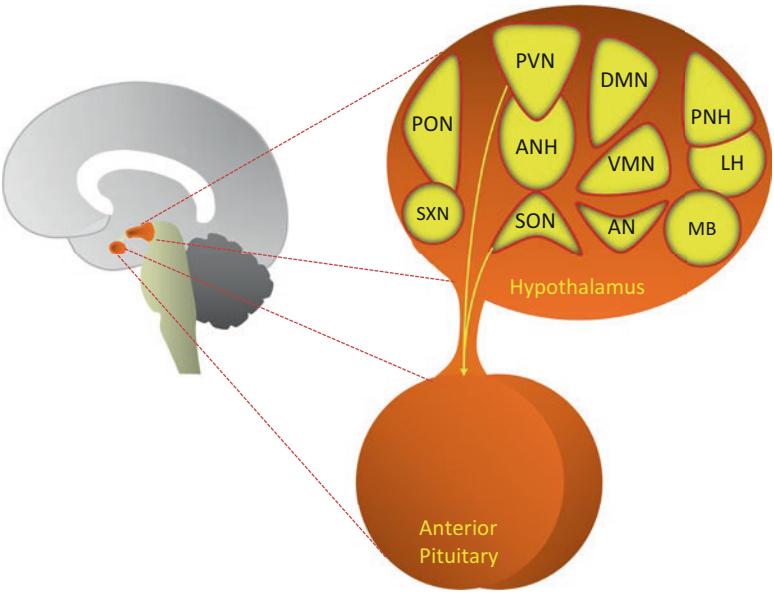

Fig. 2.40 Schematic representation of the hypothalamus and its components. The hypothalamus is a complex structure composed by more than ten different nuclei. The hypothalamus may be divided in the rostral hypothalamus, which includes the suprachiasmatic (SXN) and the preoptic (PON) nuclei, the middle part of the hypothalamus, also known as the tuberal hypothalamus, which includes the anterior and lateral areas and the ventro-medial (VMN), dorso-medial (DMN), supraoptic (SON), paraventricular (PVN) and arcuate nuclei, and the posterior part, which includes the mammillary bodies and the supramammillary, tuberomammillary and posterior nuclei

Upon exposure to stressful stimuli, the HPA axis is activated by different excitatory projections, targeting hypothalamic CRF neurons in the PVN (Herman et al., 2016). Direct mono-synaptic excitatory input involves noradrenergic projections from different nuclei located in the brainstem, mainly from the nucleus of the solitary tract (NTS) and also from the LC (Fig. 2.41). It has been shown that NA neurons in the NTS receive visceral afferent information from the sympathetic and the parasympathetic nervous system, hence allowing a rapid activation of the HPA axis in response to pathophysiological signals, associated with homeostatic challenges (Cunningham Jr & Sawchenko, 1988). In addition, the PVN may also receive direct excitatory glutamatergic projections from the NTS (Ziegler et al., 2012), as well as different excitatory neuropeptides and cytokines, from different sources, and serotonergic projections from the DRN (Herman et al., 2016) (Fig.2.41).

In response to stressful events, the HPA axis is also regulated by descending projections from different limbic structures, including the amygdala, the hippocampus and certain areas of the ACC. In this regard, although direct excitatory projections from the amygdala to the PVN have been described, mediated by CRF release from the CNA (Gray et al., 1989), activation of the HPA axis by the amygdala is mainly mediated by indirect trans-synaptic projections, implying projections from

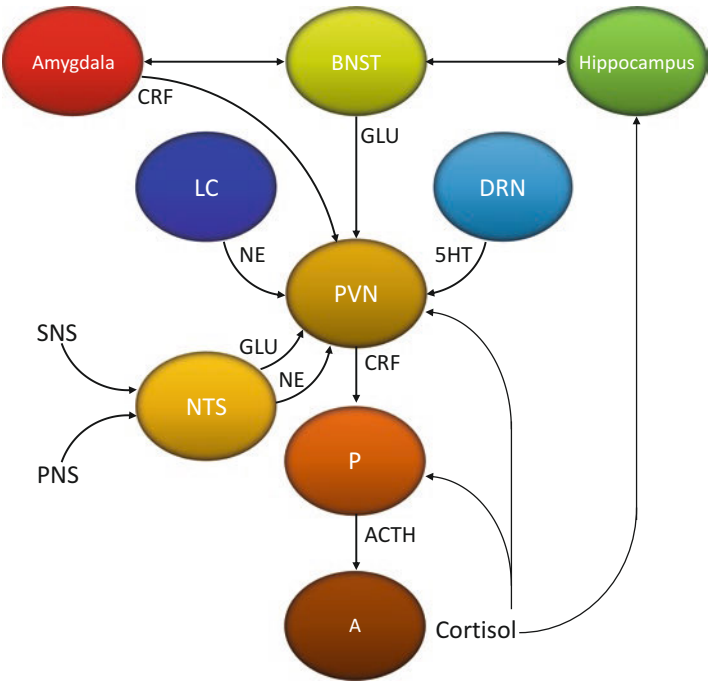

Fig. 2.41 Activation and regulation of the hypothalamic-pituitary-adrenal (HPA) axis. In response to stress, the HPA axis is activated by excitatory projections, targeting hypothalamic CRF neurons in the PVN, including excitatory noradrenergic (NA) projections from different nuclei located in the brainstem, including the nucleus of the solitary tract (NTS) and the locus coeruleus (LC). NA neurons in the NTS receive sympathetic and parasympathetic projections. The PVN may also receive excitatory glutamatergic projections from the NTS and serotonergic projections from the DRN. The HPA axis is also regulated by descending projections from the amygdala, the hippocampus and certain areas of the ACC. Although direct excitatory projections from the amygdala to the PVN have been described, mediated by CRF, activation of the HPA axis by the amygdala is mainly mediated by projections from amygdala to the BNST, which in turn sends excitatory projections to the hypothalamic PVN. After activation of the HPA axis, inhibition of the hypothalamic PVN, with the resulting decrease in CRF synthesis and release, is followed by a rapid down-regulation of ACTH in the pituitary, which in turn provokes a gradual decrease in the synthesis and release of glucocorticoids. These inhibitory effects are mediated by negative feedback mechanisms, where increased concentrations of glucocorticoids may lead to decreased synthesis and release of CRF and ACTH. In addition, inhibitory GABAergic neurons in the BNST receive excitatory glutamatergic projections from the hippocampus, as well as certain areas of the VM-PFC. Therefore, the inhibitory effect on the HPA axis by the hippocampus is mainly mediated by indirect projections, implying stimulatory projections from the hippocampus, through the subiculum, to GABAergic neurons in the BNST, which in turn send inhibitory projections to the hypothalamic PVN

amygdala to the BNST, which in turn sends excitatory projections to the hypothalamic PVN (Ulrich-Lai & Herman, 2009) (Fig. 2.41). In addition, it has been shown that GABAergic neurons located in a surrounding area next to the PVN, in the peri-PVN area, exert tonic inhibitory effect on CRF neurons in the PVN. Hence, it is likely that the stimulatory effect of the amygdala on the HPA axis, which is known

to occur in response to stressful stimuli, may be mediated by inhibitory GABAergic projections from the CNA to GABAergic neurons in the peri-PVN, therefore provoking a disinhibitory effect on CRF neurons in the PVN, with the resulting activation of the HPA axis (Herman et al., 2003; Ulrich-Lai & Herman, 2009).

Limitation of the HPA axis activity is necessary to regulate glucocorticoid synthesis and release, with their consequent effects. Hence, after activation of the HPA axis, in response to stressful situations, inhibition of the hypothalamic PVN, with the resulting decrease in CRF synthesis and release, is followed by a rapid down-regulation of ACTH in the pituitary, which in turn provokes a gradual decrease in the synthesis and release of glucocorticoids.

These inhibitory effects are mediated principally by different negative feedback mechanisms, where increased concentrations of glucocorticoids, produced by increased activation of the HPA axis, may lead to decreased synthesis and release of CRF and ACTH. In addition, CRF neurons in the PVN may be also regulated by inhibitory GABAergic projections from the peri-PVN area, from other hypothalamic nuclei, including the PON and the DMN, and from other neural structures, such as the BNST. In this regard, inhibitory GABAergic neurons in the BNST receive excitatory glutamatergic projections from the hippocampus, as well as certain areas of the VM-PFC (Herman et al., 2016). Therefore, the inhibitory effect on the HPA axis by the hippocampus is mainly mediated by indirect trans-synaptic projections, implying stimulatory projections from the ventral hippocampus, through the ventral subiculum, to specific GABAergic neurons in the BNST, which in turn send inhibitory projections to the hypothalamic PVN (Cullinan et al., 1993; Herman et al., 2016).

Molecular Biology of the HPA Axis: The Role of the CRF System

Corticotropin-releasing factor (CRF, also termed corticotropin-releasing hormone, CRH) is a 41 amino acid containing polypeptide, usually synthesized and released in the hypothalamic PVN, where it plays a critical role in the regulation of the HPA axis, and certain nuclei of the extended amygdala, such as the lateral and medial sub-nuclei of the CNA and the lateral division of the BNST. The molecular effects of CRF are mediated by two G-protein-coupled-specific receptors, known as CRF-R1 and CRF-R2, each of them constituted by seven transmembrane domains, and predominantly associated with a Gs protein, which in turn is involved in the activation of AC, with the consequent synthesis of cAMP (Bale & Vale, 2004) (Fig. 2.42).

There are CRF-containing circuits in the CNS, which have been associated with the coordination of the stress response, both as a neuroendocrine factor, through its role in the regulation of the HPA axis, and through its function as a neurotransmitter, participating in behavioural, immune and autonomic responses to stress (Nemeroff, 2004). In this regard, CRF-containing neurons have been identified throughout different neural structures, such as the amygdala and the BNST, where it plays an important role in the regulation of emotional responses (Arborelius et al., 1999). In this regard, CRF projections from the CNA to the BNST and the hypothalamic PVN

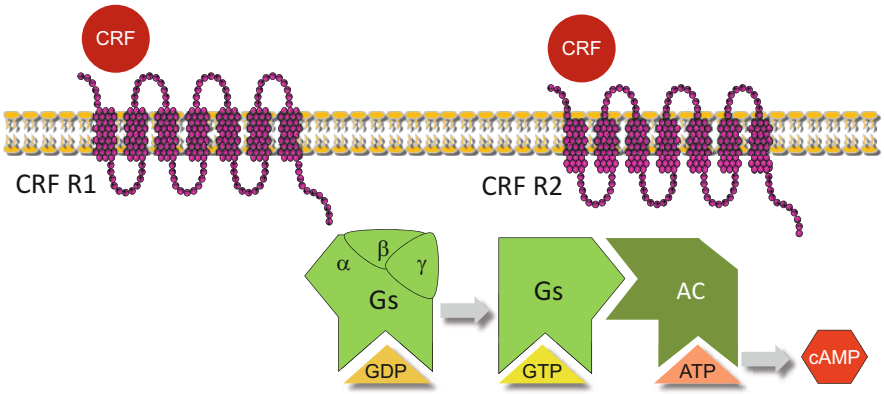

Fig. 2.42 CRF receptors and their molecular cascades. Corticotropin-releasing factor (CRF, also termed corticotropin-releasing hormone, CRH) is a polypeptide, usually synthesized and released in the hypothalamic PVN, where it plays a critical role in the regulation of the HPA axis, and certain nuclei of the extended amygdala, such as the lateral and medial sub-nuclei of the CNA and the lateral division of the BNST. The molecular effects of CRF are mediated by two G-protein coupled specific receptors, known as CRF-R1 and CRF-R2, each of them associated with a Gs protein, which in turn is involved in the activation of AC, with the consequent synthesis of cAMP

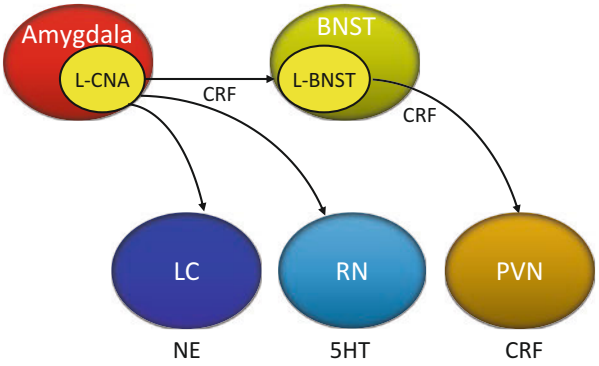

Fig. 2.43 CRF projections from the extended amygdala. Corticotropin-releasing factor (CRF) projections from the central nucleus of the amygdala (CNA) to the BNST and the hypothalamic PVN have been identified, which participate in the activation of the HPA axis in response to stress, and to the monoaminergic nuclei in the brainstem, including the LC and the RN. Therefore, CRF stimulates NA release in the LC, with the consequent noradrenergic activation of the ANS and the HPA axis while mainly inhibits 5HT neurons in the RN, which in turn may affect other structures, through serotonergic projections to the amygdala, hippocampus and PVN. Through regulatory effects on these monoaminergic systems, CRF participates in neurobiological processes underlying mood and anxiety disorders, mostly associated with anxiogenic and depressogenic effects

have been identified, which participate in the activation of the HPA axis in response to stress, and to the monoaminergic nuclei in the brainstem, including the LC and the RN (Heim & Nemeroff, 2001) (Fig. 2.43). Therefore, CRF stimulates NA

release in the LC (Valentino et al., 1993), with the consequent noradrenergic activation of the ANS and the HPA axis, while mainly inhibits 5HT neurons in the RN (Kirby et al., 2000), which in turn may affect other structures, through serotonergic projections to the amygdala, hippocampus and PVN (Heim & Nemeroff, 2001). Hence, through regulatory effects on these monoaminergic systems, CRF participates in neurobiological processes underlying mood and anxiety disorders, mostly associated with anxiogenic and depressogenic effects (Nemeroff, 2004). In addition, CRF may also be involved in anxiety and the encoding of emotional memories (Nemeroff, 2004), playing a critical role in the stress response, not only during adulthood but also mediating the long-lasting effects of trauma and other early life stressful experiences. Moreover, increased levels of CRF may be also involved in neuroplastic changes induced by chronic stress (Regev & Baram, 2014), and this effect may be also enhanced by glucocorticoids, as a component of the stress response (Timmermans et al., 2013).

The role of CRF in the regulation of the HPA axis starts when it is released from CRF neurons in the PVN. After reaching the anterior pituitary, CRF binds to CRF-R1, which activates AC, with the consequent synthesis of cAMP, which in turn activates a molecular cascade mediated by PKA (Fig. 2.42). Activation of the CRF/CRF-R1/AC/cAMP/PKA molecular pathway may lead to enhanced transcription of the POMC gene, with the consequent synthesis of ACTH (Boutillier et al., 1998), which is released into the bloodstream to reach the adrenal cortex. At the adrenal cortex, ACTH binds to melanocortin 2 receptors (MC2R), which also activates AC, with the consequent synthesis of cAMP, which in turn stimulates biosynthesis of cholesterol, the common precursor of steroid hormones, including glucocorticoids.

Molecular Biology of the HPA Axis: The Role of Cortisol and Its Receptors

Cortisol is a glucocorticoid hormone involved in the mobilization of energetic resources, including the capacity to elicit gluconeogenesis to maintain adequate glucose concentrations, necessary to keep homeostatic equilibrium and to implement successful responses to stress. This steroid hormone is synthesized from cholesterol through an enzymatic process termed steroidogenesis and released to the bloodstream by the adrenal cortex. Cortisol is released according to a circadian rhythm, with morning zeniths and evening nadirs, which in turn may be affected by physiopathological changes, particularly in response to stressful situations. In this regard, chronic stress has been associated with increased synthesis and release of cortisol and alteration of the characteristic circadian rhythm, reflected through increased levels of cortisol during the evening and mild changes in the morning (Chrousos & Gold, 1998; Tafet & Bernardini, 2003).

At the molecular level, cortisol binds to specific cytoplasmic receptors, including mineralocorticoid receptors (MRs or type I) and glucocorticoid receptors (GRs or type II) (Evans, 1988; Truss & Beato, 1993) (Fig. 2.44). Both MRs and GRs are members of the nuclear receptor family of ligand-gated transcription factors. The MR expresses higher binding affinity to glucocorticoids, in comparison to the GR,

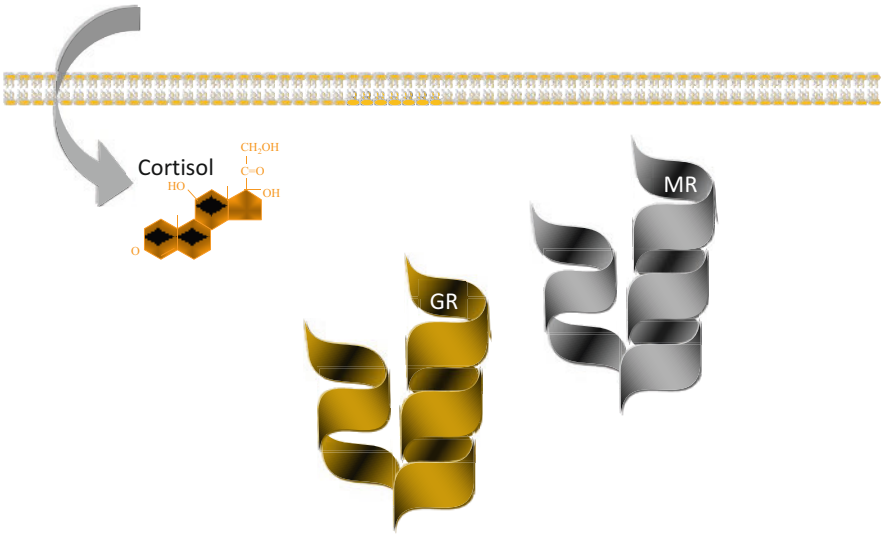

Fig. 2.44 Cortisol and its receptors. Cortisol is a glucocorticoid hormone. At the molecular level, cortisol binds to specific cytoplasmic receptors, including mineralocorticoid receptors (MRs or type I) and glucocorticoid receptors (GRs or type II). Both MRs and GRs are members of the nuclear receptor family of ligand-gated transcription factors. The MR expresses higher binding affinity to glucocorticoids, in comparison to the GR. Higher concentrations of glucocorticoids, such as the observed during stressful situations, may lead to increased binding and activation of GRs

and participates in the regulation of circadian rhythms and the HPA axis activity. Higher concentrations of glucocorticoids, such as the observed in response to stressful situations, may lead to increased binding and activation of GRs.

The GR is a protein containing three functional domains: an N-terminal transactivation domain, a central DNA binding domain and a C-terminal ligand-binding domain (Carlsted-Duke et al., 1987). In the absence of the ligand, GR is principally located in the cytoplasm, where it may be found as part of a multi-protein complex that includes chaperone molecules, such as the heat shock protein 70 (hsp70) and heat shock protein 90 (hsp90), and co-chaperones, such as the FK506-binding protein 51 (FKBP5), which participate in conformational changes of GRs, including its folding, maturation and trafficking to the nucleus and the consequent binding to specific DNA sequences, located in the promoter region of target genes (Binder, 2009). Hence, the co-chaperone FKBP5 is bound to the hsp90, which keeps bound to the GR, which, in this conformation, expresses lower affinity for cortisol. Upon binding to cortisol, the GR undergoes conformational changes, including the release of FKBP5, which is replaced by the FK506-binding protein 52 (FKBP4), which integrates dynein into the hormone-receptor complex, which in turn allows its translocation into the nucleus, with the consequent transcriptional activity (Beato, 1989; Wochnik et al., 2005) (Fig. 2.45).

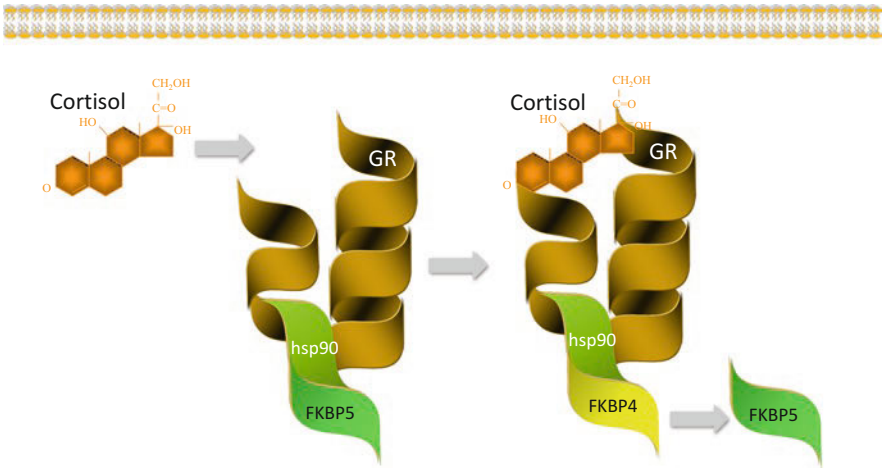

Fig. 2.45 Activation of glucocorticoid receptors (GRs). The GR is a protein containing three functional domains. In the absence of the ligand, GR is located in the cytoplasm, where it may be found as part of a multi-protein complex that includes chaperone molecules, such as the heat shock protein 70 (hsp70) and heat shock protein (hsp90), and co-chaperones, such as the FK506-binding protein 51 (FKBP5), which participates in conformational changes of GRs, including its folding, maturation and trafficking to the nucleus and the consequent binding to specific DNA sequences, located in the promoter region of target genes. The co-chaperone FKBP5 is bound to the hsp90, which keeps bound to the GR, which, in this conformation, expresses lower affinity for cortisol. Upon binding to cortisol, the GR undergoes conformational changes, including the release of FKBP5, which is replaced by the FK506-binding protein 52 (FKBP4), which integrates dynein into the hormone-receptor complex, which in turn allows its translocation into the nucleus, with the consequent transcriptional activity

In the nucleus, expression of genes may be regulated by different transcription factors, which may interact with their specific consensus sites, located in the promoter region, a DNA sequence located upstream of the coding region, which allows RNA polymerase to bind to DNA, therefore initiating transcription. Once into the nucleus, the complex GR-cortisol interacts and binds to a glucocorticoid response element (GRE), a specific nucleotide sequence located in the promoter region of different target genes (Scheidereit et al., 1986) (Fig. 2.46). The GRE constitutes a palindromic sequence containing two separated halves, therefore allowing the hormone-receptor complex to bind as a dimer, composed by two GR-cortisol units. Upon binding of a GR-cortisol complex to the GRE, the hormone-receptor complex undergoes further conformational changes, allowing the recruitment of additional co-factors at the promoter region (Holsboer, 2000), therefore leading to transcriptional regulation, translated into gene expression or repression.

Cortisol has the capacity to regulate the activity of the HPA axis, and therefore its own synthesis and release, through multiple negative feedback loops, which require binding to GRs located in the hypothalamic PVN and in the anterior pituitary, where it down-regulates the synthesis and release of CRF and ACTH, respectively (Keller-Wood & Dallmam, 1984; Dallman et al., 1985) (Fig. 2.47). It has been

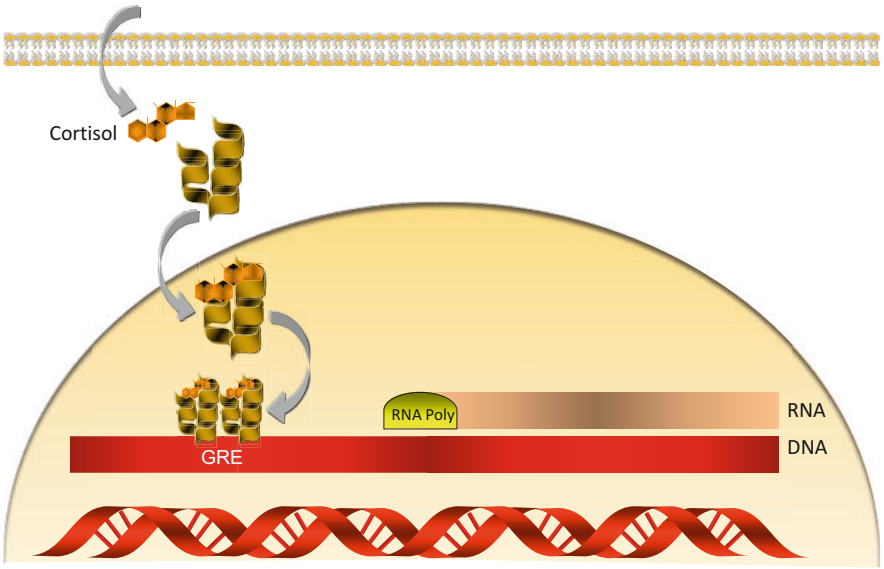

Fig. 2.46 Transcription regulation by cortisol. In the cell nucleus, the complex GR-cortisol interacts and binds to a glucocorticoid response element (GRE), a specific nucleotide sequence located in the promoter region of different target genes. The GRE constitutes a palindromic sequence which allows the hormone-receptor complex to bind as a dimer, composed by two GR-cortisol units. Upon binding of a GR-cortisol complex to the GRE, the hormone-receptor complex undergoes further conformational changes, allowing the recruitment of additional co-factors at the promoter region, therefore leading to transcriptional regulation, translated into gene expression or repression

shown that the inhibitory effect produced by GRs, translated into down-regulation of these genes, may be achieved through binding to a negative GRE (nGRE). These nGREs are composite elements, constituted by hybrid sequences, including a short sequence similar to a GRE and a short different sequence. Differing to the interactions with a GRE, where GRs may bind as dimers, GRs may bind nGREs as monomers, hence interacting with other monomers of different transcription factors. Therefore, upon binding of a GR-cortisol complex to a nGRE, this may lead to down-regulation of target genes, like in the negative regulation of the POMC gene (Drouin et al., 1993) and the CRH gene (Malkoski & Dorin, 1999). Alternatively, GRs may interfere with other transcription factors, otherwise involved in enhanced gene expression, like genes that contain an activator protein 1 (AP-1) binding site in their promoter regions (Pfahl, 1993). Therefore, several of the known effects of cortisol may be explained as a result of transcriptional regulation of different genes, including those involved in the negative feedback loops responsible for the regulation of the HPA axis (Holsboer, 2000). In addition, cortisol binds to GRs in the hippocampus, where it activates a regulatory process involving projections form the subiculum to certain GABAergic neurons in the BNST, which in turn send

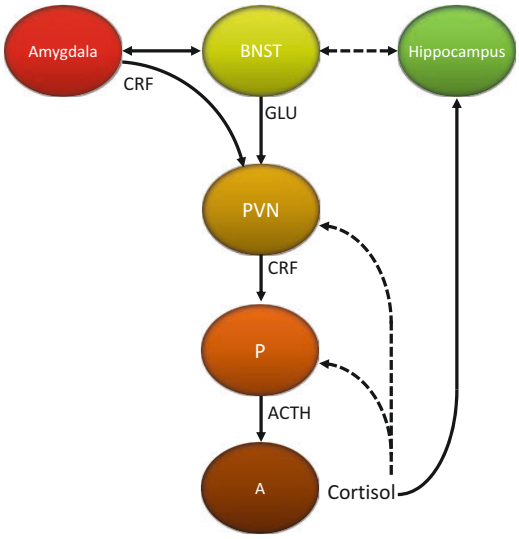

Fig. 2.47 Activation and regulation of the HPA axis by cortisol. Cortisol has the capacity to regulate the activity of the HPA axis, and therefore its own synthesis and release, through multiple negative feedback loops, which require binding to GRs located in the hypothalamic PVN and in the anterior pituitary, where it down-regulates the synthesis and release of CRF and ACTH, respectively. The inhibitory effect produced by GRs, translated into down-regulation of these genes, may be achieved through binding to a negative GRE (nGRE), constituted by a short sequence similar to a GRE and a short different sequence. Differing to the interactions with a GRE, where GRs may bind as dimers, GRs may bind nGREs as monomers, hence interacting with other monomers of different transcription factors. Upon binding of a GR-cortisol complex to a nGRE, this may lead to down-regulation of target genes, like in the negative regulation of the POMC gene and the CRH gene. In addition, cortisol binds to GRs in the hippocampus, where it activates a regulatory process involving projections from the subiculum to certain GABAergic neurons in the BNST, which in turn send inhibitory projections to the hypothalamic PVN, therefore providing an additional negative feedback mechanism in the regulation of the HPA axis. Chronic and persistent activation of the HPA system may lead to altered physiological mechanisms, including the abolition of negative feedback loops, resulting in persistent activation of the system. Circadian rhythms characterized by morning zeniths and evening nadirs are altered during chronic stress, with the consequent increase in plasma cortisol levels and blunted circadian rhythm, mostly due to increased levels of cortisol during the evening and mild changes in the morning. Therefore, sustained and prolonged exposure to stressful events may lead to dysregulation of the HPA axis, with the resulting hypercortisolism, which in turn plays a critical role in the interface between chronic stress and the origin and development of depression

inhibitory projections to the hypothalamic PVN, therefore providing an additional negative feedback mechanism in the regulation of the HPA axis.

Chronic and persistent activation of the HPA system may lead to altered physiological mechanisms, including the abolition of the aforementioned negative feedback loops, resulting in persistent activation of the system (Chrousos & Gold, 1998). Circadian rhythms normally characterized by wide variations, with morning zeniths and evening nadirs, are clearly altered during chronic stress, with the consequent

increase in plasma cortisol levels and blunted circadian rhythm, mostly due to increased levels of cortisol during the evening and mild changes in the morning.

Prolonged exposure to increased levels of cortisol may lead to harmful effects on hippocampal neurons, reducing dendritic branching and inhibiting hippocampal neuroplasticity and neurogenesis (Krugers et al, 2010). Moreover, increased levels of CRF and cortisol were also associated with reduced hippocampal volume, particularly in subjects with a history of childhood trauma. Since the hippocampus has been shown to be involved in the regulation of the HPA axis, it is possible that subjects with a history of early life trauma and depression, with reduced hippocampal volume, may also have reduced hippocampal function, therefore resulting in further sensitization of stress responses. This notion is in line with previous studies that also associated reduced expression of GRs in hypothalamus and hippocampus, with the resulting increased levels of cortisol, with the origin and development of disorders associated with the effects of chronic stress, such as depression (Chrousos & Gold, 1998; Baumeister et al., 2014). Therefore, sustained and prolonged exposure to stressful events may lead to dysregulation of the HPA axis, with the resulting hypercortisolism, which in turn plays a critical role in the interface between chronic stress and the origin and development of depression.

In conclusion, stressful life events may lead to adaptive responses, mediated by the activation of physiological, cognitive emotional and behavioural processes, which in turn are mediated by different neural pathways, mainly integrated in the CNS, and translated into the activation of the ANS and the HPA axis. These processes may be accomplished through the continuous interactions between environmental input and physiological output, cognitive processing, with the resulting appraisal and coping, emotional processing, with the consequent feelings that motivate behavioural responses, and all the underlying biological and molecular mechanisms involved in these processes. Therefore, successful adaptive responses to stress may lead to the development of resilience and the acquisition of resources aimed at improving health conditions while cultivating better quality of life. Failure to implement adaptive responses, associated with exposure to chronic stress, or overwhelming stressful conditions, may lead to traumatic experiences, which in turn may lead to increased vulnerability, associated with chronic stressful conditions, early traumatic experiences and the interactions with different biological and psychological factors of vulnerability.

References

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2002). *Molecular biology of the cell* (4th ed.). Garland Science. The Structure and Function of DNA.

Alenina, N., & Klempin, F. (2015). The role of serotonin in adult hippocampal neurogenesis. *Behavioural Brain Research, 277*, 49–57.

Alheid, G. F., & Heimer, L. (1988). New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: The striatopallidal, amygdaloid, and corticopetal components of substantia innominata. *Neuroscience, 27*, 1–39.

Amaral, D. G., & Price, J. L. (1984). Amygdalo-cortical projections in the monkey (Macaca fascicularis). *The Journal of Comparative Neurology, 230*, 465–496.

Arborelius, L., Owens, M. J., Plotsky, P. M., et al. (1999). The role of corticotropin-releasing factor in depression and anxiety disorders. *The Journal of Endocrinology, 160*, 1–12.

Baddeley, A. (1998). Recent developments in working memory. *Current Opinion in Neurobiology, 8*(2), 234–238.

Baddeley, A., & Petrides, M. (1996). Specialized systems for the processing of mnemonic information within the primate frontal cortex – Discussion. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences, 351*(1346), 1461–1462.

Bale, T. L., & Vale, W. W. (2004). CRF and CRF receptors: Role in stress responsivity and other behaviors. *Annual Review of Pharmacology and Toxicology, 44*, 525–557.

Barbas, H. (2000). Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Brain Research Bulletin, 52*, 319–330.

Barbas, H. (2007). Specialized elements of orbitofrontal cortex in primates. *Annals of the New York Academy of Sciences, 1121*, 10–32.

Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. *Cortex, 49*(5), 1195–1205.

Baumeister, D., Lightman, S. L., & Pariante, C. M. (2014). The interface of stress and the HPA axis in behavioural phenotypes of mental illness. *Current Topics in Behavioral Neurosciences, 18*, 13–24.

Beato, M. (1989). Gene regulation by steroid hormones. *Cell, 56*, 335–344.

Binder, E. B. (2009). The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology, 34*(Suppl 1), S186–S195.

Bogdan, R., Nikolova, Y. S., & Pizzagalli, D. A. (2013). Neurogenetics of depression: A focus on reward processing and stress sensitivity. *Neurobiology of Disease, 52*, 12–23.

Boutillier, A. L., Gaiddon, C., Lorang, D., Roberts, J. L., & Loeffler, J. P. (1998). Transcriptional activation of the proopiomelanocortin gene by cyclic AMP-responsive element binding protein. *Pituitary, 1*(1), 33–43.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences, 4*, 215–222.

Cabib, S., & Puglisi-Allegra, S. (2012). The mesoaccumbens dopamine in coping with stress. *Neuroscience and Biobehavioral Reviews, 36*, 79–89.

Carlsted-Duke, J., Strömstedt, P. E., Wrange, Ö., Bergman, T., Gustafsson, J. A., & Jörnvall, H. (1987). Domain structure of the glucocorticoid receptor protein. *Proceedings of the National Academy of Sciences of the United States of America, 84*, 4437–4440.

Carmichael, S. T., & Price, J. L. (1995). Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *The Journal of Comparative Neurology, 363*, 615–641.

Carmichael, S. T., & Price, J. L. (1996). Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *The Journal of Comparative Neurology, 371*, 179–207.

Cenquizca, L. A., & Swanson, L. W. (2007). Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. *Brain Research Reviews, 56*(1), 1–26.

Choi, D. C., Furay, A. R., Evanson, N. K., Ostrander, M. M., Ulrich-Lai, Y. M., & Herman, J. P. (2007). Bed nucleus of the stria terminalis subregions differentially regulate hypothalamic-pituitary-adrenal axis activity: Implications for the integration of limbic inputs. *The Journal of Neuroscience, 27*(8), 2025–2034.

Chrousos, G. P., & Gold, P. W. (1992). The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *Journal of the American Medical Association, 267*(9), 1244–1252.

Chrousos, G. P., & Gold, P. W. (1998). A healthy body in a healthy mind- and vice versa—The damaging power of uncontrollable stress. *Journal of Clinical Endocrinology and Metabolism, 83*, 1842–1845.

Cullinan, W. E., Herman, J. P., & Watson, S. J. (1993). Ventral subicular interaction with the hypothalamic paraventricular nucleus: Evidence for a relay in the bed nucleus of the stria terminalis. *The Journal of Comparative Neurology, 332*, 1–20.

Cunningham, E. T., Jr., & Sawchenko, P. E. (1988). Anatomical specificity of noradrenergic inputs to the paraventricular and supraoptic nuclei of the rat hypothalamus. *The Journal of Comparative Neurology, 274*, 60–76.

Dallman, M. F., Makara, G. B., Roberts, J. L., Levin, N., & Blum, M. (1985). Corticotropin response to removal of releasing factors and corticosteroids in vivo. *Endocrinology, 117*, 2190–2197.

Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience, 15*, 353–375.

Deakin, J. F. W., & Graeff, F. G. (1991). 5 HT and mechanisms of defense. *Journal of Psychopharmacology, 5*, 305–315.

Der-Avakian, A., & Markou, A. (2012). The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences, 35*, 68–77.

Dixon, M. L., Thiruchselvam, R., Todd, R., & Christoff, K. (2017). Emotion and the prefrontal cortex: An integrative review. *Psychological Bulletin, 143*(10), 1033–1081.

Dong, H. W., & Swanson, L. W. (2006). Projections from bed nuclei of the stria terminalis, anteromedial area: Cerebral hemisphere integration of neuroendocrine, autonomic, and behavioral aspects of energy balance. *The Journal of Comparative Neurology, 494*, 142–178.

Drevets, W. C., Savitz, J., & Trimble, M. (2008). The subgenual anterior cingulate cortex in mood disorders. *CNS Spectrums, 13*, 663–681.

Drouin, J., Sun, Y., Chamberland, M., Gauthier, Y., De Lean, A., Nemer, M., & Schmidt, T. (1993). Novel glucocorticoid receptor complex with DNA element of the hormone-repressed POMC gene. *EMBO Journal, 12*(1), 145–156.

Duman, R. S. (2004). Role of neurotrophic factors in the etiology and treatment of mood disorders. *Neuromolecular Medicine, 5*, 11–25.

Duman, R. S., & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biological Psychiatry, 59*(12), 1116–1127.

Dunlop, B. W., & Nemeroff, C. B. (2007). The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry, 64*, 327–337.

Eichenbaum, H., & Lipton, P. A. (2008). Towards a functional organization of the medial temporal lobe memory system: Role of the parahippocampal and medial entorhinal cortical areas. *Hippocampus, 18*(12), 1314–1324.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences, 15*, 85–93.

Evans, R. M. (1988). The steroid and thyroid hormone receptor superfamily. *Science, 240*(4854), 889–895.

Fanselow, M. S., & Dong, H. W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron, 65*(1), 7–19.

Ferguson, A. V., Latchford, K. J., & Samson, W. K. (2008). The paraventricular nucleus of the hypothalamus - a potential target for integrative treatment of autonomic dysfunction. *Expert Opinion on Therapeutic Targets, 12*(6), 717–727.

Ferry, B., & McGaugh, J. L. (2000). Role of amygdala norepinephrine in mediating stress hormone regulation of memory storage. *Acta Pharmacologica Sinica, 21*(6), 481–493.

Franklin, T. B., Saab, B. J., & Mansuy, I. M. (2012). Neural mechanisms of stress resilience and vulnerability. *Neuron, 75*(5), 747–761.

Garcia-Garcia, A. L., Newman-Tancredi, A., & Leonardo, E. D. (2014). 5-HT(1A) receptors in mood and anxiety: Recent insights into autoreceptor versus heteroreceptor function. *Psychopharmacology, 231*(4), 623–636.

Ghashghaei, H. T., Hilgetag, C. C., & Barbas, H. (2007). Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *NeuroImage, 34*(3), 905–923.

Goel, V., & Dolan, R. J. (2001). The functional anatomy of humor: Segregating cognitive and affective components. *Nature Neuroscience, 4*(3), 237–238.

Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron, 14*(3), 477–485.

Grabenhorst, F., & Rolls, E. T. (2011). Value, pleasure and choice in the ventral prefrontal cortex. *Trends in Cognitive Sciences, 15*(2), 56–67.

Gray, T. S., Carney, M. E., & Magnuson, D. J. (1989). Direct projections from the central amygdaloid nucleus to the hypothalamic paraventricular nucleus: Possible role in stress-induced adrenocorticotropin release. *Neuroendocrinology, 50*, 433–446.

Gray, N. A., Milak, M. S., DeLorenzo, C., et al. (2013). Antidepressant treatment reduces serotonin-1A autoreceptor binding in major depressive disorder. *Biological Psychiatry, 74*, 26–31.

Hamon, M., & Blier, P. (2013). Monoamine neurocircuitry in depression and strategies for new treatments. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 45*, 54–63.

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry, 49*, 1023–1039.

Hensler, J. G. (2006). Serotonergic modulation of the limbic system. *Neuroscience and Biobehavioral Reviews, 30*, 203–214.

Herman, J. P., Figueiredo, H., Mueller, N. K., Ulrich-Lai, Y., Ostrander, M. M., Choi, D. C., & Cullinan, W. E. (2003). Central mechanisms of stress integration: Hierarchical circuitry controlling hypothalamo-pituitaryadrenocortical responsiveness. *Frontiers in Neuroendocrinology, 24*, 151–180.

Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., & Myers, B. (2016). Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Comprehensive Physiology, 6*(2), 603–621.

Herman, J. P., Schaffer, M. K.-H., Young, E. A., Thompson, R., Douglass, J., Akil, H., & Watson, S. J. (1989). Evidence of hippocampal regulation of neuroendocrine neurons of the hippothalamo –pituitary–adrenocortical axis. *The Journal of Neuroscience, 9*, 3072–3082.

Hiser, J., & Koenigs, M. (2018). The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. *Biological Psychiatry, 83*(8), 638–647.

Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology, 23*, 477–501.

Hoover, W. B., & Vertes, R. P. (2007). Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. *Brain Structure and Function, 212*(2), 149–179.

Jacobs, B. L., van Praag, H., & Gage, F. H. (2000). Adult brain neurogenesis and psychiatry: A novel theory of depression. *Molecular Psychiatry, 5*, 262–269.

Keller-Wood, M. E., & Dallmam, M. F. (1984). Corticosteroid inhibition of ACTH secretion. *Endocrine Reviews, 5*, 1–24.

Kirby, L. G., Rice, K. C., & Valentino, R. J. (2000). Effects of corticotropin-releasing factor on neuronal activity in the serotonergic dorsal raphe nucleus. *Neuropsychopharmacology, 22*, 148–162.

Knierim, J. J. (2015). The hippocampus. *Current Biology, 25*(23), R1116–R1121.

Koenigs, M., & Grafman, J. (2009). The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural Brain Research, 201*(2), 239–243.

Kranz, G. S., Kasper, S., & Lanzenberger, R. (2010). Reward and the serotonergic system. *Neuroscience, 166*, 1023–1035.

Krishnan, V., & Nestler, E. J. (2010). Linking molecules to mood: New insight into the biology of depression. *The American Journal of Psychiatry, 167*, 1305–1320.

Krugers, H. J., Lucassen, P. J., Karst, H., & Joëls, M. (2010). Chronic stress effects on hippocampal structure and synaptic function: Relevance for depression and normalization by antiglucocorticoid treatment. *Frontiers in Synaptic Neuroscience, 2*, 24.

LeDoux, J. E., Iwata, J., Cicchetti, P., & Reis, D. J. (1988). Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *The Journal of Neuroscience, 8*(7), 2517–2529.

LeDoux, J. E. (1992). Brain mechanisms of emotion and emotional learning. *Current Opinion in Neurobiology, 2*, 191–197.

LeDoux, J. (1998). *The emotional brain: The mysterious underpinnings of emotional life*. Simon & Schuster.

LeDoux, J. (2007). The amygdala. *Current Biology, 17*(20), R868–R874.

Lesch, K. P., & Gutknecht, L. (2004). Focus on the 5-HT1A receptor: Emerging role of a gene regulatory variant in psychopathology and pharmacogenetics. *The International Journal of Neuropsychopharmacology, 7*, 381–385.

Lesch, K. P., Bengel, D., Heils, A., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*, 1527–1531.

López, J. F., Chalmers, D. T., Little, K. Y., et al. (1998). Regulation of serotonin$_{1A}$, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: Implications for the neurobiology of depression. *Biological Psychiatry, 43*, 547–573.

López, J. F., Akil, H., & Watson, S. J. (1999). Neural circuits mediating stress. *Biological Psychiatry, 46*, 1461–1471.

Mackey, S., & Petrides, M. (2010). Quantitative demonstration of comparable architectonic areas within the ventromedial and lateral orbital frontal cortex in the human and the macaque monkey brains. *European Journal of Neuroscience, 32*, 1940–1950.

Mahar, I., Bambico, F. R., Mechawar, N., et al. (2014). Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. *Neuroscience and Biobehavioral Reviews, 38*, 173–192.

Malberg, J. E., Eisch, A. J., Nestler, E. J., & Duman, R. S. (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *Journal of Neuroscience, 20*, 9104–9110.

Malkoski, S., & Dorin, R. (1999). Composite glucocorticoid regulation at a functionally defined negative glucocorticoid response element of the human corticotropin-releasing hormone gene. *Molecular Endocrinology, 19*, 1629–1644.

Maren, S., & Fanselow, M. S. (1995). Synaptic plasticity in the basolateral amygdala induced by hippocampal formation stimulation in vivo. *The Journal of Neuroscience, 15*, 7548–7564.

Marin, P., Bécamel, C., Chaumont-Dubel, S., Vandermoere, F., Bockaert, J., & Claeysen, S. (2020). Classification and signaling characteristics of 5-HT receptors: Toward the concept of 5-HT receptosomes. In C. P. Müller & K. A. Cunningham (Eds.), *Handbook of behavioral neuroscience* (Vol. 31, pp. 91–120). Elsevier.

Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., Silva, J. A., Tekell, J. L., Martin, C. C., Lancaster, J. L., & Fox, P. T. (1999). Reciprocal limbiccortical function and negative mood: Converging PET findings in depression and normal sadness. *The American Journal of Psychiatry, 156*(5), 675–682.

McCall, J. G., Al-Hasani, R., Siuda, E. R., Hong, D. Y., Norris, A. J., Ford, C. P., & Bruchas, M. R. (2015). CRH engagement of the locus Coeruleus noradrenergic system mediates stress-induced anxiety. *Neuron, 87*(3), 605–620.

McEwen, B. S., & Brinton, R. E. (1987). Neuroendocrine aspects of adaptation. *Progress in Brain Research, 72*, 11–26.

Mitchelmore, C., & Gede, L. (2014). Brain derived neurotrophic factor: Epigenetic regulation in psychiatric disorders. *Brain Research, 1586*, 162–172.

Mongeau, R., Blier, P., & de Montigny, C. (1997). The serotonergic and noradrenergic systems of the hippocampus: Their interactions and the effects of antidepressant treatments. *Brain Research Reviews, 23*, 145–195.

Motzkin, J. C., Philippi, C. L., Wolf, R. C., et al. (2015). Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biological Psychiatry, 77*, 276–284.

Myers-Schulz, B., & Koenigs, M. (2012). Functional anatomy of ventromedial prefrontal cortex: Implications for mood and anxiety disorders. *Molecular Psychiatry, 17*(2), 132–141.

Namboodiri, V. M. K., Otis, J. M., van Heeswijk, K., Voets, E. S., Alghorazi, R. A., Rodriguez-Romaguera, J., et al. (2019). Single-cell activity tracking reveals that orbitofrontal neurons acquire and maintain a long-term memory to guide behavioral adaptation. *Nature Neuroscience, 22*, 1110–1121.

Nemeroff, C. B. (1998). Psychopharmacology of affective disorders in the 21st century. *Biological Psychiatry, 44*, 517–525.

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

Nestler, E. J., & Carlezon, W. A., Jr. (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry, 59*, 1151–1159.

Ochsner, K. N., et al. (2002). Rethinking feelings: An FMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience, 14*(8), 1215–1229.

Ochsner, K. N., et al. (2004). For better or for worse: Neural systems supporting the cognitive down- and upregulation of negative emotion. *NeuroImage, 23*(2), 483–499.

Ongür, D., Ferry, A. T., & Price, J. L. (2003). Architectonic subdivision of the human orbital and medial prefrontal cortex. *The Journal of Comparative Neurology, 460*, 425–449.

Ota, K. T., & Duman, R. S. (2013). Environmental and pharmacological modulations of cellular plasticity: Role in the pathophysiology and treatment of depression. *Neurobiology of Disease, 57*, 28–37.

Paré, D., Quirk, G. J., & Ledoux, J. E. (2004). New vistas on amygdala networks in conditioned fear. *Journal of Neurophysiology, 92*(1), 1–9.

Pare, D., & Duvarci, S. (2012). Amygdala microcircuits mediating fear expression and extinction. *Current Opinion in Neurobiology, 22*(4), 717–723.

Paul, E. D., & Chen, A. (2017). Neural circuitry of stress, fear, and anxiety: Focus on extended amygdala Corticotropin-releasing factor systems. In G. Fink (Ed.), *Stress: Neuroendocrinology and neurobiology* (Vol. 2, pp. 84–96, Ch 8). Academic Press

Pfahl, M. (1993). Nuclear receptor/AP-1 interaction. *Endocrine Reviews, 14*, 651–658.

Phillips, M. L., Ladouceur, C. D., & Drevets, W. C. (2008). A neural model of voluntary and automatic emotion regulation: Implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry, 13*(9), 829–857.

Pitkänen, A., Pikkarainen, M., Nurminen, N., & Ylinen, A. (2000). Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat. A review. *Annals of the New York Academy of Sciences, 911*, 369–391.

Price, J. L. (2006). Connections of orbital cortex. In D. H. Zald & S. L. Rauch (Eds.), *The orbitofrontal cortex* (pp. 39–55). Oxford University Press.

Price, J. L. (2007). Definition of the orbital cortex in relation to specific connections with limbic and visceral structures and other cortical regions. *Annals of the New York Academy of Sciences, 1121*, 54–71.

Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology, 35*, 192–216.

Price, J. L., & Drevets, W. C. (2012). Neural circuits underlying the pathophysiology of mood disorders. *Trends in Cognitive Sciences, 16*, 61–71.

Pruessner, J. C., Champagne, F., Meaney, M. J., & Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: A positron emission tomography study using [11C]raclopride. *The Journal of Neuroscience, 24*(11), 2825–2831.

Ray, R. D., & Zald, D. H. (2012). Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. *Neuroscience and Biobehavioral Reviews, 36*, 479–501.

Regev, L., & Baram, T. Z. (2014). Corticotropin releasing factor in neuroplasticity. *Frontiers in Neuroendocrinology, 35*, 171–179.

Ressler, K. J., & Nemeroff, C. B. (1999). Role of norepinephrine in the pathophysiology and treatment of mood disorders. *Biological Psychiatry, 46*, 1219–1233.

Ressler, K. J., & Nemeroff, C. B. (2000). Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depression and Anxiety, 12*(Suppl 1), 2–19.

Richter-Levin, G., & Akirav, I. (2000). Amygdala-hippocampus dynamic interaction in relation to memory. *Molecular Neurobiology, 22*(1–3), 11–20.

Robbins, T. W., & Everitt, B. J. (1995). Arousal systems and attention. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 703–720). The MIT Press.

Rolls, E. T. (2004). The functions of the orbitofrontal cortex. *Brain and Cognition, 55*(1), 11–29.

Rolls, E. T. (2017). The roles of the orbitofrontal cortex via the habenula in non-reward and depression, and in the responses of serotonin and dopamine neurons. *Neuroscience and Biobehavioral Reviews, 75*, 331–334.

Rolls, E. T. (2019). The cingulate cortex and limbic systems for emotion, action, and memory. *Brain Structure & Function, 224*(9), 3001–3018.

Rolls, E. T. (2019a). The cingulate cortex and limbic systems for action, emotion, and memory. In B. A. Vogt (Ed.), *Handbook of clinical neurology: Cingulate cortex* (pp. 23–37). Elsevier.

Rolls, E. T. (2019b). *The orbitofrontal cortex*. Oxford University Press.

Rolls, E. T., & Grabenhorst, F. (2008). The orbitofrontal cortex and beyond: From affect to decision-making. *Progress in Neurobiology, 86*, 216–244.

Rolls, E. T., & Xiang, J. Z. (2005). Reward-spatial view representations and learning in the primate hippocampus. *The Journal of Neuroscience, 25*(26), 6167–6174.

Rolls, E. T., Cheng, W., & Feng, J. (2020). The orbitofrontal cortex: Reward, emotion and depression. *Brain Communications, 2*(2), fcaa196.

Roy, M., Shohamy, D., & Wager, T. D. (2012). Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends in Cognitive Sciences, 16*(3), 147–156.

Rudebeck, P. H., Saunders, R. C., Prescott, A. T., Chau, L. S., & Murray, E. A. (2013). Prefrontal mechanisms of behavioral flexibility, emotion regulation and value updating. *Nature Neuroscience, 16*, 1140–1145.

Rudnick, G., & Clark, J. (1993). From synapse to vesicle: The reuptake and storage of biogenic amine neurotransmitters. *Biochimica et Biophysica Acta, 1144*(3), 249–263.

Rushworth, M. F., Kolling, N., Sallet, J., & Mars, R. B. (2012). Valuation and decision making in frontal cortex: One or many serial or parallel systems? *Current Opinion in Neurobiology, 22*, 946–955.

Sah, P., Faber, E. S., Lopez De Armentia, M., & Power, J. (2003). The amygdaloid complex: Anatomy and physiology. *Physiological Reviews, 83*(3), 803–834.

Saper, C. B., & Lowell, B. B. (2014). The hypothalamus. *Current Biology, 24*(23), R1111–R1116.

Scheidereit, C., Krauter, P., von der Ahe, D., Janich, S., Rabenau, O., Cato, A. C., Suske, G., Westphal, H. M., & Beato, M. (1986). Mechanism of gene regulation by steroid hormones. *Journal of Steroid Biochemistry, 24*(1), 19–24.

Schloss, P., & Williams, D. C. (1998). The serotonin transporter: A primary target for antidepressant drugs. *Journal of Psychopharmacology, 12*(2), 115–121.

Schoenbaum, G., Roesch, M. R., Stalnaker, T. A., & Takahashi, Y. K. (2009). A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. *Nature Reviews. Neuroscience, 10*(12), 885–892.

Šimić, G., Tkalčić, M., Vukić, V., Mulc, D., Španić, E., Šagud, M., Olucha-Bordonau, F. E., Vukšić, M., Hof, R., & P. (2021). Understanding emotions: Origins and roles of the Amygdala. *Biomolecules, 11*(6), 823.

Stevens, F. L., Hurley, R. A., & Taber, K. H. (2011). Anterior cingulate cortex: Unique role in cognition and emotion. *The Journal of Neuropsychiatry and Clinical Neurosciences, 23*(2), 121–125.

Suri, D., & Vaidya, V. A. (2013). Glucocorticoid regulation of brain-derived neurotrophic factor: Relevance to hippocampal structural and functional plasticity. *Neuroscience, 239*, 196–213.

Suridjan, I., Boileau, I., Bagby, M., et al. (2012). Dopamine response to psychosocial stress in humans and its relationship to individual differences in personality traits. *Journal of Psychiatric Research, 46*, 890–897.

Suzuki, W. A., & Eichenbaum, H. (2000). The neurophysiology of memory. *Annals of the New York Academy of Sciences, 911*, 175–191.

Tafet, G. E., & Bernardini, R. (2003). Psychoneuroendocrinological links between chronic stress and depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27*, 893–903.

Tafet, G. E., & Nemeroff, C. B. (2016). The links between stress and depression: Psychoneuroendocrinological, genetic, and environmental interactions. *The Journal of Neuropsychiatry and Clinical Neurosciences, 28*(2), 77–88.

Tafet, G. E., Toister-Achituv, M., & Shinitzky, M. (2001). Enhancement of serotonin uptake by cortisol: A possible link between stress and depression. *Cognitive, Affective, and Behavioral Neuroscience, 1*, 96–104.

Taliaz, D., Loya, A., Gersner, R., Haramati, S., Chen, A., & Zangen, A. (2011). Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor. *The Journal of Neuroscience, 31*(12), 4475–4483.

Timmermans, W., Xiong, H., Hoogenraad, C. C., et al. (2013). Stress and excitatory synapses: From health to disease. *Neuroscience, 248*, 626–636.

Truss, M., & Beato, M. (1993). Steroid hormone receptors: Interaction with deoxyribonucleic acid and transcription factors. *Endocrine Reviews, 14*(4), 459–479.

Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews. Neuroscience, 10*, 397–409.

Valentino, R. J., Foote, S. L., & Page, M. E. (1993). The locus coeruleus as a site for integrating corticotropin-releasing factor and noradrenergic mediation of stress response. *Annals of the New York Academy of Sciences, 697*, 171–187.

van Riel, E., van Gemert, N. G., Meijer, O. C., et al. (2004). Effect of early life stress on serotonin responses in the hippocampus of young adult rats. *Synapse, 53*, 11–19.

Vogt, B. A. (2009). *Cingulate neurobiology and disease*. Oxford University Press.

Walker, D. L., Miles, L. A., & Davis, M. (2009). Selective participation of the bed nucleus of the stria terminalis and CRF in sustained anxiety-like versus phasic fear-like responses. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 33*(8), 1291–1308.

Waterhouse, E. G., & Xu, B. (2009). New insights into the role of brain-derived neurotrophic factor in synaptic plasticity. *Molecular and Cellular Neurosciences, 42*(2), 81–89.

Winecoff, A., Labar, K. S., Madden, D. J., Cabeza, R., & Huettel, S. A. (2011). Cognitive and neural contributors to emotion regulation in aging. *Social Cognitive and Affective Neuroscience, 6*(2), 165–176.

Wochnik, G. M., Rüegg, J., Abel, G. A., Schmidt, U., Holsboer, F., & Rein, T. (2005). FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells. *The Journal of Biological Chemistry, 280*(6), 4609–4616.

Wu, G., Feder, A., Cohen, H., Kim, J. J., Calderon, S., Charney, D. S., & Mathé, A. A. (2013). Understanding resilience. *Frontiers in Behavioral Neuroscience, 7*, 10.

Yang, Y., & Wang, J. Z. (2017). From structure to behavior in basolateral amygdala-hippocampus circuits. *Frontiers in Neural Circuits, 11*, 86.

Ziegler, D. R., Edwards, M. R., Ulrich-Lai, Y. M., Herman, J. P., & Cullinan, W. E. (2012). Brainstem origins of glutamatergic innervation of the rat hypothalamic paraventricular nucleus. *The Journal of Comparative Neurology, 520*, 2369–2394.

Chapter 3
Psychological Approach to Stress

Adaptive responses to stress are triggered by environmental stimuli, which may be interpreted as a challenge or as a threat, to which the organism reacts with a repertoire of adaptive responses. Perceived environmental stimuli may be processed through a series of memory storages, including short-term memory, which allows the retention of a limited amount of information for a limited period of time, until it may be encoded and transferred to long-term memory, depending on its potential emotional relevance. This cognitive content may be integrated with previously learned information, therefore contributing to the development of cognitive schemas. Perceived and stored information may be retrieved and consciously processed through working memory, which participates in the encoding of new information and the retrieval of stored information, hence allowing the utilization and implementation of cognitive resources. This processing is also mediated and supported by language, which plays a critical role in the encoding and retrieval of information, allowing cognitive and emotional processing of perceived stimuli, organizing past and present experiences with expectancies about future events, integrating and shaping adaptive responses to potential stressful events. In response to stressors, cognitive appraisal integrates external information, related to perceived stimuli, with internal information related to personal characteristics and available resources. Cognitive appraisal includes a primary phase, which involves basic emotional processing, and a secondary phase, which is associated with more complex cognitive processing, and the resulting coping strategies. The lack of coping options or the subjective belief that resources are not effective to respond to stressful events may be enough to feel and behave according to this perception, therefore leading to feelings of learned helplessness, which represents a strong factor of vulnerability for the development of depression. The development and implementation of coping strategies may determine the characteristics of secondary responses, which include all the repertoire of cognitive, emotional and behavioural adaptive responses. Therefore,

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the perception of controllability plays a critical role in the implementation of adaptive responses to stress, which may determine the difference between the development of learned helplessness, which may be prevented by a process of learned controllability, and the development of resilience.

Cognitive Processing of Stress: Perception and Working Memory

Adaptive responses to stress begin with the impact of a stressor, which is basically any environmental event, including simple stimuli or complex situations, which may be perceived, or imagined. These environmental events may be interpreted as challenging or threatening stimuli, which may affect in certain way the individual psychophysiological balance, to which the organism reacts with a repertoire of adaptive responses, aimed at protecting or recovering the previous equilibrium. In order to constitute a stressor, environmental stimuli require certain intensity, which may be perceived as a signal, with certain salience and valence, necessary to arouse some kind of response. Salience represents the potential relevance of stressful stimuli, which may be translated into the activation of physiological and psychological responses, while valence represents the positive or negative experience produced by the subjective interpretation of perceived stimuli. Hence, irrelevant stimuli that do not fulfil significant criteria to be considered as a signal may be perceived as background noise, which may contribute to the general perception of the surrounding environment. In this regard, it is also important to take into consideration the potential differences between the degree and kind of reaction aroused among different individuals. Hence, sensitivity and vulnerability to different stressful events may differ among individuals, as well as different social and cultural groups, including their subjective interpretations and the resulting reactions, and the objective responses expected in a certain context. In this regard, upon exposure to similar environmental stimuli, some people may respond with negative emotions, such as anger, fear or anxiety, while others may feel more challenged and less threatened, therefore responding with neutral, or even positive, emotional reactions. In order to understand the different potential reactions, aroused among different individuals in response to similar stressful conditions, it is important to take into consideration the cognitive processing that may happen between the impact of environmental events, the personal factors involved in their perception and interpretation and the consequent emotional and behavioural responses (Fig. 3.1).

Environmental stressors are perceived by sensory organs, which in turn convey perceived information through different sensory pathways, from the external world to the CNS. Perceived environmental stimuli may be processed through a series of memory storages, starting with sensory memory, which represents a brief process through which certain features of perceived information may be retained for a short instant, a very brief time span, after the original impact finished and perceived stimuli are no longer present in the environment. Focused attention on certain details of

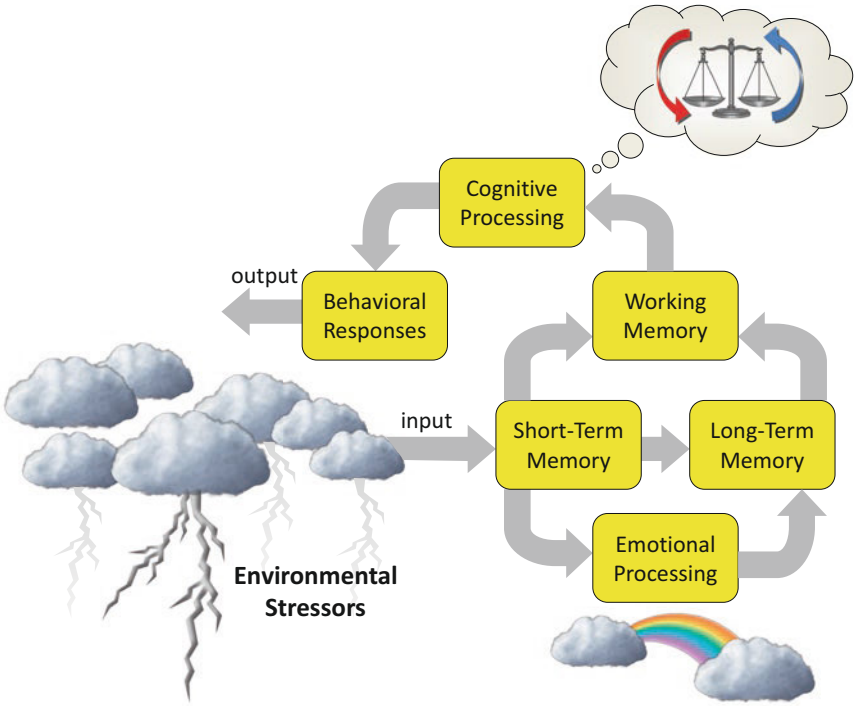

Fig. 3.1 Cognitive and emotional processing of environmental stressors. Environmental stressors may be interpreted as challenging or threatening stimuli. In order to constitute a stressor, environmental stimuli require certain intensity, with certain salience and valence, necessary to arouse some kind of response. Perceived environmental stimuli may be processed through a series of memory storages; focused attention on certain details of perceived stimuli may lead to keep information in the short-term memory, which allows the active retention of a limited amount of information, for a limited period of time, which may be kept active through continuous rehearsal, until it may be encoded and transferred to long-term memory, or eventually lost and forgotten. After brief rehearsal through short-term memory processing, these transiently stored pieces of information may be processed according to their potential relevance, which may be strongly influenced by emotional aspects. Hence, a higher salience, with a negative or positive valence, may determine the potential emotional relevance, which in turn may lead to encoding of newly acquired information in the long-term storage. Cognitive processing may allow the integration of perceived information with stored information, which may be consciously perceived and elaborated in the working memory

these perceived stimuli may lead to keep information from sensory memory to short-term memory, which represents the next step in memory processing. Hence, short-term memory allows the active retention of a limited amount of information, for a limited period of time, which may be kept active through continuous rehearsal, until it may be encoded and transferred to long-term memory, or eventually lost and forgotten. After brief rehearsal through short-term memory processing, these transiently stored pieces of information may be processed according to their potential relevance, which may be strongly influenced by emotional aspects. Hence, a higher

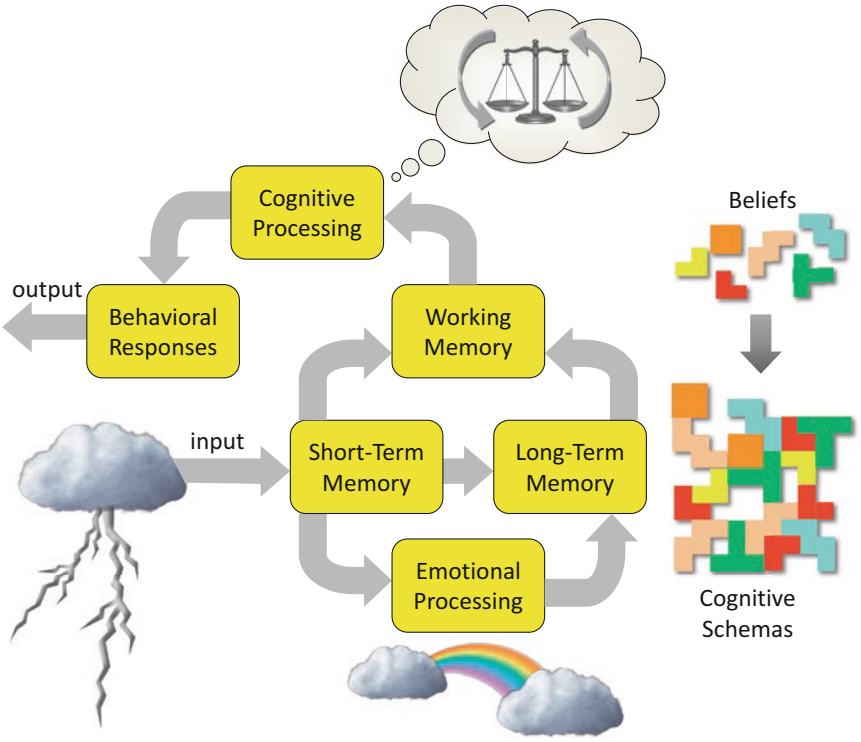

Fig. 3.2 Learning and memory in the development of cognitive schemas. Perceived information may be elaborated, held in the short-term memory for a short period and transferred to the long-term memory, according to the emotional relevance of stimuli. This cognitive content may be integrated with previously learned information, therefore transforming simple information in cognitions, capable of being accepted and learned as subjective beliefs, hence contributing to the development of more elaborated cognitive constructs, which are known as cognitive schemas

salience, with a negative or positive valence, may determine the potential emotional relevance, which in turn may lead to encoding of newly acquired information in the long-term storage. This cognitive content may be integrated with previously learned information, therefore contributing to the development of cognitive constructs, which are known as cognitive schemas (Beck, 1967) (Fig. 3.2).

Information stored in the long-term memory may be consciously retrieved, through a process of explicit memory, or unconsciously, through implicit memory. Perceived information, stored in the short-term memory, and encoded information, stored in the long-term memory, may be retrieved and consciously processed through working memory. The development of this concept provided the necessary cognitive theatre, where the newly perceived information, just stored in the short-term memory, met the previously stored information, encoded in the long-term memory, hence allowing their reciprocal integration, which may be available for conscious processing (Miller et al., 1960). Therefore, the concept of working

memory refers to the capability to transiently integrate new information, perceived from environmental or internal stimuli, with learned information, retrieved from long-term storages, to be consciously organized and utilized to serve current needs, or to achieve ongoing challenges (Baddelety & Hitch, 1974; Baddeley, 1986). Working memory has been associated with different cognitive abilities, such as analytical thinking and general intelligence (Persuh et al., 2018), which are necessary for the cognitive, emotional and behavioural components of adaptive responses to stress, including the development of coping strategies and other conscious responses. In response to stressful situations, working memory participates in the encoding of new information and the retrieval of stored information, hence allowing the utilization and implementation of cognitive resources. According to the interactions between perceived stressful events and the consequent adaptive responses, mediated by the available resources stored in long-term memory, the resulting outcomes may lead to processing and encoding of incoming information, therefore improving or modifying previously learned information, which in turn may be continuously retrieved. This processing is also mediated and supported by language comprehension, interpretation and construction, which plays a critical role in the encoding and retrieval of information. In this regard, language involves the recognition, understanding and interpretation of perceived input, which in turn, after semantic integration of perceived words, may provide certain objective and subjective meaning. Therefore, language also participates in the cognitive theatre of working memory, allowing the cognitive and emotional processing of perceived stimuli, organizing past and present experiences with expectancies about future events and integrating and shaping adaptive responses to potential stressful events (Fig. 3.3).

Cognitive Processing of Stress: Appraisal and Coping

In order to generate adequate adaptive responses, perceived sensory information should be processed through diverse neural structures, involved in different cognitive processes, which may allow each individual to discern and differentiate between positive and negative stimuli, or benign and potentially dangerous stressful events. Hence, cognitive appraisal plays a critical role in the interactions between each person and the surrounding environment, to reach successful adaptation, to survive potential threats and, if it would be possible, to develop positive emotions, such as relieve, or a sensation of well-being (Lazarus, 1984).

Cognitive appraisal is a complex evaluative process that integrates external information, related to different stimuli perceived from the environment and interpreted according to the context, with internal information related to personal characteristics, including the beliefs we developed about ourselves and about the surrounding world, our scale of values and our particular style of thinking. This concept is in line with the cognitive model (Beck, 1967), according to which, all the information we know and believe, including everything we learnt through our own experience about ourselves and our surrounding world, may be integrated and assembled, either as

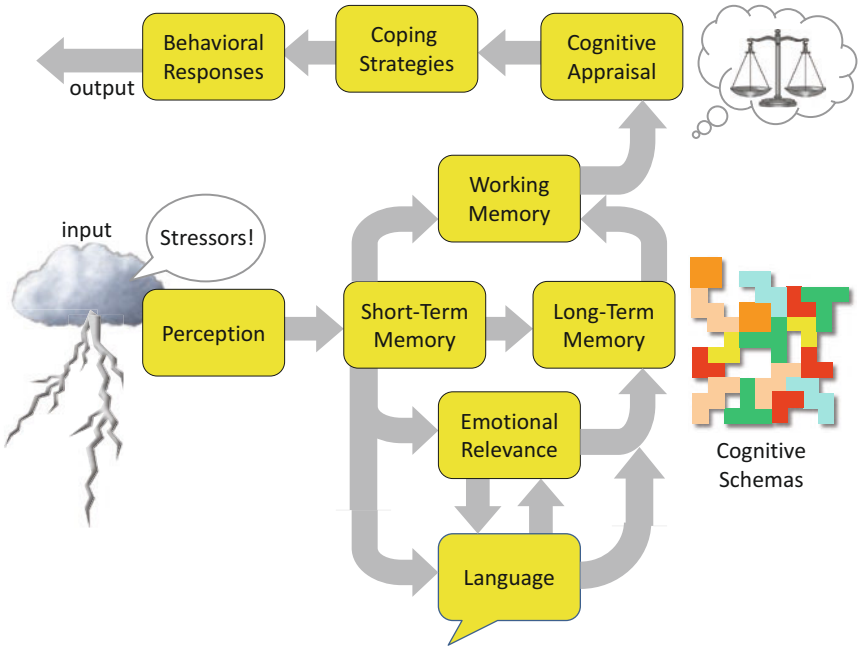

Fig. 3.3 Working memory and conscious cognitive processing. Perceived information, stored in the short-term memory, and encoded information, stored in the long-term memory, may be retrieved and consciously processed through working memory, where the newly perceived information, just stored in the short-term memory, meets the previously stored information, encoded in the long-term memory, hence allowing their reciprocal integration, which may be available for conscious processing. Working memory has been associated with different cognitive abilities, which are necessary for the cognitive, emotional and behavioural components of adaptive responses to stress, including the development of coping strategies and other conscious responses. In response to stressful situations, working memory participates in the encoding of new information and the retrieval of stored information, hence allowing the utilization and implementation of cognitive resources. According to the interactions between perceived stressful events and the consequent adaptive responses, mediated by the available resources stored in long-term memory, the resulting outcomes may lead to processing and encoding of incoming information, therefore improving or modifying previously learned information. This processing is also mediated and supported by language comprehension, interpretation and construction, which plays a critical role in the encoding and retrieval of information. Language also participates in the cognitive theatre of working memory, allowing the cognitive and emotional processing of perceived stimuli, organizing past and present experiences with expectancies about future events, integrating and shaping adaptive responses to potential stressful events

objective knowledge or as subjective beliefs, to build our cognitive schemas. This information, stored in our long-term memory, may provide the cognitive foundations to perceive, interpret and understand all the newly incoming information, which may be kept in our short-term memory. Therefore, the way we process information or, in other words, the way we think, may shape our emotional and behavioural responses. Moreover, cognitive appraisal is more than information processing, but a continuous evaluation process, focused on the particular meaning and the subjective significance of events and experiences (Lazarus & Folkman, 1984) (Fig. 3.3).

Therefore, cognitive appraisal includes a primary phase, which involves basic emotional processing, associated with survival and more basic drives, and a secondary phase, which is associated with more complex cognitive processing, and the resulting coping strategies. Primary appraisal is the necessary process to evaluate certain basic issues, including the subjective relevance of perceived stimuli, if it represents a potential source of danger, if it may cause any immediate effect or it may lead to any consequence in the far or near future, and how it may cause any potential effect. Primary appraisal is strongly influenced by subjective emotional processes, which may provide the necessary background to differentiate between relevant and irrelevant cues, with the consequent salience, the positive or negative valence of perceived stimuli, with the resulting appetitive or aversive trend we may experience in response to perceived stressful events. In this regard, primary appraisal may also include the perception and anticipation of potential harm or losses, which in turn may be associated with the perception of threat, and therefore is characterized by negative emotions, such as fear, anger and anxiety, which in turn may trigger the activation of coping efforts. Perception or anticipation of dangerous or threatening events represents undesirable situations, which may be also interpreted as unpredictable and uncontrollable, therefore constituting distressful events. On the other hand, if a stressful situation is associated with potential gains or any kind of benefit, this may be experienced as a challenge, which may be characterized by pleasurable emotions, such as excitement, eagerness and exhilaration. If these are also perceived and interpreted as predictable and controllable situations, they may be experienced as eustressful events. Both perceptions of threat and challenge are associated with the mobilization of available resources, involved in the generation of coping efforts. Therefore, a primary appraisal may lead to the subsequent activation of a primary response and a secondary appraisal (Fig. 3.4).

Primary responses are characterized by the rapid activation of physiological adaptive reactions, mediated by the successive activation of the ANS and the HPA axis. Activation of the ANS is characterized by a wide spectrum of central and peripheral sympatho-adrenergic events. At the central level, noradrenergic activation in the CNS plays a critical role to stimulate arousal and increase focused attention, necessary to improve coping functions. At the peripheral level, sympathetic activation, with the consequent increase of heart rate, blood pressure and respiratory frequency, is also required to provide the necessary energetic resources, including oxygen and glucose to different organs, for successful adaptive responses. Activation of the sympatho-adrenergic system may lead to symptoms of stress, which in turn may be also perceived as internal stressors, reinforcing the perception and interpretation of stress. Therefore, the simultaneous perception of these symptoms, strongly associated with stressful situations, alongside the perception of environmental stressors, may lead to a feedback circuit of internal and external stimuli, which in turn may be perceived and interpreted as part of an ongoing stressful experience, therefore maintaining or increasing the potential feelings of danger and threat, which are usually observed during chronic stress disorders, such as panic, generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD).

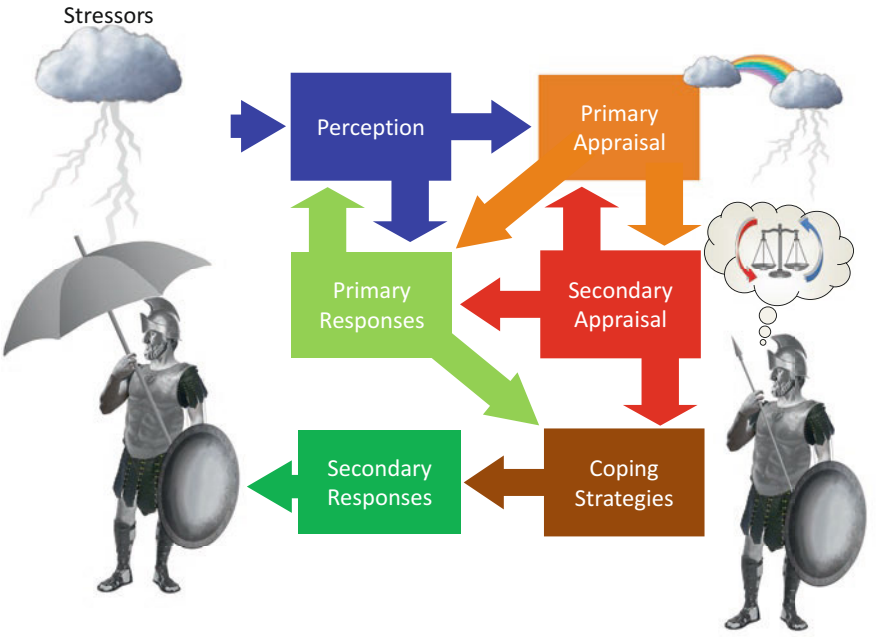

Fig. 3.4 Cognitive and emotional processing, appraisal and coping. Environmental stressors are perceived and processed through a series of stages. Primary appraisal involves the subjective relevance of perceived stimuli, if it represents a potential danger and how it may cause any potential effect. Perception or anticipation of dangerous or threatening events represents undesirable situations, which may be also interpreted as unpredictable and uncontrollable, therefore constituting distressful events. A primary appraisal may lead to the subsequent activation of a primary response and a secondary appraisal. Primary responses are characterized by the rapid activation of physiological adaptive reactions, mediated by the successive activation of the ANS and the HPA axis. Activation of the ANS may lead to symptoms of stress, which may be also perceived as internal stressors, reinforcing the perception and interpretation of stress. The perception of symptoms, associated with the perception of environmental stressors, may lead to a feedback circuit of internal and external stimuli, which may be perceived and interpreted as part of a stressful experience. A secondary appraisal represents a cognitive process involved in the evaluation of stressful situation, including perceived environmental events and the available resources to cope with them. The primary appraisal of threat or challenge and the secondary appraisal, associated with potential responses, are continuously interacting, therefore shaping the repertoire of potential coping strategies and the resulting secondary responses

Following the primary appraisal, with the consequent primary responses, it has been also described a secondary appraisal, which represents a further step in the implementation of successful responses. When we experience a stressful situation, either perceived as a threat or as a challenge, we know, and sometimes we feel and believe, that we must respond to cope with the ongoing situation. Hence, a secondary appraisal is an important cognitive process involved in a more complex evaluation of the different factors implicated in the stressful situation, including those pertaining to the perceived environmental events, usually kept in our short-term memory, the

information associated with similar events we experienced in the past, normally stored in our long-term memory, and the repertoire of available resources. In this regard, available resources include all the information we know and we learnt about similar situations, our previous experiences, and our capacity and ability to design and implement successful coping strategies. The primary appraisal of threat or challenge and the secondary appraisal, associated with perceived threat and potential responses, are continuously interacting, therefore shaping the repertoire of potential coping strategies (Fig. 3.4). The lack of coping options, or the subjective belief that our resources are not effective to respond to stressful events, may be enough to feel and behave according to this perception, therefore leading to feelings of learned helplessness, which represents a strong factor of vulnerability for the development of depression.

The development of coping represents much more than fight or flight. It is a complex cognitive process, where it is possible to identify different stages. In this regard, cognitive appraisal allows evaluating whether certain stressful events may happen, how it is expected to happen, and also takes account of contextual factors, such as when and where it may happen. In addition, secondary appraisal also allows to evaluate the available resources to cope with the potential threat and, if it would be possible, to prevent it, constituting an anticipatory stage. During this anticipation, it is possible to evaluate the potential damage of stressful events, if it would be possible to prevent the impact or, in case it would not be possible, how to improve the possibilities of a successful coping. Anticipation may also lead to improve a sense of predictability and controllability. Upon the impact of environmental stressors, it is necessary a continuous reappraisal of the characteristics of these stressors, if the impact was as harmful or threatening as it was anticipated, and if the coping strategies resulted effective or not. After every new impact, it is necessary a new reappraisal to assess what happened, its potential consequences and its subjective meaning and significance. Therefore, the development and implementation of coping strategies, together with the continuous cognitive reappraisal, may determine the characteristics of secondary responses, which include all the repertoire of cognitive, emotional and behavioural adaptive responses.

The Role of Cognitive and Emotional Resources

Cognitive appraisal may allow us to process relevant information related to environmental stimuli, including the characteristics of the stressor and their contextual variables, including the spatial situation where it takes place and the moment when it occurs. This allows the perception of stress to expand over time, so that we can anticipate an adaptive response to the extent that we can prevent a potentially stressful situation in the future. This mechanism may be highly beneficial if it generates a certain degree of arousal, which allows us to adequately prepare to cope with adversity, improving our chances of escaping, or at least minimizing the consequences of the impact. This process includes the evocation of past experiences, which may allow us to create the optimal conditions for learning from these experiences to

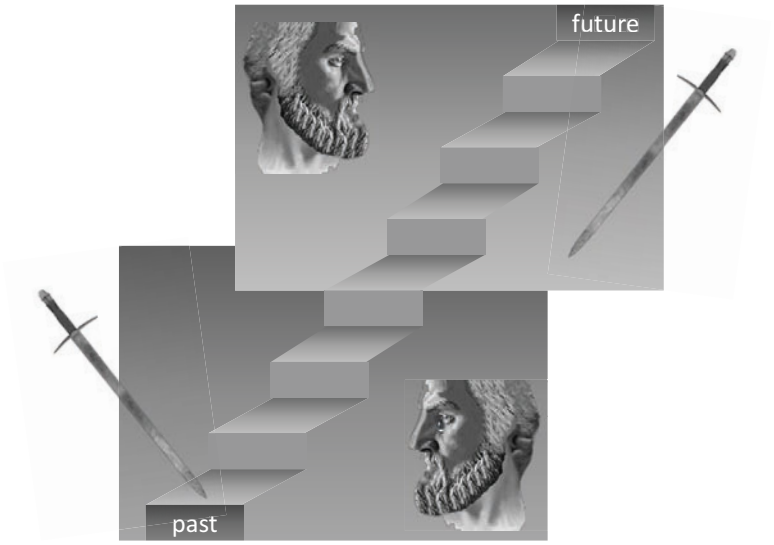

Fig. 3.5 Consciousness of the past and the future in cognitive and emotional processing. Cognitive appraisal is necessary to process information related to environmental stressor and their contextual variables, including the spatial situation where it takes place and the moment when it occurs. This allows the perception of stress to expand over time. These cognitive mechanisms involve subjective awareness of past and future. Excessive focus on past negative events, experienced as traumatic memories, or exaggerated worry about future events, may converge in the present moment, overlapping each other and interfering the possibility to be aware of the present. Cognitive appraisal requires the evocation of past information and expectancies on future events, but if these become exaggerated, overwhelming or invasive, these may lead to maladaptive responses. If the anticipatory perception of stressful events is strongly imposed on the present, it may lead to symptoms of anticipatory anxiety. If the persistent evocation of traumatic memories brings the past to the present, this may lead to symptoms of sadness and frustration, associated with the traumatic experiences, which may negatively affect the perception of the present, as it occurs in depression

avoid the recurrence of dangerous situations while significantly improving the ability to respond to similar events in the future. These cognitive mechanisms involve subjective awareness of our past and our future, although excessive focus on negative events that occurred in the past, usually experienced and referred as traumatic memories, or exaggerated worry about future events, may converge in the present moment, overlapping each other and interfering the possibility to be aware of the present situation. Cognitive appraisal requires the evocation of past information and expectancies on future events, but if these become exaggerated, overwhelming or invasive, these may lead to maladaptive responses. Therefore, when the anticipatory perception of stressful events is strongly imposed on the present, it may lead to symptoms of anticipatory anxiety. In the same way, when the persistent evocation of traumatic memories brings the past to the present, this may lead to symptoms of sadness and frustration, associated with the traumatic experiences, which in turn may influence the perception of the present situation in a negative manner, as it usually occurs in depression (Fig. 3.5).

Therefore, cognitive and emotional processing participate in response to stressful situations, playing an adaptive or a maladaptive role, to the extent that, even in the absence of real psychophysiological changes caused by present stimuli, they can provoke stress responses by their own, based on the evocation of the past or the imagination of the future, neglecting the interactions with the real world. On the other hand, the possibility to take advantage of previous experiences, including learned skills and successful copping strategies utilized in the past, may contribute to the development of better coping strategies in the face of new stressful situations. In addition, the possibility to create new projects, to envisage and preview future achievements, with genuine interest and motivation, may also contribute to reinforce successful coping strategies. Therefore, an adequate implementation of our past experiences, stored in our long-term memory, and our visualization, and positive imagination, of our desired future, may encourage a better attitude towards the present while promoting the foundations for resilience.

Stress, Trauma and Resilience: Cognition and Emotion

Stressful experiences may be a threatening and exhausting experience, characterized by dysfunctional responses, which may lead to the development of long-lasting trauma or a challenging opportunity to develop resilience (Fig. 3.6). In this regard, resilience implies molecular, biological, cognitive, emotional and behavioural changes, all of them integrated in an array of active and adaptive physiological, psychological and behavioural responses.

Resilience may be also conceived as the ability to overcome acute and chronic stressful situations without significant deleterious effects. Therefore, resilience may be developed as a result of successful cognitive processing, which in turn requires a simultaneous integration with adaptive emotional reactions, aimed at preventing stressful events from having negative psychophysiological consequences. Upon exposure to stressful situations, certain aspects of perceived stressors may be modified, allowing transforming a negative experience into a positive challenge. In this regard, effective cognitive processing may lead to significantly improving predictability, hence reducing the degree of uncertainty, while increasing the subjective perception of controllability, which may allow transforming negative stressful events into positive and enriching experiences (Fig. 3.7).

A resilient person has not been free from stress and adverse experiences, but, despite the fact of being affected by adversity, may continue developing successful adaptive responses (Feder et al, 2009). Moreover, a resilient person may demonstrate more positive outcomes than the expected, successfully coping with adversity (Rutter, 2006). It has been observed that resilient individuals express more effective cognitive skills, including greater flexibility of thinking, increased ability for problem-solving and capacity for future planning, which may allow them to implement active coping strategies. Resilient individuals have demonstrated greater capacity to handle stressful situations with better predisposition, displaying positive

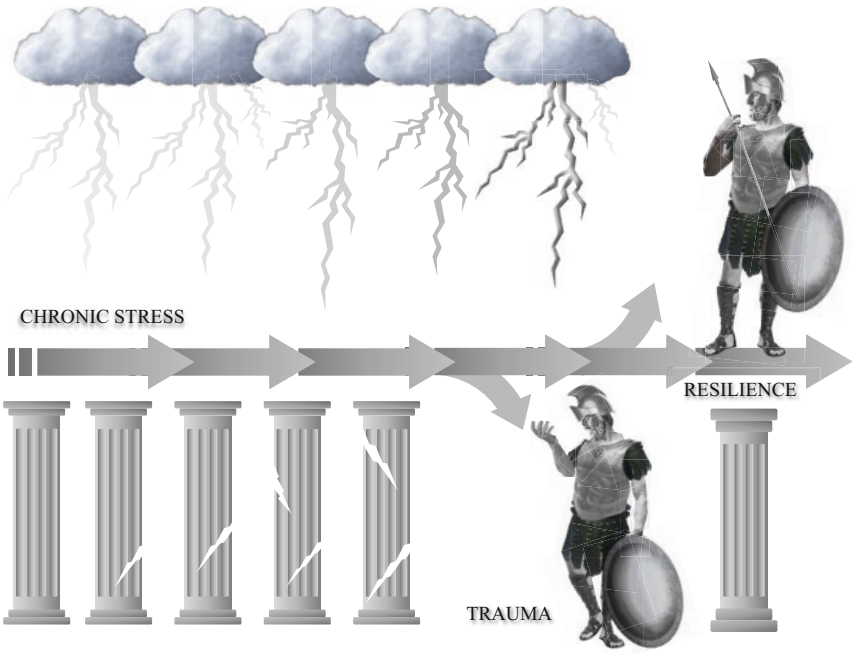

Fig. 3.6 Chronic stress in the origin of trauma and the development of resilience. Stressful experiences may be a threatening and exhausting experience, characterized by dysfunctional responses, which may lead to the development of long-lasting trauma or a challenging opportunity to develop resilience, which involves molecular, biological, cognitive, emotional and behavioural changes, integrated in active and adaptive physiological, psychological and behavioural responses

emotionality, including optimism, when it would be possible. The effective integration of these emotional and cognitive resources may allow them to face their fears, normally expressed in the face of threatening and dangerous situations, actively responding life challenges despite their fears. In addition, a resilient person is usually open to develop social relationships, providing and accepting reciprocal support, expressing higher altruism, with a healthy equilibrium with a moderated feeling of egoism, implying self-esteem and self-care, which allows them to actively participate in joint challenges with the aim to attain common goals. All these characteristics may be translated into the possibility to improve learned skills and to enhance personal resources, hence providing an opportunity for achievement and personal development, which is usually observed and referred by resilient persons.

Therefore, resilience constitutes an adaptive process, characterized by the ability and capacity to maintain a normal psychological and physiological functioning, overcoming adverse events and stressful situations. Adversity may be understood as a perceived conflict between an objective stressful situation and the subjective interpretation of perceived experiences, which in turn may be determined by the personal needs and desires, the expected goals and the particular motivation of each

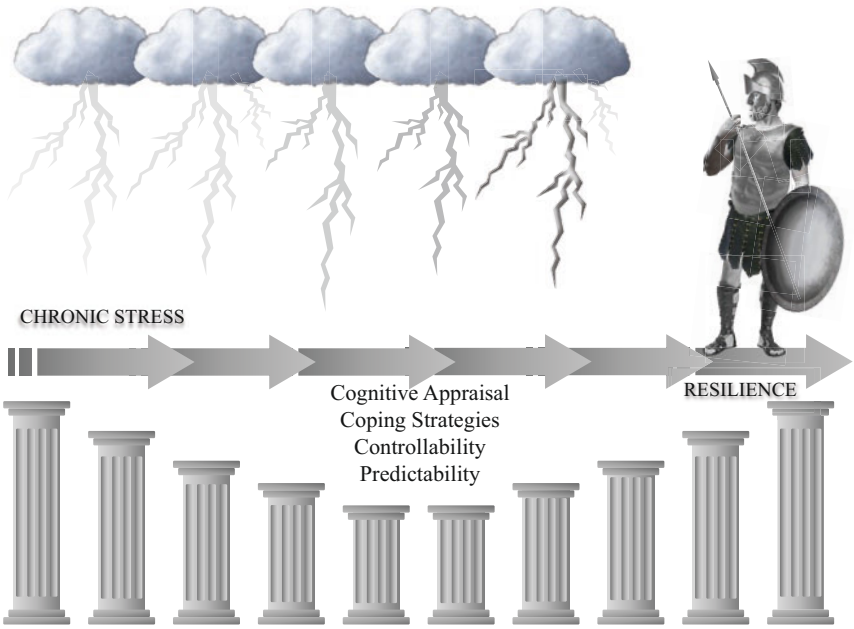

Fig. 3.7 Predictability and controllability in the development of resilience. Resilience represents the ability to overcome acute and chronic stressful situations without significant deleterious effects. Upon exposure to stressful situations, certain aspects of perceived stressors may be modified, allowing transforming a negative experience into a positive challenge. In this regard, effective cognitive processing may lead to significantly improving predictability, hence reducing the degree of uncertainty, while increasing the subjective perception of controllability, which may allow transforming negative stressful events into positive and enriching experiences

person, all of which participate in the cognitive and emotional processing involved in the subjective cognitive appraisal (Lazarus & Folkman, 1984). Hence, the adverse character of stressful situations may be determined by this subjective cognitive appraisal (Lazarus & Follkman, 1984). Despite the fact that different situations are usually considered objectively adverse, such as a war or a terror attack, the stressful impact may differ according to subjective interpretations (Bonanno, 2004), which in turn may also depend on the available resources, or their subjective assessment, including their potential efficacy to cope with adverse events.

Cognitive appraisal plays a critical role in the way we cope and react to stressful events. A cognitive appraisal characterized by deficient assessment of personal resources, or the belief that the available resources are not enough for successful coping, or the exaggerated assessment of adversity, or the belief that a stressful event may result overwhelming, unpredictable or uncontrollable, may be also determined by cognitive biases, which may be established by dysfunctional cognitive processing, which in turn may determine an additional factor of cognitive vulnerability.

Cognitive vulnerability may be founded on erroneous beliefs, based on early adverse experiences. Accordingly, traumatic events, mostly experienced during childhood, may engender erroneous beliefs about us and our surrounding world. These dysfunctional cognitions may include erroneous ideas related to a weak self-esteem, to a threatening environment, to poor skills or deficient capabilities to successfully cope with challenges, which in turn may be assembled into dysfunctional cognitive schemas. These dysfunctional cognitions may lead to maladaptive cognitive biases, which in turn may reinforce each other, in a vicious cycle, therefore leading to increased cognitive biases and emotional vulnerability. Cognitive and emotional vulnerability may affect cognitive appraisal, leading to deficient reappraisal, which in turn may be translated into decreased and downgraded assessment of available resources, and increased and exaggerated evaluation of potential danger, associated with stressful experiences.

The assessment of stressful events as a negative and undesirable experience may be exacerbated if it is also perceived as surprising and unexpected. In addition, the perception of unpredictability may be also aggravated by a deficit, or absence, of available resources to cope with stressors, with the resulting perception of lack of control. Hence, subjective interpretation of uncontrollability may lead to increased emotional vulnerability, with the resulting difficulties in the implementation of coping strategies and the consequent development of learned helplessness, which in turn represent the gateway to chronic anxiety disorders and depression.

On the contrary, active positive cognitions, associated with positive emotions, may lead to adaptive cognitive appraisals, which in turn may be translated into more efficient and effective coping strategies. The experience of successful coping, with the consequent perception of increasing controllability, may influence the perception of stressful events in a positive manner. This positive experience may allow and reinforce the belief that a stressful event may be a challenge, rather than a threat (Parsons et al., 2016), which in turn may improve the ability and capacity to successfully cope with stressful situations. Effective reappraisal, with the resulting optimization of resources and improvement of coping strategies, may lead to increased perception of controllability, which in turn may be translated into the development of resilience.

Developing Controllability: The Road Map to Resilience

As we have explained previously, stress represents a common experience in normal life, where it has been shown that positive events, characterized by desirable situations, which may be perceived and interpreted as predictable and controllable, according to our cognitive and emotional processes, may lead to positive experiences, associated with resilience and improved quality of life. The opportunity to identify a challenge, to get involved in active responses to attain a goal, expressing enhanced functioning despite exposure to adverse situations, constitutes an essential feature in the development of resilience (Maier & Watkins, 2010). On the other

hand, it has been shown that decreased controllability, or perceived lack of control, has been associated with the development of learned helplessness (Maier & Seligman, 1976). In this regard, it has been demonstrated that uncontrollable stressful situations, such as those experienced during chronic stress, may seriously affect cognitive, emotional and behavioural functioning (Henderson et al., 2012), which have been observed in learned helplessness. Moreover, it has been demonstrated that chronic exposure to uncontrollable situations may lead to impaired cognitive performance, which may be reflected through altered working memory, therefore affecting the capacity to effectively cope with stressful situations. Exposure to uncontrollable situations may lead to defective emotional regulation, which may be expressed through the development of negative feelings, including sadness and anhedonia, which represent a core aspect of learned helplessness. Uncontrollable stressful situations may also lead to maladaptive or ineffective behavioural responses, characterized by passivity, which in turn has been associated to feelings of failure and defeat. Moreover, altered cognitive, emotional and behavioural responses may be also translated into pathophysiological changes, including alterations in the regulation of the HPA axis, with the consequent hypercortisolism, and excessive activation of the ANS, with the consequent signs and symptoms associated with increased sympathetic responses. These changes may lead to a continuous vicious cycle, characterized by the continuous effects of uncontrollable stress, decreasing cognitive and behavioural efficacy, and increasing feelings of helplessness, which in turn may lead to the development of depression and anxiety disorders. In this regard, several lines of evidence support the notion that loss or lack of predictability and controllability may induce feelings of fear and anxiety (Seligman & Maier, 1967) or depression (Seligman, 1974). Therefore, the perception of controllability plays a critical role in the implementation of adaptive responses to stress, which may determine the difference between the development of learned helplessness, which may be prevented by a process of learned controllability, and the development of resilience.

Perceived controllability is based on the belief an individual holds about the ability to exert control over perceived stressful events (Weems & Silverman, 2006; Ly et al., 2019). The impact of stressors may lead to undesirable outcomes; hence, the perception of control represents the possibility to cope with adversity, to attain desired goals and to avoid aversive results. Perceived controllability allows a positive interpretation of environmental stressors, which may support the belief in the possibility to achieve desirable results, approaching rewarding stimuli, while overcoming negative situations, avoiding possible punishment or potentially threatening stimuli.

Upon experiencing stressful events, cognitive appraisal may lead to the assessment of salient characteristics of stressors, which in turn may lead to the realization and identification of over what is necessary to exercise control, and the assessment of available resources, which in turn may lead to properly evaluate if it would be possible to exert control.

The concept of controllability has long been investigated throughout different lines of research, where it has been conceived and referred through different terms.

Among these, it has been proposed the construct of internal locus of control (Rotter, 1966), according to which the perception of control over a reinforcement, represented by anything that may strengthen or reinforce a behaviour, would be correlated with personal capabilities and resources. An external locus of control, on the contrary, implies the perception that control over a reinforcement may depend on external circumstances, including real or imagined factors. The resulting perception of lack of control has been associated with uncertainty and increasing anxiety (Mandler & Watson, 1966; Weems & Silverman, 2006). Perceived lack of control has been also studied in the context of learned helplessness (Overmier & Seligman, 1967; Seligman, 1974; Abrahamson et al., 1978), according to which, individuals who were exposed to unavoidable or inescapable stressful events may predispose themselves to fail escaping subsequent similar events, even if escape is possible. This has been attributed to a learned predisposition to perceive a lack of contingency between their actions and specific effects, therefore losing their incentive and motivation to assume active responses, such as coping with adversity, and adopting a passive attitude towards stressful events. Moreover, learned helplessness may be attributed to internal or external causes, stable or unstable conditions and global or specific circumstances, therefore constituting certain attributional style. In this regard, lack of control may be attributed to internal causes, which have been associated with feelings of guilt, regret or loss, which in turn may seriously affect self-esteem. This attribution of self-responsibility over the outcomes of negative events is similar to personalizing, according to the cognitive model (Beck, 1976). The attribution to stable conditions has been associated with certain cognitive distortions, such as the belief that the causes that provoked a negative event were the same that provoked previous experiences, that there are still present, and will remain stable over time, which may lead to pessimism and hopelessness. The attribution to global circumstances may lead to extrapolate negative outcomes to different situations, in diverse contexts, either similar or dissimilar to previous negative experiences, spreading this negative perception among many other life domains. Therefore, learned helplessness has been associated with the tendency to attribute negative events, or the failure to cope with them and to reach positive outcomes, to internal, stable and global factors, which in turn constitute a negative, pessimistic attributional style (Folkman & Lazarus, 1988). This represents an important factor of vulnerability in the origin and development of depression and anxiety, especially in those individuals exposed to chronic uncontrollable stressful situations.

Learned helplessness constitutes a learned belief, a cognitive construct based on traumatic experiences, many of them suffered during childhood and many others in adulthood, closely associated with the perceived lack of controllability. In contrast, perceived self-efficacy constitutes a strong learned belief, a conviction of an individual about the abilities and capabilities to generate and exert some influence over events that may affect his or her life (Bandura, 1982), which has been shown to decrease uncertainty and anxiety by improving a cognitive sense of controllability (Bandura, 1982). The concept of self-efficacy has been also associated with self-confidence, which is supported by the belief on the ability and capability to manage available resources and learned skills to exert control. Hence, self-efficacy and

self-confidence may contribute to develop adaptive beliefs, which in turn may be assembled and integrated in adaptive cognitive schemas, associated with increased perceived control. In contrast, a person with poor self-efficacy may develop dysfunctional beliefs, which in turn may be translated into maladaptive schemas, correlated with decreased perceived control. The subjective perception of control may be coherent with real control on perceived stressful events or may be overestimated and unrealistic, constituting an illusion of control (Burger, 1986). In this regard, controllability may be accomplished as a result of a real experience of control, which may enhance perceived competence and perceived contingency, or an illusion of control, which may lead to active effortful responses, which in turn may lead to the development of real control. Therefore, real controllability is necessary to successfully cope with environmental stressors, as well as the real regulation of emotional responses, such as fear and anxiety. Hence, diminished capacity of emotion regulation may lead to excessive fear and anxiety disorders, particularly in children with decreased perception of control and diminished self-efficacy. In this regard, it has been shown that early adverse experiences, in children with limited possibilities to exert control, led to the development of a biased cognitive style, characterized by a negatively biased interpretation of stressful events, subjectively perceived as out of control. The traumatic effect of these early adverse experiences has been proposed as a factor of vulnerability for anxiety disorders (Chorpita & Barlow, 1998).

Stress in Early Periods of Life: Vulnerability or Controllability

Traumatic experiences during early periods of life may lead to decreased perception of control and diminished emotion regulation, constituting a critical factor of vulnerability for the development of depression and anxiety disorders (Heim and Nemeroff, 2001; Heim et al., 2008; Nemeroff and Binder, 2014). In this regard, certain stressful life events, which may be characterized by their unusual intensity or excessive extent, may lead to cognitive and emotional alterations, usually associated with an array of maladaptive responses. These extreme stressful events are frequently referred as overwhelming or devastating experiences, which occurred at a certain moment in life, as an acute traumatic event, or happened during an extended period, as a chronic stressful situation, also referred as a traumatic experience. A psychological trauma refers to a cognitive and emotional wound, which may be stored in the long-term memory, and therefore produce their long-lasting effects, translated into traumatic experiences. These traumatic experiences may be translated into severe psychological and neurobiological consequences, which in turn may lead to long-lasting pathophysiological processes. In this regard, it has been shown that certain adverse conditions during childhood, such as abuse, neglect or loss, may lead to the formation of dysfunctional cognitive schemas, which may be further translated into negative biases in response to additional stressful conditions at a later time, therefore constituting an important factor of cognitive vulnerability (Beck, 2008).

Various lines of research have focused on the long-lasting consequences of early life stress, where it has been shown that the effect to severe or extreme stressful conditions, such as those previously described as traumatic experiences, has been associated with increased vulnerability, while exposure to mild and brief stressful conditions may contribute to the development of resilience. In this regard, it has been shown that children exposed to certain mild or moderate stressful conditions, where they experienced the opportunity to exert control, developed better coping resources in later periods of life. The subjective experience of control, reflected in successful coping, has been associated with positive beliefs, which in turn may lead to reinforcing cognitive and emotional processes involved in the development of resilience. In this regard, the difference between early life stressful experiences, which may be associated with increased vulnerability or the development of resilience, may depend on individual and contextual factors, the interactions between them, and the characteristics of stressors. Cognitive appraisal of these reciprocal interactions may allow differentiating between overwhelming and controllable situations (Gunnar et al., 2009: Southwick et al., 2005). In this regard, exposure to controllable stressful situations during childhood, with the consequent emotional and physiological activation, and the resulting successful coping, has been shown to improve arousal regulation and resilience in the face of stressful exposures later in life (Lyons et al., 2009; Gunnar et al., 2009). This process, known as stress inoculation (Garmezy, 1991; Rutter, 1993), involves simultaneous cognitive and emotional processing, which participate in a process of learned controllability, which in turn may lead to improved coping skills, and the development of resilience.

References

Abrahamson, L. Y., Seligman, M. E. P., & Teasdale, J. D. (1978). Learned helplessness in humans: Critique and reformulation. *Journal of Abnormal Psychology, 87*, 49–74.

Alim, T. N., Feder, A., Graves, R. E., Wang, Y., Weaver, J., Westphal, M., Alonso, A., Aigbogun, N. U., Smith, B. W., Doucette, J. T., Mellman, T. A., Lawson, W. B., & Charney, D. S. (2008). Trauma, resilience, and recovery in a high-risk African-American population. *The American Journal of Psychiatry, 165*(12), 1566–1575.

Baddeley, A., & Hitch, G. (1974). Working memory. *Psychology of Learning and Motivation, 8*, 47–89.

Baddeley, A. D. (1986). *Working memory*. Clarendon Press.

Bandura, A. (1982). Self-efficacy mechanism in human agency. *American Psychologist, 37*, 122–147.

Beck, A. T. (1967). *Depression: Clinical, experimental, and theoretical aspects*. Harper & Row.

Beck, A. T. (1976). *Cognitive therapy and the emotional disorders*. International Universities Press.

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *The American Journal of Psychiatry, 165*, 969–977.

Bonanno, G. A. (2004). Loss, trauma, and human resilience: Have we underestimated the human capacity to thrive after extremely aversive events? *The American Psychologist, 59*, 20e28.

Burger, J. M. (1986). Desire for control and the illusion of control: The effects of familiarity and sequence of outcomes. *Journal of Research in Personality, 20*, 66–76.

Burger, J. M., & Cooper, H. M. (1979). The desirability of control. *Motivation and Emotion, 3*, 381–393.

Chorpita, B. F., & Barlow, D. H. (1998). The development of anxiety: The role of control in the early environment. *Psychological Bulletin, 124*, 3–21.

Feder, A., Nestler, E. J., & Charney, D. S. (2009). Psychobiology and molecular genetics of resilience.*Nat. Reviews in the Neurosciences, 10*(6), 446–457.

Folkman, S., & Lazarus, R. S. (1988). The relationship between coping and emotion: Implications for theory and research. *Social Science & Medicine, 26*, 309–317.

Garmezy, N. (1991). Resilience in children's adaptation to negative life events and stressed environments. *Pediatric Annals, 20*(459–460), 463–466.

Gunnar, M. R., Frenn, K., Wewerka, S. S., & Van Ryzin, M. J. (2009). Moderate versus severe early life stress: Associations with stress reactivity and regulation in 10-12-year-old children. *Psychoneuroendocrinology, 34*(1), 62–75.

Heim, C., & Binder, E. B. (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. *Experimental Neurology, 233*, 102–111.

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry, 49*(12), 1023–1039.

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology, 33*(6), 693–710.

Henderson, R. K., Snyder, H. R., Gupta, T., & Banich, M. T. (2012). When does stress help or harm? The effects of stress controllability and subjective stress response on stroop performance. *Frontiers in Psychology, 3*, 179.

Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal and coping*. Springer Publishing Company.

Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal and coping*. Springer.

Lyons, D. M., Parker, K. J., Katz, M., & Schatzberg, A. F. (2009). Developmental cascades linking stress inoculation, arousal regulation, and resilience. *Frontiers in Behavioral Neuroscience, 3*, 32.

Ly, V., Wang, K. S., Bhanji, J., & Delgado, M. R. (2019). A reward-based framework of perceived control. *Frontiers in Neuroscience, 13*, 65.

Maier, S. F., & Seligman, M. E. P. (1976). Learned helplessness: Theory and evidence. *Journal of Experimental Psychology. General, 105*, 3–46.

Maier, S. F., & Watkins, L. R. (2005). Stressor controllability and learned helplessness: The roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. *Neuroscience and Biobehavioral Reviews, 29*(4–5), 829–841.

Maier, S. F., & Watkins, L. R. (2010). Role of the medial prefrontal cortex in coping and resilience. *Brain Research, 1355*, 52–60.

Mandler, G., & Watson, D. L. (1966). Anxiety and the interruption of behavior. In C. Spielberger (Ed.), *Anxiety and behavior* (pp. 263–288). Academic Press.

Miller, G. A., Galanter, E., & Pribram, K. H. (1960). *Plans and the structure of behavior*. Henry Holt and Company.

Nemeroff, C. B., & Binder, E. (2014). The preeminent role of childhood abuse and neglect in vulnerability to major psychiatric disorders: Toward elucidating the underlying neurobiological mechanisms. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(4), 395–397.

Overmier, J. B., & Seligman, M. E. (1967). Effects of inescapable shock upon subsequent escape and avoidance responding. *Journal of Comparative and Physiological Psychology., 63*, 28–33.

Parsons, S., Krujit, A. W., & Fox, E. (2016). A cognitive model of psychological resilience. *Journal of Experimental Psychopathology, 7*(3), 296–310.

Persuh, M., LaRock, E., & Berger, J. (2018). Working memory and consciousness: The current state of play. *Frontiers in Human Neuroscience, 12*, 78.

Pfau, M. L., & Russo, S. J. (2015). Peripheral and central mechanisms of stress resilience. *Neurobiol Stress., 1*, 66–79.

Rotter, J. B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs: General and Applied, 80*(1), 1–28.

Rutter, M. (1993). Resilience: Some conceptual considerations. *Journal of Adolescent Health, 14*(626–631), 690–696.

Rutter, M. (2006). Implications of resilience concepts for scientific understanding. *Annals of the New York Academy of Sciences, 1094*, 1e12.

Seligman, M. E. P., & Maier, S. F. (1967). Failure to escape traumatic shock. *Journal of Experimental Psychology, 74*, 1–9.

Seligman, M. E. P. (1974). Depression and learned helplessness. In R. J. Friedman & M. M. Katz (Eds.), *The psychology of depression: Contemporary theory and research* (pp. 83–113). Winston-Wiley.

Southwick, S. M., Vythilingam, M., & Charney, D. S. (2005). The psychobiology of depression and resilience to stress: Implications for prevention and treatment. *Annual Review of Clinical Psychology, 1*, 255–291.

Weems, C. F., & Silverman, W. K. (2006). An integrative model of control: Implications for understanding emotion regulation and dysregulation in childhood anxiety. *Journal of Affective Disorders, 91*(2–3), 113–124.

Chapter 4
Clinical Approach to Stress

Stress is associated with different emotional states, where fear and anxiety are the most commonly experienced during stressful situations. Fear plays a critical role in rapid reactions to perceived threats, preparing the organism for immediate responses to face potential dangers, including the ability to get ready to cope with adversity or to escape. It may be an adaptive emotion, but chronic and uncontrollable fear has been associated with the origin and development of anxiety, which is characterized by anticipated fear and uncertainty, associated with threatening events. Anxiety may contribute to improving adaptive responses, stimulating attention and arousal, shaping cognitive processes involved in different coping strategies. If anxiety continues longer, as it is observed during chronic stress, it may interfere with cognitive and emotional processes, which, in turn, may lead to the origin and development of chronic and severe anxiety disorders. Chronic stress, mostly produced by the impact of unavoidable and uncontrollable conditions, may lead to learned helplessness, which has been associated with the origin and development of depression. Chronic stress may lead to hyper-activation of the hypothalamic-pituitary-adrenal (HPA) axis, with the resulting increased levels of cortisol, and various aminergic systems are also involved in this process, including the serotonergic, the dopaminergic and the noradrenergic systems, which, in turn, are also interconnected with cortical and limbic structures. The amygdala plays a critical role in identifying potentially stressful stimuli and detecting present threats or imminent danger, which therefore contributes to activating the necessary adaptive responses. It represents the main structure of an adaptive neural circuit involved in cognitive and emotional processing, which includes reciprocal connections with other neural structures, such as the hippocampus, the bed nucleus of the stria terminalis (BNST) and different areas of the prefrontal cortex (PFC). Activation of the amygdala, associated with feelings of fear and anxiety, may be neutralized by the ventro-medial PFC (VM-PFC), which has been involved in decreasing learned helplessness and the resulting learned control, consolidating neural pathways involved in predictability and controllability, which are crucial for the development of resilience.

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The Role of Stress in the Development of Fear and Anxiety

Stress is closely associated with an array of emotional states, where fear and anxiety are the most commonly experienced during stressful situations. Fear constitutes an emotional state, mostly characterized by uneasiness and apprehension, usually provoked by environmental stressful situations, more specifically by the presence of an imminent and genuine danger or threat (Davis et al., 2010). Anxiety is closely associated with fear, although it may be provoked by less specific stressors, perceived as less imminent and more distant, like a threat attributed to distal events, therefore representing a "future-oriented" emotional state (Davis et al., 2010); likewise, depression is characterized by excessive or long-lasting sadness, which may be associated with traumatic experiences, which, in turn, constitutes a "past-oriented" emotional state (Fig. 4.1). Hence, fear and anxiety are basic emotions that, to a certain extent, constitute an integral component of adaptive responses to stress.

Fear plays a critical role in rapid reactions to perceived threats or dangerous situations, accompanying and preparing the whole organism for immediate responses to face potential dangers. Hence, the adaptive role of fear results evident as the leading emotional component in defensive behaviours, including the ability to get ready to actively cope with adversity or to escape. Fear is usually associated with specific

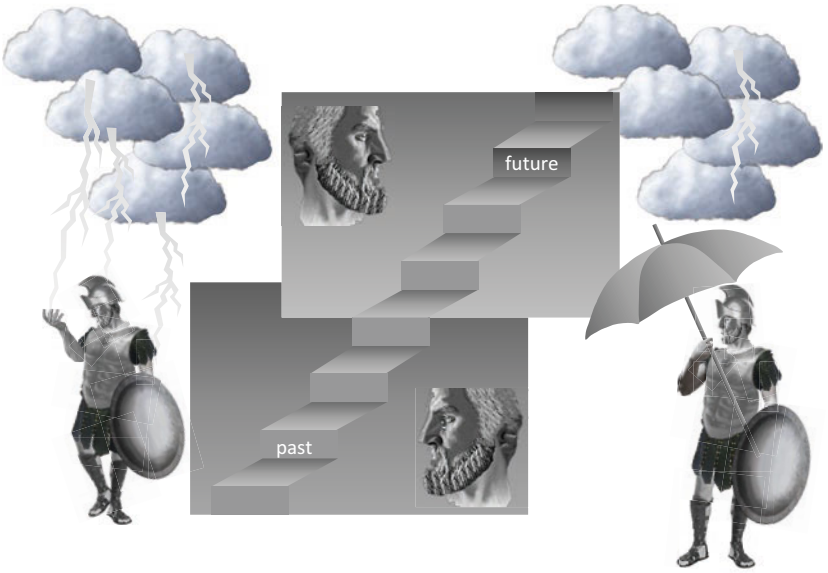

Fig. 4.1 Emotional states provoked by stress. Stress is associated with emotional states, such as fear and anxiety. Fear is characterized by uneasiness and apprehension, associated with imminent and genuine danger or threat. Anxiety is associated with fear, provoked by less specific stressors, perceived as less imminent and more distant, representing a "future-oriented" emotional state. Depression is characterized by excessive or long-lasting sadness, which may be associated with traumatic experiences, representing a "past-oriented" emotional state

events, which may be perceived through external stimuli, represented by environmental conditions, or through internal stimuli, represented by certain symptoms. These symptoms are mostly provoked by the concerted activation of the autonomic nervous system (ANS), alongside the HPA axis, which, in turn, may be interpreted as signals of imminent danger or may represent a threat or a risk for personal safety. Upon termination of the dangerous encounter, or the threatening event, fear is usually controlled, slowly decreasing to allow the organism to recover previous homeostatic conditions. Therefore, fear is an essential emotion, characterized by anticipation and a negative valence, which is necessary for survival. In the face of a stressful situation, anticipatory visualization of potential harm, with the consequent fear of undesirable outcomes, may lead to defensive reactions, including sympathetic activation, increased arousal and the development of coping strategies, aimed at protecting the organism against possible threats and preventing potential harm. Fear may be necessary for survival, although cognitive or emotional dysfunction in fear processing may lead to exaggerated interpretation of threat, which, in turn, has been associated with symptoms of chronic fear and the development of certain anxiety disorders, such as specific phobias or generalized anxiety disorder (GAD).

Fear may be an adaptive emotion, but chronic and uncontrollable fear has been associated with the origin and development of anxiety, which represents an emotional state characterized by anticipated fear, uncertainty and a negative valence, associated to threatening events. Anxiety may be less specific and longer lasting than fear, more focused on future events than imminent danger and the prediction of potential threats, with the resulting uneasiness and worry about undesirable and unpredictable consequences (Steimer, 2002). As it was previously described for fear, anxiety is also characterized by sympathetic activation and increased arousal and may lead to the development of coping strategies, aimed at protecting the organism against potentially adverse events, as well as expected and unexpected stressful situations. However, anxiety has been associated with unknown or uncertain threats, whereas fear has been associated with known, more precise and more specific environmental threats (Craig et al., 1995). Among the different characteristics of anxiety, uncertainty has been associated with the subjective perception of unpredictability and uncontrollability, which may contribute to impaired re-appraisal of stressful situations, difficulty recognizing and utilizing available resources and less effective coping strategies, which, in turn, may lead to a vicious cycle, with the resulting increased anxiety (Steimer, 2002; Craig et al., 1995). This has been extensively studied and described in depression and different anxiety disorders, such as panic attacks, specific phobias and GAD.

The adaptive role of anxiety is associated with increased attention and arousal, necessary to cope with adversity and to prevent exposure to potentially dangerous situations. Hence, anxiety may contribute to improving adaptive responses, stimulating learning and memory consolidation and shaping cognitive processes involved in the origin and development of different coping strategies, which may be necessary to cope with current and future events. If anxiety continues longer, in a sustained and prolonged manner, as it is usually observed during chronic stress, it may

interfere with cognitive and emotional processes, which, in turn, may lead to the origin and development of chronic and severe anxiety disorders (Kalin, 2020).

Anxiety disorders may be characterized by an array of emotional and cognitive symptoms, including anticipated and diffuse feelings of fear and worry, excessive arousal with impaired focused attention, difficulty concentrating, decreased tolerance to adversity with the resulting feelings of irritability, sleep disturbances and the consequent feelings of fatigue. In addition, anxiety is also associated with increased activation of the ANS, which results in various symptoms, mainly provoked by increased activation of the sympathetic nervous system. These autonomic symptoms include an increased heart rate, with the perception of heart palpitations; altered breathing, with the resulting sensation of shortness of breath; and painful feelings throughout the body, mostly in the chest, head, neck and muscles, with extreme tension, excessive sweating and dizziness. In addition, excessive worry and nervousness may lead to extreme tiredness and fatigue, all of which reinforce the subjective experience of anxiety.

Stress, Anxiety and the Development of Anxiety Disorders

It has been clearly demonstrated that fear and anxiety play a critical role in the adaptive responses to stress, providing the necessary signs of danger and threat, associated with experienced stressful events (Steimer, 2002). Fear constitutes an emotional state aroused by certain identifiable stimuli, associated with a real or perceived threat, which may lead to active defensive responses, including an array of physiological and behavioural reactions elicited in response to a stressful situation (Daviu et al., 2019; Chrousos, 2009). These adaptive responses may be triggered by internal or external stressors, which may be objectively assessed or subjectively interpreted, which represent a real or immediate danger, hence associated with feelings of fear, or may lead to potential or future danger, with the resulting anxiety.

In this regard, neurobiology of fear and anxiety has been usually studied in different species as the emotional components of adaptive responses to certain environmental stressors, mostly related to threatening stimuli associated to potential predators or aggressive con-specific individuals. Fear and anxiety may be also associated with perceived internal stressors, including pathophysiological signals of low energy supplies, which may provoke fear of starvation; symptoms of fluid imbalance, which may lead to dehydration; or signals of hypothermia, which may provoke fear of freezing, all of them representing potential risks for survival (LeDoux & Pine, 2016). In human beings, anxiety may be also experienced in relation to existential concerns, including the subjective perception of a meaningless life, the lack of accomplishment in personal projects or different concerns, real or imagined, related to health and potential diseases.

Therefore, anxiety constitutes a complex emotional state aroused by the anticipation of different stressful events, which may be perceived in the real environment or just imagined in the virtual theatre of mind, which may pose a potential threat or

may cause a possible harm. Hence, anxiety represents an emotional state of rather diffuse fear, provoked by the anticipation of uncertain stressful events, with uncertain consequences (Daviu et al., 2019).

Psychoneurobiological Bases of Fear and Anxiety

The psychoneurobiological bases of fear and anxiety may be explained through the development of specific neural circuits in the central nervous system (CNS), which have been studied and recognized as survival circuits (LeDoux, 2012). These neural circuits play a critical role in the organization of different adaptive functions, particularly those involved in the recognition and processing of relevant information, related to environmental challenges and threats, and the subsequent regulation of psycho-physiological and behavioural responses. Activation of these adaptive functions, including increased arousal and improved attention, mostly focused on relevant sensory information about environmental and internal stimuli, enhanced motivation and improved memory formation, which are necessary for successful defensive responses (LeDoux, 2012).

The adaptive role of these neural circuits may be explained in the context of information processing. As it was previously described, environmental sensory information is perceived and conveyed through sensory pathways to the CNS, particularly to the thalamus, including innate and conditioned stimuli (CS). Direct pathways from the thalamus convey basic information to the amygdala, while indirect pathways through sensory and associative cortices may also reach the amygdala conveying more elaborated sensory information (Fig. 4.2). Additional pathways from the hippocampal formation and transition cortices, which integrate sensory and contextual information, provide an even more elaborated input to the amygdala (LeDoux, 2000). In addition, there is an important interchange between the amygdala and different areas of the PFC, including the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC), where sensory information is further elaborated by different neural structures involved in emotional and cognitive processing. In this regard, the amygdala represents the main structure of an adaptive neural circuit involved in cognitive and emotional processing, which includes reciprocal connections with other neural structures, such as the hippocampal formation, the BNST and different areas of the PFC (Fig. 4.3).

The Amygdala and the Fear Circuit in the Brain

Perceived information associated with potential environmental threats may be processed through reciprocal projections between the amygdala, the BNST, the ventral hippocampus and different areas of the VM-PFC, particularly involving the ACC and the OFC, which may allow the identification and recognition of perceived

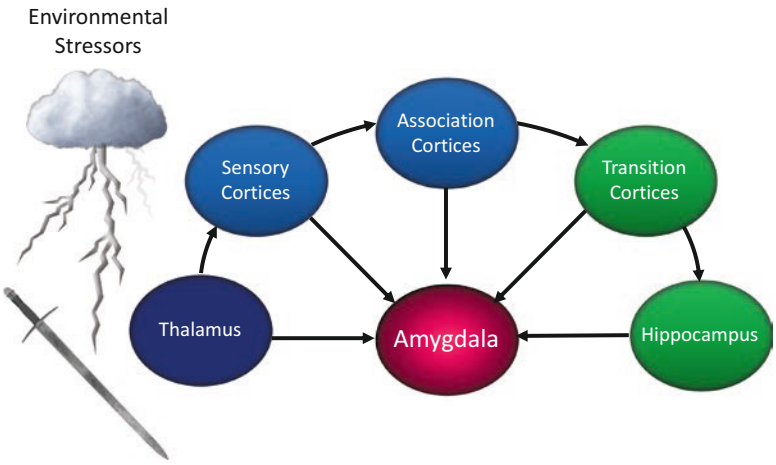

Fig. 4.2 Neural processing of environmental stressors. Environmental information is perceived and conveyed through sensory pathways to the brain, particularly to the thalamus, including innate and conditioned stimuli. Direct pathways from the thalamus convey basic information to the amygdala, while indirect pathways through sensory and associative cortices may also reach the amygdala conveying a more elaborated sensory information. Additional pathways from the hippocampal formation and transition cortices, which integrate sensory and contextual information, provide an even more elaborated input to the amygdala

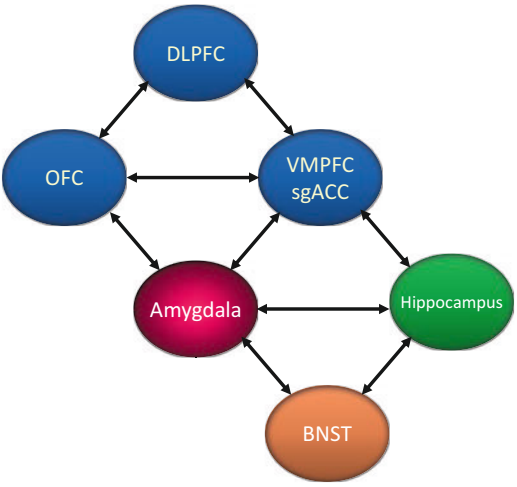

Fig. 4.3 Reciprocal projections between the amygdala and the prefrontal cortex (PFC). The amygdala shares connections with different areas of the PFC, including the ACC and the OFC, in the VM-PFC, and indirectly also with the DL-PFC. The amygdala represents the main structure of an adaptive neural circuit involved in cognitive and emotional processing, which also includes reciprocal connections with the hippocampal formation and the BNST

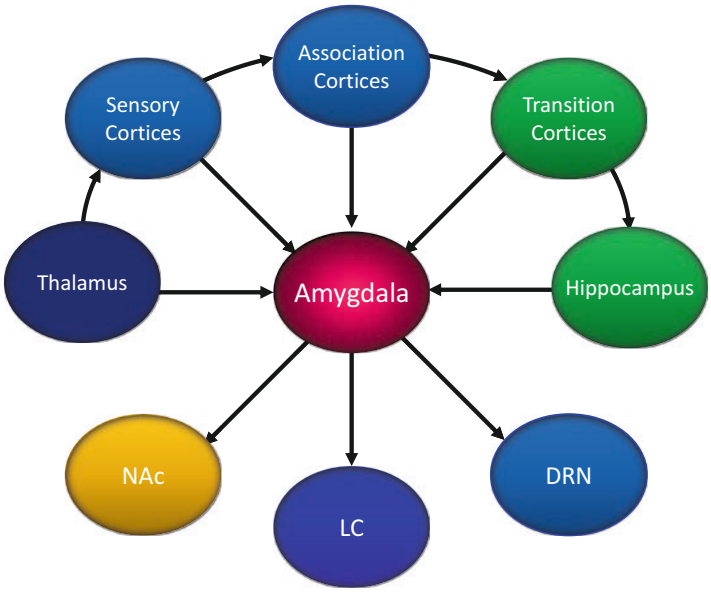

Fig. 4.4 Projections from cortical and subcortical structures to the amygdala and from the amygdala to monoaminergic systems. Perceived information is processed through reciprocal projections between the amygdala, the BNST, the hippocampus and different areas of the VM-PFC, particularly involving the ACC and the OFC. Identification of potential threats may lead to enhanced vigilance, which results in reciprocal activation of the different structures. Continuous information processing through these circuits is also regulated by reciprocal projections with aminergic nuclei in the brainstem, including the serotonergic, noradrenergic and dopaminergic systems, which is reflected in the activation and regulation of the HPA axis and the ANS

stimuli as potentially dangerous (Janak & Tye, 2015). Identification of potential threats may lead to enhanced vigilance, which results in reciprocal activation of the different structures involved in this circuit. Continuous information processing through these circuits is also regulated by reciprocal projections with aminergic nuclei in the brainstem, including the serotonergic, noradrenergic and dopaminergic systems (Fig. 4.4). Hence, the resulting integration of this continuous processing is therefore reflected in the activation and regulation of the HPA axis and the ANS.

The amygdala plays a critical role in the identification of salience, which represents the emotional relevance of potentially stressful stimuli, understanding salience as the capacity of environmental stimuli to activate physiological responses and psychological processing, due to its potential relevance (Liberzon et al., 2003) (Fig. 4.5). In this regard, a group of neurons have been identified in the amygdala, particularly in the baso-lateral amygdala (BLA), involved in the detection of salience of different stimuli, independently of their potential aversive or rewarding value, which has been associated to an increased emotional arousal in response to salient stimuli (Shabel & Janak, 2009; Janak & Tye, 2015), which, in turn, through projections from the amygdala to different areas of the PFC, may lead to an increased

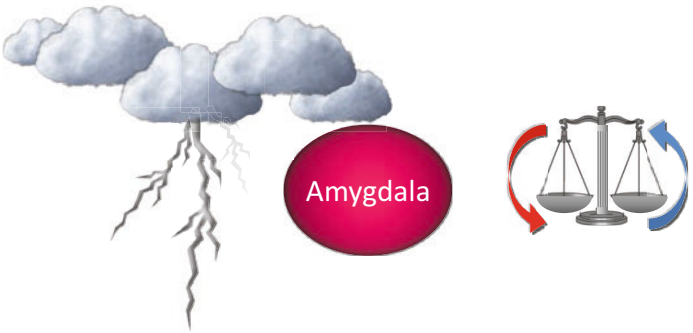

Fig. 4.5 The amygdala plays a critical role in salience and valence assessment. The amygdala plays a critical role in the identification of salience, which represents the emotional relevance of potentially stressful stimuli. The amygdala also participates in the identification of the potential valence of perceived stimuli Discrimination between positively and negatively valenced stimuli has been associated with interactions between the amygdala and the PFC, particularly with the OFC, which is closely involved in emotional processing

attention and perception, with the consequent increased awareness (Phelps & LeDoux, 2005).

In addition to salience, the amygdala participates also in the identification of the potential valence of perceived stimuli (Zald, 2003) (Fig. 4.5). In this regard, different populations of neurons have been identified in the BLA, which may be differentially activated by stimuli associated with fear or reward, therefore participating in the identification and discrimination of positively and negatively valenced stimuli (Paton et al., 2006; Janak & Tye, 2015). Discrimination between positively and negatively valenced stimuli has been also associated with interactions between the amygdala and the PFC, particularly with the OFC, which is closely involved in emotional processing (Paton et al., 2006).

The amygdala also plays a critical role in the fear circuit, detecting present threats or imminent danger, which therefore contributes to activating the necessary adaptive responses, whereas the BNST participates in the processing of uncertain threats, which results in risk assessment and behavioural inhibition. Therefore, activation of the amygdala and the BNST contributes to activate adaptive systems and functions, which, in turn, generate signals that activate neural circuits involved in the subjective feelings of fear and anxiety, respectively (LeDoux & Pine, 2016). Accordingly, the subjective experiences of fear and anxiety require the activation of subcortical circuits, mainly represented by limbic structures involved in defensive responses, which, in turn, activate higher-order cortical structures, involved in cognitive processing of perceived signals and symptoms. In this regard, different areas of the PFC involved in conscious awareness, such as the dorso-lateral PFC (DL-PFC), and areas involved in the conscious experience of somatic sensations, such as the insula, play a critical role in the experience of fear and anxiety (LeDoux & Pine, 2016) (Fig. 4.6).

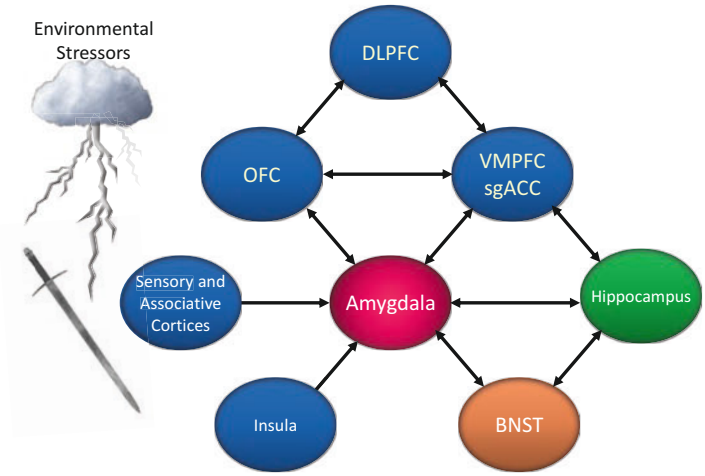

Fig. 4.6 The extended amygdala plays a critical role in the fear circuit. The amygdala plays a critical role in the fear circuit, detecting present threats or imminent danger, contributing to activate the necessary adaptive responses, whereas the bed nucleus of the stria terminalis (BNST) participates in the processing of uncertain threats, risk assessment and behavioural inhibition. Activation of the amygdala and the BNST contributes to activating neural circuits involved in fear and anxiety. The subjective experiences of fear and anxiety require the activation of limbic structures involved in defensive responses, including the amygdala, hippocampus and BNST, which, in turn, activate cortical structures, including the OFC and ACC, involved in cognitive processing. Different areas of the PFC involved in conscious awareness, such as the DL-PFC, and areas involved in the conscious experience of somatic sensations, such as the insula, play a critical role in the experience of fear and anxiety

As we described previously, the amygdala constitutes a group of well-defined nuclei, which are interconnected between them and share important connections with cortical and subcortical neural structures. During stressful situations, the lateral nucleus of the amygdala (LNA) receives information from different neural structures, particularly from the sensory thalamus, sensory cortices and associative cortices. Within the amygdala, the LNA projects to the BLA, and both of them send projections to the central nucleus of the amygdala (CNA). The hippocampus also sends projections to the LNA and the BLA, which, in turn, convey projections to the CNA, and direct projections have been also described from the entorhinal cortex to the CNA (Fig. 4.7). The BLA shares reciprocal connections with the PFC and the hippocampus and sends unidirectional projections to the nucleus accumbens (NAc), the BNST and the CNA (Janak & Tye, 2015) (Fig. 4.8).

Therefore, the LNA receives information about environmental stimuli, which is subsequently processed by the BLA and the CNA, which, in turn, sends projections to different neural structures, including the peri-aqueductal grey (PAG). Activation of the PAG may lead to innate defensive reactions, such as freezing, in response to perceived threats (LeDoux et al., 1988; Ramirez et al., 2015). Aversive stimuli may also provoke different defensive actions, such as avoidance or escape, constituting behavioural responses aimed at controlling the impact of perceived stressors

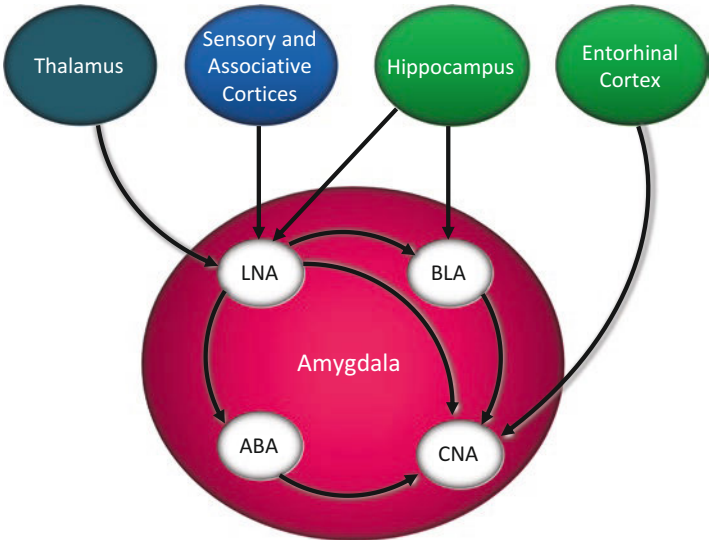

Fig. 4.7 Input from different neural structures to the amygdala. The amygdala constitutes a group of nuclei, which are interconnected between them and share important connections with cortical and subcortical neural structures. The LNA receives information from different neural structures, including the sensory thalamus, sensory cortices and associative cortices. The LNA projects to the BLA, and both of them send projections to the CNA. The hippocampus also sends projections to the LNA and the BLA, which, in turn, convey projections to the CNA, and direct projections have been also described from the entorhinal cortex to the CNA

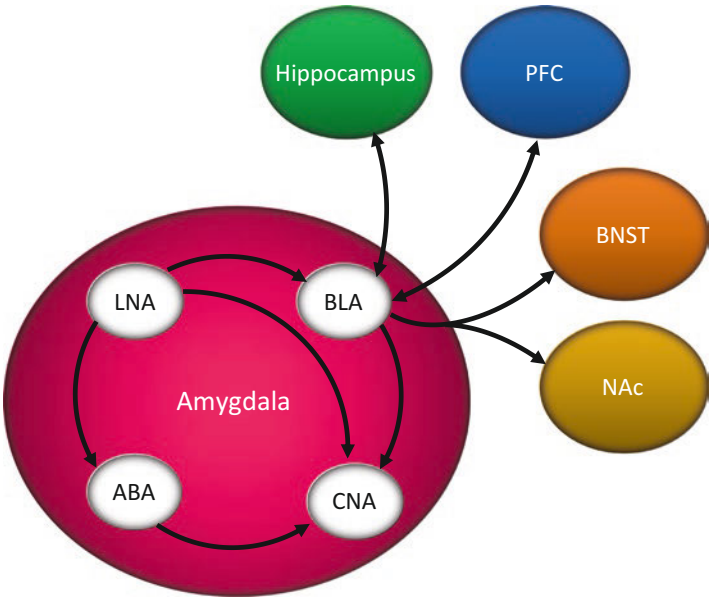

Fig. 4.8 Reciprocal connections with the amygdala. The BLA shares reciprocal connections with the PFC and the hippocampus and sends unidirectional projections to the NAc, the BNST and the CNA

(Cardinal et al., 2002). These behavioural responses depend also on the cascade of information processing involving the LNA and the BLA, but instead of projection from the BLA to the CNA, the implementation of these adaptive actions involves projections from the BLA to the NAc (Ramirez et al., 2015) (Fig. 4.9). The NAc has been mainly associated with reward and positive stimuli, playing a critical role in the reward circuit, though it has been also associated with the processing of aversive information, including negative stimuli and certain cues that may predict their impact. Moreover, the NAc receives projections from the amygdala, particularly from the BLA, hence participating in the detection of salient cues that may lead to adaptive behavioural responses (Ramirez et al., 2015; LeDoux & Pine, 2016). In this regard, it has been shown that activation of the NAc plays a critical role in the discrimination between positive and negative valence (Ikemoto & Panksepp, 1999) (Fig. 4.10). Interestingly, the positive valence attributed to any stimulus may increase with reward magnitude or probability, particularly with an increased magnitude of anticipated rewards, as well as certain motivational states (Cooper & Knutson, 2008) and an increased positive arousal (Drevets et al., 2001). Reward anticipation has been also associated with an increased dopamine (DA) release through projections from the ventral tegmental area (VTA) to the NAc, which provides a predictive signal that may influence behaviour to approach rewarding

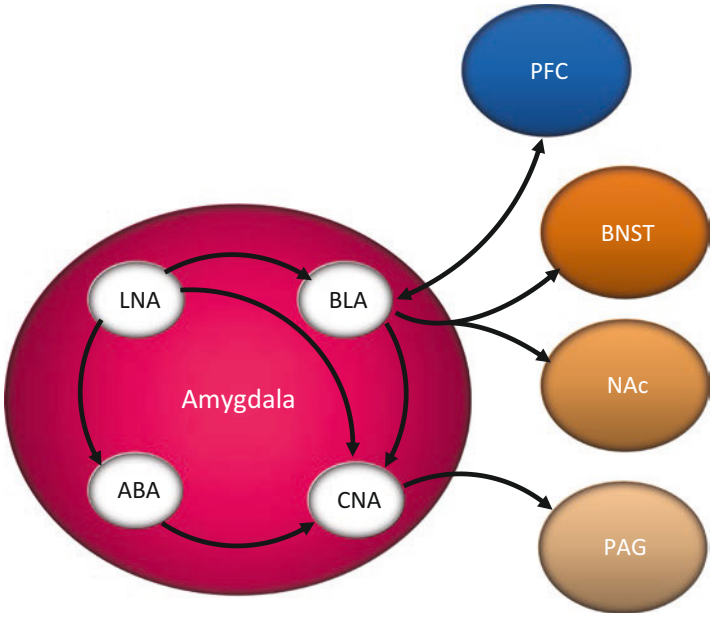

Fig. 4.9 Output from the amygdala to different neural structures. The LNA receives information about environmental stimuli, which is subsequently processed by the BLA and the CNA, which send projections to different structures, including the PAG. Activation of the PAG may lead to innate defensive reactions, such as freezing, in response to perceived threats. Aversive stimuli may provoke defensive actions, such as avoidance or escape, constituting behavioural responses aimed at controlling the impact of perceived stressors. These responses depend on information processing involving the LNA and the BLA and projections from the BLA to the NAc

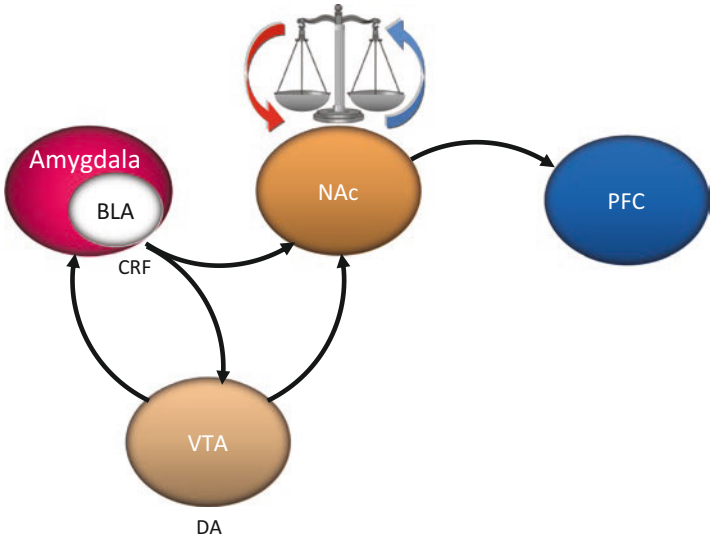

Fig. 4.10 The amygdala and the nucleus accumbens (NAc) participate in salience and valence assessment. The NAc receives projections from the amygdala, particularly from the BLA, participating in the detection of salient cues that may lead to adaptive behavioural responses. Activation of the NAc plays a critical role in the discrimination between positive and negative valence. Positive valence may increase with reward magnitude or probability, particularly with an increased magnitude of anticipated rewards, and certain motivational states and increased positive arousal. Reward anticipation has been associated with an increased DA release through projections from the VTA to the NAc, which provides a predictive signal that may influence behaviour to approach rewarding stimuli. Activation of the NAc has been also associated with detection of salience, which may lead to approach or withdrawal. Activation of the NAc has been also associated with increased attention, which may involve connections with the PFC, mostly focused on relevant or unexpected events, including novelty and anticipation

stimuli (Cooper & Knutson, 2008). Activation of the NAc has been also associated with the detection of salience, which may determine increased probabilities to elicit behavioural responses, which, in turn, may lead to approach or withdrawal. Accordingly, activation of the NAc has been associated with increased attention, mostly focused on relevant or unexpected events, including novelty and anticipation (Cooper & Knutson, 2008) (Fig. 4.9).

The CNA represents the main source of output projections from the amygdala to different neural structures. This important nucleus constitutes a significant source of corticotropin-releasing factor (CRF), which has been shown to play an important role during stress responses. In this regard, the CNA sends stimulatory CRF projections to the hypothalamic paraventricular nucleus (PVN), either directly or indirectly through the BNST, and the noradrenergic locus coeruleus (LC), which, in turn, share important stimulatory projections among them (Fig. 4.11). In addition, the amygdala also sends stimulatory projections from the CNA to the dorsal raphe nucleus (DRN), which, in turn, sends back serotonergic projections to the amygdala, particularly stimulating $5HT_{2A}$ receptors in the BLA, as well as in the BNST (Fig. 4.12), which have been associated with

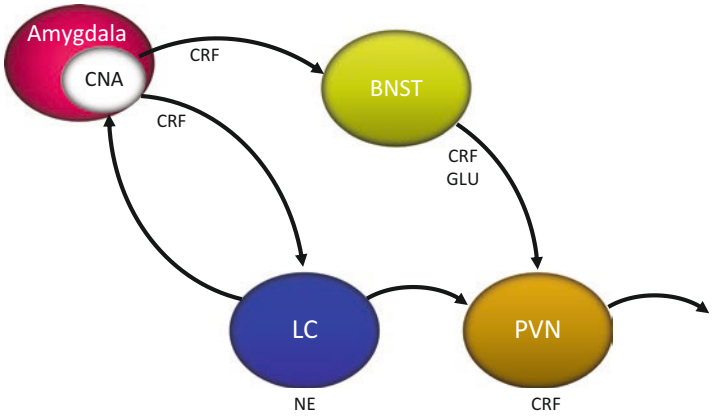

Fig. 4.11 Projections from the amygdala to the bed nucleus of the stria terminalis (BNST) and the paraventricular nucleus (PVN) of the hypothalamus. The CNA represents the main source of output projections from the amygdala to different neural structures. The CNA sends stimulatory CRF projections to the hypothalamic PVN, either directly or indirectly through the BNST, and the noradrenergic LC, which, in turn, share important stimulatory projections among them

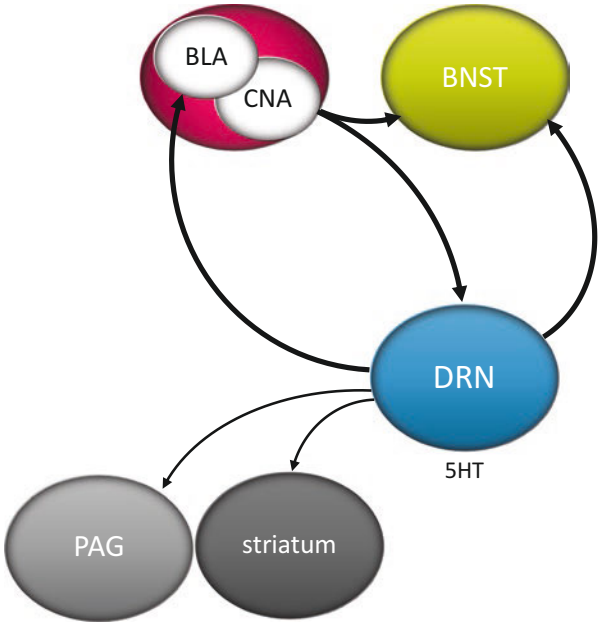

Fig. 4.12 Reciprocal projections between the amygdala and the dorsal raphe nuclei (DRN). The amygdala sends stimulatory projections from the CNA to the DRN, which, in turn, sends back serotonergic projections to the amygdala, particularly stimulating $5HT_{2A}$ receptors in the BLA, as well as in the BNST, which have been associated with increased feelings of fear and anxiety. Inhibitory projections from the DRN may also reach the striatum and the peri-aqueductal grey (PAG), leading to inhibition of active responses, such as fight or flight, with the resulting passive responses. The inhibition of active responses, with the consequent passivity and increased feelings of fear, uncertainty and anxiety, constitute the main symptoms of learned helplessness

increased feelings of fear and anxiety (Maier et al., 1993, 2005). Projections from the DRN may also send inhibitory projections to the striatum and the periaqueductal grey (PAG), which therefore leads to inhibition of active responses, such as fight or flight, with the resulting passive responses (Maier et al., 1993, 2005). The inhibition of active responses, with the consequent passivity and increased feelings of fear, uncertainty and anxiety, constitutes the main symptoms of learned helplessness (Seligman, 1974) (Fig. 4.12). This condition may be neutralized by glutamatergic projections from the VM-PFC to GABAergic interneurons in the DRN and the amygdala (Maier & Watkins, 2005; Maier & Seligman, 2016). Hence, amygdala activation, associated with feelings of fear and anxiety, may be neutralized by activation of the VM-PFC, which has been involved in decreasing learned helplessness and the resulting learned control (Fig. 4.13).

Other areas in the PFC have been also associated with learned control, such as the DL-PFC, which participates in working memory and cognitive processing and therefore is involved in cognitive aspects of inhibitory control; the OFC, which is involved in emotional features of inhibitory control; and the ACC, which plays a critical role in emotion regulation (Shi et al., 2019) (Fig. 4.14). Therefore, cognitive

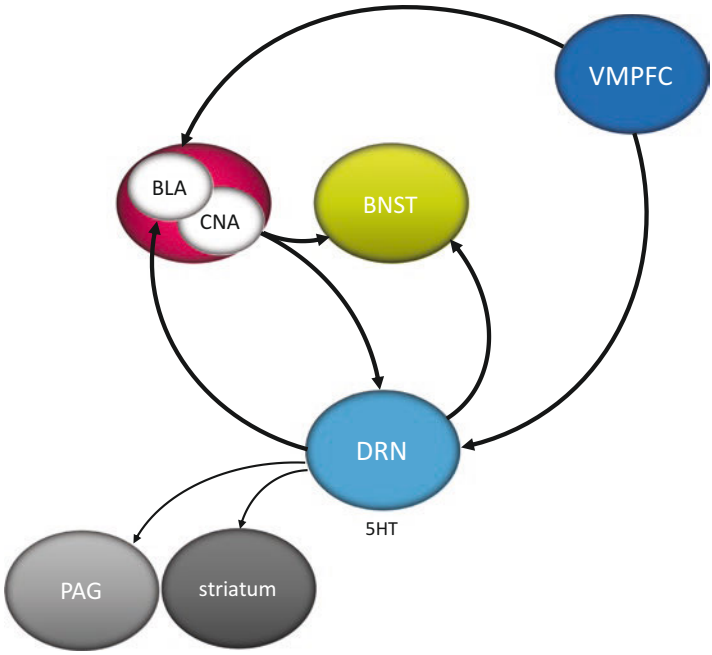

Fig. 4.13 Projections from the ventro-medial prefrontal cortex (VM-PFC) to the amygdala and the dorsal raphe nuclei (DRN). Excessive activation of the amygdala and the DRN may be neutralized by projections from the VM-PFC. The VM-PFC sends stimulatory glutamatergic projections to inhibitory GABAergic interneurons in the DRN and the amygdala, which has been involved in decreasing learned helplessness and the resulting learned control

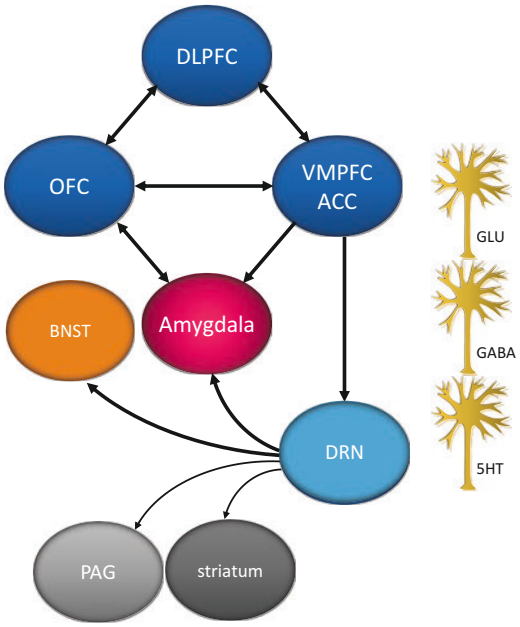

Fig. 4.14 Projections between the dorso-lateral (DL-PFC) and the ventro-medial prefrontal cortex (VM-PFC) are involved in cognitive processing and emotion regulation. Different areas in the PFC have been associated with learned control, such as the DL-PFC that participates in working memory and cognitive processing, the OFC that is involved in emotional features of inhibitory control and the ACC that plays a critical role in emotion regulation. Cognitive processing from the VM-PFC may exert regulatory control through inhibitory projections to the amygdala and the DRN

processing from the VM-PFC may exert regulatory control through inhibitory projections to the amygdala and the DRN, which, in turn, may stimulate new protein synthesis, consolidating these neural pathways involved in predictability and controllability, which are crucial for the development of resilience.

Certain regions of the VM-PFC, particularly in the ACC, are also involved in the processing of stressful stimuli. In this regard, it has been shown that the ACC plays a critical role in the assessment of potential or remote threaten stimuli, whereas the amygdala is more involved in the processing of immediate threats (Fiddick, 2011). Therefore, perception and processing of immediate threats would be associated to fear, whereas the processing and assessment of more distant potential threats would be more associated to anxiety. The ACC and the BLA share important projections, which may be relevant in the assessment of potential threats associated to perceived environmental stimuli. In addition, the ACC (encompassing BA 24, 25, 32 and 33) also receives projections from the insula, the thalamus and other parts of the PFC and shares reciprocal projections with the posterior cingulate cortex (PCC; encompassing BA 23, 29, 30 and 31), which, in turn, also receives projections from the hippocampus (Fiddick, 2011; Vogt et al., 1979, 1995). Reciprocal projections between the insula and the ACC allow the integration and processing of internal and external

stimuli. In this regard, the ACC has been associated with the processing of potential threats from internal sources, including physiological stimuli or psychological processes, whereas the PCC participates in the processing of perceived environmental threats (Fiddick, 2011; Vogt et al., 1992). Therefore, it would be possible to associate the ACC with the assessment of potential risks generated by each person, as it is usually observed in the psychosocial environment or in different challenges in daily life, while the PCC would be more involved in the assessment of external risks, usually observed in the bio-ecological environment. The ACC also participates in the regulation of the HPA axis, through projections to the BNST, and also sends projections to different neural structures involved in the activation of the ANS, including the lateral hypothalamus and the PAG (Vogt, 2018).

Neurobiology of Innate Fear Programming

It has been demonstrated that certain environmental stimuli may lead to fear and anxiety, with the resulting cognitive, emotional and behavioural responses. In order to provoke fear or anxiety, these stimuli should be associated to innate programming or learned from previous experience. Innate programming refers to specific inborn information, which may be operational without previous learning, hence allowing the individual to elicit immediate adaptive responses to specific patterns, which can make the difference between survival or not in the face of potential dangers. It has been proposed that this innate programming may be genetically determined and epigenetically modulated by different factors during development and subsequently expressed in the development of specific synaptic connections, in certain neural pathways involved in survival circuits (LeDoux, 2012).

These innate fear reactions have been studied in rodents, where it has been shown that diverse odorants, mostly associated with their natural predators, may induce innate fear responses (Silva et al., 2016). In this regard, it has been shown that innate fear reactions may be elicited in response to aggressive con-specific or predator cues, which represent powerful stressful stimuli, therefore contributing to rapid implementation of adaptive responses allowing surviving potential dangers (Sokolowski & Corbin, 2012). The perception of these odorants activates the olfactory system, conveying sensory information to the olfactory bulb, which, in turn, sends projections to the amygdala, particularly to the medial nucleus of the amygdala (MNA), which is involved in innate fear associated with aggressive conspecifics and predators (Motta et al., 2009). Sensory polymodal information is processed in associative cortices and conveyed to the BLA. The MNA sends projections to the hypothalamus, more specifically to a medial hypothalamic defensive system (MHS), which integrates information related to perceived stimuli from the MNA and the BLA. This system is integrated by the anterior nucleus, the dorsal premammillary nucleus (PMH) and the dorso-medial part of the ventro-medial hypothalamus (VMH). Therefore, the amygdala sends projections to the hypothalamus, where the VMH projects to the PMH, which, in turn, conveys information to

the dorsal part of the PAG (LeDoux, 2012) and participates in acute defensive behaviours (Canteras, 2002). This medial hypothalamic system also integrates nociceptive information from the parabrachial nucleus (PBN), which also projects this information to the CNA and subsequently to the PAG, which also participate in the recognition of internal signals associated with stress and the subsequent defensive responses (LeDoux, 2012). The medial hypothalamic system and the PAG convey information to the antero-medial thalamic nucleus (AMT), which, in turn, sends information to the ACC, entorhinal and perirhinal cortices, which participate in contextual fear learning. In addition, the BLA and the ventral hippocampus receive contextual information from cortico-thalamic inputs. These innate fear circuits may convey signals to the PFC, amygdala and hippocampus, constituting a memorization fear circuit (Fig. 4.15).

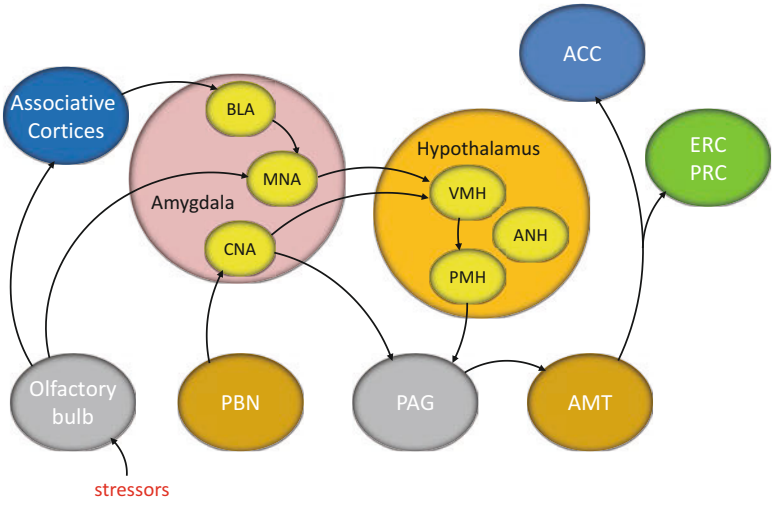

Fig. 4.15 Neural processing in the innate fear circuit. Innate fear reactions may be elicited in response to aggressive con-specific or predator cues, which represent powerful stressful stimuli, therefore contributing to rapid adaptive responses allowing surviving potential dangers. Perception of odorants associated with predators activates the olfactory system, conveying sensory information to the olfactory bulb, which projects to the medial nucleus of the amygdala (MNA). Sensory polymodal information is processed in associative cortices and conveyed to the baso-lateral amygdala (BLA). The MNA sends projections to the medial hypothalamic defensive system (MHS), which integrates information related to perceived stimuli from the MNA and the BLA. This system is integrated by the anterior nucleus (ANH), the dorsal premammillary nucleus (PMH) and the dorso-medial part of the ventro-medial hypothalamus (VMH). The amygdala sends projections to the hypothalamus, where the VMH projects to the PMH, which, in turn, conveys information to the PAG, which participates in acute defensive behaviours. The MHS also integrates nociceptive information from the parabrachial nucleus (PBN), which also projects to the CNA and subsequently to the PAG, which also participate in the recognition of internal signals associated with stress and the subsequent defensive responses. The MHS and the PAG convey information to the antero-medial thalamic nucleus (AMT), which, in turn, sends information to the anterior cingulate (ACC), entorhinal (ERC) and perirhinal (PRC) cortices, which participate in contextual fear learning. Innate fear circuits convey signals to the PFC, amygdala and hippocampus, constituting a memorization fear circuit

Innate fear reactions have been also studied with visual stimuli in rodents, where it has been shown that expanding looming shadows, also associated with their natural predators, may induce innate fear responses, such as freezing or escape, mostly if they are perceived in the upper visual field. Visual information is perceived from environmental stimuli and processed through neural pathways, starting from the photoreceptor layers of the retina, and conveyed through the optic nerves, mainly to the lateral geniculate body (LGB) of the midbrain, which is a postero-lateral extension of the thalamus, and to the superior colliculus (SC). From the LGB, visual information is conveyed through the genico-calcarine tract to the primary visual cortex (BA 17), in the occipital lobe. The LGB receives input from the foveal region of the retina, providing the necessary visual acuity for feature detection. The SC is a neural structure located in the rostral midbrain, in the upper region of the brainstem, which receives input from the periphery of the retina, providing the necessary information for movement detection. In addition, the SC also receives auditory, vestibular and somatosensory spatial information, which may be integrated with visual input, hence allowing the control of movements of the eyes and head towards salient features of perceived stimuli (Lee et al., 2020). Moreover, it has been proposed that innate fear reactions may be triggered by certain salient visual features, which may be processed through a subcortical pathway from the SC to the pulvinar of the visual thalamus, which, in turn, projects to visual cortical areas and to the amygdala, more precisely to the LNA (Wei et al., 2015). Therefore, projections from the SC to the LNA may provide a critical pathway to better understand the role of visual and auditive stimuli in the activation of innate fear responses. This innate fear system provokes defensive responses elicited by predators and aggressive conspecific, which represent powerful sources of social threats. Hence, fear and anxiety may be provoked by environmental stimuli associated to innate programming or learned from previous experience, where the perception of novel sensory events, which may be considered meaningless or neutral stimuli, may be associated with innately significant events. The experience-dependent association between novel sensory events and innate information, which provides biological relevance to certain stimuli, may lead to the development of learned defensive responses, which, in turn, may also provoke the activation of survival circuits in response to learned signals of danger (LeDoux, 2012).

Neurobiology of Fear Conditioning

It has been shown that certain environmentally aversive stimuli may trigger innate defensive responses. Since these stimuli are present in the natural environment and were not previously conditioned by experience, they are termed “unconditioned stimuli” (UCS). The impact of aversive UCS may provoke innate defensive responses, which were not previously conditioned, hence termed “unconditioned responses” (UCR). During fear conditioning, a neutral stimulus, which lacks any previous emotional relevance, may be introduced to impact at the same time, to

coincide with the impact of an aversive UCS. Therefore, after pairing with an aversive UCS, a neutral stimulus may be associated in such a way that, even in the absence of the UCS, may trigger a defensive response, similar to the UCR elicited by the aversive UCS. Hence, the learned association between both stimuli may condition a neutral stimulus, otherwise irrelevant, into an emotionally relevant stimulus, capable of triggering a defensive response, therefore becoming a "conditioned stimulus" (CS). Since the defensive response is similar to the UCR elicited by the UCS but may be provoked by the CS, even in the absence of the UCS, it has been termed "conditioned response" (CR) (Fig. 4.16). Hence, fear conditioning allows a CS to provoke a CR, characterized by fear and the typical pattern of defensive responses, usually elicited in the face of dangerous or threatening stimuli, similar to the innate fear response described as UCR (Pavlov, 1927). Therefore, the impact of

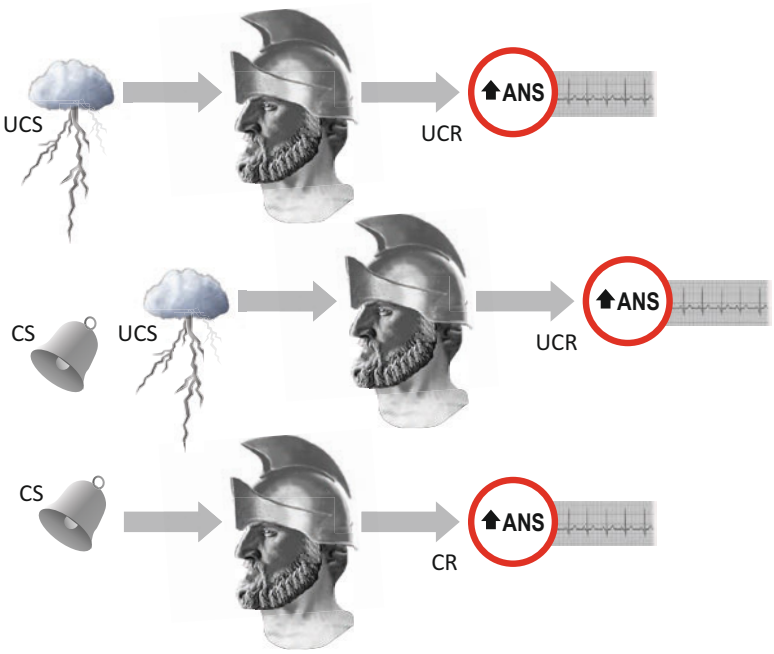

Fig. 4.16 Conditioned and unconditioned stimuli may trigger similar defensive responses. Certain environmental stimuli may trigger innate defensive responses. Since these stimuli were not previously conditioned by experience, they are termed unconditioned stimuli (UCS). The impact of UCS may provoke innate defensive responses, mainly mediated by activation of the autonomic nervous system (ANS), which were not previously conditioned, termed unconditioned responses (UCR). During fear conditioning, a neutral stimulus, which lacks any previous emotional relevance, may be introduced to impact at the same time, to coincide with the impact of an aversive UCS. After pairing with an aversive UCS, a neutral stimulus may be associated in such a way that, even in the absence of the UCS, may trigger a defensive response, similar to the UCR elicited by the aversive UCS, therefore becoming a conditioned stimulus (CS). Since the defensive response is similar to the UCR elicited by the UCS but may be provoked by the CS, even in the absence of the UCS, it has been termed conditioned response (CR)

a CS may lead to adaptive physiological responses, including activation of the ANS and the HPA axis, and defensive behavioural responses, including freezing, fight and flight, with their consequent symptoms, usually associated with the emotional experience of fear and anxiety (LeDoux, 2003). Fear conditioning may be developed after one pairing or several coincident events between the UCS and the CS and may be learned to last longer, as it is usually observed with certain traumatic events stored in long-term memory, which represent a critical factor in the development of depression and anxiety disorders, such as post-traumatic stress disorder (PTSD). It has been also observed that subsequent presentation of a CS in the absence of an associated UCS may gradually decrease the ability to provoke a CR, constituting a process of extinction (Sotres-Bayon, 2004). If extinction fails, certain CS may be perceived as threatening, therefore provoking the same CR, with the consequent fear or anxiety, even after the context changed (Milad & Quirk, 2012). It has been demonstrated that extinction is the result of a new learning process, which may inhibit the CR to the previously learnt CS, where an individual infers that a CS is no longer dangerous. Interestingly, this process has provided the basis for different psychotherapeutic strategies.

The possibility to evaluate and store fear memories is important to learn about potentially dangerous stimuli and respond accordingly to challenging conditions. It has been demonstrated that the amygdala plays a critical role in the cognitive and emotional processing of fear, particularly in fear conditioning and extinction (LaBar et al., 1998), where the hippocampus and the VM-PFC, through their reciprocal connections with the amygdala, have been also critically involved.

The amygdala represents the fear hub of the limbic system, composed of more than 12 nuclei, which may be further subdivided into more than 20 sub-nuclei, with extensive interconnections (Ressler, 2010; Pape & Pare, 2010). Among the most important nuclei, the LNA, the basal nucleus of the amygdala (BNA), also called BLA, and the CNA, with its medial (M-CNA) and lateral (L-CNA) subdivisions, play a critical role in the neural circuits of fear and anxiety (Fig. 4.17). The BLA group, composed of the lateral nucleus of the amygdala (LNA), BNA and accessory basal of the amygdala (ABA), is the main gateway for sensory input from the thalamus to the amygdala, whereas the CNA represents the main source of output from the amygdala to different neural structures (LeDoux, 2007; Sotres-Bayon et al., 2004; Pare et al., 2004).

Information associated to perceived stimuli, including CS and UCS, is conveyed from cortical and subcortical regions through glutamatergic projections to the BLA nuclei, mainly to the LNA and BNA (Fig. 4.17). Neurons in the BLA send projections to the CNA, which, in turn, activates different pathways involved in CR and UCR.

The BLA sends projections to the L-CNA, which shares reciprocal projections with the M-CNA, which, in turn, sends projections to hypothalamic and brainstem nuclei, involved in fear responses (Marek et al., 2013). The BLA sends stimulatory glutamatergic projections to the CNA and inhibitory di-synaptic projections, through intercalated GABAergic neurons (Fig. 4.17).

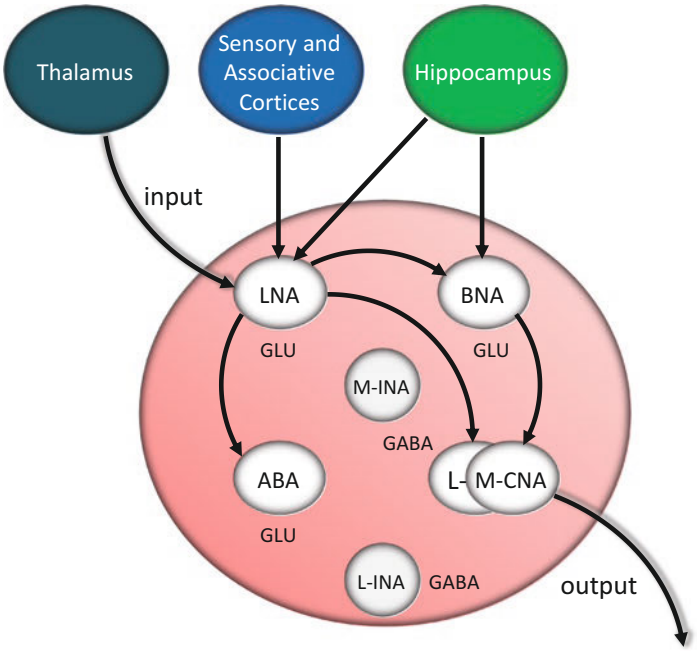

Fig. 4.17 Projections between different nuclei within the amygdala participate in the neural circuits of fear and anxiety. The lateral (LNA), basal (BNA), accessory basal (ABA) and the central (CNA) nuclei of the amygdala, with its medial (M-CNA) and lateral (L-CNA) subdivisions, play a critical role in the neural circuits of fear and anxiety. The baso-lateral (BLA) group, composed of the LNA, the BNA and the ABA, is the main gateway for sensory input from the thalamus to the amygdala, whereas the CNA represents the main source of output from the amygdala to different neural structures. Information about perceived stimuli is conveyed from the thalamus, sensory and association cortices and the hippocampus, through glutamatergic projections to the BLA, mainly to the LNA and BNA. The BLA sends stimulatory glutamatergic projections to the CNA and inhibitory projections, through intercalated GABAergic neurons. The LNA and the BLA contain excitatory glutamatergic neurons and inhibitory GABAergic interneurons; however, both nuclei send excitatory glutamatergic projections to the L-CNA and excitatory projections to the intercalated neurons, which, in turn, send inhibitory GABAergic projections to the M-CNA. Neurons in the BLA send projections to the L-CNA, which shares reciprocal projections with the M-CNA, which, in turn, sends projections to hypothalamic and brainstem nuclei involved in fear responses

During fear conditioning, certain glutamatergic neurons in the BLA have been shown to respond to the impact of CS. After extinction, these neurons decrease their response, and different neurons are activated in response to CS (Marek et al., 2013). During fear conditioning, glutamatergic neurons activated by the impact of CS send activating input to certain neurons in the L-CNA, which have been identified as "on", which inhibit a population of tonically active "off" neurons, which, in turn, send inhibitory GABAergic projections to the M-CNA (Ciocchi et al., 2010). The L-CNA also receives glutamatergic projections from other neural structures, including the insula and brainstem nuclei, such as the PBN. Hence, the impact of a CS

may lead to disinhibition of neurons in the M-CNA, which, in turn, activate fear responses (Marek et al., 2013; Ciocchi et al., 2010). After extinction, BLA activation of intercalated GABAergic neurons provokes inhibition of CNA neurons, therefore inhibiting fear responses.

The amygdala also shares important reciprocal projections with different areas in the medial PFC, particularly with the prelimbic PFC (PL-PFC; in rodents), which corresponds to the pre-genual ACC (pgACC) in primates, and the infralimbic PFC (IL-PFC; in rodents), which, in turn, corresponds to the sub-genual ACC (sgACC) in primates (Marek et al., 2013). In this regard, the PL-PFC participates in consolidation and recall of fear memories, whereas the IL-PFC participates in the consolidation of extinction of these memories. Therefore, in the fear circuit, the amygdala plays a critical role in the acquisition and expression of fear conditioning, as well as in extinction, whereas the PL- PFC does not participate in the acquisition but in the expression of fear and the IL-PFC in the consolidation of extinction.

The BLA sends reciprocal projections to the PL-PFC and the IL-PFC. The BLA also sends excitatory projections to the L-CNA, which results in disinhibition of the M-CNA. During extinction, these neurons in the BLA exhibit reduced activation in response to CS. In addition, it has been suggested that projections from the IL-PFC send also projections to intercalated GABAergic neurons, providing an additional mechanism to inhibit the CNA.

The Role of the Amygdala and the BNST in the Regulation of the HPA Axis

As previously described, the amygdala represents the fear hub of the limbic system. This almond-shaped neural structure, also known as the “amygdaloid complex”, is composed of more than 12 nuclei, which may be further subdivided into more than 20 sub-nuclei (Ressler, 2010; Pape & Pare, 2010). Among the most important nuclei, the LNA, the BNA (also called BLA) and the CNA, with its medial (M-CNA) and lateral (L-CNA) subdivisions, play a critical role in the neural circuits of fear and anxiety. The LNA represents the main gateway for sensory input from the thalamus to the amygdala, whereas the CNA represents the main source of output from the amygdala to different neural structures, including those involved in the expression of anxiety and fear responses (LeDoux, 2007; Sotres-Bayon et al., 2004; Pare et al., 2004) (Fig. 4.17).

The LNA receives excitatory glutamatergic projections from the thalamus. Thereafter, the LNA and the BLA contain excitatory glutamatergic neurons and inhibitory GABAergic interneurons; however, both nuclei send direct excitatory glutamatergic projections to the CNA, more specifically to the L-CNA, and excitatory projections to the intercalated neurons, which, in turn, send inhibitory GABAergic projections to the M-CNA (Fig. 4.17). Hence, the CNA constitutes the main source of projections from the amygdala to different neural structures,

mainly involved in behavioural and physiological responses, including innate and conditioned fear responses. It has been shown that more than 90% of neurons in the CNA express and release GABA (Šimić et al., 2021), while CRF and other neuropeptides are also synthesized and released by the CNA (McCall et al., 2015). Most of these CRF neurons are located in the L-CNA, with only few of them in the M-CNA. Under basal conditions, these neurons produce and release mostly GABA, which participates in the regulation of baseline anxiety, while under the impact of more salient events, such as the experience during stressful conditions, and these neurons may produce and release increased concentrations of CRF, which induces sustained modulatory effects, associated with anxiety-like behaviour (McCall et al., 2015; Šimić et al., 2021). In this regard, the CNA is closely connected with the BNST, constituting the core of the "extended amygdala", which plays a critical role in the psychoneurobiology of fear and anxiety. In this regard, it has been shown that the BNST receives projections from the BLA and the CNA and projections from the PFC and sends projections to the same brainstem structures as the CNA. Hence, the interconnections between the CNA and the BNST and their reciprocal connections with other neural structures may provide the bases for a better understanding of the neurobiological links between stress and anxiety.

The BNST is a complex neural structure, composed of different divisions, which, in turn, may be subdivided into more than 12 sub-nuclei. According to the earlier classifications, the BNST may be divided into medial (M-BNST) and lateral (L-BNST) regions or divisions (Dong et al., 2001; Moga et al., 1989), which, in turn, may be subdivided into sub-nuclei, including the antero-medial (AM-BNST), ventro-medial (VM-BNST), postero-medial (PM-BNST), dorso-lateral (DL-BNST), ventro-lateral (VL-BNST), antero-lateral (AL-BNST) and postero-lateral (PL-BNST), among many others. A more recent classification is based on anterior and posterior divisions, where the anterior division corresponds to the previous M-BNST and L-BNST, and the posterior division is also included in the M-BNST in the previous classification (Dong et al., 2001). According to these classifications, the DL-BNST corresponds to the oval nucleus (BNSTov), the VL-BNST corresponds to the fusiform nucleus (BNSTfu), the VM-BNST corresponds to the dorsomedial nucleus (BNSTdm), the AL-BNST corresponds to the subcomisural (BNSTsc), and the PM-BNST corresponds to the principal nucleus (BNSTpr) (Dong et al., 2001; Swanson et al., 1998).

The BNST receives projections from different nuclei of the amygdala, mostly from the CNA, and from the hippocampus and the PFC and, in turn, sends projections to the hypothalamic PVN, therefore playing a critical role in the regulation of the HPA axis, while constituting one of the main structures involved in the neurobiology of anxiety (Lebow & Chen, 2016) (Fig. 4.18). Within the amygdala, the BLA and subsequently the CNA receive information about environmental stressful stimuli from the thalamus and internal stimuli from the insular cortex. Within the CNA, the L-CNA is the origin of CRF projections to the L-BNST, which represents a pathway involved in sustained anxiety responses to long-term threats, whereas the M-CNA is the origin of CRF projections to different brainstem nuclei involved in

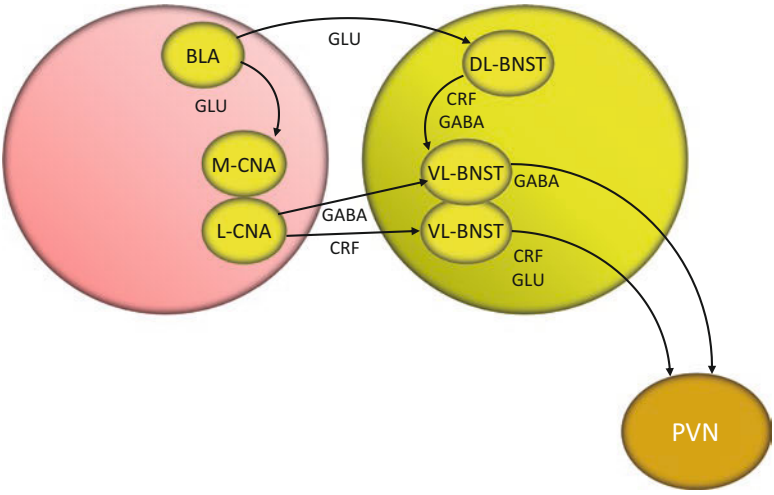

Fig. 4.18 Reciprocal projections within the extended amygdala. Within the amygdala, most of the CRF neurons in the central nucleus of the amygdala (CNA) are located in the L-CNA, with only few of them in the M-CNA. Under basal conditions, these neurons produce and release mostly GABA, which participates in the regulation of baseline anxiety. During stressful conditions, these neurons may produce and release increased concentrations of CRF. The CNA is connected with the BNST, constituting the "extended amygdala". The BNST receives projections from the BLA and the CNA and projections from the PFC and sends projections to the same brainstem structures as the CNA. The BNST may be divided into medial (M-BNST) and lateral (L-BNST) regions or divisions, which, in turn, may be subdivided into different sub-nuclei, including the dorsal lateral (DL-BNST) and ventro-lateral (VL-BNST), among many others. The BNST receives projections from different nuclei of the amygdala, mostly from the CNA, and from the hippocampus and the PFC and, in turn, sends projections to the hypothalamic PVN, therefore playing a critical role in the regulation of the HPA axis

behavioural, emotional and autonomic responses. This pathway plays a critical role in fear responses to short-term threats (Paul & Chen, 2017) (Fig. 4.19).

Excitatory glutamatergic projections from the BLA to the M-CNA and the L-BNST, but not to the L-CNA, convey information about the nature of internally and externally perceived threats. The L-CNA receives direct information about potential threats from the paraventricular nucleus of the thalamus (PVT) and from the insular cortex, the same sources that also project to the BLA. In addition, CRF projections from the L-CNA to the L-BNST may potentiate the excitatory glutamatergic input from the BLA to the L-BNST. In the L-BNST, it has been shown that CRF neurons in the dorso-lateral part (DL-BNST) co-localize with GABA, those in the ventro-lateral part (VL-BNST) co-localize with glutamate, and those in the M-CNA co-localize also with GABA (Fig. 4.19).

In the PVN, CRF neurons receive tonic inhibitory GABAergic input from neurons located next to them and excitatory CRF projections from the antero-ventral region of the BNST, which activates CRF synthesis and release in response to stressful events. In this regard, CRF neurons in the VL-BNST send CRF and

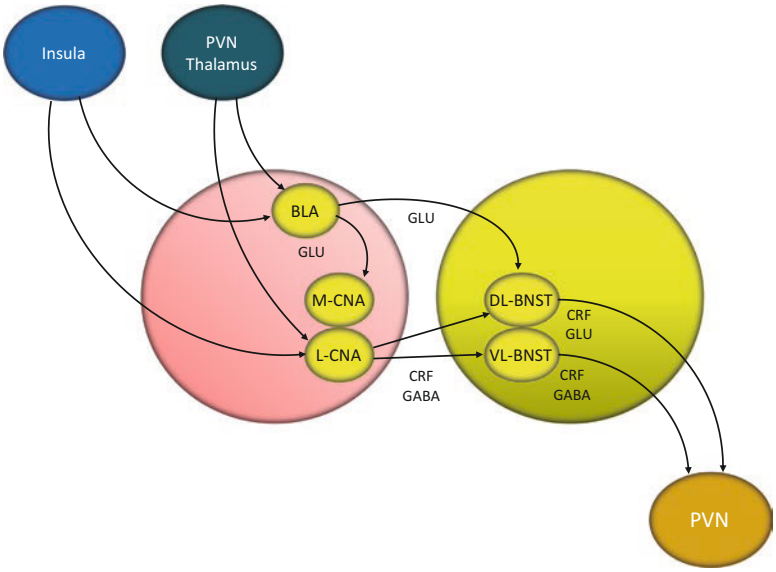

Fig. 4.19 Input to the extended amygdala and output to different neural structures. Within the amygdala, the BLA and subsequently the CNA receive information about environmental stressful stimuli from the thalamus and internal stimuli from the insular cortex. Within the CNA, the L-CNA is the origin of CRF projections to the L-BNST, which represents a pathway involved in sustained anxiety responses to long-term threats, whereas the M-CNA is the origin of CRF projections to different brainstem nuclei involved in behavioural, emotional and autonomic responses

glutamatergic excitatory projections to CRF neurosecretory neurons in the PVN, therefore stimulating the activity of the HPA axis (Paul & Chen, 2017). The DL-BNST may also affect the activity of the PVN through excitatory CRF and inhibitory GABAergic projections to CRF neurons in the VL-BNST. In addition, inhibitory GABAergic neurons in the VL-BNST receive and integrate excitatory projections from the ventral subiculum and the VM-PFC, particularly from the ACC (Radley & Sawchenko, 2011). Therefore, direct GABAergic projections from the VL-BNST to the PVN provide a pathway for the inhibitory effects of these neural structures on the HPA axis (Fig. 4.20).

The posterior region of the BNST receives and integrates projections from different structures, including inhibitory GABAergic projections from the MNA and excitatory glutamatergic projections from the CA1 of the hippocampus and the ventral subiculum. The principal nucleus, in the posterior BNST, may exert inhibition on other nuclei in the BNST, and it has been shown to exert inhibitory effect on the HPA axis, through direct inhibitory GABAergic projections to the PVN (Choi et al., 2007; Lebow & Chen, 2016). This may explain the inhibitory effect of the hippocampus and associated structures in the regulation of the HPA axis by indirect projections through the BNST (Fig. 4.21).

In the antero-ventral BNST, the VM-BNST (BNSTdm) and VL-BNST (BNSTfu) express CRF and send excitatory projections to the PVN. The stimulatory effect of

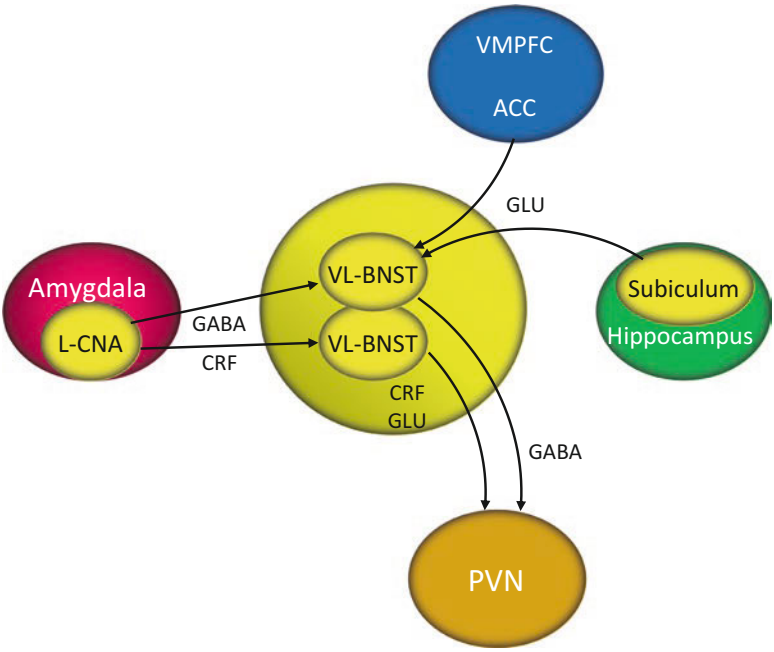

Fig. 4.20 Regulatory projections from the bed nucleus of the stria terminalis (BNST) to the paraventricular nucleus (PVN) of the hypothalamus. In the hypothalamic PVN, CRF neurons receive tonic inhibitory GABAergic input from neurons located next to them and excitatory CRF projections from the anteroventral region of the BNST, which activates CRF synthesis and release in response to stressful events. Hence, CRF neurons in the VL-BNST send CRF and glutamatergic excitatory projections to CRF neurons in the PVN, therefore stimulating the activity of the HPA axis. The DL-BNST may also affect the activity of the PVN through excitatory CRF and inhibitory GABAergic projections to CRF neurons in the VL-BNST. In addition, inhibitory GABAergic neurons in the VL-BNST receive and integrate excitatory projections from the subiculum and the VM-PFC, particularly from the ACC. Direct GABAergic projections from the VL-BNST to the PVN provide a pathway for the inhibitory effects of these neural structures on the HPA axis

the VL-BNST and the VM-BNST may be mediated by CRF projections and glutamatergic projections. The CNA may exert stimulatory effect on the HPA axis through CRF projections to the VM-BNST and VL-BNST, which also send CRF projections and excitatory glutamatergic projections to the PVN. The CNA may also exert stimulatory effect on the HPA axis through inhibitory GABAergic projections to inhibitory GABAergic neurons in the VM-BNST and VL-BNST, therefore resulting in disinhibition of the PVN with the consequent activation of the HPA axis (Choi et al., 2007).

In the posterior BNST, the principal nucleus (P-BNST) sends inhibitory GABAergic projections to the PVN (Choi et al., 2007; Dong & Swanson, 2004). The P-BNST receives inhibitory GABAergic projections from the MNA, which, in turn, may exert inhibitory effect on GABAergic projections from the P-BNST to the PVN, therefore resulting in disinhibition of the PVN and the consequent activation

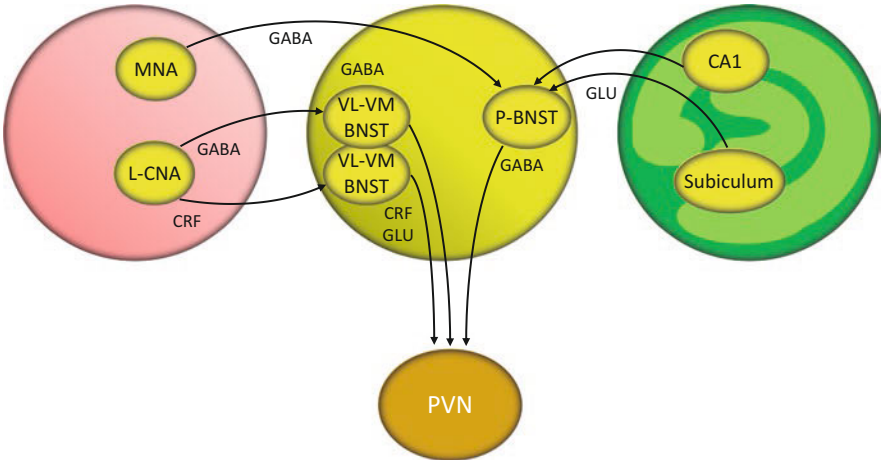

Fig. 4.21 Regulation of the hypothalamic-pituitary-adrenal (HPA) axis by projections from the amygdala, the hippocampus and the bed nucleus of the stria terminalis (BNST). The posterior region of the BNST receives inhibitory GABAergic projections from the MNA and excitatory glutamatergic projections from the CA1 of the hippocampus and the ventral subiculum. The principal nucleus, in the posterior BNST, may exert inhibition on other nuclei in the BNST and exert inhibitory effect on the HPA axis, through direct inhibitory GABAergic projections to the PVN. This may explain the inhibitory effect of the hippocampus and associated structures in the regulation of the HPA axis by indirect projections through the BNST. The VM-BNST and VL-BNST express CRF and send excitatory projections to the PVN. The stimulatory effect of the VL-BNST and the VM-BNST may be mediated by CRF and glutamatergic projections. The CNA may exert stimulatory effect on the HPA axis through CRF projections to the VM-BNST and VL-BNST, which also send CRF projections, and excitatory glutamatergic projections to the PVN. The CNA may also exert stimulatory effect on the HPA axis through inhibitory GABAergic projections to inhibitory GABAergic neurons in the VM-BNST and VL-BNST, resulting in disinhibition of the PVN with the consequent activation of the HPA axis. The principal nucleus of the BNST (P-BNST) sends inhibitory GABAergic projections to the PVN. The P-BNST receives inhibitory GABAergic projections from the MNA, which, in turn, may exert inhibitory effect on GABAergic projections from the P-BNST to the PVN, therefore resulting in disinhibition of the PVN and the consequent activation of the HPA axis. The P-BNST also receives excitatory glutamatergic projections from the hippocampus, mostly through the subiculum, which may stimulate GABAergic projections from the P-BNST to the PVN, resulting in the inhibitory effect on the HPA axis. Hippocampal projections may reach the PVN indirectly through excitatory glutamatergic projections from the ventral subiculum to the BNST, which, in turn, send inhibitory GABAergic projections to the PVN

of the HPA axis. The P-BNST also receives excitatory glutamatergic projections from the hippocampus, mostly through the ventral subiculum, which, in turn, may stimulate GABAergic projections from the P-BNST to the PVN, therefore resulting in the inhibitory effect on the HPA axis (Choi et al., 2007). In this regard, it has been shown that hippocampal projections may reach the PVN indirectly through excitatory glutamatergic projections from the ventral subiculum to the BNST, the preoptic area and the DMH, which, in turn, send inhibitory GABAergic projections to the PVN, but not through direct projections from the hippocampal formation to the

PVN (Cullinan et al., 1993). Therefore, it is well established that the amygdala and the hippocampus play a critical role in the regulation of the HPA axis, although it has been shown that these limbic structures have very sparse direct projections to the PVN, therefore relaying information to this hypothalamic nucleus mainly through the BNST (Choi et al., 2007) (Fig. 4.21).

The Role of the PVN in the Regulation of the HPA Axis

The hypothalamus is a complex neural structure, composed by more than 10 nuclei, which, in turn, are distributed in the rostral, the middle and the posterior part. The middle part, known as the tuberal hypothalamus, includes the anterior and lateral areas and the PVN, supraoptic nuclei (SON), ventro-medial nuclei (VMN), dorsal motor nuclei (DMN) and arcuate nuclei, which are involved in the integration and regulation of different autonomic and neuroendocrine functions (Fig. 4.22). The PVN comprises a magnocellular group of larger neurons, which synthesize oxytocin and vasopressin, a parvocellular group of smaller neurons, which synthesize and release different peptides involved in the regulation of different endocrine systems, and a group of parvocellular pre-autonomic neurons, involved in the regulation of the ANS. Additionally, the PVN also contains glutamatergic and GABAergic interneurons, which contribute to the regulation of the other neuronal groups (Saper & Lowell, 2014).

The PVN represents the core of the HPA axis, where parvocellular neurons produce CRF, which is released into the hypophyseal portal blood to reach the anterior pituitary, where it stimulates corticotrophic cells. In the anterior pituitary, CRF is known to up-regulate the transcription of proopiomelanocortin (POMC), which is a common precursor for the synthesis of adreno-corticotropic hormone (ACTH) and other peptides. Then, ACTH is released into the systemic blood circulation to reach the adrenal cortex, where it stimulates the biosynthesis and release of glucocorticoids, particularly cortisol.

It has been shown that the HPA axis is also regulated by limbic structures, mainly by stimulatory input from the amygdala, through direct projections from the CNA to the PVN, or indirectly through the BNST, and inhibitory input from the hippocampus, through indirect projections from the BNST to the PVN (Fig. 4.23).

The Role of the Amygdala and the Hypothalamus in the Regulation of the ANS

Activation of the ANS represents one of the principal components of adaptive reactions to stress, particularly in response to threat and potential danger. Hence, activation of the sympathetic system and the complementary activation of the parasympathetic system constitute an essential component of fear and anxiety. In this regard, it is well known that autonomic symptoms, mostly due to

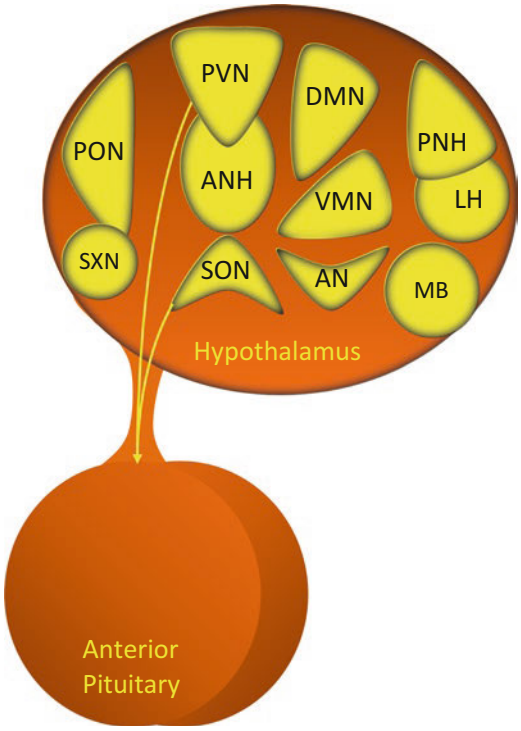

Fig. 4.22 Schematic representation of the hypothalamus and its different nuclei. The hypothalamus is a complex structure composed by more than 10 different nuclei. The hypothalamus may be divided into the rostral hypothalamus, which includes the suprachiasmatic (SXN) and the preoptic (PON) nuclei; the middle part of the hypothalamus, also known as the tuberal hypothalamus, which includes the anterior and lateral areas and the ventro-medial (VMN), dorsomedial (DMN), supraoptic (SON), paraventricular (PVN) and arcuate nuclei; and the posterior part, which includes the mammillary bodies and the supramammillary, tuberomammillary and posterior nuclei

hyperactivation of the sympathetic system, are typically observed during chronic stress and the consequent mood and anxiety disorders.

The hypothalamus plays a critical role in the activation and regulation of the ANS. In this regard, it has been shown that the PVN, through activation of a group of parvocellular pre-autonomic neurons, is critically involved in the regulation of the ANS, constituting the main integrator of stress signals (Ulrich-Lai & Herman, 2009). The PVN contains a group of parvocellular neurons involved in the regulation of the ANS through projections to both sympathetic and parasympathetic nuclei (Kreier et al., 2006). These neurons project to different neural structures in the brainstem and the spinal cord involved in the regulation of the ANS, including the nucleus of the tractus solitarius (NTS), the dorsal motor nucleus of the vagus (DMN or DMX), the nucleus ambiguus (NAm), the parabrachial nucleus (PBN) and the intermedio-lateral cell column (IML) (Ulrich-Lai & Herman, 2009; Swanson & Kuypers, 1980). It has been shown that the PVN is regulated by limbic structures,

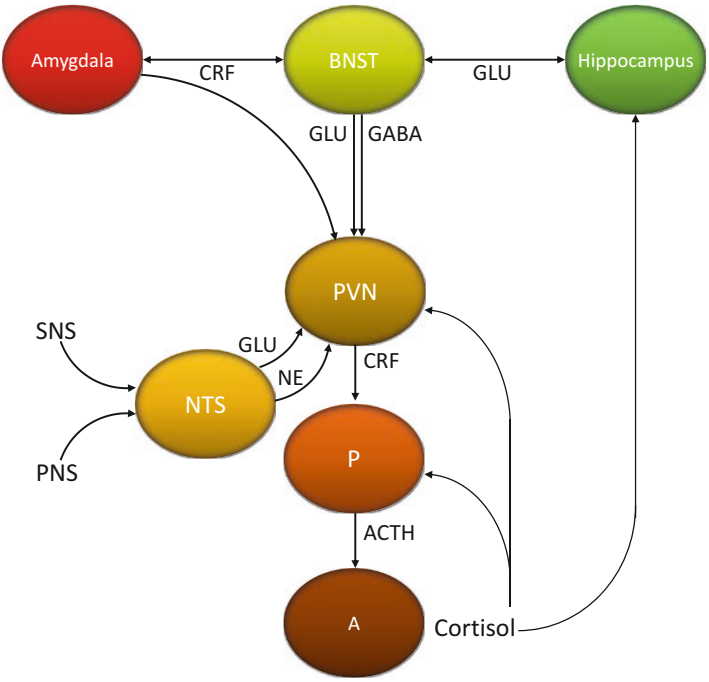

Fig. 4.23 Regulation of the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamic PVN is the core of the HPA axis, where parvocellular neurons produce CRF, which is released into the hypophyseal portal blood to reach the anterior pituitary, where it stimulates corticotroph cells. In the anterior pituitary, CRF up-regulates the transcription of POMC, which is a common precursor for the synthesis of ACTH and other peptides. Then, ACTH is released into the systemic blood circulation to reach the adrenal cortex, where it stimulates the biosynthesis and release of cortisol. The HPA axis is also regulated by stimulatory input from the amygdala, through direct projections from the CNA to the PVN or indirectly through the BNST, and inhibitory input from the hippocampus, through indirect projections from the BNST to the PVN

such as the amygdala, the hippocampus and the BNST, which, in turn, project to inhibitory GABAergic neurons, mainly located in the peri-PVN region (Roland & Sawchenko, 1993), therefore modulating the HPA axis and the ANS (Herman et al., 2002).

The DMN has been demonstrated to be also involved in the regulation of the ANS and the HPA axis in response to stressful stimuli. In this regard, stimulation of the DMN has been associated with sympathetic activation, reflected in an increased heart rate and blood pressure (Bailey & Dimicco, 2001), which have been associated with DMN projections involved in the regulation of the PVN. In this regard, different sub-nuclei in the DMN may exert different effects on the PVN, where activation of the dorsal DMN may lead to stimulation, and the ventral DMN has been associated with inhibition of the PVN, which has been, respectively, reflected in activation or inhibition of the HPA axis (DiMicco et al., 2002). Activation of the

DMN has been associated with stimuli from the amygdala, which project to the LH, which, in turn, sends excitatory projections to the DMN (DiMicco et al., 2002).

The amygdala initiates the activation of the sympathetic branch of the ANS through direct projections from the CNA to the nucleus of the solitary tract (NTS). In this regard, the BLA and the MNA may be activated by environmental psychosocial stressors, while the CNA may be directly activated by systemic stressors and indirectly by psychosocial stressors, through projections from the BLA and the MNA (Ulrich-Lai & Herman, 2009). The amygdala also shares reciprocal connections with the LC, which also sends stimulatory noradrenergic projections to the NTS. It has been shown that the amygdala also regulates the ANS and the HPA axis through direct, although sparse, projections to the PVN (Gray et al., 1989), while the strongest connections are mediated by projections from the CNA to the anterior BNST, which, in turn, sends stimulatory projections to the PVN (Fig. 4.24). The hippocampus plays also a critical role in the regulation of the ANS and the HPA axis. In this regard, the hippocampal formation sends projections from the subiculum to the posterior BNST, which, in turn, sends inhibitory projections to the PVN, which may be reflected through decreased heart rate, breathing rate and blood pressure (Ulrich-Lai & Herman, 2009). The NTS also receives direct stimulatory projections from the PVN and the LC, and all of them send stimulatory projections to the ventro-lateral medulla (VLM) (Fig. 4.24). Then, the rostral VLM, the LC and the PVN send projections to the preganglionic sympathetic nervous system (PG-SNS), particularly the intermedio-lateral cell column (IML), therefore initiating sympathetic responses. The NTS is also modulated by the VM-PFC, particularly through direct projections from infralimbic (IL) neurons, in the sgACC, and indirectly by the hippocampus, which exerts inhibitory tone on the NTS through projections to these IL neurons (Figueiredo et al., 2003) (Fig. 4.24). Hence, activation of the sympathetic system is reflected through an array of sympathetic responses, including an increased heart rate, blood pressure and breathing rate.

The parasympathetic system is mainly regulated by the NTS, which sends projections to the DMX and the NAm and direct projections from the PVN to the NTS and the DMX (Fig. 4.25). In addition, the NAm is also regulated by projections from the VM-PFC, particularly from prelimbic (PL) neurons, in the ACC. The amygdala also participates in the regulation of the parasympathetic system, through interactions with the anterior BNST, which, in turn, sends projections to the PVN and the NTS. Therefore, the PVN and the NTS send projections to the DMX and the NAm, which, in turn, send projections to the postganglionic parasympathetic system, therefore regulating the activation of target organs (Fig. 4.25).

The Role of the Locus Coeruleus and the Noradrenergic System in Stress

It has been shown that norepinephrine (NE) plays a critical role in various pathways involved in cognitive and emotional functions. Noradrenergic projections to cortical and subcortical structures are mainly originated in the brainstem nucleus LC, which

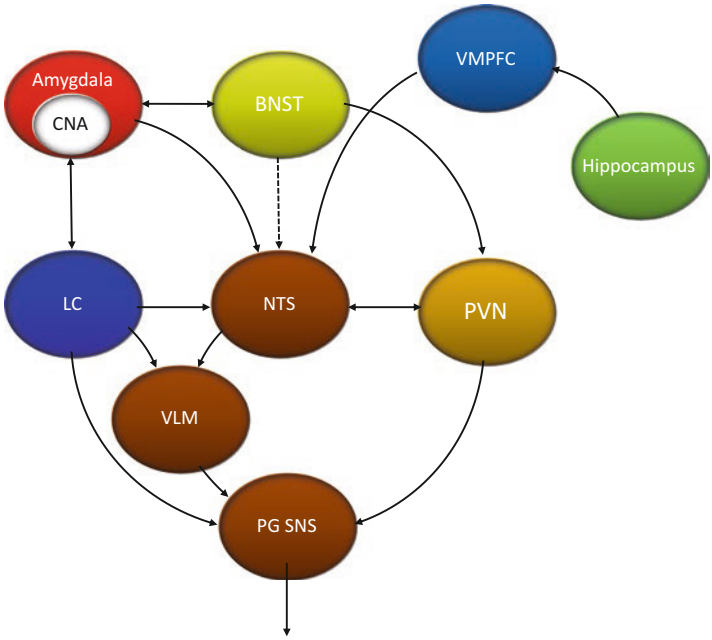

Fig. 4.24 Regulation of the sympathetic system. The hypothalamic PVN is involved in the regulation of the ANS through projections to sympathetic and parasympathetic nuclei. These neurons project to different neural structures in the brainstem and the spinal cord involved in the regulation of the ANS, including the nucleus of the tractus solitarius (NTS), the dorsal motor nucleus of the vagus (DMN or DMX), the nucleus ambiguus (NAm), the parabrachial nucleus (PBN) and the intermedio-lateral cell column. The PVN is regulated by the amygdala, the hippocampus and the BNST, which project to inhibitory GABAergic neurons, mainly located in the peri-PVN region, therefore modulating the HPA axis and the ANS. Stimulation of the DMN may lead to sympathetic activation. Activation of the dorsal DMN may lead to stimulation and the ventral DMN to inhibition of the PVN, reflected in activation or inhibition of the HPA axis. Activation of the DMN has been associated with stimuli from the amygdala, which project to the LH, which sends excitatory projections to the DMN. The amygdala initiates the activation of the sympathetic system through projections from the CNA to the NTS. The BLA and the MNA may be activated by psychosocial stressors, while the CNA may be activated by systemic stressors and by psychosocial stressors, through projections from the BLA and the MNA. The amygdala also shares reciprocal connections with the LC, which also sends stimulatory NA projections to the NTS. The amygdala also regulates the ANS and the HPA axis through direct projections to the PVN and mainly by projections from the CNA to the anterior BNST, which, in turn, sends stimulatory projections to the PVN. The hippocampal formation sends projections from the subiculum to the posterior BNST, which sends inhibitory projections to the PVN. The NTS also receives direct stimulatory projections from the PVN and the LC, and all of them send stimulatory projections to the ventro-lateral medulla (VLM). Then, the rostral VLM, the LC and the PVN send projections to the preganglionic sympathetic nervous system (PG-SNS), particularly the intermedio-lateral cell column (IML), therefore initiating sympathetic responses. The NTS is also modulated by the VM-PFC, particularly through direct projections from infralimbic (IL) neurons, in the sgACC, and indirectly by the hippocampus, which exerts inhibitory tone on the NTS through projections to the IL neurons

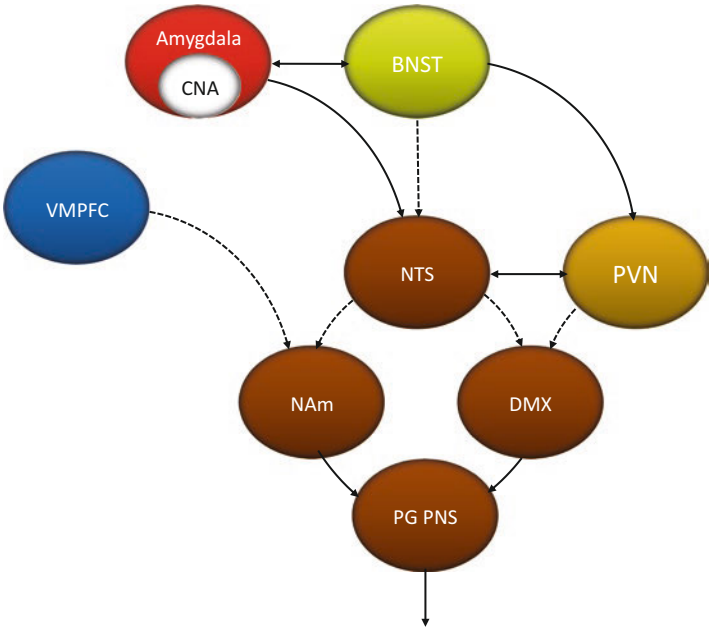

Fig. 4.25 Regulation of the parasympathetic system. The parasympathetic system is mainly regulated by the NTS, which sends projections to the DMX and the NAm and direct projections from the PVN to the NTS and the DMX. The NAm is also regulated by projections from the VM-PFC, particularly from prelimbic (PL) neurons, in the ACC. The amygdala also participates in the regulation of the parasympathetic system, through interactions with the anterior BNST, which, in turn, sends projections to the PVN and the NTS. Therefore, the PVN and the NTS send projections to the DMX and the NAm, which, in turn, send projections to the post-ganglionic parasympathetic system, therefore regulating the activation of target organs (Fig. 4.25)

has been also identified as the A6 area, and from noradrenergic cell groups in the medulla oblongata identified as A1, A2 and A5 (Bouret et al., 2003), which are known to be also involved in the regulation of autonomic functions (Fig. 4.26). The LC plays a critical role in adaptive responses to stress, which is known to be immediately activated during stressful situations, therefore producing and releasing increased concentrations of NA throughout the CNS. This has been associated with the stimulatory effects produced by increased concentrations of CRF (Valentino et al., 1992), which may reach the LC through different projections. In this regard, the LC receives stimulatory CRF projections from the amygdala, particularly from the CNA, and from the hypothalamic PVN (Morris et al., 2020) (Fig. 4.27). The LC also receives projections from different cortical areas, including the DL-PFC, the DM-PFC, the insula, and indirectly from the VM-PFC, particularly from the PL, which corresponds to the pgACC in humans. The LC also shares reciprocal connections with the other aminergic nuclei in the brainstem, such as the dopaminergic VTA and the serotonergic DRN, which play a critical role in the regulation of

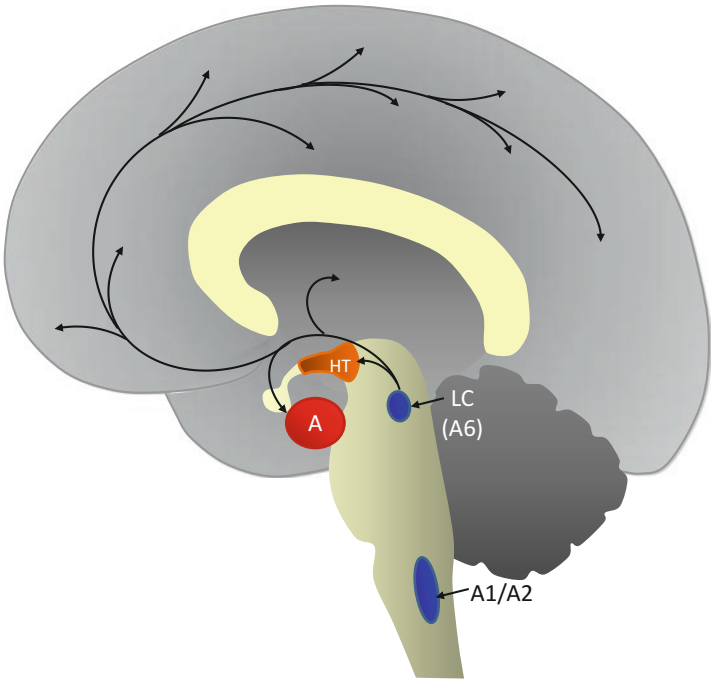

Fig. 4.26 Schematic representation of the noradrenergic system. Noradrenergic projections to cortical and subcortical structures are mainly originated in the locus coeruleus (LC), which has been also identified as the A6 area, and from noradrenergic cell groups in the medulla oblongata, identified as A1, A2 and A5, which are known to be also involved in the regulation of autonomic functions

adaptive responses to stress (Fig. 4.27). The LC also receives excitatory glutamatergic and CRF projections from the nucleus paragigantocellularis (PGN) and inhibitory GABAergic projections from the nucleus prepositus hypoglossi (PHN) (Fig. 4.27). The PGN and the PHN are located in the rostral medulla and are involved in autonomic regulation, particularly in sympathetic activation, and visceral functions. In addition, the LC also receives projections from the hypothalamic PVN, the lateral hypothalamus and the PAG, which are involved in stress responses (Ressler & Nemeroff, 1999). It has been shown that the LC also receives modulatory GABAergic projections from neurons located in the peri-coeruleus region, which exert a modulatory role on noradrenergic neurons (Bouret et al., 2003).

Reciprocally, ascending projections from the LC innervate different limbic structures, such as the amygdala, particularly through reciprocal projections to the CNA involved in salient detection and associative learning, the hippocampus involved in learning and memory, the hypothalamus involved in the regulation of the ANS and the HPA axis, and different cortical areas involved in the regulation of attention and arousal (Fig. 4.28). In addition, the LC also sends projections to the PAG, the BNST and the NTS, which participate in the regulation of the ANS (Morris et al., 2020).

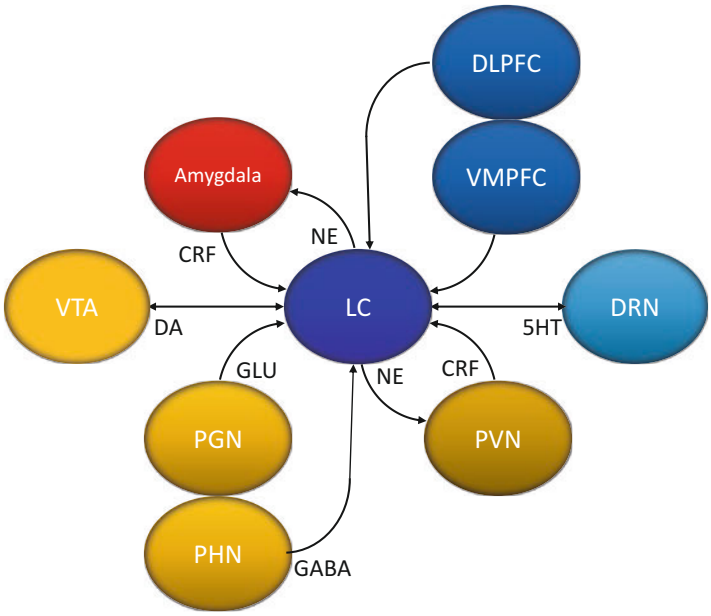

Fig. 4.27 The noradrenergic system participates in adaptive responses to stress. The locus coeruleus (LC) plays a critical role in adaptive responses to stress, releasing NA throughout the CNS. The LC receives stimulatory CRF projections from the amygdala, particularly from the CNA, and from the hypothalamic PVN. The LC also receives projections from different cortical areas, including the DL-PFC, the DM-PFC and the insula and indirectly from the VM-PFC, particularly from the PL, which corresponds to the pgACC. The LC also shares reciprocal connections with the dopaminergic VTA and the serotonergic DRN. The LC also receives excitatory glutamatergic and CRF projections from the nucleus paragigantocellularis (PGN) and inhibitory GABAergic projections from the nucleus prepositus hypoglossi (PHN). The PGN and the PHN are involved in autonomic regulation, particularly in sympathetic activation, and visceral functions. The LC also receives projections from the hypothalamic PVN, the lateral hypothalamus and the PAG, which are involved in stress responses

Therefore, the LC represents the hub of a neural system involved in the modulation of descending cortical and subcortical, cognitive and emotional input, and ascending visceral signals, implicated in the regulation of different psychophysiological functions (Morris et al., 2020) (Fig. 4.28). In this regard, tonic firing of the LC is necessary for normal vigilance, orienting and attentional functions. An increased tonic firing may lead to hyperarousal and anxiety. When a novel or disruptive stimulus is introduced, this may lead to phasic activation of the LC, with the resulting increased vigilance, with attentional and behavioural reorienting to salient or threatening stimuli, aimed at preparing a rapid behavioural response. Perceived stressful stimuli may lead to an increased NE and CRF release, with the resulting stimulation of the HPA axis, and the consequent increased synthesis and release of glucocorticoids. Increased levels of CRF may also lead to an increased tonic LC activation, and the resulting NE release, which, in turn, activates the HPA axis,

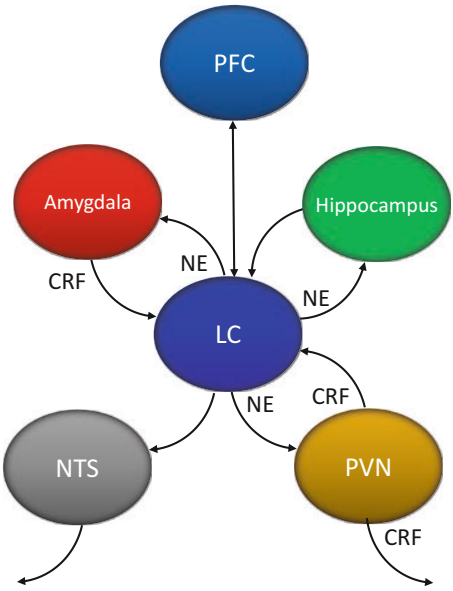

Fig. 4.28 Projections from the noradrenergic system to different neural structures. Ascending projections from the LC innervate the amygdala, particularly through reciprocal projections to the CNA, the hippocampus, the hypothalamus that is involved in the regulation of the ANS and the HPA axis and different cortical areas that is involved in the regulation of attention and arousal. The LC also sends projections to the PAG, the BNST and the NTS, which participate in the regulation of the ANS. Stressful stimuli may lead to an increased NE and CRF release, with the resulting stimulation of the HPA axis. Increased levels of CRF may lead to LC activation and the resulting NE release, which, in turn, activates the HPA axis, generating a positive feedback circuit involved in the development of anxiety. Stressful stimuli may lead to an increased LC connectivity with the amygdala, contributing to rapid responses to stress

generating a positive feedback circuit involved in the development of anxiety (Owens et al., 1994). Moreover, perceived stressful stimuli may lead to an increased LC connectivity with the amygdala (van Marle et al., 2010), therefore contributing to rapid responses to stress.

The amygdala has been implicated in stress processing, integrating information conveyed through projections from different sources, and associative learning, while the LC has been implicated in a rapid increased vigilance and arousal. In this regard, the amygdala receives and integrates environmental information from the thalamus, the hippocampus and sensory, associative and transition cortices and visceral information from the insula and subcortical structures, therefore producing conditioned associations, with the resulting learned fear responses (Cardinal et al., 2002). The amygdala may be increasingly activated by more salient stimuli, either aversive or appetitive, with the resulting increase in CRF release through projections from the CNA (Morris et al., 2020; Fitzgerald et al., 2006).

The PFC has been also implicated in stress processing. Activation of the medial PFC, comprised of the VM-PFC, with overlapping parts of the OFC and the ACC, has been associated with extinction, to regulate learned negative associations, through reciprocal connections with the amygdala and the LC (Delgado et al., 2008), which may be translated into emotion regulation and the resulting control of anxiety (Delgado et al., 2008). Activation of the DL-PFC has been associated with regulation of stress-related responses, through projections to the medial PFC, with the subsequent projections to the amygdala, therefore exerting cognitive control on negative emotions, which is critical for the development of resilience (Ochsner et al., 2004). Hence, the PFC participates in the control of emotional and autonomic responses to stress, while acute stress reactions may lead to sustained activation of the LC, with the resulting excessive release of NE. Excessive stress reactions, as usually observed during chronic stress, may lead to sustained activation of the LC, with the consequent amplified reactivity, and an increased NE release in response to subsequent stressful stimuli, which may lead to functional and structural alterations in different areas of the PFC, which, in turn, may reduce cognitive control on emotional responses (Arnsten, 2009). Prolonged and sustained activation of the LC may lead to excessive release of NE in the amygdala (McCall et al., 2017), which, in turn, may lead to excessive release of CRF in the LC, with the resulting increase in tonic LC activity, hence contributing to the development of anxiety in response to stressful stimuli (McCall et al., 2015).

The LC may be activated by novel stimuli, but if the stimulus is not aversive, this may lead to habituation and decreased LC activity (Sara & Bouret, 2012). In this regard, it has been shown that projections from the medial PFC may suppress LC activity. The LC is stimulated by CRF-mediated projections from the amygdala, particularly from the CNA, which reciprocally receives an important noradrenergic input. It has been shown that fear conditioning is associated with activation of the CNA, with the consequent activation of the LC, which, in turn, sends noradrenergic projections to the BLA and LNA. An increased noradrenergic release in the amygdala contributes to memory consolidation. An increased CRF release from the CNA to the LC contributes to an increased attention and arousal, through noradrenergic projections from the LC to different cortical and subcortical regions, and enhanced processing of sensory information, which, in turn, may lead to enhanced learning and memory. In this regard, activation of the LC may also lead to an increased release of NE in the hippocampus, more specifically in the DG, thus also contributing to memory formation. Therefore, LC projections to the amygdala and the hippocampus contribute to cognitive and emotional functions.

There are noradrenergic projections from the LC to the VTA, which potentiate the activity of dopaminergic neurons in the mesolimbic pathway, and noradrenergic projections from the LC to the DRN and medial raphe nuclei (MRN). In this regard, it has been shown that activation of α_1 noradrenergic receptors increases and α_2 receptors decreases the firing rate of serotonergic neurons in the DRN (Ressler & Nemeroff, 1999). The LC sends noradrenergic projections to different cortical and subcortical structures through the whole brain. Upon exposure to stressful stimuli,

the LC may be stimulated by an increased CRF release from the extended amygdala, including projections from the CNA and the BNST, and CRF projections from the hypothalamic PVN, through stimulation of CRFR1, which, in turn, may lead to an increased noradrenaline (NA) release in the areas innervated by projections from the LC, including the CNA and the BLA. Therefore, an increased release of CRF in the LC may lead to a higher tonic activity, which, in turn, may also lead to a heightened arousal and environmental scanning, rather than phasic activity, produced by glutamatergic stimulation, which may lead to selective attention to discrete stimuli. The LC sends excitatory noradrenergic projections to CRF neurons in the CNA, therefore constituting a positive feedback mechanism, which, in turn, may lead to an increased NE release in order to improve adaptive responses to stress. Excessive activation of this positive feedback may lead to maladaptive responses, including hypervigilant states, as observed in different anxiety disorders.

The Role of the Raphe Nuclei and the Serotonergic System in Stress

It has been shown that 5HT plays a critical role in various circuits involved in cognitive and emotional functions, and these serotonergic pathways are originated in the brainstem raphe nuclei (RN), including the DRN and the MRN (Fig. 4.29). Serotonergic projections from the MRN may reach diverse neural structures, including the thalamus, the hypothalamus and the hippocampus. It has been shown that 5HT released in the hippocampus may stimulate $5HT_{1A}$ receptors, which play a critical role in the process of adaptation to chronic adverse stimuli. This process is necessary to develop tolerance to undesirable adverse events, such as those perceived during chronic stressful experiences. Hence, alteration of this important serotonergic pathway has been associated with learned helplessness and the development of depressive symptoms, such as impaired mood and low tolerance to adversity (Deakin & Graeff, 1991). Upon exposure to chronic stressful situations, activation of this serotonergic pathway plays a critical role in adaptation through stimulation of hippocampal $5HT_{1A}$ receptors, which may contribute to inhibiting the formation and consolidation of stressful memories, therefore disconnecting the impact produced by aversive events from their emotional and behavioural outcomes (Deakin & Graeff, 1991). This process may contribute to developing coping responses to chronic stress while preventing the development of learned helplessness.

Serotonergic projections from the DRN may reach different neural structures, including the extended amygdala (Deakin, 1991; Lowry, 2005), where it has been shown that 5HT released in the CNA and the BNST may exert stimulatory effects through interactions with $5HT_{2A}$ receptors (Fig. 4.29). The activation of this serotonergic pathway has been associated with increased feelings of fear and anxiety (Maier & Watkins, 2005; Maier et al., 1993). In this regard, in response to acute stressors, an increased arousal may be associated with improved attention and

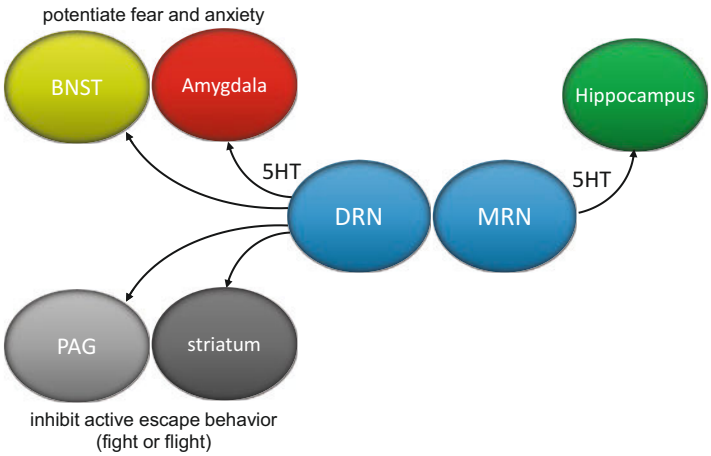

Fig. 4.29 Projections from the serotonergic system to different neural structures. Serotonergic pathways are originated in the brainstem raphe nuclei (RN), including the DRN and the MRN. Serotonergic projections from the MRN may reach diverse neural structures, including the hippocampus, which play a critical role in the adaptation to chronic adverse stimuli. Alteration of this pathway has been associated with learned helplessness and depression. Serotonergic projections from the DRN may reach different neural structures, including the extended amygdala, where it has been shown that 5HT released in the CNA and the BNST. Activation of this pathway has been associated with increased feelings of fear and anxiety. Projections from the DRN may also reach parts of the striatum and the peri-aqueductal grey (PAG), which participate in the development and modulation of active coping behavioural responses. Serotonergic input from the DRN to the striatum and PAG may have an inhibitory effect, therefore leading to inhibition of active responses, such as fight or flight, which, in turn, may lead to increased passive responses

awareness, which, in turn, may lead to subtle feelings of anxiety. In addition, any environmental stressor associated with potential danger or threat may provoke feelings of fear, which, in this context, plays an important adaptive role necessary to develop and maintain active behavioural responses, such as the activation of the typical fight-or-flight response. During chronic stressful situations, sustained feelings of fear and excessive anxiety may interfere with adaptive cognitive and emotional processing, with the consequent behavioural and pathophysiological reactions, which, in turn, may lead to excessive and maladaptive responses, usually observed in depression and anxiety disorders. In this regard, additional projections from the DRN may also reach parts of the striatum and the peri-aqueductal grey (PAG), which participate in the development and modulation of active coping behavioural responses (Graeff et al., 1996) (Fig. 4.29). In this regard, serotonergic input from the DRN to the striatum and PAG may have an inhibitory effect, therefore leading to inhibition of active responses, such as fight or flight, which, in turn, may lead to increased passive responses (Maier & Watkins, 2005; Maier et al., 1993). The inhibition of active responses, with the consequent predominance of passive responses, also defined as “passivity”, alongside increased feelings of fear, uncertainty and anxiety, constitutes the main symptoms of learned helplessness (Seligman, 1974), which represents the gateway to depression.

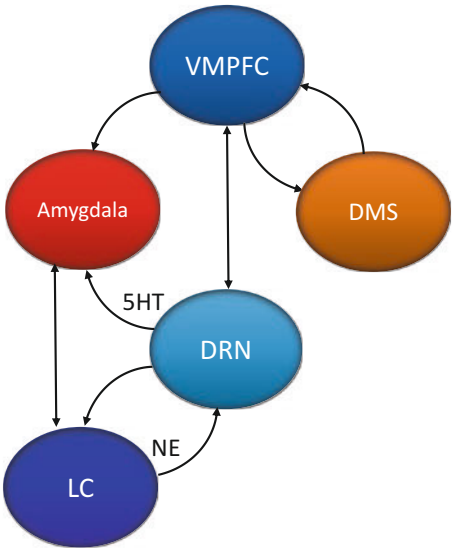

Fig. 4.30 Projections from the ventro-medial prefrontal cortex (VMPFC). Activation of the serotonergic DRN may be modulated by excitatory projections from the noradrenergic LC and inhibitory projections from the VM-PFC. The inhibitory effect exerted by the VM-PFC on the DRN is mediated by glutamatergic neurons, which stimulate GABAergic interneurons in the DRN, which, in turn, exert an inhibitory effect on serotonergic neurons in the DRN. The VM-PFC, in association with the dorsal medial striatum, participates in a neural circuit involved in detection of control, which may exert inhibitory effect on the DRN. Therefore, inhibition of active responses, with the resulting passive responses, associated with chronic stress and the consequent learned helplessness, may be neutralized by learned control, which is mediated by the inhibitory effect of the VM-PFC on the DRN. The VM-PFC also sends glutamatergic projections to GABAergic interneurons in the amygdala, which may exert an inhibitory effect. Hence, an increased activation of the amygdala, with the resulting feelings of fear and anxiety, may be neutralized by an increased activation of the VM-PFC, which has been involved in learned control

Activation of the serotonergic DRN may be modulated by projections from diverse neural structures, including excitatory input from the noradrenergic LC, which plays a critical role in adaptive responses, and inhibitory input from certain areas of the PFC, particularly from the PL area of the VM-PFC (Peyron et al., 1997) (Fig. 4.30). The inhibitory effect exerted by the VM-PFC on the DRN is mediated by glutamatergic neurons, which stimulate GABAergic interneurons in the DRN, which, in turn, exert an inhibitory effect on serotonergic neurons in the DRN. It has been shown that the VM-PFC, in association with the dorsal medial striatum, participates in a neural circuit involved in detection of control, which, in turn, may exert inhibitory effect on the DRN (Baratta et al., 2009; Maier & Seligman, 2016). Therefore, the situation provoked by inhibition of active responses, with the resulting passive responses, associated with chronic stress and the consequent learned helplessness, may be neutralized by learned control, which, in turn, is mediated by the inhibitory effect of the VM-PFC on the DRN (Maier & Watkins, 2005; Maier & Seligman, 2016) (Fig. 4.30). Moreover, it has been shown that prelimbic (PL) and

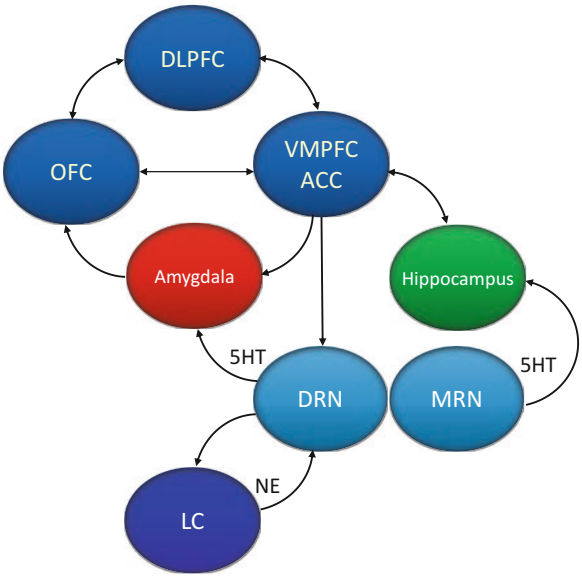

Fig. 4.31 Learned controllability is mediated by interactions between different areas of the prefrontal cortex (PFC) and aminergic systems. Other areas in the PFC have been also associated with learned control, such as the DL-PFC, the OFC and the ACC. Therefore, cognitive processing in the DL-PFC may induce activation of the VM-PFC, which, in turn, may exert regulatory control through inhibitory projections to the amygdala and the DRN. This may lead to an increased predictability and controllability, which are crucial for the development of resilience

infralimbic (IL) neurons in the VM-PFC also send glutamatergic projections to GABAergic interneurons in the amygdala, which, in turn, may exert an inhibitory effect on the amygdala (Fig. 4.30). Hence, an increased activation of the amygdala, with the resulting feelings of fear and anxiety, may be neutralized by an increased activation of the VM-PFC, which has been involved in learned control.

Other areas in the PFC have been also associated with learned control, such as the DL-PFC, which participates in working memory and cognitive processing and therefore is involved in cognitive aspects of inhibitory control; the OFC, which is involved in emotional features of inhibitory control; and the ACC, which plays a critical role in emotion regulation (Shi et al., 2019). Therefore, cognitive processing in the DL-PFC may induce activation of the VM-PFC, which, in turn, may exert regulatory control through inhibitory projections to the amygdala and the DRN. This may lead to neuroplasticity through the stimulation of a new protein synthesis, consolidating these neural pathways involved in predictability and controllability, which are crucial for the development of resilience (Fig. 4.31).

The extended amygdala shares important connections with the serotonergic system, mainly with the DRN. The CNA sends CRF projections to the DRN, through the L-CNA and M-CNA, more specifically to certain sub-nuclei, such as the dorsal and caudal DRN, associated to responses to anxiogenic stimuli, and the ventro-lateral DRN (VL-DRN) which, along with the ventro-lateral PAG (VL-PAG),

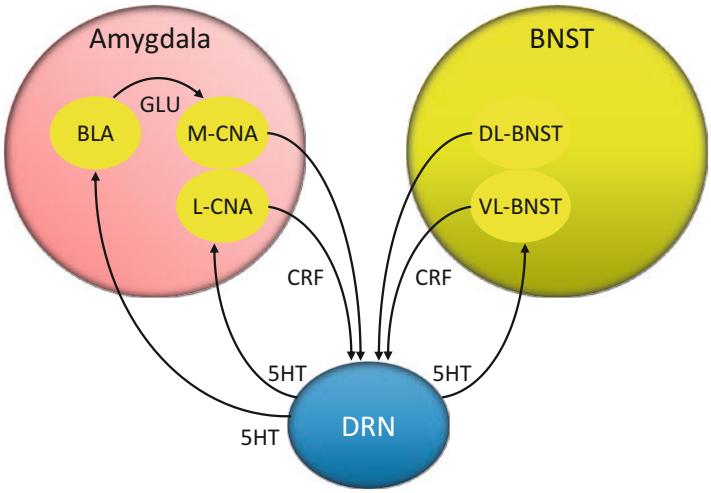

Fig. 4.32 Reciprocal projections between the extended amygdala and the dorsal raphe nuclei (DRN). The extended amygdala shares connections with the DRN. The CNA sends CRF projections to the DRN, through the L-CNA and M-CNA. The BNST also sends CRF projections from the DL-BNST and to a lesser extent also from the VL-BNST to the DRN. Excessive CRF release in the DRN, which has higher concentrations of CRF-R2, may lead to an increased release of 5HT in the amygdala, particularly in the BLA, which may be translated into chronic anxiogenic states. Stimulation of CRF-R2 in the DRN may be involved in the development of learned helplessness after exposure to uncontrollable chronic stress. CRF neurons in the CNA and BNST receive serotonergic projections from the same areas of the DRN to which they send projections, which have been suggested to participate in stress-induced emotional regulation

participate in the behavioural coping responses, such as freezing. The BNST also sends CRF projections, mostly from the DL-BNST and, to a lesser extent, also from the VL-BNST, to the DRN (Fig. 4.32).

The effects of CRF in the DRN may depend on the binding of CRF to different receptors, their actions on serotonergic and GABAergic neurons and the available concentrations of the released CRF. In this regard, it has been shown that lower concentrations of CRF may bind principally to CRF-R1, which inhibit 5HT release, and higher concentrations may bind principally to CRF-R2, which stimulate 5HT release in the DRN. Therefore, lower concentrations of CRF, associated with acute stress, may stimulate CRF-R1, with the resulting inhibitory effect on 5HT release in the DRN, while an increased CRF release, associated with chronic stressful situations, may lead to internalization of CRF-R1 and trafficking of CRF-R2 to the cell membrane, therefore stimulating serotonergic neurons, with the consequent increased release of 5HT from the DRN (Valentino et al., 2010) (Fig. 4.33). Moreover, an excessive CRF release in the DRN, more specifically in the dorsal and caudal areas, which have higher concentrations of CRF-R2, may lead to an increased release of 5HT in the amygdala, particularly in the BLA and in certain regions of the PFC, which, in turn, may be translated into chronic anxiogenic states. In this regard, it has been suggested that stimulation of CRF-R2 in the DRN may be involved in the

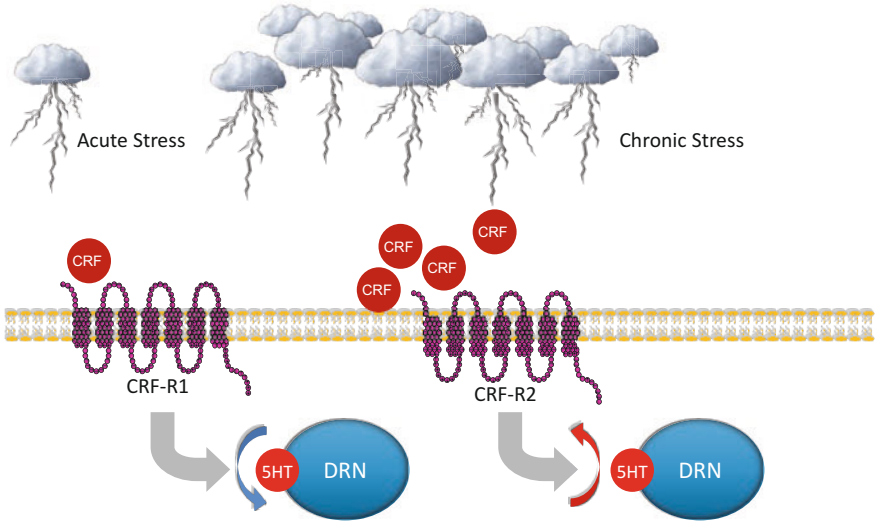

Fig. 4.33 Effects of CRF on the serotonergic system in acute and chronic stress. The effects of CRF in the DRN may depend on the binding of CRF to different receptors and their actions on serotonergic and GABAergic neurons and on the available concentrations of released CRF. Lower concentrations of CRF, associated with acute stress, bind principally to CRF-R1, which inhibit 5HT release, and higher concentrations, associated with chronic stress, bind principally to CRF-R2, which stimulate 5HT release in the DRN

development of learned helplessness after exposure to uncontrollable chronic stress (Maier & Watkins, 2005). Moreover, CRF neurons in the CNA and BNST receive serotonergic projections from the same areas of the DRN to which they send projections, which have been suggested to participate in stress-induced emotional regulation (Commons et al., 2003) (Fig. 4.32). It has been shown that serotonergic projections from the DRN to the BNST may be excitatory through stimulation of $5HT_{2A}$, $5HT_{2C}$ and $5HT_7$ receptors, which may contribute to anxiogenesis, and may be also inhibitory through stimulation of $5HT_{1A}$, which may lead to anxiolysis (Paul & Chen, 2017). In this regard, chronic stress may induce changes in the expression patterns of different 5HT receptors, associated with excitatory responses to 5HT in the BNST, which, in turn, have been associated with increased anxiety.

Therefore, anxiogenic stimuli may activate CRF neurons in the DL-BNST, which sends projections to stimulate the dorsal and caudal areas of the DRN through binding to CRF-R2. Consequently, these serotonergic neurons send inhibitory projections from the DRN to the DL-BNST, constituting a negative feedback mechanism, which may limit the activation of CRF neurons in the BNST provoked by acute stress. Chronic stress may lead to an increased expression of $5HT_{2A}$ and $5HT_7$ receptors in the DL-BNST, which, in turn, may lead to an increased CRF release from the DL-BNST to the DRN, with the consequent chronic anxiety (Hammack et al., 2009).

Serotonergic projections from the DRN to the CNA have been also involved in the regulation of the HPA axis (Feldman et al., 2000) and have been associated with

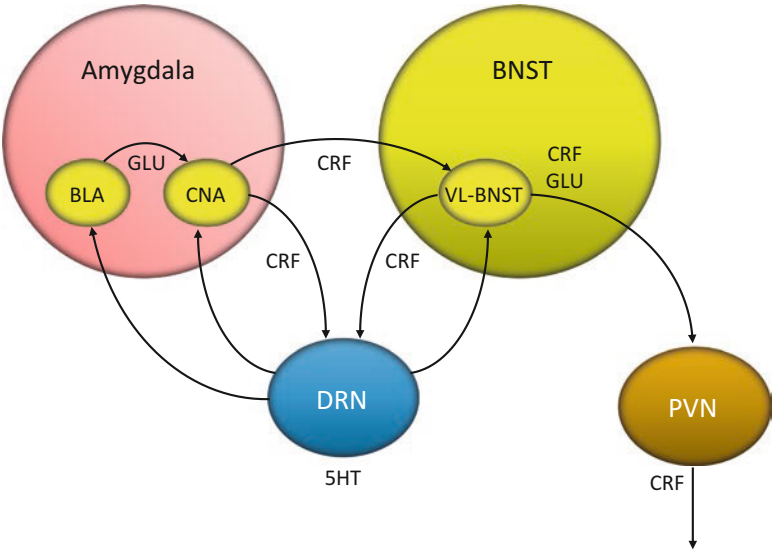

Fig. 4.34 Interactions between the extended amygdala and the serotonergic system in stress and anxiety. Anxiogenic stimuli activate CRF neurons in the DL-BNST, which sends projections to stimulate the DRN through binding to CRF-R2. These 5HT neurons send inhibitory projections from the DRN to the DL-BNST, constituting a negative feedback mechanism, which may limit the activation of CRF neurons in the BNST provoked by acute stress. Chronic stress may lead to an increased 5HT release in the DL-BNST, which may lead to an increased CRF release from the DL-BNST to the DRN, with the consequent chronic anxiety. Serotonergic projections from the DRN to the CNA have been also involved in the regulation of the HPA axis and have been associated with anxiety and fear behavioural responses, such as freezing, through projections to the PAG. An increased 5HT release in the CNA is necessary to reach its stimulatory effect on the HPA axis, and CRF stimulation is necessary to provoke an increased 5HT release from the DRN

anxiety and fear behavioural responses, such as freezing, through projections to the PAG. In this regard, the L-CNA and M-CNA send CRF projections to the VL-PAG, involved in coping responses, such as freezing (Forster et al., 2006). An increased 5HT release in the CNA is necessary to reach its stimulatory effect on the HPA axis, and CRF stimulation is necessary to provoke this increased 5HT release from the DRN (Paul & Chen, 2017) (Fig. 4.34). The CRF system of the extended amygdala is sensitive to corticosteroids, such as cortisol, therefore providing a molecular mechanism through which may be regulated by neuroendocrine input, especially during chronic stressful situations.

The Role of the Reward Pathway and the Dopaminergic System in Stress

Adaptive responses to stress, including coping strategies, involve cognitive, emotional and goal-directed behavioural responses, which, in turn, require the ability to assess reward value, potential risks, predictability and controllability, based on

perceived environmental information and long-term memory information associated with previous experiences. It has been shown that DA participates in various circuits involved in cognitive and emotional functions, and these dopaminergic pathways are mainly originated in the VTA and the substantia nigra (SN). Dopaminergic projections from the VTA constitute the source of the M-L and M-C pathways. The M-L pathway constitutes the core of the "reward pathway", which is involved in the processing and reinforcement of rewarding stimuli, motivation and subjective experience of pleasure (Dunlop & Nemeroff, 2007). In addition, dopaminergic projections are also involved in stress responses, including the regulation of the HPA axis, and also in the pathophysiological mechanisms involved in anhedonia, which is a cardinal symptom of depression.

The M-L pathway conveys dopaminergic input from the VTA to the NAc, in the ventral striatum, which may be divided into two different regions, known as the "core" and the "shell", which, in turn, may be further divided into a lateral and a medial region. The NAc also receives stimulatory glutamatergic projections from the hippocampus, the thalamus, the VM-PFC, particularly from neurons located in the OFC and the ACC, and the amygdala, particularly from the BLA (Haber & Knutson, 2010) (Fig. 4.35). Neurons in the OFC and the ACC participate in evaluating reward value, error prediction and the choice between short- and long-term outcomes. Neurons in the NAc participate in reward detection and anticipation, particularly in the integration of just received environmental information with a long-term stored information related to past experiences. After receiving excitatory glutamatergic projections, neurons in the NAc receive dopaminergic projections from the VTA, which has been associated with salience and valence related to reward information, through the M-L pathway (Fig. 4.35). Reciprocally, the NAc, through the neurons located in the shell, sends projections to the VTA, the ventro-medial pallidum (VMP), the lateral hypothalamus and the extended amygdala, including the BNST and the CNA. Therefore, the NAc shell, which is mainly composed of GABAergic neurons, is involved in the emotional and motivational value-related responses (Baik, 2020). It has been shown that DA is released, particularly in the M-L pathway, in response to stressful stimuli, depending on the intensity, duration and potential avoidability, predictability and controllability of stressors. In this regard, the impact of mild or moderate stressors, which result in novel, brief, avoidable and controllable stimuli, may lead to an activating effect, therefore stimulating DA release. On the contrary, the sustained and prolonged impact of intense and chronic stressors, which are perceived as unavoidable or uncontrollable, may lead to inhibitory effects on DA release. In this regard, it has been shown that acute or short-term stressors may lead to increased DA levels in the NAc, as well as in the VM-PFC, which has been associated with the reward-related activity, including learning and enhanced memory formation of reward-related associations (Sabatinelli et al 2007). On the contrary, chronic or long-term stressors may lead to decreased levels of DA in these neural structures, which, in turn, have been associated with depressive symptoms. In addition, it has been shown that environmental stressors may induce an increased activation of the amygdala, which, in turn, may lead to increased DA levels in the M-C pathway, particularly in the OFC and the ACC, therefore assigning

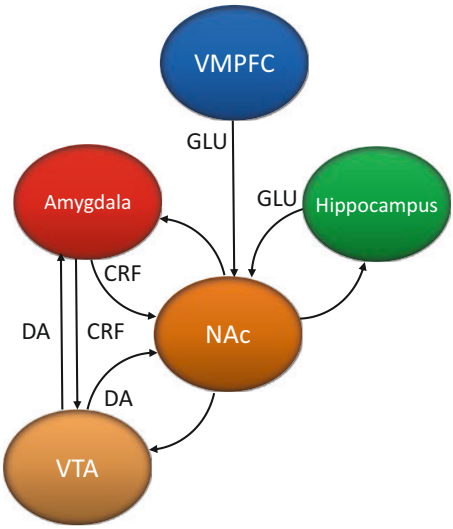

Fig. 4.35 Projections from the dopaminergic system to different neural structures. Dopaminergic projections from the VTA constitute the source of the M-L and M-C pathways. The M-L pathway is the core of the "reward pathway", involved in the processing of rewarding stimuli, motivation and the subjective experience of pleasure. The M-L pathway conveys DA input from the VTA to the NAc, in the ventral striatum. The NAc also receives stimulatory glutamatergic projections from the hippocampus, the thalamus, the VM-PFC (particularly from the neurons located in the OFC and the ACC) and the amygdala (particularly from the BLA). After receiving excitatory glutamatergic projections, the neurons in the NAc receive DA projections from the VTA, through the M-L pathway. Reciprocally, the NAc sends projections to the VTA, the ventro-medial pallidum (VMP), the lateral hypothalamus and the extended amygdala, including the BNST and the CNA. The NAc shell, which is mainly composed of GABAergic neurons, is involved in emotional and motivational value-related responses. DA is released in the M-L pathway in response to stressful stimuli, depending on the intensity, duration and potential avoidability, predictability and controllability. The impact of mild or moderate stressors, which result in novel, brief, avoidable and controllable stimuli, may stimulate DA release. The sustained and prolonged impact of intense and chronic stressors, which are perceived as unavoidable or uncontrollable, may lead to inhibitory effects on DA release

excessive salience to negative stimuli, contributing to the consequent negative bias in cognitive processing (Dunlop & Nemeroff, 2007).

Regarding the M-L pathway, the impact of unavoidable or uncontrollable stressors has been associated with a decreased DA release in the NAc and impaired response to environmental stimuli, which may lead to depressive symptoms associated with chronic stress (Cabib & Puglisi-Allegra, 2012). This may depend on the subjective appraisal of perceived stressful events and the resulting controllability or the perception of uncontrollability, which, in turn, has been associated with learned helplessness. In this regard, the difficulty or inability to experience pleasure, associated with a loss of interest and motivation in usual activities, constitutes the typical anhedonia exhibited by depressed subjects (Nestler & Carlezon Jr., 2006), and it has been demonstrated that impaired dopaminergic function is critically involved in altered reward processing underlying anhedonia (Krishnan & Nestler, 2010).

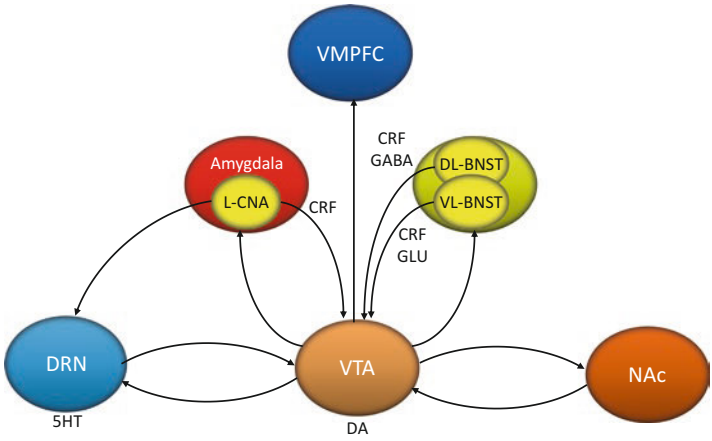

Fig. 4.36 Projections between the extended amygdala, the prefrontal cortex (PFC) and the serotonergic and dopaminergic systems involved in emotional processing. The mesolimbic (M-L) pathway is involved in the processing of rewarding and hedonic experiences, which involves reciprocal connections between the NAc and the OFC, in the VM-PFC, which, in turn, participates in the subjective assessments of hedonic and rewarding value. The OFC also shares reciprocal connections with the ACC, also in the VM-PFC, and the DL-PFC, where emotional processing participates in cognitive information processing. The DA and 5HT systems share important interactions, through reciprocal connections between the VTA and the DRN, which are critical for emotional processing. The extended amygdala also shares connections with the VTA, in the M-L system. Neurons in the L-CNA, the DL-BNST and the VL-BNST send CRF projections to the VTA, where CRF may influence the DA system through direct stimulatory effects, through mechanisms mediated by CRF1 and CRF2 receptors, or through regulatory effects on glutamatergic terminals and GABAergic interneurons. Projections from the L-CNA and the DL-BNST may also release GABA, while projections from the VL-BNST may also release glutamate as co-transmitters. Hence, the effects of CRF on the VTA may influence the DA output to the NAc and VMPFC, affecting approach and avoid behaviours associated to anxiety. Reciprocally, the VTA sends excitatory DA projections to CRF neurons in the BNST and the CNA, constituting a positive feedback mechanism, which may stimulate DA neurons in the VTA with the consequent increase in DA release in the NAc and the VM-PFC during stressful situations. The effects of CRF on the DA system may reach the VTA and the NAc through 5HT projections from the DRN, which are also modulated by CRF projections from the CNA and the BNST

Therefore, the M-L pathway is critically involved in the processing of rewarding and hedonic experiences, which involves reciprocal connections between the NAc and the OFC, which, in turn, participates in the subjective assessments of hedonic and rewarding value (Der-Avakian & Markou, 2012). The OFC also shares reciprocal connections with the ACC and the DL-PFC, where emotional processing participates in cognitive information processing. In addition, the dopaminergic and serotonergic systems share important interactions through reciprocal connections between the VTA and the DRN, which are critical for emotional processing (Fig. 4.36).

The extended amygdala also shares important connections with the mesocortico-limbic dopaminergic system, more specifically with the VTA. Neurons in the L-CNA, the DL-BNST and the VL-BNST send CRF projections to the VTA,

where it has been shown that CRF may influence the dopaminergic system through direct stimulatory effects on DA neurons, through different mechanisms mediated by CRF_1 and CRF_2 receptors, or through indirect regulatory effects on glutamatergic terminals and GABAergic interneurons (Fig. 4.36). In addition, to CRF, projections from the L-CNA and the DL-BNST may also release GABA, while projections from the VL-BNST may also release glutamate as co-transmitters. Hence, the effects of CRF on the VTA may influence the dopaminergic output to the NAc and PFC, therefore affecting approach and avoiding behaviours associated to anxiety. Reciprocally, the VTA sends excitatory DA projections to CRF neurons in the BNST and the CNA, therefore constituting a positive feedback mechanism, which, in turn, may stimulate DA neurons in the VTA with the consequent increase in DA release in the NAc and the PFC during stressful situations (Fig. 4.36). In addition, the effects of CRF on the dopaminergic system may reach the VTA and the NAc through serotonergic projections from the DRN, which, in turn, are also modulated by CRF projections from the CNA and the BNST (Paul & Chen, 2017) (Fig. 4.36).

Therefore, acute and controllable stressors have been associated with an increased DA release in the NAc, whereas chronic and uncontrollable stressors have been associated with a decreased dopaminergic activity in the M-L pathway (Suridjan et al., 2012). In this regard, the increased DA release in the M-L pathway has been associated with positive or rewarding stimuli and in response to certain negative or aversive situations that may be perceived and interpreted as controllable and escapable. Hence, controllability may be also perceived and interpreted as a rewarding experience, which plays a critical role in the development of resilience.

The Role of Stress in the Development of Depression

Depression is a mood disorder, characterized by intense feelings of sadness and usually associated with severe dysphoria and profound loss of pleasure or interest (Nemeroff, 2020). It is well known that sadness is the core symptom of depression that constitutes a negatively valenced emotion, usually associated to feelings of loss, which may be based on a real and objective experience or a biased and subjective interpretation of .a real experience. In this regard, cognitive distortions may lead to a biased interpretation of certain experiences, which, in turn, may lead to exaggerated feelings of sadness, and the consequent behavioural responses usually observed in depression. Negative emotions associated with a sad mood include feelings of frustration, unhappiness, disappointment, sorrow, hopelessness and helplessness. Feelings of hopelessness may lead to negative thoughts, including more pessimistic and less realistic interpretations. Negative thoughts may include excessive guilt and worthlessness and, in more severe cases, may lead to thoughts of death and suicidal ideation. Loss of interest, mostly in the activities that previously aroused interest, may be associated with a profound loss of the ability to enjoy and

the capacity to feel pleasure, constituting the typical anhedonia usually observed in depression. This may be also associated with loss of motivation and loss of will that may lead to decreased ability to fulfil normal functioning, including social interactions, usually observed and referred in the working environment, associated with decreased efficacy or productivity, and also in the personal environment, where it may affect normal relationship with friends and family. Depression may be also associated with sleep disturbances, decreased concentration, appetite disturbance and loss of energy. In addition, a high comorbidity between depression and anxiety disorders has been demonstrated, such as panic disorder, GAD and PTSD. Moreover, it has been demonstrated that the expression of anxiety disorders is usually previous to the origin and development of depression (Kalin, 2020). In this regard, a significant association has been observed between chronic stressful experiences, where the sustained and prolonged impact of stressful events may lead to learned helplessness, and the origin and development of chronic anxiety disorders and depression (Tafet & Nemeroff, 2016).

The links between stressful life events and the origin and development of depression have long been studied and demonstrated, including the effects produced by a personal history of early adverse experiences during childhood and chronic stressful conditions during adulthood, hence providing an increasing body of research supporting the association between both conditions (Kessler, 1997; Nemeroff, 1999; Heim & Nemeroff, 2001). Stressors may affect different individuals in different manners, with the resulting triggering of adaptive or maladaptive responses, which, in turn, may be continuously influenced by psychological and neurobiological factors, in the constant and sustained interactions between environmental stimuli and individual resources (Tafet & Nemeroff, 2016). Psychological factors are involved in the cognitive processing of perceived information, the resulting subjective appraisal of different features related to environmental stressors, including their magnitude and their chronicity, the potential predictability and controllability and the available resources to cope with them. Neurobiological factors are involved in the activation of different neural structures, with their respective synaptic connections and their molecular cascades of events, implicated in emotional and cognitive processing.

Upon exposure to environmental stressors, physiological responses play an adaptive role when they are rapidly activated, in a successful and effective manner, in response to stressful conditions, and may be consequently controlled and limited after the stressful event concluded. Their prolonged and sustained activation may turn into maladaptive responses, as observed in chronic stressful conditions, which, in turn, may lead to the development of depression and anxiety disorders. In this regard, certain individuals may display better resources to successfully cope with adverse conditions, as observed in resilient people, while others may be more susceptible to the development of pathological conditions, which may be predisposed by individual characteristics, including psychological or biological, cognitive or genetic factors of vulnerability (Fig. 4.37).

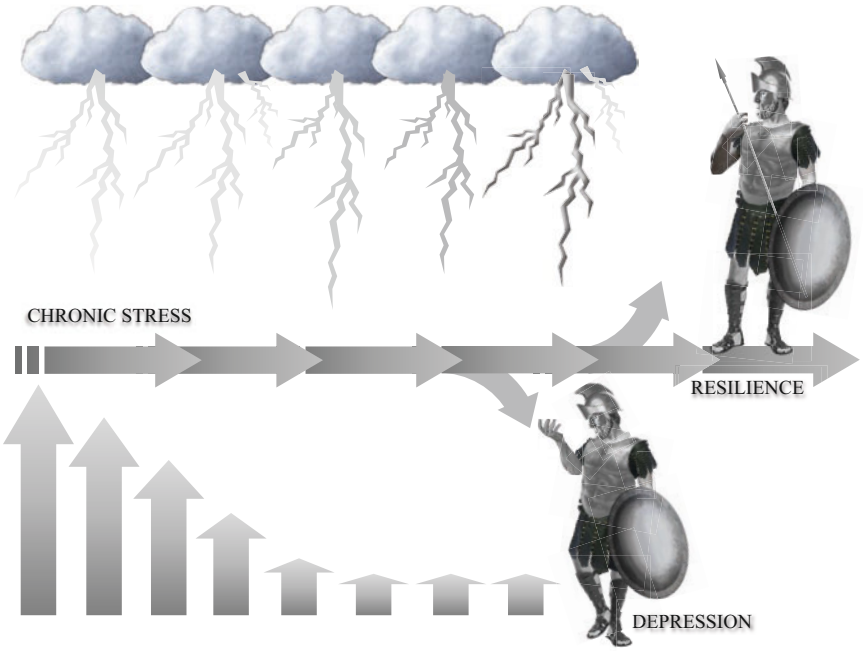

Fig. 4.37 Chronic stress may lead to depression; successful coping may lead to resilience. Environmental stressors provoke adaptive responses, which may be controlled and limited after the stressful event concluded. Their prolonged and sustained activation may turn into maladaptive responses, as observed in chronic stressful conditions. Certain individuals may display better resources to successfully cope with adverse conditions, as observed in resilient people, while others may be more susceptible to the development of pathological conditions, which may be predisposed by different factors of vulnerability as observed in depression

Chronic Stress and the HPA Axis: The Role of Glucocorticoids

During stressful situations, the excitatory input to the amygdala contributes to the activation of the ANS and the hypothalamic PVN, with the consequent activation of the HPA axis, which, in turn, is translated into an increased synthesis and release of glucocorticoids. Chronic stress may lead to dysregulation of the HPA axis, with the consequent increased levels of cortisol, particularly observed in the nadir of the circadian rhythm, and altered negative feedback mechanisms (Young et al., 1991). Increased levels of CRF have been also described, as observed in the cerebrospinal fluid of depressed patients (Nemeroff et al., 1984). Hence, hyperactivity of the HPA axis, with the resulting hypercortisolism, represents one of the most consistent findings in depression and certain anxiety disorders (Tafet & Nemeroff, 2016). In addition, alteration of various aminergic systems has been also described in these conditions, where dysregulation of the 5HT system has been closely associated with the origin and development of depression (Melzter, 1989; Owens & Nemeroff, 1994).

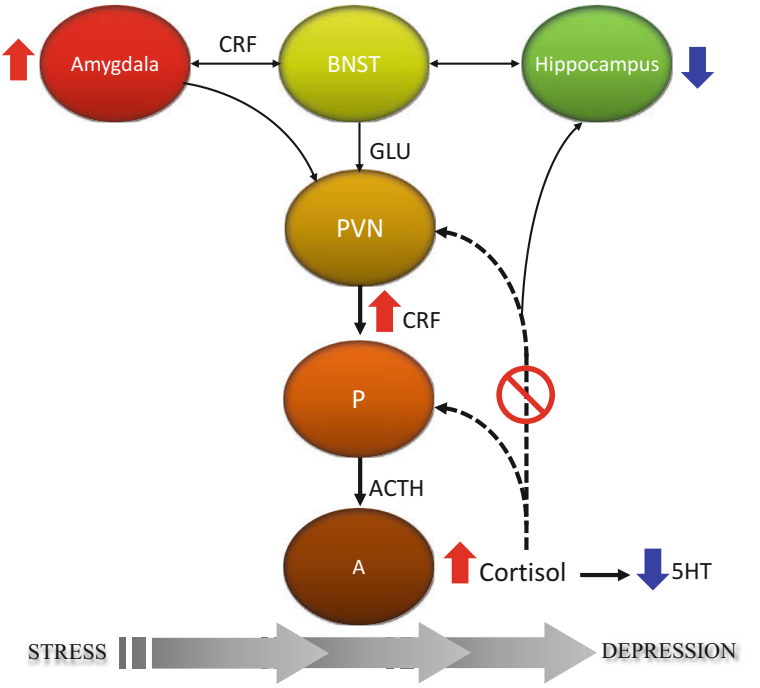

Fig. 4.38 Psycho-neuro-endocrinological links between chronic stress and depression. During stressful situations, excitatory input to the amygdala contributes to the activation of the ANS and the hypothalamic PVN, with the consequent activation of the HPA axis. Chronic stress may lead to dysregulation of the HPA axis, with increased levels of CRF and cortisol. Alteration of various aminergic systems has been also described, where dysregulation of the 5HT system has been associated with the origin and development of depression. Therefore, the interactions between these systems, particularly between hyperactivity of the HPA axis and dysregulation of the 5HT system, may provide an important psycho-neuro-endocrinological link between the effects produced by chronic stressful events and the origin and development of depression. Chronic stress may also have damaging effects on the hippocampus. Increased levels of cortisol, as well as CRF, were associated with reduced hippocampal volume and altered function, which were also associated with further sensitization of stress responses. A decreased expression of GRs in the hippocampus and hypothalamus, with the consequent alteration of the HPA system and the resulting hypercortisolism, has been also associated with depression

Therefore, the interactions between these systems, particularly between hyperactivity of the HPA axis and dysregulation of the 5HT system, may provide an important psycho-neuro-endocrinological link between the effects produced by chronic stressful events and the origin and development of depression (McEwen, 1987; López et al., 1998; Tafet et al., 2001) (Fig. 4.38).

The impact of stressful events may also have damaging effects on the hippocampus, which is a highly sensitive structure, vulnerable to the effects of aging and chronic stress (Sapolsky, 1996). It has been shown that glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) are expressed in the hippocampus

(McEwen et al., 1968), where they may be increasingly activated by glucocorticoids, which, in turn, may have profound effects on hippocampal functioning, particularly in highly sensitive processes such as neuroplasticity and neurogenesis. In this regard, it has been shown that glucocorticoids participate in a reversible form of atrophy of dendrites, which has been described in the CA3 region of the hippocampus, induced by stress (McEwen, 1999). In addition, glucocorticoids may also have inhibitory effects on neurogenesis, which has been described in granule neurons of the dentate gyrus, also induced by stress (McEwen, 1999). Both effects of glucocorticoids on hippocampal neuroplasticity and neurogenesis have been also associated with increased concentrations of excitatory neurotransmitters, such as glutamate, in response to stress (McEwen, 1999). Therefore, these molecular and biological processes induced by glucocorticoids have been associated with the effects of stress on cognitive functions, including reversible deficits in selective attention and memory consolidation during stressful experiences (Lupien & McEwen, 1997). Furthermore, increased levels of cortisol, as well as CRF, were associated with reduced hippocampal volume and altered function in subjects with a history of early traumatic experiences (Nemeroff & Binder, 2014), which, in turn, were also associated with further sensitization of stress responses (Heim et al., 2008). A decreased expression of GRs in the hippocampus and hypothalamus, with the consequent alteration of the HPA system, and the resulting hypercortisolism have been also associated with symptoms of depression (Holsboer, 2000).

Chronic activation of the HPA axis may lead to alteration of regulatory negative feedback mechanisms, which, in turn, may result in elevated concentrations of hypothalamic CRF and circulating cortisol. Hence, increased levels of cortisol in a sustained and prolonged manner may lead to an array of pathophysiological changes, which, in turn, have been associated with the effects induced by cortisol GRs, through transcriptional regulation of different target genes.

Increased levels of glucocorticoids have been associated with altered expression and signalling of brain-derived neurotrophic factor (BDNF), an important neurotrophin (NT) involved in various neurobiological process, including neuroplasticity, cell survival and neurogenesis, particularly in the hippocampal GD (Suri & Vaidya, 2013). It has been shown that acute or chronic exposure to glucocorticoids may decrease the levels of BDNF mRNA in the hippocampus, particularly in the DG, which has been also reflected through decreased levels of BDNF protein in the hippocampus (Schaaf et al., 1998). This may be achieved by direct repression, through binding of glucocorticoids to negative glucocorticoid response elements (nGREs) located in the promoter region or by indirect repression through interference with other transcription factors, such as the AP-1 complex and cAMP-response element-binding protein (CREB), which participate in the stimulation of BDNF transcription (Suri & Vaidya, 2013; Kassel & Herrlich, 2007).

Interactions between the HPA axis and the 5HT system, at various levels of both systems, have been long studied and demonstrated (López et al, 1999). Moreover,

the association between chronic stress and depression has been extensively studied and demonstrated at the psycho-neuro-endocrinological level, where increased levels of cortisol constitute one of the most consistent findings in depression and chronic anxiety disorders. In this regard, increased levels of glucocorticoids have been also associated with altered expression of different molecules involved in the 5HT system, including 5HT receptors and the 5HTT, which, in turn, have been associated with the origin and development of depression (Tafet & Bernardini, 2003).

It has been shown that chronic stress may lead to down-regulation of $5HT_{1A}$ receptors in the hippocampus, and this effect has been attributed to the effect of glucocorticoids, which, after binding to GRs and MRs, may exert an inhibitory effect on 5HT1A gene expression (López et al., 1998). The modulatory effect produced by glucocorticoids has been observed in post-synaptic $5HT_{1A}$ receptors, particularly in the hippocampus, but not in somato-dendritic pre-synaptic $5HT_{1A}$ receptors in the RN. Moreover, in vivo experiments also demonstrated an increased expression of $5HT_{1A}$ and $5HT_7$ receptors in the hippocampus after adrenalectomy, further supporting the notion that glucocorticoids exert a modulatory effect on the serotonergic system.

The effects of glucocorticoids on the 5HT system have been also reflected through the observed up-regulation of the 5HTT. In this regard, it has been shown that exposure to elevated concentrations of cortisol may lead to an increased reuptake of 5HT in vitro. This effect has been demonstrated to be mediated through the effect of cortisol in the transcriptional regulation of the 5HTT, with the resulting increased reuptake of 5HT (Tafet et al., 2001) (Fig. 4.39). This may be understood as a direct effect of the cortisol-GR complex through binding to the GRE in the promoter region of the 5HTT gene (Tafet & Bernardini, 2003), also known as the 5HTT gene-linked promoter region (5HTTLPR). The stimulatory effect of glucocorticoids on the 5HTT gene expression was also observed with the administration of dexamethasone, a synthetic glucocorticoid which specifically binds to GRs, constituting a hormone receptor complex, which, in turn, binds to the GRE in the promoter region of the 5HTT gene (Glatz et al., 2003). In line with these previous reports, it has been also shown that exposure to chronic stressful conditions, with the consequent increased concentrations of glucocorticoids, resulted in increased levels of 5HTT in vivo (Zhang et al., 2012). Moreover, exposure to experimental chronic stressful conditions was associated with increased concentrations of the 5HTT protein in different neural structures, including the DRN, amygdala, hippocampus and certain areas of the frontal cortex, which was attributed to increased levels of glucocorticoids (Zhang et al., 2012). Therefore, various lines of evidence support the notion that increased levels of cortisol, as those observed during chronic stressful conditions, may lead to an increased 5HT uptake, with the resulting decreased concentrations of 5HT at the synaptic cleft, which has been associated with the origin and development of depression (Tafet et al., 2001; Glatz et al., 2003; Zhang et al., 2012).

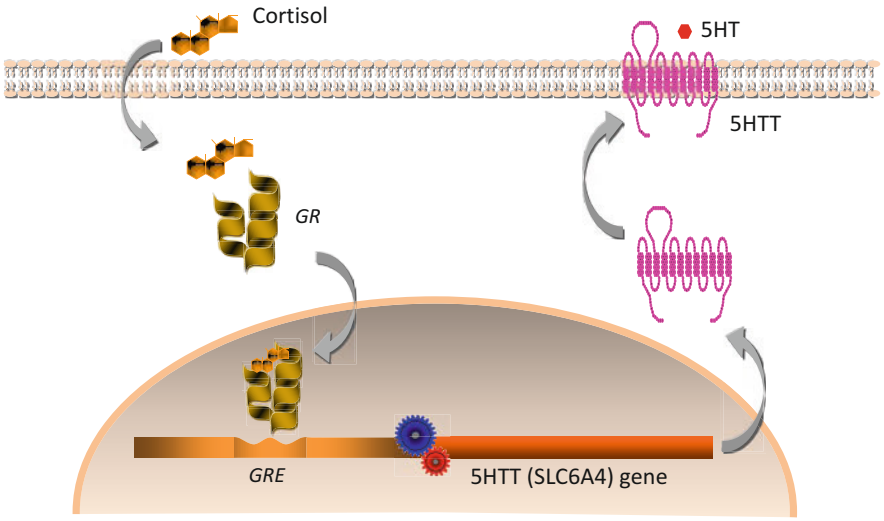

Fig. 4.39 Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, with increased levels of cortisol, may lead to alteration of the serotonergic system. Chronic activation of the HPA axis may lead to alteration of regulatory negative feedback mechanisms, which may result in elevated concentrations of hypothalamic CRF and circulating cortisol. Increased levels of cortisol may lead to pathophysiological changes associated with the effects induced through transcriptional regulation of different target genes, including different molecules involved in the 5HT system. Elevated concentrations of cortisol may lead to an increased reuptake of 5HT, mediated through the effect of cortisol in the transcriptional regulation of the serotonin transporter (5HTT), with the resulting increased reuptake of 5HT. Cortisol binds to specific receptors, such as the glucocorticoid receptor (GR), constituting a cortisol-GR complex, which, in turn, represents a transcription factor. Within the nucleus, the cortisol-GR complex binds to a glucocorticoid response element (GRE) in the promoter region of the 5HTT gene, also known as the 5HTT gene-linked promoter region (5HTTLPR). Increased levels of cortisol, as those observed during chronic stressful conditions, may lead to an increased 5HT uptake, with the resulting decreased concentrations of 5HT at the synaptic cleft, which has been associated with the origin and development of depression

Genetic Vulnerability: The Role of Polymorphisms

Research on genetic factors of vulnerability has focused on different genes, which have been shown to participate in molecular mechanisms associated with the origin and development of depression, where subtle genetic variations, known as "polymorphisms", have been described. Gene expression is regulated by the promoter region, located upstream of the coding region, which allows ribonucleic acid (RNA) polymerase to bind to a certain region in the deoxyribonucleic acid (DNA) sequence, hence initiating transcription. In this regard, various polymorphisms have been described in the promoter region of different genes. Many of these genetic variations are characterized by substitution of a single nucleotide in the genetic sequence, therefore constituting "single nucleotide polymorphisms" (SNPs). It has been demonstrated that some of these polymorphisms may be involved in the development of

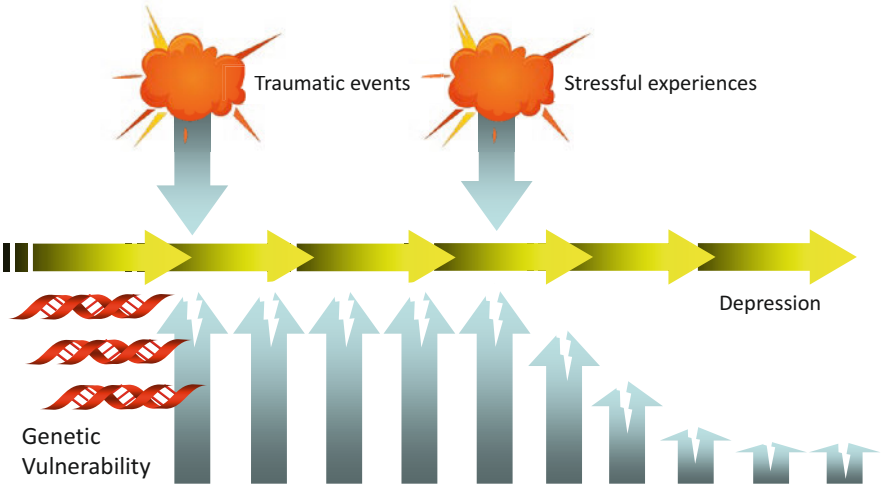

Fig. 4.40 Genetic vulnerability to stress. Genetic factors of vulnerability have been investigated, mostly focusing on different genes, involved in molecular mechanisms associated with the origin and development of depression, where subtle genetic variations, known as "polymorphisms", have been described. Many of these genetic variations are characterized by substitution of a single nucleotide in the genetic sequence, therefore constituting "single nucleotide polymorphisms" (SNPs). Some of these polymorphisms may be involved in the development of depression in response to stressful situations, including traumatic experiences during childhood and chronic stressful situations during adulthood, therefore representing genetic factors of vulnerability

depression in response to stressful situations, including traumatic experiences during childhood and chronic stressful situations during adulthood, therefore representing genetic factors of vulnerability (Heim et al., 2008; Caspi et al., 2003; Kaufman et al., 2000; Kaufman et al., 2006; Bradley et al., 2008; Nemeroff & Seligman, 2013) (Fig. 4.40).

Various genes implicated in the regulation of the HPA system have been investigated with the aim to identify potentially relevant polymorphisms. Hence, two different SNPs have been identified in the GR gene, termed BclI and Asp363Ser, which have been associated with an increased glucocorticoid sensitivity (De Rijk et al., 2012) and therefore an increased vulnerability for the development of depression. More recent studies focused on the FKBP5, which is a co-chaperone protein of hsp 90, closely involved in the regulation of the GR sensitivity (Horstmann et al., 2010), with the consequent role in the regulation of the HPA axis responsivity. It has been shown that FKBP5 is part of the heterocomplex bound to GRs, which in the presence of the glucocorticoid is replaced by FKBP4, which participates in the nuclear translocation of the GR-cortisol complex, therefore allowing its regulatory effect as a transcriptional factor (Binder et al., 2004). Any alteration of GR function may induce changes in the feedback regulation, which, in turn, may lead to hyperactivation of the HPA axis, which has been described in chronic stress and depression. In this regard, various SNPs have been observed in the FKBP5 gene, which may be

involved in an increased expression of FKBP5, which, in turn, may decrease glucocorticoid binding affinity to GRs, therefore affecting the nuclear translocation of the GR-cortisol complex. In addition, cortisol may up-regulate the expression of FKBP5, providing an intracellular negative feedback mechanism to regulate GRs (Vermeer et al., 2003). One of the SNPs, identified by the substitution of a cytosine (C) by a thymine (T), was associated with up-regulation of FKBP5 expression and altered HPA response. Other studies focused on CRF and the CRF type 1 receptor (CRHR1) genes (McEwen et al., 2012), where various SNPs have been identified in the CRHR1, including haplotypes constituted by different SNPs, associated with the effects of traumatic events experienced during childhood as vulnerability factors for depression during adulthood (Kendler et al., 2004). Upon binding of CRF to CRHR1, it participates in the activation of the HPA axis and in cognitive and emotional functions in the amygdala and the LC (Nemeroff, 2004), including arousal, attention, conscious perception of emotional experiences and memory consolidation.

Regarding aminergic neurotransmitters, it has been shown that the serotonergic system plays a critical role in the maintenance of euthymia, which is "good mood", and the adequate tolerance to adversity during stressful events. Hence, altered serotonergic neurotransmission has been associated to increased vulnerability to depression and anxiety disorders. Sufficient and effective concentrations of 5HT in the synaptic cleft are usually regulated by the 5HTT, which is responsible for its reuptake, therefore regulating its availability to stimulate specific 5HT receptors (Hamon & Blier, 2013). In addition, to be involved in cognitive and emotional functions, stimulatory projections from the DRN have been shown to innervate CRF-containing neurons in the PVN (Lesch & Gutknecht, 2004), hence stimulating the HPA axis and the ANS, and reciprocally, cortisol and NE may impact the 5HT system during stressful situations (Tafet & Bernardini, 2003). In this regard, various studies have shown that post-synaptic $5HT_{1A}$ receptors in different limbic structures may be down-regulated or desensitized by cortisol or exposure to chronic stressful conditions (López et al., 1998; Van Riel et al., 2004). In addition, it has been shown that cortisol may increase 5HT uptake in vitro, an effect attributed to an increased expression of the 5HTT gene by cortisol (Tafet et al., 2001), therefore providing further support to the reciprocal regulation of the HPA and 5HT systems, and their potential interplay in the interface between stress and depression (Tafet & Bernardini, 2003).

Regarding its role in genetic vulnerability, a polymorphism was identified in the promoter region of the 5HTT gene (Lesch et al., 1996). The promoter activity is regulated by elements located in the regulatory region, known as the 5HTT gene-linked polymorphic region (5HTTLPR), where a short ("S") and a long ("L") allele have been identified (Caspi et al., 2003). The short variant (5HTTLPR-S) was associated with altered transcriptional efficiency in comparison with the long allele (5HTTLPR-L), with the consequent altered expression of the 5HTT gene (Lesch et al., 1996), which, in turn, may alter the modulation of 5HT activity in response to stress. This has been supported by clinical and preclinical studies (Karg et al., 2011), including the observation that "S" allele carriers presented an increased amygdala

reactivity to threatening stressors, in comparison to those homozygous for the "L" allele (Hariri et al., 2005), therefore suggesting that variations in the 5HTT gene may be involved in psychological responses to stress (Caspi et al., 2003). A potential association has been observed between this polymorphism and increased reactivity of the amygdala in response to distressful events (Hariri et al., 2002, 2005). Since the amygdala plays a critical role in the emotional responses to stressful events, its increased reactivity was associated with anxiety and altered mood regulation (LeDoux, 1992). In addition, the amygdala also plays a critical role in the activation of the HPA axis, and therefore, its hyperactivation may also lead to increased levels of cortisol. It has been observed that carriers of the "S" allele presented an increased activation of the amygdala and an increased cortisol in response to certain stressors (Gotlib et al., 2008). The association between an increased vulnerability attributed to the 5HTTLPR-S variation and an altered expression of the 5HTT gene may be paradoxical. In this regard, it has been proposed that alterations in 5HTT gene regulation, with the resulting effect on synaptic 5HT concentrations, may be different between the expressed by constitutive conditions, and the provoked by stressful events. Hence, 5-HTTLPR-S carriers may have an essentially increased concentrations of 5HT, which may lead to down-regulation of post-synaptic 5HT receptors, with the resulting relative desensitization of the serotonergic system (Hariri et al., 2005), providing a potential justification for the vulnerability presented by 5-HTTLPR-S carriers. In contrast, an increased expression of the 5HTT gene, associated with the impact of environmental stressors, and the resulting hyperactivation of the HPA axis and increased levels of cortisol may result in an increased 5HT reuptake, with the resulting diminished 5HT concentrations in the synaptic cleft (Tafet et al., 2001), which has been associated with the development of depression.

It has been demonstrated that BDNF plays an important role in the regulation of neuroplasticity and neurogenesis and in mood disorders. In this regard, it has been shown that decreased concentrations of BDNF may lead to depressive symptoms, whereas increased levels of BDNF have been associated with clinical recovery (Duman & Monteggia, 2006). Chronic stress, with the consequent hyperactivation of the HPA axis, may induce a damaging effect in hippocampal neurons, which express high levels of GRs, and these changes have been associated with a decreased availability of BDNF (Ota & Duman, 2013). In addition, it has been shown that increased levels of cortisol may lead to down-regulation of BDNF (Suri & Vaidya, 2013), and it has been shown that BDNF and 5-HT may induce hippocampal neurogenesis (Mahar et al., 2014). In this regard, neurogenesis may be stimulated by enhanced hippocampal activity and increased levels of 5HT (Malberg et al., 2000; Alenina & Klempin, 2015), while it may be inhibited by stressful experiences, with the resulting increased levels of cortisol (Krugers et al., 2010). Various SNPs have been also identified in the BDNF gene, particularly an SNP identified at nucleotide position 196 in the coding region of the BDNF gene, where a guanine (G) is replaced by an adenine (A), resulting in the substitution of valine (Val) by methionine (Met) at codon 66, therefore termed "Val66Met", where the presence of a "Met" allele has been associated with a decreased secretion of BDNF (Duman, 2004; Malberg et al., 2000). Carriers of the Met-BDNF allele presented relatively smaller hippocampal

volumes, comparing to carriers of the Val-BDNF allele (Duman, 2004). This was associated with diminished hippocampal activation and deficient cognitive performance (Gatt et al., 2009; Duman, 2004), which, in turn, have been associated with decreased emotional stability and increased vulnerability to develop depression.

Inflammatory Processes: The Role of Cytokines

The association between chronic stress and inflammation has long been demonstrated, where it has been shown that acute and chronic psychological stress may lead to the activation of inflammatory responses (Haroon et al., 2012). In this regard, the sustained and prolonged impact of certain environmental stressors has been associated with increased concentrations of certain pro-inflammatory cytokines, such as IL-I, IL-6 and TNF-α, which have been observed in subjects exposed to chronic psychosocial stress (Capuron & Miller, 2011), as well as in depression (Cattaneo et al., 2015). In this regard, major depression may provoke increased inflammatory responses to stress, which has been associated to a history of early adverse experiences, which, in turn, suggested a possible link between these and increased inflammatory responses to stress later in life (Haroon et al., 2012). It has been shown that the impact of environmental stressors may lead to adaptive responses, including the activation of the SNS, with the consequent release of catecholamines, which, in turn, bind to their specific receptors. Some of these receptors are located in the cell membranes of immune cells, which may stimulate the subsequent release of pro-inflammatory cytokines (Leonard, 2010). Therefore, chronic inflammatory processes in the CNS may lead to an increased release of pro-inflammatory cytokines, which, in turn, may affect the concentrations of BDNF, therefore reducing neuroplasticity (Leonard, 2010) and neurogenesis in the hippocampus (Cattaneo et al., 2015). These have been also associated with cognitive impairment and depression. Pro-inflammatory cytokines may also exert certain regulatory effect on the HPA axis, stimulating the release of CRF, with the resulting increased levels of cortisol (Leonard, 2010), which, in turn, may lead to reduced sensitivity of GRs and glucocorticoid resistance (Leonard, 2010). Increased levels of cortisol may also lead to an reduced activity of the rate-limiting enzyme tryptophan hydroxylase, therefore leading to a decreased synthesis of 5HT. Increased levels of cortisol may also lead to an increased activity of tryptophan dioxygenase (indoleamine-pyrrole 2,3-dioxygenase or IDO), which is involved in the degradation of tryptophan to kynurenine, with the resulting decreased synthesis and release of 5HT (Leonard, 2010). Pro-inflammatory cytokines, such as IFN, participate in the regulation of this pathway, stimulating IDO, therefore leading to a reduced synthesis of 5HT and an increased synthesis of kynurenine (Loftis et al., 2010). Degradation of kynurenine results in the formation of 3-hydroxykynurenine, which produces free-radical species involved in oxidative stress, kynurenic acid and quinolinic acid, which activate the glutamatergic system, therefore leading to neurotoxicity, also involved in the origin of depression (Loftis et al., 2010; Leonard, 2010).

Other pro-inflammatory cytokines, such as IL-1 and TNF, may affect serotonergic neurotransmission by stimulating the 5HTT, therefore decreasing the synaptic concentrations of 5HT in the CNS (Leonard, 2010).

Stress, Appraisal and Coping: The Role of Psychological Vulnerability

It has been demonstrated that psychological vulnerability may depend on diverse factors related to stressful events, including their strength, intensity and length of the impact, and the availability of personal resources to cope with them, but mostly, it may depend on the cognitive appraisal, the resulting balance between perceived stressors and the available resources to cope with them and the consequent coping strategies (Folkman & Lazarus, 1988). Certain stressful conditions, including chronic stressful situations during adulthood and early adverse experiences during childhood, may represent important factors of psychological vulnerability. In this regard, chronic exposure to unavoidable and uncontrollable stressors may lead to decreasing resources, mostly due to biased appraisals, according to which the available resources are not enough, which has been associated with increasing feelings of helplessness.

Early adverse events, including neglect, sexual or physical abuse during childhood or psychological harassment, also known as bullying, may contribute to developing dysfunctional cognitive schemas, which may be latent during long periods and reactivated by new experiences at a later time, particularly those with strong emotional relevance. In response to stressful situations in later periods of life, the reactivation of dysfunctional schemas may lead to negative biases, which may influence information processing, with the resulting dysfunctional consequences expressed through cognitive processing, emotional reactions and behavioural responses, constituting the foundations of cognitive vulnerability (Beck, 2008) (Fig. 4.41).

Stress in Early Periods of Life and Its Long-Term Effects

Early adverse conditions, including traumatic events experienced during childhood, represent a major factor of vulnerability in the origin and development of depression (Heim & Nemeroff, 2001; Heim et al., 2008; Nemeroff & Binder, 2014). The association between traumatic experiences during childhood and the development of depression later in life has been particularly observed during and after exposure to stressful situations during adulthood (Heim et al., 2008). In this regard, certain stressful experiences, which may be recognized by a significant intensity or extent, which occurred as an acute event or as a chronic situation, have been associated with altered emotional and cognitive processing and the resulting maladaptive

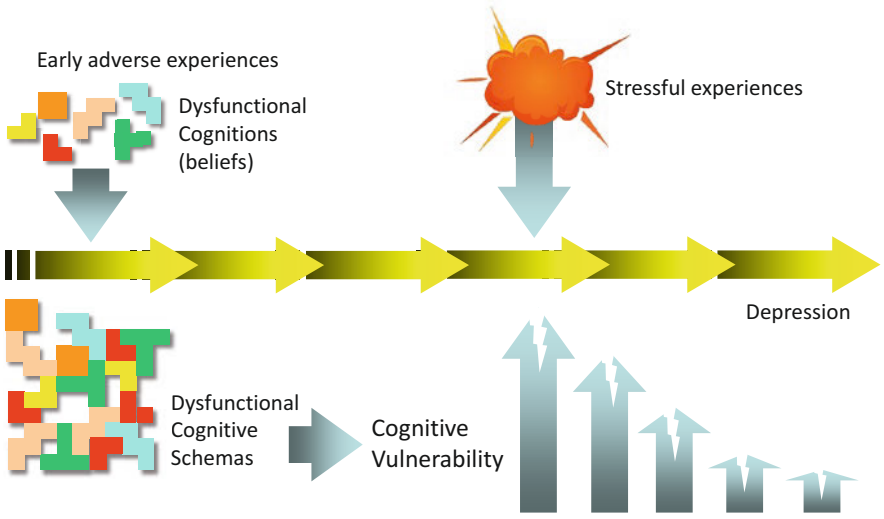

Fig. 4.41 Cognitive vulnerability to stress. Psychological vulnerability may depend on diverse factors related to stressful events, on the cognitive appraisal, on the resulting balance between perceived stressors and the available resources to cope with them, and the consequent coping strategies. Early adverse events may contribute to developing dysfunctional cognitive schemas, which may be latent during long periods and reactivated by new experiences at a later time, particularly those with strong emotional relevance. Certain stressful conditions during childhood, such as abuse, neglect or loss, may lead to the development of dysfunctional cognitive schemas, with the consequent negative biases in response to additional stressful conditions later in life. In response to stressful situations in later periods of life, the reactivation of dysfunctional schemas may lead to negative biases, which may influence information processing, with the resulting dysfunctional consequences expressed through cognitive processing, emotional reactions and behavioural responses, constituting the foundations of cognitive vulnerability

behavioural responses. Some of these traumatic experiences have been associated with severe psychological and neurobiological consequences, which, in turn, have been translated into long-lasting pathophysiological processes. It has been shown that certain stressful conditions during childhood, such as abuse, neglect or loss, may lead to the development of dysfunctional cognitive schemas, with the consequent negative biases in response to additional stressful conditions later in life (Beck, 2008) (Fig. 4.41). Moreover, some of these adverse conditions, such as neglect, may lead to dysfunctional attitudes, which have been associated with hyperactivity of the HPA axis (Peng et al., 2014).

Negative effects of early adverse events have been shown to induce long-lasting alterations in neural and neuroendocrine systems involved in adaptive responses to stress, particularly in CRF neurotransmission and other neurotransmitter systems, such as the 5HT system (Arborelius et al., 1999; Nemeroff, 1999), which, in turn, may lead to persistent sensitization and increased responsiveness to stress (Heim & Nemeroff, 2001; Heim et al., 2008). Moreover, CRF has been demonstrated to be involved in neural, endocrine, immune, autonomic and behavioural

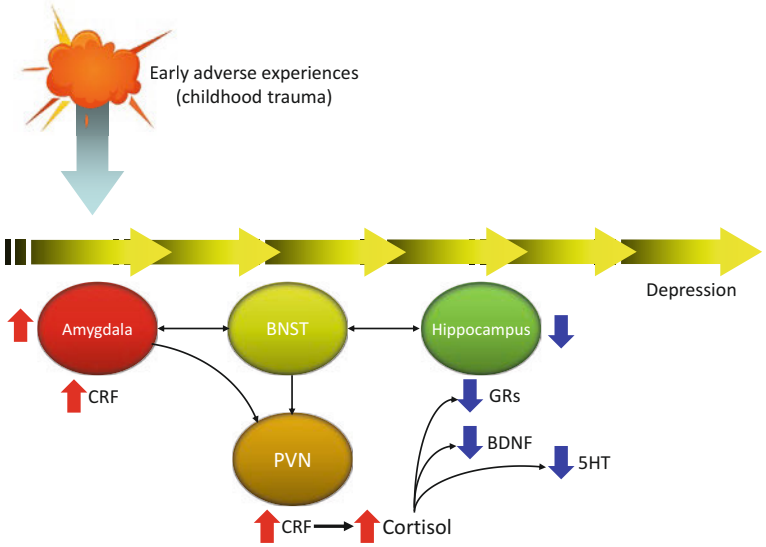

Fig. 4.42 Early adverse experiences and vulnerability to stress later in life. Traumatic experiences during childhood, such as abuse, neglect or loss, may lead to the development of dysfunctional cognitive schemas, with the consequent negative biases in response to additional stressful conditions during adulthood. Some of these adverse conditions have been associated with hyperactivity of the HPA axis. The negative effects of early adverse events may induce long-lasting alterations in neural and neuroendocrine systems involved in adaptive responses to stress, including the amygdala, hippocampal activation and increased CRF neurotransmission, which may lead to persistent sensitization and increased responsiveness to stress. Increased levels of CRF may induce hyperactivity of the HPA axis, with the consequent increased levels of cortisol, which, in turn, may lead to functional and morphological changes in the hippocampus, decreased glucocorticoid receptors (GRs) and brain-derived neurotrophic factor (BDNF), with the consequent alteration in neuroplasticity and neurogenesis and altered serotonergic neurotransmission

stress responses. In this regard, CRF neurons in the medial parvocellular region of the hypothalamic PVN play a critical role in the regulation of the HPA axis, and CRF neurons in the amygdala, particularly in the CNA, are connected with aminergic nuclei in the brainstem, including the noradrenergic LC and the serotonergic RN, and also participate in the regulation of the PVN (Heim & Nemeroff, 2001). Increased levels of CRF may induce hyperactivity of the HPA axis, with the consequent increased levels of cortisol, which, in turn, may lead to functional and morphological changes in the hippocampus (Suri & Vaidya, 2013) and altered serotonergic neurotransmission (Tafet et al., 2001) (Fig. 4.42). In this regard, a reduced hippocampal volume has been attributed to excessive exposure to excitatory amino acids, such as glutamate, or glucocorticoids, such as cortisol, which have been associated with decreased neuroplasticity and neurogenesis (Duman & Charney, 1999). Moreover, reduced neuroplasticity and neurogenesis have been observed in the hippocampus, particularly in the DG, following acute or chronic stress (Suri & Vaidya, 2013). These effects have been associated with an increased

exposure to glucocorticoids, which, in turn, may lead to decreased levels of BDNF, a neurotrophin critically involved in these processes in the hippocampus (Schaaf et al., 1998). Various studies focused on the role of hippocampal GRs, where it has been shown that increased levels of cortisol, in a sustained and prolonged manner, may lead to down-regulation of GRs in the hippocampus (Sapolsky et al., 1984). It has been suggested that the availability and efficacy of hippocampal GRs may be permanently affected by early stressful experiences (Heim & Binder, 2012), which may lead to glucocorticoid resistance and the consequent hyper-reactivity of the HPA axis in response to additional stressful situations. Increased levels of cortisol and decreased GR availability, associated with stressful conditions during childhood, have been also associated with a decreased hippocampal volume and neural activity in adulthood and an increased reactivity of the HPA axis, with the resulting alterations observed later in life (Heim & Binder, 2012; Korosi et al., 2012).

Early adverse experiences have been also associated with alterations in the amygdala. In this regard, it has been shown that the amygdala may increase in volume in response to chronic stressful conditions (Vyas et al., 2002), which has been associated also with increased levels of glucocorticoids and a high density of GRs in the amygdala (Geuze et al., 2012). Various studies have been reported on the effects of early adverse events in children, where it has been observed that the effects on amygdala volume were associated with the duration and intensity of stressful events (Lupien et al., 2009). Although, in studies performed in depressed adults exposed to early adverse events during childhood, increased amygdala volumes were observed (Evans et al., 2016). In this regard, the increased amygdala volume, associated with a history of early adverse experiences, may lead to an increased amygdala reactivity in response to stressors, particularly those associated with negative emotional cues (Guadagno et al., 2021). Preclinical studies performed with rodents in experimental conditions demonstrated that chronic stress in early periods resulted in an increased arborization in neurons in the BLA and reduced density and arborization in neurons in the hippocampus (Vyas et al., 2002). Therefore, the increased reactivity of the amygdala, with a reduced activity of the hippocampus, may be translated into an increased activation of the HPA axis, with the resulting increase in CRF and cortisol, which, in turn, may lead to down-regulation of hippocampal GRs and BNDF, and up-regulation of the SERTT, with the consequent effect on serotonergic neurotransmission.

The effects of early adverse events may also involve epigenetic mechanisms, which allow long-lasting effects produced by environmental stressors on gene expression, without altering the underlying genetic sequence. At the molecular level, epigenetic mechanisms involve biochemical changes in certain nucleotides and associated histone proteins. These changes may affect gene expression by allowing transcription factors to improve their access to regulatory elements, therefore stimulating or inhibiting gene expression, while the original DNA

sequence remains unaltered (Stankiewicz et al., 2013). Potential changes include DNA methylation, which has been associated with down-regulation of gene expression, histone acetylation that may induce up-regulation of gene expression, and histone methylation and phosphorylation that may lead to activation or repression of transcriptional events. Epigenetic mechanisms have been studied in the context of stressful situations, which may induce long-lasting changes in gene expression in different neural structures, which, in turn, have been associated with the development of stress-related conditions. In this regard, preclinical studies revealed that chronic stress may regulate histone acetylation in the hippocampus, inducing transient increases and subsequent decreases, while transient increases have been also observed in the amygdala. In addition, early adverse experiences have been associated with changes in histone markers and DNA methylation of the GR gene, particularly in the hippocampus, and changes in DNA methylation have been also observed in the GR and BDNF genes (McEwen et al., 2012). Therefore, early stressful experiences may induce epigenetic changes in different neural structures, with the subsequent effect on their respective functions, which, in turn, may predispose to an increased vulnerability to stress and the development of diverse clinical conditions, such as depression.

In summary, depression constitutes a multi-factorial condition, usually associated with the convergence of an array of different factors, where the exposure to stressful conditions plays a critical role through psychological and neurobiological features. Psychological factors include the prolonged and sustained impact of stressful events, with the resulting learned helplessness, and the long-term consequences of traumatic experiences in early periods of life, with the resulting development of dysfunctional cognitive processing. In this regard, dysfunctional cognitive schemas, with the associated cognitive distortions, may lead to deficient reappraisal of stressful events and ineffective coping strategies. Neurobiological factors include chronic alterations of the HPA axis, with the consequent sustained increase of cortisol, and dysregulation of monoaminergic systems. In this regard, dysregulation of the 5HT system includes alteration of various 5HT receptors, an increased expression of 5HTT, and decreased levels of 5HT. Neurobiological factors also include alteration in other molecular pathways, including BDNF and CRF. Genetic polymorphisms also represent an additional group of biological factors, which may interact with other molecular mechanisms through the effects produced by their defective final products. Therefore, the effects of past or current stressful experiences may lead to different adaptive or maladaptive responses, according to their potential interactions with other factors involved in the origin and development of depression. These interactions may lead to further traumatic experiences, to different pathophysiological processes, or may contribute to the development of resilience (Fig. 4.43).

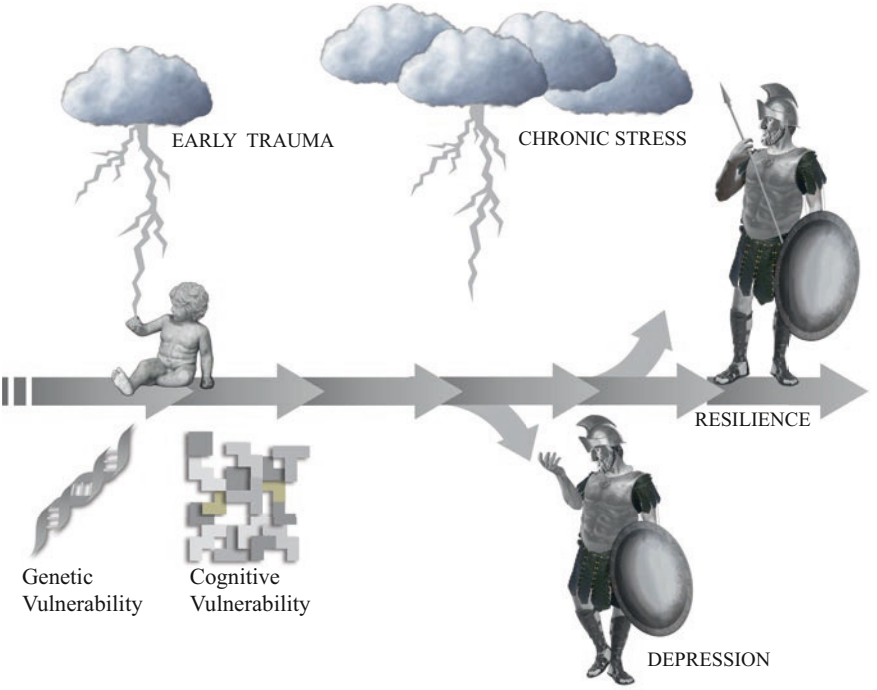

Fig. 4.43 Stress may lead to the origin and development of depression depending on various factors of vulnerability. Depression constitutes a multi-factorial condition, where the exposure to environmental stressors plays a critical role through psychological and neurobiological processes. Psychological factors include the impact of stressful events, with the resulting learned helplessness, and the long-term consequences of traumatic experiences in early periods of life, with the resulting dysfunctional cognitive processing. Neurobiological factors include chronic alterations of the HPA axis, with a sustained increase of cortisol, and dysregulation of monoaminergic systems, particularly 5HT. Cognitive vulnerability is based on dysfunctional cognitive schemas and cognitive distortions, which may lead to deficient reappraisal of stressful events and ineffective coping strategies. Genetic vulnerability is based on polymorphisms, which may interact with other molecular mechanisms through the effects produced by their defective final products. The effects of past or current stressful experiences may lead to different adaptive or maladaptive responses, according to their potential interactions with other factors involved in the origin and development of depression. These interactions may lead to further traumatic experiences or may contribute to the development of resilience

References

Alenina, N., & Klempin, F. (2015). The role of serotonin in adult hippocampal neurogenesis. *Behavioural Brain Research, 277*, 49–57.

Arborelius, L., Owens, M. J., Plotsky, P. M., et al. (1999). The role of corticotropin-releasing factor in depression and anxiety disorders. *The Journal of Endocrinology, 160*, 1–12.

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience, 10*(6), 410–422.

Baik, J. H. (2020). Stress and the dopaminergic reward system. *Experimental & Molecular Medicine, 52*(12), 1879–1890.

Bailey, T. W., & Dimicco, J. A. (2001). Chemical stimulation of the dorsomedial hypothalamus elevates plasma ACTH in conscious rats. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 280*, R8–R15.

Baratta, M. V., Zarza, C. M., Gomez, D. M., Campeau, S., Watkins, L. R., & Maier, S. F. (2009). Selective activation of dorsal raphe nucleus-projecting neurons in the ventral medial prefrontal cortex by controllable stress. *The European Journal of Neuroscience, 30*(6), 1111–1116.

Baumeister, D., Lightman, S. L., & Pariante, C. M. (2014). The interface of stress and the HPA axis in behavioural phenotypes of mental illness. *Current Topics in Behavioral Neurosciences, 18*, 13–24.

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *The American Journal of Psychiatry, 165*, 969–977.

Binder, E. B., Salyakina, D., Lichtner, P., et al. (2004). Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nature Genetics, 36*, 1319–1325.

Bouret, S., Duvel, A., Onat, S., & Sara, S. J. (2003). Phasic activation of locus coeruleus neurons by the central nucleus of the amygdala. *Journal of Neuroscience, 23*(8), 3491–3497.

Bradley, R. G., Binder, E. B., Epstein, M. P., et al. (2008). Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene. *Archives of General Psychiatry, 65*, 190–200.

Buijs, R. M., & Van Eden, C. G. (2000). The integration of stress by the hypothalamus, amygdala and prefrontal cortex: Balance between the autonomic nervous system and the neuroendocrine system. *Progress in Brain Research, 126*, 117–132.

Cabib, S., & Puglisi-Allegra, S. (2012). The mesoaccumbens dopamine in coping with stress. *Neuroscience and Biobehavioral Reviews, 36*(1), 79–89.

Canteras, N. S. (2002). The medial hypothalamic defensive system: Hodological organization and functional implications. *Pharmacology, Biochemistry, and Behavior, 71*, 481–491.

Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: Neuropsychopharmacological implications. *Pharmacology & Therapeutics, 130*, 226–238.

Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: The role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience and Biobehavioral Reviews, 26*(3), 321–352.

Caspi, A., Sugden, K., Moffitt, T. E., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*, 386–389.

Cattaneo, A., Macchi, F., Plazzotta, G., et al. (2015). Inflammation and neuronal plasticity: A link between childhood trauma and depression pathogenesis. *Frontiers in Cellular Neuroscience, 40*, 1–12.

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews. Endocrinology, 5*(7), 374–381.

Choi, D. C., Furay, A. R., Evanson, N. K., Ostrander, M. M., Ulrich-Lai, Y. M., & Herman, J. P. (2007). Bed nucleus of the stria terminalis subregions differentially regulate hypothalamic-pituitary-adrenal axis activity: Implications for the integration of limbic inputs. *The Journal of Neuroscience, 27*(8), 2025–2034.

Ciocchi, S., Herry, C., Grenier, F., Wolff, S. B., Letzkus, J. J., Vlachos, I., Ehrlich, I., Sprengel, R., Deisseroth, K., Stadler, M. B., Müller, C., & Lüthi, A. (2010). Encoding of conditioned fear in central amygdala inhibitory circuits. *Nature, 468*(7321), 277–282.

Commons, K. G., Connolley, R. K., & Valentino, R. J. A. (2003). Neurochemically distinct dorsal raphe-limbic circuit with a potential role in affective disorders. *Neuropsychopharmacology, 28*, 206–215.

Cooper, J. C., & Knutson, B. (2008). Valence and salience contribute to nucleus accumbens activation. *NeuroImage, 39*(1), 538–547.

Craig, K. J., Brown, K. J., & Baum, A. (1995). Environmental factors in the etiology of anxiety. In F. E. Bloom & D. J. Kupfer (Eds.), *Psychopharmacology: The fourth generation of progress* (pp. 1325–1339). Raven Press.

Cullinan, W. E., Herman, J. P., & Watson, S. J. (1993). Ventral subicular interaction with the hypothalamic paraventricular nucleus: Evidence for a relay in the bed nucleus of the stria terminalis. *Journal of Comparative Neurology, 332*(1), 1–20.

Davis, M., Walker, D., Miles, L., & Grillon, C. (2010). Phasic *vs* sustained fear in rats and humans: Role of the extended amygdala in fear *vs* anxiety. *Neuropsychopharmacology, 35*, 105–135.

Daviu, N., Bruchas, M. R., Moghaddam, B., Sandi, C., & Beyeler, A. (2019). Neurobiological links between stress and anxiety. *Neurobiology of Stress., 11*, 100191.

de Lima, M. A. X., Baldo, M. V. C., & Canteras, N. S. (2019). Revealing a cortical circuit responsive to predatory threats and mediating contextual fear memory. *Cerebral Cortex, 29*, 3074–3090.

De Rijk, R. H., Schaaf, M., & de Kloet, E. R. (2012). Glucocorticoid receptor variants: Clinical implications. *The Journal of Steroid Biochemistry and Molecular Biology, 81*, 103–122.

Deakin, J. F., & Graeff, F. G. (1991). 5-HT and mechanisms of defence. *Journal of Psychopharmacology, 5*(4), 305–315.

Deakin, J. F. W., & Graeff, F. G. (1991). 5 HT and mechanisms of defense. *Journal of Psychopharmacology, 5*, 305–331.

Delgado, M. R., Nearing, K. I., Ledoux, J. E., & Phelps, E. A. (2008). Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron, 59*(5), 829–838.

Der-Avakian, A., & Markou, A. (2012). The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences, 35*(1), 68–77.

DiMicco, J. A., Samuels, B. C., Zaretskaia, M. V., & Zaretsky, D. V. (2002). The dorsomedial hypothalamus and the response to stress: Part renaissance, part revolution. *Pharmacology, Biochemistry, and Behavior, 71*(3), 469–480.

Diorio, D., Viau, V., & Meaney, M. J. (1993). The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamo-pituitary-adrenal responses to stress. *The Journal of Neuroscience, 13*, 3839–3847.

Dong, H. W., & Swanson, L. W. (2004). Projections from bed nuclei of the stria terminalis, posterior division: Implications for cerebral hemisphere regulation of defensive and reproductive behaviors. *The Journal of Comparative Neurology, 471*(4), 396–433.

Dong, H. W., Petrovich, G. D., & Swanson, L. W. (2001). Topography of projections from amygdala to bed nuclei of the stria terminalis. *Brain Research Reviews, 38*(1–2), 192–246.

Drevets, W. C., Gautier, C., Price, J. C., Kupfer, D. J., Kinahan, P. E., Grace, A. A., Price, J. L., & Mathis, C. A. (2001). Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biological Psychiatry, 49*, 81–96.

Duman, R. S. (2004). Role of neurotrophic factors in the etiology and treatment of mood disorders. *Neuromolecular Medicine, 5*, 11–25.

Duman, R. S., & Charney, D. S. (1999). Cell atrophy and loss in major depression. *Biological Psychiatry, 45*(9), 1083–1084.

Duman, R. S., & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biological Psychiatry, 59*, 1116–1127.

Dunlop, B. W., & Nemeroff, C. B. (2007). The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry, 64*(3), 327–337.

Evans, G. W., Swain, J. E., King, A. P., Wang, X., Javanbakht, A., Ho, S. S., Angstadt, M., Phan, K. L., Xie, H., & Liberzon, I. (2016). Childhood cumulative risk exposure and adult amygdala volume and function. *Journal of Neuroscience Research, 94*(6), 535–543.

Feldman, S., Newman, M. E., & Weidenfeld, J. (2000). Effects of adrenergic and serotonergic agonists in the amygdala on the hypothalamo-pituitary-adrenocortical axis. *Brain Research Bulletin, 52*, 531–536.

Ferguson, A. V., Latchford, K. J., & Samson, W. K. (2008). The paraventricular nucleus of the hypothalamus – A potential target for integrative treatment of autonomic dysfunction. *Expert Opinion on Therapeutic Targets, 12*(6), 717–727.

Fiddick, L. (2011). There is more than the amygdala: Potential threat assessment in the cingulate cortex. *Neuroscience and Biobehavioral Reviews, 35*(4), 1007–1018.

Figueiredo, H. F., Bruestle, A., Bodie, B., Dolgas, C. M., & Herman, J. P. (2003). The medial prefrontal cortex differentially regulates stress-induced c-fos expression in the forebrain depending on type of stressor. *The European Journal of Neuroscience, 18*, 2357–2364.

Fitzgerald, D. A., Angstadt, M., Jelsone, L. M., et al. (2006). Beyond threat: Amygdala reactivity across multiple expressions of facial affect. *NeuroImage, 30*(4), 1441–1448.

Folkman, S., & Lazarus, R. S. (1988). The relationship between coping and emotion: Implications for theory and research. *Social Science & Medicine, 26*, 309–317.

Forster, G. L., Feng, N., Watt, M. J., Korzan, W. J., Mouw, N. J., Summers, C. H., & Renner, K. J. (2006). Corticotropin-releasing factor in the dorsal raphe elicits temporally distinct serotonergic responses in the limbic system in relation to fear behavior. *Neuroscience, 141*(2), 1047–1055.

Gatt, J. M., Nemeroff, C. B., Dobson-Stone, C., et al. (2009). Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Molecular Psychiatry, 14*, 681–695.

Geuze, E., Van Wingen, G. A., Van Zuiden, M., Rademaker, A. R., Vermetten, E., Kavelaars, A., Fernandez, G., & Heijnen, C. J. (2012). Glucocorticoid receptor number predicts increase in amygdala activity after severe stress. *Psychoneuroendocrinology, 37*, 1837–1844.

Glatz, K., Mössner, R., Heils, A., & Lesch, K. P. (2003). Glucocorticoid-regulated human serotonin transporter (5-HTT) expression is modulated by the 5-HTT gene-promotor-linked polymorphic region. *Journal of Neurochemistry, 86*(5), 1072–1078.

Gotlib, I. H., Joormann, J., Minor, K., et al. (2008). HPA axis reactivity: A mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biological Psychiatry, 63*, 847–851.

Graeff, F. G., Guimarães, F. S., De Andrade, T. G., & Deakin, J. F. (1996). Role of 5-HT in stress, anxiety, and depression. *Pharmacology, Biochemistry, and Behavior, 54*(1), 129–141.

Gray, T. S., Carney, M. E., & Magnuson, D. J. (1989). Direct projections from the central amygdaloid nucleus to the hypothalamic paraventricular nucleus: Possible role in stress-induced adrenocorticotropin release. *Neuroendocrinology, 50*(4), 433–446.

Guadagno, A., Belliveau, C., Mechawar, N., & Walker, C. D. (2021). Effects of early life stress on the developing basolateral amygdala-prefrontal cortex circuit: The emerging role of local inhibition and perineuronal nets. *Frontiers in Human Neuroscience, 15*, 669120.

Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology, 35*(1), 4–26.

Hammack, S. E., Guo, J. D., Hazra, R., Dabrowska, J., Myers, K. M., & Rainnie, D. G. (2009). The response of neurons in the bed nucleus of the stria terminalis to serotonin: Implications for anxiety. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 33*(8), 1309–1320.

Hamon, M., & Blier, P. (2013). Monoamine neurocircuitry in depression and strategies for new treatments. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 45*, 54–63.

Hariri, A. R., Mattay, V. S., Tessitore, A., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297*, 400–403.

Hariri, A. R., Drabant, E. M., Munoz, K. E., et al. (2005). A susceptibility gene for affective disorders and the response of the human amygdala. *Archives of General Psychiatry, 62*, 146–152.

Haroon, E., Raison, C. L., & Miller, A. H. (2012). Psychoneuroimmunology meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology, 37*, 137–162.

Heim, C., & Binder, E. B. (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. *Experimental Neurology, 233*, 102–111.

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry, 49*, 1023–1039.

Heim, C., Newport, D. J., Mletzko, T., et al. (2008). The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology, 33*, 693–710.

Herman, J. P., Cullinan, W. E., Ziegler, D. R., & Tasker, J. G. (2002). Role of the paraventricular nucleus microenvironment in stress integration. *The European Journal of Neuroscience, 16*, 381–385.

Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology, 23*, 477–501.

Horstmann, S., Lucae, S., Menke, A., et al. (2010). Polymorphisms in GRIK4, HTR2A, and FKBP5 show interactive effects in predicting remission to antidepressant treatment. *Neuropsychopharmacology, 35*, 727–740.

Ikemoto, S., & Panksepp, J. (1999). The role of nucleus accumbens dopamine in motivated behavior: A unifying interpretation with special reference to reward-seeking. *Brain Research. Brain Research Reviews, 31*(1), 6–41.

Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature, 517*(7534), 284–292.

Kalin, N. H. (2020). Novel insights into pathological anxiety and anxiety-related disorders. *The American Journal of Psychiatry, 177*(3), 187–189.

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry, 68*, 444–454.

Kassel, O., & Herrlich, P. (2007). Crosstalk between the glucocorticoid receptor and other transcription factors: Molecular aspects. *Molecular and Cellular Endocrinology, 275*, 13–29.

Kaufman, J., Plotsky, P. M., Nemeroff, C. B., et al. (2000). Effects of early adverse experiences on brain structure and function: Clinical implications. *Biological Psychiatry, 48*, 778–790.

Kaufman, J., Yang, B. Z., Douglas-Palumberi, H., et al. (2006). Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. *Biological Psychiatry, 59*, 673–680.

Kendler, K. S., Kuhn, J. W., & Prescott, C. A. (2004). Childhood sexual abuse, stressful life events and risk for major depression in women. *Psychological Medicine, 34*, 1475–1482.

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology, 48*, 191–214.

Korosi, A., Naninck, E. F., Oomen, C. A., et al. (2012). Early-life stress mediated modulation of adult neurogenesis and behavior. *Behavioural Brain Research, 227*, 400–409.

Kreier, F., Kap, Y. S., Mettenleiter, T. C., van Heijningen, C., van der Vliet, J., Kalsbeek, A., Sauerwein, H. P., Fliers, E., Romijn, J. A., & Buijs, R. M. (2006). Tracing from fat tissue, liver, and pancreas: A neuroanatomical framework for the role of the brain in type 2 diabetes. *Endocrinology, 147*(3), 1140–1147.

Krishnan, V., & Nestler, E. J. (2010). Linking molecules to mood: New insight into the biology of depression. *The American Journal of Psychiatry, 167*(11), 1305–1320.

Krugers, H. J., Lucassen, P. J., Karst, H., & Joëls, M. (2010). Chronic stress effects on hippocampal structure and synaptic function: Relevance for depression and normalization by anti-glucocorticoid treatment. *Frontiers in Synaptic Neuroscience, 2*, 24.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., & Phelps, E. A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. *Neuron, 20*(5), 937–945.

Lebow, M., & Chen, A. (2016). Overshadowed by the amygdala: The bed nucleus of the stria terminalis emerges as key to psychiatric disorders. *Molecular Psychiatry, 21*, 450–463.

LeDoux, J. E. (1992). Brain mechanisms of emotion and emotional learning. *Current Opinion in Neurobiology, 2*, 191–197.

LeDoux, J. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23*, 155–184.

LeDoux, J. (2003). The emotional brain, fear, and the amygdala. *Cellular and Molecular Neurobiology, 23*(4–5), 727–738.

LeDoux, J. (2007). The amygdala. *Current Biology, 17*(20), R868–R874.

LeDoux, J. (2012). Rethinking the emotional brain. *Neuron, 73*(4), 653–676.
LeDoux, J. E. (2014). Coming to terms with fear. *Proceedings of the National Academy of Sciences of the United States of America, 111*(8), 2871–2878.
LeDoux, J. E., Iwata, J., Cicchetti, P., & Reis, D. J. (1988). Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *The Journal of Neuroscience, 8*(7), 2517–2529.
LeDoux, J. E., & Pine, D. S. (2016). Using neuroscience to help understand fear and anxiety: A two-system framework. *The American Journal of Psychiatry, 173*(11), 1083–1093.
Lee, K. H., Tran, A., Turan, Z., & Meister, M. (2020). The sifting of visual information in the superior colliculus. *eLife, 9*, e50678.
Leonard, B. E. (2010). The concept of depression as a dysfunction of the immune system. *Current Immunology Reviews, 6*, 205–212.
Lesch, K. P., & Gutknecht, L. (2004). Focus on the 5-HT1A receptor: Emerging role of a gene regulatory variant in psychopathology and pharmacogenetics. *The International Journal of Neuropsychopharmacology, 7*, 381–385.
Lesch, K. P., Bengel, D., Heils, A., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*, 1527–1531.
Liberzon, I., Phan, K. L., Decker, L. R., & Taylor, S. F. (2003). Extended amygdala and emotional salience: A PET activation study of positive and negative affect. *Neuropsychopharmacology, 28*(4), 726–733.
Loftis, J. M., Huckans, M., & Morasco, B. J. (2010). Neuroimmune mechanisms of cytokine-induced depression: Current theories and novel treatment strategies. *Neurobiology of Disease, 37*, 519–533.
López, J. F., Chalmers, D. T., Little, K. Y., & Watson, S. J. (1998). Regulation of serotonin$_{1A}$, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: Implications for the neurobiology of depression. *Biological Psychiatry, 43*(8), 547–573.
López, J. F., Akil, H., & Watson, S. J. (1999). Neural circuits mediating stress. *Biological Psychiatry, 46*, 1461–1471.
Lowry, C. A., Johnson, P. L., Hay-Schmidt, A., Mikkelsen, J., & Shekhar, A. (2005). Modulation of anxiety circuits by serotonergic systems. *Stress, 8*(4), 233–246.
Lupien, S. J., & McEwen, B. S. (1997). The acute effects of corticosteroids on cognition: Integration of animal and human model studies. *Brain Research Reviews, 24*, 1–27.
Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience, 10*, 434–445.
Mahar, I., Bambico, F. R., Mechawar, N., et al. (2014). Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. *Neuroscience and Biobehavioral Reviews, 38*, 173–192.
Maier, S. F., & Seligman, M. E. (2016). Learned helplessness at fifty: Insights from neuroscience. *Psychological Review, 123*(4), 349–367.
Maier, S. F., & Watkins, L. R. (2005). Stressor controllability and learned helplessness: The roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. *Neuroscience and Biobehavioral Reviews, 29*(4–5), 829–841.
Maier, S. F., Grahn, R. E., Kalman, B. A., Sutton, L. C., Wiertelak, E. P., & Watkins, L. R. (1993). The role of the amygdala and dorsal raphe nucleus in mediating the behavioral consequences of inescapable shock. *Behavioral Neuroscience, 107*, 377–389.
Malberg, J. E., Eisch, A. J., Nestler, E. J., & Duman, R. S. (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *Journal of Neuroscience, 20*, 9104–9110.
Marcilhac, A., & Siaud, P. (1997). Identification of projections from the central nucleus of the amygdala to the paraventricular nucleus of the hypothalamus which are immunoreactive for corticotrophin-releasing hormone in the rat. *Experimental Physiology, 82*(2), 273–281.
Marek, R., Strobel, C., Bredy, T. W., & Sah, P. (2013). The amygdala and medial prefrontal cortex: Partners in the fear circuit. *The Journal of Physiology, 591*(10), 2381–2391.

McCall, J. G., Al-Hasani, R., Siuda, E. R., Hong, D. Y., Norris, A. J., Ford, C. P., & Bruchas, M. R. (2015). CRH engagement of the locus coeruleus noradrenergic system mediates stress-induced anxiety. *Neuron, 87*(3), 605–620.

McCall, J. G., Siuda, E. R., Bhatti, D. L., et al. (2017). Locus coeruleus to basolateral amygdala noradrenergic projections promote anxiety-like behavior. *eLife, 6*, e18247.

McEwen, B. S. (1987). Glucocorticoid-biogenic amine interactions in relation to mood and behavior. *Biochemical Pharmacology, 36*, 1755–1763.

McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annual Review of Neuroscience, 22*, 105–122.

McEwen, B. S., Weiss, J., & Schwartz, L. (1968). Selective retention of corticosterone by limbic structures in rat brain. *Nature, 220*, 911–912.

McEwen, B. S., Eiland, L., Hunter, R. G., & Miller, M. M. (2012). Stress and anxiety: Structural plasticity and epigenetic regulation as a consequence of stress. *Neuropharmacology, 62*(1), 3–12.

McNaughton, N., & Corr, P. J. (2018). Survival circuits and risk assessment. *Current Opinion in Behavioral Sciences, 24*, 14–20.

Melzter, H. (1989). Serotonergic dysfunction in depression. *The British Journal of Psychiatry, 155*, 25–31.

Milad, M. R., & Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. *Annual Review of Psychology, 63*, 129–151.

Moga, M. M., Saper, C. B., & Gray, T. S. (1989). Bed nucleus of the stria terminalis: Cytoarchitecture, immunohistochemistry, and projection to the parabrachial nucleus in the rat. *The Journal of Comparative Neurology, 283*(3), 315–332.

Morris, L. S., McCall, J. G., Charney, D. S., & Murrough, J. W. (2020). The role of the locus coeruleus in the generation of pathological anxiety. *Brain and Neuroscience Advances, 4*, 1–18.

Motta, S. C., Goto, M., Gouveia, F. V., Baldo, M. V. C., Canteras, N. S., & Swanson, L. W. (2009). Dissecting the brain's fear system reveals the hypothalamus is critical for responding in subordinate conspecific intruders. *Proceedings of the National Academy of Sciences, 106*, 4870–4875.

Nemeroff, C. B. (1999). The preeminent role of early untoward experience on vulnerability to major psychiatric disorders: The nature-nurture controversy revisited and soon to be resolved. *Molecular Psychiatry, 4*, 106–108.

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

Nemeroff, C. B. (2020). The state of our understanding of the pathophysiology and optimal treatment of depression: Glass half full or half empty? *American Journal of Psychiatry, 177*(8), 671–685.

Nemeroff, C. B., & Binder, E. (2014). The preeminent role of childhood abuse and neglect in vulnerability to major psychiatric disorders: Toward elucidating the underlying neurobiological mechanisms. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*, 395–397.

Nemeroff, C. B., & Seligman, F. (2013). The pervasive and persistent neurobiological and clinical aftermath of child abuse and neglect. *The Journal of Clinical Psychiatry, 74*, 999–1001.

Nemeroff, C. B., Widerlov, E., Bisette, G., et al. (1984). Elevated concentrations of CSF corticotropin-releasing-factor-like immunoreactivity in depressed patients. *Science, 226*, 1342–1344.

Nestler, E. J., & Carlezon, W. A., Jr. (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry, 59*(12), 1151–1159.

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., & Gross, J. J. (2004). For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage, 23*(2), 483–499.

Ota, K. T., & Duman, R. S. (2013). Environmental and pharmacological modulations of cellular plasticity: Role in the pathophysiology and treatment of depression. *Neurobiology of Disease, 57*, 28–37.

Owens, M. J., & Nemeroff, C. B. (1994). The role of serotonin in the pathophysiology of depression: Focus on the serotonin transporter. *Clinical Chemistry, 40*, 288–295.

Pape, H. C., & Pare, D. (2010). Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. *Physiological Reviews, 90*(2), 419–463.

Pare, D., Quirk, G. J., & Ledoux, J. E. (2004). New vistas on amygdala networks in conditioned fear. *Journal of Neurophysiology, 92*(1), 1–9.

Paton, J. J., Belova, M. A., Morrison, S. E., & Salzman, C. D. (2006). The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature, 439*(7078), 865–870.

Paul, E. D., & Chen, A. (2017). Neural circuitry of sress, fear, and anxiety: Focus on extended amygdala corticotropin releasing factor systems. In G. Fink (Ed.), *Stress: Neuroendocrinology and neurobiology* (pp. 83–96). Academic Press.

Pavlov, I. P. (1927). *Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex*. Oxford University Press.

Peng, H., Long, Y., Li, J., et al. (2014). Hypothalamic-pituitary-adrenal axis functioning and dysfunctional attitude in depressed patients with and without childhood neglect. *BMC Psychiatry, 14*, 45.

Peyron, C., Petit, J. M., Rampon, C., Jouvet, M., & Luppi, P. H. (1997). Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. *Neuroscience, 82*(2), 443–468.

Phelps, E. A., & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron, 48*(2), 175–187.

Radley, J. J., & Sawchenko, P. E. (2011). A common substrate for prefrontal and hippocampal inhibition of the neuroendocrine stress response. *Journal of Neuroscience, 31*, 9683–9695.

Ramirez, F., Moscarello, J. M., LeDoux, J. E., & Sears, R. M. (2015). Active avoidance requires a serial basal amygdala to nucleus accumbens shell circuit. *The Journal of Neuroscience, 35*(8), 3470–3477.

Ressler, K. J. (2010). Amygdala activity, fear, and anxiety: Modulation by stress. *Biological Psychiatry, 67*(12), 1117–1119.

Ressler, K. J., & Nemeroff, C. B. (1999). Role of norepinephrine in the pathophysiology and treatment of mood disorders. *Biological Psychiatry, 46*(9), 1219–1233.

Roland, B. L., & Sawchenko, P. E. (1993). Local origins of some GABAergic projections to the paraventricular and supraoptic nuclei of the hypothalamus of the rat. *The Journal of Comparative Neurology, 332*, 123–143.

Sabatinelli, D., Bradley, M. M., Lang, P. J., Costa, V. D., & Versace, F. (2007). Pleasure rather than salience activates human nucleus accumbens and medial prefrontal cortex. *Journal of Neurophysiology, 98*, 1374–1379.

Saper, C. B., & Lowell, B. B. (2014). The hypothalamus. *Current Biology, 24*(23), R1111–R1116.

Sapolsky, R. M. (1996). Why stress is bad for your brain. *Science, 273*, 749–750.

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1984). Stress down-regulates corticosterone receptors in a site-specific manner in the brain. *Endocrinology, 114*, 287–292.

Sara, S. J., & Bouret, S. (2012). Orienting and reorienting: The locus coeruleus mediates cognition through arousal. *Neuron, 76*(1), 130–141.

Schaaf, M. J. M., de Jong, J., de Kloet, E. R., & Vreugdenhil, E. (1998). Downregulation of BDNF mRNA and protein in the rat hippocampus by corticosterone. *Brain Research, 813*, 112–120.

Seligman, M. E. P. (1974). Depression and learned helplessness. In R. J. Friedman & M. M. Katz (Eds.), *The psychology of depression: Contemporary theory and research* (pp. 83–113). Winston.

Shabel, S. J., & Janak, P. H. (2009). Substantial similarity in amygdala neuronal activity during conditioned appetitive and aversive emotional arousal. *Proceedings of the National Academy of Sciences of the United States of America, 106*(35), 15031–15036.

Shi, L., Sun, J., Wei, D., & Qiu, J. (2019). Recover from the adversity: Functional connectivity basis of psychological resilience. *Neuropsychologia, 122*, 20–27.

Silva, B. A., Gross, C. T., & Gräff, J. (2016). The neural circuits of innate fear: Detection, integration, action, and memorization. *Learning & Memory, 23*(10), 544–555.

Šimić, G., Tkalčić, M., Vukić, V., Mulc, D., Španić, E., Šagud, M., Olucha-Bordonau, F. E., Vukšić, M., & Hof, P. R. (2021). Understanding emotions: Origins and roles of the amygdala. *Biomolecules, 11*, 823.

Sokolowski, K., & Corbin, J. G. (2012). Wired for behaviors: From development to function of innate limbic system circuitry. *Frontiers in Molecular Neuroscience, 5*, 55.

Sotres-Bayon, F., Bush, D. E., & LeDoux, J. E. (2004). Emotional perseveration: An update on prefrontalamygdala interactions in fear extinction. *Learning & Memory, 11*(5), 525–535.

Stankiewicz, A. M., Swiergiel, A. H., & Lisowski, P. (2013). Epigenetics of stress adaptations in the brain. *Brain Research Bulletin, 98*, 76–92.

Steimer, T. (2002). The biology of fear- and anxiety-related behaviors. *Dialogues in Clinical Neuroscience, 4*(3), 231–249.

Suri, D., & Vaidya, V. A. (2013). Glucocorticoid regulation of brain-derived neurotrophic factor: Relevance to hippocampal structural and functional plasticity. *Neuroscience, 239*, 196–213.

Suridjan, I., Boileau, I., Bagby, M., Rusjan, P. M., Wilson, A. A., Houle, S., & Mizrahi, R. (2012). Dopamine response to psychosocial stress in humans and its relationship to individual differences in personality traits. *Journal of Psychiatric Research, 46*(7), 890–897.

Swanson, L. W., & Kuypers, H. G. (1980). The paraventricular nucleus of the hypothalamus: Cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex, and spinal cord as demonstrated by retrograde fluorescence double labeling methods. *The Journal of Comparative Neurology, 194*, 555–570.

Swanson, L. W., & Petrovich, G. D. (1998). What is the amygdala? *Trends in Neurosciences, 21*(8), 323–331.

Tafet, G. E., & Bernardini, R. (2003). Psychoneuroendocrinological links between chronic stress and depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 27*, 893–903.

Tafet, G. E., & Nemeroff, C. B. (2016). The links between stress and depression: Psychoneuroendocrinological, genetic, and environmental interactions. *The Journal of Neuropsychiatry and Clinical Neurosciences, 28*(2), 77–88.

Tafet, G. E., Toister-Achituv, M., & Shinitzky, M. (2001). Enhancement of serotonin uptake by cortisol: A possible link between stress and depression. *Cognitive, Affective, & Behavioral Neuroscience, 1*, 96–104.

Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience, 10*(6), 397–409.

Valentino, R. J., Page, M. E., Van Bockstaele, E., & Aston-Jones, G. (1992). Corticotropin-releasing factor innervation of the locus coeruleus region: Distribution of fibers and sources of input. *Neuroscience, 48*, 689–705.

Valentino, R. J., Lucki, I., & Van Bockstaele, E. (2010). Corticotropin-releasing factor in the dorsal raphe nucleus: Linking stress coping and addiction. *Brain Research, 1314*, 29–37.

van Marle, H. J., Hermans, E. J., Qin, S., & Fernández, G. (2010). Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *Neuroimage, 53*(1), 348–354.

van Riel, E., van Gemert, N. G., Meijer, O. C., et al. (2004). Effect of early life stress on serotonin responses in the hippocampus of young adult rats. *Synapse, 53*, 11–19.

Vermeer, H., Hendriks-Stegeman, B. I., van der Burg, B., et al. (2003). Glucocorticoid-induced increase in lymphocytic FKBP51 messenger ribonucleic acid expression: A potential marker for glucocorticoid sensitivity, potency, and bioavailability. *The Journal of Clinical Endocrinology and Metabolism, 88*, 277–284.

Vogt, B. A. (2018). Anxiety and fear from the perspective of cingulate cortex. *Journal of Depression and Anxiety Forecast, 1*, 1–7.

Vogt, B., Rosene, D., & Pandya, D. (1979). Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. *Science, 204*, 205–207.

Vogt, B. A., Finch, D. M., & Olson, C. R. (1992). Functional heterogeneity in cingulate cortex: The anterior executive and posterior evaluative regions. *Cerebral Cortex, 2*, 435–443.

Vogt, B., Nimchimsky, E., Vogt, L., & Hof, P. (1995). Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. *Journal of Comparative Neurology, 359*, 490–506.

Vyas, A., Mitra, R., Shankaranarayana Rao, B. S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *The Journal of Neuroscience, 22*(15), 6810–6818.

Wei, P., Liu, N., Zhang, Z., Liu, X., Tang, Y., He, X., Wu, B., Zhou, Z., Liu, Y., Li, J., Zhang, Y., Zhou, X., Xu, L., Chen, L., Bi, G., Hu, X., Xu, F., & Wang, L. (2015). Processing of visually evoked innate fear by a non-canonical thalamic pathway. *Nature Communications, 6*, 6756.

Young, E. A., Haskett, R. F., Murphy-Weinberg, V., Watson, S. J., & Akil, H. (1991). Loss of glucocorticoid fast feedback in depression. *Archives of General Psychiatry, 48*, 693–699.

Zald, D. H. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews, 41*(1), 88–123.

Zhang, J., Fan, Y., Li, Y., Zhu, H., Wang, L., & Zhu, M. Y. (2012). Chronic social defeat up-regulates expression of the serotonin transporter in rat dorsal raphe nucleus and projection regions in a glucocorticoid-dependent manner. *Journal of Neurochemistry, 123*(6), 1054–1068.

Chapter 5
Integrative Approach to Stress

Resilience implies successful adaptation to stressful situations, overcoming threatening and adverse events, while maintaining psychological and physiological functioning. Resilience requires integrating different psychological and biological processes, involved in cognitive, emotional, behavioural and psychoneuroendocrinological adaptive changes. Psychoneuroimmunoendocrinology (PNIE) constitutes an integrative discipline, shaped in the interface between different scientific and clinical areas. Hence, it represents an ample and generous concept to define a new scientific discipline, which includes and integrates the distinguishing characteristics provided by the converging fields that contributed to shape it, with their respective processes and signalling molecules, involved in the major communication systems in each organism. Archaeological research demonstrated that the deciphering of the "Rosetta Stone" provided a bridge between the known and the unknown scripts. In the same way, the extraordinary progress in the study of stress, comprising several lines of research focused on psychological and neurobiological aspects, also needed a "Rosetta Stone" to bridge the remaining gaps. Therefore, PNIE represents the "Rosetta Stone" in the neuroscience of stress, which provides the necessary links between the involved factors, translating psychological concepts into neurobiological mechanisms and reciprocally molecular and biological processes into cognitive and emotional functions. In this regard, the study of PNIE involves the study of the nervous, the endocrine and the immune systems and the molecules involved in their respective signalling systems. Moreover, it is concerned with the study of neurotransmitters, neurotrophins, hormones and cytokines and the reciprocal interactions between them, their respective systems and the transcriptional regulation of different genes involved in these systems, through the bridges provided by this integrative discipline to study the interactions between all the different processes involved in the PNIE of stress.

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Cognitive and Neurobiological Integration of Stress and Resilience

Resilience represents the challenge to achieve successful adaptation to stressful situations, overcoming threatening and adverse events, while maintaining psychological and physiological functioning. In order to achieve resilience, it is necessary to integrate different psychological and biological processes, involved in cognitive, emotional, behavioural and psychoneuroimmunoendocrinological adaptive changes.

Successful cognitive processing may allow perceiving stressful events through the lens of adaptation to reality, less threatening and more challenging, which may lead to the development of more effective coping strategies. An effective cognitive processing may allow learning from aversive experiences, which, in turn, may lead to improving coping skills, emotional equilibrium and behavioural control. Moreover, resilience has been also associated not only with the ability and capacity to successfully cope with adverse situations but also with the possibility to emerge stronger from adversity, implying an opportunity for personal growth and development.

Exposure to sustained and prolonged stressful events, as it is usually observed in chronic stressful situations, may induce negatively biased cognitive processing, altered emotional equilibrium and the resulting behavioural changes, which, in turn, may be reflected in the development of learned helplessness. The ability to develop more effective cognitive processing, including an efficient reappraisal of perceived situations, and a proficient assessment of the available resources may lead to enhancing the subjective perception of predictability and improving the feeling of controllability. Therefore, successful cognitive processing, associated with improved predictability and controllability on stressful situations, may also lead to recovering the emotional equilibrium and more adaptive behavioural responses.

Upon exposure to environmental stressors, perceived information is consecutively processed through sensory, associative and transition cortices, which, in turn, project to the hippocampus and the amygdala. Reciprocal connections between the hippocampus and the amygdala and between these limbic structures with the dorsolateral prefrontal cortex (DL-PFC) and the ventro-medial (VM-PFC), including the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC), allow further emotional and cognitive processing (Fig. 5.1). Serotonergic, noradrenergic and dopaminergic projections from the brainstem are also involved in the integration of emotional and cognitive processing. Therefore, in response to stressful situations, the extended amygdala has been associated with the expression of fear and anxiety, while the dorsal peri-aqueductal grey (D-PAG) has been associated with activation of the fight-or-flight response.

During stressful situations, if aversive stimuli are perceived and interpreted as inescapable, the resulting lack of control may lead to the activation of serotonergic neurons in the dorsal raphe nuclei (DRN), which send stimulatory serotonergic projections to the extended amygdala, therefore potentiating fear and anxiety, and

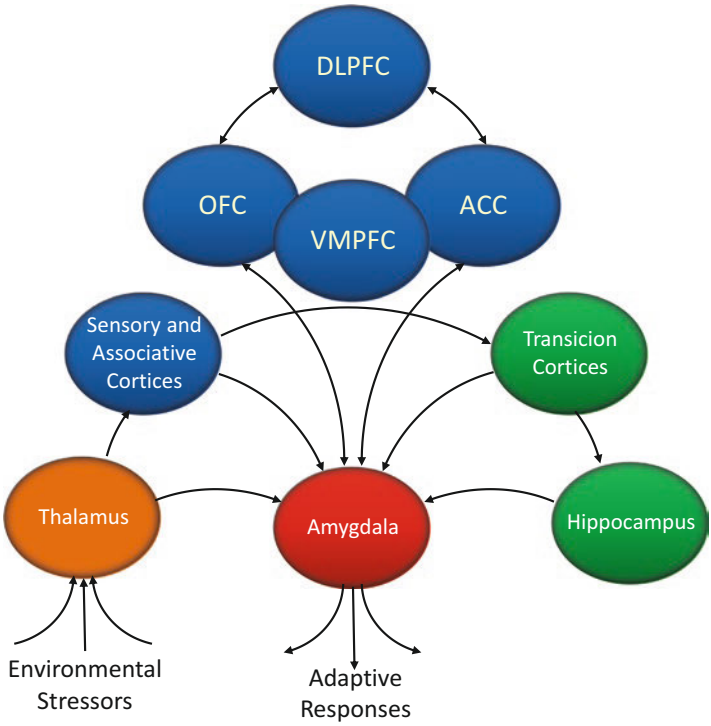

Fig. 5.1 Information processing from environmental stressors to adaptive responses. Perceived environmental information is conveyed through sensory pathways to the thalamus and is consecutively processed through sensory, associative and transition cortices, which, in turn, project to the hippocampus and the amygdala. Reciprocal connections between the hippocampus and the amygdala and between these limbic structures with the DL-PFC and the VM-PFC, including the OFC and the ACC, allow further emotional and cognitive processing

inhibitory projections to the D-PAG and striatum, hence inhibiting active coping behaviours, such as fight or flight, with the resulting passive responses (Graeff et al., 1996; Maier et al., 1993, 2005) (Fig. 5.2). The inhibition of active responses, with the consequent passivity and increased feelings of fear, uncertainty and anxiety, constitutes symptoms of learned helplessness (Seligman, 1974).

If aversive stimuli are perceived and interpreted as avoidable or escapable, the resulting perceived control may lead to the activation of neurons in the VM-PFC, particularly in the prelimbic (PL) region, which send projections to the dorsal medial striatum (DMS), which, in turn, send back stimulatory projections to the VM-PFC. After detection of controllability, a group of neurons in the PL area, which participate in this circuit with the DMS, convey updated information through projections from the VM-PFC to the DRN, where 5HT neurons, previously activated by the impact of aversive stimuli, result inhibited by updated information from the VM-PFC (Maier & Seligman, 2016) (Fig. 5.3).

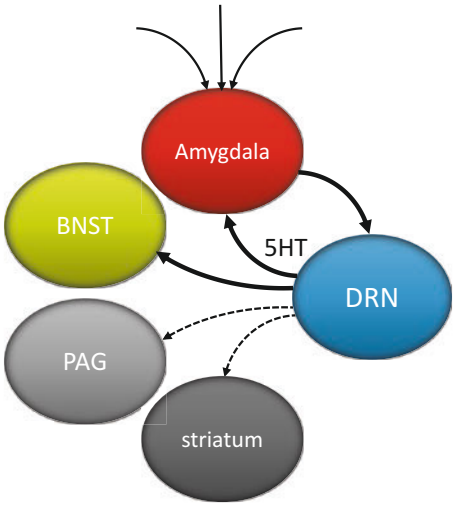

Fig. 5.2 Projections between the amygdala and the dorsal raphe nuclei (DRN) involved in fear and anxiety. In response to stressful situations, the extended amygdala has been associated with the expression of fear and anxiety, while the dorsal PAG (D-PAG) has been associated with activation of the fight-or-flight response. Stressful situations, which are perceived as unavoidable or inescapable, may lead to the activation of 5HT neurons in the dorsal raphe nucleus (DRN), which sends stimulatory serotonergic projections to the amygdala and the bed nucleus of the stria terminalis (BNST), therefore potentiating fear and anxiety, and inhibitory projections to the D-PAG and striatum, hence inhibiting active coping behaviours, such as fight or flight, with the resulting passive responses. The inhibition of active responses, with the consequent passivity, and increased feelings of fear, uncertainty and anxiety may contribute to learned helplessness

Therefore, activation of this circuit may be critical to prevent activation of serotonergic neurons in the DRN, which, in turn, is necessary to prevent sensitization of these neurons, which may lead to passivity and excessive fear and anxiety. During exposure to sustained and prolonged stressful events, if the situation is not perceived and interpreted as potentially controllable, this circuit is not activated, which results in continuous activation of serotonergic neurons in the DRN, with the consequent passivity and increased feelings of fear and anxiety. Although, if controllability is recognized, activation of projections from the VM-PFC to the DRN may lead to enduring changes in this circuit, mediated by the synthesis of new proteins, constituting a process of neuroplasticity. The strengthening of this circuit may improve its efficacy to cope with further stressful situations, therefore generating a neurobiological mechanism to improve and support a newly developed expectancy of control (Maier & Seligman, 2016), which may further support a cognitive process of "psychoplasticity". In this regard, it has been observed in rodents subjected to experimental conditions that previous experiences of controllability, in response to previous stressful events, may create an expectancy of control in the face of new stressful events, which may lead to improved behavioural responses, even to inescapable aversive stimuli, which may activate this sensitized circuit. Moreover, it has

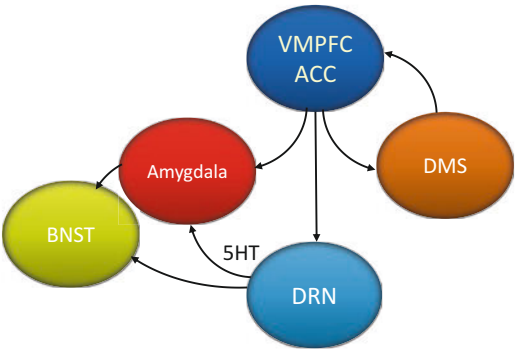

Fig. 5.3 Projections from the ventro-medial prefrontal cortex (VM-PFC) to the dorsal raphe nuclei (DRN) involved in controllability. Perception of controllable stressful situations, which may be interpreted as avoidable or escapable, has been associated with activation of neurons in the prelimbic (PL) region of the VM-PFC. These PL neurons send projections to the dorsal medial striatum (DMS), which send back stimulatory projections to the VM-PFC, which, in turn, send projections to the DRN, where 5HT neurons, previously activated by the impact of aversive stimuli, result inhibited by updated information from the VM-PFC

been also observed that both escapable and inescapable stressful stimuli may lead to activation of the DRN, with the resulting increased release of 5HT in the target neural structures, such as the amygdala. The concentrations of released 5HT decreased immediately in those subjects that learned to cope with stressful situation, therefore modifying inescapable into potentially escapable situations.

Activation of 5HT neurons, in both the DRN and the MRN, is modulated by $5HT_{1A}$ somato-dendritic autoreceptors. Increased concentrations of 5HT may lead to rapid activation of these receptors, with the resulting decreased release of 5HT due to this self-restraint mechanism. Prolonged and sustained activation of serotonergic neurons in the DRN, as it may occur during inescapable stressful situations, may lead to desensitization or down-regulation of these inhibitory $5HT_{1A}$ somato-dendritic autoreceptors, therefore suppressing its inhibitory effect, with the resulting increased release of 5HT in the amygdala, bed nucleus of the stria terminalis (BNST) and D-PAG (Rozeske et al., 2011), which have been associated with the development of learned helplessness. Therefore, the prolonged and sustained impact of inescapable stressful situations may lead to selective activation of 5HT neurons in the DRN, which, in turn, may be translated into passivity and increased feelings of fear and anxiety (Fig. 5.3).

Hence, activation of the amygdala, associated with feelings of fear and anxiety, may be neutralized by activation of the VM-PFC, which plays a critical role in the recognition and detection of controllability. In this regard, escapable stressful situations may be recognized by neurons in the VM-PFC, which exert inhibitory effect on the DRN. The VM-PFC, through projections, mainly originated in the PL region, represents the main source of cortical input to the DRN (Peyron et al., 1997; Vertes, 2004). This regulatory effect is mediated by excitatory glutamatergic projections from the VM-PFC to inhibitory GABAergic interneurons in the DRN, which, in

turn, exert inhibitory effect on 5HT neurons, and in the amygdala (Maier & Watkins, 2005; Maier & Seligman, 2016) (Fig. 5.3).

The impact of stressful stimuli, associated with recognition and detection of controllability, may lead to long-term increased connectivity between neurons in the VM-PFC and the DRN, constituting a process of learned controllability, which may be translated in certain learned immunity to further stressful situations. Of course, in order to achieve this long-term process, it is necessary to induce neuroplasticity, mediated by the synthesis of new proteins, particularly in neurons of the VM-PFC. Successful immunization, produced by the association between the impact of aversive events and the perception of controllability, may lead to the expectation that new aversive events may be also controllable, which constitutes a critical concept in the development of resilience.

The amygdala plays a critical role in this process, where the BLA is responsible of the association between a stimulus predicting the impact of an aversive event and the presence of that aversive event. Information processing regarding this associative learning is conveyed through internal projections in the amygdala, linking the BLA with the CNA, which, in turn, sends an array of multiple projections to different neural structures (Fig. 5.4). These projections, which convey information from the amygdala to the neural structures involved in the expression and regulation of adaptive responses, may lead to the expression of symptoms associated with fear and anxiety. Projections from the CNA include different targets, such as the PAG, which is involved in freezing; the BNST, which is involved in anxiety and also participates in the regulation of the HPA axis; and different nuclei involved in the regulation of the ANS.

The VM-PFC, through activated neurons in the PL and the infralimbic (IL) regions, also sends regulatory projections to the amygdala. In this regard, the IL region, corresponding to the sgACC in humans, sends glutamatergic projections to GABAergic neurons located in the intercalated cell region, which, in turn, send inhibitory projections to the CNA (Berretta et al., 2005), therefore inhibiting the expression of fear (Sierra-Mercado et al., 2011). It has been shown that previous inescapable stressful experiences may facilitate fear conditioning, whereas previous experiences of escapable stressful situations may interfere with fear conditioning, while inducing fear extinction, therefore showing certain expectation of control over new stressful events (Baratta et al., 2008). This may be achieved through the activation of a circuit involving neurons in the IL region, which shares reciprocal communications with the PL region, which, in turn, participates, in association with the dorsal medial striatum (DMS), in a circuit involved in the recognition and detection of controllability. Hence, an increased activation of the amygdala may be neutralized by an increased activation of the VM-PFC, which has been involved in learned control. Other areas in the PFC have been also associated with learned control, such as the DL-PFC (which participates in working memory and cognitive processing and therefore is involved in cognitive aspects of inhibitory control), the OFC (which is involved in emotional features of inhibitory control) and the ACC (which plays a critical role in emotion regulation) (Shi et al., 2019) (Fig. 5.5). Therefore, cognitive processing, involving the subsequent activation of the DL-PFC

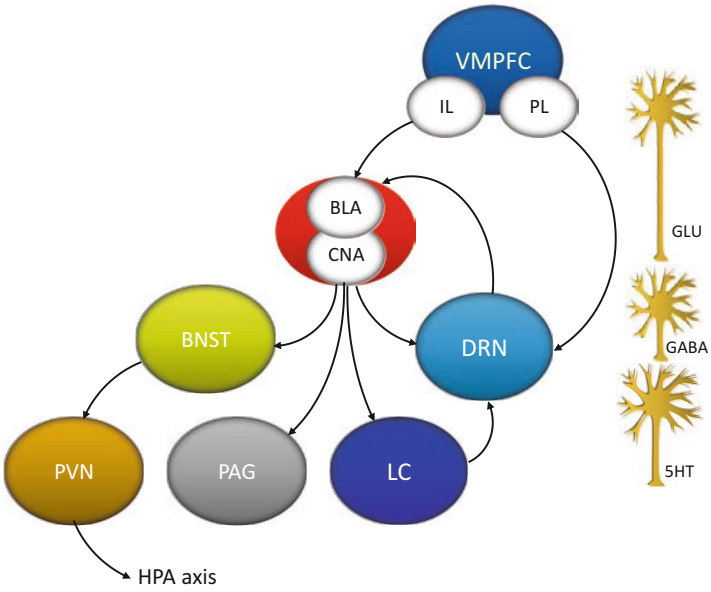

Fig. 5.4 Projections from the ventro-medial prefrontal cortex (VM-PFC) to the amygdala and the dorsal raphe nuclei (DRN) involved in controllability. Inescapable stressful situations may lead to selective activation of 5HT neurons in the DRN, which, in turn, may be translated into passivity and increased feelings of fear and anxiety. Activation of the amygdala, associated with feelings of fear and anxiety, may be neutralized by activation of the VM-PFC. Escapable stressful situations may be recognized by neurons in the VM-PFC, which exert an inhibitory effect on the DRN. The VM-PFC, through projections from the prelimbic (PL) region, exerts regulatory effect, mediated by excitatory glutamatergic projections from the VM-PFC to inhibitory GABAergic interneurons in the DRN, which, in turn, exert an inhibitory effect on 5HT neurons. Within the amygdala, the BLA projects to the central nucleus of the amygdala (CNA), which sends multiple projections to different neural structures, including the PAG (which is involved in freezing), the BNST (which is involved in anxiety and also participates in the regulation of the HPA axis) and different nuclei involved in the regulation of the ANS. The VM-PFC, through activated neurons in the prelimbic (PL) and the infralimbic (IL) regions, sends regulatory projections to the amygdala. The IL region sends glutamatergic projections to GABAergic neurons located in the intercalated cell region, which, in turn, send inhibitory projections to the CNA, therefore inhibiting the expression of fear

and the VM-PFC, may exert regulatory control through inhibitory projections to the amygdala and the DRN, consolidating these neural pathways involved in predictability and controllability, which are crucial for the development of resilience.

In response to stressful events, the amygdala also plays a critical role in the activation of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. In this regard, it has been shown that the amygdala exerts stimulatory effect on the hypothalamic paraventricular nucleus (PVN), mostly through projections to the BNST, which, in turn, sends stimulatory projections to the PVN, with the consequent synthesis and release of corticotrophin-releasing factor (CRF) (Fig. 5.6). Chronic stress may lead to increased levels of CRF, with the consequent increased levels of cortisol. After activation of the HPA axis, in response

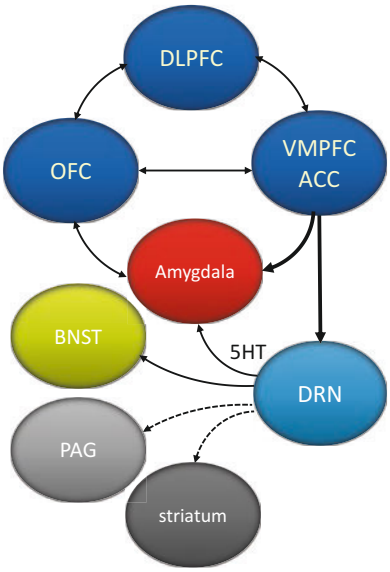

Fig. 5.5 Projections from different areas of the prefrontal cortex (PFC) involved emotion regulation. Activation of the amygdala may be neutralized by activation of the VM-PFC, which has been involved in learned control. Other areas in the PFC have been also associated with learned control, such as the DL-PFC (which participates in working memory and cognitive processing and therefore is involved in cognitive aspects of inhibitory control), the OFC (which is involved in emotional features of inhibitory control) and the ACC (which plays a critical role in emotion regulation)

to stressful stimuli, inhibition of the PVN, with the resulting decrease in CRF, is followed by a rapid down-regulation of adreno-corticotropic hormone (ACTH) in the pituitary, which, in turn, provokes a gradual decrease in the synthesis and release of cortisol. Thus, activation of negative feedback mechanisms, mostly exerted by glucocorticoids at different points of the HPA axis, is critical in the development of resilience. In this regard, resilience has been associated with the effective activation of these regulatory mechanisms, with the resulting reduction in CRF, and the consequent decrease in the synthesis and release of cortisol (Fig. 5.6). Moreover, it has been shown that resilient individuals, who exert active coping in response to environmental stressors, associated with challenging attitudes, may express lower glucocorticoid responses, in contrast to those with passive responses, associated with defeat and learned helplessness. In addition, it has been shown that dehydroepiandrosterone (DHEA) may be also released in response to stressful stimuli, which may exert compensatory antiglucocorticoid effects in the central nervous system (CNS) (Feder et al., 2009). In this regard, higher DHEA/cortisol ratios have been associated with a higher resilience. In addition, neuropeptide Y (NPY), which has been shown to exert compensatory effects in the amygdala, hippocampus and hypothalamus, opposing those produced by CRF, has been also associated with resilience.

Increased levels of brain-derived neurotrophic factor (BDNF) have been also associated with resilience. In this regard, BDNF is known to be involved in the

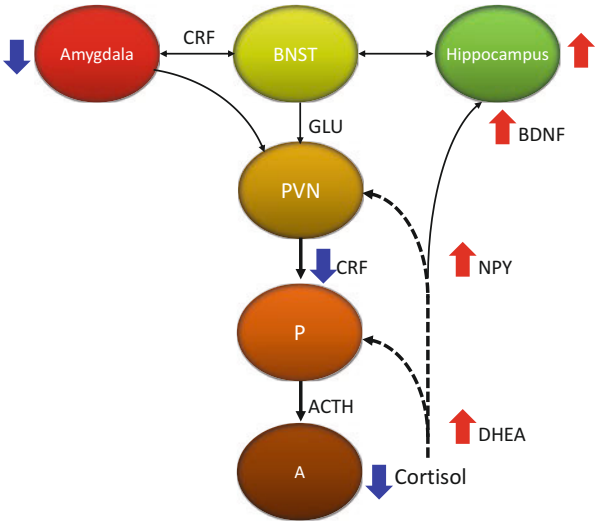

Fig. 5.6 Molecular changes involved in resilience. Resilience has been associated with a decreased activation of the amygdala and an increased activity in the hippocampus. In response to stressful events, the amygdala also plays a critical role in the activation of the ANS and the HPA axis. The amygdala exerts stimulatory effect on the hypothalamic PVN, mostly through projections to the BNST, which, in turn, sends stimulatory projections to the PVN, with the consequent synthesis and release of CRF. Chronic stress may lead to increased levels of CRF and cortisol. Activation of negative feedback mechanisms exerted by glucocorticoids at different points of the HPA axis is critical in the development of resilience, which has been associated with the effective activation of these regulatory mechanisms, with the resulting reduction in CRF and the cortisol. Dehydroepiandrosterone (DHEA) may be also released in response to stressful stimuli, which may exert compensatory antiglucocorticoid effects in the CNS. Neuropeptide Y (NPY) exerts compensatory effects in the amygdala, hippocampus and hypothalamus, opposing those produced by CRF. Brain-derived neurotrophic factor (BDNF) is involved in the development and functioning of the hippocampus through its role in neuroplasticity and neurogenesis

development and functioning of the hippocampus, particularly through its role in neuroplasticity and neurogenesis (Fig. 5.6). It has been shown that BDNF plays a critical role in neuronal proliferation and development at early ages and neuronal survival and normal functioning at later periods of life (Wu et al., 2013). In this regard, BDNF constitutes an important component of adaptive responses to stress, particularly in the hippocampus, where it has been shown to be necessary and sufficient to promote resilient adaptation to chronic stress (Taliaz et al., 2011; Franklin et al., 2012). Moreover, it has been observed that an increased BDNF expression in the ventral hippocampus, particularly in the CA3 area, in rodents resilient to chronic stress, and increased expression of BDNF in the dentate gyrus (DG) have been shown to promote resilience while blocking the anhedonic effects of stress (Taliaz et al., 2011; Franklin et al., 2012). Therefore, an increased expression of BDNF and its receptor TrkB in the hippocampus and PFC has been also associated with the therapeutic effects of antidepressants, further supporting the role of BDNF-TrkB signalling in the development of resilience (Wu et al., 2013).

Psychological and neurobiological processes underlying the development of resilience have been also investigated focusing on the reward system. In response to stressful events, resilience has been associated with effective cognitive and emotional processing, which may be translated into successful coping and subjective perception of predictability and controllability, which, in turn, may be reflected in positive and rewarding experiences. In this regard, the reward system has been shown to play a critical role in the modulation of adaptive responses to stress, particularly in the development of resilience.

Survival is associated with the ability and capacity to recognize threatening stimuli, to avoid dangerous situations, to learn about the characteristics of these stressors and to develop more effective resources to cope with them (LeDoux & Daw, 2018; Sapolsky, 2004). In the same way, survival is also associated with the ability to recognize rewarding stimuli, to learn about their characteristics and to approach them. Among these stimuli, primary rewards are those basically involved in survival, associated with satisfaction of basic needs, such as nutrition and reproduction, translated into the seek for food and sex. Secondary rewards may be not directly involved in survival but may indirectly lead to facilitating survival, such as money, power, challenge and positive experiences, associated with improving quality of life (Berridge & Robinson, 2003; Schultz, 2015; Sescousse et al., 2013). Hence, rewarding conditions may be associated with the development of resilience to stressful conditions, therefore highlighting the influence of the reward system on the stress system.

The reward system, as it has been previously described, encompasses dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), constituting the mesolimbic (M-L) pathway, and reciprocal connections between the NAc and different neural structures, including the VM-PFC, the hippocampus and the amygdala. The NAc has been involved in anticipation of positive and rewarding stimuli (Ikemoto & Panksepp, 1999). In this regard, the positive valence of anticipated rewards may lead to activation of the NAc, which, in turn, may be involved in the recognition of positive and negative valence (Ikemoto & Panksepp, 1999). Positive valence may increase with reward magnitude or probability. Hence, anticipatory activation of the NAc has been correlated with positive emotional experiences, which, in turn, may lead to approach behaviour.

Activation of the NAc has been also associated with the assessment of salience of perceived stimuli; thus, activation of the NAc may promote attention towards important or unexpected events (Berridge & Robinson, 1998; Redgrave et al., 1999). The amygdala is also involved in this mechanism, more specifically the BLA, which has been shown to be involved in reward-stress modulation (Ulrich-Lai et al., 2010). In this regard, it has been observed that rewarding stimuli may lead to an increased plasticity in the BLA and the NAc, which, in turn, have been associated with a decreased HPA reactivity (Ulrich-Lai, 2010). Moreover, it has been shown that upon stressful conditions, the presence of rewarding stimuli may decrease the intensity of subsequent stress responses, including cortisol reactivity and improved problem-solving strategies (Dutcher & Creswell, 2018).

Therefore, exposure to controllable stressful situations has been associated with an increased dopamine (DA) release in the NAc, whereas exposure to chronic and uncontrollable stressors has been associated with a decreased DA activity in the M-L pathway (Suridjan et al., 2012). Moreover, unavoidable or uncontrollable stressors may lead to a decreased DA release in the NAc and impaired response to environmental stimuli, which may result in the expression and exacerbation of certain depressive symptoms (Cabib & Puglisi-Allegra, 2012). In this regard, impaired dopaminergic function is involved in altered reward processing underlying anhedonia (Krishnan & Nestler, 2010). Moreover, the M-L dopaminergic pathway, and more specifically the NAc, is critically involved in the processing of rewarding and hedonic experiences in association with the OFC, which, in turn, is involved in the subjective assessments of hedonic and rewarding value (Der Avakian & Markou, 2012). The increased DA release in the M-L pathway has been associated with rewarding stimuli and in response to certain aversive situations, when these are perceived as controllable and escapable. The subjective perception of controllability is highly relieving, which, in turn, is also rewarding, representing a cardinal condition of resilience.

The role of early adverse experiences in the development of resilience has been also thoroughly investigated. Adverse experiences during early periods of life, including different traumatic events during childhood, have been associated with the origin of vulnerability to further stressful experiences or, in some individuals, with the development of resilience. It has been shown that the subjective degree of controllability, which may allow the person exert control over environmental stressors, plays a critical role in this process (Feder et al., 2011). Subjective perception of decreased controllability, especially during early periods of life, may contribute to developing learned helplessness (Overmier & Seligman, 1967). The development of learned helplessness has been associated with dysregulation of 5HT neurons in the DRN (Greenwood et al., 2003) and decreased neuroplasticity and neurogenesis in the hippocampus (Ho & Wang, 2010), which, in turn, may lead to long-lasting alterations in cognitive and emotional processes. In addition, early adverse experiences have been also associated with dysregulation of the HPA axis (Heim et al., 2008), with the consequent increased levels of corticotrophin-releasing hormone (CRH) and cortisol. On the other hand, it has been shown that children exposed to mild or moderate stressful situations, where they have been able to exert control, developed the capacity to be resilient in the face of different stressors in later periods of life (Feder et al., 2009; Russo et al., 2012). The development of potential immunity against later stressors has been called “stress inoculation” (Rutter, 1993) and has been associated with the ability to implement successful adaptive responses, with the consequent perception of controllability on stressful situations, and a higher tolerance to the negative effects of uncontrollable stressors (Southwick & Charney, 2012), which, in turn, has been associated with resilience. The protective effects of stress inoculation have been attributed to neuroplasticity in the PFC (Southwick & Charney, 2012). In this regard, an improved cognitive control and larger volume of

the VM-PFC has been observed in monkeys subjected to stress inoculation (Parker et al., 2005; Lyons et al., 2009). Therefore, it is conceivable that stress inoculation may lead to "learned resilience", the same way that early traumatic events may lead to learned helplessness, with the resulting increased vulnerability to further stressful events. In this regard, if resilience may be achieved as a learning process, then it may require synthesis of new proteins to generate neuroplasticity, which, in turn, may be also associated with increased levels of BDNF, and improved neurogenesis.

In summary, successful adaptive responses to stress, with the consequent development of resilience, constitute a dynamic combined process composed of multiple psychological and neurobiological mechanisms. At the psychological level, it is important to take into consideration the cognitive and emotional processing involved in the appraisal of stressful situations, the reappraisal of stressors and the available resources to cope with them and the resulting coping strategies. Successful appraisal and coping have been associated with the subjective perception of predictability and controllability, which play a critical role in the development of resilience. At the neurobiological level, successful implementation and regulation of adaptive responses, including effective regulation of the ANS and the HPA axis, play also a critical role in resilience. Cognitive and emotional processes involved in resilience depend on the effective activation of neural structures and their respective circuits underlying these processes. In this regard, cognitive processing, associated with an increased activity in the DL-PFC, with the concerted activation of the VM-PFC, associated with successful control on limbic structures, such as the amygdala, and aminergic systems, such as the DRN, may be translated into effective regulatory effects of cognitive on emotional processes (Fig. 5.7). Resilience has been associated with an increased activity in the hippocampal formation and decreased reactivity of the amygdala. Regarding the serotonergic system, it has been associated with an increased activity in the medial raphe nuclei (MRN), particularly involved in 5HT release in the hippocampus, and decreased activation of the DRN, which, in turn, projects to the amygdala and the PAG. The VM-PFC exerts inhibitory effects on the amygdala and the DRN and is also associated with the increased activity in the hippocampus (Fig. 5.7). Resilience has been also associated with an increased BDNF in the hippocampus, where it has been shown to be involved in neuroplasticity and neurogenesis. The reward system is also involved, particularly through DA projections from the VTA to the NAc, which, in turn, also participates in reciprocal connections with cortical and limbic structures, participating in the rewarding effects of controllability on stressful events (Fig. 5.7). Therefore, these psychological and neurobiological processes are reciprocally integrated in the development of resilience, which may be critical to successfully cope with the stress of life and, when it would be possible, to transform negative distressful events into positive and challenging positive experiences.

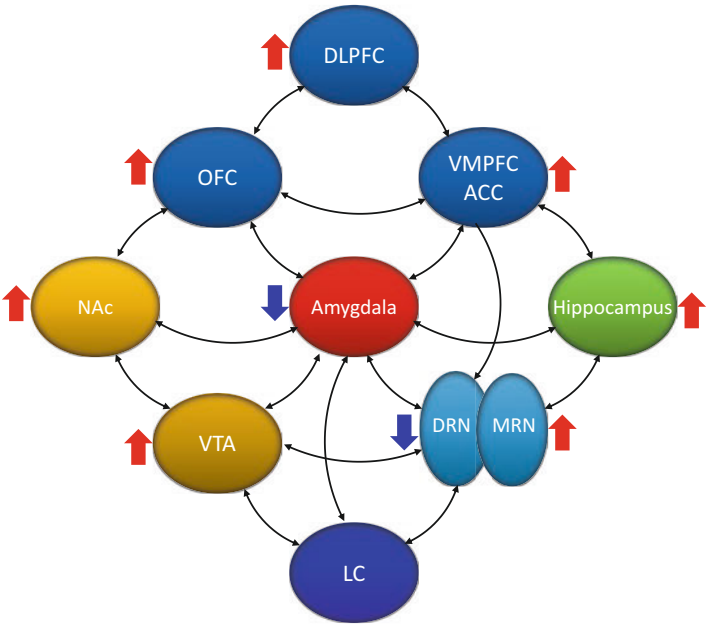

Fig. 5.7 Psychoneuroendocrinological changes involved in resilience. Successful cognitive processing associated with an increased activity in the DL-PFC and the VM-PFC exerts control on the amygdala and the DRN. The VM-PFC exerts inhibitory effects on the amygdala and the DRN and is also associated with an increased activity in the hippocampus. Resilience has been associated with an increased activity in the hippocampal formation and a decreased reactivity of the amygdala (Fig. 5.7). Resilience has been also associated with an increased serotonergic activity in the medial raphe nuclei (MRN), particularly involved in 5HT release in the hippocampus, and a decreased activation of the DRN, which projects to the amygdala. The reward system is also involved, particularly through DA projections from the VTA to the NAc, which participate in reciprocal connections with cortical and limbic structures involved in the rewarding effects of controllability on stressful events

Psychoneuroimmunoendocrinology: A "Roseta Stone" in the Neuroscience of Stress

Psychoneuroimmunoendocrinology (PNIE) constitutes an integrative discipline, shaped in the interface between different scientific and clinical areas, including psychiatry, psychology, neurology, neurobiology, endocrinology and immunology. PNIE represents an ample and generous concept to define a new scientific discipline, which includes and integrates the distinguishing characteristics provided by the converging fields that contributed to shape it, with their respective signalling molecules, involved in the major communication systems in our organism (Nemeroff, 2013).

The origins of PNIE may be closely related to the development of traditional psychosomatic medicine, which constitutes an interdisciplinary approach to understand psychological factors involved in the origin and development of somatic disorders. During the classical era, in ancient Greece, the mutual influence between the soul and the body, which may be also understood as the reciprocal influence of the mind and pathophysiological processes, was first approached by philosophers, such as Alcmeon (around 500 B.C.) and Hippocrates (469–399 B.C.) (Lindley & Schatzberg, 2003). During the second century, Galen, the Roman physician and philosopher, focused on the role of "passions" in the origin of bodily diseases and the control of passions in the recovery of health. His ideas contributed to the development of medicine and were influential on various medical writers until the nineteenth century, including the Jewish physician and philosopher Maimonides (1138–1204), who also referred to the effects produced by the "passions of the mind" in various pathophysiological processes. Therefore, the role of psychological processes in the origin and development of various medical conditions was further demonstrated in the first decades of the twentieth century by the pioneering works of Pavlov (Pavlov, 1902) and Cannon (Cannon, 1915), who focused their research on the pathophysiological correlates of emotional processes, giving rise to psychophysiology (Lipowski, 1986).

Although the expression "psychosomatic", to refer to this concept, was first introduced by Heinroth in 1818 (Margetts, 1950), the development of psychosomatic medicine started in the first half of the twentieth century (Ackerknecht, 1982). Between the 1930s and the 1960s, the development of psychosomatic medicine received a strong influence from psychoanalysis, which started with the pioneering works by Sigmund Freud and his followers, who associated bodily symptoms, referred by patients suffering from psychosomatic disorders, with intrapsychic unconscious conflicts (Freud, 1926). Among his followers, Franz Alexander proposed that unconscious conflicts may lead to chronic emotional tensions, which may be translated into specific physiological correlates, which, in turn, may lead to functional and structural changes in specific organs (Alexander, 1950). Therefore, he proposed a psychogenic theory, which associated psychological processes, represented by unconscious conflicts, the defences against them and the resulting emotions, with the origin and development of psychosomatic disorders. Hence, the development of psychosomatic medicine focused on the idea of psychogenesis of disease, which led to the concept of psychosomatic diseases, to refer to physical diseases caused by psychological factors (Fava & Sonino, 2010). According to the psychogenic model proposed by Alexander, these psychological processes, with their potential alterations, could not fully account for the origin and development of somatic disorders, since according to the assumed multicausal origin of all diseases, other biological factors should be also involved in this process (Lipowski, 1986). The role of these biological factors was largely accepted by most of the psychoanalysts involved in the development of psychosomatic medicine, although the links between these biological factors, unveiled by the increasing progress in psychophysiology and neurobiology, and their clinical correlates, provided by psychosomatic theories, remained still elusive. Moreover, the interface between

neurobiological processes and their clinical correlates, usually observed in psychiatry and clinical psychology, and conversely the interface between psychosomatic processes and their biological and molecular underpinnings, increasingly studied by a burgeoning body of research in neurosciences, still gave the impression to be spoken and written in different languages, too different between them and too difficult to reach mutual understanding, and therefore reciprocally translated. On the one hand, the language of psychosomatic medicine was a language of psychological processes, which included an array of abstract terms to define sophisticated concepts, such as emotions and thoughts, which was very difficult to translate into biological and molecular terms. On the other hand, the language of neurobiology and psychophysiology was a language to describe biological processes and molecular mechanisms, including specific references to neural structures and molecular pathways, which was very difficult to translate into psychological terms. The development of neuroscience met a critical point, where the involved scientific disciplines, which gave rise to an increasing body of unprecedented achievements, needed a "Rosetta Stone" to bridge the gaps among them, allowing the reciprocal translation and mutual understanding of these languages.

The "Rosetta Stone" is a fragment of an ancient Egyptian stele, a piece of stone engraved in three different types of writing: hieroglyphic, demotic and Greek. Hieroglyphic represents an ancient writing system, developed in Egypt around 3000 BCE, composed of a collection of pictorial scripts, each of them constituting a *hieroglyph*, which means "sacred carving" in Greek. These scripts were abundantly found in ancient Egyptian monuments, but no one was able to decipher their meaning during centuries. The second writing was demotic, which represents a simpler version of hieroglyphic, used for everyday handwriting, and the third writing was Greek, which was officially introduced in Egypt during the Hellenistic period, between 332 and 30 BCE. Unlike hieroglyphic writing, Greek was widely known and therefore could be easily understood by modern scholars. The stone was unexpectedly found in 1799 by a French soldier named Bouchard, during a military campaign led by Napoleon Bonaparte in Egypt, and received its name after it was found in Rosetta, the name that the French gave to the ancient Egyptian town of Rashid. After it was transferred to Paris, the stone arrived at the hands of Champollion, an expert Egyptologist, who carefully studied the stone and discovered that the same text, with the same possible meaning, was written in three different writings. This interesting observation and his subsequent investigations allowed him to translate the meaning of hieroglyphs for the first time initially into Greek and then into French and other modern languages. The realization that it was the same message written in different writings, and at least one of them was known, allowed them to fully deciphering an ancient code, which has been hidden for centuries, such as hieroglyphs.

The deciphering of the "Rosetta Stone" provided a marvellous bridge between the known and the unknown scripts. In the same way, the extraordinary progress in the study of stress, comprising several lines of research focused on different aspects, such as the psychological and neurobiological foundations of stress, also needed a "Rosetta Stone" to bridge the remaining gaps. In this regard, the twentieth century

witnessed a significant progress in the understanding of stress and the pathophysiological consequences of stressful experiences, including the neural structures involved in cognitive processing, emotional experiences and behavioural responses. Therefore, neurobiological research focused on the mechanisms involved in the functioning of these neural structures, including the neural circuits and pathways involved in their reciprocal communication. Cellular and molecular research also provided a comprehensive view of the interactions between different systems, including neurotransmitters and hormones involved in cell signalling, and the biological roots coded in the genes and their transcriptional regulation. Psychological research provided a comprehensive understanding of the effects produced by stress, including the cognitive and emotional processing of stressful experiences, and the potential development of trauma or resilience. Clinical research provided an important information about the effects produced by stress, including the impact of stressful experiences in the development of different diseases, various psychosomatic disorders, and particularly the role of chronic stress in the origin and development of depression and anxiety disorders. The contributions of these lines of research was amazing; however, the efforts to translate psychological concepts into the language of neurobiological mechanisms and reciprocally molecular and biological processes into the language of cognitive and emotional functions still needed a "Rosetta Stone" to overcome the remaining gaps among them.

The rise of psychoneuroendocrinology (PNE), during the 1950s, 1960s and 1970s, provided the necessary links to bridge these gaps, with strong scientific backgrounds, universally understood and recognized throughout the involved fields of knowledge (Campeau et al, 1998). Therefore, the development of PNE allowed paramount advances in the study of stress in a comprehensive manner, integrating an increasing body of research on psychoendocrinology (PE) and neuroendocrinology. Some of the most influential contributions included the studies on the regulatory effects of neural structures, such as the hypothalamus, the pituitary gland and the adrenal cortex (Harris, 1955, 1956), which provided the foundations for better understanding the communications between the brain and the body through the HPA axis, representing the core of the neuroendocrine system (Harris, 1970). The links between psychoendocrinology and neuroendocrinology were also supported through the studies on the effects produced by stressful events in the regulation of the HPA axis (Bliss et al., 1956; Ganong, 1963; Mason, 1968). Moreover, clinical and neuroendocrinological research in the field of PNE also provided evidence on the dysregulation of the HPA axis in patients with stress, anxiety (Basowitz et al., 1956; Persky et al., 1959) and depression (Gibbons & McHugh, 1962; Bridges & Jones, 1966). The regulatory effect of the nervous system on endocrine functions was further supported by the discovery of different hypothalamic peptides, which exerted stimulatory effects as releasing factors for pituitary hormones (Schally et al., 1973; Guillemin, 1978; Nemeroff & Prange, 1978), such as the CRF (Vale et al., 1981). Reciprocally, the effects of endocrine mediators on neural circuits were further supported by the finding of glucocorticoid receptors (GRs) in the hippocampal formation (McEwen et al., 1968; Gerlach & McEwen, 1972) and other neural structures involved in the regulation of cognitive and emotional functions

(Gerlach et al., 1976; McEwen, 1976), as it was reflected through the association between hormonal changes and depression (Prange et al., 1977). The development of PNE, mainly focused on the interactions between neural structures and the endocrine system, and the molecular signalling involved in their crosstalk were further enhanced with the contributions of psychoneuroimmunology (PNI). In this regard, PNI was developed as a new integrative discipline in the interface between psychology, immunology and the neurosciences, to study the interactions between the nervous, the endocrine and the immune systems (Ader, 1981). Hence, research on PNI originally focused on the effects of stressful life events on the potential vulnerability to develop infectious diseases and was further expanded during the 1970s, when several lines of research focused on the reciprocal interactions between the brain and the immune system (Ader, 2001). It has been shown that the brain interacts with the immune system via neural and endocrine signals, and reciprocally, activation of the immune system may influence the CNS through hormones and cytokines produced by activated lymphocytes (Ader, 2001). In this regard, chronic exposure to stressful conditions may lead to immunological alterations, which has been also observed in depressed patients.

Therefore, the extraordinary evolution of PNE, in conjunction with the contributions of PNI, provided the foundations for the development of PNIE as a major integrative discipline. In this sense, the study of PNIE involves the study of the nervous, the endocrine and the immune systems, the molecules involved in their respective signalling systems (including neurotransmitters, hormones, cytokines, and other peptides), their reciprocal interactions and the resulting pathophysiological processes. Regarding the PNIE of stress, this involves the cognitive and emotional processing of environmental stimuli and their appraisal on the resulting coping strategies and behavioural responses, therefore constituting the psychological component, which, in turn, may lead to the effects produced by different pathophysiological processes in the origin and development of depression and anxiety disorders. In addition, the study of the nervous system, with the complex interactions between different neural structures in the CNS, including the constellation of synaptic connections and the molecules involved in these processes, provides the bases to include PNIE in the context of neurosciences.

Therefore, PNIE represents the "Rosetta Stone" in the neuroscience of stress, which provides the necessary links between the involved factors, translating psychological concepts into neurobiological mechanisms and reciprocally molecular and biological processes into cognitive and emotional functions (Fig. 5.8). In this regard, PNIE is concerned with the study of neurotransmitters, neurotrophins, hormones and cytokines and the reciprocal interactions between them, their respective systems and the transcriptional regulation of the different genes involved in these systems, through the bridges provided by this integrative discipline to study the interactions between all the different processes involved in the PNIE of stress.

In conclusion, stress may be a common condition in normal life, which may lead to pathophysiological processes involved in an array of adverse consequences, including different somatic diseases and mental disorders, such as depression and anxiety disorders. The development of PNIE allowed the possibility to integrate the

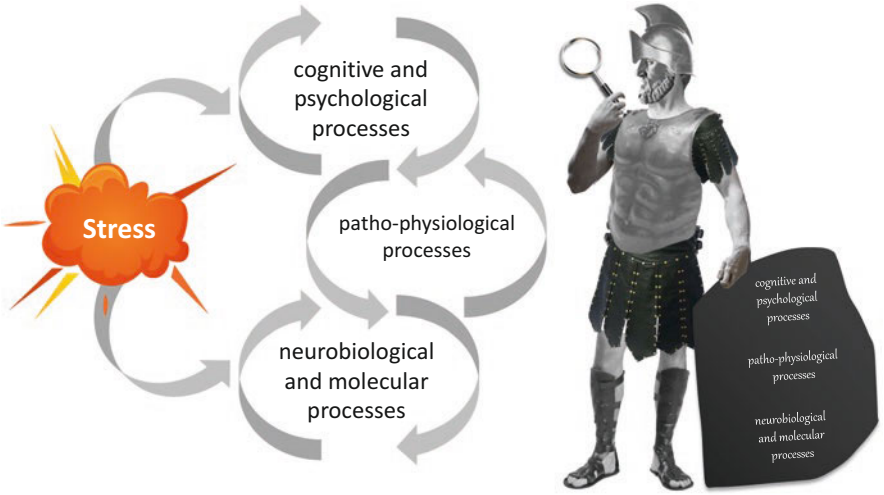

Fig. 5.8 Reciprocal bridges between neurobiological and psychological processes provide the bases to understand the pathophysiological processes involved in the neuroscience of stress and its clinical implications. Psychoneuroimmunoendocrinology (PNIE) represents the "Rosetta Stone" of the neuroscience of stress, providing the necessary links between the involved factors, translating psychological concepts into neurobiological mechanisms and reciprocally molecular and biological processes into cognitive and emotional functions

available scientific knowledge, provided by all the involved disciplines, necessary to better understand all the underlying psychological and neurobiological processes of stress. Moreover, the development of PNIE also provided the possibility to understand the processes involved in the development of resilience, which may be critical to successfully cope with the stress of life and, when it would be possible, to transform negative distressful events into positive and challenging positive experiences. This may be critical to prevent disorders provoked by stressful experiences, to develop more effective psychotherapeutic, psychopharmacological and biological strategies for the effective treatment of these disorders, significantly improving our quality of life.

References

Ackerknecht, E. H. (1982). The history of psychosomatic medicine. *Psychological Medicine, 12*(1), 17–24.

Ader, R. (Ed.). (1981). *Psychoneuroimmunology*. Academic Press.

Ader, R. (2001). Psychoneuroimmunology. *Current Directions in Psychological Science, 10*(3), 94–98.

Alexander, F. (1950). *Psychosomatic medicine*. Norton.

Baratta, M. V., Lucero, T. R., Amat, J., Watkins, L. R., & Maier, S. F. (2008). Role of the ventral medial prefrontal cortex in mediating behavioral control-induced reduction of later conditioned fear. *Learning & Memory, 15*(2), 84–87.

Basowitz, H., Chevalier, J. A., Grinker, R. R., Hamburg, D. A., Korchin, S. J., Persky, H., & Sabshin, M. A. (1956). Adrenal cortical function in anxious human subjects; plasma level and urinary excretion of hydrocortisone. *A.M.A. Archives of Neurology and Psychiatry, 76*(5), 549–558.

Berretta, S., Pantazopoulos, H., Caldera, M., Pantazopoulos, P., & Pare, D. (2005). Infralimbic cortex activation increases c-Fos expression in intercalated neurons of the amygdala. *Neuroscience, 132*(4), 943–953.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Research. Brain Research Reviews, 28*(3), 309–369.

Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences, 26*(9), 507–513.

Bliss, L., Migeon, C. J., Branch, C. H., & Samuels, L. T. (1956). Reaction of the adrenal cortex to emotional stress. *Psychosomatic Medicine, 18*, 56.

Bridges, P. K., & Jones, M. T. (1966). The diurnal rhythm of plasma cortisol concentration in depression. *The British Journal of Psychiatry, 112*(493), 1257–1261.

Cabib, S., & Puglisi-Allegra, S. (2012). The mesoaccumbens dopamine in coping with stress. *Neuroscience and Biobehavioral Reviews, 36*(1), 79–89.

Campeau, S., Day, H. E., Helmreich, D. L., Kollack-Walker, S., & Watson, S. J. (1998). Principles of psychoneuroendocrinology. *The Psychiatric Clinics of North America, 21*(2), 259–276.

Cannon, W. B. (1915). *Bodily changes in pain, hunger, fear, and rage*. Appleton.

Der-Avakian, A., & Markou, A. (2012). The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences, 35*(1), 68–77.

Dutcher, J. M., & Creswell, J. D. (2018). The role of brain reward pathways in stress resilience and health. *Neuroscience and Biobehavioral Reviews, 95*, 559–567.

Fava, G. A., & Sonino, N. (2010). Psychosomatic medicine. *International Journal of Clinical Practice, 64*(8), 1155–1161.

Feder, A., Nestler, E. J., & Charney, D. S. (2009). Psychobiology and molecular genetics of resilience. *Nature Reviews. Neuroscience, 10*(6), 446–457.

Feder, A., Charney, D. S., & Collins, K. (2011). Neurobiology of resilience. In S. M. Southwick, B. T. Litz, D. S. Charney, & M. J. Friedman (Eds.), *Resilience and mental health*. Cambridge University Press.

Franklin, T. B., Saab, B. J., & Mansuy, I. M. (2012). Neural mechanisms of stress resilience and vulnerability. *Neuron, 75*(5), 747–761.

Freud, S. (1926). *Inhibitions, symptoms, and anxiety* (Vol. 20, pp. 87–156). Standard Edition.

Ganong, W. F. (1963). The central nervous system and the synthesis and release of adrenocorticotropic hormone. In A. V. Nalbandov (Ed.), *Advances in neuroendocrinology* (Vol. 111, p. 92). Univ. Illinois Press.

Gerlach, J., & McEwen, B. S. (1972). Rat brain binds adrenal steroid hormone: Radioautography of hippocampus with corticosterone. *Science, 175*, 1133–1136.

Gerlach, J., McEwen, B. S., Pfaff, D. W., Moskovitz, S., Ferin, M., et al. (1976). Cells in regions of rhesus monkey brain and pituitary retain radioactive estradiol, corticosterone and cortisol differently. *Brain Research, 103*, 603–612.

Gibbons, J. L., & McHugh, P. R. (1962). Plasma cortisol in depressive illness. *Journal of Psychiatric Research, 1*, 162–171.

Graeff, F. G., Guimarães, F. S., De Andrade, T. G., & Deakin, J. F. (1996). Role of 5-HT in stress, anxiety, and depression. *Pharmacology, Biochemistry, and Behavior, 54*(1), 129–141.

Greenwood, B. N., Foley, T. E., Day, H. E., Campisi, J., Hammack, S. H., Campeau, S., Maier, S. F., & Fleshner, M. (2003). Freewheel running prevents learned helplessness/behavioral depression: Role of dorsal raphe serotonergic neurons. *Journal of Neuroscience, 23*(7), 2889–2898.

Guillemin, R. (1978). Peptides in the brain: The new endocrinology of the neuron. *Science, 202*, 390–402.

Harris, G. W. (1955). *Neural control of the pituitary gland*. Arnold.

Harris, G. W. (1956). Hypothalamic control of the anterior lobe of the hypophysis. In W. S. Fields, R. Guillemin, & C. A. Carton (Eds.), *Hypothalamic-hypophysial interrelationships* (p. 31). Thomas.

Harris, G. W. (1970). Effects of the nervous system on the pituitary-adrenal activity. *Progress in Brain Research, 32*, 86–88.

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology, 33*, 693–710.

Ho, Y. C., & Wang, S. (2010). Adult neurogenesis is reduced in the dorsal hippocampus of rats displaying learned helplessness behavior. *Neuroscience, 171*, 153–161.

Ikemoto, S., & Panksepp, J. (1999). The role of nucleus accumbens dopamine in motivated behavior: A unifying interpretation with special reference to reward-seeking. *Brain Research. Brain Research Reviews, 31*(1), 6–41.

Krishnan, V., & Nestler, E. J. (2010). Linking molecules to mood: New insight into the biology of depression. *The American Journal of Psychiatry, 167*(11), 1305–1320.

LeDoux, J., & Daw, N. D. (2018). Surviving threats: Neural circuit and computational implications of a new taxonomy of defensive behaviour. *Nature Reviews. Neuroscience, 19*(5), 269–282.

Lindley, S. E., & Schatzberg, A. F. (2003). Historical roots of psychoneuroendocrinology. In O. M. Wolkowitz & A. J. Rothschild (Eds.), *Psychoneuroendocrinology: The scientific basis of clinical practice* (pp. 9–25). American Psychiatric Publishing.

Lipowski, Z. J. (1986). Psychosomatic medicine: Past and present. Part I. Historical background. *Canadian Journal of Psychiatry, 31*(1), 2–7.

Lyons, D. M., Parker, K. J., Katz, M., & Schatzberg, A. F. (2009). Developmental cascades linking stress inoculation, arousal regulation, and resilience. *Frontiers in Behavioral Neuroscience, 3*, 32.

Maier, S. F., Grahn, R. E., Kalman, B. A., Sutton, L. C., Wiertelak, E. P., & Watkins, L. R. (1993). The role of the amygdala and dorsal raphe nucleus in mediating the behavioral consequences of inescapable shock. Behavioral. *Neurosciences, 107*, 377–389.

Maier, S. F., & Seligman, M. E. (2016). Learned helplessness at fifty: Insights from neuroscience. *Psychological Review, 123*(4), 349–367.

Maier, S. F., & Watkins, L. R. (2005). Stressor controllability and learned help lessness: The roles of the dorsal raphe nucleus, serotonin, and cor-ticotropin-releasing factor. *Neuroscience and Biobehavioral Reviews, 29*, 829–841.

Margetts, E. L. (1950). The early history of the word psychosomatic. *Canadian Medical Association Journal, 63*, 403.

Mason, J. W. (1968). A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosomatic Medicine, 30(5):Suppl*, 576–607.

McEwen, B. S., Weiss, J., & Schwartz, L. (1968). Selective retention of corticosterone by limbic structures in rat brain. *Nature, 220*, 911–912.

McEwen, B. S. (1976). Steroid hormone receptors in developing and mature brain tissue. In S. Snyder & B. S. McEwen (Eds.), *Neurotransmitters, hormones and receptors: Novel approaches* (pp. 50–66). Society of Neuroscience.

Nemeroff, C. B., & Prange, A. J., Jr. (1978). Peptides and psychoneuroendocrinology. A perspective. *Archives of General Psychiatry, 35*(8), 999–1010.

Nemeroff, C. B. (2013). Psychoneuroimmunoendocrinology: The biological basis of mind-body physiology and pathophysiology. *Depression and Anxiety, 30*(4), 285–287.

Overmier, J. B., & Seligman, M. E. (1967). Effects of inescapable shock upon subsequent escape and avoidance responding. *Journal of Comparative and Physiological Psychology, 63*, 28–33.

Parker, K. J., Buckmaster, C. L., Justus, K. R., Schatzberg, A. F., & Lyons, D. M. (2005). Mild early life stress enhances prefrontal-dependent response inhibition in monkeys. *Biological Psychiatry, 57*, 848–855.

Pavlov, J. P. (1902). *The work of the digestive glands. Translated by W H Thompson*. Lippincott.

Persky, H., Korchin, S. J., Basowitz, H., Board, F. A., Sabshin, M., Hamburg, D. A., & Grinker, R. R. (1959). Effect of two psychological stresses on adrenocortical function; studies on anxious and normal subjects. *A.M.A. Archives of Neurology and Psychiatry, 81*(2), 219–226.

Peyron, C., Petit, J. M., Rampon, C., Jouvet, M., & Luppi, P. H. (1997). Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. *Neuroscience, 82*(2), 443–468.

Prange, A. J., Jr., Lipton, M. A., Nemeroff, C. B., & Wilson, I. C. (1977). The role of hormones in depression. *Life Sciences, 20*(8), 1305–1318.

Redgrave, P., Prescott, T., & Gurney, K. N. (1999). The basal ganglia: A vertebrate solution to the selection problem? *Neuroscience, 89*, 1009–1023.

Rozeske, R. R., Evans, A. K., Frank, M. G., Watkins, L. R., Lowry, C. A., & Maier, S. F. (2011). Uncontrollable, but not controllable, stress desensitizes 5-HT1A receptors in the dorsal raphe nucleus. *The Journal of Neuroscience, 31*(40), 14107–14115.

Russo, S. J., Murrough, J. W., Han, M. H., Charney, D. S., & Nestler, E. J. (2012). Neurobiology of resilience. *Nature Neuroscience, 15*(11), 1475–1484.

Rutter, M. (1993). Resilience: some conceptual considerations. *The Journal of Adolescent Health, 14*, 626–631, 690–626–631, 696.

Sapolsky, R. M. (2004). *Why Zebras don't get ulcers*. Holt Paperbacks.

Schally, A. V., Arimura, A., & Kastin, A. J. (1973). Hypothalamic regulatory hormones. *Science, 179*, 341–350.

Schultz, W. (2015). Neuronal reward and decision signals: From theories to data. *Physiological Reviews, 95*(3), 853–951.

Seligman, M. E. P. (1974). Depression and learned helplessness. In R. J. Friedman & M. M. Katz (Eds.), *The psychology of depression: Contemporary theory and research* (pp. 83–113). Winston.

Sescousse, G., Caldú, X., Segura, B., & Dreher, J. C. (2013). Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 37*(4), 681–696.

Shi, L., Sun, J., Wei, D., & Qiu, J. (2019). Recover from the adversity: Functional connectivity basis of psychological resilience. *Neuropsychologia, 122*, 20–27.

Sierra-Mercado, D., Padilla-Coreano, N., & Quirk, G. J. (2011). Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 36*(2), 529–538.

Southwick, S. M., & Charney, D. S. (2012). The science of resilience: Implications for the prevention and treatment of depression. *Science, 338*, 79–82.

Suridjan, I., Boileau, I., Bagby, M., Rusjan, P. M., Wilson, A. A., Houle, S., & Mizrahi, R. (2012). Dopamine response to psychosocial stress in humans and its relationship to individual differences in personality traits. *Journal of Psychiatric Research, 46*(7), 890–897.

Taliaz, D., Loya, A., Gersner, R., Haramati, S., Chen, A., & Zangen, A. (2011). Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor. *The Journal of Neuroscience, 31*(12), 4475–4483.

Ulrich-Lai, Y. M., Christiansen, A. M., Ostrander, M. M., Jones, A. A., Jones, K. R., Choi, D. C., Krause, E. G., Evanson, N. K., Furay, A. R., Davis, J. F., Solomon, M. B., de Kloet, A. D., Tamashiro, K. L., Sakai, R. R., Seeley, R. J., Woods, S. C., & Herman, J. P. (2010). Pleasurable behaviors reduce stress via brain reward pathways. *Proceedings of the National Academy of Sciences of the United States of America, 107*(47), 20529–20534.

Vale, W., Spiess, J., Rivier, C., & Rivier, J. (1981). Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science, 213*, 1394–1397.

Vertes, R. P. (2004). Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse, 51*(1), 32–58.

Wu, G., Feder, A., Cohen, H., Kim, J. J., Calderon, S., Charney, D. S., & Mathé, A. A. (2013). Understanding resilience. Front. *Behavioral Neuroscience, 7*, 10.

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