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Impact of Physiological Changes in Various Region of The Brain Under Psychosocial Stress

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Abstract

Psychosocial stress is the body's response to psychological stressors faced by individuals due to external and internal factors that challenge psychological and emotional balance. Psychosocial stress is known to affect the structure and function of various regions in the brain, thereby affecting cognitive abilities and individual susceptibility to various psychopathological disorders. This literature review aims to examine the impact of physiological changes in various regions of the brain associated with responses to psychosocial stress. The main components of the stress system are the hypothalamus and brainstem and include corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) neurons from the paraventricular nucleus (PVN) of the hypothalamus, as well as CRH neurons from paragigantocellular and parabranchial nuclei of the medulla, as well as the locus coeruleus (LC) and another group of the cells that synthesize catecholamines, norepinephrine (NE) from the medulla and pons (central sympathetic nervous system). Furthermore, the hypothalamic-pituitary-adrenal (HPA) axis, along with the efferent sympathetic/adrenomedullary system, form the peripheral component of this interconnected system. Psychosocial stress can predispose to cognitive and emotional deficits due to disruption in the brain connectivity of the various brain regions involved such as dorsal prefrontal cortex (PFC), ventral PFC, hippocampus and amygdala.

***Keywords*:** *Psychosocial stress, amygdala, hippocampus, prefrontal cortex, physiological changes*

Abstrak

Dampak Perubahan Fisiologis Pada Berbagai Regio di Otak Pada Kondisi Stress Psikososial. Stres psikososial merupakan respons tubuh terhadap faktor-faktor stres psikologis yang dihadapi individu akibat faktor eksternal dan internal yang mengganggu keseimbangan psikologis dan emosional. Stres psikososial diketahui mempengaruhi struktur dan fungsi berbagai regio di otak, sehingga memengaruhi kemampuan kognitif dan kerentanan individu terhadap berbagai gangguan psikopatologis. Tinjauan literatur ini bertujuan untuk mengkaji dampak perubahan fisiologis di berbagai wilayah otak yang terkait dengan respons terhadap stres psikososial. Komponen utama sistem stres meliputi hipotalamus dan batang otak, serta mencakup neuron *corticotropin-releasing hormone* (CRH) dan *arginine-vasopressin* (AVP) dari nukleus paraventrikular (PVN) hipotalamus, serta neuron CRH dari nukleus paragigantocellular dan parabranchial medulla, serta *locus coeruleus* (LC) dan kelompok sel lain yang mensintesis katekolamin, norepinefrin (NE) dari medulla dan pons (sistem saraf simpatik pusat). Selain itu, sumbu hipotalamus-pituitari-adrenal (HPA) bersama dengan sistem simpatik/adrenomedular eferen membentuk komponen perifer dari sistem terintegrasi ini. Stres psikososial dapat meningkatkan risiko defisit kognitif dan emosional akibat gangguan konektivitas otak pada berbagai wilayah otak yang terlibat, seperti korteks prefrontal dorsal (PFC), korteks prefrontal ventral, hipokampus, dan amigdala.

Kata Kunci: *Stres Psikososial, Amigdala, Hipokampus,Korteks Prefrontal, Perubahan fisiologis.*

Introduction

Stress is the body's reaction to various threatening situations that can cause both physical and physiological changes that will disrupt homeostasis.[1] When a condition is interpreted as stress, the body will activate the hypothalamic-pituitary-adrenal gland (HPA) axis which is then followed by the secretion of cortisol.[2,3] This stress response is related to the state of arousal and activation of various body systems and emotions.[4,5] Thus, according to the characteristics of the stressor or source of stress, stress is categorized into two major groups, namely physiological stress and psychosocial stress.[6]

Psychosocial stress is the body's response to psychological stressors that individuals face due to external or internal factors that challenge psychological and emotional balance. It involves the interaction between psychological factors (such as anxiety, fear, or frustration) and social factors (such as work pressures, interpersonal relationship problems, or economic challenges), which can have a significant impact on an individual's well-being. Various studies have shown that psychosocial stress is closely related to physical and psychological changes, which not only affect the mental state, but also alter the physiological functions of the body.[6,7,8]

The brain is the main organ that interprets and responds to stress, as well as the target of stress hormones.[2,3] Psychosocial stress is known to affect the structure and function of various regions in the brain. The human brain has an adaptive response to stress, but under conditions of prolonged or chronic stress, the physiological changes that occur can reduce the brain's capacity to manage stress, affect cognitive abilities, and increase its vulnerability to various psychopathological disorders such as depression, anxiety and addiction.[6,9] While the entire central nervous system (CNS) is directly or indirectly involved in maintaining and restoring the body's homeostasis, specific areas of the brain have critical and distinct roles in regulating the stress response.[4]

Research on psychosocial stress has largely focused on understanding HPA axis activity as this pathway controls cortisol production. Although previous studies have shown that the cognitive and emotional deficits that occur with psychosocial stress are due to impaired brain connectivity of the various brain regions involved such as the dorsal prefrontal cortex (PFC), ventral PFC, hippocampus, and amygdala that have cortisol receptors and mediate important processes that support the perception, interpretation, and emotional response to stress.[2,6,10] Specifically, previous studies have shown that the PFC and hippocampus exhibit inhibitory control of the HPA axis, while the amygdala exerts an excitatory influence on HPA axis function.[11]

These physiological changes not only affect cognitive and emotional aspects, but also contribute to physical disorders, such as increased blood pressure, sleep disturbances, and decreased immune system. In addition, complex brain networks may also influence an individual's biological sensitivity to stress, and may ultimately mediate inter-individual differences in susceptibility to stress-related psychiatric disorders. In this regard, it is important to understand how these changes occur and their impact on an individual's long-term health, particularly in relation to the risk of mental disorders such as anxiety, depression and post-traumatic stress disorder (PTSD). A better understanding of the stress response in health may ultimately lead to a better understanding of how stress contributes to psychopathology in vulnerable individuals.

Based on this phenomenon, this literature review aims to examine the impact of physiological changes in various regions of the brain associated with responses to psychosocial stress. This literature review is expected to provide a deeper understanding of the brain mechanisms involved in the stress response, as well as the potential implications for mental and physical health, both in the context of prevention and therapeutic interventions to reduce the adverse effects of psychosocial stress

Stress Responses

The main components of the stress system are the hypothalamus and brainstem and include corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) neurons from the paraventricular nucleus (PVN) of the hypothalamus, as well as CRH neurons from the paragigantocellular and parabranchial nuclei of the medulla, as well as the locus coeruleus (LC) and another group of cells that synthesize catecholamines, norepinephrine (NE) from the medulla and pons (central sympathetic nervous system).[12,13] Furthermore, the hypothalamic-pituitary-adrenal (HPA) axis, along with the efferent sympathetic/adrenomedullary system, form the peripheral components of this interconnected system.

When a condition is interpreted as stressful, catecholamines are produced first and then followed by increased levels of corticosteroid hormones. Catecholamines are secreted and then cause *second messenger* activation in postsynaptic neurons within a few seconds, while corticosteroid hormones are secreted within minutes and cause effects for hours until they are involved in the process of gene transcription.[14,15] Epinephrine in the brain acts as an alarm system that can decrease neurovegetative functions such as eating or sleeping and also plays a role in increasing autonomic and neuroendocrine responses including the HPA system to stress. Norepinephrine can activate the amygdala which is the center for regulating fear and increasing long-term memory storage in the hippocampus.[16]

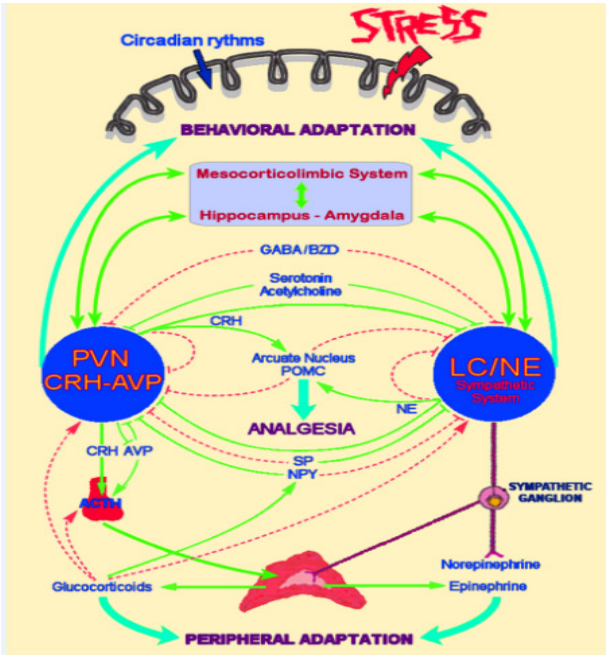

Figure 1. Central and peripheral components of Stress[12]

Furthermore, these processes lead to activation of the HPA axis. The hypothalamus will secrete CRH and AVP to the portal system and will then cause an increase in the secretion of adrenocorticotropic hormone (ACTH). ACTH will then stimulate the adrenal cortex to secrete cortisol.[16,17] Cortisol is an effector of the HPA system and plays a role in the control of body homeostasis and the organism's response to stress. Cortisol is also important in regulating the basal activity of the HPA system and for the termination of the stress response. Cortisol's negative feedback on ACTH secretion is aimed at limiting the duration of cortisol's action on tissues so as to minimize the catabolic, anti-reproductive and immunosuppressive effects of cortisol activation.[16] In chronic stress there is an increase in cortisol levels over a long period of time due to hyperactivity of the HPA system and disruption of glucocorticoid receptor (GR) function which plays a role in the negative feedback mechanism of the HPA system.[16, 18,19]

Cortisol can easily enter the brain tissue because of its lipophilic nature and then will be bound to 2 glucocorticoid receptors, namely MR and GR.[14,15,20] MR is found limited to limbic system regions such as the hippocampus, amygdala nuclei and motor nuclei of the brain stem, while GR is widespread and can be found both in neurons and cells.[17,20] MR has a high affinity, 10 times higher than GR, so it plays a role in basal cortisol levels, whereas if there is an increase in cortisol levels, the role of MR will be replaced by GR. The bond between cortisol and GR will cause different effects and even opposite to the effects of cortisol in basal conditions.[15,21] With the difference in receptor types, then in general the effect of cortisol on the hippocampus can be described by an inverted U-shaped curve (Inverted U-shaped dose dependency). Cortisol levels in mild stressors are needed as a mechanism to maintain homeostasis, while very low or very high cortisol levels will adversely affect brain tissue.[20] In chronic stress there is an increase in cortisol levels over a long period of time due to hyperactivity of the HPA system and disruption of GR function which plays a role in the negative feedback mechanism of the HPA system.[16]

Acute stress results in rapid activation of the sympathetic nervous system which activates the hypothalamic-pituitary-adrenal (HPA) axis that functions to maintain or restore homeostasis. The HPA axis is a complex system that induces wide-ranging bodily effects to interact with neurotransmitters and the immune system. It receives top-down neural regulation from the limbic system in the brain, and from the prefrontal cortex, which is strongly associated with limbic regions.[22]

Long-term elevated cortisol levels due to repeated exposure to stress can have detrimental effects on the brain.[37] The effects of chronic stress are progressive, starting with temporary (reversible) effects to permanent effects such as neuronal damage. The effects of chronic stress can be seen in various regions of the brain, especially the hippocampus which plays an important role in learning and memory storage. The hippocampus is a region in the brain that is most rich in corticosteroid receptors and has a high sensitivity to corticosteroids.[20,23] Therefore, stress is believed to be associated with decreased cognitive abilities and the emergence of diseases.[15]

Psychosocial Stress

In daily life, humans are constantly confronted with social, cognitive or physiological stressors in a variety of situations. Physiological stress is caused by unpleasant sensory, emotional and subjective experiences associated with potential damage to body tissues and threats to the body such as pain, hunger and oxidative stress.[24,25] Psychosocial stress is induced by social threat situations such as social evaluation, social exclusion and achievement situations that demand goal-directed performance.[26,27] The need to interact with others and maintain oneself in the social settings is a basic psychological need of every individual.[28,29] If the fulfilment of this need is threatened, for example by negative assessment of performance by others, social evaluation as well as cognitive achievement with unpredictable outcomes, social threat and can trigger a stress response.[27.28,29]

As previously described, stressors induce responses that activate the sympathetic nervous system and HPA axis to maintain and restore homeostasis.[30,31] The HPA axis is a complex system that interacts with various neurotransmitters and induces wide-ranging effects on the body. The HPA axis receives neural regulation from the limbic system and from the prefrontal cortex. Thus, stress responses are mediated by limbic structures, including the ventral hippocampus, infralimbic and prelimbic regions, and the amygdala; the hippocampus and anterior cingulate cortex (ACC)/prelimbic cortex inhibit HPA activation, the amygdala and infralimbic cortex may increase cortisol secretion.[30,31]

Previous studies have shown that various areas associated with the limbic system including the medial temporal lobe, insular lobe, and prefrontal cortex are activated during stress.[32] The amygdala-hippocampus complex, orbitofrontal cortex, anterior cingulate, and insula have been shown to be activated under conditions of physical and psychological stress which is useful for triggering autonomic stress responses.[32,33]

In physiological stress, various meta-analyses studying neural correlates of pain processing identified a network of activated brain areas as primary and secondary motor and somatic regions, insula, dorsal ACC, thalamus, periaqueductal substantia grisea and prefrontal cortex.[34,35] These regions process *sensory-discriminative* information as well as other pain characteristics such as affective-cognitive. Both psychosocial stress and physiological stress are related to survival-threatening situations and both stressors alter mesolimbic dopamine transmission in the striatum and prefrontal cortex.[34,35] In addition, like psychosocial stress, specific deactivation during pain processing in emotion regulation areas such as the amygdala, nucleus accumbens, and frontal regions, as well as in motor and sensory related areas has also been reported.[34]

In contrast to physiological stress, the response to psychosocial stress is more complex. Brain region activation in psychosocial stress shows inconsistent results.[34,36] Psychosocial stressors usually cause challenges to cognitive function, leading to increased activity of the medial prefrontal cortex.[32] Psychosocial stress also activates the anterior cingulate which has an important role in activating cardiovascular autonomic responses and also the insula region which works together with the anterior cingulate because these two regions are components of the system responsible for the function of consciousness.[32,37] Psychosocial stress causes deactivation of the hippocampus-amygdala complex which aims to disinhibit the hypothalamus.[38,39] This deactivation will allow the initiation of a stress response by the HPA system.[32,34,40]

Several brain regions such as the amygdala, prefrontal cortex, anterior cingulate cortex, insula, and hypothalamus are activated during *stress-inducing tasks*.[36] The amygdala, which is found to be active during acute and chronic stress, is involved in the processing of emotional information such as fear and anxiety; the prefrontal cortex, associated with higher-order cognitive processes such as attention, decision-making, and self-regulation; the anterior cingulate cortex, which is involved in emotional regulation, and plays a role in the perception of pain and anxiety; the insula, which is active during stress-inducing tasks, is associated with interceptions and processing of visceral sensations; and finally, the hypothalamus region, which is also active during stress-related tasks, is found to be involved in the regulation of stress responses.[32,34,40] Research on the relationship between stress and brain region activation has shown that as stress levels increase, there is also increased activation in brain regions associated with stress response, such as the amygdala, hypothalamus, and prefrontal cortex which is influenced by various factors such as gender, age, and previous history of stress exposure. But overall, research shows that changes in brain activation patterns are associated with stress and can vary based on individual differences and the type of stressor experienced. During the recovery period following stress, these activation patterns change, involving regions such as the ventromedial prefrontal cortex, posterior cingulate cortex, and hippocampus, which are involved in emotional regulation, cognitive control, and memory consolidation.[32,34]

In general, neuroimaging studies typically show activation of the nervous system; however, it is not uncommon for studies studying psychosocial stress to report deactivation of the nervous system.[34,40] Specifically, some studies report deactivation of limbic and cortical regions associated with emotion processing.[34,37] However, some studies also report activation in these regions.[29,34] Thus, activation and deactivation in brain regions especially in the hippocampus/amygdala, anterior cingulate cortex, and prefrontal area show inconsistent results. In addition, the interrelationship between activated and deactivated brain regions remains poorly understood.[36,38]

A meta-analysis study that quantitatively summarized fMRI and PET imaging studies of the human brain showed the right Inferior Frontal Gyrus (IFG) (pars triangularis) and right Posterior Superior Temporal Gyrus (STG) regions were consistently activated under psychosocial stress. Whereas, psychosocial stress resulted in consistent deactivation in a cluster within the striatum extending from the left Caudate Nucleus (CN) to the Putamen.[34]

The right STG region is a brain region that has been shown to have a role in cognitive regulation of emotions.[41] In conditions of psychosocial stress, activation of the right posterior STG region indicates an increase in attentional processes and regulation of emotional stimuli, which may result in focused, egocentric and goal-directed behaviour in the face of psychosocial stress situations.[34,41] The right STG region showed

stronger activation in psychosocial stress compared to physiological stress as well as negative connectivity to regions involved in social cognition. Thus, under psychosocial stress conditions attention is focused on ego-centred emotional regulation while social processing is simultaneously reduced.[34]

The IFG is a brain region known to play a role in emotion and stress regulation.[42] The right IFG cluster (pars triangularis) extending to the insula showed convergence of activation when exposed to both types of stressors. This part of the IFG, often referred to as the Ventrolateral Frontal Cortex (VLPFC) is an important brain region for action and cognitive control such as behavioural inhibition and for suppressing emotions and emotional memory.[34,43] In addition, specifically, IFG activity is also associated with processing and regulation of affective states such as, negative affect/emotion processing during negative experiences; cognitive emotion regulation; social rejection.[44] Thus IFG activation during stress exposure may indicate the processing of negative and subjective experiences, resulting from and/or accompanied by the inhibition of behavioural drives such as escape reactions.[34]

In addition to ventral IFG activation, the anterior insula (AI) is also activated under conditions of psychosocial and physiological stress. The insula region is associated with nociceptive, thermoregulatory, and cardiovascular functions, as well as regulation of peripheral activation and autonomic arousal, so the insula region is thought to play a role in mediating sensory and affective processing. The insula region, especially the ventral anterior part, is involved in processing strong emotions, playing an affective and autonomic role of the current state, i.e. how unpleasant one feels in a given situation. Therefore, AI engagement during physiological and psychosocial stress reflects emotion mapping and evaluation.[34]

Psychosocial stress consistently causes deactivation of a cluster within the striatum that extends from the left CN to the putamen. Research by Nikolova *et al.* reported a negative association between early life stress and decreased striatum activation that was also associated with decreased positive affect. In general, CN is associated with various behavioural and cognitive domains, including *reward* processing and *motivation*.[36,45] Related to these functions, Kumar *et al.* (2014) showed that psychosocial stress can affect *reward* processing, with decreased CN activity during *reward* processing.[46] Psychosocial stress can induce anhedonia behaviour and reduce positive affirmation processing and motivation.[34] This is also consistent with several studies showing that emotional complaints such as lack of motivation are related to stressful experiences. In contrast to CN, the putamen region has functions in processing and control.[36,46] In addition, the putamen region is also directly related to pain sensation and pain intensity discrimination. Thus, during psychosocial stress the processing of motor and pain-related abilities will be reduced as well as reward processing and cognitive resource capacity.[34]

The striatum is a brain region involved in processing psychosocial and physiological stress. The striatum is functionally divided into 3 distinct subzones: the dorsal sensory-motor striatum, the medial cognitive-associative striatum, and the ventral limbic and emotional-motivational striatum. There are differences in the subzones activated in the two types of stress, physiological stress activates the dorsal striatum and psychosocial stress deactivates the ventral striatum. This result may be due to physiological stress involving motor preparation and sensory processing, whereas psychosocial stress downregulates both of these processes. The ventral striatum has long been known to play a role in reward processing, emotion and executive function. Deactivation of the ventral striatum during psychosocial stress suggests suppression of cognitive and emotional processing, particularly reward processing.[34,36]

Changes in Amygdala Due to Psychosocial Stress

Neuronal and synaptic changes induced by psychosocial stress are seen with morphological changes and long-term structural adaptations in the amygdala. The amygdala has an important role in mediating the impact of stress on memory consolidation and recall processes. This impact is not limited to the amygdala region as stress also modulates memory mechanisms involving other brain regions that are sensitive to stress hormones.[47]

The findings suggest that exposure to psychosocial stress can trigger the activation of the amygdala, along with the stimulating and inhibiting effects of other brain regions, causing brain conditions that on the one hand promote long-term memory storage of emotionally arousing situations and thus retain important information, but on the other hand interfere with long-term memory retrieval and working memory. Thus, this increase in memory consolidation ability under psychosocial stress has adaptive value.[48] In contrast, stress-induced impairment of memory retrieval and working memory that occurs simultaneously is certainly undesirable in challenging situations (e.g., during an exam), but this effect should not be considered maladaptive. In fact, temporary blockade of memory retrieval processes during the consolidation and storage of new, emotionally arousing information may actually prevent memory distortions and thus aid the accurate retention of this information. However, exposure to highly unpleasant experiences, such as severe stress, can also lead to highly emotional, traumatic, or frightening memories, which contribute to the development and symptoms of anxiety disorders, such as PTSD.[49]

In psychosocial stress there are changes in neuronal activity and synaptic transmission in the form of changes in neuromodulators, stress hormones, and variations in the duration and intensity of stress that trigger electrophysiological and structural changes in the amygdala.[50] The effects of psychosocial stress on amygdala plasticity are very different from those in the hippocampus and prefrontal cortex, two brain areas that are not only sensitive to stress but also regulate psychosocial stress responses. The expression of Brain Derived Neurotrophic Factor (BDNF) induced by psychosocial stress in the amygdala is not the same as that found in the PFC and hippocampus. Much evidence has shown that BDNF expression in the amygdala increases after exposure to stress.[51] BDNF expression in the amygdala shows a tendency to increase after psychosocial stress and this detectable increase corresponds to the increase in spinogenesis in the Basolateral Amygdala (BLA) induced by psychosocial stress.[51,52]

Exposure to psychosocial stress that has a direct effect on amygdala function and causes morphological changes in cells and synapses in the amygdala has important clinical implications. Several studies have shown that after highly unpleasant experiences, the formation of strong and unpleasant memory traces is an important pathogenic mechanism for the development of anxiety disorders such as PTSD. Findings from animal studies suggest that memory consolidation and retrieval processes may be permanently altered under these conditions.[53]

Changes in Hippocampal Due to Psychosocial Stress

Prolonged and/or traumatic stressors have also been shown to cause morphological changes in the hippocampus. The hippocampus has long been known to function in learning and memory. However, the hippocampus also has an important role in mood regulation. Specifically, in human brain imaging studies, PTSD patients had smaller hippocampal volumes, which correlated with verbal memory deficits. Another study in experimental animals showed that chronic immobilization stress caused a reduction in hippocampal volume from pre-stress measures. These effects are likely mediated by the effects of stress on neuronal morphology and/or neurogenesis in the hippocampus.[54]

Neuronal structural remodelling also often occurs as a result of stress exposure. Chronic psychosocial stress transiently reduces the number of dendritic spines and branches of pyramidal neurons in CA3 and suppresses the production of new granular neurons in the gyrus dentata region of the hippocampus. These structural changes in the hippocampus after stress are also consistent with deficits in spatial navigation and episodic memory caused by psychosocial stress.[55]

The hippocampal CA3 region is not the only part of the hippocampus that shows dendritic reorganization due to chronic psychosocial stress. Psychosocial stress-induced shrinkage of dendrites of CA3 hippocampal neurons and gyrus dentata as well as loss of dendrite spines in CA1 neurons indicate aspects of structural plasticity of the brain.[56] Apical dendrites of CA1 neurons are reported to be shorter in adult rats subjected to chronic neonatal stress and stressor differences suggest differences in the hippocampus and its

functional connectivity with other brain regions. Exposure to multimodal stress (light, loud sound and immobilization for hours) compared to immobilization or loud sound alone revealed severe deficits in hippocampus-dependent object recognition memory after multimodal stress, but fewer deficits after immobilization or loud sound alone.[56] Another study using C-Fos as a marker of neuronal activity, multimodal stress was reported to reduce neuronal connectivity in the hippocampus.[57]

In addition to the structural remodelling described earlier, the hippocampal gyrus dentata is a brain region that exhibits post-natal neurogenesis, a process regulated by steroid hormone levels. The gyrus dentata undergoes a reduction in cell number under conditions of chronic psychosocial stress in response to corticosterone levels. Hippocampal neurogenesis is also associated with BDNF, whose levels are highly dynamic in response to chronic psychosocial stress, where levels are decreased at *baseline*, but with recovery after stress levels can return to *baseline*. Additionally, direct infusion of BDNF has been shown to increase hippocampal neurogenesis.[58]

The hippocampus is also an important region for understanding the effects of glucocorticoids and psychosocial stress on gene expression. Recent technological advances have enabled the analysis of gene expression changes in response to psychosocial stress for example, microarray analysis in the hippocampus after acute and chronic stress, as well as recovery from stress in rats, showed a decrease in psychosocial stress-induced neuroplasticity. Exposure to acute and chronic stress can modulate a series of genes and can alter the transcriptional response in the gyrus dentata. These studies suggest that a history of stress exposure can have a long-term impact on hippocampal function and influence future stress reactivity. Several studies have identified many of the genes that change after chronic stress exposure in relation to epigenetic studies so it is this mechanism that underlies persistent changes in expression response beyond stress exposure.[59]

Changes in Prefrontal Cortex Due to Psychosocial Stress

Psychosocial stress is known to impair cognitive flexibility and working memory, both of which require PFC function. Chronic psychosocial stress also causes morphological changes in the PFC that are seen with impaired Long-Term Potentiation (LTP) and reduced functional connectivity including reversibility after the end of the stress period. Long-term psychosocial environments can affect the PFC and its ability to exert control over amygdala activity. Exposure to psychosocial stress is associated with reduced PFC grey matter volume accompanied by increased rates of systemic inflammation and changes in white matter structure throughout the brain.[60]

Functional connectivity between the PFC and amygdala first develops as positive affect and then follows as inhibitory affect. Under typical conditions, mPFC connections with the amygdala are immature during childhood and will develop to their proper function by adolescence, and rodent models suggest that maternal deprivation accelerates this development.[60]

In some studies, the amygdala and PFC are involved in the development of psychosocial stress effects on the hippocampus. Both structures have extensive sensory circuit connections that are required to respond when receiving sensory input from various brain regions (e.g., thalamus and sensory cortex) and project to various structures associated with defensive responses (e.g., the mPFC interconnects with the amygdala projecting to the nucleus stria terminalis to activate stress hormones, the periaqueductal gray for protective behaviour, and the lateral hypothalamus for sympathetic activation).[60] In addition, the mPFC also projects to the amygdala and hippocampus through which executive function processing occurs so the mPFC may influence the hippocampus during stress.[61]

Compared to acute stress exposure, chronic stress exposure causes more extensive changes in the rat PFC, including architectural changes. Layer II/III neurons that make up the PFC network lost dendritic material i.e., dendrite length, branching, and spines density as a result due to chronic stress. Spine loss was particularly evident at distal locations (~200 μm from the soma) and involved mushroom-shaped dendrite spines known to be involved in synaptic connections. These dendritic changes in the rat PFC were associated

with apparent PFC dysfunction in abilities in attention and working memory. Chronic stress also disrupts neuroplasticity processes between the PFC and hippocampus that are necessary for flexible memory consolidation. The dendritic changes in the PFC will gradually show improvement when the stress subsides.[62]

As with acute stress, the PFC appears to be particularly sensitive to architectural changes induced by chronic stress compared to other brain regions. While structural changes in the hippocampus require several weeks of stress exposure, dendrites in the PFC begin to change after just one week of stress or even with a single exposure. In contrast to the PFC and hippocampus, dendrites in the amygdala expand in response to chronic stress exposure. Thus, chronic stress weakens structures that provide negative feedback on the stress response and strengthens structures that drive the stress response. Interestingly, recent data show that neurons in the rat infralimbic PFC that project to the amygdala do not lose their dendrites in response to stress, which highlights a distinct amygdala circuit response.[62]

Various studies have also been conducted to study the signalling mechanisms underlying dendritic changes in the PFC. Chronic psychosocial stress alters catecholamine pathways, increasing noradrenergic innervation of the PFC (although dopamine levels are decreased in severe chronic stress). This increase in noradrenaline will lead to higher levels of Protein Kinase C (PKC) and cAMP signalling. This increase in PKC signalling will lead to reduced working memory ability due to chronic stress. Stress-induced changes to dendritic morphology are thought to involve excitotoxicity or oxidative stress. Chronic stress also leads to chronic glucocorticoid exposure which reduces brain-derived neurotrophic factor levels in the PFC, contributing to the observed dendritic changes.[61]

Chronic psychosocial stress that occurs during the golden period of brain development or in childhood has profound effects on PFC structure and function in adulthood. Dendritic changes can occur in utero when the mother is exposed to stress. Chronic uncontrolled stress in childhood can cause long-term effects on the adult PFC. Studies conducted on rat pups exposed to extensive maternal deprivation had long-lasting dendritic retractions in the PFC and increased anxiety-like behaviours. In contrast, exposure to mild stress, for example when a young monkey learns that its mother will return after a short period of separation, appears to promote a resilient response to stress in adulthood and reduce glucocorticoid receptor expression in the dorsolateral PFC.[62] Similar effects have been shown to occur in rats, where very mild stress early in life increases resilience whereas more severe stressors exacerbate stress responses later in life. Changes in utero and during childhood likely contribute to vulnerability to mental illnesses that emerge during adolescence and adulthood.[63,64,65]

Conclusions

Psychosocial stress is known to affect the structure and function of various regions in the brain. Previous studies have shown that the cognitive and emotional deficits that occur with psychosocial stress are due to disruptions in the brain connectivity of the various brain regions involved such as the dorsal prefrontal cortex (PFC), ventral PFC, hippocampus, and amygdala.

Conflict of Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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