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Review

The Effects of Chronic Stress on Neuroanatomy and Cognitive Function

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Abstract

Stress plays a central role in functioning for all life forms. As humans, we experience stress in a multitude of ways through various types of stimuli. Due to the constancy of stressors in our lives, the nervous system has learned to allosterically adapt to the stimuli, but when the body cannot adapt, chronic stress can have morphological and degenerative impacts on neuroanatomy and cognitive function that may or may not be reversible. This literature review aimed to identify the specific neuroanatomical structures impacted most by the long-term effects of chronic stress and the subsequent relationship the morphological changes had on cognitive function in rodent models. We examined articles published from PubMed, Google Scholar, and Science Direct, while focusing the search on anatomical and neurodegenerative effects associated with chronic stress stimuli. The degenerative effects of various types simulated physiological chronic stress showed the most impact on neurogenesis and neuronal development, brain plasticity, and spatial learning and memory with association to the hippocampus. The hippocampus, amygdala, prefrontal cortex, and hypothalamic-pituitary-adrenal axis (HPA) all had reversible and non-reversible morphological alterations, which also had a direct impact on the brain's cognitive abilities. While studies regarding chronic stress are still being conducted, future research may be able to further highlight why stressful stimuli can particularly impact these structures and the tangential impacts that it may have on related or adjacent structures.

Keywords: Alzheimer's; aging; amygdala; brain plasticity; CA1; CA3; chronic stress; cognition; GABA; HIF-1; hippocampus; hypoxia; neurogenesis; Parkinson's; prefrontal cortex; PSA-NCAM; ROS; spatial learning

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Introduction

Chronic stress has become a commonplace occurrence from the constant pressures of the evolving world. Stress is categorized as any intrinsic or extrinsic stimulus that evokes a biological response, with the compensatory responses to these stimuli labeled as stress responses (1). Stressors can have an influence and impact on psychosocial health, physiological health, and even how the body maintains homeostasis (2). While the central nervous system is primed to produce integrated coping responses, it is the autonomic nervous system that engages in the fight, flight, or coping mechanisms that help the body adjust and adapt to the stressful stimuli that it may encounter (3). Some stress may be instantaneous, but if the stimuli persist over a long period of time, it is generally referred to as chronic stress.

How an individual reacts to the strain that long-exposed stimuli pose can affect both mental and physical health, with chronic stress having a more permanent effect on the body than short term stressors (4). Additionally, the time course of stress responses can be measured by the neuroendocrine and behavioral responses of the body, which can identify how destabilizing the stimulus makes the stress manageable or harmful (1). How the stressors are processed, in turn, can have a remarkable toll on the development and functioning of the brain and nervous systems.

The brain plays a key integratory role in processing stimuli in the adaptation to stress. Stress and stimuli, however, are information that stimulate behavioral and physiological responsiveness between the brain and other systemic functions (4). Beyond the acute responses to stress that life may pose, allostatic load is considered the integral feature of chronic stress that leads to degenerative effects (5). Allostatic load includes innate and adaptive processes that help to maintain homeostasis through mediator chemical messengers like adrenaline and cortisol (6). With allostatic load comes the heightened wear and tear on the central and peripheral nervous systems, even down to the cellular level (7, 8). In this systematic review, we identify key neurological structural changes that may be induced by chronic stress and put into context how these

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changes can impact behavioral or mental health as well.

Methods

We examined relevant articles from 1950-2021 and focused our search on the effects of chronic stress in cognitive function in associated structures in the brain. We used a combination of terms including chronic stress, stress, aging, spatial learning, brain plasticity, neuronal degeneration, hippocampus, amygdala, prefrontal cortex and used the boolean operators AND and OR. We searched three electronic databases, Google Scholar, PubMed, and ScienceDirect using keywords, backwards, and forward searches to achieve higher quality literature search following the Preferred Reporting Item for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (Figure 1). We excluded publications that were not in English, did not follow information systems (IS) framework and were not peer reviewed.

Discussion

Neuronal Deterioration

Stress is the body's normal response to stimuli. All organisms have a physiological response to stress, and in humans, stress begins from embryogenesis and continues throughout adulthood (9). During a period of chronic stress, the body physiologically accommodates to the stressor, as high levels of glucocorticoids are released into the bloodstream in a fight-or-flight response. Physiological stress is divided into three different categories: developmental stress, environmental stress, and aging (9). Developmental stress includes any changes during embryogenesis that can be influenced by nutrient availability, oxygen, and exposure to chemicals during development. Environmental stress is the physiological accommodation our body has to external environmental cues, from changes in weather to exposure to pollution and ultraviolet radiation, among others. Finally, as we become older, our cells can lose the ability to fight pathogens, protect against reactive oxygen species, and regenerate as they are affected by telomerase activity (9). Therefore, physiological stress is an accumulation of external stimuli that influence internal cues

 doi:10.20944/preprints202207.0171.v1

for our bodies to adapt. By understanding stress as a component of our lives, it is important to acknowledge its impact on the body, especially the brain, as neurons are nonregenerative and form part of the control center of the nervous system.

The impact of stress at the cellular level has been investigated for more than 40 years. Initially, researchers looked at neuronal response in the model organism, *C. elegans*, and discovered the change of processing information in response to hypoxia- environmental stress (9, 10). Neuronal cells consume 20% of glucose in the body and rely on high amounts of oxygen to generate adenosine 5′-triphosphate (ATP) during aerobic glycolysis to maintain cellular and physiological processes (11). In hypoxic or low oxygen states, there can be phenotypic changes to the brain that alter relay mechanisms (11). Factor-1 hypoxia inducible factor (HIF-1) senses low oxygen levels in neurons and induces transcriptional changes to maintain homeostasis in the brain by targeting angiogenesis, erythropoiesis, cell death and energy metabolism (12). An analysis done with mouse models found phenotypic changes in neuronal plasticity, reduction in dendrite migration, and axonal guidance through HIF-1 response (9).

From a young age, we are exposed to ultraviolet (UV) rays from the sun. As we age our cells accumulate cellular DNA damage from UV-B and UV-A rays. It is commonly thought that excessive exposure to UV radiation affects only epithelial cells and melanocytes, causing skin cancers. However, UV radiation affects neuronal cells similarly, inducing nuclear and mitochondrial damage (9). In normal cells throughout the body, UV-induced DNA damage causes cell checkpoint inhibition during the cell cycle to accommodate polymerase repair systems. Neuronal cells also undergo checkpoint inhibition, but this process has been correlated with early cell death and low response to other environmental stress (9). Research found that DNA damage in neuronal cells due to reactive oxygen species (ROS) has a role in advancement of neurodegenerative diseases, such as Alzheimer’s and Parkinson’s disease (13). Accumulation of ROS suppresses DNA

 doi:10.20944/preprints202207.0171.v1

repair and calcium cycling in electrical impulses which can lead to disease (12). Although neurodegenerative disorders are more relevant in connection to aging, it is important to note the environmental stress factors contribute to cell death. Investigations performed in mice in laboratory controlled environments found that synaptic density in the olfactory bulbs decreases with age (9). In aging humans, there is a loss of neuronal density in the cerebral cortex that manifests as memory impairments associated with neurodegeneration.

It is part of human nature to encounter stressful situations. Our bodies have developed a fight-or-flight response as a form of adaptation, and it can lead to increased levels of anxiety and depression. Long-term, stressful situations can change the brain morphology in the prefrontal cortex, ultimately affecting the limbic system (14). Gamma Aminobutyric Acid (GABA) acts on GABA receptors, inhibiting cAMP and the release of calcium. An increased imbalance of GABA is associated with anxiety and depression. An experimental study in animal models for depression that measured GABA imbalance during chronic stress, observed the effect in the cortex (13). During long periods of chronic stress, there was a decreased number of active GABAergic neurons, increased glial cell pathologies, and reduced orbitofrontal cortex volume (13, 14). In the long term, fewer GABAergic neurons affect the way we respond to stress, impacting the responsiveness of the amygdala which is responsible for emotional processing (15). The decrease of GABA in the amygdala leads to excitability and further increases the stress-induced response in the hypothalamus.

Another study measured chronic stress expression of the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) (16). This molecule was used to track molecular and morphological changes of the inhibitory amygdala interneurons associated with GABA (16). A decreased number of dendritic arborization of interneurons and PSA-NCAM expression were found to be associated with decreased neuroplasticity (17, 18).

Brain Plasticity

 doi:10.20944/preprints202207.0171.v1

While the effect of chronic stress can lead to behavioral, neuroendocrine, and autonomic changes, persistent negative stimuli can also alter the brain's innate plasticity (19). Brain plasticity can be described as the development of neuronal synapse, neuronal connections, and the contribution to brain development. Brain development is widely examined using mouse models, and it has been noted that brain structure differs in individuals, influenced by genetic and environmental components such as diet, hormones, chemical exposure and stress (20). There are seven different stages of brain development and brain plasticity from cell birth during prenatal embryogenesis to cell death and synaptic pruning. During neurogenesis, approximately 250,00 neurons are created per minute (20). These newly created neuronal cells migrate to their destination of major brain structures with the support of glial cells and astrocytes forming the brain cortex (20). At their target locations, neuronal cells grow and create synapses to form the neural crest (20). Cell pruning is a stage of brain development and neural plasticity. It balances neurogenesis and the synapse formation and is a way for the brain to create sensory pathway formation. At this stage stress influences the rate of neuronal cell death and synapse remodeling.

Brain plasticity is ubiquitously involved in our behavior, and it is known that synapse modeling is responsible for human behavior. Plasticity is directly influenced by external and internal factors, the development of neural synapses are dependent on experience, time and age, and therefore can vary from person to person at various life stages (20). In mouse model studies, the effect of stress on brain plasticity at early age showed decreased spinal density and neuronal length in the prefrontal and occipital cortex, whereas in adults, there was a decrease in mass in both in the prefrontal cortex and an increase in mass in the occipital cortex (21). Although this area of investigation allows for more research, it is important to note the influence of stress at different stages of neural plasticity and its impact in major brain areas.

Along with the dendritic spines of neurons, the structures that are commonly associated with brain plasticity include the prefrontal cortex, HPA, amygdala, and hippocampus (Figure 2)

 doi:10.20944/preprints202207.0171.v1

(22). Chronic stress can affect any of these structures in a way that alters the long-term potentiation abilities of the brain (23). The HPA axis is responsible for the interactions between the hypothalamus, pituitary gland, and adrenal glands (24). This axis is central to homeostatic processes, stress response, energy metabolism, and generalized neuropsychiatric functions via modulation by glucocorticoids (25). As the main regulator of the HPA axis, the brain is an etiological link between stress and HPA dysregulation when stress-induced plasticity affects the glucocorticoid release and regulation of the neural circuitry of the HPA axis (25). Glucocorticoids, in particular corticotropin-releasing hormone (CRH) released from the hypothalamic paraventricular nucleus, subsequently release the neurotransmitters GABA, glutamate, and norepinephrine (26). All three are involved in the body's fight-or-flight response to stress, and when the body is dealing with excessive or chronic stressors, the HPA axis is forced into overdrive which can overwhelm the brain from forming the neural circuitry required for optimal brain plasticity (27).

The amygdala is responsible for the way we react to emotional stressors and external stimuli (19). During periods of chronic stress, the amygdala is hyperactivated and further stimuli is enough to generate an activation of the limbic system leading to depression and anxiety (19). Amygdala activation, through basolateral pathways, is responsible for the creation of memories (28). This memory consolidation can be different based on the stimuli (28). The basolateral intrinsic pathway is responsible for the excitatory response of the limbic system, and *in vivo* experiments found that during prolonged periods of stress the basolateral amygdala becomes hyper-excited and shows a reduction in GABA receptor response (28). Chronic stress in the basolateral amygdala is also correlated to increased dendritic arborization and spine density in neurons, alongside increased levels of glucocorticoid levels in the blood (29). Additionally, a feedback mechanism increased excitation in the brain was also observed, producing morphological changes in the brain, and maladaptive responses relating to anxiety and hypervigilance to cope with chronic stress stimuli (30).

 doi:10.20944/preprints202207.0171.v1

The prefrontal cortex oversees cognitive control, major decision making, comprehending external stimuli, memory formation, and emotional regulation (32). During the fight-or-flight response, the prefrontal cortex can analyze the situation and formulate an appropriate response to the situation (31). During executive decision making, it is also responsible for modulating the amygdala and hippocampus (33). The stimuli and activation of the prefrontal cortex creates synapses to improve the response control of the brain, and during long periods of stress, decreased activity of the prefrontal cortex is associated with cognitive impairment and cognitive deficits (31). These maladaptive responses are predominantly correlated to HPA dysregulation (31). Although these are underlying brain functioning systems, the response to chronic stress varies among people, due to genetics, hormones, sex and social characteristics (34).

Hippocampal Degeneration and Cognitive Function

Spatial memory, according to cognitive psychology and neuroscience, is a form of memory that is used for the recording and recall of information, formation and assimilation of semantic memories, and the creation and storage of schematic spatial maps (35). The hippocampus and the adjacent medial temporal lobe are the two structures that are imperative for declarative memory; however, the functional distinctions from the hippocampus and lobe have not yet been conclusively determined (36). The hippocampus is crucial for allocentric spatial memory, which allows humans to remember spatial locations despite shifts in viewpoint (36). Electrophysiological examinations in rodents have been used to examine the modalities of hippocampal processing in the spatial domain, and consequently, have also been used to determine the effects that chronic stress has on these key parts of the brain (37). Rodent models have also helped identify the hippocampus proper, dentate gyrus, subicular complex, and the perirhinal, entorhinal, and parahippocampal cortices as parts that have been linked to degeneration when subjected to chronic stress (38, 39).

 doi:10.20944/preprints202207.0171.v1

Converging evidence from several rodent model reports have shown that over time, applied chronic stress impairs spatial reference memory while transiently impacting spatial working memory (40). Long-term exposure to stress, or even glucocorticoids produced by the adrenal cortex in response to stress, has been documented to show altered hippocampal neurochemistry, neurogenesis, neuronal morphology, neuronal apoptosis, and even neuronal excitability (41). One consideration with animal model studies is that chronic stress was previously assumed to be the direct cause of hippocampal degeneration (42). While hippocampal degradation was later proved to be affiliated with chronic stress, some study assumptions were based on the structural changes being permanent, largely ignoring the plasticity of the brain (43). Rodent models have been favored extensively in this field because of the ability to carefully control the timing and nature of the stress exposure (44). Rodents were primarily tested on radial arm mazes, T-shaped mazes, or conventional water mazes, with the motivation being to escape the maze for a food reward (45).

Chronic stress in rodent models that incorporated restraint procedures, with mesh barriers in mazes, caused CA3 neuronal dendritic retraction without disrupting motor ability and motivation to explore mazes (46). The functional significance of these findings was that chronic stress created consistent yet reversible changes on the dendritic branches of the CA3 neurons in which the dendritic branches ’length and numbers both decreased (47). The CA3 hippocampal neurons assist with pattern completion and the generation of sharp-wave ripples (SPW-Rs) that are cognitive biomarkers for episodic memory, planning, and transferring compressed waking neuronal sequences (48). During the generation of the SPW-Rs, the pyramidal CA3 neurons are activated and produce spatiotemporally structured input patterns that are processed by efferent dendrites (49). These input patterns are then translated into output patterns after the dendritic integration in thin CA3 pyramidal cells using glucocorticoid release via uncaging, which merges the input signal for further processing (49). The combined glucocorticoid release and dendritic length shortening are

 doi:10.20944/preprints202207.0171.v1

thought to disrupt the hypothalamic-pituitary-adrenal (HPA) axis which creates dysregulated glucocorticoid release and subsequently impairs spatial memory (47).

Another study conducted on male rats that were placed in a mixed-sex environment visible burrow system showed that innately formed dominance hierarchies led both the dominant and subordinate rats to show stress-related behavioral, endocrine, and neurochemical changes (50). The chronic stress, which was psychosocial in nature, caused a morphological atrophy on the Golgi apparatus of CA3 pyramidal neurons in the hippocampus while also decreasing serotonin binding to the dendritic receptors of these neurons (50). The dendritic retraction, decreased serotonin binding, and increased dysfunctional glucocorticoid release were observed during chronic stress induced studies which caused behavioral detriment on spatial learning and memory (51). It can be theorized that a link between these diminishing structural changes impacts how the brain processes and retains cognitive information.

When testing rodents through the water maze, a common trend that also emerged was that the effects of chronic stress on spatial learning impairments was reversible (52). Chronic stress is thought to impact various memory domains, but it is still relatively unknown if all the memory domains can fully recover (53). However, in terms of reference and working memories, when mice were exposed to immediate stress versus time delayed stress, the group with delayed stress showed fewer errors in the two previously stated memory domains (54). The stressors were applied as wire-mesh barriers and deemed to be psychosocial in nature (55). The rodents that were in the delayed stressor group also displayed better working and reference memories of the maze, indicating that the CA3 dendritic retraction had been restored to some degree (55, 56). The degenerative effects of chronic stress in rodents improving after a post stress recovery period is extremely promising in terms of application to human health, as it could potentially be analogous for those dealing with or recovering from cognitive decline due to long-term stress.

Psychiatric Effects

 doi:10.20944/preprints202207.0171.v1

Due to the degenerative and impedimentary ramifications of chronic stress, the human body innately and allosterically adapts to whatever situation is being encountered (57). When faced with any physical or psychological stimuli that deviates the body from homeostasis, a stress response is mediated by the activation of the sympathetic-adreno-medullary axis (57). With that activation, comes larger systemic adaptations that are engaged in order to protect the body from harm as much as possible. Chronic stress has long been linked to maladaptive reactions such as depression and other physiological issues, beyond just cognitive impairment (58). One of the major effects of chronic stress is the impact it can have on mental health. There is a broad scale overlap with neuroscience and psychiatry that has been established, as both rely heavily on neurology and its sequential behavioral effects. Major depressive disorder is one of the common mental disorders that is profoundly affected by chronic stress. A study has found that the physiopathology underlying depression can be linked to the degenerative structural alterations made when the body is dealing with long term stressors (59). Another investigation linked how the dendritic retraction points from hippocampal neurons may be critical sites for chronic stress induced depression, in addition to the basal lateral amygdala (60). Chronic stress has also been known to manifest with depressive and anxiety symptoms while eliciting neurological syndromes that are mistaken for psychiatric conditions (61). One study found the ventral CA1 neurons and the basal lateral amygdala to play such an integral role to mediating the effects of chronic stress, that stimulation of that area via chemogenetics or administration of cannabidiol could reduce the effects altogether, thus alleviating the depressive-like behaviors in mice (62). The complex nature between neuroscience and behavioral psychiatry and psychology is not yet fully understood. Future investigation should focus on finding methods of bolstering the critical neurological sites against the impact of chronic stress stimuli.

In addition to eliciting psychiatric conditions, chronic stress has also been deemed a risk factor for the development of Alzheimer’s disease (63). As microglia play a major role in provoking

 doi:10.20944/preprints202207.0171.v1

immunity reflexes and homeostasis in the central nervous system, they can be heavily impacted by chronic stress (63). Researchers have found that repeated exposure to chronic stressors creates a higher risk of developing neurodegenerative diseases like Alzheimer's, due to the stimulation of reactive microgliosis, in which microglia undergo abnormal morphology in attempts to steer the body back towards homeostasis via synaptic remodeling (64). Exposure to mild forms of chronic psychosocial stress can fully transform normal microglial phenotypes to full-fledged Alzheimer's phenotypes in rat models (65). With chronic stress being linked to various systemic disorders and morphological changes, it is important to consider some of the different sources of chronic stress and the cognitive issues that they may cause.

Proposed Therapies

Effective therapies and treatment techniques for stress management are varied, ranging from physical behavioral changes to ingestion of certain metabolites including antioxidants and vitamins (66). Cognitive behavioral therapy and mindfulness are effective strategies for dealing with long-term effects of burnout, stress, and post-traumatic stress disorders in both children and adults (67). Cognitive behavioral therapy helps to reduce mental health concerns by reframing thought processes and mindful behavioral changes (68). It has also been suggested that chronic psychological stressors can be combated with exercise. A study on the physiological shortening of telomeres due to chronic stress found that exercise had a buffering relationship with telomere length (69, 70). Individuals that participated in rigorous exercise when dealing with high stress situations were protected against aversive memory impairment and oxidative damage (71). Another study has also found that saffron and crocin could be promising target treatments for Alzheimer's disease and chronic stress related disorders (72). While these proposed therapies have been relatively effective, there may be limitations that could impact their benefits. Cognitive behavioral therapy, for example, has limits on its efficacy in which some patients may not be able to successfully cope with their stressors using its methods without additional aid (73). Patients may also not be

 doi:10.20944/preprints202207.0171.v1

able to partake in physical exercise due to various other circumstances ranging from other health issues to socioeconomic factors, as well. Future study could potentially highlight additional lifestyle and behavioral changes that patients could integrate seamlessly into their current daily routines, however, the difficulties of finding such a solution may be onerous.

Conclusion

Chronic stress, which ranges from psychosocial to physiological forms, can be identified as a stressful stimulus that persists over an extended period of time. Stress responses will cause the body to alter its behavioral, autonomic, or neuroendocrine functionalities to cope with the perceived threats of the stressful stimulus in an attempt to regain homeostasis (74). The human body has evolved to adapt allosterically, but when stress is applied frequently and is prolonged, the body is subjected to degenerative and dysregulated effects. Based on our review of the literature, chronic stress can impair spatial learning and retention memory, create maladaptive changes in terms of brain plasticity, and trigger divergent neuronal remodeling and impede neurogenesis (75, 76). However, there are more physiological changes that may be associated with chronic stress beyond neuroanatomy and cognitive function.

Chronic stress is a pervasive presence in many patients. In the future, scientists could expand on the therapies that individuals can use daily to dispel its harmful effects beyond pharmacological treatments. Clinical experiments using rodent models have been effective in determining the physiological effects of chronic stress and could also be beneficial for testing new therapeutic modalities. Research in genotypic resilience against stress could be an interesting way to learn more about how humans deal with allostatic loads and stressful stimuli, as well.

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Figure Legends:

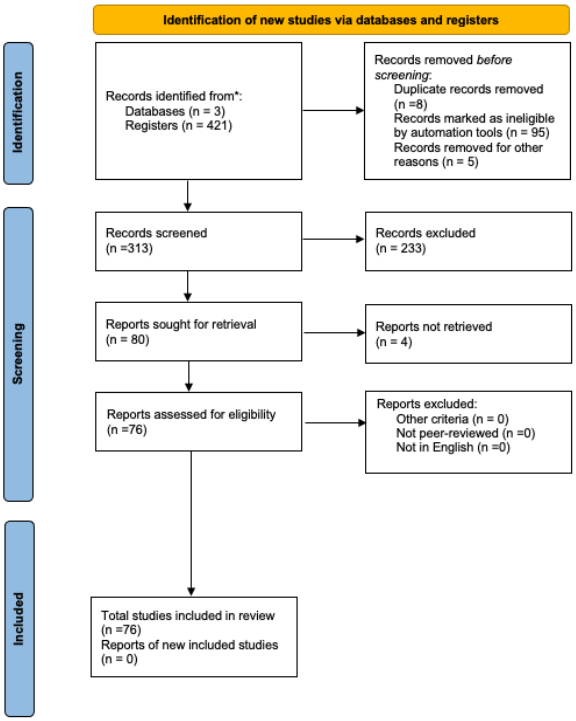

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Figure 1: PRISMA Flow Diagram. Adapted from (77)

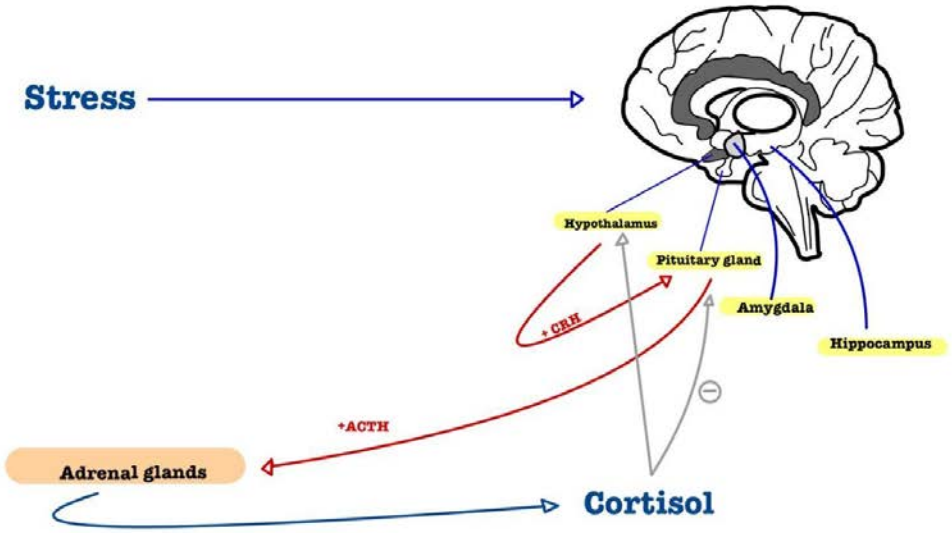

Figure 2**:** Schematic interpretation of the regulation of the HPA axis when presented with chronic stress.Stress is interpreted by the brain in the prefrontal lobe along with the hypothalamic-pituitary-adrenal axis. The input of stress triggers the hypothalamus to release corticotropin-releasing hormone (CRH) via positive feedback to the anterior pituitary gland, which releases adrenocorticotropic hormone (ACTH) via positive feedback to the adrenal cortex. The adrenal glands will eventually release cortisol, a stress hormone, which will send negative feedback signals to the pituitary gland and hypothalamus, respectively.

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