Stress and Cognition

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Introduction

Prior to becoming part of our day-to-day conversations, the term 'stress' was used by engineers to explain forces that can put strain on a structure. For example, one could place strain on a piece of metal in such a way that it would break like glass when it reached its stress level. In 1936, Hans Selye borrowed the term of stress from the field of engineering and talked about stress as being a nonspecific phenomenon representing the intersection of symptoms produced by a wide variety of noxious agents. For many years, Selye tested various conditions (e.g., fasting, extreme cold, operative injuries, and drug administration) that would produce morphological changes in the body that were representative of a stress response, such as enlargement of the adrenal gland, atrophy of the thymus, and gastric ulceration. Selye's view of the concept of stress was that the determinants of the stress response are nonspecific, that is, many unspecific conditions can put strain on the organism and lead to disease, the same way that many unspecific conditions can put strain on a piece of metal and break it like glass.

Not all researchers agreed with Selye's model, particularly with the notion that the determinants of the stress response are nonspecific. The reason for this was simple. While Selye spent his entire career working on physical stressors (e.g., heat, cold, and pain), we all know that some of the worst stressors we encounter in life are psychological in nature, and are induced by our interpretation of events. For this reason, a psychologist named John Mason spent many years evaluating stress hormone levels in humans subjected to various conditions that he thought would be stressful, in order to describe the psychological characteristics that would make any condition stressful, to anyone exposed to it.

By summarizing the results of studies measuring the circulating levels of these hormones before and after individuals were exposed to various jobs or situations that were deemed to be stressful (e.g., air-traffic controllers or parachute jumping), Mason was able to describe three main psychological determinants that would induce a stress response in any individual exposed to them. Using this methodology, he showed that in order for a situation to induce a stress response from the body, it has to be interpreted as being novel,

and/or unpredictable, and/or the individual must have the feeling that he/she does not have control over the situation. Although this work led to a general debate between Selye and Mason, further studies confirmed that the determinants of the stress response are highly specific, and therefore, potentially predictable and measurable. More recently, a meta-analysis of the determinants of psychological stress in human added the component of social evaluative threat as a fourth characteristic of a situation that is a potent inducer of a physiological stress response in humans.

The Relativity of Stress

From this short historical background, we can now define stress as being a threat, real or implied, to homeostasis. In this sense, stress can be absolute (a real threat induced by an earthquake in a town, leading to a significant stress response in every person facing this threat), or it can be relative (an implied threat induced by the interpretation of a situation as being novel, and/or unpredictable and/or uncontrollable – for example, a public speaking task).

Absolute stressors serve adaptive purposes and are those events or situations that will necessarily lead to a stress response in the majority (if not the totality) of individuals when they are first confronted with it. Being in or witnessing an accident, confronting a dangerous animal, and being submitted to extreme cold or heat are all examples of absolute stressors. These extreme and particular situations constitute absolute stressors in that, due to their aversive nature, a stress response has to be elicited for one's survival and/or well-being. In our western societies, absolute stressors are rare, but are nonetheless those that elicit the greatest physiological response and most vivid memories. Conversely, relative stressors are those events or situations that will elicit a stress response only in a certain proportion of individuals. Moreover, this response may be mild or large. For example, having to unexpectedly deliver a speech may be very stressful for a given individual, and not at all for another. Consequently, large inter-individual variations in the stress response to psychological challenges have been frequently reported.

The stressor is the event itself, such as the earthquake in the case of the absolute stress, or the public speech in the case of the relative stress. The stress response is the body's reaction to the event, and it is this body's response to stress that is the foundation for the studies that determine the impact of stress on cognitive function. The reason for this is that the

stress hormones that are secreted in response to an absolute or relative stress, and particularly the glucocorticoids, are steroids that can easily cross the blood–brain barrier and access the brain, where they can influence learning and memory by binding to glucocorticoid receptors (GRs) localized in various brain regions known to be involved in learning and memory.

Stress Hormones

When a situation is interpreted as being stressful, it triggers the activation of the hypothalamic–pituitary–adrenal (HPA) axis whereby neurons in the hypothalamus, a brain structure often termed the 'master gland,' releases a hormone called corticotropin-releasing factor (CRF). The release of CRF triggers the subsequent secretion and release of another hormone called adrenocorticotropin (ACTH) from the pituitary gland, also located in the brain. When ACTH is secreted by the pituitary gland, it travels in the blood and reaches the adrenal glands, which are located above the kidneys, and triggers secretion of the so-called stress hormones. There are two main stress hormones, the glucocorticoids (called corticosterone in animals, and cortisol in humans) and the catecholamines (epinephrine and norepinephrine). The acute secretion of glucocorticoids and catecholamines in response to a stressor constitutes the primary mediators in the chain of hormonal events triggered in response to stress. When these two hormones are secreted in response to stress, they act on the body to give rise to the fight-or-flight response whereby one would, for instance, experience an increase in heart rate and blood pressure.

Glucocorticoids have a variety of different effects in target systems throughout the organism, which can be summarized as aiming to increase the availability of energy substrates in different parts of the body, and allow for optimal adaptation to changing demands of the environment. While the activation of the HPA axis can be regarded as a basic adaptive mechanism in response to change, prolonged activation of this system presents a health risk to the organism. The highly catabolic glucocorticoids antagonize insulin and increase blood pressure, thus increasing the risk for developing diabetes, hypertension, and arterial disease. Also, growth and tissue repair are impaired. Furthermore, activation of the HPA axis suppresses immune functions, which in a chronic state can be considered harmful for the organism, since it is associated with increased risk of infection.

Given their liposoluble characteristics, the glucocorticoids can easily cross the blood–brain barrier and access the brain where they bind to receptors.

Three of the most important brain areas containing GRs are the hippocampus, amygdala, and frontal lobes, which are brain structures known to be involved in learning and memory. Although epinephrine does not readily access the brain due to absence of lipophilic properties, it can still act on the brain through its action on the sensory vagus outside of the blood–brain barrier, with information transmitted into the brain via the nucleus of the solitary tract. The most important brain area containing adrenergic receptors is the amygdala, which has been shown to play an important role in fear processing and memory for emotionally relevant information.

Important Characteristics of Glucocorticoids

Under basal conditions, glucocorticoid secretion exhibits a 24-h circadian profile in which glucocorticoid concentrations present a morning maximum in humans (the circadian peak), and slowly declining levels in the late afternoon, evening, and nocturnal period (the circadian trough), and an abrupt elevation after the first few hours of sleep. Circulating glucocorticoids bind with high affinity to two receptor subtypes, the mineralocorticoid receptor (MR or type I) and GR or type II.

Although both receptor types have been implicated in mediating glucocorticoid feedback effects, there are two major differences between MR and GR receptors. First, MRs bind glucocorticoids with an affinity that is about 6–10 times higher than that of GRs. This differential affinity results in a striking difference in occupation of the two receptor types under different conditions and time of day. Thus, during the circadian trough (the p.m. phase in humans and the a.m. phase in rats), the endogenous hormone occupies more than 90% of MRs, but only 10% of GRs. However, during stress and/or the circadian peak of glucocorticoid secretion (the a.m. phase in humans and the p.m. phase in rats), MRs are saturated, and there is occupation of approximately 67–74% of GRs.

The second major difference between these two receptor types is related to their distribution in the brain. The MR is exclusively present in the limbic system, with a preferential distribution in the hippocampus, parahippocampal gyrus, entorhinal, and insular cortices. On the contrary, the GR is present in both subcortical (paraventricular nucleus and other hypothalamic nuclei, the hippocampus, and parahippocampal gyrus) and cortical structures, with a preferential distribution in the prefrontal cortex. As we will see in the following sections, the impact of glucocorticoids on cognitive function can be best understood in terms of the differential effects of MR and GR activation.

Positive Effects of the Stress Response on Cognition

Because of their actions on brain structures known to be involved in fear detection and memory for emotionally relevant information, the stress hormones enhance the formation of the so-called 'flashbulb memories' of events related with strong emotions that are usually associated with an absolute stress. This process involves the amygdala, and the pathway for encoding these memories involves the interaction between neurotransmitters in the amygdala and in related brain areas such as the hippocampus, along with circulating levels of catecholamines and glucocorticoids. The importance of the stress hormones on memory for emotionally relevant information has been recently confirmed by studies in which blockade of either glucocorticoid or norepinephrine activity impaired the recall of emotionally relevant information. Consequently, secretion of these primary stress mediators is necessary for the adequate encoding of emotionally relevant information during an absolute stress. This enhancement of memory for stimuli inducing stressful and/or emotional responses may be essential for species' survival.

At the same time as the brain encodes information and controls the behavioral responses to stress, it is also changed structurally and chemically by those experiences. Although for a long time it was thought that the brain of adult mammals does not generate new nerve cells, more recent evidence showed that neurons are born in the adult mammalian brain. Interestingly, in the adult brain, the generation of new neurons (called neurogenesis) occurs in two regions. The first region is the subventricular zone in the wall of the lateral ventricle, where new interneurons are generated for the olfactory bulb, and the second region is the subgranular zone of the dentate gyrus of the hippocampus, which gives rise to the granule cells. Recent evidence show that adult neurogenesis in the dentate gyrus of the hippocampus is a feature of all mammalian species, occurring in rats, mice, tree shrews, marmosets, macaques, and humans. Although the functional significance of hippocampal neurogenesis has been questioned in the past, a study reported that neurogenesis in the adult is involved in the formation of trace memories, suggesting that the new neurons actually contribute to the function of the adult brain.

Comparative studies of different species show that hippocampal volume is increased in mammalian and avian species that depend critically on spatial memory for survival. Examples of such critical memory skills involve home-range navigation, migration, brood parasitism, and memory-based cache recovery in birds that hide food. This association between performance of spatial tasks and hippocampal size can be explained in terms of the impact of environmental demands (stress) on hippocampal volume, rather than the converse. For example, it has been reported that the hippocampus of titmice and chickadees increases in volume in association with the experience of storing and recovering food cache. This result shows that in animals, there can be an experience-dependent hippocampal growth that occurs at a relatively late stage in development. Similar results of experience-based changes in hippocampal volumes have been reported in humans. Maguire and collaborators tested the hypothesis that the ability of taxi cab drivers to navigate to a specific destination correlates with hippocampal volume. They showed that compared to age-matched controls, the taxi drivers had larger posterior hippocampi. Although these results surely do not confirm that the experience of driving a taxi in the complex streets of London has a significant effect on hippocampal volumes, they nonetheless raise the intriguing possibility of hippocampal plasticity in response to environmental demands.

Negative Effects of the Stress Response on Cognition

While short-term responses of the brain to novel and potentially threatening situations may be adaptive and result in new learning and acquired behavioral strategies for coping, as may be the case for absolute stress, repeated stress can cause both cognitive impairments and structural changes in the hippocampus. These processes may be occurring somewhat independently of each other and contribute in various degrees to different pathophysiological situations involving traumatic stress, depression, or aging.

The cognitive effects of long-term elevations of glucocorticoids in human populations have been studied in disorders affecting glucocorticoid levels and using exogenous administration of the synthetic compound to healthy subjects. Mental disturbances mimicking mild dementia (such as decrements in simple and complex attentional tasks, verbal and visual memory, encoding, storage and retrieval) have been described in depressed patients with hypercortisolism, and in steroid psychosis following glucocorticoid treatment. Similar cognitive deficits are also reported in patients suffering from Cushing's disease, a medical condition in which endogenous levels of glucocorticoids are chronically elevated. During human aging, a significant proportion of elderly individuals present an endogenous increase of glucocorticoid levels, and this increase has been related to impaired memory performance.

Chronic exposure to stress has also been shown to be associated with structural changes of the hippocampus. For example, treatment of adult rats with corticosterone decreases the proliferation of granule cell precursors, while removal of adrenal steroids stimulates the generation of new granule neurons. Given the suppressive actions of glucocorticoids on hippocampal neurogenesis, stressful experiences have been suggested to inhibit cell proliferation in adulthood, a hypothesis that has been demonstrated. Long-term stressful experience decreases the number of adult-generated neurons in the dentate gyrus in various species, including the rat, tree shrew, and marmoset. In a similar vein, repeated stress also produces prolonged suppression of cell proliferation in the dentate gyrus of the adult tree shrew. Stress-induced decreases in dentate gyrus cell proliferation could also contribute, in line with atrophy of the pyramidal cells of the hippocampus, to changes in hippocampal volumes observed after chronic exposure to stress.

Smaller hippocampal volumes associated with chronic elevations of glucocorticoids have also been reported in humans. Over the past two decades, many studies revealed the presence of smaller hippocampal volumes in various psychiatric disorders such as depression, posttraumatic stress disorder, and schizophrenia, all of which involve glucocorticoid level dysregulations. Hippocampal atrophy associated with chronic exposure to high levels of glucocorticoids is also reported in Cushing's patients and in elderly individuals. A recent study of Cushing's patients revealed that surgical treatment of hypercortisolism in these patients leads to a reversal of the glucocorticoid-induced hippocampal atrophy reported to occur in this population, with an average volume increase of 3.2%, and variations up to 10% in some patients. This is a significant finding since it implies the possibility of functional reorganization of the hippocampus, once the chronic stress has been taken away. Reversibility and/or preventability of such atrophy are major topics for future research, as is the implication of such treatment for cognitive function.

## Positive Effects Meeting Negative Effects: The Inverted-U Shape Function

There is a great paradox in the field of stress research that relates to the fact that stress hormones are sometimes associated with positive effects and sometimes associated with negative effects on cognition. This apparent discrepancy in the data can be explained by the fact that in both animals and humans, many studies reveal the presence of an inverted-U shape function between circulating stress hormone levels and memory performance, so that up to an optimal level, glucocorticoids can enhance cognitive performance, while above this optimal level, glucocorticoids impair cognitive performance. A model has been developed and suggests the presence of an inverted-U shape function between circulating levels of glucocorticoids and cognitive performance ([Figure 1]). More importantly, this model is based on the two types of GRs found in the brain.

Remember that given their differential affinity for glucocorticoids, the MRs will always be almost saturated (100% activated) before the GRs can start to be activated. During periods of stress or high levels of glucocorticoids (the a.m. phase in humans), both MRs and GRs will thus be saturated. Many studies performed in rodents have reported that the ratio of MR/GR occupation is a major determinant of the direction of glucocorticoid-induced cognitive changes. For example, long-term potentiation (LTP), a proposed neurobiological substrate of memory formation, has been shown to be optimal when glucocorticoid levels are mildly elevated, that is, when the ratio of MR/GR occupation is high. In contrast, significant decreases in LTP are observed after adrenalectomy, when MR occupancy is very low, or after exogenous administration of synthetic glucocorticoids, which activate GRs and deplete cortisol, again resulting in low occupancy of MRs.

Some authors have reinterpreted the well-known inverted-U shape function between circulating levels of glucocorticoids and cognitive performance, in line with the MR/GR ratio hypothesis. In this view, cognitive function can be enhanced when most of the MRs and only part of the GRs are activated (top of the inverted-U shape function; increased MR/GR ratio). However, when circulating levels of glucocorticoids are significantly decreased or increased (extremes of the inverted-U shape function; low MR/GR ratio), cognitive impairments will result. The authors suggested that the negative view of glucocorticoid actions on human cognitive function could be partly explained by limitations in previous human experimental designs, which did not allow differential manipulation of MR and GR levels. In order to do this, such studies should measure cognitive function when glucocorticoid occupancy is decreased (rather than increased), thus allowing functional measures of MR/GR occupancy on learning and memory.

Recent studies have tested this hypothesis and confirmed it. A first study measured whether memory performance in young, normal adults can be modulated by a hormone removal–replacement protocol in which one pharmacologically manipulates circulating levels of cortisol and measures subsequent memory performance. In this protocol, the authors used a
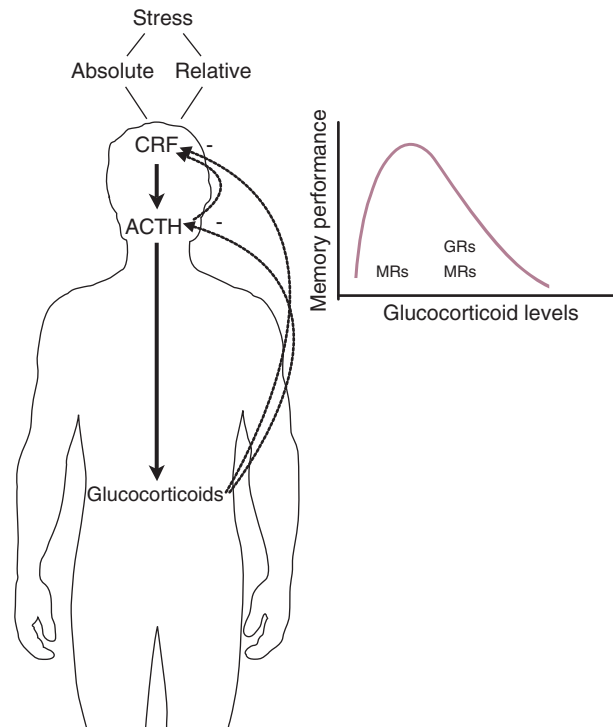
Figure 1 Schematic representation of the stress response and its impact on cognition. First, perception of an absolute or relative stressor triggers the secretion of corticotropin-releasing factor (CRF) by the hypothalamus, which then acts on the pituitary gland to induce secretion of adrenocorticotropin (ACTH). ACTH travels in the bloodstream and reaches the adrenal gland located on top of the kidneys and induces secretion of glucocorticoids. Because of their liposoluble properties, glucocorticoids easily cross the blood–brain barrier where they act on the hypothalamus and pituitary gland to shut down further secretion of CRF and ACTH, and they also access various brain regions where two types of glucocorticoid receptors (GRs) are located. The mineralocorticoid receptor (MR) has an affinity that is 6 to 10 times higher than that of the GR. Consequently, it has been proposed that the inverted-U shape function that relates circulating levels of glucocorticoids and memory performance is best explained by the differential activation of MR and GR receptors at different circulating levels of glucocorticoids. Low circulating levels of glucocorticoids mostly activate MRs and this is thought to be associated with the positive (left side of the inverted-U shape function) effects of glucocorticoids. In contrast, high circulating levels of glucocorticoids saturate MR and activate and/or saturate GRs (depending on the magnitude of the glucocorticoid increase) and this activation of MR and GR is thought to be associated with the impairing (right side of the inverted-U shape function) effects of glucocorticoids on cognition.

within-subject double-blind experimental protocol in which they first induced a chemical lowering of glucocorticoid levels by administration of metyrapone, a potent inhibitor of glucocorticoid synthesis, and then restored baseline circulating glucocorticoid levels with subsequent infusion of hydrocortisone. Memory performance of participants under each of these conditions was compared to that measured on a placebo day. The results showed that the metyrapone treatment significantly impaired memory, while hydrocortisone replacement restored performance at placebo level.

In a second study, the authors took advantage of the circadian variation in circulating levels of glucocorticoids and tested the impact of a bolus injection of 35 mg of hydrocortisone on memory performance in the afternoon. The idea behind this experiment was to test the impact of hydrocortisone in the late afternoon, at a time of very low cortisol concentrations, that is, at a time of low MR/GR ratio. It was postulated that if the ratio of MR/GR activation is involved in glucocorticoid-induced memory changes, administration of hydrocortisone in the late afternoon should increase the MR/GR ratio, and lead to increased memory performance when compared to placebo. The results confirmed the hypothesis, as it was shown that administration of hydrocortisone in the afternoon led to significantly faster detection times on the memory test when compared to administration of placebo.

In a third study, authors took advantage of the circadian variation in circulating levels of glucocorticoids and tested memory performance after exposure to a psychological stressor in participants who were stressed in the a.m. or p.m. phase. Here, the authors added a new variable in the protocol, and tested the potential differential impact of MR and GR activation on recall of neutral versus emotional information.

Young, normal adults were submitted to a psychological stress task before viewing a story composed of emotionally negative and neutral segments, and memory performance was assessed by a 1-week postlearning delayed recall. Results show that stress-induced increases in salivary glucocorticoid levels impaired delayed recall of emotionally arousing material in the a.m. group, but not in the p.m. group. There was no effect of stress on memory for neutral material. Altogether, these findings suggest that stressing participants in the a.m. phase, at a time of high circulating levels of corticosteroids, can overstimulate MR and GR receptors in the brain, impairing declarative memory for emotionally arousing material unrelated to the stressor. These findings suggest that the experimental context, that is, time of day at which the experiment occurs, the nature of the to-be-remembered material (remembering the stressful event itself or material unrelated to the stressor), and the valence of the to-be-remembered material (emotionally arousing vs. neutral), modulates the effects of stress on human memory.

Conclusion

After two centuries of research on the effects of glucocorticoids on human cognitive function, we have come to view the actions of this steroid as being modulatory rather than direct. History has taught us two important things. First, these steroids could access the brain and lead to changes in cognitive function. Second, glucocorticoids' action on cognitive process can be positive, and that the positive or negative effects of glucocorticoids depend on the balance of the two GR types known to exist today.

The story was supposed to become simpler as new discoveries were being made about the actions of glucocorticoids on the animal and human brains. Yet, it became more complex, dynamic, and difficult to grasp. Indeed, we now suspect that important variables related to the testing environment itself can have an important impact on the stress response and, consequently, can predict its impact on cognitive performance. Here, time of day, the valence, and the nature of the information to be learned were summarized as examples of the types of variables that have to be controlled when assessing the effects of glucocorticoids on cognition in humans, since these factors have been shown to impact on either the stress response itself and/or its effect on cognitive performance in humans populations. However, as complex as the story will get, it tells us that the glucocorticoid hormone is a very important player in the interface between the brain and the environment. This renders the study of its action more exciting than ever.

See also: Chronic (Repeated) Stress: Consequences, Adaptations; Hormones and Memory; Neurogenesis in the Intact Adult Brain; Stress and Vulnerability to Brain Damage; Stress and Neuronal Plasticity; Stress, Dopamine, and Puberty; Stress: Definition and History; Stress: Homeostasis, Rheostasis, Allostasis and Allostatic Load.

Further Reading

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