Effects of Chronic Stress on Prefrontal Cortex Structure and Function

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Introduction

Stress is highly present and appears to be increasing in our modern and demanding society. Different studies have shown that prolonged exposure to stress, apart from affecting our health, has significant consequences in certain brain areas. Although research has been mainly focused on the impact of stress on the hippocampus, more recently the influence of chronic stress on the prefrontal cortex (PFC) has been exhaustively investigated due to its important role in cognitive and emotional processes.

The **aims** of this review are:

- To describe the stress-induced cellular changes in prefrontal cortical pyramidal neurons.
- To analyze the impairment of prefrontal-dependent cognitive functions induced by chronic stress.
- To study the potential implication of stress-induced changes in the PFC in the pathology of some neuropsychiatric illnesses.

Methodology

The methodology consisted on a **bibliographic search**.

- Search for scientific literature on Pubmed and ScienceDirect databases from October 2014 to March 2015.
- The following keywords were used, alone or in combination: *"chronic stress"*, *"prefrontal cortex"*, *"pyramidal neurons"*, *"dendrites"*, *"executive functions"*, *"stress-related mental illnesses"*.
- Selection criteria were based on the journal impact factor, the date of publication and the relation with the main topic of this review.
- Finally, the most important reviews and articles were read and summarized and their bibliography was extensively analyzed.

Theoretical framework

Chronic stress

When the brain perceives an experience as stressful, it activates a coordinated response to cope with that challenge or stressor. This so-called **stress response** is crucial to adapt to the changing environment, but its prolonged activation may have negative effects on brain and many other organs.

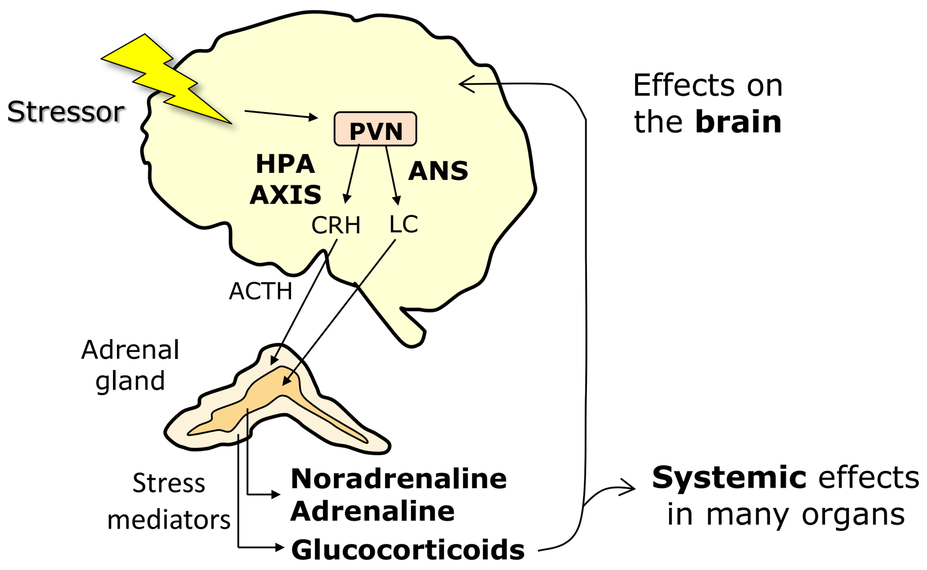

Figure 1. Stress response. The stress response consists on the activation of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis. *PVN: paraventricular nucleus; LC: locus coeruleus; CRH: corticotropin-releasing hormone; ACTH: adenocorticotropic hormone.*

The two sides of stress mediators

Protective		Damaging
Acute stress	→ *Time* →	Chronic stress
Release of many stress mediators		Sustained high levels of stress mediators
Adaptation and return to baseline levels		Wear and tear of the body
Allostasis	→	Allostatic load

Prefrontal cortex

The PFC, which is our most evolved brain region, constitutes the highest level of the cortical hierarchy dedicated to the representation and execution of actions.

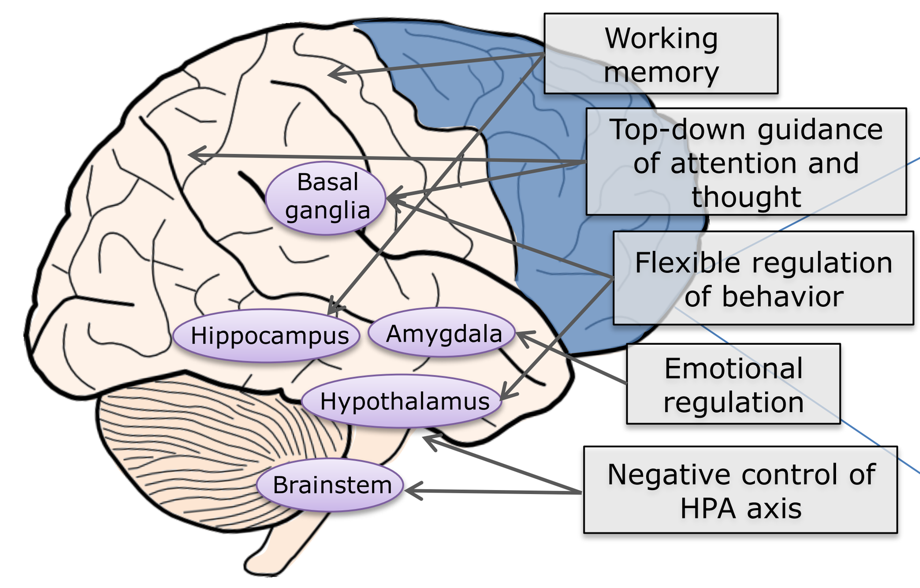

Figure 2. PFC executive functions and connections. The PFC regulates our thoughts, actions and emotions through extensive connections with many other brain regions.

PFC neuronal networks

PFC network connections can be rapidly altered, which confers great flexibility to the PFC but also high vulnerability to diverse factors such as stress.

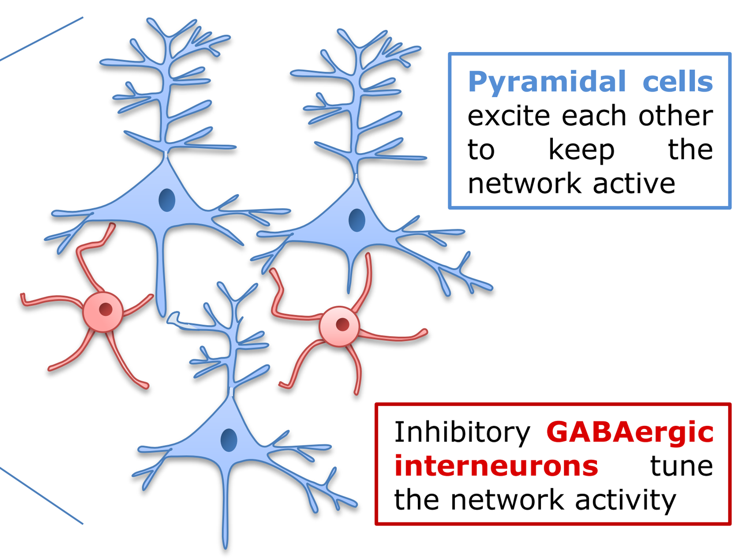

Figure 3. PFC microcircuitries. PFC networks consist basically on pyramidal excitatory neurons and inhibitory GABAergic interneurons.

Stress-induced cellular changes in the prefrontal cortex

Stressful experiences have a profound impact on neuronal plasticity in the PFC. The most remarkable effects occur on **pyramidal neurons**, which are the most abundant neuronal population of the PFC.

Changes in dendritic morphology and spine density

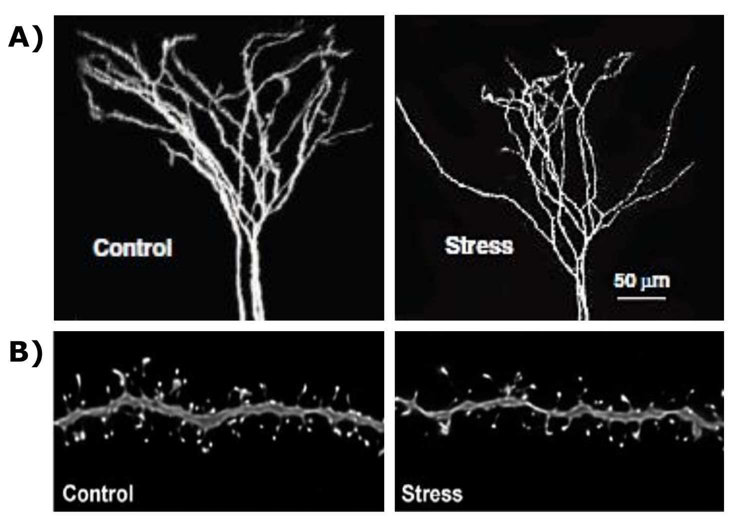

Figure 4. Morphological changes induced by chronic stress in PFC pyramidal neurons in rats. Apical dendrites of stressed animals experiment a reduction of length (A) and spine density (B) in comparison with unstressed control rats. A) *adapted from [3] and B) adapted from [4].*

- Reduction of the length of apical dendrites
- Decrease in dendritic branching of distal apical dendrites
- Basal dendrites remain unaffected

+

- Reduction of spine density at distal portions of apical dendrites
- Dendritic spines are not affected in basal dendrites

↓

Prolonged stress may impact the **axospinous synaptic input** into the PFC and this could be reflected in functional impairments

Changes in glutamate receptors expression

1. Exposure to chronic stress increases GC levels, enhancing the activation of GR.
2. GR activate the E3 ubiquitin ligases Fbx2 and Nedd4-1 which ubiquitinate NMDAR and AMPARs.
3. Enhancement of the proteasome-mediated degradation of these receptors.

↓

Decreased surface expression of different subunits of glutamate receptors in the PFC:

- **AMPAR**: ↓ GluA1, GluA2, GluA3
- **NMDAR**: ↓ GluN1, GluN2A, GluN2B

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Altered **glutamatergic transmission** can have detrimental effects on PFC-dependent functions

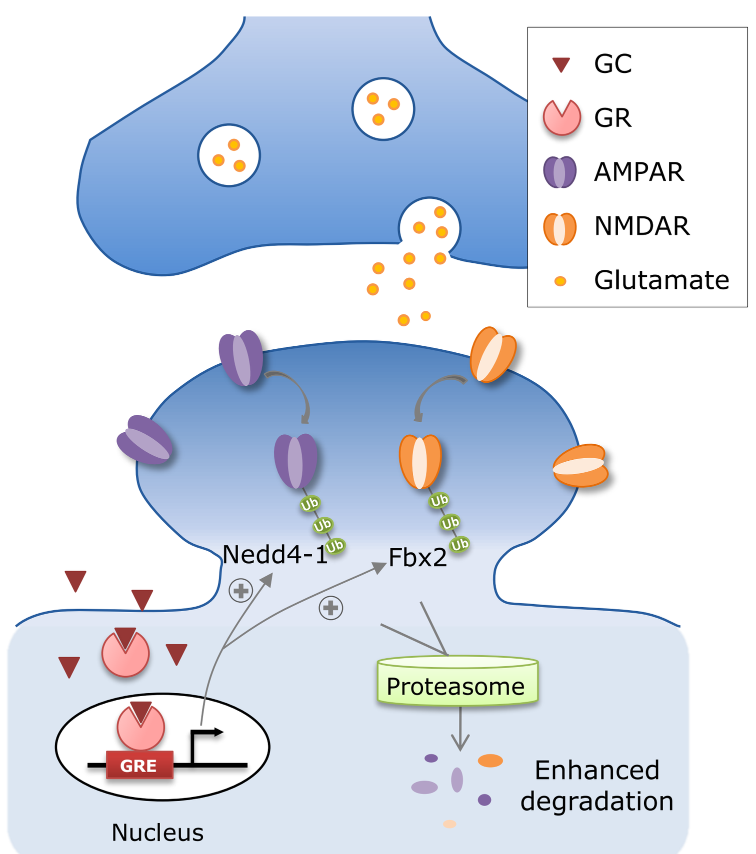


Figure 5. Effects of chronic stress on glutamate receptors. *GC: glucocorticoid; GR: glucocorticoid receptor; GRE: glucocorticoid responsive element; AMPAR: AMPA receptor; NMDAR: NMDA receptor.*

Stress effects on prefrontal-dependent cognitive functions

The executive functions of the PFC allow us to plan the future, to adapt our behavior to the circumstances and to make appropriate decisions, among others. Exposure to chronic stress can **disrupt PFC functions** and switch from slow and thoughtful PFC regulation of behavior to more reflexive and impulsive responses.

Stress → PFC FUNCTIONS

Decision-making

- Difficulty choosing the proper action based on the consequences of the choice
- Shift from goal-directed to habitual behavioral strategies

Working memory

- Impaired ability to keep information in mind and manipulate it
- Increased susceptibility to interferences

Behavioral flexibility

- Inability to adapt behavior to changing environments or demands

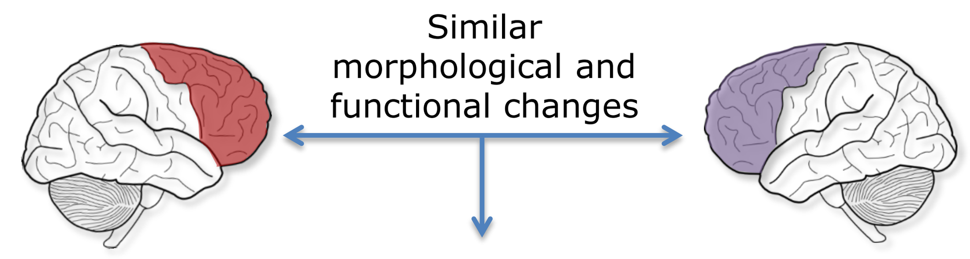
Figure 6. Stress disrupts some PFC functions. Chronic stress impairs working memory, decision-making and behavioral flexibility.

There is a **significant correlation** between stress-induced structural changes in PFC and the degree of impairment of PFC-dependent cognitive tasks. Although correlations alone cannot demonstrate that the structural changes directly cause the disruption of PFC functions, they suggest a causative link between them.

Stress-related mental illnesses

Stress is a well established **risk factor** for the development of many neuropsychiatric illnesses, such as depression, post-traumatic stress disorder (PTSD) and anxiety disorders, among others.

PFC in neuropsychiatric illnesses | PFC under chronic stress conditions



- Atrophy of pyramidal neurons and loss of synapses
- Dysfunction of glutamatergic transmission
- Dysregulation of PFC networks
- Impaired PFC functions
- Disturbed HPA axis regulation

Further exploration of the relationship between altered plasticity in the PFC after stress and pathology of stress-related mental illnesses

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New and more effective treatments

Figure 7. PFC under chronic stress and PFC in neuropsychiatric conditions. The similarity between the changes that occur in the PFC in these two situations suggest that changes caused by stress could underlie some of the typical pathological alterations that take place in neuropsychiatric illnesses and be in part responsible for their symptoms.

Conclusions

- The PFC shows a high plasticity, thereby illustrating the profound capacity of experiences to change the neural circuitries.
- The PFC is one of the most sensitive brain regions to the detrimental effects of stress, reflected in both structural and functional changes:
  - Dendritic morphological remodeling and changes in receptors expression in PFC pyramidal neurons.
  - Deficits in PFC executive functions that are associated with the structural modifications.
- Despite the tremendous advances made in understanding the impact of chronic stress on the PFC, many questions are still unanswered.
- Further understanding of the molecular mechanisms that mediate PFC stress-induced changes will provide important insights into the pathology of stress-related mental illnesses and the framework for the development of novel therapeutic approaches for these diseases.

References

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