

EXPERT REVIEW

The dynamics of the stress neuromatrix

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Stressful stimuli in healthy subjects trigger activation of a consistent and reproducible set of brain regions; yet, the notion that there is a single and constant stress neuromatrix is not sustainable. Indeed, after chronic stress exposure there is activation of many brain regions outside that network. This suggests that there is a distinction between the acute and the chronic stress neuromatrix. Herein, a new working model is proposed to understand the shift between these networks. The understanding of the factors that modulate these networks and their interplay will allow for a more comprehensive and holistic perspective of how the brain shifts 'back and forth' from a healthy to a stressed pattern and, ultimately, how the latter can be a trigger for several neurological and psychiatric conditions.

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WHAT IS STRESS?

As pointed out by Hans Selye¹ 'Stress is a scientific concept which has received the mixed blessing of being too well known and too little understood'. Indeed, there is still no perfect definition of stress that is commonly viewed as the brain's response to a demand and/or challenge (from now on here referred to as *stressors*). Stressors can be real or perceived. More so, stressors are not only subject dependent (value attribution), but also have distinct temporal dynamics (recurring, short term or prolonged) and may vary in their intensity (or at least in the individual's perception of it). That is, stressors can be mild and relatively harmless or result from major events and may have immediate and/or long-term effects on the subject's well-being. Thus, it is basically unavoidable that most individuals have/will feel stressed, at least from time to time.² However, it is also of critical importance to highlight that not all stress is 'bad' and/or detrimental. In fact, stress has been crucial to our very own survival as a species, being intrinsically linked to evolution: survival through adaptation. Indeed, all animals, and even other organisms, such as plants, have a stress response; however, as with other aspects in life, if the stress response is not moderate and controlled, it may cause harm. This prolonged, maladaptive, stress response is the focus of this review.

Some characteristics of stressors (or stress response) are determinant variables for the installation of the maladaptive response to stress: *timing*, *individual variability*, *predictability* and *controllability* (Figure 1). *Timing*, viewed not only as the temporal dynamics of the stress effects in the brain, but also how the brain will orchestrate the response to stressors in different states, will be in the center of this review. *Individual variability* is also critical as different individuals experience stress in different ways. Symptoms vary from anxious and/or depressed mood, anger and/or irritability to digestive or skin complaints or even immunosuppression.³ Importantly, there are also significant variations in the way distinct subjects cope with stress and this is a critical element for the establishment of maladaptive stress and for its impact on mental and physical health.⁴ *Predictability*, given that challenges are common events, the stress response has evolved in order to

be tightly controlled and regulated. In other words, if an individual faces repeatedly the same stressor, the organism typically develops an adaptive response.^{5,6} This is of the utmost relevance, particularly in the (translational) approaches used to study stress. A substantial number of studies use protocols of prolonged stress composed by a single stressor; these typically will not only measure the response to that stressor, but also represent the capacity of the subject to develop an adaptation to that stressor. The fourth factor to have into consideration is *controllability*. As shown by work from different laboratories,^{7–9} to have, or not to have, control over the stressor is critical for the installation of its detrimental effects. In fact, there are elegant studies reporting that animals with control over the stressor do not display any major signs or symptoms of stress.^{7–9} Thus, the monitoring of these factors is critical for the correct interpretation of the effects of stress in the brain.

Yet, these are not the only critical aspects to understand how stress can affect, and shift, the structure of the brain. In fact, the concepts of multistability, metastability and criticality will be key to understand how an individual brain network shifts (learns): depending on the individual's initial repertoire (see below), adaptive changes are governed by a shift mechanism (or a bi- or tri-furcation mechanism),^{10,11} where distinct routes occur. These alternative routes depend on each other and may be viewed as two successive phases of the learning/shifting process. A possible reason is that a minimum level of *multistability* (attained through the bifurcation mechanism) is needed to evolve gradually through the shift route; only later does the shift mechanism kick in giving rise to gradual behavioral change.^{10–12}

Obviously, brain circuits can become unstable leading to the emergence of novel states. Multistable coordination dynamics confers a capacity on the brain to lock into one of several available patterns. It goes without saying that locking in and switching capabilities can be adaptive and useful, or maladaptive and harmful. In coordination dynamics, *metastability* is the simultaneous realization of two competing tendencies: the tendency of the individual components to couple together and the tendency

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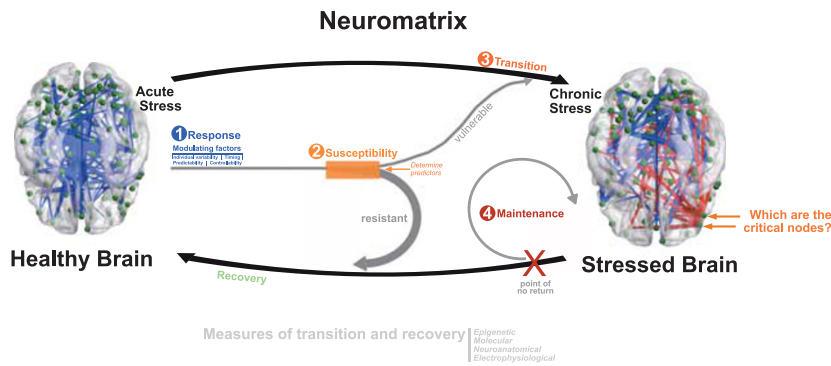


Figure 1. Proposed working model for a more dynamic, comprehensive and holistic perspective on how the brain shifts ‘back and forth’ from a healthy to a stressed pattern. In this working model, there are independent, although interacting, steps ((1) response; (2) susceptibility; (3) transition and (4) maintenance) that explain the dynamics from the acute stress condition to the chronic stress brain construct; here the critical questions related with the determination of the key nodes for the transition to chronicity and ‘points of no-return’. Whereas the response to stress depends on some factors (timing, individual variability, predictability, controllability), the transition to chronicity and the recovery are dependent on multifactorial determinants of individual susceptibility/resistance; in this case, the major research challenge is the ability to determine predictors of such individual response patterns.

for the components to express their independent behavior. Metastability emerges from multistability and, importantly, in the metastable brain, the activity of individual elements obeys neither the intrinsic dynamics of the elements nor the dynamics dictated by the assembly.¹⁰

Systems operating at the critical point of transition between ordered and random behavior are metastable with respect to a set of control parameters, and are capable of rapid qualitative change in response to fluctuations of external input.¹³ At or near the point of phase transition, the systems exhibit complex patterns of fluctuations on all scales of space and time, this being one of the indicators of an impending phase transition.¹⁴ Systems at *criticality* exhibit an optimal dynamical range for information processing, but shift as a result of plastic adaptation of synaptic strengths.¹⁵ These attributes of criticality are the reason for its rapid switching between different cooperative neuron collectives. A remarkable consequence of phase transitions is the generation of qualitative novelty in the form of networks with new properties.¹³

A NEW MODEL FOR UNDERSTANDING STRESS DISORDERS

Stressful stimuli in healthy subjects give rise to a consistent and reproducible activation of a set of brain regions^{16–18} (Figure 2). This can be considered as the stress ‘*neurosensorial-matrix*’. It is of importance to note that that this network is necessary, and probably also sufficient, for stressor perception and valuation. The nature of the stressor determines the sensorial pathway that is initially recruited. If the stressor is of physical nature (for example, a painful stimuli, hypovolemia, exposure to inflammatory cytokines, hypoglycemia), activation of the brain stem nuclei, or of circumventricular organs, takes place. These will, via ascending projections, ultimately activate corticotropin-releasing hormone and arginine vasopressin (AVP) releasing neurons in the paraventricular nucleus of the hypothalamus that control the release of adrenocorticotropin hormone in the anterior pituitary and, in turn, the release of corticosteroids in the adrenal cortex. If the stressor is a psychosocial stimulus, activation may occur in the amygdala, hippocampus and/or frontal cortex, among other limbic brain structures that modulate the activity of distinct nuclei in the bed nucleus of the stria terminalis or of the nucleus of the solitary tract, dorsomedial hypothalamic nucleus, arcuate nucleus or peri-paraventricular nucleus zone and, subsequently, the activity of the paraventricular nucleus (Figure 2). These constitute some of the initial nodes/networks of activation in response to stressors.^{16,18} Understanding how these acute stress-related

networks operate is probably helpful in uncovering pathways mediating pathological stress-related conditions. Therefore, it is not surprising that many tried to unravel functional properties and distinctions between the activated areas by studying which areas better correlate with stress intensity and which are better modulated by the exposure to previous stressful stimuli.

However, there is growing evidence that with time, the way the brain deals with stressors, in terms of regions and patterns of activation, suffers a remarkable shift, suggesting that there is a distinction between the acute and the chronic neuromatrix. In fact, in the chronic maladaptive stress state, in contrast to acute or subacute states, there is an involvement of additional neurons with distinct projections, resulting in unique modifications of stress control nodes and networks (discussed in detail below). Moreover, this transition from acute to chronic stress involves a time-dependent neural structural and functional reorganization, initiating a series of events that potentiate one neuronal pathway at the cost of another. Thus, anchored in these premises, a new working model is here proposed (Figure 1); in this model there are independent, although interacting, steps that are modulated by factors that may explain the dynamics of the chronic stress brain construct: (1) susceptibility; (2) response and initial injury; (3) transition to chronicity; and (4) maintenance of a ‘stressed-brain’.

This model was inspired in research developed in the pain field by Melzack¹⁹ and Apkarian *et al.*²⁰ More specifically, in this chronic pain there are specific brain areas and properties that are reliably linked with distinct chronic pain conditions; this pattern of activity is the result of a long-term and continued condition-specific reorganization of the brain across chronic pain that justifies the notion that chronic pain is a maladaptive neuropathological disease state.^{21,22} Similarly, and also because of the commonality between the neuronal networks in chronic pain and chronic stress,^{22,23} a model that explains how the temporal component emerges from the interplay between the network where the stressor was first perceived/processed and the networks that convey the experience-related reorganization is herein suggested; such interplay will reorganize the brain circuitry to distinct states, some of which are common to the ones observed in clinical conditions for which stress is a trigger factor. As a result, in the chronic stress stage, perception and salience of a stressor is a modified emotional and hedonic construct, where threat/value assessment and memory traces of stressful experiences are incorporated, eventually in an ‘altered mode’. Indeed, according to this model, the transition from acute to chronic stress also entails a transition in the salience of a stressor from a simple sign

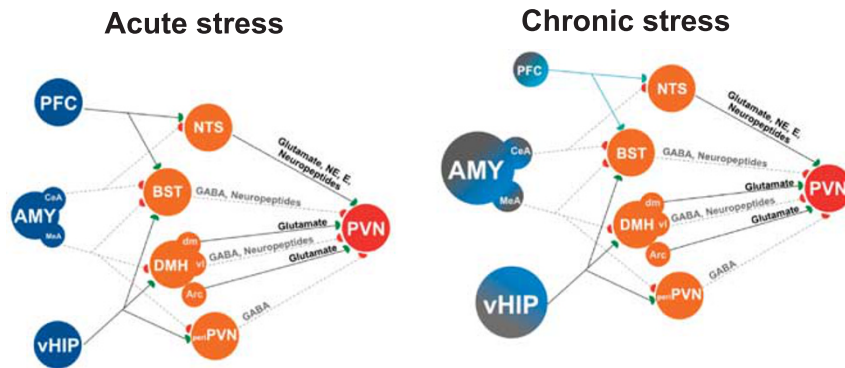


Figure 2. Schematic representation of some of the brain areas, and some of their connections, controlling one of the main aspects of the stress response: the activation of the paraventricular nucleus (PVN) of the hypothalamus. On the left panel, the normal pattern of connectivity that controls the response in an acute stress condition is illustrated. On the right side, a scheme of the altered pattern of connectivity in a chronic stress situation, where some of the major corticolimbic areas that modulate the stress response suffered a significant morphophysiological change that leads to a permanent shift in their pattern of connectivity (the *stressed neuromatrix*) that determines an altered behavior *per se* but also an inadequate control of the stress response. Please note that only some of the areas (critical nodes) that are instrumental for this shift (prefrontal cortex (PFC), central amygdaloid nucleus (CeA), amygdala (AMY: medial amygdaloid nucleus (MeA), ventral hippocampus (vHIP)) and their changes, are represented, given that many are still to be revealed. ARC, arcuate nucleus; BST, bed nucleus of the stria terminalis; DMH, dorsomedial hypothalamic nucleus: ventrolateral (vl) and dorsomedial (dm); E, epinephrine; NE, norepinephrine, NTS, nucleus of the solitary tract; peri-PVN, peri-paraventricular nucleus zone. Please see refs. 5,16,18 for further details.

of external threat/challenge into a pathological construct; this can be of relevance to understand how stress triggers several psychiatric conditions, namely depression and post-traumatic stress disorder.

SUSCEPTIBILITY OR PREDISPOSITION TO MALADAPTIVE STRESS

As indicated before, there is a remarkable variability in the individual response and predisposition to the effects of stress. This variability has a multifactorial origin, but certainly genetic and epigenetic mechanisms are implicated in it (Figure 3). It is well established that genetically transmitted patterns of reaction to stressors are highly preserved within species because they are critical for survival and evolution.^{24,25} More recently, several lines of experimental evidence have also shown the relevance of epigenetic mechanisms in the programming of stress brain circuits.^{26–29} Indeed, data obtained in various rodent models, such as models of prenatal and perinatal stress, maternal deprivation or separation and variation in maternal care, have revealed that exposure to stressful conditions in early life may lead to neuroendocrine perturbations later in life, some of them proposed to be transgenerationally transmitted.^{30,31}

Prenatal stress, or excess exogenous glucocorticoid exposure, have been consistently linked to adverse health outcomes including low birth weight, neuroendocrine dysfunction and increased risk of infectious, cardiometabolic and psychiatric diseases in later life (for reviews, see refs. 25,27–32). These observations derive from both animal and human studies and are concomitant with alterations in the activity of the hypothalamic–pituitary–adrenal (HPA) axis.^{28,29} Stress programming, however, extends further into early postnatal life. Data from models of impairment of mother–infant interaction reveal a disruption in neuroendocrine regulation(s) as a consequence of the down-regulation of the hippocampal glucocorticoid receptor (GR) and the hypothalamic corticotropin-releasing hormone, resulting in a HPA overactivation.^{33,34} Such early stress-induced neuroendocrine alterations are linked to behavioral problems and/or disease-state in adulthood, such as impaired memory, learning and anxiety- and depressive-like behaviors.³⁵ Lasting effects associated with natural variations in postnatal maternal care in rodents (namely, high or low levels of licking and grooming) have also been noted. In

adulthood, male rats reared by high-licking/grooming dams exhibit lower levels of stress response, better cognitive performance and increased exploratory activity as compared with the offspring of low-licking/grooming dams.^{36–38} Nonetheless, more recent studies have proposed that negative experiences early in life might also confer some preparation to face stressors later in life.³⁹ Certainly, the interplay of early-life events with long-lasting programming of brain circuits is much more complex than what preliminary data seem to have indicated, involving crucial ‘check and balances’ of individual variability, predictability, controllability and timing.

Epigenetic mechanisms, which started to be revealed in this context in the past two decades, seem to operate and be decisive contributors in mounting the stress response.⁴⁰ It has been shown that these early-life events trigger a developmental deregulation of epigenetic pathways that result in discrete or genome-wide changes in gene expression in various tissues, including the brain. These may influence the connectivity and functioning of neural circuitry and conferring a risk for both psychiatric and physical disorders in later life.⁴¹ The observation of an increased methylation of a CpG-rich region in the promoter and exon 1F of the GR gene (*NR3C1*) in the cord blood of newborns of mothers with depressed mood during the third trimester of gestation constitutes one of the first examples in humans of a functional consequence of epigenetic variation on stress reactivity.⁴² Importantly, this pattern on *NR3C1* gene methylation, which occurred only in the offspring, was correlated with levels of response to stress throughout and beyond infancy.⁴² Similarly, increased methylation of *NR3C1* promoter was also observed in childhood-abused suicide victims in comparison with nonabused individuals; this was also linked to decreased nerve growth factor-IA-inducible gene transcription.⁴³ These findings suggest a common effect of parental care in both rodents and humans on the epigenetic regulation of hippocampal GR expression. Moreover, to illustrate other potential effects of stress on the epigenome, there is evidence that the exposure to maternal depressed mood during the second trimester of gestation leads to decreased levels of methylation in the promoter of the *SLC6A4* gene, which encodes for the serotonin transporter, in maternal peripheral leukocytes and in offspring umbilical cord leukocytes.⁴⁴ Similar epigenetic effects have also been observed in cord blood as a consequence of pregnancy-related anxiety.⁴⁵

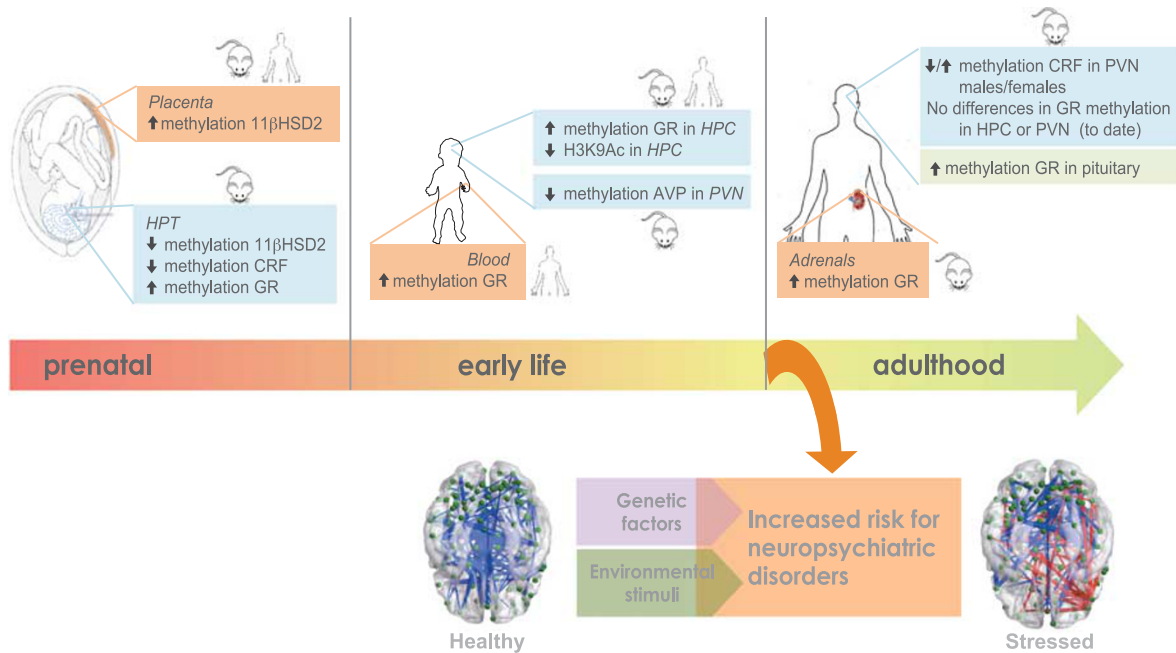


Figure 3. Schematic representation, along with different stages of neurodevelopment, of emblematic (epi)genetic determinants of individual susceptibility/resistance to develop a stressed neuromatrix. 11βHSD2, 11β-Hydroxysteroid dehydrogenase type 2; CRF, corticotropin-releasing factor; GR, glucocorticoid receptor; H3K9Ac, H3 lysine 9 acetylation; HPC, hippocampus; PVN, paraventricular nucleus of the hypothalamus.

Finally, prenatal glucocorticoid (GC) exposure also leads to differential methylation of dopamine receptor D2, suggesting that different neurotransmitter systems may be programmed by early-life stressors.⁴⁶

Shifts in glucocorticoid levels affect globally gene transcription and cell function; these are also likely associated with epigenetic changes in a number of tissues. The GR has been shown to induce stable demethylation in and around glucocorticoid receptor binding sites, leading to an increased transcriptional sensitivity of the target gene.⁴⁷ A similar mechanism may also mediate the lasting effects of childhood abuse on DNA demethylation at intronic glucocorticoid response element of the *FKBP5* gene, a co-chaperone regulating GR sensitivity, in both peripheral blood cells and in a hippocampal progenitor cell line.⁴⁸ Several mechanisms have been proposed for this transcription factor-guided active demethylation and involve protein–protein interactions with methyl-DNA binding proteins and DNA repair mechanisms as well as an intermediate introduction of hydroxymethylation marks.^{49–52}

Epigenetic modifications in response to traumatic experience and stress are emerging as important factors in the long-term biological trajectories leading to stress-related psychiatric disorders, reflecting both environmental influences and individual genetic predisposition.⁴⁹ In addition, epigenetic modifications are now recognized to be highly dynamic and also occurring in fully differentiated neurons. Such new form of plasticity has been implicated in the formation and function of synapses in the developing and adult brain⁵³ and in synaptic remodeling in stress disorders.⁵⁴ An emerging view also supports the existence of a complex epigenetic modulation of the adult neurogenesis process.⁵⁵ Indeed, it has been postulated that epigenetically controlled reprogramming restricts developmental options in proliferation and terminal cellular differentiation during neurogenesis. In this way, environmental stressors can affect the epigenetic regulation of adult neurogenesis, mediating neurogenesis imbalances that participate in the development of

depressive symptomatology.^{56–58} In parallel, there have been advances in our knowledge on the regulation of epigenetic modifications and, as an example, it is now established that dynamic epigenetic regulation of the glial cell-derived neurotrophic factor (*Gdnf*) promoter plays an important role in determining both the susceptibility and the adaptation responses to chronic stressful events.⁵⁹ It is, therefore, not surprising that later postnatal stressful experiences may also have potential for long-term programming and to increase the risk of developing physical and mental problems in adulthood (reviewed in refs. 60–64), namely when facing subsequent stressors later in life.⁶⁵

Obviously, genetic variability is influenced by other mechanisms. In fact, certain polymorphisms are reported to change HPA axis reactivity and stress response; for example there are single nucleotide polymorphisms in the mineralocorticoid receptor gene,⁶⁶ glucocorticoid receptor⁶⁶ and *arginine vasopressin receptor 1b* (*AVPR1b*) gene single-nucleotide polymorphisms.⁶⁷ Of note, such changes in stress responses are known to have important implications for the risk of developing mental disorders.

In summary, these observations show that previous exposure to stressful conditions induce substantial biological changes that modify the maturation of systems involved in *allostasis* (active process of adaptation and maintaining homeostasis), particularly those of the stress neuromatrix. This supports the notion that each individual is endowed with a particular stress response pattern and, more relevant, that the subsequent activation of this network later in life may confer a particular predisposition for the development of maladaptive stress-related disorders. This opens new avenues of research in the stress field (Figure 1): can the predictors of stress maladaptive responses be determined? If yes, can these risk factors be modulated? These are certainly open (and exciting) research questions for the field to tackle in the next decade. But now, it is important to review the networks implicated in the initial stress response and the transition to a stressed neuromatrix.

THE ROADMAP FROM THE INITIAL STRESS INJURY TO CHRONICITY

As discussed previously, there are initial nodes/networks of activation in response to stressors.^{16,18} Moreover, the activation of the HPA axis is a known target of programming effects that may result in distinct susceptibility to stressors. Such may translate into distinct levels of corticosteroids produced both in basal conditions and in response to stressful stimuli. Ultimately, these variations in the levels of corticosteroids, and other stress hormones, either direct or through indirect alterations, will trigger other nodes in the central nervous system and drive a new set of changes in the stress neuromatrix.

The hippocampus as the starting point of mapping of stress effects in the brain

In this scenario, the best way to map the activational effects of stress in the brain is to take into account the pattern of distribution of stress-mediating receptors, namely corticosteroids,⁶⁸ that are important (although not exclusive) mediators of maladaptive response.^{2,5} This exercise clearly highlights the hippocampal formation, rich in corticosteroid receptors,⁶⁸ as a target of the stress. And, indeed, much of the research focused on the effects of stress in the brain has been directed to the hippocampal formation. Almost 30 years ago, Sapolsky *et al.*⁶⁹ 'kick-started' the field with the notion that chronic stress disrupts hippocampal structure and function, eliciting a vicious cycle that results in an unabated secretion of GCs. The central idea indicated for the loss of corticosteroid receptor-bearing hippocampal neurons after prolonged exposure to high levels of GC,⁷⁰ resulting in a loss of the feedback inhibition that this brain region drives over the HPA axis. Subsequently, this view was strengthened by observations that GC can directly promote apoptosis⁷¹ and render hippocampal neurons more vulnerable to both excitotoxicity^{72,73} and oxidative stress.⁷⁴ Importantly, links between high GC levels and hippocampal degeneration have also become evident from magnetic resonance imaging studies in humans. In fact, for instance, GC hypersecretion, resulting from either Cushing's syndrome⁷⁵ or recurrent major depression,⁷⁶ triggers hippocampal atrophy and declarative memory deficits.⁷⁷ Notably, cognitive improvements are seen after remedy of the hypercortisolismic state in Cushingoid subjects.⁷⁸ More so, there is evidence toward restoration of hippocampal volumes in depressed patients who received pharmacological treatment.^{79,80} Of note, the impact of stress or excessive GC exposure in the hippocampal formation is not confined to loss of neurons, as several studies have also shown that stress exposure strongly reduces neurogenesis in the subgranular zone of the hippocampal dentate gyrus.^{81–83}

Whether the variation in neuron numbers is of relevance to the stress effects in the brain has been disputed,⁸⁴ and the emerging view is that the plasticity of brain network in response to stress involves other mechanisms. A much more common, faster and dynamic plastic event in neuronal adaptation is the synaptic remodeling of neurons, including changes in synaptic proteins, astroglia contacts at the tripartite synapse and alterations in the number of dendrites and in the type of spines. The idea that stress impairs brain function by compromising neuronal plasticity stems from reports that chronic stress or prolonged exposure to high GC levels impair cognitive performance and trigger dendritic atrophy and synaptic loss in dorsal hippocampal circuits;^{85–88} interestingly, more recently it was shown that an opposite phenomenon takes place in the ventral hippocampus,⁸⁹ a critical node to stress and emotional response control.⁹⁰ Notably, in this process two distinct outcomes can occur: if the stress context is sustained, changes at the dendritic and synaptic level tend to evolve to more definite states in neuronal structure and function, progressing along transsynaptic pathways;⁵ in contrast, in conditions in which the context that triggered the stress response is altered (either by an

intervening stress-free period and/or through therapeutic intervention), these changes are largely reversible and are associated with functional rescuing.⁸⁷ Thus, the transient effects of stress/GC on the structure and function of the hippocampus, as well as in other brain regions, tend to support the view that dendritic atrophy and synaptic changes, rather than variations in neuronal numbers, are the critical mechanism(s) through which the transition from the initial insult of stress to the chronicity phase takes place; a good example of this transition and temporal dynamics is seen in the stress effects on depressive-like behavior.^{91–93}

From the hippocampus to other brain regions

As a result of this view highlighting the relevance of the interconnectivity patterns in dynamic neuronal networks, a growing interest in generating systematic maps of stress-responsive brain circuits has developed.⁵ These efforts take into account the classic slow actions triggered by stress/corticosteroids through cytoplasmic receptors located in the cell membrane⁹⁴ as well as the novel fast actions of corticosteroid receptors.⁹⁴ They also include other stress modulators operating in the hippocampus and in brain regions to which the hippocampus is interconnected, namely through changes in glutamate release⁹⁵ that trigger distinct glutamate receptors⁹⁶ and contribute to a better understanding of the events that occur from the perception of stress to the adaptive neuroendocrine and behavioral responses. Certainly, the direct effects mediated by receptors are of relevance for the shifts in network structure and function, but ultimately there are other indirect effects resulting from the changes in the pattern of the activity of nodes within networks that *per se* will lead to changes in cascade in other nodes/networks. These effects on neuronal (or better said, on neuroglial) networks are likely to explain why the disruptive effects of stress are generally not restricted to a single location or function. For example, stress initially interferes with hippocampus-dependent declarative memory but, eventually, also impairs frontocortical-dependent cognitive functions (for example, working memory, behavior flexibility and decision making)^{97–99} as well as behavioral domains that are regulated by multiple brain areas (for example, mood, anxiety, fear).^{91,100} Importantly, these stress-induced behavioral deficits are underpinned by the morphological reorganization of dendrites, spines and synapses in the medial prefrontal cortex (mPFC),^{98,101–103} orbitofrontal cortex,⁹⁷ dorsal and ventral striatum,^{46,97,104} amygdala^{100,105} and bed nucleus of the stria terminalis.¹⁰⁶

Interestingly, at this level of interconnectivity it is possible to recognize the spatiotemporal and step-wise manner by which stress disrupts behaviors that require more than one brain area. A previous study demonstrated that whereas acute stress (3 days) in rats only impairs spatial reference memory (a hippocampal-dependent function), chronic stress (28 days) produces impairments in both spatial working memory and behavioral flexibility (functions in which the mPFC is implicated).⁹⁸ These structural alterations are paralleled by electrophysiological changes, namely by decreased theta coherence (crucial for performance in spatial working memory and long-term memory^{107,108}), in the hippocampal-to-PFC link.¹⁰⁹ Altogether, these findings point to the high sensitivity and/or earlier response of the hippocampus to the deleterious actions of this stress protocol; thereafter, the impact of stress progresses to the mPFC. The progressive pattern of the stress disruption within one brain region or within different brain regions is further supported by other studies. One example derives from studies in the mPFC where changes in spine and dendritic morphology in the apical trees of pyramidal neurons, namely in the infralimbic compartment, may be seen after acute exposure to stress.^{110,111} Importantly, these structural changes are also accompanied by resistance to and retrieval of fear extinction^{111,112} and by electrophysiological alterations that also

display a temporal progression.¹¹³ Another example is the demonstration that the effects of stress on the corticostriatal networks evolve in the first weeks of exposure to stress; specifically, electrophysiological alterations are first observed in the mPFC, and then progress to the dorsomedial striatum. As a result, the activity of corticostriatal associative network decreases in favor of the activity of sensorimotor network, underlying the observation that stress promotes habit formation.⁹⁷ Notably, similar observations were described in the amygdala-to-PFC projection,¹¹⁴ highlighting the broad, but specific, effects of stress on neuronal networks. But even more important is the notion that this transsynaptic evolution of stress effects with time also applies to its implication in pathological processes. For example, regarding the role of stress as a risk factor of Alzheimer's disease, a recent study reveals that the stress-induced amyloid precursor protein misprocessing and abnormal Tau hyperphosphorylation, characteristic neuropathological biomarkers of Alzheimer's disease, are first observed in the hippocampus and parahippocampal regions, from where they spread to frontocortical areas.¹¹⁵

The unexplored areas of the stress neuromatrix

One critical question is whether these stress-triggered effects are (1) reversible and/or (2) whether there is a 'point of no return' (Figure 1). Unfortunately, although a few laboratories have been exploring the issue of reversibility, none has specifically addressed the establishment of the critical 'point of no-return', where changes become irreversible. More precisely, it was shown that similarly to the hippocampus⁸⁷ the stress-induced changes in the PFC morphology are reversible when (young) animals are allowed a period of recovery after stress.^{116–118} Of note, the same experimental protocols failed to induce recovery in older animals.¹¹⁸ This indicates that the critical point of reversibility is probably influenced by several factors, one of which is age(ing) in itself. Also relevant is the observation that the spontaneous recovery of plasticity can be augmented by antidepressant drugs,⁹¹ including fast-acting antidepressants,^{119–121} a finding that may be relevant in the context of pharmacological interventions for the management of stress-induced disorders in which impaired neuroplasticity is implicated.¹²² In humans, it has also been shown that the impact of stress in corticostriatal networks (both at structural and functional levels) is reversible,¹²³ but that some sequel of the detrimental effect of stress on resting-state networks were still present after a stress-free period.^{124,125} Importantly, therapeutic interventions, namely the use of antidepressants, are also known to produce important reorganization in the neuronal circuits,^{126,127} relevant in the context of the stressed neuromatrix. As for the point of no return, its clinical relevance and whether all individuals experience it (and a similar or distinct level) are open questions for which future research is needed. Such studies should not only include brain functionality analysis of phase transition, but also longitudinal imaging studies where the impact of stress (and stress recovery) in brain networks can be followed in association with functional (endocrine, electrophysiological and behavioral) outcomes. Such approaches will determine the different factors influencing the point of no return in distinct individuals to stress (see more in refs. 116,128) and, certainly, affect the way we deal with stress-related disorders.

The design of better, and eventually customized, therapeutic interventions that may induce recovery or remediation from stress exposure is critically dependent on our knowledge of the mechanisms underlying stress detrimental effects.^{129,130} A large number of studies have been done on the molecular and cellular mechanisms mediating its effects at the synapse, in the extracellular matrix, at the cascades triggered by distinct corticosteroids receptors, in the production of neurotrophins and pathological mechanisms (reviewed in refs. 2,5,131–133). Herein, a couple of recent findings will be highlighted. The first

relates with the dual effects of stress changes at the synaptic levels (Figure 4). On one hand, acute stress, by activating GRs, activates serum-and-glucocorticoid-inducible kinase (SGK) and increases Rab4 levels, augmenting the trafficking and function of NMDA (*N*-methyl-D-aspartate) and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and leading to potentiated synaptic transmission.¹³⁴ On the other, chronic stress reduces AMPA and NMDA receptor expression and synaptic transmission through the enhancement of ubiquitin/proteasome-mediated degradation of some of its subunits (GluR1 and NR1), a process that is under the control of the E3 ubiquitin ligase Nedd4-1 and Fbx2, respectively, leading to synaptic dysfunction and eventually synaptic loss¹³⁴ (Figure 4). The second set of exciting findings in the field relate with unbiased proteomic and lipidomic analysis. A proteomic study using a dynamic approach¹³⁵ showed that prenatal stress exposure led to two distinct patterns of changes in protein expression: some were transiently changed, whereas others were consistently altered. These findings support the progressive nature of stress changes in the brain, namely in proteins implicated in calcium homeostasis, redox status, secretory protein synthesis and glucose or energy deprivation. Although this study represents a whole-brain analysis, other studies on specific brain regions have also largely confirmed the impact of stress in proteins implicated in these functions,^{136,137} even at the synaptic level¹³⁸ and with potential predictive value for vulnerability to stress-related disorders.¹³⁹ In addition, more recently, and largely due to the technical advances in lipid analysis, the impact of stress in brain lipidomics has been revealed. Specifically, it was shown that the PFC and the hippocampus presented significant alterations in their lipidome, with an impairment in sphingolipid and phospholipid metabolism.¹⁴⁰ The identification of impaired lipid signaling pathways opens a new avenue of potential targets of stress pathology. Remarkably, decreasing the levels or inhibiting the lipid modulating enzyme acidic sphingomyelinase prevented chronic stress-induced behavior and pathological hippocampal alterations.¹⁴¹

In summary, the above-described findings ultimately lead, in a yet to be better characterized spatiotemporal pattern, to a new 'stress connectome' paradigm. The existence of this stress neuromatrix has two distinct implications: (1) it is at the center/origin of the pattern of response to stress, of relevance for the maintenance and hyperactivation of stress nodes and networks, and (2) it facilitates the appearance of signs and symptoms typically associated with neuronal and psychiatric disorders, because these stress signaling and neuronal pathways are also implicated in the etiopathogenesis of such conditions.

THE STRESSED CONNECTOME

Brain function results from the pattern of activity generated in interconnected brain nodes. This view is clearly observed in functional brain imaging research that permits to examine localized brain activity and integrate such activity into networks.^{142–147} These approaches indicate that the brain can be regarded as a network with fast signal processing, able to synchronize. The resting brain state and its properties are recent extensions on the topic and, perhaps, some of the most exciting new developments in our understanding of the functional human brain as a dynamic network. In the next paragraphs, using the resting-state networks as an example, attention will be given to the following questions: is the chronically stressed brain a healthy brain? Even if not, is it still able to go back to a healthy state?

Recent studies show that stress increases the activation of the default mode network (DMN) at rest in different nodes, including the ventral mPFC, posterior cingulate cortex, adjacent precuneus and inferior parietal cortex. Based on previous studies highlighting the role of the DMN at rest,^{148–151} these results suggest an

augment in self-reflective thoughts and also an increased dynamic interaction between emotional processing (that is, ventral regions) and cognitive functions (that is, dorsal regions) in stressed individuals, as a result of increased activity in the anterior components of the DMN. The increases in the posterior regions of the DMN, particularly the posterior cingulate cortex and the inferolateral parietal lobes, are likely associated with longer processing of emotionally salient stimuli and episodic memory retrieval.^{152,153} Interestingly, after stress recovery, a global rescuing of the resting functional connectivity in the DMN has been noted, except for connectivity of the right anterior cingulate cortex. Notably, a volumetric contraction, with specific reductions in the left posterior cingulate cortex and left and right parietal inferior regions, paralleled the increase in functional connectivity in the DMN, after chronic stress. This is likely to reflect the

stress-induced atrophic effects in cortical regions, as observed in previous reports,^{124,154} that appear more resistant to recovery.¹²⁵

The characterization of changes in functional connectivity between brain networks subserving distinct psychophysiological functions is of relevance to understand the symptoms triggered by stress. For example, a recent study in rodents revealed an altered (increased) pattern of resting-state network connectivity in chronic stress rats.¹⁵⁵ Similarly, in humans the finding of an increased functional connectivity between dorsal mPFC (part of the 'dorsal nexus') and posterior cingulate cortex in stressed participants¹²⁴ has also been reported in depressed subjects¹⁵⁶ and to be rescued by antidepressants.^{157–159} In addition, the observation of increased connectivity in nodes of the dorsal attention network in stressed individuals suggests alterations in emotional regulation and in vigilance and awareness, typical of stress-induced hyperemotionality. Interestingly, the dorsal attention network did not reveal a functional recovery after the cessation of the exposure to stress,¹²⁵ maintaining a sustained pattern of increased functional connectivity that might affect emotional regulation in response to future stressors or pathological conditions.

Differences in deactivation of resting-state networks after stress have also been described, particularly in the ventral attention network and DMN, that are of relevance for task control function^{160–162} and "salience" processing.¹⁶³ Importantly, the greater functional connectivity found in the ventral attention network during resting-state functional magnetic resonance imaging in stressed participants¹⁰⁴ suggests a greater difficulty in moving from more oriented, self-related processes toward a task-focused behavior. Given that the ventral attention network has an important role in cognitive control related to switching between the DMN and task-related networks,¹⁶⁴ this has a potential impact on cognitive performance; for example, a stronger DMN deactivation in a working memory task predicts better performance.^{165,166}

Importantly, the triggering effect of an acute stress episode to the development of clinical disorders, namely post-traumatic stress disorder, is a matter of relevance. Several studies have

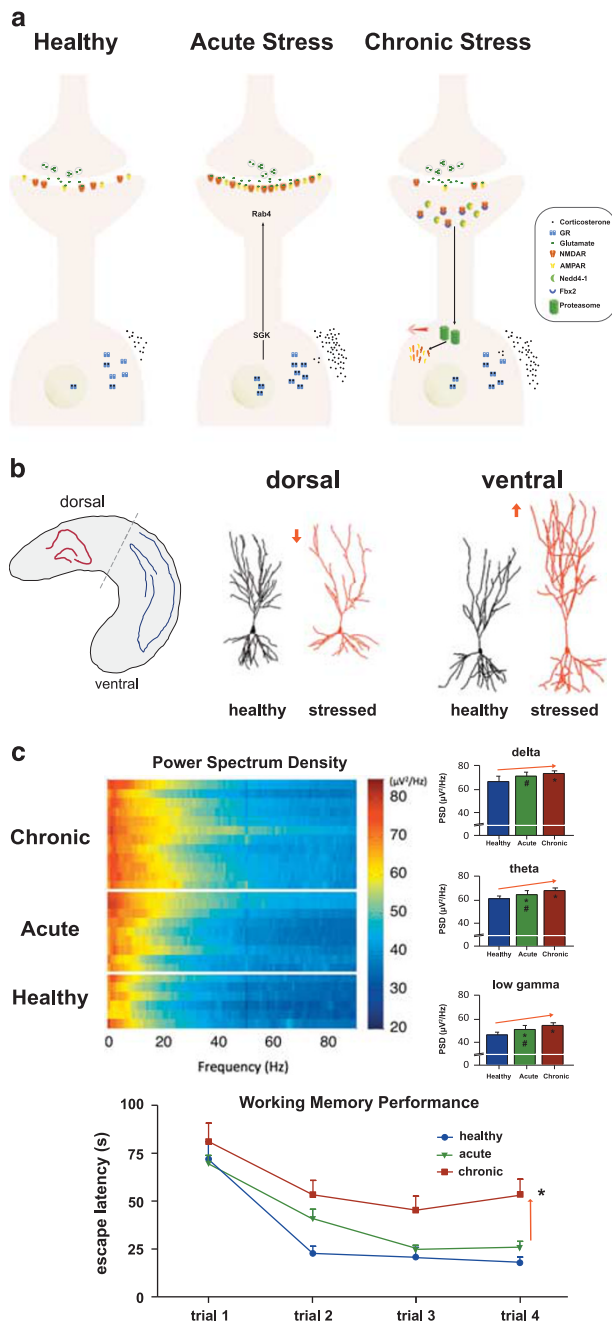


Figure 4. Schematic representation of the different levels that anchor the transition from a healthy to a stressed neuromatrix. **(a)** At the molecular and synaptic level, there is growing evidence that stress has a dual effect on the glutamatergic transmission in prefrontal cortex (PFC) pyramidal neurons: on one hand, acute stress, by activating glucocorticoid receptors (GRs), increases serum- and glucocorticoid-inducible kinase (SGK) and Rab4 that augments the trafficking and function of *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and leads to potentiated synaptic transmission; on the other, chronic stress reduces AMPA and NMDA receptor expression and synaptic transmission through the enhancement of ubiquitin/proteasome-mediated degradation of some of its subunits (GluR1 and NR1), a process that is under the control of the E3 ubiquitin ligase Nedd4-1 and Fbx2, respectively. **(b)** At the neuroanatomical level, the progressive exposure to stress triggers a morphological reorganization of dendritic arbors and spines; as an example of the complexity of the structural reorganization, although in the dorsal hippocampus chronic stress induces an atrophy of apical dendrites in CA3 pyramids, the opposite occurs in the ventral hippocampus. **(c)** At the functional level, an example of a power spectral density map in ventral hippocampus of controls (healthy), acute stressed (acute) and chronic unpredictable stressed (chronic) rats for delta (1–4 Hz), theta (4–12 Hz) and low gamma (20–40 Hz) frequency bands showing that exposure to stress progressively increases power in this brain node. At the behavioral level, an example of progressive spatial working memory deficits from a healthy condition to a chronic stressed state. **(a)** Is an illustration of results presented in refs. 134,170, **(b)** in refs. 87,89 and **(c)** in refs. 98,109.

addressed this issue and it seems clear that exposure to a major episode of stress is a relevant antecedent for the development of future acute and chronic forms of post-traumatic stress disorder.^{167,168} The key question seems to be why some individuals develop such disorders whereas others seem to be more resilient to the acute stress episode. Several predictors (gender, previous psychiatric problem, intensity and nature of exposure to the traumatic event and lack of social support) are implicated in such variability. Importantly, individuals who face trauma do develop changes in the dynamics of functional brain networks, independently of developing clinical symptoms; some brain areas, such as the amygdala and parahippocampal cortex, distinguished post-traumatic stress disorder patients from other individuals.¹⁶⁹ Again, issue-related multi- and metastability seem to be of relevance to understand such transitions.

In summary, altogether, these observations strengthen the view that the pattern of brain activity in chronic stress is quite distinct from the one observed in healthy conditions, reinforcing the view that a shift toward a stressed neuromatrix also underlies a transition in the salience of a stressor from a simple sign of external threat/challenge into a pathological construct.

FINAL REMARKS

Taking into account that the brain is a complex and dynamic matrix, where detailed connectivity is constantly being modified by the instantaneous experience of the organism, it becomes obvious that quantifying chronic stress as an activation of sensorial node perception and HPA outflow is simplistic and inadequate. Preliminary studies looking at the brain connectome in distinct stress states reveal both the dynamic alterations and the particular properties/responses that take place in the stressed neuromatrix (Figure 1). By integrating preclinical and clinical evidence, an overall working model for the transition from acute to chronic stress is proposed. This model can be adapted and, hence, mechanistically reflect differences between subjects experiencing stress to varying extents, including in the context of different clinical conditions.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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