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A salience hypothesis of stress in PTSD

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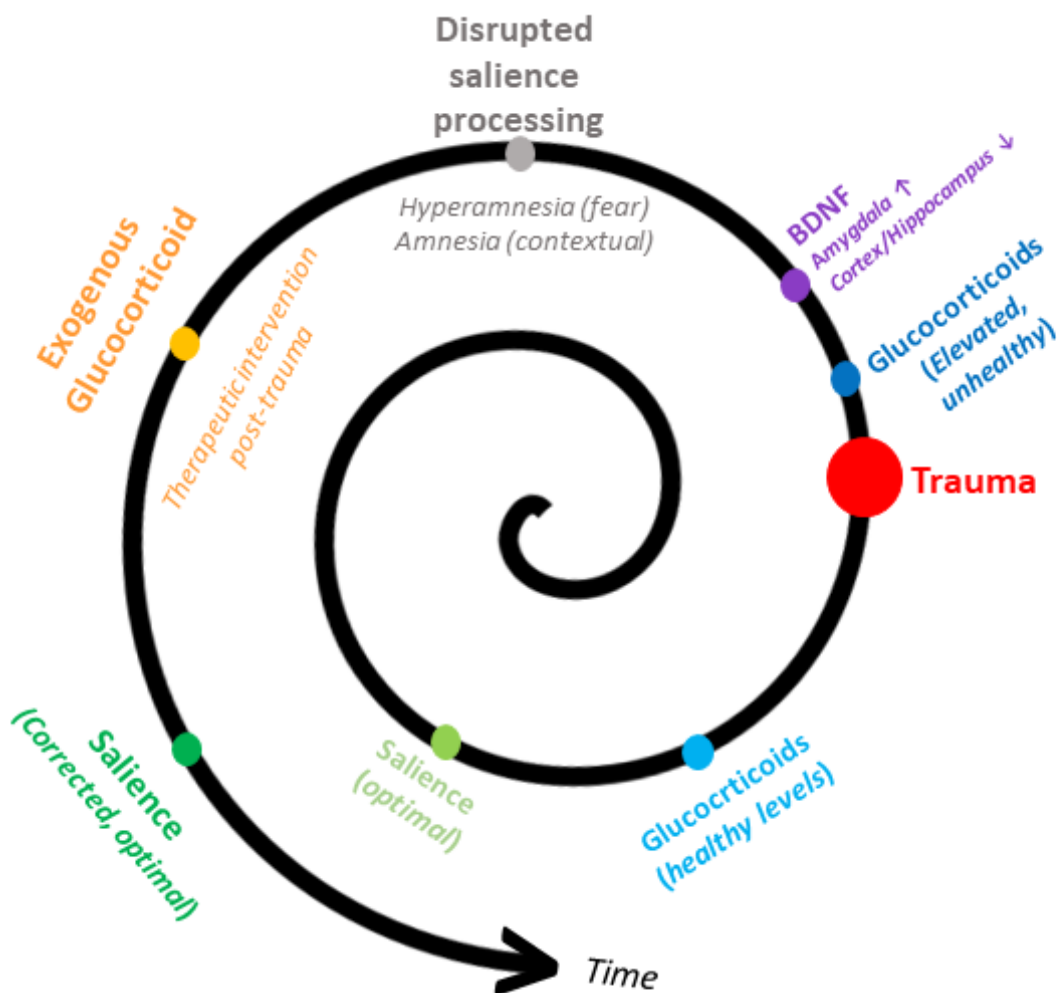
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Abstract

Attention to key features of contexts and things is a necessary tool for all organisms. Detecting these salient features of cues, or simply, salience, can also be affected by exposure to traumatic stress, as has been widely reported in individuals suffering from Post-Traumatic Stress Disorder (PTSD). Interestingly, similar observations have been robustly replicated across many animal models of stress as well. By using evidence from such rodent stress paradigms, in the present review we explore PTSD through the lens of salience processing. In this context, we propose that interaction between the neurotrophin BDNF and glucocorticoid determines the long lasting cellular and behavioural consequences of stress salience. We also describe the dual effect of glucocorticoid therapy in the amelioration of PTSD symptoms. Finally, by integrating *in vivo* observations at multiple scales of plasticity, we propose a unifying hypothesis that pivots on a crucial role of glucocorticoid signalling in dynamically orchestrating stress salience.

Keywords – PTSD, Animal models, Amygdala, Cortex, Glucocorticoids, BDNF



Graphical abstract – A disruption of glucocorticoid function due to trauma leads to disrupted processing of salience in PTSD. This can be corrected by additional exogenous intervention with glucocorticoids after trauma.

Introduction

Survival in the natural world involves a constantly adapting response to emotionally salient cues. It involves first, detecting the relevance of a stimulus ('Is this a reward or a threat?', 'Is this context safe or dangerous?', and so on) and then engaging an appropriate action towards it (if reward/safe, then approach; if threat/dangerous, then avoid). This ability to optimally detect and process the key, salient characteristics of cues, or simply, salience, is a central tenet that guides adaptive behaviour. In humans, a dedicated central 'salience network' is involved in directing attention and purpose to such stimuli that are relevant to the context (1). Functionally, this involves a number of different brain regions including, but not limited to, cingulate and insular cortices, hypothalamus, ventral tegmental area, hippocampus and the amygdala (1). Under conditions of psychological duress, both the detection and response to relevant stimuli must be reset to fit with the demands of the internal and external worlds. Stress, for instance, not only enhances the salience of aversive cues, but also diminishes appetitive salience. This disequilibrium has been widely documented in individuals suffering from Post-Traumatic Stress Disorder (PTSD) – a stress-induced condition that has a significant global burden and lacks effective pharmacological treatment.

Although it had been prevalent since much earlier with names like ‘shell shock’ and ‘irritable heart of soldiers’, the earliest clinical diagnosis and classification of PTSD occurred as late as the 1980s (2,3). PTSD patients exhibit symptoms like hypervigilance, insomnia, enhanced anger and increased arousal (2,3), which can emerge from anywhere between a few weeks to a few years after trauma exposure (4). The nature of trauma varies widely too, ranging from war-related trauma to occupational stress (5) and even road traffic accidents (6). Indeed, the altered behavioural responses exhibited by PTSD-subjects could be attributed to a miscomputation of particularly salient elements of the event that are not predictive of the event. But hypermnesia of these elements is often comorbid with declarative amnesia for the context in which the trauma occurred (7), resulting in difficulty to erase fearful experiences (8) and reduced positive affect (9–11). Expectedly, such individuals also show a stronger connectivity of the salience network in functional imaging studies (12–15), in line with the idea that stress would alter the expression of synaptic plasticity required for adaptation to trauma. This involves hyperactivity in the amygdala consistent with emotional hypermnesia and decreased activity in the hippocampus contributing to contextual amnesia, such that PTSD patients would exhibit persistent fear memories out of context.

In such a pathological state, it is now clear that the mechanistic underpinnings involve an imbalanced activity between regions like the amygdala and hippocampus, by engaging direct or indirect neurocircuits which respond to the stress-altered salience. Rodent preclinical models of stress have been instrumental in shedding light on these processes. These involve either repetitive application of a stressor(s) over days (chronic stress paradigms) or an acute, one-time exposure to a traumatic stressor (acute stress paradigms). The wealth of evidence from such studies point towards a shift in salience-response of stressed rodents too, similar to observations from humans. The real power of these models, however, lie in their ability to determine both *ex vivo* and *in vivo* functional mechanisms that underlie the stress-induced changes. An intriguing role in this milieu is played by glucocorticoids – a class of steroid hormones critical not just in the onset of stress-effects but also in the amelioration of PTSD symptoms (16). In this regard, glucocorticoids are thought to prepare cellular responses towards future demands by programming metabolic fitness, fostering synaptic plasticity and shutting down unnecessary energetic costs.

Thus, in the light of these accumulating evidence, the present review examines a ‘stress-salience hypothesis’, by specifically focusing on animal models of PTSD. By doing so, we attempt to integrate existing evidence from preclinical studies in a new framework that synthesizes context-specific alterations in neuronal plasticity and behavioural function.

Stress effects on behaviour: the ‘*what*’ and the ‘*when*’

Hallmarks of behavioural impairment seen in PTSD patients include an exaggerated fear response that is resistant to extinction (8) and an increase in anxiety (17). Moreover, these individuals also exhibit an inability to discriminate between cues associated with safety and danger, leading to increased fear generalisation (18). Together, they suggest a failure to process salience - a state that could last for a considerable length of time beyond trauma impact. Modelling these behaviours in rodents allows us to first dissect their neuronal mechanisms and then test pre-clinical efficacies of different treatment regimens. To study fear learning, for instance, animals recall a previously learnt association between a fearful unconditioned stimulus (typically a shock) and a previously innocuous conditioned stimulus (typically a tone, image or odour). Subsequently during extinction, unreinforced presentation of the conditioned

stimulus leads to a gradual reduction of fear. As seen in human PTSD subjects, stressed rodents also show high fear which is difficult to extinguish (19–25). A decrease in fear during extinction involves an ability to optimally interpret a change in salience of the same cue over time, and this seems to be impaired following stress. Interestingly, however, rodents typically undergo fear conditioning *after* being subjected to stress in most reports exploring fear extinction (26). Indeed, this would lead to an unequal strength in salience of the fear-associated cue in animals which have experienced stress before, versus animals which only experienced conditioning in the absence of stress. Could it be, therefore, that this difference in internal state during learning contributed to a subsequent failure to extinguish fear?

A set of recent studies revealed that indeed, rats failed to extinguish a fear memory that was formed *after* chronic stress (thereby in agreement with conventional designs). Very interestingly, however, when fear learning occurred *before* stress (thereby creating an equivalent salience of the conditioned stimulus in all animals prior to stress onset), stressed rats could extinguish it as successfully as controls (20,21). In striking similarity to these observations, Bryant et al. 2007 also observed that PTSD-subjects showed no impairments in the recall of negative autobiographical memories which were formed *before* trauma (27), although enhanced recall of trauma-associated memory in PTSD has been well documented (28). This indicates that the modulation of salience is not just governed by the stressed state of the animal, but also depends on *when* the stress occurred.

Such temporal modulation is evident for stress-induced anxiety-like behaviour as well (**Table 1**). While chronic stressors over multiple days robustly enhance anxiety (29), a single, 2 hour long episode of immobilisation stress also increases anxiety 10 days, but not 1 day later (30–35). Similar delayed effects are also reported after exposure to other types of acute stressors including acute predator stress and one-time injection of the stress hormone corticosterone (36–39), and can be detected even 30 days afterwards (40). Rodents also show enhanced social anxiety (a symptom often reported in PTSD patients (41)) which is quantified by a decrease in social interaction of a stressed animal with an unfamiliar conspecific (35,42–45) (**Table 1**). So, while stress does alter salience-processing of both social and non-social cues, could social and asocial anxiety divergently evolve over time after the same stressful experience? A recent study provides support to this idea wherein acutely stressed animals showed an immediate deficit in social interaction 1 day later that persisted even 10 days after stress (42). Asocial measures of anxiety, on the other hand, only emerged at the delayed time-point (42). Thus stress effects on behavioural salience can also be modulated temporally – an intriguing idea that we shall expand on in the next few sections.

Amygdala, cortex and hippocampus: opposite roles in stress-salience

What underlies the stress-induced behavioural changes discussed above? While ‘altered neuronal plasticity’ may be a simple answer, it falls short of describing the functional divergence seen across different brain regions. Take the amygdala, for instance. Following chronic stress, excitatory neurons in the rodent basolateral amygdala (BLA) show increased dendritic arborisation as well as dendritic spine density on principal neurons (19,21,46–51) (**Table 1**). Acute stress, on the other hand, shows no effect on BLA neurons 1 day later (30). Similar to anxiety, stress effects build up over time such that principal neurons in the BLA now show an increased density of dendritic spines 10 days afterwards (30–33,52). Injection of glucocorticoids alone also recapitulates a temporally delayed evolution of morphological plasticity within the amygdala that is not evident proximal to trauma-exposure (36,53). Accompanying such an increase in morphological plasticity is also an increase in physiological

activity of BLA excitatory neurons, with an enhancement in excitatory synaptic activity and a decrease in synaptic inhibition (54). This temporal evolution of plasticity between neuronal excitation and inhibition noticeably mirrors the emergence of stress-induced behavioural phenotypes over time, as discussed above.

In contrast to strengthening the amygdala, stress weakens plasticity in the dorsal hippocampus (**Table 1**). Some of the earliest reports showed that daily injections of corticosterone (55) and three weeks of chronic restraint stress (56) both led to loss of dendritic arbour from dorsal hippocampal pyramidal neurons. First evidences from the prefrontal cortex (PFC) also showed similar effects: chronic corticosterone (57) and a 21 day chronic restraint stress paradigm (58,59) both significantly atrophied apical dendrites and resulted in a loss of dendritic spines of PFC pyramidal neurons (21,60). Subsequently, dendritic atrophy and spine loss from dorsal hippocampus (32,46,61–64) and PFC (22,36,65) were routinely validated and consistently reported across various other rodent chronic and acute stress paradigms (66). These reports are further strengthened by supporting clinical evidence indicating loss of hippocampal (7,67) and cortical volume (68–70) in a number of clinical studies involving stress-disorder patients. This loss of volume is distinct from neurodegenerative loss, in that it is largely contributed by changes in morphological plasticity due to altered excitation-inhibition.

Interestingly, the hippocampus shows a dorso-ventral specialisation in both anatomy and function. In contrast to dorsal hippocampus, rodent pyramidal neurons in the ventral CA1 have longer apical dendrites, lesser number of branches, and are *more* excitable than dorsal CA1 cells (71). The ventral hippocampus also plays a significant role in the regulation of anxiety (72), and heavily projects to regions like the amygdala which regulate neuroendocrine responses to emotionally salient experiences (73). However, while there has been a decade-wide interest in studying the impact of stress on dorsal hippocampus (largely due to its key role in memory-related cognitive processes), reports on stress-induced plasticity in the ventral hippocampus are fewer. Some chronic stress paradigms (social isolation, maternal separation, chronic immobilisation) report weakened morphological plasticity in the ventral hippocampal neurons (21,74,75). Others like chronic restraint stress has a gender-dependent effect such that stressed female rats showed a decrease in spine density and an increase in dendritic arborisation of ventral CA1 neurons (76). Even other stress paradigms (acute restraint, chronic unpredictable stress) have reported no effect on neuronal morphology (77,78). Such dorso-ventral distinction extends to stress-induced physiological changes as well. In contrast to suppressing LTP and enhancing long-term depression (LTD) in the dorsal division, stress enhances LTP and converts LTD into LTP in the ventral hippocampus (79–82). This regional contrast is further supported by strikingly different patterns of change in stress-induced expression of molecular players (proteins, mRNA, epigenetic markers) between the two hippocampal sub-divisions (83).

In sum, these stress-altered effects across functionally interconnected brain regions lead to a tempting question: could it be that functional interaction *between* these areas are also affected by stress? Indeed, it has been observed that the directional influence of BLA on the dorsal hippocampus grows stronger during chronic stress, and remains so even afterward (while intra-hippocampal network interactions become weaker with stress) (84). Stress and glucocorticoids alter interactions between amygdala and PFC as well (85–87). Additionally, these interactions could be modulated by the *timing* of experience with respect to stress exposure. In the context of an earlier example: when fear learning occurred *after* stress, the consequent deficit in fear extinction could be explained by a disrupted neuronal synchrony between the PFC and BLA (20). However, when the same fear was acquired *before* stress, such a disrupted network activity was not evident (20). This, consequently, allowed for unimpaired fear extinction despite stress exposure.

The gamut of behavioural deficits seen in PTSD patients hence results from a summed impact of divergent patterns of neuronal plasticity across the corticolimbic circuitry (54,88). So it can further be predicted that pharmacotherapy in PTSD might employ different mechanisms for reversing stress-effects in the amygdala versus the hippocampus/cortex. This is interesting, particularly because the initial systemic response to stress is the same, involving an immediate elevation in systemic corticosterone in rodents and cortisol in humans (33,89–92). But what happens next, and how do glucocorticoids interact with other molecular players? We discuss this in the following section, with a particular focus on its interaction with a neurotrophin.

Glucocorticoids and BDNF: a dynamic relationship in stress salience

Upon its release from adrenal cortex after activation of the Hypothalamus-Pituitary-Adrenal axis, glucocorticoids enter the brain by diffusing across the blood-brain-barrier (93). It then binds to its cognate receptors, of which GRs are distributed from the olfactory bulb to cerebellum, although their expression is particularly dense in limbic nodes like the hippocampus and amygdala (94). GRs are expressed both as cytosolic as well as membrane-found forms, and can therefore act via genomic or non-genomic mechanisms respectively (95,96). Interestingly, GRs are present not just in neurons, but also in astrocytes, oligodendrocytes, endothelial cells and pericytes (97). Their distinct roles in excitatory versus inhibitory neurons may differently affect salience (98) - deletion of GRs in the glutamatergic but not GABA-ergic neurons in the amygdala, for instance, reduced behaviours with exaggerated negative salience processing, like fear and anxiety (98). The second receptor type, mineralocorticoid receptors, are topographically more restricted than GRs, with a significant distribution observed in hippocampus, lateral septum, various nuclei of the amygdala and a few other regions (99). Given the receptor-distribution, therefore, it is not surprising that glucocorticoids can also affect network activity. In *ex vivo* preparations, corticosterone (acting via GRs) has been shown to increase hippocampal gamma oscillations (100,101). *In vivo*, stress affects hippocampal excitability in a temporal fashion on one hand (102), while at a network level decreases the ratio of theta to delta power on the other (103). Together, these imply that glucocorticoids exert an influence on all scales of functional organisation - starting from a cellular to a global, systems level. A unifying view came recently with the characterization of glucocorticoid effects in behaviourally-cued engram cells using an immediate early gene (*c-fos*) based trapping system. Neighbouring cells of the hippocampus equipped with similar glucocorticoid receptors contents produced very different responses to glucocorticoids at the molecular, physiological and structural scales, depending on whether they belonged to the engram network, or not (104). This indicates that the glucocorticoid-mediated response to stressors is cell type specific and cued to its targets' experience and activity (105).

One key molecular interactor of glucocorticoids is the neurotrophin Brain-Derived Neurotrophic Factor (BDNF), a widely studied example of activity-dependent secretory molecule in the brain. A decrease in BDNF has been reported as a biomarker for mood-disorders (106), and lower BDNF levels has been observed in the plasma of PTSD patients too (107). BDNF also directly conditions glucocorticoid signaling in stress-related neuropsychiatric diseases. Within the brain, however, cells produce a variety of responses depending on their state of activity within changing networks, even though receptors and the hormones are readily accessible. This activity-dependent glucocorticoid response of stress varies with the salience of cues from the external and internal worlds. Such a variation is often reflected across different brain areas of stressed rodents, where variable BDNF levels often mimic the direction of plasticity at multiple scales (108–113). Furthermore in this context, the BDNF-Glucocorticoid receptor (GR) phosphorylation pathway provides a complete picture of the coincidence

detection between the two signalling systems, for instructing a stress response fit to the cellular environment (114–116) and thus, processing of salience. So, what are the existing mechanisms that underlie the crosstalk between BDNF and glucocorticoid, and how can we study it?

Interestingly, the BDNF receptor TrkB uses kinases of the MAPK pathway to phosphorylate GR on target serine sites in the transactivation domain (**Figure 1**), while glucocorticoids deactivate the serine/threonine phosphatase PP5 bound constitutively to the receptor (115). Coinciding pathways produce a net effect in favor of increased phosphorylation at the BDNF-responsive serine sites, reflecting a dynamic balance of activities between the kinases and phosphatases which make it a transient effect marked in time. *In vivo*, GR phosphorylation is associated with the learning phase when BDNF and corticosterone reach the same cells, including both c-fos positive pyramidal neurons and parvalbumin interneurons (114). These sites also serve as binding sites for protein cofactors like CREB1 to instruct downstream effects (117). While this mechanism is likely to occur in any cells equipped with the appropriate actors, yet the activity-dependent release of BDNF makes an appealing case for an activity-dependent glucocorticoid response being distinct from that of non-phosphorylated GR. Intriguingly, 60% of GR was observed to be phosphorylated at the BDNF-responding sites following 30 minutes of stimulation *in vitro*— indicating not a black-and-white effect but a far more complex relationship. So, what happens if these crucial BDNF-responsive serine sites in GR transactivation domain are deleted? It was observed that deleting these sites impaired encoding and retention of memory during the learning phase, with no discernable effects in absence of learning (114). This suggests activity-state-dependent effects of glucocorticoids in cells are part of an engram, as compared to the neighboring engram-negative cells (104). However, beyond cellular mechanisms, these effects of glucocorticoids in relation with BDNF are far less understood at the network level, although correlative data provide ground for speculation (118). Traumatic stressors (chronic, inescapable, social or extreme) tend to suppress the neurotrophic pathway in the cortical areas processing sensory information, decision making and contextual memory, whereas it would strengthen the neurotrophic pathway in regions encoding for emotional expression and anticipatory prediction-error system like the amygdala and ventral tegmental area (VTA). As GR is expressed in pyramidal neurons and parvalbumin interneurons of all these regions where phosphor-GR is most abundant, it is speculated that GR activity could vary accordingly in these brain areas – an idea that needs to be explored in future research.

Finally, what can be learned from the versatility of the BDNF-GR interaction? Can BDNF mimetics influence GR activity? If so, could it specifically influence an engram network? A reduction in GR activity in dorsal hippocampus due to chronic stress (quantified by temporal monitoring of a luciferase reporter tagged to glucocorticoid responsive element (GRE)) is accompanied by a reduction in GR phosphorylation (116) - both of which can be restored upon fluoxetine treatment (a classical antidepressant that acts via BDNF (119–121)). Indirect evidence also backs a role of GR-phosphorylation in affecting emotionally salient experiences: a pharmacologically-induced increase in anxiety is accompanied by a decrease in GR-phosphorylation, and both can be rescued by activating the BDNF-pathway (122). Furthermore, mice expressing Val66Met mutation (a human variant strongly linked to stress-induced neuropsychiatric diseases) provides additional argument, wherein GR-phosphorylation in cortex and hippocampus is diminished cued to behavioural experience, as we will discuss later (114,115). This latter observation is also cued to neuronal activity, given that the Val66met variant impairs activity-dependent secretion of BDNF and adaptation to stress (123). All these lines of evidence point towards future research which needs to focus more on studying the dynamics of glucocorticoid activities, rather than simply relying on glucocorticoid levels, receptor expression and their subcellular distribution. Such insights will help us better understand precise BDNF-GR interactions at the highest resolution with behavioral precision,

more so in the context of PTSD. Beyond such a role, yet another intriguing aspect of glucocorticoid function lies in its therapeutic potential to ameliorate stress effects. We next focus on glucocorticoid-targeted strategies that alleviate stress response by taking a closer look first, in the amygdala and then, in the cortex.

Reaching the ups and downs in stress salience with glucocorticoids in the amygdala

As the action of glucocorticoids sets in during stress, the level of extracellular glutamate increases across brain regions, including the hippocampus (124) and the amygdala (125). Given enough time, the amygdala gets sensitized such that pharmacologically blocking glucocorticoid signalling in the rodent BLA prevents stress-induced behavioural deficits (126). This suggests that stress-initiated, and glucocorticoid-dependent changes in the amygdala is a key factor that contributes to disrupted salience in PTSD. Intriguingly, these very same emotional symptoms can also be ameliorated in PTSD patients by using glucocorticoids as a drug. Indeed, a seemingly counterintuitive set of clinical studies since the early 2000s have consistently documented a role of the glucocorticoid analogue hydrocortisone in treatment of PTSD symptoms (16,127–131). But if stress (and thus glucocorticoid secretion) sensitizes the amygdala and disrupts stress-salience (by increasing anxiety, for instance), how does a second, additional dose of glucocorticoid revert it?

To address this question, a set of recent studies used glucocorticoid-based intervention strategies within the time-period *after* stress, using the same 2-hour acute immobilisation stress paradigm described previously. As mentioned before, such acute stress increases both anxiety-like behaviour and density of dendritic spines on BLA excitatory neurons 10 days later (30,33,35,52,132,133). This increase in amygdalar morphological plasticity is a known neuronal correlate that accompanies an enhanced state of anxiety (48). Within this experimental framework, a first study employed an indirect strategy in which stressed male rats received oral gavage of vehicle 1 hour after acute immobilisation (33). Oral gavage, being a stressful manipulation in itself, led to a systemic elevation of corticosterone (33). Quite remarkably, this single dose of gavage (and thus, the additional post-stress surge of corticosterone) was sufficient not only in preventing the delayed increase in anxiety-like behaviour, but also in reversing the enhanced spine density within the BLA (33).

In a second study built on these observations, stressed rats received an oral dose of corticosterone in drinking-water 24 hours after acute immobilisation (35). Interestingly, this direct treatment with glucocorticoids as late as 1 day after stress could successfully prevent the increase in anxiety on the elevated plus-maze on day 10 (35), thereby reversing stress-altered salience. As the plus-maze measures anxiety of an animal in a non-social context, could it be that the treatment effects also extended to social correlates of anxiety? It does, as testing the corticosterone-treated (Cort-treated) rats on a juvenile social interaction test 10 days after stress showed a significant rescue of the social deficit as well (35). This suggests an ability to now correctly process salience for both social and asocial behavioural contexts upon Cort-treatment, despite prior stress. These observations are also in accordance with work by Cohen and colleagues, who report that administration of antidepressants (134), benzodiazepines (135) and atypical anxiolytics (39) after predator scent stress (PSS) all effectively reduced anxiety-like behavior on the plus-maze, while antidepressants like ketamine (136) or β -adrenoreceptor blockers like propranolol (137) failed to do so. Specifically in support of a therapeutic role of glucocorticoids, systemic dose of hydrocortisone given 1 hour after PSS or a low-pressure blast wave was sufficient in preventing anxiety-like behavior (17,138,139). Could elevation of corticosterone by other stressful experiences also exert similar protective effects? Indeed, sleep

deprivation after stress, another perturbation which enhances corticosterone (140), successfully prevented the delayed increase in anxiety due to PSS (141). Even more remarkably, post-stress glucocorticoid treatment corrected morphological plasticity too. While hydrocortisone injection after PSS reversed spine loss in the dorsal dentate gyrus (17), oral corticosterone 24 hours post-acute immobilisation reversed increased spine density in the BLA of the same animal in which it also reversed anxiety 10 days later (35). Subsequent investigations in the latter study revealed that while vehicle-treated stressed animals showed a lasting elevation in corticosterone levels, Cort-treatment 24 hours afterwards could successfully prevent this surge and bring it back to baseline (35).

How do such preclinical findings align with reported clinical observations? While trauma affected individuals also show elevated glucocorticoids soon after (142,143), PTSD patients are known to have suppressed internal glucocorticoid levels (144) as well as an overactive inflammatory response (145). Interpreting these lines of evidence together leads us to predict that post-trauma glucocorticoid therapy works at three levels. We firstly predict that glucocorticoids break a further stress-enhanced increase in its levels by engaging inhibitory mechanisms, possibly via endocannabinoids and/or GABA-ergic signaling pathways, by modifying the negative feedback on HPA axis at the level of the pituitary. This could be mediated by upregulating inhibition via GR-dependent endocannabinoid signalling, GABA_A-signalling, or both. Such a homeostatic ‘correction’ protectively incubates against future stresses, as oral corticosterone given even *before* the onset of stress also protects against a subsequently delivered acute stressor (31). Secondly, post-stress application of glucocorticoids may lead to a desensitization of GRs, thus re-stabilizing GR-mediated signaling and correcting the stress-induced deficits. That would depend on the cellular past and present history of activity in their network and the typical molecules that would be engaged in plasticity-related processes (BDNF, endocannabinoids, neurosteroids etc.) for resetting cellular homeostasis to the new environment. And finally, hydrocortisone treatment in PTSD patients has been shown to reduce levels of the interleukin IL-6 (16,146), signifying a correction of stress-induced inflammatory responses too. We hypothesize that it is these set of actions which collectively contribute towards the beneficial effects of post-stress glucocorticoids, in an individual who has been exposed to trauma.

Integrated into the above framework lies the fact that a common aim of treatment strategies would then be to reverse the enhanced excitation in the amygdala. Of note in this regard is the fact that the activity-dependent neurotrophin BDNF is also upregulated in the stressed amygdala (91), paralleling an increased state of excitation (**Table 1**). So does post-stress glucocorticoid also reverse BDNF levels? While that remains to be explored in the BLA, we do know that post-stress hydrocortisone reverses the *depleted* BDNF pool in the hippocampus (147). Additionally, post-stress Cort may also upregulate inhibition by GR-dependent activation of endocannabinoid signalling, thus putting a brake on stress-enhanced glutamate release (148,149). Endocannabinoid levels, particularly that of Anandamide, is significantly reduced in a stressed amygdala (150), contributing to a shift of the excitatory-inhibitory balance leftwards (more excitation). Not surprisingly, bypassing glucocorticoids and directly augmenting Anandamide in the BLA was found to be equally effective in preventing the delayed increase in amygdalar spine density (133). A third possibility suggests involvement of GABA_A-receptor (GABA_A-R) mediated signalling to offset the excitation-inhibition disequilibrium. On one hand, positive allosteric modulators of GABA_A-R like allopregnanolone, a neurosteroid, have been found to be reduced in PTSD patients (157,158). In animal experiments on the other hand, not only have neurosteroids been shown to enhance tonic inhibition via GABA_A-R (159–162), but level of neurosteroids have also shown to decrease due to stressors like social isolation (163). Interestingly, a reduction in allopregnanolone levels also follows a reduction in the

endocannabinoid N-palmitoylethanolamine (PEA) and its receptor peroxisome-proliferator activated receptor-alpha (PPAR-alpha) (164). Integrating this into our present discussion leads to the prediction that post-stress glucocorticoids may also have stimulated the synthesis of PPAR-alpha mRNA via activation of GRs (165). This, in turn, may have reversed levels of allopregnanolone, rescued stress-induced deficits in GABA_A-R signalling, and corrected the excitation-inhibition disequilibrium. Apart from endocannabinoids, another possibility is that glucocorticoids could also directly upregulate functional plasticity of inhibitory neurons (115). In sum, it is such a correction of the excitation-inhibition disequilibrium in the amygdala that would enable an individual to now optimally process salience again (150). Negating the hyperactivation of amygdala by muscimol (a GABA_A agonist), direct inhibitors of glutamate signalling or by upregulating endocannabinoid signalling has been very frequently shown to counteract stress-induced plasticity and behavioural changes (52,150–153). Interestingly, targeting some of the above described pathways have shown promise in clinical trials too. Glucocorticoid treatment has not only been recently suggested as one of the most promising lines of pharmacotherapy in PTSD (130,154), but both glucocorticoids and Anandamide have also been implicated in reducing fear in humans (155,156). Synthetic allopregnanolone analogues, on the other hand, have been shown to be effective in the remission of post-partum depression, and early evidence suggests its beneficial effects on major depression as well (162). This opens up multiple therapeutic strategies lying at the interface of steroid hormones and endocannabinoid signalling that may hold future promise in correcting salience defects in PTSD.

Finally, an opposite perspective on PTSD and pharmacotherapy is presented within the cortex/hippocampus where chronic stress itself weakens plasticity. What interactions occur between glucocorticoid and neurotrophin signalling in these brain regions? And what clues can it provide to better our understanding of stress salience in PTSD? To obtain an answer, exploring these dynamics in superficially located cortical areas might allow us to directly reconnect functional and morphological plasticity by *in vivo* imaging strategies.

Priming of glucocorticoids receptors in the cortex: a code for stress-salience

Tracking dynamics of dendritic spines in real time by using 2-photon microscopy provides visual precision on neuronal plasticity that is technically limited by the depth of accessible neuronal tissue. One such region which could be studied is the primary motor cortex - an area that is involved in motor skill learning. Interestingly, stress-induced deficits are also observed in motor skills. PTSD patients, for one, report impaired verbal learning and memory as well as reduced psychomotor speed (166). In parallel, stressed rodents also show deficits in motor learning when tested on the accelerating Rotarod test (167–169).

Within this brain region of interest, a set of recent investigations first tested naïve, unstressed mice who could successfully retain skills of a motor task (trained on the accelerating Rotarod test) on subsequent days of recall. More importantly, this recall was paralleled by an increase in newly formed dendritic spines in the motor cortex (114). At a molecular level, GRs showed an increased phosphorylation specifically at two BDNF-dependent sites in naïve mice who showed normal motor skill retention and spine dynamics. Interestingly, when subjected to 10 days of chronic unpredictable stress, this site-specific phosphorylation of GR by BDNF was found to be disrupted (115) (**Table 1**). Blocking BDNF signalling or GR-phosphorylation led to the same outcome as stress, suggesting that the effects of stress result from an inhibition in the interaction of these two molecular species. Conversely, treatment with fluoxetine, a classical anxiolytic, was found to rescue this defect and increase phosphorylation at the same GR residues (115). This process, dubbed ‘priming’ of GR by BDNF, was hence concluded to

contribute towards the adaptive effect of glucocorticoids by specifying the transcriptional response outcome (170)

The impact of disrupted neurotrophic priming of GR span other scales of plasticity too. The same chronic unpredictable stress that disrupted GR-priming also caused a significant loss of dendritic spines *in vivo* in the motor cortex (114). These spines were specifically formed in response to motor learning, and thus were experientially-tagged. Coupled with their loss, therefore, was also an inability to retain a previously acquired motor skill (114). To mimic the effects of stress next, a knockin deletion of BDNF-dependent phosphorylation sites in mice was generated to suppress the priming of GR. In these animals, serine-to-alanine mutations were created within exon 2 of GR, in the BDNF-dependent phosphorylation sites S152 and S284 (mouse numbering scheme, S134 and S267 in humans). This impeded the phosphorylation of GR by BDNF, thus preventing a cell autonomous specification of the transcriptional response outcome. Predictably, knock-in phospho-deficient mice recapitulated the above described patterns of cellular and behavioural deficits even in the absence of stress. These animals showed not just impaired skill-retention, but also loss of newly-formed spines and exaggerated spine elimination (114). There were deficits in long-term plasticity too: while trained wild-type mice showed an occlusion of long term potentiation (LTP) in the motor cortex (suggesting a ceiling-effect due to previous training/learning), successive trains of stimulation could still induce LTP in knock-in mice beyond the ceiling effect of wildtype controls (suggesting lack of any plasticity due to learning itself, and thus room for additional plasticity to occur) (114). To precisely test plasticity consequences on single dendritic spines, local uncaging of glutamate evoked a significantly slower rate of spine enlargement in trained knockin phospho-deficient mice as opposed to wild-type animals (114). Remarkably, glutamate-evoked enlargement shown by wild-type mice could also be blocked by a GR antagonist delivered *before* training, but not after – a deficit that was occluded in the knock-in phospho-deficient mice (114). Thus, there exists a critical window *when* the priming of GR is necessary and crucial. It is within this temporal period that GR-priming shapes the detection of salient cues that are relevant to the context. But if indeed priming of GR by BDNF is crucial to functional plasticity, would a deficiency in BDNF *also* recapitulate similar effects?

To address this final piece of the puzzle, another transgenic mouse model that manipulates expression of BDNF was studied. These mice carry a single nucleotide polymorphism (valine to methionine) in the pro-domain of the precursor form of BDNF, which impairs its sorting and packaging in vesicles for activity-dependent release from neurons (171,172). Interestingly, human Val66Met carriers show memory deficits, reduced hippocampal activation (173) and could also show increased vulnerability to and enhanced symptomatology of PTSD (174,175) (but also see (176,177)). Transgenic mice expressing Val66Met show very similar traits, including decreased dendritic arbours of hippocampal neurons, impaired long-term potentiation, impaired recall of memory and increased anxiety-like behaviour (173,178). Low BDNF levels in these mice would predict a deficiency in priming of GR. And indeed, Val66Met mice do display reduced phosphorylation of GRs at the BDNF-dependent sites (114). Furthermore, these animals have impaired memory retention and decreased survival of learning-associated new spines in the motor cortex (due to exaggerated elimination of dendritic spines) (114), mirroring the same cellular and behavioural patterns of change described above with stress.

A key fact to be noted is that naive knock-in GR phospho-deficient mice do not show any baseline deficits in morphological plasticity. Rather, it is only when the animals are challenged with a task that the impaired spine dynamics emerge, thus suggesting two things. First, it implies that experience of the challenge demanded an activity-dependent release of BDNF, which being insufficient in these animals, resulted in the deficit. It secondly implies that the priming of GR

is crucial only when salient, contextual information is acquired, but not at a baseline state. These conclusions allow us to further hypothesize that phosphorylation of GR serves as a molecular signature of stress-salience. In fact, the presence or absence of this precise molecular interaction can robustly predict normal or disrupted processing of salient learning cues. Neurotrophic priming of GR, therefore, gives rise to the cross-talk between glucocorticoids, neurotrophins and neuronal plasticity in stress and PTSD.

Sex as a biological variable

A significant bias in the current neuroscience research lies in a large predominance of studies focussing primarily on male animals (179). This often arises from a wrongful notion that circulating estrus hormones result in more variable data in females than males (180). It is necessary to address this bias, as both sexes do not respond to the same behavioural challenge (like stress) in the same way. For instance, the same acute stress that causes delayed anxiety in males does not do so in female rats (34), and the same stress which enhances fear learning in males only disrupts the innate cyclicality of fear learning in females (181). Interestingly, there also lies an intrinsic difference how both sexes express fear, with female rats being more likely to ‘dart’ instead of freeze as compared to their male counterparts (182). Does this imply intrinsic neurophysiological differences between both sexes too?

Indeed, while intermittent tail shocks decreases apical dendritic spines in the dorsal hippocampus of proestrus female rats, it increases spines on the male hippocampal neurons (183). A similar contrast exists in the amygdala too. Reports indicate that acute stress does not affect synaptic excitation in the amygdala of female rats (34), while repeated stressful experience decreases the firing rate of lateral amygdala neurons (181) (both acute and chronic stresses *increase* excitation in males (34,181)). Furthermore, repeated stress *decreases* dendritic arborisation of lateral amygdala neurons in female rats too, in sharp contrast to the *increase* observed in males (181). This points at sharp gender differences at the level of circuits which regulate anxiety, fear and extinction (184). Could then pharmacological interventions to mitigate PTSD also have a gender bias? Clinical studies involving post-trauma glucocorticoids have often included patients of both genders in their study cohort (16,131), indicating the efficiency of such an approach for both sexes. In support of this, administration of hydrocortisone 1 hour after PSS was found to rescue delayed anxiogenesis in both sexes (185). The underlying cellular mechanisms, however, might still be gender-specific. Systemic elevation of the endocannabinoid Anandamide, for instance, impairs fear extinction in female rats while not affecting males (186). Moreover, treatment with the GR-agonist dexamethasone triggers a gender-specific expression of target genes, albeit in the liver, leading to a sex-specific difference in the cellular stress response of both sexes (187). Together, these emphasise on the importance of addressing sex as a biological variable in all future studies of stress-disorders, more so because female individuals are more susceptible to not only PTSD but mood disorders in general as well (188).

Concluding remarks and future studies of the stress-salience hypothesis

We summarize that the eventual outcome of salience misprocessing seen in animal models of PTSD starts from a single common point. Stress interacts with the homeostatic experience-dependent processes that integrate salient cues from the external and internal worlds to adapt. This, for instance, is clearly evident in the unique response of glucocorticoids in engram cells, where hormonal signalling intersects with neuronal activity and plasticity mechanisms at the molecular and cellular levels (104). Evidence suggests a key role of BDNF-GR interaction in this process as well, which is thought to impact multiple layers of downstream pathways

(epigenetic, transcriptomic, synaptic plasticity). These can eventually feedback directly or indirectly through the cellular networks (excitation-inhibition balance, neurosecretions of hormones, peptides and neurotransmitters, and so on), and are regionally and temporally determined by past, present and future behavioural experiences. Integrated at a network level, the interaction between hormonal response and activity-dependent signalling should adjust the coding of stress-salience across a diverse range of aversive and appetitive tasks (**Table 1**). This process of coincidence detection between neuronal and hormonal activities can go awry in many ways, which means it could also be corrected in many ways. In this context, while clinical and preclinical studies indicate that post-stress interventions are effective across both genders, only do stress-coping strategies vary between males and females (189,190), but stress also engages divergent sex-specific circuits and mechanisms (191,192). Thus, a critical factor which orchestrates stress-salience is gender, and a significant proportion of investigations into PTSD and its treatment should be dedicated to this in the near future.

When considering pharmacotherapy in PTSD, timing, in fact, is of crucial importance, especially with glucocorticoids. We hypothesize that correct timing-based intervention with glucocorticoids could not only desensitize receptors in a hyperactive amygdala but also re-sensitizes receptors throughout the hypoactive regions like cortex and dorsal hippocampus. Exogenously delivered glucocorticoid could, at a systems level, also alter the innate diurnal oscillation of glucocorticoids, whose trough and peak are essential for long-term retention of memory and acquisition phase, respectively. Excess corticosterone during such a trough following learning disrupts long-term memory, reduces the formation of learning-associated new spines and decreases spine pruning (193). It is likely that post-stress glucocorticoids, which was in fact delivered through the diurnal oscillations, also corrected dendritic spine plasticity by a similar process. We also propose that it engages priming of GR by BDNF by elevating the level of this neurotrophin in the hippocampus/cortex, and possibly decreasing its levels in the amygdala – hence restoring the excitatory-inhibitory balance. Underlying such divergent spatial effects are interactions with array of other molecular interactors, including, but not limited, to endocannabinoids and neurosteroids. As a sum of these effects, behavioural salience stands corrected in stressed animals, who now respond within normal limits in behavioural tasks (optimal levels of anxiety on the plus-maze and normal social interaction). Thus the duality of glucocorticoids presents a unique attribute for adjusting plasticity to the context in the realm of PTSD.

Together, we infer that glucocorticoid function is indispensable in both facets of stress-salience (onset and correction), and a generalist view only provides an incomplete picture of its role. Moreover, it is only when additional factors like neurotrophins and endocannabinoids are taken into account does the picture become truly complete. Building on the observations discussed here, future studies should aim at integrating brain-wide quantification of functional plasticity in targeted neuronal subsets by using genetically-encoded cell-type specific trapping tools and GR activity sensors. These approaches hold promise for addressing the many questions which still persist in our current understanding of stress-salience. For instance, do different rules of plasticity apply for different kinds of salient cues (stress-induced decrease in food reward versus social reward, for example)? Can brain-wide circuits *predict* the gradual emergence of salience miscomputation seen in PTSD? How do other markers of stress-induced plasticity, like epigenetic modifications, integrate within our present framework, since subjects who develop PTSD show distinctive patterns of epigenetic changes (altered methylation of the GR gene (194) as well as the GR-regulatory gene *FKBP5* (195))? How would, then, novel and promising modes of pharmacotherapy (like pharmacological inhibitors of epigenetic modifications that reduce fear (196)) alter functionality in the salience pathways? We finally propose that instead of adopting a single broad approach, future therapeutic strategies could

benefit from targeted correction of brain-region specific correlates of neuronal function that underlie specific defects in processing salience, in a sex-dependent manner. And we also believe that future investigations would be empowered by a strengthened dialogue between cutting-edge preclinical findings and contemporary clinical advances. Only then will it lead to a unifying synthesis of ideas, providing directions on how to combat not just PTSD, but perhaps all stress-related psychiatric conditions.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

P.C., S.C and F.J. conceptualised the manuscript. P.C. and F.J. wrote the manuscript.

List of abbreviations

BDNF – Brain-derived Neurotrophic Factor

BLA – Basolateral Amygdala

Cort – Corticosterone

GR – Glucocorticoid receptor

IL-6 – Interleukin 6

LTP – Long Term Potentiation

PFC – Prefrontal cortex

PTSD – Post-Traumatic Stress Disorder

TrkB – Receptor Tyrosine kinase B

Figure Legend

Figure 1 – Stress-altered salience and neurotrophic priming. Stress activates different arms of the BDNF/GR signaling, chiefly moderated by a decrease in BDNF in the cortex/hippocampus (*left*) and an increase in its levels in the amygdala (*right*). BDNF could also independently affect transcription and plasticity. Together, these result in behavioral rigidity (eg., impaired spatial memory in a water-maze) as well as behavioural maladaptation (eg., increased fear and anxiety), together giving rise to altered stress-salience. This is accompanied by opposite effects on neuronal plasticity, involving a weakening of morphological plasticity and synaptic depression in the hippocampus, and by contrast, an overall strengthening of plasticity in the amygdala. *GR* – *Glu cocorticoid receptor*, *Cort* – *Corticosterone*, *TrkB* – *Receptor Tyrosine kinase B*.

Data sharing statement

Figures are available online in a public access repository.

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Table 1: Divergent effects of chronic and acute stress on the amygdala, hippocampus and cortex in animal models, and their reversal by pharmacological strategies, as reported/predicted.

Metric analyzed	Stress (Chronic/Acute)		Stress + Pharmacology (Glucocorticoids/ endocannabinoids/ anxiolytics (eg., fluoxetine))	
	Effect	Reference	Effect	Reference
Behavior				
Anxiety	↑	(17,30,199,200,33,34,48,5 2,132,138,197,198)	↓	(17,33,132,138,1 85,198)
Fear	↑	(19–21,23,65,201–203)	↓	(126,208,209)
Social interaction	↓	(35,42,204–207)	↑	(198,210–212)
Motor learning	↓	(115,167–169)	↓	(213)
Physiology				
Excitation in amygdala	↑	(19,52,133,214–216)	↑	(133,149)
Excitation in Cortex/Hippocampus	↓	(80,103,217–221)	↓*	Predicted
Structure				
Dendritic and spines in amygdala	↑	(21,23,133,222,223,30– 33,35,46,49,52)	↓	(31,33,35,133)
Dendrites & spines in Cortex/Hippocampus	↓	(17,21,228,46,60,74,213,2 24–227)	↑	(17,115,213)
Molecular				
BDNF in amygdala	↑	(76)	↓*	Predicted
BDNF in Cortex/Hippo	↓	(17,108–110,199,229,230)	↑	(17)
Phosphor-GR at BDNF-sensitive sites in amygdala	↑*	Predicted	↓*	Predicted
Phosphor-GR at BDNF-sensitive sites in Cortex/Hippocampus	↓	(114,115)	↑	(114,115)

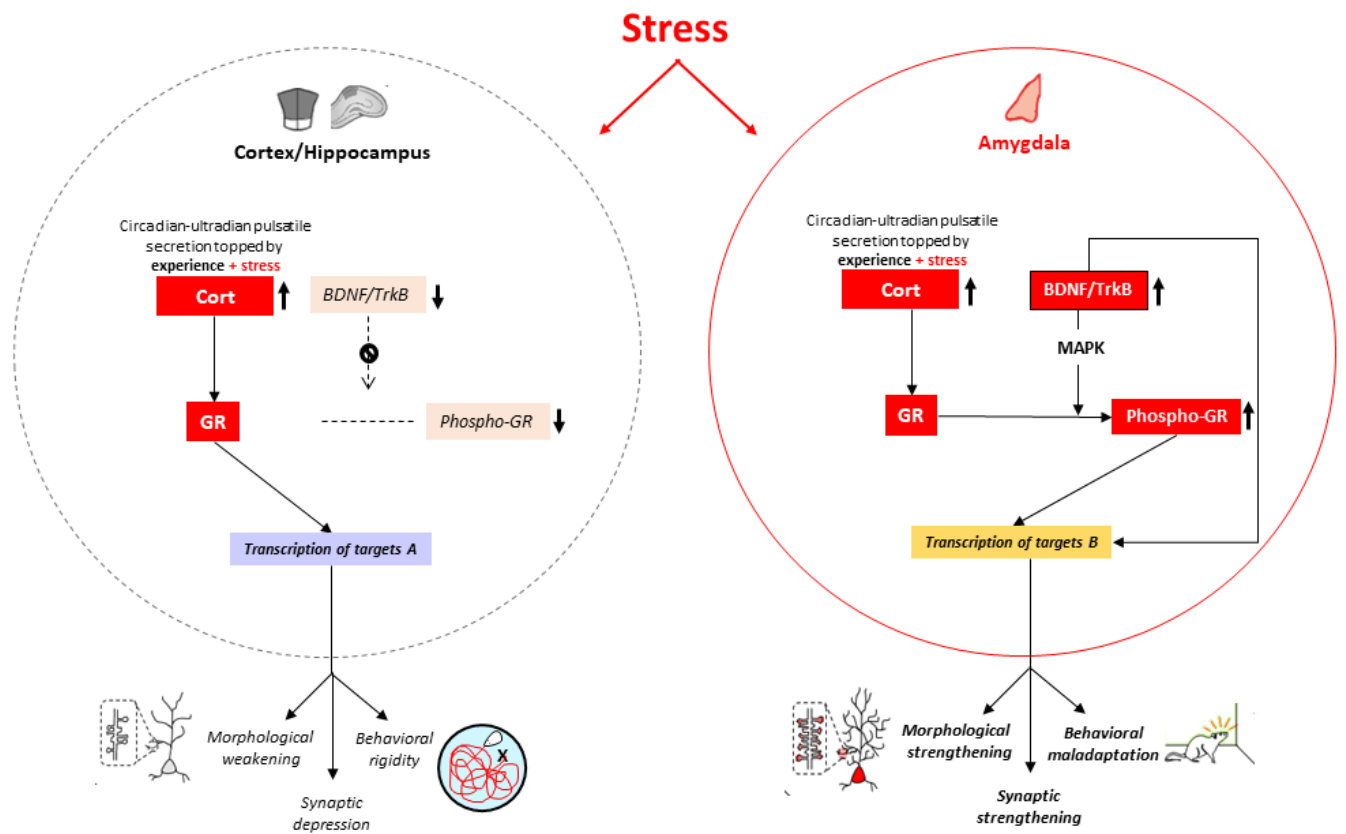


Figure 1 – Stress-altered salience and neurotrophic priming. Stress activates different arms of the BDNF/GR signaling, chiefly moderated by a decrease in BDNF in the cortex/hippocampus (*left*) and an increase in its levels in the amygdala (*right*). BDNF could also independently affect transcription and plasticity. Together, these result in behavioral rigidity (eg., impaired spatial memory in a water-maze) as well as behavioural maladaptation (eg., increased fear and anxiety), together giving rise to altered stress-salience. This is accompanied by opposite effects on neuronal plasticity, involving a weakening of morphological plasticity and synaptic depression in the hippocampus, and by contrast, an overall strengthening of plasticity in the amygdala. *GR* – *Glu cocorticoid receptor*, *Cort* – *Corticosterone*, *TrkB* – *Receptor Tyrosine kinase B*.