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
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# **Fast signaling by glucocorticoids shapes neural representations of behaviors**

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## **Abstract**

Glucocorticoids are stress hormones that play central roles in the immediate and slower adaptive responses of the brain and body to new behavioral experience. The exact mechanisms by which the rapid and slow processes underlying glucocorticoid mnemonic effects unfold are under intensive scrutiny. It is possible that glucocorticoids rapidly modify memory representations in the brain by interfering with synaptic functions between inhibitory and excitatory neurons in a timing and context dependent manner. In particular, activity-dependent trans-synaptic messengers appear to have all the necessary attributes to engage in the rapid signaling by glucocorticoids and regulate the brain and behaviors. Novel frameworks for the treatment of stress-related disorders could emerge from a better characterization of the dynamic interplay between the rapid and slow signaling components by glucocorticoids on large-scale brain networks. Here I present some of the exact factors that could help reach this objective.

## Introduction

Glucocorticoids have robust but complex effects on learning and memory [1]. They can facilitate or deteriorate memory retention depending on timing, dose and duration of exposure [2]. Glucocorticoids trigger rapid non-genomic and slower genomic effects in the brain that yet remain to be functionally integrated with timely behavioral components [3]. Opposite effects on brain and behaviors can be explained by the interaction between glucocorticoids and multiple neurotransmitters systems and neuromodulators [4, 5]. The memory enhancing effects of glucocorticoids follow an inverted U-shaped dose-response relationship. Moderate doses are optimal for brain and behavior compared to too low or too high levels [6]. It is possible that a biphasic response reflects the engagement of multiple binding sites with distinct pharmacological profiles like the high affinity mineralocorticoid receptor (MR) and the low affinity glucocorticoid receptor (GR) [7]. However, this phenomenon is common to most paracrine systems, and a more universal explanation remains unknown. We proposed that pleiotropic effects of glucocorticoids in human and rodent memory consolidation involve multi-sites binding across several types of synapses that shape neural representations of behaviors [8]. Here, I extend the viewpoint of putative synapse-specific glucocorticoid mechanisms of action to the construct of timing and context.

## Molecular and cellular components for rapid glucocorticoid effects

We have used single cell RNA sequencing data made publicly available in the Allen Brain Atlas from the Allen Institute for Brain Science to report on the expression and distribution of signaling components of glucocorticoids, and to help clarify signaling possibilities across brain regions and cell types [8]. A similar approach previously focused on the nuclear regulators for MR and GR [9], and downstream regulated genes [10]. Here, I focus on a selection of potential synaptic components for the rapid signaling by glucocorticoids ([Figure 1](#)).

Rapid non-genomic glucocorticoid effects are well characterized in neuro-endocrine cells [11], in the hypothalamus [12], amygdala [13], hippocampus [14] and cortex [15]. These effects concentrate at the synapse (inhibitory and excitatory) in the amygdala [16], hippocampus [17], cortex [18], hypothalamus [19], where GR and MR are enriched in the forms of cytoplasmic as well as hypothetical membrane-bound receptors [20, 21]. Molecular mechanisms of rapid signaling involve G-proteins, membrane receptors, kinases and phosphatases, changes of local ion concentrations, exchange of gas, vesicular trafficking, GTPases and cytoskeletal remodeling to name a few [22]. In the hypothalamus, some of these components (endocannabinoid-CB1 system) are used by GR to signal the suppression of presynaptic glutamate release while others (Nitric oxide-soluble Guanylate cyclase system) are used to regulate GABA release [23]. The duality of these effects could ensure the accelerator and the brake onto neurotransmission are coordinated. In the hippocampus, another rapid signaling pathway made of kinases facilitates presynaptic neurotransmitter release by a hypothetical membrane-bound MR (mMR) [24-26]. Beyond glutamate and GABA, rapid signaling by glucocorticoids has been shown to interact with several neurotransmitter systems (*e.g* norepinephrine, serotonin, dopamine) to influence specific behaviors [4, 27]. Rapid signaling by glucocorticoids also interacts with the kinase pathway triggered by the neurotrophic factor BDNF for promoting synaptic plasticity at least in the cortex [18, 28].

The levels of GR and MR across cell types are consistent with varying ratios in the whole hippocampus and cortex (Figure 1). Both receptors need to be balanced to work alone and together at the levels of transcriptional regulation [29]. However, the role of the GR versus MR ratio on the rapid signaling by glucocorticoids remains incompletely understood. GR is most abundant in pyramidal neurons (PN) whereas MR is most abundant in VIP interneurons. Non-neuronal cell types can also present with an excess of GR over MR (e.g. oligodendrocytes, microglia and endothelial cells), and a more balanced ratio occurs in astrocytes, smooth muscle and pericytes (Figure 1).

Rapid signaling engaged by MR and GR converges on trans-synaptic *retrograde* messenger systems to influence neurotransmitter release. Synthetic enzymes for endocannabinoids are most abundant in PN and SST cells whereas the CB1 receptors are enriched in VIP cells (CCK subtype) as well as in other cells types at much lower levels (Figure 1). The distribution of these components for the rapid suppression of glutamate release by GR would argue that this mode of regulation favors the PN→PN and VIP→SST connections. However, astrocytes could compensate at the other types of synapses with the expression of the monoacylglycerol lipase (MAGL) to produce local endocannabinoids. Remarkably, the enrichment of nitric oxide synthase (NOS) and its receptor sGC in PN suggests that gaseous control of neurotransmitter release could be favored by PN→PN connections but counter example has been described in the hypothalamus [23].

The *anterograde* trans-synaptic factor BDNF also uses GR as signaling platform to influence the mobilization of AMPA receptors and regulate the polymerization of the actin cytoskeleton in the post-synaptic compartment of cortex [15, 18]. BDNF is mostly made in PN whereas its full-length receptor TrkB is widespread in neuronal subtypes, suggesting that this mode of rapid signaling by glucocorticoids could be enriched in PN→PN and PN→IN (inhibitory neuron) connections. Given that BDNF is secreted in an activity-dependent manner, it also suggests that rapid signaling by GR is conditioned by the state of neuronal activity in the local network. Indeed, mutation of the wildtype BDNF-Val66 variant into polymorphic Met66 variant that prevents activity-dependent secretion of BDNF, phenocopied the impairment of the rapid GR signaling on dendritic spine maintenance and long-term potentiation caused by the mutation of BDNF-dependent GR phosphorylation sites [18].

In absence of neurotransmission, the importance of the retrograde and anterograde messenger systems for signaling by glucocorticoids would be limited. Predominant exploitation of these signaling pathways is expected when neural networks are activated by behavioral experience [30]. For instance, BDNF-dependent phosphorylation of GR occurs in Fos-activated neurons of the motor cortex in response to motor training whereas glucocorticoid-dependent phosphorylation of GR is widespread in the brain [18]. It would therefore be instructive to overlap the expression levels of receptors for various neurotransmitter systems with that of glucocorticoid rapid signaling components (Figure 1). For example, adrenergic receptors are expressed in specific cell types of the whole hippocampus and cortex with  $\beta$ -ADR mostly in PN and  $\alpha$ -ADR mostly in interneurons. Serotonergic receptors are also specifically expressed with HTR3 in VIP cells, HTR2C in SST cells, and HTR2a in PN. The expression of other relevant neurotransmitters systems are described elsewhere [10]. The specific enrichment of receptors in distinct neuron types suggests that norepinephrine and serotonin signaling would intersect with the rapid

signaling components of glucocorticoids at restricted focal points in neuronal networks.

### **Role of the rapid signaling by glucocorticoids on neurotransmission**

The exploitation of *trans-synaptic* messengers ensures that glucocorticoids influence functional connectivity in both the pre- and the post-synaptic sides ([Figure 2 left](#)). The selection of target connectivity in the brain is given by the coupling of glucocorticoid signaling with neuronal activity. This way, low glucocorticoid concentration binds to mMR in order to facilitate glutamate release whereas at higher concentration it also occupies mGR for suppressing it. The utilization of cGR in dendritic spines by BDNF anterograde signaling serves to scale pre-synaptic activity with post-synaptic plasticity at the level of structural dynamics [28], metabolism [31] and long-term potentiation [18].

To clarify the inverted U-shaped mode of action, one must distinguish glucocorticoid impact on excitatory and inhibitory neuronal subtypes *-individually* and *collectively*- in various circuit configurations. The geometry of interneurons innervation at dendritic territories of PN enables network specificity. Parvalbumin (PV) cells innervating basal dendrites are permissive to signal integration from the apical inputs, while somatostatin (SST) cells would enable the opposite because they mostly innervate the apical tufts. Recruitment of the cholecystokinin (CCK) cells innervating the primary apical dendrite should override the SST effects, while the PV cells should override them all. If one-order of inhibition –via PV, CCK or SST cells- filters incoming signals, two-orders of inhibition -through VIP cells- enable raw excitation via disinhibition ([Figure 2 middle](#)).

I envision scenarios in which rapid signaling by glucocorticoids would enforce or weaken functional connectivity based on the network configurations. *Direct* default of excitation at targeted PN cells would justify the attrition of dendritic territories, low BDNF levels and low glucocorticoid sensitivity observed in chronic stress studies [27]. However, *indirect* default of excitation at targeted PN cells relayed by one-order of inhibitory neurons would drive the opposite response [32]. This model is supported by the morphological data on stress-induced dendritic spine loss at the apical tufts of PN in cortex that an artificial activation of PV cells overrides [33]. Therefore, it is possible that the local circuitry could be optimally or poorly engaged by behavioral experience depending on the timing, dose, and duration of exposure to glucocorticoids ([Figure 2 right](#)).

### **Network components for rapid glucocorticoid effects**

The hippocampal micro-circuitry, for example, involves well-established excitatory inputs to DG, CA1 and CA2 from the deep layers of entorhinal cortex (EC), and excitatory outputs from CA1 to superficial layers of EC [34]. Local excitatory circuitry also shunts CA2 to make a DG→CA3→CA1 polysynaptic connection in separate dendritic territories compared to CA2→CA1 and EC→CA1 projections ([Figure 3](#)). Local inhibitory cells are also recruited by the excitatory cells to increase control of neurotransmission at each level of the polysynaptic circuit. In CA1, rapid signaling by GR increases spontaneous inhibitory currents in PN via the retrograde release of NO from PN to CCK cells, which in turn, increase GABA release on PN soma and CCK release on PV cells to further enhance their activity on PN soma [32].

Regional expression of GR and MR in the hippocampus is also likely to modify how the local micro-circuitry responds to the rapid signaling by glucocorticoids. If GR and MR levels are equivalent in CA1, MR is almost exclusive in CA2, and predominant in CA3 and DG subfields (Figure 3). Consequently, excitatory PN→PN connections from CA2→CA1 distinguish from that of CA3→CA1 and EC→CA1 by the GR versus MR ratios across synapses, and also by their innervation territories in CA1 (*e.g.* stratum orientes, radiatum or lacunosum). Such regional differences in expression patterns provide anatomical boundaries for the engagement of rapid glucocorticoid signaling components in selective parts of neuronal networks.

One consequence is that rapid signaling by glucocorticoids enforces or weakens the allocation of neuronal networks to a specific behavioral experience. During learning, rapid glucocorticoid signaling increases the number of DG cells allocated to the acquisition of contextual fear. This so-called “engram network” composes with a mixture of excitatory and inhibitory neurons [35]. However, during retrieval, rapid glucocorticoid signaling decreases the excitability of DG cells prior allocated to the acquisition of contextual fear, and thus their reactivation on memory replay [36]. This decrease of excitability in DG engram cells could take multiple forms, with the recruitment of inhibitory cells in real time to silence memories [37], and/or the prior production of gene products that lower the threshold of excitability as previously suggested [38, 39]. This phenomenon has important consequences for the encoding, retention and retrieval of contextual memory precision by the hippocampus [40, 41].

### **Systems components for rapid glucocorticoid effects and clinical relevance**

I then further zoom out of hippocampal circuitry to discuss its integration with other connected brain regions (Figure 4). Retrieval of memory representations dependent of hippocampus are expected to provide the contextual precision of episodic memories [42]. In contrast, neural representations independent from hippocampus but dependent of cortical regions are associated with degraded memories because they lack the precise details of the learning context while retaining the central theme of the event, in part due to the mistiming of glucocorticoids signaling with neural activity in the arousal norepinephrine system [43]. This is particularly true for emotional memories, better remembered with glucocorticoid surge (*e.g.* induced by stress). For example, injection of glucocorticoids with the  $\alpha$ -adrenergic antagonist Yohimbine prevents the enhancement of object recognition memory in the emotional arousing context of novelty but not if animals were prior habituated to the context chamber, and therefore less emotionally aroused [44]. Roozendaal and colleagues have speculated that glucocorticoid injection enhances the effect of norepinephrine on the consolidation of emotional memory but at the cost of accuracy by disengaging the hippocampus from the amygdala functional network while engaging cortical areas [43]. On the contrary, injection of norepinephrine in the amygdala consolidates memory precision by enforcing the engagement of the hippocampus with the amygdala functional network [45]. It is further expected that in conditions of supra-normative elevation of circulating glucocorticoid concentration or reduced expression of glucocorticoid receptors or its desensitization for extended periods of time (*e.g.* glucocorticoid resistance) prior acquisition of new emotional memories would alter the engram network allocation toward cortical regions independently from the hippocampus, and thereby facilitating the storage of imprecise generalized memories (Figure 4).

Imaging of the human brain during emotionally charged memory tasks implicated stress hormones (e.g glucocorticoids and norepinephrine) in the shift of memory systems from cognitive-to-habit by acting on large-scale neural correlates [46, 47]. Notably, acute stress promotes the utilization of a *salience network* linking the hypothalamus, amygdala, cingulate cortex, striatum, and inferotemporal regions for threat processing over the utilization of a *central executive network* consisting of the prefrontal and parietal cortices for goal-directed decision-making [48]. A shift of responses from cognitive goal-directed toward more compulsive habit-directed could overtime trigger stress coping responses unfit with the experience and even become pathogenic in vulnerable individuals due to a loss of self-control when making emotional choices under duress. Resting state imaging studies also reported effects of stress and glucocorticoids on functional connectivity in the *default mode network* that assembles large distributed regions of the association cortex with reduced activity during attention-demanding tasks relative to steady state for integrating new information with existing knowledge [49]. Rising glucocorticoid levels associate with increased functional coupling in sensory salience detection systems and promote performance improvement in subsequent attention tasks [50]. Chronic stress uses glucocorticoids to switch the configuration of neural systems at play from a default cognitive executive network to a *compulsive habit network* that integrates dorsal striatum, cortical and subcortical projections forming an emotional-reward-habit system. This shift is reverted by successful antidepressant treatment and normalization of circulating glucocorticoid levels [51, 52]. Therefore, the modification of the rules of engagement of specific neuronal networks by glucocorticoid rapid signaling has implications for discriminating between vulnerability and resilience to stress-related neuropsychiatric disorders and neurodegenerative diseases [53, 54]. For example, susceptibility to post-traumatic stress disorders could be due to the increased generalization of fearful memories by the rapid glucocorticoid effects [55].

## Conclusions

Novel frameworks for the treatment of stress-related disorders will emerge from a better characterization of the dynamic interplay between the rapid and slow signaling by glucocorticoids on large-scale brain networks [3, 30]. Targeting the rapid signaling by glucocorticoids could have more profound effects than targeting the slow genomic signaling components, as they are upstream and intertwined [56]. Clinical studies for the treatment of phobia with synthetic glucocorticoids during specific memory phases of extinction learning are very encouraging examples of the recent developments [57].

**Declaration section.** The author has no competing interests to declare that are relevant to the content of this article.

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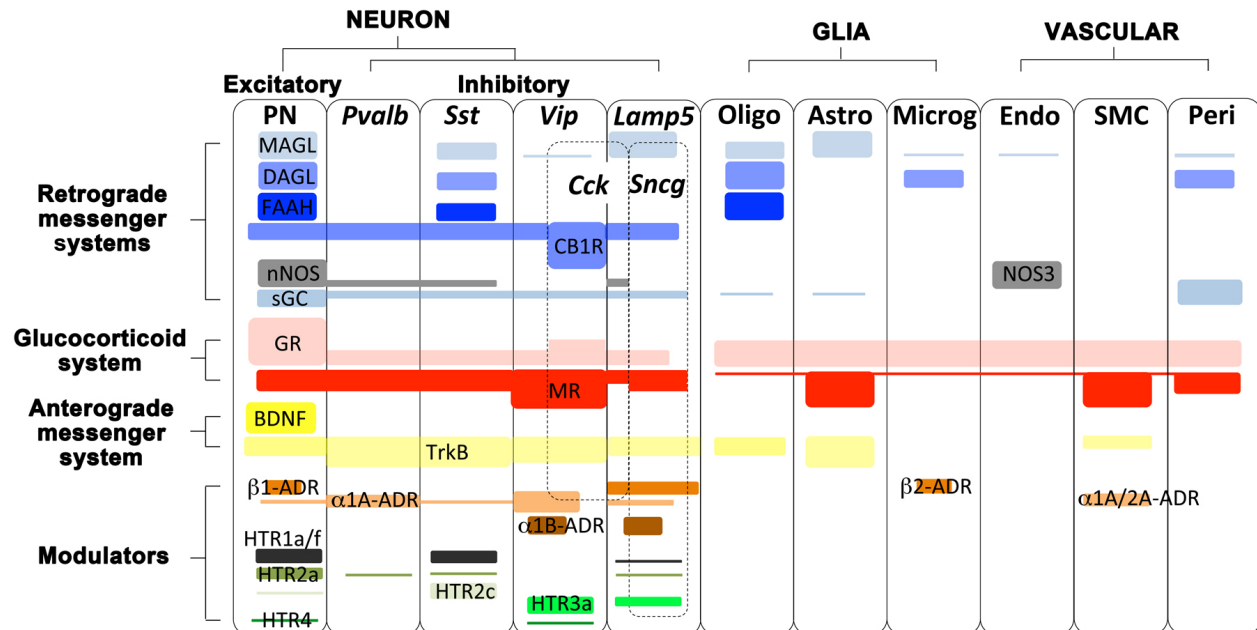
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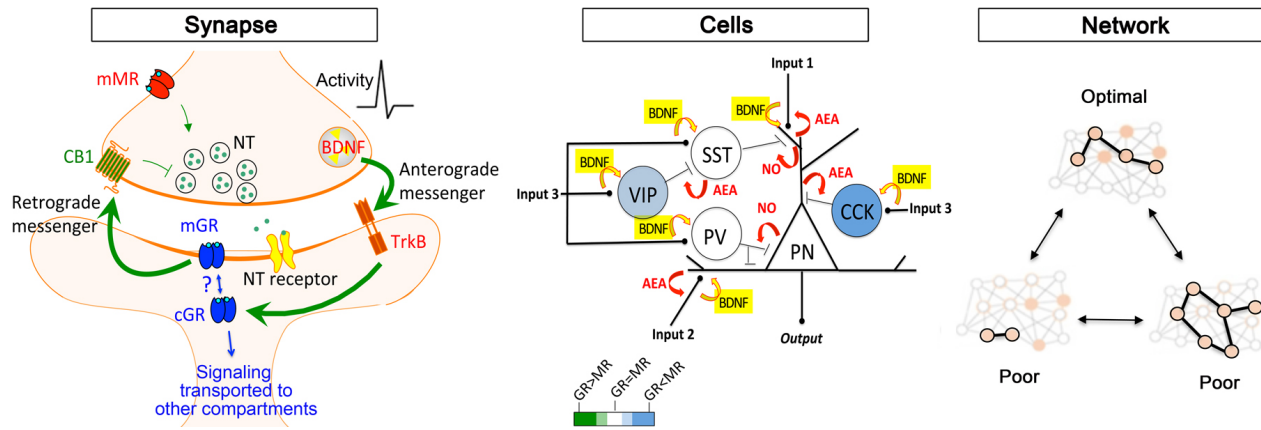
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## Figures



### Figure 1. Expression patterns of synaptic signaling components for glucocorticoids

Steady state RNA expression of the indicated genes in the mouse and human whole hippocampus and cortex based on the Transcriptomic Explorer Brain Map at the *Allen Institute for Brain Science*. Genes are categorized by systems according to their functional attributes. GR are more abundant in principal neurons (PN) than in interneurons and non-neuronal cells. MR are highest in interneuron subtypes and also in astrocytes, smooth muscle cells and pericytes. Co-expression within the same cells and projection neurons creates a variety of GR-MR ratio on each side of the synapse. Components of retrograde synaptic signaling exploited by the fast glucocorticoid actions are abundant in all cell types with nitric oxide synthase (NOS) isoforms and its receptor, the soluble guanylate cyclase (sGC) while endocannabinoids synthesis enzymes [Monoacylglycerol lipase (MAGL), Diacylglycerol Lipase (DAGL), Fatty Acid Amide Hydrolase (FAAH)] are highest in PN and SST cells with its receptor (CB1R) found in VIP, CCK and PN cells. Endocannabinoid synthesis enzymes are also high in oligodendrocytes, and selective isoforms expressed in other non-neuronal cells. Neuromodulators conditioning the fast glucocorticoid behavioral response like adrenergic receptors are present in PN ( $\alpha 1a/\beta 1$ -ADR) and inhibitory cells ( $\alpha 1a$ -ADR in all and  $\alpha 1b$ -ADR in VIP); others like the neurotrophic factor BDNF is exclusive of PN while its high-affinity receptor TrkB is in all types (truncated isoforms TrkB.T1 and TrkB.T2 dominate in astrocytes); serotonin receptors equip all types of neurons (HTR1a/f in PN, HTR2c in SST cells, and HTR3a in VIP, LAMP5 cells).

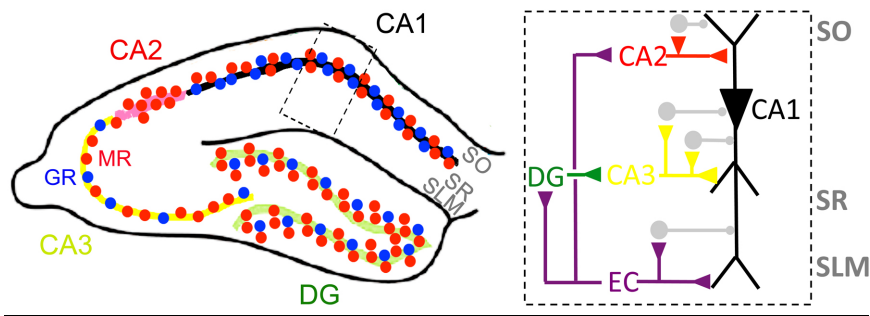


**Figure 2. Role of fast signaling by glucocorticoids on neurotransmission**

*Left:* Rapid glucocorticoid signaling must be studied on the scale of the synapses, cell types and neural networks to comprehend pleiotropic actions on brain and behaviors. Neural activity engages neurotransmitter (NT) release and plasticity within minutes, with the recruitment of trans-synaptic messengers (anterograde and retrograde) that scale the response on both sides of the synapse. Glucocorticoids act on a hypothetical membrane-associated receptor (mGR) that engages kinase-phosphatase pathways to increase endocannabinoid-mediated suppression of presynaptic NT release, and use the neurotrophic factor BDNF as anterograde signal to strengthen the post-synapse via kinase-phosphatase pathways converging on the cytoplasmic GR (cGR) and the actin cytoskeleton. Both mechanisms converging to and diverging from GR update signaling possibilities to the ongoing biochemical environment modified by neural activity. This is made possible though the allosteric remodeling of GR protein-protein interaction N-terminal domain [56]. Then, GR assembles a platform of dynamic signaling components that moves to other subcellular compartments. In the nucleus and mitochondria, slower responses take form with the recruitment of transcriptional effectors ordered to adjust metabolism and biomass with the experience.

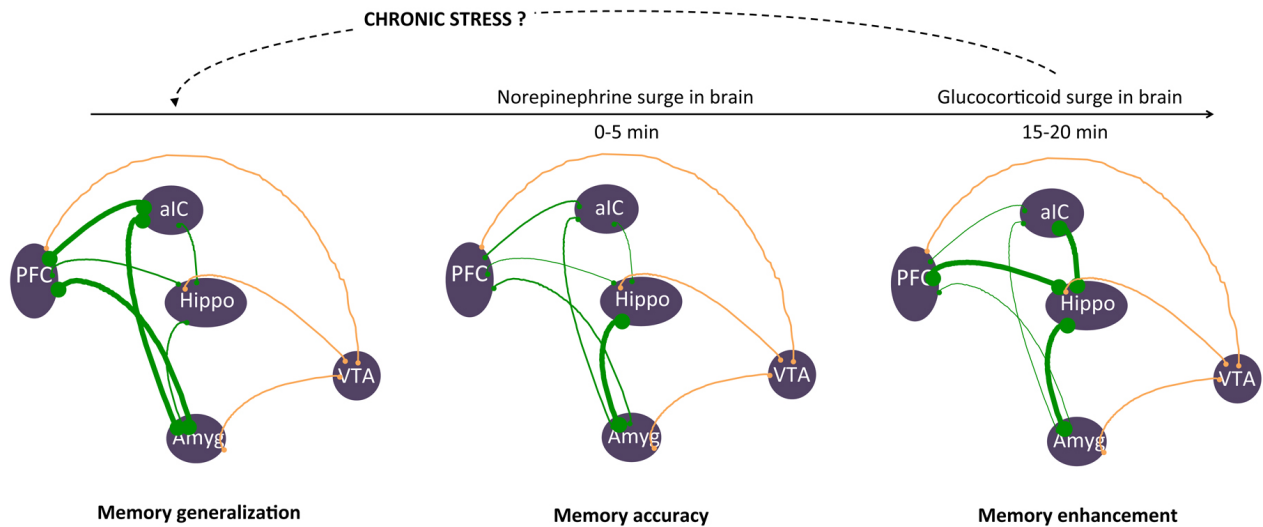
*Middle:* Glucocorticoids rapidly moderate functional connectivity as a function of the GR/MR ratio and the availability of synthesis enzymes and receptors for trans-synaptic messengers (EAE, endocannabinoids; NO, nitric oxide; and BDNF). Color code is representative of the GR:MR ratio in the hippocampus. If the membrane-bound MR (mMR) facilitates NT release, mGR contributes to its termination and post-synaptic plasticity. At low dose, glucocorticoids bind only to mMR whereas at higher doses, it would bind to mMR and mGR, both acting as accelerator and brake on neurotransmission. Based on this model, the expression patterns of glucocorticoid signaling components on each side of a synapse would dictate the overall output across neuronal networks. PV, parvalbumin; SST, somatostatin; PN, principal neuron; CCK, cholecystokinin; VIP, vasoactive intestinal peptide.

*Right:* Depending on glucocorticoid dose, timing and duration of exposure, the local circuitry could be optimally or poorly engaged by behavioral experience resulting in a wide range of possible behavioral outputs.



**Figure 3. Fast signaling by glucocorticoids depends on the type of synapse and regional anatomy**

Asymmetrical RNA expression of GR (blue dots) and MR (red dots) in hippocampal subfields creates a variety of patterns across synapse types in the local circuitry. For instance, CA2 neurons, enriched with MR, synapse with basal dendrites of CA1 neurons, enriched with GR or MR or both. This CA2-CA1 glutamatergic synapse would contain MR in the axon terminal to facilitate glutamate release, and GR in the dendritic spine to mobilize AMPA receptors and remodel the cytoskeleton via the LIMK1-cofilin-actin pathway. On the contrary, a DG-CA3 glutamatergic synapse would contain MR on both sides of the synapse resulting in a different response because it lacks the GR-mediated retrograde signal that limits neurotransmission. The asymmetry also concerns GABAergic synapses (grey cells). For instance, MR is enriched in VIP cells whereas GR is most abundant in PN. Together, the anatomical distribution of GR and MR on each side of a synapse is expected to influence the rapid response to glucocorticoids. EC, enthorinal cortex; CA, Cornu Ammonis; DG, dentate gyrus; SO, stratum oriens; SR, stratum radiatum, SLM, stratum lacunosum.



**Figure 4. Fast signaling by glucocorticoids across large-scale brain regions determines neural representations of behaviors**

Glucocorticoids enhance the effect of norepinephrine on memory consolidation when the surge is proximal to learning (within minutes). Together, they engage the hippocampus micro-circuitry with the amygdala to link emotional processing with contextualization, and also with the frontal cortex to link emotional contextualization with action control (green connections are excitatory) [58]. The enhancement of memory consolidation by glucocorticoids depends on the dose, timing and duration of exposure such that too much before learning (because of chronic stress) would redefine the rules of engagement of the hippocampus micro-circuitry by norepinephrine, preventing contextualization of emotional contents resulting in memory generalization about the most salient theme of the event regardless of context (loss of accuracy) [43]. This idea fits with the prioritization of resources commanded by the stress-glucocorticoid system to increase vigilance, awareness and learning of dangers. In this situation, the order of presentation of glucocorticoids with norepinephrine would change the engagements of micro- and macro-circuits between the amygdala, hippocampus and cortex [57]. Mistiming of glucocorticoid signaling with norepinephrine signaling would impair their synergistic actions [59]. When dangers involve reward, the dopaminergic macro-circuitry (orange connections) would superimpose with the effects of glucocorticoids and norepinephrine, again changing the geometry of neural network engagement. The passing of time also reduces memory accuracy, like stress does, by reducing the engagement of the hippocampus to the profit of cortex for the storage and retrieval of episodic or context-dependent information [60]. Given that steady state levels of glucocorticoids increase with aging as well as chronic stress, it is possible that a loss of memory accuracy could result from the shift of memory representations in the brain by notably making the storage and retrieval of emotional memories dependent of cortical areas and independent from the hippocampus [42]. aIC, anterior insular cortex; PFC, prefrontal cortex; Hippo, hippocampus; Amyg, Amygdala; VTA, ventral tegmental area.