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Opinion

Cognitive Adaptation under Stress: A Case for the Mineralocorticoid Receptor

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Corticosteroid hormones, released during stressful encounters, have profound and far-reaching effects on cognition. They are often thought to accomplish these effects primarily via glucocorticoid receptors (GR), but recent findings from rodent and human studies argue for an additional, critical role of the mineralocorticoid receptor (MR) in cognitive changes in response to stress. We propose that the MR initiates rapid changes in the recruitment of specific neural systems, inducing a shift towards cognitively less-demanding processing and allowing a quick and adequate response to the situation. In combination with slower and longer-lasting actions mediated by GR, this shift leads to optimal coping with the ongoing stressful event.

Stress as a Key Modulator of Cognition

Stress is ubiquitous in our everyday lives and known to have a profound impact on a variety of cognitive processes, ranging from attention and cognitive control to memory and social cognition [1,2]. In particular, stress effects on learning and memory are well documented [3,4]. For instance, stress enhances memory consolidation [3,5,6], but markedly deteriorates memory retrieval and working memory [7,8] when it is experienced shortly before or during the task. Many of these effects require the stress-induced surge of **corticosteroids** (cortisol in humans, corticosterone in rodents; see Glossary), acting in concert with **catecholamines** and other neurotransmitters, hormones, and neuropeptides, which are released in response to stressful encounters [9–13]. Corticosteroids induce a multitude of cognitive effects by activating two types of receptor in the brain, the **GR** and the **MR** [14] (Box 1). For decades, stress research centered on the GR, because the intracellular MR was thought to be substantially occupied already at rest, given its high affinity for corticosteroids. However, recent years saw the discovery of membrane-associated MRs with much lower affinity, comparable with that of GRs, thus allowing the MR to respond to stress-induced corticosteroid releases [15]. Accordingly, activation of membrane-associated MRs was found to induce rapid, nongenomic effects on neural excitability, cognition, and behavior (reviewed in [16]). Since then, tremendous progress has been made in understanding how the MR affects cognition when individuals are stressed.

The effects of stress on cognition, and aberrations thereof, are thought to be a crucial factor in stress-related mental disorders, such as **post-traumatic stress disorder** (PTSD) or **major depressive disorder** [17,18]. In line with this view, directly after stress, higher-order cognitive functioning depending on the prefrontal cortex (PFC), such as mental flexibility or multitasking, is impaired (e.g., [1,19,20]), and this needs to be normalized afterwards to achieve optimal coping. Importantly, however, many cognitive changes occurring under acute stress are at least partially beneficial and promote acute cognitive adaptation [21]. For instance, stress enhances focused

Trends

Adaptive cognitive changes under stress require the brain MR for corticosteroids and its interaction with other neuromodulators released in response to stress, such as catecholamines.

Under stress, the MR induces a rapid shift from 'cognitive' systems based at the hippocampus and, most likely, the prefrontal cortex, towards less-demanding 'habit' systems depending on the **amygdala** and the dorsal striatum. This shift is reflected in distinct changes in neural activity and connectivity within and between these brain circuits.

Although this MR-dependent shift is often beneficial and promotes coping during acute stress, it might come at the cost of less access to flexible cognitive processes depending on the hippocampus and other regions involved in more reflective processing, such as the prefrontal cortex.

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Box 1. One Hormone, Two Receptor Types

Upon stressful encounters, corticosteroids are released from the adrenal cortex, travel through the blood stream and readily enter the brain to induce their effects on cognition. Early on, it was discovered that two receptor types differing in expression and affinity mediate corticosteroid actions [118]: the MR and the GR. The MR was found to be comparable to the kidney mineralocorticoid system and expressed in brain regions essential for memory functions and regulating the stress response, that is, mainly the hippocampus, but also to a lesser extent in the amygdala, lateral septum, and parts of the PFC [119]. This receptor type displays such a high affinity for corticosteroids that it was assumed to be substantially activated even at the circadian nadir of corticosteroid release. The GR is similar to the liver glucocorticoid system, but also abundantly expressed throughout the rat brain. In contrast to the MR, the GR demonstrates lower affinity, allowing it to respond to stress-induced rises in corticosteroid levels. Therefore, research on stress and its impact on cognition was long focused on the GR because it was not understood how the MR could mediate stress-induced changes in view of its high affinity [120].

Classically, both receptor types were considered to be only intracellular receptors mediating relatively slow genomic changes by **transactivation** or **transrepression** of responsive genes (Figure I). However, this traditional view was challenged by the discovery of (presumably) membrane-bound MRs inducing rapid, nongenomic effects on neural excitability, cognition, and behavior (reviewed in [16]). Surprisingly, and of key significance, the membrane-bound MR mediating nongenomic effects appears to have a lower affinity for corticosteroids than its nuclear version and, thus, can mediate rapid stress-induced changes that facilitate cognitive adaptation under stress.

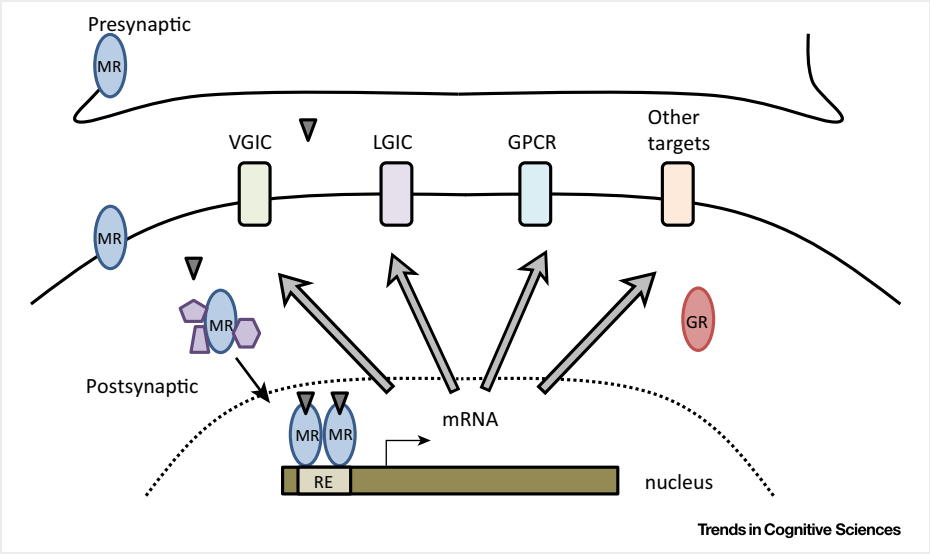

Figure I. Pathways of Corticosteroid Action. Corticosteroids (triangles) are lipophilic and easily enter the plasma membrane where they bind to intracellular receptors [i.e., mineralocorticoid (MR) and glucocorticoid receptors (GR)]. In the unbound form, these receptors are associated with other molecules, such as heat shock proteins (angular shapes). Upon binding, the receptor complex dimerizes and translocates to the nucleus, where the dimer binds response elements (RE) in responsive genes. Alternatively, MR (or GR) interacts with other transcription factors (not shown). Through both pathways, gene transcription is altered for a prolonged period of time. Corticosteroids transcriptionally regulate many molecules involved in neurotransmission, including voltage-gated ion channels (VGIC), ligand-gated ion channels (LGIC), G-protein-coupled receptors (GPCR), and, for example, receptors for growth factors or ion pumps (here indicated as 'other targets'). In addition to transcriptional regulation, there are direct nongenomic pathways through which corticosteroid receptors can affect information transfer. This involves receptors that are associated with the plasma membrane, either post- or presynaptically.

attention on threat-related information and memory formation, thus leading to improved remembrance of the stressful event for future use [9]. Furthermore, stress promotes the recruitment of well-learned habits and routines that enable rapid responding and spare valuable cognitive resources when faced with high demands [22]. Even the transient impairment of memory retrieval under stress might be beneficial, in that it reduces distraction and interference with efficient memory formation [4].

Glossary

Amygdala: a crucial brain structure involved in threat detection, emotion processing, and the modulation of memory processes in other brain structures, such as the hippocampus.
Antagonist: drug that blocks a receptor.
Catecholamines: monoamine neurotransmitters derived from tyrosine, such as noradrenaline.
Corticosteroids: steroid hormones that are released during stressful situations from the adrenal cortex as the end product of the hypothalamus–pituitary–adrenal axis. To exert their multifaceted effects, they can bind to MR or GR.
Dorsal striatum: subcortical structure involved in habit learning and motor control.
Functional connectivity: correlated activity of distinct brain regions during task performance or rest periods as measured with fMRI.
Glucocorticoid receptor (GR): receptor type that binds corticosteroids, such as cortisol, in the brain (Box 1, main text).
Habit learning: encoding of the relation between stimuli and consecutive responses independent of the outcome following the response. Compared with other forms of learning, this type of learning is rather rigid but cognitively less demanding.
Hippocampus: brain structure crucial for episodic memories and spatial navigation.
Major depressive disorder: mental disorder characterized by low mood, a persistent loss of energy, and decreased interest in things that were enjoyed previously.
Mineralocorticoid receptor (MR): receptor type that binds corticosteroids, such as cortisol, in the brain (Box 1, main text).
Post-traumatic stress disorder: mental disorder characterized by recurring flashbacks, avoidance, and hyperarousal, which can develop after experiencing trauma.
Spatial memory: encoding the relation between two or more stimuli in the environment to learn the location of target items. This type of learning depends on the hippocampus and is not only more flexible, but also more cognitively demanding compared with habit learning.

In this review, we focus on the mechanism underlying cognitive adaptation to stress and argue that the MR has a critical role in this process. We first integrate recent findings from rodent and human experiments suggesting the importance of the MR in cognitive changes under stress. Thereafter, we introduce the latest results from human neuroimaging studies that have begun to unravel how these MR-mediated corticosteroid effects on cognition may be neurally implemented. Specifically, we argue that MR stimulation under stress drives the amygdala, which then switches the balance of multiple memory systems in favor of the **dorsal striatum**, at the expense of the **hippocampus** (and, possibly, the PFC). Based on these data, we propose a model of the MR as an important player in the rapid behavioral, cognitive, and neural adaptation to stressful experiences, complementary to the more established role of the GR (for a detailed review on the GR, see [23]) and, most likely, in close interaction with the known catecholamine actions [19].

Stressor: physical or psychological event or stimulus that is perceived as threat to the homeostasis of the organism.
Transactivation: a classic, genomic way of action of corticosteroid receptors resulting in enhanced gene expression. Upon binding of corticosteroids, MRs and GRs translocate into the nucleus, bind to responsive elements in promoter regions of target genes, and increase their expression.
Transrepression: in contrast to transactivation, this genomic way of action of corticosteroid receptors results in decreased gene expression.

The MR and Cognition in Nonhuman Animals

The first important insights into the role of the MR in cognition came from rodent studies that tested the involvement of the MR in neuroplasticity and behavior at rest (i.e., under nonstressful conditions). For instance, the MR was implicated in hippocampal neurogenesis, spine elimination, the regulation of neural excitability, and synaptic plasticity in several brain structures, including the hippocampus, amygdala, and motor cortex ([15,24–30] but see [31]). These MR-mediated effects promote memory formation and serve to maintain integrity and plasticity in brain regions that are critical to memory [15,26,27,30,32,33]. The involvement of the MR at rest in modulating memory formation and retrieval was consequently confirmed by behavioral studies in rodents [34–45] and chicks [46,47]. Moreover, MR blockade in rodents can impair working memory, at least after repeated administration and most strongly when combined with GR blockade [40]. Insights gained from rodents with genetically altered MR expression further support a role for the MR in explorative behavior, **spatial memory** [48–56], and working memory [53]. However, the impaired working memory performance displayed by animals overexpressing the MR may stem from increased behavioral perseverance due to enhanced striatal actions, rather than impaired working memory performance *per se*.

These studies indicating a role of the MR in cognitive processes at rest, in combination with the discovery of lower-affinity MRs that allow a response to stress-induced corticosteroid levels, made it tempting to speculate that the MR is also critically involved in cognitive changes after stress. Indeed, studies investigating the MR during stress indicated that the MR is important for neuronal survival [29,54] and synaptic plasticity under stress [57–59]. In addition, corticosterone administration impaired hippocampus-dependent memory retrieval via an MR-mediated mechanism [60]. Moreover, whereas previous findings concerning MR functions at rest supported the hypothesis that the MR is involved in the degree to which memory is formed, the MR appeared to be also a regulator of which memory system is used to learn new information, especially under stress, when resources need to be reorganized to allow successful coping. For instance, stress or the injection of corticosterone favored the engagement of a rather rigid but simple, effective stimulus–response ('habit') learning system based on the dorsal striatum, at the expense of a more complex and cognitively demanding spatial learning system involving the hippocampus [61,62]. Pharmacological MR blockade abolished this stress-induced shift towards the cognitively less-demanding memory system [62]. Interestingly, stress *per se* did not alter quantitative learning performance in the dual-solution task, but blocking the MR before stress induction or before corticosterone injection resulted in a pronounced learning impairment [62]. Furthermore, performance of stressed animals that switched to the striatum-dependent system was comparable with that of nonstressed control animals, indicating that the strategy shift from hippocampal to striatal systems allowed the preservation of performance as measured by percent correct in the task used. By contrast, stressed animals that kept using their hippocampal memory system were impaired in learning. These findings provide evidence that the MR-operated shift

from hippocampus-based to dorsal striatum-based learning is highly adaptive with respect to performance in this task. However, there may be other conditions where such a strategy shift may come at a cost, for instance in tasks that require intact mental flexibility where habitual responses would cause errors [53]. An involvement of the MR in switching between memory systems is further supported by studies investigating stress effects in MR-knockout mice, although the picture here is less clear [55,56].

In sum, recent behavioral studies in rodents point to the MR in regulating the use of different memory systems, exploratory behavior, working memory, memory encoding, and recall, which are all critical for successful adaptation to novel, potentially threatening environments.

The MR and Human Cognition

The rodent findings were recently extended and translated to humans and a range of cognitive functions was found to involve the MR. In line with the rodent data, human studies are largely consistent with the hypothesis that the MR is involved in regulating memory formation in healthy individuals under baseline conditions (i.e., even when not subjected to stressful circumstances; [63–66], but see [67] for data showing no effect of MR activation on memory). Furthermore, there is evidence to some extent for an involvement of the MR in other cognitive domains, including working memory ([63,67], but see [65,69] for data showing no effect of MR blockade), aspects of social cognition [68], attention ([69,70] but see [64] for data showing no effect of MR blockade), and executive functions [64]. However, the MR seems to have a particularly crucial role in cognitive changes under stress. For instance, working memory was found to be most strongly impaired when psychosocial stress was combined with MR blockade, suggesting that an intact MR alleviates some of the deteriorating influences of stress [69], which is in line with positive effects of MR activation on working memory performance at rest [63,67]. Similarly, selective attention, executive functioning, and memory recall were impaired after MR blockade in individuals who underwent a panic induction procedure [71]. Finally, human carriers of a genetic loss-in-function variant of the *MR* gene were severely impaired in modulating their behavior as a function of the current situational demands under stress [72], again arguing for a crucial role for the MR in flexibly adapting behavior to the given situational characteristics.

To summarize, recent pharmacological and genetic studies in humans support the hypothesis of the MR regulating processes important for attention, working memory, and long-term memory formation both at rest and under stress. In addition, corroborating prior behavioral data in rodents [62,71], the MR appears to mediate a stress-induced shift from cognitively more-demanding, declarative memory strategies towards less-demanding, procedural strategies [73,74] (see below).

On Autopilot: The MR as a Switch from 'Cognitive' to 'Habitual' Brain Systems

Recently, the human neuroimaging field has begun to unravel how MR-dependent cognitive changes might be implemented in the human brain. In a series of studies that combined pharmacological manipulations of the MR with functional magnetic resonance imaging (fMRI), the neural mechanism underlying the MR-dependent stress-induced shift towards less-demanding cognitive strategies was uncovered. In the first of these studies, neural activity was measured while participants learned how to categorize stimuli based on trial-by-trial feedback [73], a task that can be achieved both by a hippocampus-dependent 'cognitive' or a dorsal striatum-dependent 'habit' system [75]. Stress induced a shift from hippocampus-based to dorsal striatum-based learning strategies [76]. More specifically, task performance in control participants was positively correlated with hippocampal activity, whereas, under stress, performance correlated positively with dorsal striatal activity. Furthermore, hippocampal activity was reduced and even negatively correlated with performance under stress. This suggests, in

line with previous rodent data [62], that attempts to recruit the hippocampus during stress are associated with impaired performance and, hence, that the shift towards striatum-based learning is adaptive and rescues cognitive performance in this task under stress. Most importantly, however, a follow-up study showed that the MR antagonist spironolactone blocked this shift from hippocampal to striatal learning and resulted in markedly impaired performance shortly after **stressor** exposure [73]. In line with rodent findings [62], these data support the hypothesis that the MR operates an adaptive shift from cognitively demanding learning based on the hippocampus towards rather simple, yet effective, 'habitual' learning mediated by the dorsal striatum.

Although the stress-induced shift towards cognitively less-demanding learning processes has mainly been studied in spatial and category learning, it can also be observed in fear learning. More precisely, MR activation under stress induced a switch towards a dominance of cognitively less-demanding delay fear-learning over more complex trace fear-learning strategies, accompanied again by a decrease in hippocampal activity during learning [77] (Figure 1). The MR-dependent shift between neural systems under stress may not even be limited to the memory domain, because it was also found during tasks not involving memory components (vigilance processing) [78], indicating that it may be a more general phenomenon affecting a range of cognitive functions [79].

How are the stress-induced changes in hippocampal and striatal contributions to behavior orchestrated? Earlier findings suggested a crucial role of the amygdala in modulating the balance between multiple memory systems under stress or emotional arousal [80–83]. Indeed, imaging data confirmed that stress increased **functional connectivity** between the amygdala and the

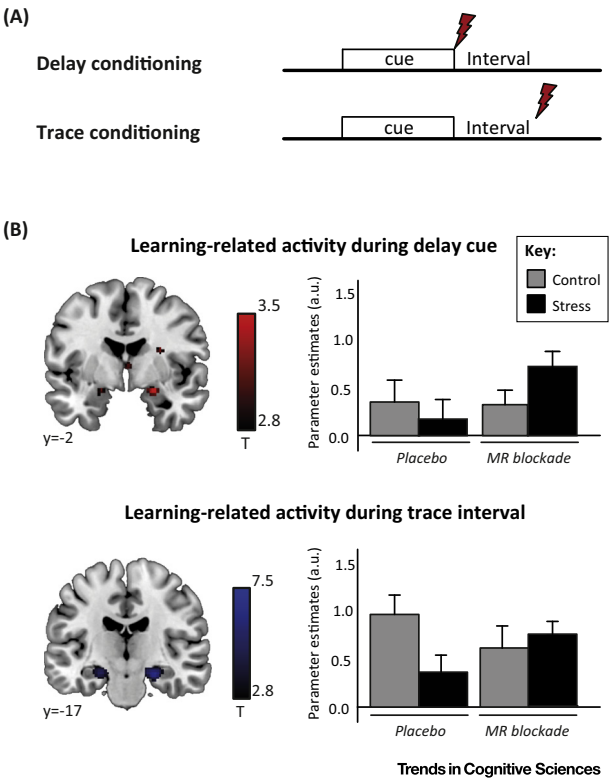

Figure 1. The Mineralocorticoid Receptor (MR) Mediates a Stress-Induced Shift away from more Complex Types of Fear Learning. (A) Healthy participants underwent a stress or control procedure before they performed a fear-conditioning paradigm that comprised both amygdala-dependent delay conditioning as well as more complex, hippocampus-dependent trace conditioning. (B) Whereas stress did not affect learning-related activity of the amygdala during delay conditioning, stress decreased hippocampal learning-related activity during the trace interval. This relative stress-induced shift away from hippocampal learning was blocked in those participants who had received spironolactone before stress induction. Error bars represent standard error of the mean (SEM). Adapted, with permission, from [77].

dorsal striatum, whereas it decreased amygdala connectivity with the hippocampus [73] (Figure 2). Importantly, these opposite changes in amygdala connectivity with hippocampus and striatum under stress were also blocked by spironolactone and, thus, appear to be MR dependent, whereas the stress-induced change in the hippocampus itself appeared to be independent of MR activation [73]. Recent data replicated and extended these findings by showing that a similar stress-induced increase in amygdala connectivity with the dorsal striatum developed rapidly, within less than 20 min after stressor onset [78] and, therefore, might mediate rapid behavioral changes under stress. However, the underlying mechanism of how the MR activates the amygdala is still under debate. At the cellular level, MR activation rapidly increases the excitability of amygdala neurons [30]. Whether this is translated to changes in information transfer is still unclear, because a behavioral pharmacology study reported no effect of MR antagonist injections into the (basolateral) amygdala on rodent freezing behavior [84]. By contrast, injecting MR antagonists into the ventral tegmental area (VTA) reduced dopamine release in the basolateral amygdala and decreased conditioned freezing [84]. Thus, it is tempting to speculate that the MR-mediated increase in amygdala-striatal coupling may partly stem from MR effects in the VTA, strengthening amygdala function [85] and possibly its connectivity with the dorsal striatum. Moreover, MR stimulation in the VTA may also directly increase dopamine release in the ventral striatum, which could in turn promote the formation and retrieval of emotional habits [84,86].

In sum, these studies show, across different types of tasks, that corticosteroids induce wide-ranging neural, cognitive, and behavioral changes, favoring cognitively less-demanding

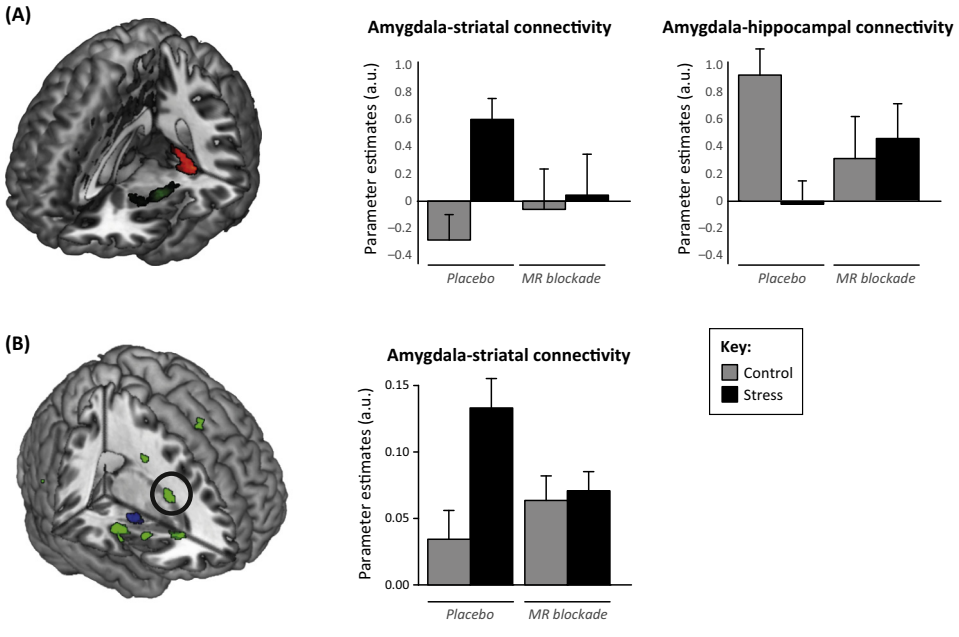

Figure 2. A Mineralocorticoid Receptor (MR)-Dependent Stress-Induced Shift towards Habit Memory Systems May be Orchestrated by Rapid Changes in Amygdala Connectivity. (A) Stress increased amygdala-striatal connectivity (putamen shown in red) during learning, whereas amygdala-hippocampal connectivity was decreased (hippocampus shown in green) [73]. Importantly, these stress-induced changes were abolished in participants who received an MR antagonist before the stress induction. (B) Another study investigated vigilance processing rapidly after stressor onset in healthy men [78]. Stress increased connectivity between the centromedial amygdala (green) and the caudate (circled) less than 15 min after stressor onset, indicating rapid, nongenomic MR-mediated effects. Again, this increase in amygdala-striatal connectivity could be blocked by the administration of an MR antagonist. Error bars represent standard error of the mean (SEM). Adapted, with permission, from [73] (A) and [78] (B).

processing over more complex cognitive processes. These effects are likely triggered by stress-induced changes in amygdala activity and connectivity. Critically, these effects are blocked by MR antagonists, suggesting that these influences rely at least partly on the MR, which thus contributes importantly to rapid cognitive adaptation under stress. The MR exerts this effect most likely in concert with catecholamines, such as noradrenaline or dopamine [19,85–87]. In fact, several studies suggested that catecholamine release during stress induces a shift from the PFC to habitual responding of the amygdala and the striatum [19,79,87–89], in interaction with GR-mediated corticosteroid effects [90,91]. In line with these data, recent evidence indicated that stress may favor a shift from goal-directed learning based on the PFC to **habit learning** based on the dorsolateral striatum [92] and that this shift requires noradrenergic activation, interacting with corticosteroids [89,93,94]. However, for this stress-induced bias from goal-directed to habit learning, the involvement of the MR has not been directly tested yet.

The MR and Rapid Cognitive Adaptation under Stress

Encountering stressful events necessitates well-orchestrated behavioral, cognitive, and physiological changes to adapt to the increased demands posed on the individual. For instance, increased attention to threat-related information and memory encoding are beneficial in stressful situations, and an improved availability of 'habitual' responses allows for rapid retrieval of well-learned, previously reinforced behaviors. Obtaining a better understanding of how adaptive effects of stress on cognition arise has critical implications for society, for instance for educational settings or occupations with performance pressure under high levels of stress.

We have illustrated above that the MR may be important for stress-induced changes in cognitive functioning. Crucially, we propose that the MR controls a rapid stress-induced shift towards an increased use of striatal learning systems at the expense of cognitively more-demanding strategies based on the hippocampus. This shift could be mediated, at least partly, by dopaminergic action in the amygdala, which in turn modulates the engagement of these different brain systems [62]. Thus, the MR appears to quickly promote the enhanced engagement of simple yet efficient learning and memory systems that are less affected by stress [22]. Thereby, the MR may allow for intact performance in the face of increased environmental demands. Furthermore, by switching towards less-demanding systems under stress, the MR may allow the organism to focus on efficient coping with the ongoing stressor. Moreover, it can be speculated that the shift towards less-demanding systems might even make resources available for better adaptation. For instance, by optimizing the availability of relevant cognitive resources, otherwise occurring stress-related impairments in other cognitive domains, such as working memory, may be partially alleviated [69] and yet other cognitive functions, such as controlling ongoing behaviors, might even be improved [95], again allowing for better performance in stressful situations. However, these seemingly MR-mediated effects on prefrontal functions possibly also recruit indirect pathways, because direct prefrontal administration of an MR antagonist did not change PFC functioning after corticosterone injection [90].

In sum, we argue that, by focusing attention, increasing vigilance, avoiding distraction, and shifting to less-demanding cognitive strategies, the MR rapidly induces a cognitive state that is ideally suited to optimize behavioral responses in the face of stress.

At a more general level, we propose that the MR facilitates cognitive adaptation shortly after stress by reorganizing cognitive resources (Figure 3, Key Figure). Several authors have argued that distinct cognitive processes share a common pool of cognitive resources [96–98]. Under nonstressful conditions, these resources may be flexibly allocated to the ongoing cognitive processes (i.e., all of these resources are available for the cognitive process most relevant at the time, allowing deliberate cognitive processing). However, under stressful conditions, when high demands are posed on several cognitive processes simultaneously, these shared resources

Key Figure

A Model of the Mineralocorticoid Receptor (MR) as a Key Player in Cognitive Adaptation under Stress

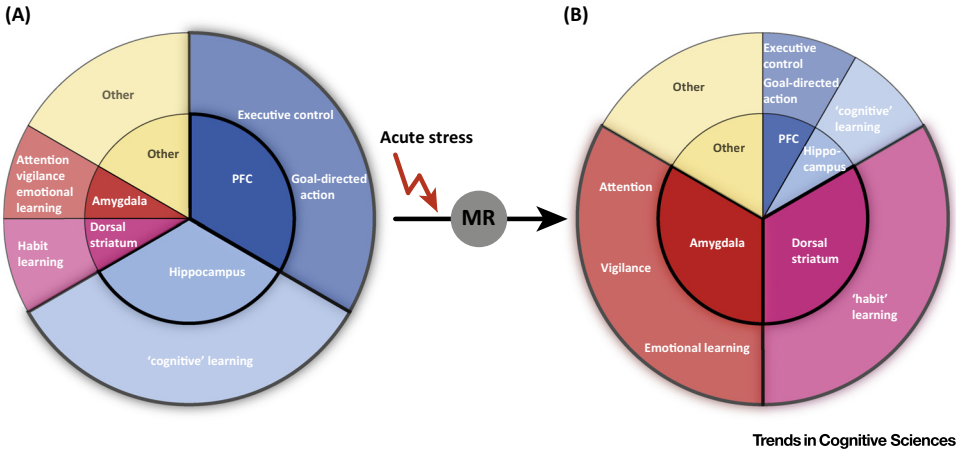

Figure 3. Circles represent hypothetically available cognitive and neural resources, respectively. (A) At rest, resources are predominantly allocated to the hippocampus and the prefrontal cortex (PFC), allowing executive control processes, goal-directed actions, and cognitively more demanding types of learning ('cognitive' learning). (B) In response to an acute stressor, the MR induces a shift in resource allocation towards the amygdala and the dorsal striatum, supporting increased vigilance and more efficient 'habit' learning. At the same time, fewer resources are available for cognitively more-demanding processes mediated by the hippocampus or the prefrontal cortex under stress.

need to be divided between different processes, which potentially hampers the functioning of each. In such situations, the MR may initiate a redistribution of resources towards simple, rather reflexive systems dependent on the dorsal striatum, at the cost of flexible, cognitively demanding systems based on PFC and the hippocampus. This shift towards less-demanding systems, initiated by MR-dependent and possibly dopamine-mediated changes in amygdala connectivity with other brain areas, is highly adaptive in the face of an acute threat, but would be less beneficial if it was long lasting or when complex decisions have to be made under stress. Thus, it is essential that this shift towards simpler systems is followed by a reallocation of resources to brain areas supporting higher cognitive functions, such as PFC and the hippocampus, to improve elaborated cognition after the stressful situation has passed [99]. Most likely, this reallocation is a critical function of the GR, accomplished through genomic pathways [99], but the specific differential roles of MR and GR and their interactions remain to be further investigated.

Although this model clearly needs to be directly tested in future studies, most findings implicate intact MR functioning in enhanced cognitive abilities under stress, whereas dysfunctional or blocked MRs generally lead to deteriorated cognitive performance under stress. Therefore, these studies underscore the role of the MR in the rapid behavioral, cognitive, and neural adaptation to stress.

Relevance for Psychopathology

In support of the idea that the MR is critical for successful cognitive adaptation, impaired MR functionality is associated with maladaptation to stressful events and an enhanced risk for stress-related mental disorders. For instance, prenatal or chronic stress in rodents induces downregulation of hippocampal MR expression accompanied by increased anxiety-like

behaviors in adulthood [100,101], whereas rats that cope with chronic stress show enhanced hippocampal MR expression [102]. In line with this, human participants carrying a mild loss-in-function genetic variant of the MR are prone to increased neuroticism during adulthood and more depressive symptoms in old age [103,104]. Similarly, brain MR expression is decreased in patients with depression ([105–107], but see [108]) and a genetic variant possibly impairing MR regulation is related to increased emotional memories, which represents a cognitive phenotype associated with depression [109,110]. In line with these findings, a first randomized clinical trial in patients with depression showed that MR activation accelerated the positive effects of antidepressant treatment [111], corroborating a causal role of the MR in adaptation to stressful environments. There is also first neuroimaging evidence implicating a dysfunctional MR with maladaptation in a large sample of children and adolescents [112]. While neural activity was measured in the MRI scanner, all participants viewed pictures of human faces expressing anger or fear, a procedure that reliably activates the amygdala [113]. In line with previous research, participants with experiences of prolonged stress during a critical period of development showed enhanced amygdala reactivity, indicating a heightened risk for stress-related mental disorders [114]. Importantly however, this effect of early life stress was dependent on the individual MR genotype [112]. Only participants with normally functional MRs displayed the well-known increase in amygdala reactivity with previous childhood stress. By contrast, participants with less-functional MRs displayed enhanced amygdala reactivity even when no early life stress was experienced, suggesting a generally increased sensitivity for psychopathology. Finally, it can be speculated that the stress-induced shift towards habit memories, particularly the lack of reverting to more flexible systems in the aftermath of stress, might be related to psychiatric conditions. For instance, patients with drug addiction may be prone to relapse under stress by recalling dysfunctional drug-seeking habits [115,116]. Thus, whereas the stress-induced shift is generally assumed to be adaptive in healthy individuals, it may maintain psychopathology in vulnerable individuals with strong maladaptive habits.

Concluding Remarks

To conclude, recent data from rodents and humans indicate a clear role of the MR in successfully adjusting behavior, cognition, and neural resources to the increased demands posed by stressful situations. In addition to their relevance for basic science, these findings point to the MR as a potential target for novel treatment approaches of psychiatric disorders. Of course, several fundamental questions remain (see Outstanding Questions). First, the presented findings show that the MR is involved in regulating several cognitive functions, such as attention, working memory, memory performance, and the engagement of multiple memory systems. Yet, exactly how the MR alters these functions both at rest and under stress is unclear and remains a challenge for future research. Furthermore, the interactions between the MR on the one hand and catecholamines and the GR on the other hand need to be better understood. Another important issue is the sex dependency of MR functionality. Nearly all of the rodent literature reviewed here pertains to male animals, and human studies often also focus on men. However, there is some evidence that the effects of alterations in MR expression are even stronger in female mice, at least in certain behavioral domains, such as fear learning [50,52]. This agrees with human studies showing that the relation between genetic MR variants and depressive symptoms is sex dependent and particularly prominent in females [104,117]. Answering these and related questions will aid our understanding of the pivotal role of the brain MR in cognitive adaptation, and maladaptation, to stressful encounters.

Outstanding Questions

Exactly how does the MR affect cognitive functions, such as attention, working memory, memory encoding, and mental flexibility, both at rest and under stress?

How do genomic and nongenomic MR-mediated effects interact to alter behavior and cognition?

How do rapid MR-mediated effects interact with catecholamines and other neuromodulators released under stress?

When is MR activation critical? When is GR activation critical? And, under what specific conditions do they interact to produce specific effects on cognition and behavior?

What is the exact timing of MR-dependent effects in humans? When do nongenomic effects set in and how long do they last?

How can brain MR expression or functionality be affected in humans and what are the consequences of short-term up- or downregulation of the brain MR?

How can we explain interindividual differences in the regulation of MR signaling after acute and chronic stress?

To what extent are the reported effects of the MR on cognitive adaptation sex (hormone) dependent?

What is the role of the MR in stress effects in cognitive domains other than learning and memory, such as decision-making?

Do MR-mediated corticosteroid effects differ depending on the specific brain site?

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