Review

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Shaping Memories via Stress: A Synaptic Engram Perspective

Niek Brosens, Sylvie L. Lesuis, Priyanka Rao-Ruiz, Michel C. van den Oever, and Harm J. Krugers

ABSTRACT

Stress modulates the activity of various memory systems and can thereby guide behavioral interaction with the environment in an adaptive or maladaptive manner. At the cellular level, a large body of evidence indicates that (nor)adrenaline and glucocorticoid release induced by acute stress exposure affects synapse function and synaptic plasticity, which are critical substrates for learning and memory. Recent evidence suggests that memories are supported in the brain by sparsely distributed neurons within networks, termed engram cell ensembles. While the physiological and molecular effects of stress on the synapse are increasingly well characterized, how these synaptic modifications shape the multiscale dynamics of engram cell ensembles is still poorly understood. In this review, we discuss and integrate recent information on how acute stress affects synapse function and how this may alter engram cell ensembles and their synaptic connectivity to shape memory strength and memory precision. We provide a mechanistic framework of a synaptic engram under stress and put forward outstanding questions that address knowledge gaps in our understanding of the mechanisms that underlie stress-induced memory modulation.

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Stress can be defined as any disturbance of internal homeostasis that occurs following exposure to salient interoceptive or external stimuli. It influences the interpretation of salient experiences that serves as a reference for future events via memory (1–3). In turn, memory can frame a perceptual constraint of the environment, thereby influencing the response to a stressor (4,5). The resulting interplay between stress and memory drives experience-dependent behavioral adaptation to the environment, which is essential for survival (3) and also shapes the risk for stress-related psychopathology such as anxiety disorders, posttraumatic stress disorder, and depression (6,7). Because the prevalence of stress-related psychopathology is increasing in modern society (8,9), understanding the mechanistic interactions between stress and memory is of great importance for the development of preventive and therapeutic tools.

Box 1 provides some key definitions of terms used in this article.

Stress exposure activates the autonomic nervous system, leading to the release of various neuromodulators in the periphery and brain to support behavioral adaptation (10). Noradrenaline (NA) is released in the brain from terminals of noradrenergic neurons that are localized in the locus coeruleus, an arousal-promoting nucleus that projects extensively throughout cortical and subcortical areas (Figure 1A) (11). Therein, NA acts on functionally distinct adrenergic receptors (ARs) (i.e., α_1-, α_2-, and β-ARs) that exert rapid modulation of neuronal function and plasticity (12,13). This, in turn, may induce lasting neuromodulation via secondary genomic mechanisms (14). Subsequently, slower activation of the hypothalamic-pituitary-adrenal axis is initiated by the sequential release of corticotropin-releasing hormone from the hypothalamus and adrenocorticotropic hormone from the pituitary gland, culminating in elevated release of glucocorticoids (GCs) from the adrenal cortex (6,10). The lipophilic GCs easily pass the blood-brain barrier (Figure 1A), where they act on high-affinity mineralocorticoid receptors (MRs) and low-affinity glucocorticoid receptors (GRs) (6) to influence neuronal function through both immediate nongenomic and delayed genomic actions (15).

Synapses are critically involved in memory and constitute a main neuromodulatory site of these stress hormones (16). Within specific time domains (Figure 1B), GCs and NA synergistically and complementarily modulate synaptic transmission and plasticity in brain areas that are critical for memory (14), including the hippocampus, amygdala, and prefrontal cortex (PFC) (16–18). These modulations are associated with alterations of distinctive memory systems and processes ranging from memory encoding to retrieval (3). In particular, NA and GCs affect memory processing of emotionally arousing events according to an inverted U-curve (14), which is dependent on stressor type, as well as its timing, duration, and intensity (19). Generally, relatively low to moderate stress levels can enhance memory strength and precision (20,21), while high stress levels hamper memory processing and decrease memory precision. This can cause the generalization of aversive memories to novel nonaversive experiences (22,23). Excessive stress levels (e.g., prolonged or intense) can decrease memory strength and reduce memory precision (24,25).

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Box 1. Key Definitions

Acute stress: A transient and specific emotional, physical, or psychological event that disrupts homeostasis, with a discrete onset and offset and often including transient actions of stress hormones on receptors of the stress system.
Chronic stress: A prolonged state of physiological or psychological distress induced by ongoing or repetitive emotional, physical, or psychological stressors that often surpass the coping ability of an organism.
Low to moderate stress: Mild physical or psychological arousal, e.g., induced by exposure to novelty.
High stress levels: Very strongly elevated arousal, often reflecting a traumatic experience.
Memory processes/processing: An umbrella term for memory-related processes ranging from memory encoding and consolidation to (recent and remote) retrieval, including the strength and precision at which the processing occurs.
Memory encoding: The process by which external or interoceptive information is transformed into a physical memory trace, supported by the memory allocation to sparsely distributed learning-activated neurons that are connected through a discrete set of synapses to form a so-called engram cell ensemble with its respective synaptic engram.
Memory consolidation: The transformation of labile, newly encoded experiences into stable, durable memories through the strengthening of synaptic connectivity of engram cell ensembles.
Memory retrieval: Accessing and recalling stored information in response to an external or interoceptive cue through partial reactivation of the same engram cell ensemble that was initially recruited upon memory encoding.
Memory strength: The durability and accessibility of encoded and stored information over time in support of memory retrieval.
Memory precision: The accuracy and extent of detail of retrieved memories that can either be specific (i.e., highly accurate and detailed to support the ability to discriminate between events) or generalized (i.e., extracted commonalities in broader categories or contexts).
Engram cell ensemble: A discrete set of neurons dispersed throughout the brain that are activated upon learning and that are physically modified as a consequence. These changes support the consolidation of experiences into a memory and ensure (partial) reactivation of the engram cell ensemble to support information recall.
Synaptic engram: Discrete learning-induced changes in synaptic connectivity (e.g., synapse formation or strengthening) of an engram cell ensemble to support memory storage of an experience and facilitate reactivation of an engram cell ensemble to enable information recall.
Synaptic crosstalk: The exchange of signaling molecules by neighboring synapses that may support heterosynaptic plasticity (i.e., activity-dependent changes at inactive synapses through neighboring active synapses).

Physical memory traces are represented by networks of sparsely distributed, yet highly interconnected, neurons that support memory processing (26–28). Given the causal role of these specific cells in memory encoding and subsequent retrieval, they are thought to harbor the experience-induced physical changes, i.e., engrams, required for information storage and recall and are therefore referred to as engram cells (29,30). Newly developed technologies that enable the identification and modulation of synapses belonging to learning-activated neurons, such as dual-eGRASP (31), and

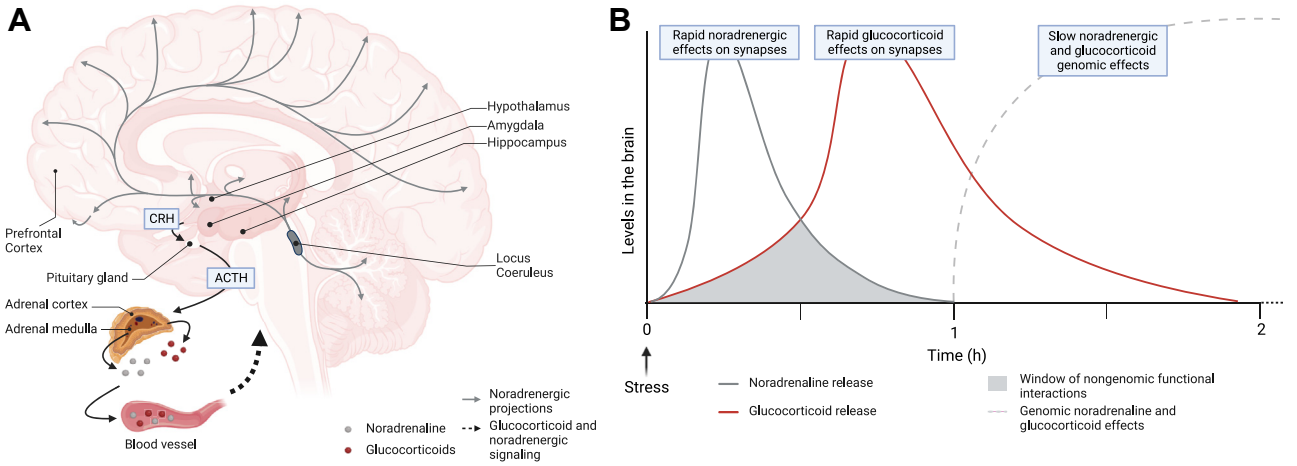

Figure 1. Stress signaling in the brain. **(A)** Schematic overview of stress signaling in the brain. Arousal-induced NA release from noradrenergic cells in the locus coeruleus and from the adrenal medulla reaches cortical and subcortical areas (10,11). Subsequently, the hypothalamic-pituitary-adrenal axis is activated by the release of CRH from the hypothalamus and ACTH from the pituitary, culminating in the release of GCs from the adrenal cortex, which pass the blood-brain barrier easily (6,10). Together, NA and GCs, in addition to other neuromodulators such as CRH and ACTH, modulate neuronal and synaptic function in areas that are critical for recent and remote memory processing, including the hippocampus, amygdala, and prefrontal cortex. **(B)** Timeline of NA and GC signaling in the brain. NA level peaks rapidly after stress, after which it subsides relatively quickly. GCs peak shortly thereafter, resulting in a time-restricted overlap of the stress hormones that allows functional interactions. Finally, delayed genomic effects of NA and GCs lastingly affect brain function and structure. Figure reproduced/adapted from Krugers *et al.* (146), licensed under CC BY-SA 4.0. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; GCs, glucocorticoids; NA, noradrenaline.

learning-activated synapses, such as AS-PaRac1 (32), have uncovered distinctive synaptic properties of a physical memory trace, termed a synaptic engram. These learning-induced synaptic changes may promote stability of an engram cell ensemble and its maintenance, thereby supporting memory consolidation and reactivation (33,34). Formative studies suggest a critical role for synaptic engrams in learning and memory (32,34,35). These findings suggest that synaptic engrams may also be involved in the impact of acute stress and stress hormones on the strength and precision of emotional memory, mediated via engram cell ensembles (5,23,36,37).

In this review, we build a framework for the effects of acute stress on emotional memory using the concept of a synaptic engram. First, we briefly summarize findings on how acute stress alters memory, synaptic function, and structure. Although the effects of stress on memory are mediated by multiple neuromodulators, we focus here primarily on the role of NA and GCs. Then, we integrate these effects with the mechanistic properties of engram cell ensembles in relation to memory strength and memory precision. Finally, we discuss outstanding questions that need to be addressed to address knowledge gaps in the impact of stress on memory via synaptic engrams in health and disease.

NA, MEMORY, AND SYNAPSES

Release of NA enhances attention to prioritize emotionally salient information (38), driving preferential encoding of emotionally salient events. While memories typically generalize and lose strength over time (39), NA also promotes emotional memory precision and strength at remote time points (40). The selective enhancement of emotional memory by NA is associated with changes in synaptic transmission and plasticity (41).

Activation of hippocampal glutamatergic synapses promotes the local release of NA (42), which activates presynaptic β-ARs to further amplify local NA and glutamate release (Figure 2A) (43). Postsynaptically, β-AR stimulation activates CaMKII (calcium/calmodulin-dependent protein kinase II) (44) and G_s-mediated cAMP (cyclic adenosine monophosphate)-induced activation of the protein kinase A (PKA) pathway, resulting in CREB (cAMP response element binding protein)–mediated gene transcription (45), a major pathway for synaptic plasticity (46). Specifically, β-AR activation increases the synaptic recruitment of glutamatergic AMPA and NMDA receptors (AMPARs and NMDARs, respectively), thereby reducing the induction threshold for long-term potentiation (LTP) and increasing neuronal excitability (47). Accordingly, stimulation of β-ARs enhances memory formation in rodents (48) and humans (49). β-ARs also enlarge the paraspinal zone, a dendritic shaft region in the vicinity of a potentiated spine, extending the synaptic crosstalk range of signaling molecules to influence neighboring synapses (Figure 2A) (50). This could facilitate heterosynaptic plasticity via β-ARs to promote subthreshold LTP induction in neighboring synapses (51). Combined with a β-AR–mediated increase in spine density (52,53), the structural and functional clustering of synapses can synchronize input and/or output properties (54), which may enhance memory consolidation.

Given that glutamatergic activity promotes local NA release (42), synapses that are relatively less active have lower NA levels that activate presynaptic α_2-ARs. This inhibits presynaptic glutamate release in the hippocampus (55) and amygdala (56). Postsynaptically, α_2-AR activation decreases PKA activation (57) and promotes the induction of long-term depression (58). Together, these findings suggest that NA may locally enhance the signal-to-noise ratio in support of information processing and memory encoding (59).

GCs, MEMORY, AND SYNAPSES

Elevated levels of GCs enhance memory consolidation (2,60–62) and promote fear memory generalization (23,63). These effects are dose-dependent because moderately elevated GC levels enhance the consolidation of emotional memory (61,64), while highly elevated GC levels may induce generalization (65). Moreover, elevated GC levels at retention testing can impair memory retrieval (66,67). Thus, the effects of GCs depend on the memory phase during which they are elevated.

Via the activation of MRs, glucocorticoids increase hippocampal synaptic transmission within minutes (68) and promote the mobility and activity-dependent synaptic retention of AMPARs and NMDARs (Figure 2B) (69–72). These synaptic alterations may facilitate LTP (73). Elevated GCs also activate GRs that modulate glutamate and GABA (gamma-aminobutyric acid) release in the PFC (74,75), amygdala (76), and hippocampus (77,78). In the hippocampus, GR activation initiates several molecular pathways that modulate synaptic transmission and plasticity, including CaMKII-BDNF (brain-derived neurotrophic factor)-CREB (79), MAPK-EGR-1 (80), and mTOR signaling (62). GR activation leads to a delayed increase in AMPAR-mediated synaptic transmission (81) and an increase in AMPAR mobility and retention (62,69,70). Similar effects have been observed in the PFC (21) and may contribute to enhanced memory consolidation via GRs (21,62,80). The GR-mediated enhancement of memory consolidation is further dependent on the interaction with NA (82), and GCs and NA together exert synergistic and complementary actions on synaptic modulation. For example, co-application of NA and GCs enhances hippocampal synaptic transmission and LTP (83,84).

However, GR activation can also decrease neuronal excitability by enhancing the afterhyperpolarization of action potentials (85), thereby increasing the threshold for LTP induction (73). Thus, it has been suggested that stress-induced GR activation affects subsequent synaptic plasticity by occluding synaptic potentiation (18). This may involve suppressed synaptic potentiation upon exposure to a second stressor via activation of GRs in the hippocampus (86) and amygdala (87). Similarly, excessively elevated GCs can induce hippocampal long-term depression through activation of extra-synaptic NMDARs via glutamate spillover (88). Together, these mechanisms may serve as a protective mechanism under highly stressful circumstances to suppress the encoding of accumulating novel information and/or avoid interference from stressful experiences.

GC signaling also can increase spine turnover (89), possibly via cofilin, an actin-depolymerization factor, to mediate

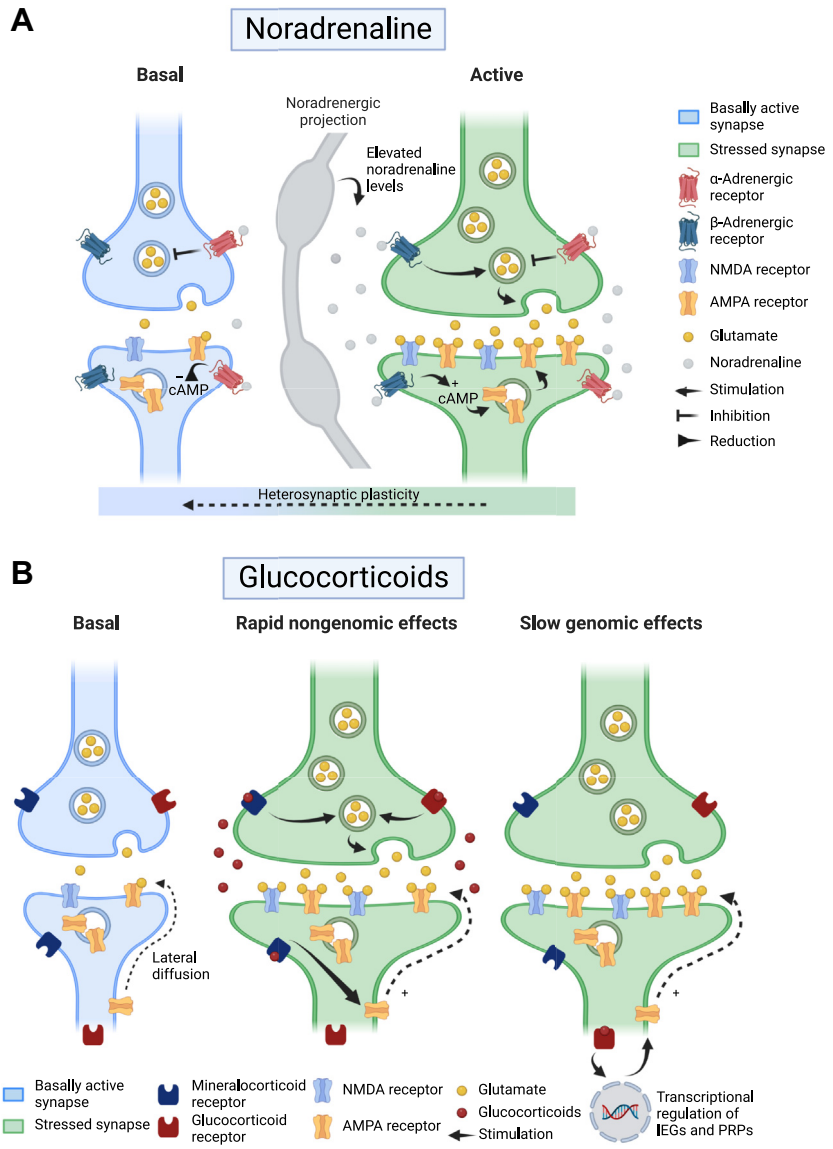

Figure 2. Noradrenaline and glucocorticoid modulation of synapses. **(A)** Schematic overview of synaptic modulation by noradrenaline. In the absence of stimulation, basal noradrenaline levels result in low synaptic activity via α-ARs, low presynaptic glutamate release, and postsynaptic cAMP signaling (56). In neighboring active synapses, noradrenaline levels are elevated, which activates β-ARs. β-ARs further enhance synaptic potentiation by enhancing glutamate release, stimulating cAMP signaling and promoting AMPA receptor trafficking (43,45,47). β-ARs also enlarge the potentiated paraspinal zone and facilitate heterosynaptic plasticity in neighboring synapses (50,51). **(B)** Basally active synapses are supported by glutamate release from the presynapse and continuous lateral diffusion of AMPA receptors in the postsynapse. In the hippocampus, rapid nongenomic effects of glucocorticoids potentiate synaptic activity via mineralocorticoid and glucocorticoid receptors by enhancing presynaptic glutamate release (77). Mineralocorticoid receptors also promote AMPA receptor and NMDA receptor mobility and retention (69,71,72). Slow genomic effects of glucocorticoid receptors promote AMPA receptor mobility and retention (62,69–71). ARs, adrenergic receptors; cAMP, cyclic AMP; IEG, immediate early gene; PRP, plasticity-related proteins.

clustered spine formation, maintenance, and loss (90). Synergistic effects of GCs together with selective β-AR activation can also increase hippocampal spine number (53). Genomic action of GRs can further modulate structural and functional changes via feedback loops, regulating gene expression that in turn modulates GR function (91), which may outlast effects on local synaptic transmission (Figure 2B). For example, BDNF-mediated GR phosphorylation promotes the maintenance of newly formed spines following learning in support of memory retention (92). Thus, while GR activation increases spine turnover, spine clusters in active dendritic zones are maintained. The resulting structural and functional clustering may facilitate memory processes (54).

Collectively, the history and degree of GR activation in addition to MR activation determines the level and direction of synaptic and structural plasticity and may influence how memory is affected. GCs may rapidly promote the capacity to encode information through enhanced AMPAR and NMDAR function and more slowly facilitate information storage through regulation of synaptic AMPARs. Moreover, GCs interact with NA both synergistically and complementarily to modulate synaptic function and excitability and shape regulatory control of memory systems in rodents (20,82,146) and humans (93). Finally, GCs and NA also interact with other neuromodulators such as corticotropin-releasing hormone (94) and dopamine to shape memory (95), but that topic is beyond the scope of this review.

SYNAPTIC PROPERTIES OF AN ENGRAM

The causal role for engram cell ensembles in memory has been extensively studied using gain- and loss-of-function studies [for a review, see (29)]. Studies targeting neuronal excitability,

e.g., by CREB overexpression (96), have revealed that enhanced neuronal excitability is critical for neuronal allocation during learning (97), engram cell maintenance during memory consolidation (97), and engram cell reactivation during memory retrieval (98), thereby influencing memory strength and precision. Neuronal excitability is closely intertwined with synaptic connectivity and plasticity because the integration of synaptic inputs influences intrinsic excitability, which in turn shapes synaptic transmission and plasticity (99,100). As such, synapses emerge as significant players in neuronal allocation, engram cell ensemble maintenance, and reactivation to support memory. It has been suggested that imbalanced excitatory-inhibitory synaptic inputs (101) and the degree of synaptic connectivity (33) of engram cell ensembles modulate memory processing, highlighting the pivotal role of synaptic engrams in memory.

During memory encoding, the synchronized activity of sparsely dispersed neurons promotes neuronal recruitment into an engram cell ensemble (102). These neurons already display relatively high and stable excitatory synaptic connectivity with slow synaptic turnover prior to learning (103). The recruitment of neurons into an engram cell ensemble may be supported by their capacity to form spines that are in close proximity to preexisting spines and induce spine clustering (34). It has been suggested that spine clusters induce local dendritic calcium and depolarization spikes that enhance neuronal excitability (54). Moreover, synaptic activity may enhance CREB signaling (104), which enhances excitability to prime neurons for recruitment into an engram cell ensemble (105–107). Neuronal excitability influences synaptic transmission (99,100), and CREB may modulate retrograde synaptic mechanisms that promote neuronal recruitment into an engram cell ensemble (33). Thus, while natural fluctuations in excitability as well as prior neuronal activity likely contribute to memory allocation (108), (prior) synaptic connectivity, activity, and plasticity can affect excitability to promote the recruitment of neurons for memory allocation.

Synaptic mechanisms also support memory consolidation through engram cells. CREB drives the expression of immediate early genes (IEGs) (109,110), which are primary responsive factors to neuronal activity that are commonly used to study engram cells. Acting largely as transcription factors, IEGs can facilitate LTP (111), which possibly contributes to the engram cell-specific, learning-induced increase in spontaneous excitatory synaptic transmission in the hippocampus (23,28,31) and evoked excitatory synaptic transmission in the amygdala (112) and PFC (113). This is accompanied by an engram cell-specific increase in spine density in the hippocampus (114) and PFC (115) and spine size in the hippocampus (34) and amygdala (36). Moreover, hippocampal engram cell-specific synaptic transmission facilitates the gradual strengthening and refinement of cortical engram networks (113), thereby supporting the functional maturation of PFC engram cell ensembles in support of remote memory retrieval (106,115). Post-learning CREB-dependent gene transcription in PFC engram cells is required for subsequent remote memory expression (106) and increases synaptic connectivity between these engram cells (34). Thus, memory consolidation via engram cell ensembles involves signaling cascades from synapse to nucleus and vice versa.

Furthermore, different neuronal ensembles that may undergo distinct synaptic modifications during consolidation to shape memory have been described. For example, engram cell ensembles that express the IEG *Npas4* have been shown to receive enhanced inhibitory synaptic input and contribute to memory discrimination following fear conditioning (116). Conversely, c-Fos–expressing ensembles receive enhanced excitatory synaptic input and contribute to fear memory generalization (116). Together, these findings imply that the balance of excitatory/inhibitory inputs onto engram cell ensembles may regulate memory precision.

Synaptic connectivity of engram cells has been reported to be correlated with memory strength upon retrieval (31), and the extent of engram cell ensemble reactivation is correlated with memory precision (117). This is consistent with the engram accessibility hypothesis, which poses that memory retrieval is in part contingent on engram cell ensemble activity and synaptic connectivity (118). Linked memories, which are distinct memories that are allocated into an overlapping engram, are dependent on distinctive sets of synapses in shared engram cells (119). These findings suggest that memory strength and precision may be supported by selective synaptic engrams. Thus, a single neuron can be multimodal and incorporated into multiple engram cell networks via distinct synaptic engrams. Cooperative and competitive synaptic interactions between engram cell ensembles could then regulate memory processing in response to environmental stimuli through neuromodulators such as GCs and NA.

STRESS-INDUCED MODULATION OF A SYNAPTIC ENGRAM

While there is substantial evidence that stress, via NA and GCs, alters synaptic transmission and plasticity, it remains largely unknown whether and how stress alters engram cell ensembles and their synaptic connectivity. Understanding the interaction between stress and engram cell ensembles, ranging from acute changes in synaptic transmission and excitability to enduring changes in protein expression and dendritic structure, would help increase understanding of how stress (hormones) alters memory strength and precision.

NA release upon stress exposure locally increases excitatory synaptic transmission (59), potentially priming these synapses for recruitment into a synaptic engram. Specifically, β-AR activation may induce the early potentiation and plasticity of synapses during learning and tag synapses via CaMKII (120) to support the gradual strengthening of synaptic engram connectivity during memory consolidation. NA release in the PFC upon fear conditioning mediates early tagging of PFC engram cell ensembles via β-ARs in support of remote memory (121). Following this rapid NA mechanism, synergistic action with the rapid and delayed elevation of GCs may (further) potentiate these synapses, as well as other, relatively less active synapses, to promote and/or stabilize their recruitment into a synaptic engram. Increased glutamate release probability (16,72,81) paired with MR/GR-dependent increase in AMPAR mobility (69) and a GR-mediated increase in CaMKII activation (79) may promote the recruitment of otherwise dormant synapses. Moreover, GR activation is enhanced by

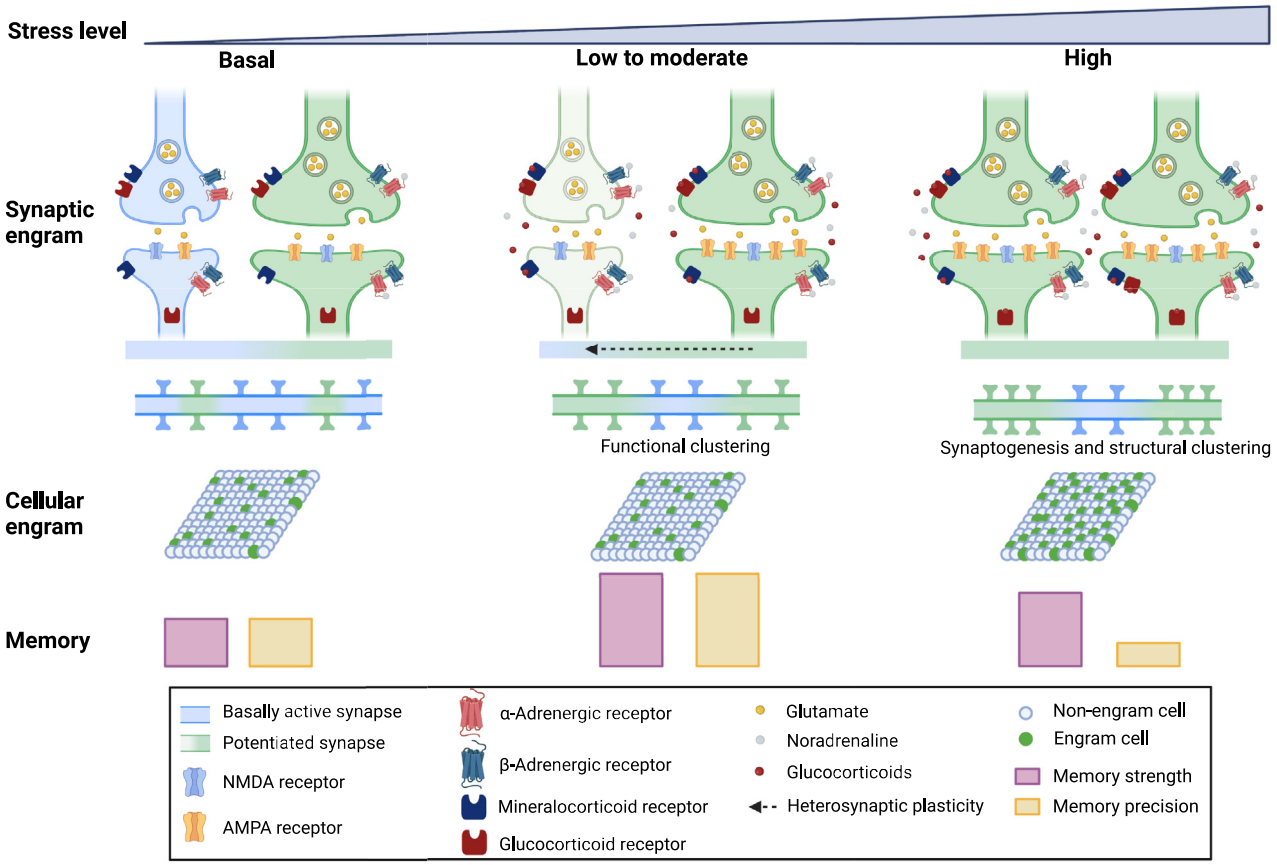

Figure 3. Hypothetical mechanistic framework of stress modulation of hippocampal synaptic engrams, memory strength, and memory precision. Left: AMPA and NMDA receptors are critical for synaptic transmission and plasticity. Under basal conditions, synaptic engrams display enhanced synaptic strength (28,31). Middle: Low to moderate stress levels enhance noradrenaline and glucocorticoid release, increasing presynaptic glutamate release via β-adrenergic receptors in active synapses (43) and increasing overall glutamate release via mineralocorticoid and glucocorticoid receptors (77). Postsynaptically, AMPA receptor mobility and retention is enhanced to further potentiate synaptic strength. β-adrenergic receptors enlarge the potentiated paraspinal zone and facilitate heterosynaptic plasticity via cyclic AMP (50,51), potentially promoting the recruitment of otherwise dormant synapses and enhancing functional clustering of synaptic engrams. As a result, low to moderate stress may enhance the activity and size of a synaptic engram ensemble to promote memory strength and precision without affecting the size of the respective cellular engram. Right: High stress levels further potentiate synapses, induce synaptogenesis, and facilitate structural clustering of synapses. Enhanced synaptic potentiation increases the likelihood of synaptic and neuronal recruitment into an engram ensemble, increasing the size of the engram cell ensemble at the cost of memory precision (23). Excessive and chronic stress levels can disrupt synaptic plasticity and induce long-term depression, potentially impairing synaptic engram mechanisms. Consequently, an engram cell ensemble cannot be maintained, and memory strength and precision are reduced.

cAMP signaling (122). Thus, through β-AR activation-increased cAMP levels (45) and an enlarged potentiated paraspinal zone (50), NA and GCs may synergistically enhance heterosynaptic LTP to functionally cluster synapses, thereby promoting synaptic engram connectivity. As a result, low to moderate levels of stress may enhance the activity and size of a synaptic engram to promote memory strength and precision without affecting the size of the respective cellular engram (Figure 3).

Persistent synaptic activation following stress, as well as activation of β-ARs and GRs, can enhance CREB signaling (123,124). This may increase neuronal excitability and facilitate the recruitment of neurons into an engram population (34,107–109). Acute GC administration after fear conditioning increases the size and reactivation of a dentate gyrus c-Fos–expressing ensemble, which causes fear generalization (23). In the current study, these effects were accompanied by increased synaptic transmission in nonengram cells to the level observed in engram cells. This may enhance neuronal recruitment into a cellular engram and reduce specificity of the synaptic engram, thereby decreasing memory precision and increasing memory generalization. Highly elevated GCs also decrease hippocampal Npas4 expression (125). This may result in the loss of Npas4-espressing engram cells and may imbalance excitatory/inhibitory synaptic inputs of an engram cell ensemble and increase the recruitment and relative contribution of c-Fos–expressing engram cells, thereby enhancing fear generalization (116). In addition to functional and structural clustering of synapses, NA and GC signaling can stimulate spine formation (53,89), and this may facilitate the increase in size and reactivation of an engram cell ensemble to alter the strength and precision of emotional memory (Figure 3).

Excessive levels of stress or prolonged stress can facilitate long-term depression and reduce synaptic transmission (25,88) and induce spine loss (126), which may disrupt the formation and maintenance of synaptic engram ensembles and decrease memory expression. Thus, similar to the behavioral effects of stress on memory, stress may also affect synaptic engrams ranging from increased to decreased function and regulate memory strength and precision (Figure 3).

Due to the distinct roles of MRs and GRs in synaptic transmission and (meta)plasticity, the ratio of synaptic MR/GR and history of GR activation may determine the direction and strength of downstream signaling upon elevated GCs. Moreover, the availability, conformation, and localization of both NA and GC receptors as well as their potential downstream interactors could determine their synaptic effects. For example, PKA-mediated β-AR phosphorylation can couple β-ARs to inhibitory instead of excitatory intracellular signaling pathways (127), which may alter GC-induced potentiation. Together, these factors would allow for synapse-specific stress modulation that may ultimately influence the size and activity of an engram cell ensemble to shape memory strength and precision.

Memory is relatively unstable upon formation (128), allowing for interference with overlapping or functionally connected patterns of activity at the level of an engram cell ensemble (129). This may facilitate the linkage of memories for closely timed events (130), which is dependent on enhanced excitability of engram cell ensembles (131). Stress-induced synaptic potentiation may extend this window of memory linking to increase encoding of the ongoing context during a stressor. This also facilitates interactions with other memories to extract common features during memory encoding and retrieval (132), thereby contributing to memory generalization. This may occur via cooperative interactions between synaptic engrams that encode distinctive memories on shared engram cell ensembles (119). Conversely, stress-induced synaptic potentiation prior to memory retrieval may disrupt the coordinated reactivation of a synaptic engram, thereby competitively suppressing information recall.

Stress (hormones) may also modulate synaptic engram accessibility to shape memory strength upon retrieval. For example, exposure to a social stressor suppresses an engram cell ensemble by increasing activity of RAC1 (133), a cytoskeletal modulatory protein that facilitates synaptic remodeling (134). In contrast, GR activation regulates fear memory by decreasing RAC1 in the hippocampus (135). In addition, enhanced BDNF signaling in the hippocampus via GR activation (136) may promote transsynaptic messaging molecules to enhance the connectivity of synaptic engrams specifically (137). These factors could retain accessibility of an engram cell ensemble, thereby contributing to enhanced fear memory retention.

In summary, synaptic modulation via NA release and β-AR activation may initially prime synapses for engram recruitment under stressful circumstances. Synergistic activity with GCs may subsequently modulate synaptic activity according to synaptic MR/GR ratios as well as the history of GR activation to control synaptic recruitment and neuronal recruitment into an engram and differentially regulate heterogenous neuronal ensembles within an engram cell ensemble during consolidation. Cooperative and competitive synaptic engram mechanisms may be utilized by stress to influence the size and activity of an engram cell ensemble to shape memory strength and memory precision.

OUTLOOK

While the memory engram field has focused predominantly on the role of engram cell ensemble size in memory performance, recent evidence has highlighted the relevance of their synaptic properties in regulating memory processes (31,34,103,113). Although empirical evidence is still scarce, recent studies have shown that stress hormones modulate engram cell ensembles to influence memory (5,23,36,37). We suggest that these effects may be at least in part due to changes in the synaptic properties of an engram cell ensemble.

To further substantiate the results of these studies, technological advances contingent on synaptic potentiation, such as synaptic optogenetics, enable investigation of synaptic engrams (32,119). In addition, in vivo mapping of synaptic activity during behavior (138) and the combination of calcium imaging with IEG-based tagging systems has enabled targeted assessment of synaptic engrams (139). Finally, dual-eGRASP technology enables synaptic input-specific analysis of engram cell ensembles (31). Integrating these approaches with molecular techniques, electrophysiology, and 2-photon in vivo calcium imaging will enable detailed multilevel examination of synaptic engram mechanisms and how they are affected by stress. These approaches would also enable the investigation of stress effects on other engram-modulating factors, such as inhibitory action and other cell types that affect synaptic function like astrocytes and microglia, which contain receptors for NA and GCs and regulate memory (140,141). In addition to episodic emotional memories, investigating how stress affects engrams of other memory types, memory processes (e.g., forgetting), or phases (e.g., consolidation and retrieval) is equally important for understanding how stress alters memory. For example, GC peaks and troughs in circadian oscillations facilitate learning-dependent synapse formation and maintenance, respectively, thereby supporting motor memory (90).

In these studies, not only acute but also chronic stress will be important to consider because they often have opposing effects at the level of the synapse (25,69,70,81). For example, while acute stress and stress hormone elevation often potentiate synaptic function (18), chronic stress disrupts synaptic function by reducing AMPAR- and NMDAR-mediated synaptic transmission and receptor expression (25) and leads to spine loss of learning-activated cells (142). This may disrupt synaptic engram mechanisms, thus leading to memory impairments. In addition, not all individuals are equally sensitive to stress-related disorders, which may be related to differences in adapting to stressors. Understanding the role of engram cell ensembles in individual differences in coping with stressors, which is also modulated by experiences early in life (147), will be important to achieving a better understanding of the mechanisms that underlie stress-related pathologies.

Pharmacological interventions that target NA and GC signaling suggest therapeutic potential for the treatment of stress-related psychopathology (143). In fact, the use of β-AR blockers has been explored in fear- and anxiety-related psychopathology such as posttraumatic stress disorder (144), and

GC administration prior to memory reactivation may be effective in reducing fear memory (2). Whether and how such interventions interact with synaptic engrams will be important to explore from the therapeutic point of view.

Finally, stress may alter memory in a sex-dependent manner because women have higher basal and stress-induced hypothalamic-pituitary-adrenal axis activity than men (145). Therefore, sex-dependent differences in stress-induced modulation of synaptic engrams to shape stress responsivity and susceptibility will be important for future research and clinical translation.

CONCLUSIONS

Stress alters memory strength and precision. These effects are at least in part mediated by the release of NA and GCs, which alter synaptic function and may influence engram cell dynamics. Accordingly, stress can prime synapses to regulate memory allocation and alter memory consolidation and retrieval. Low to moderate stress levels may drive NA and GCs to potentiate synapses to promote their recruitment into a synaptic engram and facilitate consolidation to promote memory strength and precision, whereas high levels can potentiate synaptic engrams and increase the size of an engram cell ensemble, causing memory generalization. Excessive or chronic stress may disrupt synaptic function, potentially leading to memory impairments and stress-related psychopathology. Technological advances related to studying synaptic engrams are now available to unravel the underpinnings of the effects of stress on memory by examining synaptic properties of engram cell ensembles. Understanding the modulatory capacity of the stress system to affect a specific engram provides clinical opportunities for developing novel avenues for the treatment of stress-related memory disorders.

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ARTICLE INFORMATION

From the Brain Plasticity Group, Swammerdam Institute for Life Sciences-Center for Neuroscience, University of Amsterdam, Amsterdam, the Netherlands (NB, SLL, HJK); the Cellular and Cognitive Neuroscience group, Swammerdam Institute for Life Sciences-Center for Neuroscience, University of Amsterdam, Amsterdam, the Netherlands (SLL); and the Department of Molecular and Cellular Neurobiology, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands (PR-R, MCvdO).

MCvdO and HJK jointly supervised this work.

Address correspondence to Niek Brosens, M.Sc., at a.a.d.brosens@uva.nl, or Harm J. Krugers, Ph.D., at h.krugers@uva.nl.

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