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Trends in Neurosciences

Review

The impact of stress on the hippocampal spatial code

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Hippocampal function is severely compromised by prolonged, uncontrollable stress. However, how stress alters neural representations of our surroundings and events that occur within them remains less clear. We review hippocampal place cell studies that examine how spatial coding is affected by acute and chronic stress, as well as by stress accompanying fear conditioning. Emerging data suggest that chronic stress disrupts the acuity and specificity of CA1 spatial coding, both in familiar and novel contexts, and alters hippocampal oscillations. By contrast, acute stress may have a facilitatory impact on spatial representations. These findings encourage a fresh look at the documented stress-induced changes in hippocampal anatomy and *in vitro* excitability, and offer a new perspective on the links between stress and memory.

Highlights

Chronic stress alters the activity of hippocampal place cells, leading to firing rate changes (rate remapping) in familiar contexts and impaired global remapping between distinct contexts.

Acute stress improves the spatial information carried by place cells, making their activity more predictive of the location of an animal in its surroundings, whereas chronic stress decreases it, suggesting that acute and chronic stress have differential impacts on CA1 spatial coding.

Associative fear learning induces partial remapping of the place cell map by altering the firing rates and preferred firing locations of a subpopulation of place cells.

The remapped place cell population following associative fear learning is preferentially activated during consolidation-associated sharp-wave ripples.

Both stress and associative fear alter CA1 neural oscillations during exploratory behavior.

Stress impacts on hippocampal function at multiple levels

A common theme across stress neurobiology research is that, although moderate levels of arousal caused by a mildly stressful or threatening situation can have a positive impact on cognition and memory, repeated exposure to stress leads to maladaptive changes [1,2]. Brain areas implicated in both stress and memory include the hippocampus, **amygdala** (see Glossary), and prefrontal cortex. This troika of circuits regulates stress responses by providing feedback to the **hypothalamic–pituitary–adrenal (HPA) axis** and are, in turn, themselves affected by stress [3–6]. We focus here on the hippocampus, which plays a crucial role in cognition and memory and contains neurons that encode spatial and temporal representations crucial for the formation of episodic memory [7].

Previous reviews have extensively covered the effects of stress on hippocampal synaptic plasticity, morphology, and molecular signaling pathways, as well as hippocampus-dependent memory [8–13]. In brief, there is general consensus that repeated exposure to stress (specifically chronic stress) disrupts hippocampus-dependent spatial memory [14], alters activity-dependent synaptic plasticity [**long-term potentiation (LTP)**] [15,16], induces hippocampal volume loss [14], and leads to dendritic atrophy and spine loss [3,17]. The impact of acute or shorter-term stress is less clear. A study, for instance, indicated that as few as three consecutive days of stress in rodents results in hippocampal volume decreases before observable spatial learning deficits [14]. Other work has found that even a single exposure to stress alters hippocampal LTP and leads to memory deficits if spatial learning occurs in a context that significantly differs from the context in which the stress was delivered [18]. Moreover, fear-learning studies, which induce stress, consistently find robust memory of the spatial context in which a rodent encounters a threatening/stressful stimulus [19,20]. These distinctions may be because fear-learning studies test the association between a context and an aversive stimulus formed during conditioning, whereas acute and chronic stress studies typically avoid spatial and temporal overlap between the stressor and the spatial context of memory acquisition/recall.

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Understanding how stress and fear alter spatial coding, both at the single-cell and population levels, can be helpful in linking stress-induced behavioral changes, such as generalization and impaired memory encoding, with physiological correlates such as place cell remapping [21]. In this review we first discuss studies that have used various animal models of stress (Box 1 and Figure 1) to evaluate the impact of acute and chronic stress on hippocampal spatial coding by examining the place cell remapping phenomenon (Box 2). Next, we assess the impact of stress on various hippocampal neural oscillations that dominate hippocampal local field potentials (LFPs) during different behavioral states, thus providing a glimpse of excitability and information flow in neural circuits (Box 3). We highlight possible reasons for the differential impacts of acute and chronic stress on hippocampal place cell activity and neural oscillations. Subsequently, we focus on the impact of threatening/aversive stimuli on hippocampal place cell activity and oscillations by discussing fear associative learning studies. We conclude with a summary and questions to be addressed by future studies.

Box 1. Different animal models of stress

A life-threatening situation, such as the presence of a predator, immediately activates the sympathetic nervous system and the release of catecholamines from the medulla of adrenal glands, initiating fight and flight responses, followed within a few minutes by the release of corticosteroids from the cortex of the adrenal glands [99,100]. Such acute stress responses have evolved to favor survival in the wild and can be modeled in rodent laboratory studies by exposing the animal to a stimulus mimicking a looming predator. Modified versions of this naturalistic stressor involve rodents encountering an artificial predator or a predator odor (cat or fox urine) in their environment. Another common protocol, although less naturalistic, involves rodents receiving aversive stimuli, such as electric foot-shocks. These paradigms, aimed to model stress responses in animals, often activate amygdala circuitry and thus are often used to examine amygdala-related functions ([100,101] for review).

The stressors we encounter as humans in daily lives, however, vary widely in both severity and duration. In animal models, chronic types of stress are known to activate the hippocampus–amygdala–prefrontal cortex circuitry, and a variety of reproducible and well-validated models have been established that attempt to capture the essence of real-life stress, at least in some circumstances – uncontrollable, unrelenting, and repeatedly occurring – as well as the ability of stress to induce anxiety, depression, addiction, and memory disruption [3,8,11]. Such animal models of stress are broadly categorized into psychological stress and physical stress (see next and Figure 1).

Psychological stressors

These stressors are typically chronic and, in laboratory animal studies, involve repeatedly exposing subjects to events such as social defeat or maternal separation. Social defeat stress involves a hostile, but non-lethal, interaction between conspecifics by typically employing a resident–intruder paradigm [102]. It results in social avoidance, reflecting depressive-like behavior, generalized anxiety, and addictive behavior; symptoms commonly reported in post-traumatic stress disorder (PTSD) patients. In rodent studies, another chronic stress paradigm is social isolation stress, which involves an adult animal being exposed to social isolation typically lasting from weeks to months [103]. Maternal separation, mentioned earlier, is a chronic neonatal stress paradigm that involves separating and isolating rodent pups from their dam and siblings for ~1–6 h per day for several days to weeks [104,105]. Maternal separation stress has been shown to affect the stress response system and alter both affective and cognitive functions.

Physical stressors

These stressors often involve repeated exposure to stimuli such as loud noise, bright light, or electric shock, and have been reported to impair hippocampal synaptic plasticity. In rodent studies, photic stress is induced by exposure to bright light (e.g., ~120 cd) typically for ~30 minutes [34]. Audiogenic stress involve delivering very loud (~100 dB) bursts of tone or white noise for ~30–120 minutes [18]. Inescapable shock stress involves delivering multiple electric shocks to the tails of restrained rodents [41] or foot-shocks in a closed chamber [33]. Restraint and the closely related immobilization stress paradigms physically restrict the movement of an animal, rendering it isolated, in physical discomfort, and unable to escape, making these stress paradigms extremely potent. Restraint stress involves completely restricting the movement of the animal for ~2–6 h, whereas immobilization stress is often delivered for ~1–2 h. Chronic restraint stress (CRS) administers the stress daily for approximately three consecutive weeks, resulting in learning and memory deficits, hippocampal atrophy, dendrite and spine loss, and impaired synaptic plasticity ([3] for review). To avoid habituation caused by repeated exposure to stress, researchers sometimes combine exposure to multiple types of stress, for instance one type per day, leading to a protocol termed 'chronic unpredictable stress'. In addition, artificially increasing stress hormones by systemic administration of corticosteroids in the absence of an overt stressor is also used in animal studies to assess the impact of stress on neural circuits [60].

Glossary

Amygdala: an almond-shaped conglomerate of multiple brain nuclei located in the temporal lobes. Among other functions, the amygdala is involved in assigning valence (negative or positive) to an ongoing event and is primarily implicated in processing emotions as well as mediating fear responses, aggression, and anxiety-like behaviors.
Contextual fear conditioning (CFC): a behavioral paradigm that is routinely used in animal studies to test the memory of a spatial context in which the subject previously encountered an aversive stimulus (foot shock, eyelid shock). CFC requires activation of both the hippocampus and the amygdala.
Corticosterone: a hormone that is rapidly released (<1 minute after encountering stress) by the adrenal glands of rodents (also found in amphibians, reptiles, and birds) that regulates glucose levels, immune system function, and the stress response. Typically, blood corticosterone levels peak at ~30 minutes from the time of encountering a stressor and remain elevated for at least 2 h.
Hypothalamus–pituitary–adrenal (HPA) axis: a stressful situation leads to activation of the HPA axis that releases a cascade of hormones culminating in secretion of glucocorticoid stress hormones (corticosterone in rodents and cortisol in human) from the adrenal glands. Overactivation of the HPA axis, often caused by chronic stress, can lead to physiological and cognitive impairments.
Linear tracks (LTs): place cell studies often employ linear tracks (LT1, LT2, etc.), to assess 1D spatial coding. The tracks can be either real/physical, for assessing coding in freely moving rodents, or virtual linear tracks to test place cell activity in head-fixed subjects.
Long-term potentiation (LTP): a persistent strengthening of synaptic efficacy based on the pattern of activity that occurred recently in that synapse. LTP was first discovered in rabbit hippocampal slices and is thought to be one of the main physiological mechanisms underlying hippocampal learning and memory.
Neuronal ensembles: electrophysiological and imaging studies often detect coordinated activity by groups of neurons, often termed neuronal ensembles (or cell assemblies). Neuronal ensembles are thought to

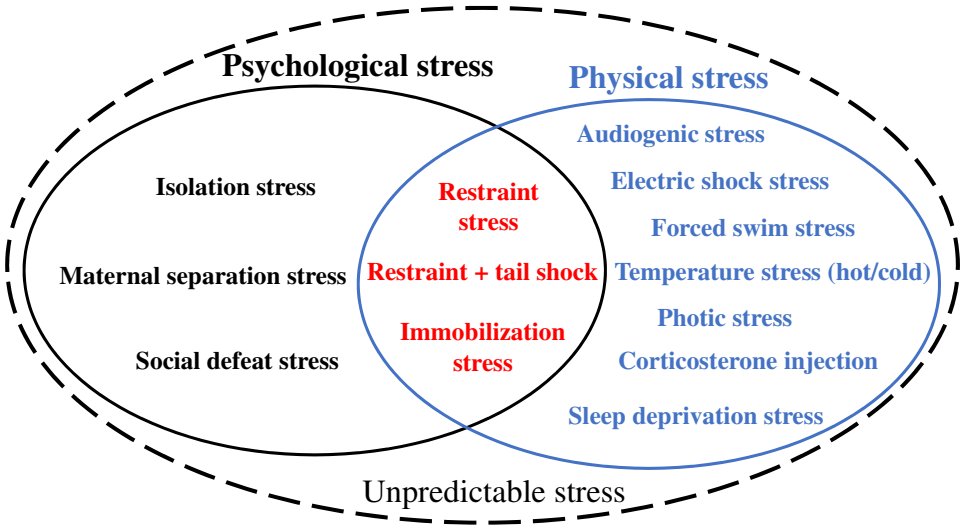

Figure 1. Stress models in rodents. A variety of approaches have been employed in rats and mice to study the impact of acute stress (single exposure) and chronic stress (multiple exposures) on the structure and function of the hippocampus. These can be broadly divided into more naturalistic psychological stressors (listed in the black oval) and physical stressors (listed in the blue oval). Immobilization stress and the closely related restraint stress are widely used rodent stress models (red text) because they not only have a physical stress component, in the form of physical restriction of rodent movement, but also involve psychological stress by rendering the stressed subject isolated and unable to escape from the stressor. The unpredictable stress model (dotted black oval) involves exposing rodents to multiple stressors across different episodes.

Disrupted place cell remapping in the hippocampus under stress

The hippocampal neural circuit is composed of densely packed pyramidal neurons across the CA subfields and granule cells in the dentate gyrus. Within each subregion, the neurons share a similar orientation with stratified excitatory inputs [22]. This layered anatomy, particularly in the CA1 subfield, and the location of the hippocampus immediately beneath the neocortex, make the structure a tractable target for high-density *in vivo* physiological recordings. Since the initial characterization of the context-specific, spatially receptive firing patterns of CA1 place cells [23], five decades of work have provided a deep understanding of the role of place cells in forming representations. These representations are based on the rate and temporal coding of the geometry/topology of physical space (spatial context), as well as on the ability of place cells to reflect changes in

represent a functional unit of the neural circuits that are involved in a specific neural computation.

Non-rapid eye movement (NREM): a stage of sleep which is thought to be crucial for memory consolidation. During NREM, place cell sequences are replayed (both forward and backward replay) during ripples – high-frequency (120–250 Hz) ripple oscillatory transients (~50–250 ms) that have been shown to play a key role in learning and memory.

Box 2. Representing changes in spatial and non-spatial information through place cell remapping

Hippocampal pyramidal cells can demonstrate highly tuned and context-specific spatially receptive fields characterized by spiking whenever the subject enters a specific location in its surroundings (Figure 2), but remaining virtually silent elsewhere in the environment. The preferred location of this enhanced firing by a place cell is called the 'place field', and although this field can show stability across repeated visits to a context, a place cell can change the location of its place field in response to changes in its surroundings. Various studies have employed a population vector analysis in which the simultaneously recorded activity of place cells is combined, and each spatial location is represented by the combined activity of all the recorded place cells. Using this approach, it has been shown that even minor modifications to familiar surroundings can result in rate remapping – changes (either a decrease or increase) in the firing rates of place cell populations without affecting the location of place fields. Further, hippocampal place cells can also represent changes in non-spatial information through rate remapping [28,29,98]. However, spatial remapping, a change in both the locations of place fields and average firing rate, is observed when substantial modifications are made in the surroundings of an animal – a phenomenon termed global remapping [29,30]. Thus, global remapping is thought to encode spatial changes and plays a crucial role in context discrimination. Importantly, disruption in global remapping between substantially different surroundings has been suggested to underlie context generalization [29]. Further, partial remapping, that involves only a fraction of place cells displaying place remapping, while others remain stable, is often observed during and after fear/aversive context conditioning and is thought to reflect episodic learning [24,73,74].

other non-spatial aspects of the physical space through a phenomenon called remapping [21,24] (Box 2). For example, place cells can modulate their firing rates in response to modifications of features in the environment of the animal, a phenomenon termed rate remapping [25]. Moreover, these changes in rate, but not in the location of the place field, can also reflect changes in the motivational state or physical point of view of the subject [26–28]. Further, significant modifications in the features of spatial contexts lead to 'global remapping' in which place cell populations display changes in both firing rates and place field locations [29,30] (Figure 2).

Chronic stress leads to instability of firing rates in a familiar context

Hippocampal synaptic plasticity plays a crucial role in the stabilization of spatial representations [31,32] and, because stress disrupts synaptic plasticity [16,33], a straightforward hypothesis is that stress may prevent the formation and/or retrieval of a stable hippocampal map. Among the early experiments that tested this idea, a study in rats deployed an audiogenic model of stress [18] in which rats were exposed repeatedly to 2 h of audiogenic stress over the course of several weeks and CA1 place cell activity was recorded before and after the stress episodes. No rate or place remapping was observed after stress; however, compared to days when stress was not administered, larger changes in unsigned firing rates were observed across the place cell population, suggesting greater rate variability after stress. The authors reasoned that this stress-induced increase in rate variability interferes with the storage of stable place maps, which in turn could lead to poor spatial memory. However, subsequent studies employing different animal models of stress noticed a consistent decrease in the firing rates of place cells following stress [15,34,35]. For example, repeated exposure to 30 minutes of photic stress resulted in a decrease in the firing rates of place cells in areas CA3 and CA1 [34], and repeated exposure to 6 h of restraint stress led to a qualitatively similar result [15]. Likewise, mice subjected to chronic immobilization stress (CIS; 2 h per day for 10 days) displayed suppressed pyramidal cell firing during the stress episodes [36] and decreased firing rates of place cells following the last day of stress [35]. These studies show that stressful experiences alter place cell firing, resulting in rate remapping in a previously encountered spatial context. However, the direction and magnitude of these firing rate changes may differ according to the type of stressor and/or the duration of stress exposure.

Chronic stress disrupts global remapping between different spatial contexts

Given that stress can alter the place cell representations of a familiar environment, a next question that arises is how stress impacts the encoding of novel surroundings. A study in mice assessed the impact of CIS on the spatial representations of two distinct **linear tracks (LTs)** – a familiar track and a novel one [37]. The authors employed a population vector (PV) analysis approach in which the tracks were divided into an equivalent number of spatial bins and a vector of firing rates was generated across all recorded place cells in each bin [29]; repeated runs on the same track resulted in high PV correlation coefficients, whereas low PV correlation coefficients were associated with changes in the population code for space. Interestingly, although the tracks used in this experiment were distinct, one day after the termination of chronic stress, significantly higher correlation coefficients were observed in the stress group compared to controls (Figure 2). Thus, after experiencing chronic stress, hippocampal place cells showed deficient global remapping, suggesting a likely mechanism by which chronic stress causes poor contextual discrimination.

Acute and chronic stress differentially alter place cell activity

Moderate levels of arousal caused by mild stress can have a positive impact on cognition and memory [2]. However, evidence from acute stress studies at different levels of hippocampal neural organization offers a mixed picture: increased neurogenesis and stable spines [38–40],

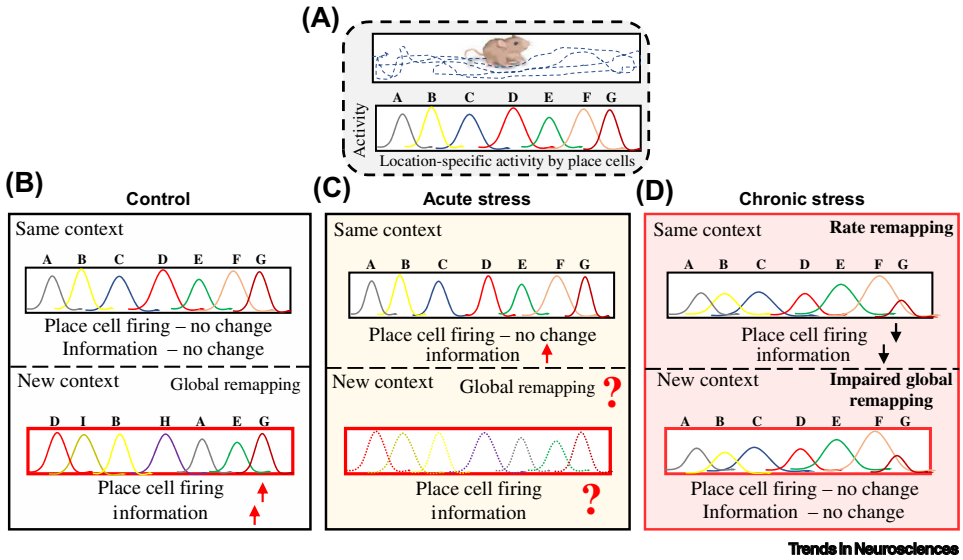

Figure 2. Impact of stress on hippocampal spatial coding. Experimental studies involving rats and mice demonstrate that acute and chronic stress differentially affect the activity of CA1 place cells. (A). Schematic depicting the exploratory activity by a rodent on a linear track (above) and a cartoon of place fields on the track showing the location-specific activation of seven place cells. (B) Re-exposure to a familiar track does not significantly alter the firing rate of place cells, the information content of place cells, or the location of place fields (top), whereas exposure to a novel track leads to increased firing, enhanced information content, and rearrangement of place fields, where some cells stop firing and new cells become active, leading to global remapping [29] (bottom). (C) After acute stress, re-exposure to the familiar track does not alter firing rate but leads to increased information content without affecting the place field arrangement [35] (top). Whether acute stress in adult subjects alters the location of place fields in a novel track remains unknown (bottom). (D) After chronic stress, re-exposure to familiar track leads to decreased firing rate [15] and lower information content [38] without significantly changing place field location (top). Chronic stress alters global remapping [36] because place cells do not significantly alter their firing rate, information content, or the location of place fields (bottom).

but impaired learning and LTP [18,41,42]. Accordingly, it is unclear at this stage whether acute stress facilitates or disrupts spatial coding. A recent study [35] found that, although acute stress did not result in rate remapping in a familiar context, it did lead to an increase in place cell spatial information [43] – that is, the ability of neuron spiking to predict information about the location of the animal. However, with repeated stress, spatial information decreased, likely caused by the broadening of place fields (Figure 2). Importantly, altered spatial information after chronic restraint stress was also reported in a study that employed head-mounted wide-field optical imaging and assessed the activity of hippocampal pyramidal cells in freely moving mice [38]. Thus, acute and chronic stress appear to have differential and opposing impacts on the acuity of CA1 spatial coding.

Stress alters hippocampal neural oscillations

Oscillatory activity in hippocampal LFPs can serve as a signature of the behavioral state of an animal [44] (Box 3). Active exploration and attentive states are associated with high-amplitude theta (6–12 Hz) and gamma (30–90 Hz) oscillations, whereas idle states (awake immobility/slow-wave sleep) and long pauses during exploration display irregular activity punctuated by high-frequency (120–250 Hz) sharp-wave ripples (ripples). It is not yet clear if neural activity during stress resembles that of an attentive state, including enhanced theta and gamma oscillations, or that of an idle state dominated by ripple activity. A recent study employing immobilization stress in mice reported that hippocampal LFP signals broadly resembled the latter, and displayed low power in the theta band and sporadic ripple activity [36]. However, subtle but

Box 3. Hippocampal neural oscillations during behavior

Local field potentials (LFPs) are extracellular potentials that are present around neurons. LFPs not only reflect spiking activity but also provide a measure of summated synaptic inputs into a local region and are thought to mediate behavioral metaplasticity [44]. During movement, rodent hippocampal LFPs are dominated by large-amplitude theta (6–12 Hz) oscillations and occasional bursts of higher-frequency (30–90 Hz) gamma oscillations that often occur at specific times during theta cycles [106]. Theta oscillations are thought to provide a clock-like mechanism through which distant cells can synchronize their activity, leading to formation of Hebbian cell assemblies and aiding in information coding in neuronal circuits. The interplay between theta and the activity of hippocampal pyramidal cells is reflected in temporal coding mechanisms, such as theta phase preference, theta phase precession, and theta sequences; all these phenomena are related to the precise temporal organization of place cell activity. Similarly, a substantial fraction of pyramidal cells (~30–50% of cells) also display phase-locking to ongoing gamma oscillations [35,106], which is also thought to contribute to the formation of cell assemblies. CA1 gamma oscillations have been shown to manifest in distinct sub-bands – slow gamma (25–50 Hz) and fast gamma (55–90 Hz), although the two rarely co-occur in a single theta cycle. It has been suggested that CA1 gamma oscillations reflect dynamic changes in information inflow to area CA1 by switching between the Schaffer collateral (SC) and temporoammonic (TA) pathways that relate to slow and fast gamma, respectively [66].

During idle states such as quiet wakefulness and NREM sleep, rodent hippocampal LFPs become more irregular but exhibit periodic high-frequency (120–250 Hz) oscillatory transients termed sharp-wave ripples (SPW-Rs or ripples) [55]. Sequences of hippocampal place cell firing, which occur over tens of seconds during exploratory behavior, are reactivated in a compressed manner during ripples, typically ~150 ms in duration, suggesting that they play a role in memory consolidation [85]. It has been reported that suppression of ripples, during both sleep and exploratory pauses (awake ripples), affects spatial learning; these findings provide support for the hypothesis that ripples are crucial for memory consolidation [55]. Previous studies have demonstrated that reactivation of place cell sequences (both forward and backward replay) during spatial tasks take place during pauses in active exploration when awake ripples occur at the locations where the rodent makes a choice. This has led researchers to suggest that ripples may be crucial for memory recall as well as for future planning ([85,107]; *cf* [108]). Interestingly, slow gamma (20–50 Hz) oscillations have also been noted at the beginning of awake ripples [109], further suggesting that coordinated activity between the CA3 and CA1 circuits plays a role during memory retrieval, especially when the animal takes long pauses during exploratory sessions (*cf* [110]). Although some studies have reported gamma oscillations primarily during retrieval, others have observed gamma oscillations during the encoding phase. However, the functional significance of hippocampal gamma oscillations is still debated ([66] for review).

significant differences from idle-state activity were also observed, suggesting that, although activity during restraint stress is rest-like, it is unique. Further, CA1 pyramidal cells displayed low firing rates, but enhanced coactivity during ripples. However, a study that combined restraint and tail-shock stress noted increased theta power during stress [41], again suggesting that the type of stressor employed can led to unique physiological effects.

The theta and gamma oscillations that are present in the hippocampus during exploration are crucial for the temporal organization of neuronal activity, both at the single-cell and population levels [45]; thus, stress-induced changes in neural oscillations during exploratory behavior may provide additional information about altered spatial coding in the hippocampus under stress. A study in rats examined auditory evoked potentials, short-latency LFP signals obtained in response to auditory signals, and found that acute immobilization stress enhanced beta/gamma, but not theta, oscillatory power in CA1 and CA3, likely indicating enhanced information processing [46]. Further, another acute immobilization stress study also did not find altered theta power during subsequent exploration of a familiar track in mice, but observed a stronger influence of these oscillations on ongoing neuronal activity as the phase-locking of place cell spiking to theta strengthened [35]. The theta phase-preference of place cell spiking is thought to facilitate hippocampal information processing by dynamic grouping of distant place cells [47]. Together, the sharpening of place cell activity in the form of increased information content by place cells (rate code) and the facilitation of spiking to theta (temporal code) support the idea that acute stress does not disrupt hippocampal information coding, and instead may facilitate it.

Stress can also alter the gamma oscillations that often co-occur with theta during exploratory behavior. For example, a study in rats reported that prenatal stress (PS) altered neural oscillatory activity in the developing hippocampus [48]. Specifically, offspring of rats that experienced

restraint stress during gestation days 15–21 reported altered coherence between theta and gamma oscillations in areas CA3 and CA1. A study in adult rats that employed auditory evoked potentials to assess the responses of the hippocampus–amygdala circuitry after CIS observed a decrease in gamma power in both areas CA3 and CA1 [46]. Similarly, in a study on mice, CIS was shown to be followed by a decrease in gamma band (30–90 Hz) power, as well as by an increase in the variability of place cell modulation by slow gamma (30–50 Hz) oscillations [35]. Much like theta modulation, the gamma phase-locking of place cell oscillations is hypothesized to facilitate the formation of cell assemblies (**neuronal ensembles)** that are thought to underlie information coding [49]. Thus, observations that chronic stress disrupts gamma oscillations concurs with earlier literature on the detrimental effect of stress on hippocampal information processing. Notably, the negative impact of chronic stress on gamma oscillations is not limited to the hippocampal circuits because recent chronic stress studies have reported altered gamma oscillations in disparate brain regions, including the nucleus accumbens (NAc) [50] and anterior cingulate cortex (ACC) [51].

A recent study that examined the impact of immobilization stress on pyramidal cell coactivation during ripples found that, after chronic stress, the coactivity of pyramidal cells was significantly greater than that observed in an idle state before the onset of stress [36]. A caveat to these experiments is that no exploratory place data were included, therefore it is unclear whether, and if so how, chronic stress may affect ripple-associated replay of place cells. Thus, although stress studies have begun to gain insights into the altered representation of spatial context, close examination of the impact of stress on the role of hippocampal circuits in the retrieval of spatial representations is still lacking.

Mechanisms mediating stress-induced disrupted spatial coding

How does chronic stress disrupt global remapping? A key region to consider is CA3, which, via anatomical heterogeneity along its transverse axis, can contribute to both pattern completion and pattern separation [52,53]. Briefly, proximal CA3 receives input predominantly from the dentate gyrus and lacks extensive recurrent connectivity, thus biasing it towards separation and context discrimination, whereas distal CA3 receives strong input from the medial entorhinal cortex (MEC) and has robust autoassociative connectivity, thus favoring recognition of previous input patterns and pattern completion. Moreover, these distinctions are passed on to CA1, where proximal CA3 targets distal CA1 and distal CA3 targets proximal CA1 [54]. Thus chronic stress-induced loss of anatomical connectivity in the form of dendritic shrinkage and spine loss within regions CA3 and CA1 [3,17] can impact both the pattern-completion and pattern-separation processes, thus disrupting global remapping and preventing stressed subjects from unambiguously discriminating between novel and familiar contexts [37].

After chronic stress, hippocampal neural activity during idle states [awake immobility/**non-rapid eye movement (NREM) sleep**] begins to show physiological phenotypes that are typically only observed during stress exposure [36]. Idle states have been shown to be involved in memory consolidation (extensively reviewed in [55]) as well as in the downregulation of global synaptic plasticity [56–58] through homeostatic processes to prepare circuits for subsequent information coding. This line of reasoning suggests that, after chronic stress, hippocampal synapses may have limited capacity to undergo subsequent plasticity and new encoding. Consistent with this link between plasticity and remapping, it has been shown that, during exploratory behavior, optogenetic inhibition of a subset of CA1 place cells led to place remapping in the inhibited neurons, rate remapping in a disinhibited subpopulation, and no remapping in the remaining cells, suggesting that ongoing plasticity is necessary to maintain a stable map [59]. In view of this report, chronic stress likely altered the ability of hippocampal synapses to undergo synaptic

plasticity [15,16] during encoding, which could disrupt the stabilization of novel spatial representations, resulting in poorer spatial discrimination.

Why do stressful experiences lead to rate remapping when rodents are re-exposed to the same spatial context? To gain a mechanistic understanding of this phenomenon, a study examined whether elevated levels of **corticosterone**, a rodent stress hormone, led to rate changes [60]. Indeed, corticosterone administration in behaving rats led to rate remapping, and the majority of place cells increased their firing rates post-corticosterone injection. Interestingly, a recent study that exposed mice to 8 weeks of corticosterone and performed calcium imaging noticed decreased recruitment of place cells during linear track exploration [61]. Thus, although elevations of corticosterone levels do modulate place cell firing, the trend emerging from these studies is not entirely consistent with findings from studies in animals exposed to stress [18], suggesting that corticosterone is not the sole contributor to the effects of stress on place cell coding. It has also been suggested that norepinephrine, which is also released during stress, may play a crucial role in suppressing hippocampal activity during and after stress [36]. Further, the amygdala may also play a role in hippocampal stress phenotypes: first, the influence of the amygdala on hippocampal functionality increases as chronic stress progresses [46,62]; second, amygdala stimulation induces rate remapping by decreasing place cell firing in a familiar recording chamber [60].

What leads to disrupted CA1 gamma oscillations after chronic stress, and what does it signify? Mechanistically, perisomatic inhibition is hypothesized to play a key role in the generation of gamma oscillations [49,63]. Previous stress studies have reported a significant decrease in the number of parvalbumin-positive (PV^+) interneurons after exposure to chronic stress [64,65]. Thus, a shift in inhibitory–excitatory balance induced by chronic stress is a primary suspect in LFP phenotypes, including decreased gamma power and altered phase locking between gamma oscillations and place cell spiking in area CA1 [36]. Functionally, because the presence of neural oscillations in a circuit reflects ongoing information flow [66], disrupted CA1 gamma oscillations, both in the low- and high-gamma bands, after chronic stress suggests poorer communication between area CA1 and its major inputs – area CA3 (via the Schaffer collaterals, SC) and the MEC (via the temporoammonic pathway, TA). Reports that chronic stress alters physical connectivity within hippocampal circuits by inducing dendritic atrophy, spine loss, and impaired CA1 LTP [3,8], and reduces TA excitability [67], are consistent with the altered information flow hypothesis [35].

The observation that acute stress leads to increased spatial information and theta phase locking of place cells [35] appears to contradict earlier observations of impaired spatial learning and LTP after a single stressful experience [18]. However, apart from differences in the type of stressor used, these studies also differed in the order of stress delivery and spatial encoding. In the spatial learning study [18], rats experienced audiogenic stress before spatial learning, whereas the place cell study first exposed mice to a linear track and then administered immobilization stress. Why is the order of stress experience a potentially crucial factor? It has been hypothesized that stress itself may produce LTP in the hippocampal synapses coding the stressful situation, thus occluding subsequent LTP induction [68]. Altered post-stress LTP after audiogenic stress exposure concurs with this idea [18]. However, in the place cell study the mice formed their initial spatial representation before experiencing acute stress. As a result, following stress, the map showed high stability but decreased place field size, leading to an increase in spatial information. Further, in the audiogenic stress study, although the authors performed place cell recordings when rats first experienced a spatial context before stress, the pre-stress and post-stress data were combined across multiple recording days, preventing comparison of the impact of the first/acute stress versus subsequent repeated stress episodes. Nonetheless, the interpretation that acute stress may

have facilitatory effects on hippocampal spatial coding is based on limited data, and this conclusion should therefore be further tested in future work.

Associative fear learning alters hippocampal spatial coding

The hippocampus plays a crucial role in remembering the locations where life-threatening stimuli are encountered. Experimental studies often assess such learning in rodents by employing associative fear-learning paradigms such as **contextual fear conditioning (CFC)** and inhibitory avoidance. CFC probes the memory of a subject of encountering an aversive stimulus (e.g., electric shock, exposure to predator or predator odor) in a specific context, typically using the innate freezing response of an animal to assess memory [69]. Inhibitory avoidance differs from CFC in that memory is assessed by the tendency of an animal to avoid the region of the recording chamber where the aversive stimulus was encountered [70]. Importantly, both tasks invoke acute stress and have been used to model post-traumatic stress disorder [71,72]. Further, place cell studies using fear conditioning or inhibitory avoidance tasks report that fear learning alters hippocampal spatial coding.

Associative fear learning induces place remapping

A recent study reported partial remapping – in other words, a fraction of CA1 place cells changed the location of their place fields – after rats experienced a foot shock on a linear track, whereas other neurons displayed increased firing rate variability following the shock [73]. Another study in rats employed a spatial decision-making task that included the avoidance of a shocked arm and also found partial remapping of the CA1 place cell population [74]. A similar shock-avoidance approach was used in a recent calcium-imaging study in mice to assess hippocampal spatial coding [75]. During the acquisition phase, after receiving foot-shock in any quadrant of the shock chamber, the mouse could escape to other quadrants. This study found a decrease in firing rate of place cells and smaller place fields, as well as increased information content. Thus, associating a previously known spatial context with a threatening/aversive stimulus often leads to spatial remapping by a significant fraction of CA1 place cells. Interestingly, a study that assessed spatial coding following tone-cued foot shock found that some place cells in the conditioned context became additionally responsive to the auditory tone, but only when the subject displayed a freezing response in the place field of the cell [76].

Another study which exposed rats to an artificial predator (robotic gator) in a familiar context, and later recorded place cell activity in the same surroundings without the robot present, observed place cell remapping, but only in the zone where the robot was previously encountered [77]. These data are in agreement with the inhibitory avoidance calcium-imaging study that noted stronger remapping closer to the location where foot-shock was encountered [75]. Encountering predator odor, even in absence of the physical predator, leads to spatial remapping. For example, in a predator odor contextual fear-conditioning study, mouse place cell activity was recorded during the conditioning phase in the presence of a predator odor (coyote urine) [78]. This study reported spatial remapping by ~60% of its place cells during conditioning, as well as partial remapping during testing in the same context in the absence of the odor. Another study along similar lines that also extended spatial coding analysis to the extinction phase found that, although some place cells displayed remapping during conditioning with predator odor, others remapped specifically during extinction, and a subpopulation did not undergo remapping at all [79].

Associative fear learning alters hippocampal neural oscillations

Prominent theta oscillations in the mouse hippocampus have been observed during fear recall in a cued version of the fear-conditioning paradigm [80], as well as during testing of anxiety-like behavior on the elevated plus maze [81,82,84]; also [111]. Further, presentation of an artificial

predator (robotic gator) also enhances power in the theta band, measured indirectly by the temporal profile of spiking across neuronal populations ([77]; more information on altered theta oscillations associated with stress is provided in [112]). Predator odor contextual conditioning studies have also reported altered hippocampal neural oscillations, including increased amplitude of beta oscillations [83], as well as significant coupling between low-gamma oscillations and place cell spiking [79]. Thus, hippocampal oscillatory activity and the place cell spiking associated with these oscillations are altered during threatening situations, although the *in vivo* physiology data differ according to the threatening stimulus used.

Recent work has suggested that ripples occurring during pauses in exploratory behavior are crucial for both memory consolidation and decision making [85]. These pauses often occur at locations where the animal must make a goal-directed decision. Hippocampal pyramidal cell activity during these ripples can be temporally ordered to reflect a compressed sequence of place cell spiking similar to that observed during earlier exploration – a phenomenon termed replay [85,86]. A recent fear-learning study that recorded hippocampal activity in rats trained to avoid a shock-delivery arm found increased place cell replay during awake ripples [74]. Interestingly, this increase in ripple-associated replay was selective for place cells that remapped during the learning phase of the task, emphasizing the role of awake ripple-associated replay during learning. Relatedly, another fear-learning study that examined the role of awake ripples in memory retrieval employed avoidance of a shock zone on a linear track [73] and reported that, after experiencing the shock, replay sequences preferentially began with place cells representing the current location of the animal and extended with the trajectories terminating in the shock zone. Thus, the ripple-associated spiking of place cells has been key in elucidating the role of fear in memory retrieval and decision making. Extending these investigations to the domain of stress remains a goal for future work.

Experimental studies have reported functional differences across the dorsoventral axis of the hippocampus [87,88], finding that the dorsal hippocampus is crucial for the encoding of space [89] and time [90], whereas the ventral hippocampus mediates (among other functions) defensive [91] and anxiety-like behaviors [84,92,93]. Place cell studies have also found differences across the dorsoventral axis, where ventral hippocampal pyramidal cells display poorer spatial selectivity than those in dorsal hippocampus [94,95]. Interestingly, unlike disrupted LTP in the dorsal hippocampus, acute stress and corticosterone application facilitate ventral hippocampal LTP [96]. Thus, it is likely that the impact of stress on ventral hippocampal neural activity may differ from that of the dorsal hippocampus; future studies collecting in *vivo* electrophysiology data from the ventral hippocampus during associative fear learning in animal models of stress are needed for addressing these possibilities.

Concluding remarks and future perspectives

We have assessed recent hippocampal spatial coding studies involving stress and fear-learning paradigms. Although there is much variation in protocols across laboratories, and exact definitions of acute versus chronic stress in these paradigms differ, we have considered that the first exposure to stress relates to acute stress, whereas repeated exposure to either the same or multiple stressors reflects chronic stress. Chronic stress exposure consistently impairs the acquisition of novel spatial representations and leads to poor spatial discrimination. In acute stress studies, the temporal ordering of spatial acquisition and encountering the stressor or threatening stimulus appears to be a crucial factor in determining whether acute stress facilitates or impairs hippocampal spatial coding. How this occurs is not fully clear and merits further investigation, but enhanced level of noradrenaline and attention-related processes could be at play. In addition, an associative fear experience consistently results in a substantial fraction of place cells undergoing spatial remapping.

Outstanding questions

How does stress alter the consolidation of newly acquired spatial representations? The studies discussed in this review have focused on neural activity during encoding and recall of spatial representation; however, the impact of stress on consolidation processes that occur during idle states, such as awake immobility and sleep, remain largely unexplored.

Does stress alter temporal coding in the hippocampus? Hippocampal pyramidal neurons are reported to encode both spatial and temporal representations; it is thus plausible that stress may also alter hippocampal temporal coding.

Do the impacts of stress differ across the dorsoventral axis of the hippocampus? Whereas the dorsal hippocampus plays a key role in the encoding of space and time, the ventral hippocampus mediates (among other functions) anxiety-like behavior. Because chronic stress causes dendritic atrophy in both regions, systematic studies will be necessary to assess the impact of acute and chronic stress on neural activity across this axis.

Does the amygdala contribute to stress-induced hippocampal place remapping, and if so how? The amygdala sends glutamatergic inputs to the hippocampus and is thought to play a role in the effects of stress on hippocampal learning and memory and synaptic plasticity; however, its role in stress-induced place cell changes is poorly understood.

Although the number of studies examining the impact of stress on hippocampal spatial coding has been increasing, relatively little is known about how stress changes the neural oscillations that dominate the hippocampal LFPs during information coding and retrieval. Accordingly, much remains to be elucidated in relation to the neural mechanisms underlying disrupted information coding in hippocampal circuits (see Outstanding questions). Further progress, we would argue, will require that advances in information coding analysis are incorporated into stress neurophysiology studies. The role of theta sequences, for instance, which are thought to support spatial navigation [97], remains to be examined in the context of stress. Similarly, how stress alters the occurrence and properties of place cell replay – the sequential reactivation of place cells during ripples which is hypothesized to mediate consolidation of previously acquired information and decision-making processes [85,86] – should be studied in depth.

Some of the key questions that require attention in future work include elucidating the impact of stress on consolidation processes and temporal coding [7,98], characterizing the differential impact of acute and chronic stress on spatial and non-spatial representations across the dorsoventral axis of the hippocampus [92,93], and probing the contributions of the amygdala in mediating hippocampal stress phenotypes.

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Declaration of interests

The authors declare no competing interests.

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