Stress, memory and the amygdala

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Abstract | Emotionally significant experiences tend to be well remembered, and the amygdala has a pivotal role in this process. But the efficient encoding of emotional memories can become maladaptive — severe stress often turns them into a source of chronic anxiety. Here, we review studies that have identified neural correlates of stress-induced modulation of amygdala structure and function — from cellular mechanisms to their behavioural consequences. The unique features of stress-induced plasticity in the amygdala, in association with changes in other brain regions, could have long-term consequences for cognitive performance and pathological anxiety exhibited in people with affective disorders.

Stress has many effects on the brain. In addition to preparing an individual for the acute consequences of dangerous or threatening situations and the return to homeostasis, an important function of stress is to induce long-term adaptive responses[1]. Enhanced memory for stressful or emotionally arousing events is a well-recognized, highly adaptive phenomenon that helps us to remember important information. Findings from experimental studies indicate that people have good recollection of where they were and what they were doing when they experienced an earthquake[2] or witnessed an accident[3]. Similarly, rats remember the place in a piece of apparatus where they received a footshock or the location of an escape platform in a tank filled with water[4,5]. Such memory enhancement is not limited to experiences that are unpleasant or aversive: pleasurable events also tend to be well remembered.

There is extensive evidence that the amygdala, a group of nuclei located in the medial temporal lobe (FIG. 1), is crucially involved in regulating stress effects on memory[6]. Findings indicate that stress hormones and stress-activated neurotransmitters enhance the consolidation of memory for emotionally arousing experiences through actions involving the amygdala. Such amygdala activation strengthens the storage of different kinds of information through the amygdala's widespread network of efferent projections to other brain regions. However, stress and emotional arousal do not only induce strong memories of new information: they can also impair our remembering through amygdala interactions with other brain regions.

But the brain is not a static organ: it has structural and functional plasticity that can have both adaptive and maladaptive consequences[7,8]. It is now evident that intensely emotional events or chronic exposure to stressful experiences can create traumatic memories and even result in the development of mood and anxiety disorders, including post-traumatic stress disorder (PTSD) and major depressive illness. Animal models indicate that acute and chronic stress induce long-term functional and morphological alterations in specific amygdala nuclei, together with associated changes in other brain regions such as the hippocampus and the prefrontal cortex, which might underlie the cognitive changes, increases in anxiety-like behaviour and mood alterations that are found in these conditions. Importantly, stress-induced functional and structural changes in the amygdala have a pattern that differs entirely from that observed in these other brain regions.

In this Review we first summarize the role of the amygdala in mediating the effects of acute stress on learning and memory, and the neurotransmitters and hormones involved in this process. Next we describe how acute and chronic stress exposure induces functional and morphological changes in the amygdala as well as neuronal remodelling in other, associated brain regions. We then discuss how such changes in amygdala function and morphology, and the associated changes in these other brain regions, might contribute to maladaptive responses after exposure to severe or chronic stress.

The amygdala in memory consolidation

Acute stress exposure induces the activation of many different hormonal and neurotransmitter systems[9]. Lots of these systems are known to influence memory consolidation processes. Extensive evidence indicates that the basolateral complex of the amygdala (BLA; consisting of the lateral, basal and accessory basal nuclei) is an important locus for integrating these modulatory influences on memory consolidation[10].

A central role for noradrenaline. Noradrenaline released into the amygdala in response to stressful or emotional stimulation[11] has a central role in regulating stress effects

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Inhibitory avoidance task
A learning task in which animals are placed in a small starting compartment or on a small platform and receive a single footshock after entering a larger compartment or stepping down from the platform. Memory of the one-trial training experience is usually tested by placing the animals back in the same position and recording the delay before they move to the place where they received the footshock.

Contextual fear conditioning
A learning paradigm in which animals are placed in a piece of apparatus and given a series of footshocks. Memory of the training experience is typically assessed by measuring how long the animals freeze when they are subsequently replaced in the apparatus.

on memory consolidation. Infusions of noradrenaline into the BLA, but not the adjacent central nucleus of the amygdala (CeA), of mice and rats immediately after training on emotionally arousing learning tasks enhance the consolidation of memory of such training experiences, whereas blocking training-induced noradrenaline with β-adrenoceptor antagonists impairs this consolidation[12,13]. Activation of β-adrenoceptors in the BLA post-training enhances memory consolidation through stimulation of the cyclic AMP-dependent protein kinase pathway[14]. Activation of α1-adrenoceptors in the BLA also enhances memory; however, activation of this receptor type seems not to directly activate cAMP, but to enhance memory consolidation through a potentiation of the β-adrenoceptor cAMP response[14,15].

Extensive evidence indicates that noradrenergic activity in the BLA is essential in mediating the modulatory effects of other hormones and neurotransmitters on memory consolidation. Many studies have reported that intra-BLA infusions of the GABA (γ-aminobutyric acid)-ergic receptor antagonist bicuculline enhance memory consolidation and that GABAergic receptor agonists impair memory[16,17]. Antagonists for β-adrenoceptors infused into the amygdala block the memory-enhancing effects of bicuculline infused concurrently[10]. Stress exposure also induces rapid increases in BLA levels of endocannabinoids, a family of membrane-derived retrograde messenger molecules[18]. Recently it has been reported that activation of the CB1 endocannabinoid receptor in the BLA enhances memory consolidation whereas blockade of CB1 receptors induces memory impairment[19]. As CB1 receptor activation is known to decrease GABA release in the BLA and other brain regions[20,21], such findings suggest that endocannabinoids might enhance memory consolidation by inhibiting GABAergic activity in the BLA, thereby presynaptically increasing noradrenergic transmission.

Effects of stress hormones. The effects of adrenal stress hormones (such as adrenaline and glucocorticoids) on the enhancement of memory consolidation also depend on the integrity of the amygdala noradrenergic system[10]. Williams and colleagues[22] reported that adrenaline administered systemically immediately after inhibitory avoidance training increases noradrenaline levels in the amygdala, whereas others showed that infusions of a β-adrenoceptor antagonist into the amygdala block the memory-enhancing effects of peripherally administered adrenaline[23]. As adrenaline is a polar substance that does not readily cross the blood–brain barrier, a pathway running from the periphery to the CNS is most likely involved in mediating adrenaline's effects on amygdala modulation of memory consolidation[24,25]. It is now well established that systemic adrenaline can activate peripheral β-adrenoceptors located on vagal afferents that terminate in the nucleus of the solitary tract. In turn, noradrenergic cell groups in this brain region send direct projections to the amygdala. In addition, the nucleus of the solitary tract regulates the noradrenergic activity of the forebrain through indirect projections to noradrenergic cell groups in the locus coeruleus[26], the main source of noradrenaline inputs to the BLA[27].

Unlike adrenaline, glucocorticoid hormones readily enter the brain and bind directly to adrenal steroid receptors in the BLA and other brain regions[28]. A specific glucocorticoid receptor (GR) agonist administered into the BLA immediately after inhibitory avoidance training or contextual fear conditioning enhances memory consolidation, whereas a GR antagonist impairs the consolidation of memory of these and other learning experiences[29,30]. Furthermore, neurotoxic lesions of the BLA, but not the CeA, block the memory enhancement that is induced by systemically administered glucocorticoids[31,32]. Glucocorticoids also require noradrenergic activity in the BLA to enhance the consolidation of memory for emotionally arousing training[33,34]: post-training activation of GRs in the BLA facilitates memory consolidation through a rapid potentiation of the noradrenaline signalling cascade[34]; conversely, intra-BLA infusions of a GR antagonist attenuated the dose–response effects of a β-adrenoceptor agonist on retention enhancement for inhibitory avoidance training[34]. These findings suggest that glucocorticoids facilitate the effects of noradrenergic stimulation in the BLA on memory consolidation through an interaction with the β-adrenoceptor–cAMP cascade.

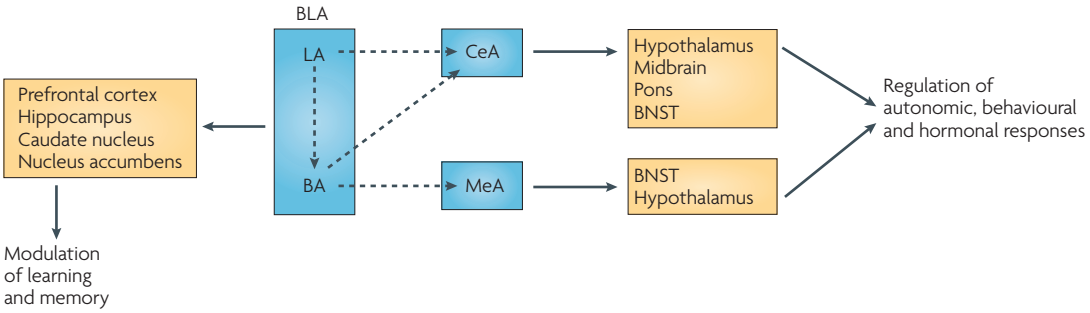


Figure 1 | **The main subdivisions of the amygdala and their intrinsic and extrinsic connections.** The basolateral complex of the amygdala (BLA) consists of the lateral amygdala (LA) and basal amygdala (BA) and projects to many different brain regions involved in learning and memory, including the prefrontal cortex, the hippocampus, the caudate nucleus and the nucleus accumbens. The BA also projects to the central amygdala (CeA) and the medial amygdala (MeA). The CeA projects to autonomic, behavioural and hormonal regulatory centres in the hypothalamus, the midbrain, the pons and the bed nucleus of the stria terminals (BNST). The MeA sends efferents to the BNST and hypothalamus.

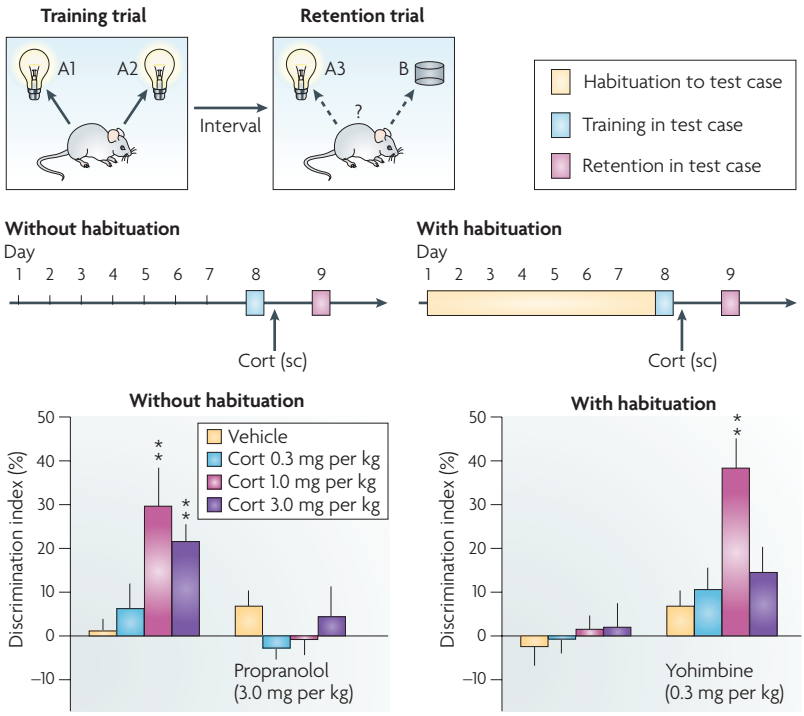


Figure 2 | **Glucocorticoid effects on memory consolidation for object recognition training require arousal-induced noradrenergic activation.** Rats were either habituated to the training context for 7 days or not habituated. On day 8 they were given a 3 min training trial during which they could freely explore two identical objects, followed by systemic drug administration. Retention was tested 24 h later by placing the rats back into the apparatus for 3 min; now one object was similar to that explored during training whereas the other object was novel. Corticosterone (Cort) injections selectively enhanced memory consolidation in context-naive rats, which showed greater emotional arousal response during training. Systemic post-training administration of the β-adrenoceptor antagonist propranolol blocked this memory enhancement in naive (emotionally aroused) rats. Co-administration of the α2-adrenoceptor antagonist yohimbine with corticosterone enhanced object recognition memory in habituated (emotionally non-aroused) rats. The data represent the discrimination index (%) on a 24 h retention trial, expressed as the mean ± the standard error. The discrimination index was calculated as the difference in time spent exploring the novel and the familiar object, expressed as the ratio of the total time spent exploring both objects. ** $p<0.0001$ vs vehicle[41]. Figure is modified, with permission, from REF. 41 © (2006) National Academy of Sciences.

Recent findings indicate that the memory-modulating effects of the neuropeptide corticotropin-releasing factor (CRF), which is released in the amygdala after stress, also depend on interactions with the β-adrenoceptor–cAMP cascade in the BLA[35]. Moreover, it was found that the CRF and glucocorticoid systems in the BLA interact in influencing β-adrenoceptor–cAMP effects on memory consolidation: a blockade of GRs in the BLA prevents concurrently administered CRF from enhancing memory consolidation of inhibitory avoidance training[35].

Role of emotional arousal. The evidence that arousal-induced noradrenergic activation in the BLA is essential in mediating the modulatory effects of stress hormones and many neurotransmitters on memory consolidation has important consequences. For example, recent findings indicate that adrenal stress hormones modulate the consolidation of memory for emotionally arousing experiences that induce the release of noradrenaline into the amygdala, but do not affect memory consolidation of neutral information[36–38]. A study that examined this issue in rats reported that corticosterone administered systemically immediately after object recognition training enhanced the consolidation of memory of this experience in emotionally aroused rats that had not been habituated to the context[39] (FIG. 2). By contrast, post-training administration of corticosterone did not enhance the retention of object recognition in habituated rats, which showed an attenuated arousal response during the training. Habituation of rats to the experimental context significantly reduced noradrenergic activity in the BLA during object recognition training, as assessed by reduced activity of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of noradrenaline[40]. In non-habituated (that is, emotionally aroused) rats, the β-adrenoceptor antagonist propranolol, administered systemically or directly into the BLA, blocked the corticosterone-induced memory enhancement[41]. To determine whether the failure of corticosterone to enhance memory consolidation under low-arousal conditions was due to insufficient training-induced noradrenergic activation, low doses of the α2-adrenoceptor antagonist yohimbine, which increases noradrenaline levels in the brain, were co-administered with the corticosterone to well-habituated rats immediately after object recognition training. The crucial finding of this study was that such an augmented noradrenergic tone was sufficient to mimic the effects of emotional arousal, in that simultaneously administered corticosterone enhanced memory consolidation[41]. Further, in habituated rats corticosterone activated BLA neurons, as assessed by phosphorylated CRE-binding protein immunoreactivity levels, only in animals that also received yohimbine. Findings of human studies are consistent with those of animal studies and have provided evidence that stress hormone effects on memory enhancement of emotionally arousing training require noradrenergic[42,43] and amygdala activity[44].

BLA interactions with other brain regions. Many of the experiments that investigated BLA involvement in memory consolidation used inhibitory avoidance and fear conditioning training and testing, but comparable effects of post-training amygdala treatments have been obtained in experiments using different kinds of aversive or appetitive training tasks. Several recent studies have indicated that the BLA can influence the consolidation of memory of different kinds of information through its many efferent projections to other brain regions[10] (FIG. 3). The BLA projects directly to the caudate nucleus and both directly and indirectly to the hippocampus[45,46], and there is considerable evidence that these two areas are involved in different kinds of learning[47,48]. In studies of rats given water-maze training, Packard and colleagues[49] found that amphetamine infused post-training into the caudate nucleus selectively enhanced memory of visually cued training, whereas infusions into the dorsal hippocampus selectively enhanced memory of spatial training. By contrast, amphetamine infused into the amygdala post-training enhanced memory for both

Water-maze task
A spatial learning and memory task that depends on the hippocampus. Rodents are trained to learn the location of an escape platform that is hidden beneath the surface in a pool of water. The cued version of the water maze task measures a form of implicit learning and memory that depends on the caudate nucleus; here, animals are trained to swim to a visible platform that is moved from one location to another across trials.

types of training. Thus, these early findings suggested that the amygdala can modulate the consolidation of memory for both caudate nucleus-dependent and hippocampus-dependent tasks.

Subsequent studies found direct evidence that interactions between the BLA and the hippocampus regulate emotional-arousal effects on memory consolidation of spatial or contextual information. Noradrenergic stimulation of the BLA, in a dose that enhances memory consolidation, increased dorsal hippocampal levels of activity-regulated cytoskeletal-associated protein (ARC)[50], an immediate-early gene product implicated in hippocampal synaptic plasticity and memory consolidation[51]. Additionally, pharmacological inactivation of the BLA impaired memory consolidation and decreased ARC mRNA and protein levels in the dorsal hippocampus[50,52]. Other studies indicated that an intact and functional BLA is required to enable memory modulation that is initiated by a manipulation of hippocampal activity: infusions of a GR agonist into the hippocampus post-training enhanced memory consolidation of inhibitory avoidance training but, most importantly, inactivation of the BLA blocked this effect[53,54].

It is now well established that post-training infusions of drugs into various cortical regions can impair or enhance the consolidation of memory for several kinds of training[55–59]. The findings of several studies indicate that the BLA modulates cortical functioning involved in memory consolidation. Neurons in the BLA project directly to the entorhinal cortex[45,60], and lesions of the BLA prevent the memory enhancement that is induced by post-training pharmacological activation of the entorhinal cortex[61]. Other recent studies indicated that the BLA interacts with the insular cortex in regulating memory consolidation of conditioned taste aversion[62] and with the anterior cingulate cortex in regulating memory consolidation of nociceptive stimulation[56]. Moreover, some studies suggested that the BLA interacts with the prefrontal cortex in regulating memory consolidation of affective training[63,64]. Together, these findings indicate that the BLA interacts with different brain regions to mediate stress or emotional arousal effects on the consolidation of memory of different types of training[65].

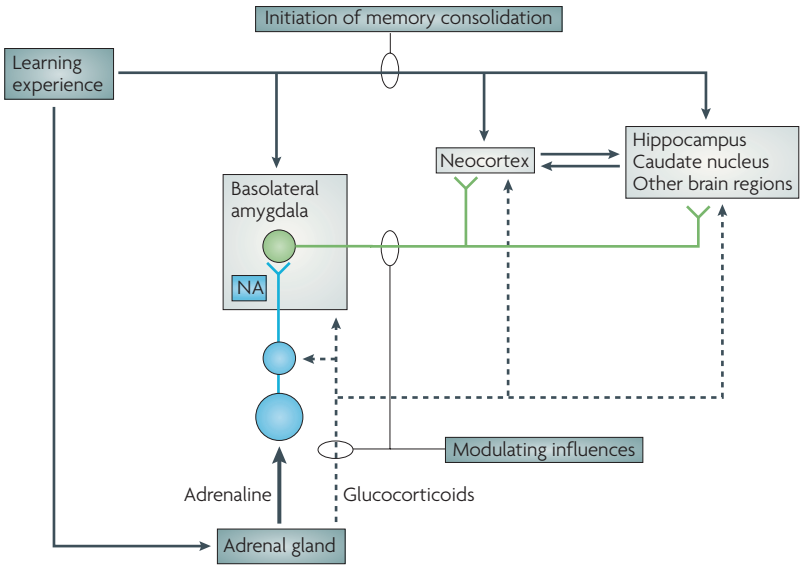


Figure 3 | **Emotional arousal-induced modulation of memory consolidation.** Experiences initiate memory storage in different brain regions. For example, spatial or contextual information recruits the hippocampus, whereas procedural information activates the caudate nucleus. Emotionally arousing experiences also release adrenaline and glucocorticoids from the adrenal gland and induce the release of noradrenaline (NA) in the basolateral complex of the amygdala (BLA). Adrenaline, which does not cross the blood–brain barrier, induces the release of noradrenaline in the BLA by activating vagal afferents to the nucleus of the solitary tract. Noradrenergic neurons in the nucleus of the solitary tract project both directly and indirectly to the BLA. Glucocorticoids freely enter the brain and can directly bind to glucocorticoid receptors in the BLA. Such stress-induced BLA activity modulates memory consolidation by influencing neuroplasticity in other brain regions. In addition, stress hormones directly activate other brain regions to enhance memory consolidation (dotted arrows); these effects also depend on intact BLA functioning[10]. Figure is modified, with permission, from REF. 10 © (2000) American Association for the Advancement of Science.

The BLA in memory retrieval and working memory

Most studies that have investigated the role of the BLA in memory have focused on its involvement in mediating the influences of stress on the consolidation of recent experiences. However, several findings indicate that the BLA, through its projections to other brain regions, also has an important modulatory role in regulating stress hormone effects on other memory functions, such as retrieval and working memory.

Stress exposure or administration of glucocorticoids shortly before retention testing impairs memory retrieval[66–69]. In contrast to the lasting effects of stress on memory formation, stress-induced impairment of memory retrieval seems to be temporary, as corticosterone injections impaired the acute retrieval of a contextual fear memory without affecting retrieval performance 48 h later[70]. Although these stress effects on memory retrieval of spatial or contextual information in rats or of declarative information in humans mainly involve the hippocampus[71–73], evidence from animal studies indicates that the BLA interacts with the hippocampus in mediating them. Indeed, lesions of the BLA or infusions of a β-adrenoceptor antagonist into the BLA block the impairing effect of a GR agonist infused into the hippocampus on memory retrieval[72,73]. Such findings indicating that stress (hormone) effects on memory retrieval require amygdala activity are consistent with evidence from human studies suggesting that glucocorticoids or psychosocial stress impair the retrieval of only emotionally arousing information or impair retrieval in only emotionally arousing test conditions[66,74,75]. Other human studies indicated that successful retrieval of emotionally arousing information induces greater activity in and connectivity between the amygdala and the hippocampus than successful retrieval of emotionally neutral information[76,77].

Certain stressors and high doses of glucocorticoids also impair prefrontal cortex-dependent working memory in rodents[78,79] and humans[80]. Animal studies have shown that glucocorticoid effects on working memory depend on functional interactions between the BLA and the medial prefrontal cortex, as a disruption of BLA activity blocks working memory impairment induced by a GR agonist administered into the medial prefrontal cortex[78].

Impact of stress on amygdala neurons

Two important themes emerge from the findings discussed so far. First, the amygdala has a pivotal role in mediating the effects of stress on the consolidation and recall of memories. Second, these effects are not confined to the amygdala: stress also modulates memory mechanisms involving other brain regions that are sensitive to stress hormones. Such findings suggest that stress exposure can induce amygdala activation, in concert with excitatory and inhibitory effects on other brain regions, to create a brain state that on the one hand promotes the long-term storage of memories of these emotionally arousing events and thus preserves significant information, but on the other hand impairs memory retrieval and working memory. It is obvious that enhanced consolidation of memory of emotionally arousing events has an adaptive value. By contrast, the stress-induced impairments of memory retrieval and working memory that occur simultaneously are certainly unwanted in challenging situations (for example, during an examination), but these effects should not *a priori* be regarded as maladaptive. In fact, a temporary blockade of memory retrieval processes during the consolidation and storage of new, emotionally arousing information might actually prevent memory distortion and thereby aid accurate storage of this information.

However, exposure to extremely aversive experiences, such as severe stress, can also lead to highly emotional, traumatic or fearful memories, which contribute to the development and symptoms of anxiety disorders, such as PTSD. Thus, important questions that arise are whether and how the neurobiological mechanisms that underlie the adaptive influence of acute stress and emotional arousal on amygdala activity — which strengthens memories of emotionally significant experiences — relate to the mechanisms that are induced by severe or prolonged stress. These questions highlight the importance of examining the impact of stress on amygdala neurons and how it compares with that on other brain regions affected by stress. A large body of evidence regarding the hippocampus has given rise to a framework in which the consequences of stress can be either adaptive or maladaptive depending on the level of glucocorticoids[81]. Although similar analyses are yet to be done for the amygdala, recent studies have begun to examine how neuromodulators, stress hormones and variations in the duration and intensity of behavioural stress trigger electrophysiological and structural changes in the amygdala.

Changes in neuronal activity and synaptic transmission. As described in earlier sections, manipulations that reduce or enhance the activity of the BLA after training have been shown to respectively impair or facilitate memory consolidation. Evidence that arousal changes electrical activity in the BLA came from a study that used a feline analogue of the inhibitory avoidance task. Single-unit activity was recorded *in vivo* in the BLA before and after a single inescapable footshock. The recordings revealed that the firing rate of many BLA neurons gradually increased after the footshock, peaking 30–50 min post-shock and then subsiding to baseline levels 2 h later. During this period of increased activity, the discharges of simultaneously recorded BLA cells were more synchronized than before the shock[82].

As described earlier, noradrenergic activation of the BLA mediates the modulatory effects of stress hormones at the behavioural level. To study this at the level of single neurons, *in vivo* single-unit recordings can be made in behaving rodents that undergo Pavlovian fear conditioning. Such recordings have shown increases in action potential firing evoked by conditioned stimuli in neurons of the lateral division of the BLA[83]. Interestingly, *in vivo* iontophoresis of noradrenaline attenuated both spontaneous and evoked firing of action potentials in BLA neurons[84]. These inhibitory effects were mediated by α2-adrenoceptors, but noradrenaline also had smaller, excitatory effects that were mediated by activation of β-adrenoceptors. These results are in agreement with *in vitro* electrophysiological recordings in BLA slices, which showed that noradrenaline enhanced excitatory neurotransmission through β-adrenoceptors[85–87] and produced inhibitory effects through α2-adrenoceptors[87]. Thus, β-adrenoceptors mediate both the facilitative effects of noradrenaline on memory consolidation and the excitatory effects in the BLA. Further mechanistic insight comes from another study that revealed how activation of β-adrenoceptors inhibits small-conductance Ca^{2+}-activated K^+ channels (SK channels) and enhances long-term potentiation (LTP) of cortical inputs to lateral amygdala pyramidal neurons[88]. The latter effect is particularly interesting because SK channels seem to be located in the immediate proximity of NMDA (*N*-methyl-D-aspartate) receptors in the dendritic spines of BLA neurons, which explains how they can regulate synaptic plasticity so efficiently. Taken together, these findings indicate that noradrenaline could have an overall inhibitory effect on spontaneous spiking in most BLA neurons but an excitatory effect on a smaller subset of neurons to amplify the signal-to-noise ratio in those neurons that are involved in memory modulation.

Although excitatory synaptic transmission could play an important part in stress-induced synaptic plasticity in the amygdala, several lines of evidence also point to a central role for GABAergic inhibitory transmission in gating these effects[89]. In whole-cell recordings from amygdala slices, noradrenaline was shown to suppress GABAergic inhibition of projection neurons in the lateral amygdala, thereby enabling the induction of LTP at thalamus–amygdala synapses[90]. Further evidence of a role for synaptic inhibition comes from findings that immediate post-training infusions of GABAergic agonists into the BLA impair memory consolidation of emotionally arousing training, whereas local administration of GABAergic antagonists enhances memory consolidation[16,17]. Other studies indicated that the enhanced memory for contextual fear conditioning caused by previous exposure to restraint stress was mimicked by infusing a $GABA_A$ receptor antagonist into the BLA; pretreatment with a positive modulator of $GABA_A$ sites prevented both of these facilitating effects[91]. Importantly, these stress-induced facilitatory effects were paralleled by GABAergic disinhibition, which resulted in a lowering of

Pavlovian or classical fear conditioning
A robust learning paradigm in which an animal rapidly learns to associate a previously neutral or innocuous sensory stimulus (conditioned stimulus), such as light or an auditory tone, with a coincident aversive stimulus (unconditioned stimulus) such as a mild footshock. Subsequent exposure to the same conditioned stimulus or cue alone elicits a conditioned response (freezing) that provides a measure of the learned association.

Iontophoresis
A process by which charged molecules are ejected onto tissue by passing electric current through the electrolyte solution containing the molecules. This causes a spurt of charged molecules to be transported out of the pipette tip.

the threshold for LTP induction in BLA slices; these cellular effects were prevented by *in vivo* pharmacological treatments that enhanced GABAergic inhibitory tone. These findings raise the possibility that a stress-induced reduction in GABAergic regulation could facilitate memory consolidation processes by triggering neuronal hyperexcitability and increased plasticity at excitatory synapses in the BLA. This view is supported by a study that examined how CRF-induced synaptic plasticity in the amygdala can translate stress into anxiety-like behaviour[92]. Repeated local infusions of urocortin (a CRF type 1 and 2 receptor agonist) into the BLA led to a persistent increase in anxiety in rats. Electrophysiological recordings from BLA neurons of these anxious animals revealed a pronounced reduction in both spontaneous and evoked inhibitory postsynaptic potentials, leading to a hyperexcitability of the BLA network. These observations are also consistent with more recent evidence for an inverse relationship between GABAergic inhibitory tone in the BLA and behavioural anxiety[93].

In vivo recordings and immunocytochemical labelling have shown that the ability of serotonin to inhibit glutamatergic activity in the lateral amygdala is dependent on the presence of corticosterone: although serotonin inhibited both synaptically evoked and glutamate-evoked action potentials in BLA neurons, it failed to do so in adrenalectomized rats. Strikingly, high but not low corticosterone doses given to adrenalectomized animals reinstated the inhibition by serotonin of excitatory transmission[94]. Conversely, recent electrophysiological studies using whole-cell recordings have demonstrated that *in vitro* application of high, stress levels of corticosterone leads to a reduction in GABAergic inhibitory synaptic transmission, along with an increase in the intrinsic excitability of excitatory principal neurons in brain slices of the lateral amygdala[95]. These findings raise the intriguing possibility that the direction of corticosterone effects on amygdala function and corticosterone's impact on memory consolidation depend on its concentration[34], and that stress-induced amygdala activation and inhibition might be tightly coupled. Under conditions of severe and repeated stress this disruption of the balance between synaptic excitation and inhibition might lead to more persistent changes in synaptic connectivity in the amygdala that are manifested as structural plasticity (discussed below).

Finally, there is growing evidence that BLA activation can also modulate synaptic plasticity in other brain regions. According to one recent study, activation of BLA inputs greatly facilitates LTP induction at corticostriatal synapses[96]. Electrophysiological findings also indicate that BLA activity influences stress- or perforant path stimulation-induced LTP in the hippocampus[97–100] and facilitates impulse transfer through the rhinal cortices of neocortical inputs to the hippocampus[101]. Recent findings that Pavlovian fear conditioning increases synchronization of theta-frequency activity in the lateral amygdala and CA1 region of the hippocampus strongly suggest that activation of an amygdala–hippocampus circuit is involved in fear-based learning[102]. More generally, studies of synchronized oscillatory activity occurring in the BLA suggest that such activity might facilitate temporal lobe as well as neocortical processes involved in consolidating explicit or declarative memory[103,104]. These findings are consistent with the evidence summarized above that the BLA influences hippocampal and cortical function by modulating stress effects on memory consolidation[24,50,53,54,105]. Consistent with this view, electrolytic lesioning of the amygdala before exposure to uncontrollable restraint and tail shock stress prevented

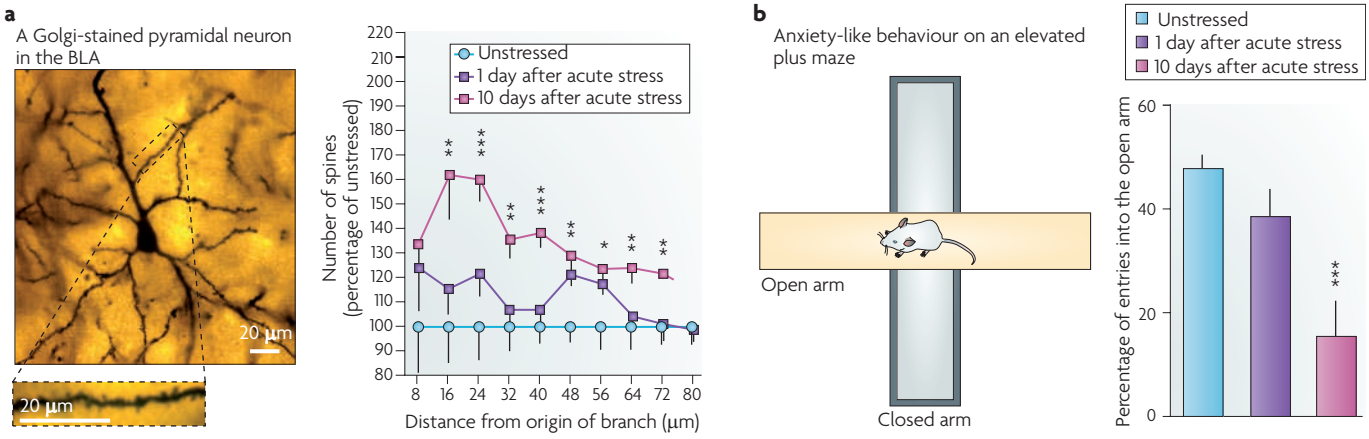


Figure 4 | **A brief exposure to stress triggers a delayed increase in anxiety and spine density in the BLA.** **a** | A single episode of acute stress (immobilization for 2 h) had no significant effect on spine density on principal neurons in the basolateral complex of the amygdala (BLA) 1 day later, which was quantified by counting the number of spines per unit length of dendrite in Golgi-stained neurons. However, 10 days after the same acute stress there was an increase in spine density that was localized to proximal dendritic segments of BLA neurons. **b** | The delayed increase in spine density was paralleled by a gradual build-up in anxiety-like behaviour measured on the elevated plus maze — there was a significant reduction in the number of entries into the open arm of the plus maze 10 days but not 1 day after acute stress[115]. * p<0.05; ** p<0.01; ***p<0.001 (all versus control). Figure is modified, with permission, from REF. 115 © (2005) National Academy of Sciences.

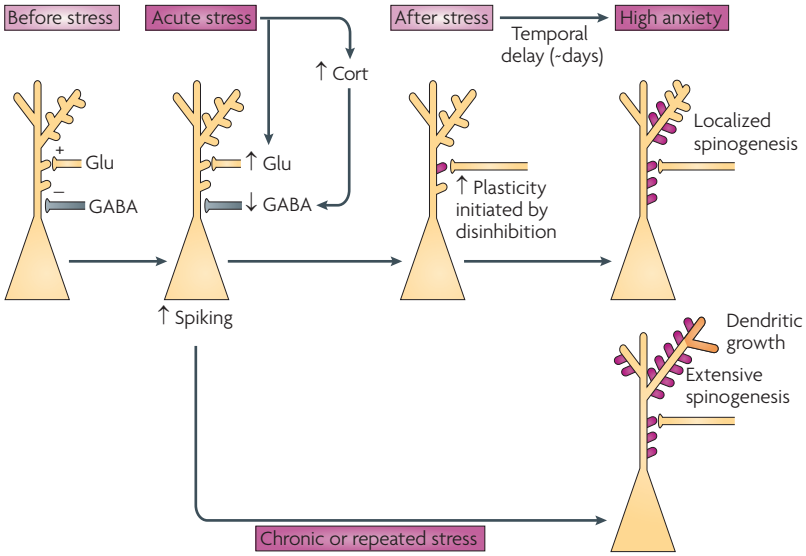


Figure 5 | **Effects of acute and chronic stress on BLA principal neurons.** Brief but severe stress (top), such as 2 h of immobilization, triggers a surge of high corticosterone (Cort) and glutamate release. High corticosterone, in turn, causes a reduction in GABA (γ-aminobutyric acid)-ergic inhibitory synaptic inputs to basolateral complex of the amygdala (BLA) cells, which also exhibit enhanced intrinsic excitability by way of enhanced action potential firing. Stress-induced disinhibition frees up the excitatory glutamatergic synapses to undergo plasticity that eventually leads to a delayed strengthening of these inputs through biochemical signalling mechanisms. These plasticity mechanisms, once triggered, continue despite restoration of normal levels of inhibition, glutamate and corticosterone after the termination of acute stress. Eventually this leads to strengthening of the structural basis of synaptic connectivity, manifested as newly formed spines (shown in purple) in the BLA, which are restricted to dendritic segments that are close to the soma[115]. If the same acute stress is repeated for several days (for example, 2 h per day for 10 consecutive days) (bottom), it has a cumulative effect in that the changes in synaptic inhibition and excitation now act on a cellular substrate that is already undergoing plasticity as a result of the earlier exposures to stress. Thus, chronic exposure to stress acts on a sliding, and continuously strengthening, baseline of plastic inputs that quickly add up to give rise to more robust and widespread structural changes (new spines; shown in purple). These plastic changes are eventually manifested as extensive spinogenesis across both primary and secondary dendrites[115]. Finally, chronic stress-induced strengthening of the physiological and structural basis of synaptic connectivity might also lead to persistent dendritic elongation (shown in orange)[108,110].

stress-induced impairment of hippocampal LTP and spatial memory in rats[106]. In more recent experiments, micro-infusions of the $GABA_A$ receptor agonist muscimol into the BLA before stress prevented stress-induced impairment of LTP in hippocampal slices[107]. Consistent with these physiological effects, at the behavioural level stress failed to impair spatial memory in the water maze in animals receiving muscimol infusions into the amygdala[107].

Changes in neuronal morphology. The modulation of neuronal and synaptic activity, discussed above, can culminate in morphological changes that persist as a longer-lasting cellular trace of stress-induced plasticity in the amygdala. Indeed, the effects of acute and chronic stress result in neuronal remodelling of synapses and dendritic branching in the BLA and medial amygdala (MeA) that are accompanied by increases in anxiety[108–111] and enhancement of fear conditioning[112–114]. A single 2 h episode of immobilization stress in rats led to a delayed increase in spine density on principal neurons of the BLA (FIG. 4), and this was accompanied by greater anxiety-like behaviour[115]. Interestingly, the increase in anxiety and BLA spine density only became evident 10 days after the acute stress. Further, this delayed formation of new spines was restricted to dendritic segments that lie proximal to the cell soma and occurred in the absence of any dendritic remodelling (FIG. 4). Thus, a single brief exposure to stress elicits modest structural changes at the synaptic level that take time to build up and that therefore have delayed anxiogenic effects at the behavioural level (FIG. 5). However, if the same 2 h stress is repeated for 10 consecutive days, the cellular and behavioural consequences are more robust. Unlike acute stress, such chronic stress caused a significant increase in anxiety within 24 h after the cessation of the stress exposure. Chronic stress also elicited increases in spine density that were more widespread than those elicited by acute stress, spanning both primary and secondary dendrites of BLA principal neurons[115] (FIG. 5).

Strikingly, the impact of chronic stress was not restricted to spines — it also triggered robust dendritic growth in pyramidal and stellate neurons of the BLA[108,110,111]. Importantly, only those forms of chronic stress that triggered dendritic growth in the BLA also led to greater anxiety-like behaviour[108,109]. These changes probably involve increased corticosterone levels as a recent study showed that chronic treatment with 10 daily doses of high physiological levels of corticosterone also leads to dendritic hypertrophy in the BLA and to enhanced anxiety[116]. The impact of chronic stress on the amygdala is also striking in its temporal persistence: even after 21 days of stress-free recovery, animals exposed to chronic stress continued to exhibit heightened anxiety and dendritic hypertrophy in the BLA[110]. Thus, the total impact of chronic stress (more spines per unit length of dendrite multiplied by more dendrites) is manifested as a significant strengthening of the structural basis of synaptic connectivity in the BLA, which in turn might serve as a cellular substrate for enhanced anxiety[117,118]. These findings suggest that an acute episode of severe stress initiates plasticity mechanisms that might not be readily evident soon after the end of stress but might eventually give rise to delayed and restricted spinogenesis (FIGS 4,5), and this in itself might be sufficient to have a long-term impact on anxiety-like behaviour. But repeated exposure to the same acute stressor pushes this cellular machinery to scale up to more robust structural plasticity, manifested as extensive spinogenesis along with enlargement of the dendritic tree in the BLA[119] (FIG. 5).

Although the BLA has been the focus of many studies on the cellular effects of stress, it is important to note that the output nuclei of the amygdala differ considerably in their response to stress. For example, 10-day chronic immobilization stress enhances dendritic arborization in neurons of the bed nucleus of the stria terminalis (BNST) but not in the CeA[120]. Further, although repeated restraint stress for 21 days leads to the formation of spines in the BLA, it has the opposite effect — a loss of spines — in the MeA, another major output nucleus of the amygdala. These divergent morphological

effects highlight distinctions between various amygdala nuclei, and they also leave open the question as to which of these changes is more important for the anxiety that results from stressful experiences, including the possibility that they are all important to some degree. First, in terms of cytoarchitecture, the BLA has been described as a 'cortical' nucleus whereas the CeA and MeA have been classified as 'non-cortical' nuclei[121]. Second, these region-specific differences in cytoarchitecture are paralleled by variations in the expression patterns of specific molecular markers that are implicated in morphological plasticity and synaptic reorganization. For example, stress-induced spine loss in the MeA depends on the extracellular matrix protease tissue plasminogen activator (TPA; also known as PLAT), which has no role in spine formation in the BLA[122,123]. Importantly, stress-induced upregulation of TPA is restricted to the MeA and CeA — it is not evident in the BLA. A similar regional gradient was reported for polysialylated neural cell adhesion molecule (PSA–NCAM), which can be a substrate for TPA-mediated proteolysis[124], with the CeA and MeA showing the highest levels of expression[125]. Chronic restraint stress causes a significant downregulation of PSA-NCAM in these nuclei but not in the BLA. These observations highlight the need to examine the subtle region specificity, possibly even cell specificity, of these molecular effects of stress in the amygdala network.

Implications and future directions

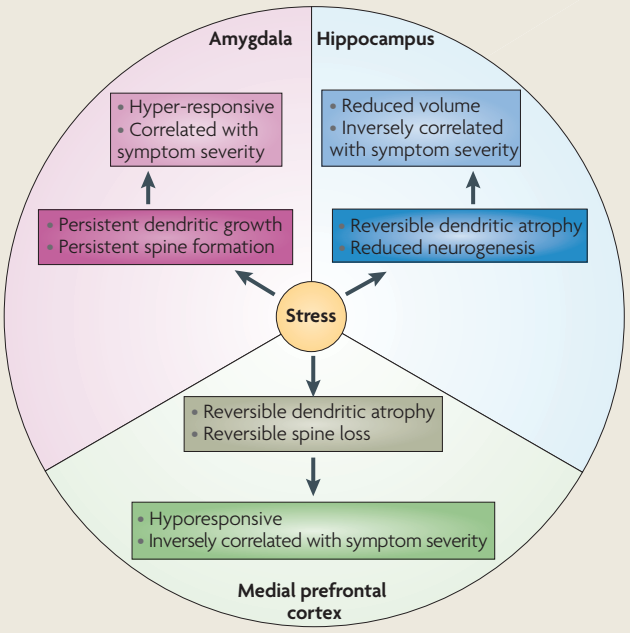
The findings summarized above — that stress exposure has direct effects on amygdala function and induces more enduring morphological effects on cells and synapses in the amygdala — has important clinical implications. Several lines of evidence indicate that after an intensely aversive experience the formation of a strong, aversive memory trace is an important pathogenic mechanism for the development of anxiety disorders such as PTSD[126]. PTSD is a chronic response to a traumatic event and is characterized by the following features: re-experiencing the traumatic event, avoidance of stimuli associated with the trauma, and hyperarousal[127]. The findings from animal studies suggest that memory consolidation and recall processes might be permanently altered in these conditions. Although it is likely that stress-induced functional and structural changes in the amygdala play a pivotal part in many of these symptoms[119], other brain regions are also involved in the plasticity and in the storage and recall of memories. Although largely unexplored, the stress-related remodelling of amygdala, prefrontal cortex and hippocampal neurons is likely to influence their memory-processing capabilities. This is particularly important because, as already noted, the morphological effects of stress on amygdala plasticity are strikingly different to those in the hippocampus and the prefrontal cortex, two brain areas that are not only sensitive to stress but also regulate the stress response (BOX 1). In turn, these findings have implications for the understanding, diagnosis and treatment of anxiety and mood disorders (BOX 2).

There are many fascinating unanswered questions. First, are the same hormone and neurotransmitter systems that have a role in adaptive learning and memory responsible for the structural changes that occur in the BLA after chronic exposure to stress? Studies on learning and memory have focused on the crucial role of arousal-induced noradrenergic activation, but morphological studies have not investigated this. It is important to investigate whether noradrenaline has a central role in inducing structural changes in the amygdala.

Second, acute and chronic stress increase anxiety in open-field and plus-maze tests (FIG. 4), but it is unclear how these increases in anxiety might translate to changes

Box 1 | **Structural changes in interconnected brain regions**

Repeated stress of the type that causes remodelling of neurons and connections in the amygdala produces concurrent neuronal remodelling in the prefrontal cortex and hippocampus (see the figure), two structures that regulate the activity of the hypothalamus-pituitary-adrenal axis[117]. These changes include shrinkage of dendrites and a reduction of spine density in medial prefrontal cortex neurons and, in the hippocampus, shrinkage of dendrites in CA3 pyramidal neurons and dentate gyrus granule neurons. Chronic stress also decreases neurogenesis and neuron number in the dentate gyrus. However, dendritic branching in the orbitofrontal cortex increases as a result of chronic stress. For the most part, these stress-induced changes in the hippocampus and medial prefrontal cortex are reversible over time, at least in the animal models that have been investigated so far. As these brain regions are interconnected, it is likely that the structural remodelling in one region will influence the functions of other brain regions.



Box 2 | **Translational aspects of research into anxiety and mood disorders**

Stress hormone effects on the activity of the amygdala and that of brain regions interconnected with the amygdala might directly alter the consolidation and recall of emotional memories, one of the core features of chronic anxiety, including post-traumatic stress disorder (PTSD)[126]. Moreover, the unique features of stress-induced neuronal remodelling in the amygdala and associated brain regions could be of relevance to studies of humans with mood disorders and PTSD. First, although neurons in the basolateral complex of the amygdala (BLA) undergo dendritic growth, neurons in the hippocampus and prefrontal cortex show atrophy following chronic stress. Consistent with these results, human neuroimaging studies have revealed enhanced responsiveness of the amygdala and diminished responsiveness of the prefrontal cortex in patients with PTSD. There is also evidence for reduced hippocampal volume and function in patients with PTSD[129–131]. Overactivity of the amygdala has also been reported in people with major depressive illness, along with atrophy of the hippocampus and prefrontal cortex[8,132].

Although each of these brain areas shows specific changes in function and morphology in association with PTSD-like symptoms, the significant neuroanatomical interconnections between these areas raises the possibility that some of the changes triggered by stress in one brain area might, at least in part, induce changes in others. This too is in broad agreement with results from animal models in which amygdala activation seems to trigger many of the physiological and behavioural changes involving other brain regions. Finally, although PTSD is triggered by a single, intensely traumatic event, its symptoms persist well beyond the original event. This temporal feature is captured by the delayed manifestation of enhanced anxiety and BLA spinogenesis initiated by a single episode of stress in animal studies. Moreover, BLA hypertrophy and anxiety, unlike changes in the hippocampus, last for weeks after termination of chronic stress[110]. Thus, the amygdala seems to have special features — especially with respect to the temporal manifestation and persistence of its effects — that fit well with the delayed and prolonged enhancing effects on fear and anxiety observed in patients with PTSD.

in learning, memory and extinction of fear-related or other memories. As noted above, limited evidence suggests that both acute and chronic stress enhance fear conditioning, but the degree to which they might affect learning and memory processes requires more extensive analysis.

Third, the findings of stress effects on amygdala functioning in learning and memory clearly indicate that amygdala activity induces learning-associated changes in the activity of other brain regions, but presently it is unclear whether the structural changes found in the amygdala are causally linked to those in the hippocampus and prefrontal cortex, particularly as the structural remodelling in these two brain regions reverses after stress even though the remodelling in the amygdala persists.

Fourth, it is important to note that, despite intriguing parallels between neuroimaging results in patients with PTSD and stress-induced changes in animal models, only a minority of humans will develop PTSD and related anxiety disorders after trauma. Detailed morphological and behavioural analyses focused on the amygdala and other brain regions in both vulnerable and resilient animal strains[128] might help us to resolve this important gap in knowledge.

Finally, it is unclear whether the morphological alterations in the amygdala are indicative of maladaptive amygdala functioning or whether such changes, perhaps to a lesser extent, also occur as a result of adaptive effects of stress on memory consolidation. Likewise, we need to find out whether and to what extent these structural changes selectively affect stress- or arousal-influenced learning and memory, as they might also have an impact on the consolidation or recall of memory of non-emotional information.

In conclusion, the amygdala has unique features of structural and functional plasticity that make it especially relevant to our understanding of memory of emotionally arousing and fearful experiences, but also of the pathological consequences of chronic and severe stress. Furthermore, whatever happens in the amygdala seems to occur in concert with functional changes in other, interconnected brain regions. Therefore, future studies aimed at investigating the role of the amygdala in stress effects distributed across wider neural networks will not only help us to understand the complex interactions between stress and memory, but may also reveal common targets for therapeutic interventions against stress-related psychiatric disorders.

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