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CRITICAL BRAIN CIRCUITS AT THE INTERSECTION BETWEEN STRESS AND LEARNING

Debbie A. Bangasser, PhD[1] and **Tracey J. Shors, PhD**[2]

[1] Department of Anesthesiology, The Children's Hospital of Philadelphia, Philadelphia, PA 19104

[2] Department of Psychology and Center for Collaborative Neuroscience, Rutgers University, Piscataway, New Jersey, 08854, USA

Abstract

The effects of stressful life experience on learning are pervasive and vary greatly both within and between individuals. It is therefore unlikely that any one mechanism will underlie these complicated processes. Nonetheless, without identifying the necessary and sufficient circuitry, no complete mechanism or set of mechanisms can be identified. In this review, we provide two anatomical frameworks through which stressful life experience can influence processes related to learning and memory. In the first, stressful experience releases stress hormones, primarily from the adrenals, which directly impact brain areas engaged in learning. In the second, stressful experience indirectly alters the circuits used in learning via intermediary brain regions. Importantly, these intermediary brain regions are not integral to the stress response or learning itself, but rather link the consequences of a stressful experience with circuits used to learn associations. As reviewed, the existing literature provides support for both frameworks, with somewhat more support for the first but sufficient evidence for the latter which involves intermediary structures. Once we determine the circumstances that engage each framework and identify which framework is most predominant, we can begin to focus our efforts on describing the neuronal and hormonal mechanisms that operate within these circuits to influence cognitive processes after stressful life experience.

Indexing terms

Associative learning; stress; amygdala; hippocampus; bed nucleus of the stria terminalis; post-traumatic stress disorder; depression; eyeblink conditioning; sex difference

Introduction

It is not surprising that stressful life events can affect processes of learning and memory. In fact, it is easy to think of many everyday examples wherein a stressful experience alters our ability to acquire or remember new information. In some situations, stress impairs learning. For example, one often forgets the names associated with faces while nervously attending a social event. However, in other situations, stress increases our ability to learn and remember, as may occur when one is asked to recall the details of a car accident or personal trauma. After

Corresponding Author: Debbie Bangasser, PhD, The Children's Hospital of Philadelphia, 3615 Civic Center Blvd., ARC 402E, Philadelphia, PA 19104, Phone: 215-590-0654; Fax: 215-590-3364, dbangasser@yahoo.com.

an extremely stressful event, some people develop enduring psychopathology. The most poignant example is post-traumatic stress disorder (PTSD), a disease marked by ruminations or flashbacks of the trauma which prevent the person from leading a healthy productive life. The neuronal and hormonal markers of stress have been studied for decades and numerous important reviews have been presented. These reviews have focused on the specific biological consequences of stress and how they relate to learning and memory (e.g., Conrad, 2008; Hains and Arnsten, 2008; Howland and Wang, 2008; Joels et al., 2006; Lupien et al., 2005; Lupien and Lepage, 2001; Sandi and Pinelo-Nava, 2007). In this review, we instead focus on the overall anatomical framework through which stressful life experience can modify processes of learning and memory. In doing so, we propose two models. In the first more traditional model, exposure to a stressful event initiates the stress response, which results in the release of stress-related hormones. These hormones, via their receptors, act directly on the circuitry used to form, store, and/or retrieve memories. In the second model, exposure to a stressful event indirectly modulates learning circuitry through intermediary brain regions. These so-called "intermediary structures" are not necessary for initiating the stress response or for learning in and of themselves, but are capable of enhancing or impairing learning by influencing activity in distant brain regions used in the learning process. This review will provide evidence for both models and describe how each may improve our understanding of the mechanisms associated with stress and learning. Lastly, these models may help lay the groundwork for developing more effective treatments for humans suffering from stress-related psychiatric disorders.

Various effects of stress on learning

Before addressing the models, it should be noted that stress does not always have the same effect on learning and memory. For example, sometimes stress enhances learning, while other times stress impairs learning. Properties of the stressor itself, such as intensity, are important, as is its duration (Cordero et al., 1998; Diamond, 2005; Joels, 2006; Sandi and Pinelo-Nava, 2007). In general, longer duration stressors (i.e., chronic) tend to result in memory impairments (Conrad et al., 1996; Joels et al., 2004; Luine et al., 1996; McEwen, 2005). The source of the stressor is also important (Sandi and Pinelo-Nava, 2007). When the act of training is intrinsically stressful, as it is during fear conditioning, the learning process tends to be facilitated by stressful experience. However, when the training is not as stressful or the stressful experience occurs at a time distant from training, the consequences become less predictable (Sandi and Pinelo-Nava, 2007). The stage of the learning process is also important. Stressful experiences tend to enhance processes related to acquisition but often impair those related to recall (Roozendaal, 2002, 2003). Finally, demographic factors, such as sex and age, can alter the way stress modulates learning (Jackson et al., 2006; Lupien et al., 2005; Shors, 2006; Zorawski et al., 2005). Regardless of these many variables, most published studies implicate similar brain regions at the intersection between stress and learning. These regions include but are not limited to the hippocampus, amygdala, and prefrontal cortex. Thus, it would appear that the degree to which stress affects learning and the direction of that effect does not necessarily result from differences in brain circuitries, but rather from differences in physiological and cellular processes within the same or similar circuitries. It is under this premise that we propose the two general anatomical frameworks.

Stress hormones modulate learning and memory

There is a large and overwhelming literature indicating that glucocorticoids (cortisol in humans and corticosterone in rodents) modulate processes related to learning and memory. These stress hormones are released from the adrenal glands following activation of the hypothalamic-pituitary-adrenal (HPA) axis, after which they enter the brain to act on their respective receptors. One clear example of such hormonal modulation is Cushing's syndrome. People with this disease release excessive amounts of cortisol, and as a consequence, they have difficulty learning and performing during training on various cognitive tasks (Starkman et al.,

1992; Starkman et al., 2001). The types of learning that are affected include declarative memory and other tasks such as, visual-spatial tests and trace conditioning (Grillon et al., 2004; Starkman et al., 1992; Starkman et al., 2001). Importantly, the learning deficits expressed by Cushing's syndrome patients can be reversed when the cortisol concentrations are managed within a normal physiological range (Starkman et al., 2003). Thus, the learning deficits are likely mediated by the presence of excessive amounts of endogenous glucocorticoids. In healthy humans, the release of stress hormones from the adrenals can also influence processes of learning, again typically expressed as deficits in declarative memory. For example, high concentrations of glucocorticoids as well as stressful manipulations elicit poor retrieval of declarative information in healthy participants (Kirschbaum et al., 1996; Kuhlmann et al., 2005; Maheu et al., 2004). In rodents, exposure to either chronic or acute stressors tends to impair the recall of spatial memories (Conrad et al., 1996; Diamond et al., 1999), although there are also a number of reports showing that stress or stress hormones can enhance learning and/or memory. For instance, exposure to either an acute or a chronic stressor enhances an animal's ability to remember the context associated with a stressful stimulus such as a foot shock, a type of learning referred to as contextual fear conditioning (Conrad et al., 1999; Cordero et al., 2003a; Cordero et al., 2003b; Sandi et al., 2001). Many of these effects are mediated by corticosterone. For example, injecting corticosterone peripherally enhances the acquisition of a classically conditioned eyeblink response, in which an animal learns to associate an auditory stimulus with an aversive stimulation to the eyelid (Beylin and Shors, 2003). If the training conditions themselves are intrinsically stressful learning can be affected, such that animals trained in a cold water maze task learn better than those trained in warmer water (Conboy and Sandi, 2009; Sandi et al., 1997). The enhanced learning and memory after training in colder water is mediated by the presence of glucocorticoids, as is the increase in classical eyeblink conditioning that occurs after exposure to an acute stressful event (Beylin and Shors, 2003; Conboy and Sandi, 2009) (Fig. 1). Thus, glucocorticoids play a central role in regulating learning after stressful life experience.

Model 1: Stressful experience directly affects learning circuitry via stress hormones

Structures required for learning contain stress hormone receptors

The above examples link stress and stress hormones, particularly glucocorticoids, with altered learning and memory processes. Based on these studies and others, a model has been proposed which assumes that stress affects learning directly by acting on brain regions used for learning and memory itself (Fig. 2a). The learning circuit most often includes the hippocampus because it is necessary for many of the types of learning that are affected by stress, including declarative and spatial memory tasks. Also, for decades it has been well documented that there is a high concentration of corticosterone and density of its receptors within the hippocampus (McEwen et al., 1968;Veldhuis et al., 1982). From these findings, the hippocampus is considered a primary site for regulating learning after stressful experience. However, other regions, such as the amygdala and the prefrontal cortex, have been implicated (Patel et al., 2008;Patel et al., 2000;Sarrieau et al., 1986). Like the hippocampus, these brain regions are necessary for various types of learning that are affected by stress, and they also possess receptors for glucocorticoids and other stress-related compounds such as corticotropin-releasing factor (CRF) and norepinephrine (Arnsten, 1997;Gray and Bingaman, 1996;Roozendaal et al., 2002).

Stressful experience induces physiological, morphological, and cellular changes in learning circuitry

The fact that many stress compounds and their receptors are located in regions involved in learning has led to the general hypothesis that stress hormones and neurotransmitters act directly on learning circuitry to modify processes of learning and memory. The hypothesis is

strengthened by overwhelming evidence for physiological, morphological, and cellular changes within those structures as a result of a stressful experience. For example, exposure to an acute stressful experience and peripheral exposure to exogenous glucocorticoids persistently decreases the expression of long-term potentiation (LTP)—a form of synaptic plasticity often promoted as a model of learning in the mammalian brain—in the hippocampus and amygdala (Kavushansky et al., 2006; Shors et al., 1989; Smriga et al., 1996). Furthermore, acute stress increases neuronal excitability in the hippocampus, which is also associated with enhanced learning (Weiss et al., 2005). Stress and glucocorticoid release also alter the production of new neurons in the hippocampus (Gould and Tanapat, 1999; Mirescu and Gould, 2006), and these new cells have been linked to some processes of learning (Leuner et al., 2006; Shors, 2009; Shors et al., 2001b). Additionally, stress can modify the morphology of dendrites in the hippocampus as well as the prefrontal cortex (Radley et al., 2004; Watanabe et al., 1992). In the hippocampus, chronic stress induces dendritic retraction within the CA3 region, an effect associated with deficits in performance on a spatial learning procedure (Lupien et al., 2005; Watanabe et al., 1992; Wright and Conrad, 2005). Additionally, chronic stress induces dendritic retraction and decreases volumetric measurements in the prefrontal cortex (Cerqueira et al., 2007; Radley et al., 2004; Wellman, 2001). These changes are accompanied by deficits in working memory, behavioral flexibility, and attentional set shifting (Cerqueira et al., 2007; Liston et al., 2006). Chronic stress also alters frontostriatal circuits, which then changed decision-making strategies (Dias-Ferreira et al., 2009). At a more reduced level, dendritic spines in these brain regions have been implicated in stress/learning interactions. Acute stressor exposure changes the density of spines on apical dendrites in the CA1 region of the hippocampus in a sex-specific manner (Leuner and Shors, 2004; Shors et al., 2001a; Shors et al., 2004) (Fig. 3). Whereas stress increases the density of dendritic spines in the male hippocampus, it decreases density in the female hippocampus. These changes in spine density are consistent with the effects of stress on learning, as assessed with trace eyeblink conditioning, a task that requires the hippocampus (Leuner and Shors, 2004; Wood and Shors, 1998). Thus, the animals that have more dendritic spines after a stressful experience tend to learn faster, whereas those that have fewer spines tend to be learning impaired. It has been suggested that the presence of dendritic spines provide a biological substrate for rapid encoding of associations after stressful experience and learning in general (Leuner and Shors, 2004).

In addition to anatomical substrates, molecular responses to stress are likewise prevalent in brain regions that are involved in learning and memory. Stress and stress hormones alter the expression of receptors within these structures, and these alterations in turn influence learning ability. For example, acute stressful experience increases the expression of both AMPA and NMDA receptor subunits in pyramidal neurons of the prefrontal cortex which thereby increases glutamatergic transmission (Yuen et al., 2009). This same stressor facilitates performance on working memory tasks, which depend on the prefrontal cortex (Yuen et al., 2009). The increase in neurotransmission and the increase in working memory are both mediated by activation of glucocorticoid receptors (Yuen et al., 2009). Another cellular mechanism implicated in stress/learning interactions is neural cell adhesion molecule (NCAM). Chronic restraint stress decreases NCAM expression in the hippocampus (Sandi et al., 2001; Venero et al., 2002), and mice without hippocampal NCAM have difficulty learning a spatial orientation task (Bukalo et al., 2004). Thus, a decrease in NCAM in the hippocampus may impair learning directly because the hippocampus is necessary for this type of learning (Bisaz et al., 2009; Sandi, 2004). Similarly, MAPK has been implicated in stress/learning interactions. Revest et al. (2005) reported blocking MAPK activation specifically within the hippocampus prevented the enhancement of contextual fear in response to glucocorticoids (Revest et al., 2005). Thus, it would appear that specific molecular events within the hippocampus itself are necessary to enhance learning in response to glucocorticoids. Overall, these studies (and others not discussed here) support the first model, which proposes that stress hormones act directly on molecular and cellular processes within brain structures that are used for learning itself.

Evaluation of evidence for direct effect of stress hormones on learning circuitry

Although there is much support for this model, there are some exceptions. For one, it is well established that stressful experience impairs the induction of LTP in the hippocampus (Shors et al., 1989; Smriga et al., 1996). Because LTP is often considered a physiological model (if not a mechanism) for learning, it would seem reasonable that stress would impair learning that depends on the hippocampus. But it does not always do so. In fact, stress tends to enhance trace eyeblink conditioning, which depends on the hippocampus for learning (Shors and Matzel, 1996; Shors et al., 1992). As another example, stressful experience reduces the number of new cells that are produced in the hippocampus but again tends to enhance rather than impair learning which is associated with those new cells (Leuner et al., 2004; Shors et al., 2007). Minimally, these two examples rule out any overarching rule indicating that the modulation of learning is necessarily mediated by an observed change in response to stress at the neurophysiological or cellular level. That said, we have so far discussed several lines of evidence which suggest that stress does modulate learning via the direct actions of stress hormones on learning circuitry. First, structures involved in learning contain stress hormones receptors, which make direct effects of hormones possible. Second, exposure to a stressful event induces physiological, morphological, and cellular changes within regions critical for learning, and these changes often mirror the effects on learning (e.g., decreases in dendritic spines are associated with impaired learning and vice versa).

Although compelling, these lines of evidence do not *directly* test the model that stress hormones act within specific brain regions to alter mnemonic processes. Establishing a direct and causal connection is difficult and in some cases impossible because of technical limitations. There are not many, if any, methods to transiently and selectively prevent morphological changes that occur as a result of stress. Brain lesions or inactivation techniques are also ineffective if the brain region is necessary for learning. However, other techniques do exist and are being used. With remarkable success, drugs that mimic or block stress hormones are being injected directly into brain regions that are used during learning tasks that are intrinsically stressful, like fear conditioning and passive avoidance (e.g., Donley et al., 2005; Ferry and McGaugh, 1999, 2000; Ji et al., 2003; Liang et al., 1986; McGaugh, 2004; Mueller et al., 2008; Rodrigues et al., 2009; Yang et al., 2006). Other studies have used local drug infusions to examine how stress or stress hormones modulate hippocampal-dependent learning. Roozendaal et al. (2003) found that infusing a glucocorticoid agonist into the hippocampus impaired the recall of spatial memory. As noted, Revest et al. (2005) reported that a decrease in MAPK activation in the hippocampus prevented an increase in contextual fear in response to glucocorticoids (Revest et al., 2005). These studies suggest that stress hormones directly modify activity within the hippocampus to influence learning. However, not all of the aforementioned effects have been examined with local drug infusions, so it remains to be determined whether these same principles hold in all instances.

Model 2: Stress hormones affect learning circuitry via intermediary structures

In the second proposed model, we suggest that stressful experience affects learning indirectly though intermediary structures (Fig. 2b). These intermediary structures are not required for stress responses or learning itself, but instead link the consequences of a stressful experience with a specific learning circuitry. Recent work from our laboratory has identified the amygdala, hippocampus, and bed nucleus of the stria terminalis (BNST) as critical components within the circuit. In the standard version of these experiments, adult rats are exposed to an acute stressor of restraint and periodic low-intensity tailshocks or swim stress for 30 minutes (Servatius and Shors, 1994;Shors, 2001;Shors et al., 1992). Twenty-four hours later, rats are trained for the first time on a classical eyeblink conditioning task in which a white noise

conditioned stimulus (CS) precedes and predicts a periorbital eyelid stimulation, the unconditioned stimulus (US). After many training trials, the rats learn to emit an eyeblink response in anticipation of the US, a response referred to as the conditioned response (CR). The number of CRs emitted over trials is an indirect measure of an animal's ability to associate the CS with the US and correctly time the CR within milliseconds of the US. Using this procedure, the acute stressful event reliably alters learning and does so very differently in male vs. female rats. In all male species tested (rats, mice, and humans), acute stressor exposure enhances subsequent eyeblink conditioning (Duncko et al., 2007;Shors et al., 1992;Weiss et al., 2005), whereas the same stressful event reduces and in most instances, prevents learning in females (Wood et al., 2001;Wood and Shors, 1998). This phenomenon has been reviewed elsewhere (Shors, 2004,2006) and will be discussed here only as it relates to brain circuitry.

The learning circuit used to associate the CS with the US in eyeblink conditioning is well characterized and includes the cerebellum (Christian and Thompson, 2003; Mauk and Thompson, 1987; Thompson, 2005). Specifically, mossy fibers from the pontine nucleus and climbing fibers from the inferior olive carry information about the CS and US respectively to the interpositus nucleus of the cerebellum, wherein the plasticity occurs. From there, efferents from the interpositus project to motor areas necessary for generating the CR. During a slightly different version of the task, a trace interval (or temporal gap) is placed between the CS and the US. When trained under these conditions, animals without a hippocampus cannot learn (Bangasser et al., 2006; Beylin et al., 2001; Solomon et al., 1986). Moreover, neuronal activity in the hippocampus predicts the acquisition of the learned response during trace conditioning (McEchron and Disterhoft, 1999). Thus, the cerebellum and its brainstem connections are necessary to learn both the delay and trace conditioned response, whereas the hippocampus is not necessary to learn the delay response.

The hippocampus as an intermediary structure

Because the circuitry is known, eyeblink conditioning can be used to identify intermediary structures that potentially link stress with learning. Recently, we demonstrated that the hippocampus is used in this way to connect a stressful event with learning. We were able to test this hypothesis because the hippocampus is not necessary for the simple delay version of the task, though performance of this task is still modulated by stress. Males and females were given complete hippocampal lesions and then tested for the effects of stress on learning (Bangasser and Shors, 2007) (Fig. 4). These lesions prevented both the enhanced conditioning after stress in males, as well as the deficit in females after stress. Importantly, neither learning itself nor the corticosterone response to stress was disrupted by the lesion procedure (Bangasser and Shors, 2007). Thus, the role of the hippocampus in learning and HPA activation was dissociated from its role in the modulation of learning by stress. To our knowledge, this was the first lesion study to demonstrate that the hippocampus can serve as an intermediary structure that links stressful experience with learning circuitry.

The amygdala as an intermediary structure

Studies suggest that the basolateral nucleus of the amygdala (BLA) is also an intermediary brain structure between stress and learning. Rodriguez Manzanares et al. (2005) found that blocking BLA activity during stress prevented the subsequent enhancement of contextual fear conditioning (Rodriguez Manzanares et al., 2005). Similarly, Waddell et al. (2008) found that neuronal activity within the BLA during the stressor was necessary in order for male rats to express the enhanced learning after stress, as well as for females to express a deficit in performance (Fig. 5). Excitatory neuronal activity within the BLA was temporarily prevented with a GABA agonist during the stressor, and animals were trained the next day. Because training occurred in the absence of the compound, the treatment could not have altered the learning process itself. It also does not disrupt the release of corticosterone during the stressor

(Kim et al., 2005). These results support the idea that the BLA serves as an intermediary structure linking the consequences of stressful experience with the anatomical circuitry used to acquire new information.

The bed nucleus of the stria terminalis as an intermediary structure

The bed nucleus of the stria terminalis (BNST) has long been associated with stress and anxiety, and more recently with processes of learning and memory (Casada and Dafny, 1991; Davis and Shi, 1999; Davis et al., 1997). Because it is the major output structure from the amygdala, it was predicted that the BNST might also be an intermediary structure to link stressful experience with learning (Krettek and Price, 1978; Weller and Smith, 1982). Indeed, permanent lesions of the BNST prevent the enhanced trace eyeblink conditioning that occurs after exposure to a stressful experience in male rats (Bangasser et al., 2005). However, the BNST is only necessary during specific time periods. Using a temporary inactivation technique, we found that inactivation of the BNST during the stressful event did not prevent the enhancement of conditioning. Only inactivation during training was effective (Bangasser et al., 2005). Importantly, BNST inactivation did not disrupt the HPA stress response or conditioning itself. Thus, these data indicate that the BNST acts as an intermediary structure that mediates the lasting effects of stress on conditioning. Interestingly enough, the BNST is not critical under all conditions – or at least not in all animals. Females, which express a profound learning deficit after stress, were unaffected by the BNST inactivation procedure (Bangasser and Shors, 2008) (Fig. 6a). Thus, unlike in males, the BNST does not mediate the effect of stress on conditioning in females.

To our knowledge, a specific stress/learning circuit in one sex and not the other is unprecedented. However, given the sexually dimorphic nature of the structure, one might have predicted this outcome. The BNST is masculinized by a perinatal surge in testosterone, which increases its volume and changes its neurochemical profile (del Abril et al., 1987; Han and De Vries, 2003). This same perinatal surge organizes the stress effect on classical eyeblink conditioning (Shors and Miesegaes, 2002). Thus, females that are exposed to testosterone at birth behave like males as adults, i.e. they learn better after the stressor. Moreover, these same females now require activity within the BNST to express the enhancement in learning (Bangasser and Shors, 2008) (Fig. 6b). These results indicate that a masculinized BNST, rather than a feminized one, is required for stress to enhance acquisition of this simple associative response. Notably, a loss of BNST activity did not cause masculinized females or males to respond with a learning deficit, as observed in cycling females. In other words, inactivation of the BNST did not feminize the male response. Note that we did not provide estrogen to masculinized females or males, but the data nonetheless suggest that brain regions other than the BNST are being engaged by females to impair learning after a stressful event. Overall, these studies demonstrate that males and females use different brain regions to modulate learning after a stressful event. Moreover, they underscore the importance of considering sex when identifying the critical brain circuitry used for a given behavioral response.

Intermediary structures at the intersection between stress and learning

In this model system, we have determined that the hippocampus, amygdala, and BNST are necessary to modulate learning after stress. How they interact with one another to do so remains unknown. Each of these brain regions projects to the cerebellar eyeblink conditioning circuit via monosynaptic or polysynaptic connections (Fig. 7). The hippocampus sends afferents to the subiculum, which then projects via the retrosplenial cortex to the pontine nuclei that are critical for CS processing (Berger et al., 1986). The BLA projects via the central nucleus of the amygdala (CeA) to both the lateral tegmental field of the brainstem and the pontine nuclei, parts of the US and CS pathways, respectively (Krettek and Price, 1978;Steinmetz et al., 1987;Tracy et al., 1998;Whalen and Kapp, 1991). The BNST can affect the cerebellar eyeblink

circuitry via direct afferents to the pontine nuclei (Holstege et al., 1985). Thus, the three brain regions that we know to be involved at some level in the stress/learning interaction (the amygdala, hippocampus and BNST) interact with the eyeblink circuitry. They could do so independently of one another, but it seems more likely that they form an elaborate network that is used to more generally monitor stressful experiences, remember that experience and relate it to future learning opportunities. One network might begin in the hippocampus, which projects to the BLA via the entorhinal cortex and the subiculum (Aggleton et al., 1987;Canteras and Swanson, 1992). The hippocampus and BLA project to the BNST via the fimbria/fornix and CeA, respectively. In this case, the BNST would serve as a final output to eyeblink conditioning circuitry, at least in males (Cullinan et al., 1993;Krettek and Price, 1978;Weller and Smith, 1982). Alternatively, the network may involve the retrosplenial cortex, since both the hippocampus and BNST send afferents to the retrosplenial cortex, which in turn projects to the pontine nuclei. In this scenario, the retrosplenial cortex would be an intermediary structure much like the BNST (Berger et al., 1986;Swanson and Cowan, 1977). Regardless of the specifics, it appears that an extended circuit of intermediary brain regions, in addition to those used to elicit the stress response and orchestrate learning, are being used to modify learning after stressful experience, at least in some cases.

Potential mechanisms within circuits

How these intermediary structures are influenced by stress to affect learning in efferent structures is not known, but several possibilities have been proposed. For example, stress hormones and neurotransmitters released from peripheral targets can alter neurophysiological responses within the BLA and the hippocampus (Buffalari and Grace, 2007; Karst et al., 2002; Kavushansky and Richter-Levin, 2006; Shors et al., 1989; Smriga et al., 1996). These same substances also have relatively dramatic effects of stress on dendritic morphology in these brain regions (Magarinos and McEwen, 1995; Mitra and Sapolsky, 2008). The BNST has a relatively high concentration of receptors for corticosterone, norepinephrine, and corticotropin-releasing factor, activation of which can in turn modify gene expression and cellular responses within the structure (Davis and Shi, 1999; Davis et al., 1997; Egli et al., 2005; Shepard et al., 2006). Thus, these cellular alternations within intermediary structures may connect stress hormones and transmitters to learning circuitry. Alternatively, the process may be more psychological. By this, we mean that the intermediary structures may process information about the stressful event which is then relayed to efferent brain regions. When an animal is experiencing a stressor, it simultaneously records many aspects of the experience, such as contextual information about where and when the stressful event occurred. If the contextual cues that were associated with the stressful event are presented to the animal during training, they can react more intensely to the training experience because the cues serve as reminders of the stressful event. This reminder may actually cause a stress response in the animal during learning. Accordingly, it is not the stress response that occurred days earlier that alters learning but rather the stressful state triggered by the memory of the stressful context. There is some evidence to support this hypothesis. Typically in our procedure, the stressor and the training occur in different contexts (as different as is possible) and the effects of stress on eyeblink conditioning only persist when training begins two days after the stressful event has ceased. However, if the animals are trained in the same context as the stressor, the effects persist for a longer time period (Shors and Servatius, 1997; Wood et al., 2001). Interestingly, the hippocampus and amygdala are known to be critical for encoding the contextual cues associated with emotional events (Anagnostaras et al., 2001; Davis, 1994; Fanselow and Kim, 1994; Phillips and LeDoux, 1992). Moreover, neuronal activity within the amygdala, which decreases during the stressor, is also reduced when the animal is re-exposed to the context in which the stressful event occurred (Shors, 1999). Antagonizing NMDA receptors in the BLA during the stressor prevents enhanced learning and the decrease in neuronal activity within the BLA, indicating that neuronal plasticity is required (Shors and Mathew, 1998). Thus, the amygdala

(and potentially the hippocampus) may be critical for encoding contextual information about a stressful event which is later used to modify future learning processes, even when the amygdala is not necessary for learning the specific task. More generally, these results suggest that intermediary structures serve not only as relay stations but rather, as sites for learning about the stressful experience itself.

Implications for the treatment of stress-related mental illness

As noted, PTSD is induced by stressful experience and is expressed as a cognitive disorder. Other stress-related illnesses such as depression and generalized anxiety disorder are also characterized by cognitive disturbance (Austin et al., 2001; Bemelmans et al., 1996). If we could identify the brain circuits used at the intersection between stress and learning, we might be able to better understand how stressful life events impact cognitive function in humans. More critically, we might be able to design interventions that target specific brain structures or even circuits in humans with stress-related illness or, ideally, prevent the illness before it is established. In preclinical animal models, local administration of the β-adrenergic blocker, propranolol, into the amygdala attenuates the enhancing effect of norepinephrine on memory consolidation (Liang et al., 1986; Miranda et al., 2003; Salinas et al., 1997). Similarly, blocking glucocorticoid receptors in the amygdala after reactivation of a fearful memory prevents the consolidation of a recalled memory (Tronel and Alberini, 2007). Others have begun to use similar approaches in humans. For example, Pitman and colleagues (2002) treated people with propranolol with the hope of blocking the consolidation of a traumatic memory. The treatment begins within hours of the trauma and then the drug is continuously administered for days afterward (Pitman et al., 2002). Amazingly, they found that even months later, these humans emitted a blunted autonomic response to images related to the trauma, i.e. contextual cues (Pitman et al., 2002). It would appear that the stress hormones released during the trauma could not access their receptors afterward, and as a consequence, the memory for the trauma was not as intensely consolidated, lessening its impact later in life.

Others have begun to intervene with stress hormones themselves. As noted, stress hormones tend to impair retrieval of fear memories (Roozendaal, 2002, 2003). De Quervain and colleagues administered patients with PTSD and phobias with systemic low doses of cortisol (Aerni et al., 2004; de Quervain and Margraf, 2008; Soravia et al., 2006). They found that treated patients had less salient memories of the event and were less likely to experience cognitive disruption (Aerni et al., 2004; de Quervain and Margraf, 2008; Soravia et al., 2006). With imaging, these researchers observed that the drug had its most notable effects in medial temporal lobe structures, including the hippocampus (de Quervain et al., 2003; Oei et al., 2007; Roozendaal et al., 2003). Although suggestive, it is not possible to verify that the drug is working via activity in this specific brain region. In the meantime, pharmaceutical companies are aggressively pursuing ways to target compounds into discrete brain regions. If successful, it might be useful to target the intermediary structures because, at least in principle, this would lessen the interaction between stress and learning but leave the stress response and learning itself intact.

Finally, we consider a third option for treating stress-related cognitive disruption. Rather than manipulating hormones or their receptors, another approach has been to target the mnemonic processes that occur during cognitive training and/or therapy. For example, there is renewed interest in D-cycloserine, a partial agonist to the NMDA receptor. In general, this drug is used as a cognitive enhancer in normal healthy animals, but it is also being used to facilitate extinction learning during exposure therapy for phobias and other anxiety-related disorders (Hofmann et al., 2006; Ressler et al., 2004; Wilhelm et al., 2008). Recently, we found that the drug not only enhances learning in general but reverses the negative effect of stress on learning. As discussed, stress profoundly disrupts classical eyeblink conditioning in females. However,

if they are trained in the presence of D-cycloserine, they learn very well, comparable to female rats that were not stressed (Waddell et al., 2009). Since the drug was given long after the stressful event occurred, it is not just preventing the deficit in learning but reversing it. However, the drug was given systemically, and thus, we do not know where in the brain it is acting to reverse the effects of stress on learning. It may act on the learning circuit directly (i.e. the hippocampus and cerebellum in this case), or it may intervene via intermediary structures (e.g., amygdala or BNST) to modify processes of learning. If the latter case is supported, then intermediary structures may be targeted with pharmaceutical compounds during cognitive behavioral therapy.

Conclusion

This review has examined the anatomical frameworks by which stress modulates learning by delineating two models. In the first model, stressful experience directly impacts the circuits used for learning. In the second model, stressful experience alters processes of learning via activity within intermediary structures, which are neither necessary for learning nor for the stress response. As discussed, the first model has a great deal of empirical support, but the second model is not far behind. If we can determine when each framework is engaged and which one predominates, we can begin to consider how mechanisms operate within these circuits to modify learning after stressful experience. It is certainly possible that neither model is entirely correct and that some combination of circuits and interactions between those circuits act together to modify learning after stressful life events. However, by delineating, defending, and potentially rejecting one or the other of these two models, we may come to a greater understanding about how brain regions interact with one another to influence future learning after stress.

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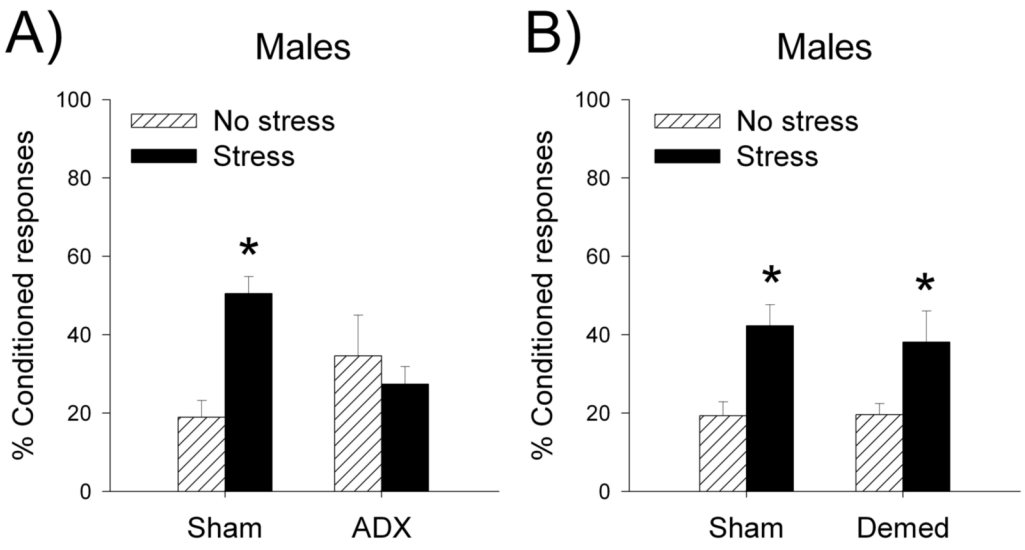

Figure 1. Adrenalectomy, but not demedullation, prevents the stress-induced enhancement of hippocampal dependent trace eyeblink conditioning (Beylin and Shors, 2003)

Stress increased the percentage of CRs emitted in sham operated but not in adrenalectomized (ADX) male rats (A). Note that basal levels of corticosterone were provided in drinking water. Demedullation (Demed), which leaves the adrenal cortex and corticosterone production intact, while removing adrenal catecholamine production, failed to prevent the stress-induced enhancement of trace conditioning, indicating that these effects are specific to corticosterone (B). Data are represented as Mean ± SEM percentage of CRs averaged across 300 training trials. Asterisks indicate a significant difference ($p<0.05$).

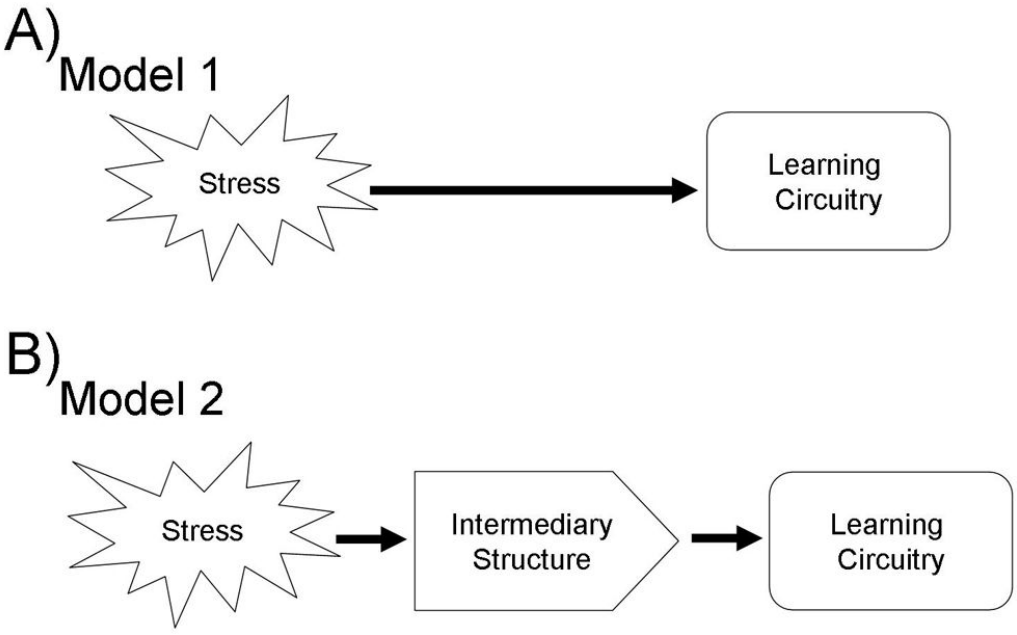

Figure 2. This is a schematic representation of the two models of stress and learning interactions
In model 1 stress hormones directly impact learning circuitry (A). In model 2 stress hormones act via intermediary structures to impact learning circuitry (B).

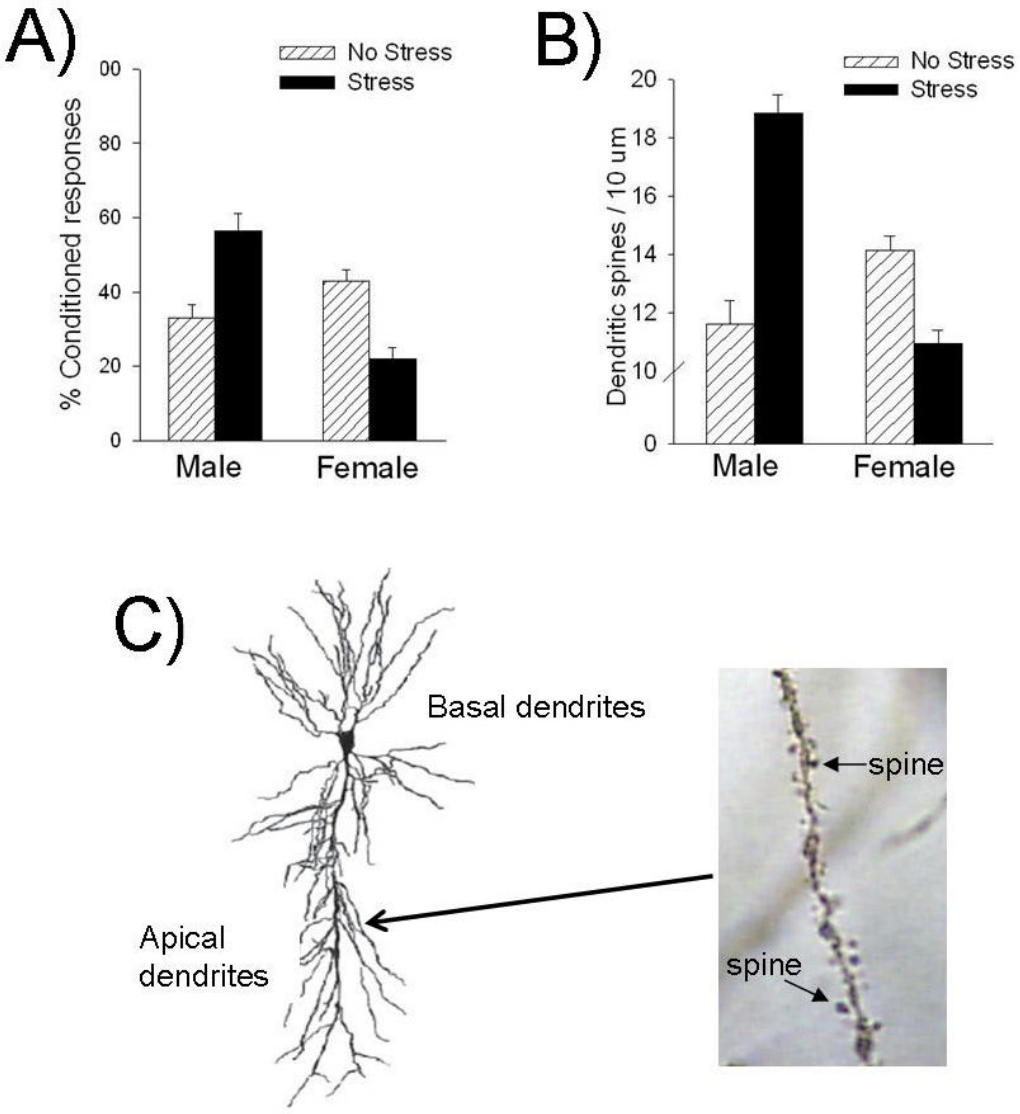

Figure 3. Opposite effects on stress on hippocampal-dependent trace conditioning and dendritic spines in the hippocampus in males vs. females (Shors et al., 2001a; (Waddell et al., 2008)

Under unstressed conditions, females emit more CRs than males. However, stressor exposure enhances trace conditioning in males, but impairs it in females (A). Similarly under unstressed conditions, females in proestus have greater spin density than males. Stressful experience increases spine density in males, while it decreases spine density in females (B). The altered spine density following stress is observed on apical dendrites of CA1 pyramidal neurons (C).

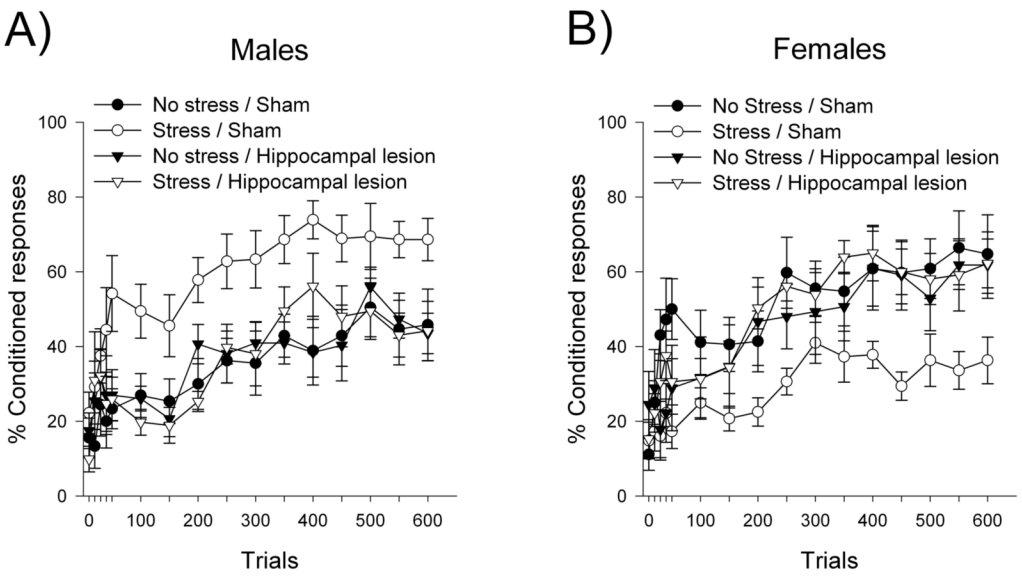

Figure 4. The hippocampus is required for stress to modulate learning, even when learning itself is independent of the hippocampus (Bangasser and Shors, 2007)

Hippocampal lesions prevented the stress-induced enhancement of delay eyeblink conditioning in male rats (A) and the stress-induced impairment of conditioning in female rats (B). Data are represented as Mean ± SEM percentage of CRs over 600 training trials (150 trials per day).

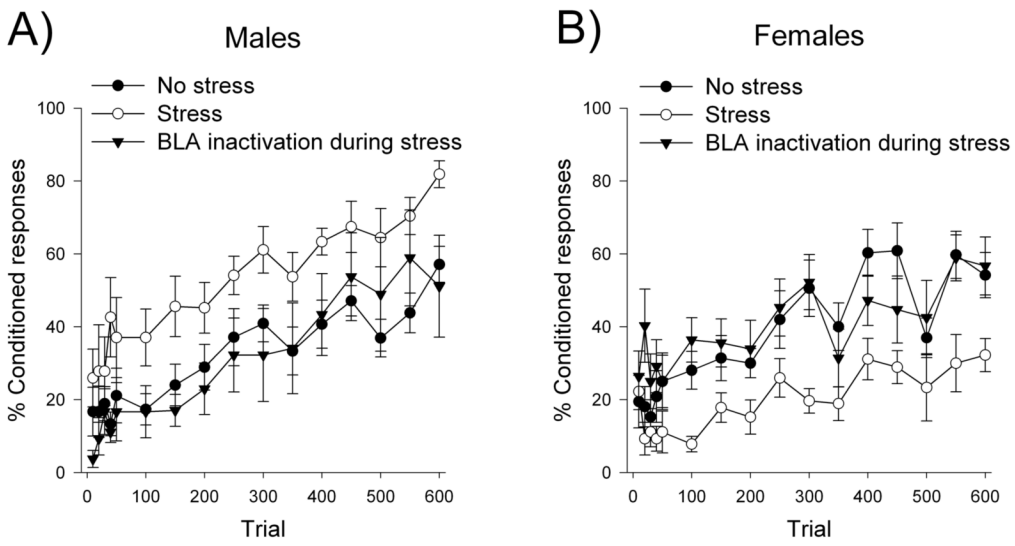

Figure 5. Activation of the amygdala during stressor exposure is required for stress to modulate learning (Waddell et al., 2008)

Temporary inactivation of the amygdala during stressor exposure prevented enhanced conditioning in males (A) and impaired conditioning in female rats (B). Data are represented as Mean ± SEM percentage of CRs over 600 training trials (150 trials per day).

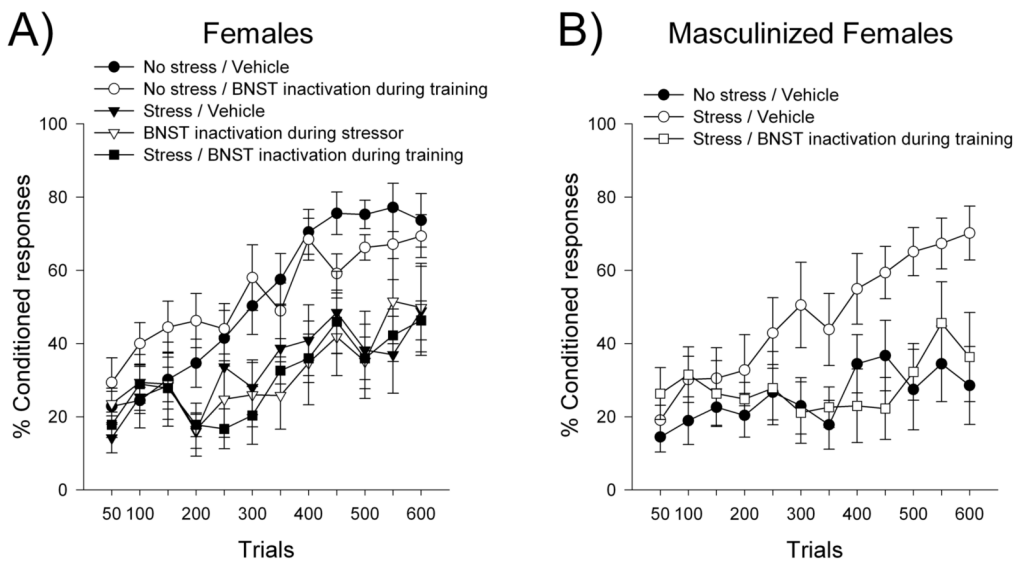

Figure 6. The BNST is required for stress effects on learning in masculinized, but not in cycling (i.e., normal) female rats (Bangasser et al., 2005)

In cycling females, BNST inactivation at any timepoint failed to prevent impaired conditioning (A). Just like in males, masculinized females require their BNST during training for enhanced conditioning after stress (B). Data are represented as Mean ± SEM percentage of CRs over 600 training trials (150 trials per day).

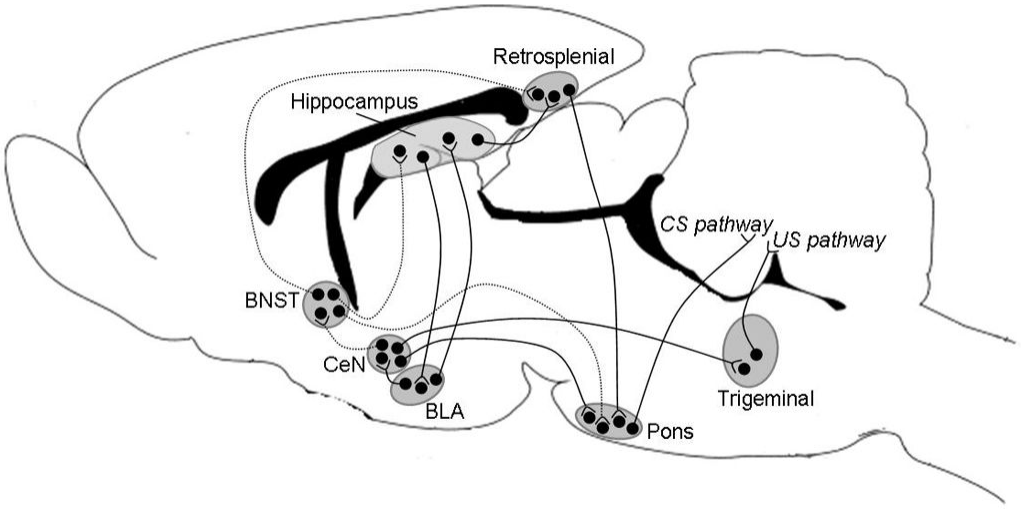

Figure 7. This figure illustrates how the hippocampus, amygdala, and BNST could affect the circuitry necessary for classical eyeblink conditioning

Solid lines represent possible connections in males and females, dashed lines represent possible connections in males only.