Chapter

AMYGDALA-INDUCED MODULATION OF COGNITIVE BRAIN STRUCTURES UNDERLIES STRESS-INDUCED ALTERATIONS OF LEARNING AND MEMORY: IMPORTANCE OF STRESSOR TIMING AND SEX DIFFERENCES

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ABSTRACT

Stress exerts complex effects on cognition. While stress can enhance learning and result in powerful memories that last a lifetime, it can also impair learning and cause us to be forgetful in our everyday lives. Over the past several years, it has become apparent that the types of effects that

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stress exerts on learning and memory depend critically on several factors related to the organism being studied, the learning experience, and the timing of the stressor. For instance, post-learning stress often facilitates long-term memory, while pre-learning and pre-retrieval stress effects are more variable and can involve enhancements or impairments of memory. In addition, stressors that are administered immediately before learning seem to result in amygdala-induced enhancements of hippocampal neuroplasticity, which promote learning, whereas stressors that are temporally separated from the learning experience result in amygdala-induced suppression of hippocampal neuroplasticity, which impairs learning. In the present review, we provide a comprehensive discussion of factors that mediate stress-induced alterations of hippocampus-dependent learning and memory and contend that the neurochemicals released following stress (e.g., cortisol, norepinephrine, glutamate, etc.) exert temporally distinct effects on brain areas devoted to processing emotional and cognitive information, such as the amygdala, hippocampus, and prefrontal cortex. We also propose that such stress-memory interactions differ significantly between males and females, which may be attributable, at least in part, to differences in amygdala activity and temporal dynamics of the stress response. Collectively, understanding the neurobiological basis of stress-memory interactions and how sex mediates such effects will facilitate the scientific community's understanding of traumatic memory formation and the onset of stress-related psychological disorders, such as post-traumatic stress disorder.

**INTRODUCTION**

The effects of stress on cognition are profound, yet complex. For instance, stress can strengthen learning and produce memories that last a lifetime, but it can also hinder learning and lead to significant memory impairments. Today, scientists are faced with the task of understanding when stress enhances versus impairs learning and memory and what ramifications such phenomena have for psychological health. We approach this issue with the prediction that stress-induced changes in learning and memory are adaptive in nature and have facilitated organisms’ survival over time. Thus, stress-induced enhancements of learning allow organisms to remember information pertaining to threatening situations, which later facilitates survival by helping them avoid similar, potentially dangerous, circumstances. On the other hand, stress-induced impairments of learning result from brain memory systems giving priority to the consolidation of stressor-related information, thereby compromising the storage or retrieval of other, less important, information.
Although these types of effects on learning are adaptive, they can also have serious inadvertent consequences. For instance, the enhancement of learning that occurs during a stressful event can lead to the production of traumatic memories that are difficult to extinguish and promote the onset of psychological disorders, such as post-traumatic stress disorder (PTSD). Thus, developing a better understanding of stress-induced alterations of learning and memory could lend important insight into factors governing the development of stress-related psychological illness.

It has become apparent that stress-induced alterations of learning and memory depend on several factors related to the stressor (e.g., type, timing, intensity, duration), the information being learned (e.g., emotional nature of the information, learning strategy required), and the organism under investigation (e.g., sex, age, physical health). In recent years, researchers have made significant progress describing how these factors interact with the neurobiological stress response to influence cognition. In the present chapter, we will present a developing comprehensive theory on how stress, primarily of the acute variety, interacts with these factors to influence learning and memory, especially in humans.

**WHAT IS STRESS?**

Stress is an ill-defined term that has come to mean many things. A common component of stress is arousal. Stress results in significant activation of two major physiological systems commonly associated with arousal-inducing stimuli, the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal (HPA) axis. Upon SNS activation, there is a rapid, almost immediate, release of epinephrine and norepinephrine from the adrenal medulla, which mobilizes metabolic resources that are necessary for the fight-or-flight response (Gunnar and Quevedo, 2007). This results in a significant increase in heart rate and blood pressure and prepares an organism to act. The HPA axis activation is a slower response that eventually, minutes later, leads to the synthesis and secretion of corticosteroids (de Kloet, Oitzl, and Joels, 1999; Joels, 2001). Upon activation of the HPA axis, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland to release adrenocorticotropic hormone, which then travels to the adrenal cortex to induce glucocorticoid synthesis and release (i.e., cortisol in humans, corticosterone in rodents). Similar to epinephrine and norepinephrine, glucocorticoids are involved in an organism’s
stress response, but one of their main functions is to act as a homeostatic mechanism and regulate the stress response by inhibiting SNS activity (Brown and Fisher, 1986; Komesaroff and Funder, 1994; Kvetnansky et al., 1993). In laboratory studies of stress, investigators frequently measure SNS and HPA axis activity to verify the induction of a stress response.

However, it is important to emphasize that although these responses are characteristic of stress episodes, their occurrence does not necessitate the presence of stress. Many activities other than stress (e.g., sex, exercise) can produce significant SNS and/or HPA axis activity. Therefore, arousal, alone, is not sufficient to define stress. In addition to arousing, a stressful experience must be aversive, meaning that, if given the opportunity, an organism would avoid the situation that is leading to the arousing response. This characteristic of stress introduces the importance of perception in defining stress. As certain situations are aversive to some people but not others, not every individual will consider the same situations to be stressful. Public speaking is an example of this concept. Some individuals would do anything to avoid public speaking, whereas others thrive in such situations. Therefore, how an organism views the situation plays an important role in whether or not stress is experienced. Finally, even situations that are both aversive and arousing, under some circumstances, can have minimal effects on physiology and behavior. Another important variable related to the stress concept is controllability (Maier and Watkins, 2010). Extensive work has shown that uncontrollable, but not controllable, aversive and arousing experiences exert significant effects on physiology and behavior. Thus, having the sense of control over a situation acts as a buffer against the stress response. Ultimately, based on the framework put forth by Kim and Diamond (2002), we would contend that stress is a perceived lack of control over an arousing, aversive experience.

**NEUROBIOLOGY OF STRESS – USING CHRONIC STRESS EFFECTS ON BRAIN STRUCTURE AS AN EXAMPLE**

Stress exerts powerful effects on learning and memory, in large part, because it results in the release of neurochemicals that have dramatic effects on cognitive brain areas, such as the amygdala, hippocampus, and prefrontal cortex (PFC). Each of these brain structures contains at least a moderate density of corticosteroid receptors, making them highly susceptible to the
effects of stress (Diorio, Viau, and Meaney, 1993; McEwen, Macewen, and Weiss, 1970; McEwen, Weiss, and Schwartz, 1968, 1969; McGaugh, 2004). The hippocampus, which is necessary for the formation of spatial and/or declarative memories (Broadbent, Squire, and Clark, 2004, 2006; Eichenbaum, 2004; Kaut and Bunsey, 2001; Moser and Moser, 1998; Squire, Stark, and Clark, 2004), and the PFC, which is important for higher-order cognitive function and working memory (Bechara, 2005; Muller and Knight, 2006; Nebel et al., 2005; Rowe, Owen, Johnsrude, and Passingham, 2001), regulate the stress response cycle through a negative feedback loop that is initiated by corticosteroid receptor binding. The amygdala, in contrast, is important for emotion (primarily fear) (McGaugh, 2004; Roozendaal, McEwen, and Chattarji, 2009) and can exacerbate the HPA axis response to stress through corticosteroid receptor-mediated positive feedback.

Preclinical animal models have reported a dissociation between the effects of stress on hippocampal / PFC and amygdala structure and function. For instance, chronic stress significantly reduces the length, spine density, and arborization of dendrites on neurons in the hippocampus and PFC (Cerqueira, Mailliet, Almeida, Jay, and Sousa, 2007; Conrad, LeDoux, Magarinos, and McEwen, 1999; Cook and Wellman, 2004; Kole, Costoli, Koolhaas, and Fuchs, 2004; Lambert et al., 1998; Liston et al., 2006; Magarinos and McEwen, 1995a, 1995b; Magarinos, McEwen, Flugge, and Fuchs, 1996; Radley et al., 2005; Radley et al., 2006; Radley et al., 2004), while increasing each of these parameters on neurons in the amygdala (Vyas, Bernal, and Chattarji, 2003; Vyas, Jadhav, and Chattarji, 2006; Vyas, Mitra, Shankaranarayana Rao, and Chattarji, 2002). Unsurprisingly, the same chronic stress regimens have been shown to produce significant impairments on hippocampus-dependent tasks (e.g., spatial learning) and PFC-dependent tasks (e.g., attention set-shifting, working memory, reversal learning) (Bodnoff et al., 1995; Cerqueira et al., 2007; Krugers et al., 1997; Liston et al., 2006; Luine, Villegas, Martinez, and McEwen, 1994; Park, Campbell, and Diamond, 2001; Sousa, Lukoyanov, Madeira, Almeida, and Paula-Barbosa, 2000; Zoladz, Conrad, Fleschner, and Diamond, 2008), while enhancing performance on amygdala-dependent tasks (e.g., fear conditioning) (Conrad, LeDoux et al., 1999; Sandi, Merino, Cordero, Touyarot, and Venero, 2001). Additionally, the same chronic stress that leads to hypertrophy of cells in the amygdala increases the expression of anxiety-like behaviors in rats tested on the elevated plus maze (Vyas et al., 2003; Vyas et al., 2006; Vyas et al., 2002). Importantly, the effects of chronic stress on hippocampal and PFC morphology have been found to be reversible – that is, the dendrites re-grow
when the stress is discontinued (Conrad, LeDoux et al., 1999; Radley et al., 2005; Sousa et al., 2000). This is not the case, however, for the effects of chronic stress on amygdala morphology or the amygdala-mediated expression of anxiety-like behavior (Vyas, Pillai, and Chattarji, 2004). Given the amygdala’s involvement in emotion, particularly fear, these differences have important implications for understanding how stress can facilitate the onset of psychological illness.

Most of the aforementioned effects of chronic stress on brain structure and function have been observed in male rodents. This highlights an important bias that has been present in the stress literature for some time, and one that we will address throughout the chapter. Specifically, very few investigators have attempted to understand the differential effects of stress on males and females, likely because of the inconvenience and difficulty in dealing with the influence of the estrus (rodents) or menstrual (humans) cycle on such effects. The few investigators who have examined the effects of stress on females have often reported effects opposite to the ones observed in males. For instance, in preclinical work, chronic stress has been reported to have no effect on or enhance dendritic arborization in the hippocampus and PFC of female rodents (Galea et al., 1997; Garrett and Wellman, 2009; McLaughlin, Baran, and Conrad, 2009) and enhance their spatial learning and memory (Bowman, Beck, and Luine, 2003; McLaughlin, Baran, Wright, and Conrad, 2005). The differential effects observed in males and females are likely attributable to the influence of ovarian hormones in females, as some work has indicated (Garrett and Wellman, 2009; Luine, Beck, Bowman, Frankfurt, and Maclusky, 2007; McLaughlin et al., 2009).

The effects of chronic stress on cognitive brain regions, especially the hippocampus, appear to be mediated by corticosteroid and excitatory amino acid activity, although most of this work, again, has been conducted in male rodents. In hippocampal neurons, chronic stress and chronic elevations of corticosteroids result in excessive glutamatergic activity, in part due to a reduction of glutamate reuptake and altered GABA signaling (Magarinos and McEwen, 1995b; Reagan et al., 2004); thus, the dendrites of such neurons retract to avoid toxic increases in glutamate-induced increases in intracellular calcium (Conrad, 2006). Accordingly, chronic corticosteroid administration mimics the effects of chronic stress on hippocampal and PFC morphology (Magarinos, Orchinik, and McEwen, 1998; Sousa et al., 2000; Watanabe, Gould, Cameron, Daniels, and McEwen, 1992; Woolley, Gould, and McEwen, 1990), and the stress-induced dendritic retraction in the hippocampus of male rats can be blocked by steroid synthesis inhibitors, as well as N-methyl-D-
aspartate (NMDA) receptor antagonists and agents that significantly reduce extracellular levels of glutamate (Magarinos and McEwen, 1995b; Magarinos et al., 1996; Watanabe, Gould, Cameron et al., 1992; Watanabe, Gould, Daniels, Cameron, and McEwen, 1992).

**GENERAL CORRELATES OF ACUTE STRESS EFFECTS ON LEARNING AND MEMORY**

Over the past couple of decades, considerable research has accumulated indicating that stress can influence many different types of learning (e.g., hippocampus-dependent, striatum-dependent, PFC-dependent), oftentimes in different manners. The majority of this chapter will focus on how acute stress influences hippocampus-dependent learning and memory, as this seems to be the most complex and least understood form of stress-memory interaction. Nonetheless, at the end of the chapter, we will briefly address the influence of acute stress on multiple memory systems and how alterations of hippocampal function may be related to this phenomenon.

One important distinction to make when considering how stress affects learning and memory is to consider how stress affects one’s memory for events or information that is unrelated to the stressor versus how stress affects one’s memory for the stress experience itself. In most cases, stress enhances one’s memory for the stress-inducing stimulus (e.g., terrorist attack, crime that has taken place), whereas the effects that stress has on one’s memory for events or information that is unrelated to the stressor are more variable (Wolf, 2008). Thus, when considering the influence of stress on learning and memory, one must distinguish between intrinsic and extrinsic stressors (Joels, Pu, Wiegert, Oitzl, and Krugers, 2006). Intrinsic stressors are stressors that are inherent to the learning experience. In rodents, intrinsic stress has been manipulated by decreasing the water temperature in a water maze for a spatial learning task or by increasing the shock intensity in a Pavlovian fear conditioning experiment (Cordero, Merino, and Sandi, 1998; Sandi, Loscertales, and Guaza, 1997). In humans, intrinsic stress (or perhaps “arousal” in this case) has often been manipulated by having participants learn words or pictures that vary in emotional arousal [i.e., positive (e.g., kiss), negative (e.g., poison), and neutral (e.g., chair) words or pictures] (Cahill and McGaugh, 1995; Kuhlmann and Wolf, 2006a). In general, intrinsic stress enhances learning and long-term memory. Thus, as the water temperature
decreases in a water maze or the shock intensity increases in a fear conditioning experiment, the organisms exhibit a greater stress response and consequentially better learning. In addition, humans exhibit significantly greater learning and memory for words or pictures that are emotionally arousing, relative to emotionally neutral information. The enhancing effects of intrinsic stress on long-term memory have been associated with corticosteroid and noradrenergic activity in the amygdala (Cahill et al., 1996; Cahill and McGaugh, 1996; Canli, Zhao, Brewer, Gabrieli, and Cahill, 2000; Strange and Dolan, 2004; van Stegeren et al., 2005). These mechanisms will be a recurring theme throughout the chapter, as they explain many of the stress-induced alterations of learning and memory that have been observed.

Extrinsic stress, on the other hand, includes stressors that are not part of the learning experience but exert some sort of influence on that experience. For instance, preclinical investigators have exposed rats to stressors such as predator stress (e.g., cat), tailshock, or restraint to examine their effects on learning that takes place in another context (e.g., spatial learning in a water maze, object recognition learning, etc.) (Campbell et al., 2008; de Quervain, Roozendaal, and McGaugh, 1998; Diamond et al., 2006; Diamond, Park, Heman, and Rose, 1999; Kim, Koo, Lee, and Han, 2005; Kim, Lee, Han, and Packard, 2001; Woodson, Macintosh, Fleshner, and Diamond, 2003). In humans, investigators have exposed participants to social evaluative stressors (e.g., Trier Social Stress Test; TSST) or physical stressors (e.g., cold pressor test – hand placed in ice-cold water) to examine their effects on learning a list of words or pictures (Cahill, Gorski, and Le, 2003; Schwabe, Bohringer, Chatterjee, and Schachinger, 2008; Schwabe et al., 2009; Zoladz, Clark et al., 2011; Zoladz et al., 2013). One of the dogmas in the field of stress-memory interactions used to be the notion that extrinsic stressors globally impair hippocampal function; however, over the past decade or so, it has become apparent that stressors experienced outside of the learning context can either enhance or impair hippocampus-dependent learning and memory, depending on numerous factors (Diamond, Campbell, Park, Halonen, and Zoladz, 2007; Joels, Fernandez, and Roozendaal, 2011; Joels et al., 2006; Schwabe, Joels, Roozendaal, Wolf, and Oitzl, 2012). Similar to the concept described in the previous paragraph, some investigators have shown that extrinsic stress can enhance learning and memory if the information being learned is conceptually related to the stressor. For instance, Smeets and colleagues exposed participants to social evaluative stress before learning a list of words that were either (a) stressor-related or stressor-unrelated and (b) highly arousing or low arousing (Smeets et al., 2009). The results showed that stress enhanced
participants’ long-term memory for stressor-related, high arousing words only, supporting the idea that extrinsic stress can facilitate the acquisition of information that is conceptually related to the stressor.

Several studies in both humans and rodents have reported that stress-induced (intrinsic and extrinsic) enhancements and impairments of hippocampus-dependent learning and memory are associated with endogenous levels of circulating corticosteroids (Diamond et al., 2007; Wolf, 2009; Zoladz and Diamond, 2008). Comparable electrophysiological studies have provided strong evidence for an involvement of corticosteroids in the stress-induced modulation of long-term potentiation (LTP), a well-studied physiological model of memory in which an enhancement of synaptic transmission is produced by high-frequency stimulation of afferent fibers (Diamond et al., 2007; Kim and Diamond, 2002; Kim, Song, and Kosten, 2006). Studies have reported that both abnormally low and abnormally high levels of corticosteroids impair hippocampal synaptic plasticity, suggesting an inverted U-shaped relationship between corticosteroid levels and hippocampal function (Diamond, Bennett, Fleshner, and Rose, 1992).

Corticosteroids exert their effects by acting on mineralocorticoid (MR, Type I) and glucocorticoid (GR, Type II) receptors (Joels, 2001; Joels, Karst, DeRijk, and de Kloet, 2008). MRs exhibit a much higher affinity for corticosteroids than GRs and are nearly saturated at baseline. In contrast, GRs have a much lower affinity for corticosteroids and become extensively occupied only during times of corticosteroid elevation (e.g., stress). This led early investigators in the field to formulate the opposing receptor hypothesis, which suggested that MR activity is responsible for maintaining optimal hippocampal function, while GR activity is responsible for stress- and corticosteroid-induced impairments of hippocampal function (Conrad, Lupien, and McEwen, 1999). This hypothesis was initially supported by replacement studies reporting that, in adrenalectomized rats, the administration of the MR agonist aldosterone enhanced hippocampal LTP and rescued spatial memory impairment induced by corticosteroid depletion, while the administration of GR agonists impaired hippocampal LTP and enhanced hippocampal long-term depression (LTD), a decrease in synaptic transmission that is produced by low-frequency stimulation of afferent fibers (Conrad, Lupien, Thanasoulis, and McEwen, 1997; Pavlides, Kimura, Magarinos, and McEwen, 1995; Pavlides, Watanabe, Magarinos, and McEwen, 1995). However, other work did not support such a simple dichotomy between MR and GR activity and suggested that some GR occupancy is necessary for optimal hippocampal function. In a series of experiments, Conrad and colleagues found that, when GRs were
either completely blocked or highly occupied, rats exhibited impaired spatial memory in the Y-maze, an effect that was independent of the level of MR activation (Conrad, Lupien et al., 1999). In other words, only when there was a moderate level of GR occupancy did rats exhibit intact spatial memory. Collectively, these findings indicated that both MR and GR activity are necessary for hippocampus-dependent learning and memory. MR activity seems to be more involved in encoding / acquisition of hippocampus-dependent information (e.g., context), while GR activity seems to be involved in consolidating (i.e., storing) hippocampus-dependent information for subsequent retrieval (de Kloet et al., 1999; Oitzl and de Kloet, 1992).

Although corticosteroids are typically considered “stress” hormones, they circulate throughout the body on a regular basis according to a circadian rhythm. In humans, corticosteroids are the highest in the morning (i.e., awakening) hours, but decrease throughout the day and reach their nadir sometime during the late evening hours. Thus, in the morning, MRs are saturated, while GRs tend to be approximately 70% occupied. In the afternoon / evening, MRs are approximately 90% occupied, while GRs are only around 10% occupied.

Given these circadian-based differences in corticosteroid receptor activity, researchers speculated that stress or the administration of corticosteroids might have different effects on hippocampus-dependent learning and memory in the morning versus the afternoon / evening. Specifically, investigators predicted that significant elevations of corticosteroids would result in impairment primarily in the morning (as GRs would likely be close to saturation as a result) but may enhance learning and memory in the afternoon (as GRs would likely be only moderately activated). Two preliminary studies provided support for this prediction. Lupien and colleagues found that afternoon administration of hydrocortisone resulted in faster recognition of previously studied words during a delayed free recall assessment (Lupien et al., 2002), and Maheu and colleagues reported that social evaluative stress prior to learning a series of pictures impaired memory for the emotional pictures when administered in the morning, but had no effect on memory when administered in the afternoon (Maheu, Collicutt, Kornik, Moszkowski, and Lupien, 2005). In contrast to these studies, however, Smeets recently found that socially evaluated cold pressor stress impaired memory retrieval for emotional and neutral words independent of the time of day (i.e., morning or afternoon) (Smeets, 2011). This latter finding suggested that stress (and corticosteroid elevation) could impair memory regardless of when it occurred. However, there were some important differences between these studies that warrant
attention. For instance, both Lupien et al. (2002) and Maheu et al. (2005) examined males only, while Smeets (2011) included males and females in his study. In addition, Lupien et al. (2002) employed a within-day design, and Maheu et al. (2005) studied the effects of pre-learning stress on long-term memory. Smeets (2011), in contrast, assessed the effects of pre-retrieval stress on long-term memory. Thus, when considering the disparate findings of Smeets (2011), the differences between the three studies suggest that the effects of corticosteroid elevations at different times of the day may depend on sex and the stage of learning and memory that is influenced by such elevations. Additional work is necessary, however, to validate such speculation.

Despite the well-established involvement of corticosteroids in the stress-induced modulation of hippocampus-dependent learning and synaptic plasticity, it is important to note that an increase in corticosteroid levels, alone, is not sufficient to significantly alter hippocampal processes and often depends on concurrent activation of β-adrenergic mechanisms in the amygdala. The necessary involvement of the amygdala in the stress- and corticosteroid-induced modulation of hippocampal function has been addressed in studies revealing that inactivating or lesioning the basolateral amygdala (BLA), as well as administering β-adrenergic receptor antagonists directly into the BLA, despite leaving corticosteroid levels unaffected, prevents the effects of stress and corticosteroids on hippocampus-dependent learning and synaptic plasticity (Kim et al., 2005; Kim et al., 2001; Roozendaal, 2003; Roozendaal, Hahn, Nathan, de Quervain, and McGaugh, 2004; Zoladz, Park, and Diamond, 2011).

**EFFECTS OF STRESS DEPEND ON STAGE OF LEARNING**

The process of learning and memory can generally be divided into three major stages: encoding, consolidation, and retrieval. Encoding involves the acquisition phase, during which information is initially learned (e.g., studying a list words, associating a tone with a shock). Consolidation is when the learned information is stored, or consolidated, in order to be successfully retrieved (the third stage) at a later point in time. Most of the early studies on stress-memory interactions did not allow investigators to determine which stage was affected by the stress. For instance, many studies involved within-day stress manipulations, which hindered the ability to know whether the effects of stress were due to its effects on encoding, consolidation, or retrieval. As research in this area progressed, most investigators switched to the use of
two (or more)-day paradigms, in which participants were stressed before (pre-
learning stress; encoding / consolidation effects) or after (post-learning stress;
consolidation effects) learning and then tested 24 hr (or more) later, sometimes
following stress (pre-retrieval stress; retrieval effects), for their memory of the
learned information. This methodology has enabled investigators to show that
stress exerts differential effects on learning and memory depending on the
stage that is directly influenced.

Pre-Retrieval Stress (Retrieval Effects)

Most research, in both humans and rodents, has reported deleterious
effects of pre-retrieval stress or corticosteroid administration on memory
(Buchanan and Tranel, 2008; Buchanan, Tranel, and Adolphs, 2006; Buss,
Wolf, Witt, and Hellhammer, 2004; de Quervain et al., 1998; Diamond et al.,
2006; Kuhlmann, Kirschbaum, and Wolf, 2005; Kuhlmann, Piel, and Wolf,
2005; Park, Zoladz, Conrad, Fleshner, and Diamond, 2008; Smeets, Otgaar,
Candel, and Wolf, 2008; Tollenaar, Elzinga, Spinhoven, and Everaerd, 2008).
The memory-impairing effects of pre-retrieval stress have been positively
associated with endogenous corticosteroid levels, and administration of
corticosteroid antagonists can prevent the deleterious effects of pre-retrieval
stress on testing (de Quervain et al., 1998). Pre-retrieval stress or
corticosteroid effects on hippocampus-dependent memory appear to depend on
an interaction of corticosteroids and noradrenergic mechanisms in the
amygdala. Indeed, lesions of the BLA or systemic / intra-BLA administration
of β-adrenergic receptor antagonists, such as propranolol, eliminates the
impairing effects of stress or corticosteroids on memory (Roozendaal, 2003;
Roozendaal et al., 2004). In addition, the effects of pre-retrieval stress or
corticosteroids on memory are often selective for emotionally arousing (i.e.,
amygdala-activating) information (Buchanan et al., 2006; Kuhlmann,
Kirschbaum et al., 2005; Kuhlmann, Piel et al., 2005; Smeets et al., 2008;
Tollenaar et al., 2008), and testing subjects under non-arousing conditions
abolishes the adverse effects of stress on memory testing (Kuhlmann and
Wolf, 2006b). For instance, testing participants in the same context as that
which was utilized during encoding (supposedly reducing novelty stress
induced by participating in an experiment) eliminates pre-retrieval stress
effects on memory (Schwabe and Wolf, 2009a). These findings suggest that
arousal, and more specifically noradrenergic activity in the BLA, is a co-
requisite for stress or corticosteroid-induced alterations of retrieval.
The effects of stress or corticosteroid administration on retrieval, however, are not unequivocal. Some studies have reported that stress can impair retrieval without a concurrent increase in corticosteroid levels; others have shown that pre-retrieval stress has no effect on memory; and, still others have shown that pre-retrieval stress can enhance memory. In preclinical work, Diamond and colleagues found that systemic administration of stress-level corticosterone prior to water maze testing had no effect on spatial memory in rats. These investigators also reported that stress impaired spatial memory retrieval in adrenalectomized rats that were not able to manifest a stress-induced increase in corticosteroids, suggesting that corticosteroid elevation is not even necessary for stress-induced retrieval deficits (Zoladz, Park, Munoz, Fleshner, and Diamond, 2008). In humans, Beckner and colleagues reported that exposing participants to social evaluative stress (TSST) had no effect on recall 48 hr later (Beckner, Tucker, Delville, and Mohr, 2006). Schwabe and colleagues even found that exposing participants to a brief stressor 30 min prior to testing enhanced 24-hr recall of emotionally arousing words, an effect that was prevented by administration of a β-adrenergic receptor antagonist (Schwabe et al., 2009). Recently, Schilling et al. (2013) reported that intravenous administration of cortisone prior to retrieval dose-dependently enhanced memory in participants. These findings resonate with previous work demonstrating an inverted, U-shaped relationship between corticosteroids and memory retrieval (Domes, Rothfischer, Reichwald, and Hautzinger, 2005; Wolf, 2009; Zoladz and Diamond, 2008). In fact, recent work by our group has revealed that brief stress immediately before memory testing can enhance declarative memory (Zoladz, Kalchik et al., submitted, unpublished findings). This is consistent with the work from Schwabe and colleagues (Schonfeld, Ackermann, and Schwabe, 2014), who found that stress near the time of retrieval enhanced memory, an effect that was associated with increased autonomic arousal. The enhancing effects of pre-retrieval stress on memory may also be related to rapid, non-genomic effects of corticosteroids, which have been associated with enhanced hippocampus-dependent learning and synaptic plasticity, rather than classic delayed, gene-dependent corticosteroid signaling, which often results in impairments of hippocampal function.

As with most of the stress-memory literature, much of the research examining stress effects on retrieval has been conducted in males. In those studies that have examined the possibility of sex differences in these effects, some have revealed that pre-retrieval stress exerts similar effects on males and females, whereas others have shown that pre-retrieval stress can have differential effects on males and females, especially when considering
hormone levels in females. Kuhlmann and Wolf (2005) reported that cortisol administration impaired retrieval in naturally cycling women (mensis and luteal phases), but had no effect on memory in women using oral contraceptives. Schoofs and Wolf (2009) later found that stress had no effect on females during the luteal phase of the menstrual cycle. Finally, Wolf et al. (2001) showed that pre-retrieval stress led to a negative correlation between corticosteroids and memory in men, but not women. Collectively, these studies show that pre-retrieval stress effects on memory can depend on sex and circulating hormone levels.

Theoretical views on how stress impairs memory retrieval have focused on the idea of metaplasticity. Researchers have shown that stress activates mechanisms in common with models of synaptic potentiation, such as LTP (Diamond, Park, Campbell, and Woodson, 2005; Diamond, Park, and Woodson, 2004). One might suggest that stress results in such activity because a memory of the stress must be formed. Therefore, investigators have contended that stress activates endogenous plasticity, which leads to an increased threshold for subsequent plasticity to occur (i.e., metaplasticity); there may even be a shift toward a suppression of synaptic potentiation following stress, thus facilitating plasticity such as LTD (Kim and Yoon, 1998; Schmidt, Abraham, Maroun, Stork, and Richter-Levin, 2013). According to this view, pre-retrieval stress prevents access to stored information by saturating the neural synapses that are necessary for retrieving the memory. In other words, stress impairs memory by forming a new memory, and it is the formation of this new memory that results in retrieval failure. While some research has supported this view (Diamond et al., 2004), such a perspective fails to account for pre-retrieval stress-induced enhancements of memory, even though they have rarely been reported.

Post-Learning Stress (Consolidation Effects)

Most of the research examining the effects of post-learning stress on consolidation has reported enhancements of long-term memory, and these enhancements have frequently been associated with an organism’s corticosteroid response to the stressor (Beckner et al., 2006; Cahill et al., 2003; Hui, Hui, Roozendaal, McGaugh, and Weinberger, 2006; Preuss and Wolf, 2009; Smeets et al., 2008). Indeed, the administration of corticosteroids can mimic the post-learning stress-induced enhancement of long-term memory (Roozendaal, Barsegian, and Lee, 2008). Much evidence indicates that
noradrenergic activity in the BLA, along with subsequent activation of GRs by cortisol, plays a central role in this effect, as GR antagonists, BLA lesions, or β-adrenergic receptor antagonists block the effect (Roozendaal, 2003; Roozendaal, Okuda, Van der Zee, and McGaugh, 2006). In human work, the importance of amygdala activity in the enhancement of memory consolidation has been demonstrated by studies showing that endogenous elevations of cortisol are associated with enhanced memory only in participants exhibiting heightened arousal (Abercrombie, Speck, and Monticelli, 2006). In addition, Cahill and colleagues found that participants exposed to cold pressor stress immediately following learning recalled more arousing slides and more details from arousing slides than control participants (Cahill et al., 2003). These findings support the notion that stress or corticosteroids result in an amygdala-induced enhancement, or emotional tagging, of recently learned information.

The ability of post-learning stress to enhance long-term memory appears to be time- and sex-dependent. The enhancement has been observed when stress is administered up to 30 min following learning, but subsides when longer time intervals are employed (Nielson and Powless, 2007). Thus, for memory enhancement to occur, there needs to be a convergence in time between the learned information and the stress experience. It is likely that the neurochemicals released during stress must converge on brain areas (i.e., convergence in space) engaged during learning at the right time (i.e., convergence in time) to promote storage of the information (Joels et al., 2006). Studies examining sex differences in post-learning stress effects on long-term memory have been mixed. Felmingham and colleagues reported that post-learning cold pressor stress enhanced memory for negative images in females, but not males (Felmingham, Tran, Fong, and Bryant, 2012). However, others have reported similar effects of post-learning stress in males and females (Beckner et al., 2006; Trammell and Clore, in press) or greater effects in males (Preuss and Wolf, 2009). If females were more sensitive to stress-induced enhancements of long-term memory, it may explain why females are more likely to develop stress-related psychological disorders, such as PTSD (Tolin and Foa, 2006). More research is warranted to explore how sex and hormonal differences influence post-learning stress effects on consolidation.

Not all studies examining post-learning stress effects on long-term memory have reported enhancements. Indeed, a paper recently published by Trammell and Clore (in press) challenged the well-accepted notion that stress administered after learning enhances long-term recall. These investigators found that cold pressor stress administered shortly after learning led to impaired 48-hr recall. Importantly, this effect was independent of the type of
information being learned (i.e., words or pictures), the valence / arousal of the learned information, the duration of the stressor (1- or 3-min stressor), and the sex of the participant. These findings suggest that the enhancement of consolidation by stress may be more restricted than once thought and requires additional work to disentangle.

**Pre-Learning Stress (Encoding / Consolidation Effects)**

In studies examining the effects of pre-learning stress on long-term memory, one cannot determine the specific stage of learning that is affected by the stressor. That is to say, pre-learning stress could influence encoding or the consolidation of information. In an attempt to verify that stress has influenced the consolidation rather than the encoding of information, some investigators show that the pre-learning stress has no effect on memory testing during day 1 (i.e., short-term memory) of an experiment and selectively influences memory testing during day 2 (i.e., long-term memory). However, even in such studies, it is impossible to conclusively verify that the information has not been encoding differentially as a result of stress exposure.

Pre-learning stress effects on encoding or consolidation, regardless of which stage is actually being influenced, are still meaningful. However, studies examining pre-learning stress effects on long-term memory have been more inconsistent than studies examining the effects of post-learning or pre-retrieval stress on memory, which were discussed above. Studies have shown that pre-learning stress can enhance, impair, or have no effect on long-term memory, and this inconsistency appears to depend on several factors (Diamond et al., 2006; Duncko, Johnson, Merikangas, and Grillon, 2009; Elzinga, Bakker, and Bremner, 2005; Jelicic, Geraerts, Merckelbach, and Guerrieri, 2004; Kim et al., 2005; Kim et al., 2001; Nater et al., 2007; Park et al., 2008; Payne et al., 2007; Payne et al., 2006; Schwabe et al., 2008; Zoladz, Clark et al., 2011; Zoladz et al., 2013). One factor is the emotional nature of the learned information. Some work has shown that pre-learning stress, or corticosteroid administration, can enhance long-term memory for emotionally arousing information, at the cost of (i.e., impairing) memory for emotionally neutral information (Jelicic et al., 2004; Payne et al., 2007; Payne et al., 2006). This phenomenon has been referred to as the “emotional trade-off” effect and does seem to be adaptive in that exposure to stress would intuitively result in an individual focusing on emotionally arousing, potentially threatening information, rather than emotionally neutral, innocuous information. That pre-
learning stress can exert selective effects on emotionally arousing information further supports the involvement of amygdala-induced modulation of cognitive brain structures in stress effects on learning. However, not everyone has replicated the effect. In fact, some have shown that pre-learning stress can enhance long-term memory for emotionally neutral information, while exerting little to no effect on memory for emotionally arousing information (e.g., Schwabe et al., 2008).

Two other factors that appear to mediate pre-learning stress effects on long-term memory are the timing of the stressor relative to learning and the sex of the individual being examined. As will be described more thoroughly below, investigators have proposed that stress exerts time-dependent, multiphasic effects on several brain regions involved in cognition. According to this view, stress that occurs in close temporal proximity to a learning experience will result in an enhancement of long-term memory, while stress that is temporally separated from learning will result in an impairment of long-term memory. Some investigations have corroborated this speculation, but it is apparent that the sex of the individual under study is important as well. For instance, we recently reported that brief stress administered 30 min prior to learning impaired long-term memory in males who exhibited a robust cortisol response to the stressor, while having no effect on females (Zoladz et al., 2013).

**TEMPORAL DYNAMICS OF ACUTE STRESS EFFECTS ON LEARNING**

Much of the early research on stress and cognition led scientists to conclude that stress exerted global deleterious effects on hippocampal function. However, a shift in thought has occurred over the past couple of decades with the realization that stress, even when occurring outside the context of the learning experience, can enhance or impair hippocampus-dependent learning and memory. Although numerous studies have shown that acute stress impairs synaptic plasticity in the hippocampus, most of these studies did not deliver tetanizing (i.e., high-frequency) stimulation to the neural fibers until long after (e.g., ≥ 20 min) the onset of stress (see Diamond et al., 2007 for a review). Indeed, a closer examination of the literature, as indicated by Diamond and colleagues, reveals that when high-frequency stimulation is delivered shortly after a stressful or arousing event, hippocampal
synaptic plasticity is actually enhanced (Ahmed, Frey, and Korz, 2006; Almaguer-Melian et al., 2005; Davis, Jones, and Derrick, 2004; Frey, 2001; Li, Cullen, Anwyl, and Rowan, 2003; Seidenbecher, Balschun, and Reymann, 1995; Seidenbecher, Reymann, and Balschun, 1997; Straube, Korz, and Frey, 2003; Uzakov, Frey, and Korz, 2005). Because the induction of synaptic plasticity, such as LTP, is considered to be a well-established physiological model of learning, one might reason that stress effects on learning might also be time-dependent.

As a result of their thorough examination of the research literature, Diamond and colleagues (Diamond et al., 2007) developed the temporal dynamics model of emotional memory processing to address how the timing of a stressor might influence the effects of stress on learning. The temporal dynamics model was inspired by research demonstrating an amygdala-induced biphasic response pattern of hippocampal function. Specifically, Akirav and Richter-Levin found that electrical stimulation of the BLA immediately prior to high-frequency stimulation of the perforant pathway enhanced LTP in the dorsal dentate gyrus (DG) of the hippocampus, while stimulating the BLA 1 hr before high-frequency stimulation impaired dorsal DG LTP (Akirav and Richter-Levin, 1999). Subsequent work revealed that both the enhancement and impairment of dorsal DG LTP that was induced by BLA stimulation depended on corticosteroids and norepinephrine, most likely interacting in the amygdala (Akirav and Richter-Levin, 2002). Also, these investigators showed that basal, but not lateral or central, amygdala stimulation was responsible for the effects on hippocampal plasticity (Akirav and Richter-Levin, 1999, 2002). Interestingly, Richter-Levin and colleagues found that the same BLA priming stimulation that enhanced DG LTP impaired LTP induction in the CA1 region of the hippocampus, a region known to be involved in spatial learning and memory, and that this effect was independent of corticosteroid and norepinephrine activity (Vouimba and Richter-Levin, 2005; Vouimba, Yaniv, and Richter-Levin, 2007). Importantly, however, the investigators in these studies examined the effects of BLA stimulation on plasticity in the ventral part of the CA1 region, and because extensive work has reported a dissociation between the functions of the dorsal and ventral hippocampus (Maggio and Segal, 2012; Segal, Richter-Levin, and Maggio, 2010), the finding may be less related to memory and more associated with emotional functions of the structure.

The amygdala-induced biphasic effects on hippocampal plasticity resonated with the relatively recent discovery that corticosteroids could induce biphasic effects on hippocampal plasticity as well (de Kloet, Karst, and Joels,
2008; Karst et al., 2005; Morsink et al., 2006). The traditional view of corticosteroid action was that it exerts effects on cells in a delayed manner by binding to intracellular receptors which enter the nucleus and act as transcription factors to modulate gene expression. However, it was discovered that corticosteroids could also bind to membrane-bound receptors and exert rapid, non-genomic effects on neuronal transmission, effects that were dependent on MR-induced increases in glutamatergic transmission.

Thus, according to Diamond and colleagues (Diamond et al., 2007), stress induces two phases of hippocampal function: an excitatory phase (Phase 1) and an inhibitory phase (Phase 2). At the onset of a stress experience, the amygdala is rapidly activated, which, in addition to activating the SNS and HPA axis, would stimulate and enhance hippocampal function (excitatory Phase 1). Enhanced hippocampal function would be fueled by a dramatic increase in the levels of numerous excitatory neurochemicals (e.g., glutamate, acetylcholine, CRH, norepinephrine, dopamine), all of which have been shown to enhance hippocampal LTP (Ahmed et al., 2006; Blank, Nijholt, Eckart, and Spiess, 2002; Gray and Johnston, 1987; Hopkins and Johnston, 1988; Li et al., 2003; Ovsepian, Anwyl, and Rowan, 2004; Wang, Tsai, and Lee, 2000; Wang, Wayner, Chai, and Lee, 1998; Ye, Qi, and Qiao, 2001) and would, hypothetically, activate endogenous forms of hippocampal neuroplasticity and facilitate memory storage. Corticosteroid-mediated effects on the hippocampus would not be observed immediately, as there is a several minute delay from the onset of stress to the release of corticosteroids from the adrenal cortex (Cook, 2001). Nevertheless, when the newly synthesized corticosteroids reached the hippocampus, they would exert immediate, non-genomic excitatory effects on synaptic plasticity by enhancing glutamate transmission and facilitating NMDA receptor-dependent synaptic plasticity (Joels et al., 2011; Joels et al., 2008). Learning that occurred during this phase would theoretically be enhanced. This would explain why individuals exhibit very strong memories for stressful experiences by forming so-called “flashbulb memories” (Brown, 1977). It would also potentially explain how intensely stressful events can lead to traumatic memory formation and, as a result, psychological disorders such as PTSD.

As the time from stress onset increased, corticosteroid levels would significantly rise, resulting in extensive GR activation. In addition, there would be a buildup of glutamate and calcium, promoting the desensitization of NMDA receptors (Alford, Frenguelli, Schofield, and Collingridge, 1993; Nakamichi and Yoneda, 2005; Price, Rintoul, Baimbridge, and Raymond, 1999; Rosenmund and Westbrook, 1993; Zorumski and Thio, 1992). These
events would result in an inhibition of hippocampal function (Phase 2), which would lead to impaired learning and memory. Despite the seemingly negative effects of Phase 2, they would theoretically have adaptive consequences. For instance, Diamond and colleagues (Diamond et al., 2007) suggested that an inhibition of hippocampal function following stress would allow for the region to properly consolidate the information that had been acquired around the time of the stressor, information that would hypothetically be more important for an organism’s survival. In addition, Phase 2 would occur to protect hippocampal cells from the threat of excitotoxicity. As glutamate levels steadily rose, the increase in intracellular calcium levels would endanger cell survival. Thus, desensitization of NMDA receptors could be viewed as a compensatory mechanism to counter this threat. Finally, as a foreshadowing of a subsequent section, it is during Phase 2 that one might predict an organism to switch learning strategies from a hippocampus-dependent to a hippocampus-independent strategy (Packard, 2009). This type of adaptive mechanism would allow an organism to still learn during stress-induced hippocampal impairment by utilizing a different style of learning.

Although the focus of the temporal dynamics model is how stress influences hippocampal function, it also includes the prediction that stress exerts differential effects on amygdala and PFC function. As discussed by Diamond and colleagues, stress would exert biphasic effects on amygdala activity, rapidly activating the amygdala shortly after stress but eventually inhibiting amygdala function over time. Support for this prediction comes mainly from preclinical research demonstrating time-dependent effects of stress on amygdala plasticity (Kavushansky and Richter-Levin, 2006; Schroeder and Shinnick-Gallagher, 2005; Tsvetkov, Carlezon, Benes, Kandel, and Bolshakov, 2002); however, there is also some evidence that corticosteroids result in decreased amygdala activity in humans (Henckens, van Wingen, Joels, and Fernandez, 2010, 2012). It is not clear how the timeline of amygdala activity would vary following stress onset, and it is likely, as the authors of the model suggest, that the amygdala would undergo a longer excitatory phase than that of the hippocampus before entering its refractory state (Diamond et al., 2007). Nevertheless, the prediction that the amygdala undergoes a biphasic response pattern following stress relates well with human studies in which stress administered immediately before fear conditioning enhanced fear memory, while stress administered more than 30 min before fear conditioning impaired fear memory (Antov, Wolk, and Stockhorst, 2013). In terms of stress effects on PFC function, Diamond and colleagues predicted that stress turns the PFC “offline” and impairs PFC
function from the onset of the stressor. This prediction is consistent with extensive work revealing that acute stress impairs PFC-dependent working memory in both humans and rodents and blocks LTP induction in the PFC (Maroun and Richter-Levin, 2003; Moghaddam and Jackson, 2004). Moreover, BLA stimulation 30 sec or 1 hr prior to high-frequency stimulation impairs LTP in the medial PFC (Richter-Levin and Maroun, 2010).

Most of the support for the temporal dynamics model has come from preclinical work in non-human animals examining hippocampal synaptic plasticity or hippocampus-dependent learning and memory in males. As described above, in electrophysiological studies, an enhancement of the magnitude and duration of hippocampal LTP has resulted only when tetanizing electrical stimulation occurred in conjunction with the onset of the arousing experience. In contrast, when tetanizing stimulation was delivered 30 min or more after the onset of stress or corticosteroid administration, then LTP has primarily been inhibited. Behaviorally, investigators have shown that brief stress applied immediately, but not 30 min, prior to learning enhanced water maze memory and novel object recognition in male rats (Bullard, Park, and Diamond, 2013; Diamond et al., 2007). Subsequent work revealed that these pre-learning stress-induced enhancements of long-term memory were dependent on β-adrenergic receptor activity, as the administration of propranolol blocked the effects (Bullard et al., 2013; Halonen, Zoladz, Park, and Diamond, 2007). More recently, some investigators have shown that stimulating the BLA immediately after rats learn a novel object recognition task enhances long-term recognition memory, an effect that is dependent on an intact hippocampus (Bass, Nizam, Partain, Wang, and Manns, 2013; Bass, Partain, and Manns, 2012). These latter findings provide perhaps some of the most conclusive evidence for amygdala-induced modulation of hippocampal function as a pre-requisite for stress-induced enhancements of memory.

In general, human work in which the timing of stress has been experimentally manipulated is limited. Our laboratory was the first to experimentally manipulate the timing of stress before learning to examine its effects on long-term memory in humans (Zoladz, Clark et al., 2011). We found that when participants were exposed to brief (i.e., 3-min) socially evaluated cold pressor stress immediately before learning, they exhibited enhanced memory for positive words 24 hr later, an effect that was positively associated with their heart rate response to the stressor. In contrast, when participants were exposed to the same stressor 30 min prior to learning, they exhibited impaired memory for negative words 24 hr later, an effect that was negatively associated with their corticosteroid and blood pressure responses to the
stressor. That the effects were present only for emotionally arousing information again implicates an involvement of amygdala activity in the findings. Overall, the findings of this study suggested that the rapid enhancement of hippocampus-dependent learning is associated with stress-induced increases in autonomic activity (likely noradrenergic signaling), while the delayed impairing effects are associated with stress-induced increases in both corticosteroids and autonomic activity.

Our laboratory recently provided additional support for the temporal dynamics model by showing that brief (i.e., 3-min) cold pressor stress administered 30 min before learning impaired overall long-term memory 24 hr later (Zoladz et al., 2013). Additional work in humans, though limited, has further supported these findings. For instance, Quaedflieg et al. (2013) found that stress administered immediately or 30 min prior to learning a series of images, overall, impaired long-term memory. However, they reported that stress-induced cortisol responses were positively associated with memory when stress was administered immediately before learning and negatively associated with memory when stress was administered 30 min before learning, suggesting that rapid versus delayed corticosteroid actions could be associated with different effects on learning. Wolf and colleagues (Pabst, Brand, and Wolf, 2013) also reported that stress administered 5 or 18 min prior to a decision-making task led to an improvement of decision-making, while stress administered 28 min prior to the task led to more risky decisions. As decision-making is often dependent on PFC function, these findings suggest that stress could exert biphasic effects on PFC-dependent, in addition to hippocampus- and amygdala-dependent, tasks. Additional work is necessary, however, to corroborate such speculation.

In addition to the aforementioned studies, much human work related to the temporal dynamics model has focused on time-dependent effects of corticosteroids, as opposed to stress, on physiology and behavior. For instance, Henckens and colleagues have conducted several studies on the rapid (i.e., non-genomic) versus delayed (i.e., genomic) effects of corticosteroids on learning and brain activity in male participants. These investigators found that rapid corticosteroid activity led to decreased functioning of the amygdala toward both positive and negative stimuli, while delayed corticosteroid activity only continued to block amygdala response to positive stimuli, as the response to negative stimuli returned to baseline levels (Henckens et al., 2010). These researchers also found that working memory and PFC activity increased as a result of delayed corticosteroid action ( Henckens, van Wingen, Joels, and Fernandez, 2011). In addition, delayed corticosteroid activity led to decreased
activity in the hippocampus when compared to a placebo condition, but not when compared to rapid corticosteroid effects (Henckens et al., 2012).

Some of these findings concerning time-dependent effects of corticosteroids on brain function seem contrary to what one would predict based on the temporal dynamics model. However, it is important to emphasize that studies examining the influence of corticosteroids on physiology and behavior, though useful for understanding basic stress processes, are not synonymous with the effects of stress. Indeed, as mentioned above, stress induces the release of an overabundance of neurochemicals that likely interact with each other in a complex manner. Therefore, the effects of corticosteroids on learning, memory, and brain activity do not allow for a full picture of the consequences that stress can have on the very same processes. It is also important to note that Henckens and colleagues did not consistently use the same dosage of corticosteroids across their studies. As described above, Schilling et al. (2013) demonstrated that, when administering cortisol before retrieval, the non-genomic effects of cortisol follow a dose-dependent, inverted U-shaped function. Participants who received a moderate amount of cortisol, equivalent to what would be experienced during moderate stress, showed the greatest cued-recall performance. Participants who received either more or less cortisol recalled fewer items. Therefore, it is possible that different effects could be seen in the brain regions examined by Henckens and colleagues if participants are given different amounts of cortisol.

**NUANCES OF THE TEMPORAL DYNAMICS MODEL**

The temporal dynamics model is a general approach to understanding how stress can influence cognitive brain areas, which then influence learning and memory capabilities. It is important to emphasize that, depending on several factors, the timing and duration of Phase 1 and Phase 2 of the model could vary considerably. For instance, as illustrated in Figure 1, a very intense stressor could result in a more short-lived excitatory phase of hippocampal function and a faster onset of its inhibitory phase. In fact, it is possible that traumatic stressors could force the hippocampus into a refractory phase immediately following the onset of stress, which may explain the phenomenon of traumatic amnesia (Bryant et al., 2009; Layton, Krikorian, Dori, Martin, and Wardi, 2006). In addition, individual differences, such as different physiological responses to stress, different perceptions of the stressor, or different perceived controllability over the stress, could also influence the
model. Thus, in most cases, stress results in an immediate excitatory phase of hippocampal function that is followed by a delayed inhibitory phase; however, the specifics of these phases are likely guided by several factors related to the stressor and the organism under investigation.

The temporal dynamics model of emotional memory formation is clearly applicable to how pre-learning stress influences the acquisition and consolidation of information, but is it relevant to post-learning or pre-retrieval stress effects on long-term memory? With regards to post-learning stress, we have already described the requirement of a convergence in time between the learning experience and the stressor for an enhancement of long-term memory to be observed. Thus, in this respect, the temporal dynamics model does appear applicable. That is to say, following learning, the application of a stressor would enhance amygdala and hippocampal function and facilitate memory storage. One major difference between the temporal dynamics of pre-versus post-learning stress may relate to the time window for enhancement. In other words, post-learning stress may result in an excitatory phase of hippocampal function that is more prolonged than the excitatory phase time window observed following pre-learning stress. Of course, the recent finding that post-learning stress impairs memory consolidation by Trammell and Clore (in press) suggests that the typical temporal dynamics model, with an excitatory and inhibitory phase, could apply. More work regarding how post-learning stress affects consolidation processes is needed to further test this possibility.

Figure 1. Figure 1A (left) illustrates the general model for the temporal dynamics of acute stress effects on hippocampal function. Shortly following stress onset, amygdala activity coupled with the rapid actions of several stress-related neurochemicals [e.g., norepinephrine (NE), glutamate (Glu)] would enhance hippocampal function and, consequentially, result in enhanced learning during this time frame. As the time from
stress onset increased, the hippocampus would eventually enter a refractory phase, during which learning would be impaired. The refractory phase would result from delayed effects of corticosteroids (CORT), as well as NMDA receptor desensitization. Figure 1B (right) illustrates how the general temporal dynamics model may differ if a very intense stressor is experienced. In this case, the stress-induced enhancement of hippocampal function may be more short-lived, and the refractory phase may have a more rapid onset. Of course, a similar pattern of stress-induced alterations of hippocampal function could result from other factors, such as individual differences (e.g., sex, genetic variation).

The traditional view has been that stress influences retrieval in a time-dependent manner, but any effect that occurs is likely to be impairment. For instance, researchers have shown that stress shortly before retrieval has no effect on memory, but when the stress occurs approximately 30 min before retrieval, providing enough time for endogenous corticosteroid levels to rise, impairment results (de Quervain et al., 1998). However, recent work from our laboratory and from that of others has suggested that this is an issue requiring further examination. Schilling and colleagues reported that intravenous cortisol administration shortly before retrieval dose-dependently enhanced recall (Schilling et al., 2013). This enhancement is likely a result of rapid, non-genomic effects of corticosteroids exerting a facilitative effect on cognitive brain function. In addition, our laboratory recently found that exposing participants to brief (i.e., 3-min), cold pressor stress immediately prior to 24-hr retrieval enhanced memory in males who exhibited a robust cortisol response to the stressor, thus suggesting a role of rapid, non-genomic corticosteroid actions in this enhancement (Zoladz, Kalchik et al., submitted, unpublished findings). These findings, though preliminary, do indicate that pre-retrieval stress or corticosteroid administration can enhance memory. Of course, pre-retrieval stress effects on memory might not follow the exact same temporal dynamics that have been put forth for pre-learning stress, as such a model does not necessarily fit with the finding that brief stress administered 30 min before retrieval enhances memory (Schwabe et al., 2009). Future work must delineate the timeline for pre-retrieval stress effects on human memory and the mechanisms or factors that could mediate different directions of the effects observed.
Throughout the stress-memory literature, there has been a clear bias toward studying male, as opposed to female, subjects. This has likely resulted from the inconvenience and difficulty in controlling for the influence of the estrus / menstrual cycle on any observed effects. Those investigators who have explored the influence of sex in stress-memory interactions have shown that stress exerts sex-specific effects on learning and memory; however, the differences observed in these studies have been inconsistent and difficult to unravel. Preclinical work has shown that acute stress enhances classical eyeblink conditioning in male rats, while impairing such conditioning in female rats (Wood and Shors, 1998). These effects may be related to baseline differences that have been observed between males and females in eyeblink conditioning paradigms, as females tend to exhibit greater performance than males under such conditions. Neurobiologically, researchers have shown that the differential effects of stress on eyeblink conditioning in males and females require an intact BLA (Waddell, Bangasser, and Shors, 2008). Moreover, acute stress has been reported to exert differential effects on hippocampal spine density in male and female rodents (Shors, Chua, and Falduto, 2001; Shors, Falduto, and Leuner, 2004). While such stress increases CA1 spine density in males, it decreases this spine density in females. Research examining sex differences in mediating stress-induced alterations of other types of learning has been less conclusive. For instance, some investigators have shown that acute stress impairs spatial learning and memory in males, while enhancing it in females (Conrad et al., 2004); others have shown that acute stress exerts comparable effects on both sexes or that females are less severely affected than males, yet not enhanced (Park et al., 2008). Many of the differences observed in the stress-induced alterations of learning and memory in male and female rodents has been attributed to the influence of ovarian hormones (Shors, Lewczyk, Pacynski, Mathew, and Pickett, 1998; Wood, Beylin, and Shors, 2001).

Like preclinical work, research in humans has also been biased against the inclusion of females in stress-memory investigations, perhaps even to a greater degree. Nevertheless, several studies have reported greater stress-induced alterations of learning and memory in males, relative to females. Investigators have frequently reported negative or curvilinear relationships between stress-induced cortisol and memory in males, while observing no relationship...
between these variables in females (Andreano and Cahill, 2006; Wolf et al., 2001). On the other hand, females tend to recall emotional information better than males, an effect that has been associated with greater noradrenergic activity in females (Felmingham, Tran et al., 2012; Schwabe, Hoffken, Tegenthoff, and Wolf, 2013). Similar to preclinical work, ovarian hormones may play a role in mediating these effects. Cahill and colleagues observed a positive correlation between stress-induced cortisol and memory only when female participants were in the mid-luteal phase of the menstrual cycle, a time when progesterone levels are elevated (Andreano, Arjomandi, and Cahill, 2008). Later work substantiated these findings by reporting that females exhibiting high levels of progesterone demonstrate better memory for emotional information, greater stress-induced elevations of salivary cortisol, and stronger stress-induced enhancements of memory than women with low levels of progesterone (Ertman, Andreano, and Cahill, 2011; Felmingham, Fong, and Bryant, 2012). Females also exhibit stronger responses of the amygdala-hippocampus neural network to emotional stimuli when they are in the luteal phase (Andreano and Cahill, 2010). These findings may collectively explain why females are more susceptible to stress-related psychological disorders such as PTSD (Tolin and Foa, 2006).

It is also possible that the female brain does not respond to emotion in the same manner that the male brain does. Some research has shown that the brain responses of males and females to emotional stimuli are hemisphere-specific. For instance, Cahill and others have reported that, when presented with emotional stimuli, males tend to exhibit greater activity in the right amygdala, while females tend to exhibit greater activity in the left amygdala (Cahill et al., 2001; Cahill, Uncapher, Kilpatrick, Alkire, and Turner, 2004; Canli, Desmond, Zhao, and Gabrieli, 2002; Mackiewicz, Sarinopoulos, Cleven, and Nitschke, 2006). Interestingly, the right amygdala has been associated with one’s memory for gist, while the left amygdala has been associated with one’s memory for details (Fink et al., 1996; Fink, Marshall, Halligan, and Dolan, 1999). Thus, it may not be surprising to note that, under emotionally arousing conditions, males exhibit greater memory for the central aspects of a scene, while females exhibit greater memory for the details (Cahill and van Stegeren, 2003). This differential activation of brain areas in response to emotional stimuli could play an important role in sex influences on stress-memory interactions.

We have recently observed sex differences in pre-learning stress-induced alterations of hippocampus-dependent memory. In one study, we were interested in testing the time-dependent influences of stress on false memory
production (Zoladz, Peters et al., submitted, unpublished findings). Based on the temporal dynamics model, we hypothesized that stressing participants immediately before encoding would reduce false memory production, as opposed to increasing it (Payne, Nadel, Allen, Thomas, and Jacobs, 2002). We exposed participants to brief cold pressor stress immediately before having them perform the Deese-Roediger-McDermott (DRM) false memory paradigm (Deese, 1959; Roediger and McDermott, 1995). In this paradigm, participants are exposed to several lists of semantically-related words (e.g., candy, sour, sugar, bitter, chocolate, cake) and subsequently given free recall and recognition tests for the word lists. Experiments employing this paradigm have reported that many participants falsely recall / recognize semantically-related, non-presented “critical lures” (e.g., sweet) as being a part of the original word list. In the study, participants were stressed, given 10 of the DRM word lists to learn (one at a time) and tested for their memory after the presentation of each list. As predicted, we found that stress, overall, reduced false memory. We then analyzed the data in a slightly different manner, by comparing the effects of stress on false memory for critical lures from the first half of the word lists studied, relative to the second half of the word lists studied. Hypothetically, if the temporal dynamics model is accurate, one would expect stress to enhance learning for the first five word lists that were presented, as they would be temporally more proximal to the stress experience. We found that stressed males recalled fewer critical lures from the first five word lists, while stressed females recalled fewer critical lures from the second five word lists. This suggested to us that the temporal dynamics of acute stress, and its neurobiological consequences, could differ between the sexes.

For instance, as illustrated in Figure 2, it is possible that while males exhibit a temporal pattern that more closely aligns with the traditional temporal dynamics timeline described above, females might demonstrate a temporal pattern in which stress-induced enhancements of hippocampal function are delayed, relative to males, or simply last longer than those of males. This hypothesis is supported by other work from our laboratory in which we found that brief cold pressor stress administered 30 min prior to learning led to impaired long-term memory in males, but not females. In this case, the hippocampal function of females may not have yet entered the predicted refractory phase, which is why their long-term memory was not influenced. Further research is necessary to address this speculation and to ascertain the influence of menstrual cycle activity on such effects.
Figure 2. Figure 2A (top left) illustrates how genetic variation might influence the temporal dynamics of stress effects on hippocampal function. The deletion variant of the ADRA2B gene, for instance, could enhance the excitatory phase as a result of greater amygdala and noradrenergic activity and promote even greater stress-induced enhancements of learning. Other genetic polymorphisms could lead to alterations of the refractory phase as well. Importantly, depending on the type of genetic variation, the alterations in each phase could be facilitative or inhibitory. Figures 2B (top right) and 2C (bottom) provide additional examples of how individual differences, such as genetic variation or sex, could influence the dynamics of stress effects on hippocampal function. As an example, following stress onset, females might display either a longer-lasting excitatory phase with a delayed-onset inhibitory phase (Figure 2B) or simply a delayed-onset excitatory phase (Figure 2C), relative to males.

**GENETIC VARIATION AND STRESS-INDUCED ALTERATIONS OF LEARNING AND MEMORY**

One of the reasons why generating conclusions about stress-memory interactions is so difficult is because different individuals are often affected
differently by the same stressor. Thus, a topic of increasing importance in the field of stress-memory interactions is that of genetic variation and its influence on such effects. Over the past several years, researchers have established a clear association between certain genetic polymorphisms, emotional memory, and the onset of stress-related psychological disorders, such as PTSD (Amstadter, Nugent, and Koenen, 2009; Skelton, Ressler, Norrholm, Jovanovic, and Bradley-Davino, 2012; Wilker, Elbert, and Kolassa, in press). While it is beyond the scope of this review to elaborate extensively on how such polymorphisms might be involved in stress-induced alterations of learning and memory, it is potentially an important avenue for future research in terms of discerning why different individuals respond differently to stress.

There are several examples of associations between genetic polymorphisms, emotional memory, and PTSD in the literature. For instance, a deletion variant of the *ADRA2B* gene, which affects *ADRA2B* (α2B-adrenergic) receptor function in a way that leads to greater norepinephrine availability, results in enhanced emotional memory (de Quervain et al., 2007), greater amygdala reactivity to stress (Cousijn et al., 2010) and emotional stimuli (Rasch et al., 2009), and greater intrusiveness of traumatic memories in people with PTSD (de Quervain et al., 2007). Polymorphisms of the gene that codes for FK506 binding protein 5 (FKBP5), a co-chaperone of the GR that interacts with heat shock protein 90 to influence GR sensitivity (Binder, 2009), have been associated with altered baseline cortisol levels (Mahon, Zandi, Potash, Nestadt, and Wand, 2013), prolonged physiological responses to stress (Ising et al., 2008), increased amygdala reactivity (White et al., 2012), and greater risk for PTSD (Binder et al., 2008; Boscarino, Erlrich, Hoffman, Rukstalis, and Stewart, 2011; Boscarino, Erlrich, Hoffman, and Zhang, 2012; Levy-Gigi, Szabo, Kelemen, and Keri, in press; Mehta et al., 2011; Xie et al., 2010). As a final example, a single nucleotide polymorphism (SNP) (Val66Met) in the gene coding for brain-derived neurotrophic factor (BDNF), a protein involved in neurogenesis and synaptic plasticity, is associated with greater amygdala activity and impaired extinction learning (Felmingham, Dobson-Stone, Schofield, Quirk, and Bryant, 2013; Lonsdorf et al., 2010; Soliman et al., 2010). Despite the clear association of these genetic polymorphisms with emotional memory and the onset of PTSD, very little work has addressed the role of such genetic variation in the stress-induced alteration of learning and memory. Those studies that have investigated genetic predictors of stress-memory interactions have assessed the involvement of such genetic variation in the effects of pre-retrieval stress on memory (Li, Weerda, Guenzel, Wolf, and Thiel, 2013) or have measured PFC-
dependent working memory (Buckert, Kudielka, Reuter, and Fiebach, 2012), as opposed to hippocampus- or amygdala-dependent memory. We would contend that an examination of how such polymorphisms interact with pre-learning stress effects on learning would provide more relevant information with regards to the formation of traumatic memories and therefore be more applicable to understanding the onset of stress-related disorder like PTSD. However, as of yet, there has been no research in this area.

It is our speculation that some of the aforementioned polymorphisms may increase the risk for PTSD by influencing stress effects on learning and facilitating traumatic memory formation. For instance, the deletion variant of *ADRA2B* may, through its effects on norepinephrine availability, interact with the temporal dynamics model outlined above to augment the excitatory phase of amygdala and hippocampal function, thereby facilitating the formation of a powerful emotional memory following stress (see Figure 2). Other polymorphisms related to the stress response, such as those for *FKBP5*, could influence stress-memory interactions in such a way that exacerbates stress-induced impairments of hippocampal function and learning. Variants of stress response genes could increase and/or prolong the excitatory and/or inhibitory phases of hippocampal function that theoretically follow stress onset. Of course, these effects could result from alterations of physiological mechanisms underlying the stress response, which thereby influences amygdala-induced modulation of hippocampal plasticity.

**STRESS AND MULTIPLE MEMORY SYSTEMS**

The presence of multiple brain memory systems is well supported by research in both humans and non-human animals (Packard, 2009; Schwabe, Wolf, and Oitzl, 2010). These memory systems often support different types of learning (e.g., explicit vs. implicit), yet can interact and are thus not completely independent of one another. For instance, researchers have frequently differentiated between a hippocampus-based learning system, which is a “cognitive” system that supports declarative or spatial learning strategies, and a striatum-based learning system, which is a “habit” system that supports response- and cue-based learning strategies. Using clever experimental apparatus and methodologies, investigators have been able to examine subjects’ performance on tasks that can be acquired via either of these strategies. Early studies employing such techniques revealed that organisms
begin training by adopting a hippocampus-based spatial strategy, but over time, shift to a hippocampus-independent, striatum-based response strategy.

Research has demonstrated that the amygdala, a brain area heavily implicated in the stress response, can influence each of these memory systems. For instance, Packard and colleagues found that amphetamine infusions into the amygdala enhanced rat performance on cue- (i.e., striatum-dependent) or spatially- (i.e., hippocampus-dependent) based water maze tasks (Packard, Cahill, and McGaugh, 1994). Thus, investigators speculated that stress, due to its association with amygdala activity, might influence the type of learning strategy that an organism adopts for a task that can be learned in one of multiple ways. Such studies have generally shown that stress administered prior to learning or retrieval biases organisms toward a striatum-based response strategy, as opposed to a hippocampus-based spatial strategy. For instance, Kim et al. (2001) exposed rats to restraint stress combined with tailshock for 1 hr prior to water maze learning. When the water maze task could be solved only by employing a hippocampus-dependent spatial strategy, stressed rats exhibited an impairment of long-term memory, an effect that was prevented by lesioning the amygdala. In contrast, pre-learning stress enhanced long-term memory in the water maze when the task could be solved by adopting a striatum-dependent cue strategy, suggesting that stress shifted rats’ learning strategy from a hippocampus-based to a striatum-based strategy. Packard and colleagues observed similar effects in a T-maze when an anxiogenic pharmacological agent, an α2-adrenergic receptor antagonist, was injected in the animals systemically or directly into their BLA (Elliott and Packard, 2008). In addition, inactivation of the BLA prevented the shift from a hippocampus-dependent spatial strategy to a striatum-dependent response strategy that resulted from the anxiogenic agent (Packard and Gabriele, 2009). Collectively, these findings suggest that acute episodes of stress induce amygdala activity that, when resulting in an impairment of hippocampus-dependent learning, shifts organisms’ learning strategy to one that involves striatum-dependent response learning.

Recent work in humans has reported similar effects. In these studies, acute stress administered before learning led to a shift from spatial strategies to response-based strategies (Schwabe and Wolf, 2012). Interestingly, investigators found that administration of an MR antagonist blocked the stress-induced shift from hippocampus-dependent to striatum-dependent learning (Schwabe, Tegenthoff, Hoffken, and Wolf, 2013), suggesting an involvement of corticosteroids in the effects. Other work also revealed that stress impaired goal-directed (i.e., PFC-dependent) learning and favored habit-based learning.
(Schwabe and Wolf, 2009b, 2010), which was associated with concurrent corticosterone and β-adrenergic receptor activity (Schwabe, Hoffken, Tegenthoff, and Wolf, 2011; Schwabe, Tegenthoff, Hoffken, and Wolf, 2010). These results in humans corroborate the abovementioned findings in rodents and indicate that stress impairs hippocampus- and PFC-dependent learning, while promoting striatum-dependent strategies.

With regards to the temporal dynamics model of emotional memory, the shift in learning strategy that occurs following stress would likely take place during Phase 2. That is, once stress forced hippocampal or PFC function into a refractory state, organisms might switch to a striatum-based strategy as a compensatory and adaptive response to the stressor, which would still allow the organism to acquire important information during hippocampal or PFC impairment. As discussed above, the switch in learning strategy that occurs is likely due to amygdala-induced modulation of hippocampal, PFC, and striatum function and reveals that stress not only can affect how much an organism learns (i.e., quantity), but also the way in which an organism learns (i.e., quality) (Schwabe, Wolf et al., 2010).

**CONCLUSION**

Stress-induced alterations of learning and memory are complex, and although research over the past couple of decades has allowed us to make great strides in our understanding of such effects, there is still a great deal about stress-memory interactions that is as of yet unknown. In the present chapter, we have reviewed the literature on acute stress effects on hippocampus-dependent learning and memory in an attempt to provide a developing theory on factors that mediate such effects. Clearly, there are some common elements underlying most stress-induced alterations of learning and memory, including corticosterone and noradrenergic interactions in the amygdala. However, it is our speculation that the timing of stress relative to learning or testing results in differential effects on long-term memory due to differential time courses of neurochemical-induced effects on amygdala interaction with cognitive brain structures. These effects may also be shaped by individual differences (e.g., genetic variation) and the sex of the organism. Additional work is essential in order to elucidate how the timing of stress interacts with factors related to the individual to influence learning and memory.


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