STRESS AND EPISODIC MEMORY: THE FATE OF NEUTRAL VERSUS EMOTIONAL INFORMATION

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ABSTRACT

This paper describes two experiments, each of which investigated the impact of stress on human episodic memory. All participants watched narrated slide shows containing emotional and neutral information. Experiment 1 demonstrated that pre-learning exposure to a psychological stressor (the Trier Social Stress Test or "TSST"; Kirschbaum, Pirke & Hellhammer, 1993) preserved or enhanced memory for emotional aspects of the slide show, but impaired memory for neutral aspects of the slide show. Moreover, stress exposure disrupted memory for information that was visually and thematically central to the slide show. Memory for peripheral information, on the other hand, was unaffected by stress. Experiment 2 replicated these results and extended them to a similar paradigm, where participants viewed separate emotional and neutral slide shows, and saliva was tested for the stress hormones cortisol and norepinephrine. Similar to the results of Experiment 1, stress disrupted memory for the neutral slide show, but enhanced memory for the emotional slide show. Salivary cortisol levels at retrieval were negatively correlated with memory for the neutral slide show. These results are consistent with theories invoking differential effects of stress on brain systems responsible for encoding and retrieving emotional memories (the amygdala) and non-emotional memories (e.g. the hippocampal formation, frontal cortex), and inconsistent with the view that memories formed under high levels of stress are qualitatively the same as those formed under ordinary emotional circumstances. These data, which are also consistent with results obtained in a number of studies using animals and humans, have implications for the traumatic memory debate and theories regarding human memory.

INTRODUCTION

Stress affects memory. This has been known for some time, but only recently has it been possible to ask and answer pointed questions about why and how memory is influenced by stress. Only by elucidating the neurological consequences of stress, which until recently had been deemed a purely "psychological" event, can we unravel its effect on memory.

For at least the last two decades, the impact of stress on memory has been understood as largely disruptive. Both animal (e.g. Diamond, Park, Heman & Rose, 1999; Sapolsky, Krey & McEwen, 1986) and human (e.g. Lupien et al., 1994, 1998; Newcomer et al, 1994, 1999) studies have demonstrated that exposure to high levels of stress can impair memory. "Stress" is typically induced by exposing subjects either to stress hormones (e.g. cortisol) or to anxiety-provoking psychosocial tasks (e.g. public speaking). Both techniques influence the functioning of the medial temporal lobe (see de Quervain et al., 2003), which, as this brain region is critical for intact memory ability, likely underlies the memory deficits which can emerge after stress exposure (de Quervain et al., 2000, 2003; Kirschbaum et al., 1996; Newcomer et al., 1994, 1999; Payne et al., 2002).

In spite of this general pattern of memory disruption, other studies show that high levels of stress can enhance memory for emotionally arousing experiences. Various studies performed in rodents, for example, report a positive impact of stress on memory when the tasks require emotional learning (e.g. Bohus et al., 1983; De Kloet et al., 1988; Micco et al., 1979; Micco & McEwen, 1980; Mitchell & Meaney, 1991; Roozendal et al., 1996; Veldhuis et al., 1985).

Emotional memory appears to be facilitated by stress in humans as well (e.g. Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003). Although the experimental evidence examining the relationship between emotional memory and stress in humans is still relatively scarce, a recent study demonstrated that a one-time, low dose (20mg) of the stress hormone cortisol enhanced memory for emotional stimuli (in this case emotional pictures) relative to placebo. Subjects given cortisol recalled significantly more emotional pictures than did subjects in a placebo group, while both groups recalled a similar number of neutral pictures. To date, however, Buchanan & Lovallo (2002) is one of very few studies investigating the effect of cortisol on emotionally neutral versus emotionally salient information in humans. The stress hormone norepinephrine also facilitates emotional memory function. For example, norepinephrine agonists typically lead to superior memory for emotional, but not neutral, scences compared to placebo, whereas norepinephrine antagonists abolish this effect (e.g. Cahill et al., 1994; Southwick et al., 2002).

These findings suggest that the affective quality of the memory task is important, and indeed, a close comparison of studies finding memory impairment with those finding memory enhancement reveals that the former typically use neutral memory materials (de Quervain et al., 2000, 2003; Kirschbaum et al, 1996; Newcomer et al., 1994, 1999; Payne et al., 2002; Wolkowitz et al., 1990, 1993), while the latter use materials that are emotionally arousing (Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003; Gold & van Buskirk, 1978; McGaugh, 2000). Consider, for example, the varied effects of administering a comparable orally administered, one-time low dose of cortisol (i.e. 20/25mg) to human subjects. de Quervain et al. (2000, 2003) administered a 25mg dose of cortisol to subjects learning word lists composed of unrelated, emotionally neutral nouns. Those who had received the cortisone retrieved significantly *fewer* of these neutral words than participants who received a placebo. Buchanan & Lovallo (2001), on the other hand, showed that a 20mg dose of cortisol enhanced memory for emotional relative to neutral pictures.

Most investigations into stress and memory have used pharmacological manipulations (e.g. administering cortisol in humans, corticosterone in animals) as a method of inducing stress. Yet elevating cortisol, while an important part of the stress response, is not the same as inducing the subjective, emotional state of stress. In fact, elevated cortisol is not necessarily associated with subjective feelings of stress or arousal, nor the decreases in mood that often accompany stressors like public speaking (Wolf et al., 2001; Buss et al., 2004; Kuhlmann et al., 2005; Kuhlmann, Piel & Wolf, 2005). Several studies have used more naturalistic, psychosocial stressors to raise stress hormone levels while also creating the sensation of being stressed. In humans, these stressors include performing complicated mathematical tasks or giving speeches in front of an audience (e.g. the Trier Social Stress Test (TSST), see Kirschbaum et al., 1993; Kirschbaum et al., 1996). Such stressors elevate cortisol levels (Kirschbaum et al., 1993; Kirschbaum et al., 1996; see also Mason, 1968), but they also elevate other stress hormones and related neurotransmitters (McGaugh, 2000; Nater et al., 2005). Of these, norepinephrine (NE) is perhaps the most important. Unlike cortisol, increases in NE are associated with the sensation of physiological arousal. Like cortisol, however, NE plays an important role in the formation and consolidation of emotional memories (Hamann, 2001; McGaugh, 2000). Thus, rather than administering cortisol directly, as in most of the studies mentioned above, other investigators have used psychological stressors to elevate stress hormone levels and achieve the subjective experience of stress.

Exposing human subjects to psychological stress can impair memory. For example, public speaking has been shown to disrupt memory for word lists, both by reducing the amount of material recalled (Kirschbaum et al., 1996; Kuhlmann, Piel & Wolf, 2005), and by producing gist-based false memory errors (Payne et al., 2002). To our knowledge, psychosocial stress has not yet been used to examine emotional episodic memory; thus, its impact on emotional tasks remains to be determined. However, to the extent that social stressors effectively raise levels of stress hormones like cortisol and NE, it follows that they should facilitate emotional memory.

Taken together, these results suggest that high stress levels should disrupt neutral memory and facilitate emotional memory, even if these two memory types are components of the same experience. However, the studies leading to this assumption are separate and cross-sectional, with many methodological differences between them. As mentioned, some researchers administered stress hormones directly, while others used more naturalistic social stressors to induce stress. Moreover, many of the studies tested memory for simple word-lists or pictures, while others tested memory for events (Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003). It thus remains to be seen what pattern of results will be obtained in more complex episodic memory experiments, after the administration of a specific psychosocial stressor. The primary goal of this dissertation and its two experiments is to answer these questions. The main prediction of these studies is that acute stress exposure (induced via public speaking) will disrupt memory for neutral information, and enhance memory for emotional information.

The Neurobiology of Stress and Memory: An Overview

These predictions are well grounded in the neurobiology of stress and memory. Both the stress-based enhancement of emotional memory and the stress-based disruption of neutral memory have been attributed specifically to the impact of stress hormones and neuromodulators on brain regions important for memory function (Buchanan & Lovallo, 2001; de Quervain et al., 2000, 2003; Kim & Diamond, 2002; Kirschbaum et al., 1996; Lupien & Lepage, 2001; Lupien & McEwen, 1997; Roozendaal, 2002; 2003). For example, both norepinephrine and cortisol facilitate the functioning of the amygdala – a structure known to modulate emotional memory (Cahill & McGaugh, 1998; Canli et al., 2000; Kensinger & Corkin, 2004; McGaugh, 2000; Roozendaal, 2002, 2003; Strange & Dolan, 2004). High levels of cortisol, on the other hand, disrupt the functioning of the hippocampus and prefrontal cortex, structures integral to memory for neutral materials (Kim & Diamond, 2002; Lupien & Lepage, 2001). In the next section, we take a closer look at the impact of stress on these structures and on the memory functions they support.

Effects of Stress on Brain Physiology and Anatomy

One of the most important stress response systems in humans is the hypothalamic-pituitary-adrenal (HPA) axis. When activated, this system initiates a cascade of stress hormones, culminating in the release of cortisol from the adrenal cortex. Stress triggers the release of corticotropin-releasing factor (CRF) from the hypothalamus when then subsequently triggers adrenocorticotropic hormone (ACTH) release from the pituitary gland. In response to ACTH, glucocorticoids (GCs) such as cortisol are secreted and released from the adrenal glands. Circulating glucocorticoids then feed back onto the pituitary and hypothalamus to inhibit further secretion of CRF and ACTH. The hippocampus (and certain cortical areas, particularly frontal cortex) plays an important role in this negative feedback system, helping the pituitary and hypothalamus inhibit HPA activity (Feldman & Conforti, 1980, 1985; Jacobson & Sapolsky, 1991; Sapolsky & Meaney, 1986).

Hippocampal involvement in the regulation of the stress response turns out to be critically important to any discussion of stress and memory because this structure has long been implicated in explicit memory. In particular, the hippocampal formation has been linked to episodic memory, to memory for context, and to spatial maps (Buckner & Wheeler, 2001; O'Keefe & Nadel, 1978; Schacter & Tulving, 1994; Zola & Squire, 2000). Debate rages over various aspects of this story, but the link between the hippocampal system and episodic memory seems firm. The seminal studies of Scoville and Milner (1957), for example, showed that bilateral ablation of the hippocampal complex resulted in profound loss of memory. We now know that damage to the hippocampus results in a rather specific form of memory dysfunction, in particular that involving spatial/contextual and episodic memories (Hirsch, 1974; Nadel, 1991, 1994; Nadel & Willner, 1980; Rosenbaum et al., 2000), and further, that stress appears to impair precisely these types of memory (Buss, Wolf, Witt & Hellhammer, 2004; Lupien

& McEwen, 1997; de Quervain et al., 2003; Kuhlmann, Piel & Wolf, 2005)[i]. Together with the discovery of dense concentrations of stress hormone receptors in the hippocampus (e.g., McEwen, Weiss, & Schwartz, 1968)[ii], these findings provide a basis for the claim that stress hormone modulation of hippocampal activity underlies the effects of stress in animals and humans (see Bremner, 1999; McEwen, 2000 for reviews).

The presence of glucocorticoids at abnormally high or abnormally low concentrations can, by changing the physiological characteristics of large populations of hippocampal neurons, disrupt the functioning of the hippocampus. A moderate level of circulating glucocorticoids appears to enhance memory whereas maximal or minimal levels appear to disrupt it (e.g. Kim & Diamond, 2002; Lupien et al., 2005). At high enough levels, glucocorticoids can also produce changes in hippocampal neuronal physiology and anatomy, such as alterations in hippocampal morphology, disruption of neurogenesis, and blockage of the synaptic plasticity thought to underlie memory formation (see McEwen, 2000, 2001 for reviews).

Both glucocorticoid exposure and restraint stress over 21 days have been shown to result in reduced dendritic branching in pyramidal neurons of the CA3 region of the rat hippocampus (Magarinos & McEwen, 1995; Watanabe, Gould, & McEwen, 1992; Woolley, Gould, & McEwen, 1990). Psychosocial stress leads to atrophy of dendrites as well, both in the tree shrew (Magarinos, McEwen, Flugge, & Fuchs, 1996) and in rats (McKittrick et al., 2000). In addition, stress and glucocorticoid elevations can produce alterations in synaptic terminal structure in CA3 (Magarinos, Verdugo, & McEwen, 1997).

Several early studies suggested that even longer periods of exposure to stress and glucocorticoids results in overt loss of hippocampal neurons (e.g., Sapolsky, Krey, & ; McEwen; Uno et al., 1989). Such findings led to the assertion that neuronal death associated with glucocorticoid release might underlie the severe memory impairments seen in stress related conditions such as major depression and post-traumatic stress disorder (PTSD). More recent work, however, raises questions about whether glucocorticoids are themselves toxic or simply create conditions for other factors to exert neurotoxic effects (Sapolsky, 1996). Nonetheless, chronic exposure to stressors is undoubtedly associated with hippocampal impairment. For example, post-mortem analysis of chronically-stressed monkeys showed extensive damage in the CA3 region of the hippocampus. Subsequent research has suggested that high cortisol levels were responsible for the hippocampal damage, as cortisol-secreting pellets implanted in the monkey hippocampus resulted in the same pattern of damage.

In addition to having neurotoxic effects on existing hippocampal neurons, chronic exposure to stressors may also inhibit the growth of new neurons (granule cells) in the dentate gyrus, thereby changing its structure. A stress-induced decrease in neurogenesis has been demonstrated in the dentate gyri of rats, tree shrews and primates (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998; Gould & Tanapat, 1999; Tanapat, Hastings, Rydel, Galea, & Gould, 2001), and some believe that disrupted neurogenesis is the primary mechanism of stress-related hippocampal impairment (Gould & Gross, 2002; Gould & Tanapat, 1999). Glucocorticoids have been shown to mediate these stress-induced changes in neurogenesis. Normalizing glucocorticoid levels prevents predator odor stress from inhibiting granule cell production (Tanapat et al., 2001). In addition, corticosterone treatment has been shown to decrease dentate cell proliferation, whereas adrenalectomy increases the production of new granule cells (Cameron & Gould, 1994; Cameron & McKay, 1999).

In addition to these structural effects, stress and stress hormones also modulate the excitability of hippocampal neurons. Acute stress and glucocorticoid release can impair hippocampal plasticity (Diamond, Fleshner & Rose, 1994; Foy, Stanton, Levine, & Thompson, 1987). Long-term potentiation (LTP), and the related phenomenon of primed burst potentiation (PBP), are two processes by which hippocampal neuronal responsiveness changes in response to experience (McEwen, 2001). These forms of potentiation are often conceptualized as physiological models of memory. Hippocampal LTP can be impaired by the administration of glucocorticoids (e.g., Diamond & Rose, 1994; Filipini et al., 1991). Diamond, Bennet, Fleshner, and Rose (1992) reported an inverted U-shaped relationship between the level of circulating glucocorticoids and the extent of LTP, demonstrating that glucocorticoids facilitated LTP at moderate levels but disrupted it at low and high levels. Stress-induced disruption of LTP targets CA1 and the dentate gyrus and has been shown to last up to 48 hours in rats and 24 hours in mice (e.g., Garcia, Musleh, Tocco, Thompson & Baudry, 1997; Shors, Gallegos, & Breindl, 1997). Stress-induced disruption of LTP and changes in plasticity can last for days; however, these changes are typically not permanent. More recent studies suggest that PBP may be even more sensitive to psychological stress (e.g., predator exposure) than is LTP (Mesches, Fleshner, Heman, Rose, & Diamond, 1999). Importantly, these changes in plasticity can take place immediately. In both the dentate gyrus and CA1 and CA3 fields of the hippocampus, LTP can be modulated rapidly (e.g. within 1 hour) by corticoterone (Pavlides et al, 1995, 1996), thus providing a neurobiological basis for the acute effects of stress that we turn to next.

Effects of Stress on Memory Function

A growing body of randomized, placebo-controlled studies has begun to demonstrate that exposure to stressors can impair various forms of memory. This research has proceeded along two separate but related paths, one dedicated to the study of relations between episodic memory and long-term/chronic stress and the other to relations between episodic memory and short-term/acute stress.

The ethics inherent in human research make experimental studies of relations between memory and *chronic* stressors difficult if not impossible, leaving the field to naturalistic research designs. An example is the above-noted study conducted by Lupien et al (1998), who followed a large sample of aged (60-87 years), healthy subjects over 3-6 years and found that subjects whose cortisol levels steadily increased over time were significantly impaired in their declarative memory performance when compared to subjects whose cortisol levels were fairly stable or decreasing.

Experimental studies of relations between memory and *acute* stress, on the other hand, while difficult ethically, are at least possible. The administration of stress-related hormones, for example, permits well-controlled studies of relations among memory and acute stress in humans. Low to moderate doses of various stress hormones, such as cortisol, can be safely administered to humans over relatively brief periods of time. In some studies, agonists (corticocortisone) or antagonists (e.g., dexamethasone) of naturally occurring glucocorticoids are used instead of cortisol. Glucocorticoid antagonists reduce the level of circulating glucocorticoids, and both abnormally high and abnormally low levels of glucocorticoids have been shown to produce memory deficits (Conrad & Roy, 1996; Luine, Villegas, Martinez, & McEwen, 1994; Vaher, Luine, Gould, & McEwen, 1994).

Acute Stressors: Memory Disruption in Humans

As mentioned, inducing acute stress in the laboratory typically involves exposing the subject, whether animal or human, to a brief, one-time stressor (e.g., a speech task, a predator's odor), or administering a single dose of glucocorticoids. In both cases an increase in glucocorticoid levels occurs, usually lasting no longer than several hours in humans. However, the cognitive effects of acute stress or glucocorticoid administration are often apparent for a time span ranging from several hours to a day, and are usually reversible (McEwen, 2001). Moreover, these effects are typically specific to memory function, with spatial and verbal-episodic memory often showing the greatest impairment (e.g. Lupien et al., 1997).

Wolkowitz et al. (1990, 1993), for example, examined recall of previously learned verbal-episodic material after the administration of dexamethasone or prednisone and found that the presence of either of these glucocorticoids interfered with word recall. In the dexamethasone study, participants learned a list of 12 semantically associated words, which they were first asked to *recall* following a 90-second distractor task and then asked to *recognize* in a larger list of related distractor words. Participants were tested 1 week before and 1 day after administration of 1 mg of dexamethasone. Although this single dose of dexamethasone did not produce a change in recall, it did produce an increase in errors of commission, or false recognition of related words that were not presented on the study list.

The prednisone study used a similar test of memory, but here both recall and recognition of previously learned words were required 24 hours after presentation of the list, a manipulation that made the procedure a test of longer-term episodic memory. Participants were given 80 mg of prednisone daily for 5 days. Word recognition and recall were tested once during an initial 5-day placebo period, again after 4 days of prednisone administration, and once again 7 days after discontinuation of the treatment. Again, participants receiving prednisone showed no differences in free recall, but falsely recognized more semantically related words than did controls. Thus, administration of dexamethasone and prednisone resulted in difficulties recognizing words presented in standard word lists (see also Bender et al., 1991), and this difficulty seemed to be characterized by an impaired ability to discriminate previously studied information from new information of a similar nature (see also Nadel & Payne, 2002; Nadel, Jacobs & Payne, 2002; Payne et al., 2002).

Newcomer et al. (1994) also investigated the effects of dexamethasone on memory, as well as attention and perceptual function. Dexamethasone treatment administered over 4 days (in successive doses of 0.5, 1, 1, and 1 mg) was associated with impaired recall of verbal material originally presented in a paragraph (Wechsler, 1945). This impairment was strongest on the fourth day of treatment, and was specific to memory for verbal material. The presence of dexamethasone did not affect measures of attention or perception.

Unlike Wolkowitz et al. (1990, 1993), Newcomer et al. (1994) found that dexamethasone treatment resulted in errors of omission (information in the paragraph was forgotten), but not errors of commission (related but non-presented information was added to the material presented in the paragraph). The discrepancy between the Wolkowitz et al. (1990) and Newcomer et al. (1994) studies is likely due to differences in the strategies required by the two tasks. The recall task used by Newcomer et al. (1994) required the *verbatim* recall of story-like information that was presented in paragraph format. Given these instructions, normal subjects usually make more omission than commission errors, as thematically related intrusions errors rarely occur in this type of task. By comparison, semantically associated word lists, like the ones used in Wolkowitz et al. (1990), are known to produce commission errors at high rates (see Deese, 1959; Roediger & McDermott, 1995). Indeed, we have recently shown that psychologically induced stress increases commission errors on semantically associated word lists (Payne et al., 2002).

Results of the first few experimental studies indicate that pharmacological doses of the glucocorticoids dexamethasone and prednisone impair verbal episodic memory. However, caution should be used when thinking of this memory impairment as causally related to stress-induced increases in cortisol. Although changes in recall and recognition could result from increased glucocorticoid receptor binding in a manner similar to the direct administration of cortisol (the traditional explanation), an alternative explanation is possible. Dexamethasone suppresses cortisol, and because very high or very low levels of cortisol can affect the biological structures upon which memory depends, the observed changes could result from dexamethasone-induced decreases in cortisol secretion – and hence, a failure to bind to glucocorticoid receptors. This uncertainty, along with differences in the binding of dexamethasone and cortisol to type I and type II glucocorticoid receptors in the hippocampus, limits our confidence in the generality of conclusions reached when dexamethasone and similar ligands are used to examine the effects of cortisol or stress in humans (Newcomer et al., 1999).

Similar concerns motivated a second study by Newcomer et al. (1999), which examined interactions between hydrocortisone (cortisol) and explicit memory for words, again using a paragraph recall task. Two fixed oral doses of hydrocortisone (160 mg/d or 40 mg/d) were administered over 4 days. The lower-dose treatment was selected to approximate physiological levels of cortisol associated with mild to moderate stress, and the higher-dose treatment was selected to approximate physiological levels of cortisol associated with severe stress. Sampling of plasma cortisol and memory testing were conducted at baseline (day 0), on days 1 and 4, and after a 6-day washout period (day 10). Impaired paragraph recall was reported in the presence of the higher, but not the lower, dose of hydrocortisone. As in their previous study (Newcomer et al., 1994), this effect was maximal on the fourth day of treatment. Newcomer et al. (1999) did not observe the immediate effects of glucocorticoids seen in some studies (e.g., Wolkowitz et al., 1990), but instead showed that several days of cortisol exposure at doses and plasma concentrations associated with high stress could impair the recall of verbal material presented in a paragraph format.

An earlier study by Kirschbaum et al. (1996), however, reported that a single, low dose of hydrocortisone (10mg) led to a deficit in verbal episodic memory. In this study, subjects who received hydrocortisone recalled fewer words (via a cued recall test) from a previously learned word list than did control subjects when recall occurred 60 minutes after receiving the drug. Thus, it seems that hydrocortisone can produce a deficit in at least one type of verbal memory (cued word recall) at smaller doses and with shorter delays between administration and test than suggested by the results of the Newcomer et al. (1999) experiment. Again, the differences in these two experiments might depend on the nature of the material recalled, the delay between learning and test, or different task-demands. Although the details vary from experiment to experiment, the administration of drugs simulating acute stress clearly changes the recall pattern of words presented via word-lists or paragraphs, both of which measure aspects of explicit verbal memory.

Many of the glucocorticoid-administration studies are limited in that the physiological effects of cortisol are longer-lived than the standard memory experiment (which typically lasts no longer than an hour or two). Consider the designs used by Kirschbaum et al. (1996) and Newcomer et al. (1999) described above. In each case cortisol levels were probably elevated continuously throughout the study, making it difficult to determine what stage of memory was impaired. In an attempt to sort this out, de Quervain et al. (2000) administered 25 mg doses of cortisone (which is quickly absorbed and transformed into cortisol) at different stages of a verbal delayed free-recall experiment. In this way they could evaluate the impact of elevated cortisol on each of three distinct memory processes: acquisition, storage, and retrieval. Participants learned word lists composed of unrelated words, and received cortisone either: 1) before list learning, 2) immediately after list learning, or 3) 24-hours later, but immediately before recall. Impairment in recall was found only when cortisone was given immediately before recall, thus implicating retrieval as the memory stage most affected by a low dose of cortisol.

It is notable that although a 25 mg dose of hydrocortisone administered at *encoding* did not affect recall of verbal material presented in paragraphs (Newcomer et al., 1999), the same low dose of cortisone did affect the *retrieval* of words presented in lists (de Quervain et al. 2000). This discrepancy could have arisen from differences in the kind of information recalled (stories versus word lists), or from stress having a greater impact on retrieval than on encoding or consolidation.

In addition to explicit memory for words, spatial memory also appears to suffer in the presence of stress. To our knowledge, spatial memory in humans has not yet been assessed with the direct administration of glucocorticoids. However, Laurance, Hardt, Nadel, and Jacobs (2001) found that exposure to a social stressor (public speaking) slows the rate at which spatial information is acquired in a virtual environment. The impact of stress in this study was specific to hippocampally-mediated, spatial map-based performance, while performance based on individual cues, which depends on different neural circuits, remained intact. Similar to the pharmacological studies described above, public speaking tasks also result in hippocampally-based verbal episodic memory deficits, as measured by list-learning tasks in healthy elderly subjects (Lupien et al., 1997), and in younger adults (Kirschbaum et al., 1996; Kuhlmann, Piel, & Wolf, 2005). The critical role of the medial temporal lobe in mediating stress-induced memory impairments is supported by a recent human neuroimaging study (de Quervain et al., 2003). This study used PET to demonstrate that cortisol's impairing effect on memory for words is associated with reduced blood flow in the medial temporal lobe.

Stress and Memory in Non-Human Animals

Animal studies of stress and memory yield results that are generally consistent with the human studies. Exposure to glucocorticoids, be it acute or long-term, is often associated with deleterious effects on memory tasks dependent on hippocampal integrity (e.g., Bodnoff et al., 1995; Luine, Villegas, Martinez, & McEwen, 1994; Ohl & Fuchs, 1999; see Kim & Diamond, 2002; Lupien & Lepage, 2001 for reviews). As in humans, however, acute stress effects are often short-term and reversible, whereas repeated and/or long-term stress effects can lead to cognitive dysfunction (McEwen & Sapolsky, 1995) that may result from changes in hippocampal morphology similar to those described above.

Spatial memory, also known to depend upon the hippocampus, is impaired in rats exposed to stressors (Nadel & Willner, 1989) or given corticosterone, and in transgenic mice with elevated corticosterone levels. Twenty-one days of restraint stress was correlated with impairments in spatial memory as measured by performance in the radial arm maze task (Luine, Villages, Martinez, & McEwen, 1994). Exposure to stressors has also been shown to disrupt hippocampal-dependent object recognition (e.g., Clark, Zola & Squire, 2000), and working memory (Diamond et al., 1996, 1999; Lupien, Gillin &

Hauger, 1999; Young, Sahakian, Robbins & Cowen, 1999). Likewise, long-term subcutaneous implants of glucocorticoids, which mimic the effects of chronic stress, impair new learning and memory for maze escape behaviors in rats. In one study for example, the severity of such deficits was correlated with the number of damaged cells in the CA3 region of the hippocampus (Arbel et al, 1994). A thorough review of the effects of stress in animals is beyond the scope of this dissertation, but the reader is directed to several excellent reviews (de Kloet, Oitzl, & Joels, 1999; Kim & Diamond, 2002; Lupien & Lepage, 2001; Lupien & McEwen, 1997; McEwen, 2000).

Collectively, findings from these studies converge on the idea that elevated levels of glucocorticoids released during stress disrupt normal hippocampal physiology, which, in turn, leads to impairment in hippocampally-dependent forms of memory. However, new evidence is beginning to suggest that stress hormones may facilitate emotionally arousing forms and features of memory. As mentioned, the amygdala is known to modulate emotional memory (Buchanan & Adolphs, 2004; Fanselow & LeDoux, 1999; LeDoux, 2000; McGaugh, 2000). It is active during stressful and emotionally charged conditions (LeDoux, 1996), and recent studies suggest that activity in this region is associated with enhanced remembering later on (e.g. Canli et al., 2000; Hamann et al., 1999; Kensiner & Corkin, 2004). This is at least partly mediated by the stress hormone norepinephrine, which, as noted earlier, also reaches high levels during stressful experiences (McGaugh, 2000).

Norepinephrine is released from the locus coeruleus (a nucleus in the pontine region of the brainstem), and this is often thought of as the “first wave” response to stress. The norepinephrine system responds almost immediately to a stressor, whereas the "second wave" response, via the HPA axis, occurs more slowly. Norepinephrine binds to receptors throughout the brain and facilitates motor responsiveness, thus governing the "flight or fight" response (e.g., Stoddard, Bergdall, Townsend & Levin, 1986). More importantly for our purposes, norepinephrine has potentiating effects on memory for emotional experiences, a finding that appears to be mediated by the numerous norepinephrine receptors located in the amygdala (e.g., McGaugh, 2000).

Andrenergic activity enhances (e.g., O'Carroll et al., 1999; Southwick et al., 2002), and blockade of adrenergic activity reduces (e.g, Cahill et al., 1994), the consolidation of explicit memory for emotional materials in humans. The activation of beta-adrenergic receptors, which are located on neurons in the basolateral nucleus of the amygdala (BLA), appears critical for this noradrenergic mediation of emotional memory consolidation (McGaugh, 2002; McGaugh & Roozendaal, 2002).

In addition to norepinephrine, growing evidence suggests that cortisol may also be involved in potentiating amygdala function and enhancing memory for emotional information (e.g. Buchanan & Lovallo, 2001). Again, the basolateral amygdala is the specific nucleus thought to underlie these effects. The BLA is not only a locus of interaction between norepinephrine and cortisol (McEwen, 2000), but is also a major hub of communication between the amygdala and hippocampus. As such, the BLA may be a critical locus regulating norepinephrine and glucocorticoid influences on emotional memory enhancement effects.

In sum then, the two prominent stress hormones – cortisol and norepinephrine -

may have opposing effects on different structures in the brain. High levels of cortisol, as reviewed in detail earlier, disrupt hippocampal function, impairing neutral forms of episodic memory (e.g. de Quervain et al., 2001, 2003). In contrast, high levels of both norepinephrine and cortisol may facilitate amygdalar function and the emotional memories it modulates (Nadel & Jacobs, 1998; Jacobs & Nadel, 1998; Metcalfe & Jacobs, 1996, 1998, 2000).

At this point we can return to the predictions of the dissertation, which are that stress will disrupt neutral memory and enhance emotional memory. Given the data discussed thus far, we assume that *stress specifically*, likely via the opposing effects of the hormones cortisol and norepinephrine, underlies this predicted pattern. As mentioned, this is the primary hypothesis of the dissertation.

Nonetheless, drawing solely on the impact of stress hormones on brain function may not be the only, or best, way to understand the effects of stress on human memory. Indeed, there is another possibility that deserves close attention because it leads to an alternative, yet related prediction. A large body of evidence, stemming from cognitive studies of emotion and memory, demonstrates that *arousal*, much like stress, has an uneven impact on memory. These studies show that arousal enhances memory for emotional experiences, but that within these experiences, central information is well remembered, whereas peripheral information is not. In the following section, we attempt to map these findings onto the stress findings presented previously.

Memory Enhancement: Remembering Central Vs. Peripheral Information

Arousal can be dissociated from stress physiologically, with stress activating the hypothalamic-pituitary-adrenal (HPA) axis and ultimately resulting in the release of cortisol (Bondi & Picardi, 1999; Lovallo & Thomas, 2000). Arousal, on the other hand, while sharing some physiological functions with stress, such as increased heart rate and norepinephrine release, does not inevitably activate the HPA axis nor necessarily produce cortisol release. Notwithstanding these differences, the effects of arousal and stress on memory are strikingly similar. Given this similarity, could it be that physiological arousal alone can account for the stress and memory findings discussed above? This is a possibility we must consider. In addition, the neutral versus emotional memory distinction may not be the best way of delineating the effects of stress on memory. Studies of arousal and memory show that memory for "central" aspects of a stimulus or event are enhanced, often at the expense of more "peripheral" aspects. It could thus be the case that stress produces the same, albeit undetected result, with emotional information being confounded with central information, and neutral information being confounded with peripheral information.

An early finding in the emotion and memory literature was that individuals initially remember highly arousing, unpleasant events more poorly than neutral events - but that over time the pattern reverses, with enhanced recall for arousing events after a delay (e.g., Goodman, Hirschman, Hepps & Rudy, 1991; Osborne, 1972). Clark, Milberg, and Ross (1983) and Kleinsmith and Kaplan (1963, 1964) demonstrated that highly arousing events are initially less well remembered than low-arousal or neutral events, but a recovery effect for the high-arousal events occurs after a delay. The eventual enhancement of memory by arousal is not surprising given that such memories may be essential for survival. For instance, remembering to avoid a certain poisonous food could be life saving (Bremner, Southwick, & Charney, 1997, 1999; McEwen, 2000). Given these results, it seems safe to assume that emotional arousal leads to overall enhanced memory for these negative events, particularly after a delay.

More recent research, however, suggests that the story isn't quite so straightforward. First, newer studies show that emotional arousal can promote *immediate* memory enhancement, implicating an affect of arousal on encoding, in addition to longer term consolidation, processes (see Hamann, 2001 for a review). Second, and more importantly, many studies support the idea that emotion enhances episodic memory, but in a way that is often limited to the central and thematic features of such experiences (Burke, Heuer, & Reisberg, 1992; Christianson & Loftus, 1987, 1991; Loftus, Loftus, & Messo, 1987). People tend to remember the gist or affective significance of a stimulus or event at the expense of peripheral details (Christianson, 1992, Goodman et al., 1991; Ochsner & Schacter, 2000).

The central versus peripheral breakdown stems from laboratory studies of emotional memory that have aimed to test two intertwined hypotheses. The first concerns subjects' memory for the gist or "central" information contained within an event. The bulk of the evidence on this claim is reasonably clear at this point: in general, emotional arousal seems to enhance memory for an event's gist or center (cf. Reisberg & Heuer, 2004). The second derives from data showing that arousal causes a narrowing of attention, so that an aroused subject attends less to information at the "periphery" of an event and more to information at the center of an event. This is known as the Easterbrook hypothesis (Easterbrook , 1959; Loftus, 1982; Mandler, 1975). This attention to central details results in the "weapon focus" phenomenon, where eyewitnesses to crimes can often vividly remember the gun or knife used to perpetrate a crime, but not the features of the assailant (see Loftus, 1979; Stanny & Johnson, 2000). Loftus and Burns (1982), for example, reported that subjects who watched an emotionally arousing videotape of a violent bank robbery (in which a little boy is shot in the face) did not recall the events immediately preceding the attack as well as control subjects who watched a less emotional videotape (in which bank robbers simply ran past the little boy, leaving him unharmed). Similarly, Goodman et al. (1991) showed that receiving an unpleasant inoculation leads to enhanced memory for central information related to the procedure (see also Christianson & Loftus, 1991).

There is considerable evidence demonstrating enhanced memory for central information under conditions of emotional arousal. However, the data are mixed as to whether memory for peripheral information is substantially decreased under the same conditions (see Reisberg & Heuer, 2004). It seems to depend, at least in part, on how the terms "central" and "peripheral" are defined.

There are two major ways of defining what is central and what is peripheral to a particular stimulus or event (see Reisberg & Heuer, 2004 for a review). The first is based on visual centrality, for example the focal point of a threatening picture, such as a gun or knife depicted in a picture of an attack. Peripheral details, on the other hand, would be any other aspect of the picture, such as background objects or even the physical appearance of the perpetrator. Christianson and Loftus (1991) studied memory for central versus peripheral features of an emotional event involving a bicycle accident. They defined these categories strictly in visual terms; peripheral details were those that were truly in the background (e.g. a car located in the distant background or extreme "periphery" of the slide). The second definition is more conceptual, and based on the theme or plot of an episode. Heuer and Reisberg (1990) defined as central any aspects of the story that were directly relevant to the plot, or in any way important for how the story unfolded; they defined as peripheral any information that could be changed without changing the story. The data suggest that emotional arousal enhances central information, regardless of whether it is conceptualized as visual or thematic. Conversely, impaired memory for peripheral information (memory narrowing) seems to emerge only when testing memory for the visual periphery (see Reisberg & Heuer, 2004).

It is possible that an overlap exists between the emotional content of an event and what is central to that event. In the Heuer and Reisberg (1990) study, for example, much of the central, thematic and plot-relevant information was emotional in nature, as the story is about a boy visiting his father, a surgeon, at a hospital and witnessing a gruesome surgery. Indeed, Christianson (1992) points out that central information represents the source of the emotional arousal, including the most relevant information for extracting the emotional significance of an event. Likewise, there may be overlap between what is neutral and what is peripheral, as many of the details that can be changed without altering the gist of the story are neutral in nature.

Clearly then, studies of arousal and memory show that memory for "central" aspects of a stimulus or event are enhanced, often at the expense of more "peripheral" aspects. This produces a pattern that is strikingly similar to that from the stress literature, which suggests that emotional memory features are preserved relative to neutral memory features under stress. It may thus be the case that stress and arousal are producing the same result, with emotional/neutral information being confounded with central/peripheral information. Experiment 1 of the dissertation examines this possibility as a second hypothesis.

The Experiments

The dissertation consists of two experiments. Given the animal and human evidence outlined above, it was hypothesized that stress would disrupt neutral aspects, but enhance emotional aspects of depicted episodes. In Experiment 1, this pattern of enhancement and disruption was predicted to occur both when memory was tested immediately and after a 2-week delay (Hamann, 2001). Given the cognitive data described above, we further predicted that there would be overlap between neutral and peripheral detail information on the one hand, and between emotional and central information on the other. We reasoned that such overlap would produce similar patterns of memory performance for both delineations. In Experiment 2, we sought to replicate and extend Experiment 1 using a modified version of the memory task, taking salivary cortisol and catecholamine measures and attempting to relate the findings of both experiments to the actions of stress hormones.

EXPERIMENT 1: THE IMPACT OF PSYCHOSOCIAL STRESS ON NEUTRAL AND EMOTIONAL ASPECTS OF EPISODIC MEMORY

The first study aimed to test the effect of stress on memory for emotional versus neutral information in a complex episodic memory experiment, where the episode unfolds in space and time and emotional and neutral features are part of the same experience. We also tested the effect of stress on memory for central versus peripheral information, thus enabling us to determine which dichotomy better accounts for the data - the emotional/neutral distinction or the central/peripheral distinction. A larger, conceptual question follows from this distinction, namely, which account will better describe the data, the stress account or the arousal account? As discussed, the stress account posits that neutral information should be disrupted, and emotional information enhanced, by the actions of stress-related neuromodulators at different brain sites (i.e. hippocampal regions and prefrontal cortex, amygdala). To the extent that stress per se (and not just physiological arousal) is an important manipulation, neutral, but not emotional, memory should suffer in the current experiment.

The arousal account, while similarly positing that emotional information should be preserved relative to neutral information due to high levels of emotional arousal, also posits that stress should lead to an enhancement of central information, and possibly (according to the Easterbrook hypothesis) a disruption of peripheral information. If peripheral memory suffers and central memory improves under stress, we will have to consider at least two different possibilities: 1) that stress is an intense form of arousal having the same, uneven impact on central versus peripheral memory, or 2) that overlap necessarily exists between central and emotional information, and between peripheral and neutral information.

Experiment 1 thus examined the impact of highly emotional, psychosocial stress on memory for different aspects of a single event. As stated above, we hypothesized that stress would disrupt memory overall, but we also suspected that analyzing "memory" part by part (e.g. emotional vs. neutral information, and central vs. peripheral information) would reveal a more complex interplay between stress and memory. Specifically, we expected stress to disrupt neutral aspects but not emotional aspects of memory, which would be preserved, if not enhanced, by the same stressor. We also expected to see a significant overlap between emotional information and central information, and between neutral information and peripheral information, thus resulting in a similar pattern of preserved central information and disrupted peripheral information.

METHOD

Participants and Design

Participants were 117 undergraduate students recruited from lower-division psychology classes who received course credit for their participation. They were randomly assigned to a 2 (stress group: stress vs. control) x 2 (delay condition: immediate memory test vs. 2-week delay) x between-subjects factorial design. There were 61 participants in the stress condition and 56 in the no-stress control condition. We tried to ensure relatively equivalent numbers of males and females in each of the four groups. Of the 33 participants in the stress/immediate memory condition, 14 were males and 19 were females. Of the 28 participants in the stress/1-week delay condition, 12 were males and

16 were females. In the control condition, 17 males and 11 females were tested in the immediate memory condition, and 10 males and 18 females were tested in the delay condition.

Stimulus Materials

All participants viewed a narrated slideshow containing emotional and neutral information. The slides were taken from Heuer and Reisberg (1990), who kindly provided copies of their materials. In contrast to Heuer & Reisberg's procedure, where subjects viewed two different slideshows, one neutral and one emotionally arousing, participants in the present study viewed only the emotional version.

The slideshow contained 12 detailed slides, the middle 3 of which were emotionally arousing. The material in the remaining 9 (4 shown before the emotional slides and 5 after) was neutral. Cahill and McGaugh (1995) have shown that the middle emotional slides (along with their corresponding narrative) account almost entirely for participants' enhanced memory for the arousing story relative to the neutral story. Heuer and Reisberg (1990) showed the same pattern in their own data, where recognition memory was most pronounced for the emotionally arousing middle slides (see Heuer & Reisberg, 1990, Figure 2). The emotionally neutral slides in this version of the story are typically no better remembered than the corresponding slides in the neutral version of the story. Using a single set of slides thus allowed us to compare emotional and neutral slides as a within-subjects variable, eliminating the interpretive difficulties posed by using different stimuli in the emotional and neutral slideshows.

Each of the 12 slides was accompanied by a recorded narration. The slideshow depicted a mother taking her young son to visit his father (a surgeon) at work. Midway through the slideshow, participants learn that a terrible car accident has occurred, and the father must fight to save the victims. The son watches his father work, and at this point participants see the emotionally arousing slides (the car accident, a team of surgeons operating on the open chest cavity of a victim, and a victim's reattached severed legs).

Procedure

Participants in the experimental group were exposed to the Trier Social Stress Test (TSST) (Kirschbaum et al. 1993), a procedure that reliably elicits moderate psychological stress in laboratory settings (Kirschbaum et al., 1996). These subjects were required to deliver a speech in front of a one-way mirror. They were told that three trained investigators, located behind the mirror, would evaluate the speech. Ten minutes were given for speech preparation, notes were abruptly taken from participants at the end of this time, and they were told to give the speech extemporaneously. Participants also believed that the speech was video and audio recorded and that verbal and nonverbal aspects of their performance were being analyzed. All speeches were made under intense lighting, in the presence of two tripod-mounted 1000-watt halogen stage lights. Following the 5-minute speech, participants performed a moderately difficult subtraction task aloud, also for 5 minutes. Control participants sat and listened to relaxing music for a corresponding amount of time (ca. 20 minutes).

All participants were tested individually. After completing the TSST (or the relaxation period in the case of controls), participants sat at a computer and two Ag-AgCl electrodes were attached to their fingers. They were told (deceptively) that physiological measurements, including heart rate and skin conductance, were being taken to assess sensitivity to various types of auditory and visual stimulation, that they would be watching a slideshow, that they might find some slides pleasant, some unpleasant, and some neutral, and to carefully attend to each slide for the duration of its presentation. After indicating they understood the instructions, participants viewed the slideshow while listening to an accompanying narration through headphones. Each slide was presented for 6 seconds via computer; the narration began immediately after presentation of each slide. Subjects were not informed that their memory would be tested for the materials later on.

Subjective state anxiety reports, using the Speilberger state-trait anxiety scale (Speilberger, 1983), were collected at 1) the beginning of the experiment, before the experimental manipulation, 2) immediately after the manipulation (participants were asked, “How do you feel *now*?”), 3) after the manipulation, immediately after the 2nd form (participants were asked, “How did you feel *during* the speech?” and 4) after viewing the slides, at the end of the experiment (see Table 1). Although saliva samples were not analyzed for cortisol content in this study, a sister study (Jackson, Payne, Nadel & Jacobs, 2004) demonstrated that, in this laboratory, the TSST reliably elevates cortisol (see also Kirschbaum et al., 1996).

Depending on experimental condition, participants were administered the memory test immediately after viewing the slides or asked to return 2 weeks later for “additional physiological testing”. Participants in the delay condition were told they were participating in an experiment of sensory sensitivity. As part of this deception, they took home journals to record episodes of sensitivity.

The memory assessment consisted of both a recall and a recognition memory test. After Heuer and Reisberg (1990) and Cahill et al. (1994), participants were first asked to recall all they could about the narrated story they had previously seen, both about the general story line and any details they recalled. They were then reminded that they had seen a total of 12 slides, and were asked to remember each slide in as much detail as possible. Recall data were taped for later transcription and analysis[1]. Participants were credited with remembering a slide if they described visual information that could only be known from having viewed that particular slide (Cahill et al., 1994). Two judges, blind to experimental condition, scored these data. Each judge also scored the data for false recall errors. Memories were considered "false" only if participants recalled information that was clearly not part of the slideshow or narration (e.g. "an ambulance came and took the boy away"). Percent agreement between the judges was greater than 90% in both cases. The few disagreements were discussed until a consensus was reached and were ultimately decided by the second judge (JP).

Following free recall, participants were given a 4AFC recognition questionnaire (137 questions), where questions pertained to visual elements of the slideshow as well as the narration. The questions and answer choices were read aloud to all participants in the same order. For each question, a confidence judgment was made, indicating whether the participant was 1 (not at all confident of the answer) to 5 (extremely confident in the answer). These confidence ratings were used to construct a "false memory" variable.

[1] With the exception of 4 subjects, who were excluded from the analysis due to problems with the recording equipment.

False memories were considered confident answers (i.e., a rating of 5) that were nonetheless incorrect.

An emotional memory score was obtained for each subject by computing the average number of correct responses on the emotionally arousing slides 5, 6, and 7. A neutral memory score was obtained by computing the average correct responses to all other slides. Finally, two variables were created to measure “central information” and “peripheral information”. The first of these defined “central information” as information that was central to the plot of the story. Three scorers assessed each question on the recognition questionnaire, and determined whether it “could be removed without changing the gist or plot of the story”. If not, the question received a score of “central”. If so, it received a score of “peripheral”. For example, a question asking whether mother and son (as opposed, for example, to a mother and daughter, or a father and son) were depicted is central to this story. So, for that matter, is the fact that a car accident occurred and that father performs surgery on the victims. Changing these items would change the plot of the story. Examples of peripheral facts, on the other hand, are that mother was wearing a pink collar, that the boy had blonde hair, that he was carrying a soccer ball, and so on. One could change these details without changing the gist or theme of the story.

The questions were next scored for visual centrality. In this case, the three scorers were instructed to determine whether each question corresponded to a feature that was “visually central or visually peripheral relative to what the viewer would see assuming fixation at the center each slide”. By this second scoring system, facts that were learned via the narration (as opposed to looking at the slides) would necessarily be peripheral because they were not visible on the slides. Scorers placed a “VC” (for visually central) next to central questions and a “VP” (for visually peripheral) next to peripheral questions. There was approximately 95% agreement between scorers for both thematically and visually defined central/peripheral variables. Again, disagreements were discussed and ultimately settled by the second judge (JP).

RESULTS

Exposure to the TSST produced a robust increase in mean subjective stress ratings (see Table 1). Although stress and control participants gave equivalent stress ratings at the beginning of the experiment, before stressor administration, those in the experimental condition rated themselves as significantly more stressed, both during ($\underline{M} = 59$) and immediately after ($\underline{M} = 51$) the speech, than those in the control condition at the same two times ($\underline{Ms} = 26$ and 27, respectively). T-tests comparing groups at each time point confirmed that these were significant differences (ts $(114) = 16.6$ (during) and 12.8 (after), ps both $< .0001$). The difference between the groups disappeared on the 4^{th} subjective anxiety measure, given shortly before participants left the lab, indicating that subjective stress had returned to baseline by the end of the experiment.

Recall Memory Overall

We first analyzed free recall memory with a 2 x 2 x 2 between subjects ANOVA comparing group (stress, control), sex (male, female), and delay (immediate memory, 1-week delay). Exposure to the stressor significantly disrupted recall memory, predominantly in males, producing a significant group x sex interaction effect, $F(1,105) = 4.54$, $p < .05$. Follow-up analyses revealed a trend toward recall memory suffering more in males, $t(50) = 1.9$, $p = .069$ than in females, $t(59) = -1.1$ (ns), for whom recall memory was statistically equivalent in both stress and control conditions. We next analyzed false recall using a similar 2 (group) x 2 (sex) ANOVA. Analyses of false recall errors revealed further memory impairments in stressed subjects, with subjects in the stress group recalling more false information than those in the control group, $F(1,105) = 4.11$, $p < .05$. This false memory effect was unrelated to sex or memory type.

Emotional vs. Neutral Recall Memory

We next examined the effect of stress on the type of memory presented in the different phases of the slideshow. Recall that recognition memory scores were computed for emotional and neutral information, yielding a 2-level within subjects "memory type" variable. We thus used a 2 x 2 x 2 x 2 mixed ANOVA, this time comparing stress group (stress, control), sex (male, female), delay (immediate memory test, one-week delay), and memory type (emotional, neutral) as a within subjects variable (See Table 2). This analysis revealed that emotional information ($M = .81$) was better recalled than neutral information overall ($M = .66$), $F(1, 105) = 45.3$, $p < .0001$, an effect that did not interact with delay condition. We also found a significant group x memory type interaction ($F(1,105) = 4.4$, $p < .05$). As can be seen in Figure 1, neutral memory, but not emotional memory, was impaired by the stress manipulation. Unlike neutral information, emotional information was preserved under stress. Participants in the stress ($M = .807$) and control ($M = .809$) groups remembered an equivalent amount of emotional information.

This result was accompanied by a marginally significant group x memory type x sex interaction, $F(1,109) = 3.6$, $p = .059$ and a significant group x memory type x sex x delay interaction, $F(1, 109) = 4.6$, $p < .05$ (See Table 2). Splitting the data by "delay" showed that the group x sex interaction reached significance only in the 1-week delay condition, $F(1, 50) = 9.3$, $p < .01$. Stressed females carried this effect, apparently by showing facilitated memory for the emotional slides recalled after a 1-week delay. As depicted in Figure 2, follow-up t-tests confirmed that stressed females recalled significantly more emotional information than both stressed males ($p < .01$), and control females ($p < .01$). Importantly, then, stress did enhance emotional recall, although only in females.

Recognition Memory Overall

We next analyzed overall recognition memory scores with a 2 x 2 x 2 between subjects ANOVA, comparing stress group (stress, control), sex (male, female), and delay (immediate memory test, one-week delay). Exposure to the stressor significantly disrupted recognition memory overall, as revealed by a main effect of stress condition, $F(1, 109) = 6.03$, $p < .02$. Stressed subjects remembered significantly less information from the slideshow overall than did non-stressed control subjects. There was also a significant effect of delay. Participants tested immediately after viewing the slides remembered more information than those tested after a one-week delay, $\underline{F}(1,109) = 91.69$, $\underline{p} < .0001$. The delay variable, however, did not interact with the other variables of interest. Finally, there was no main effect of sex ($\underline{p} = .37$), nor did sex interact with any of the other variables.

Emotional vs. Neutral Recognition Memory

We next examined the effect of stress on the type of memory presented in the different phases of the slideshow. We used a 2 x 2 x 2 x 2 mixed ANOVA, this time comparing group (stress, control), sex (male, female), delay (immediate memory test, one-week delay), and memory type (emotional, neutral) as a within subjects variable. In addition to the main effects of stress and delay noted above, a main effect of memory type emerged, $F(1, 109) = 117.7$, $p < .0001$, which was qualified by a significant stress by memory type interaction, $F(1, 109) = 4.78$, $p < .05$. As can be seen in Figure 3, and consistent with our predictions, only neutral information suffered under stress. Memory for emotional information was preserved relative to neutral information.

Strange et al. (2003) reported that memory for neutral information suffers when it precedes emotional information. We thus recreated the memory type variable, this time yielding a 3-level variable where the neutral slides were further broken into "pre" and "post" emotional information (neutral pre, emotional, neutral post). "Pre" refers to the neutral content (slides 1-4) preceding the emotional slides, and "post" refers to the neutral material (slides 8-12) following the emotional slides (4-7). We conducted another 2 (stress group; between subjects) x 2 (sex; between subjects) x 2 (delay; between subjects) x 3 (memory type with 3 levels, pre, emotional, and post; within subjects) mixed ANOVA to assess the impact of stress, sex and delay on the 3-level memory type variable.

Regardless of its position relative to the emotional material, memory for neutral information was marginally impaired under stress $F(1, 109) = 3.35$, $p = .07$. To clarify this result, we analyzed the three story phases (neutral pre, emotional, neutral post) in separate ANOVAs (after Cahill & McGaugh, 1995), which revealed that stressed participants remembered significantly less neutral information in both the pre ($F(1, 109) = 13.59$, $p < .01$) and post ($F(1, 109) = 5.74$, $p < .02$) phases but remembered an equivalent amount of information in the emotional phase ($F(1, 109) = .71$, $p = .40$ ns) (See Figure 4).

Finally, despite the changes to the Reisberg & Heuer (1990) procedure, we obtained an "emotional memory enhancement effect." Emotional information was better remembered (in this case recognized) than neutral memory, $F(1, 114) = 75.2$, $p < .0001$. Interestingly, this main effect of memory type did not interact with delay, suggesting that the emotional memory enhancement effect was present in both the immediate and delay conditions (See Figure 5). Follow up ANOVAs confirmed this to be the case in both the immediate memory condition, $F(1, 59) = 55.1$, $p < .0001$) and the 1-week delay condition $F(1, 54) = 24.6$, $p < .0001$.

Remembering emotional information well does not, however, mean that it is remembered accurately. Looking at false memories, which we defined as confident false recognition responses (i.e. false recognition responses that had a confidence rating of 5 or "extremely certain"), a group x sex interaction emerged, $F(1,109) = 6.69$, $p < .01$. Stressed females falsely recognized significantly more emotional information than control females ($p < .05$). Correlational analyses revealed that these false memories were positively related to the *details* of the emotional slides (e.g. the color of a door, the number of cars in a particular slide) ($r = .32$, $p < .01$), but not the gist (e.g. general questions about the story line) ($r = .13$, ns). This finding did not apply to males, nor did it reach statistical significance for neutral information.

Central Vs. Peripheral Recognition Memory

We next examined the effect of stress on memory for central versus peripheral information, as assessed by the recognition questionnaire. A 2 (group; stress vs. control) x 2 (sex; male vs. female) x 2 (delay; immediate memory test vs. 1-week delay) x 2 (memory type; central vs. peripheral, within subjects) mixed ANOVA revealed a main effect of group, qualified by a two-way interaction between group and memory type; $F(1,109) = 3.84$, $p < .05$. Stress significantly *disrupted* memory for central, thematic information ($M = .71$ versus $M = .77$ in the control condition). Memory for thematically peripheral information, on the other hand, though reduced relative to thematically central information, was not significantly impaired by the stress manipulation ($M = .36$ in the stress group, $M = .385$ in the control group). A similar pattern emerged for visually defined central and peripheral information (e.g. $M = .487$ for visually central information in the stress condition, $M = .534$ in the control condition), though in this case the relevant interaction was not significant. Also similarly, visually peripheral information was unaffected by stress ($M = .52$, stress group; $M = .55$, control group).

Stress did not simply disrupt memory for the comparatively trivial details of the story; the detrimental effect of stress applied even to the most central elements – the who, what, when and where – of the story. For example, individual chi-square analyses confirmed that stressed subjects were significantly less able than control subjects to remember critical facts, such as the fact that the son watched the father perform the surgery (91% of stressed subjects remembered this fact as compared to 100% of control subjects, ($\chi^2 = 3.15$; $df = 1$; $p = .06$), that the father was pleased that his son watched

(77% compared to 90%), ($\chi^2 = 4.85$; $df = 1$, $p <$ 05), that the father was smiling after the surgery (42% compared to 66%), ($\chi^2 = 6.59$; $df = 1$, $p < .01$), and that the mother left the hospital alone (78% compared to 93%), ($\chi^2 = 4.72$; $df = 1$, $p < .03$).

DISCUSSION

In the past decade, cognitive and neuroscientific studies have shown that both stress and arousal augment emotional memory (e.g. Cahill & McGaugh, 1998; Reisberg & Heuer, 2004). We replicated this effect here, demonstrating that memory for emotional material is superior to memory for neutral material both immediately and after a one-week delay. In typical experiments using this design, memory is tested only after a delay on the assumption that emotion specifically augments long-term consolidation processes (Cahill & McGaugh, 1998). Only recently have encoding effects been considered (e.g. Cahill, 2003; Strange et al., 2003; Quevedo et al., 2003; Strange & Dolan, 2004). Our immediate memory findings thus add to the burgeoning evidence that emotional arousal can act on both short-term and long-term memory processes (see also Hamann, 2001).

Our data also demonstrate that stress has differential effects on memory for the various features or components of what, in its entirety, is an emotional episode. The episode depicted in our slides is complex, containing features presented in different modalities (visual and auditory), and containing both emotional and neutral information – much as would be the case during a stressful episode in the real world. As predicted, stress disrupted memory for neutral, but not emotional, features of the episode.

Contrary to our predictions, however, stress failed to disrupt memory for peripheral information relative to central information. In fact, the opposite was true:

While stressed subjects had worse memory than control subjects overall (i.e. worse memory for both central and peripheral information), they had particular difficultly remembering central information, performing more poorly than controls. This pattern applied to central information regardless of whether it was defined conceptually or visually. So while memory for emotional information was preserved, and in some cases even enhanced under stress, memory for central information suffered under stress. These rather different patterns may indicate that there is not substantial overlap between what is emotional about an event and what is central to an event, at least in this particular paradigm.

Interestingly, Heuer and Reisberg (1990) found that arousal *enhanced* both central and peripheral features of the emotional slideshow. Here, stress *disrupted* both central and peripheral features of the slideshow. Taken together, these results suggest that the arousal induced by our stress manipulation cannot account for the current findings. Rather, stress appears to have a unique impact on memory. The stressed subjects in our experiment had difficulty remembering even the most central facts about the story – critical facts such as who, what, when and where – not just the minor details. The fact that experimental and control subjects did not differ significantly in terms of their memory for peripheral details (e.g. the fact that the little boy was carrying a soccer ball or was wearing tennis shoes) suggests that these details are difficult to remember regardless of whether or not one is under stress. Stress' most detrimental impact was on the more important, central information that was critical to the plot of the story. Thus, while general emotional arousal facilitates memory for these central story elements, stress appears to disrupt them.

The Easterbrook hypothesis also failed to find support in the current experiment, in that peripheral information was not selectively impaired relative to central information. This is a particularly surprising result given that stress induces physiological and emotional arousal. Consistent with the current study, Heuer and Reisberg (1990) found that arousal failed to impair memory for peripheral information. While this might have been due to their definition of central information (defined thematically rather than visually), it may also have been because the magnitude of arousal in their study (generated simply by viewing the emotional slides) was not sufficient to produce the attentional narrowing effect found in other experiments. As stress undoubtedly produces intense physiological arousal, however, this latter explanation now seems unlikely.

It appears, then, that the stress account provides a better explanation of our data than the arousal account. As the stress account predicts, we found preserved (or enhanced) emotional memory and impaired neutral memory after the stress manipulation. This is not to say that arousal makes no contribution to the preservation of emotional information seen in the stress group – it almost certainly does. However, it does suggest that arousal alone cannot account for the full pattern of findings, particularly the pronounced disruption of neutral information. Nor can it account for the disruption of central information we observed. Given these findings, we suggest that arousal and stress have somewhat distinct effects on memory, with stress adding to and changing the impact of arousal.

It is worth noting that most studies of arousal and memory have used forms of arousal that derive from the studied memory materials (i.e. the arousal is generated by viewing the emotional materials), and it is these studies that have led to the established pattern of enhanced memory for central relative to peripheral information. Several studies, however, have aroused subjects via extrinsic means, such as the administration of stimulants or vigorous exercise (e.g. Christianson & Mjorndal, 1985). These studies typically fail to have any impact on memory, suggesting that arousal must be intrinsic to the to-be-remembered materials to have an effect on memory. The current data show a strong effect of the stress manipulation, which is independent of the to-be-remembered materials. This may be another hint that a critical difference exists between the impact of "arousal" and "stress" on memory, even though the stress response includes an increase in physiological arousal. On top of this increase, however, is the activation of the HPA axis, which occurs specifically during the stress response. The stress response triggers the release of cortisol and norepinephrine, both of which influence memory in specific ways. High levels of cortisol have repeatedly been shown to disrupt memory for neutral materials, and we believe that cortisol elevations are most likely behind the neutral memory impairments found here[2]. The Trier Social Stress Test (TSST) is associated with average cortisol elevations of around 12-13 nmol/L – a level that has produced memory disruption both in our lab (Jackson, Payne, Nadel & Jacobs, 2003; Payne et al., 2002) and in other labs (e.g. Kirschbaum et al., 1993, 1996). Thus, while we did not take cortisol samples in the current experiment, we have good reason to believe that cortisol was

[2] Given cortisol's facilatory effect on the amygdala (McGaugh, 2000), cortisol elevations probably also help explain why emotional information was preserved in our experiment.

elevated by the TSST.

Previous studies on the neural mechanisms of stress and memory (e.g. Jackson, Payne, Nadel & Jacobs, 2003; Kirschbaum, Wust & Hellhammer, 1992; Wolf et al., 2001), and emotion and memory (e.g. Cahill & van Stegeren, 2003; Canli et al., 2002; Shors et al., 1998) have pointed to substantial sex differences. In line with these findings, we found three differing response patterns between the sexes.

The first was a pattern of enhanced emotional memory for women, but not men, after a 2-week delay. Examining both sexes together, emotional memory appeared to be “preserved”, but not enhanced, by stress. Examining them separately, however, revealed that women showed the emotional memory enhancement effect. This is consistent with Buchanan & Lovallo’s (2001) finding of enhanced emotional memory following a low dose of the stress hormone cortisol, and other studies showing an augmenting effect of stress on memory for emotional materials (e.g. Cahill, Gorski & Le, 2003; see McGaugh, 2000). The question, however, is why this effect emerged only in women. Although we did not measure cortisol in the current study, it is well documented that females give greater subjective stress ratings to social stressors than males (Kirschbaum et al., 1992; Stroud et al., 2002). That our speech task resulted in stronger memory effects in females than in males might reflect this difference perceived stress.

The second sex difference emerged in the proportions of false recognition errors men and women made under stress. Stressed females falsely recognized more emotional information than stressed males, particularly for peripheral detail (as opposed to central information or gist). Cahill and van Stegeren (2003) have shown that, in women, the effect of arousal on emotional memory is modulated by the left amygdala, whereas in men it is modulated by the right amygdala. As the left hemisphere is also associated with the processing of detail information (as opposed to gist information, which is the domain of the right hemisphere, see Hellige, 1993; Sergent, 1983), it may be that stress specifically impaired the processing of emotional detail information in women. This, however, is probably not the best explanation, as stressed females, in spite of their false memories for emotional detail, also showed generally superior overall emotional memory (see above). This superiority may have led to a false confidence in their memory, even for difficult to remember, highly specific details.

The third sex difference emerged in the overall recall data, and suggested that men's recall memory was more impaired by stress than females' recall memory. While this result did not emerge in the recognition memory data, or in any of the analyses where memory type (whether emotional/neutral or central/peripheral) was assessed, it is nonetheless consistent with other findings in the literature. For instance, Wolf et al. (2001) demonstrated a sex difference in the relationship between cortisol and short-term memory. In spite of an overall negative correlation between cortisol and memory in a mixed-sex sample, additional analyses showed that the effect was specific to men. Thus, higher cortisol values were associated with poorer memory performance in men, but not in women. Cahill, Gorski & Le (2003), however, in a study of post-learning stress administration (cold pressor stress), failed to find this sex difference, although this may have been due to a small number of male subjects in the sample. Further studies are clearly needed to pinpoint the impact of stress and cortisol on memory in male versus female human participants.

In summary, exposure to psychosocial stress had the predicted, uneven impact on human memory. Memory for neutral aspects of the depicted episode were disrupted, while emotional aspects were preserved.

EXPERIMENT 2: THE IMPACT OF PSYCHOSOCIAL STRESS ON NEUTRAL AND EMOTIONAL EPISODIC MEMORY: THE ROLE OF CORTISOL AND CATECHOLAMINES

The goal of Experiment 2 was to replicate, extend and improve upon Experiment 1. Experiment 1 demonstrated that psychosocial stress disrupts memory for neutral information, but preserves, if not enhances (see Figures 1 and 2) memory for emotional information. Experiment 2 sought to replicate this finding, and extend it to a different (and in some ways improved) memory task (see below).

Experiment 2 also sought to build on Experiment 1 by directly investigating the impact of stress hormones on human memory. In Experiment 1, we assumed that our results were attributable to cortisol and catecholamine elevations, and speculated that high levels of these neuromodulators, produced in response to the TSST, likely led to the disruption of neutral memory and to the preservation/enhancement of emotional memory. However, we did not take cortisol samples in Experiment 1. We thus cannot be certain that stress hormones moderated the results, nor that stress hormones were sufficiently elevated by the stressor (although they are in most TSST experiments, see Kirschbaum et al., 1996; Kulhmann, Piel & Wolf, 2005; Nater et al., 2005). In Experiment 2, we sampled cortisol at 4 different time points, and catecholamines (e.g. norepinephrine) at 2 time points, including immediately after the TSST, and attempted to relate these values to memory performance. In this way, Experiment 2 investigated a putative neurobiological mechanism underlying the behavioral results obtained in Experiment 1.

Experiment 1 detected a reduction in neutral memory under stress. The hypothesized enhancement of emotional information, however, did not emerge as robustly as we had predicted, perhaps because we did not test truly separable emotional and neutral memory conditions. To accomplish this, Experiment 2 used a modified version of Cahill et al. (1994). Although this test is similar to Heuer & Reisberg's (1990) paradigm, it employs closely matched emotional and neutral versions of the same slide show. This allows comparison of stress' impact on two identical episodes, varying only in emotionality. In Experiment 1, a single slide show containing neutral and emotional information was used. All subjects (stressed and control) saw and heard the exact same stimuli. While this modification addressed one confound – that the slide shows may have differed on more dimensions than "emotionality" (a weakness of Heuer & Reisberg's procedure), it failed to address another potential confound - the lack of a closely matched "neutral" condition.

This new memory testing procedure allowed a comparison of an "emotional" slide show with an entirely separate "neutral" slide show. All slides in the slide show were visually identical. Emotionality was varied by way of the narration. Though participants saw identical stimuli, what they *heard* was different. Like the within-subject procedure used in Experiment 1, the procedure used in Experiment 2 removed much of the variability between slide shows and constitutes an additional improvement upon the original Heuer and Reisberg (1990) design.

METHOD

Participants and Design

Participants were 76 (44 females, 32 males) undergraduate students at the

University of Arizona, who received course credit for their participation. Participants were randomly assigned to a 2 (stress group: stress vs. control; between subjects) x 2 (story type: neutral slide show vs. emotional slide show; between subjects) factorial design. Thus, nineteen (13 female, 6 male) participants were assigned to the stress/emotional story condition, 17 (10 female, 7 male) to the stress/neutral story condition, 20 (12 female, 8 male) to the control/emotional story condition, and 20 (9 female, 11 male) to the control/neutral story condition. Stress group was the main variable of interest, and consisted of 36 participants in the stress condition (23 females, 13 males) and 40 in the no-stress control condition (21 females, 19 males).

Stimulus Materials

Participants viewed one of two versions of a story – a neutral version or an emotional version – each consisting of 11 slides and each accompanied by one sentence of narration played over headphones (see Cahill & McGaugh, 1995; Cahill et al., 1994; van Stegeren, Everaerd, Cahill, McGaugh & Gooren, 1998). Both the neutral and the emotional story depicted a mother taking her young son to visit his father at work. All but two slides were taken from the Heuer and Reisberg (1990) slide show used above. In addition to the improvements noted above, Cahill and colleagues (e.g. Cahill & McGaugh, 1995; van Stegeren et al., 1998) modified the Heuer and Reisberg (1990) to eliminate several shortcomings. First, slide #7 (the picture of the surgery) was left out because it was not well remembered by any of the subjects in Cahill and McGaugh (1995, experiment 2). Second, slide number 5 (the picture of the accident scene) was slightly modified to improve story continuity. Finally, as mentioned, the visual aspects of the neutral and emotional slide shows were identical; only the narration differed. In the emotional story, participants were told that the boy had been injured in a terrible car accident and that the depicted injuries were real. In the neutral version, participants were told that the victim was a mere dummy being used in a hospital “disaster drill”.

The emotionally arousing elements of this narration, and the emotional pictures themselves (e.g. the car accident) were introduced in the second phase of this three-phase slide show. The first and the third phases had the same narration as the neutral version. The first four slides made up phase 1, slides 5-8 phase 2 (the emotional phase), and the final 3 slides composed phase 3.This procedure has been used extensively to examine emotional memory in laboratory settings (Cahill & McGaugh, 1995; van Stegeren et al., 1998, 2002; Rimmele et al., 2004).

As in the first study, each slide was shown for 6 seconds, with a 1-second interstimulus interval. Each corresponding sentence began approximately 500 milliseconds after the slide was displayed, and ended approximately 4 seconds later.

Procedure

Participants in the stress conditions (i.e. the stress/emotional story and the stress/neutal story conditions) were exposed to a variation of the Trier Social Stress Test (Kirschbaum et al., 1993). As in Experiment 1, participants were required to prepare a speech and then deliver it in front of a one-way mirror. They were again led to believe that three trained investigators were located behind this mirror, and that their speeches would be evaluated. In addition, a fourth investigator wearing a lab coat sat directly in front of participants, looking rather stern and taking notes on the speech.

Participants arrived at the lab, gave informed consent and filled out several initial questionnaires. They were told (this time truthfully) that we would be monitoring their physiological responses during the speech and throughout the first part of the experiment. Three electrodes were attached to the stomach area (2 on the ribs, the 3rd on the stomach proper), and alcohol was used to clean the three areas before electrodes were attached. We were thus able to collect heart rate data while simultaneously deceiving participants into believing that the experiment was investigating physiological sensitivity – not memory. Again, this deception was necessary to achieve surprise when participants returned one week later for the memory test.

As before, ten minutes were then given for speech preparation, and notes were abruptly taken from participants at the end of this time. Participants believed they were being video and audio recorded and that verbal and nonverbal aspects of their performance were being analyzed. All speeches were made under intense lighting, in the presence of two tripod-mounted 1000-watt halogen stage lights. Following the 5-minute speech, participants performed a moderately difficult subtraction task aloud, also for 5 minutes. As before, participants were required to count backward from 1022 by 13's as quickly and accurately as possible for 5 minutes. If a mistake was made, the experimenter bluntly stated, "No, that is not correct. Start over with 1022." Control participants simply sat and perused non-arousing magazines for a corresponding period of time (ca. 20 minutes). They were allowed to rest in the chair but the experimenter monitored subjects to ensure that they did not sleep, write, draw, talk, or put their heads down. Relaxing music was not used in experiment 2 due to complaints about the genre of music (meditation/new age) and concerns that music, if perceived as annoying, might lead to a stress response.

All participants were tested individually. After completing the TSST (or control period), participants sat at a computer. They were told that they would be watching a slideshow and that they would likely find some slides pleasant, some unpleasant and some neutral. They were told to carefully attend to each slide for the duration of its presentation. After indicating that they understood the instructions, participants viewed the slideshow and listened to the corresponding narration via headphones. Each slide was presented via computer, with the narration beginning immediately after each slide's presentation. At the end of the slideshow, participants rated (on a scale of 0-10) the emotionality of the story as well as how emotionally they reacted to it.

Memory Testing

All participants were administered the memory test exactly one week after viewing the slides. Because an incidental learning procedure was used (as in Experiment 1), all participants were told that they were participating in an experiment on sensory sensitivity. To prevent rehearsal across the week delay, participants took home journals and were encouraged to report any episodes of visual, olfactory or auditory sensitivity they experienced. They were instructed to bring the journals on their return visit (all participants complied and most returned with detailed journals). This procedure was intended to persuade participants that we were interested in their reactions to different types of stimulation both inside and outside the laboratory.

When participants returned 1 week later, they expected to view additional slides and participate in a follow-up study of sensory sensitivity. Instead, they were given a surprise memory test. The surprise memory assessment consisted of three parts - a free recall memory test followed by a cued-recall memory test and then a recognition memory test.

Participants were first asked to write down all they could about the slide show they had seen 1 week earlier, focusing both on the general story line and the specific details of the story (Heuer & Reisberg, 1990; Cahill et al., 1994).

Memory Scoring of Free Recall Data

Initially, the experimenters compiled a list of 140 elements of information about each story. Some elements were descriptive of specific details, such as “the boy had blonde hair”, whereas others were gist-like (e.g. “there was a car accident”), and considered central to the plot or theme of the story. If a participant recalled an element that was not originally on the list, then the element was added to the list. If an element originally on the list was not recalled by any participant (e.g. “the name of the hospital was Victory Memorial”), then it was removed from the list. This procedure resulted in a final list of 125 story elements. Participants were credited with recalling a story element if it was clearly mentioned in their responses. Two judges, blind to experimental condition, scored these data. Percent agreement between the judges was 97%. The few disagreements were discussed until a consensus was reached.

Participants were next reminded that they had seen a total of 11 slides, and were asked to remember each slide in as much detail as possible. This cued-recall method of testing was included because such prompting has been shown to elicit additional memory for the slide shows (e.g. Cahill & McGaugh, 1995).

Memory Scoring of Cued-Recall Data

Cued recall responses were scored for the number of slides recalled and the number of false slides recalled. Participants were credited with remembering a slide if they described visual information that could only be known from having viewed that particular slide (Cahill et al., 1994). In cases where participants gave ambiguous descriptions, such as "there was a slide with a car", free recall responses were consulted for verification. Reports of slides that were clearly not part of the slide show (e.g. "a slide showing an ambulance") were scored as false slide recalls. The slides recalled were summed separately for each story phase and are represented as the percent recalled out of the total number of slides in that phase. Two judges, blind to experimental condition, scored these data. Percent agreement between the judges was approximately 95% in both cases. Disagreements were discussed until a consensus was reached.

Memory Scoring of the Recognition Data

Finally, participants were given a 4AFC recognition questionnaire (88 questions) via computer, with one question presented at a time (This was necessary, as some questions presupposed others). This version of the questionnaire (Cahill et al., 1994; Cahill & McGaugh, 1995) included eight questions per slide. For each question, a confidence judgment was made, indicating whether the participant was 1 (not at all confident of the answer) to 5 (extremely confident in the answer). All participants received the questions in the order of the original slide presentation and in the same sequence within any given slide. The order of questions was the same for all subjects.

Questions and answer choices were presented on a computer screen and participants responded using a keyboard.

Measures of Stress Responsivity

Subjective state anxiety reports (Speilberger, 1983) were administered at four time-points; 1) at the beginning of the experiment, before the experimental manipulation, 2) immediately after the manipulation, 3) 30 minutes following the manipulation, and 4) at the beginning of the second visit, 1-week later immediately prior to memory testing. Salivary cortisol samples were taken at the same four time periods (see Kirschbaum et al., 1996), while participants were filling out the subjective anxiety questionnaires. Ten minutes prior to the first and 4th cortisol samples, participants were instructed to rinse their mouths out with water for precisely 15 seconds. After this procedure, participants were not permitted to have drinks, food or gum. All saliva samples were collected with Salivette collection devices (Sarstedt Inc., Germany), and samples were immediately frozen in a standard freezer at approximately 10 degrees Fahrenheit.

Using our in-house facilities, all saliva samples were assayed for cortisol in duplicate with a commercially available, highly sensitive, enzyme immunoassay (Salimetrics LLC, PA). The test used 25μl of saliva per determination, had a lower limit of sensitivity of 0.003 μg/dl, standard curve range of from 0.007 to 1.8 μg/dl, and average intra- and inter-assay coefficients of variation 5.1% and 8.2% respectively. Method accuracy, determined by spike recovery, and linearity, determined by serial dilution were 103% and 96% respectively. Values from matched serum and saliva samples show the expected strong linear relationship, $r(63) = 0.89$, $p < 0.0001$.

The saliva from each subject was also used to assess alpha-amylase, which is considered another measure of stress responsivity (Nater et al., 2005). Alpha-amylase is an enzyme secreted from salivary glands in response to activation of the sympathetic nervous system (Schneyer and Hall, 1991). Stress-related increases in salivary alpha-amylase can be inhibited by adrenergic antagonists and can be stimulated by beta-adrenergic agonists (Speirs et al 1974; Gallacher & Petersen 1983). Correspondingly, in response to psychological stress, salivary alpha-amylase is a correlate of norepinephrine and epinephrine release but not cortisol release (Chatterton 1996; Nater et al 2005). Given these findings, salivary alpha-amylase was included in this study as a surrogate marker of catecholamine response to stress, a stress response system distinct from the cortisol system.

A testing service (Salimetrics LLC, PA) was used to analyze the alpha amalyse data. The saliva samples collected before and after the experimental manipulation (2 time points only) were assayed for alpha-amylase in singlet with a highly sensitive enzyme immunoassay. The test used 25µl of saliva per determination, and had an average intra- and inter-assay coefficients of variation 5.5% and 4.7% respectively. Method accuracy, determined by spike recovery, and linearity, determined by serial dilution were 101% and 96% respectively.

RESULTS

A total of 11 subjects out of 87 were excluded from analysis for various reasons: six because of technical problems during the experiment (e.g. subjects were unable to hear the narration), and five because of a failure to return for the 1-week memory testing session. Thus, the following analyses were performed on the 76 remaining subjects.

Subjective Stress Ratings

As in Study 1, TSST treatment produced a significant increase in mean subjective stress ratings (see Figure 6). A repeated-measures ANOVA with sex and stress group as between-subject factors and assessment time (four levels: pre-manipulation, post-manipulation, 30-min post-manipulation, and return visit) as the within-subject factor detected a significant main effect of stress group ($F[1,72] = 45.7$, $p < .001$), and a significant stress group by assessment time interaction ($F[1,72] = 81.7$, $p < .001$). Post hoc t-tests indicated that exposure to the stressor significantly elevated subjective stress levels immediately after ($t(74) = 14.0$, $p < .001$), and 30-min after ($t(74) = 3.6$, $p = .001$) the TSST manipulation as compared to the control group. Stress and control participants gave statistically equivalent stress ratings at the beginning of the experiment, before TSST administration ($t(74) = .37$, $p = .71$), and at the 1-week return visit ($t(74) = .48$, $p = .63$). There was also a significant 3-way interaction among sex, stress group, and assessment times ($F[1, 72] = 4.2$, $p = .01$). Post hoc t-tests indicated that while both males and females exhibited the same pattern as above (see Figure 7), females reported significantly higher levels of stress than males after the TSST manipulation ($t(74) = 3.3$, $p = .002$).

Cortisol Levels

The results confirm the expected stress-induced cortisol increase. A repeated-measures ANOVA with cortisol assessment time as the within-subject factor (four levels: pre-manipulation, post-manipulation, 30-min post-manipulation, and 1 week return visit) compared cortisol levels across stress group and sex (between-subject factors), controlling for time since waking. There was a significant main effect of stress group ($F[1,72] = 9.85$, $p = .003$) and a significant stress group by assessment time interaction ($F[1,72] = 8.0$, $p < .001$) (see Figure 8). Post hoc t tests indicate that exposure to the stressor significantly elevated cortisol levels immediately after the stressor (Time 2) and 30-min after the stressor (Time 3) ($t(74) = 3.7$, $p < .001$; $t(74) = 4.1$, $p < .001$, respectively). The stress group did not differ from the control group, however, either at baseline (Time 1) or at the beginning of the return visit (Time 4) ($t(74) = .2$, $p = .85$; $t(74) = .4$, $p = .70$).

There were also significant cortisol by sex ($F[1,72] = 6.02$, $p < .001$) and cortisol by sex by stress group interactions ($F[1,72] = 5.7$, $p < .01$) (see Figure 9), which indicate two things: one, that stressed males had a more pronounced cortisol response to the stressor than females, and two, that stressed males' cortisol levels were still more elevated than females' at the 1-week return. In fact, stressed males' average cortisol level at the return was greater that 12 nmol/l, which is still rather high. This result may be responsible for the strong relationship between elevated cortisol levels and memory retrieval at the one-week delay, an issue we return to later.

Catecholamines

Analysis of catecholamines, as indexed by salivary alpha-amylase, used a repeated-measures ANOVA with sex and stress group as between-subject factors and assessment time (two levels: pre-manipulation and post-manipulation) as the within-subject factor. This ANOVA detected a significant stress group by assessment time interaction (F[1,74] = 17.8, p < .001). Post hoc t-tests indicated that the stress group experienced the predicted increase in catecholamine levels after the TSST manipulation (t(35) = 3.5, p = .003), whereas the control group experienced a significant decrease (t(39) = 2.6, p = .02). No significant sex differences were detected in this analysis.

Heart Rate

Analysis of heart rate data used a repeated-measures ANOVA with sex and stress groups as between-subject factors and assessment time (baseline, during the speech preparation, during the speech, and post-TSST) as the within-subject factor. The ANOVA detected a significant main effect of time (F[1,72] = 5.9, p < .0001). Post hoc t-tests indicated that exposure to the TSST significantly elevated heart rate over that of the control group (baseline: t(64) = 1.6, ns; speech preparation: t(64) = 4.8, p < .001; speech task: t(64) = 7.8, p < .001; post-TSST: t(64) = 3.6, p < .001). No significant sex differences were detected.

MEMORY DATA

Recall Memory: Emotional Versus Neutral Slides

We first analyzed free recall memory with a 2 x 2 x 2 x 3 mixed ANOVA comparing group (stress, control), story type (emotional, neutral) and sex (male, female), with “phase of story” (phase, 3 levels) as the within subjects factor. This analysis detected significant main effects of story type F[1, 74] = 13.2, p < .01), and phase (F[1, 73] = 32.4, p < .0001), demonstrating that the emotional story was better recalled than the neutral story, and that phase 2 (the phase containing the emotional slides) was better recalled than phases 1 and 3. Critically, there was also a significant interaction between stress group and story type (F[1,74] = 5.1, p = .03) (see Figure 10). Post hoc t tests indicated that stress significantly increased the recall of slides from the emotional story (t(37) = 2.1, p < .05) compared to controls, and significantly decreased recall of slides from the neutral story compared to controls (t(35) = 2.0, p < .05). Finally, there was also a significant story type by phase interaction (F[1, 74] = 14.0, p < .0001), which demonstrates, consistent with Cahill and colleagues (e.g. Cahill & McGaugh, 1995), that Phase 2 of the emotional story was better recalled than Phases 1 and 3.

We next analyzed cued recall memory with a 2 x 2 x 2 x 3 mixed ANOVA comparing group (stress, control), story type (emotional, neutral) and sex (male, female) on overall slide recall, with "phase of story" (phase, 3 levels) as the within subjects factor. As expected, there was a main effect of story type, $F(1,74) = 7.7$, $p < .01$, demonstrating that the emotional story was better recalled than the neutral story overall, and, in line with Cahill and colleagues (e.g. Cahill et al., 1994; Cahill & McGaugh, 1995), a significant story type by phase interaction confirming again that phase 2 of the emotional story (which contains the emotionally salient slides) is remembered best $F(1,74) = 6.6$, $p < .01$.

As was the case for free recall, there was also a story type x group interaction, $F(1,74) = 8.2$, $p < .01$, showing that, compared to the control group, stressed subjects recalled fewer of the slides from the neutral story, but more of the slides from the emotional story. However, while post hoc t-tests indicated that stress significantly increased recall of slides from the emotional story (t(37) = 2.4, p = .02), it only tended to decrease recall of slides from the neutral story (t(35) = 1.3, p = .14). Note that, in spite of their different scoring methods, the free and cued recall results are highly similar. Sex differences did not emerge in any of the recall analyses.

False slide recalls were next analyzed using a similar 2 (group) x 2 (story type) x 2 (sex) x 3 (phase) mixed ANOVA, which, by means of a significant group x story type interaction, $F(1,74) = 5.8$, $p < .02$, demonstrates an additional memory impairment in the stressed subjects (see Figure 11). Follow up t-tests revealed a significantly greater number of falsely recalled neutral slides in the stress group than in the control group ($t(36) = 4.7$, $p < .05$). However, stress and control subjects falsely recalled an equivalent number of emotional slides ($p = .21$, ns). Again, stressed subjects appear to have a deficit in neutral, but not emotional, memory.

Recognition Memory: Emotional Versus Neutral Slides

We next analyzed recognition memory scores with a 2 x 2 x 2 between subjects ANOVA, comparing stress group (stress, control), story type (emotional, neutral), and sex (male, female). Similar to recall memory, we found the expected main effect of story type, $F(1,74) = 15.1$, $p < .0001$, showing that slides from the emotional story were better remembered than slides from the neutral story, and the critical significant story type x group interaction, $F(1,74) = 9.6$, $p < .01$ (see Figure 12). As was the case for free recall memory, independent t-tests confirmed that stressed subjects' recognition memory was *both* significantly impaired for the neutral slide show ($t(36) = 5.1$, $p < .05$), and significantly enhanced for the emotional slide show ($t(36) = 4.5$, $p < .05$), relative to control subjects. There was no main effect of sex, nor did sex interact with the other variables.

The Relationship Between Cortisol Levels and Memory Performance at Retrieval

The only robust relationship to emerge between cortisol and memory occurred at the time of retrieval. This is a curious finding because retrieval took place 1 week after TSST exposure and initial learning of the slides. Nonetheless, the patterns of correlations between cortisol and memory performance at retrieval were consistent with our predictions. Cortisol levels at retrieval were negatively correlated with memory in the stress group, regardless of story type. This was true for all memory measures: cued-recall (stress: $r = -.42$, $n = 28$, $p = .03$; control: $r = .19$, $n = 35$, $p = .30$), free-recall (stress: $r = -.53$, $n = 28$, $p = .005$; control: $r = .32$, $n = 35$, $p = .07$), and recognition (stress: $r = -.59$, $n = 27$, $p = .002$; control: $r = .15$, $n = 35$, $p = .42$). The only exception to this generally disruptive relationship between cortisol levels and memory performance was in Phase 2, which, interestingly, is where the arousing narration occurs in the emotional slide show, and where the arousing pictures occur in both slide shows (e.g. the car accident). For example, although free recall of Phases 1 ($r = -.62$, $n = 30$, $p = .000$) and 3 ($r = -.46$, $n = 30$, $p = .005$) were strongly negatively correlated with cortisol, Phase 2 was not ($r = -.13$, $n = 30$, *ns*). This finding may hint at a resistance to the negative impact of cortisol on emotional memory, at least at retrieval.

We failed to find robust correlations between cortisol and memory measures at any of the other time points. Nor did we find reliable correlations between catecholamines (alpha amalyse values) and measures of memory, or between heart rate and measures of memory.

DISCUSSION

The TSST and Stress Responsivity

The TSST, as expected, significantly activated the endogenous stress hormone response. Our findings provide new evidence (Gold & McGaugh, 1975) that hormones released by emotionally stressful events modulate memory consolidation, and support the view that stress hormones are part of an endogenous memory modulating system for emotionally arousing events that helps insure memory strength that is proportional to memory importance (Cahill & McGaugh, 1995).

As has been found in previous studies (Kirschbaum et al., 1996; Kuhlmann, Piel & Wolf, 2005; Nater et al., 2005), the TSST treatment successfully elevated levels of both cortisol and catecholamines, and increased subjective stress ratings compared to a control condition. Thus, we can safely say that the TSST achieved its goal. Not only did it trigger a stress response in our subjects, but it was also perceived as stressful. Consistent with findings from other studies (Kirschbaum et al., 1992; Stroud et al., 2002), women perceived the TSST as more stressful than men.

Emotional and Neutral Episodic Memory under Psychosocial Stress

As in Experiment 1, psychosocial stress disrupted neutral episodic memory but facilitated emotional episodic memory. Here, rather than looking at neutral versus emotional aspects of a single experience, we investigated the effects of stress on separate neutral and emotional experiences. As predicted, stress disrupted memory for the neutral slide show, but greatly facilitated memory for an equivalent slide show that was emotional in nature. This interaction emerged in free and cued recall memory, and in recognition memory. The fact that we used different scoring methods for free and cued recall suggests that this pattern is rather robust. The most important result of Experiment 2 is thus as follows: In spite of the modifications made to the memory testing procedures, we replicated and extended the findings obtained in Experiment 1. We therefore conclude that stress indeed has a differential impact on neutral and emotional episodic memory – disrupting the former but enhancing the latter.

In spite of the general similarities across Experiments 1 and 2, there are several notable differences in the results. In Experiment 2, the facilitation of emotional memory under stress appears to be somewhat stronger than the disruption of neutral memory under stress, especially in the cued-recall data. This is contrary to what we found in Experiment 1, where neutral memory disruption was more pronounced than emotional memory enhancement. Although significant on some memory measures (free recall and recognition), and nearly significant on others (cued-recall), the disruption of neutral memory in the stress group was not as pronounced in Experiment 2 – a result that may make sense when one considers that the "neutral" slide show in Experiment 2 is neutral only in its auditory content. Participants still see the graphic (emotional) pictures, even in the neutral version of the slide show, which means that there is still some emotional content in the neutral condition.

This difference between the Heuer and Reisberg (1990) and Cahill et al. (1994) procedures may explain why the disruption of neutral memory is more pronounced in Experiment 1, where "neutral stimuli" are neutral in both narration and visual quality. In spite of these potentially important differences between the two experiments, it should be kept in mind that the overall pattern of disruption and enhancement under stress is similar. Additional evidence for a neutral memory impairment under stress emerged in the false memory analyses. Stressed subjects falsely recalled more slides from the neutral slide show than control subjects, but this was not the case for the emotional slide show. Stressed subjects apparently had more difficultly than controls accurately recalling the neutral, but not the emotional, slide show. Emotional memory appears to be better remembered and more accurately remembered than neutral memory under stress. In both experiments then, emotional memory tends to fare quite well under stress, whereas neutral memory tends to suffer.

Interestingly, stress exposure produced an increased rate of false memories in a previous experiment in our lab (see Payne et al., 2002). This experiment also tested memory for neutral stimuli (in this case semantically related word lists), and showed that pre-learning TSST exposure produced more falsely recognized words than exposure to a relaxation control condition. The falsely recognized words were similar in theme to the presented words but were nonetheless not on the lists presented for study. Likewise, most false slide recalls in Experiment 2 were semantically related to the theme of the slide show, but were nonetheless never presented for study. For example, some subjects remembered a slide depicting an ambulance, even though no ambulance was present in any of the slides nor mentioned in the narration. Ambulances are nevertheless often present at the scene of car accidents, so this type of error is not particularly surprising. What is surprising is that stressed subjects made this type of error more often than control subjects. We argued previously that this type of gist-based error suggests that hippocampal and prefrontal areas may not be functioning efficiently under stress (see Nadel & Payne, 2002; Nadel, Payne & Jacobs, 2003; Payne et al., 2002; Payne et al., 2004). The malfunctioning of these neural systems may give rise to what Jacobs and Nadel (1998) have termed "narrative smoothing", where retrieved memories are composed of incomplete representations cobbled together by a narrative based upon gist, inference, and educated guesswork (Jacobs & Nadel, 1998; Nadel & Jacobs, 1998. The false memory finding in Experiment 2 replicates our original finding (Payne et al., 2002), and extends it to a slide show paradigm. Together, both experiments strongly suggest that certain types of false memories (e.g. gist-based) are increased under stress.

The pattern of disrupted neutral information/enhanced emotional information is similar to that recently obtained by Jelicic, Geraerts, Mercelbach & Guerrieri (2004), who used word lists. These researchers found that the TSST facilitated memory for emotional words but disrupted memory for neutral words. Participants were exposed either to the TSST or a control task, and then required to learn and immediately recall 15 neutral and 15 emotional words. Subjects in the stress condition recalled fewer neutral words, and more emotional words, than control subjects. In spite of methodological differences such as the type of stimuli (words versus slide shows), and timing of the memory test (immediate test of memory versus a 1 week delay), these results are highly similar to those found here.

This pattern of neutral memory disruption and emotional memory enhancement after stress may be specific to experiments using the TSST or other social stressors. Pharmacological studies of stress, on the other hand, return rather mixed results. For example, two other recent studies found that cortisol administration impaired memory for neutral and positive words but did not impact memory for negative words (Tops et al., 2003, 2004). Another study (Kuhlmann, Kirschbaum & Wolf, 2004) found that cortisol administration impaired retrieval of emotional (negative) words while having no effect on neutral words, and still another (Abercrombie et al., 2003) found that cortisol administration enhanced both emotional and neutral words. We will return to the potential differences between studies using social stressors versus those administering cortisol in the general discussion, but for now, simply note that TSST studies, such as Experiments 1 and 2 here, and Jelicic et al (2004), seem to produce different patterns of results than studies of cortisol administration.

The Relationship between Cortisol and Memory Retrieval

Elevations in cortisol were predicted to correlate with deficits in memory for the neutral slide show. However, the only evidence for this occurred 1-week after viewing the slide show, when participants returned for memory testing. This time point turns out to be particularly illuminating, as it targets memory retrieval processes specifically. Interestingly, as in Kuhlmann, Kirschbaum & Wolf (2004), our results demonstrate an overall disruption of memory retrieval in the stress group. As predicted, increased cortisol values at the 1-week delay were strongly negatively correlated with memory retrieval overall (free recall, cued-recall and recognition). This is highly consistent with results from previous studies. Indeed, five studies in humans have now observed an impairing effect of cortisol treatment on delayed memory retrieval (de Quervain et al., 2000, 2003; Wolf, Convit et al., 2001; Kuhlmann, Kirschbaum & Wolf, 2004; Kuhlmann, Piel &

Wolf, 2005).

Given that we administered the TSST prior to learning, we were obviously unable to directly evaluate the impact of cortisol on memory retrieval. However, we were able to investigate the relationship between memory performance and basal cortisol levels at the 1-week return, when participants retrieved information about the slide shows. Generally speaking, cortisol levels should not have been elevated 1-week later as there was no stress manipulation at this point. Nonetheless, some participants had elevated cortisol levels at the return. Stressed males in particular showed such elevations. This finding is difficult to understand, unless one assumes either 1) that these men feared that they would have to give another stressful speech, although we said nothing to lead participants to believe this, or 2) that these men were randomly under more stress (unrelated to the experiment) than women at this time point. Males did have a more intense cortisol response to the stressor initially, so perhaps there is some reason to believe they feared having to give another speech. Or, perhaps they experienced a context-specific cortisol response on their return to the laboratory in which they were originally stressed.

Variations in basal cortisol levels have been shown to impact memory function. For example, one study showed that participants with high levels of basal cortisol (mean = 12.8 nmol/l) had better memory for emotional faces than participants with low levels of basal cortisol (mean = 7.6) (Putman et al., 2003). Similarly, basal cortisol levels impacted memory in the present study, although here higher levels were associated with poorer memory overall (except for Phase 2 information, see below). Further studies are needed to evaluate the role of cortisol specifically at retrieval. While elevated cortisol generally has a disruptive impact on retrieval, as we also show here (see also de Quervain et al., 2000, 2003; Kuhlmann, Kirschbaum & Wolf, 2004), it remains unclear if the emotional nature of stimuli moderates this effect.

The only exception to this generally disruptive relationship between increased cortisol levels and memory performance at retrieval was in Phase 2, which, interestingly, is where the arousing narration occurs in the emotional slide show, and where the arousing pictures occur in both slide shows. Although Phases 1 and 3 were strongly negatively correlated with cortisol, Phase 2 was not. There were no significant correlations between cortisol and any of the Phase 2 measures (cued-recall, free recall, recognition).

Given the strong negative correlations between cortisol and the emotional slide show overall (determined mainly by negative correlations in Phases 1 and 3), it is interesting that Phase 2 is resistant to the negative impact of cortisol. Although speculative, this may hint that emotional memory is resistant to the deleterious influence of cortisol. This idea should be cautiously considered, however, as cortisol was often more strongly correlated with memory for the emotional slide show than the neutral slide show overall. Nevertheless, there may be something special about Phase 2, and the data do seem to suggest that Phase 2 is buffered from the effects of cortisol in a way that the other phases are not.

It is important to keep in mind that our cortisol findings are correlational and thus should not be viewed as a final pronouncement on the relationship between cortisol elevations and memory. Cortisol levels are notoriously variable, differing depending on basal circulating level, weight, time of day, previous sleep patterns and current stress level, and future studies should at least assess weight and administer questionnaires to detect variations in sleep and stressors, and take note of the time of day when testing occurs. These variations are important, because we know that the relationship between cortisol level and memory change is not a linear one. Numerous studies have shown that very low and very high levels of circulating cortisol have impairing effects on memory, whereas a moderate level seems to facilitate it (Kim & Diamond, 2002). It is important to keep in mind that the TSST is a considered a stressor of moderate intensity (see Kirschbaum et al., 1993, 1996; Kuhlmann, Piel & Wolf, 2005). If cortisol levels in our stress group were higher, stronger correlations may have emerged. Indeed, variability may be one reason for the mixed results in the several studies of cortisol and human memory to date (e.g. de Quervain et al., 2000; Kuhlmann, Piel & Wolf, 2004; Wolf et al., 2001). Additional studies, that carefully control the various factors affecting cortisol level, are thus needed to clarify the role of cortisol in memory.

In summary then, a psychosocial stressor increased memory for the emotional story and decreased memory for the neutral story. A robust relationship between cortisol levels and the various measures of memory was only clear at retrieval. Future studies should systematically vary cortisol and catecholamine levels using experimental designs (rather than relying on correlations). Examining the influence of cortisol and catecholamines in this manner is necessary before their role in memory can be thoroughly understood.

Although it is too early to switch focus entirely to another neuromodulator, the impact of cytokines on memory function should at least be mentioned in closing. In addition to cortisol, stress-induced increases in proinflammatory cytokines may contribute to the memory deficits that occur in response to stress. Specifically, interleukin-1 (IL-1), which is released by macrophages in response to stress, may mediate stress-induced memory impairments (e.g. Linthorst, Flachskamm, Holsboer, & Reul, 1994), particularly hippocampus-specific memory impairments. For example, IL-1 induction has been found to impair performance on spatial (i.e. hippocampal-dependent) versions of the Morris water maze task, but to leave performance on the non-spatial versions unaffected (Gibertini, Newton, Friedman, & Klein, 1995). Thus, cytokines like IL-1 should at least be kept in mind when considering interactions between stress and memory, as they may help explain some of the findings that are difficult to account for with cortisol alone.

GENERAL DISCUSSION

A growing body of evidence suggests that stress influences memory function in animals (Lupien & McEwen, 1997; McGaugh, 2000; Roozendaal, 2000) and humans (Cahill & Alkire, 2003; Cahill, Gorski & Le, 2003). Yet there is still much debate about precisely *how* stress influences memory. Experiments 1 and 2 clearly demonstrate that pre-learning psychosocial stress disrupts memory for neutral episodes and information, but facilitates memory for emotional episodes and information. We now attempt to fit these novel findings into the recent literature on stress and memory. In so doing, we will focus on several studies that were published after Experiments 1 and 2 were conducted (see below).

As discussed at length in the introduction, a large and growing body of evidence demonstrates that acute stress can be disruptive to memory (Lupien & McEwen, 1997; Lupien & LePage, 2001 for reviews). However, a close reading of the literature reveals a confusing mix of data, with some studies showing a disruptive effect of stress on memory (e.g. Buss, Wolf, Witt & Hellhammer, 2003; de Quervain et al., 2000, 2003; Lupien et al., 1994, 1997; Newcomer et al., 1999; Wolf et al., 2001), and others finding an enhancing effect of stress on memory (e.g. Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003; Putman, van Honk, Kessels, Mulder & Koppeschaar, 2003).

These mixed data have led to several theoretical attempts to explain the fact that stress can have enhancing as well as impairing effects on memory (Lupien & Lepage, 2001; Wolf, 2003). De Kloet, Oitzl & Joels (1999), for example, focus on the importance of the context of learning. These researchers suggest that stress within the context of a specific learning experience enhances memory, while stress outside of the context impairs it. By this view, novel stressful experiences promote consolidation of information relevant to that specific experience. If stress originates from outside a context, on the other hand, the focus of learning will switch to the source of the new stressor, leading to impaired memory for the original experience. In this way, stress hormones bias information processing toward adaptive behavior that is most relevant to the situation at hand (De Kloet, Oitzl & Joels, 1999).

Whether or not De Kloet Oitzl & Joels' (1999) theory helps explain the impact of stress on memory depends, in part, on how one defines context. If context includes the entirety of the laboratory experience, including both the administration of the stressor and study of the memory materials, then this theory has much explanatory power. If, however, context is restricted to the learning materials themselves, then the theory fails to explain much. This second definition of context would dissociate the stressor (e.g. public speaking) from the study materials (e.g. an emotional series of pictures or an emotional story), rendering them separate and unrelated experiences. To use our Experiment 2 as an example, subjects would not associate the stressful experience of public speaking with the emotional events unfolding in the slide show. Another way of saying this is that stress was not engendered by the viewing of the slides themselves. By De Kloet Oitzl & Joels' (1999) theory, stress would have originated from outside the relevant learning context (the slide show), and thus memory should be impaired. This is not, of course, what we found. Nor is it what others have found. De Quervain et al (2000, 2003), for example, administered cortisol before delayed retrieval of word lists, so clearly the pharmacological manipulation was separate from the learning experience, which occurred 1 week earlier. Nonetheless, memory was impaired by this manipulation. Likewise, Cahill, Gorski and Le (2003) administered cold pressor stress shortly after the viewing of pictures. The stress associated with sticking one's hand in freezing water is not meaningfully related to the study of pictures, and in fact, these procedures were separated in time. Nonetheless, this stressor enhanced memory for emotional relative to neutral pictures.

Interestingly, most studies of *arousal* and memory have used forms of arousal that derive from the studied memory materials (i.e. arousal is generated simply by viewing the emotional materials themselves), and these studies have led to the well established pattern of enhanced memory for central relative to peripheral information discussed in Experiment 1. Conversely, the few studies that have aroused subjects via extrinsic means, such as the administration of stimulants or vigorous exercise (e.g. Christianson & Mjorndal, 1985), typically fail to have any impact on memory. This suggests that arousal must be intrinsic to the to-be-remembered materials to have an effect on memory (Reisberg & Heuer, 2004). This does not appear to be the case for stress, however, which, although an intense form of emotional and physiological arousal, is independent of the to-be-remembered materials in most studies of stress and memory. Interestingly, this suggests that stress and arousal have at least somewhat separable effects on memory. Moreover, it suggests that subjects participating in stress studies *do* connect stressors with studied emotional materials, combining them into a single event or experience in their memories. This is precisely what we found in Experiments 1 and 2, where the speech had a powerful impact on stressed subjects' ability to remember information that was unrelated (in content and in time) to the stressful experience of public speaking.

Thus, the De Kloet Oitzl & Joels' (1999) account does help us understand why stress promotes memory for emotionally arousing and stressful experiences (Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003; Experiments 1 & 2 here). It does less well, however, in accounting for the well-documented disruptive effects of stress. Indeed, as we have shown in Experiment 1 here, the disruptive influence of stress can manifest in the neutral aspects of memory for an emotional experience (see also Jelicic, Geraerts, Mercelbach & Guerrieri, 2004).

Another account (Roozendaal, 2002, 2003) proposes that GCs, interacting with noradrenergic activation in the basolateral nucleus of the amygdala, enhance the process of memory consolidation, but impair the process of memory retrieval, seemingly via identical mechanisms (Roozendaal, 2002). Roozendaal (2002) suggests that the release of stress hormones may put the brain into a 'consolidation mode' that is accompanied by impaired retrieval. Much evidence supports Roozendaal's (2002, 2003) account. For example, both Buchanan & Lovallo (2001) and Cahill, Gorski & Le (2003) investigated the effect of stress on memory *consolidation* after a significant delay between learning and test. Buchanan & Lovallo (2001) administered cortisol prior to learning and Cahill, Gorski & Le (2003) administered cold pressor stress immediately after learning. While Buchanan & Lovallo's (2001) procedure likely impacted encoding processes, we can assume that both studies targeted storage/consolidation processes. Both of these studies found that stress enhanced memory for the memory materials. However, subjects in both experiments studied emotional slides. Thus, the memory enhancement could be attributed to the emotionality of the to-be-remembered stimuli rather than the consolidation processes specifically, or some interaction between the two. Indeed, the consolidation process is thought to take time, which is why experimenters typically impose an extended delay period (usually 1 or 2 weeks) before testing memory. Experiment 1 did so as well, but we also included a condition where memory was tested immediately after learning. Here, too, the stressor led to enhanced emotional memory, so long-term consolidation processes may not be necessary to produce this result (see Strange & Dolan, 2004). And there may be something special about emotionally arousing information that is preferentially enhanced by stress and stress hormones, whether memory for this information is assessed immediately or after a significant delay.

Roozendaal (2002, 2003) also argues that the disruptive influence of stress takes place specifically at retrieval. Many studies support this notion, showing that psychosocial stress/cortisol administered prior to recall has a negative impact on memory (de Quervain et al., 2000, 2003; Kuhlmann, Kirschbaum & Wolf, 2005; Kuhlmann, Piel, & Wolf, 2005). We found evidence of the same disruptive influence here, as basal cortisol levels at the time of retrieval (1 week post-study, in Experiment 2) were negatively associated with memory overall. However, cortisol was also positively correlated with Phase 2 (the arousing phase) of both (neutral and emotional) conditions, suggesting that the emotionality of stimuli may play an additional role in mediating the effects of stress on memory. Our results thus support Roozendaal's (2002, 2003) theory, but suggest that emotional arousal may play an additional and equally important role in capturing the full relationship between stress and memory.

Given this, a final account focuses on the role of the emotionality of to-be-remembered stimuli, and suggests that emotional arousal modulates the effect of stress on memory (see Payne, Britton, Nadel & Jacobs, 2004). This is the perspective taken in the dissertation, and as noted previously, a close examination of stress and memory studies does suggest a break down along these general lines: Studies that find memory impairment typically use neutral memory materials (de Quervain et al., 2000, 2003; Kirschbaum et al, 1996; Newcomer et al., 1994, 1999; Payne et al., 2002; Wolkowitz et al., 1990, 1993), whereas those that find memory enhancement typically use emotional memory materials Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003; Expeirments 1 & 2 here).

This account is closely tied to the neurobiology of stress and to the location and density of stress hormone receptors in various areas of the brain. As mentioned, receptors for stress hormones are densely concentrated in both the hippocampus and amygdala. These medial temporal lobe structures are important for memory; the amygdala interacts with the hippocampus to modulate memory for emotional information and experiences, and the hippocampus is generally important for episodic memory (Schacter & Tulving, 1994; Strange & Dolan, 2004).

Memory for word lists and memory for personal experiences involve the medial temporal lobes (particularly the hippocampus) (Tulving & Schacter, 1994), and findings collectively suggest that cortisol can impair the functioning of this brain region (Lupien & McEwen, 1997). For example, cortisol administration has now been shown to impair word retrieval in several laboratories (e.g. de Quervain et al., 2000, 2003; Lupien et al., 1999; Wolf, Convit et al., 2001), and more recently, cortisol was shown to impair autobiographical memory retrieval as well (Buss, Wolf, Witt & Hellhammer, 2003). Thus, cortisol's impact on episodic remembering has been attributed to the activation of GC receptors in the medial temporal lobe. de Quervain et al (2003) were the first to show direct evidence for this assumption in humans. These authors used PET to demonstrate that 25 mg of cortisol given at retrieval led to a reduction of blood flow in the medial temporal lobe, specifically the right parahippocampal gyrus. Moreover, the 25 mg dose of cortisol produced marked memory impairment for studied words relative to a placebo condition (see also de Quervain et al., 2000). Thus, the impact of stress on hippocampal-dependent forms of memory is likely due to the influence of cortisol in this region (de Quervain et al., 2003).

Likewise, both norepinephrine and cortisol have an impact on the amygdala. New evidence suggests that cortisol may potentiate amygdala function and enhance memory for emotional information (e.g. Buchanan & Lovallo, 2001; de Quervain et al., 2003). As stated, the basolateral amygdala (BLA) is the specific nucleus thought to underlie these facilitatory effects, as it appears to regulate norepinephrine and glucocorticoid influences on emotional memory. Thus, the enhancing impact of stress on forms of memory involving the amygdala are likely due to the combined influence of stress hormones in this region.

Given these findings, we made two informed predictions: one, that stress would produce a pattern of emotional memory enhancement and neutral memory disruption, and two, that stress hormones would correlate strongly with these behavioral effects. Specifically, we expected cortisol to be negatively associated with neutral memory, and cortisol and norepinephrine to be positively associated with emotional memory in both experiments. The results of Experiments 1 and 2 provided strong support for the first prediction, but failed to support the second prediction. Both experiments yielded the expected pattern of facilitated emotional memory/impaired neutral memory, but Experiment 2 failed to strongly connect these findings to the presence of elevated stress hormones prior to encoding. However, evidence in support of our second prediction emerged in the retrieval data. Here we found the expected overall deleterious effect of elevated cortisol, and a positive relationship between cortisol values and Phase 2 (the arousing phase) in both slide shows.

To review, Experiments 1 and 2 demonstrated that psychosocial stress disrupts memory for neutral information. This result is consistent with several other studies showing that psychosocial stress disrupts neutral memory materials (e.g. Kirschbaum et al., 1996; Kuhlmann, Piel & Wolf, 2005; Payne et al., 2002). Moreover, we have shown that psychosocial stress preserves or enhances emotional memory materials. This result is in line with two other studies in the literature - Cahill, Gorski & Le (2003), and Buchanan and Lovallo (2001). These studies showed that stress manipulations produce memory facilitation for emotional pictures but not neutral pictures. Post-stressor cortisol levels did not correlate with memory performance in the Cahill, Gorski & Le (2003) study, as was the case in Experiment 2.

There are three major differences across these studies that might account for the differences between them, and help clarify the unexpected relationship between cortisol levels assessed after the stressor and memory performance in Experiments 1 and 2. First, some researchers used pictoral stimuli to assess memory while others used word-lists. Second, some researchers used psychosocial stress while others administered stress hormones directly. Third, some researchers investigated the impact of cortisol on the retrieval process, whereas others investigated its impact on memory when administered prior to, or shortly after, learning (thus targeting encoding and/or consolidation processes). In order to gain clarity on the stress hormone results, then, we turn first to several studies that examined the impact of stress and memory for word-lists rather than pictures.

The findings reviewed thus far suggest that emotional memory is overwhelmingly facilitated by stress and GCs (Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003; Experiments 1 and 2 here). However, all four of these studies assessed the impact of stress on memory for emotional pictures or slides. The impact of stress on emotional words, conversely, is not quite as clear. Similar to Experiment 1, one recent study found that the TSST facilitated memory for emotional words but disrupted memory for neutral words (Jelicic, Geraerts, Mercelbach & Guerrieri, 2004), and two others found that cortisol administration impaired memory for neutral and positive words but did not impact memory for negative words (Tops et al., 2003, 2004). The two Tops et al (2003, 2004) studies are thus similar to our Experiment 1, where memory for neutral information was disrupted by stress whereas memory for emotional information was preserved. However, another study (Kuhlmann, Kirschbaum & Wolf, 2004) found that cortisol administration impaired retrieval of emotional (negative) words while having no effect on neutral words, and still another (Abercrombie et al., 2003) found that cortisol administration enhanced both emotional and neutral words.

There were many small differences between these studies, such as time of cortisol or TSST administration (e.g. morning vs. afternoon), and length of the delay between study and test (2 hours 5 hours or 2 days after study) that might help account for the mixed results. However, stress may simply impact pictures differently than words, either because visual scenes are more arousing and threatening than words (Kuhlmann, Kirschbaum & Wolf, 2004), or because emotionally arousing words are often more semantically related to one another than are neutral words (Tops et al., 2003). In any case, some have suggested that emotional pictures or stories might produce stronger and more reliable effects of arousal and valence on memory than words, and therefore might be better suited for the investigation of stress and GC effects on emotional memory (Buchanan & Lovallo, 2001; Kuhlmann, Kirschbaum & Wolf, 2004).

A second potentially important variable concerns whether cortisol is administered directly or subjects are exposed to a social stressor like the TSST. Kirschbaum et al. (1996) found a negative relationship between TSST-induced cortisol levels and recall of neutral words. Lupien et al (1997) found similar results in healthy elderly subjects. More recently, Jelicic et al., (2004) found that administering the TSST prior to study led to enhanced memory for emotional words but disrupted memory for neutral words relative to controls. However, Kuhlmann, Piel & Wolf (2005) found that when the TSST was administered prior to retrieval, memory for words – particularly emotional words – was disrupted. The differences between the Jelicic et al (2004) and Kuhlmann et al (2005) studies suggests that memory stage might be a more powerful predictor of how stress impacts memory than how researchers go about stressing their subjects (i.e. administering stress hormones versus administering psychosocial stress).

Indeed, growing evidence suggests that stress has differential effects on discrete memory phases (de Quervain et al., 2000, 2003; Roozendaal, 2000). De Quervain et al (2000, 2003) convincingly demonstrated that recall of long-term memory for word lists was impaired when subjects were tested under the influence of acutely elevated cortisol levels. Cortisol-induced memory retrieval impairment was also found by Wolf et al. (2001), who showed that cortisol administration impaired recall of neutral words learned 2 hours earlier. Wolf and colleagues (Kuhlmann, Kirschbaum & Wolf, 2004; Kuhlmann, Piel & Wolf, 2005) recently confirmed these findings, again highlighting retrieval as potentially the most important for the disruptive influence of stress.

However, Jelicic et al (2004) administered the TSST prior to learning, as we did in Experiments 1 and 2, and found that the stressor disrupted neutral words (but not emotional words). Furthermore, Tops et al (2003, 2004) administered a low dose of cortisol (10 mg) prior to learning and found that this treatment impaired neutral and positive words, but did not influence negative words, relative to control subjects. Thus, it seems that memory can be disrupted by cortisol or psychosocial stressors, if they are given prior to encoding. Indeed, this is what we found for neutral information in both of the experiments presented here[iii].

Given the extant data, what do we know about stress and memory? First, we know that stress appears to have its most powerfully disruptive impact at retrieval (see de Quervain et al., 2000, 2003; Kuhlmann, Kirschbaum & Wolf, 2004; Kuhlmann, Piel & Wolf, 2005; Wolf et al., 2001; Experiment 2 presented here). In fact, the only case of disrupted *emotional* information occurred at retrieval (Kuhlmann, Kirschbaum & Wolf, 2004; Kuhlmann, Piel & Wolf, 2005). In spite of these two studies, it is too soon to conclude that stress reliably disrupts emotional memory. There are several reasons for this: 1) both of the Kuhlmann et al (2004, 2005) studies found a significant impairing impact of cortisol or psychosocial stress on memory overall, but no significant interaction between treatment (stress versus control) and word valence (emotional versus neutral). Therefore, their inquiry into stress' impact on valence must be viewed as exploratory and interpreted with caution; 2) stress may impact memory for word lists differently than pictures, stories or scenes, yet the only studies to find emotional memory disruption used word lists. The many others that consistently find emotional memory enhancement used pictures or slide shows (e.g. Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003; Experiments 1 and 2); 3) not all word list studies find that stress disrupts memory for emotional words. Jelicic et al (2004), using the same psychosocial stressor as Kuhlmann, Piel & Wolf (2005), found enhanced memory for emotional words under stress, although Jelicic et al (2004) administered the TSST prior to learning rather than before retrieval, as in Kuhlmann, Piel & Wolf (2005); and 4) the only other study to assess the relationship between emotional memory and stress level at retrieval is Experiment 2 presented here, which, as mentioned, showed that the generally disruptive association between stress and memory overall was not found for Phase 2 of the slide show, where the emotional content resides.

The exact relationship between stress and emotional valence remains to be worked out. Nonetheless, it is clear that stress can disrupt memory, and that this disruption is most often seen when stressors or stress hormones are administered at delayed retrieval.

Some studies, however, demonstrate that neutral memory impairment can occur when stress is administered prior to study (rather than at delayed retrieval). Interestingly all three studies to find an impact of stress administered prior to encoding (Jelicic et al (2004); Experiments 1 and 2) returned identical patterns of disrupted neutral information and enhanced emotional information. The use of a psychosocial stressor administered prior to learning appears to consistently produce this pattern of memory findings.

We also know that stress typically has an enhancing effect on emotional memory materials, particularly when the stressor/stress hormone manipulation is administered prior to learning or shortly after learning and when memory is tested after a delay. This effect can also be seen, however, when memory is tested immediately (Experiment 1), which suggests that stress may influence encoding and short-term consolidation processes in addition to the longer term consolidation processes most often investigated in past work (e.g. Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003; Cahill et al., 1994). As mentioned, the only exception to the enhancing effect of stress on emotional memory is when stressors/stress hormones are administered prior to the delayed recall of emotional words (Kuhlmann, Kirschbaum & Wolf, 2004; Kuhlmann, Piel & Wolf, 2005). Further studies are needed to determine if this result is valid and reliable. Such follow-up studies are especially warranted because while the two Kuhlmann et al (2004, 2005) studies suggest that emotional words might be impaired by stress under some conditions (e.g. when word-lists are used), Experiment 2 hints that the emotional phase of a slide show might be preserved relative to more neutral phases of the slide show.

While these studies are far from conclusive, they suggest that emotionality of stimuli interacts with stress to determine its ultimate influence on memory. We have provided further evidence that stress has unique effects on different types of memory. Generally speaking, we have shown that pre-learning stress disrupts memory for neutral information, but preserves or enhances memory for emotional information both immediately and after a delay. This pattern of neutral memory disruption/emotional memory enhancement emerged regardless of whether these memory types were aspects of a single episode (Experiment 1), or comprised different episodes (Experiment 2).

We turn next to a closer examination of the enhancing impact of stress on emotional memory, and consider our findings in a larger theoretical context – one that takes us into the impact of extreme stress on memory and the traumatic memory debate.

Emotional Memory Enhancement and Stress

Both cognitive and neuroscientific studies have demonstrated that stress and arousal enhance emotional memory (e.g. Cahill & McGaugh, 1998; Reisberg & Heuer, 2004). Indeed, a key finding in the emotion and memory literature is that memory for emotionally arousing events is superior to memory for similar, neutral events. We replicated this effect here, demonstrating that memory for emotional material is superior to memory for neutral material both after a one or two-week delay (Experiments 1 and 2), and when tested immediately (Experiment 1).

In typical experiments using this design, memory is tested only after a delay on the assumption that emotion specifically augments consolidation processes (Cahill & McGaugh, 1998). Only recently have encoding effects been considered (e.g. Cahill, 2003; Strange et al., 2003; Quevedo et al., 2003; Strange & Dolan, 2004). For example, Quevedo et al (2003) found enhanced memory for emotional slides after a one-week delay (LTM), but not after a one-hour delay (STM), suggesting that emotional arousal effects are not related to STM. Given this, the authors concluded that the amygdala does not modulate short-term emotional memory mechanisms. However, Strange, Hurleman & Dolan (2003) found enhanced memory for emotional relative to neutral words after a very brief delay. Even more importantly, using beta-adrenergic antagonists and fMRI, they were able to relate this enhancement to adrenergic and amygdala mechanisms that are already known to participate in long-term emotional memory enhancement (Strange & Dolan, 2004; Strange, Hurleman & Dolan, 2003; Cahill, 2003). They showed that successful encoding of emotional, as compared to neutral, verbal stimuli evoked increased amygdala responses in humans. Items that evoked amygdala activation at encoding evoked greater hippocampal responses at retrieval compared to neutral items. Administering propranolol at encoding abolished the enhanced amygdala encoding and hippocampal retrieval effects, in spite of the fact that propranolol was no longer present at retrieval (which occurred 10 hours after the memory test at 7:30 am, see Strange & Dolan, 2004). Thus, encoding and/or very short-term consolidation processes are likely impacted by arousal and do indeed require norepinephrine and the activation of the amygdala.

Our immediate memory findings thus add to the burgeoning evidence that emotional arousal can act on both short-term and long-term memory processes (see also Hamann, 2001). Our use of a pre-learning stressor may have encouraged amygdala involvement at encoding, which may help explain the enhancement of emotional information in the immediate memory condition. However, further studies, perhaps that administer β-adrenergic antagonists as in Strange, Hurleman & Dolan (2003) and in Strange & Dolan (2004), are needed to investigate this assumption directly.

Theoretical Implications: Traumatic Memory

Given these findings, it seems safe to assume that emotional memory thrives under conditions of stress and arousal. This idea fits nicely with our subjective experience of remembering. Most people have ready examples of highly arousing, emotional events that are remembered vividly 'as if they happened yesterday', and a substantial literature confirms that some emotional experiences are unforgettable (see Reisberg & Heuer, 2004). Some authors have noted the persistence of highly emotional and stressful memories, and argued that traumatic memories, far from being forgotten, are remembered wholly and in excruciating detail (e.g. McNally, 2003; Shobe & Kihlstrom, 1997). Yet our evidence from Experiment 1 demonstrates that stress can cause important elements of an emotional story to be forgotten. Thus, the claims made by Shobe and Kihlstrom (1997) and McNally (2003) may be overstated.

Most of the studies cited by these authors used slide show paradigms, similar to those used in this dissertation. Subjects watch a series of slides depicting successive moments in a story that is either emotionally arousing or emotionally neutral. A tape-recorded narrative accompanies the slides, helping subjects interpret the scenes and synthesize them into a story. As mentioned, these studies focus mainly on consolidation processes, so after waiting for a period of time, participants receive a substance that either enhances or blocks adrenergic (or glucocorticoid) activity. Participants then receive a single test of memory, usually after a long delay. The typical result shows enhanced memory for the emotional slide sequence with adrenergic facilitation and decreased memory for the emotional slide sequence under adrenergic blockade. Neutral slides, on the other hand, remain unaffected by adrenergic alterations (e.g. Cahill & McGaugh, 1995; Cahill, Prins, Weber, & McGaugh, 1994; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998).

These studies have made critical contributions to our understanding of the neural and hormonal mechanisms underlying emotional memory enhancement. Nevertheless, they tempt us to believe, perhaps prematurely, that emotional arousal and stress improve memory *overall*.

These experiments have mostly employed high-level aggregate measures of memory, measures that may not be sensitive to subtle nuances obtained when assessing the various components of memory directly (although see Adolphs, Denbury, & Tranel, 2001). For example, Cahill and colleagues typically assess memory using traditional recall and recognition measures, focusing on the overall “amount” of memory preserved post-treatment. In contrast, others examine qualitative differences *within* memory – for example differentiating memory for central or gist-like information from memory for peripheral detail, or examining neutral aspects of an event separate from emotional aspects of that event, as we did here. These analyses paint a more complex picture, showing that memory under stress is not simply enhanced across the board. Rather, stress' impact is uneven. Even within an experience that is emotional overall (i.e. Experiment 1), neutral aspects of the experience can be disrupted whereas emotional aspects can be enhanced by stress.

The fact that stress has a variable impact on different types of memory seems relevant to the traumatic memory debate, and casts doubt on the idea that intensely stressful or traumatic memories will be remembered completely and well. Shobe and Kihlstrom (1997) have argued that "…the preponderance of laboratory evidence indicates that memory is more likely to be enhanced than impaired by high levels of emotion and stress". However, we have shown, in numerous experiments including the two presented here, that stress leads to complex patterns of memory disruption and enhancement (Jackson, Payne, Nadel & Jacobs, 2003; Nadel & Jacobs, 1998; Payne et al., 2004; Payne, Nadel, Britton & Jacobs, 2004; Payne et al., 2002).

Shobe and Kihlstrom's (1997) argument has a long history, dating back at least to Livingston's (1967) "Now print!" concept. This notion argued that the brain 'prints' all information immediately preceding and following an arousing event. According to Livingston, "The brain 'prints' remembrance of all events immediately preceding and that following a 'Now print!' order, everything that has been ongoing in the recent past will receive a 'Now print!' contribution in the form of a growth stimulus or a neurohormonal influence that will favor future repetitions of the same neural activities"

(Livingston, 1967). Livingston's theory would clearly argue that stress and arousal have a net facilitating effect on *all* types and *all* aspects of memory.

Livingston's concept is closely related to "flashbulb memories", which are vivid, long-lasting memories for emotionally arousing and significant events. Like the "Now print!" concept, flashbulb memories were once thought to strongly and faithfully represent past emotional experience. However, it appears that neither of these original conceptions is completely accurate. Emotional arousal may only facilitate memory for those emotional aspects of events that engender arousal at the time of encoding (Cahill & Alkire, 2003), and flashbulb memories, while maintaining perceived vividness and detail, are often highly inconsistent across time (Talarico & Rubin, 2003). Thus, it seems overly general, and overly simplistic, to argue that stress will always enhance memory and that stressful experiences are unlikely to be forgotten.

How victims remember trauma has been termed the "most divisive issue facing psychology today" (McNally, 2003). While both cognitive and neuroscientific studies have made it clear that emotional arousal and stress augment memory (e.g. Cahill & McGaugh, 1998; Reisberg & Heuer, 2004), it seems premature to imply that traumatic memories are always well remembered, or that "…people remember horrific experiences all too well" (McNally, 2003).

Our findings show that stress can simultaneously impoverish memory for neutral aspects, and preserve emotional aspects of an emotional episode. Given this result, we ask the following question: What might a traumatic memory look like when recalled? It would almost certainly not be a perfect rendition of the original emotional experience.

Rather, it might be vague for important neutral details, like time of occurrence, spatial context, or perhaps details about a perpetrator (e.g. what he or she was wearing), while being relatively sharp for focal emotional information (e.g. the pain of being hurt, the fact that one was assaulted). Further, while we have provided evidence that stress enhances memory for emotional material, we also showed that these memories are not entirely accurate. Inaccuracies in emotional memory were observed in the data from Experiment 1, albeit only in women, and only in memory for minor emotional details – not emotional gist (see also Payne et al., 2004). Further evidence comes from studies of flashbulb memories, which lack accuracy and consistency even when people believe they remember emotionally arousing experiences in sharp detail (e.g. September 11th, Talarico & Rubin, 2003).

The two studies presented here highlight the fact that stress has complex effects on memory. Memory for emotional experience may be preserved or even strengthened, while memory for the neutral elements of that emotional experience are diminished. This pattern of results can be understood if one assumes that these two aspects of memory may be modulated by the amygdala and hippocampus respectively, and that a sufficiently high concentration of stress hormones might potentiate the former but inhibit the latter. These findings dovetail nicely with clinical evidence. Clinicians often report that memory for trauma is characterized not only by intrusive, indelible emotional memory fragments, but also by gaps in memory and general memory impairment (see Payne et al., 2004). Our data suggest that a brain-based account reflecting the role of stress hormones and their actions in different memory-relevant systems in the brain, might explain why this is so.

The Caveats: Methodological Problems and Other Considerations

An important methodological problem in both experiments concerns the order of recall and recognition memory testing. In both studies, measures of recall memory preceded the recognition questionnaire. Although all studies using this and similar procedures have tested recall first, followed by recognition (e.g. Cahill et al., 1994; Cahill & van Stegeren, 1998; Heuer & Reisberg, 1990; Southwick et al., 2002) several landmark experiments make it clear that recall can have an impact on subsequent recognition. Tulving and Wiseman (1975) were among the first to demonstrate that a moderate amount of dependency exists between recall and recognition memory (see also Flexser & Tulving, 1978). Humphreys and Bowyer (1980) later showed that sequential testing (e.g. recall preceding recognition or the other way around) results in a subset of items that are both recalled and recognized, and argued that a degree of dependency is introduced by the very nature of any paradigm that allows one form of memory testing to follow another.

One might wonder what effect recall has on subsequent recognition, as this is the format used in both Experiments presented in the dissertation. According to a series of experiments conducted by Wenger, Thompson and Bartling (1980), recall typically facilitates recognition memory. These researchers showed that recall trials, if the set of test items was kept small and the items could be remembered with approximately 90% accuracy, were consistently as good as additional presentation trials at enhancing later recognition memory. In other words, and more specifically, these researchers first showed that when a long list of studied words is used, a recall trial will not facilitate subsequent recognition as much as a presentation trial. However, they went on to show in 3 additional experiments that the superiority of a presentation trial occurs only because relatively few items are recalled on the recall trial due to long list length. When the frequency of item occurrence was roughly equated for presentation and recall trials (by making the word sets smaller and thus the memory test easier), self-generated recall trials were superior to presentation trials in facilitating subsequent recognition.

Although we did not use word lists in the current experiment, it stands to reason that our recall tasks might have influenced the amount, and perhaps even the type (Schacter, 1999), of information remembered on the recognition questionnaire. This confound necessitates that our recognition data be interpreted with caution. It is also advised that more emphasis be placed on the recall data, which, as discussed, generally show the same uneven relationship between stress and type of memory assessed (e.g. emotional versus neutral) as the recognition data. Reasoning that the recognition data may have been compromised in both experiments, we conducted additional scoring of the recall data, which yielded (as one example) the free recall scoring system described in Experiment 2. As our recall findings remained quite strong, our interpretation of the data is not greatly influenced by this confound. Nonetheless, it is important to be aware of this confound and to caution other researchers about the impact of recall on later recognition memory. Moreover, future studies wishing to examine the impact of stress on detailed recognition memory should either treat recall and recognition as separate conditions (i.e. employ the appropriate crossover), or test recognition memory only.

Stress and the Frontal Cortex: Stress-Induced Forgetting Beyond the Hippocampus

Another caveat involves the nearly exclusive attention devoted to certain brain structures to the exclusion of others. Up to this point in the dissertation, we have focused almost exclusively on the hippocampus and amygdala. The frontal lobes, however, have received increasing attention in the stress and memory literatures. Recent experiments using fMRI (Henson, Shallice & Dolan, 1999) and electrophysiological techniques (Otten & Rugg, 2002) have demonstrated an important role for the prefrontal cortex (PFC) in memory (Raye, Johnson, Mitchell, Nolde, & D'Esposito, 2000; Buckner et al., 2000). Traditionally, the prefrontal cortex was thought to contribute mainly to encoding processes through its presumed role in 'working memory', which allows information to be maintained temporarily in an active state (Baddeley, 1986). New evidence from PET and fMRI studies, however, shows that the PFC is also involved in memory retrieval (see Henson, Shallice & Dolan, 1999; Nyberg & Cabeza, 2000; Rugg, Flethcer, Chua, & Dolan, 1999), and that the PFC may share, with the hippocampus, responsibilities for binding episodic material (Mitchell, Johnson, Raye, & D'Esposito, 2000).

The frontal cortex is also involved in the modulation of emotion and inhibitory responses (e.g. Arnsten, 2001; Rosenkranz & Grace, 2002). Moreover, damage to this area, particularly if it is confined to the prefrontal region, leads to perseveration, difficulty choosing correct responses, and distortions and confabulations of memory. For example, patients with frontal lobe damage tend to make an abnormally large number of confident false recognition errors, in spite of good recall and recognition generally (Curran, Schacter, Norman, & Galluccio, 1997; Delbecq-Derouesne, Beauvois, &

Shallice, 1990; Melo, Winocur, & Moscovitch, 1999; Parkin, Bindschaedler, Harsent, & Metzler, 1996). Given the existence of glucocorticoid receptors in the frontal lobes (reviewed below), it is likely that stress-related increases in false memories, such as those seen in Experiments 1 and 2 and in Payne et al (2002) are not caused solely by disrupted hippocampal processing.

An important review by Lupien and Lepage (2001) underscores the contribution of frontal regions to stress-related effects on episodic and emotional memory. These authors argue that the hippocampus has been studied at the expense of other brain regions likely involved in glucocorticoid action, and that any attempt to explain stress impairments on memory solely on the basis of the impact of stress on the hippocampus may be incomplete.

Lupien and Lepage note that both Type I (mineralocorticoid, MR) and Type II (glucocorticoid, GR) stress receptors are present in cortical regions, with a preferential and dense distribution in the prefrontal cortex (PFC). Hence, stress may exert effects not only on hippocampal neurons, but also on neurons critical for the normal functioning of the PFC. If one takes the influence of stress and corticosteroids on human memory to reflect the action of GRs, then one must acknowledge that both hippocampal and PFC function are likely involved.

Differential MR and GR action in the hippocampus and PFC may underlie some of the differences in the magnitude and nature of memory impairments reviewed in this dissertation. The hippocampus, mainly via MR, but also moderate GR, receptor binding, may be a primary site of short-term, reversible effects that occur in response to stress (e.g., de Quervain, 2000; Newcomer, 1994, 1999; Payne et al., 2002; Wolkowitz, 1990, 1993). MRs must be totally saturated before GRs become activated, and significant reductions in long-term potentiation, for example, do not take place until both MRs and GR receptors are occupied. Thus, it may be the case that experiments using humans (for obvious ethical reasons) rarely if ever attain the levels of stress needed for lasting memory changes to occur.

On the other hand, exposure to trauma may lead to the widespread and sustained saturation of *both* MR and GR receptors in PFC and hippocampus. These conditions cannot be ethically reproduced in the laboratory and thus may only emerge in the context of naturally occurring chronic stress seen in the patient populations described earlier (e.g. Cushing's syndrome, PTSD, major recurrent depression, etc.). In such cases, extensive binding of cortisol to both receptor types in the hippocampus *and* PFC may lead to long-lasting and harmful changes in neuronal functioning in the entire memory circuit, resulting in dramatic changes in the way environmental information is encoded, stored, and retrieved. Evidence that excessively high levels of norepinephrine (e.g. as seen during exposure to uncontrollable stress) impair cognitive functions of the PFC as well (Arnsten, 1998) makes this concept all the more feasible. Consequently, exposure to intense stress appears to impact the prefrontal cortex as well as the hippocampus and amygdala, and this important fact should be kept in mind when considering the influence of stress in Experiments 1 and 2, and in the various papers reviewed in the dissertation.

CONCLUSION

To the best of our knowledge, the present experiments are the first to examine the effects of pre-learning stress on complex episodic memory tasks that require the recall and recognition of a series of events. This was an important advance, because, as mentioned, most stress and memory studies to date have examined stress' impact on simple word list or paragraph recall tasks, and often only recognition memory was tested. We have demonstrated that stress can have a disruptive impact on memory for neutral information or experiences, while simultaneously having an enhancing impact on memory for emotional information or experiences. Both studies also have important theoretical significance, demonstrating that stress has a complex and uneven impact on memory. Stress neither impairs memory across the board, nor invariably leads to indelible memories that cannot be forgotten.

ENDNOTES

i. Human data demonstrate quite convincingly that glucocorticoids affect hippocampally mediated learning but have scant effects on non-hippocampally mediated cognitive tasks, such as implicit memory or vigilance (e.g. Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Lupien et al., 1997; Newcomer et al., 1999; Wolkowitz et al., 1990).

ii. Recent evidence cautions us that differences exist in the concentrations of glucocorticoid receptors in the hippocampi of different species. For example, using in situ hybridization, Sanchez, young, Plotsky, and Insel (2000) recently found very low concentrationsn of GC mRNA in the hippocampus of the rhesus monkey, but Patel and colleagues (2000) found high concentrations of GC mRNA in the squirrel monkey hippocampus. The density of GCs in the human hippocampus is currently unknown (for review, see Lupien & Lepage, 2001).

iii. It should be emphasized that because we administered the TSST prior to learning, its impact upon memory in these experiments cannot be attributed to a specific phase. That is, stress may have influenced encoding, storage or retrieval process in the immediate memory condition of Experiment 1, and either encoding or storage in Experiment 2 or the LTM condition of Experiment 1. Retrieval was most likely not influenced by the stressor in Experiment 2 or the LTM condition of Experiment 1 because subjects returned 2 weeks after the TSST manipulation, and cortisol levels are typically elevated for no more than several hours in humans (McGaugh, 2000), whereas in Experiment 1, encoding, storage, and retrieval phases all took place within the 2-hour experiment.

APPENDIX A

Table 1

Mean (standard deviation) subjective stress ratings at the 4 different time points during the experiment.

	1st stress assessment, before manipulation.	2nd stress assessment, after manipulation.	3rd stress assessment, “how did you feel during?”	4th stress assessment, prior to leaving lab.
Control Group	35 (8.7)	26 (6.5)	27 (5.2)	34 (9.8)
Stress Group	37 (8.3)	59 (13.1)	51 (13.3)	36 (9.9)
p-value	NS	< .0001	< .0001	NS

Table 2

Mean (standard deviation) Recognition Memory Scores for Neutral and Emotional Memory, Broken Down by Stress, Sex, and Delay Conditions

Neutral Memory

Stress				Control			
Males		Females		Males		Females	
No Delay	Delay	No Delay	Delay	No Delay	Delay	No Delay	Delay
.49(.08)	.42(.06)	.55(.07)	.43(.07)	.60(.08)	.45(.07)	.60(.06)	.47(.07)

Emotional Memory

Stress				Control			
Males		Females		Males		Females	
No Delay	Delay	No Delay	Delay	No Delay	Delay	No Delay	Delay
.64(.09)	.52(.1)	.68(.06)	.52(.1)	.68(.06)	.54(.1)	.68(.08)	.52(.09)

Table 3

Mean (std. error) Recall Memory Scores for Neutral and Emotional Memory, Broken Down by Stress, Sex, and Delay Conditions

Neutral Memory

Stress				Control			
Males		Females		Males		Females	
No Delay	Delay	No Delay	Delay	No Delay	Delay	No Delay	Delay
.67(.06)	.52(.07)	.78(.05)	.54(.06)	.77(.06)	.68(.07)	.88(.07)	.61(.06)

Emotional Memory

Stress				Control			
Males		Females		Males		Females	
No Delay	Delay	No Delay	Delay	No Delay	Delay	No Delay	Delay
.88(.06)	.61(.06)	.88(.05)	.85(.06)	.92(.06)	.80(.07)	.93(.07)	.58(.06)

Figure 1

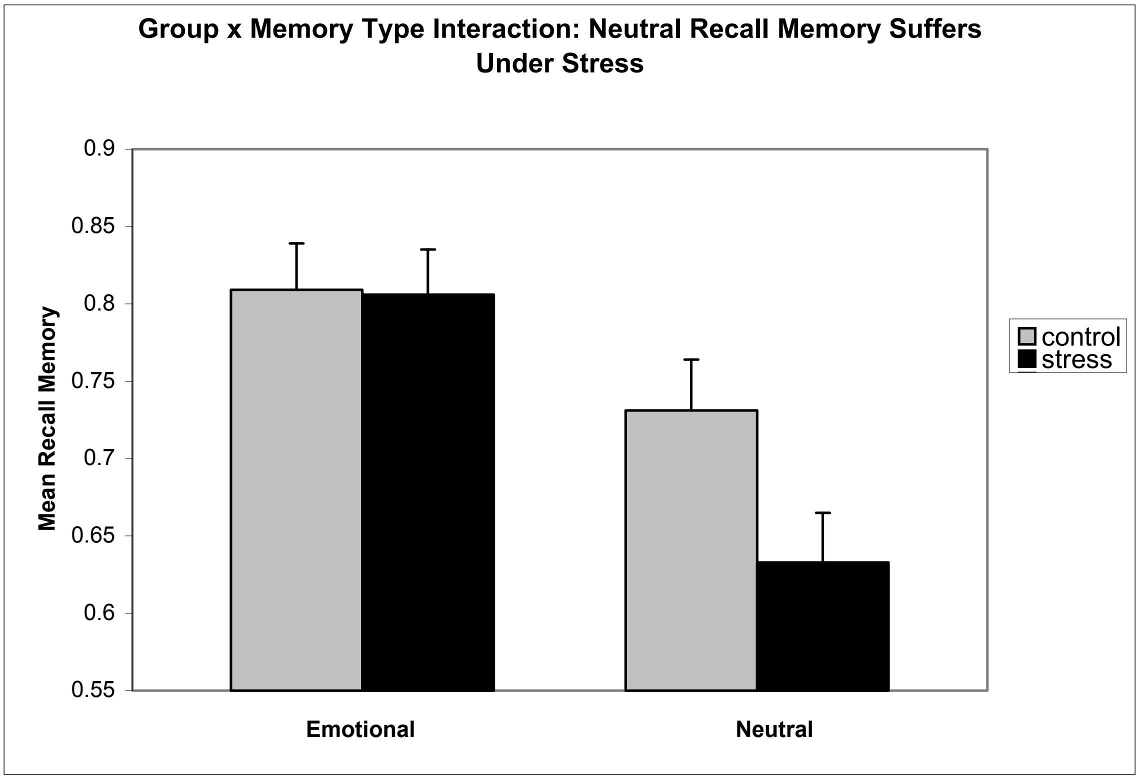

Group x Memory Type Interaction: Neutral Recall Memory Suffers Under Stress
Mean Recall Memory
0.9
0.85
0.8
0.75
0.7
0.65
0.6
0.55
Emotional
Neutral
control
stress

Figure 2

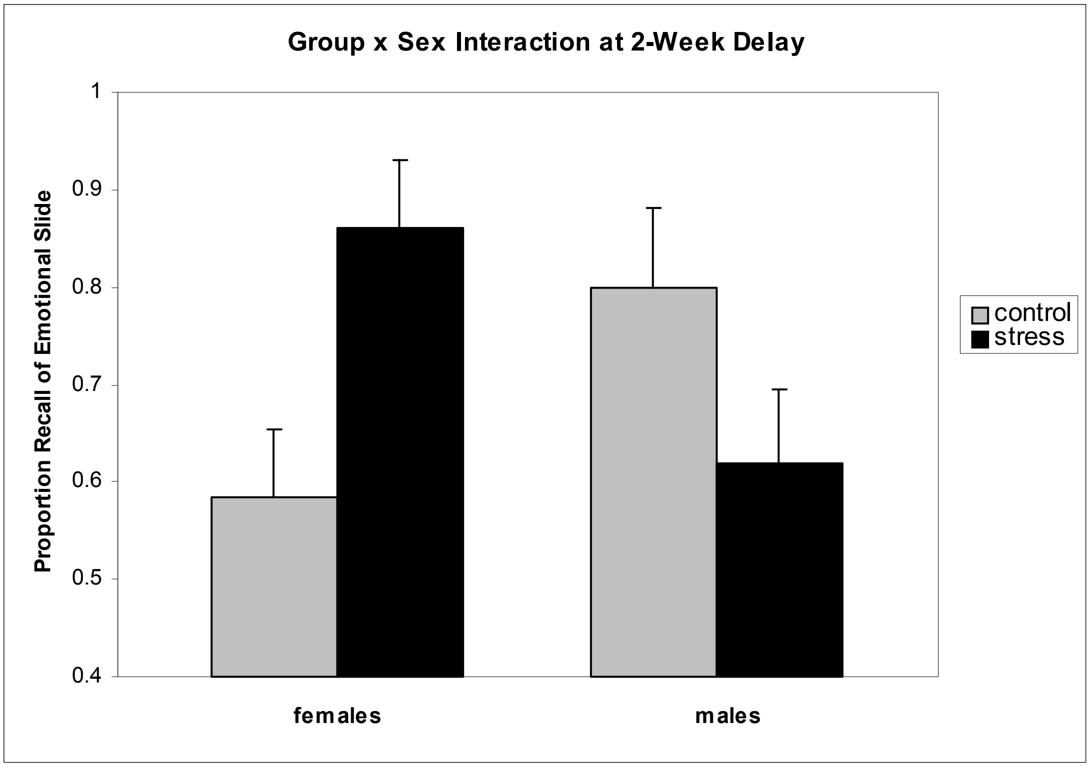

Group x Sex Interaction at 2-Week Delay
Proportion Recall of Emotional Slide
1
0.9
0.8
0.7
0.6
0.5
0.4
females
males
control
stress

Figure 3

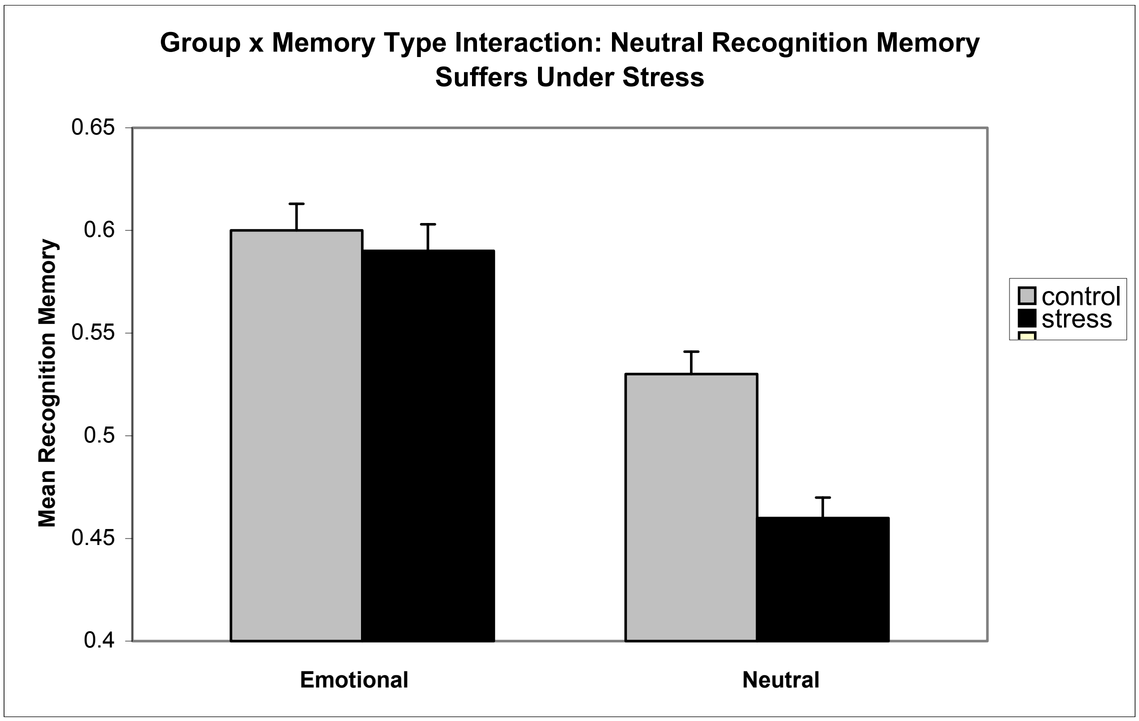

Group x Memory Type Interaction: Neutral Recognition Memory Suffers Under Stress
Mean Recognition Memory
0.65
0.6
0.55
0.5
0.45
0.4
Emotional
Neutral
control
stress

Figure 4

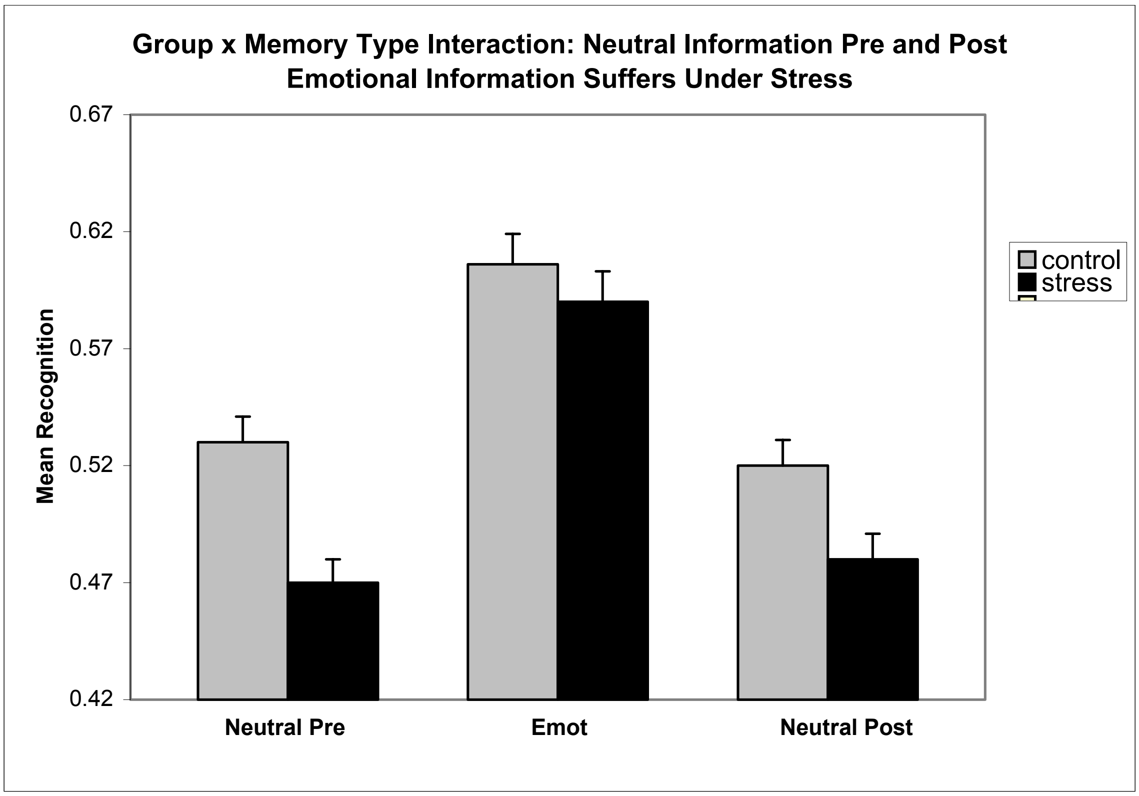

Group x Memory Type Interaction: Neutral Information Pre and Post
Emotional Information Suffers Under Stress
Mean Recognition
0.67
0.62
0.57
0.52
0.47
0.42
Neutral Pre
Emot
Neutral Post
control
stress

Figure 5

Emotional Memory Enhancement Effect: Immediately and After a Delay

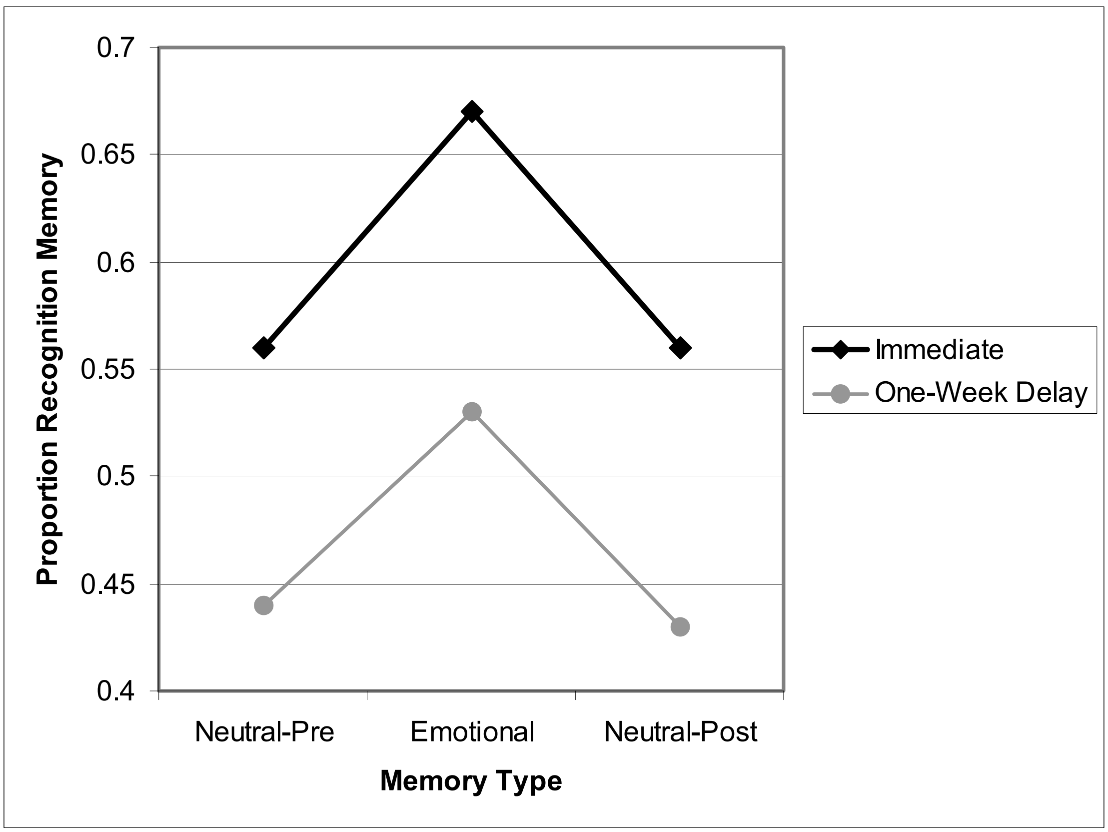


Figure 6

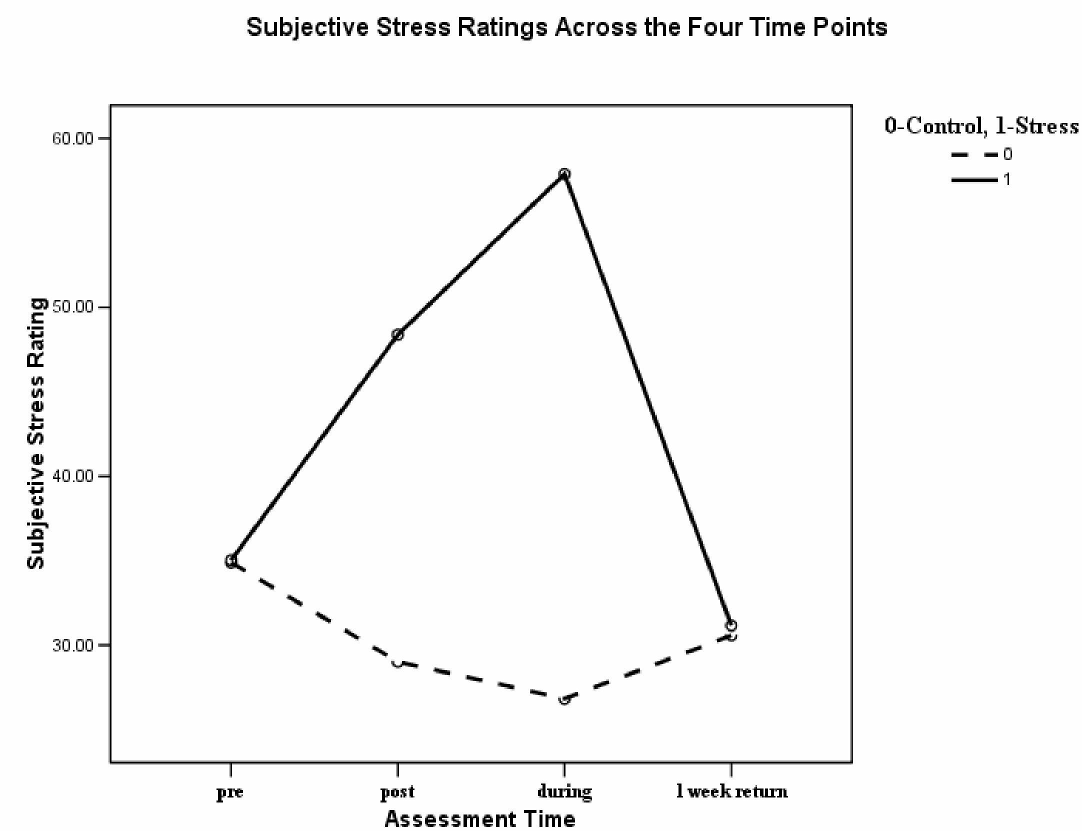
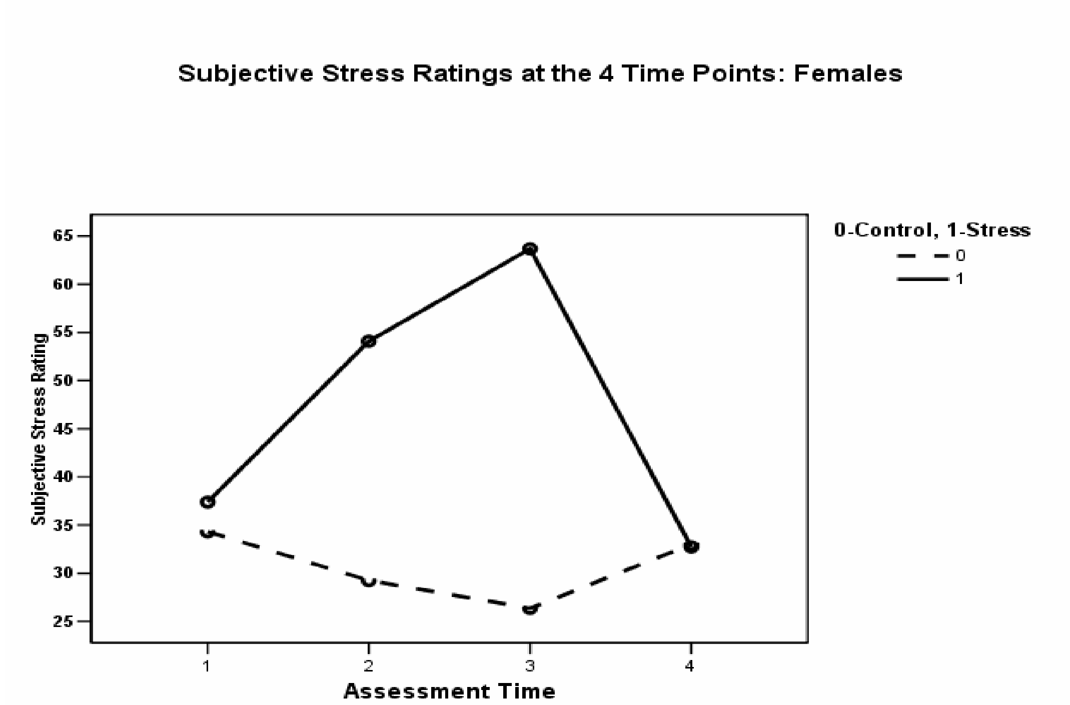

Subjective Stress Ratings Across the Four Time Points
0-Control, 1-Stress
0
1
60.00
50.00
40.00
30.00
Subjective Stress Rating
pre
post
during
1 week return
Assessment Time

Figure 7


Subjective Stress Ratings at the 4 Time Points: Females
0-Control, 1-Stress
0
1
Subjective Stress Rating
65
60
55
50
45
40
35
30
25
1
2
3
4
Assessment Time

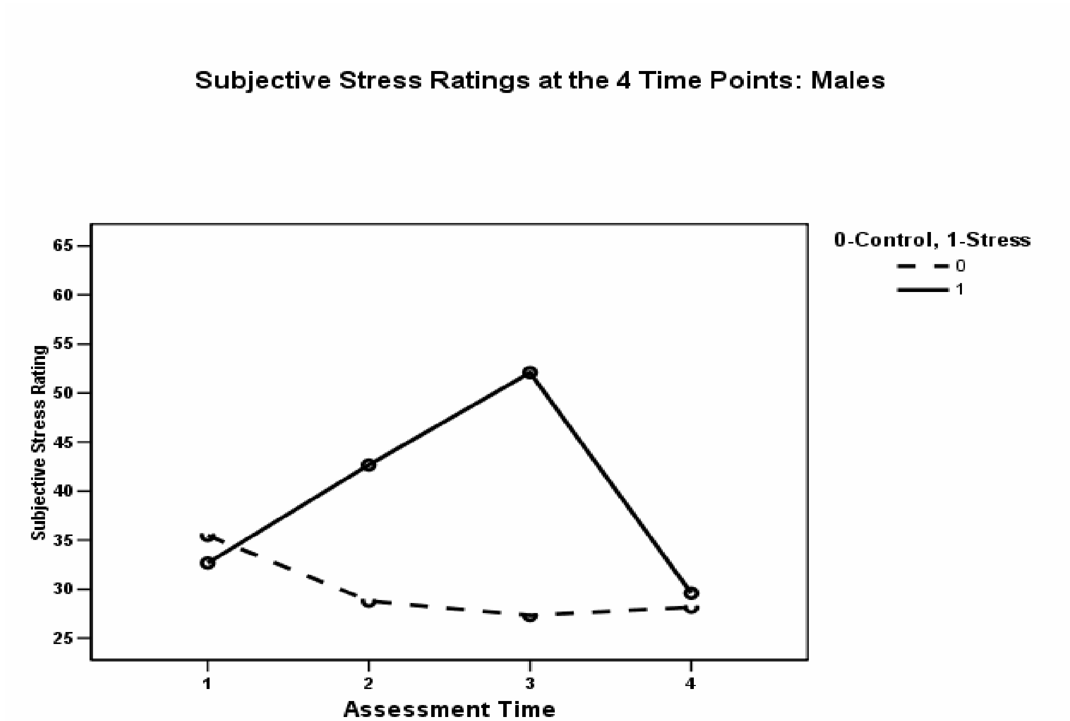

Subjective Stress Ratings at the 4 Time Points: Males
0-Control, 1-Stress
0
1
Subjective Stress Rating
65
60
55
50
45
40
35
30
25
1
2
3
4
Assessment Time

Figure 8

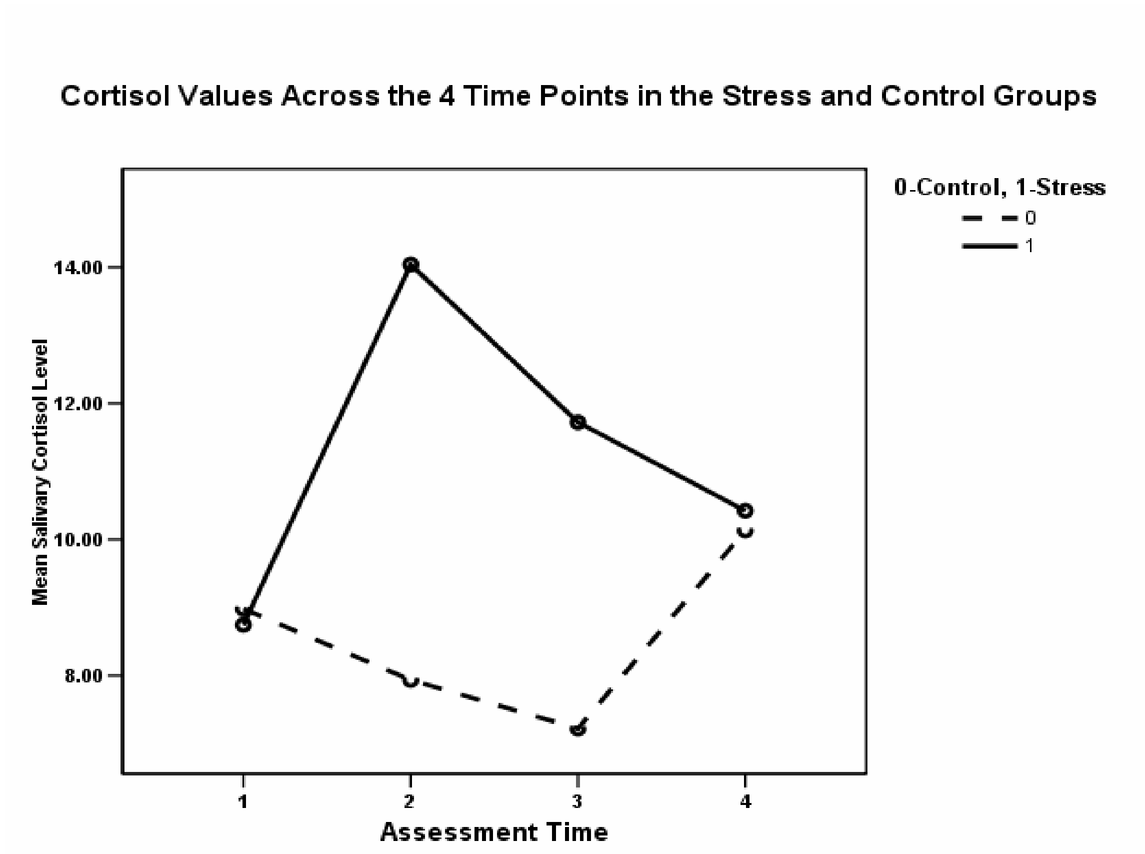
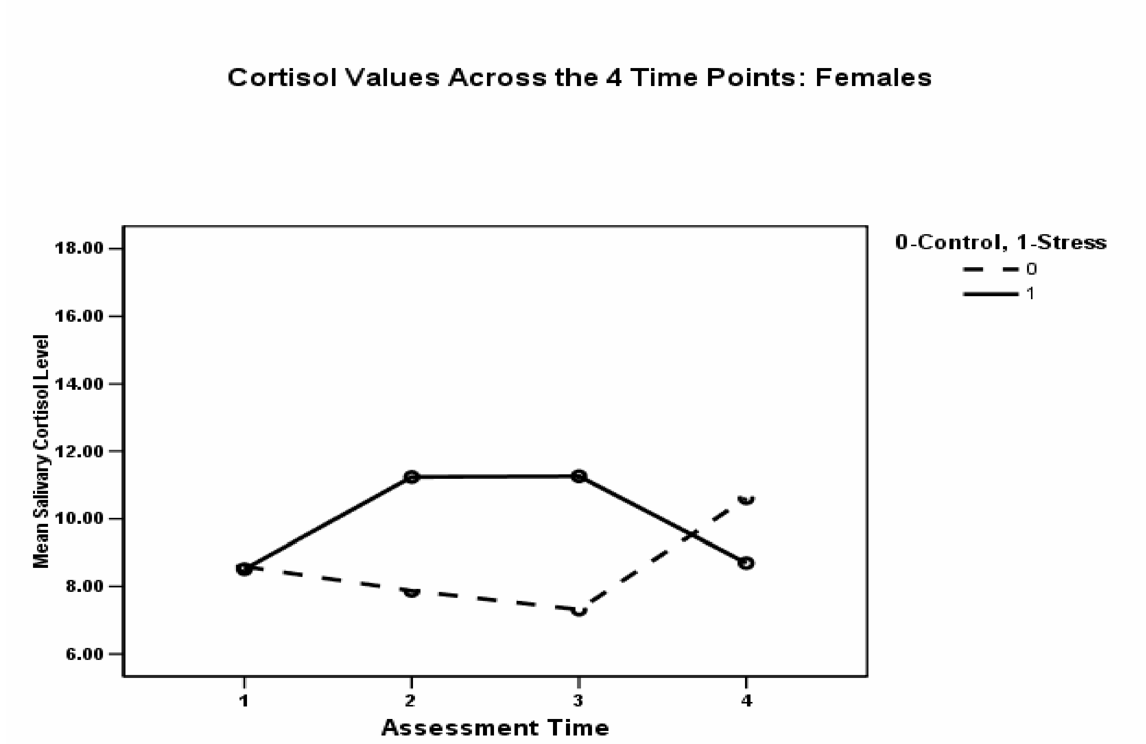

Cortisol Values Across the 4 Time Points in the Stress and Control Groups
0-Control, 1-Stress
0
1
14.00
12.00
10.00
8.00
Mean Salivary Cortisol Level
1
2
3
4
Assessment Time

Figure 9


Cortisol Values Across the 4 Time Points: Females
0-Control, 1-Stress
0
1
Mean Salivary Cortisol Level
18.00
16.00
14.00
12.00
10.00
8.00
6.00
1
2
3
4
Assessment Time

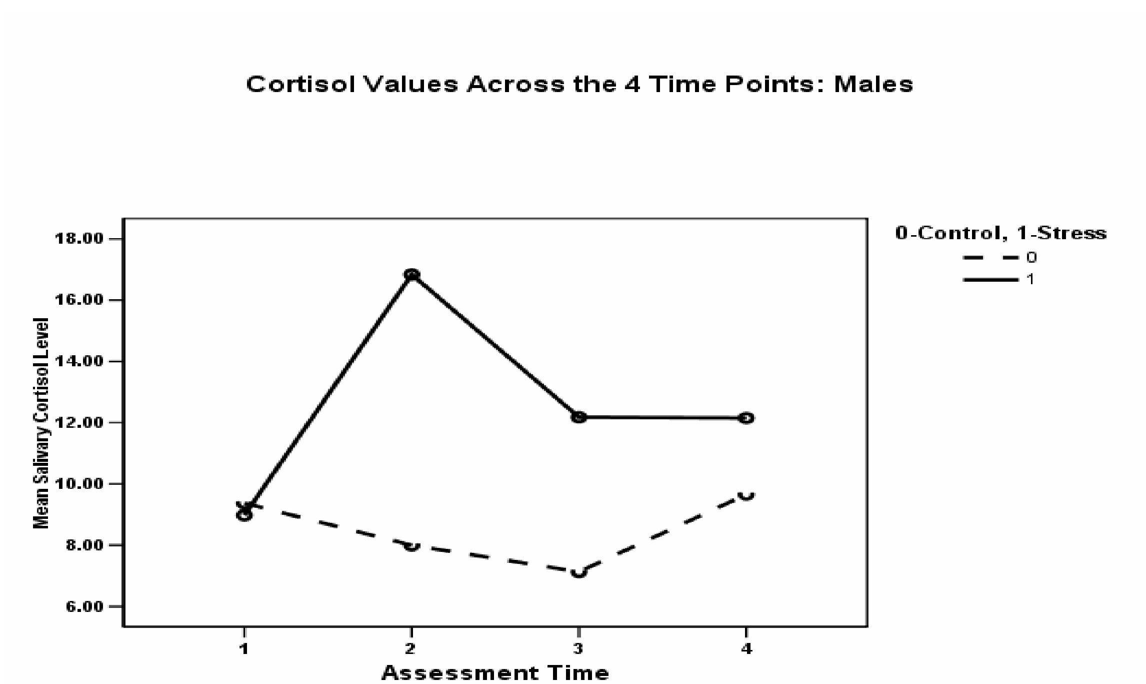

Cortisol Values Across the 4 Time Points: Males
0-Control, 1-Stress
0
1
Mean Salivary Cortisol Level
18.00
16.00
14.00
12.00
10.00
8.00
6.00
1
2
3
4
Assessment Time

Figure 10

Group x Memory Type Interaction: Stress Enhances Memory for the Emotional Story but Disrupts Memory for the Neutral Story (Free Recall)

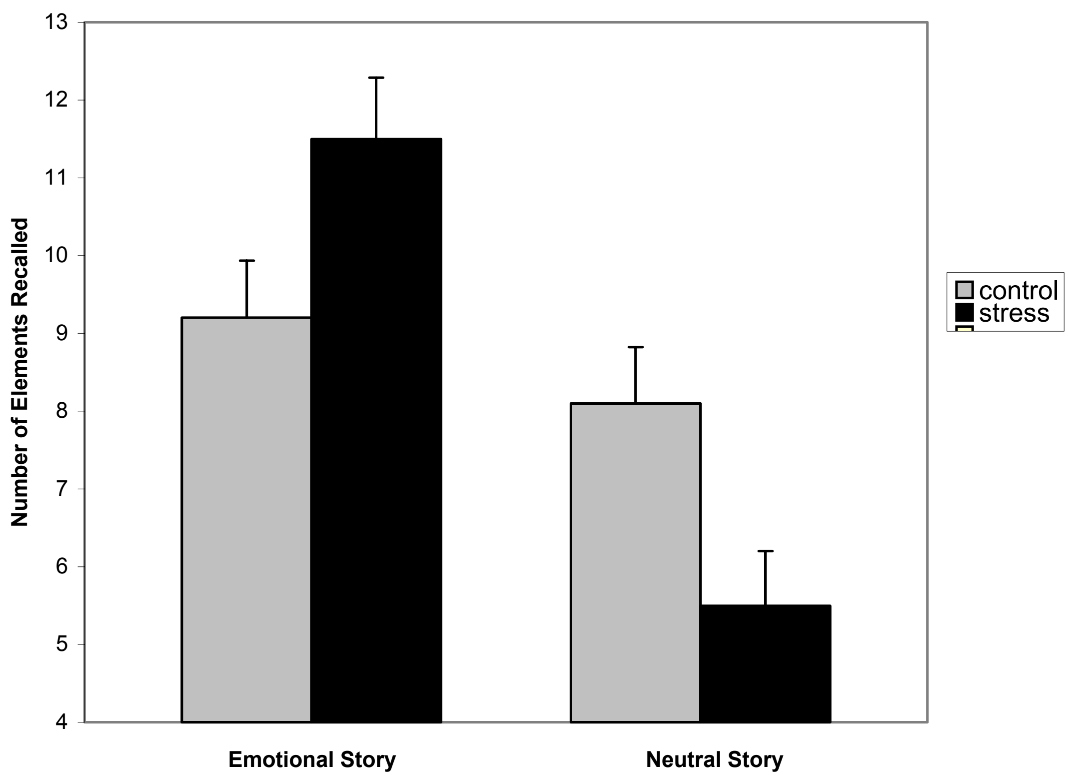


Figure 11

Stress Increases Falsely Recalled Slides from the Neutral Story

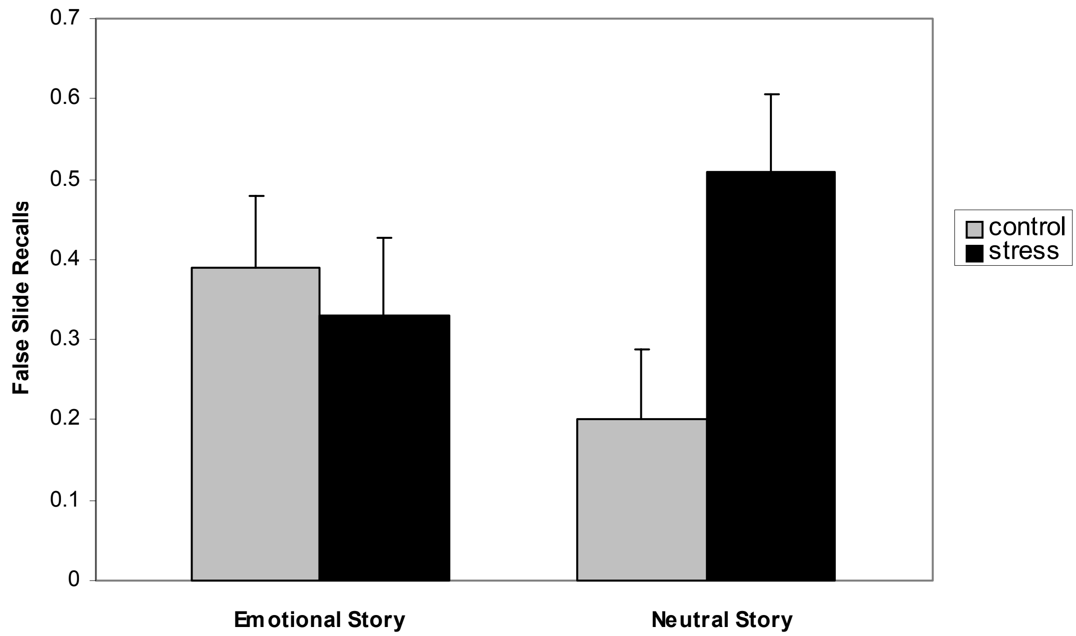
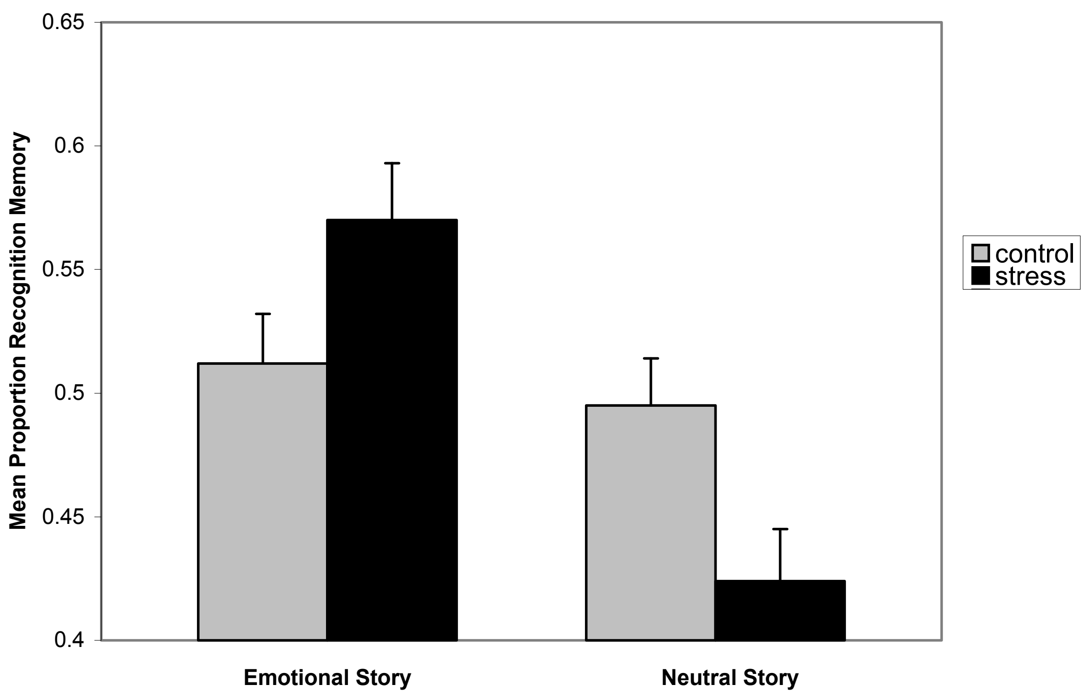


Figure 12

Group x Memory Type Interaction: Stress Enhances Memory for the Emotional Story but Disrupts Memory for the Neutral Story (Recognition Memory)



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