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THE EFFECTS OF STRESS

ON DIFFERENT STAGES OF MEMORY

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THE EFFECTS OF STRESS

ON DIFFERENT STAGES OF MEMORY

by

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DEDICATION

This dissertation is dedicated to my dad Morton Orvan Beckner, whom sadly passed away during the course of this study. His curious spirit, passion for science, and lifelong philosophical explorations of the mind-body problem continue to be the underlying inspiration for my research and clinical work in psychology.

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THE EFFECTS OF STRESS

ON DIFFERENT STAGES OF MEMORY FORMATION

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Research suggests that memory is influenced by stress and the associated rise of glucocorticoids, such as cortisol. While human studies have generally found a negative effect of stress and elevated cortisol on memory, animal studies have demonstrated a dose-dependent facilitative effect. These discrepant findings may be a result of methodological limitations in the human literature, which often confound the different stages of memory by elevating cortisol levels prior to encoding, consolidation *and* retrieval. The purpose of the current study was to parse the effects of an acute psychosocial stressor on these separate memory processes by varying the timing of the stressor. Based on recent evidence, we predicted that stress would enhance encoding and consolidation, but impair retrieval. 208 college students (63 male, 138 female, mean age = 18.9) were randomly assigned to a no-stress control group (n = 51) or one of three groups stressed at different time points: prior to stimulus presentation (encoding/ consolidation, n = 51), immediately after stimuli presentation (consolidation, n = 56), or just before memory testing 48 hours later (retrieval, n = 50). Salivary cortisol was measured at baseline and 20 minutes after the stressor. Both verbal and visual memory was measured at the 48-hr delay using a film stimulus developed by the investigator and

with the WMS-III narrative. Results demonstrated that the group stressed prior to consolidation significantly outperformed controls on the film recognition at delay for verbal and total scores. This effect may have been related to cortisol response, as this was the only stress group to exhibit a significant increase in cortisol (40%) following the stressor. No significant differences in memory were found between the other stress conditions and controls. Within-group correlations between change in cortisol and memory were not significant, but exploratory analyses revealed a small but significant positive correlation for cortisol and verbal scores on the film recognition test across all groups (r_{xy} = .18). Results support the hypothesis that stress enhances consolidation of new information, and provides the first evidence of this for verbal memory. Findings did not support a detrimental effect of stress on retrieval.

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CHAPTER 1: INTRODUCTION

Stress is a fundamental and ubiquitous part of human experience. Whether we are preparing to give a presentation, chasing down our evening meal, or fleeing the scene of a botched date proposal, our bodies are physiologically designed to respond to stressful situations. Although research has elucidated much of the physiological stress response including the release of stress hormones (catecholamines and glucocorticoid steriods), less is known about the cognitive sequelae of stress. Evidence from animal and human research suggests that memory is affected by stress hormones. From an evolutionary perspective, it certainly seems adaptive for organisms to better remember emotionally significant events--attaining essential goals and avoiding threats. Alternatively, one might argue the adaptive benefits of forgetting extremely stressful events (making it more likely, for example, that women continue to have children after experiencing painful childbirth). The data provides support for both theories, thus raising a number of important questions. Which memory processes are affected by stress (i.e., encoding, consolidation, or retrieval), and might these processes be differentially affected by stress? Are the effects related to the intensity of the stressor? To what extent do stress hormones mediate these effects? These questions are important not only to our scientific understanding of the nature of stress and memory, but also shed light on a number of important societal issues. These include (but are not limited to) the reliability of traumatic memories and eyewitness testimony, the intrusive memories associated with post-traumatic stress disorder, and the everyday effects of mild-moderate stress on academic and job performance.

The present proposal is intended to examine the effects of a moderate psychosocial stressor on different stages of memory in humans. Specifically, the study is intended to clarify what memory processes are affected by stress, and whether cortisol (the most important human glucocorticoid steroid) is related to these effects. It is first important, however, to take a closer look at how stress is defined, and how it is distinguished from associated emotions both theoretically and for the purposes of this

proposed study. The physiological stress response will then be examined, including the process by which cortisol acts on the brain--the presumed mechanism by which stress affects cognition. The dominant explanation for the effects of stress on memory presumes that cortisol acts on the hippocampus to affect consolidation. In the human literature, this stress effect appears to be adverse, suggesting that *cortisol disrupts consolidation*. This explanatory model will be challenged first by an examination of the brain regions associated with the processes of encoding, consolidation, and retrieval, which together suggest a more complex dynamic between many structures at each stage of memory formation and recall. A review of the animal literature also reveals a *facilitative* effect of stress on encoding and consolidation, although the timing of the stress or administered corticosteroid in most of these studies makes it difficult to conclude which stage of memory is being affected. Finally, a review of the human literature demonstrates a generally detrimental effect of stress on memory, but again, these studies stress participants throughout the learning and recall process. Several recent studies that have separated the stress manipulation from retention testing by several days (but continue to confound encoding and consolidation, and did not manipulate stress during retrieval) present mixed findings. The proposed study addresses this methodological limitation in the literature, and tests the hypothesis that consolidation is facilitated by stress, while *retrieval* is the memory process disrupted by stress.

1. What is Stress?

Although the research literature on stress is vast, the concept itself can be slippery. Theorists differ in their definition of stress, and operational definitions can vary widely (sometimes leading to apparently inconsistent results). One problematic conceptual issue is the relationship between stress and emotion. Each has its independent body of literature and studies, even though the two processes have much in common. It is therefore important to take a brief look at the history of stress research to clarify the construct, and to consider its overlap with emotion. Fortunately, this analysis suggests a way to empirically separate the two phenomena physiologically (a detailed account of the physiological systems underlying stress is left for the subsequent section). This section concludes with a theoretical and operational definition of stress for the present study.

History of the Stress Concept

Historically, psychologists have distinguished the stress *stimulus,* or external stressor, from the individual's resulting *stress response*. Following World Wars I and II, research with veterans conceptualized the emotional (and physiological) reaction many veterans experienced as the direct result of exposure to traumatic stimuli associated with war (Lazarus, 1999). In the 1960's and 1970's, focus turned to the idea that many events associated with work, school, and relationships can be stressful (not just traumatic events) (Lazarus, 1999). The Social Readjustment Rating Scale (Holmes & Rahe, 1967), for example, is a ranking of common life challenges (requiring "readjustment") as rated by individuals from various countries. The top two are death of a spouse and divorce, respectively, although it's noteworthy that some on the list are also positive events (marriage, vacation). Certainly the common view of stress includes the idea that some events are inherently more stressful than others.

Researchers were also interested in the physiological processes associated with the stress *response*. As early as the 19th Century, Claude Bernard theorized that the body

is designed to seek and maintain a kind of physiological balance (ideal levels of oxygen, temperature, etc.), which Walter Cannon later called "homeostasis.” When a stimulus or event (such as disease, extreme cold, hunger, the presence of a predator) moves an organism out of balance, it is the stress response that returns the organism to homeostasis (the modern term is "allostasis") (Cannon, 1929). He called this emergency physiological response, which he observed as involving increased respiration, cardiac output, and blood flow to the muscles, the “fight or flight” response (Cannon, 1929). In the 1930's, Hans Selye exposed laboratory animals to a variety of physical (cold, shock, forced exercise, surgical procedures) and psychological (restraint, social competition) stimuli, and noted the same nonspecific response, which he described as the general adaptation syndrome (Selye, 1936, 1950). By varying the length of the stressor in dozens of experiments, Selye noted a change in the stress response over time (Selye, 1950). First the organism notes the stressor in the alarm stage; the full stress response is then mobilized and moves toward restoring allostatic balance in the resistance or adaptation stage. If the stressor is prolonged and uses up available resources, the organism moves into the exhaustion phase where disease processes begin to emerge (Sapolsky, 1998).

Although recent studies suggest some specificity of response to different stressors (Stern & Sison, 1990), research supports Selye’s idea that the stress response always involves physiological changes intended to ready the organism for action. Those changes include increased arousal from rapid activation of the sympathetic adrenal medulla system (SAMS), and activation of the hypothalamic pituitary adrenal axis (HPA), which initiates the slower release of glucocorticosteriods from the adrenal cortex (Sapolsky, 1998; Nelson, 2000).

It wasn't until the 1950's that Richard Lazarus first proposed a theory of stress that placed cognitive mediation at the center of the concept, and eliminated the stimulus-response dichotomy. In his landmark book with Folkman, Lazarus argued that the severity of the stressor depends upon the *cognitive appraisal* of the threat stimulus and one's ability to cope with it (Lazarus & Folkman, 1984). Thus two people faced with an incoming storm while hiking will appraise the threat differently, depending on their

attention to the darkening clouds, knowledge about the nature of storms in the area, and beliefs about how dangerous storms can be. These "primary appraisals" involve an assessment of the threat or challenge itself—its immediacy, severity, etc (Lazarus, 1966). The hikers also assess their ability to cope psychologically and physically with the storm, which Lazarus termed "secondary appraisals" (Lazarus, 1966). Thus each person's physical strength, dispositional optimism, skills at seeking shelter—all of which provide a sense of control and coping efficacy (Bandura, 1988)—also affect the severity of the stress response. Indeed, studies show that low perceived control over a threat increases distress and anxiety in humans (Telch, Silverman, & Schmidt, 1996; Sanderson, Rapee, & Barlow, 1989; Mineka, 1985), while rats with no control over the administration of shocks will show a stronger stress response (and more ulcers) than rats that have some control (Laudenslager & Reite, 1984).

It is important to emphasize that Lazarus did not consider "appraisal" a process that required conscious reflection: any animal must continually appraise a situation and its ability to respond in order to determine how best to meet its goals—whether this is obtaining food or avoiding a predator (Lazarus, 1999). Recent work on the neurobiology of stress and emotion suggests that parallel conscious and unconscious processing of stress-related stimuli occurs in the brain (LeDoux & Armony, 1999). Sensory information reaching the thalamus follows dual pathways: a subcortical route to the amygdala facilitating an instant response, and a slower cortical route to sensory cortices and executive centers. Thus appraisals occur at different levels of analysis in the brain, allowing the organism to react and modify its response accordingly.

Stress & Emotion

The above account of stress is not unlike the conceptualization of emotion. Most agree that emotion involves cognitive appraisals, physiological changes, and species-typical behavioral expressions (Myers, 2002). Certainly it is common to experience certain emotion-states when stressed—not only anxiety, but also anger, frustration, even excitement. Many researchers in fact use the terms "stress" and "anxiety"

interchangeably. This can be problematic for research, however. When a stress induction results in an observed effect, how can one rule out co-occurring emotions as possible confounds?

Consider the following problem: the cognitive appraisals that characterize stress and emotion overlap and thus commonly lead to their co-occurrence. Evidence suggests that different cognitive appraisals give rise to different emotions: if one appraises a situation as threatening, one will experience fear; if one appraises a situation as unjust or demeaning, one might experience the emotion anger. In contrast, many different appraisals can initiate the stress alarm (cold, pain, approaching lion or advisor). The stress response only indicates that the organism is being forced to adapt to some situation—that some type of "challenge" has been perceived. This is perhaps why stress is considered a broader concept than anxiety in the clinical psychology literature: anxiety is a response to a threat, while stress can be a response not only to a threat but also to positive challenges or novelty (Cannon, 1929; Seyle, 1936). What this means, however, is that the perception of a threatening event will evoke both stress and anxiety, the appraisal of a situation as unjust will evoke both stress and anger, and so on. Indeed, Lazarus argues that stress is always *accompanied* by certain emotions, which he calls "stress emotions":

> It should be obvious that certain emotions—for example, anger, envy, jealousy, anxiety, fright, guilt, shame, and sadness—could be called stress emotions, because they usually arise from stressful, which refers to harmful, threatening, or challenging conditions (Lazarus, 1999, p. 36).

Fortunately, stress and emotion can be distinguished physiologically. The physiological correlate common to the different emotions is sympathetic arousal (Myers, 2002), although evidence suggests that there is some physiological specificity for individual emotions (Siegel & Mirsky, 1990; Le Doux, 1986). Thus both stress and emotion involve activation of the sympathetic nervous system. However, the stress response also involves activation of the HPA axis and the release of glucocorticoid hormones that ready the organism for prolonged activity. It is important to note here that this "slow" system takes time to exert its effect and is not easy to "turn off" in the way

that one can reappraise a threatening situation as benign and instantly reduce sympathetic arousal. Thus it can take as long as 30 minutes after cessation of the stressor for cortisol levels to peak, and hours for levels to return to baseline (Kirschbaum & Hellhammer, 2000). This suggests two ways of separating stress from emotion methodologically. The first is by inducing stress with a threat (which will evoke both the stress response and anxiety), and then remove the threat (thus reducing anxiety but not the stress response) prior to cognitive testing. The other approach is the direct administration of a stress hormone, which bypasses the threat evaluation and concurrent anxiety (and sympathetic arousal).

A Theoretical Definition of Stress for the Proposed Study

Drawing from the above conceptual overview of stress and emotion, the following conceptual outline of stress is proposed. Stress is defined as response to environmental (or internal) events that the organism appraises as "challenging." This challenge might be a threat to existing resources (such as food, status, a mate, or information), an opportunity to obtain the missing resources with effort, or simply any event (extreme cold, pain) that requires a response that may exceed the resources of the organism. The response involves sympathetic arousal for quick action (consistent with emotion), but also the release of slower-acting glucocorticoid hormones for sustained action. Although it does not involve a specific affect, stress is often associated with certain emotions, depending upon the specific appraisals of the stressor. Thus a *threat appraisal* triggers both the stress response and anxiety. Once the threat is removed, anxiety (and autonomic arousal) diminishes, but the glucocorticoid stress response will already be in full swing. The present study will thus use a social threat (anticipation of giving a speech to an audience) in order to initiate the stress response (with associated anxiety), but will distinguish the effects of stress from anxiety by removing the threat prior to cognitive testing.

Operationalizing Stress: Stress Induction versus Glucocorticoid Administration

By far, most studies examining the effects of stress on cognition manipulate glucocorticoid levels directly through the administration of cortisol (in humans) or corticosterone (animals), or glucocorticoid agonists and antagonists. The advantage and limitation of administering a specific stress hormone is that it only reveals the effects of that particular hormone. This has been helpful in confirming the potent effects of glucocortioids in the stress response. It is likely, however, that other hormones and physiological effects are also influencing observed stress effects. Thus in the present study, a psychosocial stress manipulation will be used to generate the full stress response, and cortisol will be considered one measure of stress and a potential predictor of cognitive effects. It is quite possible, however, that stress exerts its effects on memory through mechanisms other than cortisol release. These might include other hormones (CRF, ACTH, epinephrine, norepinephrine) or subjective psychological states such as anxiety.

2. The Physiology of Stress

Although stressors vary widely, the physiological response is relatively nonspecific. Whether the stressor involves an approaching lion or an unhappy research advisor, the physiological response is designed to cause a number of important changes that will help the organism respond. Initiated by the brain and largely mediated by stress hormones, these changes include an increase in oxygen intake, redirecting blood flow to favor the muscles, an increase in blood sugar levels to provide the organism energy, and a behavioral urgency to act (flee, practice, argue, fight). Because all of these activities involve expending energy, there must be conservation elsewhere in the body. Thus digestion, tissue repair and growth, reproductive activities, and immune function are all inhibited by the stress response (Sapolsky, 1998). The stress response also acts on the brain to presumably affect certain cognitive operations and predispose certain types of behavior. Thus to understand the effects of stress on cognition, it is critical to understand the physiological stress response. Although a number of hormones are released during stress, there are two primary systems that provide a "fast" and "slow" response: the sympathetic (catecholamine) and the glucocorticoid response respectively.

SAMS

The first system to kick into action in response to a stressor is the Sympathetic Adrenomedullary System, or SAMS (Nelson, 2000). The sympathetic response is the "fast" system, in which the hypothalamus directly stimulates internal organs via the sympathetic nervous system to initiate physiological arousal, or the "fight or flight" response. This is accomplished via a two-neuron pathway: a hypothalamic neuron synapses on a post-ganglionic neuron in the peripheral nervous system (the "sympathetic chain"); the post-ganglionic neuron innervates target organs, releasing norepinephrine (which binds to adrenergic receptors on the organ) (Sherwood, 1997). Sympathetic activation has a widespread effect on the body and is intended to prepare the organism for action. Physiological changes include an increase in heart rate and vasoconstriction

(thereby increasing blood pressure), dilation of respiratory pathways to maximize oxygen intake, and vasodilation of heart and skeletal muscle vessels to deliver oxygen and glucose to these muscles (Sherwood, 1997). The sympathetic response also involves inhibiting maintenance activities such as digestion and immune function while the organism confronts the stressor (Sapolsky, 1998).

An important target organ for sympathetic activation is the adrenal medulla, which releases the catecholamine hormone epinephrine (adrenalin). Because hormones are released into the bloodstream and must find their target tissues in sufficient concentration, their effect is relatively slower than direct neural stimulation, but lasts longer. Epinephrine reinforces and maintains the sympathetic response (i.e., promoting cardiovascular changes which redirect blood flow away from peripheral sites to skeletal muscles and the heart and inhibiting competing functions). Epinephrine also plays a critical metabolic role by increasing blood glucose levels in order to provide the organism energy (Nelson, 2000).

Catecholamines (both epinephrine and norepinephrine) also have an effect on the brain. In general, epinephrine increases alertness as part of the arousal response. More recent research has focused on the role of catecholamines in memory formation (Roozendaal, 2000). Because catecholamines do not readily pass across the blood-brain barrier (Weil-Malherbe, Axelrod, & Tomchick, 1959), they exert their effect on the brain indirectly. Epinephrine released peripherally activates the B-adreneric receptors on vagal nerve cells, which are part of the sensory autonomic nervous system. The vagal afferents project to the solitary nucleus in the brainstem (medulla), and cause the release of norepinephrine in the basolateral amygdala (Roozendaal, Quirarte, & McGaugh, 1997). Experimental research suggests that the basolateral amygdala plays an important role in modulating hormonal influences on memory consolidation in the hippocampus (Roozendaal & McGaugh, 1996a). The solitary nucleus and the basolateral amygdala also have glucocorticoid receptors, and are thus directly affected by adrenal steroid release during stress (Roozendaal, et al. 1997).

HPA

The second hormonal system to be activated during the stress response is the Hypothalamus-Pituary-Adrenal cortex (HPA) axis. Unlike the SAMS, which instantly initiates an autonomic response via direct neural stimulation of organs (followed and reinforced by epinephrine release), the HPA stress response relies exclusively on the relatively slower action of adrenal hormones to exert their effect (Sapolsky, 1998). HPA activity thus maintains and builds upon the sympathetic response. The hypothalamus first releases Corticotropin Releasing Factor (CRF), which in turn stimulates the pituitary to release Adrenocorticotropin Hormone, or ACTH into the bloodstream. ACTH makes its way to the adrenal glands, causing the adrenal cortex to release adrenocortical hormones, which are steroids (lipids derived from cholesterol). There are three classes of hormones produced and released from the adrenal cortex: mineralocorticoids (which help to maintain electrolyte balance), sex hormones, and glucocorticoids (the most important of these in humans is cortisol, while in rodents it is corticosterone) (Sherwood, 1997).

As the name implies, glucocorticoids such as cortisol play a critical role in raising circulating levels of glucose in the blood to provide muscles and the brain energy for the stress response. Cortisol does this by stimulating the liver to convert glycogen into glucose (which is then released into the blood), inhibiting the secretion of insulin (which takes up glucose for storage), and promoting hepatic gluconeogenesis (converting amino acids into glucose when carbohydrate sources are depleted) (Sherwood, 1997). Cortisol also promotes the break-down of protein (muscle) into amino acids for later gluconeogensis, and fat into fatty acids to provide an additional source of energy for some tissues (although the brain can only use glucose) (Sherwood, 1997).

While cortisol works to make energy available, it also contributes to the shut-down of bodily activities that compete for resources—longer-term “building projects” or maintenance activities that can be delayed until after the emergency. These include immune function, tissue repair, digestion and energy storage, and certain reproductive activities (Bullock, 2001). Consider the immune system. While cortisol’s anti-

inflammatory effects are well-known (steroids are the drug of choice for treating excessive or damaging inflammation), researchers have become increasingly interested in the effect of cortisol on immunosuppression. Cortisol inhibits the production of new lymphocytes (T-helper cells, T-suppressor cells), pulls existing lymphocytes out of circulation, and can also cause lymphocytes to commit suicide (Sapolsky, 1998). It also inhibits the activity of interleukins and interferons, dampening the immune alarm response (Sapolsky, 1998). Clearly, if such acute effects of the stress response were to continue under conditions of *chronic* stress, the result could be very damaging to the organism.

Elevated levels of cortisol eventually trigger a negative feedback inhibition process to keep hormone levels from rising out of control. High levels of cortisol thus signal the hypothalamus to stop releasing CRF, essentially down-shifting the HPA response. This maintains cortisol at the level necessary to cope with the stressor, or returns cortisol levels to their basal level once the stressor has passed (Bullock, 2001). Several disorders are characterized by abnormalities in this negative feedback system, including depression (see section on *Stress and Memory in Humans*).

Corticosteroid Receptors

Unlike the catecholamines, adrenocortical hormones pass readily through the blood-brain barrier (Roosendaal, Quirarte, & McGaugh1997). As Lupien & McEwen describe in their review (1997), evidence suggests that corticosteroids have two methods of receptor activation. The first is genomic: once the hormone binds with the receptor, the receptor separates from its attached protein and moves into the cell nucleus, initiating transcription and mRNA protein synthesis. This genomic action eventually alters neuron receptor structure and activity, thus taking hours to weeks to observe an associated behavioral change. The more rapid receptor activation involves corticosteroid interaction with the cell membrane, affecting transmitter response.

The brain has two types of corticosteroid receptors relevant to stress research: mineralocorticoid receptors and glucocorticoid receptors. These corticosteroid receptors

have different affinities for endogenous and synthetic corticosteroids and vary in their distribution in the brain. Both, however, are found extensively in the hippocampus. Recent theoretical and experimental work suggests that the way these receptors function and interact might explain the varied and sometimes inconsistent relationship between corticosteroids and cognition (Lupien & McEwen, 1997; De Kloet, Oitzl, & Joels, 1999; Roozendaal, 1999).

The mineralocorticoid receptors (MRs) are found largely in the hippocampus, with some expression in other limbic and brainstem nuclei (McEwen, de Kloet, & Rostene, 1986). MRs bind to cortisol (in humans) and corticosterone (in rodents) with high affinity, and are thus largely occupied under non-stressful conditions when corticosteroid levels are low (see McEwen, et al., 1986, for review). MR activation via low levels of corticosteroids generally results in reduced calcium currents and thus more stable responses to excitatory glutamatergic and biogenic amine inputs. This has lead some to suggest that activation of MRs play a role in maintaining homeostasis (De Kloet et al., 1999).

Glucocorticoid receptors (GRs) have one-tenth the affinity for cortisol and corticosterone (Reul & de Kloet, 1985). Thus as endogenous corticosteroid levels rise under stress and most of the MRs become occupied, GRs gradually become activated. If the stressor is moderate to severe (or a corticosteroid is administered in comparable levels), the percentage of GR occupation increases substantially. GRs are distributed widely throughout the brain, including the limbic system, brainstem, hypothalamic nuclei, and cortex, although they are most concentrated in the hippocampus (McEwen, Weiss, & Schwartz, 1968). GR activation leads to enhanced calcium currents and responsiveness to excitatory neurotransmitters. This activation is generally followed by a decrease in cellular activity, helping to restore cells to their homeostatic state (De Kloet et al., 1999). There is evidence, however, that the increase in excitatory activity associated with GR activation can lead to neuron atrophy and death in the hippocampus (see section below). Because MRs are largely occupied during rest and GRs become activated during stress, most researchers have concluded that activation of GRs, rather

than MRs, are responsible for stress-related brain and behavioral changes (see Roozendaal, 1999).

Glucocorticod Effects on Hippocampal Neurons

Because the two types of corticosteroid receptors are found in high density in the hippocampus, many researchers have studied the *in vivo* effects of corticosteroids on hippocampal neurons. These effects include changes in neuron activity, morphology, neurogenesis, and cell death. Such findings provide a likely mechanism by which stress hormones affect (at minimum) hippocampal-supported memory functions.

Corticosteroids have been found to affect hippocampal neuron activity. Following enhanced calcium influx, corticosteroids seem to faciliate a return to homeostasis by reducing cellular activity (de Kloet et al., 1998). Thus Chen and colleagues found that corticosteroids reduce neuron firing immediately following administration (Chen, Hua, Wang, Wu, Gu, & Zing, 1991), which suggests interaction at the membrane level. Others have found suppressed neuron firing in the hippocampus after a 30-minute delay (Pfaff, Silva, & Weiss, 1971), consistent with genomic action. Adrenal steroids can also affect the plasticity of hippocampal neurons. Long term potentiation (LTP) or the lower-threshold prime-burst potentiation (PBP) of a neuron occurs when afferent stimulation enhances the neuron's responsiveness to subsequent stimulation. Researchers have demonstrated a dose-dependent biphasic effect of adrenal sterioids on LTP in the dentate gyrus, CA1, and CA3 fields of the hippocampus. At low levels, there is a positive correlation between corticosterone and PBP (Diamond, Bennett, Fleshner, & Rose, 1992), while higher levels and acute stress are associated with impaired PBP and LTP (Diamond et al., 1992; Diamond, Fleshner, & Rose, 1994; Bennett, Diamond, Fleshner, & Rose, 1991). Others have shown that this biphasic excitatory response relates to receptor type: MR activation occurs at low levels of corticosteroids and leads to increased LTP, while GR activation at increasingly higher level of adrenal steroids reduces LTP (Pavlides, Kimua, Magarino, & McEwen, 1994; Pavlides, Watanabe, Magarinos, & McEwen, 1995).

Following observations that aging rats show loss of pyramidal neurons in the hippocampus which can be prevented by adrenalectomy (Landfield, 1987), researchers began investigating the role of chronic corticosteroid exposure and hippocampal neuron atrophy and loss. Three weeks of daily corticosterone injections result in atrophy of the CA3 neuron dendrites (Woolley, Gould, & McEwen, 1990), while 3 weeks of restraint stress (6 hours per day) result in similar atrophy of pyramidal cells. When cyanoketone is administered to partially inhibit the release of corticosterone during stress, the atrophy is blocked (Magarinos & McEwen, 1995). Sapolsky and colleagues found that young adult rats exposed to daily corticosterone injections for 12 weeks demonstrated pyramidal neuron loss comparable to aging rats (Sapolsky, Krey, & McEwen, 1985). It is important to note that granule neurons in the dentate gyrus of the hippocampus depend on low levels of adrenal steroids (MR activation) for their survival (Woolley, Gould, Sakai, Spencer, & McEwen, 1991). Consequently, adrenalectomy results in rapid neuron death (Gould & McEwen, 1993).

Thus stress sets in motion a number of physiological responses, including sympathetic and HPA activation and the release of stress hormones. These hormones exert their action in the brain by activating corticosteroid receptors. The distribution of these receptors in structures involved in memory, particularly the hippocampus (which has the largest concentration of receptors) is an important link in understanding the connection between glucocorticoids and cognition.

3. Memory Processes and the Brain

Research on the physiological stress response and corticosteroid action in the brain points to the hippocampus as a potential site where glucocorticoids may exert their effect on memory. The dominant assumption in the stress literature—that the function of the hippocampus is to consolidate information—has led researchers to conclude that because stress hormones act on the hippocampus, consolidation is the affected memory process. The problem with the model is that it oversimplifies: data from human amnesia and animal lesion studies do not suggest a clear association between specific brain structures (such as the hippocampus) and specific memory processes (i.e., consolidation). This is partly due to the fact that amnesia cases have suggested the dissociation of different types of memory (e.g., declarative vs. procedural), and thus researchers have focused on the different neural structures that support these memory *systems*. For example, there is robust evidence that the hippocampus and other temporal lobe structures play an essential role in declarative—but not procedural—memory (Bauer, Tobias, & Valenstein, 1993). Thus fewer studies have attempted to identify the specific neural substrates supporting the putative stages of memory formation and recall: encoding, consolidation, and retrieval. In general, the data yields a complex picture. A brief review of these findings suggest that 1) each memory stage (including consolidation) involves many brain regions that also have corticosteroid receptors, and 2) the hippocampus itself may play a role in more than consolidation. Thus stress could in principle be predicted to affect all of the stages of memory.

Learning & Memory: Terminology

Before reviewing the brain structures associated with specific memory processes, it is important to clarify the memory terminology that can vary in usage within and between the human and animal literature.

"Learning" vs. "Memory"

In animal research, "learning" typically refers to associative conditioning (classical and operant) and is traditionally distinguished from "memory" for information (spatial location of food or escape route, contextual cues). There is certainly evidence that different neural structures are specialized for learning and memory thus defined: the amygdala for acquiring a conditioned response (particularly fear conditioning) vs. the hippocampus for remembering which arm of a maze contained food (Roozendaal & McGaugh, 1996a). However, in recent reviews summarizing animal and human research on the effect of *glucocorticoids on memory*, authors have consistently included data from inhibitory avoidance training and other associative learning paradigms (Lupien & McEwen, 1997; Lupien & Lepage, 2001; Roozendaal, 2002; Wolf, 2003). Roozendaal describes this learning as evidence of the "consolidation and /or storage of novel information" (Roozendaal, 2002). Thus associative learning will be defined here as one type of non-declarative memory, consistent with Searleman & Herrmann's (1994) definition, and will be included in the chapter summarizing animal research on stress and memory.

It is also important to note that "learning" in the human neuropsychological literature generally refers to the *initial acquisition or encoding of information*, such as learning in new word list. In terms of memory phases, this is akin to the term "training" in the animal research. In humans it is generally measured using an immediate recall test. (Of course the difficulty with immediate recall tests as measures of learning is that retrieval processes are also required.)

Declarative vs. Nondeclarative Memory

Before reviewing the brain structures associated with specific memory processes, it is also important to distinguish the two memory systems which depend (at least partly) upon different neural structures: declarative (explicit) and nondeclarative (implicit) (Kolb & Whishaw, 1998). This is relevant to the interpretation of stress and memory studies: the majority of human studies employ declarative memory tests (as does the proposed

study), while animal researchers have studied the effects of stress on nondeclarative spatial memory and conditioning tasks.

Declarative memory involves the storage of consciously learned facts, and includes both semantic and episodic knowledge (Cohen & Squire, 1980). Semantic memory is general knowledge about the world (historical figures, word meanings, object uses, scientific facts, social roles), while episodic memory is knowledge about the specific events that make up one's personal experience (Searleman & Herrmann, 1994). Episodic memory generally draws upon semantic knowledge (learning a new word list requires knowledge of word meanings), and over time and repetition becomes semantic knowledge (the episodic meeting of many mothers of teenage soccer players develops into to a semantic construct such as "soccer mom"). Most standard verbal and visual neuropsychological memory tests are measures of episodic declarative memory. Research suggests that the hippocampus, rhinal cortex, and areas of the neocortex all play an important role in declarative memory (see below).

Nondeclarative memory can be considered the default category of memory. It includes the incidental acquisition of new knowledge, also referred to as implicit memory, and often tested with priming tasks. Non-declarative memory also includes the acquisition of new behaviors or skills through repeated exposures or trials (procedural memory, motor skills) and associative learning (classical and operant conditioning, and related contextual memory) (Searleman & Herrmann, 1994). Often there is no subjective awareness of acquiring nondeclarative memory, as in the case of H.M., who demonstrated priming effects and implicit memory while having no conscious memory of the learning experience (Scoville & Milner, 1957). Not surprisingly, data suggests that the basal ganglia and cerebellum, structures associated with motor behavior, are important in procedural memory and skill learning (Petri & Mishkin, 1994). Evidence suggests that the amygdala is essential for associative learning, particularly fear conditioning (Armony & LeDoux, 1997). There is emerging evidence that the amygdala also plays a role in emotional declarative memory (discussed below).

Encoding

Encoding is the initial acquisition stage in which information is "registered"—transformed into a form that can be retained in memory (Searleman & Herrmann, 1994). External stimuli first activate peripheral sensory receptors, which transmit to the thalamus (through different routes) and then to respective sensory areas of the cortex (Kolb & Whishaw, 1998). Atkinson & Shiffrin (1968) called the initial, temporary registration of sensory stimuli in the brain the "sensory register." Research shows that much of this visual and auditory information is lost within 1-2 seconds (Searleman & Herrmann, 1994). A number of processes likely influence what information initially enters the sensory register. An organism cannot encode all of the stimuli bombarding it from the environment at any given moment. Thus mechanisms exist to help filter stimuli in order to encode what is most relevant to meeting important goals (Revelle & Loftus, 1992). *Selective attention* focuses awareness to a select set of relevant stimuli while inhibiting competing input or activity (Kolb & Whishaw, 1998). Organisms do this automatically (for example, neurons fire more rapidly in response to changing stimuli), although attention is often consciously directed, as when you turn your head to listen in on someone's conversation. A minimum level of physiological arousal is also required to *sustain attention* (also called vigilance), although too much arousal can impair attention (Revelle & Loftus, 1992).

The information that does not fade from the sensory register is held briefly in a temporary "store," commonly referred to as short term memory (STM), for further encoding (Atkinson & Shiffrin, 1968). Miller was initially responsible for demonstrating the limited capacity of STM: he consistently found that the number of digits or letters people could recall was the "magical number seven, plus or minus two," although more information can be retained if "chunked" together (Miller, 1956). Following up evidence suggesting the acoustic nature of STM encoding (Conrad & Hull, 1964), Baddeley and others theorized that time might be the limiting factor of STM—specifically, the time it takes for the auditory trace to fade. Consistent with this, they found that STM fades after several seconds (Baddeley, 1990; Schweickert & Boruff, 1986). Baddeley went on to

define different component systems of STM, including a phonological loop and visul-spatial pad, coordinated by a "central executive" that directs attention and operates on the temporarily held information (Baddeley, 1992). Badderley called this "working memory" to emphasize the active manipulation of information that is held only temporarily in memory. Similarly, in their "levels of processing approach," Craik & Lockhart (1972) argue that memory strength depends upon the depth of the encoding processes at this stage through rehearsal, effective chunking, or training (for nondeclarative memory). *Processing speed* also influences encoding from STM: given its limited capacity (memory span), the faster one can operate on information in working memory, the greater the amount of information that can processed in any given interval of time.

Thus brain regions associated with sensory registration, selective attention, vigilance, processing speed, and rehearsal / elaboration processes all contribute to successful encoding. Interference with any of these regions and their associated functions could contribute to memory impairment.

Thalamus

Given its putative designation as the "sensory relay station" of the brain, it is no surprise that the thalamus also plays an important role in encoding. Lesions of the medial thalamus (from either vascular accidents or alcohol-related Korsakoff's syndrome) is reliably associated with memory impairments (Kolb & Whishaw, 1998). Studies of patients with Korsakoff's syndrome, characterized by anterograde amnesia (inability to form new memories) and retrograde amnesia (impaired of remote memory), also suggest problems with *depth* encoding. Utilizing the "levels of processing" paradigm, researchers have shown that Korsakoff patients demonstrate only superficial processing of verbal information (Cermak & Butters, 1972; Cermak, Butters, & Gerrein, 1973; Cermak, Naus, & Reale, 1976). However, because Korsakoff patients commonly show frontal lobe atrophy (and possibly sustain damage to the mammilary bodies of the hypothalamus), it is difficult to conclude that thalamic damage is responsible for this observed encoding impairment (Kolb & Whishaw, 1998).

Cortical regions

Many studies have associated different areas of the cortex with attention & working memory. Electrophysiological studies with monkeys have shown posterior cortical activity on different types of visual attention tasks (Corbetta, Miezin, Shulman, & Petersen, 1993). In a series of PET studies with humans, Shulman and Petersen (1993) demonstrated increased activity in the posterior parietal cortex during a selective attention task for location, while others have found occipital-temporal activation in humans for visual features such as color and form (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991). PET studies with humans have implicated the ventrolateral frontal cortex in the left hemisphere with encoding words (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Finally, Posner and Petersen (1990) have proposed a central role for the frontal lobe in attentional tasks related to short term (working) memory. They review evidence supporting this model, including studies that show activation of the motor cortices and the anterior cingulate cortex during response selection, activation of the dorsolateral prefrontal cortex during divided attention tasks, and inferior frontal cortex activation during verb generation. It is important to note that glucocorticoid receptors are distributed throughout these cortical regions (Lupien & McEwen, 1997).

Amygdala

Research on the amygdala implicates this structure in the encoding of emotionally arousing stimuli. Many studies have associated the amygdala with emotional states such as fear and rage (Kluver & Bucy, 1939; Le Doux, 1996). There is strong evidence that the amygdala is essential for acquiring a conditioned response—in other words, "tagging" neutral stimuli as emotionally significant to facilitate implicit learning (see Armony & LeDoux, 1997). Not surprisingly, both types of corticosteroid receptors are found in the amygdala (Lupien & McEwen, 1997). Activation of the amygdala during stress would thus be expected to *improve* learning and memory. Indeed, lesions to the basolaterial and medial nuclei of the amygdala in rats blocks glucocorticoid enhancement of implicit memory (inhibitory avoidance) (Roozendaal & McGaugh, 1996a; McEwen, Albeck, Cameron, Chao, Gould, et al., 1995). Stress activates the amygdala via catecholamine

action as well also enhancing emotional memory in animals (Roozendaal, et al., 1997). If the amygdala signals the hippocampus (and other regions) to remember emotionally relevant stimuli (LeDoux, 1992), it seems likely this would not be restricted to implicit or conditioned memories. Indeed, there is evidence that the amydala is involved in the acquisition of declarative memory as well (see below).

Consolidation

Mueller and Pilzecker (1990) originally proposed the "perseveration-consolidation" hypothesis at the turn of the 20th Century. They argued that memory traces are initially weak after learning, and require time and neural activity to solidify the memory (see also Milner, 1965). Clinical evidence for this theory came from head-injury patients demonstrating retrograde amnesia for events preceding the accident. Amnesia for events initially encoded before the injury typically "shrinks" during recovery along a temporal gradient, such that the farther out in time from the injury the event occurred, the more likely it will be recovered in memory (McGaugh, 1966). Presumably these distant events had more time to undergo consolidation, and thus were less vulnerable to disruption. Researchers have also demonstrated that when an electroconvulsive shock is given to rats immediately after learning, it impairs their retention of the learned behavior, but not if the shock is administered two hours after training (Duncan, 1949). Consistent with this idea is evidence that drugs such as amphetamine which enhance memory are most effective when administered immediately after learning (McGaugh, 1966). Squire (1987) reports that information is vulnerable to disruption up to several years after initial learning.

Hippocampus

The first evidence to strongly implicate the hippocampus in the consolidation of new information came from several dramatic amnesia cases, including the famous case of H.M. In 1954, William Scoville removed both of H.M.'s medial temporal lobes as an experimental treatment for his refractory epilepsy. The resection area included the anterior two-thirds of the hippocampus, the entorhinal and perirhinal cortices, the uncus,

and the amygdala (the temporal neocortex was spared; Scoville & Milner, 1957). The result was severe anterograde amnesia—the inability to consolidate new visual or verbal explicit memories— with intact remote memory, intelligence, language skills, and social behavior (Scoville & Milner, 1957; Milner, Corkin, & Teuber, 1968). In addition, H.M.'s anterograde amnesia did not affect nondeclarative memory: he performed similarly to normal controls on priming tasks and procedural memory tests such as mirror drawing and the Tower of Hanoi puzzle (Milner, et al., 1968). This dissociation between declarative and nondeclarative memory impairment has continued to be a consistent finding for anterograde amnesia, providing evidence that the medial temporal lobes are not essential for the latter (Kolb & Whishaw, 1998). Several additional individuals underwent bilateral medial temporal lobectomies, and again showed the same pattern of deficits and spared abilities (Milner, 1970). To avoid causing the debilitating anterograde amnesia, clinicians began conducting unilateral temporal lobectomies on epileptic patients, providing additional evidence for the role of these structures in the consolidation of new memories. Although most did not show the same type of dense anterograde amnesia, some showed a material-specific deficit: difficulty consolidating (spatial) information with removal of the non-dominant hemisphere (Milner, 1965). For those unilateral temporal lobectomy patients that continued to show serious anterograde amnesia, it was later discovered that the spared temporal lobe had substantial lesion damage as well (Penfield,& Matheison, 1974).

Perhaps because the hippocampus is the most conspicuous medial temporal lobe structure, researchers began to assume that this structure was primarily responsible for the observed amnesia—thus was born the hippocampal-consolidation model (Kolb & Whishaw, 1998). There was some support for this assumption. A number of anterograde amnesia cases were reported in which damage appeared to be localized to the hippocampus (bilaterally) from vascular disease (Zola-Morgan, Squire, & Amaral, 1989) or anoxic accident (Cummings, Tomiyasu, Read, & Benson, 1984). Several animal studies involving hippocampal lesions have also demonstrated impaired spatial memory (Petri & Mishkin, 1994).

There are several problems with concluding that the hippocampus is the primary structure supporting consolidation. First, it is difficult to localize dysfunction in patients suffering from neurological disease in which various brain regions may be affected (for example, in vascular disease). In addition, in all of the medial temporal lobectomy cases, more than the hippocampus was resectioned. Finally, animal studies that have examined the effects of discrete lesions in the hippocampus and adjoining regions implicate other neural structures as well (Kolb & Whishaw, 1998).

Rhinal Cortex & Neocortex

Research suggests that the rhinal cortex and the temporal neocortex are also important to consolidating memory. For example, there is evidence from primate models of medial temporal amnesia that the entorhinal cortex and the perirhinal cortex are involved in visual object recognition (Meunier, Bachevalier, Mishkin, & Murray, 1993). (Unfortunately, such animal studies cannot shed light on verbal memory.) Milner and colleagues have demonstrated that damage to the left temporal neocortex (normally spared in temporalobectomy) impairs verbal recall, while damage to the right impairs visul-spatial memory (Milner, 1965; Milner, 1970). And again, all of these regions have corticosteroid receptors (Lupien & McEwen, 1997).

Consolidation only?

A question remains regarding the assumption that anteriograde amnesia is an impairment involving consolidation only. It is certainly possible that a deficit in forming new memories might also arise from poor encoding. Indeed, Craik & Lockhart's (1972) notion of depth encoding begins to sound like consolidation, raising conceptual issues about the distinction between the two processes. It is thus possible that temporal lobe structures such as the hippocampus are involved in both the encoding and consolidation of information, although this remains to be researched. The issue is raised here to underscore the possibility that the hippocampus and other regions associated with anteriograde amnesia may be contributing to encoding as well.

Amygdala

While the role of the amygdala in "tagging" emotional events for enhanced encoding was described above, the extensive reciprocal projections between the amygdala and hippocampus (Roozendaal, Quirarte, & McGaugh, 1997) also implicate this limbic structure in the *consolidation* of declarative emotional memory as well (Roozendaal, 2000; Roozendaal 2002). Thus if the amygdala signals the hippocampus (and other regions) to remember emotionally relevant stimuli (LeDoux, 1992), it seems likely this would not be restricted to implicit or conditioned memories alone. Indeed, people show better declarative memory for affective visual stimuli compared with neutral stimuli (Buchanan & Lovallo, 2001;), and PET studies demonstrate a high correlation between activation of the amygdala and retention of an emotional film—but no correlation with memory for the neutral film (Cahill, et al., 1996). A recent review summarizes animal study findings that the glucocorticoid facilitation of memory consolidation is modulated by noradrenergic activation in the basolateral amygdala (Roozendaal, 2002).

Retrieval

Retrieval involves accessing stored (consolidated) information. Retrieval often occurs automatically without effort, such as recalling the name of your sibling or the general layout of your apartment (Searleman & Herrmann, 1994). Other memories may be "weaker" from poor encoding (the layout of a museum you visited once), gradual decay when not rehearsed (the name of your 5th grade teacher), or require systematic search (all states that begin with "M"). Retrieval that requires effort is facilitated by cues which presumably activate networks related to the target item; thus free recall tasks (without cues) are more challenging than cued or recognition tasks (Searleman & Herrmann, 1994). There are several reasons that one might have difficulty in freely recalling information from memory. Poor encoding or consolidation might account for it (the memory trace is "weak"), or the relevant retrieval mechanism itself might be impaired. Recovery from retrograde amnesia (or transient global amnesia) is an example

of impaired retrieval: the temporarily "forgotten" information had to be encoded and stored for it to be recovered later (Bauer, Tobias, & Valenstein, 1993). One way to test for a retrieval deficit related to recalling newly learned declarative information is to compare performance on a free recall test with recognition performance. For example, if after reading a story, a subject cannot freely recall many details but subsequently identifies them in a multiple choice test, this provides evidence that information was consolidated but hard to retrieve (Bauer, et al., 1993).

Of note, Lupien and colleagues have used a working memory task as a measure of short-term memory retrieval (Lupien, et al., 1999). This supports the idea that similar processes and brain structures may be involved in selective attention and retrieval (see below).

Associated Brain Regions

Specific brain regions have not been consistently associated with retrieval, although many of the same regions activated during memory formation—including sensory systems, thalamus, limbic and cortical regions—are also activated during recall (Kolb & Whishaw, 1998). Tulving and colleagues have demonstrated activation of the right dorsolateral frontal cortex and the parietal cortex bilaterally during retrieval of words, which *differed* from areas activated during encoding (Tulving, et al., 1994). Korsakoff patients commonly demonstrate a temporally graded retrograde amnesia (Albert, Butters, & Brandt, 1981; Butters & Cermak, 1986), and this raises the possibility that the thalamus (which is damaged in Korsakoff's) may also be important to retrieval. Warrington & Weiskrantz (1970) have argued that anteriograde amnesia itself may be due to a retrieval deficit (related to interference effects and poor matching between learning and recall conditions), rather than a consolidation deficit. Although their findings are equivocal, the authors did demonstrate retrieval interference effects in anteriograde patients (Warrington & Weiskrantz,1978). This would implicate temporal lobe structures such as the hippocampus in retrieval. Richard Hirsh (1974) has also proposed that the hippocampus is responsible for contextual retrieval.

Conclusion

It is clear from this brief review that the neuropsychology of memory is far more complicated than the dominant stress and memory explanatory model would suppose. Many brain regions have been associated with each stage of memory processing, and most of these structures have receptors for stress hormones. Even the temporal lobe cases of anterograde amnesia that gave birth to the hippocampus-consolidation model suggest that other structures may be involved in consolidation, and that encoding or retrieval deficits may also contribute to the observed memory deficits. This takes the question of how stress might act on the brain to affect memory, and blows it wide open.

4. Stress & Memory: Animal Studies

Introduction

The animal literature on stress and cognition is vast, providing robust evidence that stress or admininstered corticosteroids affect both associative learning and spatial memory. Stress manipulations include social stress (dominance struggle), physical restraint, shock, and certain stressful tasks, while corticosteroid administration involves either injection, implanted hormone "beads," or intracerebral administration. Investigators have examined the *modulatory* effects of corticosteroids following adrenalectomy (or other lesion procedure), and the *direct* effects of administered hormones or stress in healthy animals. Researchers have also experimented with the *timing* and *dose* of the manipulation. Together, these studies provide a complex picture, but suggest a facilitative effect of moderate doses of corticosteroids (or moderate stress) on encoding and consolidation, and possibly an adverse effect on retrieval.

Adrenalectomy

Studies demonstrating the negative effects of adrenalectomy (ADX) on memory in animals provide indirect evidence for the importance of corticosterone's role in animal cognition. Removal of the adrenal glands causes a dramatic reduction in endogenous circulating corticosterone. ADX rats trained to find a platform partially submerged in clouded water (the Morris water maze task) show impaired spatial memory for the platform location during retention testing (Oizl & de Kloet, 1992; Roozendaal, Portillo-Marquez, McGaugh, 1996; Conrad, Lupien, Thanasoulis, & McEwen, 1997). It is important to note that in the Oizl & de Kloet study (1992), no impairment was observed when only the adrenal medulla was removed (thus sparing the adrenal cortex and endogenous corticosterone levels). ADX rats also show impairments in associative learning tasks, such as passive avoidance (Borrell, de Kloet, & Bohus, 1984; Borrell, de Kloet, Versteeg, & Bohus, 1983) and acquired immobility response (Mitchell & Meaney, 1991; De Kloet, De Kock, Schild, & Veldhuis, 1988). Thus a certain minimum level of

corticosteroids is required for normal memory function. ADX-induced impairments can sometimes be reversed by glucocorticoid replacement therapy. Studies using this paradigm provide evidence of the *modulatory* effects of corticosteroids on animal cognition (see sections below).

Associative Learning

There is robust evidence that glucocorticoid levels affect associative learning. Most of the conditioning paradigms in these studies involve having an animal learn either a positive (appetitive) or negative (aversive) association between two stimuli (training period), followed by retention testing for the conditioned response. A common learning paradigm is the inhibitory avoidance task: an animal is trained to avoid a naturally preferred behavior, such as entering a dark compartment, through shock administration; latency to enter the dark compartment measures retention of the conditioned response. Often researchers also track the rate at which the learned behavior is extinguished: rapid extinction may indicate weak learning, rapid decay of information, or interference associated with new learning.

Many researchers have studied the modulatory effects of glucocorticoid replacement therapy on associative learning in ADX animals. Corticosterone treatment normalizes extinction rate in ADX rats when administered prior to training in an appetitive task (Micco, McEwen & Shein, 1979) and in a conditioned avoidance task (Bohus & Lissak, 1968). When corticosterone is administered post-training (presumably returning levels to normal baseline during consolidation and retrieval), it restores the ability of ADX rats to retain acquired immobility behavior (Mitchell & Meaney, 1991; Veldhuis, De Korte, & De Kloet, 1985), and extinction is similarly normalized (Bohus & De Kloet, 1981). There is thus indirect evidence that non-stress levels of glucocortioids are important in associative learning. Others, however, have not found corticosterone replacement to affect retention of a passive avoidance response in ADX rats (Borrell, et al., 1984; Borrell, et al., 1983).

Researchers have also demonstrated direct effects of glucocorticoids administered to healthy animals, generally finding an inverted-U shape relationship between dose and memory in conditioning paradigms. When a moderate dose of corticosterone or dexamethasone (a synthetic glucocorticoid) is administered immediately after training, it improves memory for inhibitory avoidance behavior in rats during retention testing the next day (Kovaks, Telegdy & Lissak, 1976; Flood, Vidal, Bennett, Orme, Vasquez & Jarvik,1978; Roozendaal & McGaugh, 1996b). Memory was not enhanced in these studies when administered at the lower or higher doses. Sandi & Rose (1994a) extended these findings in day-old chicks. Intracerebral administration of corticosterone either pre- or post-training enchanced memory for the learned avoidance behavior when tested 24 hours later, implicating encoding and consolidation processes. This effect held even when treatment was given up to 60 minutes following training (but not 120, 180, or 360 minutes post-training). Several studies have also looked at the effects of glucocorticoid agonists or antagonists on contextual conditioning. Evidence suggests that while the amygdala is involved with conditioning, the hippocampus plays an important role in forming memories of contextual cues associated with the conditioning event (Phillips & LeDoux, 1992, 1994). Pugh and colleagues thus conditioned rats to an auditory cue while placed in a white cooler (context). A glucocorticoid antagonist administered prior to conditioning or immediately after did not affect auditory cue conditioning 24 hours later (freezing behavior in response to tone in a novel environment). The treatment did, however, impair contextual fear conditioning (failing to freeze when put inside cooler without the tone) in treated animals compared to vehicle-treated controls (Pugh, Fleshner, & Rudy, 1997). Others have replicated this finding and have demonstrated a biphasic effect between corticosterone levels and contextual inhibitory avoidance (Cordero & Sandi, 1998).

Spatial Memory

Similar findings have been obtained on the effects of corticosteroids on spatial memory, as measured using different types of mazes. It should be noted that although these studies are typically distinguished from “associative learning” studies in the animal

literature, spatial memory paradigms in animal research typically involve some type of associative learning. Generally, a behavior is learned over several trials through operant conditioning (location of food in a radial arm maze or escape routes). Successful recall of the learned behavior then requires memory for spatial information in these tasks, which some consider explicit (episodic) memory.

A number of researchers have provided evidence of modulatory effects of corticosteroids on spatial memory in their study of ADX rats. Corticosterone receptor agonists (administered continuously during training and testing) restore previously impaired performance on the water maze task (McCormick, McNamara, Kelsey, & Kleckner, 1995; Roozendaal, Portillo-Marquez, et al., 1996) and the Y-maze (Conrad, et al., 1997). Conrad and colleagues found evidence for the inverted-U shape relationship between glucocorticoid levels and memory function. They administered either stress-levels of corticosterone, a glucocorticoid agonist, or a glucocorticoid antagonist to ADX rats prior to learning the Y-maze, and found that memory was restored with corticosterone and impaired when glucocorticoid receptors were either blocked or highly occupied (Conrad, Lupien, & McEwen, 1999).

There is also evidence for the direct effect of glucocorticoids on spatial memory in healthy animals. In contrast to the general trend in data indicating a facilitative effect of glucorticoids on associative learning, Roozendaal and colleagues found that moderate doses of dexamethasone administered post-training in intact rats produced impairment in the water maze during testing 24 hours later (Roozendaal, Bohus, & McGaugh, 1996). Roozendaal (2000) points out that the water maze task is a fairly stressful task itself (inducing the endogenous release of corticosterone). Presumably, glucocorticoid receptors are highly occupied when hormones are administered under already stressful conditions. Thus moderate doses of corticosterone improved consolidation of spatial memory in the water maze task under conditions which make this task less stressful (warming the water; Sandi, Loscertales, & Guanza, 1997). Others have also found the acute administration of glucocortioid antagonists to impair spatial memory (Oitzl, Fluttert, Sutanto, & de Kloet, 1998; Oitzl & de Kloet, 1992).

In contrast, *chronic* stress appears to be exclusively adverse to spatial memory. Bodnoff and colleagues found that a 3-month treatment of corticosterone (dose level mimicking mild stress) produced impaired performance on the water maze task in mid-aged, but not young, rats (Bodnoff, Humphreys, Lehman, Diamond, Rose, & Meaney, 1995). This was replicated in young adult rats with the 8-arm radial maze (Endo, Nishimura, & Kimura, 1996). Mid-aged rats exposed to social stress (cage rotation with novel pairing of males) also show spatial memory impairment compared to low-stress controls and ADX rats (Bodnoff, et al., 1995). Restraint stress applied over 21 days prior to maze training caused a similar impairment in spatial memory (Luine, Villegas, Luine, & McEwen, 1993). Evidence suggests that the impaired memory following chronic stress is related to reduced hippocampal plasticity, rather than neuron loss (Bodnoff, et al., 1995).

Timing & Receptor-type Effects

There is thus evidence for the direct role of glucocorticoids in enhancing associative and spatial memory. The data also suggests that this relationship is time- and dose-dependent. Evidence that the administration of glucocorticoid (or stress) treatment both before and immediately after training affects memory certainly implicates consolidation as the affected memory process (although encoding may also be affected in pre-training conditions). However, the studies cited above typically did not manipulate stress or corticosterone during the retrieval phase (generally 24 hours later). This has spurred researchers to investigate the time-dependent effects more carefully in order to differentiate the effect of stress on different stages of memory formation.

These recent studies have also examined both glucocortiocoid receptor (GR) and mineralocorticoid receptor (MR) treatments in order to test whether the inverted-U shape relationship between dose and memory may relate to differential activation of these two receptor types. (MR receptors are mostly occupied as basal levels of circulating glucocorticoids, while GR receptors become occupied with increasing levels associated with stress).

Faciliative Effects on Encoding & Consolidation

Oitzl & De Kloet (1992) administered either a MR or GR antagonist to rats through intracerebroventricular injection during different points in the training and recall procedure using the Morris water maze. One group was injected prior to training on day 1 (during encoding and consolidation), another group was injected after training on day 1 (consolidation only), and a third group was injected 30-45 minutes before retention testing on the second day (retrieval). The authors found that a GR antagonist administered either pre-training or immediately after had a determinental effect on spatial memory in rats compared to vehicle controls when tested 24 hours later, providing evidence that consolidation was compromised. GR antagonist administration prior to retention testing (after acquisition and consolidation) had no effect, arguing against the importance of activating glucocorticoid receptors during retrieval. The MR antagonist had no effect on memory when administered at any time points in the procedure. The authors did find, however, that the MR antagonist increased swimming behavior around the maze. This suggested to the authors that MR receptor activation may influence attention to relevant stimuli, evaluation of the situation, and response selection (and conversely, that MR blockage with an antagonist would result in increased reactivity to non-specific aspects of the learning situation). Others obtained similar findings regarding MR activation: MR agonist administration in ADX rats restored efficient exploratory behavior during acquisition of the water maze task (Conrad et al., 1997), while an MR antagonist increased chicks' reactivity to irrelevant stimuli (increased approach and pecking behavior) during acquisition of passive avoidance task (Sandi & Rose, 1994b). Lupien & McEwen (1997) draw this conclusion in their review of the animal literature:

> These results suggest that the dose-dependent relationship previously observed between corticosteroids and memory process in the animal may in fact be explained by the differential activation (or blockade in the case of antagonist administration) of Type I [MR] and Type II [GR] adrenal steroid receptors, particularly in the hippocampus. Type I receptor activation may be implicated in the process of memory formation through the process of sensory integration...In contrast, the activation of Type II receptor is thought to be related to the process of acquisition and consolidation of the memory trace. The time-dependent effects of Type II

> corticosteroid receptor activation on animal behavior goes along with such a suggestion (p. 13).

Detrimental Effects on Retrieval?

Because few studies manipulated stress or cortisone during the retrieval phase (the hippocampus-consolidation model would not have predicted this), until recently little data implicated stress effects on retrieval processes. In the one study reviewed above that separated all three stages of memory, a glucocortiocoid antagonist was not found to affect retrieval when given on the second day, prior to retention testing (Oitzl & De Kloet,1992). Thus retrieval was not impacted by a *decrease* in baseline glucocorticoid levels. De Quervain and collaborators recently employed a similar method but increased corticosterone, and found evidence that stress impaired retrieval in rats trained in the water maze (De Quervain, Roozendaal, & McGaugh, 1998). In their procedure, healthy rats were first trained to find the submerged platform, and memory was tested 24 hours later; stress (footshock) was administered either 2 minutes, 30 minutes, or 4 hours before *retention* testing (retrieval) on the second day. The authors found that only the rats stressed 30 minutes before testing (consistent with the time necessary to see an increase in circulating corticosterone following the shock) showed impaired memory for the platform compared with non-stressed rats. They replicated this finding with administered corticosterone, and found a dose-dependent impairment when given 30 minutes, but not 2 minutes or 4 hours, before retention testing (the two higher doses were comparable to shock). Metyrapone, which interferes with the synthesis of corticosterone, blocked the shock-induced impairment in retrieval. The authors concluded that while the effect of glucocorticoids on acquisition and consolidation appears to be facilitative (in moderate doses), stress hormones may be primarily detrimental to retrieval.

Summary

Together, the research provides strong evidence that corticosteroids exert an effect on nondeclarative conditioning and spatial memory in animals. The evidence suggests that this effect follows an inverted-U shape function: moderate doses facilitate memory, while very low and high doses often have no or adverse effects. Chronic

treatment appears to be uniformly negative. The two corticosteroid receptor types, both found extensively throughout the hippocampus, play a role in this process. Under no-stress conditions, basal circulating corticosteroids largely occupy mineralocorticoid receptors (MRs), fostering normal memory function. If levels are too low and MRs are not activated (i.e., following adrenalectomy or administration of corticosteroid antagonists), memory is impaired, possibly by interfering with selective attention and exploratory behavior. As stress increases the level of circulating corticosteroids, they begin binding to glucocorticoid receptors (GRs), facilitating the acquisition and consolidation of information following an inverted-U shape function. If the stressor becomes too severe and GRs become fully occupied, however, the memory system becomes "overwhelmed" and memory is impaired. A more recent study suggests that stress and elevated corticosteroids may uniformly impair the retrieval of learned information (de Quervain, et al., 1998).

What the animal literature cannot test directly, however, is the effect of stress on declarative memory—in particular, verbal memory. Thus we turn to research with humans.

5. Stress & Memory: Human Studies

While the animal literature is extensive, the question remains: what is the effect of stress on memory in humans? The first evidence of an association between cortisol and cognition came from disease cases involving altered cortisol regulation. These studies suggested, consistent with the animal research, that chronic exposure to elevated glucocorticoids impairs memory. Experimental studies subsequently provided more direct evidence for the effect of the acute effects of glucocortioids on declarative memory in humans. Many researchers presume that the affected memory process is consolidation, based on the hippocampal-consolidation model (i.e., given evidence that the hippocampus has a high concentration of cortisol receptors in the brain, and the assumption that the hippocampus is responsible for consolidation). But while animal studies provide evidence that mild-moderate stress or corticosteroid administration improves both encoding and consolidation, human studies suggest a *detrimental* effect. It will be argued here that this discrepancy may be explained by methodological problems in human studies—a failure to experimentally distinguish the effects of stress on different stages of memory—which this proposal seeks to address. Preliminary evidence from several recent studies which have also sought to parse memory phases suggests a revised model: consolidation may be enhanced by stress or cortisol in dose-dependent manner as in the animal literature, while retrieval may be uniquely impaired by stress.

Chronic Effects of Cortisol

The first evidence of an association between glucocorticoid steroids and cognition in humans came from case studies and later correlational studies of individuals with conditions that affect circulating cortisol levels. Clinicians also noted cognitive symptoms associated with chronic steroid treatments for allergies, asthma and auto-immune diseases.

Cushing's syndrome is a condition of chronic, abnormally high cortisol secretion resulting from adrenal or pituitary tumors, prolonged treatment with corticosteroid drugs,

or other endocrine problems. Cushing's syndrome has been associated with hippocampal atrophy in several studies (Starkman, Gebarshi, Berent, & Schteingart, 1992; Bentson, Reza, Winter, & Wilson, 1978). Individuals with the disorder also demonstrate significant cognitive symptoms. In an interview of 35 Cushing's patients, 66% reported concentration difficulties and 83% reported memory problems; symptoms correlated with plasma cortisol (Starkman & Schteingart, 1981). Starkman et al. (1992) found a negative correlation between cortisol levels and verbal memory in Cushing's patients with decreased hippocampal volumes. Others have also shown a negative correlation between cortisol levels and both verbal memory (Martignoni, et al., 1992) and visuospatial memory (Starkman & Schteingart, 1981; Whelan, Schteingart, Starkman, & Smith,1980; Martignoni et al., 1992) in patients with Cushing's syndrome.

Depression is also frequently associated with both abnormalities of the HPA axis and cognitive dysfunction. Depressed individuals often show increased levels of ACTH (Fang, Tricou, Robertson, & Meltzer, 1981); Reus, Joseph, & Dallman, 1983) and cortisol, the latter of which has been measured in CSF and brain tissues of successful suicide victims (Carroll, Curtis, & Mendels, 1976; Rubinow, Post, Savard, & Gold, 1984). There is also a subset of individuals with depression that fail to suppress cortisol in response to dexamethasone administration. Dexamethasone, a synthetic glucocorticoid, acts like cortisol to inhibit CRF and thus cortisol release as part of the negative feedback system. The nonsuppression of cortisol in response to a dexamethasone challenge suggests HPA dysregulation. Depression is also marked by cognitive symptoms, including attention, concentration, and memory difficulties (Weingartner, Cohen, & Martello, 1981; Roy-Byrne, Weingartner, Bierer, Thompson & Post, 1986). There is evidence that among depressed patients, dexamethasone nonsuppressors show greater cognitive impairment than those who show normal suppression in response to the drug (Sikes, Stokes, & Lasley, 1989; Winokur, Black & Nasrallah, 1987; Reus, Peeke, & Miner, 1985; Reus, 1984). The dexamethasone suppression test has also provided evidence for a relationship between HPA abnormalities and cognitive symptoms in other

conditions, including schizoprenia (Newcomer, Faustman, Whiteford, Moses, & Csernansky, 1991; Tandon et al., 1989) and dementia (Davis et al., 1986).

Indeed, there is evidence that aging is often accompanied by hypercortisolemia (Lupien, Gillin, Frakes, Soefje & Hauger, 1995)—a tempting explanation for the cognitive decline generally observed in the elderly. Several studies have examined this potential relationship in healthy, aging individuals. In a 5-6 year longitudinal study, Lupien and colleagues found that individuals with progressively increasing and high levels of cortisol showed impairments in declarative memory compared to those with either increasing but moderate levels, or those with progressively decreasing levels of cortisol (Lupien et al., 1994; Lupien, et al., 1998). There were no differences between groups on implicit memory tests. In a follow-up study, the authors found a significant correlation between chronic cortisol elevations and hippocampal atrophy (Lupien, et al., 1998).

A number of researchers have also noted cognitive symptoms associated with chronic corticosteroid treatments. Varney and colleagues studied 6 patients undergoing corticosteroid treatment for different diseases, and found that all demonstrated problems with attention, mental speed, and memory—symptoms which resolved following treatment cessation (Varney, Alexander & MacIndoe, 1984). An extreme condition known as "steroid psychosis" in patients receiving high doses of glucocorticoids has been described, which includes dementia-like symptoms of memory loss, attentional problems, and impaired reasoning (Ling, Perry, & Tsuang, 1981). But even milder treatment with prednisone for asthma and other conditions has been found to be associated with memory impairment in controlled studies (Keenan, et al., 1996; Bender, Learner, & Poland, 1991).

Thus there is indirect (correlational) data associating abnormalities in cortisol, hippocampal atrophy, and impaired cognition—particularly memory. It is difficult to determine, however, whether cognitive symptoms are a result of elevated cortisol, or related to other aspects of the disease process. An additional confound with conditions involving *chronic* exposure to cortisol is that sustained high levels of glucocorticoids can lead to the down-regulation of receptors (glucocorticoid resistance), rendering the body's

tissues (including the hypothalamic PVN) insensitive to cortisol. Thus the cognitive findings may be a result of insufficient glucocorticoid signaling that develops over time (Raison & Miller, 2003). Whatever the mechanism, the evidence suggests that chronic exposure to elevated cortisol has a negative effect on memory. Less clear were the *acute effects* of elevated cortisol, which might mimic the action of transient stressors. In addition, experimental studies were needed to establish a causal role for the stress hormone in human verbal and visual declarative memory. Thus began the first randomized, placebo-controlled glucocorticoid studies, starting in the 1980's.

Glucocorticoids & Declarative Memory

When researchers turned their attention to studying the direct effects of glucocorticoids on human cognition, their focus was on declarative memory. This followed theoretically from evidence demonstrating the role of the hippocampus in the formation of declarative memories, and as a primary site for glucocorticoid action.

Extended Pharmacological Treatment Studies

In order to mimic chronic stress or the hypercortisolemia of various diseases, researchers examined the amnestic effects of administering glucocorticoids over a period of several days, and found evidence for a resulting impairment in verbal memory. Newcomer and colleagues gave participants an oral dose of dexamethasone or placebo pill for 4 days. Memory testing was conducted at baseline and days 1, 4, and 7 (washout). The dexamethasone group scored significantly lower than the placebo group on immediate and 30-minute delayed recall of a paragraph story, but only on day 4. No differences were found on a visuoperception task, or on two attention measures (serial addition and vigilance tasks). The authors suggested that the lack of observed acute effects (day 1) may be related to the slower mechanisms through which dexamethasone binds with hippocampal receptors, compared with endogenous glucocorticoids (Newcomer, Craft, Hershey, Askins, & Bardgett, 1994). The authors obtained similar results, however, in a dose-response study using cortisol and the same paradigm. A significant difference between high-dose treatment (160mg of cortisol) and placebo

groups was found for immediate and delayed paragraph recall, but on the fourth day only after 4 days of cortisol administration. No differences were found between the lower-dose (40mg) treatment and placebo groups. Other cognitive measures were not affected by drug administration. The authors concluded that declarative memory (in these studies--verbal memory) is selectively impaired by glucocorticoid levels approximating moderate to high stress (Newcomer, Selke, Melson, Hershey, Craft, Richards, & Alderson, 1999).

Extended treatment studies, however, face some of the potential confounds of the disease studies previously reviewed. Elevated cortisol activates negative feedback mechanisms, including reduced production of CRF and thus ACTH and cortisol. Over time it can also lead to the down-regulation of receptors as mentioned above (although elevations over days may not constitute enough time for such resistance to develop). Thus Newcomer's findings may represent the cognitive sequele of reduced cortisol action from negative feedback. More recently, Newcomer and colleagues found that at a higher dose, chronic exposure to dexamethasone caused impairment in verbal declarative memory in healthy young individuals on the *first* day (Newcomer, Selke, Kelly, Paras, & Craft, 1995). This anticipated several single-dose studies demonstrating the acute effects of gluccocorticoids on declarative memory.

Acute Pharmacological Treatment Studies

Additional support for the effect of glucocorticoids on *verbal* declarative memory comes from several randomized, single-dose, placebo-controlled studies. Kirschbaum and colleagues adminstered either 10mg of cortisol (orally) or placebo pill to participants, and then tested them 1 hour later (peak circulating cortisol levels) on procedural memory, verbal declarative memory, and spatial thinking. The memory test involved having participants rate 26 nouns for "musicality," then after the non-memory tests were administered (approximately 30 minutes), participants were given a surprised cued-recall of the nouns learned incidentally. The cortisol group demonstrated impairment relative to the control group on the memory test. No differences were found between groups on a procedural stem-completion memory test, again supporting the dissociation between declarative and nondeclarative memory observed in anteriograde patients (Kirschbaum,

Wolf, May, Wippich, & Hellhammer, 1996). Tops and colleagues also found impaired immediate recall and recognition of neutral and pleasant nouns following 10mg cortisol treatment 2 hours earlier (Tops, et al., 2003). However, Hsu and colleagues found no effect of cortisol on verbal memory (tested within an hour of stimulus presentation) in a study using 100mg hydrocortisone treatment and a noun recall measure similar to the Kirschbaum study (Hsu, Garside, Massey & McAllister-Williams, 2003).

Acute Psychosocial Stress

Kirschbaum and colleagues in Trier, Germany have developed and tested a brief, laboratory psychosocial stressor, the Trier Social Stress Test (TSST), to examine the effects of stress on memory. The TSST involves having participants prepare a 5-minute speech over a 10-minute period, which they subsequently deliver to an audience of 3-5 while being videotaped, followed by a 5-minute arithmetic exercise in front of the audience. The TSST has proven to be a reliable moderate stressor resulting in significant cortisol elevation in over a dozen independent studies (for a review, see Kirschbaum, Pirke, & Hellhammer, 1993).

In a companion study to their cortisol study cited above, Kirschbaum and colleagues exposed healthy participants to the TSST, and then had them learn a list of 24 nouns ten minutes after cessation of the stressor. Following a 5-minute distraction task, participants were given a cued-recall test in which they wrote down all words beginning with “Mo”(10 words). The investigators found a significant negative correlation ($r = -.7$) between TSST-induced cortisol levels and number of correctly recalled words (Kirschbaum, et al., 1996). Wolf and colleagues replicated this finding, showing a negative correlation ($r = -.43$) between TSST-induced cortisol response and immediate free recall of a word list, although they did not obtain a main effect for group (TSST vs. controls) (Wolf, Schommer, Hellhammer, McEwen & Kirschbaum, 2001). Interestingly, they found that the correlation was due almost exclusively to the association observed in the men in the study, with no association found for the women. Others found a decrease in visual memory performance (picture presentation and immediate recall) following the

TSST compared with testing prior to the stressor in an elderly population (Wolf, Kudielka, Hellhammer, Hellhammer, & Kirschbaum, 1998).

In contrast, Domes and colleagues found that although there were no group differences between participants who underwent the TSST induction compared with controls on the same word recall task in Kirschbaum et al. (1996), when they divided participants into high and low cortisol responders using a median split, high responders performed better on the verbal memory task than low responders regardless of condition (Domes, Heinrichs, Reichwald & Hautzinger, 2002).

Recent Studies Testing Consolidation Effects More Directly

While there appears to be evidence that stress negatively affects short-term declarative memory, it is not clear why the authors are concluding that consolidation is the memory process being affected. In all of the studies cited above, memory was tested within 2 hours of stress or cortisol manipulation, and thus cortisol was elevated during encoding, consolidation, and retrieval of the information. Several recent studies have attempted to address this methodological confound by introducing a longer interval between stimulus exposure / acquisition and later retention-testing, thus testing retrieval after cortisol levels have returned to baseline. This provides more direct evidence of the effect of stress on consolidation processes (although it may still conflate encoding and consolidation stages).

In a study by Lupien and colleagues, participants learned word-pairs either during hydrocortisone infusion (which is rapidly converted into cortisol) or 4 hours later. Memory was tested following learning (immediate recall) and 4 days later (delayed recall). Those who learned the words during infusion showed poorer cued-recall 4 days later compared with controls; no group differences were found for those who learned the words 4 hours after infusion compared with controls (Lupien, Gillin, Frakes, Soefje & Hauger, 1995). No group differences were found on immediate recall measures, in contrast to the studies cited above. Because retention-testing was conducted days after cortisol treatment, the researchers felt more confident in interpreting these findings as

additional evidence that elevated levels of glucocorticoids have an adverse effect on the consolidation of new verbal information. Others found no significant differences between groups administered cortisol either before or immediately after learning a noun list and controls when tested 24 hours later (De Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000).

Others have found a facilitative effect of on memory for *visual* information (picture recall) in studies that separated retention testing from acquisition. Buchanan & Lovallo (2001) found that participants given 20mg of cortisol prior to presentation of pictures varying in emotional affect performed significantly better than controls during the cued recall of emotional (but not neutral) pictures learned incidentally 1 week previously. This finding was replicated in another study for 20mg dose, but not 40mg dose, for the recognition of both negative and neutral pictures two days later (Abercrombie, Kalin, Thurow, Rosenkranz & Davidson, 2003). Similarly particiants who underwent a cold presser stress (which significantly elevated cortisol) after viewing slides of varying stimulus valence demonstrated enhanced recall of emotional slides (but not neutral slides) when memory was tested one week later (Cahill, Gorski & Le, 2003).

This data need not be contradictory. It is quite possible that under stress, long-term memory for emotionally arousing material is enhanced while memory for more neutral information is weakened (although this may be a selective attention effect). There may also be domain-specific effects, with the consolidation of visual memory enhanced and verbal memory impaired by stress. The question remains whether encoding or retrieval is specifically affected by stress and glucocorticoid elevations. The human literature provides evidence implicating non-specific arousal and attentional effects, while only one recent human study (and one previously reviewed animal study) applied the stress manipulation at the point of retrieval, providing preliminary evidence that this process is negatively effected by stress.

Glucocorticoids and Attention

Early research on glucocorticoids and cognition came from psychophysiological studies. Researchers looking at evoked potentials following presentation of auditory, visual, or taste stimulation found a negative effect of administered glucocorticoids on sensory processing—specifically a latency of evoked potentials and a decrease in reaction time (Born, Hitzler, Piertrowsky, Pauschinger, & Fehm, 1988; Fehm-Worfsdorf, Scheible, Zenz, Born, & Fehm, 1989; Kopell, Wittner, Lunde, Warrick, & Edwards, 1970). Born and colleagues found evidence that cortisol may have a hypoarousal effect (slowing sensory processing and decreasing vigilance), as opposed to interfering with selective attention to relevant stimuli (Born, Kern, Fehm-Wolfsdorf, & Fehm, 1987). In support of the hypoarousal explanation, Wolkowitz et al. (1988) found a positive correlation between prednisone infusion (over 5 days) and negative alpha waves, or brain slowing. Several studies, however, did not find vigilance to be affected by glucocorticoid administration (Newcomer et al., 1994; Newcomer et al., 1999; Lupien, Gillin, & Hauger, 1999).

The evidence for the impact of glucocorticoids on selective attention is more robust. In a study by Wolkowitz and colleagues, subjects were given either 1mg of dexamethasone, a synthetic steroid, or placebo, followed by memory testing the following day. Memory was tested with a free recall of 12 semantically-related words followed by a 24-word recognition test (12 correct, 12 distracters). During the list learning, half of the words were repeated, and subjects indicated a repeated word with a raised hand as a measure of attention. No differences were found between groups on vigilance, free recall or recognition of correct words. The dexamethasone group did, however, have significantly more errors of commission (intrusions) compared with the placebo group during the free recall, which the authors interpreted as a failure of selective attention during encoding (Wolkowitz, et al., 1990). The researchers repeated this procedure with prednisone (80mg) administered over 5 days followed by memory testing, and again found no differences in attention or memory for target words. The predisone group had significantly more errors of commission on the recognition test (false

positives). This again suggested to the authors an impairment in attending to and encoding relevant stimuli, thus making it difficult to distinguish target words from semantically-related distracters during retrieval. An alternative interpretation for these findings is possible: the intrusion of non-target words during these tasks occurs *during retrieval*, and may reflect a disruption of this process (for example, a failure to inhibit competing responses during retrieval). They also proposed that an inverted-U shape relationship between dose and attention performance (Wolkowitz et al., 1990).

Recently, however, Lupien and colleagues also found that high doses of cortisol (600 mg) negatively impacted selective attention on an item-recognition working memory test, but did not affect declarative memory or vigilance (Lupien, et al., 1999). Lower doses did not have this effect, again providing additional evidence for the inverted-U shaped relationship between dose and cognitive function. The selective attention test involved varying the number of targets (symbols or letters) displayed or the number required to attend to (or both type and number) for later recall, effectively straining the limited-capacity working memory. Vigilance was measured using a continuous performance test, while declarative memory was tested with a paired-associate recall task. The authors concluded that working memory (selective attention) is more sensitive to an increase in corticosteriod levels than declarative memory systems, and there is evidence that this implicates the prefrontal cortex (Owen, Downes, Sahakian, Polkey, & Robbins, 1990). Others have also found acute negative effects of hydrocortisone on measures of attention including Digit Span (Wolf, Convit, McHugh, Dandil,Thorn et al., 2001), dichotic listening task (Al'absi, Hugdahl, & Lovallo, 2002) and the Stroop task (Hsu et al., 2003).

However, several human studies have failed to find this glucocorticoid effect on selective attention (Newcomer et al., 1999; Newcomer et al., 1994), and the above findings also contradict the observed facilitative effects of stress on acquisition behaviors in animals.

Glucocorticoids and Retrieval

In their 1997 review of the animal and human literature on corticosteroids and cognition, Lupien & McEwen propose that glucocorticoids exert an inverted-U shape effect on arousal, selective attention (thus influencing the encoding or acquisition of information), and consolidation (Lupien & McEwen, 1997). They did not consider retrieval an additional candidate for corticosteroid effects, given the implicit hippocampal model guiding the research. However, in all of the human studies using short-term memory tests (recall testing within an hour of learning), the stressor or drug treatment was active during all phases of learning and recall (including retrieval). While several recent studies cited above introduced a longer delay between learning and retention testing that allowed glucocorticoid levels to return to baseline during retrieval, they did not manipulate stress or cortisol at the time of retrieval. Thus it remained unclear whether retrieval processes may be affected by stress or increases in cortisol.

De Quervain and colleagues recently conducted the first human study to examine this question, and found evidence that retrieval is impaired, consistent with two animal studies (De Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000). The authors utilized a placebo-controlled repeated measures design, which involved having participants learn 60 unrelated nouns for immediate and 24-hour delayed recall (both free recall and recognition were tested). The 36 participants were randomly assigned to receive either 25 mg of cortisol or pill placebo at 3 different times: 1 hour before word presentation, immediately after word presentation, or 1 hour before delayed recall the next day. Two weeks later participants were then assigned to the treatment they did not receive before (pill or placebo), and the procedure was repeated (same timing of intervention) with a new word list. The authors found that cortisol significantly impaired memory compared with placebo, but only in the group that received the treatment before the delayed recall. The impairment was only observed for free recall, and not recognition, the latter of which minimizes retrieval demands. No differences between the cortisol and placebo groups were observed when doses were administered before or immediately after

word presentation. The authors confirmed that salivary cortisol levels rose significantly in the cortisol groups.

Roozendaal (2002) has proposed an adaptive explanation for why cortisol might disrupt retrieval. In a stressful situation, consolidation of novel information related to the situation is enhanced so that one is more likely to later remember where the lion naps or when the hostile supervisor takes his coffee break. However, in order to facilitate this new learning during arousing situations, competing processes of retrieving old information may be inhibited. As Roosendaal summarizes:

> It is plausible that a temporary disruption of memory retrieval during stressful conditions may diminish retroactive interference, thereby facilitating memory consolidation of such arousing experiences. In this view, glucocorticoid-induced downregulation of memory retrieval is thus not simply detrimental but serves an important adaptive value (p. 589).

Summary

The story of stress and memory in humans has thus become more complex in recent years. The majority of studies have tested memory within an hour of stress or cortisol manipulation, thus confounding encoding, consolidation and retrieval processes. Of the dozen or more of these studies, all but two demonstrated impairing effects on memory, and all but one looked at verbal recall of word lists or narratives. Several recent studies, however, have manipulated stress or cortisol prior to stimulus presentation, and then tested memory after a significant delay (allowing cortisol levels to return to baseline for retrieval). Results from these studies are mixed. One study found a detrimental effect (and another no significant effect) on verbal memory, while several others have demonstrated a facilitative effect on visual memory (particularly with affective material). This method allows for a more direct test of the effects of stress on consolidation, and the data suggesting a facilitative effect on visual memory consolidation are consistent with the animal literature. However, this method continues to confound consolidation with encoding. (Research examining the effect of cortisol on working memory or selective attention suggests that glucocorticoids disrupt working attentional processes.) In addition,

none of the studies with the retention interval manipulated cortisol prior to retention testing to examine retrieval effects. Only one human study administered cortisol at each stage of memory formation (prior to list learning, immediately after, and just before retention testing the next day), and found no effect on encoding or consolidation, but an impairing effect on word retrieval. No study to date has used a similar methodology to parse the effects of a *stressor* (rather than a pharmacological intervention) on the different memory processes, as the present study does.

6. Summary & Integration of Human and Animal Studies: Issues Motivating Present Study

Discrepancy in the Animal & Human Literature

There is thus strong evidence that stress and cortisol affect both visual and verbal semantic memory in humans. However, unlike the animal research, which generally demonstrates a facilitative effect of moderate doses of corticosteroids on spatial memory and associative learning, most of the human studies have found a detrimental effect. There are several possibilities that might resolve these discrepancies. It may be that stress facilitates nondeclarative memory (conditioning and procedural learning in the animal literature), while impairing declarative (semantic) memory in humans. Indeed, the logic of the dominant hippocampal-consolidation explanatory model in the human literature goes as follows: the hippocampus has been implicated in the consolidation of declarative memory and not procedural memory; the hippocampus has a large concentration of glucocorticosteroid receptors in the brain; thus stress activates the hippocampus and disrupts consolidation (de Kloet, Oitzl, & Joels, 1999; Kirschbaum, et al., 1996; Newcomer et al., 1994). Research on the neuropsychology of memory, however, disputes the theory that the hippocampus is the primary neural structure supporting consolidation, and instead suggests that many regions are involved in all stages of memory formation and recall. Thus there is no strong theoretical reason to expect consolidation effects alone (whether positive or negative).

Dose-dependent Effects?

Another way to potentially resolve the discrepant human-animal findings is suggested by studies that have manipulated the dose levels of glucocorticoids and the effect on memory. A number of animal studies suggest dose-dependent effects on memory following an inverted-U shape function. Studies with corticosteroid receptor agonists and antagonists suggest that low levels of corticosteroids (in which mineralocorticoid receptors are fully occupied) may influence attention and encoding of

relevant stimuli, while increasing levels associated with stress (in which glucocorticoid receptors start to become occupied) act on consolidation processes (with moderate doses facilitating memory and very high doses impairing it).

The few dose studies in the human literature also demonstrate an inverted-U shape relationship between glucocorticoids and cognition (Lupien, et al., 1999; Abercrombie et al., 2003). Additional support for dose-dependent effects in humans comes from a study by Fehm-Wolfsdorf and colleagues demonstrating higher cognitive performance during morning hours compared with the night. This corresponds to the natural diurnal hormone cycle: cortisol levels peak upon waking and rapidly (and then more gradually) decrease, hitting the lowest level before sleep. When subjects were given additional cortisol in the morning (presumably increasing levels beyond the morning peak of the inverted-U), cognitive performance decreased compared to those administered the cortisol at night (Fehm-Wolfsdorf, Reutter, Zenz, Born, & Dubrovsky, 1993).

Thus the majority of human studies reviewed above, in attempting to approximate moderate stress, may be raising cortisol levels beyond the peak of the inverted-U, resulting in detrimental effects on memory. Animal studies showing a facilitative effect of stress-levels of corticosterone on memory may instead be achieving the peak for those species. Clearly more research on dose-dependent effects in humans is needed to shed light on this issue.

Different Stages, Different Effects

Another possibility—and the motivating force behind the proposed study—is that the discrepancies in the animal and human literature may be related to a methodological issue. In most of the human studies, the stressor or cortisol is applied *before learning*, and recall is tested generally within an hour. Thus, cortisol levels are elevated during encoding, consolidation, and retrieval. Disruption in *any* one of these processes could account for memory impairment, the dominant model not withstanding. In contrast, animal studies have administered corticosteroids or stressor prior to and / or immediately

after training, followed by retention testing the following day (retrieval thus occurs after corticosterone levels have returned to baseline). These studies provide strong evidence for a dose-dependent, facilitative effect of stress on both encoding and consolidation.

Several recent human studies have attempted to address the confounding of memory stages by administering the stress or cortisol manipulation prior to acquisition, and then testing memory after a long interval (48 hours or more). These studies provide stronger evidence of encoding and consolidation effects of stress, although the findings are mixed. While one study found a detrimental effect on verbal memory (Lupien et al., 1995), several others found a facilitative effect on visual memory (Buchanan & Lovallo, 2001; Abercrombie et al., 2003; Cahill et al., 2003). These studies (with the exception of Cahill et al. 2003), however, continue to conflate encoding and consolidation processes. Studies examining attentional effects have generally found stress and cortisol to interfere with selective attention and working memory. In addition, none of the studies cited above manipulated stress or cortisol levels on the day of memory testing to investigate retrieval effects. Only one human study (de Quervain et al., 2000) and two animal studies (de Quervain et al., 1998; Oitzl & De Kloet, 1992) have directly tested for the effects of stress during each stage of memory formation and recall. These researchers found evidence of impaired *retrieval*.

Need for Ecologically Valid Memory Measures

The majority of the human studies use traditional neuropsychological tests to measure declarative memory. These tests were originally designed to detect brain damage, rather than detect subtle but important differences in memory function of healthy individuals. There is also the issue of ecological validity. Neuropsychological memory tests typically use word lists or line drawings—stimuli that are simplified and isolated from the complex, context-laden bombardment of information we normally encounter in our daily lives. A new memory measure was thus developed for the proposed study (see pilot studies) to better approximate the conditions under which we

typically form memories: participants will watch a brief film, and then be tested on visual and verbal information in the film.

Summary & Purpose of Current Study

Given the robust research evidence that stress and glucocortiocoids affect memory, and recent studies which have sought to parse the effects on different stages of memory, a revised model is proposed which integrates the animal and human data. Stress and associated glucocorticoid elevations may enhance the encoding and consolidation of new information in a dose-dependent manner, so that moderate to strongly arousing events will be better remembered. In order to facilitate this new learning, however, retrieval processes may be inhibited or disrupted, so that old knowledge does not interfere with the acquisition of new information. Thus the current study is designed to test whether stress will facilitate encoding and consolidation, but impair retrieval. And while most of the human studies have generally found detrimental effects with verbal memory, and the few that have separated consolidation from rentention-testing have only found support for stress-enhancement of visual memory, in this study verbal memory is predicted to be more sensitive than visual memory based on trends in the pilot data. Finally, it is hypothesized that change in cortisol will predict memory scores. Cortisol and anxiety were not expected to correlate, based on findings from the pilot study (see Chapter 2).

CHAPTER 2: PILOT STUDIES

1. FILM PILOT STUDY

Purpose

Most of the existing neuropsychological memory tests utilize word lists, short narratives, or line drawings to measure people's memory. Although these tests have robust psychometric properties, the memory stimuli lack the context, meaning, and complexity that characterizes real events outside the laboratory. For this reason, the investigator sought to develop a more ecologically valid measure of memory for the proposed study. Because Films come very close to mimicking verbal and visual stimuli as they naturally occur during an experience, a short Film (the "Dinner Party") was developed by the investigator as the memory stimulus. The purpose of this study was to pilot 126 verbal and visual memory questions based on the Film in order to develop immediate recall (IR) and delayed recall (DR) questionnaires. Item analysis data was collected on the difficulty level and inter-item reliability (discrimination value) for each question. This data was used to assign questions to the Dinner Party (Film) IR and DR Recognition Tests for the stress and memory pilot.

Method

Design

Questions (126) were designated as verbal or visual items, and divided equally into two pilot questionnaires, Film Pilot Questionnaires 1 & 2, in order to reduce fatigue. (The intention was not to compare these questionnaires, but simply to pilot a large number of questions.) Different subjects were used for an immediate recall condition and a 48-hour delay condition, in order to establish the difficulty level of the items at delay without previous rehearsal at the immediate recall point. Participants in each condition randomly received one of the two questionnaires. Thus four groups of participants were used to gather data on the pilot questions (see Table 1 below).

Table 1: Film Pilot Study Participant Groups		
	Film Pilot Questionnaire #1	**Film Pilot Questionnaire #2**
Immediate Recall	G1	G3
Delayed Recall	G2	G4

Participants

Undergraduate students (N=115) from the University of Texas at Austin were recruited for this study and received experimental credit for their introductory psychology course. Students signed up for the experiment (either immediate or delay condition) on posted sign-up sheets and received 1-2 hours research credit for participating. There were no exclusion criteria. The number (and gender) of the participants per group, defined above, were: G1: n = 38 (27 male / 11 female); G2: n = 22 (13 male / 9 female); G3: n = 32 (19 male / 13 female); G4: n = 23 (11 male / 12 female).

Measures

Film stimulus

A seven-minute Film, “The Dinner Party,” was developed and produced by the investigator for the proposed study. The Film was directed by Alan Klenk of Picturebox Productions, and performed by 5 professional actors and one child from Austin, TX. The Film portrays a couple having a dinner party for several invited (and surprise) guests, and includes six brief scenes (to make for a more complex stimulus): the hosts discussing the dinner party that night (kitchen); arrival of an uninvited friend (kitchen); arrival of expected couple and their son (front door, living room); small talk among guests (living room); hosts telling 2 contradictory stories about their first date to one guest (living room); the hostess straightening up (kitchen). The dialog and action was loosely scripted, and is therefore largely improvised and fairly quick-paced. Verbal information includes

the content of many short, unrelated conversations; visual information includes room furnishings, clothing, and props handled by the actors. The content of the Film is not intended to arouse strong emotion, and there is some ambiguity regarding the story-line (i.e., the "dinner" never happens; one character keeps pulling strange objects out of his bag and handing them to party guests).

Memory test questions

One hundred and twenty-six questions testing visual (67) or verbal (59) information presented in the "Dinner Party" Film were the items of interest in this study. The questions followed the chronology of the Film, and were presented in recognition format with 5 possible answers. Every question included an optional answer indicating that that verbal or visual item was not present in the Film (this was the correct answer for several of the questions. These "false positive questions" (so named because an incorrect answer suggests a false memory for information not presented in the Film) were included so that participants would not know whether a question was providing a real cue. To reduce fatigue and pilot alternative questions testing the same information, the test items were divided into two alternative questionnaires, Film Pilot Questionnaire 1 & 2, with 63 questions each. The two questionnaires were generally matched on content according to face value, and had a similar number of visual and verbal questions.

Information & Heart-rate Form

This form was included as part of the deception in the study, and to collect demographic information. It included spaces for the heart rate to be recorded, gender, age, and checkboxes for problems or disorders that might affect memory performance.

Procedures

Participants signed up for one of two conditions: immediate recall or delayed recall, and were run in groups of 5-20. When participants arrived at the classroom where the experiment was conducted, they were given a fictitious rationale for the study to disguise the upcoming memory test. Participants were told that the purpose of the study was to examine gender differences in physiological reactivity in response to a short Film.

The experimenter then distributed the Information & Heart-rate Forms for participants to record their two heart-rate measures. Participants were instructed how to take their heart rate, and subsequently recorded their baseline measure. The Film "The Dinner Party" was then shown.

In the immediate recall condition, participants were administered either Film Pilot Questionnaire 1 or 2 (randomly assigned). In the delayed recall condition, participants left following the Film and were asked to return in 48 hours in order to watch a new Film. Upon returning on the second day, they randomly received either Film Pilot Questionnaire 1 or 2. Following the questionnaire administration in both conditions, participants were debriefed and any questions were answered.

Analyses & Results

An item analysis of the questions from Film Pilot Questionnaires 1 and 2 was conducted. The difficulty level for a question was calculated as the percentage of participants that correctly answered the item at immediate recall and delay. Inter-item reliability, a measure of how well individual items measure the same dimension, was determined with an item-total coefficient of correlation value. This is also known as a discrimination index, because it is a measure of how well the item discriminates between individuals who score high on the test overall from those who score low. Inter-item reliability is calculated by first subtracting a participant's score on the item from their total score, and using this pair of scores across all participants to obtain a Pearson's correlation.

The item analysis data was then used to select test items for the Dinner Party Film Immediate Recall (IR) and Delayed Recall (DR) Recognition Tests for the subsequent stress and memory pilot. Items were selected if they met two criteria. First, items had to have an individual interitem reliability of .2 or greater at immediate recall. This ensured that all items were tapping essentially the same construct when first recalled. (Discrimination value declined substantially at delay with the rapid forgetting curve—answers became more random at delay—and was therefore not included as an exclusion

criteria.) Next, items had to have a difficulty level (percentage correct) at immediate recall between p = .4 and p = .9. This range was determined by starting with the optimum difficulty level range for an item (which is approximately halfway between 1.00 and the guessing level for that item—in this case, p = .2 for a 5-choice answer—which comes to p = .6), and expanding out from this ideal to provide greater sensitivity to changes in either direction. Questions which were answered correctly by less than 40% of the participants (fairly difficult), or by more than 90% (fairly easy), were excluded.

Sixty-four questions met these two criteria and were assigned to either the Film IR or DR Recognition Tests according to the following procedure. All items were divided first into verbal or visual categories. Within each category, items were paired according to their difficulty value at immediate recall, and then by their difficulty value at delay. Drafts of the Film IR and DR Recognition Tests were thus assembled "blind" based on above criteria. Minor changes were made to the final tests after a review of the content, due to overlapping information or cueing within a test. A statistical analysis of the two tests is shown below (Table 2).

Table 2: Statistics on Dinner Party Immediate Recall & Delayed Recall Recognition Tests

Statistic	**IR Recognition Test**	**DR Recognition Test**
Mean difficulty (immediate)	.69	.69
Mean difficulty (delay – forgetting curve)	.51	.53
Mean interitem reliability	.40	.40
Number of "False Positive" Items	8	6
Number of Questions	33	32
Verbal/Visual Questions	16/16	16/16

Discussion

The statistical analysis of the Dinner Party IR and DR Recognition Tests demonstrates that they are well matched on difficulty and interitem reliability (item discrimination). The mean difficulty level of the items at immediate recall for both the IR and DR tests (.69) is slightly higher than the recommended .6, but this is to accommodate the expected forgetting curve for the information at delay (mean difficulty level of .51 and .53 respectively). It is of note that the most neuropsychological measures of memory test identical information at immediate recall and delay. Such a design, however, yokes the DR score to the IR scores: information one recalls shortly after presentation is rehearsed and thus more likely to be recalled later while poor performance at immediate recall virtually guarantees forgetting at delay, revealing little about consolidation processes. Thus testing different visual and verbal information during immediate the delayed recall reduces (but does not eliminate, due to cueing) this effect.

The issue of test validity is also an important one. The rationale for developing the "Dinner Party" Film stimulus and related memory tests was to have a measure of memory that better approximated real-world situations than current neuropsychological (or cognitive) tests. When people attempt to remember details from experienced events, the target details are imbedded in a complex array of visual and verbal information unfolding in particular social and non-social contexts. Watching a Film about a social event comes close to capturing this complexity (from an observer's perspective). For this reason, however, a Film is a more "messy" stimulus than a word-list. The amount of information presented in a Film is large, and thus places more demands on attention and working memory. Characters or events in the Film may be more or less salient or distracting. And although the Film was intended to be neutral in affect, it is possible that aspects of story might evoke an emotional response in the observer, which might also influence memory. So with an increase in ecological validity comes a greater difficulty in interpreting experimental results. In addition, because the Film IR and DR Recognition Tests are new, no standardization data or information on their predictive validity is available.

2. STRESS AND MEMORY PILOT

Purpose

The purpose of the second pilot study was to test out the procedures of the proposed study, including the effectiveness of the stress induction, and to determine whether the preliminary data suggested differences between groups on memory.

Method

Design

The pilot study utilized a between-groups design with four conditions. Participants signed up for a particular condition according to scheduling fit, and were run in groups of 5-20. Memory was tested with the questionnaires based on the "Dinner Party" Film and developed from the Film Pilot Study data. All participants first observed the Film stimulus, and were then administered an immediate recall test and a delayed recall test 48 hours later. Groups differed in the timing (or absence) of the psychosocial stress induction (see Table 3 below). The Pre-Film group was stressed before the Film (prior to encoding). The Post-Film group was stressed after the Film and immediate recall test (during the period of consolidation after leaving the experiment). The Return group was stressed upon returning 2 days later (just before retrieval of the delay recall test). The Control group received no stress induction. Salivary cortisol was measured immediately before and approximately 10 minutes after the stress induction in the stress groups (and prior to viewing the Film in the control group). Although only a subset of the cortisol samples were analyzed for this pilot study, samples were obtained from all participants to keep the procedure (and cover story) consistent.

Table 3: Stress & Memory Pilot Study Design			
Group	**First Day**		**48-hours Later**
Pre-Film	c X c	Film / IR TEST	DR Test
Post-Film		Film / IR TEST c X c	DR Test
Return		Film / IR TEST	c X c DR Test
Control	c c	Film / IR TEST	DR Test
c = cortisol sample X = stress induction			

Participants

A total of 101 undergraduate students from a large southwestern university were recruited for this study. Participants were part of a large subject pool (N > 3000) of introductory psychology students, and received course credit for their participation in the study. Students signed up for the experiment on posted sheets if they met the following criteria: English had to be their native language (in order to easily follow the Film), and their history had to be negative for neurological disease, head injury, or Attention Deficit Hyperactivity Disorder. The demographics of the final sample per group are shown in Table 4 below.

Table 4: Stress & Memory Pilot Sample Demographics					
	Pre-Film	**Post-Film**	**Return**	**Control**	**Total**
Male / Female ratio	13 / 8	22 / 9	17 / 6	21 / 5	73 / 28
Mean Age	19.19	19.27	19.35	19.15	19.24
Caucasian	12	21	16	17	66
Asian	3	1	4	5	13
Hispanic	3	4	2	3	12
African American	0	2	1	1	4
Other	2	2	0	0	4
Total n per group	21*	31*	23	26	101
* 1 participant in each of these groups declined to state ethnicity					

Measures

Film Stimulus

See description above (*Film Pilot Study*).

Memory Tests

Memory for information on the Film was tested with the Dinner Party (Film) Immediate Recall (IR) and Delayed Recall (DR) Recognition Tests, developed by the investigator using data from the Film pilot described above. The tests have 32 questions in a multiple-choice format. Each question has 5 possible answers, and taps either visual or verbal information from the Film. See *Film Pilot Study* above for difficulty and reliability data on the tests.

Cortisol Measure

See proposed study for description (*Chapter 3: Methods*).

Subjective Anxiety

Just before participants thought they were about to give their speech (the height of the stress induction), they were asked to rate their subjective anxiety (SUDS) on a 0-100 scale. They were told that "0" represents no stress or anxiety, while "100" would be fear of death.

Demographic & Other Information

Participants recorded their age, gender, and ethnicity on scantron forms at the beginning of the experiment. Information regarding conditions (pregnancy, depression) and medications which can affect cortisol levels was collected in the Post-Experiment Questionnaire.

Manipulation check

At the end of the experiment, participants were given the Post-Experiment Questionnaire and asked to rate their belief in the likelihood that they would have to give the speech. They also indicated the presence of other stressors (and their severity) prior to and over the 3 days of the experiment, and whether they ate, drank, or exercised 1 hour prior to either experimental session.

Procedure

Preparation, Consent, & Cover Story

Participants signed up for the experiment on posted sign-up sheets. They selected one of the four conditions (groups) available each week based on scheduling fit; all groups were run between 3:00 and 6:00 PM. On the sign-up sheets, participants were instructed not to eat, drink (especially caffeine drinks), or exercise at least one hour before the experiment. Participants in the same condition were run together in groups of 5-20, in one of two classrooms. The classrooms were similar in size (seating a maximum of 20 people), each with a large projection screen to show the Film.

When the participants arrived at the appointed time, the experimenter explained the purpose of the experiment. This description was designed to disguise the real purpose of the study, in order to maximize the stress induction and discourage participants from

rehearsing information before memory testing. Participants were told that the investigator was interested in the relationship between the role of food in Film and hunger, and that this was of particular interest to the food concessionaire industry. This provided a rationale for collecting the saliva samples (hunger enzymes) and speech induction (topic: food and Film, hence the "dinner party" theme). Participants were informed that the procedure would require them to return 48 hours later, and would involve watching a Film, completing questionnaires, providing several saliva samples, and possibly an activity that would cause them to become anxious. The experimenter then provided participants written consent forms covering this information, and answered any questions.

First Day

- All participants were first given the Scantron Information Form to fill out with their demographic data and the last 4 digits of their social security number.
    - Participants in the Pre-Film, Post-Film, and Control groups were provided a Salivette, and instructed on how to collect their baseline saliva sample. Participants were told to chew the cotton insert of the Salivette until saturated (1-2 minutes), and then deposit the cotton into the Salivette tube.
    - Participants in the Pre-Film group underwent the stress induction (see below).
- All participants then watched a 7-minute Film, "The Dinner Party."
- All participants were administered the Film IR Recognition Test, with the explanation that the questionnaire was necessary to determine how engaged people were with the Film. The test took approximately 10-15 minutes to complete.
    - A second salivary sample was obtained from the Pre-Film group (approximately 20 minutes after cessation of the stressor) and the Control group (approximately 20 minutes after the first sample).
    - The Post-Film group participants underwent the stress induction. A second saliva sample was obtained following a 15-minute waiting period.
- Participants were then thanked and asked to return 48 hours later to complete the experiment, at which time a "tantalizing" Film would be shown. They were also told

that if they chose to withdraw at this time and not return, they would need to contact the experimenter to obtain credit for the first half of the experiment.

Return Day (48-hours later)

- The Scantron information forms were first returned to all participants, and the experimenter described the "change" in procedure for the second half of the experiment.
    - Participants in the Return group provided their first saliva sample, then underwent the stress induction, followed by a 7-minute waiting period.
- All participants were then administered the Film Delayed Recall Test without explanation. The test took approximately 10-15 minutes to complete.
    - A second saliva sample was obtained from the Return group, approximately 20 minutes after cessation of the stressor.
- The experimenter debriefed participants verbally and in writing, explaining the true purpose of the study and the rationale for the deception. The Post-Experiment Questionnaire was distributed to check the believability of the stress manipulation and to check for any experiences, conditions, or medications that might affect cortisol levels.

Stress Induction

The psychosocial stress induction was loosely based on the Trier Social Stress Test (TSST - in which participants prepare for a speech and then deliver it in front of a small audience), but without requiring participants to actually give the speech. This allowed participants to be run in groups, to maximize social anxiety during the preparation period. Participants were first given the following instructions:

> Now we would like you to prepare a short speech. The topic is: "The Role of Food in Film." I will pass out examples of topics and themes that students in other groups have come up with. The speech should be approximately 5 minutes long and well organized. We ask that you write out an outline with detailed notes in order to prepare. We will be collecting your notes and they are important to the study. We have several rooms set aside with assembled audiences to listen to your talk, and we will be videotaping it as well. The people in the audience are undergraduates and graduate students who are also researching this topic.

> Please take out some paper to prepare for your talk. Be sure to write the last 5 digits of your social on the paper. You will have 10 minutes to prepare the speech, and then 1 minute to commit it to memory. We will then collect your notes for analysis, and take you to the speech rooms. Please do not talk during this preparation period. I will call out the time every 2 minutes, and will circulate to help anyone who is having difficulty.

The example topics included a number of lofty and intellectual arguments, such as "How the movie *Chocolat* used chocolate as a metaphor for indulging in the sensual aspects of life and shedding the dogmatic constraints of a conservative small village." At the end of 10 minutes, participants were instructed to take the next minute to commit their speeches to memory. They were also asked to write down their subjective anxiety on a scale from 0-100. After collecting their notes, participants were told:

> Thank you for preparing the talk. We will NOT actually have you give the speech. We needed to have you believe this so that you would prepare the best outline and notes possible. We are interested in what people write on the topic, and we will analyze your notes as part of our results, so thank you! We had you rate your anxiety because this can affect how well people write.

Hypotheses

Stress was predicted to negatively affect the retrieval of both verbal and visual information. Thus the Pre-stress group was predicted to perform more poorly than all other groups (not stressed) at immediate recall on verbal and visual test scores, but not at delay (when cortisol levels should be close to baseline). The Return group was predicted to perform more poorly on verbal and visual DR test scores compared with all other groups at delay. No group differences were hypothesized between post-Film group and controls at delay. Increase in cortisol levels following the stress induction was expected to predict memory performance (negative correlation).

Analyses and Results

Analysis of memory performance includes all participants in the study. Cortisol was only analyzed for participants in the Pre-Film group (n = 20) and a subset of the

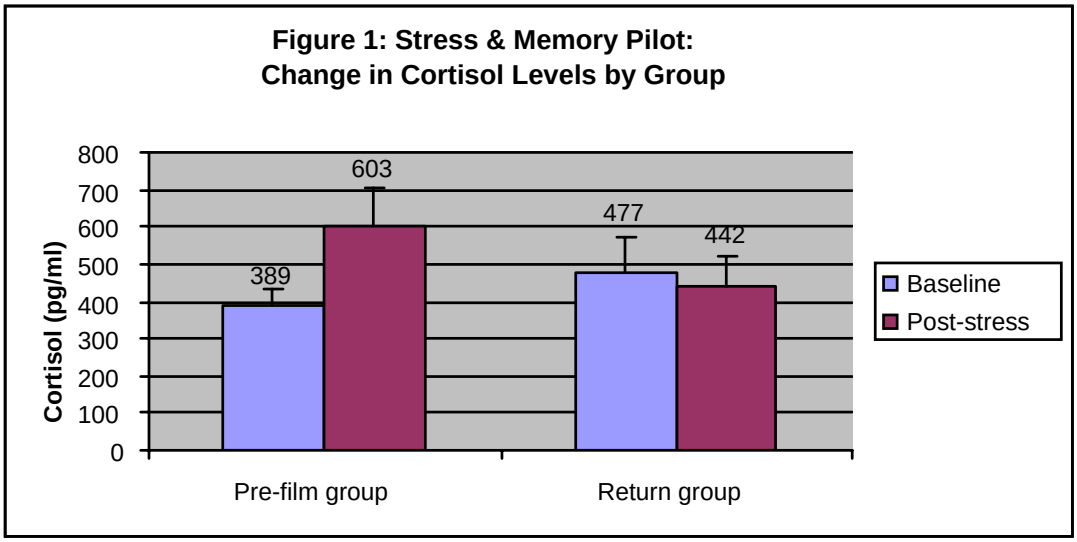
Return group (n = 13) to provide preliminary data for stress response. Intra-assay variation was less than 8%; inter-assay variation was less than 15%.

Validity Check

A chi-square test was used to assess differential dropout rates (number of participants that did not return after the first day) between groups. No significant group differences were found in dropout rates. A one-way ANOVA was also conducted on mean baseline cortisol levels between the two groups with cortisol data. No significant group differences were found (Pre-Film group: M = 389 pg/ml, SE = 43; Return group: M = 477 pg/ml, SE = 97).

Stressor Potency

A repeated measures ANOVA with stress condition as the between-group factor and time (pre-post cortisol levels) as the within-subjects factor determined no significant change in cortisol levels across all participants, but did show a group X time interaction approaching significance ($p = .06$). Thus change in cortisol levels from baseline to post-stress showed an unexpected trend toward differing between groups, and were therefore analyzed separately for the Pre-Film group and the Return group using a repeated measures ANOVA. A significant increase in cortisol was found for the Pre-Film group ($F = 4.84$, $p < .05$), while no differences in pre-to-post cortisol scores were found for the Return group (see Figure 1 below). This is certainly a problematic finding, and suggests that the manipulation was not effective in the Return group.



The question remains as to how biologically relevant the significant change in cortisol is for the Pre-Film group. In previous studies with the TSST social stressor, observable and significant cognitive effects have been observed with a doubling of cortisol values. In the present study, cortisol increased following the stressor by 55% in the Pre-Film group.

Anxiety (SUDS) ratings were also analyzed for all subjects in the 3 stress conditions as a subjective measure of the stressor. The mean anxiety rating (on a scale of 0-100) across groups was M = 39 (SD = 31), in the mild-moderate range. No significant group differences were observed. It is noteworthy that participant anxiety was not correlated with the cortisol response ($r = .2$, $p = .26$).

Memory Performance (all participants)

Differences among the groups were examined using a multivariate analysis of variance (MANOVA) for the immediate recall (IR) visual and verbal memory scores (which together make up the total score). A multivariate analysis of covariance (MANCOVA) was conducted for delayed recall (DR) visual and verbal scores, with IR scores as covariates. Group mean IR and DR total scores are shown in Table 5 below.

Table 5: Stress & Memory Pilot Group Means for IR & DR Scores						
	Immediate Recall			**Delay Recall**		
	n	Verbal	Visual	n	Verbal	Visual
Pre-Film	21	10.67 (.56)	11.71 (.69)	20	8.70 (.56)	8.25 (.57)
Post-Film	31	11.94 (.35)	12.29 (.56)	29	8.86 (.47)	8.52 (.48)
Return	23	11.65 (.67)	10.91 (.64)	18	8.83 (.65)	7.78 (.52)
Control	26	11.77 (.46)	12.50 (.41)	25	9.20 (.38)	8.92 (.46)
*Standard error in parentheses						

Contrary to the hypotheses, no significant differences were found between groups at immediate recall for total score ($F = 1.54$, $p = .17$; F values are estimated from Pillai's trace). Similarly, no significant differences were found between groups at delay ($F = .22$, $p = .97$).

Memory Performance (responders)

Planned comparison MANOVAs were conducted between controls and participants in the Pre-Film group and Return group that demonstrated a strong cortisol response to the stressor ("responders"). A strong response was defined as a 25% or greater increase in cortisol levels from pre-to-post stress, which included 39% of the participants for whom we analyzed cortisol (9 / 20 in the Pre-Film group, and 4 / 13 in the Return group). To examine group differences at immediate recall, the Pre-Film group was compared to controls on visual and verbal recall. Return group responders were excluded from these analyses because they do not represent a control group at immediate recall (i.e., they are a *selected* group based on their stress response on the return day). At delayed recall, all three groups were compared on visual and verbal DR scores, controlling for IR scores. Group means are presented below (Table 6).

Table 6: Stress & Pilot Study Group Means for Responders and Controls						
	Immediate Recall			**Delay Recall**		
	n	Verbal	Visual	n	Verbal	Visual
Pre-Film	9	9.78 (.72)	12.33 (.99)	9	8.22 (.64)	8.89 (.42)
Return	4	10.25 (1.25)	10.75 (1.03)	4	7.25 (1.70)	7.25 (.75)
Control	26	11.77 (.46)	12.50 (.41)	25	9.20 (.38)	8.92 (.46)
*Standard error in parentheses						

No significant differences were found between Pre-Film group responders and controls at immediate recall ($F = 1.87$, $p = .167$), although there was a trend for group differences on verbal IR scores ($F = 3.87$, $p = .057$). Given the small sample sizes of the responder groups, this finding is encouraging. No differences were observed between groups at delay ($F = 1.31$, $p = .273$).

Cortisol & Memory

Pre-to-post percentage increase in cortisol was analyzed for all participants (with cortisol data) within groups a predictor of verbal and visual memory performance. A simple regression analysis found that cortisol predicted *verbal* memory at immediate recall ($t = -2.54$, $p < .05$) for the Pre-Film group, but not visual memory ($t = -.30$, $p = .76$). Cortisol failed to predict DR scores for the Pre-Film group. Increase in cortisol also predicted verbal at delay for the Return group scores ($t = -2.42$, $p < .05$), with a trend toward predicting total DR scores ($t = -1.95$, $p = .077$).

Discussion & Changes Made for the Current Study

Given the substantial evidence that stress and cortisol affect memory, the lack of any significant differences between groups on recall scores was surprising. Several methodological problems are considered below, and may account for the null findings. In

particular, only 39% of the participants analyzed for cortisol response (all of the Pre-Film group and a subset of the Return group) were "responders" (those who showed a 25% or greater increase in cortisol levels). In all stress studies, a certain percentage of participants do not show a strong cortisol response to various stressors, depending on personality features, individual differences in cortisol responsivity, and how threatening a particular stressor is to the individual (Van Eck, Berkof, Nicolson, & Sulon, 1996). Given this methodological limitation, it still seems clear that the stress induction in this study could be more robust. Based on responses from the Post-Experiment Questionnaire, many of the participants suspected that they might not have to give the speech, thus lowering their stress level. This was particularly true for the Return group, which showed no significant increase in cortisol. This may have been an experimenter effect: the same individual conducted all of the Return groups, while several different experimenters ran each of other groups. This underscored the importance of experimenter training and randomly assigning experimenters to groups for the final study.

The current study therefore modified the speech induction to make the speech more tangible: participants were taken to the "speech room" which was set up with an audience table, video camera, TV monitor, and speech podium. It was expected that this would improve the believability of the stressor, thereby intensifying the stress response and increasing the number of responders for the analyses. The pilot results also suggested that it would be fruitful to conduct a separate set of analyses "responders." Indeed, we did find a trend toward differences between the Pre-Film group responders and control on immediate recall of verbal information.

Another methodological issue involves the timing of the Film stimulus presentation and recall testing. Although the second cortisol measure was taken 15-20 minutes after the cessation of the stressor in all three groups (allowing for the delayed cortisol increase), participants in the Pre-Film group observed the Film immediately after the stress induction, and took the IR test after that (7 minutes after the stressor). It is quite likely that cortisol levels did not have enough time to elevate during the stimulus presentation, and is possible that levels were still climbing during the testing. Similarly, participants in the Return group

were also administered the DR test only 7 minutes after the end of the stressor, which again may not have provided enough time for cortisol to affect retrieval. This timing issue would not account for the lack of difference between Post-Film group (stressed before leaving on the first day) and the control group on delay recall scores, however. The current study was designed to address this timing issue: the Film stimulus was shown 10 minutes after the cessation of the stressor (for the Pre-Film group), while memory and cortisol testing was conducted approximately 20 minutes after cessation of the stressor in all groups.

Finally, there is the issue of the validity and sensitivity of the dependent measures. The investigator developed the Film and related recall questionnaires in order to test memory under conditions which better approximated "real world" situations than standard neuropsychological tests (word lists, line drawings). The dependent measures were thus intended to maximize ecological validity. However, because these are new tests, they lack data on sensitivity to memory disruption (and specifically, hippocampal function). In addition, recognition memory tasks are less challenging than free recall or cued recall tests when it comes to retrieval. Indeed, when recognition scores show improvement over recall scores, this is an indication of a retrieval deficit. For these reasons, several changes to the dependent measures were made for the current study. The Film memory tests were first given in a cued-recall format (fill in the blank), followed by the recognition tests. In addition, a standardized neuropsychological measure of memory with known sensitivity to detecting hippocampal dysfunction, the narrative recall test from the Wechsler Memory Scale-III, was also included to test free recall and recognition.

CHAPTER 3: METHOD

Purpose & Design

The purpose of the present study was to isolate the effects of stress on different stages of memory (encoding, consolidation, and retrieval). The study utilizes a randomized between-groups design with four conditions; participants will be run in condition groups of 1-6 people. Memory was measured with a standard neuropsychological memory test (WMS-III Logical Memory narrative recall), and with a newly developed measure tapping memory for an observed social event, intended to be a more "ecologically" valid measure of memory. The latter used a short film (developed by the author) as the stimulus and questionnaires testing cued and recognition memory for visual and verbal information from the film (see *Film Pilot Study*). Both sets of memory measures were administered immediately following the film to ensure learning (immediate recall), and 48 hours later for the primary memory measures (delay recall). Groups differed in the timing (or absence) of the 15-minute psychosocial stress induction during the experiment procedure (see Table 7 below). The Pre-film group was stressed before the film (prior to stimulus-presentation/encoding and consolidation). The Post-film group was stressed after the film (to elevate cortisol during consolidation over the two-day interval). The Return group was stressed upon returning 48 hours later (just before retrieval of the delay recall tests). The Control group received no stress induction. Salivary cortisol levels were measured just before and 20 minute following cessation of the stress induction.

Table 7: Timing of Stress Induction By Condition					
Group	**First Day**			**48-hours Later**	
Pre-film	c **X** c	Film / IR Tests			DR Tests
Post-film		Film / IR Tests	c **X** c		DR Tests
Return		Film / IR Tests		c **X** c	DR Tests
Control	c c	Film / IR Tests			DR Tests
c = cortisol sample **X** = stress induction					

Sample Size

The proposed sample size for the present study was N=180, based on a power analysis using data from the stress pilot and literature. In the stress pilot study, the effect size for the difference between the stressed and non-stressed groups at immediate recall was .42, while differences in delayed recall were in the .36-.38 range. Effect sizes observed in studies using a drug manipulation are generally in the .7-.8 range. Because this study employed a more robust stressor than in the pilot study, and excluding participants with little or no public speaking anxiety, the proposed study was expected to yield effect sizes somewhat between the pilot and published studies. The estimated effect size was .6, and given an 80% desired power to detect a real difference between groups, 45 participants per group was required.

Participants

Participants for this study (N=208) were undergraduate students from a large southwestern university enrolled in Introduction to Psychology, identified using an on-line pretesting survey (N = 3003). A preliminary selection process was used select participants who indicated any level of fear of public speaking (score > 0 on a 9-point scale for fear *or* a score > 0 for avoidance 9-point scale) in order to ensure at least a

minimal stress response to the public speaking stress induction, leaving 2214 potential subjects. An invitation to participate in the study was then sent to this group via e-mail. The e-mail identified exclusion criteria, including pregnancy and conditions associated with impaired memory function such as a history of neurological disease, head injury, substance abuse, attention deficit disorder or learning disability. In addition, participants were required to speak English as their first language. Paticipants who responded were then randomly assigned to condition and scheduled. They were instructed in subsequent e-mails prior to the experiment to refrain from smoking, drinking caffeine or alcoholic drinks, eating, or vigorously exercising one hour before the experiment time. Although 237 participants were run in the experiment, 26 were dropped from the analyses for failing to comply with the requirements (i.e., they ate right before the experiment), and 3 failed to return to complete the delayed recall tests. Of the final sample of 208, 72% were Caucasian and 67% female, with a mean age of 18.78.

Demographic data was obtained through the on-line survey prior to the experiment. At the end of the experiment, data was collected on level of current life stress ("basal stress") over the 3 days of the experiment, speech expectation (manipulation check), current medications, and compliance with the preparation requirements. Participants received experimental credit for their psychology course for completing the experiment.

Measures

Dependent Measures (Memory)

Immediate vs Delayed Recall Tests

In the current study, memory tests were administered at immediate recall on the first day of the experiment and at delay 48 hours later. The immediate recall measures are not primary dependent measures, but were administered to ensure that adequate learning of the material took place on the first day, and for post-hoc analyses. The primary dependent measures for this study are the delayed-recall tests.

Film Memory Questionnaires

Cued-recall and recognition questionnaires testing memory for information in the film (description below) were administered at immediate recall and delayed recall. The recognition test was piloted and is described first (below). The cued recall test was developed for the current study in order to have a more challenging memory test, and to compare cued-recall and recognition performance to detect possible retrieval effects.

Film stimulus

A seven-minute film, "The Dinner Party," was developed and produced by the investigator for the proposed study. The film was directed by Alan Klenk of Picturebox Productions, and performed by 5 professional actors and one child from Austin, TX. The film portrays a couple having a dinner party for several invited (and surprise) guests, and includes six brief scenes (to make for a more complex stimulus): the hosts discussing the dinner party that night (kitchen); arrival of an uninvited friend (kitchen); arrival of expected couple and their son (front door, living room); small talk among guests (living room); hosts telling 2 contradictory stories about their first date to one guest (living room); the hostess straightening up (kitchen). The dialog and action was loosely scripted, and is therefore largely improvised and fairly quick-paced. Verbal information includes the content of many short, unrelated conversations; visual information includes room furnishings, clothing, and props handled by the actors. The content of the film is not intended to arouse strong emotion, and there is some ambiguity regarding the story-line (i.e., the "dinner" never happens; one character keeps pulling strange objects out of his bag and handing them to party guests).

Film Immediate Recall (IR) & Delayed Recall (DR) Recognition Tests

Recognition memory for information based on the "Dinner Party" film will was tested with the Film Immediate Recall (IR) and Delayed Recall (DR) Recognition Tests, developed by the investigator using data from the film pilot described in Chapter 2. The questionnaires each have 30 questions in a multiple-choice format: each question has 5 possible answers, and taps either visual or verbal information from the film. Each test has 15 verbal questions (e.g., "Where does Melissa work?"), and 15 visual questions ("What

does Phillip hand Susan as she is walking to answer the door?"). Each question always included an answer indicating that the information was not in the film (so for the question "what room was the TV in?" one answer, and in this case the correct answer, was "there was no TV"). There were six "false positive" questions on each test which asked about objects or topics discussed which were not in the film. The 30 questions on each test also included 8 "relational" questions. These questions went beyond asking *whether* a cowboy hat was *present* in the film, but who was wearing it or who handing the hat to whom.

Questions have a range of difficulty from .4-.9 (percentage of people who answered the item correctly), with a mean difficulty level of .69 when tested at immediate recall and .51 when tested 48 hours later. DR test questions have a range of difficulty from .4-.9 and a mean difficulty level of .69 when tested at immediate recall and .53 when tested at delay. Both tests have an excellent inter-item reliability of .4 when items were tested immediately following film presentation.

Film Immediate Recall (IR) & Delayed Recall (DR) Cued-Recall Tests

The Film IR Test and DR Cued-Recall Test each has 20 fill-in-the-blank (cued-recall) questions about the "Dinner Party" film. Each test has 10 verbal and 10 visual items. The questions were originally piloted in multiple-choice format (see above and *Chapter 2*) and used as the dependent measures in the stress and memory pilot study (see *Chapter 2*). Although many of the questions in the cued-recall tests are identical to the recognition questions, some were re-worded to be more specific (in order to narrow the test takers' possible answers).

Wechsler Memory Scale (WMS-III) Logical Memory Test (Narrative recall)

Logical Memory from the Wechsler Memory Scale (WMS-III) is a standard measure of verbal memory. The test includes two paragraph-long narratives comparable in recall difficulty, each with 44 pieces of information. Each narrative is normally read aloud by the tester and then repeated (as close to verbatim as possible) by the subject. In a modification of the standard procedure, the narratives were taped and played aloud to the groups; participants were then instructed to write down verbatim everything they remember from the narrative. The first narrative (Story A) was used as a baseline

measure of memory (free recall). The second narrative (Story B) was used as a measure of immediate recall (free recall) and delayed recall (free recall, 10-question cued, and 10-question recognition).

Cortisol Measure

Circadian fluctuations

Cortisol follows a robust circadian cycle (as measure in either the blood or saliva) in humans. Circulating cortisol increases 50-100% upon waking, and peaks approximately 30 minutes later (Kirschbaum & Hellhammer, 2000). Cortisol levels decrease steadily throughout the day, with another (smaller) increase following the lunch meal. This steady drop in cortisol levels is most rapid before midday, and gradually slows in the afternoon and evening (Kirschbaum, et al.). Studies show that individuals demonstrate remarkable stability in their daily cortisol rhythm (Pruessner, et al., 1997). Because of the steep drop in cortisol during the early part of the day, the experiment was conducted between 3:00 and 6:00 PM when levels were more stable.

Saliva vs. blood sampling

Several reasons favor saliva sampling over blood sampling of cortisol. Obtaining blood samples is a more invasive technique than saliva sampling, and can trigger the cortisol stress response itself (Toglia, Payne, Nightingale, & Ceci, 1989). In addition, blood and saliva cortisol levels are highly correlated ($r \geq .9$), although absolute values are lower in saliva (Kirschbaum & Hellhammer, 2000). The high correlation results from the ease with which cortisol passes into peripheral tissues, and is described by Kirschbaum et al. in their review of salivary cortisol and summarized here. Once cortisol is released from the adrenal glands into the bloodstream it quickly becomes bound to carriers such as albumin; a small fraction, however, remains “free.” This unbound (and highly lipid-soluble) cortisol passes readily through cell membranes and thus appears rapidly in all body fluids including CSF, urine, sweat, and saliva. Most pertinent to this study: saliva shows comparable changes in cortisol concentration 2-3 minutes after levels rise in the

blood. It is this free cortisol that also crosses the blood-brain barrier, and is thus responsible for the neural effects of cortisol.

Cortisol stress response

Following exposure to a stressor, peripheral ACTH levels peak within 5 minutes, while an increase in cortisol levels shows a delay of 5-20 minutes (Kirschbaum & Hellhammer, 2000). Cortisol levels continue to increase even after the stressful experience is over, peaking 10-30 minutes after cessation of the stressor. Kirschbaum et al. report that this peak is slightly less than a doubling of the baseline cortisol levels. They report a similar pattern for prolonged stress (such as during a marathon run), with cortisol levels increasing steadily for the duration of the stressor (hours) and peaking shortly after. Negative feedback of the HPA axis eventually reduces circulating cortisol. In a number of studies using a 15-minute psychosocial stressor, salivary cortisol returned to levels only slightly higher than baseline 60 minutes after the stress induction was completed (Kirschbaum, Pirke, & Hellhammer, 1993).

Sampling

Because groups were run between 3:00 and 6:00 PM, all salivary cortisol samples were measured during this afternoon window. Baseline samples were taken just prior to the stressor; the second sample was taken approximately 20 minutes after cessation of the stressor, which was approximately 35 minutes after the baseline sampling. The control group had two samples taken 35 minutes apart (with no intervening stress induction). Samples were obtained using the commercially available Salivette® (Sarstedt, Germany). The Salivette collection device includes a highly absorbent cotton roll for the participant to chew (until saturated), a plastic retainer to deposit the cotton, and a plastic centrifuge tube that the cotton retainer is placed within.

Cortisol storage & analysis

The saliva samples were stored at -20°C until the analysis was conducted. The samples were assayed by the investigator, under the training and direction of Dr. Yvon Delville, using an enzyme immunoassay kit by Assay Designs, Inc. The assay kit includes 96 wells per plate that contain an enzyme (goat anti-mouse IgG) attached to the

well walls. A cortisol antibody (monoclonal mouse) was added to each well, which binds to the enzyme on the wall. A known amount of cortisol labeled with an alkaline phosphatase molecule was then added to each well, together with a saliva sample containing an unknown amount of cortisol. The labeled cortisol molecules compete with the unlabeled cortisol from the saliva sample to bind with the high affinity antibody during a 2-hour incubation period. If the amount of cortisol in a sample is low, more of the labeled cortisol will bind to the antibody; if the sample concentration is high, less binding sites will be available for the labeled cortisol. Following incubation, the wells were washed to remove excess reagents and a substrate was added that reacts with the phosphate label. After a 1-hour incubation, the reaction was stopped. The density of the yellow phosphate tag was then read on a microplate reader at 405nm. The density is inversely proportional to the amount of non-labeled cortisol from the sample. The actual concentration of cortisol was obtained by comparing the sample wells to a standard curve (wells on the same plate with known concentrations of cortisol).

All samples were assayed in duplicate and the mean concentration was used as the cortisol measure. If the variation between two measurements of one sample exceeded 10%, the sample was assayed again. Because the pre and post levels of cortisol for each participant were being compared (difference scores), the two cortisol samples for each participant were always assayed together.

Subjective Anxiety

Just before participants thought they were about to give their speech (the height of the stress induction), they were asked to rate their subjective anxiety (SUDS) on a 0-100 scale. They were given a graph of the scale with the following anchors: 0 = “none, perfectly calm”; 15 = “slightly”; 30 = “somewhat”; 50 = “moderately”; 65 = “very”; 80 = “severely”; 100 = “extreme, fear of death.”

Demographic, Covariate & Other Measures

Demographic & other information

Participants were given a Participant Information Form at the beginning of the experiment which asked their age, gender, and ethnicity. Participants also indicated whether they had any conditions which might affect memory performance (depression and anxiety disorders), and factors that might affect cortisol levels, including medications. The questionnaire also asked participants about whether they complied with the pre-experiment instructions (not to eat, drink, smoke, or exercise one-hour prior to each experimental session). Participants were excluded from the analyses if they were currently using corticosteroid medication or faied to comply with instructions. SAT scores were obtained during the on-line screening process as a baseline measure of general intelligence.

Covariate Measures

Baseline Memory

The first narrative from the Wechsler Memory Scale (WMS-III), Logical Memory Test (see dependent measures above) was used as the stimulus for a baseline measure of memory ability (free recall). This measure was included as a covariate in the analyses of memory outcome.

Current Daily Stress

Participants were asked to rate their mean level of stress *not* related to the experiment (upcoming class tests, relationship conflicts, etc.) for each day of the study on a 10-point scale (0 = no stress; 10 = maximum stress). Their ratings for the 3 days (first day of the experiment, the in-between day, and the return day of the experiment 48 hours later) were averaged for each subject and used as a covariate in the memory analyses.

Social competency measure (deception)

A questionnaire asking participants to rate their social competency on a 7-point Likert Scale was included as part of the deception regarding the purpose of the study. (During the speech induction, they were told that we would be comparing their self-ratings with their actual filmed speech performance). Example questions include: “Please

rate your ability to speak in a natural and articulate manner when socializing in a small group," and "Please rate your ability to entertain others in social situations (your humor, charisma, etc.").

Manipulation check

At the end of the experiment, participants were given the Post-Experiment Questionnaire and asked to rate their belief in the likelihood that they would have to give the speech.

Procedure

Procedures for the first and return day, including the timing of the stressor and cortisol measures for each group, are summarized in Figure 1.

Screening & preparation

Participants were initially screened through an on-line pretesting procedure. Those who scored greater than "0" on a 9-point fear scale or on a 9-point avoidance scale for public speaking were contacted via e-mail and invited to participate. Participants who responded and expressed interest in participating were randomly assigned to one of the four conditions. Participants were instructed not to eat, drink (especially caffeine drinks), smoke, or exercise at least one hour before the experiment time.

First Day

Experimenters followed an exact script for giving directions and explanations for the procedures. Points in the procedure where groups differed (timing of cortisol measures and stressor) are bolded.

- Overview & Consent: Upon arrival, the experimenter provided participants an explanation of the purpose of the experiment. This description was designed to disguise the real purpose of the study in order to maximize the stress induction and discourage participants from rehearsing information before memory testing. Participants were told that the investigator is interested in social competence,

hormones, and different cognitive functions related to social behavior. This provided a rationale for collecting the saliva samples, memory tests, and later the speech induction (to compare their self-rated social competency to their actual performance). Participants were then informed of the procedures for both days (completing several questionnaires, listening to a story, watching a film, providing several saliva samples, and "possibly an activity that might cause some to become anxious"). The experimenter explained that if anyone fails to return 48 hours later to complete the experiment or decides to withdraw, they would need to contact the investigator to obtain credit for the first half of the experiment. Participants were then given written consent forms covering this information, and the experimenter answered any questions before obtaining consent.

- Scantron: Following consent, participants were handed out a scantron and were instructed to record the last 5 digits of their social security number, experiment date, experimenter number, and condition.
- **Cortisol Sample 1 (Controls):** Participants in the Control group were provided a Salivette, and instructed on how to collect their baseline saliva sample. Participants were told to chew the cotton insert of the Salivette until saturated (1-2 minutes), and then deposit the cotton into the Salivette tube.
- Baseline Memory: The WM S-III Logical Memory test (Story A) was then administered to obtain a baseline measure of memory.
- Social Competency Scale: The experimenter next distributed the Social Competency Questionnaire as part of the speech deception.
- **STRESS INDUCTION (Pre-Film group):**
    - **Cortisol Sample 1:** A baseline cortisol sample was then obtained from participants in the Pre-film group.
    - **Stress Induction:** Participants then underwent the stress induction (see description below).

- **Wait Period:** Participants were then told that they were to relax for about 13 minutes. They were provided entertainment and news magazines and coloring books to pass the time. They were asked not to talk or do homework.

- Film: All participants then watched the 7-minute film, "The Dinner Party."
- **Cortisol Sample 2 (Pre-Film group):** A second cortisol sample was obtained from this group approximately 20 minutes after cessation of the stressor, 35 minutes after the first sample.
- Film Immediate Recall (IR) Tests: The experimenter immediately administered the Film IR Cued-recall Test, followed by the Film IR Recognition Test. Participants were told that the purpose of these tests was to determine how closely they observed and remembered the film.
- WMS Narrative IR Test: The experimenter then played the tape of the second narrative from the WMS-III Logical Memory (Story B) and administered the free recall test.
- **Cortisol Sample 2 (Control group):** A second cortisol sample was obtained from this group approximately 20 minutes after cessation of the stressor, 35 minutes after the first sample.
- **STRESSOR (Post-Film group):**
  - **Cortisol Sample 1:** A baseline cortisol sample was then obtained from participants in the Post-film group.
  - **Stress Induction:** Participants then underwent the stress induction.
  - **Wait Period:** Participants were then told that they were to relax for about 20 minutes. They were provided entertainment and news magazines and coloring books to pass the time. They were asked not to talk or do homework.
  - **Cortisol Sample 2:** A second saliva sample was obtained from the Post-Film group
- Preparation for Return: All participants were asked to return 48 hours later to complete the experiment. They were told that if they chose to withdraw at that time

and not return, they would need to contact the experimenter to obtain credit for the first half of the experiment.

Return Day (48-hours later)

- Overview: Upon returning, participants were given a brief overview of the experiment procedures for the second day.
- **STRESSOR (Return group):**
    - **Cortisol Sample 1:** A baseline cortisol sample was then obtained from participants in the Return group.
    - **Stress Induction:** Participants then underwent the stress induction.
    - **Wait Period:** Participants were then told that they were to relax for about 20 minutes. They were provided entertainment and news magazines and coloring books to pass the time. They were asked not to talk or do homework.
    - **Cortisol Sample 2:** A second saliva sample was obtained from the Return group
- Film Delayed Recall (DR) Tests: All participants were then administered the Film DR Cued-recall Test, followed by the Film DR Recognition Test.
- WMS Narrative DR Tests: The experimenter then administered the free, cued, and recognition tests based on Story B of the WMS-III narrative.
- Debriefing: All participants were debriefed verbally and in writing, explaining the true purpose of the study and the rationale for the deception, and any questions were answered.
- Post-Experiment Questionnaire: The PEQ was administered.

Stress Induction

The psychosocial stress induction was inspired by the Trier Social Stress Test (TSST), in which participants give a speech (5 minutes) followed by an arithmetic task (5 minutes) in front of a small audience. In the current study, an emphasis was placed on anticipatory stress: participants *prepared* for 10 minutes for the expected speech (they

were also shown the speech room), but at the last minute were told that a scheduling conflict meant we had to "skip" this part of the experiment. This deception was introduced to maintain participant morale, based on feedback in the Stress and Memory Pilot. Not having participants give the speech allowed them to be run in groups (if they actually gave the speech in groups, it would have been impossible to control for factors that would influence anxiety, such as the order a subject went in giving the speech, how good/bad other speakers were, etc.). Running participants in groups also maximized the social anxiety during the preparation period by making the audience of peers more salient. Experimenters followed a detailed script for the stress induction, summarized here:

- Explanation: The speech was introduced with the following explanation:

  > "Do you remember the measure we gave you which asked about how you act in social situations? This was a social competency scale. In this segment of the experiment, we are interested in comparing how you rated yourself on social competency, and how you actually perform while giving a public speech. So we are now going to give you 10 minutes to prepare a speech, and then you will deliver the speech in front of the group and several graduate students. The speech will also be videotaped so we can rate your speech and non-verbal behaviors. First, let's determine the order in which you will be giving your speeches."

- Order Selection: Participants were asked to draw a number out of a "hat" to determine the order in which they would give their speeches.

- Viewing Speech Room: Participants were told they would next be shown the Speech Room so they could get a "feel" for the setting. They were lead down the hall to a room with a one-way mirror that looked into the speech room. This room was set up for speech phobia treatment studies in the Laboratory for the Study of Anxiety Disorders. Experimenters were instructed to point out the podium, audience seats, video camera, and video monitor. They viewed the room for approximately 1 minute.

- Speech Preparation Instructions: Once seated again, participants were handed out a list of seven speech topics representative of different majors, which they could choose

from ("current or past U.S. foreign policy issue," "emerging theory in the sciences"). They were given the following instructions:

> "Now you will have 10 minutes to prepare the speech. You can pick from one of seven topics on this sheet, so pick the topic you have the most expertise in. You must be able to compose a clear, well-organized speech that will last 3 minutes. The audience is made up of graduate students who are interested in comparing how people rate their social skills, and how they actually perform. They will be rating you on your language skills, nonverbal behaviors such as eye contact and facial expression, humor, and how interesting your speech is. The videotape will be analyzed as well, to check the validity of the audience ratings. While each of you gives your speech, the rest of you will remain in the room as well. We would like to have all of you in the group to also rate each speaker on these behaviors."

Participants were then told to take out a piece of paper and begin outlining their talk. They were also told: "You will not be able to take your notes with you because this will interfere with your eye contact and overall performance, but I'll give you 1 minute to memorize your notes before we go."

- Speech Preparation Period (10 minutes): During this time, participants were told not to talk to one another, but could ask the experimenter questions if they need help with picking a topic or organizing their material. The experimenter called out the time every 2 minutes. After 10 minutes, the experimenter asked everyone to memorize their notes before going to the speech room.

- Peak Anxiety (SUDS): Before leaving to go to the speech room, the experimenter said:

  > "Because anxiety can affect your performance, we just want to get a measure of your stress or anxiety level. Using this 100-point scale, please write down your anxiety level on the back of the Scantron and turn it over."

- Speech Cancellation: Experimenters then lead everyone into the hallway outside the speech room, and told them wait while he/she unlocked the door. The experimenter then disappeared into the suite of rooms in the Laboratory for the Study of Anxiety Disorders, and returned after several minutes. Looking frustrating, the experimenter explained that there was a scheduling conflict with the room—it was currently being used for speech phobia treatment. The experimenter apologized for this, but stated that this was only one part of the experiment, and that it would not affect other aspects of

the study. They were also told that they would not have to give the speech later, because they had already prepared once, and we could not repeat the procedure twice.

Figure 2: Experimental Procedure Showing Stress & Cortisol Timing By Group

Day	Pre-Film	Post-Film	Return	Control
First	Overview & Consent	Overview & Consent	Overview & Consent	Overview & Consent
				Cortisol (sample 1)
	Baseline Memory & SCS	Baseline Memory & SCS	Baseline Memory & SCS	Baseline Memory & SCS
	Cortisol (sample 1)			
	Speech (15 min)			
	Rest Period (13 min)			
	Film (7 min)	Film (7 min)	Film (7 min)	Film (7 min)
	Cortisol (sample 2) [1]			
	Film IR Tests	Film IR Tests	Film IR Tests	Film IR Tests
	WMS IR Test	WMS IR Test	WMS IR Test	WMS IR Test
		Cortisol (sample 1)		**Cortisol (sample 2)** [2]
		Speech (15 min)		
		Rest Period (20-min)		
		Cortisol (sample 2)		
	Overview of next session	Overview of next session	Overview of next session	Overview of next session
Return	Overview	Overview	Overview	Overview
(48 hrs)			**Cortisol (sample 1)**	
			Speech (15 min)	
			Rest Period (20-min)	
			Cortisol (sample 2)	
	Film DR Tests	Film DR Tests	Film DR Tests	Film DR Tests
	WMS DR Tests	WMS DR Tests	WMS DR Tests	WMS DR Tests
	Debriefing	Debriefing	Debriefing	Debriefing
	Post-Experiment Form	Post-Experiment Form	Post-Experiment Form	Post-Experiment Form

[1]Time of second cortisol measure in stress groups: 20 minutes after stressor

[2]Time between two cortisol samples for all groups: approximately 35 minutes

CHAPTER 4: ANALYSES & RESULTS

Hypotheses

The hypotheses of the current study are the following:

1. Stress will facilitate encoding and consolidation, particularly for verbal information. Specifically, scores at delayed recall on the memory measures will be significantly higher for the Pre-Film and Post-Film Groups, compared with the Control Group,
2. Stress will impair retrieval, especially verbal memory. Scores at delayed recall on the memory measures will be significantly lower for the Return Group (stressed at the time of retrieval) compared with all other groups.
3. Change in cortisol will be associated with memory performance within groups. Cortisol will be positively correlated with encoding/consolidation (Pre-Film and Post-Film groups), and negatively correlated with retrieval (Return group).

Analyses & Results

Participants

Participant demographics (N = 208) are listed in Table 8. The sample was predominately Caucasian (72%) and female (67%), with a mean age of 18.78. Demographics were obtained through an on-line questionnaire prior to acceptance into the study, and 7 of the participants did not answer some or all of the questions. No significant group differences were found for gender ($\chi^2 = 2.350$, $p = .503$), ethnicity ($\chi^2 = 10.78$, $p = .767$), or age (F (3, 197) = .166, $p = .919$). Drop-out numbers were very low and similar across groups.

Table 8: Participant Demographics By Condition					
	Pre-film	**Post-film**	**Return**	**Control**	**Total**
N (completers)[1]	51	56	50	51	208
Drop-outs[2]	1	1	0	1	3
Male / Female ratio[3]	11/37	19/36	18/32	15/33	63/138
Mean Age	18.87	18.80	18.86	18.65	18.78
Caucasian	34	36	39	35	144
Asian	6	9	5	8	28
Hispanic	4	5	4	4	17
African American	1	1	2	1	5
Other	3	4	0	0	7

[1]Number of participants who completed entire experiment.

[2]Number of participants who came for the first day of experiment but did not return.

[3]Demographic data (age, ethnicity, gender) missing for 7 subjects.

Validity Check

To confirm the integrity of the randomization process, a one-way analysis of variance (ANOVA) was conducted separately for measures of mean participant intelligence (SAT scores, current GPA), baseline memory (WMS first narrative score), public speaking fear / avoidance, stress on days of the experiment, and pre-stress cortisol levels (see Table 9 below). No significant differences were found between groups on these measures. Of note is the extreme variability of baseline cortisol levels, measured in pg/ml, of participants in all of the groups.

Table 9: Group Means and Standard Deviations for Baseline Measures					
Measure	**Pre-Film**	**Post-Film**	**Return**	**Control**	***p* value**
SAT scores	1230 (142)	1243 (126)	1245 (129)	1208 (134)	.54
Current GPA	3.18 (.64)	2.97 (.56)	3.04 (.62)	3.25 (.53)	.21
Baseline memory	13.84 (3.93)	13.93 (3.75)	13.60 (3.93)	12.94 (3.95)	.56
Pub speaking fear	3.42 (1.90)	3.71 (2.07)	3.98 (1.91)	3.50 (2.11)	.51
Pub speak avoidance	2.31 (1.95)	2.69 (2.32)	2.74 (2.40)	2.38 (1.92)	.68
Stress: first day	2.46 (2.73)	2.85 (2.57)	2.86 (2.70)	2.54 (2.64)	.83
Stress: return day	2.29 (2.68)	2.96 (2.83)	2.93 (2.91)	2.06 (2.47)	.26
Mean stress all 3 days	2.63 (2.17)	3.14 (2.16)	3.25 (2.32)	2.79 (2.02)	.47
Baseline cortisol	745 (634)	584 (389)	583 (398)	660 (410)	.29

Cortisol & Anxiety Response to Stressor

Groups were compared on cortisol change from time 1 (baseline) to time 2 (following stressor for the Pre-Film, Post-Film and Return groups, or after the same period of time without the stress induction in the Control group). Cortisol data was not available for all participants. Some failed to produce enough saliva for analysis (Pre-film = 4, Post-Film = 1, Return = 6, Control = 2), and 6 of the estimated cortisol concentrations were outside the standard curve for the particular assay (very high or very low) even after repeated assays (Pre-film = 2, Post-Film = 0, Return = 2, Control = 2). Stress groups were also compared on peak subjective anxiety (SUDS) during speech induction (see Table 10).

Table 10: Stressor Potency:
Group Means & Standard Deviations for Cortisol (pg/ml) & Subjective Anxiety

Measure	**Pre-Film**	**Post-Film**	**Return**	**Control**
N[1]	45	55	42	47
Cortisol: Time 1 (Pre-baseline)	745 (634)	584 (389)	583 (398)	660 (410)
Cortisol: Time 2 (post)[2]	719 (615)	729 (541)	738 (616)	549 (232)
Cortisol: Post-Pre Difference	-27 (552)	145 (472)	155 (664)	-110 (338)
Cortisol: Percentage-Change	.07 (.59)	.40 (.94)	.43 (1.09)	-.03 (.66)
Cortisol: Responders[3]	13	20	16	5
Peak anxiety during speech	58 (20)	62 (18)	62 (18)	N/A

[1]Some subjects did not produce enough saliva for analysis or had values (upon repeat assay) that were outside of the standard curve (could not obtain accurate level)

[2]Post-stressor for stress groups; post rest-period for controls

[3] A cortisol "responder" is one who showed a 25% increase or greater in cortisol between the two time points

To determine whether the stressor was *sufficiently potent* to cause a significant increase in cortisol, a repeated-measures ANOVA was conducted with time as the within-subjects factor (pre- and post-stress cortisol measures) and condition as the between-subjects factor. There were no main effects for time or condition, but a significant time x group interaction was obtained (F (3, 185) = 3.077, $p < .05$). To test the nature of the interaction, change in cortisol was examined in each group separately using paired t-tests. As expected, controls (Figure 3) showed a significant *decrease* in cortisol (M = -110, t_{46} = -2.246, $p < .05$). This suggests that cortisol levels were naturally dropping in participants, likely due to expected circadian rhythms (cortisol levels drop throughout the day, although less so in the afternoon when the experiment was conducted), but also possibly due to habituation to the experimental situation. However, of the stress groups only the

Post-Film group (Figure 4) showed a significant *increase* in cortisol (M = 143, t_{46} = 2.283, $p < .05$). The Pre-Film group (Figure 5) showed no significant change (M = -27, t_{44}= .323, p=.748), nor did the Return group (M = 155, t_{41} = 1.515, p =.137; Figure 6).

Figure 3:
Control Group Change in Cortisol

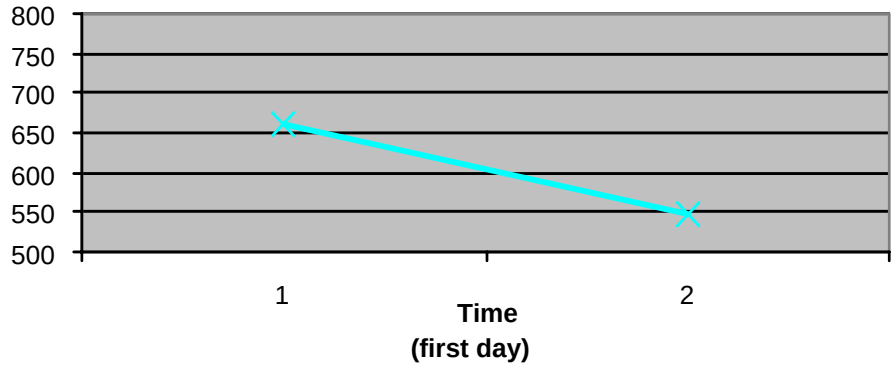


Figure 4:
Post-Film Group Change in Cortsiol

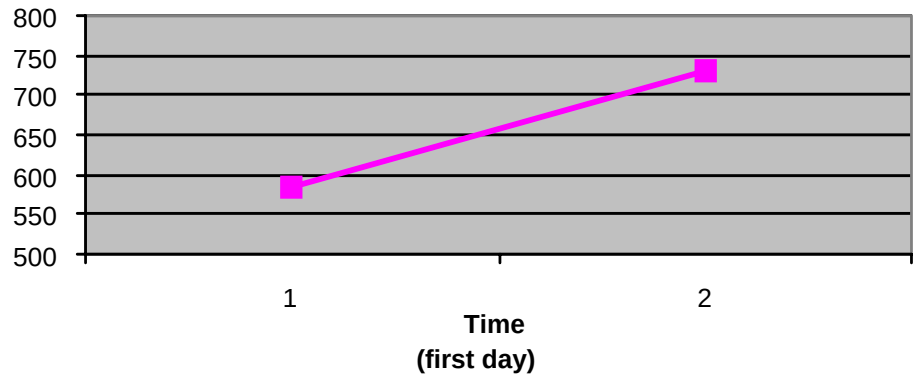


Figure 5:
Pre-Film Group Change in Cortisol

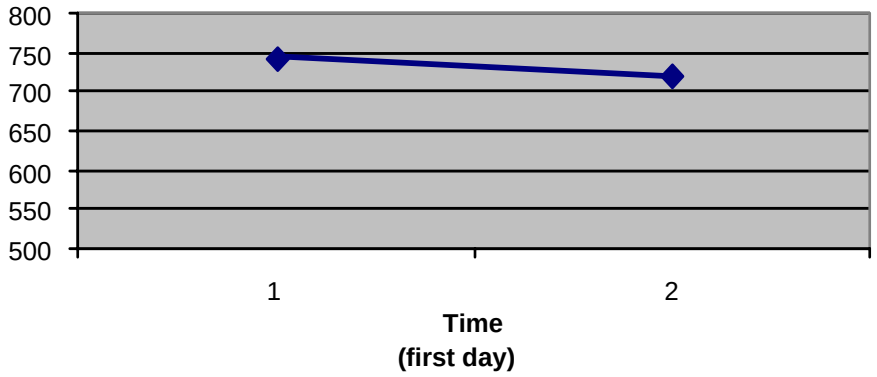
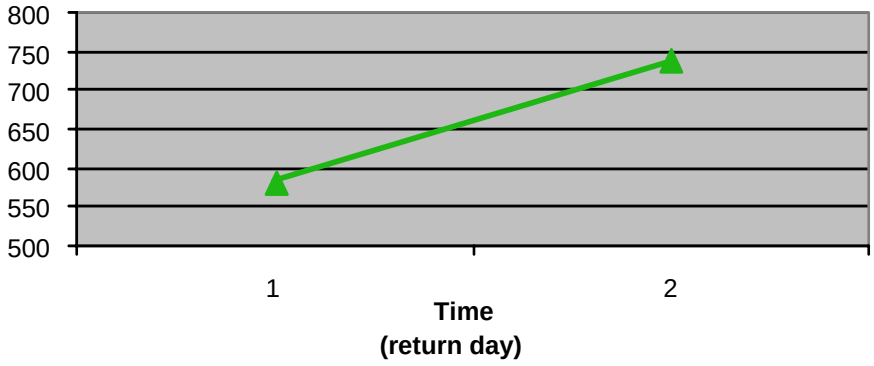


Figure 6:
Return Group Change in Cortisol



An ANOVA comparing groups on percentage change in cortisol was also conducted, with a main effect for group (F (3, 185) = 3.544, $p < .05$). Pairwise comparisons showed a trend toward a greater cortisol response in the Return group compared to controls (*MD* = .4671, $p = .060$) and in the Post-Film group compared to controls (*MD* = .1680, $p = .067$). . The percentage of responders (those who showed a 25% increase in cortisol from time 1 to time 2) in each group were as follows: 38% in the Return group, 36% in the Post-Film group, 29% in the Pre-Film group, and 11% in the Control group. Because of heterogeneous variance of the cortisol data between groups (and from pre-to-post within groups), cortisol was also examined using log-transformed scores to reduce variance. This approach did not succeed in homogenizing variance or in changing the outcomes presented above.

Comparison between the Pre-film, Post-film and Return groups on mean peak subjective anxiety (SUDS) during the speech induction showed no significant difference between these groups, suggesting participants were similarly anxious (in the moderate-to-very anxious range) in the three stress groups.

Relationship between Cortisol and Subjective Anxiety

A Pearson's Product Moment Correlation was conducted with cortisol (pre-post difference scores) and peak subject anxiety during the stressor to determine whether the two measures were related. A trend toward a small positive correlation was found ($r_{xy} = .15$, $p = .086$).

Memory Performance

The primary dependent measures in this study were delayed recall scores on the WMS narrative (free, cued, recognition) and film (cued, recognition) tests (see Table 11).

Table 11: Group Means & Standard Deviations for Delayed Recall Measures

Measure	Pre-Film	Post-Film	Return	Control	*p* value
Narrative free recall	10.39 (3.37)	11.30 (4.40)	10.56 (3.17)	11.40 (3.85)	.195
Narrative cued recall	6.39 (1.78)	7.04 (1.62)	6.95 (2.15)	6.69 (1.69)	.279
Narrative recognition	8.15 (1.37)	8.42 (1.13)	8.23 (1.40)	8.15 (1.22)	.765
Film cued recall	9.37 (2.25)	8.68 (3.35)	8.43 (3.04)	7.65 (3.17)	.135
Film recognition	18.39 (3.53)	19.87 (3.84)	18.50 (4.03)	17.59 (3.53)	.023*
Film recog-cued diff	9.07 (3.64)	11.19 (3.65)	10.07 (3.45)	9.93 (3.21)	.026*
Film recog – verbal	9.37 (2.29)	10.25 (2.34)	9.52 (2.62)	8.87 (2.03)	.031*
Film recog – visual	9.02 (1.94)	9.62 (2.14)	8.98 (2.15)	8.72 (2.46)	.255
Film recog – false pos	3.59 (1.55)	4.36 (1.24)	3.86 (1.36)	3.74 (1.36)	.039*
Film recog –relational	3.76 (1.41)	3.85 (1.71)	3.50 (1.28)	3.54 (1.54)	.663

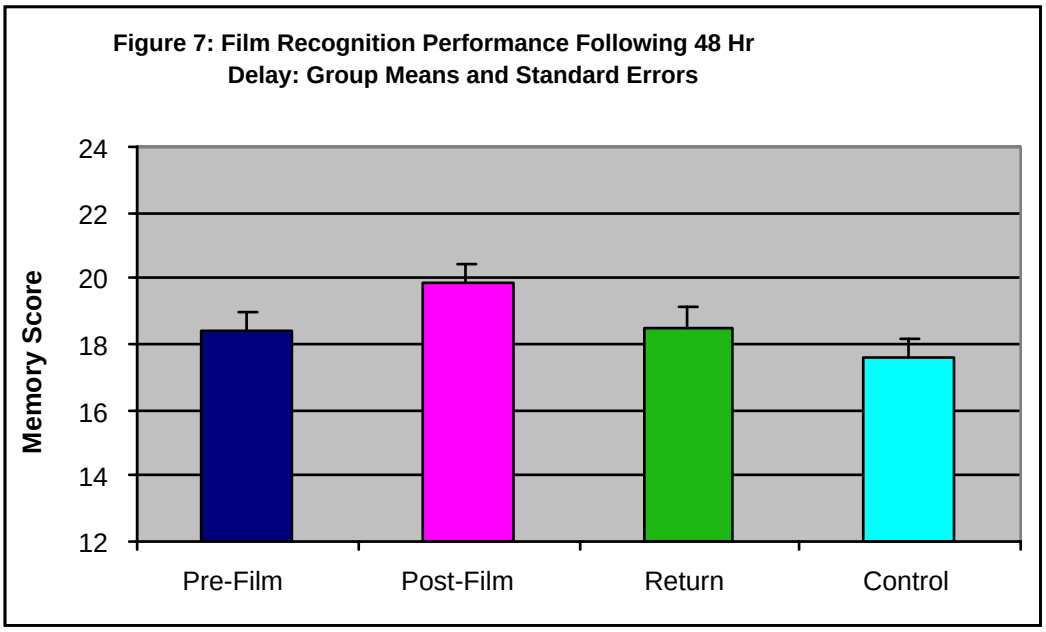
*significant at the .05 level

Hypothesis 1: Stress will facilitate encoding and consolidation, particularly for verbal information. The Pre-Film Group (stressed during encoding and consolidation) and the Post-Film Group (stressed only during consolidation) will each outperform the Control Group.

To test this hypothesis, separate ANCOVAs were conducted for each of the memory measures obtained on the return day (delay recall), covarying baseline memory and basal stress (stress not related to the experiment, estimated by subjects on a 10-point scale for each of the experiment days, and averaged over the 3 days). A main effect for group was obtained on the DR film recognition test (F (3,178) = 3.259, $p < .05$) and both covariates were significantly associated with memory outcome. Pair-wise comparisons for the DR film recognition test using a Bonferroni correction showed that while the Pre-Film group did not differ significantly from any other group, the Post-Film subjects performed significantly better than controls (MD = 2.141, $p < .05$; see Figure 7). When the verbal and visual items of this test were analyzed separately, a main effect for group

on the verbal items was found (F (3, 178) = 3.032, $p < .05$) with the Post-film group significantly outperforming controls (MD = 1.287, $p < .05$); there was no main effect for visual items. No main effects for condition were found for the WMS narrative measures or for the film cued-recall measure.

Figure 7: Film Recognition Performance Following 48 Hr Delay: Group Means and Standard Errors



Hypothesis 2: Stress will impair retrieval, particularly for verbal information. The Return Group (stressed only at the time of retrieval) scores will be significantly lower than all other groups.

Pair-wise comparisons based on the ANCOVAs described above using a Bonferroni correction showed that the Return group did not differ significantly from any of the other groups on any measure.

Hypothesis 3: Change in cortisol will predict memory performance within groups.

A simple Pearson's correlation was conducted to determine whether change in cortisol was associated with memory performance within each condition. A positive correlation was predicted for the Pre-Film and Post-film groups (encoding and

consolidation), while a negative correlation was predicted for the Return group (retrieval). No correlations with any of the dependent measures were significant for the different groups. Correlations between pre-post cortisol difference scores and the Film Recognition Test (for example) were as follows: Pre-film group (r = .004, p = .982), Post-film group (r = .124, p = .372), Return group (r = .197, p = .211).

Analyses with Responder Subset

The same analyses on the dependent variables (memory) were conducted for the subset of the subjects in the stress conditions who showed a robust cortisol response to the stress induction (percentage increase of 25% or greater) compared with all 51 controls (see Tables 12). A main effect for group was obtained for the verbal questions on the film recognition questionnaire (F (3, 85) = 2.726, $p < .05$), with a trend for the greatest difference between the Post-film group and controls in the post-hoc comparison with Bonferroni correction (MD = 1.495, p = .066). All other ANCOVAS were not significant. Correlation between change in cortisol and memory in responders across all 4 groups was not significant for any measure.

Table 12: Responder Group Means & Standard Deviations for Delayed Recall Measures

Measure	Pre-Film	Post-Film	Return	Control	*p* value
N[1]	13	20	16	51 (all)	
Narrative free recall	9.73 (4.31)	10.88 (4.87)	10.93 (2.31)	11.40 (3.85)	.284
Narrative cued recall	6.18 (2.18)	7.18 (1.88)	7.00 (2.20)	6.69 (1.69)	.558
Narrative recognition	8.00 (1.41)	8.24 (1.15)	8.33 (1.88)	8.15 (1.22)	.960
Film cued recall	9.55 (4.68)	8.35 (3.65)	8.87 (3.36)	7.65 (3.17)	.502
Film recognition	18.80 (4.24)	19.50 (4.38)	20.33 (3.66)	17.59 (3.53)	.172
Film recog-cued diff	8.50 (2.88)	11.15 (4.73)	11.47 (3.16)	9.93 (3.21)	.117
Film recog – verbal	9.30 (2.95)	10.60 (2.85)	10.47 (2.26)	8.87 (2.03)	.049*
Film recog – visual	9.50 (1.90)	8.90 (2.29)	9.87 (2.13)	8.72 (2.46)	.499
Film recog – false pos	3.70 (1.70)	4.00 (1.52)	4.27 (1.33)	3.74 (1.36)	.778
Film recog –relational	4.10 (1.66)	3.65 (1.42)	4.07 (1.22)	3.54 (1.54)	.722

[1]Includes all control subjects and participants in the stress conditions who showed a 25% increase or greater in cortisol between the two time points ("responders")

*significant at the .05 level

Exploratory Analyses

Other Memory Processes

Exploratory ANCOVAs were conducted comparing groups on additional measures of memory for the film, including false positives (recalling information bits not in the film), relational items (recalling that there was not only a basketball in the film, but who handed it to whom), and retrieval facilitation (difference score between the film cued and recognition tests) (see Table 11 above). A main effect for group was found on false positive items on the film recognition test (F (3, 178) = 2.847, $p < .05$); covariate baseline memory was significantly related to false positives but average stress over the 3 days was not. The Post-Film group had significantly more false positives than the Pre-film group

(*MD* = .773, $p < .05$). There were no significant effects for relational items (F (3, 178) = .529, $p = .663$). There was also a main effect for group on retrieval facilitation (F (3, 178) = 3.155, $p < .05$); the post-film group again showed significantly greater improvement from cued scores to recognition scores, this time compared with the pre-film condition (*MD* = 2.184, $p < .05$). Covariate baseline memory was not significant, while average stress was.

Cortisol and Memory Across Groups

Given no evidence of different relational trends in the four conditions, an exploratory correlational analysis was conducted across all groups. A small but significant correlation between change in cortisol and verbal questions on the film recognition test was obtained ($r = .18$, $p < .05$), with a trend for total score ($r = .14$, $p = .063$).

S*ubjective anxiety and memory*

Correlations between peak subjective distress during the speech (SUDS) and the memory measures were conducted, and a negative correlation was found for the total score on the film recognition measure ($r = -.18$, $p < .05$), and on the visual items as well ($r = -.19$, $p < .05$). Note that controls were not included in this analysis because the anxiety measure was only taken for individuals in the speech (stress) condition.

Gender and cortisol

Because previous studies have found gender to moderate cortisol response, gender was also examined in exploratory analyses (see Table 13). In an ANOVA with gender as the between-subjects factor and cortisol difference scores as the dependent measure, no main effect for gender was found across all groups (F (1, 181) = .598, $p = .440$). A similar non-significant finding was obtained when percentage change in cortisol was examined (F (1, 181) = 1.712, $p = .192$). When females were divided into groups according to whether they were taking oral contraceptives or not, no main effect for contraception status was found across groups for change in cortisol (F (1,116) = .375, $p = .541$). Chi-Square analysis of the number of male and female cortisol "responders" was similarly not significant ($\chi^2 = .719$, $p = .475$). Males and females did not differ on

subjective anxiety during the speech induction (F (1, 126) = .798, p = .373). When the primary hypotheses were examined in a 4 (group) x 2 (gender) model, gender was not found to moderate outcome on any memory measure (no significant interaction).

Table 13: Gender and Cortisol Stress Responses (pg/ml)

Measure	**Males**	**Females**	***p* value**
Cortisol: Post-Pre Difference	89 (660)	23 (463)	.440
Cortisol: Percentage-Change	.35 (1.06)	.17 (.78)	.192
Cortisol: Responders[1]	18 / 55	34 / 128	.475
Peak anxiety during speech	59 (19)	62 (18)	.373

[1]A cortisol "responder" is one who showed a 25% increase or greater in cortisol between the two time points

Immediate Recall: Negative Effect on Encoding?

Because the Pre-film group showed no significant difference in delay recall performance from controls, this suggested consolidation was not enhanced in this group. Alternatively, if stress negatively impacts *encoding* processes (as many of the human studies on attention suggest), this might have cancelled out the facilitation effect upon consolidation seen in the Post-Film group. To examine this question more directly, immediate recall scores were analyzed, comparing the Pre-film group (stressed) with the other 3 groups (not stressed at this point in the procedure). This comparison is essentially a replication of the majority of human studies, in which the stress group received stress or glucocorticoid administration prior to stimulus presentation and retention testing (immediate recall or recall within an hour), compared to controls. Separate ANCOVAs for each IR memory measure were conducted, with baseline memory and basal stress on the first day as the covariates. The post-hoc hypothesis predicted impaired immediate recall in the Pre-Film group (stressed prior to stimulus presentation) compared with the non-stressed participants. Consistent with this hypothesis, a trend toward a main effect

for group was found on the IR Film Recognition Test (F (1, 179) = 3.162, p = .077), with the Pre-Film group recalling fewer items than the non-stressed groups combined (Pre-Film M = 18.49, SD = 4.47; Non-Stressed M = 19.62, SD = 3.82.

CHAPTER 5: DISCUSSION

Background & Purpose of Current Study

The goal of the current study was to examine the effects of an acute, moderate psychosocial stressor, and associated changes in cortisol, on different memory processes in a sample of young adults. Results of studies using animals have generally revealed facilitative, dose-dependent effects of moderate stress and corticosterone on memory. The consistent finding of facilitative effects of stress on memory in the animal literature may be partially attributable to the methodological characteristics. Typically, animal studies separate learning from retention testing, applying the stressor or glucocorticoid administration during the encoding and/or consolidation process, and testing retrieval after a 24-hour interval. This separation allows investigators to distinguish between the different stages of memory.

In contrast, most human studies have found both stress and glucocorticoid administration to impair memory. The dominant theory is that stress-induced cortisol release causes disruption in memory consolidation due to the high concentration of glucocorticoid receptors in the hippocampus (presumably interfering with proper functioning). In the majority of human studies, the stressor or glucocorticoid is applied prior to stimulus presentation, and recall is tested within an hour of the manipulation. Thus, cortisol levels are elevated during encoding, consolidation, and retrieval processes, making it difficult to determine which processes are affected. This discrepancy in methodology between the animal and human literatures may account for the different results between them (e.g. enhance vs. impair memory). The several recent human studies to have examined the effects of stress or glucocortiocoids on the consolidation process specifically have found facilitative effects on visual memory (Buchanan & Lovallo, 2001; Abercrombie et al., 2003; Cahill et al., 2003), yet an impairing effect on verbal memory (Lupien et al., 1995). However, to date, only one human study has administered cortisol at each stage of memory (including *retrieval*), and the results suggest a detrimental effect on retrieval (De Quervain et al., 2000) consistent with two animal studies (Oitzl & De

Kloet,1992; De Quervain, Roozendaal, & McGaugh, 1998). Roozendaal (2002) has proposed that during a stressful event, retrieval processes may be disrupted to reduce retroactive interference, so that consolidation of the novel information related to the stressful experience will be facilitated.

The current study was designed to test this revised model by addressing several of the methodological and theoretical issues in the human literature on stress and memory. First, the present study sought to parse the effects of an acute stressor on *each stage of memory separately*. The psychosocial stressor (preparation for an expected public speech) was applied at 3 different time points (and compared with no-stress controls): prior to stimulus presentation and initial learning, immediately after stimuli presentation/learning, and just before memory testing 48 hours later. Specifically, it was hypothesized that stress would have a facilitative effect on encoding and consolidation processes and a detrimental effect on retrieval. While De Quervain and colleagues (2000) have used a similar paradigm using glucocorticoid administration as the manipulation, this study is the first to do so using a *psychological stressor* to investigate the effects of stress and endogeneously-released cortisol on each memory phase in a human sample. Moreover, to potentially enhance the ecological validity of the memory findings, memory was tested using a film stimulus developed by the investigator together with a standard neuropsychological measure of verbal memory. Finally, to investigate whether stress has differential effects on domain-specific information, the current study examined both verbal and visual memory processes.

Summary of Main Findings

The first hypothesis predicted a facilitative effect of stress on encoding and consolidation processes, particularly for verbal information. Results support the consolidation hypothesis, as the group that underwent the psychosocial stressor after exposure to the film stimulus (Post-film group – consolidation condition) significantly outperformed controls on a recognition test of the film 48 hrs later, both in total score and the verbal subset of questions. However, the group stressed prior to stimulus presentation

(Pre-film group – encoding and consolidation) unexpectedly showed no significant differences in memory performance compared to controls. It is notable, however, that while the Post-Film group showed a significant increase in cortisol following the stressor (40%), the Pre-Film group did not.

The second hypothesis predicted that stress applied just prior to retrieval (48 hours after stimulus presentation) would impair recall. Contrary to the this hypothesis, results revealed that the Return group (retrieval condition) showed no impairment in memory relative to controls, either on the film tests or the standard neuropsychological narrative memory test. While this contradicts the preliminary data from several studies, it may also be due to the insignificant change in cortisol following the stressor, which was also noted in this group.

Indeed, the third hypothesis predicted that change in cortisol would be associated with memory performance, with a positive association in the Pre-film and Post-film groups (encoding and consolidation) and a negative association predicted for the Return (retrieval) group. However, none of the within-group correlations were significant. An exploratory analysis revealed a small but significant positive correlation *across groups* between change in cortisol following the stressor and verbal scores on the film recognition test (r_{xy} = .18), with a trend for total score. This suggests (contrary to prediction) that stress-induced cortisol may be positively related to memory across all phases of learning and retention. It is also notable that the only group to show a significant increase in cortisol (Post-Film group) was also the group to show significant differences on memory compared with controls.

Thus, the results of the current study lend additional support to a revised model of stress and memory in humans that argues for a facilitative effect on consolidation, and that this may be related to a significant rise in cortisol. The current study does not, however, provide evidence that stress impairs retrieval processes. Finally, while the literature finds support for cortisol-enhanced consolidation of visual memory, this study provides the first evidence that stress enhances the consolidation of *verbal* information.

While the three stress groups differed in terms of the timing of their stressor (the intended manipulation), there exist other sources of variability that may have confounded the results. For example, group differences in memory may be partially attributable to unintended variation in the robustness of stress manipulation in these groups. First, the lack of cortisol response observed in the Pre-film and Return groups suggest that these groups may not have been sufficiently stressed. While the control group showed a significant decline in cortisol over the two time periods of testing (consistent with the circadian decrease in cortisol and possibly experiment habituation), the Pre-Film and Return group cortisol levels measured prior to and after the stressor did not change. Thus while the stress induction may have maintained cortisol levels (rather than allowing them to drop naturally as with controls), it failed to boost them significantly. Only the Post-film group showed a significant increase in cortisol following the stressor. Comparison of the number of responders in each group, however, did not indicate significant differences: 38% in the Return group, 36% in the Post-Film group, 29% in the Pre-Film group, and 11% in the Control group.

Surprisingly, separate analyses examining memory outcomes with cortisol "responders" (those subjects in the stress groups that showed a 25% increase or greater in cortisol following the stress induction) did not yield any additional findings beyond what was found with the entire sample (a main effect for group was obtained for verbal questions on the film recognition questionnaire, with Post-Film group outperforming controls). In addition, the correlation between change in cortisol and memory failed to reach significance with the responder subset, although a trend was found for verbal questions on the film recognition test. Other research comparing subjects that had undergone the TSST stress induction (public speech) that found no memory differences between the stress group and control have found better word recall in high cortisol responders compared with low responders regardless of condition (Domes et al., 2002). The current study's lack of findings with responders in the present study may be related

to the small number of responders in each group, thereby reducing power in these analyses.

It is not clear why the Pre-film and Return groups failed to show a robust cortisol response to the stress induction. In all stress studies, a certain percentage of participants do not show a strong cortisol response to various stressors, depending on personality features, stressful events outside the experiment, individual differences in cortisol responsivity, and how threatening a particular stressor is to the individual (Van Eck, Berkof, Nicolson, & Sulon, 1996). However, there were no differences between groups on baseline cortisol levels or mean current life stress on each day of the experiment days, suggesting integrity of the randomization process. In addition, participants were required to indicate some level of speech anxiety during pre-screening of subjects in order to ensure at least a minimal response to the stressor. Finally, the data showed similar peak anxiety levels during the speech induction between the three stress groups. Some researchers have found sex differences in cortisol response, with men more likely to be responders than women (Zimmer et al., 2003). The post-hoc analyses did not find this gender effect between or within groups. In addition when gender was entered into the stress and memory analysis of variance as a fixed factor, it did not contribute significantly to outcome. Kirshbaum and Hellhammer (1993) have also demonstrated a blunted cortisol response in women who were on oral contraceptives; post-hoc analyses did not replicate this finding.

It is possible that procedural variations may account for group differences in cortisol response. In the Pre-film group, it is notable that the mean baseline cortisol level for these subjects, although not significantly different from other groups (very high variability of both cortisol measures), it was similar to the post-stress cortisol levels of the other two stress groups. It is possible that there was some initial stress associated with coming to the experiment (a novel and unpredictable event), and this was the only group to undergo the stress induction within 10 minutes of arrival on the first day. Because cortisol testing was tied to the stressor (cortisol measured just prior to the stressor and 20 minutes after cessation of the 15-minute stressor in stress groups, and 35 minutes apart

during non-stressful activities for controls), only the control group had cortisol measured at the beginning of the experiment similar to the Pre-Film group. The Post-film group was sampled at two time points at the end of the first session (approximately 45 and 80 minutes after arrival), possibly giving subjects in this group time to habituate to the experiment before undergoing the stress induction. In contrast, the Return Group subjects were returning after the first experiment day and had some idea of what to expect. Mean baseline cortisol levels and increase for this group (43%) were similar to the Post-film group, but the within-group variability in cortisol was greater (thus rendering the pre-post difference insignificant).

Stress Facilitates Consolidation

The current study provides support that an acute psychosocial stressor and accompanying increase in cortisol levels, when applied immediately following stimulus presentation and learning, facilitates memory. These results contradict the dominant theory in the human literature that stress impairs consolidation, but are consistent with the animal literature which finds a dose-dependent facilitative effect on consolidation. Thus animal studies have demonstrated the impairing effects of dramatically reduced glucocorticoid levels on associative learning and spatial memory through adrenalectomy (Borrell et al., 1984; Versteeg, & Bohus, 1983; Oizl & de Kloet, 1992; Roozendaal et al., 1996; Conrad et al., 1997) or with intact animals using glucocorticoid antagonists (Oitzl et al., 1998; Oitzl & de Kloet, 1992). They have also shown a facilitative effects of post-training glucocorticoid administration on memory (Sandia et al., 1997; Roozendaal et al., 1996; Conrad et al., 1997; Conrad et al., 1999).

The current findings which show a facilitative effect on consolidation also support recent data from several human studies that manipulated cortisol levels during the initial encoding / consolidation period, and then tested memory at least 24 hrs later once cortisol levels had returned to baseline. However, while several of these studies have found that cortisol enhanced the consolidation of *visual* information (Buchanan & Lovallo, 2001; Abercrombie et al., 2003; Cahill et al., 2003), of the two that examined verbal memory,

one found no effect (De Quervain et al., 2000), and one found a negative effect (Lupien et al., 1995). In addition, the animal findings are based on associative and spatial memory. This study provides the first evidence for enhanced consolidation of *verbal* memory when the stages of memory have been separated methodologically. And although earlier studies have generally found a negative correlation between cortisol and verbal recall (Kirschbaum et al., 1996, Wolf et al., 2001), there is recent support for a positive correlation (Domes, 2002, Hsu et al., 2003) including the current study. Clearly the failure to measure both visual and verbal memory may be another confound in the literature, and examining both in a given experiment (thus controlling for different methodologies) might shed light on the relationship between stress, cortisol and domain-specific aspects of memory.

It is also notable this is the first stress and memory study to have used a brief film as a memory stimulus in order to strive for more ecologically valid data compared with the standard neuropsychological tests or experimental word lists. A film can better approximate the rich and complex barrage of sensory inputs, semantic information and social cues that normally confronts us as we move through the world, and from which we must selectively attend and remember. In this study's "Dinner Party" film, participants observed a typical social event with six characters interacting against a backdrop of changing scenes and activities. Guests arrived and told each other stories, people handed each other hats and toys, picked up books, moved in and out of scenes together, a child played on the couch in the background while the phone rang and one host left to answer it, and all of this occurred in a certain temporal order. At any given moment many activities were happening at once. Questions about the film ("What did Phillip hand Susan?" "How did Phillip and Melissa meet before the party?") turned out to be sensitive to the effects of stress, possibly lending greater confidence that such a laboratory finding has relevance in the real world.

The evidence obtained here for the facilitative effects of mild stress on memory may not contradict other findings. There is certainly growing evidence that the cognitive effects of stress are dose-dependent, with mild to moderate increases in cortisol

associated with improved memory and larger doses associated with a decline in performance in animals (Conrad et al., 1999; Sandi et al., 1997) and humans (Abercrombie et al., 2003). It may be that under conditions of moderate cortisol release and partial occupation of glucocorticoid receptors, memory systems are appropriately activated. If receptors become fully occupied under high cortisol release, this may cause associated brain regions to become "overwhelmed" and fail to function efficiently. In addition, because glucocorticoids eventually inhibit the initial catecholamine response to stress, excessive cortisol release may jump-start the negative feedback of catecholamines, thus interfering with their facilitative effects.

Does Stress Impair Encoding?

Setting aside the cortisol data, one possible explanation for the lack of difference in memory performance between the Pre-Film group and controls is that stress had a facilitative effect on consolidation (similar to the Post-Film group), but interfered with encoding. Thus the effects of stress on different memory processes may have cancelled each other out. Several pharmacological studies provide support for the impairing effects of stress on attention and selective encoding of stimuli. Wolkowitz and colleagues (1990) found that 4 days of prednisone treatment was associated with more errors of commission (identification of distractor targets or false positives) during memory testing, while free recall and errors of commission were similar to testing conducted prior to and 7 days after treatment. The authors interpreted this finding as a failure to adequately discriminate 'signal' and 'noise,' consistent with McEwen's theory (McEwen, 1982) that corticosteroids interfere with the work of the hippocampus to filter out irrelevant stimuli during encoding. However, this could also be a failure of retrieval processes to discriminate at the time of recall. Others have found more direct evidence of the acute negative effects of hydrocortisone on measures of working memory including performance on Digit Span (Wolf, et al., 2001), Stroop (Hsu et al., 2003, and with an experimental item recognition task that varied processing load (Lupien et al. 1999).

It is therefore possible that for participants in the Pre-Film group, the stressor resulted in some disruption of attentional processes during stimulus presentation, but enhanced consolidation of what was encoded, essentially resulting in a wash when memory was tested 2 days later compared with controls. To explore this possibility, post-hoc analyses were conducted with immediate recall scores, comparing the Pre-film group (stressed) with the other 3 groups (not stressed at this point in the procedure). Given that an immediate recall measure provides little time for consolidation, such an analysis was intended to shed light on encoding effects. As might be predicted from the above explanation, there was a trend toward the Pre-Film group recalling fewer items on the immediate recall film recognition test than the non-stressed groups combined.

Stress Effects on Retrieval

One of the primary hypotheses of this study—that retrieval would be impaired by stress relative to controls—was not supported. It has already been noted that although cortisol levels showed a similar rise in the Return group, the variability in this group rendered the change insignificant. It is therefore difficult to conclude how robust an effect the stressor had in this group, and thus how to interpret the results. It is possible that given the moderate-high peak anxiety level during the speech induction in this group (similar to the other stress groups), the manipulation did succeed but failed to alter memory performance in this group. This would suggest that stress has little effect on retrieval processes. However, the only two studies (other than the present experiment) to have examined the effects of stress and/or corticosteroid treatment during the retrieval phase alone (retention testing one or more days following stimulus presentation / learning) both found a negative effect on retrieval (De Quervain, et al., 1988; De Quervain et al., 2000). Clearly additional studies are needed to examine the effects of stress and cortisol on memory retrieval.

It is interesting to note that the Post-Film group showed more retrieval facilitation at recall than all other groups, as measured by improved score from cued recall to recognition on measures of the film. It is unlikely, however, that this group was showing

a “retrieval deficit.” It is more likely that this may simply be an artifact of the group’s relatively better consolidation compared to the other groups.

Revised Model of Stress & Memory

The findings of the current study fit well with the evolutionary notion that organisms are designed to remember events vital to their survival—events that pose a threat to (or opportunity for) basic survival, resources or social dominance. Threatening events stimulate the activation of the HPA access and cortisol release, as well as autonomic activation and the release of catecholamines (epinephrine and norepinephrine). These hormones in turn bind to receptors in brain regions involved in learning and memory in order to facilitate the consolidation of these relevant events. Roozendaal (2002) adds to this an explanation for stress-induced retrieval deficits: in order to ensure that novel information is attended to and properly processed into memory, competing processes such as the retrieval of old information must be inhibited or disrupted. While the current study did not support the later part of this revised model of stress and memory, this new model encourages a similar methodological approach to test its predictions.

Subjective Anxiety and Memory

It is interesting to note that although stress groups differed in their cortisol response, participants in all 3 stress groups reported similar peak anxiety levels during the speech induction (mean of 61 on a 100-point Subjective Units of Distress Scale), and exploratory analyses revealed that this one-point measure of anxiety was associated with memory across all groups. Indeed, peak anxiety was significantly and negatively correlated with memory two days later on the film recognition total score (r_{xy} = -.18) and visual questions (r_{xy} = -.19). Thus lower psychological distress and stronger cortisol responses were associated with better memory peformance across all subjects.

There is certainly evidence demonstrating the effects of arousal on performance while the individual is in a *state of anxiety* , including the well-known inverted-U shape

function (Myers, 2002). In a recent dissertation study, Gore (2002) found that a strong affective response to highly arousing slides did not affect cortisol or glucose levels but was associated with enhanced recall. In the present study, however, subjects were released from the threat of giving the speech *prior* to subsequent activities. No learning or memory testing was conducted while subjects were in a state of anxiety; presumably the subjective distress associated with the 15-minute stressor was quickly reduced once subjects learned that a "scheduling conflict" prevented them from conducting the speech.

There are several possible explanations for why subjective anxiety may be related to subsequent memory performance. It is certainly possible that psychological processes alone contribute unique variance to learning and memory, independent of neuroendocrine response. It is also likely that there are other biological factors associated with the psychosocial stressor and anxiety that influence memory, but which were not measured in this study. While this study examined the final effect of the "slow" HPA hormone system (cortisol), stress and anxiety also activate the immediate sympathetic response including catecholamine release. It is possible that while direct neural stimulation of heart rate and skin conductance may have returned to baseline following cessation of the stressor, the release of norepinephrine in the brain may have had longer-acting effects cognition (although none of these were measured in the present study). Indeed, there is a growing literature on the facilitative effects of catecholamines on memory (Roosendaal, 2002; Cahill et al., 2003). The current study also did not measure the other two hormones in the HPA system that may have an affect on memory: CRF and ACTH. It is therefore important to consider the possibility that although the stress groups responded differently on the cortisol measure, there may have still been a stress effect.

Weaknesses of the Current Study

As discussed above, the lack of cortisol response in two of the stress groups raises the possibility that the stress induction was not sufficiently robust in these groups, making interpretation of the memory findings in these groups difficult. This is one of the drawbacks to using a psychosocial stressor rather than direct hormone manipulation

through pharmacological intervention. While the psychosocial stress induction (anticipated speech) is a better analogue to real-world stress and naturally activates all of the psychological and biological response associated with stress, the experimenter has greater control and precision with a drug treatment. For this reason, the unique cognitive effects of specific stress hormones can be studied (CRF, ACTH, epinephrine, cortisol), specific receptors can be targeted with agonists and antagonists, and dose-levels can be manipulated. There is something inherently "messier" about a psychosocial stressor, which by its nature involves so many individual factors (cognitive appraisal of threat and coping ability, to name only two). While some of these factors were assessed to confirm the integrity of the randomization process (public speaking fear and avoidance, trait anxiety, intelligence, mean stress unrelated to the experiment), others were not anticipated (initial anxiety related to the novelty of the experiment).

Another potential weakness of the current study was that subjects were run in groups of 2-7, rather than individually. While size of group and experimenter was not related to memory scores, individual group dynamics may have influenced outcome. For example, if a group had one member who vocally doubted the speech induction, this might have undermined other members' anxiety. Conversely, groups with several highly anxious or competitive individuals might have driven up anxiety levels for the whole group. Certainly there were subjective reports by experimenters that one group seemed very "freaked out" by the speech, while another group was disengaged. The intent of using groups was to enhance the evaluative intensity of the speech stressor, but it may have introduced greater variability in the manipulation.

As mentioned above, because the timing of the stressor varied between conditions, the timing of the cortisol sampling differed between conditions. The Pre-Film and Control groups had their cortisol measured in the beginning of the session on the first day, while the Post-Film group was measured at the end. The Return group was measured at the beginning of the session, but on the second experiment day. Ideally cortisol samples should have been taken several times throughout the session and on both days. In addition, different activities were conducted before and in-between cortisol sampling

(filling out forms, wait periods in which participants could read magazines, watching the film, memory testing). Although these activities were deemed "benign" in relation to the stress induction, they also introduced variation in the procedure between groups.

Finally, more focus should have been placed on subjective anxiety as a potential variable related to memory (as suggested by the exploratory findings). A subjective anxiety rating was only obtained during the peak of the speech induction (and thus only in the stress groups), providing no information about baseline anxiety or the presumed increase in anxiety during the stressor. Anxiety should have been measured twice in order to provide a difference score similar to the cortisol measure, and should have been measured in control subjects as well to allow for comparative analyses.

Future directions

Clearly the effects of stress and cortisol on different memory processes is complex. The current study sought to parse these effects, and provides additional support for the facilitative effect of stress on the consolidation of information and a revised model of stress and memory in humans. Unfortunately, the results are equivocal regarding the effect of stress on encoding and retrieval processes. Future research should continue to focus on differentiating the effects of stress on different stages of memory. To do this, it is necessary to separate stimulus exposure and learning periods (i.e., list learning) from retention testing (free recall or other testing) by enough time to allow for application of a stress or drug manipulation to be related only to the particular memory process of interest. Varying the timing of the stressor, however, does introduce additional variation into the procedural order of the experiment, and as this study suggests, it may be important to provide time for subjects to habituate to the experiment before introducing the manipulation.

More research is also needed to better specify the dose-dependent response curve of glucocorticoids on memory. There are a number of animal studies investigating this question, suggesting this relationship is an inverted-U shape function. The question remains whether a similar relationship between cortisol and memory exists in humans,

and at what levels of stress *intensity* or hormone secretion. Certainly this is most easily studied with pharamacological interventions. However, studies varying the level of psychological stress (with accompanying autonomic and neuroendocrine measures) have not been conducted to date, but would help to provide a better idea of how intense a psychosocial stressor might need to be in order to affect cognition.

There is also the question of whether different *types* of stressors (physical, mental, social) have varying effects on biological and neurocognitive systems. Studies with animals have used restraint, forced swimming and dominance challenge as stressors, while the most common stress inductions in human research has been arm immersion in cold water or social evaluation/performance tasks such as public speaking. While theoretically these different stressors should activate the same autonomic and HPA stress systems, there is evidence for some specificity of physiological response to differing stressors (Stern & Sison, 1990). Indeed, different challenges require different types of behavioral responses by the organism: while severe cold results in a shivering and reduced behavioral activity, a challenge to one's social position will activate submissive or aggressive behaviors. To this investigator's knowledge, no studies have directly compared different types of stressors in one experiment and their associated neuroendocrine responses and cognitive correlates.

It is also clear that cortisol may not be the only mediator of stress-induced memory effects. Subjective distress during the speech induction predicted memory performance in this study, and underscores the importance of psychological and affective states to subsequent memory performance. Future studies should also measure the effects of catecholamine release on cognitive function as well as other hormones associated with HPA activation (CRF, ACTH).

Closer attention to the type of memory measures is also warranted. Many have used standard neuropsychological measures with known external validity, but which were originally designed to test for neurological impairments and may thus lack sensitivity with healthy subjects. Indeed, this study did not find the WMS-III Logical Memory narrative to be a sensitive measure, insofar as it showed no change with the manipulation.

Other researchers have developed experimental memory tests using word lists that appear to have good sensitivity. However, their ecological validity is still questionable. The current study provided evidence that stress can affect memory using a film stimulus that captures the complex rush of sensory, semantic, and social information we normally confront in the world. Similar studies are needed to better approximate how memory functions outside the laboratory. This study also provided additional evidence that stress may affect verbal and visual memory differently, and future studies should consider including memory measures that tap both of these domains separately.

Finally, the memory findings for this study and other human experiments have generally found a statistically significant but clinically small effect for memory (on a test of 30 questions, group means differed by no more than 2-3 correct answers). This may mean the effect of stress is real but very small. Alternatively, stress may selectively affect the type of information being processed (beyond visual vs. verbal). In the stress and memory literature, few researchers have manipulated demand characteristics during stimuli presentation or recall (competing tasks, processing load, instructions to attend to specific stimuli) or measured memory for content-specific information beyond visual vs. verbal information. In the current study, for example, we separately analyzed memory questions tapping "relational" content ("Cary handed the basketball to whom?"), but found no effect for stress between groups. However, several researchers have studied the effects of stress or glucocorticoids on stimuli with positive, negative or neutral affective valence. Tops and colleagues (2004) found cortisol to enhance the recall of pleasant words (but not unpleasant words) compared to placebo-controls, while another study found that the stimulus value of nouns in a recognition test was not sensitive to cortisol effects (Abercrombie et al., 2003). Others have found an association between stress and false memories (Payne et al., 2002), and the current study found that participants stressed after encoding had significantly more false positive answers than those stressed prior to encoding. This is a rich direction of investigation. Future research should continue to explore not only the effects of the timing and dose of stress on memory, but also its effects on specific cognitive processes and content.

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