# PAIN ANTICIPATION AND MEMORY: AN EVENT-RELATED POTENTIAL STUDY

by

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## LIST OF ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| ERP | Event-Related Potential |
| ANOVA | Analysis of Variance |
| SD | Standard Deviation |
| HPA | Hippocampal-Pituitary-Adrenal |
| EEG | Electroencephalogram/Electroencephalography |
| TSST | Trier Social Stress Test |
| H | Hits |
| FA | False Alarms |
| HEOG | Horizontal Electrooculogram |
| VEOG | Vertical Electrooculogram |
| μV | Microvolts |

## ABSTRACT

It is known that physical stress enhances episodic memory, but less is known about effects of psychological stressors such as pain anticipation on episodic memory and associated neural activity. The current study examined the effect of pain anticipation on episodic memory using event-related potentials (ERPs). Eighteen participants encoded 240 emotional words. Half of the words appeared in a font color that signaled threat of electric shock (threat words), although shock was only delivered on six randomly-determined threat trials. Recognition memory for the words was tested shortly after encoding. It was hypothesized that stress induced by pain anticipation would improve memory for threat over safe (no threat of shock) words, recognition ERPs would show typical old/new effects in the 500-700 ms time window, and that these old/new effects would be larger for threat than for safe words. However, results indicated better memory for safe than for threat words, and ERP amplitudes were more negative for old compared with new words in the 500-700 ms time window; typical old/new effects show the reverse pattern (more positive amplitudes for old compared with new stimuli). The observed ERP effect was also larger for safe than for threat words. Whereas previous research shows memory benefits due to stress at encoding, here, memory impairment was observed. Explanations for results could include lingering acute stress at retrieval, shallow encoding of threat words, or the devotion of resources to stress suppression during threat-word encoding. These results suggest that acute stress at encoding can impair memory in some circumstances.

# CHAPTER I

## PAIN ANTICIPATION AND MEMORY

Stress is known to have numerous effects on human physiology. For instance, heart rate quickens, breathing becomes labored, and the body begins to sweat. The root of these physiological reactions is the fight-or-flight response orchestrated by the sympathetic division of the peripheral nervous system. However, stress also has effects in the central nervous system, which can affect cognitive processes such as memory. Little is known about psychological stressors such as the anticipation of pain, which may also elicit a physiological stress response and affect memory. The current study explores how the anticipation of pain may affect memory. This information is important because it could increase knowledge about how memory is influenced by psychological stress. It also has implications for understanding how anxiety disorders may affect memory, and it could provide insight into possible evolutionary advantages of stress.

This thesis will first review previous research on memory and stress and then outline a study designed to examine how the anticipation of pain affects memory, both behaviorally and through changes in electrical activity in the brain. The first section will provide background information on memory, including a brief discussion of the distinctions between different kinds of memory and the different stages of memory. The next section will detail the known effects of stress on memory, including how aspects of physiology are involved in the modulation of memory. The anticipation of pain will then be considered, with respect to how this stressor in particular may influence memory. A brief description of how electroencephalographic measures of brain activity known as

event-related potentials can be used to examine stress-memory relationships will follow, concluding with the rationale and design of the proposed experiment. *Memory*

Long-term memory is generally divided into two categories: implicit and explicit (Schacter & Tulving, 1994). Implicit, or nondeclarative, memory can be described as the acquired knowledge of procedures, skills, and associations that do not require conscious executive control. It is typically an automatic response, such as performing a skill or a conditioned response (Schacter, 1987). Explicit, or declarative, memory is also sorted into two categories: episodic and semantic. Episodic memory can be described as a person's knowledge of experiences and autobiographical events, whereas semantic memory is knowledge of concepts, facts, and ideas, devoid of contextual information (Tulving, 1972). Episodic memory will be the focus of this manuscript.

Memory formation begins with encoding, when new knowledge is first acquired. New information reaches the brain and causes changes in the strength and number of synaptic connections. When an explicit memory trace is first formed, it is very fragile. Over time, the memory is stabilized and strengthened through consolidation, which occurs at the cellular and systems levels (McGaugh, 2000; Purves, Cabeza, Huettel, LaBar, Platt, & Woldorff, 2013). Cellular level (synaptic) consolidation begins immediately after encoding and involves changes in the number and strength of synaptic connections to create long-lasting memories at the neuronal level. Systems-level consolidation of long-term memories takes much longer, months or possibly years. During this process, the hippocampus, which is critical for encoding new information (Scoville & Milner, 1957), becomes less involved in memory maintenance, as cortical sites responsible for representing different aspects of the memory become more

thoroughly bound together. Eventually, these cortical connections become strong enough that the memories can be retrieved without a contribution from the hippocampus (Nadel, Winocur, Ryan, & Moscovitch, 2007; Purves et al., 2013). The retrieval, or access, of stored memories can lead to behavioral changes and conscious recollection (Purves et al., 2013; Tulving, 1983).

The effects of psychological stress on implicit memory have received much attention, primarily through the study of fear conditioning, which is a form of learning in which a threatening stimulus is repeatedly paired with a previously neutral stimulus, such that the neutral stimulus eventually elicits fear via a learned implicit association (LeDoux, 1996). However, less is known about the effects of psychological stress on explicit episodic memory. Therefore, the current study examined how psychological stress during encoding affects both the encoding and retrieval of explicit memories for words.

*Effect of Stress on Memory*

Although it has been demonstrated that chronic stress can impair memory functions (e.g., Mackenzie, Wiprzycka, Hasher, & Goldstein, 2009), acute stress has been shown to improve explicit memory encoding and consolidation (Birkett, 2011; Jelicic, Geraerts, Merckelbach, & Guerrieri, 2004; McEwen, 2007; Payne, Jackson, Hoscheidt, Ryan, Jacobs, & Nadel, 2007; Smeets, Giesbrecht, Jelicic, & Merckelbach, 2007). For example, one study separated participants into three groups: one that would experience personality-related stress, one that would experience memory-related stress, and a no-stress control group (Smeets et al., 2007). Participants then completed the Trier Social Stress Test (TSST; Birkett, 2011) in which they had to perform mental math and give a

presentation in front of an audience. During the TSST, the personality stress group had to give a five minute presentation about their own personality, whereas the memory stress group had to give a five minute presentation about their own memory ability. Afterwards, they studied a list of personality- and memory-related words. A day later, participants performed a memory task. Acute stress just prior to encoding enhanced memory performance for context-congruent information (for example, personality words were better remembered by the personality stress group). In another study, to examine the effects of stress on memory consolidation in particular, participants watched a film and memory for the film was tested 48 hours later (Beckner, Tucker, Delville, and Mohr, 2006). Some participants gave a public speech before a peer audience immediately after watching the film, others gave a speech immediately before retrieving memories for the film, and a final group gave no speech at all. Results showed that the participants who gave the speech immediately after watching the film had better memory for the film than the other groups, indicating that stress can enhance consolidation. Collectively, these and other studies suggest that acute stress during encoding and/or consolidation can enhance memory.

The memory benefit accrued by acute stress is mediated by the fight-or-flight response of the sympathetic nervous system (Joels, Wiegert, Oitzl, & Krugers, 2006), which includes the release of the hormones norepinephrine, epinephrine, and cortisol (Von Euler & Gaddum, 1931; Joels, et al., 2006). At the induction of an acute stressor, cortisol is secreted immediately, but does not reach peak levels until approximately 20 to 30 minutes after the onset of the stressor. These elevated cortisol levels then return to baseline within an hour (Smyth, Hucklebridge, Thorn, Evans, & Clow, 2013). This chain

of events is considered the brain's defense system (Lang & Bradley, 2010). It is thought that the memory enhancing effects of stress are mediated by cortisol, via its effects on the amygdala and the close interactions between the hippocampus and amygdala (de Quervain, Roozendaal, & McGaugh, 1998; Roozendaal, 2002). Indeed, stress-related memory enhancements disappear when the amygdala is lesioned or otherwise pharmacologically inactivated in rodents (Roozendaal, 2000).

Increased cortisol levels have been shown to mediate the stress-induced memory enhancement during encoding and consolidation in humans (Lupien & Lepage, 2001; McEwen, 2007; Roozendaal et al., 2006). For example, one study reported that, after performing a psychosocial stress task and having a saliva test confirm an increase in cortisol, participants had significantly better recognition memory for words (Jelicic et al., 2004). Similarly, another study demonstrated that doses of cortisol immediately before encoding led to fewer errors in a free-recall task (Abercrombie et al., 2003). Other studies have demonstrated that increases in cortisol shortly after encoding can also improve subsequent memory, presumably by influencing memory consolidation. In one study, participants encoded a vignette, and then shortly after received a physical stressor by performing a cold pressor task, a procedure in which the participant must submerge his or her hand in ice water for as long as they can tolerate (Andreano & Cahill, 2006). After the cold pressor task, saliva samples were obtained to measure cortisol levels, and then participants took a memory test for the vignette. Results demonstrated a positive correlation between cortisol level and memory performance. In another study, participants encoded slides, and then completed a cold pressor task immediately after encoding (Cahill, Gorski, & Le, 2003). Saliva was tested before and after the cold pressor

task to ensure that cortisol levels had increased. A week later, memory for the slides was better for participants who did the cold pressor task than participants who did a control task. Collectively, the results from these studies demonstrate that increases in cortisol can enhance memory encoding and consolidation.

Whereas memory encoding and consolidation are enhanced via the release of cortisol that occurs during acute stress, elevated cortisol at retrieval appears to have the opposite effect. Studies that administer cortisol at retrieval typically find decrements in memory, suggesting that cortisol increases during retrieval impede memory (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Kuhlmann, Kirschbaum, & Wolf, 2005). For instance, in one study (de Quervain et al., 2000), participants encoded words and then the next day, ingested cortisol one hour before a recognition test. Participants who were administered cortisol performed significantly worse on the recognition test than participants given a placebo. In another study, cortisol administered to participants just before recall, 5 hours after encoding, significantly impaired explicit memory (Kuhlmann, Kirschbaum, & Wolf, 2005). Therefore, it appears that an increase in cortisol just prior to or immediately after encoding can improve memory performance, whereas increases in cortisol before retrieval can impair episodic memory.

*Emotion and Memory*

It is well known that emotionally salient memories are preferentially encoded and stored over neutral memories (LaBar & Cabeza, 2006). It is believed that this benefit is mediated by the amygdala, as emotionally arousing stimuli activate the amygdala during encoding, and the extent of amygdala activation predicts subsequent recall success (Murty, Ritchey, Adcock, & LaBar, 2011). Once activated, the amygdala influences

memory via signals sent to the hippocampus and the surrounding medial temporal lobe that influence explicit memory encoding and consolidation (McGaugh, 2004; Murty et al., 2011).

Furthermore, stress may benefit emotional memories more so than neutral memories. As described above, the influence of cortisol on the amygdala and hippocampus is believed to modulate memory. Emotional stimuli are known to be more arousing and more stressful than neutral stimuli (Cahill & McGaugh, 1998), which can lead to memory benefits for emotional over neutral events, similar to that of stressful over non-stressful events. In support of this view, one study implemented the TSST in order to induce stress in participants before they encoded emotional and neutral vignettes (Payne et al., 2007). The results indicated enhanced memory for emotional over neutral vignettes. Another study administered cortisol to participants before showing them emotionally laden images, in order to induce stress immediately before the encoding of emotional stimuli (Buchanan & Lovallo, 2001). Results demonstrated that, under stress, memory was better for emotional than neutral stimuli. Collectively, these studies suggest that stress at encoding improves memory for emotional information in particular.

It has also been suggested that the valence of an emotional event may influence how well it is remembered. Typically, negative events are remembered better than positive events (Kensinger, 2007; Ochsner, 2000), although positive events are still remembered better than neutral (Buchanan & Adolphs, 2002). This phenomenon, whereby negative events are remembered more strongly than positive events, is referred to as a negativity bias (Rozin & Royzman, 2001). It is speculated that this negativity bias

may be driven by amygdala activation during encoding (Kensinger, 2007), as the amygdala may be tuned to detect threatening stimuli in the environment (Whalen, 1998).

*Dissociating the Effects of Pain and Pain Anticipation on Memory*

Pain is the nervous system's response to noxious, or potentially harmful, stimuli (Purves et al., 2013) and can be chronic or acute. Chronic pain is typically described as any form of pain that lasts more than 6 months, and can persist for years (Crombez, Eccleston, Van Hamme, & De Vlieger, 2008). It is often reported to feel like a dull throbbing ache, and, although at times a clear cause of chronic pain is not distinguishable, it may be accompanied by other health problems, such as fatigue, sleep disturbances, and changes in mood. Acute pain is a short-term painful sensation that alerts a person to the possibility of an injury. It is described as much more intense than chronic pain, and can last minutes to hours, but will fade away as the injury is tended to (Crombez et al., 2008). To create a stress response in participants, the current study implemented anticipation of acute, rather than chronic, pain.

The experience of acute pain when encountering something dangerous is indirectly beneficial, because it leads to an aversion to the noxious stimulus in the future. Evolutionarily, this phenomenon promotes survival. This physiological response is seen in the activation of the brain's defense system, which provides feedback to the sensory systems, significantly increasing vigilance and information gathering in the presence of a noxious stimulus (Lang & Bradley, 2010). This increased awareness prompts the brain to respond appropriately to the stimulus (e.g., pulling hand away from a hot stove; Lang & Bradley, 2010). Therefore, one possibility is that, in addition to the release of stress-

related hormones, heightened awareness caused by the anticipation of painful stimuli also leads to better memory encoding.

When a person anticipates pain, it is typically followed by a painful experience. Thus, it is possible that pain itself influences memory performance. However, the anticipation of pain is neurally different from actual pain. Neuroimaging research has shown that the anticipation of pain and the experience of pain activate distinct neural networks (Ploghaus, Tracey, Gati, Clare, Menon, Matthews, & Rawlins, 1999). For instance, brain areas that are active during the experience of acute pain include the somatosensory cortex, insular cortex, anterior cingulate cortex, prefrontal cortex, and the thalamus. Brain areas active during the anticipation of pain include the basal ganglia, cerebellum, amygdala, and hippocampus (Tracey, 2008). Furthermore, acute pain has not been shown to improve either short-term or long-term memory. Studies that induce acute pain via cold pressor tasks do not show significant effects on cognitive functions such as processing speed or working memory (Etherton, 2013; Ishizuka, Hillier, & Beversdof, 2007). Collectively, research suggests that the experience of pain does not strongly influence memory. Therefore, memory improvements in circumstances in which pain anticipation is followed by actual pain likely reflect the anticipation of pain, rather than pain itself, on episodic memory.

It should also be noted that pain-related anxiety frequently intensifies the level of actual pain experienced, when pain actually follows anticipation (Sternbach, 1968; Melzack, 1973). This intensified pain experience occurs through activation of the hippocampal formation, which is thought to prime memory representations of the aversive events (Ploghaus, Narain, Beckmann, Clare, Bantick, Wise, Matthews, Rawlins,

& Tracey, 2001). Therefore, the current study also examined fear of pain and pain catastrophizing (a tendency to consider pain in hyperbolic proportions). Participants who demonstrate a fear of pain or pain catastrophizing may have a stronger stress reaction to the anticipation of pain than other participants. If this is the case, then their results may be different than participants who do not fear or catastrophize pain. Specifically, if the anxiety generated during pain anticipation improves memory, then participants who have higher anxiety levels due to pain anticipation (those who score high for fear of pain and pain catastrophizing) might have significantly better memory than participants who do not fear or catastrophize pain.

*Event-Related Potentials*

Event-related potentials (ERPs) reflect brain activity associated with the processing of different experimental conditions, and can provide useful information regarding how different classes of stimuli are processed that may not be evident with purely behavioral measures. ERPs are voltage fluctuations in electroencephalogram activity that occur in response to a particular class of stimuli. Electrical activity is typically examined from 0-1000 ms post-stimulus onset, and averaged across several trials to reduce noise from processing not related to the event of interest. The peaks and troughs in the ERP waveforms are known as components, and separate components are typically associated with different aspects of cognitive processing.

For instance, the P2 component (also known as P200) is a positive peak, occurring approximately 200 milliseconds (ms) after the onset of a stimulus (Luck, 2005). In previous studies, during word encoding, words that signal threat (an impending painful stimulus) as opposed to safety (not followed by a painful stimulus) showed larger

P2 components over anterior brain areas (Baas, Kenemans, Böcker, & Verbaten, 2002). This suggests that the P2 may reflect increased salience for threatening stimuli, which could lead to better memory. The P3 component (or P300) is a positive peak, and usually occurs around 300ms after the onset of a stimulus (Luck, 2005). There is a distinction between P3a and P3b components. The P3a component occurs over frontal and central areas of the cortex, and is thought to reflect attentional orienting to novel stimuli, regardless of task relevance (e.g., a novel distractor during a train of stimuli in which a participant searches for a target; Picton, 1992; Polich, 2007). On the other hand, the P3b component occurs over parietal regions and is only present for target stimuli. It is thought to reflect the allocation of attention and subsequent updating of working memory representations (Polich, 2007).

During recognition, ERPs occurring between 300 and 800 ms after stimulus onset during recognition are thought to index the retrieval of long-term memories, and different components have been associated with the processes of familiarity and recollection (Curran & Friedman, 2003). Old/new effects are differences in ERP amplitudes as a function of memory, such that old items elicit significantly more positive amplitudes than new items (Rugg & Curran, 2007). Old/new effects apparent in the early FN400 component (peaking between 300-500 ms in the frontal region) are believed to be sensitive to memory processes involving familiarity, whereas old/new effects occurring during the late positive component (LPC; 500-800ms; centro-parietal regions) are associated with conscious recollection (Rugg & Curran, 2007).

One previous study examined the anticipation of pain on explicit memory by examining ERPs in addition to memory performance during a memory task that involved

a signal of oncoming pain, a possible electric shock (Weymar, Bradley, Hamm, & Lang, 2013). Participants encoded a list of words (half emotional, half neutral) in which certain words appeared in a color that signaled an upcoming electric shock, although no actual shock was ever administered. Threat of shock did not significantly affect memory performance, but it did affect ERPs recorded during both encoding and recognition. During encoding, ERPs for threat words showed enhanced P2 and P3 components compared to safe words. Consistent with prior studies examining threat versus safety cues (Baas et al., 2002; Bocker, Baas, Kenemans, & Verbaten, 2004; Bublatzky & Schupp, 2012), the enhanced P3 component for threat versus safe words during encoding found by Weymar et al. (2013) was prominent over the parietal area, and is thought to reflect the P3b component, indicating greater attentional resources allocated to threat words. Weymar et al. (2013) also found larger old/new ERP effects in the LPC (500-700 ms) time window at parietal recording sites for threat words compared with safe words. After old/new effects were calculated, Weymar and colleagues (2013) conducted a median split, and, using only the participants with the largest old/new effects, it was demonstrated that more threat words were recognized than safe words. However, this effect was only found for emotional words; it was not present for neutral words.

Collectively, these results suggest that the anticipation of pain may improve memory, but several limitations preclude drawing strong conclusions regarding whether pain anticipation facilitates memory. For example, the Weymar et al. (2013) study could have suffered from extinction effects because the electric shocks were never actually applied during the encoding task; thus, maintenance of an anticipatory state is questionable. In other words, a participant may have stopped anticipating a shock if no

shocks were delivered during encoding, attenuating both behavioral and ERP indices of memory. Another limitation is that the improved memory for threat versus safe words found only for emotional words (Weymar et al., 2013). However, it was unclear if the memory benefit was equivalent for positive and negative emotional words.

*Current Study*

The current study sought to expand on the work of Weymar et al. (2013) to find evidence that the anticipation of pain will increase performance on a recognition memory task using a similar paradigm, with the exceptions that shocks were actually administered sometimes following threat words, and only emotional words were encoded and tested. It was predicted that the anticipation of painful electric shocks would lead to increased memory accuracy for threat versus safe words. It was also expected that larger old/new effects for threat versus safe words would be present during retrieval, as was observed by Weymar et al. (2013). Although Weymar et al. (2013) did not observe a memory benefit for threat versus safe words overall, better memory for emotional threat words than emotional safe words was observed when only participants with large old/new effects were examined. It was predicted that the inclusion of only emotional words as stimuli as well as including trials in which shocks would actually be delivered would lead to larger differences in these measures in the current study. Additionally, the magnitude of these differences will be compared for negative versus positive words. Based on previous studies suggesting that negative emotional events are remembered better than positive events (Rozin & Royzman, 2001), it was expected that memory would be better for negative than for positive words, and associated ERP effects would be larger for negative than for positive words.

In addition, the current study also included exploratory correlational analyses to examine pain-related anxiety. Participants filled out questionnaires related to the fear of pain and pain catastrophizing, which may provide evidence that participants who fear or catastrophize pain will show more effects of anticipation. Specifically, participants who demonstrate higher than average fear of pain and pain catastrophizing were expected to exhibit larger than average stress responses to the anticipation of pain. This may be evidenced in larger old/new effects and/or better recognition memory of threat words compared to safe words for these individuals compared with individuals who show average or less than average fear of pain and pain catastrophizing.

# CHAPTER II

## METHOD

### *Participants*

Data collection involved 30 right-handed participants recruited from the student population at Texas State University. Six participants were excluded because of missing data due to technical error, and 6 more participants were excluded after artifact rejection due to fewer than 20 useable trials per condition. This resulted in a final group of 18 participants (13 female), with an average age of 20.7 and average number of years spent in post-secondary education of 3.1. Monetary compensation of $20 was offered as participation incentive. Exclusion criteria included individuals with chronic pain, recent acute pain, or a history of seizures. All participants provided informed written consent for the protocol, which was approved by the Texas State Institutional Review Board.

### *Materials*

From the Affective Norms for English Words (ANEW; Bradley & Lang, 1999), 480 nouns were selected, consisting of 240 negative words and 240 positive words. Words were divided into two sets. For each set of 240 words (120 positive, 120 negative), half were shown at encoding (old words), and the other half were used as new words during recognition. The word sets were matched on the basis of absolute valence (negative and positive words were matched according to deviation from neutral), arousal, and word frequency (Bradley & Lang, 1999).

Additionally, two questionnaires were used, the Pain Catastrophizing Scale (Sullivan, Bishop, & Pivik, 1995), and the Fear of Pain Questionnaire-III (McNeil & Rainwater, 1998). The Pain Catastrophizing Scale is a 13-item questionnaire that

measures responses on a 4-point Likert scale. It has been tested for psychometric effectiveness and is a reliable and valid measure of pain catastrophizing (Osman et al., 2000). The Fear of Pain Questionnaire-III is a 30-item scale that also measures responses on a 5- point Likert scale and is a reliable and valid measure of the fear of pain (Osman et al., 2002).

*Memory Task*

During the encoding phase, participants viewed a series of 240 words presented one at a time on a computer screen. Each word was presented in Times New Roman 80 point font. In each trial, a fixation cross appeared on the screen for 500 ms and then the word appeared for 2 seconds, followed by a 500 ms inter-trial interval. Superlab 5.0 (Cedrus, San Pedro, CA) was used to present words to the participants. Positive and negative words were presented during separate blocks of 40 words during encoding in an alternating manner (e.g., positive, negative, positive…; or negative, positive, negative…). Valence of the first block was counterbalanced across participants. Within each group of words, half were threat and half were safe words. For half of the participants, threat words appeared in yellow font and safe words appeared in blue font. For the remaining participants, font color was reversed, such that threat words appeared in blue font and safe words appeared in yellow font. Participants were given 2-minute breaks after each block to prevent fatigue.

In the recognition phase, 480 words (240 old, 240 new) were presented in random order one at a time on the screen for 2.5 seconds each, preceded by a 500 ms fixation cross. Prior to the start of the recognition phase, participants were instructed that, following each word, they should decide whether the word had been seen previously in

the experiment. They were instructed to press the yes button (the "Y" button on the keyboard) if they remembered seeing the word before, or the no button ("N" button on the keyboard) if they did not remember seeing the word before. After the yes or no button was pressed, a 500 ms inter-trial interval preceded the subsequent trial.

*Electroencephalogram (EEG) Recording*

EEG data was recorded continuously using a SynAmps2 system from 64 channels embedded in a cap (Ag/Ag/Cl Quik-Cap), with Acquire version 4.5 (Compumedics Neuroscan, Charlotte, NC), referenced to the vertex and re-referenced off-line to linked mastoids. There were also two electrodes on the outside corner of each eye to detect horizontal eye movements (horizontal electrooculogram, or HEOG), and two additional electrodes placed above and below one eye to record vertical eye movements (vertical electroocuologram, or VEOG). Impedance was at or below 5 kΩ for all electrodes. Data was sampled at a rate of 1000 Hz, and was filtered off-line to include a bandwidth of 0.01-50 Hz. Any trials that showed movement artifacts in any recording channel (absolute value > 100 μV) were excluded. Participants with fewer than 20 trials per condition ($n$ = 6) after artifact rejection were excluded from subsequent analyses.

*Electrical Stimulation*

Electrical stimulation was delivered with a Biopac STIM-ISO-C electrical stimulator via a separate computer running Acknowledge 4.3 (Biopac, Goleta, CA). Shocks were administered via two 8mm Ag/Ag/Cl electrodes placed on the inside of the non-dominant wrist. The participant's threshold for electrical stimulation tolerance (i.e., the level of stimulation that the participant was willing to receive) was determined just prior to the memory task. To do this, a thresholding script was developed, in which the

participant experienced gradually increasing mild electrical stimulation pulses, beginning at 0 V and increasing at 5 V increments. After each pulse, the participant reported to the experimenter if he/she was willing to tolerate that level of stimulation. Once a participant reached a level he or she did not wish to exceed, the experimenter used that level for the stimulation delivered during the experiment. If a participant received a level of stimulation that he or she decided was intolerable and did not want to experience again, the experimenter went back down to the stimulation level before it and used that level during the experiment. Each stimulation pulse lasted for 2.5 ms.

*Procedure*

Upon arrival at the laboratory, participants were fully briefed on the procedures of the study and were screened for previous chronic pain conditions, recent acute pain, or neurological conditions. Informed consent was obtained, along with self-reported demographic information such as age, number of years in post-secondary education, gender, and handedness. Next, they were prepped for EEG recording and electrical stimulation, including the thresholding procedure for electrical stimulation tolerance.

Participants then completed the memory task. Before the experiment began, participants were told which font color indicated threat (potential for a shock to be delivered). Although participants would anticipate the electrical stimulation every time a word appeared in the threat color (yellow or blue; a "threat word"), they only actually experienced the stimulation 6 times (3 positive words, 3 negative words) on randomly determined threat-word trials. For each of these 6 trials, the electrical stimulation pulse occurred 2 s after the onset of the threat word, coinciding with the disappearance of the

word from the screen. There was then a 500 ms inter-trial interval before the onset of the next word.

To encourage participants to pay attention to the words, participants were told to press the space bar every time the word "window" appeared on the screen (this word was never actually presented). When the encoding phase was complete, they completed the Pain Catastrophizing Scale and the Fear of Pain Questionnaire-III, which served to distract them from thinking about the information they just studied, in addition to gathering information about participant attitudes towards pain. These questionnaires typically took 3-5 minutes to complete. Immediately after completing the scale and the questionnaire, participants performed the recognition phase of the memory task. Finally, participants were debriefed and compensated for participating.

*Analytic Strategy*

*Behavioral analyses*. Behavioral data from the recognition test was analyzed with three independent repeated measures Analyses of Variance (ANOVAs) using valence (positive, negative) and cue (threat, safe) as within-subjects independent variables. The first ANOVA used hit rate as the dependent variable and the second and third ANOVAs used estimates of response bias and discrimination index, respectively, as the dependent variables. Response bias is the tendency to produce "old" or "new" answers in a recognition test (or as in the current study, "yes" or "no" responses). Analyses of hit rates could thus be influenced by differences in response bias across conditions. Discrimination index, or sensitivity, is a participant's ability to discriminate between old and new items in a recognition test, and reflects a measure of memory independent of response bias. To determine whether response bias differed across conditions and

whether these differences influenced hit rates in the present experiment, sensitivity and response bias were estimated using *Pr* and *Br* (Snodgrass & Corwin, 1988). *Pr* was calculated by subtracting false alarms (FA) from hits (H) for each condition (*Pr* = H - FAs), with increasing values representing an increasing ability to discriminate between old and new words. *Br* was estimated by dividing false alarms by the inverse of the discrimination index [*Br* = FA/(1-*Pr*)]. *Br* values above .5 indicate a tendency to endorse items as old, whereas *Br* values below .5 indicate a tendency to endorse items as new. Neutral bias is represented by a *Br* value of .5.

*ERP analyses.* ERP data during recognition were averaged across 500-700 ms, the time window in which old/new effects were reported in the Weymar et al. (2013) study. Electrodes to be included in analyses were selected based on preliminary *t*-tests that were conducted to determine whether there were significant differences between old and new words for each electrode. Electrodes that showed significant differences between either of the old word conditions (threat and safe) and the new word condition were selected for analysis and proximal electrodes were averaged together based on location, resulting in four locations that were submitted to subsequent repeated measures ANOVAs: centro-parietal (CP5, CP3, CP1, CP4, CP6), parietal (P5, P3, P1, Pz, P2, P4, P6, P8), parietal-occipital (PO7, PO5, PO3, PO4, PO6, PO8), and occipital (O1, Oz, O2).

# CHAPTER III

## RESULTS

*Memory Test*

Mean memory performance by condition is listed in Table 1. To assess differences in memory performance across conditions, a 2 x 2 repeated measures ANOVA was conducted with valence (positive, negative) and cue (threat, safe) as within-subjects independent variables, and hit rate as the dependent variable. A significant main effect of valence was found, $F(1, 17) = 18.8$, $p < .001$, indicating that hit rate was significantly higher for negative than for positive words. Additionally, a significant main effect of cue was found, $F(1, 17) = 6.9$, $p < .05$, indicating that hit rate was significantly higher for safe than for threat words. There was no significant interaction between valence and cue, $F(1, 17) = 2.8$, $p > .1$.

To assess response bias, a 2 x 2 repeated measures ANOVA using *Br* as the dependent variable was conducted with valence (positive, negative) and cue (threat, safe) as within-subjects variables. As reported in Table 1, there was a bias to respond "no" across nearly all conditions (there was no bias to respond "yes" or "no" to negative words in the safe condition). A significant main effect of valence was found, $F(1, 17) = 22.3$, $p < .001$, such that there was a higher tendency to respond "no" to positive words than to negative words. A significant main effect of cue was also present, $F(1, 17) = 4.7$, $p < .05$, indicating a higher tendency to respond "no" to threat words compared with safe words. Additionally, a significant interaction between valence and cue was found, $F(1, 17) = 4.7$, $p < .05$. To determine the nature of this interaction, the difference in response bias between positive and negative words was calculated for both threat (.10) and safe (.16)

conditions. A paired *t*-test indicated that the difference in response bias between positive and negative words was significantly larger in the safe condition than the threat condition, $t(17) = 2.2$, $p < .05$.

To assess whether the observed difference in response bias influenced the analysis of hit rates, a third 2 x 2 repeated measures ANOVA was conducted using the discrimination index *Pr* as the dependent variable, with valence (positive, negative) and cue (threat, safe) as within-subjects variables. Mean *Pr* values for each condition are reported in Table 1. As was observed in the hit rate analysis, a significant main effect of cue was found, $F(1,17) = 6.9$, $p < .05$, indicating that discrimination ability was higher for safe than for threat words. However, in contrast to the analysis of hit rates, there was no significant main effect of valence, $F(1, 17) = 1.7$, $p > .2$, indicating that the ability to discriminate between old and new words did not differ as a function of valence. This suggests that the higher hit rate for negative than for positive words reported above was driven by response bias. There was no significant cue x valence interaction, $F(1, 17) = 2.8$, $p > .1$.

Table 1: Memory Performance by Cue Type for Positive and Negative Words

| | Positive | | Negative | |
|---|---|---|---|---|
| | Threat | Safe | Threat | Safe |
| Hit Rate | .45 (.15) | .46 (.15) | .55 (.11) | .62 (.16) |
| *Pr* | .18 (.11) | .18 (.10) | .18 (.12) | .25 (.17) |
| *Br* | .34 (.13) | .34 (.14) | .44 (.12) | .5 (.15) |

*Note.* Numbers represent proportions; standard deviations in parentheses.

*Event-Related Potentials*

ERP data from the encoding phase were not analyzed due to technical error. Additionally, after artifact rejection, only 5 participants had > 20 trials in the positive valence conditions and only 6 participants had > 20 trials in the negative valence conditions. Therefore, the effects of valence on ERPs were not examined.

A 3 x 4 repeated measures ANOVA including condition (old threat hit rate, old safe hit rate, new correct rejections) and location (centro-parietal, parietal, parietal-occipital, occipital) as within-subjects independent variables was conducted to determine whether ERP amplitudes differed between conditions and across locations. A significant main effect of condition was found, $F(2, 34) = 9.7$, $p < .001$, indicating that the mean amplitudes differed across old threat hit rates, old safe hit rates, and new correct rejections. The ERP waveforms (Figure 1) suggest that mean amplitude was more positive for new correct rejections than for either old threat or old safe hit rates. Follow-up paired *t*-tests comparing old threat hit rates versus new correct rejections and old safe hit rates versus new correct rejections revealed significant differences in both comparisons, $t(17) = -3.3$, $p < .05$, and $t(17) = -3.4$, $p < .001$, respectively. However, old/new effects are defined as an enhanced positivity for old items compared with new items (Rugg, 2000; Rugg, Cox, Doyle, & Wells, 1995). Therefore, typical old/new effects were not present. Instead, old/new differences took the form of an old word negativity, in that old items were more negative than new items. There was no main effect of brain region, $F(3, 51) = .9$, $p > .4$, nor was there a significant interaction between condition and brain region, $F(6, 102) = .3$, $p > .9$, indicating that the main effect of condition was similar across brain regions.

To determine whether the magnitude of the old word negativity effect differed between threat and safe conditions, differences in the magnitude of this effect were computed by subtracting the average old word amplitude from the average new word amplitude for both threat and safe words. A 2 x 4 repeated measures ANOVA was conducted, including cue (threat, safe) and brain region (centro-parietal, parietal, parietal-occipital, occipital) as within-subjects variables and old word negativity difference as the dependent variable. A significant main effect of cue was present, $F(1, 17) = 5.9$, $p < .05$, indicating that there was a larger old/new difference for safe than for threat words. There was no main effect of brain region, $F(3, 51) = .5$, $p > .6$, and no significant cue x brain region interaction, $F(3, 51) = .2$, $p > .8$. Table 2 depicts average ERP amplitudes in old threat, old safe, and new conditions across each of the 4 locations included in these analyses in the 500-700 ms time window. Figure 1 depicts ERP amplitude data, from 0-1000 ms post-stimulus onset, averaged across location.

Table 2: Average Recognition ERP Amplitudes in Microvolts (μV) for Old Threat Hits, Old Safe Hits, and New Correct Rejections Across Locations in Late Positive Component (500-700 ms).

| | Old Threat | Old Safe | New |
|---|---|---|---|
| Centro-Parietal | -0.63 (1.03) | -1.23 (2.12) | -0.18 (0.74) |
| Parietal | -0.56 (0.96) | -1.18 (1.84) | -0.03 (0.70) |
| Parietal-Occipital | -0.57 (0.87) | -1.13 (1.22) | -0.04 (0.66) |
| Occipital | -0.74 (0.80) | -1.24 (1.04) | -0.27 (0.65) |

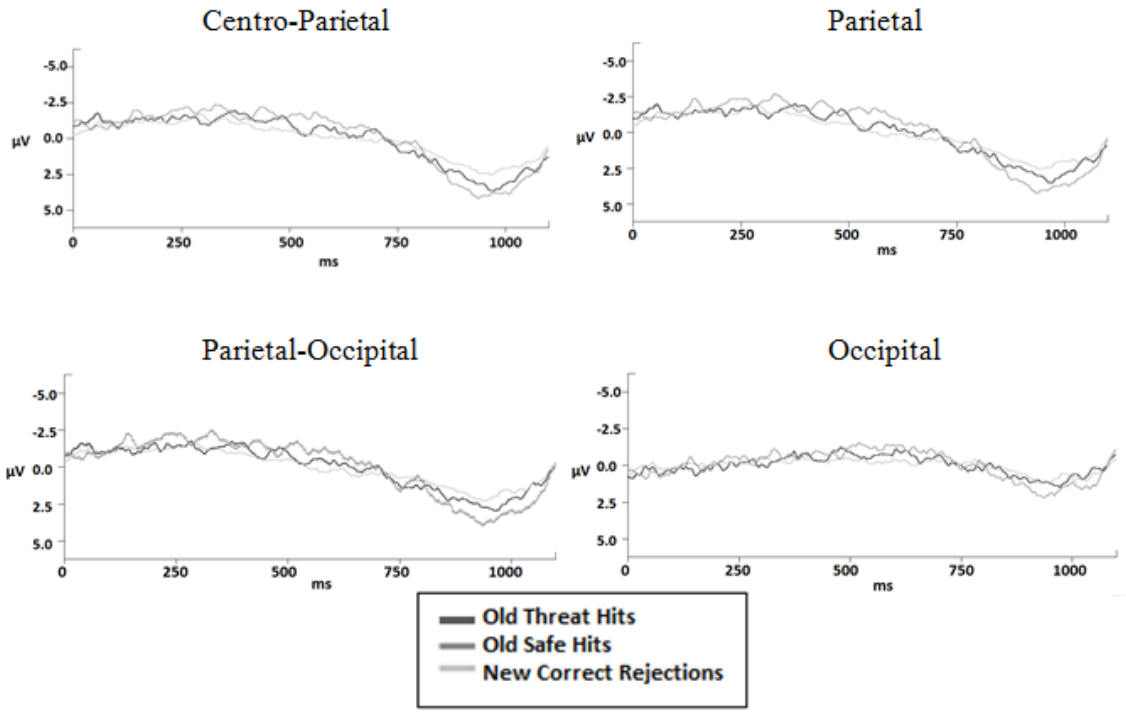


Figure 1: Grand Average Recognition ERPs for Old Threat Hits, Old Safe Hits , and New Correct Rejections by Location

*Exploratory Analyses*

Survey results from the Pain Catastrophizing Scale (mean = 27.9, SD = 11.1) and the Fear of Pain Questionnaire-III (mean = 70.6, SD = 19.9) were scored. The Pain Catastrophizing Scale has a maximum score of 50, and a score equal to or greater than 30 is thought to represent a clinically relevant level of catastrophizing, suggesting that the current sample is not prone to catastrophizing (Sullivan, Bishop, & Pivik, 1995). The Fear of Pain Questionnaire-III has a maximum score of 150. The standard mean for undergraduates is 79, with a standard deviation of 19 (McNeil & Rainwater, 1998). This suggests that the current sample does not have a high fear of pain.

Each scale was correlated with threat-word hit rates, threat-word response bias, threat-word sensitivity, and threat-word ERP amplitudes averaged across all locations

showing differences between conditions (centro-parietal, parietal, parietal-occipital, occipital) during recognition to determine whether fear of pain or pain catastrophizing were associated with ERPs or memory performance for threat words. Neither the Pain Catastrophizing Scale nor the Fear of Pain Questionnaire-III correlated with hit rate ($r$ = .007, $p$ > .9; $r$ = .03, $p$ > .8; respectively), *Br* ($r$ = .04, $p$ > .8; $r$ = .15, $p$ > .5; respectively), or *Pr* ($r$ = .03, $p$ > .8; $r$ = .27, $p$ > .2; respectively). Additionally, there was no correlation between threat-word ERP amplitude and Pain Catastrophizing scores ($r$ = .04, $p$ > .8) nor Fear of Pain scores ($r$ = .3, $p$ > .3), after the removal of one outlier in which the value of the threat-word ERP amplitude was greater than 2 standard deviations above the mean.

# CHAPTER IV

## DISCUSSION

The current study was designed to test whether the stress associated with the anticipation of an electric shock improves recognition memory and modulates associated ERPs, as suggested by Weymar et al. (2013). The primary hypothesis was that the inclusion of actual shocks during encoding and the use of only emotional words as stimuli would replicate and extend the findings of Weymar et al. (2013). In the Weymar et al. (2013) study, greater memory for words associated with a fear of electric shock than for other words was observed, but only for emotional words in individuals who also exhibited large old/new effects. Surprisingly, in the current experiment, behavioral indices of memory and associated ERP differences between conditions were stronger for words that were not associated with the anticipation of an electric shock compared with words that were, suggesting that in some circumstances, stress associated with the fear of pain can actually impair memory encoding and/or consolidation.

The findings of Weymar and colleagues (2013) are consistent with previous work demonstrating that stress and increased cortisol levels associated with stress can enhance memory encoding and consolidation (Birkett, 2011; Jelicic, Geraerts, Merckelbach, & Guerrieri, 2004; McEwen, 2007; Payne, Jackson, Hoscheidt, Ryan, Jacobs, & Nadel, 2007; Smeets, Giesbrecht, Jelicic, & Merckelbach, 2007). By making a few small changes to the Weymar et al. (2013) paradigm, it was predicted that a behavioral memory benefit for threat words would be observed in all participants. Changes included actually administering electric shocks during some encoding trials and simplifying stimuli, such that only emotional words were studied and tested. The addition of shocks was

hypothesized to prevent extinction of the stress response, which may have occurred in Weymar et al. (2013). Only emotional words were used because Weymar et al. (2013) only observed a memory benefit due to stress for emotional words. However, these changes led to results in contrast to Weymar et al. (2013). Here, memory was significantly better for safe than for threat words in analyses of both hit rates and recognition sensitivity.

The effects of stress on memory are known to vary widely across different circumstances, and in some cases, stress can impair memory. For instance, chronic stress has been shown to impair memory (Mackenzie, Wiprzycka, Hasher, & Goldstein, 2009), and acute stress at the time of retrieval also significantly impairs memory (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Kuhlmann, Kirschbaum, & Wolf, 2005). A spike in cortisol at encoding appears to enhance memory, suggesting the hippocampus-pituitary-adrenal (HPA) activation and interactions between the amygdala and hippocampus are beneficial for the formation of new memory traces. However, at retrieval, increases in this same hormone interfere with memory mechanisms in the hippocampus and amygdala (de Quervain, Roozendaal, & McGaugh, 1998; Roozendaal, 2002).

Although stress at encoding typically enhances memory, one potential explanation for the poorer memory for threat words compared with safe words in the present experiment may be the timing of the recognition test. The recognition phase occurred 3-5 minutes after the completion of the encoding phase, with only two brief questionnaires as distractors. Considering that acute stress at retrieval typically impairs memory (de Quervain et al., 2000; Kuhlmann, Kirschmann, & Wolf, 2005; Kuhlmann, Piel, & Wolf,

2005), perhaps the recognition phase occurred too soon after encoding. It's possible that the increased cortisol due to the anticipation of pain carried over from the encoding phase and persisted during the recognition phase. In fact, one study demonstrated that even a low dose (25 mg) of cortisone can significantly affect cognitive functioning—including memory—up to an hour after ingestion (de Quervain et al., 2000; Newcomer, Selke, Melson, Hershey, Craft, Richards, & Anderson, 1999). Cortisol levels peak at around 20 to 30 minutes after the onset of the stressor, and typically do not return to baseline levels until an hour has elapsed (Smyth et al., 2013). If psychologically induced cortisol levels are similar, then it could be argued that the memory benefit for safe over threat words was due to lingering stress hormones at retrieval. The time between encoding and recognition in the Weymar et al. (2013) study was not reported; it is possible that more time elapsed between encoding and retrieval in the Weymar et al. (2013) study compared with the present study, lessening the potential for stress levels from encoding to remain elevated during the recognition test. Furthermore, the application of actual shocks in the present study likely increased the amount of acute stress that the participants experienced compared with the Weymar et al. (2013) study, leading to a higher likelihood of lingering cortisol during recognition. This could be examined in the current paradigm with the inclusion of measurements of arousal and/or cortisol levels before and after stress induction.

Another reason why stress at encoding improves memory in some studies but impaired memory in the current study could be due to the inverted-U shape function between arousal and performance. This function, known as the Yerkes-Dodson Law (Yerkes & Dodson, 1908), suggests that as stress increases, memory performance

increases up to a certain point, at which it begins to reverse its relationship with stress. After this point, as stress increases, memory decreases. Therefore, it could be argued that in the current study, acute stress at encoding was at a high enough level to impair later memory. However, it is unclear why this would occur in the present study but not in the Weymar et al. (2013) study, unless the actual delivery of shocks increased stress significantly more in the present study compared with the Weymar et al. study. Again, the inclusion of arousal measurements would be necessary to test this possibility.

Another possible reason behind the memory benefit for safe over threat words could be differences in how threat versus safe words were encoded. According to depth of processing theory (Craik & Lockheart, 1972), during word encoding, primarily attending to surface features such as font color is referred to as "shallow" processing, whereas primarily attending to the meaning of the word is referred to as "deep" processing. There is typically a recognition advantage for words encoded using deep processing compared with words encoded with shallow processing (Craik & Tulving, 1975). Before the encoding phase began, participants were instructed that a certain font color would represent the threat of shock, and a different color font would represent a safe word. If participants felt stress about the threat of shock, it is possible that when threat words appeared, they focused attention on the color of the word, rather than on the meaning of the word. If threat words were processed more shallowly than safe words at encoding, this would lead to poorer memory for threat words during recognition, as suggested by depth of processing theory (Craik & Lockheart, 1972). Given that the Weymar et al. (2013) study did not actually administer shocks, threat words may have been encoded more deeply in that experiment compared with the present experiment.

The present study is not the first to report a memory decrement due to increased stress during encoding and/or consolidation. Trammell and Clore (2014) conducted three experiments that used a cold pressor task in conjunction with an explicit memory test, in which they varied the valence of the stimuli (positive, negative, and neutral) and time between the encoding phase and stress induction (0-1 min; time between encoding and recognition testing was always 48 hours). In all three experiments, across all conditions, they found that acute stress immediately after encoding impaired, rather than enhanced, later memory. They concluded this impairment could be due to suppression of stress, such that participants might have devoted cognitive resources to suppressing their stress, which otherwise could have been devoted to memory encoding and consolidation. It has previously been demonstrated that suppressing emotions at encoding can impair subsequent memory (Richards & Gross, 2000), suggesting that it may also be possible that stress could be suppressed during encoding. In the current experiment, it is possible that participants devoted resources to stress suppression during the encoding of threat words, leading to poorer memory performance for threat words compared with safe words.

Analyses of ERPs revealed an old-word negativity, such that old word amplitudes were more negative than new word amplitudes across central and posterior brain regions, and this difference was larger for safe words than for threat words. This negativity was found in the 500-700 ms time window, where old/new effects related to recollection are typically found (Rugg & Doyle, 1994). Old/new effects reflect more positive-going ERPs for old words than for new words, and are associated with the processes used in correct identification of old words (Rugg, Cox, Doyle, & Wells, 1995). It is unclear why old

items exhibited a greater negativity than new items in the present study rather than the typical old/new effect pattern observed in previous studies (Rugg, 2000; Rugg, Cox, Doyle, & Wells, 1995). One possibility is that the greater negativity for old items could be reflective of memory control processes, as has been observed previously (Curran, DeBuse, & Leynes, 2007). However, control processes are typically not evident in ERPs until 1000 ms. Thus, it seems unlikely that the old word negativity observed here can be attributed solely to control processes. Regardless, large differences were observed between old and new word ERP amplitudes, suggesting differential processing associated with old and new words. Furthermore, these differences were larger for safe words than for threat words. Just as Weymar et al. (2013) observed larger old/new effects for threat words compared with safe words, reflecting stronger encoding and/or consolidation of threat words compared with safe words, here, it appears that participants encoded and/or consolidated safe words better than threat words. It should also be noted that these differences were found primarily in the centro-parietal to occipital regions of the brain, consistent with studies reporting typical old/new effects in the parietal area (Rugg & Doyle, 1994).

With regard to emotional valence, the analysis of hit rates suggested memory was stronger for negative words than for positive words, consistent with previous studies that have shown memory benefits for negative relative to positive stimuli (Kensinger, 2007; Ochsner, 2000; Rozin & Royzman, 2001). However, when measures of response bias and sensitivity were computed, it was revealed that although there was a larger bias to endorse negative words as old compared with positive words, the actual ability to discriminate between old and new words did not differ for negative versus positive

words. Although memory benefits for negative compared with positive stimuli have frequently been reported (Kensinger, 2007; Ochsner, 2000; Rozin & Royzman, 2001), it is noteworthy that this finding is not universal. For example, another study examining stress and memory found no significant difference between sensitivity for positive and negative words (Abercrombie et al., 2003). It is possible that the lack of difference between negative and positive words in the present study was due to the fact that positive and negative words were equally likely to be accompanied by shock, whereas in other situations, negatively valenced items may be considered more threatening (Whalen, 1998). In the Weymar et al. (2013) study, both hit rate and sensitivity were higher for unpleasant than pleasant words.

Limitations of the current study include the inability to examine encoding ERPs. The presence of ERP components related to the encoding of threat words, such as enhanced P2 and P3 components, would have allowed more comparisons between the Weymar et al. (2013) study and the current study. If similar P2 and P3 effects at encoding were found, this would suggest that participants in both studies encoded threat words in the same manner, and would support the assertion that the memory benefit for safe over threat words was due to processes occurring at retrieval. However, if a different pattern of results were observed at encoding, this would provide support for the hypothesis that threat words were encoded differently than in the Weymar et al. (2013) study (e.g., if threat words were encoded more shallowly than safe words, or if participants suppressed stress during encoding). Also missing was an examination of the effect of valence on ERP amplitudes during recognition because of extensive artifacts due to blinking and other movements; including more trials of each condition would prevent this problem.

Differences between positive and negative ERP amplitudes during recognition could help elucidate why there is a larger bias to respond old to negative words compared with positive words. Finally, the use of a blocked design with respect to valence may have contributed to the larger response bias seen for negative words compared with positive words.

In conclusion, acute stress at the time of encoding can impair memory in some circumstances. Future research is necessary to discern in which circumstances stress during encoding leads to memory enhancements versus memory impairments. For instance, lengthening time between encoding and recognition would help to determine whether elevated stress during encoding persisted into the retrieval phase in the current experiment. In addition, measures of arousal via galvanic skin response or salivary cortisol during both encoding and retrieval would also help to gauge how stress may be related to memory improvements and impairments, and systematically manipulating different levels of stress could help isolate the circumstances in which stress during encoding may enhance or impair memory. Sympathetic nervous system responses to stress are part of the brain's defense system; both memory enhancements and impairments in response to arousal are vital to survival, whether a person needs to remember to avoid something dangerous or forget a bad experience for the sake of emotional self-preservation.

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