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Timing and Gender Determine if Acute Pain Impairs Working Memory Performance

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Abstract

The effects of pain on memory are complex and little is known about the vulnerability of working memory performance (WM) when individuals complete a WM test while concurrently experiencing pain. Here, we subjected 78 healthy non-smoking participants to either acute pain or a control condition while administering a WM test. In this context, we also tested WM 20 minutes after pain in order to determine if timing of pain affected WM performance, and assessed objective and subjective measures of pain. We hypothesized that pain would impair WM performance during pain. Further, women's WM performance would be impaired more than men. Importantly, there was an interaction between gender and condition, with women exposed to pain experiencing impairments during but not after the cold pressor task. Our data imply that timing and gender are critically important in whether acute pain is costly to WM performance. Our findings have interesting clinical, professional and educational implications, and understanding the influence of pain could help to improve the interpretation of WM tests in these diverse settings.

Keywords

Working memory; impairment; cold pressor; gender; letter-number sequencing

Introduction

Pain is debilitating to overall health, can interfere with everyday life⁴⁹, and impairs memory³⁸. Emerging evidence suggests that working memory (WM) is particularly vulnerable to acute pain^{16,37,45,55,56}. WM is the retention and manipulation of recent information, attentional control, and suppressing irrelevant information. Baddeley's⁴ pivotal work first described this multicomponent model. Early animal experiments²¹ and

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neuroimaging research¹¹ have identified the prefrontal cortex (PFC) as a crucial for these WM processes.

Experimental research has shown that the PFC is involved in pain modulation⁴⁷. Even mild, uncontrollable pain decreases PFC functioning². There are high densities of glucocorticoid (GC) receptors in the PFC, and in rats, these receptors bind with high affinity to corticosterone¹³. Rising levels of GC during pain rapidly affect the PFC neurons that mediate WM⁶⁷. Taken together, these data propound that pain affects PFC mediated WM processes. Foremost in the physiological response to pain are the endocrine and sympathetic autonomic nervous (SAS) systems. The SAS triggers the “fight-or-flight” response when faced with a stressor, and the body produces cortisol through the hypothalamic-pituitary-adrenocortical (HPA) axis²⁰.

Recent research has sought to understand how pain affects memory. However, the results are diverse and equivocal. Some studies found that pain enhanced memory^{7,43,60}. In contrast, much work found that psychosocial^{16,66}, chronic^{32,35}, and acute experimental^{51,56} pain impaired memory. Methodological differences, such as multiple memory tasks used within and across studies^{28,45}, differential timing of pain²⁸, and small sample single-sex populations^{14,37,43}, could likely account for the disparate findings.

Consistent across studies is the use of the cold pressor test (CPT)^{7,14,56,57}. The CPT has demonstrated activation of both the HPA axis and SAS⁴⁰. Due its dependability, and to remain congruous with other studies, we used the CPT in our paradigm. In order to administer pain throughout WM testing we used a forehead cold pressor,^{23,36,46,54}. To determine whether timing of pain was important we tested WM twice (during and 20 minutes after pain), and used a no-pain control condition to determine whether WM was impaired during pain or whether WM was enhanced following pain.

Another goal was to examine gender differences in WM, as women consistently report more pain than men^{52,53}. The reasons for these differences include developmental, psychological, and biological factors, type of pain, and hypervigilance²⁹. Despite these findings, women are often underutilized in research assessing WM and pain^{14,37,43}. In order to assess WM, we administered the Letter Number Sequencing test⁶⁴. This test was constructed to fit Baddeley’s WM framework²⁷, is commonly researched in clinical populations^{1,42,58}, was a strong predictor of a WM-criterion of experimental cognitive measures that included the n-back and listening span tasks²⁵, and in the prediction of fluid intelligence it was the best measure of WM⁵⁹. Although much variance seems attributable to the Digit Span¹⁰, it has been argued that Digit Span does not require as much executive processing¹⁷. Further, unlike computer-based cognitive tests, the Letter-Number Sequencing test requires no movement, and we required stillness for accurate physiological measurements. In order to detect biological responses to pain, we collected salivary cortisol samples, and heart rate and skin conductance measurements (HPA and SAS activity). Finally, we controlled for anxiety and depression given their link to impaired WM in previous research^{6,63}.

Hypotheses

Empirical research testing memory while concurrently experiencing acute pain is scarce; however, one study found pain disrupted memory⁴⁵. We predicted that WM during acute pain would be impaired in the present study, especially for women due to their heightened pain. As there is conflicting evidence about whether pain enhances or impairs memory after pain^{14,16}, we did not have a directional hypothesis for WM after pain; although we predicted increased cortisol levels through HPA activity following pain.

Methods

Participants

One hundred and nine university students from a state university volunteered for the study to gain course credit. Nineteen participants did not meet all inclusion criteria and so their data was not collected. A standardized interview checked for inclusion. Participants were excluded if they had circulatory problems (e.g., Reynaud's disease), peripheral neuropathy, thyroid problems, diabetes, lupus, other connective tissue disorder, cardiovascular disorder, high blood pressure and/or hypertension, or currently taking any pain or psychotropic medications. In addition, participants could not have a history of fainting or seizures, significant trauma or history of pain disorders, significant weight loss or major surgery within the last 6 months, substance abuse, a neurological condition, be pregnant and could not eat or drink anything but water for one hour before the study.

Because of previously shown differences in cortisol levels between men and women and because of differences due to oral contraceptive use³³, we noted women's menstrual cycle and contraceptive use. All women included in the study had a regular menstrual cycle in the month prior to the study (28 ± 2 days). Women stated whether they used contraceptives, the type of contraceptive, and indicated the date of their last menstruation using calendars. Research assistants provided more detailed recall instructions when needed. We classified women as either in a contraceptive cycle or a menstrual phase based on the women's self-reports (see Table 1.). Previous research has demonstrated that self-report of cycles can be accurate, with the majority of women estimating their cycle length within one day^{30,65}.

Twelve participants completed the entire study but their data is not included in any analyses. Of the twelve excluded participants, two participants had Beck Anxiety⁵ scores that indicated "severe anxiety". One participant had a depression score on the Center for Epidemiologic Studies Depression Scale⁵⁰ that indicated "severe depression". Three women had irregular menstrual cycles (cycle lengths greater than 40 days). One participant was more than double the mean age and was excessively sleepy. One participant could not tolerate CPT for the entire test. Four participants were excluded because independent video raters of the WM test found that the research assistant had not correctly followed all instructions (procedures described in section 2.4.3). This led to an incorrect WM score for those participants. Seventy-eight participants met all inclusion/exclusion criteria and constituted healthy non-smoking participants in this study (see Table 1 for sample characteristics).

Measures and Apparatus

The McGill Pain Questionnaire- Short-Form—The McGill Pain Questionnaire-Short Form (MPQ-SF) is a pain rating scale that consists of 15-descriptor items, 11 items relate to sensory pain dimensions (e.g. shooting), and four items relate to affective pain dimensions (e.g. fearful)⁴¹. Participants rated items on a 4-point scale, ranging from zero (no pain) to four (severe). Total scores can range from 0 to 60, with higher scores representing higher pain levels. The Cronbach's alpha in this study was .88.

Pain Rating—Immediately after the cold pressor task participants verbally indicated the pain of the cold pressor task using a 0 – 100 pain index, with zero being no pain at all, and 100 the worst pain imaginable.

Forehead Cold Pressor—The forehead cold pressor apparatus is temperature regulated and maintained a continuous $32 \pm 1^\circ\text{F}$. The Polar Care 500 unit (Breg®) includes a low voltage submersible pump with in-line thermometer and flow valve for temperature control.

The unit contained 2.3 kg of ice and 10.5 liters of water. A pad had cold water distributed throughout the entire surface, and researchers strapped the pad on the participants' forehead while they completed the WM test (see Figure 2). Participants in the control condition wore the apparatus, but the pad did not contain any water. The WM test took less than five minutes, which supported safety guidelines for exposure in cold pressor tasks.

Skin Conductance and Heart Rate Measurements—The Powerlab 26T (AD Instruments Inc.) continuously collected skin conductance (SC), units in microsiemens (μS) and heart rate (HR) recordings (beats per minute). The Chart (Version 5) application recorded, displayed, and summarized recordings and the units of measurement. We used averages for each of the three measurements and visually inspected the data offline to exclude artifacts.

For the SC measurements, there was an attached exterior Bioamplifier Transducer, which is fully isolated with low voltage 75Hz AC excitation and automatic zeroing. 2mm silver electrodes attached to the medial phalanges of the thumb and right index finger. In order to obtain a signal that reflected increases in SC, we replaced negative values with a value of 0.

For the HR measurements, the MLT1020FC Plethysmograph, an infrared photoelectric sensor that detects changes in infrared absorption as the blood content of the subcutaneous vascular bed changes with the pulse, attached to the medial phalange of the middle finger that plugged directly into the Powerlab Pod Port. A clip screened against variations in ambient light. The Plethysmograph operates by recording changes in blood volume as the arterial pulse expands and contracts the microvasculature.

WM Test

Letter-Number-Sequencing—The Letter-Number Sequencing test is a measure of verbal working memory, which also assesses attention span, and sequencing abilities. It involves mental manipulation, attention, visuospatial imaging, and processing speed. In the Letter-Number Sequencing test⁶⁴, the researcher verbally presented different sets of increasingly longer sequences of intermixed letters and numbers at a rate of one per second. After each sequence, participants repeated the numbers and letters in the same exact order. The test consists of 21 trials with sequences that range from two stimuli (e.g., B-4) up to a maximum length of eight stimuli. Researchers presented three trials at each length and discontinued the test when the participants failed on three consecutive trials of the same length. To minimize the possibility for practice effects, researchers administered alternate forms of the test. Researchers used formulated scaled scores for each individual based on his or her age.

The subtest has a norm-referenced mean of 10 and a standard deviation of 3⁶⁴. The test-retest stability coefficient in the original standardized sample of healthy adults aged 16–29 years over 2–12 week interval was $r = .70$ ⁶⁴. In the present study, the correlation between WM 1 and WM 2 scores was $r = .72$ for the no-pain control condition, indicating comparable stability. Additionally, the letter-number sequencing test has strong utility as a repeated measure using alternate forms⁴⁴.

Video Rating of WM Test—In order to ensure the standardized administration of the WM test, three independent raters watched a portion of 156 total video-recordings to ensure compliance with the administrative guidelines from the Wechsler manual⁶⁴. One rater watched half of the videos and the other raters split the remaining recordings. Each video rating could have a maximum total correct score of 15, if the researcher had followed the instructions perfectly. Research assistants had 99.78% accuracy on the all tests used in

analyses, and no participants WM scores were used if the research assistant's deviation from the administrative guidelines influenced the final WM score.

Cortisol Assessment—To collect saliva samples for cortisol measurement, research assistants had participants passively drool for one minute through a short straw into a cryovial tube. Participants chewed on a waxed sheet (Parafilm®) to stimulate saliva and provided salivary samples at baseline, immediately after WM 1, and following WM 2, which was 25 minutes after the forehead apparatus had been removed. After collection, researchers capped, labeled and froze samples at -20°C in a non-self-defrosting freezer. Before the assay, samples thawed at room temperature. Saliva was diluted 1:2 or 1:4 in B3 dilution buffer and free cortisol concentrations were measured using a high sensitivity cortisol immunoassay kit (Enzo® Life Sciences, Plymouth Meeting, PA) and an ELx800 plate reader (Bio-Tek, Winooski, VT) following the manufacturer's protocol. The intra-assay co-efficient of variation was $< 15\%$ and the corresponding inter-assay coefficient was $< 15\%$.

Procedures

Before arrival, researchers randomly assigned participants to either a control or an experimental condition. Researchers told participants that they may or may not experience discomfort, and participants did not have prior knowledge about condition assignment. This reduced potential carryover effects associated with multiple WM administrations in a crossover design and decreased the possibility of participants anticipating pain. After participants arrived at the laboratory, researchers explained the procedure and obtained written informed consent. At the beginning of the session, the research assistant recorded participants' heart rate (HR) and skin conductance (SC), and obtained the first salivary sample. Next, participants completed a counterbalanced questionnaire packet that contained measures of demographics, the BAI, and the CES-D. While wearing the forehead apparatus, participants completed WM 1 and researchers recorded participants' HR and SC. After the test, participants gave a verbal pain rating, and researchers obtained the second salivary sample and participants then completed the McGill Pain Questionnaire, which took an average of five minutes. Following a 15-minute break, in which participants read neutral magazines, they then completed the WM 2 while researchers recorded HR and SC. After WM 2 test, participants gave the final salivary sample (see Figure 1 for timeline). Participants were video-recorded during the WM tests and the entire study took about one hour.

All testing took place between 11am and 3pm to control for the diurnal variation of the stress hormone cortisol. Previous work has shown that cortisol levels are most stable during this period^{15,61}. In this study, baseline cortisol levels did not differ based on time of testing, $p > .60$, $\eta^2 = .02$. Before the start of the study, all participants received written and oral information about the study and provided written informed consent. The California State University San Marcos Institutional Review Board approved the protocol.

Statistical Analyses

A Repeated Measures ANOVA with WM as the within subject factor (two levels; WM 1 and WM 2), and condition (experimental or control) and gender as the between subject factors analyzed the effect of the forehead cold pressor on WM. Repeated Measures ANOVAs with cortisol levels, SC and HR as the within subject factors (three levels; baseline, WM 1 and WM 2), and condition (experimental or control) and gender as the between subject factors analyzed the HPA-axis and SAS responses to acute pain. Due to positively skewed distributions for cortisol data, analyses for cortisol values were $\log_{10}$ -transformed. In addition, we added a constant of one, as some baseline cortisol values were

close to zero: $\log(X_i + 1)^{26}$. The results follow the same trend and remain significant with or without the transformation. However, with the $\log_{10}$ transformation the data pass Mauchly's sphericity test.

Follow-up analyses consisted of Bonferroni corrected paired-samples t-tests to analyze the within-group differences, and Bonferroni corrected independent-samples t-tests to analyze between group differences. Three independent-samples t-tests tested *a priori* differences in female WM performance when exposed to acute pain. One-way ANOVAs analyzed subjective pain reports, menstrual phases, and use of oral contraceptives. Pearson correlations examined the relationship between the hormones, SC, HR and pain ratings and WM performance. We estimated practice effects for the experimental and control condition by calculating a percentage change score between WM 1 and WM 2. In addition to this metric, we calculated a Cohen's *d* statistic for the same data.

We determined statistical significance at an alpha level of $p < .05$ two-tailed. Analyses included partial eta-squared (η^2) and Cohen's *d* as the measures of effect size. Following Cohen's conventions⁸ $\eta^2 = .01$ or $d = .20$ is a small effect, $\eta^2 = .06$ or $d = .5$ is a medium sized effect and $\eta^2 = .14$ or $d = .80$ is a large effect. A Power analysis¹⁸ for a mixed-model repeated measures ANOVA was conducted to determine the sufficient sample size using an alpha of 0.01 two-tailed, a power of 0.90, with a medium effect size ($d = 0.5$). Based on these assumptions, the desired sample size was 72 participants⁸.

Results

Subjective pain ratings

As expected, participants in the experimental condition ($M = 35.90$, $SE = 2.88$) verbally rated the forehead cold pressor as more painful than participants in the control condition ($M = 2.06$, $SE = 2.81$), $F(1, 74) = 70.57$, $p < .001$, $\eta^2 = .49$. Further, participants in the experimental condition ($M = 11.54$, $SE = .84$) reported more pain on the MPQ-SF than participants in the control condition ($M = 2.39$, $SE = .82$), $F(1, 69) = 60.83$, $p < .001$, $\eta^2 = .47$. There was not a main effect of gender, or a condition x gender interaction for the verbal pain ratings or MPQ-SF total scores, all $\eta^2 < .008$, $p > .05$. There was a strong correlation between participant's verbal pain rating and their scores on the MPQ-SF, $r = .83$, $p < .001$.

Heart rate and Skin Conductance Responses

Before conducting analyses we determined that there were no differences in baseline SC and HR between men and women, $p > .20$. Subsequent analyses showed that for SC, there was a significant main effect of time, $F(2, 146) = 63.25$, $p < .0001$, $\eta^2 = .46$. There was not a significant time x condition interaction, $p > .05$, $\eta^2 = .007$. All participants SC significantly increased compared to baseline, regardless of condition. There was a significant difference between men and women's SC, $F(2, 146) = 6.77$, $p < .0001$, $\eta^2 = .22$. A follow-up analysis showed that experimental men had significantly higher SC compared to experimental women $t(28.92) = 2.37$, $p = .025$, $d = .78$ and control women, $t(25.28) = 2.86$, $p = .006$, $d = .94$ after WM 2 (see Figure 2a). For HR, there was a significant main effect of time, $F(2, 146) = 13.50$, $p < .0001$, $\eta^2 = .16$, but no time x condition interaction, $p = .64$. All participants HR increased compared to baseline regardless of condition.

Cortisol results

Statistical analyses were conducted on $\log_{10}$ transformed cortisol values. We first wanted to assess if there were any differential cortisol responses in the present study that could possibly account for differences in WM performance. Cortisol levels at baseline, immediately following WM 1, and WM 2 between women using oral contraceptives,

women not using a contraceptives and men were all similar $p > .60$. Further, after exposure to pain, experimental men and women (using and not using oral contraceptives had very similar cortisol levels, $p > .90$. There were no differences at baseline cortisol levels between ovulating women in the follicular and luteal menstrual phases, $p > .31$.

Next, we assessed cortisol levels separated on condition. Figure 2b shows un-transformed salivary cortisol values across task conditions. There was a significant main effect of time, $F(2, 144) = 6.24, p = .003, \eta^2 = .08$, as well as a significant condition x time interaction, $F(2, 144) = 10.22, p < .0001, \eta^2 = .12$. Experimental participants cortisol values were significantly higher after pain compared to baseline, $t(37) = -3.91, p < .0001, d = .81$, and compared to immediately following the pain, $t(36) = -.360, p = .001, d = .82$. Experimental participants cortisol values were significantly higher than controls only after pain, $t(75) = 3.22, p = .002, d = .74$.

WM Practice Effects Analysis

The magnitude of the percentage change score for WM 1 and WM 2 for the experimental condition was 17.32%. The magnitude of the percentage change score for WM 1 and WM 2 for the control condition was only 3.04%. The Cohen's d statistic for the control condition was .14. Using Cohen's overlap values⁸, this d values represents an 89.5% overlap between the distributions of WM 1 and WM 2 for the control condition. Further, the control participants WM performance (9.88 to 10.18) was similar to the Wechsler norm-referenced mean of 10 across both administrations.

Effects of Cold Pressor on WM

For WM performance, there was a significant main effect of time, $F(1, 74) = 20.70, p < .0001, \eta^2 = .22$, as well as a significant condition x time interaction, $F(1, 74) = 9.71, p = .003, \eta^2 = .12$. Experimental participants' WM performance was significantly lower during pain ($M = 9.21, SE = .37$) than after ($M = 10.82, SE = .37$), $t(37) = -4.71, p < .0001, d = .64$. There were no significant differences between controls WM 1 ($M = 9.88, SE = .36$) and WM 2 ($M = 10.18, SE = .36$), $p = .23, d = .15$. Although the experimental condition had lower WM performance during pain than after there were no significant differences in WM between experimental and controls during the WM 1, $p = .21, d = .29$, or between experimental and controls during WM 2, $p = .22, d = .29$. Experimental men's WM performance was better than experimental women, control women, and control men. However, this difference did not reach significance, $p > .05$ (see Figure 3).

Experimental Women's WM performance and correlations analyses

Analyses supported *a priori* hypotheses about experimental women's WM performance. As depicted in Figure 3, experimental women had significantly worse WM performance compared to experimental men, $t(1, 36) = 2.50, p = .02, d = .81$, control men $t(1, 37) = -2.36, p = .02, d = .75$, and control women, $t(1, 37) = -2.07, p = .05, d = .66$. Associations between experimental women's SC and cortisol measures, verbal pain ratings, and WM performance are displayed in Table 2. Of note, experimental women's WM performance during pain was negatively associated with significantly higher verbal pain ratings. Further, verbal pain ratings were positively correlated with higher SC and cortisol immediately following and after pain, and higher SC was significantly negatively correlated with WM during pain. Despite not being significant, the data do indicate a trend that shows that as SC, cortisol, and ratings increase WM performance decreases during and after pain.

Discussion

The present study aimed to elucidate if the timing of acute forehead cold pressor pain and gender influenced WM. We found strong support for an interaction between these hypotheses. Exposure to the noxious stimuli produced WM impairments in women during pain compared to after pain. Control participants WM performance remained stable across both administrations of the WM task, and was similar to published norms. The pattern of our results suggests that WM is compromised in women during pain, rather than WM being improved after pain. If WM were enhanced following pain, we might expect post-pain WM performance to be significantly higher than controls. This was not the case. For women, timing appears critical in whether acute pain is costly to WM.

Subjective verbal pain ratings did not differ based on gender or condition. However, for women in the experimental condition, a higher verbal pain rating was related to impaired WM performance. Physiological responses to pain were evident in differential cortisol responses; the experimental condition displayed significantly higher cortisol levels after pain. Findings from the present study indicate that SC and HR (SAS arousal) significantly increased for both conditions compared to baseline, but not to a differential response between conditions during WM 1. However, following pain, experimental men did have significantly higher SC during WM 2 compared to experimental and control women. The skin conductance orienting response, which is an autonomic response to stimuli and indirectly reflects how a person attends to and processes novel environmental events, could have played a role¹².

Our findings reveal an important WM impairment for women in acute pain. Effects were large and experimental women's WM scores were nearly one standard deviation below the normed mean for the Letter Number Sequencing Test⁶⁴, which could have important clinical implications. Some researchers have found that women who are not in the late luteal phase of their menstrual cycle or women taking an oral contraceptive may have lower cortisol levels than men in response to a psychosocial stressor^{9,33}. Due to these findings, the majority of subsequent memory studies chose to only include men^{37,56} or women in the late luteal phase⁵⁷. Our use of a forehead cold pressor did not elicit the differential cortisol responses to acute pain between men and women.

Our data imply that the cortisol increase in saliva did not directly influence the observed WM impairment in our experimental women during pain. However, one caveat is that as cortisol is first released in the blood, and there is a lag between cortisol in blood and saliva, it is possible that the biologic action of cortisol in blood could have influenced WM impairment. This action would not be detected in salivary cortisol levels immediately following pain. Nevertheless, the memory impairments in this study have been shown in previous work⁵⁶, although earlier work did not find these marked effects in women.

On the surface, our results might appear in contrast with some previous findings. Some research has found that pain can enhance memory performance. However, the majority of these studies found benefits for memory consolidation⁷ and context-related declarative⁶⁰ prospective⁴³ and spatial memory¹⁴ not WM. Further, these studies only tested men, and so could not detect gender differences. This study used forehead pain, so it is conceivable that this stimulus was especially disruptive to WM. However, we know of no empirical research that supports the contention that the site of cold pressor pain is important in WM. There is more evidence that WM is particularly susceptible to temporally close acute pain. This interpretation is supported by a number of other studies that found WM impairments in response to acute pain^{16,37,45,56}. In fact, our study extends upon a recent human study that found WM impairments in menstruating women, but not in men, when they were exposed to

a psychosocial stressor using an n-back paradigm. However, it is significant that the present study found WM impairments for normally cycling women and those women taking a contraceptive, and is the first study to find these WM impairments for women during the experience of pain⁵⁵.

The PFC appears critical to the executive attentional component of the WM system, and this system maintains information in an accessible and active state. This system works best when it is able to manipulate and filter out irrelevant information³¹. Acute pain may have limited the ability of women to engage in demanding and conscious processing. Of interest, recent work has found gender-based brain activation differences in both muscle and cutaneous pain. Pain evoked differences in the cingulate cortex, dorsolateral prefrontal cortex (DLPFC), hippocampus, and cerebellar cortex²⁴. Other separate, but complementary research demonstrated bilateral activation or right-sided dominance in the lateral prefrontal cortices (LPFC), the parietal cortices (PC), and the caudate in men, whereas women showed activation primarily in the left hemisphere⁶². Additional neuroimaging work found that women exhibited greater signal intensity changes in middle, inferior, and orbital prefrontal cortices compared to men. This body of work suggests that both cognitive and pain processing are differential based on gender, and this may be one of the reasons for the present study's findings.

Another possible explanation for our findings is that experimental women may not have felt in control over their acute pain. This possible perceived uncontrollability could have been influenced by a negative anticipatory evaluation of the pain experience^{48,49}. Much research in human and animal studies shows that control over pain or stress reduces memory impairment³⁹. Importantly, women tend to be more hypervigilant to pain, conduct more monitoring of bodily functions, and so react to negative events with increased pain responsiveness. These responses may have occurred alone or in combination and reduced WM performance²⁹. However, as the present study did not assess participants' feelings of control or hypervigilance, further research is needed.

Along with possible cognitive disruptions, there could be biological influences on WM not tested in this study. Noradrenaline and dopamine rapidly increase in PFC regions during pain and may regulate some changes in PFC functioning². Additionally, we did not measure estradiol and that is a limitation in interpreting our findings. Estradiol may modulate HPA axis functioning³⁴ and certain types of pain⁹. Gasbarri found that high levels of estradiol in the follicular phase could impair the performance of working memory for facial expressions²². Future studies that look to utilize our experimental paradigm should include estradiol analyses.

In terms of our experimental design, another limitation is that we tested participants WM on the same day. It might have been more advantageous to test participants on two separate days to reduce any possible practice effects. However, analyses indicated that practice effects were low. With regards to the Letter-Number Sequencing Test, it along with other measures of WM are most likely not pure measures of the construct, and tap into other executive abilities such as processing speed and attention. In the same context, working memory is thought to underlie other cognitive processes such as reading ability³. Our participants were college-students with demonstrated aptitude for college-level work, but having an estimate of reading ability would be helpful in the interpretation of our findings. Finally, our study sampled a young healthy population, so we advise caution in generalizing our results to chronic pain populations.

Conclusion

Our novel data suggest that concurrent exposure to experimental pain results in WM impairment in women. Shortly after pain, WM deficits were no longer present. Psychosocial responses to pain are possible mechanisms through which WM impairment in women occurred. Women's pain experience and ability to engage in cognitively demanding tasks were reduced compared to men during exposure to acute pain. These findings have interesting clinical, professional, and educational implications, especially as more women generally suffer from chronic pain¹⁹. Understanding the influence of pain could help to improve the interpretation of working memory tests in these diverse settings.

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References

1. Abeare CA, Cohen JL, Axelrod BN, Leisen JCC, Mosley-Williams A, Lumley MA. Pain, executive functioning, and affect in patients with rheumatoid arthritis. *The Clinical Journal of Pain*. 2010; 26:683–689. [PubMed: 20862788]
2. Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*. 2009; 10:410–422.
3. Baddeley AD. Working memory. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences*. 1983; 302:311–324.
4. Baddeley AD, Hitch GJ. Working memory. *The psychology of learning and motivation*. 1974; 8:47–89.
5. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*. 1988; 56:893–897. [PubMed: 3204199]
6. Brown CA, Jones AKP. A role for midcingulate cortex in the interruptive effects of pain anticipation on attention. *Clinical Neurophysiology*. 2008; 119:2370–2379. [PubMed: 18752995]
7. Cahill L, Gorski L, Le K. Enhanced Human Memory Consolidation With Post-Learning Stress: Interaction With the Degree of Arousal at Encoding. *Learning & Memory*. 2003; 10:270–274. [PubMed: 12888545]
8. Cohen J. Statistical power analysis for the behavioral sciences. Lawrence Erlbaum. 1988
9. Craft RM. Modulation of pain by estrogens. *Pain*. 2007; 132:S3–S12. [PubMed: 17951003]
10. Crowe SF. Does the letter number sequencing task measure anything more than digit span? *Assessment*. 2000; 7:113–117. [PubMed: 10868248]
11. D'Esposito M, Postle BR, Rypma B. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Experimental Brain Research*. 2000; 133:3–11.
12. Dawson ME, Schell AM, Filion DL. 7 The Electrodermal System. *Handbook of psychophysiology*. 2007; 159
13. Diorio D, Viau V, Meaney MJ. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *The Journal of Neuroscience*. 1993; 13:3839–3847. [PubMed: 8396170]
14. Duncko R, Cornwell B, Cui L, Merikangas KR, Grillon C. Acute exposure to stress improves performance in trace eyeblink conditioning and spatial learning tasks in healthy men. *Learning & Memory*. 2007; 14:329–335. [PubMed: 17522023]
15. Van Eekelen APJ, Kerkhof GA, Van Amsterdam JGC. Circadian variation in cortisol reactivity to an acute stressor. *Chronobiology International*. 2003; 20:863–878. [PubMed: 14535359]
16. Elzinga BM, Roelofs K. Cortisol-Induced Impairments of Working Memory Require Acute Sympathetic Activation. *Behavioral Neuroscience*. 2005; 119:98–103. [PubMed: 15727516]

17. Engle RW, Tuholski SW, Laughlin JE, Conway ARA. Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. *Journal of Experimental Psychology: General*. 1999;128–309.
18. Faul F, Erdfelder E, Lang AG, Buchner A. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods*. 2007; 39:175–191. [PubMed: 17695343]
19. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL III. Sex, gender, pain: a review of recent clinical and experimental findings. *The journal of pain*. 2009; 10:447–485. [PubMed: 19411059]
20. Fukuhara K, Kvetnansky R, Cizza G, Pacak K, Ohara H, Goldstein DS, Kopin IJ. Interrelations between Sympathoadrenal System andHypothalamo-Pituitary- Adrenocortical/Thyroid Systemsin Rats Exposed to Cold Stress. *Journal of Neuroendocrinology*. 1996; 8:533–541. [PubMed: 8843022]
21. Funahashi S, Chafee MV, Goldman-Rakic PS. Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature*. 1993; 365:753–756. [PubMed: 8413653]
22. Gasbarri A, Pompili A, d’Onofrio A, Cifariello A, Tavares MC, Tomaz C. Working memory for emotional facial expressions: Role of the estrogen in young women. *Psychoneuroendocrinology*. 2008; 33:964–972. [PubMed: 18667277]
23. Gedney JJ, Logan H. Pain related recall predicts future pain report. *Pain*. 2006; 121:69–76. [PubMed: 16480824]
24. Henderson LA, Gandevia SC, Macefield VG. Gender differences in brain activity evoked by muscle and cutaneous pain: a retrospective study of single-trial fMRI data. *Neuroimage*. 2008; 39:1867–1876. [PubMed: 18069004]
25. Hill BD, Elliott EM, Shelton JT, Pella RD, O’Jile JR, Gouvier WD. Can we improve the clinical assessment of working memory? An evaluation of the Wechsler Adult Intelligence Scale-Third Edition using a working memory criterion construct. *Journal of Clinical and Experimental Neuropsychology*. 2010; 32:315–323. [PubMed: 19657913]
26. Howell DC. *Statistical methods for psychology*. Wadsworth Publishing Company. 2012
27. Hudetz JA, Hudetz AG, Klayman J. Relationship between relaxation by guided imagery and performance of working memory. *Psychological Reports*. 2000; 86:15–20. [PubMed: 10778243]
28. Ishizuka K, Hillier A, Beversdorf DQ. Effect of the cold pressor test on memory and cognitive flexibility. *Neurocase*. 2007; 13:154–157. [PubMed: 17786773]
29. Jones KS. Sex and Gender Differences in Responses to Experimentally Induced Pain in Humans. 2000
30. Jukic AMZ, Weinberg CR, Wilcox AJ, McConaughy DR, Hornsby P, Baird DD. Accuracy of Reporting of Menstrual Cycle Length. *American Journal of Epidemiology*. 2008; 167:25–33. [PubMed: 17928401]
31. Kane MJ, Engle RW. The role of prefrontal cortex in working-memory capacity executive attention general fluid intelligence An individual-differences perspective. *Psychonomic Bulletin & Review*. 2002; 9:637–671. [PubMed: 12613671]
32. Kewman DG, Vaishampayan N, Zald D, Han B. Cognitive impairment in musculoskeletal pain patients. *International Journal of Psychiatry in Medicine*. 1991; 21:253–262. [PubMed: 1955277]
33. Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Hellhammer DH. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamic-pituitary-adrenal axis. *Psychosomatic Medicine*. 1999; 61:154–162. [PubMed: 10204967]
34. Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: A review. *Biological Psychology*. 2005; 69:113–132. [PubMed: 15740829]
35. Libon DJ, Schwartzman RJ, Eppig J, Wambach D, Brahini E, Peterlin BL, Alexander G, Kalanuria A. Neuropsychological deficits associated with complex regional pain syndrome. *Journal of the International Neuropsychological Society*. 2010; 16:566–573. [PubMed: 20298641]
36. Logan HL, Gedney JJ, Sheffield D, Xiang Y, Starrenburg E. Stress influences the level of negative affectivity after forehead cold pressor pain. *The Journal of Pain*. 2003; 4:520–529. [PubMed: 14636820]

37. Luethi M, Meier B, Sandi C. Stress effects on working memory, explicit memory, and implicit memory for neutral and emotional stimuli in healthy men. *Frontiers in Behavioral Neuroscience*. 2009; 2
38. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*. 2009; 10:434–445.
39. McEwen BS, Sapolsky RM. Stress and cognitive function. *Current Opinion in Neurobiology*. 1995; 5:205–216. [PubMed: 7620309]
40. McRae AL, Saladin ME, Brady KT, Upadhyaya H, Back SE, Timmerman MA. Stress reactivity: Biological and subjective responses to the cold pressor and Trier Social stressors. *Human Psychopharmacology: Clinical and Experimental*. 2006; 21:377–385. [PubMed: 16915579]
41. Melzack R. The short-form McGill Pain Questionnaire. *Pain*. 1987; 30:191–197. [PubMed: 3670870]
42. Murtagh A, Hurley AL, Kinsella A, Corvin A, Donohoe G, Gill M, O'Callaghan E, Murphy KC. The Letter-Number Sequencing Test and its association with potential to work among people with psychotic illness. *European Psychiatry*. 2010; 25:101–104. [PubMed: 19720503]
43. Nater UM, Okere U, Stallkamp R, Moor C, Ehler U, Kliegel M. Psychosocial stress enhances time-based prospective memory in healthy young men. *Neurobiology of Learning and Memory*. 2006; 86:344–348. [PubMed: 16753313]
44. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S, Fenton WS, Frese FJ III, Gold JM, Goldberg T, Heaton RK, Keefe RSE, Kraemer H, Meshulam-Gately R, Seidman LJ, Stover E, Weinberger DR, Young AS, Zalcman SR, Marder SR. The MATRICS consensus cognitive battery part 1 Test selection, reliability, and validity. *The American Journal of Psychiatry*. 2008; 165:203–213. [PubMed: 18172019]
45. Patil PG, Apfelbaum JL, Zacny JP. Effects of a cold-water stressor on psychomotor and cognitive functioning in humans. *Physiology & behavior*. 1995; 58:1281–1286. [PubMed: 8623033]
46. Peckerman A, Saab PG, McCabe PM, Skyler JS. Blood pressure reactivity and perception of pain during the forehead cold pressor test. *Psychophysiology*. 1991; 28:485–495. [PubMed: 1758926]
47. Petrovic P, Ingvar M. Imaging cognitive modulation of pain processing. *Pain*. 2002; 95:1–5. [PubMed: 11790461]
48. Porro CA, Baraldi P, Pagnoni G, Serafini M, Facchin P, Maieron M, Nichelli P. Does anticipation of pain affect cortical nociceptive systems? *The Journal of Neuroscience* 2002. 2002; 22:3206–3214.
49. Pud D, Sapir S. The effects of noxious heat, auditory stimulation, a cognitive task, and time on task on pain perception and performance accuracy in healthy volunteers: A new experimental model. *Pain*. 2006; 20:155–160.
50. Radloff LS. The CES-D Scale A self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977; 1:385–401.
51. Richardson AE, VanderKaay Tomasulo MM. Influence of acute stress on spatial tasks in humans. *Physiology & behavior*. 2011; 103:459–466. [PubMed: 21440564]
52. Riley JL III, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: A meta-analysis. *Pain*. 1998; 74:181–187. [PubMed: 9520232]
53. Ruau D, Liu LY, Clark JD, Angst MS, Butte AJ. Sex differences in reported pain across 11,000 patients captured in electronic medical records. *The Journal of Pain*. 2012; 13:228–234. [PubMed: 22245360]
54. Ruiz JM, Uchino BN, Smith TW. Hostility, sex differences in the magnitude, duration, determinants of heart rate response to forehead cold pressor Parasympathetic aspects of risk. *International Journal of Psychophysiology*. 2006; 60:274–283. [PubMed: 16125263]
55. Schoofs D, Pabst S, Brand M, Wolf OT. Working memory is differentially affected by stress in men and women. *Behavioural Brain Research*. 2013; 241:144–153. [PubMed: 23238042]
56. Schoofs D, Wolf OT, Smeets T. Cold pressor stress impairs performance on working memory tasks requiring executive functions in healthy young men. *Behavioral Neuroscience*. 2009; 123:1066–1075. [PubMed: 19824773]
57. Schwabe L, Wolf OT. Learning under stress impairs memory formation. *Neurobiology of Learning and Memory*. 2010; 93:183–188. [PubMed: 19796703]

58. Schweitzer JB, Hanford RB, Medoff DR. Working memory deficits in adults with ADHD: is there evidence for subtype differences. *Behav Brain Funct* 2006. 2006; 2:43.
59. Shelton JT, Elliott EM, Hill BD, Calamia MR, Gouvier WD. A comparison of laboratory and clinical working memory tests and their prediction of fluid intelligence. *Intelligence*. 2009; 37:283–293. [PubMed: 20161647]
60. Smeets T, Giesbrecht T, Jellic M, Merckelbach H. Context-dependent enhancement of declarative memory performance following acute psychosocial stress. *Biological Psychology*. 2007; 76:116–123. [PubMed: 17689852]
61. Smyth JM, Ockenfels MC, Gorin AA, Catley D, Porter LS, Kirschbaum C, Hellhammer DH, Stone AA. Individual differences in the diurnal cycle of cortisol. *Psychoneuroendocrinology* 1997. 1997; 22:89–105.
62. Speck O, Ernst T, Braun J, Koch C, Miller E, Chang L. Gender differences in the functional organization of the brain for working memory. *Neuroreport* 2000. 11:2581–2585.
63. Stout DM, Rokke PD. Components of working memory predict symptoms of distress. *Cognition and Emotion*. 2010; 24:1293–1303.
64. Wechsler D. WMS-III: Wechsler memory scale administration and scoring manual. Psychological Corporation. 1997
65. Wegienka G, Baird DD. A Comparison of Recalled Date of Last Menstrual Period with Prospectively Recorded Dates. *Journal of Women's Health*. 2005; 14:248–252.
66. Wolf OT, Schommer NC, Hellhammer DH, McEwen BS, Kirchbaum C. The relationship between stress induced cortisol levels and memory differs between men and women. *Psychoneuroendocrinology*. 2001; 26:711–720. [PubMed: 11500252]
67. Yuen EY, Liu W, Karatsoreos IN, Feng J, McEwen BS, Yan Z. Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *PNAS Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106:14075–14079.

Perspective

Results of this study support the growing body of work that attests to the detrimental effect of pain on working memory performance. Further, this study provides new evidence that concurrently experiencing cold pressor pain impairs working memory in regularly menstruating women and women taking a contraceptive.

Figure 1.

Timeline of study protocol and photograph of the forehead cold pressor. BAI: Beck Anxiety Inventory, WM 1 and 2: Letter Number Sequencing Test, MPQ-SF: McGill Pain Questionnaire Short Form, HR: Heart Rate, SC: Skin Conductance.

Panel A

Panel B

Figure 2.

- a. Skin conductance in the acute pain and control conditions separated by gender at baseline, during and after acute pain. * Indicates a significant difference ($p < .05$) between experimental men and experimental women and controls.
- b. Salivary cortisol values in the experimental and control conditions at baseline during WM 1 and WM 2. * Indicates a significant difference ($p < .05$) between experimental and controls' cortisol levels after WM 2 and a significant difference between experimental cortisol levels at baseline and WM 2, and WM 1 and WM 2.

Error Bars Represent 95% Confidence Intervals

Figure 3.

Effects of forehead cold pressor on WM performance separated by gender during WM 1 and WM 2. * Indicates a significant difference ($p < .05$) between experimental women and experimental men and controls during exposure to acute pain.

Table 1

Sample Characteristics

	Control (<i>N</i> = 40)	Experimental (<i>N</i> = 38)	Total (<i>N</i> = 78)
Gender			
Male	20	19	39
Female	20	19	39
Age ($M_{years} = 20.13$, $SD = 2.34$)			
18–24	37	34	71
24–29	3	4	7
Ethnicity			
Caucasian/White	15	20	35
Hispanic/Latino	14	12	26
Asian American	5	1	6
Native American/Pacific Islander	2	2	4
African American	1	1	2
Bi-Multi-racial	2	2	4
Other	1	0	1
Women (Total <i>N</i> = 39)			
Using a contraceptive			
Yes	10	6	16
No	10	13	23
Type of contraceptive			
Oral *	8	6	14
Diaphragm	1	0	1
Nuvaring®	1	0	1
Menstrual Phase (ovulating women)			
Follicular	3	4	7
Luteal	8	9	17
Contraceptive Cycle **			
0–15 days	5	2	7
16–32 days	4	4	8

Note:

* These oral contraceptives could be progesterone only, or estrogen and progesterone combined. No women reported taking extended or continuous cycling pills and all had an oral cycle ≤ 30 days.

** The contraceptive cycle represents 0–15 or 16–32 days since the last self-reported period and includes the Nuvaring® user. The diaphragm user is included with the ovulating women as this contraceptive uses a barrier method.

Table 2

Correlations for women exposed to pain

	1.	2.	3.	4.	5.	6.	7.	8.
1. WM during stressor	--							
2. WM post stressor	.46*	--						
3. Verbal pain rating	-.57*	-.27	--					
4. MPQ-SF total score	-.30	-.44	.60*	--				
5. SC during stressor	-.27	-.50*	.47*	.10	--			
6. SC post stressor	-.38	-.42	.48*	.06	.75*	--		
7. Cortisol during stressor	-.23	-.38	.49*	.15	.51*	.40	--	
8. Cortisol post stressor	-.03	-.23	.44*	.33	.21	.31	.43	--

Note:

* = $p < .05$