

By

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Abstract

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Introduction

Our experiences, positive and negative, create the individuals who we are today. For instance, adverse childhood experiences (ACEs), affecting about 20% to 30% people in the general population (Felitti et al., 1998), have significant repercussions on the lives of those who have experienced them. Such consequences include dysfunctional emotion regulation, reduced cognitive functions, and proneness to psychopathological conditions (Björkenstam, 2017). Although the negative effects of ACEs on overall mental health are well recognized, it remains less clear whether and how ACEs influence cognition. The latter issue has gained considerable attention in recent years given the importance of cognitive deficits and impairments in predicting everyday functional outcomes (Hartley et al., 2017). The proposed study is thus intended to evaluate how ACEs influences working memory (WM), the core of human cognition (Cowan, 2001), as a proxy to understand how ACEs impact cognitive functions.

As a system to retain information over a short time period at the service of other mental activities (Baddeley, 2012), WM is critical for various cognitive and affective processes, including attention (Kane, Poole, Tuholski, & Engle, 2006), fluid intelligence (Conway, Kane, & Engle, 2003), optimal processing of affective information (Xie et al., 2017), and emotional regulation (Schmeichel, Volokhov, & Demaree, 2008). With a better understanding of how ACEs impact WM, potential interventions can be developed to improve the cognitive functions in individuals with ACEs. Based on previous findings in the literature (Majer, Nater, Lin, Capuron, & Reeves, 2010), there are several possible ways that ACEs may impact WM.

First, ACEs may have a *direct* influence on WM (i.e., direct effect hypothesis). Specifically, chronic stress associated with ACEs may disrupt the function of the Hypothalamic-Pituitary-Adrenal (HPA) Axis (Carpenter et al., 2007), leading to structural and functional

changes in a wide range of brain regions including the medial temporal lobe and the prefrontal cortex (Arnsten, 2009). Consequently, cognitive functions supported by these structures, such as WM, would be compromised. This direct impact can manifest as 1) fewer items simultaneously encoded and stored in WM (i.e., quantity) and/or degraded memories (i.e., quality), which are related to the storage aspect of WM, and/or 2) compromised encoding of information into WM, a processing aspect of WM. Although neurocognitive dysfunctions associated with ACEs have been widely documented in the literature, it is unclear whether these functional impairments result from WM storage or processing.

Second, in addition to the direct effects, ACEs may also indirectly influence WM via their interaction with acute stress responses (i.e., indirect effect hypothesis). In contrast to the damaging effect of chronic stress, certain levels of acute stress can benefit overall cognitive functions, due to increased alertness and vigilance (Yuen et al., 2009). However, this transient enhancement in alertness under acute stress could be affected by chronic stress associated with ACEs (Carpenter et al., 2010). Consequently, ACEs may reduce the WM boost under a moderate level of acute stress (Yuen et al., 2009).

This study thus systematically investigates the effects ACEs on WM to test these two hypotheses (i.e., direct effect vs. indirect effect). First, this study evaluates which aspects (storage, processing, or both) of WM may be associated with ACEs. Specifically, this study adopts a modified change detection task (Vogel, Woodman, & Luck, 2006) that assesses both the speed of WM consolidation and WM capacity (see Figure 1). In this task, pattern masks are inserted at different time points after the onset of memory stimuli to disrupt encoding of fragile sensory inputs into WM, namely the WM consolidation process. As the stimulus onset asynchrony (SOA) between memory and mask items increases, more items can be encoded into

WM (see Figure 1). Consequently, the difference of number of encoded items at different SOAs can be used a proxy for the speed of WM consolidation. Furthermore, the number of items encoded into WM without any masking manipulation may be used to estimate WM capacity, which usually plateaus around 3 to 4. This study examines how ACEs may directly influence these two critical aspects of WM, namely the speed of WM consolidation and WM capacity.

Second, this study also tests how ACEs may interact with acute stress responses in the influence of WM. Specifically, in addition to measuring participants' ACEs, this study uses pupillometry to capture acute stress responses to standard emotion induction stimuli during a WM task. The rationale is that pupil dilation is closely associated with the level of norepinephrine (NE), a stress hormone (Einhäuser, Stout, Koch, & Carter, 2008). Acute stress responses can thus be measured objectively as changes in pupil size. To avoid potential measurement confounds of pupil size due to visual inputs, emotion inducing audio clips are used to induce an acute stress response. These emotion-inducing audio clips are from the International Affective Digital Sounds (IADS), which have been standardized and validated to induce changes in subjective emotional experience and pupil size (Bradley & Lang, 2007).

Method

Participants

Sixty undergraduate students (32% male, on average 19.05 years old with a standard deviation, SD, as 2.23) took part in the study at the University of California, Riverside for course credits (1 unit/hour) or paid compensation (\$10/hour). All participants reported normal (or corrected-to-normal) visual acuity and normal color vision. Participants also provided written informed consent prior to the study, following a procedure approved by the Institutional Review Board of the University of California, Riverside.

Apparatus

The experiment was conducted in a moderately lit windowless room with a background luminance of about 500 lx. A chin rest was used to maintain participants' head positions. A video-based EyeLink 1000 (SR Research Ltd., Ontario, Canada) eye tracker recorded eye movements and pupil size at a sampling rate of 500 Hz. The EyeLink 1000 assesses gaze position by measuring the reflection of an infrared illuminator on the cornea with a video camera that is sensitive to light in the infrared spectrum. The eye tracker also records the size of the pupil in arbitrary units (AU) that is linearly associated with absolute pupil diameter. Visual stimuli were controlled by Psychtoolbox in Matlab (Mathworks, Boston, MA). These visual stimuli were presented on a 60-Hz LCD monitor (calibrated with a X-Rite I1Pro spectrophotometer) with a grey background (42 cd/m^2) at a viewing distance of 80 cm. Auditory stimuli were presented via headphones at a noise level comfortable to the participant.

Stimuli

Emotional Sounds. Forty-eight 6-second sound clips were selected from the International Affective Digital Sounds (IADS) systems. Half of these sound clips are moderately arousing with a negative valence and include sounds from screams, crying babies, explosions, etc. The normative ratings of valence for these negative arousing sounds are 2.40 [Inter-quartile range, IQR: 1.71, 3.08] on a 9-point valence scale in which smaller numbers indicate more negative emotional values. The remaining half of the sound clips are emotionally neutral and include everyday sounds, such as running water, a ticking clock, typewriting, etc. These neutral sounds had an average normative valence rating close to the central point of the scale (5.05 [IQR: 4.78, 5.47]). Furthermore, all the negative sounds were more arousing (6.10 [IQR: 6.24,

6.48]) compared to the neutral sounds (4.43 [IQR: 4.14, 4.65], $p < .0001$) on a 9-point arousal scale.

Stimuli for Visual WM Task. The study array for the visual WM task consisted of four distinct colors randomly chosen from 180 colors that were evenly distributed (at least 24° of visual angle from each other) on a circle in the Commission Internationale de l'Eclairage (CIE) Lab color space (see Zhang & Luck, 2008, for details). These colors were presented in squares ($2^\circ \times 2^\circ$ of visual angle) at locations randomly selected from 6 possible locations that were equally spaced on an invisible circle with a radius of 6° of visual angle. All colors had equal luminance and varied mainly in hue and slightly in saturation.

The consolidation-masking stimuli consisted of four masking patterns at the original locations of the memory items. Each masking pattern ($2.3^\circ \times 2.3^\circ$ of visual angle) consisted of four colored squares ($1.15^\circ \times 1.15^\circ$ of visual angle) in a 2×2 arrangement. The colors of these squares were randomly selected from the 180 colors, without repetition, and completely uncorrelated with the colors from the memory array.

The test array of the change-detection task also contained four squares the same size as the memory items at the original locations. One of the squares contained a color that was either the same as (no-change trials) or different from (change trials) the corresponding memory color (at the same location) from the memory array. Change and no-change trials were equally likely. On change trials, the new color was randomly sampled from the 180 colors, with at least a 40° difference from the corresponding color from the memory array and with at least a 24° difference from the other colors in the memory array.

Procedure

Visual WM Task. As shown in Figure 1, each trial began with a 500-ms fixation display followed by a 6-second IADS sound clip with only a static central fixation circle ($\sim 0.3^\circ$ of visual angle in diameter) on the screen. Subjects were instructed to look at this central circle during the fixation display and the presentation of the sound clip. Four seconds after the onset of the sound, the central fixation circle changed in size increasing 0.1° , 0.2° , and then 0.3° of visual angle in diameter for 200 ms, 300 ms, and 400 ms, respectively. After this dynamic central fixation display, the memory array containing 4 color squares was presented on the screen for 83.3 ms. In the consolidation masking conditions, pattern masks were presented after the memory array at two different stimulus onset asynchronies (SOAs): 100 ms (short SOA condition, namely the mask occurred 16.7 ms after the memory display) or 340 ms (long SOA condition). After a delay interval with a fixed memory-and-test SOA at 1000 ms, a test display with 1 color square at a randomly selected location and 3 outlined placeholders at the remaining locations were presented on the screen. In half of the trials, the test color would be identical to the color at the same location in the memory display (“*old*”). In the other half of the trials, the test color would be a new color (“*new*”) with at least 24° difference from the original color in the CIE Lab color space. Participants were instructed to recognize whether the test color was “*new*” or “*old*” and to input their answers by using a computer mouse to click a scale presented below the test display. No feedback was provided for the visual WM change detection response. In the non-masking condition, all the timing parameters and test procedures were identical to those in the consolidation masking conditions, except that no pattern masks would be presented during the retention interval of the task.

Immediately following the visual WM change detection response, participants were

sequentially presented with the arousal and valence Self-Assessment Manikin (SAM) 9-point scales. Participants used a computer mouse to click on the scales to evaluate the arousal and valence of the sound clip presented at the beginning of the trial (i.e. how emotionally arousing the sound was and what the emotional valence of the sound was).

The emotional conditions (negative/arousing vs. neutral/non-arousing) of the sounds were organized into 2-trial mini-blocks. These emotional condition mini-blocks were randomly intermixed within an experimental block, which included 32 trials for each block. Other experimental factors, including change or no-change of the test color and the masking conditions (short SOA, long SOA, and no-masking), were randomly intermixed within an experimental block. Every participant completed 6 experimental blocks, yielding a total of 192 trials with 96 trials for each emotion condition.

Other Measures. Following completion of the experimental trials, participants completed a survey for demographic information (e.g., age and gender) and questionnaires including the Patient Health Questionnaire-9 (PHQ-9), and the Generalized Anxiety Disorder-7 (GAD-7) scale, as well as the Adverse Childhood Experiences (ACEs) questionnaire.

PHQ-9. This is a self-report measure of depressive symptoms over the previous two weeks (Kroenke, Spitzer, & Williams, 2001). Participants respond to 9 symptom questions by indicating how often in the past two weeks they have been bothered by these symptoms using a 4-point scale (from “*Not at all* = 0” to “*Nearly Every Day* = 3”). Possible scores range from 0-27, with a larger number indicating more severe depression.

GAD-7. This is a self-reported questionnaire for screening and severity measuring of generalized anxiety (Spitzer, Kroenke, Williams, & Löwe, 2006). It has seven items, which

measures the severity of various signs of generalized anxiety on a 4-point scale (from “*Not at all* = 0” to “*Nearly Every Day* = 3”). Larger values represent higher levels of anxiety. Possible scores range from 0 to 21.

ACEs. This questionnaire measures childhood exposure to abuse and family dysfunction experienced by respondents before the age of 18 years. Responses were reduced to 8 ACE categories: emotional abuse, physical abuse, sexual contact abuse, exposure to alcohol or other substance abuse, mental illness, violent treatment of mother or stepmother, criminal behavior in the household, and parental separation or divorce (Anda et al., 2006). The number of ACEs (range: 0–8) was summed to create the ACE scores.

Data Analysis

Visual WM Measures. Participants’ performance in the visual WM change detection task was assessed as Cowan’s K (set size [4] \times [hit rate – false alarm rate]) representing the number of remembered stimuli (Cowan, 2001; Rouder, Morey, Morey, & Cowan, 2011). Two measures were derived from the Cowan’s K s across three experimental conditions. First, the speed of visual WM consolidation was estimated using the difference in K s between long SOA and short SOA masking conditions. Second, the storage capacity of visual WM was estimated based on the K in the no-masking condition.

Pupil Data. The pupil data was prepared and analyzed using methods from Granholm, Asarnow, Sarkin, & Dykes (1996). As shown in Figure 1, a 4,200-ms epoch time-locked to 200 ms before the onset of the sound clip was extracted from each trial. These pupil data were Z scored to normalize individual differences. Baseline correction was conducted by subtracting the average pupil size within 200 ms before the onset of the luminance probe from all epochs.

Artifacts, including blinks, were identified using established algorithm (see Siegle, Steinhauer, & Thase, 2004). A linear interpolation was applied to the rest of the trials with blinks (see Siegle et al., 2004). Trials composed of more than 50% interpolated area within the analysis time window were excluded in the final analysis (see Siegle et al., 2004). Overall less than 5% of the data were rejected for all participants. Of primary interest, arousal responses were measured by the extent of pupil dilation following the presentation of IADS sounds, calculated as the mean pupil size in the last 2000 ms of the measurement epoch.

Results

Effectiveness of Induced Arousal

As shown in Figure 2, participants' pupil response to negative arousing sounds were generally greater than that to emotionally neutral sounds. This observation was supported by a significant mean pupil size during the 2000 ms to 4000 ms time window following the onset of the IADS sound clip in the negative condition, as compared to the neutral condition ($p < .0001$). This observation is consistent with findings in the literature, such that negative arousing sounds may trigger great arousal responses, manifested as larger dilated pupil sizes (Bradley, Miccoli, Escrig, & Lang, 2008). Furthermore, participants' subjective ratings for the sound clip following the visual WM task also showed more negative valence and higher arousal for the negative sounds as compared to neutral sounds ($ps < .0001$). Overall, these results suggest a certain level of effectiveness of emotion induction using the IADS sound clips on a trial-by-trial basis.

Visual WM Task Performance

Overall Performance. Participants' average performance in the visual WM task across different conditions is summarized in Figure 3. First, the number of items an observer retained in

WM increased as the amount of time allowed for WM consolidation increased (e.g., from short SOA to long SOA). This observation was supported by a significant main effect of masking conditions in a 2 (masking conditions: short vs. long SOA) by 2 (emotion conditions: negative vs. neutral) repeated-measured Analysis of Variance ($F_{(1, 59)} = 109.19, p < .001$). Second, the rate of visual WM encoding/consolidation was higher in the negative condition than that in the neutral condition, supported by a significant interaction effect between masking and emotion conditions ($F_{(1, 59)} = 5.13, p = .027$). However, the main effect of emotion was not statistically significant ($F < 1$). Third, there also seemed to be no substantial difference in total number of items one can retain in visual WM between negative and neutral conditions when sufficient encoding/consolidation time was given in the no-masking condition, as indicated by the lack of statistical significance in the estimate of K in the no-masking condition across emotion conditions ($t < 1$).

Level of Induced Negative Emotion and WM. To more specifically examine how induced negative emotion has impacted participants' WM performance, the sample was further trisected into three folds based on the pupil size difference between negative and neutral conditions. As such, three groups of participants were identified. They were less, moderately, or overly responsive to the selected negative IADS sounds. A linear contrast of -1, 0, and +1 could nicely capture these difference scores across three subject groups (see Figure 4, $p < .0001$). As shown in Figure 5, this trisection of sample revealed a quadratic pattern for the levels of induced negative emotion and the emotional effect on WM consolidation ($p < .05$). That is, participants who were under a medium level of induced arousal due to negative IADS sounds seemed to have the fastest WM encoding/consolidation, as compared to those who were less or overly responsive to the IADS sounds. Adding gender, PHQ score, and GAD-7 score as covariates did not seem to

substantially change the finding. Again, this quadratic pattern was not observed for WM capacity measure (see Figure 6).

ACEs and WM

Evidence was not found for adverse effects of ACEs on overall visual WM functions in that the correlations between ACEs and participants' WM measures (consolidation speed and capacity) in the neutral condition were not statistically significant ($r_s < .15$, $p_s > .26$).

Furthermore, ACEs also did not seem to modulate the effect of induced negative emotion on visual WM consolidation speed or capacity, such that the correlation between ACEs and WM measures (consolidation speed and capacity) in the negative condition relative to the neutral condition was also not statistically significant ($r_s < .16$, $p_s > .25$).

Discussion

The present study has examined how acute and chronic stressors may impact WM based on a visual WM change-detection task, pupillometry, and measures of ACEs. The results showed that induced negative emotional arousal could profoundly impact on moment-by-moment information processing, manifested as a faster visual WM consolidation speed under moderate arousal. This moderate emotional arousal could potentially improve cognitive abilities, such as fluid intelligence and performance in tasks requiring fast-paced responses (e.g. catching a baseball, avoiding obstacles while driving, etc.). Critically, these effects could not be explained by gender, current mood state, or a lifelong experience of stress. In comparison, no significant effects were found for the storage capacity of visual WM under induced negative emotion. Furthermore, chronic stress associated with ACEs also did not substantially damage WM functions in terms of either consolidation speed or capacity as much as we were concerned.

These results have some implications for further research in this field. For instance, the lack of significant effects of chronic stressors, such as ACEs, on WM may suggest a certain level of resilience among individuals with ACEs. That is, it is possible that individuals with ACEs may develop abilities to recover from difficult situations, and therefore are more capable to handle at-the-moment induced negative emotion. This interpretation suggests that the relationship between ACEs and cognitive functions may be more complicated as predicted by the direct and indirect effect hypotheses, because both hypotheses assume a negative impact of ACEs on WM. It is thus of great interest and importance for future research to elaborate how resilience may restore core cognitive functions such as WM among individuals with ACEs. Answers to this question may foster a sense of confidence for individuals with ACEs such that difficult life experiences may not necessarily lead to deteriorated cognitive function, especially WM that is highly association with intelligence (Conway, Kane, & Engle, 2003).

Beyond these implications, several limitations of this study should be noted. First, some additional factors may influence participant performance in the visual WM change-detection task, such as lack of sleep, time of day, lack of motivation, time in regard to the school year, etc. Second, there is a relatively small number of participants included in the current study. Larger amounts of data may be needed to increase statistical power.

Conclusion

Overall, the current study demonstrated clear evidence for the effect of induced negative emotion on visual WM consolidation speed but not storage capacity. However, this study did not obtain evidence for the direct or indirect impact of ACEs on visual WM measures. Although this lack of significant effects of ACEs on visual WM may be related to modulation of additional factors or a relatively small sample size, it allures to a more hopeful possibility that ACEs may

not necessarily impair WM. This interpretation may inspire future studies to further examine resilience as a critical factor in the interaction between stress and cognition.

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Appendix
Figures

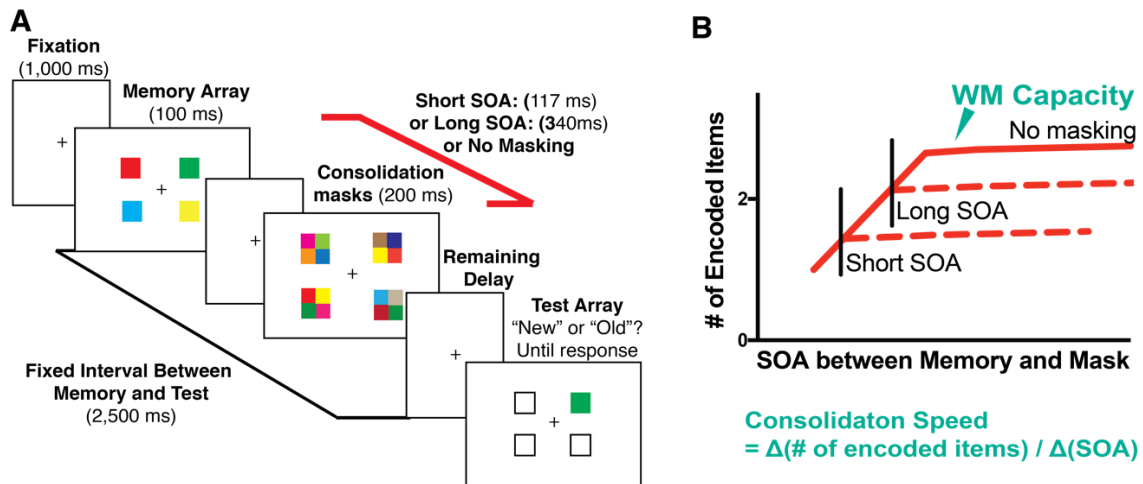


Figure 1. Change detection paradigm (A) and measure of the task (B). In A, a fixation display, memory array, consolidation mask, and then test array is presented on the screen. Participants are asked to detect if there is a change in color in the test array from the memory array. The time between the memory array and consolidation mask is changed to create varied SOAs (short, long, and no masking conditions). As the SOA between memory and mask items increases, the number of encoded stimuli increases, shown in B.

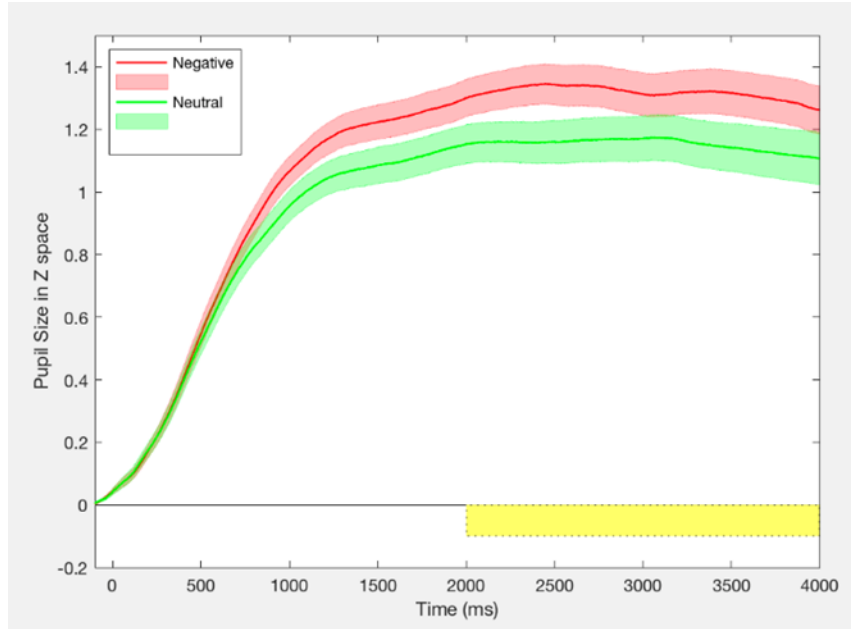


Figure 2. Pupil size during negative and neutral conditions. Participants' pupil response to negative arousing sounds were generally greater than that to emotionally neutral sounds.

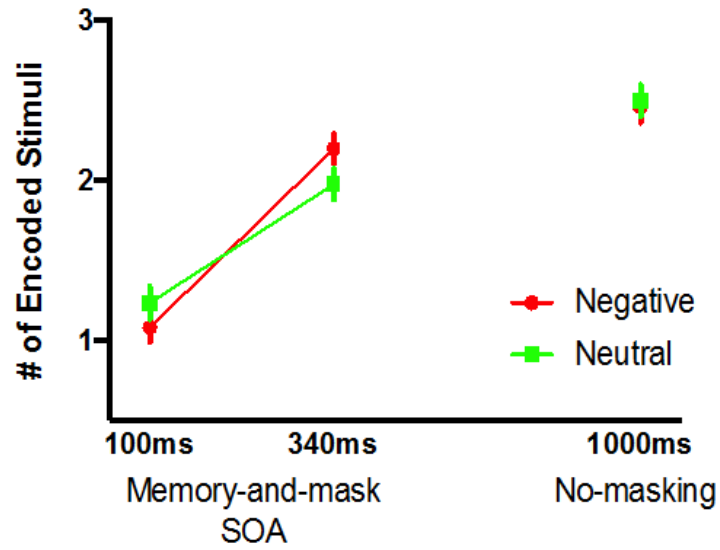


Figure 3. Number of encoded stimuli across different conditions. Number of items an observer retains in WM increases over time. Rate of visual WM encoding/consolidation is greater in negative conditions. No substantial difference in total number of encoded stimuli retained in visual WM when given sufficient consolidation time.

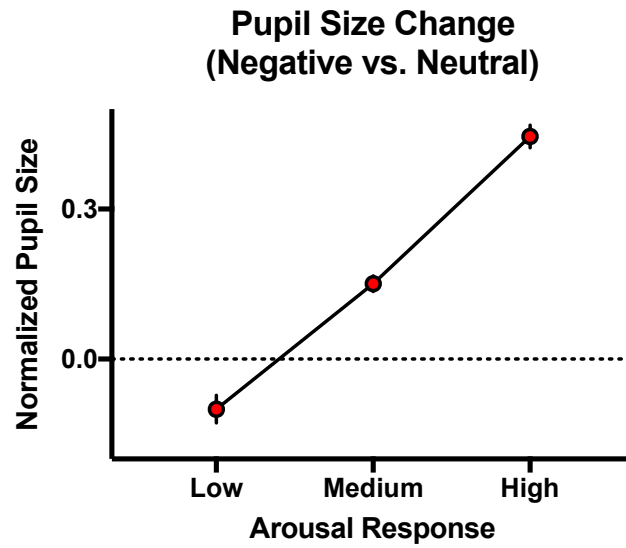


Figure 4. Individual pupil size differences for low, medium, and high arousal responses to negative IADS sounds. As arousal size increases, pupil size increases.

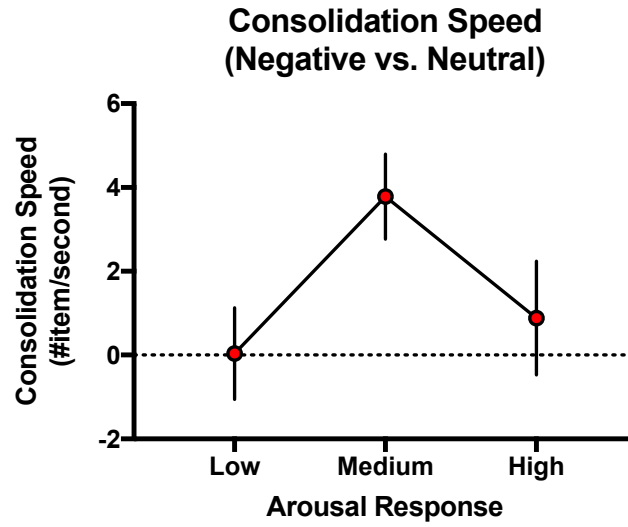


Figure 5. Levels of WM consolidation speed under low, medium, and high arousal. Participants who were under medium levels of arousal due to the negative IADS sound stimuli have the fastest WM consolidation speed.

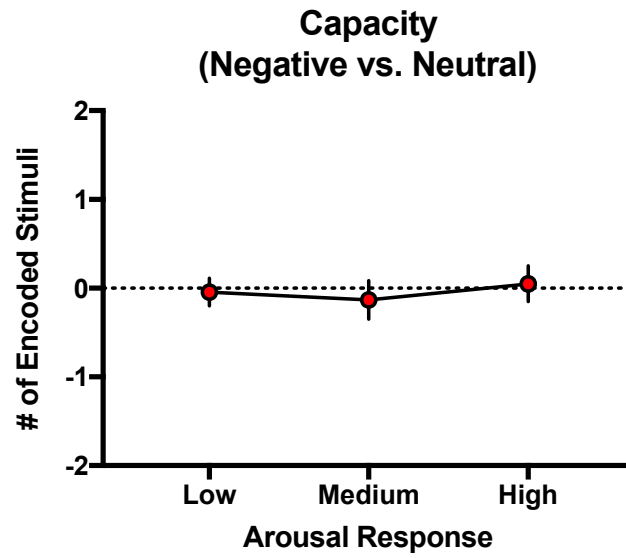


Figure 6. Levels of WM capacity under low, medium, and high arousal. There is no significant difference in WM capacity under all arousal conditions.