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Sympathetic arousal increases a negative memory bias in young women with low sex hormone levels

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ABSTRACT

Emotionally arousing events are typically better attended to and remembered than neutral ones. Current theories propose that arousal-induced increases in norepinephrine during encoding bias attention and memory in favor of affectively salient stimuli. Here, we tested this hypothesis by manipulating levels of physiological arousal prior to encoding and examining how it influenced memory for emotionally salient images, particularly those that are negative rather than positive in valence. We also tested whether sex steroid hormones interact with noradrenergic activity to influence these emotional memory biases in women. Healthy naturally cycling women and women on hormonal contraception completed one of the following physiological arousal manipulations prior to viewing a series of negative, positive and neutral images: (1) immediate handgrip arousal—isometric handgrip immediately prior to encoding, (2) residual handgrip arousal—isometric handgrip 15 min prior to encoding, or (3) no handgrip. Sympathetic arousal was measured throughout the session via pupil diameter changes. Levels of 17β-estradiol and progesterone were measured via salivary samples. Memory performance was assessed approximately 10 min after encoding using a surprise free recall test. The results indicated that handgrip successfully increased sympathetic arousal compared to the control task. Under immediate handgrip arousal, women showed enhanced memory for negative images over positive images; this pattern was not observed in women assigned to the residual and no-handgrip arousal conditions. Additionally, under immediate handgrip arousal, both high estradiol and progesterone levels attenuated the memory bias for negative over positive images. Follow-up hierarchical linear models revealed consistent effects when accounting for trial-by-trial variability in normative International Affective Picture System valence and arousal ratings. These findings suggest that heightened sympathetic arousal interacts with estradiol and progesterone levels during encoding to increase the mnemonic advantage of negative over positive emotional material.

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1. Introduction

People are more likely to attend to and remember emotionally arousing events or stimuli compared to neutral ones (Markovic et al., 2014; Labar and Cabeza, 2006). Current theories of arousal–cognition interactions posit that the release of norepinephrine (NE) during emotionally arousing experiences contributes to these attention and memory effects (Mather et al., 2015 in press; McGaugh, 2002; Markovic et al., 2014). In particular, the Biased Attention via Norepinephrine (BANE; Markovic et al., 2014) and Glutamate Amplifies Noradrenergic Effects (GANE; Mather et al., 2015 in press) models both propose that increased norepinephrine under arousal should enhance affect-biased attention and memory.

According to BANE, emotionally salient stimuli effectively bias attention and memory to boost their own processing; however, this model focuses exclusively on how NE biases mental processing in favor of the emotionally salient stimuli that induced its release (Markovic et al., 2014). In contrast, the GANE model covers a broader range of salience and arousal types to account for arousal's simultaneous ability to enhance memory of affective stimuli at the expense of memory for distracting or mundane information. Specif-

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ically, GANE predicts that memory of salient stimuli should benefit from NE release around the time of encoding, regardless of whether NE release was stimulated by the emotionally arousing stimulus or not.

The prediction that higher levels of NE enhance emotional memory effects is consistent with recent studies using genotyping technology. These studies examined carriers of a deletion variant of the ADRA2b gene, which codes for the α2b-adrenoreceptor and is associated with greater extracellular NE availability (Todd et al., 2014). Compared to non-carriers, carriers of the deletion variant not only show a greater capacity for emotionally enhanced memory of images (De Quervain et al., 2007), but also greater amygdala activation when viewing negatively valenced scenes (Rasch et al., 2009); deletion carriers also show enhanced perceptual encoding of negative words over both positive and neutral words (Todd et al., 2013). These findings suggest that increased NE availability biases attention towards affectively salient stimuli, particularly those of negative valence.

However, there are issues with drawing broad conclusions about the mechanisms of emotional memory from this genotyping approach. The previous genotyping studies focused exclusively on the α2b-adrenoreceptor, but other adrenoreceptors (e.g., β-adrenoreceptor) have significant contributions to noradrenergic influences on emotional memory (Cahill et al., 1994; Chamberlain et al., 2006; Strange et al., 2003) and likely play a role in the modulatory effects of NE on biased attention and memory for emotionally salient stimuli (Mather et al., 2015 in press; Tully and Bolshakov, 2010). Additionally, these genotyping studies have only examined how NE increases induced by emotional stimuli themselves modulate subsequent emotional memory. They have not addressed whether NE increases induced by an external physiologically arousing stimulus affect memory for emotionally salient stimuli. Separating the stimulus that induces arousal from the memoranda eliminates any potential confounds created due to differences in the perceptual qualities or semantic nature of emotional versus neutral stimuli.

Thus, our first aim was to build upon the genotyping findings by experimentally manipulating levels of physiological arousal prior to encoding and examine how the resulting changes in sympathetic arousal (and NE level) affect memory for emotionally salient images. Intriguingly, the noradrenergic genotyping studies found a valence-specific effect of NE, such that individuals with ostensibly higher NE availability showed selectively enhanced processing of only negative stimuli. Therefore, we assessed memory for negative and positive images in this study to examine how stimulus valence interacts with sympathetic arousal state. To induce sympathetic arousal and increase NE levels, we utilized an isometric handgrip paradigm (Nielsen and Mather, 2015). GANE predicts that arousal-induced NE increases will bias memory in favor of whatever stimulus is prioritized, or highly salient. Previous research indicates that young adults generally have a *negativity bias* such that they process and attend to negative stimuli more deeply than positive stimuli (Baumeister et al., 2001; Rozin and Royzman, 2001). Given this greater attentional salience of negative over positive valenced stimuli, GANE predicts that increased physiological arousal will amplify the effects of priority and enhance memory of negative stimuli more than positive stimuli.

Our second aim was to examine the role of sex steroid hormones in modulating the influence of NE activity on emotional memory biases. Steroid hormones, specifically estradiol and progesterone, affect autonomic nervous system activity in various ways. For example, in a study using static isometric handgrip with young women, levels of estradiol during the mid-luteal phase of the menstrual cycle were negatively correlated with muscle sympathetic nerve activity whereas changes in progesterone trended toward a significant positive relationship with muscle sympathetic nerve activity (Carter et al., 2013). In another study, estrogen replacement therapy decreased sympathetic activity in postmenopausal women (Vongpatanasin et al., 2001), indicating that estradiol may be sympathoinhibitory.

However, other studies provide evidence to the contrary. For example, one study showed that women in the mid-luteal phase (when estradiol and progesterone are elevated) exhibited increased sympathetic baroreflex sensitivity, increased resting muscle sympathetic nerve activity, and increased resting plasma NE levels compared to women in the early follicular phase (when estradiol and progesterone are low), indicating that hormone fluctuations across the menstrual cycle alter sympathetic nervous activity (Minson et al., 2000). In addition, hormonal contraception users (characterized by reduced levels of endogenous estradiol and progesterone) exhibited blunted sympathetic activity in response to both cardiovascular exercise (Otterstetter et al., 1999) and emotional images (Nielsen et al., 2013b). Even though these studies did not assess the specific relationship between sex hormone levels and noradrenergic activity, the results suggest that together, lower levels of progesterone and estradiol are associated with reduced sympathetic responses.

In women, sex steroid hormones levels are associated not only with sympathetic activity but also with emotional memory (Andreano and Cahill, 2009). Looking first at the role of progesterone, some studies found that in naturally cycling women, higher progesterone levels predicted enhanced memory for negative emotional images (Ertman et al., 2011) and increased intrusive memories for negative emotional events (Ferree et al., 2011; Soni et al., 2013); in these studies, there was no relationship between estradiol and memory. Other work showed that, under sympathetic arousal, women on hormonal contraception exhibited enhanced long-term memory for negative, but not positive, images compared to their non-aroused counterparts (Nielsen et al., 2013b). Thus, both high and low levels of endogenous progesterone have been associated with enhanced memory for negative stimuli.

Other research suggests that estradiol attenuates memory for negative emotional stimuli. For example, in a recent study of intrusive memories, women with lower estradiol levels showed stronger intrusive memories for violent film clips over a three-day period (Wegerer et al., 2014). These data suggest that estradiol may promote fear extinction processes such that intrusive memories are less likely to be extinguished when estradiol levels are low. Other studies testing the effects of sex steroid hormones on fear extinction processes support this notion; in both rodents and humans, estrogens, but not progesterone, were necessary for fear extinction (Graham and Milad, 2013; Milad et al., 2010; Glover et al., 2012). Thus, our second aim here was to test how levels of both estradiol and progesterone interact with sympathetic arousal at encoding to modulate emotional memory in women.

To address our two aims, we recruited women on and off of hormonal contraception so we could assess the effects of high and low levels of sex steroid hormones on arousal and memory (Kirschbaum et al., 1999). Although the mixed findings in the literature made it difficult to predict overall sympathetic activity differences by hormone group, previous evidence does suggest specific predictions regarding differences in emotional memory. Our primary prediction was that under immediate physiological arousal induced by isometric handgrip, or increased NE, women would show enhanced memory for negative, but not positive, relative to the residual handgrip arousal (handgrip 15 min before encoding) and no handgrip arousal (no-handgrip control task) conditions. We also predicted that, under immediate handgrip arousal, enhanced memory for negative images would occur predominantly in women in a low estradiol and progesterone state.