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Sex differences in extinction recall in posttraumatic stress disorder: A pilot fMRI study

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ABSTRACT

Recent research has found that individuals with posttraumatic stress disorder (PTSD) exhibit an impaired memory of fear extinction compounded by deficient functional activation of key nodes of the fear network including the amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC) and dorsal anterior cingulate cortex (dACC). Research has shown these regions are sexually dimorphic and activate differentially in healthy men and women during fear learning tasks. To explore biological markers of sex differences following exposure to psychological trauma, we used a fear learning and extinction paradigm together with functional magnetic resonance imaging (fMRI) and skin conductance response (SCR) to assess 31 individuals with PTSD (18 women; 13 men) and 25 matched trauma-exposed healthy control subjects (13 women; 12 men). Whereas no sex differences appeared within the trauma-exposed healthy control group, both psychophysiological and neural activation patterns within the PTSD group indicated deficient recall of extinction memory among men and not among women. Men with PTSD exhibited increased activation in the left rostral dACC during extinction recall compared with women with PTSD. These findings highlight the importance of tracking sex differences in fear extinction when characterizing the underlying neurobiological mechanisms of PTSD psychopathology.

1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder that develops following exposure to psychological trauma (American Psychiatric Association [APA], 2013), with women facing higher risk for developing PTSD than men (Breslau & Anthony, 2007; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Olff, Langeland, Draijer, & Gersons, 2007; Tolin & Foa, 2006). Although the mechanisms underlying increased PTSD risk in women are not fully understood, research has identified the potential role of sexually dimorphic neurobiology in the stress systems of animals (Dalla & Shors, 2009; Graham & Milad, 2013; Milad, Igoe, Lebron-Milad, & Novales, 2009; Zeidan et al., 2011) and humans (Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004; Goldstein, Jerram, Abbs, Whitfield-Gabrieli, & Makris, 2010; Goldstein et al., 2001; Graham & Milad, 2013; Lebron-Milad et al., 2012; Milad et al., 2006, 2010; Stevens et al., 2013). Recent work suggests that varying levels of female gonadal hormones, particularly estrogen, may influence fear extinction in women with PTSD (Glover et al., 2012; Lebron-Milad, Graham, & Milad, 2012). Specifically, women with PTSD who have low estradiol levels exhibit impaired extinction learning (Glover et al., 2012). No study has yet applied neuroimaging and psychophysiology to examine sex differences in fear conditioning, extinction, and recall in PTSD.

Fear conditioning and extinction paradigms have proven extremely valuable in revealing underlying circuitries of anxiety pathology and for understanding the development and maintenance of PTSD (Pitman et al., 2012; Shvil, Rusch, Sullivan, & Neria, 2013). Recent evidence specifically associates PTSD with impaired capacity to recall extinction memory, demonstrated by increased skin conductance levels to previously extinguished conditioned stimuli (Milad, Pitman, et al., 2009). Neuroimaging studies of PTSD using fear conditioning and extinction paradigms have reported functional and structural irregularities in neural regions demonstrated

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in the preclinical literature to mediate conditioned fear and extinction, including the ventromedial prefrontal cortex (vmPFC) and hippocampus (Milad & Quirk, 2012). During extinction recall, patients with PTSD show reduced activation in the hippocampus and vmPFC compared with trauma-exposed healthy controls, whereas dorsal anterior cingulate (dACC) and amygdala activity are greater (Milad & Quirk, 2012).

Importantly, activity in key fear network regions appears to be sexually dimorphic, with distinctive neural activations in these regions between healthy men and women when under acute stress (Goldstein et al., 2010) and during fear learning tasks (Cahill et al., 2004; Glover et al., 2012; Goldstein et al., 2001; Zeidan et al., 2011). For example, Lebron-Milad et al. (2012) found greater right rostral anterior cingulate (rACC) activity differences in healthy women than healthy men during extinction recall. However, the two groups did not differ significantly in skin conductance response (SCR) during extinction recall (Lebron-Milad et al., 2012). Among PTSD patients, Inslicht et al. (2013) recently reported significantly greater acquisition of conditioned fear (higher SCR) in women with PTSD compared to men with PTSD.

To clarify the potential role of sexually dimorphic neurobiology and psychophysiology in PTSD, the present pilot study explored sex differences during conditioning, extinction learning, and extinction recall using event-related fMRI and SCR in PTSD patients and matched trauma-exposed healthy control participants.

Based on previous studies, it was predicted that across the trauma-exposed healthy controls (TE-HC) and PTSD groups, men would exhibit better extinction recall than women as measured by SCR, with top-down control manifested by greater activation in the vmPFC and hippocampus, as well as diminished activation in the amygdala and dACC compared with women during extinction recall.

2. Material and methods

2.1. Participants

PTSD patients (18 females and 13 males) and TE-HCs (13 females and 12 males) subjects were recruited via advertisement and fliers. All participants met PTSD criterion A1 for adult traumatic events, including vehicular accidents, sexual or physical assaults, and witnessing serious injuries or deaths. Medical history, review of systems, physical examination, and laboratory tests determined participant health status. Raters with reliability training in psychometric assessments administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1995) and the Clinician-Administered PTSD Scale (CAPS; Weathers, Keane, & Davidson, 2001) to assess PTSD diagnosis and clinical severity. For PTSD subjects, exclusion criteria included substance/alcohol dependence within the past six months or abuse within past two months, use of any psychotropic medication 4 weeks prior to participation (6 weeks for fluoxetine), a Hamilton Depression Rating Scale (HAM-D-17; Hamilton, 1960) score greater than 24, or a CAPS score less than 50. Exclusion criteria for TE-HC subjects were current or past Axis I disorders including substance use disorders, and CAPS scores greater than 19. The New York State Psychiatric Institute Institutional Review Board approved all procedures, and all participants provided written informed consent.

2.2. Task procedures

The protocol employed an established two-day fMRI fear conditioning and extinction paradigm (See Fig. 1; Milad, Orr, Pitman, & Rauch, 2005; Milad et al., 2007). On Day 1, subjects participated in the conditioning and extinction phases of the paradigm. On the following day (Day 2), subjects were tested for level of extinction recall. Digital images of two different rooms served as the visual contexts (CXs) within which the conditioned stimuli (CSs) were presented. A lamp, which turned on and off, served as the cue and CSs were differentiated by the color of the light (e.g., red, blue, and yellow). The unconditioned stimulus (US) was a 500 ms shock delivered via electrodes attached to the second and third fingers of the dominant hand.

The US intensity was determined by a calibration procedure for each participant, after announcing that a mild electric stimulus would be used and reminding the participant that he or she could terminate the experiment at any time. Participants were instructed: "For this experiment, you will set your own level of electric stimulation. You should choose a level that is highly annoying, but not painful. I will start the stimulation at a very low level and gradually increase the level until you say 'stop.' The level that you set will then be used throughout the remainder of the experiment." The technician then recorded the participant-selected intensity level, ranging from 0.8 to 4.0 mA. A *habituation phase* followed the US calibration, consisting of 12 CS presentation trials, presenting the two to-be CS+s and the to-be CS- (4 of each of the three CS types) in counterbalanced trials.

The *conditioning phase* paired each of the two CS+s with the US at a partial reinforcement rate of 60% in the *conditioning* CX. One of the two CS+s was then extinguished during the subsequent extinction phase (CS+E), whereas the other was not extinguished (CS+NE). A third CS presented during the conditioning phase was never paired with the US (CS−). As in Milad et al. (2007), the study presented CSs in the following order: eight trials of the first CS+ were intermixed with 8 trials of the CS−, followed by eight trials of the second CS+ intermixed with 8 additional trials of the CS−. The shock (US) in the reinforced trials was delivered immediately following the CS+ offset, with no delay between CS offset and US onset. The shock electrodes remained attached to the subject's

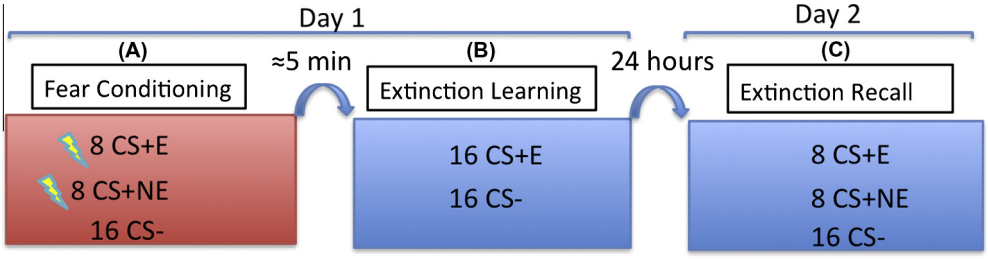

Fig. 1. Schematic diagram of the experimental design. (A) Fear conditioning phase, two CSs (e.g., red light and blue light) were paired with a shock (CS+E, CS+NE) at a partial reinforcement rate of 60%. A third CS (e.g., a yellow light) was never paired with a shock (CS−). This phase consisted of 32 trials: 8 CS+E, 8 CS+NE, and 16 CS−. (B) Extinction learning phase, the CS+E was presented in absence of a shock along with the CS− for 32 trials: 16 CS+E and 16 CS. The CS+NE was not presented in this phase. On Day 2, the (C) Extinction Recall phase 32 trials: 8 CS+E, 8 CS+NE, and 16 CS− were presented in the absence of a shock. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)