Observational Study

Medicine®

OPEN

Sex differences in extinction to negative stimuli

Event-related brain potentials

Nan Sun, PhD[a,b], Hong Lu, PhD[a,b], Chen Qu, PhD[c,*]

Abstract

There are controversial observations regarding whether females have a longer time to extinction than men, which may be related to different levels of conditioning acquisition and/or the influence of the menstrual cycle. We explored the electrophysiological evidence of sex differences in extinction.

In this study, females in the luteal phase and menstrual phase were examined for event-related potential (ERP) and evidence of attention allocation in the conditioning model using electroencephalogram recordings. A group of male participants was also included and compared.

Women in the luteal phase had a higher difference waveform of P3 amplitude to conditioned stimulus (CS) in the extinction phase than women in the menstrual phase and men. There was a shorter latency of P3 to CS+ in men than in women in the extinction phase, suggesting that men react faster than women to unconditioned stimulus (US) expectation. Our study revealed that women in the luteal phase allocated more attentive resources to the expectation of a US. In contrast, men displayed faster expectation of the extinguished US than women. Our results support the superiority of ERP technology in documenting the neural mechanism of the extinction process.

Abbreviations: ANOVA = analysis of variance, CS = conditioned stimulus, EEG = electroencephalogram, ERP = event-related potential, STAI = State-Trait Anxiety Inventory, US = unconditioned stimulus.

Keywords: estrogen, extinction, negative stimuli, progesterone

1. Introduction

A conditioned extinction model has been widely used to study many processes including memory acquisition, storage, retrieval, and extinction.[1,2] The model is based on Pavlov notion of conditioned reflex, which refers to the repeated presentation of a conditioned stimulus (CS) in the absence of the unconditioned stimulus (US) with which it was previously paired. Dalla and Shors[3] investigated whether there were sex differences in response to negative CS and reported that time to extinction was longer for women. The study supported the notion by many previous investigations that there are sex differences in response to negative CS.[3–7] However, a recent study reported inconsistent results in this regard.[8] The inconsistencies in time to extinction are thought to be closely related to the influence of menstrual cycle on the extinction procedure.

Some reports have shown that estrogen and progesterone in different menstrual cycles can affect the effectiveness of fear extinction,[9–12] making women fears more difficult to extinguish than men.[12] The amygdala, ventromedial prefrontal cortex, and hippocampus have been shown to be sexually dimorphic in humans.[13] These brain regions exhibit a different pattern of activation in response to emotional stimuli in men and women. In addition to their reproductive functions, gonadal steroids have also been implicated in neuroactive effects and are thought to be responsible for changes in decision making and attentive resource allocation over the course of the menstrual cycle.[14,15] Levels of estrogen and progesterone are low during menses compared to the follicular phase, which is characterized by high estradiol levels.[16] Some evidence from animal studies[9,11,17] suggest that gonadal hormones in different menstrual cycles may influence or contribute to sex differences in conditioned fear extinction, as well as the recall of conditioned fear. In the present research, women in 2 different phases of the menstrual cycle were compared to each other and to a group of men. According to previous studies of female menstrual cycles, the cycle is stable between 24 and 35 days,[15,18,19] and hormone levels are stable in each cycle; thus, the study can be calculated according to the number of days of menstruation.

Previous studies have suggested that extinction involves new learning,[20–22] as the process requires cognitive resources to be allocated to the extinguished US. Importantly, in testing CSs in the extinction phase, there was a selective partial return of US expectancy for CS+ but not for CS−.[6,20–23] After the CS+/US compound appeared several times, expectation of US arose, even when only the US appeared. A previous study[23] used subjective evaluation of the CS+ to predict US expectation. In addition, skin conductance responses have also been used to express US

Editor: Lucy Troup.

Funding/support: This study was supported by the Planning Project of Philosophy and Social Science in Guangdong in "Ten Two Five" (Number GD13YXL01) and National Natural Science Foundation of China (Number 31571144).

The authors have no conflicts of interest to disclose.

[a] School of Education, [b] Center for Brain and Cognitive Sciences, School of Education, Guangzhou University, [c] Psychology Research Center, South China Normal University, Guangzhou, China.

[*] Correspondence: Chen Qu, Psychology Research Center, South China Normal University, Room 508, No.4 Building, West Area, No.55, Zhongshan Xi Road, Shipai Campus, Guangzhou 510631, China (e-mail: fondest@163.com)

Medicine (2018) 97:17(e0503)

Received: 2 November 2017 / Received in final form: 24 March 2018 / Accepted: 26 March 2018

http://dx.doi.org/10.1097/MD.0000000000010503

expectation.[24] The present study used event-related potential (ERP) technology to test sex differences in the neural mechanism of extinction using the amplitude to the CS+ to predict US expectation. The P300 (P3) wave is a ubiquitous ERP component elicited in the process of decision making that reflects the stimulus-driven neural activity that can be observed in scalp electrophysiological recordings. For generalized anxiety disorder patients, the P3 amplitudes in response to recently changed trials were higher than those in response to trials with no change.[25] In contrast, normal controls had no significant difference in P3 amplitudes in response to the different trials. The effects of anxiety on extinction were thus included in our study and determined by the Spielberger State-Trait Anxiety Inventory (STAI), a commonly used measure of trait and state anxiety. STAI has been evaluated as a helpful method to study the effects of anxiety on extinction by the trait subscale.[26,27]

In the present research, ERP was assessed during 3 experimental phases: habituation, acquisition, and extinction. P3 scalp distribution is the amplitude change over the midline electrodes (Fz, Cz, and Pz), which typically increases in magnitude from the frontal to parietal electrode sites. Therefore, (Fz, Cz, and Pz) were chosen in our study as previous research indicates a P3 is maximal at those electrodes and is closely related to cognitive processes (to CS+)[28,29]; thus, the P3 waves to CS+ in the extinction phase and habituation phase represent the US expectation. Therefore, the present study used a different waveform of P3 amplitude in response to CS+ for the US expectation, in addition to the subjective assessment and skin conductance to measure US expectation to CS+.

2. Methods

2.1. Subjects and materials

2.1.1. Subjects. This study was approved by the Human Research Ethics Committee of South China Normal University. Informed consent was obtained from all participants. Ten men (age: 18–30 years; mean: 22 years) and 23 women (age: 18–30 years; mean: 22 years) participated in this study. Eleven of the women were in the menses stage (2nd to 4th day of menstruation), and 12 were in the luteal stage (3–9 days before the onset of the next menstrual cycle).[15,30] The day of onset of the subsequent menstrual period was used retrospectively to confirm the luteal stage. The following selection criteria were used for the female participants: no hormonal contraceptives, no lactation, no pregnancy during the last year, consistent menstrual cycle (between 24 and 35 days apart), no diagnosed premenstrual syndrome, no chronic illnesses (apart from allergies), no neurological, psychiatric, or endocrinological illnesses, no smoking, no subjective hearing problems, and normal body weight (body mass index between 18 and 24 kg/m^2). All subjects were right handed. Three tones were used in this research: 1 and 2-kHz pure tones as the CSs, as well as a 400-ms white noise as US.

2.1.2. EEG recording. Recordings were made at a 500-Hz sampling rate with application of a bandpass filter from 0.01 to 250 Hz. Electroencephalogram (EEG) data were acquired using a 32-channel cap and a BrainAmp MR plus EEG amplifier. For ERP determination, the EEG was recorded from Ag/AgCl electrodes (diameter 8 mm, Falk Minow Services, Germany) attached at the midline positions (Fz, Cz, and Pz) according to the 10 to 20 system. The reference electrodes were placed at each mastoid, the horizontal electrooculogram was used to the right of the reference electrodes, and the ground electrode was placed on the forehead. Additionally, PO8 and VEOL were placed separately 2 cm above and 2 cm below the left lateral canthus. The subjects were instructed to refrain from blinking as much as possible and to keep their eyes on a fixation mark during the main trials. Skin impedance was set up below 5 kΩ for each electrode and each subject. The recordings were stored for later analysis.

2.2. Procedure

Participants completed the trait version of the Spielberger STAI. They were then seated approximately 85 cm from the computer screen with a 5° visual angle. Next, the experimenter attached the electrodes. Before the experimental manipulation, the subjects were instructed to listen and differentiate 3 tones: 1-kHz, 2-kHz, and white noise. These 3 tones, with an intensity of 75 dB, were measured using a tone detector. The experiment comprised 3 phases: habitation, acquisition, and extinction. During the habitation phase, 300 tones were presented randomly; 80% of these were 1-kHz tones as CS−, and 20% were 2-kHz tones as CS+. Each trial started with a fixation cross, which was presented for 400 to 600 ms, followed by either CS+ or CS− for 200 ms. During the acquisition phase, the US was presented for 400 ms and only followed CS+ at 1-s intervals. Participants were instructed to differentiate the tones; they were then instructed to press a button as soon as possible to hear the white noise. There were 20 practice trials and 300 formal experimental trials. During the extinction phase, no US was presented.

2.3. Statistical analysis

A repeated-measures 3 (men/luteal phase/menstrual phase) ×2 (acquisition/extinction phase) analysis of variance (ANOVA) was applied with P3 amplitude as the dependent variable. Bonferroni correction (Bonferroni post hoc test) was applied to refer to the calibration of the test level alpha for multiple comparisons. Statistical analyses were conducted separately by phase.[31] The different waves were calculated by subtracting CS+ in the acquisition phase from CS+ in the extinction phase to represent expectation of the US.[6,23] For the extinction phase, a repeated-measures 3 (men/luteal phase/menstrual phase) ×3 (Cz/Fz/Pz) ×2 (CS+/CS−) ANOVA was applied to predict the wave of the P3 amplitude derived by subtracting CS+ in the acquisition phase from CS+ in the extinction phase. A repeated-measures 3 (men/luteal phase/menstrual phase) ×3 (Cz/Fz/Pz) ×2 (CS+/CS−) ANOVA was applied to predict the latency of P3 in the extinction phase. STAI scores and reaction times were used as additional factors in the ANOVA. We used Greenhouse–Geisser-corrected F- and *P*-values.

2.4. ERP analysis

The off-line analysis consisted of a segmentation of each tone (from a −150 ms prestimulus to a 1000 ms poststimulus), ocular correction, baseline correction (a 400–600 ms prestimulus until the onset of the stimulus), and artifact rejection (±80 μV). Each trial and each electrode position were then averaged separately. The peaks of the different components were defined as the maximal negativity or positivity in a defined time interval (P3 peak amplitude: negative peak within 350–400 ms poststimulus). We use the difference in the waveform of the P3 amplitude (negative peak within 350–400 ms poststimulus) to the CS+ between the acquisition phase and the extinction phase as the US

expectation, which is the same principle used in previous research.[23]

3. Results

3.1. Behavioral data

STAI scores were analyzed using ANOVA with the participant group as the main factor. No significant differences in anxiety were found between the 3 groups (men: 80.2 ± 9.82; luteal phase: 85.0 ± 23.26; menstrual phase: 83.45 ± 19.28, [F (2, 62) = 0.181; $P = 0.835$, $\eta^2_p = 0.012$]). These findings are in accordance with previous research.[27]

3.2. ERP results

A 3 (men/luteal phase/menstrual phase) × 2 phase (habitation phase/extinction phase) repeated-measures ANOVA was used with P3 amplitude as the dependent measure. The results showed a significant main effect for the group [$F(2, 62) = 8.34$; $P < .001$, $\eta^2_p = 0.53$] and a significant main effect for phases [$F(1, 31) = 4.96$; $P = .037$, $\eta^2_p = 0.28$]. There was no interaction effect between participant group and the phases [F (2, 62) = 1.63; $P = .372$]. The results were the basis of the following statistical analyses, which were conducted separately by phase.

3.3. Extinction phase

Negative valence of the CS+ was a predictor of the extent of US expectation.[6,23] In the present experiment, US expectation was calculated by subtracting the average ERP to CS+ in the habitation phase from that to the CS+ in the extinction phase. US expectation was measured in the 350 to 400 ms time window at Cz with maximal amplitude. Results showed no main effect for electrode position and no interaction between electrode position and sex. However, a significant main effect of CS+/CS [F (2, 62) = 2.058; $P < .001$, $\eta^2_p = 0.23$] and an interaction between CS+/CS and sex [F (2, 62) = 5.596; $P = .009$, $\eta^2_p = 0.55$] were observed. The simple effect showed that no significant differences were found in sex or CS− by Syntax [F = 0.24; $P = .79$], but a significant difference was found in sex and CS+ by Syntax [F = 4.9; $P = .01$] (Fig. 1). Further Bonferroni multiple comparisons showed a significant difference between women in the luteal phase and men ($P = .018$), as well as between women in the menstrual phase and in the luteal phase ($P = .002$), while no significant differences were found between women in the menstrual phase and men ($P = .44$) (Fig. 2).

A repeated-measures 3 (men/luteal phase/menstrual phase) × 3 (Cz/Fz/Pz) × 2 (CS+/CS−) ANOVA was applied to predict the latency of P3 in the extinction phase. Results showed no main effect for electrode position and no interaction between electrode position and sex; however, an interaction between CS+/CS and

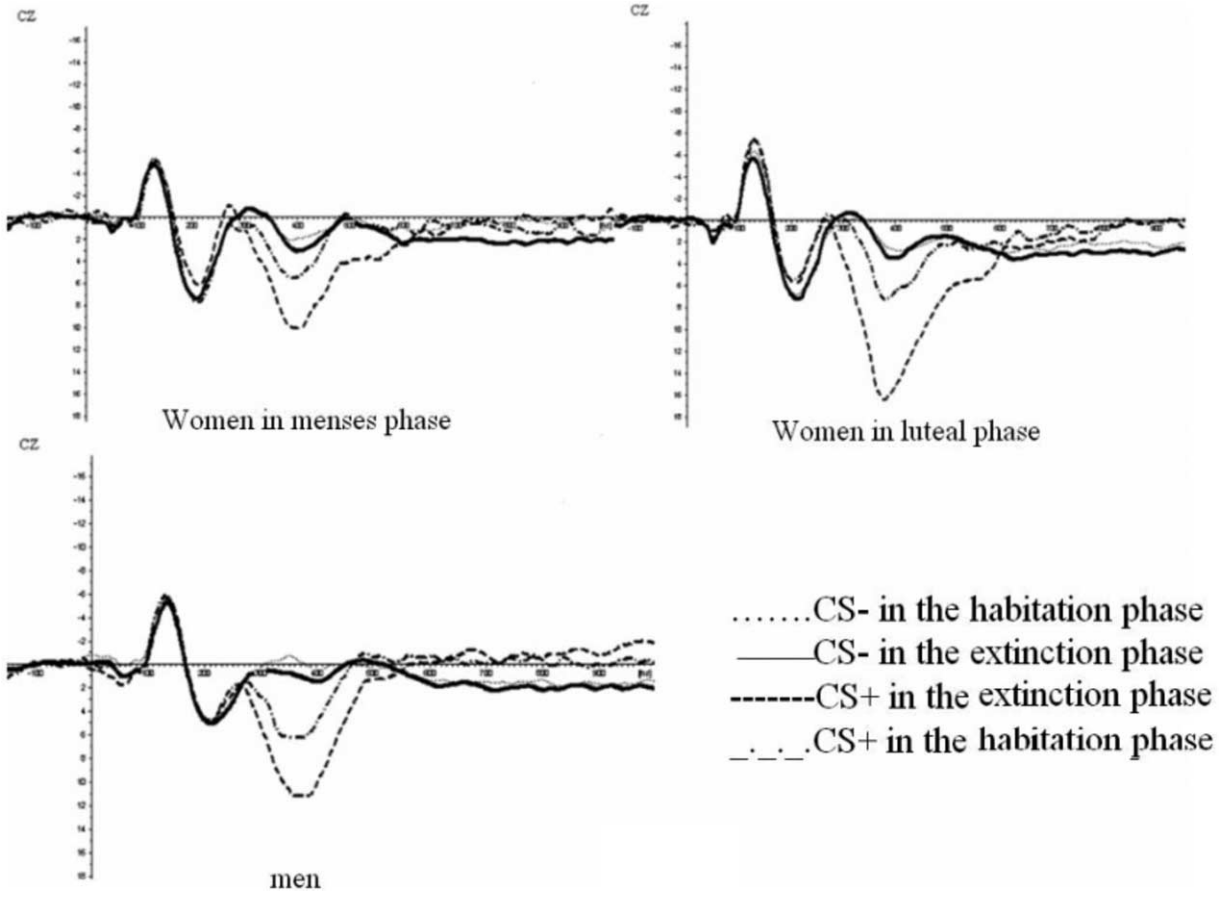

Figure 1. Grand averages to CS+ and CS− in the habitation phase and extinction phase in women in WL and women in WM for the Cz electrode. CS = conditioned stimulus.

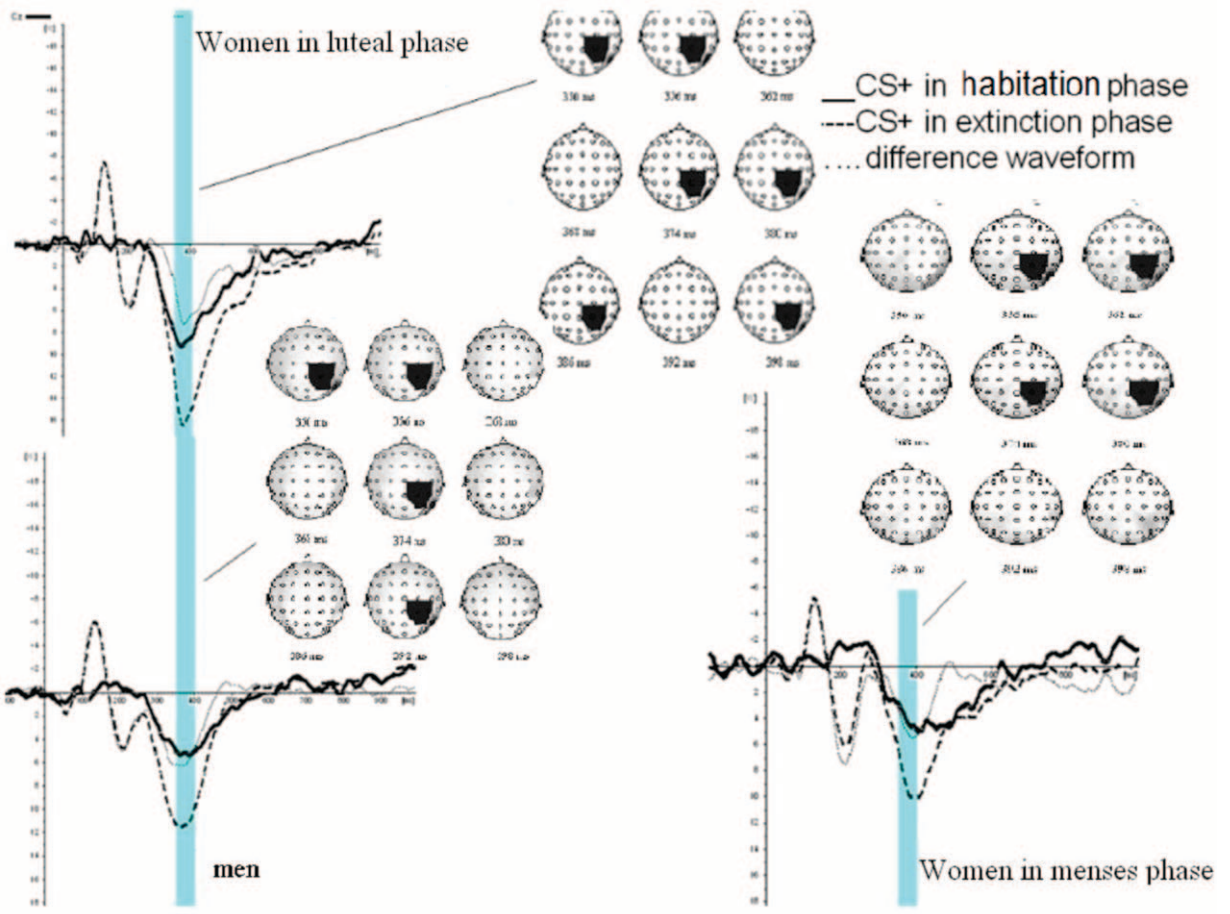

Figure 2. The difference in waveform between the habitation phase and extinction phase in men and women for the Cz electrode.

sex [F (2, 62) = 6.325; $P = .017$, $\eta^2_p = 0.29$] was observed. Follow-up analyses showed no significant differences between sex and CS− by Syntax [F = 1.37; $P = .47$], but a significant difference was found between sex and CS+ by Syntax [F = 3.85; $P = .02$, $\eta^2_p = 0.27$]. Further Bonferroni multiple comparisons showed differences between men and women in the menstrual phase ($P = .042$) and between women in the luteal phase and men ($P = .045$) but not between women in the luteal phase and women in the menstrual phase ($P = .895$).

4. Discussion

In the present research, we used state-of-the-art ERP techniques to characterize the neural mechanism of negative stimuli extinction in women during different phases of the menstrual cycle and in men. The waveform of P3 amplitude to CS+ in the extinction phase was higher in women in the luteal phase than in the other 2 groups. The brain electrical activity mapping of the P3 showed a similar trend (Fig. 2). A shorter P3 latency to CS+ in the extinction phase was observed in men compared with women. These results suggested that women in the luteal stage give more attentive resources to US expectation and that men display much shorter expectation to the extinguished US than women. The assessment criteria of the amplitude and the latency to CS+ in the present research are more precise than the index of the valence to the CS+.

An important contribution of the present research is the measure of the extinguished US: in the habitation phase, this allows subjects to establish stronger connections between CS and US. Based on the signal model proposed by Harris (2005),[32] a strong CS+/US connection could increase the reaction to CS+ in subjects compared with the reaction to CS when not followed by the US. The valence of the CS+ in extinction was predictive of the extent to US expectation.[6,23] To overcome the interaction effect of P3 amplitude and phase (habitation vs extinction), we first conducted a repeated measure ANOVA to rule out the connection effects. The US expectation, expressed by both the amplitude and latency to the CS+, indicated that brain electrical technology is more sophisticated in assessing US expectation than previously used behavioral measures.[33,34] The US expectation to the CS+ in extinction should mitigate the basic amplitude of the CS+ in the habitation phase. As such, each wave of the 2 phases would predict the extent of US expectation. Additionally, in an effort to balance fatigue and task difficulty, we used different waves of CS− in the 2 phases.

In the present research, the decreased P3 amplitude in response to CS+ was greater in women in the luteal phase than in the other groups. The brain electrical activity mapping of the difference in the waveform of P3 showed the same trend as the amplitude of the difference in the waveform of P3 (Fig. 2). The results suggest that women in the luteal stage give more attentive resources to the expectation of an US than either women in the menses stage or

men. Gonadal hormones in different menstrual cycle therefore appear to make fear extinction more difficult. Our results are in accordance with previous reports in animal models of the neurophysiological basis of sex differences in extinction.[30] More interestingly, our findings suggest a shorter P3 latency to CS+ in men than in women; however, no difference in latency to CS− in the extinction phase and men displayed faster expectation of the extinguished US than women. This discovery reflects the advantage of the ERP technology in documenting the neural mechanism of this process.

4.1. Clinical significance

Pathological extinction is one of several important factors thought to form the basis of anxiety disorders,[17,35–37] and sex differences in pathological extinction may help explain the higher incidence of anxiety disorders in women than in men. Most (75%) women with affective disorders experience significant symptoms in the luteal phase of the menstrual cycle.[16] Compared to men, women in the luteal phase show more abnormalities in decision making and spend more attentive resources on ERPs.[14,15] These findings, together with our earlier report,[38] provide a sound explanation of the neural mechanism by which extinction, not acquisition, is more difficult in women than in men. The present ERP study of women and men may provide important clues about why women are a high-risk group for anxiety disorders and could help researchers adopt differential exposure therapy strategies for men and women.

This current study has a limitation. The phases of the menstrual cycle were calculated solely based on days due to the unwillingness of the female subjects in testing luteinizing hormone levels. Women are known to have very varied menstrual cycles, and hormonal levels cannot be attributed to days alone. Ovulation can occur with a long or short luteal phase. Defining menstrual phases based on days alone would result in a lack of uniformity, consistency, and duration. In future studies, we anticipate to include hormone levels together with days to establish strictly defined menstrual cycle phases.

In conclusion, our results suggest that women in the luteal stage allocate more attentive resources to the expectation of an US than women in the menses stage or men. Men displayed faster expectation of the extinguished US than women, indicating the superiority of ERP technology in documenting the neural mechanism of this process.

Acknowledgments

The authors thank the financial support from the Planning Project of Philosophy and Social Science in Guangdong in "Ten Two Five" (Number GD13YXL01) and National Natural Science Foundation of China (Number 31571144).

Author contributions

Conceptualization: Hong Lu.
Data curation: Nan Sun, Hong Lu.
Formal analysis: Nan Sun.
Funding acquisition: Chen Qu.
Investigation: Nan Sun, Hong Lu.
Methodology: Hong Lu.
Project administration: Chen Qu.
Resources: Chen Qu.
Software: Nan Sun, Chen Qu.
Supervision: Hong Lu, Chen Qu.
Validation: Chen Qu.
Visualization: Hong Lu.
Writing – original draft: Nan Sun.
Writing – review & editing: Nan Sun, Hong Lu, Chen Qu.

References

[1] Kim JJ, Jung MW. Neural circuits and mechanisms involved in Pavlovian fear conditioning: a critical review. Neurosci Biobehav Rev 2006;30: 188–202.
[2] LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci 2000; 23:155–84.
[3] Dalla C, Shors TJ. Sex differences in learning processes of classical and operant conditioning. Physiol Behav 2009;97:229–38.
[4] Cahill L. Why sex matters for neuroscience. Nat Rev Neurosci 2006; 7:477–84.
[5] Cosgrove KP, Mazure CM, Staley JK. Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol Psychiatry 2007;62:847–55.
[6] Hermans D, Dirikx T, Vansteenwegen D, et al. Reinstatement of fear responses in human aversive conditioning. Behav Res Ther 2005;43: 533–51.
[7] Toufexis D, Davis C, Hammond A, et al. Sex differences in hormonal modulation of anxiety measured with light-enhanced startle: possible role for arginine vasopressin in the male. J Neurosci 2005;25:9010–6.
[8] Trask S, Thrailkill EA, Bouton ME. Occasion setting, inhibition, and the contextual control of extinction in Pavlovian and instrumental (operant) learning. Behav Processes 2017;137:64–72.
[9] Anderson LC, Petrovich GD. Sex specific recruitment of a medial prefrontal cortex-hippocampal-thalamic system during context-dependent renewal of responding to food cues in rats. Neurobiol Learn Mem 2016;139:11–21.
[10] Goldstein JM, Seidman LJ, Horton NJ, et al. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cereb Cortex 2001;11:490–7.
[11] Merz CJ, Wolf OT. Sex differences in stress effects on emotional learning. J Neurosci Res 2017;95:93–105.
[12] Jasnow AM, Schulkin J, Pfaff DW. Estrogen facilitates fear conditioning and increases corticotropin-releasing hormone mRNA expression in the central amygdala in female mice. Horm Behav 2006;49:197–205.
[13] Lang S, Kroll A, Lipinski SJ, et al. Context conditioning and extinction in humans: differential contribution of the hippocampus, amygdala and prefrontal cortex. Eur J Neurosci 2009;29:823–32.
[14] Maeng LY, Cover KK, Taha MB, et al. Estradiol shifts interactions between the infralimbic cortex and central amygdala to enhance fear extinction memory in female rats. J Neurosci Res 2017;95:163–75.
[15] Walpurger V, Pietrowsky R, Kirschbaum C, et al. Effects of the menstrual cycle on auditory event-related potentials. Horm Behav 2004;46:600–6.
[16] Lagowska K, Kapczuk K. Testosterone concentrations in female athletes and ballet dancers with menstrual disorders. Eur J Sport Sci 2016; 16:490–7.
[17] Milad MR, Igoe SA, Lebron-Milad K, et al. Estrous cycle phase and gonadal hormones influence conditioned fear extinction. Neuroscience 2009;164:887–95.
[18] Anderer P, Semlitsch HV, Saletu B, et al. Effects of hormone replacement therapy on perceptual and cognitive event-related potentials in menopausal insomnia. Psychoneuroendocrinology 2003;28:419–45.
[19] Tillman GD. Estradiol levels during the menstrual cycle differentially affect latencies to right and left hemispheres during dichotic listening: an ERP study. Psychoneuroendocrinology 2010;35:249–61.
[20] Sotres-Bayon F, Bush DE, LeDoux JE. Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. Learn Mem 2004;11:525–35.
[21] Myers KM, Davis M. Mechanisms of fear extinction. Mol Psychiatry 2007;12:120–50.
[22] Raes AK, De Raedt R, Verschuere B, et al. Failure to loose fear: the impact of cognitive load and trait anxiety on extinction. Behav Res Ther 2009;47:1096–101.
[23] Dirikx T, Hermans D, Vansteenwegen D, et al. Reinstatement of extinguished conditioned responses and negative stimulus valence as a pathway to return of fear in humans. Learn Mem 2004;11:549–54.
[24] Marin MF, Zsido RG, Song H, et al. Skin conductance responses and neural activations during fear conditioning and extinction recall across anxiety disorders. JAMA Psychiatry 2017;74:622–31.

[25] Han HY, Gan T, Li P, et al. Attentional bias modulation by reappraisal in patients with generalized anxiety disorder: an event-related potential study. Braz J Med Biol Res 2014;47:576–83.
[26] Indovina I, Robbins TW, Nunez-Elizalde AO, et al. Fear-conditioning mechanisms associated with trait vulnerability to anxiety in humans. Neuron 2011;69:563–71.
[27] Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 2007;118:2128–48.
[28] Kashihara K. A brain-computer interface for potential non-verbal facial communication based on EEG signals related to specific emotions. Front Neurosci 2014;8:244.
[29] Strozak P, Francuz P, Augustynowicz P, et al. ERPs in an oddball task under vection-inducing visual stimulation. Exp Brain Res 2016;234: 3473–82.
[30] Milad MR, Rauch SL, Pitman RK, et al. Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol Psychol 2006;73:61–71.
[31] Wong PS, Bernat E, Snodgrass M, et al. Event-related brain correlates of associative learning without awareness. Int J Psychophysiol 2004;53: 217–31.
[32] Harris JB. Differential conditioning of alpha amplitude: a fresh look at an old phenomenon. Clin Neurophysiol 2005;116:1433–43.
[33] Chang SD, Liang KC. The hippocampus integrates context and shock into a configural memory in contextual fear conditioning. Hippocampus 2017;27:145–55.
[34] Briggs JF, Fava DA. Immediate extinction attenuates spontaneous recovery and reinstatement in a passive avoidance paradigm. Percept Mot Skills 2016;123:5–16.
[35] Lissek S, Powers AS, McClure EB, et al. Classical fear conditioning in the anxiety disorders: a meta-analysis. Behav Res Ther 2005;43:1391–424.
[36] Milad MR, Quinn BT, Pitman RK, et al. Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. Proc Natl Acad Sci U S A 2005;102:10706–11.
[37] Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research–past, present, and future. Biol Psychiatry 2006;60:376–82.
[38] Sun N, Qu C, Zhao S, et al. Allocation of attention in response to novel neutral stimuli and predictive negative stimuli in men and women: an event-related potentials research study. Biol Rhythm Res 2011;1–9.