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Social support facilitates threat extinction retention in humans: an fMRI study

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Extinction is a recognized process for extinguishing threat memories; however, the process of extinction can be emotionally challenging, and the effect is usually short-lived. Animal studies have shown that peer presentation can inhibit freezing behavior and prevent return of the threat memories, suggesting that social support may enhance threat extinction. However, the role of social support in maintaining human threat extinction remains unclear. The present study examined the effect of social support on threat memory extinction in humans, and its underlying neural substrates. Succeeding threat conditioning on Day 1, participants were randomly assigned to the social support and no-support groups using random numbers and experienced either a social support intervention or no intervention before threat extinction procedure on Day 2, subsequently, they underwent spontaneous recovery and reinstatement tests on Day 3. A total of 96 participants completed the three-day threat extinction retention tests; 59 participants completed Day 3 tests within the fMRI scanner; 77 participants returned to the laboratory two weeks later and participated long-term threat extinction retention tests. Results showed that friend interaction significantly increased individuals' social support perception, which then reduced threat response and prevented the return of threat memories; and the effect was long-lasting. The fMRI results suggested that emotional memory-related brain regions, including the hippocampus, thalamus, and precuneus, were inhibited in the support group. By extracting these differential brain areas between support and no-support groups as regions of interest, connectivity analyses showed a significant difference in the functional connectivity of the thalamo-cortical circuits between the support and no-support group. This research highlights the positive role of social support in human threat extinction retention and related neural activations, which provides a potential strategy for treating threat- and trauma-related disorders.

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INTRODUCTION

Individuals may experience various traumatic events throughout their lives (e.g., car accidents, dog bites) that give rise to threat memories [1]. Appropriate retention of threat memories can help individuals avoid similar risks in subsequent experiences and is conducive to survival [2]. However, excessive threat memories towards traumatic stress exposure are related to the development of threat- and trauma-related disorders, such as post-traumatic stress disorder (PTSD) [3]. Thus, exploring ways to modulate threat memories is essential. A recognized approach is to weaken the connections between traumatic events and threat responses, known as the extinction of threat memories [4]. Threat extinction training refers to the process in which a conditioned stimulus (CS) is repeatedly presented without pair of unconditioned stimuli (US), resulting in a decreased conditioned response (CR) [5]. Extinction is the major mechanism for the large evidence of exposure-based psychological interventions in treating threat- and trauma-related disorders clinically [6, 7].

Some problems have been encountered when using traditional extinction procedures; for example, extinguished threat memories easily reappear with the passage of time (spontaneous recovery), return when CS appears in a different environment (renewal), and return after re-experiencing US (reinstatement) [8]. Moreover, the threat extinction procedure itself can be a source of stress for many patients in clinical settings and can cause them to drop out of treatment. Hence, facilitating strategies are required to increase the efficacy of threat memory extinction, reduce subjective suffering during the procedure, and prevent the return of threat memories. Some studies have applied pharmacological interventions to assist threat extinction. Although effective, many of the drugs used can be toxic and difficult to use in humans [9]. Therefore, non-invasive strategies should be further explored.

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Individuals experience and evaluate threatful/traumatic life events in a social network [10]. Animal studies have shown that the social presence of another conspecific in the extinction context can facilitate experimental animals' threat extinction through synergism with prefrontal oxytocin [11, 12], which inspired a new facilitating strategy on threat extinction. In clinical settings, it was demonstrated that individuals who had higher levels of social support would be less likely to develop PTSD symptoms following trauma exposure, suggesting the buffering role of social support in threat conditioning [13, 14]. In addition, several studies have revealed that high-level pretreatment social support was associated with great reduction in PTSD symptoms during exposure-based interventions for PTSD [15–17]. Therefore, providing social support may be an effective strategy for facilitating the extinction of memories related to traumatic experiences. Using a social support figure, researchers have demonstrated that social support can prevent the formation of threat associations by serving as a member of a prepared fear suppressor category [18–20]. Although inspiring, they recognized social support as a static figure rather than a multi-dynamic process (a better simulation of real-life events). Moreover, they did not explore the underlying neural basis of social support that facilitate threat extinction.

Social support in human society is far more complex than a mere presence, which refers to taking care of other people in a community to offer them what they need or to make them feel loved, cared for, esteemed, and have a sense of belonging [21]. Social support generally plays a significant role in promoting physical and mental health [22]. Regardless of the type (emotional, instrumental, informational, or appraisal support), one of the most important aspects of social support is the supported individuals' feelings or perception [23]. Functional support is believed to be the most essential aspect of social support—that is, the degree to which interpersonal relationships serve particular functions [24]. Besides, Social Identity Theory emphasizes the importance of maintaining a positive identity, such as friends and family, in social interaction [25]. Positive social interaction with supporting others can be an ideal approach to promote social support because it is usually rewarding and reciprocal, especially when interacting with close friends [26].

Therefore, the present study investigated the role of social support as a dynamic supporting strategy for threat memory extinction in humans, as well as the underlying neural substrates regulating this process. Our primary hypothesis was that positive interaction with close friends would facilitate the extinction of threat memories, and that this effect would be mediated through brain regions that are involved in social emotion regulation.

MATERIALS AND METHODS

Participants

One hundred and six participants from universities and nearby communities were recruited through posters and advertisements. The inclusion criteria were as follows: (1) healthy young adults of 18–35 years; (2) generally good health as determined by a physician; (3) junior high school education or above; and (4) volunteered to participate and provided informed consent. The exclusion criteria were as follows: (1) any history of or current psychiatric disorder diagnosed by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Axis I Disorders; (2) serious somatic or neurological comorbidities; (3) use of psychotropic drugs with no complete elution; (4) pregnancy or lactating; and (5) contraindications to magnetic resonance imaging (MRI) scanning. The recruited participants were scheduled for a screening interview at the beginning, during which they were informed of the details of the study protocol and signed an informed consent form approved by the Institutional Review Board of Peking University Sixth Hospital (**registration number: 2020122208535526**). Participants were paid 200 RMB (equivalent to US$27.67) after completing all study procedures. Additionally, all participants completed questionnaires that collected their basic demographic information, including sex, age, and education level. Data on their basic mental health conditions were collected using the Self-Rating Depression Scale (SDS) [27], Self-Rating Anxiety Scale (SAS) [28], Pittsburgh Sleep Quality Index (PSQI) [29], and Perceived Social Support Scale (PSSS) [30]. Furthermore, we did ask participants in the support group to rate their relationship with the invited friends on a Likert scale ranging from 0 to 10 at the beginning (0 = feel not comfortable to interact at all; 10 = feel extremely comfortable to interact), and only those with a rating of more than 8 were included in this study to ensure the stable relationship between participants and their friends. **All participants provided informed consent before the respondents began the questionnaire. The study was carried out in accordance with the principles of the Declaration of Helsinki and following institutional guidelines and regulations**.

Threat conditioning, extinction, spontaneous recovery test, and reinstatement test

The threat conditioning protocol was modified from our previous studies [31, 32], in which participants were expected to learn about the relationship between CSs (two different colored squares) and a US (a mild electric shock to the wrist). Shock intensity was determined individually before threat learning to meet the criteria of uncomfortable but not painful (the highest level was 70 V). During threat learning, blue and red squares were presented on a computer screen and participants were instructed to pay attention to them. One color was paired with an electric shock (CS+) on a partial reinforcement schedule (50% reinforced), whereas the other color was not (CS-). Two different presenting orders, red and blue, were applied to counterbalance which color square was CS+ and which was CS-, to counteract the effect of color on memory. Twelve reinforced presentations of the CS+, 12 nonreinforced CS+, and 12 nonreinforced CS- were included in threat acquisition. Only the skin conductance response (SCR) of the nonreinforced CS+ was used for comparison with CS- when assessing the expectation of the reinforcer to avoid the influence of the electric shock. Nonreinforced CSs were divided into four blocks, with 3 CS+ and 3 CS- in each block. The mean differential SCR between CS+ and CS- was calculated and represented threat response. A greater SCR for the CS+ than for the CS- was regarded as representing successful threat learning (mean differential SCR ≥ 0.05) [33]. Threat extinction was composed of 15 nonreinforced CS+ and 15 CS-, divided into five blocks with 3 CS+ and 3 CS- in each block. The spontaneous recovery test also consisted of 15 nonreinforced presentations of each CS (CS+ and CS-), with no electric shock throughout the process. During the reinstatement test, four presentations of the US alone were given before the following presentations of 15 nonreinforced CS+ and 15 CS-. All CSs were presented for 4 s, with an intertrial interval of 8–12 s, and the US was presented for 200 ms. There was a fixation point on the computer screen during the intertrial interval. After threat conditioning, five participants were excluded from the study because their difference in SCR values between the CS+ and CS- was less than 0.05.

Social support intervention and assessment

The social support intervention was designed to involve interacting with friends for 10 min on a positive topic. Participants in the support group were asked to invite close friends with whom they were comfortable interacting to visit the laboratory. Before the interaction, participants and the friends were instructed with the following guiding words: *"You have 10 min to share with each other about a supporting moment that impressed you the most and/or the happiest moment that you experienced. No matter which topic you talk about and no matter whether the topic is related to both of you, just make sure to discuss as many details of the event as possible and include a complete storyline."* This instruction was designed to ensure that the participants felt autonomous during the interaction and devoted themselves to the conversation as much as possible. Participants were asked to rate their perceived social support on a Likert scale ranging from 0 to 10 both before and after interaction (0 = not feeling supported at all; 10 = feeling supported all the time). The social support intervention took place in a laboratory standard room with monitoring system; experimenters were able to follow the whole procedure in another room via monitoring screen to handle any emergency, such as participants' overreaction during interaction. There was a debriefing session about this arrangement at the end of whole experiment.

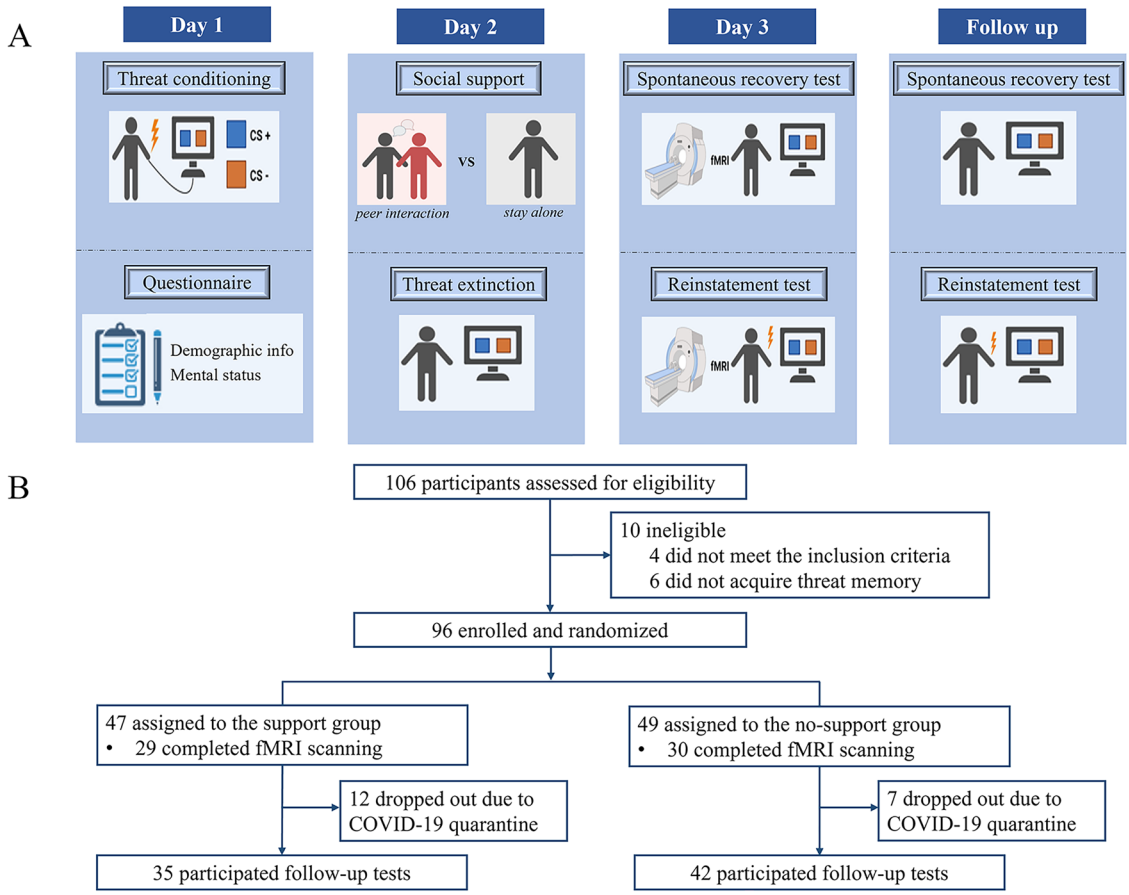

Fig. 1 Experimental workflow and participant enrollment. A Procedure and timeline of the experiments. **B** Diagram of the number of participants. 106 Participants were trained in threat conditioning on day 1 and 96 participants acquired threat memory successfully. Social support intervention and extinction training were assigned 24 h later (day 2). 24 h after extinction training, participants were tested for short-term treat extinction retention (day 3). In which, 59 participants volunteered to be tested within fMRI and were analyzed for fMRI results. 77 participants accepted the invitation to return to the laboratory 2 weeks later for long-term threat extinction retention test. No missing/lost data were encountered.

Experimental design

We first investigated the short-term effects of social support on threat memory extinction and threat return. Ninety-six participants were randomly allocated into two groups using random numbers (social support group, $n = 47$; no-support group, $n = 49$). An a priori power calculation with G*Power [34] indicated that a sample size of 96 is sufficient to detect a medium-sized effect with a power of 0.95. On Day 1, participants in both groups underwent a threat acquisition procedure by themselves and provided basic demographic information (sex, age, and education) as well as basic mental health status (depression, anxiety, sleep condition, and perceived social support). On Day 2, participants in the social support group underwent a 10 min friend interaction procedure before threat extinction, whereas participants in the no-support group waited for 10 min by themselves without using electronic devices. All participants underwent the experimental procedures in an official laboratory room with identical settings. The friend interaction in the support group was completed orally—that is, no physical touch was encouraged. Afterward, all participants experienced threat extinction alone. Spontaneous recovery and reinstatement tests were performed 24 h after extinction training. No missing or lost data were encountered in this part of the study.

We also investigated the long-lasting effect of friend interaction on threat memory extinction and return of the threat memory. Seventy-seven participants agreed to return to the laboratory two weeks after the initial tests (social support group, $n = 35$; no-support group, $n = 42$) and underwent spontaneous recovery and reinstatement tests. Except for the participants who were not able to return for the follow-up tests, no missing or lost data were encountered.

We further investigated the neuroimaging markers of social support in threat memory extinction and return prevention. Fifty-nine participants (social support group, $n = 29$; no-support group, $n = 30$) accepted the invitation to complete the spontaneous recovery test and reinstatement test within the fMRI scanner for simultaneous brain recording. The two tests lasted for 7.33 min and 8.87 min within the scanner, respectively. Figure 1 shows the general procedure and timeline of the experiments. No missing or lost data were encountered in this part of the study.

Psychophysiological stimulation and assessment

A constant-current STM200 stimulator (BIOPAC Systems, Goleta, CA, USA) was used to deliver electric shocks. A stimulating electrode was attached to the inner wrist of the participant's non-dominant arm. E-Prime software (Psychology Software Tools, Sharpsburg, PA, USA) was used for stimulus presentation. The SCR, the reflection of threat response, was recorded using two electrodes (BIOPAC TSD203 electrodes) attached to the second and third fingers of the participant's left hand using a BIOPAC MP160 system and AcqKnowledge software (BIOPAC Systems). The greatest trough-to-peak change in the SCR in an 8-s time window was recorded after an interval of 2-s post each CS onset [35]. These SCR values were then square-root transformed to normalize the distribution.

MRI data acquisition and preprocessing

MRI data were acquired using a 3.0 Tesla MR scanner (General Electric, MR750). Structural scans were acquired using a T1 MPRAGE sequence with the following acquisition parameters: matrix size, 256×256; 192 contiguous axial slices; slice thickness, 1 mm; voxel resolution, $1 \times 1 \times 1$ mm^3; flip angle, 12°; echo time, min full; and repetition time, 6.7 ms. The fMRI scans were obtained using a gradient-recalled echo-planar imaging sequence with a repetition time of 2000 ms, echo time of 30 ms, and flip angle of 90°. The slice thickness was 4.5 mm (no gap) with a matrix size of 64×64 and a field of view of 224×224mm^2, resulting in a voxel size of $3.5 \times 3.5 \times 4.5$ mm^3.

Image preprocessing was performed using the Data Processing & Analysis of Brain Imaging (DAPBI) toolbox. The DAPBI toolbox provides the Friston 24-parameter motion correction, which includes regression with autoregressive models of motion incorporating 6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items. Additionally, it performs voxel-specific head motion calculation and correction at the individual level. Beyond head motion correction, we also regressed out several other nuisance variables, including white matter (WM) and cerebrospinal fluid (CSF) signals. The first five volumes of each set of fMRI data were used for signal equilibrium and adaptation to the scanning state. The remaining 250 volumes in the spontaneous recovery test and 261 volumes in the reinstatement test were then processed including slice timing, realignment, and head motion correction. Individuals with translation or rotation parameters more than 3.0 mm or 3.0°were excluded. T1-weighted images were then co-registered to the functional MRI data, segmented into gray matter, WM, and CSF, and spatially normalized to the Montreal Neurological Institute space with a voxel size of 3 × 3 × 3 mm. Functional images were spatially smoothed using a 6 × 6 × 6 mm Gaussian kernel to decrease spatial noise.

Statistical analysis

Quantitative data including demographic data, perceived social support, and shock intensity were presented as the mean ± standard error of the mean (SEM) and analyzed using SPSS 20.0 software (SPSS, Chicago, IL, USA). Independent-sample t-tests were used to analyze differences in demographic data; SDS, SAS, PSQI, and PSSS scores; perceived social support level; and shock intensity between social support and no-support groups. The χ^2 test was used to analyze differences in sex frequencies between the two groups. Mean differential SCRs (CS+ minus CS- in corresponding trials) were calculated for all threat conditioning and test procedures. For threat acquisition, the SCRs of the 12 reinforced CS+ were excluded from the calculation to avoid the direct effect of the electric shock. The remaining 24 trials (12 CS+, 12 CS-) were divided into four blocks, with 3 CS+ and 3 CS- in each block. As for threat extinction, SCRs of 30 trials (15 CS+, 15 CS-) were divided into five blocks, with 3 CS+ and 3 CS- in each block. The first trial of the first block was excluded from the analysis as it may have been susceptible to trial sequence effects. Similar to threat extinction, the CSs in the spontaneous recovery and reinstatement tests were divided into five blocks and the first CS trial in both tests was not included in the analysis. Repeated-measures analysis of variance (ANOVA) was used to analyze threat response throughout threat acquisition, extinction, and tests, with group as the between-subjects factor and blocks (the comparison of blocks 1 and 5 of threat acquisition, the comparison of blocks 1 and 4 of threat extinction, the comparison of blocks 1 and 4 of the spontaneous recovery test, and the comparison of block 4 of the spontaneous recovery test and block 1 of the reinstatement test, respectively) as the within-subjects factor. Significant effects in the ANOVAs were further tested using *post hoc* t-tests.

For task-fMRI data analysis, SPM8 software (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/sp) was used. A general linear model (GLM) was applied to identify blood oxygen level dependence (BOLD) activation in relation to the CS+ and CS-. The first-level GLM design matrix included two task-related regressors. Six head-movement regressors derived from the realignment stage (head movement parameters) were included as covariates of no interest. The CS+ > CS- contrast computation was performed at the single-subject level. These were then entered into a second-level (random-effects) analysis by calculating one-sample t-tests on individual contrast images for contrasting results. We then compared the support group with the no-support group in the CS+ versus CS- conditions. Clusters were considered significant if they reached $p < 0.05$ at the cluster level and $p < 0.005$ at the voxel level (GRF corrected). We extracted brain areas that were significantly different between the social support and no-support groups in the spontaneous recovery and reinstatement tests as seed regions; and then performed connectivity analyses of and correlation analyses between the BOLD activity of these seed regions and a set of quantitative measures including perceived social support level and threat expressions. Multiple corrections were applied based on the number of brain regions included in the analyses using Bonferroni correction.

RESULTS

Social support facilitated threat extinction retention in the short term

There were no significant differences in sex; age; education; SDS, SAS, PSQI, and PSSS scores; or shock intensity between the support and no-support groups (all $p > 0.05$, Table 1). Both groups achieved successful and comparable threat acquisition, which was indicated by a significant main effect of the threat conditioning block ($F_{(1,94)} = 104.631$, $p < 0.001$) but no main effect of group ($F_{(1,94)} = 0.004$, $p = 0.947$) or block × group interaction ($F_{(1,\ 94)} = 0.404$, $p = 0.527$; Fig. 2A). The perceived social support level significantly increased in the support group following friend interaction compared with the no-support group ($F_{(1,94)} = 36.945$, $p < 0.001$; Fig. 2B).

Table 1. Demographic data and shock intensity.

	Support ($n = 47$)	No-support ($n = 49$)	t/χ^2	p
Age (years)	23.40 ± 0.43	23.35 ± 0.50	0.09	0.93
Sex (female%)	34/47	32/49	0.55	0.51
Education (years)	17.13 ± 0.32	16.88 ± 0.34	0.54	0.59
SDS	39.41 ± 1.03	37.09 ± 1.10	1.53	0.13
SAS	35.43 ± 1.02	33.90 ± 0.84	1.15	0.25
PSQI	4.06 ± 0.30	3.82 ± 0.31	0.57	0.57
PSSS	69.15 ± 1.29	70.90 ± 1.43	−0.91	0.37
Shock intensity (V)	47.07 ± 1.55	48.60 ± 1.51	−0.24	0.81

SDS self-rating depression scale, *SAS* self-rating anxiety scale, *PSQI* pittsburgh sleep quality index, *PSSS* perceived social support scale. Unless otherwise indicated, results are expressed as mean ± standard error of the mean.

On Day 2, both groups achieved successful threat extinction at the end of the extinction training, which was indicated by a significant main effect of the threat extinction block ($F_{(1,94)} = 39.633$, $p < 0.001$). However, the extinction trend was different in the two groups, as mainly manifested in the first block of extinction training—the support group showed a lower threat expression than the no-support group, suggesting that friend interaction may have a briefly inhibiting effect on threat expression (0.06 for support group and 0.15 for the no-support group; group main effect $F_{(1,94)} = 12.585$, $p = 0.001$; Fig. 2C).

A comparison of the two groups in the spontaneous recovery test showed a marginally significant main effect of group ($F_{(1,93)} = 3.241$, $p = 0.075$; Fig. 2D), suggesting a more obvious return of the threat memory in the no-support group following threat extinction. A comparison of threat responses between the social support group and no-support group in the reinstatement test showed a significant main effect of block ($F_{(1,93)} = 24.131$, $p < 0.001$), group ($F_{(1,93)} = 19.495$, $p < 0.001$), and block × group interaction ($F_{(1,93)} = 7.120$, $p < 0.01$; Fig. 2E), which means the threat memory was reinstated only in the no-support group. Correlation analysis on social support and threat responses showed there was a negative association between the change of perceived support level and threat responses in the reinstatement test ($r = -0.307$, $p < 0.01$), suggesting the significant relationship between return of threat memory and low support level (Supplementary Fig. 1).

Social support facilitated threat extinction retention in the long term

A comparison of the two groups in the follow-up spontaneous recovery test showed a significant main effect of the group with a higher threat expression in the no-support group ($F_{(1,75)} = 6.358$, $p = 0.014$; Fig. 3A), suggesting that the threat memory spontaneously recovered in individuals with no social support intervention before extinction training. A comparison of threat responses between the social support group and no-support group in the follow-up reinstatement test showed that there was also a

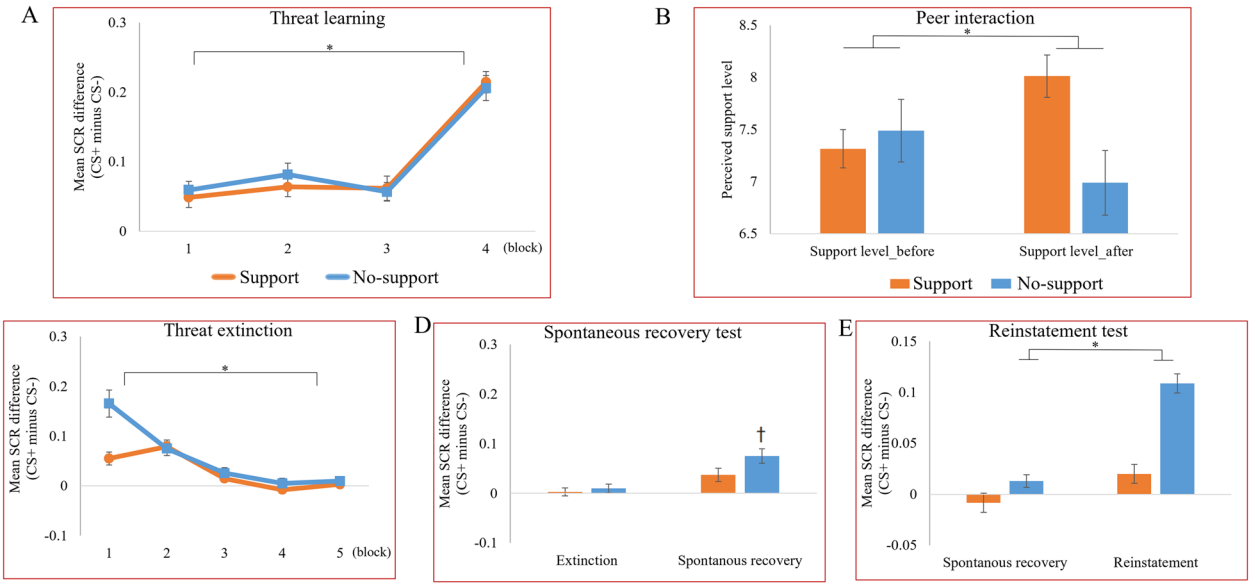

Fig. 2 Social support facilitated threat memory extinction and prevented the return of threat responses. A Mean differential SCR (CS+ minus CS–) during threat conditioning. **B** Perceived social support before and after interaction/staying alone. **C** Mean differential SCR during threat extinction. **D** Mean differential SCR during spontaneous recovery test. **E** Mean differential SCR during reinstatement test. Data are expressed as mean ± standard error of the mean (n = 47 to 49 per group). *p < 0.05, comparison between the last 3 trials of threat learning and the first 3 trials of the threat learning, the last 3 trials of threat extinction and the first 3 trials of threat extinction, the last 3 trials of threat extinction and the first 3 trials of the spontaneous recovery test, and between the last 3 trials of the spontaneous recovery test and the first 3 trials of the reinstatement test (all within-group); †p < 0.05, comparison of mean differential SCR between support group and no-support group. CS+ conditioned stimulus with electric shock, CS– conditioned stimulus without electric shock.

significant main effect of group ($F_{(1,75)} = 10.783$, $p = 0.002$; Fig. 3B), which means that the threat memory was reinstated only in the no-support group. The combination of these two results showed that social support facilitated threat extinction retention in the long term.

Neural substrates during spontaneous recovery test and reinstatement test

In the spontaneous recovery test within fMRI scanning, compared with no-support group, there was a deactivation in the bilateral thalamus, bilateral hippocampus, right precuneus, left superior frontal lobe, right calcarine, and left inferior parietal lobe in the support group when processing CS+ pictures than when processing CS- (GRF corrected, significant level was set at $p < 0.05$ at cluster level and $p < 0.005$ at voxel level; Fig. 4A and Table 2). We further analyzed the functional connectivity between key brain areas that were significantly different between the social support group and no-support group, showing that there were significant increases in the frontal-hippocampus, and significant decreases in the frontal-calcarine, hippocampus-precuneus, and precuneus-thalamus ($p < 0.0001$, $= 0.0004$, 0.0004, 0.0005, respectively, Bonferroni corrected; Fig. 4B).

In the reinstatement test within fMRI scanning, compared with the no-support group, participants in the support group had significantly lower activation levels of the right inferior frontal lobe (opercular part), left middle frontal gyrus, left thalamus, left inferior occipital gyrus, right superior frontal gyrus (dorsolateral part), right thalamus, left inferior parietal lobe, and right precuneus when processing CS+ than when processing CS- (GRF corrected, significant level was set at $p < 0.05$ at cluster level and $p < 0.005$ at voxel level; Fig. 4C and Table 3). Significant decreases in functional connectivity between the thalamus and cortical areas were detected in the support group, including in the thalamus-inferior frontal lobe, thalamus-precuneus, and thalamus-inferior occipital lobe ($p = 9.80E-05$, 4.03E-06, 0.0006, respectively, Bonferroni corrected). However, functional connectivity among the cortical areas increased in the support group, including in the inferior frontal lobe-inferior occipital lobe, and inferior occipital lobe-precuneus (both $p < 0.0001$, Bonferroni corrected; Fig. 4D). Correlation analysis suggested that threat responses were positively correlated with thalamus-precuneus connectivity (support group: $r = 0.102$, $p = 0.300$; no-support group: $r = 0.472$, $p = 0.010$), which were inhibited in the support group (Fig. 4E). In addition, brain activations and deactivations of the support group and no-support group during these two tests were also listed respectively (Supplementary tables 1-4).

DISCUSSION

In this study, we tested the effects of social support on threat extinction and its return prevention in humans. Our results demonstrated the facilitating effect of social support on the extinction retention of threat memories. In addition, the thalamo-cortical circuit was shown to regulate this process by inhibiting memory-related brain regions. The current findings can provide more understanding of applying social support in the exposure-based interventions for threat- and trauma-related disorders, such as PTSD, to help the process more emotionally tolerable and to promote the reduction of treat responses.

Social factors or social elements are essential in exploring threat memories, including threat learning and extinction. For example, social threat learning, known as learning the value of stimuli and actions from others, can help animals and humans realize deadly threats around them and avoid the risk; social transmission of safety, such as extinction learning that previously threatening stimuli are safe, is also ubiquitous across species [36, 37]. Inspired by this theoretical model, we believed that social support could play a vital role across threat conditioning. Moreover, the selection of conspecifics who provide the social support is also important. Animal studies which explored the phenomenon of social support usually use conspecifics from the same cage to prevent aggressive behaviors among unfamiliar subjects [11, 38]. In addition, decades of human studies have consistently found that support provided by friends can significantly and effectively improve an individual's

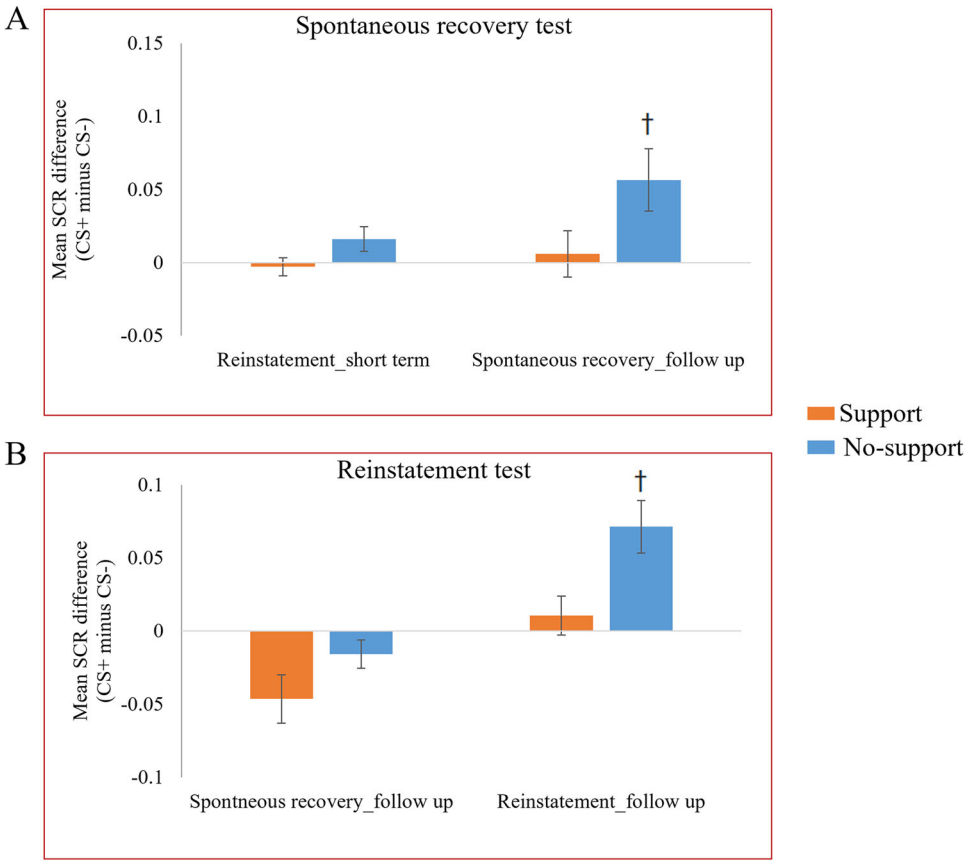

Fig. 3 Social support facilitated threat extinction retention in long term. A Mean differential SCR during spontaneous recovery test in 2 weeks. **B** Mean differential SCR during reinstatement test in 2 weeks. Data are expressed as mean ± standard error of the mean (n = 35 to 42 per group). *p < 0.05, comparison between the last 3 trials of day 3 reinstatement test and the first 3 trials of follow-up spontaneous recovery test, and between the last 3 trials of follow-up spontaneous recovery test and the first 3 trials of follow-up reinstatement test (all within-group); †p < 0.05, comparison of mean differential SCR between support group and no-support group. CS+ conditioned stimulus with electric shock, CS− conditioned stimulus without electric shock.

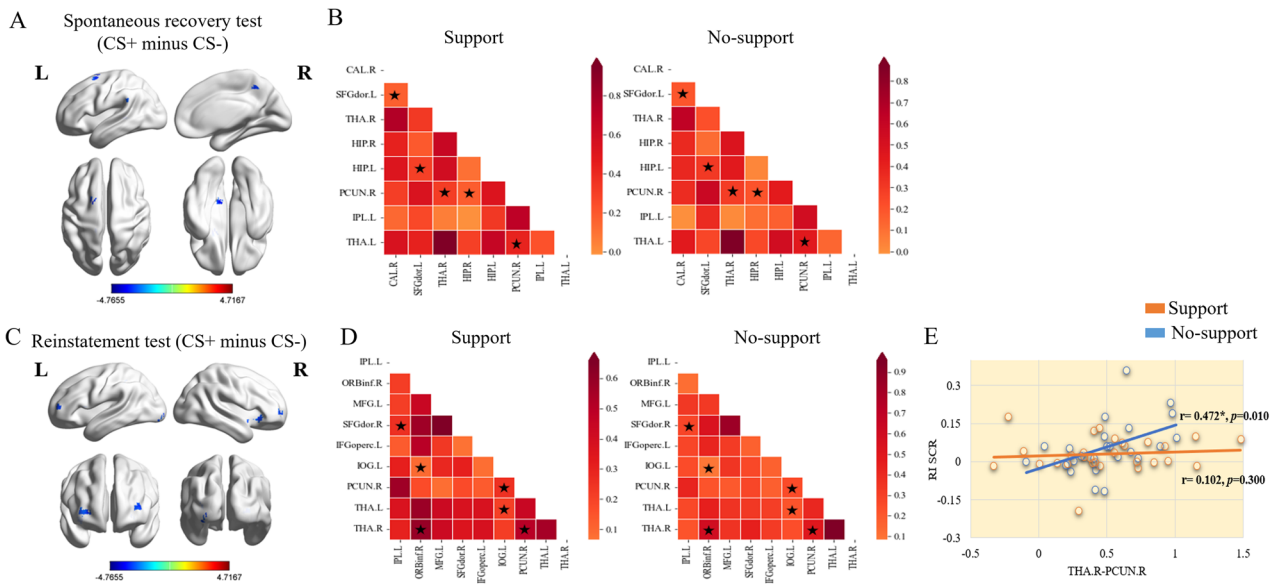

Fig. 4 Neuroimaging results of threat expression tests, *GRF corrected, $P_{(cluster)} < 0.05$, $P_{(voxel)} < 0.005$.* A Brain activations in spontaneous recovery test (CS+ > CS-). **B** Functional connectivity in spontaneous recovery test. **C** Brain activations in reinstatement test (CS+ > CS-). **D** Functional connectivity in reinstatement test. **E** Correlation between right precuneus-right thalamus and threat expression in reinstatement test. ⋆Reaching significance level after Bonferroni corrections. *Significant level was set at p < 0.05.

Table 2. Activation and deactivation of brain regions during spontaneous recovery test.

	Brain Regions	MNI	T	Voxel number		
		X	*Y*	*Z*		
Spontaneous recovery test						
Support > No-support	THA.R	24	−33	6	−4.1369	47
	HIP.R	36	−27	−12	−3.5966	33
	THA.L	−18	−27	15	−3.7197	25
	HIP.L	−12	−36	3	−3.8576	24
	PCUN.R	9	−48	48	−3.2443	17
	SFGdor.L	−18	3	66	−3.9395	17
	CAL.R	30	−54	9	−3.3898	15
	IPL.L	−63	−40	30	−3.2829	10

The negative value of T represents reduced activation of the brain regions when processing CS+ vs. CS-. *THA.R* right thalamus, *HIP.R* right hippocampus, *THA.L* left thalamus, *HIP.L* left hippocampus, *PCUN.R* right precuneus, *SFGdor.L* left superior frontal lobe, *CAL.R* right calcarine, *IPL.L* left inferior parietal lobe. GRF corrected, significant level was set at $p < 0.05$ at cluster level and $p < 0.005$ at voxel level.

Table 3. Activation and deactivation of brain regions during reinstatement test.

	Brain Regions	MNI	T	Voxel number		
		X	*Y*	*Z*		
Reinstatement test						
Support > No-support	ORBinf.R	36	36	−9	−3.463	48
	MFG.L	−33	60	9	−3.386	42
	THA.L	−3	−21	3	−3.7557	36
	IOG.L	−27	−90	−3	−3.5281	34
	SFGdor.R	24	54	0	−3.7542	34
	THA.R	21	−24	12	−3.1064	13
	IPL.L	−6	−42	48	−3.0646	13
	PCUN.R	18	−51	18	−3.4001	12
	IFGoperc.L	−39	12	9	−3.2071	10

The negative value of T represents reduced activation of the brain regions when processing CS+ vs. CS-. *ORBinf.R* right inferior frontal gyrus, orbital part, *MFG.L* left middle frontal gyrus, *THA.L* left thalamus, *IOG.L* left inferior occipital gyrus, *SFGdor.R* right superior frontal gyrus, dorsolateral part, *THA.R* right thalamus, *IPL.L* left inferior parietal lobe, *PCUN.R* right precuneus, *IFGoperc.L* left inferior frontal lobe, opercular part. GRF corrected, significant level was set at $p < 0.05$ at cluster level and $p < 0.005$ at voxel level.

perceived social support level. Friend support can increase an individual's sense of esteem, belonging, confidence, and hope within a community, which may even have physiological benefits, such as alleviating cardiovascular reactivity [39, 40]. Therefore, in the current study, we recruited a pair of close friends as the social support group, to increase participants' level of perceived support as much as possible.

The facilitating role of social support on the retention of threat extinction and the suppression of threat expressions demonstrated in the current study may be explained by the buffering effect of social support [41, 42], which believes that social support can help individuals avoid terrible consequences in adverse environments through buffering their stress levels. In the current study, the whole procedure of threat conditioning can be stressful for individuals. Compared to those in the no-support group, friend support can serve as a buffering component for participants under such stressful situation to relieve their stress and alleviate their threat responses. A previous study exploring the relationship between the level of social support and the psychological response of individuals encountering injury also indicated this buffering effect. It was found that social support can significantly alleviate the injured athletes' feelings of restlessness, loneliness, and betrayal after injury, which confirmed the buffering effect of social support on pressure [43]. Similarly, an investigation on the relationship between social support and stress of older adults with a family member incarcerated suggested that higher levels of social support buffered against stress for older adults [44]. As for the underlying mechanisms of the buffering effect of social support, it was demonstrated that the social buffering regulation might be accompanied by increased oxytocin release in the paraventricular nucleus of the hypothalamus [45]. In addition, social support could regulate activation of the hypothalamic–pituitary–adrenocortical system which is regarded as a primary stress-responsive neuroendocrine system [46].

Neuroimaging analysis in the current study revealed that the activities of the bilateral thalamus, bilateral hippocampus, several areas of the frontal lobes, inferior occipital lobe, and inferior parietal lobe were inhibited in the social support group when processing CS+ compared with CS-. In addition, we also found that thalamo-cortical functional connectivity, including the thalamus-inferior frontal lobe, thalamus-precuneus, and thalamus-inferior occipital lobe, decreased in the social support group; and the decreased thalamus-precuneus connectivity was significantly related to the level of threat expression. Previous studies demonstrated the importance of the interactions among frontal lobes such as the medial prefrontal cortex (mPFC), hippocampus, and thalamus in regulating emotional memories, in which, thalamus was significant in sustaining bidirectional interactions

between mPFC and hippocampus [47, 48]. Besides, thalamo-cortical circuits were indicated to play a critical role in threat regulation [48–50]. Similarly to the current study, Padilla-Coreano et al. [51] inhibited the activity of the dorsal part of the midline thalamus (dMT), a thalamic region that projects prominently to mPFC, and found a significant participation of dMT in threat memory regulation. Besides, it was revealed that the activation of the paraventricular nucleus (PVT) in the thalamus would exacerbate the retrieval of threat memories [52]. In addition, Tao et al. [53] found that silencing PVT neurons and disrupting infralimbic cortex-PVT projections could suppress extinction retrieval. Whereas, the investigation on thalamo-cortical circuits and perceived social support is not as sufficient as threat regulation. Indirect association between the neural circuits and social support can be obtained from previous literatures. For instance, Yamamuro et al. [54] found that 2-weeks social isolation of juvenile male mice had reduced sociability in their adulthood, which was regulated by mPFC-PVT circuits.

The innovations of the current study lie in the following aspects. First, as people experience various life events in a social network, social support is a social resource that almost everyone needs and can be easily accessed. Compared to drugs, physical therapy, and other advanced technologies, the provision of social support is inexpensive, has no side effects, and is noninvasive. Hence, the application of social support for threat extinction can be highly cost-effective. Second, this study identified the neural networks and circuits that played a role in the process of social support promoting threat memory extinction and inhibiting return of threat memories. The discovery of thalamo-cortical circuit may promote our understanding of the underlying neural basis of threat regulation. Third, considering that a number of studies on family/ partner enhanced treatments for patients with threat- or trauma-related disorders have come out in recent years, findings of the current study may also provide further inspiration for the clinical application of social support for exposure-based interventions.

LIMITATIONS

There were a few limitations of the present study. First, we didn't assess participants' subjective emotional valence or arousal throughout conditioning phases, and hence we were not able to detect a clearer relationship between friend support and lower threat expression in the first block of extinction learning in the support group, such as whether there was a mediating role of emotional stress level. Second, the interaction between participants and the friends was not monitored in order to avoid any intentional and/or involuntary interaction brought by the experiment in their daily lives. Although we asked the participants whether there was any unexpected experience regarding social interaction in their lives, it was performed orally and not in detail. It would be better to collect more detailed information towards participants' social interactions throughout the experimental procedure to eliminate potential confounding factors related to social support. Third, we did not limit the types of friends or for how long they became friends because we did not aim at investigating a certain type of friend support in the current study. However, more information can be collected for further/ secondary analysis in the future. Fourth, although we explored the neural basis of the alleviating effect of social support on threat extinction retention, we did not identify a specific mechanism of social support except for the discussion on social buffering model. For example, it is also possible that social support took an effect because it provided subjects with a positive mood or it distracted subjects' attention. In the future, more comparisons would be established for deeper exploration. Finally, there was no fMRI scanning during baseline, threat acquisition, and extinction training. Even though participants were randomly allocated to two groups using random numbers and no baseline difference was found between groups regarding demographic data and shock intensity, a baseline fMRI evaluation would be preferred to control for any unexpectedness. Collection of fMRI data during acquisition and extinction would also be more helpful for understanding differences of brain activation during threat memory tests.

CONCLUSION

In conclusion, social support facilitates threat extinction retention by preventing spontaneous recovery and reinstatement of threat memories. The thalamo-cortical circuit, including brain regions of the thalamus, several frontal areas, and the inferior occipital and parietal lobes, plays a significant role in regulating the facilitating effect of social support on threat extinction retention. The findings highlight the potential of social support, as a highly cost-effective strategy, for regulate threat memories. This study can provide an inspiration for exposure-based interventions treating trauma- and threat-related disorders.

DATA AVAILABILITY

The dataset analyzed in the present study as well as scripting and plotting code are available from the corresponding authors via email on reasonable request.

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AUTHOR CONTRIBUTIONS

YG, SS, and PL designed the experiment and interpreted the results. YG wrote the initial draft of the manuscript. YG, SS, PL, YZheng, YZhang, and WL contributed to recruit participants and data collection. YG, SS, PL, and ZY conducted the statistical analysis. XLiu, XLin, SZ, KY, and JD commented on and revised the manuscript. LL and LS commented on the study, revised the manuscript, and wrote the final version. All of the authors contributed to the final draft of the manuscript.

COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study involving human participants was reviewed and approved by the ethics committee of Peking University Sixth Hospital and carried out in accordance with the principles of the Declaration of Helsinki and following institutional guidelines and regulations. All participants provided written informed consent before the respondents began the research. The registration number is 2020122208535526.

ADDITIONAL INFORMATION

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