



## Research article

# Social support favors extinction and impairs acquisition of both short- and long-term contextual fear conditioning memory

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## ABSTRACT

Fear memory has an essential role on animal's survival once it induces defensive behavior in response to threats. Among other factors, social support is known to down-regulate the expression of fear conditioned response, representing an important modulator of fear memories. Here we studied the effects of social support during acquisition, retrieval and extinction of contextual fear conditioning (CFC) memory in rats, by exposing the animals to the CFC task either in the absence or in the presence of a conspecific during the training, extinction and/or test sessions. The presence of a conspecific during the training session of CFC resulted in impairment to memory retention as verified in the short- and long-term memory test, suggesting that social support exerts a suppressive effect on the acquisition of CFC. On retrieval, social support decreased the expression of the conditioned fear response - as also seen in the extinction session. Nevertheless, the animals were able to learn the extinction memory as verified in the retention test. Therefore, this study demonstrates the effects of social support at crucial moments in CFC: impairing memory acquisition and favoring its extinction, by reducing the expression of the conditioned fear response with no impairment to the extinction learning.

## 1. Introduction

The ability of an animal to adapt its behavior accordingly to learned information about unusual circumstances of the context is one of the main keys to the survival of species [1]. Fear memories are essential for this process, since they provide appropriate responses to threatening situations; however, when their expression is recurrent and indiscriminate, the animals can be lead to serious psychopathological conditions such as anxiety, phobias [2] or posttraumatic stress disorder [2–4]. Therefore, inhibiting the acquisition of these memories or restricting their retrieval to appropriate situations represents an efficient approach to this condition [5,6].

Pavlovian fear conditioning is the behavioral model most widely used to study fear memories in rodents [4,7,8]. In contextual fear conditioning (CFC) the animals learn to associate a conditioned stimulus (CS; such as a context) and an unconditioned stimulus (US; such as mild electric footshocks). This generates a conditioned fear response (CR; freezing) which persists even when the CS is presented alone

[9–11].

Previous studies have shown that fear responses can be modulated by the presence of conspecifics and by social memory [12–15], a phenomenon called “social support” [16]. This involves the animal's behavior in the presence of a conspecific [17] and the endogenous consequences of social interaction, such as the suppression of cortisol release in response to a novel environment for instance [18]. In CFC, the CR has a reduced expression when there is a pair-exposure to a stressor stimulus [19,20] and the familiarity between animals influences on social transmission of the fear [20–22].

Many studies have shown that social support down-regulates the fear conditioned response during the retrieval of the memory under different protocols [23–27], however, little is known about its influence during the acquisition and extinction of the memory. Here we studied the influence of social support on the acquisition of short- and long-term CFC memory, as well as its effects during the retrieval and extinction of the CFC memory.

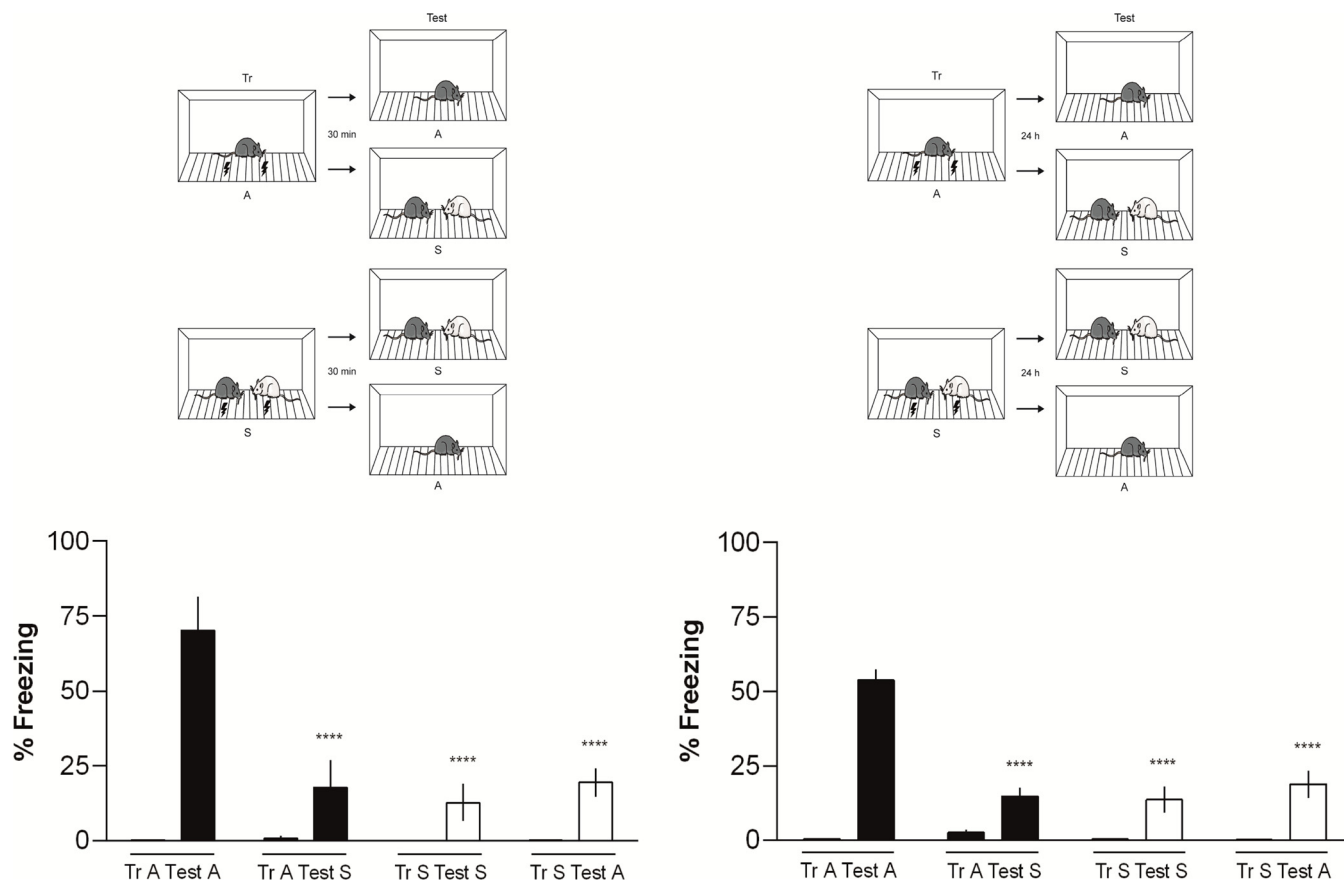
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**Fig. 1.** Effect of social support on the acquisition of short- and long-term memory of contextual fear conditioning. Animals were trained in CFC either Alone (Tr A) or with social support (Tr S). After 30 min (A; TrA/TestA n = 7, TrA/TestS n = 5, TrS/TestS n = 7, TrS/TestA n = 9) or 24 h (B; TrA/TestA n = 15, TrA/TestS n = 12, TrS/TestS n = 10, TrS/TestA n = 12) they were subjected to a 3-min retention test alone (Test A) or with social support (Test S). The figure shows the percentage of time spent freezing in the first 2 min of the Tr and in the retention test. Data are expressed as mean ± SEM. Three-way ANOVA followed by Bonferroni's post hoc test; \*\*\*\*p < 0.0001 vs. TrA/TestA. (Upper) Schematic illustration of experimental design.

## 2. Experimental procedures

### 2.1. Subjects

Male CrlCembe: Wistar rats (3 months-old, 300–330 g), purchased from the Centro de Modelos Biologicos Experimentais (CeMBE) of Pontifical Catholic University of Rio Grande do Sul (PUCRS) were used. The animals were housed 4 to a cage with free access to food and water, under 12/12 h light/dark cycle (light onset at 7:00 a.m.). All behavioral procedures were conducted in the light cycle. The temperature of the animals' room was maintained at 22–23 °C. Animals were handled once a day for 7 consecutive days and then subjected to a contextual fear conditioning.

All procedures were approved by the Animal Committee on Ethics for the Care and Use of Laboratory Animals of PUCRS and followed the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

### 2.2. Contextual fear conditioning apparatus

The apparatus was a chamber (Albarsch®, Porto Alegre, Brazil) with black Plexiglas walls (50 × 25 × 58 cm) and a transparent plastic front lid. The floor of the chamber consisted of 0.3 cm caliber bronze bars spaced 0.8 cm apart. The bars were connected to an electric device to delivery the foot shocks. The box was cleaned with a solution of 70% ethanol wipes and dried with paper towels after its use by each animal. The percentage of time that the animals spent freezing (no visible movement except for respiration) [7] in the apparatus was measured by

Startfear System Packwin (Panlab®).

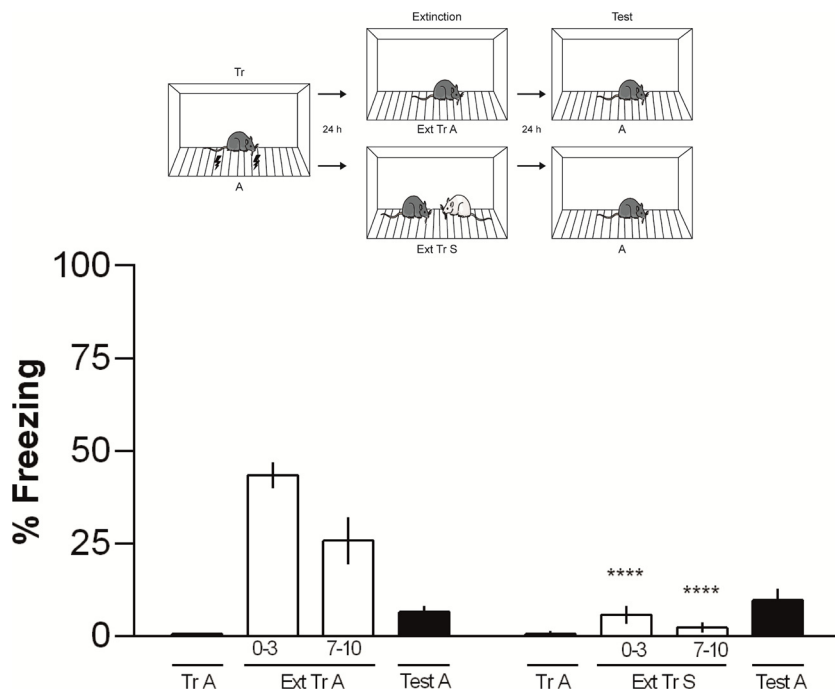
### 2.3. Behavioral procedures

#### 2.3.1. Acquisition of contextual fear conditioning memory

On the training session (Tr) animals were allowed to freely explore the apparatus Alone (A) or in the presence of a familiar conspecific (Social Support, S) for 2 min and then received three 0.5 mA (2 s duration) foot shocks with a 30-s interval between them. After 30 min (for short-term memory; STM) or after 24 h (for long-term memory; LTM) animals were placed again in the conditioning chamber either A or with S for a 3-min retention test (Test) session, with the absence of foot shocks. This yields for both STM and LTM a total of 4 groups: TrA/TestA, TrA/TestS, TrS/TestS and TrS/TestA. In order to avoid aggressive behavior all animals that were trained or tested in pairs were from the same cage [28,29]. The animals used as social support in the Test were never trained or exposed to CFC before [25,30,31].

#### 2.3.2. Extinction of contextual fear conditioning memory

On the Tr animals were allowed to freely explore the apparatus Alone for 2 min and then received three 0.5 mA (2 s duration) foot shocks with a 30-s interval between them. After 24 h animals were placed in the same conditioning chamber for a 10-min extinction training session either Alone (Ext Tr A) or with social support (Ext Tr S), with no foot shocks. Twenty-four hours later, animals were placed again in the same apparatus for a 3-min extinction retention test Alone (Test A), also with no foot shocks. This yields a total of 2 groups: TrA/ExtTrA/TestA and TrA/ExtTrS/TestA. All animals in the social support



**Fig. 2.** Effect of social support on the extinction of contextual fear conditioning memory. Animals were submitted to training session alone (Tr A) and 24 h later they were submitted to a 10-min extinction training alone (Ext Tr A;  $n = 11$ ) or with social support (Ext Tr S;  $n = 10$ ) and 24 h later the animals were submitted to a 3-min retention test alone (Test A). The figure shows the percentage of time spent freezing in the first 2 min of the Tr, in the first 3 min (0–3 min) and last 3 min (7–10 min) of the Ext Tr and in the retention test. Data are expressed as mean  $\pm$  SEM. Two-way ANOVA followed by Bonferroni Test; \*\*\*\* $p < 0.0001$  Ext Tr A 0–3 vs. Ext Tr S 0–3; \*\*\*\* $p < 0.0001$  Ext Tr A 7–10 vs. Ext Tr S 7–10. (Upper) Schematic illustration of experimental design.

group underwent Ext Tr S in the presence of a naïve unconditioned partner [25,30,31].

#### 2.4. Statistics

Data are presented as mean  $\pm$  standard error of the mean and were analyzed statistically by two-way or three-way ANOVA followed by Bonferroni Test and unpaired *t*-test using GraphPad Prism® software. Freezing behavior data in the short- and long-term memory were statistically analyzed using a three-way ANOVA with Tr vs. Test as a repeated factor while Acquisition vs. Retrieval and Alone vs. Social as between-subjects factor. Freezing behavior data in the Ext Tr were statistically analyzed using a two-way ANOVA with Ext Tr (0–3 min vs. 7–10 min) as the within-subjects factor and Alone vs. Social as the between-subjects factor. Comparisons of the freezing behavior during Tr and Test between TrA/ExtTrA/TestA and TrA/ExtTrS/TestA groups were conducted via Unpaired *t*-test.  $P < 0.05$  was considered statistically significant.

### 3. Results

#### 3.1. Effect of social support on acquisition and retrieval of short- and long-term memory of contextual fear conditioning

In order to verify whether the presence of a conspecific could affect the short-term memory (STM) or long-term memory (LTM) during CFC, animals were submitted to training session alone (Tr A) or in the presence of a familiar conspecific (Social Support; Tr S) and 30 min (STM; TrA/TestA  $n = 7$ , TrA/TestS  $n = 5$ , TrS/TestS  $n = 7$ , TrS/TestA  $n = 9$ ; Fig. 1A) or 24 h later (LTM; TrA/TestA  $n = 15$ , TrA/TestS  $n = 12$ , TrS/TestS  $n = 10$ , TrS/TestA  $n = 12$ ; Fig. 1B) were subjected to a 3-min retention test A or with S. In the STM (Fig. 1A) and LTM (Fig. 1B), animals whose Tr and/or Test occurred with S expressed less freezing behavior than animals submitted to Tr and Test A. The freezing behavior from each session were analyzed by a three-way ANOVA 2 (Tr vs. Test) \* 2 (Acquisition vs. Retrieval) \* 2 (Alone vs. Social).

Fig. 1A shows that freezing behavior during sessions revealed a significant main effect of Tr vs. Test ( $F_{(1,48)} = 55.25$ ,  $p < 0.0001$ ), Acquisition vs. Retrieval ( $F_{(1,48)} = 7.924$ ,  $p = 0.0071$ ) and Alone vs.

Social ( $F_{(1,48)} = 12.63$ ,  $p = 0.0009$ ). There was a significant Tr vs. Test and Acquisition vs. Retrieval interaction ( $F_{(1,48)} = 8.470$ ,  $p = 0.0055$ ), Tr vs. Test and Alone vs. Social interaction ( $F_{(1,48)} = 11.84$ ,  $p = 0.0012$ ), Acquisition vs. Retrieval and Alone vs. Social interaction ( $F_{(1,48)} = 13.48$ ,  $p = 0.0006$ ) and also Tr vs. Test and Acquisition vs. Retrieval and Alone vs. Social interaction ( $F_{(1,48)} = 13.88$ ,  $p = 0.0005$ ). Bonferroni *post hoc* revealed significant differences between groups during retention test: TrA/TestA vs. TrA/TestS ( $p < 0.0001$ ), TrA/TestA vs. TrS/TestS ( $p < 0.0001$ ) and TrA/TestA vs. TrS/TestA ( $p < 0.0001$ ).

In LTM (Fig. 1B) freezing behavior during sessions revealed a significant main effect of Tr vs. Test ( $F_{(1,90)} = 154.4$ ,  $p < 0.0001$ ), Acquisition vs. Retrieval ( $F_{(1,90)} = 16.73$ ,  $p < 0.0001$ ) and Alone vs. Social ( $F_{(1,90)} = 24.56$ ,  $p < 0.0001$ ). There was a significant Tr vs. Test and Acquisition vs. Retrieval interaction ( $F_{(1,90)} = 20.87$ ,  $p < 0.0001$ ), Tr vs. Test and Alone vs. Social interaction ( $F_{(1,90)} = 18.43$ ,  $p < 0.0001$ ), Acquisition vs. Retrieval and Alone vs. Social interaction ( $F_{(1,90)} = 28.63$ ,  $p < 0.0001$ ) and also Tr vs. Test and Acquisition vs. Retrieval and Alone vs. Social interaction ( $F_{(1,90)} = 35.15$ ,  $p < 0.0001$ ). Bonferroni *post hoc* revealed significant differences between groups during retention test: TrA/TestA vs. TrA/TestS ( $p < 0.0001$ ), TrA/TestA vs. TrS/TestS ( $p < 0.0001$ ) and TrA/TestA vs. TrS/TestA ( $p < 0.0001$ ).

This result suggests that the presence of a familiar non-fearful conspecific impairs the CFC acquisition and also hinders the expression of the conditioned response during both short- and long-term memory of CFC.

#### 3.2. Effect of social support on the extinction of contextual fear conditioning memory

In order to find out whether the social support could affect the extinction of CFC, animals were submitted to training session alone (Tr A) and 24 h later were submitted to a 10-min extinction training session alone (Ext Tr A;  $n = 11$ ) or with social support (Ext Tr S;  $n = 10$ ) and after another 24 h animals were subjected to a 3-min retention test alone (Test A). As shown in Fig. 2, there is no difference in freezing behavior between TrA/ExtTrA/TestA and TrA/ExtTrS/TestA groups during the Tr session (Unpaired *t*-test:  $t_{(19)} = 0.1785$ ,  $p = 0.8602$ ).

However, during the extinction session the group TrA/ExtTrS/TestA expressed less freezing behavior than the group TrA/ExtTrA/TestA. Two-way ANOVA showed a significant main effect of Ext Tr ( $F_{(1,38)} = 6.856$ ;  $p = 0.0126$ ) and Alone vs. Social ( $F_{(1,38)} = 57.72$ ;  $p < 0.0001$ ), while there was no significant interaction between Ext Tr and Alone vs. Social ( $F_{(1,38)} = 3.106$ ;  $p = 0.0861$ ).

Bonferroni's post hoc revealed significant differences in the first 3 min (0–3 min) of Ext Tr between TrA/ExtTrA/TestA vs. TrA/ExtTrS/TestA ( $p < 0.0001$ ) groups, in the last 3 min (7–10) of Ext Tr between TrA/ExtTrA/TestA vs. TrA/ExtTrS/TestA groups ( $p = 0.0012$ ) and also in the first 3 min vs. the last 3 min of Ext Tr between TrA/ExtTrA/TestA vs. TrA/ExtTrS/TestA ( $p < 0.0001$ ) groups. However, during the retention test there was no differences between groups (Unpaired  $t$ -test:  $t_{(19)} = 0.9242$ ,  $p = 0.3670$ ).

These results suggest that even in the absence of retrieval animals were able to learn the extinction of CFC.

#### 4. Discussion

Emotional states of animals are highly influenced by their conspecifics [32–34]. Social learning has been demonstrated in numerous studies involving imitational [35] and observational learning [34,36] in social transmission of fear. Rats transfer emotional information about imminent danger through vocal [37], visual [38,39], and odor or pheromone cues [40], thereby influencing defensive responses. Social support was suggested by Tolsdorf [16] like any collective action or behavior that functions to assist the individual in meeting his goals or dealing with demands of any particular situation, including in the form of emotional support.

For the social support, we use animals from the same cage, because it is known that the interaction with a familiar conspecifics is more effective to inhibit the fear conditioned response than an unfamiliar one [21,23,39]. Furthermore, previous studies have shown that the presence of a calm companion provided a greater attenuation of the stress responses than companions that had been through the same traumatic event [20,25,30,31,35], hence the animals used as support in the experiments were not trained in the CFC task.

Our findings begin with the learning of contextual fear conditioning (CFC) memory, demonstrating that social support causes an impairment in the acquisition, since the animals trained in pairs have a lower CFC response compared to those trained alone, both in short- and long-term memory. A few studies already investigated alternative interventions implemented shortly after the occurrence of the trauma, considered the secondary prevention of posttraumatic stress disorder, which aim to avoid the development of the disorder in individuals who have already been exposed to the traumatic event and reduce occasional harms resulting from the experience [41–44]. Considering the detrimental nature of traumatic memories, the social support can be an interesting secondary preventive approach, seeing its suppressing influence over the acquisition of CFC memory.

When it comes to an already consolidated memory, social support acts in the moment of retrieval by inhibiting the conditioned response, once rats trained alone but exposed to the retrieval test session with a conspecific presented a reduced freezing behavior when compared to those exposed alone to both sessions. The same was observed in the extinction of the CFC memory, when animals that went through the extinction session in pairs also presented lower levels of freezing compared to animals that went alone, corroborating with previous similar studies [19,27]. Interestingly, even when this conditioned response was reduced, the animals were able to learn the extinction memory. That is, when extinction occurs in pairs, it still provides an effective inhibition of the original fear association exempting the aversive symptoms related to retrieval. This result is in agreement with previous study that demonstrates that the expression of the CFC response is not imperative for the learning of extinction [45].

Despite many studies describing social transmission of fear between

familiar conspecifics [13,21,32] and a recent study by our group demonstrating that social support generates a form of learning that differs from extinction acquired without support in terms of the brain structures involved [46] it is important to raise the possibility that the change in the context might in part account for the behaviors observed. Still, even if added to the change in the context, we believe that the main key for social support influence is the decreased stress responses induced by the social interaction, in agreement with other results demonstrating that the social presence actually facilitates the extinction of fear memories [19,23,27,31,36].

#### 5. Conclusion

These results may state an important perspective over the approaches used on trauma disorders, seeing it allows the retrieval of these memories – which is ideal for therapeutic purposes, considering extinction emphasizes the reduction of avoidance through exposure [47] – but curbs the stress and anxiety manifestations associated with them.

Furthermore, because studies addressing the effects of social support on the acquisition of CFC memory are scarce, our findings may help to shed a light on several interesting issues, such as possible physiological regulation mechanisms of this system, intervention approaches and the conformation of this process in other species. Therefore, further studies are required to fully explore the possibilities related to social support on fear memories.

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