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Research report

Emotional learning enhances stimulus-specific top-down modulation of sensorimotor gating in socially reared rats but not isolation-reared rats

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ABSTRACT

Prepulse inhibition (PPI), the suppression of the startle reflex by a preceding sensory stimulus (prepulse), can be top-down modulated in both humans and rats. This study investigated whether emotional-learning-induced enhancement of PPI in rats is prepulse specific. The results show that in socially reared rats, PPI elicited by a narrowband-noise prepulse on the broadband-noise background (masker) was enhanced after the prepulse became fear conditioned. This fear-conditioning-modulated PPI was further enhanced by introducing a perceived spatial separation between the conditioned prepulse and the broadband-noise masker. However, these PPI enhancements disappeared if the conditioned prepulse was replaced by a different narrowband-noise prepulse that was not fear conditioned. In isolation-reared rats, who had both enhanced baseline startle and reduced PPI before conditioning, neither fear conditioning of the prepulse nor perceived spatial separation between the conditioned prepulse and noise masker could enhance PPI. Thus, the emotional-learning-induced enhancement of PPI in socially reared rats is prepulse specific, indicating that auditory processing interacts with mnemonic signaling in the formation of top-down modulation of PPI. Since the deficiency of attentional modulation of PPI in schizophrenic patients is correlated with the symptom severity, the deficiency of top-down modulations of PPI in isolation-reared rats is useful for modeling schizophrenia.

1. Introduction

Learning is important for both humans and animals to acquire the ability and knowledge to discriminate biologically meaningful sensory stimuli from irrelevant stimuli. For example, associative learning builds association between a sensory cue (the conditioned stimulus, CS) and a biologically significant event (the unconditioned stimulus, US), leading to both selective attention to the occurrence of the CS and enhanced sensitivity to the sensory cue [57]. According to the "protection-of-processing" theory, receiving a sensory stimulus can trigger not only the information processing for the stimulus signal but also a gating mechanism that dampens the information of disruptive inputs [28]. To further our understanding about functions of learning, it is important to know whether sensory gating is also modulated by learning.

Prepulse inhibition (PPI) is the reduction of the amplitude of the startle reflex in response to an intense startling stimulus (pulse) when this intense stimulus is shortly preceded by a weaker, non-startling sensory stimulus (prepulse) ([11,63], for reviews, see [37,40,51,54]). Since the consequences of PPI include the reduction of behavioral responses to disruptive stimuli by regulating the motor system and/or the pre-motor system, PPI has been generally recognized as a simple operational measure of sensorimotor gating (e.g., [73]). The magnitude of PPI has also been widely used as a measure of the salience of the prepulse stimulus in rodents (e.g., [2,12,38,41,48,77,85,86]).

Although the pathway mediating PPI resides in the brainstem, PPI can be modulated by higher-order central processing (for a recent review see [54]). For example, in humans, greater PPI is produced by an attended prepulse than an ignored prepulse (e.g., [16,22,23,32,33,69,75]) and PPI is more pronounced when the prepulse is emotionally salient than neutral stimulus (e.g., [5,6]). Interestingly, even anticipation of electrical shock can increase general vigilance, enhance processing of the prepulse stimulus, and augment PPI [30]. While in rats, following the prepulse becomes fear conditioned [20,38,56,86] or fear-extinction conditioned [68], PPI is markedly enhanced, indicating that emotional learning (fear conditioning) indeed top-down modulates sensory gating. Furthermore, one of our recent studies [20] has confirmed that the emotional-learning-induced modulation of PPI is due to a formation of selective attention to the conditioned prepulse (see below).

In a noisy, reverberant environment, listeners receive not only sound waves that directly emanate from various sources but also reflections from surfaces at various locations. When the time interval between the direct wave coming from the source and a reflected

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wave of the source is sufficiently short, attributes of the delayed reflection are perceptually captured by the direct wave [53], leading to a single fused image whose point of origin is perceived to be around the location of the leading source. This phenomenon is called the "precedence effect" [4,51,58,82]. In humans, the precedence-effect-induced perceived spatial separation between target speech and masking stimuli (e.g., irrelevant speech or broadband noise) facilitates selective attention to the signal stream and improves recognition of target speech (e.g., [25,39,52,65,84]). For example, when both the target (e.g., speech) and the masker are presented by a loudspeaker to the listener's left and another loudspeaker to the listener's right, the perceived location of the target and that of the masker can be manipulated by changing the inter-loudspeaker interval for the target and that for the masker [52,84]. More specifically, for both the target and masker, when the sound onset of the right loudspeaker leads that of the left loudspeaker by a short time (e.g., 3 ms), both a single target image and a single masker image are perceived by the human listener as coming from the right loudspeaker. However, if the onset delay between the two loudspeakers is reversed only for the masker, the target is still perceived as coming from the right loudspeaker but the masker is perceived as coming from the left loudspeaker. The perceived co-location and perceived separation are based on perceptual integration of correlated sound waves delivered from the two loudspeakers. It has been confirmed that perceived target-masker spatial separation facilitates the listener's selective attention to target signals and significantly improves recognition of target signals, even though neither the masker energy at each ear nor the stimulus-image compactness/diffusiveness is substantially changed [25,52].

One of our recent studies [20] has shown that in rats, precedence-effect-induced spatial separation between the sound image of the fear-conditioned prepulse and the sound image of the noise masker facilitates selective attention to the location of the image of the conditioned prepulse, causing an additional enhancement of PPI.

However, it is still not clear whether the emotional-learning-induced attentional enhancement of PPI results from either a general elevation of rats' vigilance to surroundings (see [30]) or a prepulse-specific enhancement of selective attention only to the conditioned prepulse. In the present study, we further improved the paradigm for studying attentional modulation of PPI in rats with a within-subject design using intermixed fear-conditioned prepulse stimulus (narrowband-noise burst with a particular center frequency) and other prepulse stimuli (narrowband-noise bursts with different center frequencies) without being conditioned. The prediction is that if the emotional-learning-induced top-down modulation of PPI is prepulse specific, the attentional enhancements of PPI occur only when the prepulse is the one that has been fear conditioned, otherwise, the attentional enhancements of PPI occur for any types of prepulse stimuli, including ones without being conditioned.

Moreover, the present study also used this new PPI paradigm in isolation-reared rats, which are valuable in establishing animal developmental models for studying schizophrenia (for reviews, see [54,83]). PPI deficits occur in schizophrenics and schizotypal personality-disordered subjects (e.g., [7,8,17,45,74]) and rats with either early maternal separation or social isolation (e.g., [13,20,56,78]). Particularly, attentional modulation of PPI is impaired in schizophrenic patients (e.g., [16,17,31,32,33,59]), and PPI modulation induced by either emotional learning or perceived spatial separation between prepulse and masker is deficient in isolation-reared rats [20,56]. This study was also to investigate whether impairments of emotional-learning-induced prepulse-specific modulations of PPI occur in isolation-reared rats.

2. Materials and methods

2.1. Subjects

Thirty-six male Sprague–Dawley rats (Vital-River Experimental Animals Technology Ltd., Beijing, China) at the age of weaning (21 days old) were randomly assigned into the socially reared group (18 rats) and isolation-reared group (18 rats). The 18 rats in each of the main groups were further divided randomly into two subgroups with 9 rats in each: the high-frequency-conditioning subgroup (the high-frequency narrowband noise was the conditioned prepulse) and the low-frequency-conditioning subgroup (the low-frequency narrowband noise was the conditioned prepulse).

For isolation-reared rats, each individual was housed in a single transparent plastic cage (48 cm × 30 cm × 18 cm). For socially reared rats, three individuals were housed in a cage with the same dimensions. All the rats were kept in the same room for eight weeks before testing, under a temperature of 24 ± 2 °C and a 12-h light/dark cycle with food and water freely available.

2.2. Stimuli and apparatus

The rat's whole-body startle reflex, which was induced by a 10-ms broadband-noise burst (0–10 kHz, 100 dB SPL) delivered by a loudspeaker above the rat's head, was measured by a custom-made electrical scale (the National Key Laboratory on Machine Perception, Peking University) in a soundproof chamber. The prepulse stimulus was delivered by each of the two additional loudspeakers which were placed horizontally in the frontal field with a 100° separation angle and 52 cm away from the rat's head position (Fig. 1A).

The 50-ms-long narrow-band (1.14/3 octaves) noises with the center frequency of 1 kHz (the low-frequency, ranged from 870 to 1130 Hz), 3 kHz (the middle-frequency, ranged from 2610 to 3390 Hz), or 5 kHz (the high-frequency, ranged from 4350 to 5650 Hz) were used as the prepulse stimuli. They were digitally generated by Matlab software and converted by a custom-developed sound-delivery system (the National Key Laboratory on Machine Perception, Peking University) with the 16-kHz sampling rate and 16-bit resolution. Sound levels were calibrated using a B&K sound level meter (Type 2230) whose microphone was placed at the central location of the rat's head when the rat was absent, using a "Fast"/"Peak" meter response. The single-source sound level of the prepulse for each of the two horizontal loudspeakers was fixed at 60 dB SPL.

2.3. Procedures

After 8-week social rearing or isolation rearing, each rat went through an 8-day testing procedure (see Fig. 2). For the first three successive days, the rat was placed into the restraining cage in which the rat was held during the measurement of the startle reflex [38,86] and exposed to a broadband noise (56 dB SPL), which was continuously presented by each of the two horizontal loudspeakers for 30 min each day. During the restraining period, neither the prepulse nor the startling noise was presented. This procedure was to adapt the rat to the cage and testing chamber.

On the fourth day, pre-manipulation PPI was measured. The rat was placed in the cage for 5 min, receiving ten presentations of startling stimulus without prepulse presentation on the broadband-noise background whose intensity was 56 dB SPL. The interval between startling stimuli varied between 25 and 35 s (mean = 30 s). Then six testing sessions were conducted in a random order.

In each of the six testing sessions, two of the following three narrow-band noises were selected as the two prepulse stimuli: low-frequency (1 kHz), middle-frequency (3 kHz), and high-frequency (5 kHz) narrowband noises. Thus, each of the three types of two-prepulse combinations (low-frequency/high-frequency, low-frequency/middle-frequency, middle-frequency/high-frequency) was used in two testing sessions and the two types of prepulse stimuli were presented within a single testing session in a random order.

The same prepulse was presented from each of the two horizontal loudspeakers with the prepulse-onset delay between the two loudspeakers being either +1 ms (left leading) or −1 ms (right leading) in one testing session. Due to the precedence effect, a single fused prepulse image would be perceived as coming from the left loudspeaker in some trials and from the right loudspeaker in other trials. The 1-ms inter-sound delay was within the range for producing perceptual fusion in behaving rats [36,44]. In addition to the prepulse, the broadband noise (0–10 kHz, 56 dB SPL) was continuously delivered from each of the two horizontal loudspeakers throughout the whole testing session as the masker. For the two testing sessions for a typical type of prepulse combination, the masker-onset delay between the two loudspeakers was +1 ms (left leading) in one testing session and −1 ms (right leading) in the other testing session, leading to a single fused noise image as being perceived at the left loudspeaker in one testing session (Fig. 1B and C) and at the right loudspeaker in the other testing session, due to the precedence effect. Thus two types of perceived spatial relationships between the prepulse image and the masker image were induced in a single testing session: perceived spatial separation and perceived co-location (Fig. 1).

In a testing trial, the startling noise burst was presented by the top loudspeaker 50 ms after the offset of the prepulse, making the inter-stimulus onset interval 100 ms (50 + 50 ms). Then a new trial started about 30 s (varying from 25 to 35 s)

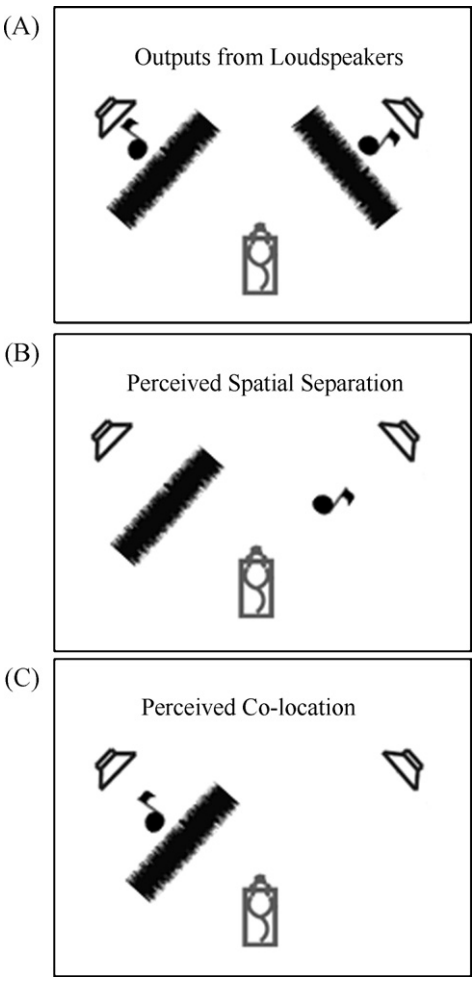

Fig. 1. Diagrams showing the physical (panel A) and perceived (panels B and C) spatial relationship between the prepulse (represented by the music note) and the broadband-noise masker (represented by the noise waveform). (Panel A) Both the prepulse and the masker were delivered by each of the two horizontal loudspeakers. The startling stimulus (a 10-ms broadband-noise burst, 100 dB) was delivered by a third loudspeaker above the rat's head. (Panel B) When the onset of the prepulse delivered from the left loudspeaker lagged behind that from the right loudspeaker by 1 ms and the onset of the masker delivered from the left loudspeaker led that from the right loudspeaker by 1 ms, the image of the prepulse was on the right and the image of the masker was on the left, causing a perceived spatial separation between the prepulse and masker. (Panel C) When the onset of the prepulse delivered from the left loudspeaker led that from the right loudspeaker by 1 ms and the onset of the masker delivered from the left loudspeaker led that from the right loudspeaker by 1 ms, both the image of the prepulse and the image of the masker were on the left, causing a perceived co-location between the prepulse and masker.

after the offset of the prepulse. In each testing session, 20 trials were assigned to the condition of perceived spatial separation (10 trials for one type of prepulse and 10 trials for the other type of prepulse), 20 trials were assigned to the condition of perceived co-location (10 trials for one type of prepulse and 10 trials for the other type of prepulse), and 10 trials were assigned to the no-prepulse (startling stimulus only) condition.

On the fifth day, all the four subgroups of rats underwent both the manipulation of fear conditioning and the manipulation of conditioning control (so called combined conditioning/conditioning-control manipulations). The CS was the prepulse delivered by each of the two horizontal loudspeakers with balanced left–right leading. Based on previous studies [38,72,80,86], the US was 6-mA rectangular-pulse (duration = 3 ms) footshock using Grass S-88 stimulator (Grass, Quincy, MA, USA). The short duration of footshock applied in this and our previous studies [20,38,56,86] removed any potential effects of escaping movement, which might occur if the duration of footshock was long (e.g., 500 ms).

For each of the two high-frequency-conditioning subgroups (social rearing, isolation rearing), 10 temporally synchronized (paired) combination of the high-frequency CS (5-kHz narrow-band noise) and the US were presented every 30 s in the fear-conditioning session (US started 3 ms before CS ending, and co-terminated with CS), and 10 temporally random (unpaired) combination of the low-frequency CS (1-kHz narrow-band noise) and the US were presented every 30 s in the conditioning-control session (Fig. 3). For the two low-frequency-conditioning subgroups, 10 paired combination of the low-frequency CS (1-kHz narrow-band noise) and the US were presented every 30 s in the fear-conditioning session (US also started 3 ms before CS ending, and co-terminated with CS), and 10 unpaired combination of the high-frequency CS (5-kHz narrow-band noise) and the US were presented every 30 s in the conditioning-control session.

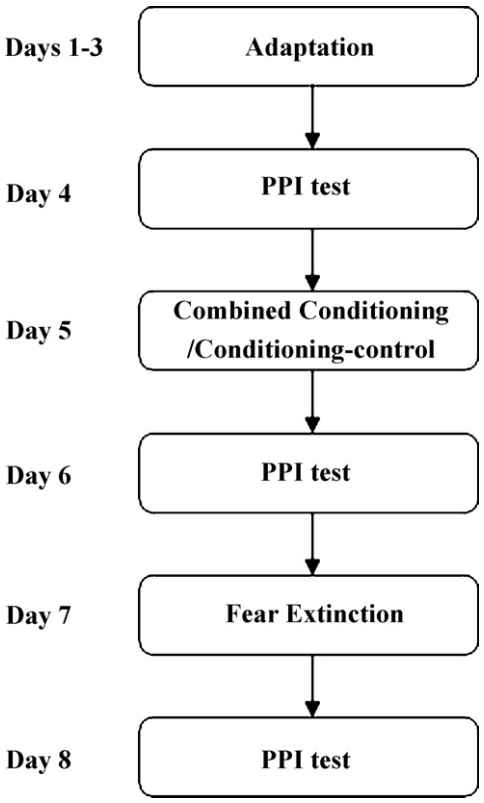

Fig. 2. Illustration showing the 8-day testing procedure.

On the sixth day (24 h after the manipulations of fear conditioning and conditioning control), PPI was measured using the same six-session procedures as used on the fourth day.

On the seventh day, all subgroups underwent the manipulation of auditory fear extinction. Without pairing the US, the CS (5-kHz narrow-band noise for the high-frequency conditioning subgroups and 1-kHz narrow-band noise for the low-frequency conditioning subgroups) was presented 60 times and the CS control (1-kHz narrow-band noise for the high-frequency conditioning subgroups and 5-kHz narrow-band noise for the low-frequency conditioning subgroups) was presented 20 times with the inter-stimulus interval of 30 s. For each rat, the total 80 prepulse presentations (60 for CS and 20 for CS control) were evenly divided into 4 extinction sessions with the inter-session interval of 10 min.

On the eighth day (24 h after the extinction manipulation), PPI was measured using the same six-session procedures as used on the fourth and sixth days.

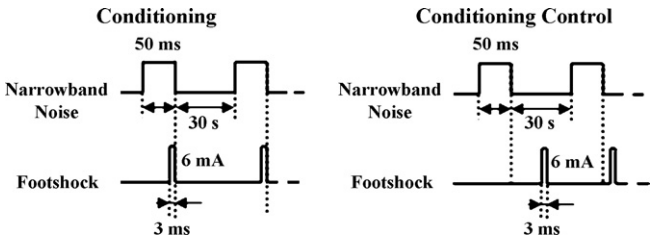

Fig. 3. Illustrations showing the fear-conditioning manipulation (paired presentations of the narrowband noise and footshock) and the conditioning-control manipulation (unpaired presentations of the narrowband noise and footshock).

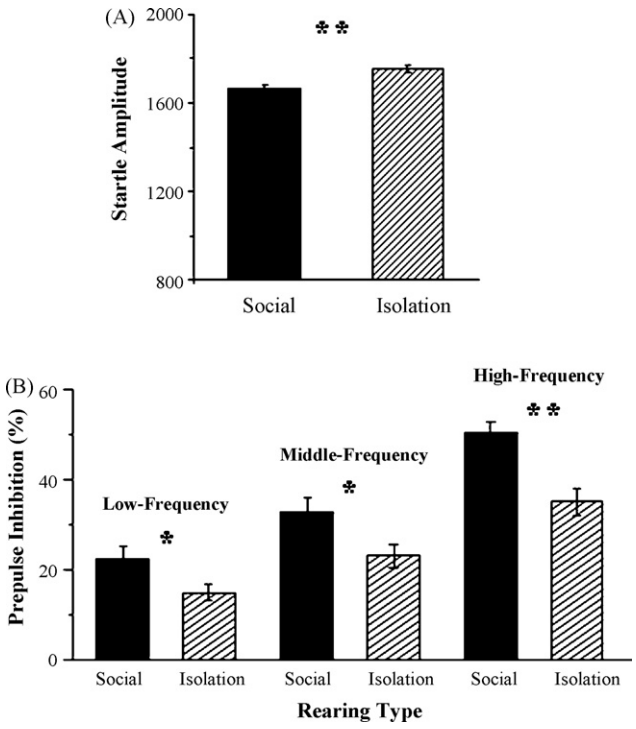

Fig. 4. (Panel A) The group-mean magnitude of the baseline startle reflex (when the prepulse was not presented) for socially reared rats and isolation-reared rats before the conditioning/conditioning-control manipulations. (Panel B) The group-mean magnitude of prepulse inhibition (PPI) for each of the three prepulses (low-frequency, middle-frequency, and high-frequency narrowband noises) for socially reared rats and isolation-reared rats before the manipulations. Error bars represent the standard errors of the mean. $^{*}P<0.05$, $^{**}P<0.01$ by one-way ANOVA.

2.4. Data analyses

The amount of PPI was calculated with the following generally used formula:

$$\text{PPI}(\%) = \frac{\text{amplitude to startling sound alone} - \text{amplitude to startling sound preceded by prepulse}}{\text{amplitude to startling sound alone}} \times 100\%$$

Analyses of variance (ANOVAs) were performed and followed by Bonferroni post hoc tests by using SPSS 13.0 software (for details see Section 3). The null-hypothesis rejection level was set at 0.05.

3. Results

3.1. Effects of social isolation on startle reflex and PPI before manipulations

Panel A in Fig. 4 shows the group-mean amplitude of the startle reflex for all the socially reared rats and that for all the isolation-reared rats before manipulations. An one-way ANOVA confirms that before the combined conditioning/conditioning-control manipulations, the startle amplitude was significantly larger in isolation-reared rats than in socially reared rats [$F(1,106)=9.403$, $P<0.01$].

Panel B in Fig. 4 shows the group-mean PPI associated with each of the three types of prepulses for all the socially reared rats and all the isolation-reared rats before the manipulations. As one-way ANOVAs confirm that, for each of the prepulse types, isolation-reared rats had significantly lower group-mean PPI magnitudes than socially reared rats before the combined conditioning/conditioning-control manipulations [low-frequency prepulse: $F(1, 34)=5.113$, $P<0.05$; high-frequency prepulse: $F(1, 34)=14.150$, $P=0.001$; middle-frequency prepulse: $F(1,34)=5.548$, $P<0.05$]. These results are consistent with previous reports that isolation rearing both enhances the baseline startle reflex and reduces PPI in rats.

3.2. Modulation of the startle reflex

Fig. 5 shows the amplitudes of startle responses to the startling stimulus alone typically for each of the four subgroups before and after the combined conditioning/conditioning-control manipulations and after the conditioning-extinction manipulation. Generally, the baseline startle was enhanced by the combined conditioning/conditioning-control manipulations, and then reduced by the conditioning-extinction manipulation.

Separate 3 (testing-session type (i.e., prepulse-combination type): low/high, low/middle, middle/high) × 3 (testing time: before conditioning/conditioning-control, after conditioning/conditioning-control, after extinction) within-subject repeated-measures ANOVAs for the four subgroups show similar results: the interaction between testing-session type and testing time was not significant ($P>0.05$ for all), the main effect of testing-session type was not significant ($P>0.05$ for all), but the main effect of testing time was significant [for low-frequency-conditioning socially reared subgroup: $F(2, 16)=7.971$, $P<0.01$; for high-frequency-conditioning socially reared subgroup: $F(2, 16)=7.897$, $P<0.01$; for low-frequency-conditioning isolation-reared subgroup: $F(2, 16)=5.227$, $P<0.05$; for high-frequency-conditioning isolation-reared subgroup: $F(2, 16)=4.896$, $P<0.05$]. Thus, the startle responses to the startling stimulus alone were significantly affected by the manipulations but not the testing-session type (the type of prepulse combination in a testing session).

3.3. Modulation of PPI in socially reared rats

Fig. 6 shows the values of PPI induced by each of the three types of prepulse stimuli in the two socially reared subgroups with either low-frequency-noise conditioning (left panels) or high-frequency-noise conditioning (right panels), when the prepulse and masker were either perceptually co-located (filled bars) or perceptually separated (diagonal bars). For each of the two subgroups under each of the three testing stages, because the PPI values for each prepulse type under the two different prepulse-combination conditions were similar, they were averaged across the two prepulse-combination conditions. As shown in Fig. 6, only PPI elicited by the conditioned prepulse exhibited both the post-conditioning enhancement and the perceived-separation enhancement following the combined conditioning/conditioning-control manipulations. Also, these two types of PPI enhancements disappeared following the extinction manipulation.

For the low-frequency-conditioning subgroup, a 3 (testing time: before conditioning/conditioning-control, after conditioning/conditioning-control, after extinction) × 2 (perceptual location: co-location, separation) repeated-measures ANOVA for low-frequency-prepulse-elicited PPI (Fig. 6, left top panel) indicates that the interaction between testing time and perceptual location was significant [$F(2, 34)=19.334$, $P<0.001$]. Further one-way ANOVAs and pairwise comparisons show that both PPI elicited by the low-frequency prepulse perceptually co-located with the masker and PPI elicited by the low-frequency prepulse perceptually separated from the masker were significantly enhanced following the combined conditioning/conditioning-control manipulations ($P<0.001$ for all) and decreased to the pre-conditioning level after the extinction manipulation ($P<0.001$ for all). Moreover, low-frequency-prepulse-elicited PPI under the condition of perceived separation (with the masker) was significantly larger than that under the condition of perceived co-location only when

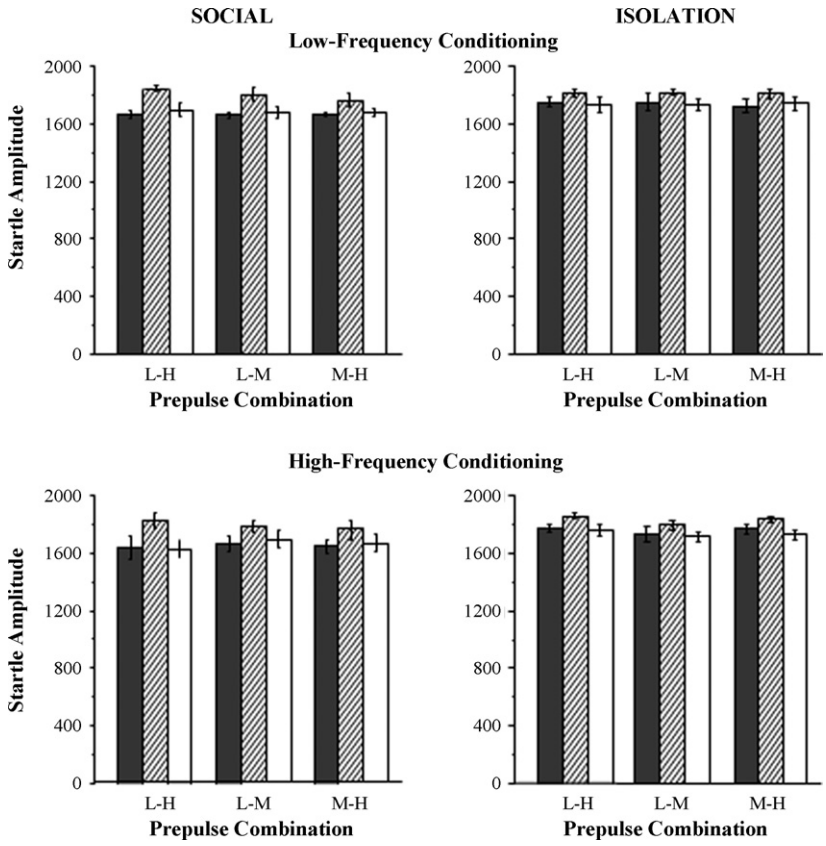

Fig. 5. Amplitudes of startle responses to the startling stimulus alone in each of the four subgroups before the combined conditioning/conditioning-control manipulations (black bars), after the combined conditioning/conditioning-control manipulations (diagonal bars), and after conditioning extinction (white bars) in each of the three types of testing sessions with different prepulse combinations. L–H: the testing sessions containing both low-frequency and high-frequency narrowband-noise prepulses; L–M: the testing sessions containing both low-frequency and middle-frequency narrowband-noise prepulses; M–H: the testing sessions containing both middle-frequency and high-frequency narrowband-noise prepulses. Error bars represent the standard errors of the mean.

the low-frequency prepulse was fear conditioned ($P < 0.001$). On the other hand, separate 3 (testing time) × 2 (perceptual location) repeated-measures ANOVAs for high-frequency-prepulse-elicited PPI (Fig. 6, left middle panel) and middle-frequency-prepulse-elicited PPI (Fig. 6, left bottom panel) show that the interactions between testing time and perceptual location, the main effects of testing time, and the main effects of perceptual location were not significant ($P > 0.05$ for all).

For the high-frequency-conditioning subgroup, a 3 (testing time) × 2 (perceptual location) repeated-measures ANOVA for high-frequency-prepulse-elicited PPI (Fig. 6, right middle panel) indicates that the interaction between testing time and perceptual location was significant [$F(2, 34) = 18.549$, $P < .001$]. Further one-way ANOVAs and pairwise comparisons show that both PPI elicited by the high-frequency prepulse perceptually co-located with the masker and PPI elicited by the high-frequency prepulse perceptually separated from the masker were significantly enhanced after the combined conditioning/conditioning-control manipulations ($P < 0.001$ for all) and decreased to the pre-conditioning level after the extinction manipulation ($P < 0.001$ for all). Moreover, high-frequency-prepulse-elicited PPI under the condition of perceived separation (with the masker) was significantly larger than that under the condition of perceived co-location only when the high-frequency prepulse was fear conditioned ($P < 0.001$). On the other hand, separate 3 (testing time) × 2 (perceptual location) repeated-measures ANOVAs for low-frequency-prepulse-elicited PPI (Fig. 6, right top panel) and middle-frequency-prepulse-induced PPI (Fig. 6, right bottom panel) show that the interactions between testing time and perceptual location, the main effects of testing time, and the main effects of perceptual location were not significant ($P > 0.05$ for all).

Thus, for socially reared rats, the fear-conditioning manipulation, but not the conditioning-control manipulation, selectively strengthened PPI elicited by the conditioned narrowband-noise prepulse with a particular center frequency without influencing PPI elicited by another narrowband-noise prepulse with a different center frequency, which was not conditioned. In other words, PPI enhancement by auditory fear conditioning is sound-feature specific (center-frequency dependent in this study). Moreover, the effect of perceived spatial separation between prepulse and masker images (perceptual spatial unmasking) on PPI was not significant until the prepulse became biologically "relevant" (fear conditioned). Finally, the emotional-learning-induced enhancements of PPI were abolished by the extinction manipulation.

3.4. Modulation of PPI in isolation-reared rats

Fig. 7 shows the values of PPI induced by each of the three types of prepulse stimuli in the two isolation-reared subgroups with either low-frequency-noise conditioning (left panels) or high-frequency-noise conditioning (right panels), when the prepulse and masker were either perceptually co-located (filled bars) or perceptually separated (diagonal bars). For each of the two subgroups at each of the three testing stages, because PPI values for each prepulse type under the two different prepulse-combination conditions were similar, they were averaged across the two prepulse-combination conditions.

For either isolation-reared rats with low-frequency-noise conditioning (Fig. 7, left panels) or those with high-frequency-noise

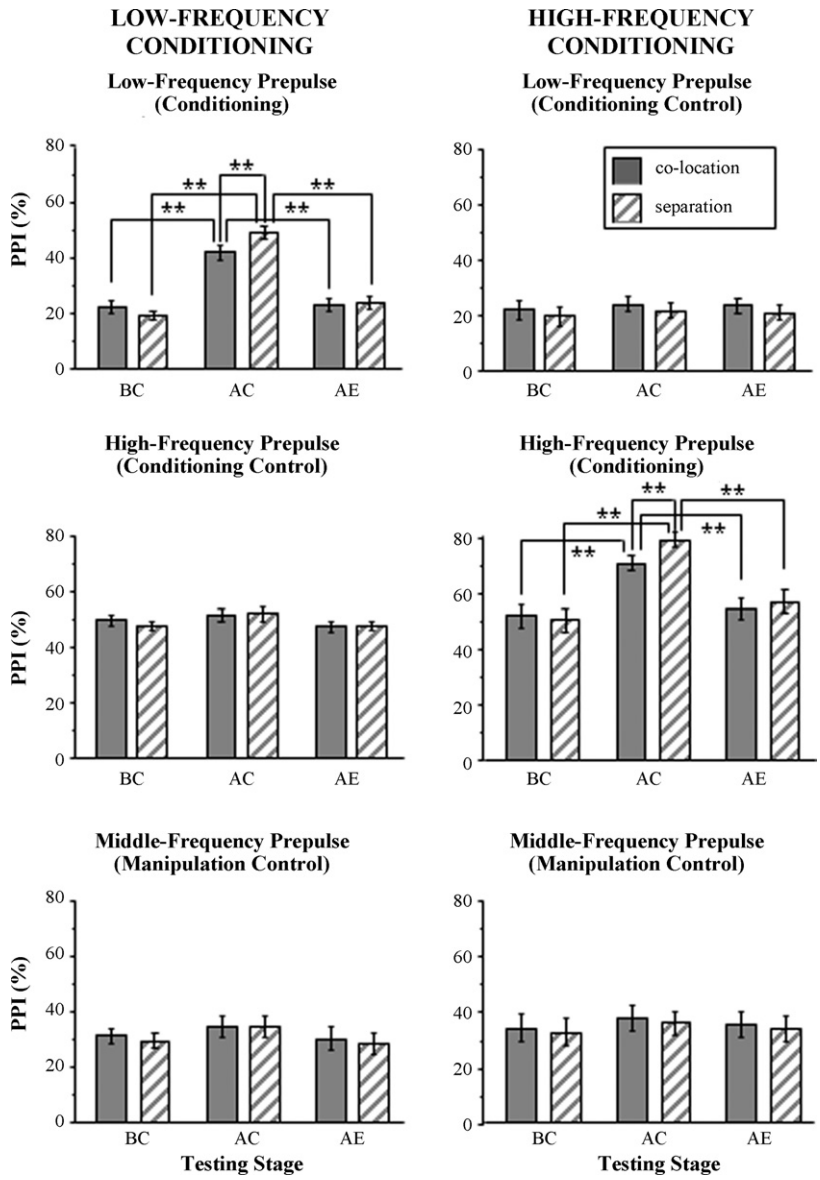

Fig. 6. Values of prepulse inhibition (PPI) in the low-frequency-conditioning socially reared subgroups (left panels) and the high-frequency-conditioning socially reared subgroups (right panels) at the three testing stages: before the combined conditioning/conditioning-control manipulations (BC), after the combined conditioning/conditioning-control manipulations (AC), and after extinction (AE). When the prepulse was the low-frequency (1 kHz) narrowband noise (top panels), middle-frequency (3 kHz) narrowband noise (bottom panels), or high-frequency (5 kHz) narrowband noise (middle panels), it was either perceptually co-located with (filled bars) or perceptually separated from (diagonal bars) the broadband-noise masker. Error bars represent the standard errors of the mean. Note that in each of the two socially reared subgroups, only PPI elicited by the conditioned prepulse was significantly enhanced after the combined conditioning/conditioning-control manipulations and further enhanced by the perceived spatial separation from the noise masker. While both conditioning-induced and separation-induced PPI enhancements disappeared after the extinction manipulation. $^{**}P < 0.01$ by one-way ANOVA and Bonferroni pairwise comparisons.

conditioning (Fig. 7, right panels), PPI elicited by each of the three prepulse stimuli did not differ significantly across the testing times under each of the two perceptual-location conditions (repeated-measures ANOVAs, $P > 0.05$ for all), and any significant PPI enhancements elicited by perceived spatial separation were not observed for each of the prepulse stimuli ($P > 0.05$ for all). These results suggest that both baseline PPI and emotional-learning-induced modulation of PPI were impaired in isolation-reared rats.

4. Discussion

The results of this study are consistent with our previous reports that in socially reared rats, fear conditioning of the prepulse stimulus enhances PPI [20,38,56,86] and the precedence-effect-induced perceptual separation between the conditioned prepulse and the noise masker facilitates selective attention to the prepulse, leading to a further enhancement of PPI [20]. Also, isolation rearing impairs both the emotional-learning-induced enhancement of PPI [20,56] and the perceptual-separation-induced enhancement of PPI [20]. Although there was a general startle enhancement in both socially reared and isolation-reared rats following the combined conditioning/conditioning-control manipulations, showing the occurrence of fear potentiation of startle (e.g., [10,15]), this general enhancement of the baseline startle was not correlated with the emotional-learning-induced enhancement of PPI. First, in socially reared rats only PPI elicited by the conditioned prepulse, but not those without being conditioned, exhibited the learning-induced enhancement. In addition, in isolation-reared rats, the learning-induced enhancement of PPI was not present even though the enhancement of the baseline startle was. Thus, the neural net-

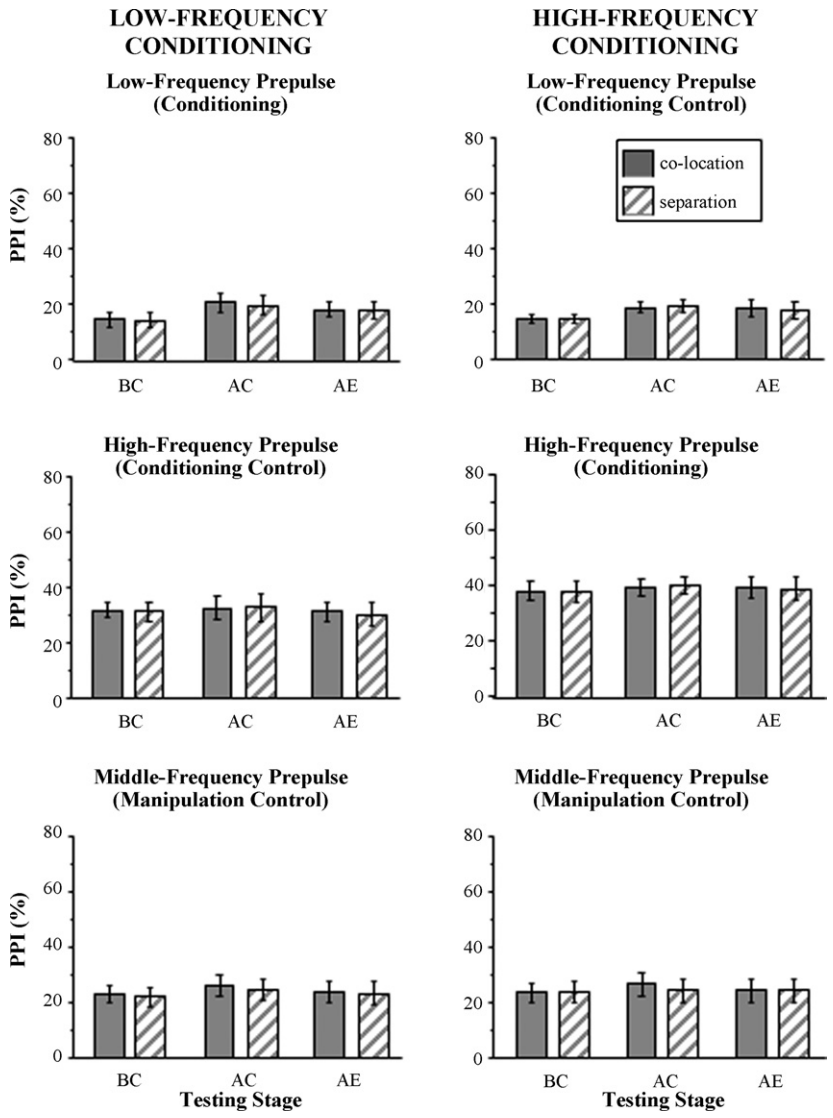

Fig. 7. Values of prepulse inhibition (PPI) in the low-frequency-conditioning isolation-reared subgroups (left panels) and the high-frequency-conditioning isolation-reared subgroups (right panels) at the three testing stages. See the legend of Fig. 6 for explanations of symbols and abbreviations. Note that neither fear conditioning nor perceptual spatial separation had effects on PPI in any subgroup of isolation-reared rats.

work for top-down modulation of PPI is very different from that for modulation of startle.

More importantly, using the within-subject experimental design, the present study for the first time demonstrates that the PPI enhancement that is induced by either emotional learning or perceived prepulse-masker spatial separation is prepulse specific: these two PPI enhancements occur only when the fear-conditioned stimulus is used as the prepulse. Thus, the emotional-learning-induced PPI enhancements are not due to general elevations in vigilance, emotion and/or attention during testing.

Previous studies have shown that in humans perceived spatial separation between the sound target and the masker facilitates listeners' selective attention to the target even when the signal-to-noise ratio (in sound level) is not substantially changed [25,52], and either perceptual processing of or selective attention to the prepulse enhances PPI [5,6,16,22,23,32,33,34,69,75]. The findings of the present study are also consistent to the reports of these human studies. Particularly, the finding that in socially reared rats introducing a difference in perceived location between the conditioned prepulse and the noise masker further enhanced PPI confirms that emotional learning builds a signal-processing link between sensory processing of the CS, memory retrieval of ecological meanings of the CS, elicitation of selective attention to the CS, and stimulus-specific top-down modulation of sensorimotor gating associated with the processing of the CS. In other words, emotional-learning functions as the "processing organizer" for handling ecologically significant sensory inputs, including initiating selective attention to the occurrence of the CS and enhancing sensitivity to the CS [57].

In the present study, the onset interval between the prepulse stimulus and startling stimulus was 100 ms, which was shorter than the interval of 120 ms at which the attentional-modulation effect on PPI in humans has been well demonstrated [22,69]. However, Filion and Poje reported that even at the inter-stimulus interval of 60 ms PPI in task-based protocol (when the prepulse was attended or ignored) was larger than that in passive, no-task protocol, and they suggested that PPI at the short interval of 60 ms in task-based protocol is a sign of sensorimotor gating enhanced by the initial nonselective allocation of attention to both attended and ignored prepulses [23]. Thus, considering the species difference in brain size, it is possible that the attentional-modulation effect on PPI in rats can also be observed at inter-stimulus onset intervals shorter than 100 ms.

It is well known that schizophrenic patients often suffer from impaired sensory gating that filters out distracting stimuli to ensure useful information processing (for reviews, see [9,27]) and perform worse than normal controls in noise-masking tasks [43]. Particularly, when instructed to selectively attend to the prepulse stimulus, compared to normal controls, schizophrenic patients and schizotypal personality-disordered subjects exhibit not only reduced baseline PPI but also declined attentional modulation of PPI (e.g., [16,17,31,32,33,59]). For example, McDowd et al. [59] examined PPI in both passive and active attentional paradigms within the same schizophrenic patients and found that the patients showed less PPI particularly in the active attention phase. In addition, Dawson et al. [17] reported that in patients with schizophrenia under the condition when the prepulse was attended but not the condition when the prepulse was ignored, impaired prepulse inhibition was significantly correlated with heightened delusions, conceptual disorganization, and suspiciousness as measured with the expanded Brief Psychiatric Rating Scale. They proposed that impaired attentional modulation of PPI reflects basic neurocognitive processes related to thought disorder in schizophrenia. Indeed, some recent studies have confirmed that the PPI deficiency that occurs when the prepulse is attended is associated with the symptom severity in the schizophrenia spectrum (e.g., [33]). Thus, in patients with schizophrenia, the disability to focus on what is important (i.e., attentional deficits) can be reflected by deficient attentional modulation of PPI. As attentional deficits are the key features of schizophrenia, it is convincing that the impaired attentional modulation of PPI is more specifically correlated with the symptom severity of this disorder than impaired baseline PPI. In the present study, we found that attentional enhancements of PPI in isolation-reared rats disappeared. The results not only are in consistence with our previous reports [20,56] but also suggest that isolation-rearing-induced changes in top-down modulations of PPI are useful for modeling schizophrenia. Since isolation rearing in rats also results in various schizophrenic-like cognitive/behavioral abnormalities including spontaneous hyperactivity in open field environments, recognition memory deficits, reduced PPI, deficits in attentional set-shifting performance (impaired inhibitory control in attentional selection), and impaired reversal learning in the rotating T maze (e.g., [1,3,13,26,42,46,55,56,60,70,78,79], for reviews, see [24,83]), it is important to know whether the various isolation-induced behavioral impairments are based on deficits of a general signal-processing organization that is related to the function of associative learning.

Here we discuss four issues that may be related to the causes for the deficiency of the learning-induced top-down-modulating effect on PPI in isolation-reared rats:

(1) In rats, the medial prefrontal cortex participates in the formation of fear conditioning, attentional control, and sends direct axonal projections to the amygdala (for a recent review see [54]). Melendez et al. [61] have found that the capacity of Group I metabotropic glutamate receptors (mGluR) to elevate extracellular glutamate levels significantly decreases in the prefrontal cortex (PFC) of isolation-reared rats compared to rats reared in normal environmental conditions. It has been known that mGluR subtype 5 (mGluR5) are critical for the formation of auditory fear conditioning [21,47,66,71], and particularly, conditioning-induced PPI enhancement can be abolished by systemic administration of the mGluR5 antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), in normal rats [56,86].

On the other hand, the amygdala plays a critical role in both forming fear conditioning (e.g., [67]) and modulating PPI (for a recent review see [54]). Although systemic injection of the D2-receptor agonist, quinpirole, decreases fear and impairs the recall of emotional memories [62], chemical block of dopamine D2 receptors in the amygdala with the D2-recepor antagonist, raclopride, disrupts emotional learning measured with fear-potentiated startle [29]. These reports suggest that D2-receptors in the amygdala participate in fear-conditioning-induced modulation of PPI. Moreover, it has been recently reported that social isolation results in significant neurotransmission abnormalities in the rat's amygdala, including increased dopamine D2 receptor density in both the central nucleus and basolateral nucleus of amygdala [19].

Thus, in isolation-reared rats, the mGluR5- and D2-receptor-involved abnormality in the interaction between the prefrontal cortex and amygdala may bring about abnormal functional integrations between conditioning of the prepulse, memory retrieval of ecological meanings of the CS, and selective attention to the CS, leading to impaired stimulus-specific top-down modulation of sensorimotor gating.

(2) It has recently reported that in isolation-reared rats, both defensive reaction to aversive stimuli [76] and level of conditioned fear [50] are reduced. However, it is still unclear whether these two reported reductions are due to a weakening of CS–US association or emotional responses to the CS. To clarify whether isolation-rearing affects fear conditioning of a prepulse, it is also critical for future studies to investigate whether emotional responses to the conditioned prepulse is really weakened by isolation rearing, leading to ignorance of the conditioned prepulse.

(3) Since isolation rearing impairs the inhibitory control in attentional selection [60,70] and the testing paradigm used in the present study requires rat to inhibit the attention-drawing influence of the noise image in order to maintain selective attention to the fear-conditioned prepulse image, isolation-reared rats may not be able to efficiently shift and/or maintain selective attention to the prepulse image. Indeed, isolation rearing results in both structure abnormalities [18,61,64] and neurotransmitter abnormalities (involving serotonin, dopamine, and glutamate) [14,35,42,49,61] in the medial prefrontal cortex (mPFC), which is involved in attention control (e.g., [81]). Thus, isolation-rearing-caused mPFC abnormalities may be associated with the lack of attentional enhancement of PPI. Thus, impaired learning-induced top-down modulation of PPI in isolation-reared rats may be due to isolation-related changes in the weighted distributions of attentional resources to the CS and irrelevant stimuli.

(4) Finally, it should not be excluded that isolation rearing causes substantial impairments within the neural circuitry mediating PPI, making certain top-down neural inputs ineffective, even though the underlying top-down-modulation mechanisms are presumably intact. In other words, it needs further investigation of whether isolation rearing impairs the primary PPI circuitry, which is located in the brainstem (for a recent review see [54]).

In summary, emotional-learning-induced top-down modulations of PPI is prepulse specific, and the modulation effects are impaired in isolation-reared rats. In the future, the emotional-learning-organized interaction between sensory processing of conditioned prepulses and mnemonic signaling of conditioned prepulses in the formation of top-down modulations of PPI needs further investigation, which is also critical for understanding both psychological and neurobiological mechanisms underlying schizophrenia.

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