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Research report

The role of the deeper layers of the superior colliculus in attentional modulations of prepulse inhibition

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ABSTRACT

Prepulse inhibition (PPI) is the suppression of the startle re ex, when a weaker non-startling sensory stimulus (the prepulse) precedes the intense startling stimulus. Although the basic PPI neural circuitry resides in the brainstem, PPI can be enhanced by selective attention to the prepulse, indicating that this sensorimotor-gating process is in uenced by higher-order perceptual/cognitive processes. Along with the auditory cortex, the brain structures involved in attentional modulations of PPI include both the lateral nucleus of the amygdala (LA), which contributes to the fear-conditioning modulation, and the posterior parietal cortex (PPC), which contributes to the spatially attentional modulation. The deeper layers of the superior colliculus (DpSC), which has been suggested as a midbrain component in the PPI circuitry, receive descending axonal projections from some forebrain structures associated with auditory perception, emotional conditioning, or spatial attention. This study was to examine whether the DpSC are also involved in attentional modulations of PPI in rats. The results showed that both fear conditioning of a prepulse sound and precedence-e ect-induced perceptual separation between the conditioned prepulse and a noise masker facilitated selective attention to the prepulse and consequently enhanced PPI. Reversibly blocking glutamate receptors in the DpSC with 2-mM kynurenic acid eliminated both the conditioning-induced and the perceptual-separation-induced PPI enhancements. However, the baseline magnitudes of startle and PPI were not a ected. The results suggest that the DpSC play a role in mediating the attentional enhancements of PPI, probably through both receiving top-down signals from certain forebrain structures and modulating the midbrain representations of prepulse signals.

1. Introduction

The startle re ex is a strong whole-body re exive response that can be e ectively elicited by sudden and intense sensory stimuli [1–3]. The neural circuitry mediating the startle re ex is simple and short [4] with the giant neurons in the caudal pontine reticular nucleus (PnC) being the most essential for mediating the startle re ex. The PnC giant neurons receive axonal projections from the cochlear nucleus, trigeminal nucleus, and vestibular nucleus, and send projections to motor areas of the cranial nerve nuclei and the spinal cord [4–6].

Prepulse inhibition (PPI) is the suppression of the startle re ex in response to an intense startling stimulus (pulse) when this startling stimulus is shortly preceded by a weaker, non-startling sensory stimulus (prepulse) [7,8]. According to Graham's "protection of processing" theory, the weak prepulse can trigger not only the information processing for the prepulse signal but also the gating mechanism dampening the e ects of the intense disruptive startling inputs. Since PPI protects the early processing of the prepulse signal from startling interferences by regulating the motor system and/or the pre-motor system, it has been generally recognized as an operational measure of sensorimotor gating [9,10].

PPI can be observed in laboratory rats with either acutely surgical de-cerebration [11–13] or chemical suppression of the cortex [14], indicating that the basic neural circuitry mediating PPI resides in the brainstem. One of the anatomical models for explaining the circuitry mediating PPI includes the three serially connected midbrain structures: the inferior colliculus (IC [15–17],) sends vast axonal projections to the deeper layers of the superior colliculus (DpSC [18–21],), the DpSC in turn project to the pedunculopontine tegmental nucleus (PPTg [22–24],), and nally the PPTg plays a role in inhibiting the PnC [22].

However, ber-sparing lesions of the SC only attenuate PPI by approximately 45% [19], while lesions of the IC totally disrupt PPI [15].

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Moreover, GABAergic neurons in the lateral globus pallidus (LGP) project to the PPTg and play a crucial role in the regulation of PPI [25] without involving the DpSC. Thus, the role of DpSC in mediating PPI still needs further investigation.

Although the primary circuitry mediating PPI resides in the brainstem, numerous studies in humans [26–31] and those in rats [32–35] have shown that PPI can be top-down modulated by higher-order perceptual/cognitive processes, such as fear conditioning-induced attention and spatially selective attention. Specifically, in rats, after fear conditioning of the prepulse sound, the conditioned prepulse-induced PPI is enhanced by drawing more attention to conditioned prepulse (which becomes ecologically significant after the conditioning) [33–36]. Moreover, when the prepulse sound is co-presented with a masking noise, an auditory precedence effect-induced perceived spatial separation between the conditioned prepulse and the noise masker further enhances PPI by facilitating selective attention to the prepulse signal [4,37–42]. Obviously, the neural circuitry mediating PPI in the brainstem must receive descending axonal projections from certain forebrain structures, which play a role in top-down attentional modulation of PPI.

In rats, the fear-conditioning-induced PPI enhancement is mediated by the lateral nucleus of the amygdala (LA), and the perceptual-separation-induced PPI enhancement is mediated by the posterior parietal cortex (PPC), indicating that the LA and the PPC contribute to the attentional modulation of PPI differently [37]. More importantly for motivating the present study, both the LA and the PPC have either direct or indirect neural connections with the DpSC [43–45], which may also be a relay site in the pathway mediating PPI [18,19,46]. Previous animal studies have also suggested that PPI is modulated by the cortico-striatal-pallido-thalamic circuitry [47]. Correspondingly, functional magnetic resonance imaging (fMRI) studies in humans have suggested that humans have the similar brain circuits modulating PPI [48–51].

Kynurenic acid (KYNA) is an endogenous antagonist of excitatory glutamate receptors [52], which blocks both non-NMDA and NMDA receptors, reducing excitation of neurons in the area [53–55]. This study was to examine the hypothesis that the DpSC may play a role in the attentional modulation of PPI in rats. If DpSC play a key role in the attentional modulation of PPI, then blocking excitatory transmissions in the DpSC should lead to a reduction or elimination of the attentional modulation effects.

2. Materials and methods

2.1. Animal preparation

Twenty-six young-adult male Sprague Dawley rats (10 weeks; 250–300 g) were randomly assigned into two groups: the experimental group (n = 16) and the anatomically control group (n = 10).

During the surgical procedures, each of the rats was anesthetized with the 10% chloral hydrate (500 mg/kg, i.p.). Microinjection guide cannulae (C317 G guide cannula; Plastics One) were bilaterally implanted into the DpSC in the experimental group, and in the superficial layers of the superior colliculus (superSC) in the anatomically control group. Referenced to bregma, the stereotaxic coordinates of the inner cannula aimed structures were the following: (1) DpSC: anteroposterior, −6.3 mm; mediolateral, ± 1.5 mm; depth, −4.8 mm. (2) superSC: anteroposterior, −6.3 mm; mediolateral, ± 1.5 mm; depth, −3.0 mm [43].

Rats were given 1 week for recovery from surgery in a room with the temperature of 24 ± 2 °C and a 12 h light/dark cycle, with food and water continuously available. The treatments of animals in this study were in accordance with the Guidelines of the Beijing Laboratory Animal Center, and the Policies on the Use of Animals and Humans in Neuroscience Research approved by the Society of Neuroscience (2006). All experimental procedures were approved by the Committee for Protecting Human and Animal Subjects in the School of Psychology and Cognitive Sciences at Peking University.

2.2. Stimuli and apparatus

The apparatus of PPI testing have been described in details elsewhere [37,39]. Briefly, all the startle-response tests were conducted in a sound proof chamber. The rat's whole-body startle reflex, which was measured by a custom-made electrical scale (the National Key Laboratory on Machine Perception, Peking University), was induced by an intense 10-ms broadband noise burst (0–10 kHz, 100 dB SPL) delivered by a loudspeaker above the rat's head. The prepulse stimulus, which started 100 ms before the onset of startling noise (pulse), was a 50-ms three-harmonic-tone complex with either lower frequency components (1.3, 2.6, and 3.9 kHz, 60 dB SPL) or higher frequency components (2.3, 4.6, and 6.9 kHz, 60 dB SPL). These two harmonic complexes are within the audible frequency range for rats [56,57] and can be distinguished by rats [37,39].The prepulse stimulus and the broadband background (masking) noise (60 dB SPL) were delivered by each of the two spatially (i.e. left, right) separated loudspeakers in the frontfield, with a 100° separation angle and 52 cm away from the rat's head position. All the sound stimuli were digitally generated by MATLAB software and converted by a custom-developed sound delivery system (National Key Laboratory on Machine Perception, Peking University). Calibration of sound levels was conducted with a Larson Davis Audiometer Calibration and 3091 Electro-acoustic Testing System (AUDit & System 824, Larson Davis, Depew, NY, USA) whose microphone was placed at the central location of the rat 's head when the rat was absent, using a "Fast"/"Peak" meter response.

2.3. Procedures

After 1 week of recovery from surgery, each rat went through the 7-day testing procedure.

For the first 3 successive days, the rat was placed into the restraining cage, whose dimensions matched the rat's body sizes. The rat could not reorient their body position inside the cage. For 30 min on each of the 3 days, the rat was exposed to the background noise only (neither the prepulse nor the startling noise was presented), which was continuously delivered by the two spatially separated loudspeakers. This procedure allowed the rats to adapt to the restraining cage, testing chamber, and the background noise.

On the fourth day, startle responses and PPI at the stage before conditioning (procedure stage BC) were examined. The rat was placed in the restraining cage for 5 min, receiving 10 presentations of the startling stimulus on the background noise without the prepulse presentation. The interval between startling stimuli varied between 25 and 35 s (mean = 30 s). Then the rats went through 4 testing blocks, whose order was arranged by the Latin Design. Each testing block contained 15 trials: 5 trials with the startling stimulus (pulse) alone, 5 trials with the lower-frequency prepulse stimulus 100 ms preceding the startling pulse, and 5 trials with the higher-frequency prepulse stimulus 100 ms preceding the startling pulse. All the trials in each block were presented in a random order, with the inter-trial interval varied between 25 and 35 s (mean = 30 s).

The prepulse was presented from each of the two spatially separated loudspeakers with the inter-loudspeaker onset delay being either + 1 ms (left leading) or −1 ms (right leading). Due to the auditory precedence effect [58], a single fused prepulse image would be perceived at the left loudspeaker locations in two testing blocks and at the right loudspeaker locations in the other two testing blocks.

In each block, the background noise was continuously presented from the two loudspeakers with the inter-loudspeaker onset delay being either + 1 ms (left leading) or −1 ms (right leading), leading to a fused auditory image of the background noise being perceived at the left loudspeaker location in two testing blocks and at the right loudspeaker location in the other two testing blocks.

Therefore, there were four (2 × 2) combinations of the perceived locations between the prepulse stimulus and background noise across the four testing blocks: two blocks with perceptual separation (when the prepulse stimulus and background noise had di erent leading loudspeakers) and the other two blocks with perceptual co-location (when the prepulse stimulus and background noise had the same leading loudspeaker). By doing so, the change between perceived spatial separation and co-location did not a ect the impact of bottom-up sensory inputs (i.e., the shift between the two types of conditions did not change the signal-to-noise ratio in sound pressure level at the ear) but facilitated selective spatial attention to the attended signal [58].

On the fth day, rats received both fear-conditioning and conditioning-control manipulations. The conditioning stimulus (CS) was one of the prepulse stimuli (either the lower- or the higher-frequency prepulse) delivered by each of the two horizontal loudspeakers with a left/right-leading balance, and the unconditioned stimulus (US) was a 6-mA rectangular-pulse footshock with a duration of 3 ms provided by a Grass S-88 stimulator (Grass, Quincy, MA, USA). For each rat, during the fear-conditioning manipulation, 20 temporally synchronized (paired) combinations of the footshock (US) and one of the prepulse stimuli (CS) were presented every 30 s (US started 3 ms before CS ending, and co-terminated with CS). During the conditioning-control manipulation, 20 temporally random (unpaired) combinations of the footshock and the other prepulse were presented every 30 s. In each group, one-half of the rats received fear conditioning of the lower-frequency prepulse and conditioning control of the higher-frequency prepulse, and the other one-half of the rats received the contrary manipulations.

PPI in the next four procedure stages was examined on the sixth and seventh days (between 24 h and 48 h after the conditioning and conditioning-control manipulations): PPI after conditioning (procedure stage AC), PPI after injecting KYNA (procedure stage KY), PPI after injecting Locke's solution (procedure stage LK), and PPI after recovery (procedure stage RE), with the order of either AC-KY-LK-RE or AC-LK-KY-RE balanced across individual rats. All the four procedure stages were measured with the procedure used in the stage before conditioning (BC) as described above. Note that both the conditioned prepulse and the conditioning-control prepulse were always presented in each of the four blocks.

In the procedure stage KY or LK, either the KYNA (2 mM in Locke's solution; Sigma-Aldrich) or Locke's solution was injected slowly into the bilateral DpSC (2.0 μl on each side) in the experimental group over a period of 2 min, but only KYNA was injected into the bilateral superSC (2.0 μl on each side) in the anatomical control group. According to the previous studies, local and slow injection of 2.0 μl of KYNA does not spread too much to the surrounding brain areas [37]. Drug administration was made by a 5.0 μl microsyringe which connected to the inner cannula with a polyethylene tubing (inner diameter, 0.38 mm; outer diameter, 1.09 mm; Clay Adams, division of BD Biosciences).

PPI after injecting KYNA (procedure stage KY) or PPI after injecting Locke's solution (procedure stage LK) was tested 15 min after the injection. Since the blocking e ect of KYNA is reversible [59,60], PPI testing was conducted again no less than 3 h after the injection of KYNA or Locke's solution (procedure stage KY or LK) when the injected structure recovered from blocking e ects (procedure stage RE). Each procedure stage (BC, AC, KY, LK, and RE) was about 45 min, and the interval between two successive stages was no less than 3 h.

For the anatomical control group, only procedure stages BC, AC and KY were performed, with the order of BC-AC-KY or BC-LK-AC balanced across individual rats. At the procedure stage KY, KYNA (2 mM in Locke's solution; Sigma-Aldrich) was injected slowly into bilateral superSC (2.0μl on each side) over a period of 2 min. Other details were the same as used in the experimental group.

2.4. Data analyses

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

PPI (%) = (amplitude to startling noise alone - amplitude to startling noise preceded by prepulse) / (amplitude to startling noise alone) × 100%.

Mixed and within-subject repeated-measures ANOVAs followed by Bonferroni's pairwise comparisons (for comparisons between procedure stages) and Bonferroni's pairwise comparisons (for comparisons between perceived colocation and spatial separation) were performed using SPSS 20.0 software. Multivariate tests were conducted, and the null-hypothesis rejection level was set at 0.05.

2.5. Histology

When all data collections were completed, rats were killed with an overdose of chloral hydrate (i.p.). Lesion marks were made via the cannula by an anodal DC current (500 μA, 10 s). Brains were stored in 10% formalin with 35% sucrose, and then sectioned at 50 μm in the frontal plane in a cryostat (−20 °C). Sections were examined to determine locations of injection cannulae.

3. Results

3.1. Histology

According to histological examination (Fig. 1), injection cannulae were precisely located within the bilateral DpSC in 16 rats and bilateral superSC in 10 rats. Thus, descriptions and statistical analyses were based on data from 16 rats in the experimental group and 10 rats in the anatomically control group.

3.2. Responses to the startling stimulus alone

Fig. 2 shows the mean amplitude of the startle response to the startling stimulus alone (when the prepulse was not presented) in each of the procedure stages in the experimental group. A repeated-measures

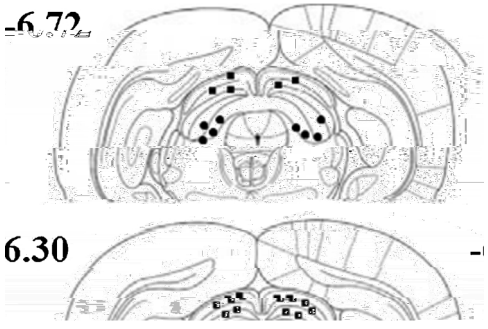

Fig. 1. Histological locations of injection cannulae in all 26 rats, showing bilateral injection cannula placements in the deep layers of the superior colliculus (DpSC, lled circles) and super cial layers of the superior colliculus (superSC; lled squares).

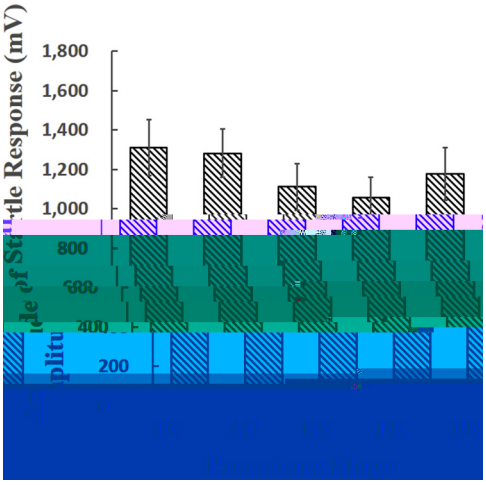

Fig. 2. Startle amplitudes to the startling stimulus alone in the experimental group (DpSC, n = 16). BC, before conditioning; AC, after conditioning; KY, after injecting KYNA; LK, after injecting Locke's solution; RE, after recovery. Note that half of the rats were tested in the order of "BC-AC-KY-LK-RE", and the other half were in another order of "BC-AC-LK-KY-RE". Data for all rats are shown in the figure. Error bars represent the standard errors of the mean (SEM).

ANOVA with one within-subjects factor (procedure stage: BC, AC, KY, LK, RE) showed that the effect of the procedure stage on the startle response to the startling sound alone was not significant in the experimental group ($p > 0.05$). Thus, no significant changes in the baseline-startle amplitude were induced by the conditioning/conditioning control manipulation, the injection of either KYNA into the DpSC or Locke's solution into the DpSC.

3.3. Effects of KYNA injection on PPI

Fig. 3 shows the effects of fear conditioning, perceptual separation, and blocking the DpSC on PPI in the experimental group. At the procedure stage BC, the perceived spatial separation between the prepulse and noise masker did not enhance PPI. However, when the prepulse

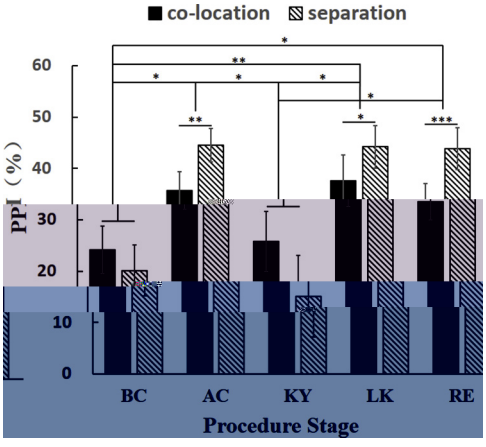

Fig. 3. PPI induced by the fear-conditioned prepulse at different procedure stages in the experimental group (DpSC, n = 16). The black bars represent the PPI magnitudes when the prepulse was perceptually co-located with the noise masker, while the diagonal bars represent the PPI magnitudes when the prepulse was perceptually separated with the noise masker. BC, before conditioning; AC, after conditioning; KY, after injecting KYNA; LK, after injecting Locke's solution; RE, after recovery. Note that half of the rats were tested in the order of "BC-AC-KY-LK-RE", and the other half were in another order of "BC-AC-LK-KY-RE". Data for all rats are shown in the figure. Error bars represent the SEM. *: $p < 0.05$; **: $p < 0.01$, ***: $p < 0.001$ (by repeated-measures ANOVA, Bonferroni's pairwise comparisons).

became fear conditioned (procedure stage AC), PPI was remarkably enhanced, and the enhancement was further increased by the perceived spatial separation. Next, injection of KYNA into the DpSC markedly eliminated the two types of PPI enhancements (procedure stage KY), leading to that PPI reduced to the level at the procedure stage BC. In contrast, the injection of Locke's solution into the DpSC did not influence the two types of PPI enhancements (procedure stage LK). Finally, at the procedure stage RE, the KYNA effects disappeared and PPI returned to the level at the procedure stage AC.

A 5 (procedure stage: BC, AC, KY, LK, RE) × 2 (perceived spatial relationship, simply called separation type: co-location, separation) within-subject repeated-measures ANOVA showed that the interaction between the two factors was significant ($F(4,12) = 3.947$, $p = 0.029$, $\eta_p^2 = 0.568$) and the main effect of the procedure stage was significant ($F(4,12) = 7.120$, $p = 0.004$, $\eta_p^2 = 0.704$). Pairwise comparisons (for comparisons between procedure stages) and Bonferroni's pairwise comparisons (for comparisons between separation types) showed that: (1) at procedure stage BC, the effect of separation type on PPI was not significant ($F(1,15) = 0.534$, $p = 0.476$, $\eta_p^2 = 0.034$), (2) the PPI level at procedure stage AC was significantly larger than that at procedure stage BC ($p = 0.019$), and (3) at procedure stage AC, the effect of separation type on PPI was significant ($F(1,15) = 10.01$, $p = 0.006$, $\eta_p^2 = 0.400$).

Following the injection of KYNA into the DpSC (procedure stage KY), the perceived spatial separation-induced PPI enhancements disappeared ($F(1,15) = 3.390$, $p = 0.085$, $\eta_p^2 = 0.184$). Also, the PPI level at procedure stage KY became significantly smaller than that at procedure stage AC ($p = 0.016$), but not significantly different from that at procedure stage BC ($p > 0.05$).

Three or more hours after the injection of KYNA (procedure stage RE), the PPI level returned to that at the procedure stage AC ($p > 0.05$) and became significantly larger than that at procedure stage KY ($p = 0.022$). Moreover, the significant effect of separation type reappeared, showing that the difference in PPI magnitude between the co-location condition and separation condition became significant ($F(1,15) = 16.033$, $p < 0.001$, $\eta_p^2 = 0.517$). Thus, blocking the DpSC completely abolished both the conditioning-induced PPI enhancement and the perceptual separation-induced PPI enhancement.

On the other hand, the injection of Locke's solution into the DpSC did not significantly change either the conditioning-induced PPI enhancement (procedure stage LK vs procedure stage AC, $p > 0.05$) or the separation-induced PPI enhancement (at the procedure stage LK, PPI under the separation condition was still larger than that under colocation condition; ($F(1,15) = 8.126$, $p = 0.012$, $\eta_p^2 = 0.351$). Also, the PPI level at procedure stage LK was significantly larger than that at procedure stage BC ($p = 0.004$) and stage KY ($p = 0.047$).

3.4. PPI induced by conditioning-control prepulse

Fig. 4 shows the PPI levels at different procedure stages when the prepulse was the conditioning-control tone complex. After the conditioning-control manipulation, the PPI magnitude was not enhanced. A 5 (procedure stage: BC, AC, KY, LK, RE) × 2 (separation type) within-subject repeated-measures ANOVA showed that the main effect of procedure stage was significant ($F(4,12) = 4.827$, $p = 0.015$, $\eta_p^2 = 0.617$), the main effect of separation type was not significant ($F(1,15) = 1.309$, $p = 0.271$, $\eta_p^2 = 0.080$), and the interaction between the two factors was not significant ($F(4,12) = 1.302$, $p = 0.324$, $\eta_p^2 = 0.303$). Pairwise comparisons showed that only the PPI level at the procedure stage KY was significantly lower than those at the procedure stage RE ($p = 0.026$).

3.5. Effects of blocking the superSC on PPI

To examine the anatomical specificity for the KYNA injection into the DpSC, PPI was tested in 10 rats with KYNA injected into the

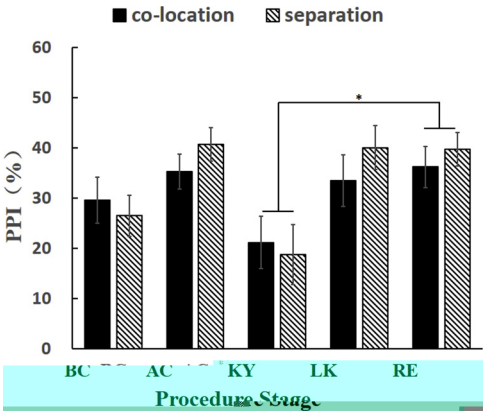

Fig. 4. PPI induced by the conditioning-control prepulse at di erent procedure stages in the experimental group (DpSC, n = 16). The black bars represent the PPI magnitudes when the prepulse was perceptually co-located with the noise masker, while the diagonal bars represent the PPI magnitudes when the prepulse was perceptually separated with the noise masker. BC, before conditioning; AC, after conditioning; KY, after injecting KYNA; LK, after injecting Locke's solution; RE, after recovery. Note that half of the rats were tested in the order of "BC-AC-KY-LK-RE, and the other half were in another order of "BC-AC-LK-KY-RE. Data for all rats are shown in the gure. Error bars represent the SEM. *: p < 0.05 (by repeated-measures ANOVA, Bonferroni's pairwise comparisons).

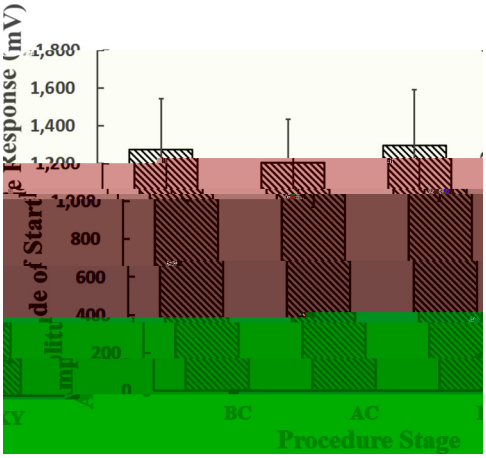

Fig. 5. Startle amplitudes to the startling stimulus alone in the anatomical control group (superSC, n = 10). BC, before conditioning; AC, after conditioning; KY, after injecting KYNA. Note that half of the rats were tested in the order of "BC-AC-KY, and the other half were in another order of "BC-KY-AC. Data for all rats are shown in the gure. Error bars represent the SEM.

superSC.Fig. 5 shows the group-mean amplitude of startle response to the startling stimulus alone (when the prepulse was not presented) in each of the testing procedure stages in the anatomical control group. A repeated-measures ANOVA with one within-subjects factor (procedure stage: BC, AC, KY) showed that the e ect of procedure stages was not signi cant (all $p > 0.05$). There were no signi cant changes in the baseline startle amplitude after the conditioning/conditioning control manipulation. Also, injection of KYNA into superSC did not signi cantly in uence the startle amplitude to the startling stimulus alone.

Fig. 6 shows the e ects of fear-conditioning/conditioning-control manipulations, perceptual separation, and blocking the superSC on PPI in the anatomically control group. At the procedure stage BC, the perceived spatial separation between the prepulse and masker did not enhance PPI. When the prepulse became fear conditioned (procedure stage AC), PPI was remarkably enhanced, and the enhancement was further increased by the perceived spatial separation (Fig. 6, left panel).

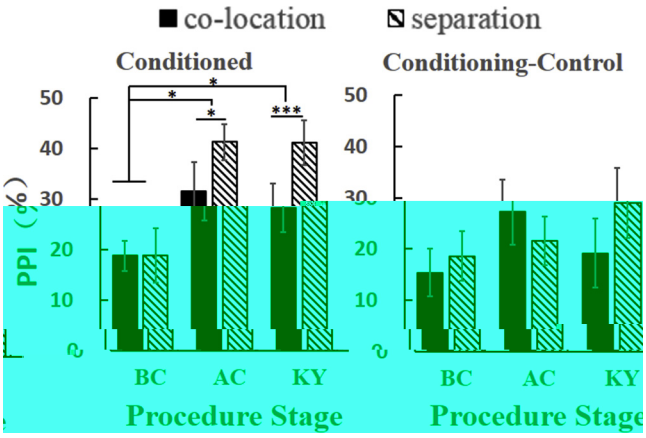

Fig. 6. PPI at di erent procedure stages in the anatomical control group (superSC, n = 10). The black bars represent the PPI magnitudes when the prepulse was perceptually colocated with the noise masker, while the diagonal bars represent the PPI magnitudes when the prepulse was perceptually separated with the noise masker. Left panel: PPI induced by the conditioned prepulse; right panel: PPI induced by the conditioning-control prepulse. BC, before conditioning; AC, after conditioning; KY, after injecting KYNA. Note that half of the rats were tested in the order of "BC-AC-KY, and the other half were in another order of "BC-KY-AC. Data for all rats are shown in the gure. Error bars represent the SEM. *: p < 0.05; ***: p < 0.001 (by repeated-measures ANOVA, Bonferroni's pairwise comparisons).

However, the conditioning-control manipulation did not a ect the PPI magnitude (Fig. 6, right panel).

Following either the fear-conditioning manipulation (Fig. 6 left panel) or the conditioning-control manipulation (Fig. 6, right panel), injection of KYNA into the superSC did not change the PPI.

A 3 (procedure stage: BC, AC, KY) × 2 (separation type) within-subject repeated-measures ANOVA showed that for the experimental condition with fear conditioning, the main e ect of procedure stage was signi cant ($F(2,8) = 5.006$, $p = 0.039$, $\eta_p^2 = 0.556$), the main e ect of separation type was signi cant ($F(1,9) = 7.035$, $p = 0.026$, $\eta_p^2 = 0.439$), and the interaction between the two factors was not signi cant ($F(2,8) = 1.815$, $p = 0.224$, $\eta_p^2 = 0.312$). Pairwise comparisons showed that (1) at the procedure stage BC, the e ect of separation type on PPI was not signi cant ($F(1,9) < 0.001$, $p = 0.995$, $\eta_p^2 < 0.001$); (2) the PPI level at procedure stages AC and KY was signi cantly larger than that at procedure stage BC (AC:$p = 0.030$; KY: $p = 0.030$); (3) at procedure stages AC and KY, the e ect of separation type on PPI was signi cant (AC: $F(1,9) = 6.415$, $p = 0.032$, $\eta_p^2 = 0.416$; KY: $F(1,9) = 38.851$, $p < 0.001$, $\eta_p^2 = 0.812$).

Another 3 (procedure stage: BC, AC, KY) × 2 (separation type) within-subject repeated-measures ANOVA showed that for the experimental condition with the fear conditioning-control manupulation, the main e ect of procedure stage, the main e ect of separation type, and the interaction between the two factors were all not signi cant ($p > 0.05$).

As Fig. 6 shows, when PPI was induced by either the conditioned prepulse or the conditioning-control prepulse, bilateral injection of 2- µl KYNA into the superSC did not signi cantly alter the PPI magnitude under either the co-location or the separation condition. Thus, the results con rmed the anatomical speci city of the blocking e ect of the KYNA injection into the DpSC.

4. Discussion

4.1. Do the deep layers of SC contribute to the baseline PPI?

KYNA is a reversible broad-spectrum antagonist of glutamate receptors [60,61] and can block both NMDA and non-NMDA receptors

[53–55]. In this study, KYNA was used to block glutamate receptor-mediated excitatory neurotransmissions in either the DpSC or the superSC. Since KYNA does not influence axonal action-potential conductions, it does not affect the activity of axons bypassing the injected area. Moreover, the reversibility of the blocking effect of KYNA has been confirmed in this and previous studies [37,59–61].

In this study, surprisingly, although injection of KYNA into the DpSC eliminated the two types of PPI enhancements in the experimental group, it did not significantly affect the baseline PPI. Under the conditioning-control condition, no significant decline in PPI was observed following the injection of KYNA into the DpSC. However, also under the conditioning-control condition, the PPI magnitude following the injection of KYNA into the DpSC (at the procedure stage KY) was significantly smaller than that over 2 h after the injection (at the procedure stage RE). Thus, blocking the DpSC may only have a weak effect on the baseline PPI.

It has been known that PPI can be observed in laboratory rats with acutely surgical decerebration [11–13], indicating that the basic neural circuitry mediating PPI resides in the brainstem. As mentioned in the Introduction, one of the anatomical models about the circuitry mediating auditory PPI includes the serially connected three midbrain structures: the IC [15–17], DpSC/intermediate layers of the SC [18–21], and PPTg [22–24]. However, some studies have also shown that certain components in the circuitry mediating PPI bypass the DpSC [21] or even the PPTg and PnC [62]. Thus, there may be multiple pathways mediating PPI. More specifically, as suggested by Yeomans et al. [20], there are at least two parallel midbrain pathways mediating PPI, a faster pathway containing direct axonal projections from the IC to the PPTg, and a slower pathway through DpSC [21]. If the DpSC is involved in the slower mediation of PPI, the blockage of excitatory glutamate neurotransmissions within the DpSC may not affect the faster mediation of prepulse signals.

4.2. Two types of attentional enhancements of PPI

The results of this study are in agreement with the previous animal studies showing that fear conditioning of the prepulse stimulus specifically improves the ecological salience of the prepulse signal, thereby enhancing PPI induced by the conditioned prepulse, and the perceived spatial separation between the fear-conditioned prepulse stimulus and a noise masker further enhances PPI by facilitating spatially selective attention to the conditioned prepulse [32,37–39,42,63].

4.3. Contributions of the DpSC in attentional modulations of PPI

This study, for the first time, reveals that the DpSC, but not the superSC, contribute to each of the two types of attentional enhancements of PPI. Previous studies have suggested that the DpSC affects neural activation of the pedunculopontine tegmental nucleus (PPTg) [21],), which in turn mediates PPI [22–24]. How are the DpSC modulated by top-down attentional processes?

It has been known that the LA specifically contributes to fear-conditioning-induced PPI enhancement, the PPC specifically contributes to perceptual-separation-induced PPI enhancement after the prepulse becomes fear conditioned, and the A1 generally contributes to these two types of PPI enhancements [37]. Anatomically, the LA sends projections to the central nucleus of the amygdala (CeA) [64],), and the CeA assumedly has neural connections with the DpSC [43,65].

Auditory inputs to the LA originate from both the medial geniculate nucleus (MGN) and the auditory association cortex (AAC) [44,66–70]. Both the MGN and AAC play roles in the formation of fear-conditioning-related the neural plasticity in the LA [71,72]. Moreover, in rats, the TE2 area of AAC (or called the "posterodorsal" auditory area, PD), which receives auditory signals from the A1, has not only cortical projections to the PPC [73], but also subcortical projections to the DpSC [73,74]. The direct descending projections from auditory cortical regions to the DpSC have also been discovered in Mongolian gerbil [75]. Thus, the descending projection from the AAC to the DpSC may play an important role in both the fear-conditioning-induced PPI enhancement and the perceptual separation-induced PPI enhancement.

On the other hand, the PPC projects to the medial agranular frontal cortex (AGm) [76], and the AGm sends descending axonal projections to the DpSC [77,78]. Thus, the PPC may top-down modulate the activity of the DpSC through the AGm, leading to that the DpSC is involved in perceptual-separation-induced PPI enhancement.

Since the results of this study showed that both the fear-conditioning-induced and the perceptual-separation-induced PPI enhancements were completely eliminated by injecting the broad-spectrum antagonist of excitatory glutamate receptors (i.e., KYNA) into the DpSC, the top-down modulations of the DpSC activation are mediated by excitatory glutamate synaptic transmissions.

4.4. New animal models for studying schizophrenia

In people with schizophrenia, impaired PPI induced by the attended prepulse, but not ignored prepulse, is more correlated with the symptom severity in the schizophrenia spectrum [26,79,80]. Therefore, the top-down attentional modulation of PPI in rats can be used for establishing animal models for the diagnosis of schizophrenia [32,34,39,42]. Recently, Lei et al. (2018) have discovered that in humans the perceived spatial separation between the prepulse sound and the masking noise can enhance both PPI induced by the attended prepulse and the cortical responses to the prepulse signal [29]. Also, the perceptual-separation-induced PPI enhancement is reduced in people with schizophrenia [81]. Since the DpSC bridges the forebrain attentional system with the brainstem PPI circuitry, this study opens a new avenue for further deeply studying the mechanisms underlying the deficits of attentional enhancement of PPI in people with schizophrenia.

5. Summary

(1) Blocking excitatory glutamate neurotransmissions in the DpSC does not affect either the baseline startle reflex or the baseline PPI, suggesting that the DpSC is not the critical midbrain structure involved in either the mediation of the primary startle reflex or the faster mediation of prepulse signals.
(2) Fear conditioning of the prepulse stimulus enhances PPI induced by the conditioned prepulse, and under the noise-masking condition, the perceived spatial separation between the fear-conditioned prepulse stimulus and the noise masker further enhances PPI, confirming that PPI in rats can be top-down enhanced by various types of attentional processes.
(3) Blocking excitatory glutamate neurotransmissions in the DpSC reduces each of the two types of attentional enhancements of PPI, suggesting that the DpSC is involved in both the fear-conditioning-induced PPI enhancement and the perceptual-separation-induced PPI enhancement.
(4) Since the DpSC receives descending projections from both the auditory cortical areas and the AGm, the involvement of the DpSC in mediations of PPI enhancements may be based on bridging the higher-order cortical functions and the brainstem prepulse-signal processing.
(5) In the future, new animal models for studying PPI-modulation deficits in schizophrenia will involve the DpSC.

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