Brief Communication

# Post-training reversible disconnection of the ventral hippocampal–basolateral amygdaloid circuits impairs consolidation of inhibitory avoidance memory in rats

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**The ventral hippocampus (VH) and the basolateral amygdala (BLA) are both crucial in inhibitory avoidance (IA) memory. However, the exact role of the VH–BLA circuit in IA memory consolidation is unclear. This study investigated the effect of post-training reversible disconnection of the VH–BLA circuit in IA memory consolidation. Male Wistar rats with implanted guide cannulae were trained with a one-trial IA task, then received immediate intracerebral injections of muscimol or saline, and were tested 24 h later. Muscimol injection into the bilateral BLA, or the unilateral VH and contralateral BLA, but not the unilateral VH and ipsilateral BLA, significantly decreased the retention latencies (versus saline treatment). The results suggest that the VH–BLA circuit could be an important circuit to modulate consolidation of IA memory in rats.**

The ventral hippocampus (VH) and basolateral amygdala (BLA, including the lateral and basal nuclei of the amygdala) are two crucial temporal lobe structures in modulation of emotion-related learning and memory (such as fear conditioning and inhibitory avoidance [IA]) (LeDoux 2000; McGaugh 2004). Both structures are connected by direct reciprocal circuit, which is called ventral hippocampal–basolateral amygdaloid (VH–BLA) circuit (Canteras and Swanson 1992; Pikkarainen et al. 1999; Pitkänen et al. 2000; French et al. 2003; Herry et al. 2008). In the VH–BLA circuit, the VH is one of the primary providers of contextual information to the BLA (especially to the basal nucleus), and the BLA is the main input region of the amygdala, which receives extensive afferent projections from other brain areas (Maren and Fanselow 1995; Pitkänen et al. 2000; Maren 2001; Herry et al. 2008). Therefore, different sensory and regulatory information can converge in the BLA to form new emotion-related mnemonic traces (Davis 2008; Herry and Johansen 2014). Meanwhile, the BLA also regulates hippocampal neuronal activity, synaptic plasticity, and memory functions. A series of animal experiments conducted by Abe and colleagues showed that the induction of long-term potentiation in the dentate gyrus was partially impaired by lesion or inactivation of the BLA, or injection of the NMDA receptor antagonist or the β-adrenoceptor antagonist into the BLA (Abe 2001). Experiments combining in vivo/in vitro electrophysiological and behavioral methods showed that theta oscillations of the lateral amygdala were synchronized with the hippocampus following cued and contextual fear conditioning in rodents, which suggested that the theta synchronization means the activity in amygdalo–hippocampal pathways is associated with consolidation of fear memory (Seidenbecher et al. 2003; Pape et al. 2005; Narayanan et al. 2007). Furthermore, functional imaging researches also showed that there is enhanced amygdala–hippocampal connectivity in emotion-related memory-retrieval tasks in humans (Smith et al. 2006; de Voogd et al. 2016). Optogenetic activation of the BLA → VH projection has been proven to enhance consolidation of foot-shock learning, anxiety levels, and social interactions in rodents (Felix-Ortiz et al. 2013; Felix-Ortiz and Tye 2014; Janak and Tye 2015; Huff et al. 2016). These studies supported that there is a close relationship between the BLA and VH, and the VH–BLA circuit is involved in emotion-related memory and behaviors.

The VH and BLA have frequently been reported to be involved in the consolidation of IA memory in animal and human experiments. IA memory is a kind of contextual memory with emotional (fear/aversion) arousal tested by an instrumental conditioning task, which depends on the functional intactness of the hippocampus and amygdala (Bianchin et al. 1999; Tovote et al. 2015). Inactivation of the BLA can impair consolidation of IA memory in rats (Liang et al. 1994; Parent and McGaugh 1994; Wilensky et al. 2000; Rossato et al. 2004; Lalumiere and McGaugh 2005). Post-training optogenetic manipulation (stimulating/inhibiting) of the activity of BLA neurons can enhance or impair IA retention, respectively (Huff et al. 2013); and the right, but not left, BLA is mainly involved in modulation of IA memory consolidation by the cholinergic, and catecholaminergic systems (Lalumiere et al. 2004; Lalumiere and McGaugh 2005). However, Lalumiere and McGaugh (2005) reported that only bilateral, but not unilateral, inactivation of the BLA by sodium channel blocker lidocaine or $GABA_A$ receptor agonist muscimol can impair IA memory consolidation in rats. Han et al. (2009) reported that the contextual and auditory fear memory were impaired by selective erasure of the cyclic adenosine monophosphate response element-binding protein (CREB) overexpressed neurons from the bilateral, but not unilateral, BLA. Those works indicated that the inhibitory roles (such as the GABAergic agonism effect of muscimol) of BLA on consolidation of fear memory were different from the enhancement effect of the cholinergic and catecholaminergic systems (which is right

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hemisphere lateralization). That is, either the right BLA or the left BLA could independently accomplish the inhibitory role of IA memory consolidation. Hence, if one side of the BLA does not work, it will be compensated by the other side.

Similarly, previous work has shown that inactivation of bilateral, but not unilateral, VH impaired the IA performance, especially the consolidation of IA memory, in rats (Ambrogi Lorenzini et al. 1997; Wang and Cai 2008). Moreover, disconnection of the VH-prefrontal cortical circuits could impair spatial learning and working memory, but not IA memory (Floresco et al. 1997; Wang and Cai 2006, 2008). Therefore, there may be other circuits connected with the VH being in charge of IA memory. In view of the importance of the VH and BLA in IA memory consolidation, as well as the association of enhanced amygdala–hippocampal synchronized activities at theta frequencies and emotional memory consolidation, we speculated that the VH–BLA circuit is a potential candidate circuit for IA memory consolidation. Furthermore, the role of the VH–BLA circuit in IA memory has not been studied by direct disconnection methods. We hypothesized that IA memory consolidation would be impaired by bilateral disconnection of the circuit, but not unilateral circuit inactivation. To verify this hypothesis, we used post-training infusion of muscimol to disconnect the VH–BLA circuit in rats asymmetrically (see Fig. 1A), and the animal behavioral performances in a step-through IA task were evaluated.

Sixty male adult Wistar rats (aged 10 wk at the beginning of the experiment, purchased from Dossy Biological Technology, Chengdu, China; License number: SCXK (Chuan) 2015-030) were used in this study. The rats were group housed in a temperature (23 ± 1°C) and light (12 h light–dark cycle, 8 a.m. to 8 p.m.)-controlled animal room with water and food available ad libitum. The animal care and experimental protocol was approved by the Animal Ethics Supervision Committee of Yunnan Normal University. All procedures were performed in accordance with the *Yunnan Province Guidelines for Use and Care of Laboratory Animals*.

All animals were stereotaxically implanted with guide cannulae before behavioral training. They were deeply anesthetized with sodium pentobarbital (55 mg/kg, intraperitoneally [i.p.]) after pretreatment with sulfate atropine (0.2 mg/kg, i.p.). An incision was made along the midline of the scalp, and two stainless steel guide cannulae (outside diameter: 0.48 mm; RWD Life Science) were implanted into two target brain regions (see Fig. 1A). The stereotaxic coordinates were derived from a rat brain atlas (Paxinos and Watson 1986). For inactivation of the unilateral VH–BLA circuit (uVH–BLA group), a cannula was unilaterally implanted in the VH (AP, −5.4 mm from the bregma; ML, ±5.2 mm from the midline; DV, −7.6 mm from the surface of the skull), and another one was implanted in the ipsilateral BLA (AP, −2.4 mm; ML, ±5.0 mm; DV, −8.0 mm). For BLA inactivation, two cannulae were bilaterally implanted in the BLA (bBLA group). For bilateral disconnection of the VH–BLA circuits, two cannulae were asymmetrically implanted in the unilateral VH and the contralateral BLA (cVH/BLA group). There were 10 saline animals and 10 muscimol animals in each of the three groups (uVH–BLA, bBLA, and cVH/BLA). Such an asymmetrical treatment procedure would bilaterally disconnect the VH–BLA circuit but reserve other connections with the VH and the BLA unilaterally, on account of the compensatory effects of their intact contralateral parts. The cannulae were affixed to the skull using dental cement secured with sterile stainless steel screws. A sterile stylet (outside diameter: 0.29 mm) was inserted into the guide cannula to prevent occlusion (0.5 mm beyond the tip of guide cannula). Surgical incisions were painted with mupirocin ointment mixed with Yunnan baiyao, and benzylpenicillin sodium (intramuscularly) was applied on four consecutive postoperative days. The animals were given at least 7 d to recover from surgery before the start of behavioral training.

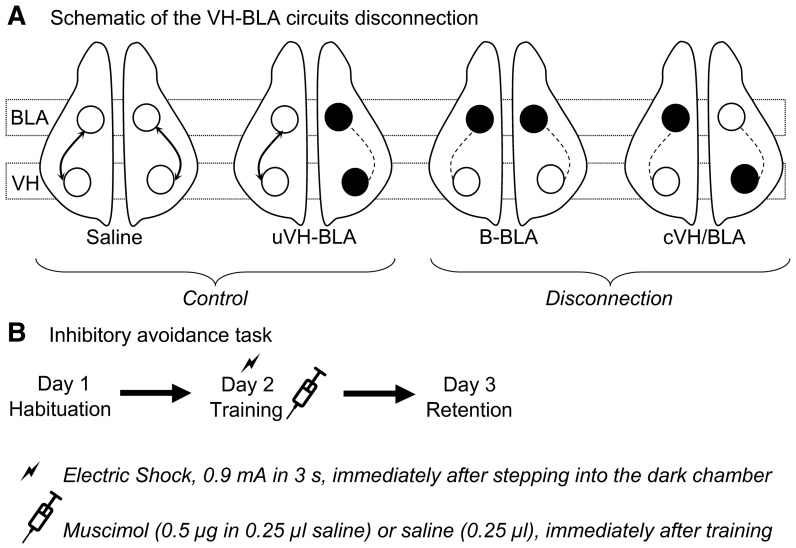


**Figure 1.** A schematic of the VH–BLA circuits in saline rats and rats in which the circuits were disconnected (*A*), and a timeline depicting the behavioral testing procedures in the step-through inhibitory avoidance task (*B*). In intact rat brains (Saline), there are ipsilateral, reciprocal projections (double-headed arrows with solid lines) between the VH and BLA. Control rats with unilateral inactivation of the VH–BLA circuit (unilateral VH–BLA, uVH–BLA) maintained normal connectivity between the VH and BLA in the intact hemisphere. However, along with bilateral inactivation of the BLA (bBLA), contralateral inactivation of the VH and BLA (cVH/BLA) disconnected the VH–BLA circuits in both hemispheres. The little lightning symbol means an electric shock will be given immediately after the animal's four limbs have stepped into the dark chamber and the door has automatically closed in the training phase. The little syringe symbol indicates infusions into the target brain areas immediately after the training phase.

Before drug injection, the animals were habituated initially to the injection procedure using a mock method. On injection days, the animals were gently restrained by hand while the stylets were replaced with sterile injection needles (outside diameter: 0.29 mm) that extended 0.5 mm below the tips of the guide cannulae. Either saline (0.25 µL) or muscimol (0.5 µg dissolved in 0.25 µL saline, Sigma Chemical) was injected (0.25 µL/side) into the target areas at a rate of 0.125 µL/min driven by a microsyringe pump (Longer Precision Pump) using 5 µL microsyringes. The dosage, volume, and injection rate of muscimol have been validated by local EEG power analysis and behavioral tasks in our previous experiments (Wang and Cai 2006). After completion of the injection, the injection needle remained in place for 1 min for drug diffusion. Then, the injection needles were retracted and stylets were immediately replaced into the guide cannulae. The injection procedure was performed immediately after the training phase of the IA task (see Fig. 1B). After injection, the animals were returned to their home cages. The peak inactivation effect of muscimol could last for 6 h, and completely disappear 24 h after injection (Martin and Ghez 1999). The critical period of memory consolidation in the

hippocampus or BLA is <6 h (Igaz et al. 2002; Zheng et al. 2008; Huff et al. 2013; Benetti et al. 2015); hence, the muscimol could fulfill the requirements of the present tasks.

After recovery from surgery, the animals were trained with a one-trial step-through IA task. The apparatus was a computer-controlled system (San Diego Instruments), in which two adjacent chambers (26 × 20 × 19 cm) were connected by an automatic guillotine door (9 × 8 cm). The grid floor was connected by an inbuilt constant current stimulator. On the day before training, each animal was placed into the right chamber with the light on (lighted chamber). The left chamber was a dark chamber. The guillotine door was opened for 300 sec so that the animal could move freely between the two chambers. In the training phase, each animal was placed into the lighted chamber with the guillotine door open and with its tail toward the door. When the four limbs of the animal stepped into the dark chamber, the door was closed immediately and a shock (constant current: 0.9 mA, 3 sec) was given (see Fig. 1B). Then the animal was removed to receive drug injection. The animal would be excluded from the task if it did not enter the dark chamber within 300 sec. Twenty-four hours later, animals were placed into the apparatus again for a retention test, with the situation the same as the training phase, but without a shock. The latency of entering the dark chamber was recorded. If an animal did not enter the dark chamber within 300 sec, the trial was terminated with its latency recorded as 300 sec.

After the behavioral tasks, each animal was killed by overdose of sodium pentobarbital, and a stainless steel electrode (outside diameter: 0.25 mm) was inserted into the same position of the injection needle in order to mark the injection point using an anodal current (6 V, 10 sec). The rat bodies were treated with intra-ascending aorta infusions of physiological saline followed by a formaldehyde solution (4%) containing potassium ferrocyanide (1%). The brains were stored in a formaldehyde solution for several days, and then sectioned for histological verification. The positions of the injection needle tips were marked with Prussian blue against a background of cresyl violet staining.

The latencies in entering the dark chamber in the IA task were analyzed using either independent or paired-samples $T$ tests, or one-way analysis of variance (ANOVA) followed by a Post Hoc Dunnett's test. All data were shown as mean ± SEM with $P < 0.05$ as the standard of significance.

The positions of the injection needle tips in the animals are shown in Figure 2. Six rats (two saline rats and two muscimol rats from the bBLA group, a muscimol rat from the uVH–BLA group, and a muscimol rat from the cVH/BLA group) were excluded from the data analysis as their injection positions were not in the target area. Before the IA task, no abnormal behavior was observed in any of the animals. During the training phase of the IA task, the latencies of the animals in the three groups were similar between saline and muscimol treatments (unpaired-sample $T$ test, All $T \leq 0.992$, $P \geq 0.338$). There was no significant difference between the three groups in the similarly treated animals (ANOVA: Saline, $F_{(2,25)} = 0.708$, $P = 0.502$; Muscimol, $F_{(2,19)} = 0.421$, $P = 0.662$). These data showed that all animals could rapidly step into the dark chamber, and their vision and motor abilities and scototaxis (preference for dark environments) would be normal and similar.

During the retention phase, the latencies of all saline animals were significantly longer than during the training phase in all groups (paired-sample $T$ test, All $T \geq 4.151$, $P \leq 0.004$). There was no significant difference between the three groups in saline animals (ANOVA, $F_{(2,25)} = 0.378$, $P = 0.689$). So the saline animals in the three groups formed IA memory normally. In muscimol animals, significant difference emerged between the groups (ANOVA, $F_{(2,20)} = 8.454$, $P = 0.002$). Post hoc analysis showed that the latencies of the bBLA group ($P = 0.003$) and cVH/BLA group ($P = 0.007$) were significantly shorter than that of the uVH–BLA group. At the same time, unpaired-sample $T$ test showed that the latencies

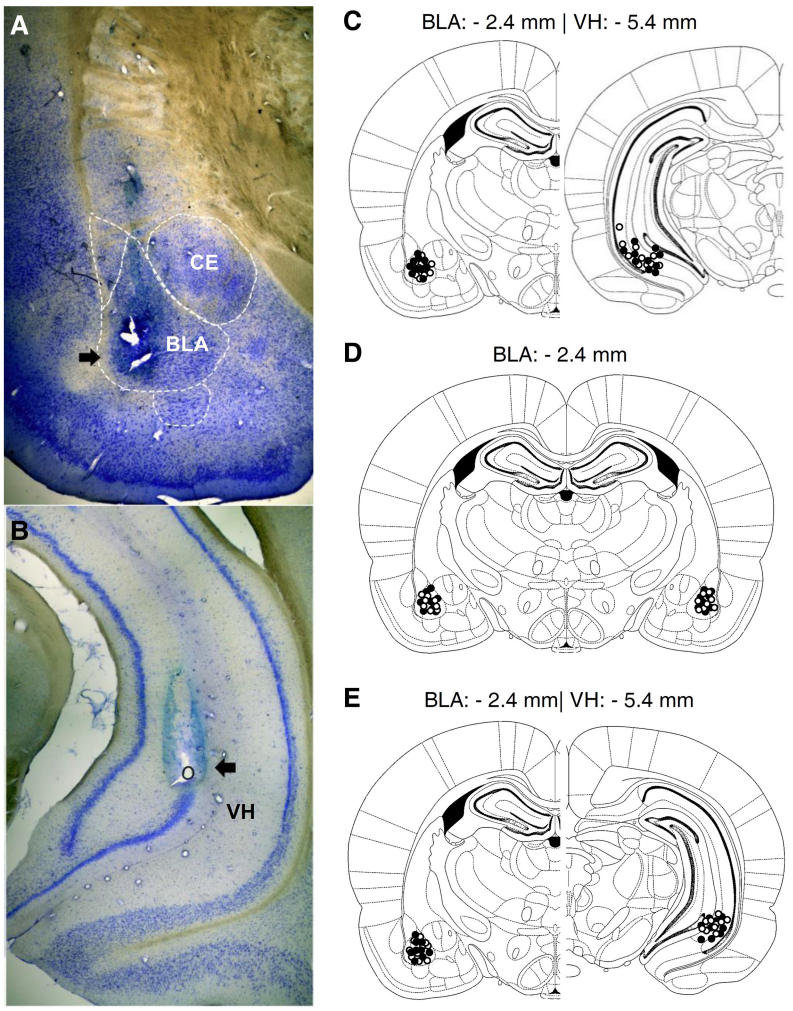


**Figure 2.** The locations of the tips of injected needles in the rat brain areas. On the *left* are the representative microphotographs (4×) of the tracks of injected needle tips in the BLA (*A*) and VH (*B*); on the *right* are overlaid locations of the injected needle tips in the unilateral VH and ipsilateral BLA (*C*), in the bilateral BLA (*D*), or in the unilateral VH and contralateral BLA (*E*), marked by open or solid dots ([○] saline; [●] muscimol). The maps of brain coronal sections were adapted from Paxinos and Watson (1986). Each section was marked with distance to the bregma (mm). (BLA) Basolateral amygdala; (CE) central amygdala nucleus; (VH) ventral hippocampus.

of muscimol animals were significantly shorter than that of the saline animals in the bBLA group ($T_{(14)} = 2.785$, $P = 0.015$) and cVH/BLA group ($T_{(17)} = 3.596$, $P = 0.002$). However, there was no such effect on the uVH–BLA group ($T_{(17)} = 0.232$, $P = 0.819$). Compared with their training phase, a similar tendency in muscimol animals was shown in uVH–BLA group, but not in bBLA and cVH/BLA groups (paired-sample $T$ test: uVH–BLA, $T_{(8)} = 3.741$, $P = 0.006$; bBLA, $T_{(7)} = 1.173$, $P = 0.279$; cVH/BLA, $T_{(8)} = 2.076$, $P = 0.072$; see Fig. 3). These results show that post-training inactivation of the bilateral BLA or contralateral VH and BLA, but not ipsilateral VH and BLA inactivation, could decrease IA retention latencies, indicating an impairment effect on memory consolidation.

Bilateral BLA inactivation impaired consolidation of IA memory, which was similar to previous studies on amnesia effects of post-training BLA optogenetic modulation or inactivation by lidocaine or muscimol, infusion of glutamate receptor antagonists or inhibition of the protein kinase C in the BLA (Liang et al. 1994; Parent and McGaugh 1994; Roesler et al. 2000; Wilensky et al. 2000; Rossato et al. 2004; Bonini et al. 2005; Lalumiere and McGaugh 2005; McIntyre et al. 2005; Huff et al. 2013; Nazari-Serenjeh and Rezayof 2013). And other researchers have reported that inactivation of the VH, or changes of the cannabinoid CB1 receptor and histamine receptor in it, could impair or modulate IA memory consolidation (Ambrogi Lorenzini et al. 1997; Alvarez and Banzan 2008; Wang and Cai 2008; Mohammadmirzaei et al. 2016). The data in this study, in combination with that of previous studies, supports that BLA and VH are key anatomical structures in IA memory consolidation.

Similar to the findings from the BLA and VH, an important discovery in this study is that the VH–BLA circuit also contributes to IA memory consolidation (Ambrogi Lorenzini et al. 1997; Lalumiere and McGaugh 2005; Wang and Cai 2008; Han et al. 2009). The VH and the BLA are the two ends of this reciprocal circuit (Canteras and Swanson 1992; Pikkarainen et al. 1999; Pitkänen et al. 2000; French et al. 2003; Herry et al. 2008). Thus, inactivation of either of these regions will block the neural transmission through the VH–BLA circuit. Consequently, bilateral inactivation of the VH or the BLA could result in bilateral disconnection of the VH–BLA circuit (Ambrogi Lorenzini et al. 1997; Lalumiere and McGaugh 2005; Wang and Cai 2008; Han et al. 2009). Ipsilateral inactivation of the VH and the BLA produced little effect on IA memory consolidation, which could be explained by the compensation effect from the intact side of the VH–BLA circuit. However, although there was an intact VH on one side and an intact BLA on the other side in rats with inactivation of the cVH/BLA, these arrangements could not compensate for the impairment of memory consolidation resulting from bilateral VH–BLA circuit disconnection. Therefore, the impairment effect of asymmetrical disconnection of the VH–BLA circuit would not result from the accumulative effect of inactivation of the two regions, but be the effect of bilateral circuit disconnection. As the route of BLA modulation on the hippocampus, the BLA → VH projection is the indispensable part of the reciprocal VH–BLA circuit, which is involved in anxiety, social interaction, and consolidation of footshock learning in contextual fear conditioning in rats (Felix-Ortiz et al. 2013; Felix-Ortiz and Tye 2014; Huff et al. 2016). The results of our study further proved that post-training reversible disconnection of the bilateral VH–BLA circuit could produce similar impairment effects as bilateral BLA inactivation in consolidation of IA memory.

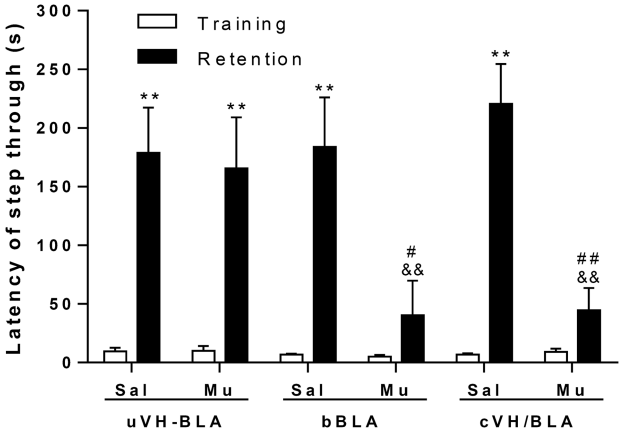


**Figure 3.** Effects of injection of muscimol into the uVH–BLA, bBLA, or cVH/BLA on the latency of entering the dark chamber during the training phase and retention phase of the one-trial inhibitory avoidance task. The data from each group is summarized by mean ± SEM. (**) $P < 0.01$ versus training phase; (#) $P < 0.05$, (##) $P < 0.01$ versus matching saline animals; (&&) $P < 0.01$ versus muscimol animals from the uVH–BLA group. (bBLA) Bilateral BLA; (cVH/BLA) contralateral VH and BLA; (uVH–BLA) ipsilateral VH and BLA; (Mu) muscimol; (Sal) saline.

However, in some situations as reported by Roozendaal and McGaugh (1996), animals with pretraining lesion of the BLA could perform IA tasks normally, but lost the memory enhancement or impairment effect of stress hormones (Roozendaal and McGaugh 1997; Roozendaal et al. 1998). In reality, the BLA is more like a gathering node of different emotional information, by which, the BLA can modulate memory formation, anxiety, and social interaction (McGaugh 2004; Davis 2008; Felix-Ortiz et al. 2013; Felix-Ortiz and Tye 2014; Huff et al. 2016). There would be some other circuits connected with the hippocampus to afford the IA memory independently in a nonemotional way if the BLA does not work (such as permanent lesion). According to the memory modulation hypothesis, the amygdala, especially the BLA, is a pivotal temporal lobe structure to facilitate the processes of stressful and emotionally arousing experiences forming long-term memory by modulation of memory-related brain regions in a permissive-like way (Gerard 1961; McGaugh 2004). These results, consistent with previous works, support that the BLA GABAergic system plays a critical inhibitory modulation role in fear memory consolidation (Wilensky et al. 2000; Rossato et al. 2004; Lalumiere and McGaugh 2005; McIntyre et al. 2005; Nazari-Serenjeh and Rezayof 2013). Our present study further verified our hypothesis, proving that the VH–BLA circuit can also play a prominent role in inhibitory modulation of IA memory consolidation in rats.

In general, our results suggest that the VH–BLA circuit, as well as the BLA, would be regulated by the GABAergic system in emotionally arousing memory consolidation. However, the detailed mechanism of the VH–BLA circuit in memory modulation is not clearly known. This knowledge would help to develop useful methods to prevent or cure memory and emotion-related diseases, such as post-traumatic stress disorder, in future (Parsons and Ressler 2013).

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