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Research report

The effect of acute stress on LTP and LTD induction in the hippocampal CA1 region of anesthetized rats at three different ages

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Abstract

Not all experiences are memorized equally well. Especially, some types of stress are unavoidable in daily life and the stress experience can be memorized for life. Previous evidence has showed that synaptic plasticity, such as long-term potentiation (LTP) that may be the major cellular model of the mechanism underlying learning and memory, is influenced by behavioral stress. However, the effect of behavioral stress on age-related synaptic plasticity in vivo was primarily known. Here we found that the LTP induction in the hippocampal CA1 region of anesthetized rats obviously showed inverted-U shape related to ages (4, 10 and 74 weeks old rats), but low-frequency stimulation was unable to induce reliable long-term depression (LTD) in these animals. Furthermore, acute elevated platform (EP) stress enabled reliable LTD significantly and completely blocked LTP induction at these ages. Importantly, LTD after exposure to acute EP stress showed similar magnitude over these ages. The present results that stress enables LTD but impairs LTP induction at these three ages strengthen a view that stress experience-dependent LTD (SLTD) may underlie stress form of aberrant memories.
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1. Introduction

Changes in synaptic efficacy have long been hypothesized to be important for memory formation in the CNS [9,11,21]. It is well known that activity-dependent long-term potentiation (LTP) of hippocampus underlies certain types of learning and memory [9,40]. On the other hand, growing evidence has showed that long-term depression (LTD) of hippocampus plays role in hippocampal-dependent learning and memory[34,41], although it remains elusive [42].

In the past years, the investigations have increased attention to the age-related hippocampal synaptic plasticity (LTP and LTD) and memory [5,20,32,42,50,57]. Most studies have focused on the relation between LTP impairment and memory deficits in adult and aged rats in vivo and in vitro [5,6,14,47]. In addition, the role of LTD in hippocampal-dependent learning and memory also has been studied in adult rats [34]. LTD induction has shown age-dependent in naïve in vitro [23,42].

Since the hippocampus enriches the glucocorticoid receptors and crucially plays role in the effects of stress on synaptic plasticity and memory [3,29,46,55], it is significant to understand the effect of stress on age-related LTP and LTD induction in anesthetized rats at different ages.

It is well known that stress forms strong memories (e.g., stress form of aberrant memories in post-traumatic

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stress disorder, depression, etc.), and disturbs cognitive processes, then limits the quality of human life. Because LTP was inhibited under stressful condition or administration of corticosterone [3,13,17,29,43,48]. Contrarily, LTD induction was facilitated by behavioral stress [24–26,36,43,53–55]. Moreover, many forms of experience-dependent plasticity were suggested to involve in chronic pain, drug addiction, etc [16,44,49,52,57]. Thus, the stress experience-dependent LTD (SLTD) might relate to stress form of aberrant memories [53]. In the present report, we examined the effect of acute elevated platform (EP) stress on LTP and LTD induction in hippocampal CA1 region of anesthetized rats at 4, 10 and 74 weeks old rats.

2. Materials and methods

2.1. Animals

Experiments were carried out on male Wistar rats (Animal House Center, Kunming General Hospital, Kunming), aged 4, 10 and 74 weeks. Animals were group-housed with free access to water and food in an established animal house having a 12:12-h light/dark cycle and a thermo-regulated environment. The animal care and experimental protocol were approved by the Yunnan Health Department, China.

2.2. Electrophysiology and surgery

The method in detail for electrophysiological and surgical procedures was previously described [51,53,54]. Experiments were carried out under pentobarbitone sodium (50–60 mg/kg, i.p.) anesthesia and core temperature was maintained at 37 ± 0.5 °C. Recordings of the field excitatory postsynaptic potential (fEPSP) were made from the CA1 stratum radiatum of the hippocampus in response to ipsilateral stimulation of the Schaffer collateral/commissural pathway. The electrode implantation sites were identified by using stereotaxic coordinate. Two stainless steel screws (1.5 mm diameter) were inserted into the skull through a drill hole without piercing the dura. One served as a ground electrode (7 mm posterior to bregma and 5 mm left of the midline), the other served as the reference electrode (8 mm anterior to bregma and 1 mm left of the midline). Recording and stimulating electrodes were glued together with a pair of twisted Teflon-coated 90% platinum/10% iridium wires (50 μm inner diameter, 75 μm outer diameter, from Sigma). The recording electrode was inserted ~3.5–4.0 mm posterior to bregma and ~2.5–3.0 mm right of the midline, and the stimulating electrode was inserted ~4.3–4.8 mm posterior to bregma and ~3.5–3.8 mm right of the midline at these three ages. The optimal depth of the electrodes in the stratum radiatum of the CA1 area of the dorsal hippocampus was determined by using electrophysiological criteria and was verified by postmortem examination [33,53,54]. In all experiments, test fEPSP were evoked by stimulating, a square wave of constant current pulse of 0.1 ms duration, at a frequency of 0.033 Hz and at an intensity adjusted to given the fEPSP amplitude of 40–50% of maximum response.

2.3. LTP/LTD induction and stress protocols

High-frequency stimulation (HFS) (10 bursts of 20 pulses at 200 Hz, each burst separated by 2 s) was used to induce LTP, whereas low-frequency stimulation (LFS) (900 pulses at 3 Hz) was applied to induce LTD. The stimulation was delivered at basal stimulation intensity, and the timing was controlled by Scope Software (PowerLab/MacLab/4sp, ADInstruments, USA). Before the induction of LTP and LTD, a baseline fEPSP was recorded at least for 40 min. In the stress groups, rats were placed on an elevated platform, which was 10×10 cm and about 1.6 m high in the middle of a bright room, for 30 min, and then were anesthetized immediately after the procedure.

2.4. Statistics

Data were expressed as mean ± SEM % of baseline fEPSP amplitude. Statistical comparisons were made by using Student's *t*-test or ANOVA. Significance level was set at $P < 0.05$.

3. Results

3.1. The different magnitudes of LTP at three ages were blocked by acute EP stress

We examined the differences in LTP induction of 4, 10 and 74 weeks old rats between naïve and EP stress in the Schaffer collateral/commissural-CA1 synapses. Same as previous methods in our laboratory [51,53], after the HFS episode, responses to HFS were averaged respectively at three different time points (15–20, 30–35, and 55–60 min of post-HFS) and were compared with the averaged responses of baseline. Analyses showed that the responses at each of the three time points were significantly increased. This indicated that the potentiation persisted for at least 1 h.

HFS (arrow, Fig. 1, 10 bursts of 20 pulses at 200 Hz, each burst separated by 2 s) failed to induce LTP at 74 weeks old rats compared with 4 and 10 rats in naïve (4 weeks: $108.88 \pm 1.96\%$, $n = 6$, $P < 0.05$, open circles, Fig. 1A; 10 weeks: $124.49 \pm 3.55\%$, $n = 11$, $P < 0.05$, open triangles, Fig. 1B; 74 weeks: $102.49 \pm 2.35\%$, $n = 3$, $P > 0.05$, open squares, Fig. 1C; compared with the averaged baseline responses). The result showed the different magnitude of LTP at 4, 10 and 74 weeks old rats. Interestingly, LTP was unable to induce in all groups of stressed animals ($96.51 \pm 2.93\%$, $n = 3$, $P > 0.05$; $100.75 \pm 5.66\%$, $n = 3$,

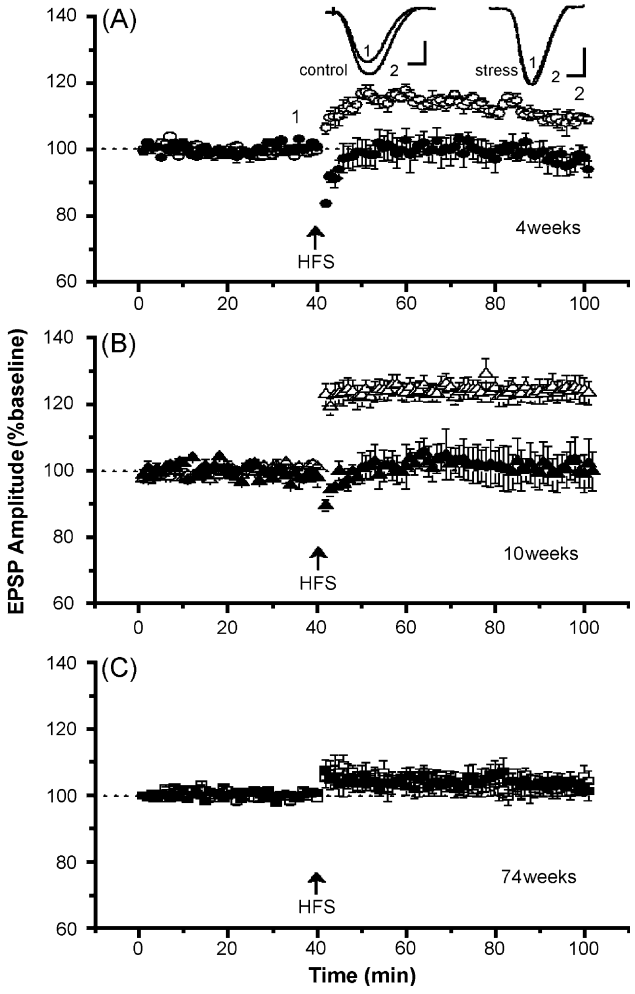

Fig. 1. The different magnitudes of LTP at three ages were blocked by acute EP stress. (A) At 4 weeks old rats, rats showed a slight significant LTP in naïve after HFS (arrow, 10 bursts of 20 pulses at 200 Hz, each burst separated by 2 s) (108.88 ± 1.96%, $n=6$, $P<0.05$, ○); and acute EP stress impaired the LTP induction (96.51 ± 2.93%, $n=3$, $P>0.05$, ●). The upper traces represented the sample traces before (1) and after (2) HFS in naïve and stressed group, respectively of 4 weeks old rats. Scale bar: 1 mV, 10 ms. (B) However, rats exhibited larger potentiation at 10 weeks old rats than LTP at 4 weeks old animals (124.49 ± 3.55%, $n=11$, $P<0.05$, △); also, LTP induction was impaired after acute EP stress (100.75 ± 5.66%, $n=3$, $P>0.05$, ▲). (C) Different from 4 and 10 weeks old animals, 74 weeks old rats showed no reliable LTP after HFS (102.49 ± 2.35% $n=3$, $P>0.05$, □); no changes occurred after acute EP stress (103.08 ± 2.50%, $n=5$, $P>0.05$, ■). All data was respectively compared with baseline themselves. Thus, the data showed the different magnitudes of LTP induction at 4, 10 and 74 weeks old rats, and all LTP was impaired after exposure to acute EP stress.

$P>0.05$; 103.08 ± 2.50%, $n=5$, $P>0.05$ at 4, 10 and 74 weeks old rats, respectively, compared with the averaged baseline responses or LTP in naïve, filled circles/triangles/squares, respectively).

The result suggested that the magnitude of LTP exhibited an inverted-U shape related to age of the rats, which may relate to the dissimilar abilities of hippocampal-dependent learning and memory among different ages [5,17,24,32]. On the other hand, since acute stress impaired LTP induction in all ages, it is necessary to investigate the stress-related LTD (SLTD) at different ages because SLTD might underlie stress experience-dependent form of aberrant memories [53].

3.2. Acute EP stress facilitated LTD at three ages

Similarly, we examined the LTD induction (bar, Fig. 2, 3 Hz, 900 pulses) of 4, 10 and 74 weeks old rats between naïve and acute EP stress. As shown in Fig. 2, there were no significant differences among 4, 10 and 74 weeks old rats in LTD induction, in naïve (4 weeks: 95.43 ± 1.08%, $n=6$, open circles, $P>0.05$, Fig. 2A; 10 weeks: 94.67 ± 1.61%, $n=7$, open triangles, $P>0.05$, Fig. 2B; 74 weeks: 96.74 ±

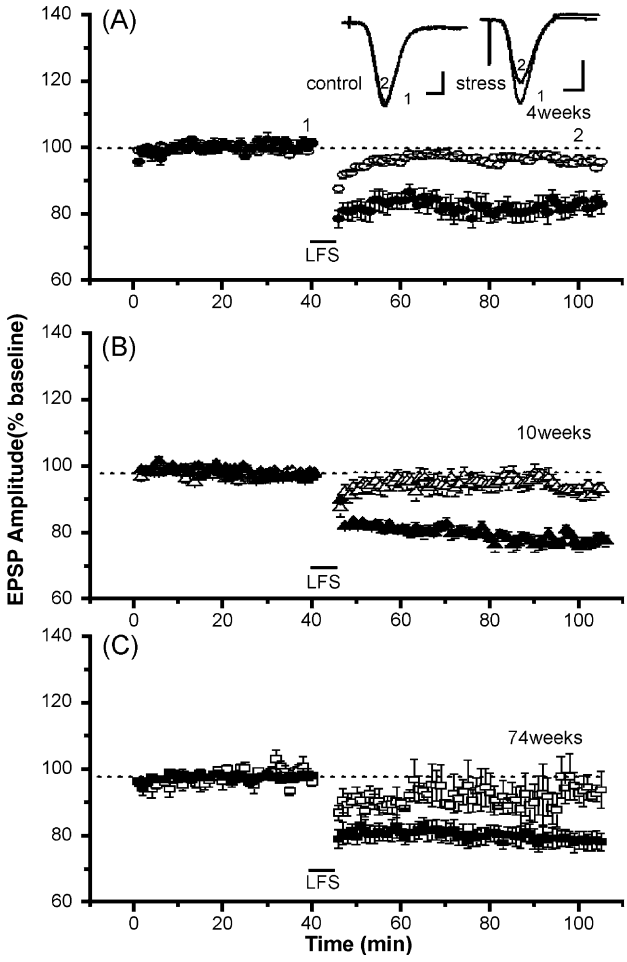

Fig. 2. Acute EP stress facilitated similar magnitude of LTD at three ages. (A) Rats did not show LTD without EP stress at 4 weeks old rats (95.43 ± 1.08%, $n=6$, $P>0.05$, ○), but acute EP stress facilitated the LTD induction after LFS (bar, 900 pulses at 3 Hz) (81.45 ± 2.89%, $n=5$, $P<0.05$, ●). The upper traces represented the sample traces before (1) and after (2) LFS in naïve and stressed animals, respectively, of 4 weeks old rats. Scale bar: 1 mV, 10 ms. (B) Same as at 4 weeks old rats, 10 weeks old rats exhibited no LTD in naïve but reliable LTD with acute EP stress (94.67 ± 1.61%, $n=7$, $P>0.05$ in naïve, △; 78.96 ± 1.64%, $n=6$, $P<0.05$ in stressed group, ▲). (C) 74 weeks old rats showed no LTD in naïve but LTD with acute EP stress (96.74 ± 4.56%, $n=3$, $P>0.05$ in naïve, □; 79.88 ± 2.81%, $n=9$, $P<0.05$ in stressed rats, ■). All data was respectively compared with baseline themselves. The results concluded that acute EP stress facilitated similar magnitude LTD at these three ages.

4.56%, $n=3$, open squares, $P>0.05$, Fig. 2C, respectively, compared with their baselines). However, exposure to acute EP stress enabled significant LTD induction ($81.45 \pm 2.89\%$ in 4 weeks, $n=5$, $P<0.05$, filled circles; $78.96 \pm 1.64\%$ in 10 weeks, $n=6$, $P<0.05$, filled triangles; $79.88 \pm 2.81\%$ in 74 weeks, $n=9$, $P<0.05$, filled squares, respectively, compared with their baselines). Interestingly, no difference of LTD magnitude was observed among these three stressed groups ($81.45 \pm 2.89\%$, $78.96 \pm 1.64\%$ and $79.88 \pm 2.81\%$ at 4, 10 and 74 weeks old rats, $P>0.05$, compared with each others).

The present data demonstrated that rats showed no LTD in naïve, whereas all the rats exhibited a similar magnitude of LTD after acute EP stress, suggesting this type of synaptic plasticity (i.e., SLTD) may relate to stress experience form of aberrant memory since the stress experience can be memorized for life whenever it happened at young, adult or old ages.

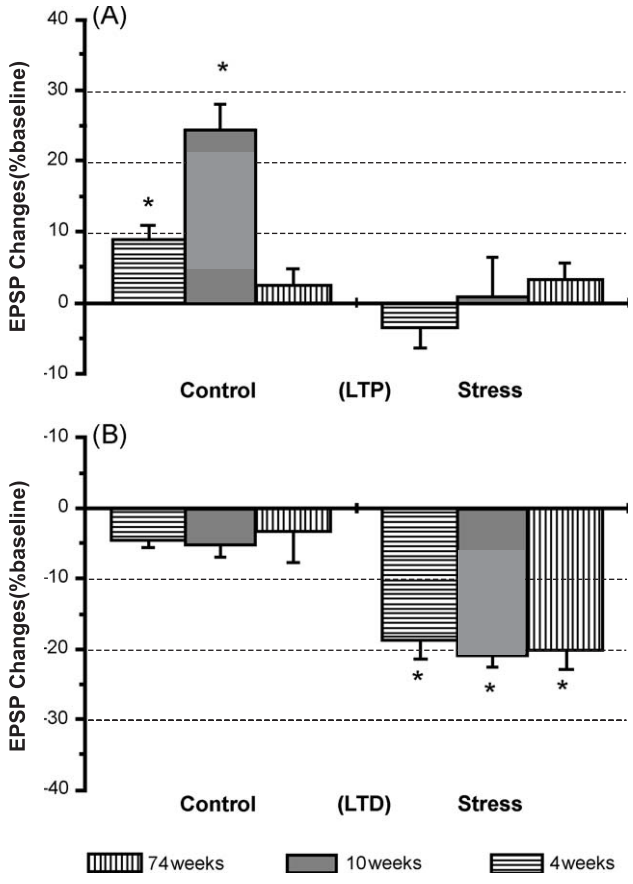

Fig. 3. Summaries of LTP and LTD induction in naïve and stressed animals at three ages. (A) Again, LTP induction after 200 Hz HFS appeared notably inverted-U shape related to three ages in naïve ($108.88 \pm 1.96\%$, $n=6$; $124.49 \pm 3.55\%$, $n=11$ and $102.49 \pm 2.35\%$, $n=3$, at 4, 10 and 74 weeks old rats, respectively, $P<0.05$, compared with each others). All rats showed no LTP in acute EP stressed rats ($96.51 \pm 2.93\%$, $n=3$; $100.75 \pm 5.66\%$, $n=3$; $103.08 \pm 2.50\%$, $n=5$, at 4, 10 and 74 weeks rats individually, $P>0.05$, compared with their baselines). (B) However, the animals exhibited no LTD after 3 Hz LFS ($95.43 \pm 1.08\%$, $n=6$; $94.67 \pm 1.61\%$, $n=7$; $96.74 \pm 4.56\%$, $n=3$, $P>0.05$, compared with their baselines individually) at 4, 10 and 74 weeks old rats. All rats showed similar magnitude of LTD after LFS in stressed rats ($81.45 \pm 2.89\%$, $n=5$; $78.96 \pm 1.64\%$, $n=6$; $79.88 \pm 2.81\%$, $n=9$; $P<0.05$, compare with their baselines; $P>0.05$ compared with each other at these three ages). The asterisk (*) represents the significance ($P<0.05$).

3.3. Summaries of LTP and LTD induction

We summarized the LTP and LTD induction between naïve and stressed animals at 4, 10 and 74 weeks old rats, respectively. LTP induction showed inverted-U shape in naïve but not in stressed animals (Fig. 3A); LTD was reliably induced in stressed but not in naïve rats (Fig. 3B), at these three ages.

4. Discussion

Our findings demonstrated that: first, stress impaired LTP induction and facilitated LTD induction at 4, 10 and 74 weeks old rats; secondly, the magnitude of LTP exhibited inverted-U shape related to these three ages in naïve rats. Importantly, although stress impaired the LTP induction of 4 and 10 weeks old rats, and the LTP induction was impaired both in naïve and stressed rats of 74 weeks old, the LTD induction significantly appeared a similar magnitude among 4, 10 and 74 weeks old rats after exposure to acute EP stress, strengthening our previous finding that the stress experience-dependent LTD (SLTD) may underlie the stress form of aberrant memory [53].

4.1. The inverted-U shape of LTP related to these ages

Hebbian hypothesis has described that synaptic activity is related to learning and memory (1949) [21]. Subsequently, two forms of synaptic plasticity (LTP and LTD), which well supported the hypothesis and implicated the role of synaptic plasticity in learning and memory, were found in 1980s [10].

As showed in Fig. 3, the magnitude of LTP obviously exhibited inverted-U shape related to three ages (at 4, 10 and 74 weeks old rats) in anesthetized rats, consent with previous studies in vitro from young (2 month) and old (24 month) Fischer 344 rats and Teyler's results about the *N*-methyl-D-aspartate (NMDA) and voltage-dependent calcium channel (VDCC)-dependent LTP [39,47]. Most researches have showed LTP impairment at aged animals in vitro and in vivo [6,31,42,45], but LTP is induced easily in adult animals [8]. Moreover, a developmental switch in the signaling cascades exists for LTP induction, and the stability of LTP in slice increasing with age relates to different ratios of the α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) and NMDA receptors, in the hippocampus of very young rats [19,20,30,58]. Recently, the developmental change shows in spike-timing-dependent LTP induction of juvenile and young adult rats [37]. These reports indicate the rationality of the different magnitudes of LTP among 4, 10, and 74 weeks old rats in the present findings. In addition,

stress blocked LTP induction at these ages, in agreement with previous reports [13,29,45].

4.2. The similar magnitude of LTD after stress at these ages

It is well known that LTP plays a necessary role in hippocampal-dependent learning and memory [9,11,40], whereas, although LTD has been suggested in certain types of learning and memory [34,41], it remains elusive.

Some sorts of stress are unavoidable in daily life and the experience can be memorized for life. Since stress impairs LTP induction and forms strong memory [35], and many forms of experience-dependent synaptic plasticity have been suggested to involve chronic pain [52], drug addiction [44,49], etc., stress experience-dependent LTD (SLTD) may be also related to this form of aberrant memory [53]. In the present studies in vivo, EP stress significantly enabled a similar magnitude of SLTD at 4, 10 and 74 weeks old rats. It is known that the induction of LTD is somewhat difference between in vivo and in vitro, and among different ages. Norris et al. [42] reported age dependence of LTD which can be reliably elicited in the CA3–CA1 synapses of old (~ 108 weeks), but not of adults (~ 28 weeks) Fischer 344 rats, in vitro. Furthermore, low-frequency stimulation (1–5 Hz) also failed to induce LTD in the hippocampus of adult rats in vivo, except very young rats (10–11 days) [15].

Why stress always enabled LTD at different ages? (1) Stressful events, caused the release of adrenal hormones (e.g., glucocorticoids), block the induction of LTP and facilitate LTD induction in the hippocampus [29,35,43,55], since the area enriches glucocorticoid receptors, a target of corticosterone [28]. Moreover, we have reported the corticosterone levels show similar increases after elevated platform stress (used in the present studies) at 4, 10 and 76 weeks old rats [57]. This suggests that the activation of the glucocorticoid receptor may effectively lower the threshold of LTD induction [12,26]. (2) The metaplasticity that prior synaptic activity can influence the subsequent induction of synaptic plasticity is the plasticity of synaptic plasticity, and stress may change the metaplasticity to enable LTD induction [1,25,26]. Metaplasticity has been observed as an inhibition of LTP and a facilitation of LTD by prior activation of the NMDA receptor [18,38] or, conversely, a facilitation of LTP induction by prior activation of the metabotropic glutamate receptor [2]. Thus, the Bienenstock, Cooper, and Munro (BCM) theory of synaptic plasticity, similar to the ABS rule suggested by Artola and Singer [4,7], may well explain the effects of stress on LTD induction. That is, stress may regulate the threshold of BCM model, and then contribute to the facilitation of LTD induction [12]. (3) It has been documented that theta rhythm changes in the hippocampus during/after stress [27,56]. A same burst stimulation at the peak and trough of theta activity induced LTP and LTD, respectively, suggesting the importance of theta rhythms in synaptic plasticity [22]. Exposure to acute stress increased theta activity and the cessation of stress transiently decreased synaptic efficacy [48]. Thus, stress may facilitate LTD induction through theta activity. All these mechanisms could happen to enable LTD induction under stressful condition at different ages.

Present findings that stress facilitates LTD but impairs LTP induction at different ages strengthen a view that SLTD may underlie stress form of aberrant memories [53,57].

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