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Stress reverses plasticity in the pathway projecting from the ventromedial prefrontal cortex to the basolateral amygdala

Mouna Maroun
The Brain and Behaviour Research Center, Department of Neurobiology and Ethology, Faculty of Science and Science Education, University of Haifa, Haifa 31905, Israel

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Abstract

We have previously shown that high-frequency stimulation to the basolateral amygdala (BLA) induces long-term potentiation (LTP) in the ventromedial prefrontal cortex (vmPFC) and that prior exposure to inescapable stress inhibits the induction of LTP in this pathway [Maroun & Richter-Levin (2003) *J. Neurosci.*, **23**, 4406–4409]. Here, we show that the reciprocal pathway projecting from the vmPFC to the BLA is resistant to the induction of LTP. Conversely, long-term depression (LTD) is robustly induced in the BLA in response to low-frequency stimulation to the vmPFC. Furthermore, prior exposure to inescapable stress reverses plasticity in this pathway, resulting in the promotion of LTP and the inhibition of LTD. Our findings suggest that, under normal and safe conditions, the vmPFC is unable to exert excitatory synaptic plasticity over the BLA; rather, LTD, which encodes memory of safety in the BLA, is favoured. Following stressful experiences, LTP in the BLA is promoted to encode memory of fear.

Introduction

Previous exposure to both acute and chronic stressful events can facilitate amygdala-dependent memory processes such as the classical conditioning of tasks, including fear conditioning (Shors *et al*., 1992; Beylin & Shors, 1998; Shors, 2001; Cordero *et al*., 2003; Rodríguez Manzanares *et al*., 2005). Moreover, exposure to acute inescapable stress has also been reported to enhance the induction of long-term potentiation (LTP) in the basolateral amygdala (BLA; e.g. Vouimba *et al*., 2004; Rodríguez Manzanares *et al*., 2005).

Recent rodent studies show that exposure to inescapable stress, which activates the amygdala, causes dendritic retraction in the infralimbic subregion of the ventromedial prefrontal cortex (vmPFC), and resistance to fear extinction (Izquierdo *et al*., 2006; Miracle *et al*., 2006) and to inhibition of the induction of LTP in the vmPFC (Maroun & Richter-Levin, 2003; Rocher *et al*., 2004).

There are close anatomical and functional interactions between the vmPFC (composed of the infralimbic and the prelimbic subdivisions) and the amygdala (Krettek & Price, 1977; Porrino *et al*., 1981; Ottersen, 1982; Kita & Kitai, 1990; Davis *et al*., 1994; Garcia *et al*., 1999; Martijena *et al*., 2002; Charney, 2003; Maroun & Richter-Levin, 2003; Gabbott *et al*., 2005). It has previously been reported that the vmPFC is capable of modulating activity in the amygdala as part of reducing fear. This notion is based on findings that: (i) lesions of the vmPFC prolong the maintenance of a conditioned aversive response (Morgan *et al*., 1993); (ii) vmPFC stimulation inhibits conditioned fear (Milad & Quirk, 2002); and (iii) subjects with post-traumatic stress disorder have reduced vmPFC activity during trauma recall (Bremmer *et al*., 1999).

Notwithstanding the burgeoning understanding of the functional interaction between the vmPFC and the BLA, and of the recent findings demonstrating that stress can affect fear conditioning and extinction, a number of critical questions remain. These questions relate to how the vmPFC may influence activity and plasticity in the BLA under normal, nonstressful conditions and, particularly, whether exposure to inescapable stress influences the way the vmPFC can affect activity and plasticity in the BLA.

We undertook the present series of experiments: (i) to assess whether the vmPFC–BLA pathway is amenable to the induction of LTP and LTD; and (ii) to further explore whether plasticity in this pathway is modified following exposure to stress, similarly to what occurs in the hippocampus (e.g. Foy *et al*., 1987; Bennett *et al*., 1991; Diamond *et al*., 1992; Diamond & Rose, 1994; Kim *et al*., 1996; Pavlides *et al*., 1996; Garcia *et al*., 1997; Xu *et al*., 1997, 1998; Kim & Yoon, 1998; Manahan-Vaughan, 2000; Yang *et al*., 2004, 2005). To this end, we delivered a range of high- or low-frequency stimulation (HFS or LFS) protocols, known to be effective in inducing LTP/LTD, respectively in other brain pathways, to the vmPFC of anaesthetized rats and measured the evoked field potential responses in the BLA.

HFS protocols failed to induce LTP in the vmPFC–BLA pathway, whereas the application of LFS reliably induced LTD. Our results also show that 30 min of exposure to an elevated platform reliably and robustly promoted the induction of LTP and inhibited the induction of LTD in the BLA.

Materials and methods

Electrophysiology

Male Sprague–Dawley rats (280–380 g) were anaesthetized (with 40% urethane and 5% chloral hydrate in saline; 0.5 mL/100 g, i.p.) and placed in a stereotaxic frame, with body temperature maintained at 37 ± 0.5 °C. The procedures were performed in strict accordance with University of Haifa regulations and National Institute of Health guidelines (NIH publication number 8023). In brief, small holes were

Correspondence: Dr Mouna Maroun, as above.
E-mail: mmaroun@psy.haifa.ac.il

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drilled into the skull to allow the insertion of electrodes into the brain. A single recording microelectrode (glass, tip diameter of 2–5 μm, filled with 2 M NaCl; resistance of 1–4 MΩ) was slowly lowered into the BLA (anteroposterior, −3 mm relative to bregma; lateral, 5.0 mm; ventral, −7.6 mm; Paxinos & Watson, 1998).

A bipolar 125 μm stimulating electrode was implanted in the area of the vmPFC (anteroposterior, +3 mm relative to bregma; lateral, 0.05 mm; ventral, −5 mm). The evoked responses were digitized (10 kHz) and analysed, using the Cambridge Electronic Design (Cambridge, UK) 1401+ and its Spike2 software. Offline measurements were made of the amplitude of field postsynaptic potentials (fPSPs), using averages of five successive responses to a given stimulation intensity applied at 0.1 Hz. Test stimuli (monopolar pulses; 100 μs duration) were delivered at 0.1 Hz. After positioning the electrodes, the rats were left for 30 min before commencing the experiment.

Protocols for LTP induction

HFS protocols

A. Theta-like HFS at 100 Hz (TS-100) to the vmPFC (three sets of 10 trains; each train consisted of 10 pulses at 100 Hz; intertrain interval of 200 ms; interset interval of 1 min).

B. Theta-like HFS at 400 Hz (TS-400) to the vmPFC (three sets of 10 trains; each train consisted of 10 pulses at 400 Hz; intertrain interval of 200 ms; interset interval of 1 min).

C. HFS at 100 Hz (HFS-100) to the vmPFC (three trains at 100 Hz, 1 s, at 3-min intervals).

LFS

This consisted of 900 pulses delivered at 1 Hz, at the same stimulation intensity and pulse duration (100 μs) as the test stimuli. This protocol was previously shown to effectively induce LTD in the hippocampal CA1 subregion *in vivo* (Manahan-Vaughan *et al*., 2000).

For all the experiments, baseline responses were established by means of delivering a stimulation intensity (50–150 μA) sufficient to elicit a response representing ∼25–30% of the maximal amplitude of the evoked field potentials.

The different protocols for HFS and LFS were delivered at the same intensity and pulse duration as the test stimuli during establishment of the baseline responses. Evoked field potentials at the baseline intensity were recorded from the BLA for up to 60 min following the application of HFS or LFS. LTP and LTD were measured as an increase or decrease, respectively, in fPSP amplitude. Changes in the fPSP amplitude were measured as a percentage change from the baseline.

Stress protocol

Rats were exposed to stress in a brightly lit room. Stress was evoked by placing the rats on an elevated platform (12 × 12 cm) for 30 min. This protocol has been shown to induce behavioural (freezing, urination and defecation) and endocrinal (elevated serum corticosterone levels) signs of stress in rats (Xu *et al*., 1997).

After the termination of the stressor, rats were immediately anaesthetized and taken for electrophysiological testing.

Histology

Histological verification of the locations of both the recording and stimulating electrodes was performed in all of the rats. After the electrophysiological testing, marking lesions were made by passing anodal currents (10 mA for 3 s and 10 mA for 2 min) through the metal bipolar stimulating electrode and recording electrode, respectively. The rats' brains were removed, postfixed for three nights in formaldehyde (10%), and sectioned (120 μm) on a sledge microtome. The sections were then mounted on gelatin-coated slides, stained with Cresyl Violet, dehydrated and cover-slipped. Following this procedure, the electrode tract and lesion locations were identifiable under a light microscope. The locations of the recording and stimulating sites in the vmPFC and BLA are shown in Fig. 1.

Statistical analysis

Differences were determined using ANOVA and *t*-tests. All *post hoc* comparisons were made using the least significant difference multiple comparison test.

Results

The vmPFC–BLA pathway was resistant to the induction of LTP

Stimulation of the vmPFC elicited negative fPSPs in the BLA, and these peaked after 18–25 ms. The shape, amplitude and latency of

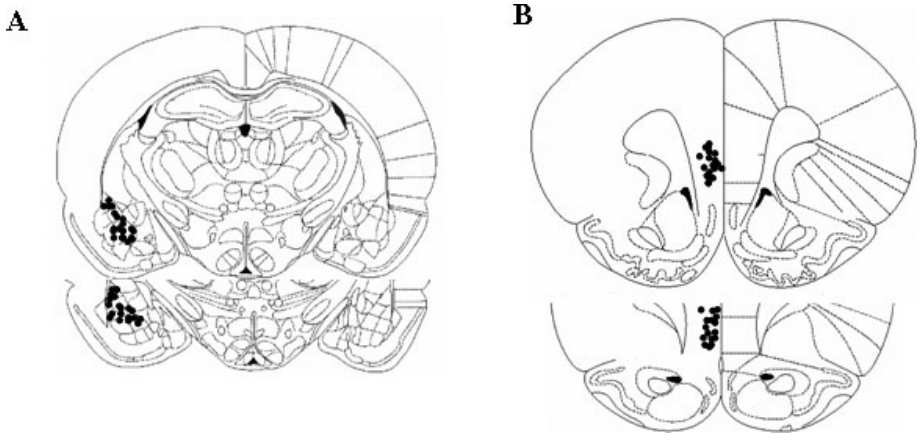

FIG. 1. Schematic diagram presenting the location of the electrodes (indicated by solid black circles in A and B). (A) Recording electrodes in the BLA (anteroposterior, −3 mm relative to bregma; lateral, 5 mm; ventral, −7.6 mm). (B) Stimulating electrodes in the ventromedial prefrontal area (anteroposterior, +3 mm relative to bregma; lateral, 0.05 mm; ventral, −5 mm).

these potentials were highly reproducible and remained stable over time.

After establishing that vmPFC stimulation induces evoked field potentials in the BLA, we assessed whether the vmPFC–BLA pathway was amenable to the induction of LTP. Overall, four groups of rats were tested. One group was utilized for baseline intensity control (base intensity, $n = 4$) with the remaining three groups receiving one of the HFS protocols (described above) that induce LTP, namely: a theta-like pattern at 100 Hz (TS-100; $n = 7$); a theta-like pattern at 400 Hz (TS-400; $n = 7$); or HFS at 100 Hz (HFS-100; $n = 6$).

An ANOVA conducted on the fPSP amplitudes from the different time points following HFS [groups × time (4 × 5)] did not reveal a significant difference at any time point [$F_{3,20} < 1$; NS (not significant)]; see Fig. 2. The three HFS groups did not differ from the baseline-intensity stimulation group. Hence, HFS to the vmPFC failed to induce LTP of the fPSP amplitude in the BLA.

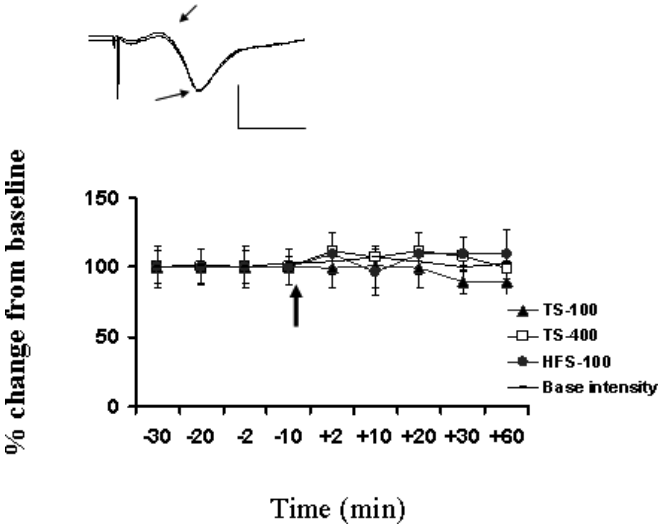

FIG. 2. HFS failed to induce LTP in the vmPFC–BLA circuitry. Main graph, application of a varying range of HFS and theta-like protocols to the vmPFC failed to induce LTP in the BLA. The level of potentiation in the four groups tested (TS-100, TS-400, HFS-100 and stimulation at baseline intensity) was not significantly different from 100% at any time point. Arrow denotes the time of the application of electrical stimulation. Top left corner, representative evoked field potentials in the BLA during vmPFC stimulation immediately before and 60 min after electrical stimulation. The baseline and the response following electrical stimulation are superimposed and are averages of 20 evoked responses each. The dashed line is the baseline and the thick line is the response following electrical stimulation. Arrows denote the points taken for amplitude measurement. Calibration bars, 0.2 mV, 10 ms.

Acute stress induced LTP and blocked LTD in the vmPFC–BLA pathway

The previous experiment showed that different protocols of HFS and theta-like stimulation failed to induce LTP in the vmPFC–BLA pathway. Here, we were interested in addressing the following: (i) whether the vmPFC–BLA pathway is resistant to the induction of all forms of plasticity, including LTD; (ii) whether, similarly to what occurs in other pathways projecting to the BLA (i.e. the entorhinal cortex–BLA pathway; Vouimba *et al*., 2004), exposure to inescapable stress promotes the induction of LTP; and (iii) whether LTD is affected by prior exposure to behavioural stress.

Four groups were tested: TS-100 (using TS-100, as it is the weakest of the HFS protocols; $n = 8$); TS-100 following exposure to the elevated platform stressor (Stress–TS-100; $n = 9$); LFS (1 Hz; $n = 9$); and LFS following exposure to the elevated platform stressor (Stress–LFS; $n = 8$; Fig. 3).

We first assessed whether stress enhanced the fPSP amplitude of the baseline for the stressed vs. the unstressed groups and found that it did not (mean ± SEM; TS-100, 0.89 ± 0.087; Stress–TS-100, 0.966 ± 0.081; LFS, 0.908 ± 0.82; Stress–LFS, 1.047 ± 0.094 mV). To confirm this observation, we performed an overall mixed ANOVA [groups × time (4 × 4)] comparison between the groups before application of TS-100 or LFS. This did not reveal a significant difference in the fPSP amplitude at any time point ($F_{3,30} < 1$, NS), indicating a similar baseline for all groups. We further found that the stimulation intensity used to elicit a baseline response was not different between the different groups ($F_{3,33} < 1$, NS; stimulation intensity 50–150 μA).

We then considered the post-TS-100 and post-LFS results. ANOVA conducted on the fPSP amplitude results at the different time points post-TS-100 and post-LFS [groups × time (4 × 5)] revealed a significant difference between the groups ($F_{3,30} = 13.762$, $P = 0.001$; Fig. 3). *Post hoc* analysis showed these differences to be significant: the TS-100 group significantly differed from the Stress–TS-100 group ($P < 0.05$) and the LFS group significantly differed from the Stress–LFS group ($P < 0.001$).

Analysis of the difference between the post-TS-100 results of the TS-100 group compared to those from the Stress–TS-100 group revealed a significant difference at all the time points tested (+2 min, $F_{1,15} = 9.09$, $P < 0.001$; +10 min, $F_{1,15} = 13.01$, $P < 0.005$; +20 min, $F_{1,15} = 16.23$, $P > 0.005$; +30 min, $F_{1,15} = 6.58$, $P > 0.05$; +60 min, $F_{1,15} = 6.81$, $P < 0.05$; Fig. 3). By contrast, 30 min exposure to stress did not affect the amplitude of the evoked field potentials in the vmPFC–BLA pathway recorded during baseline recordings taken prior to application of TS-100 or LFS ($F_{1,15} < 1$; NS).

These results for the TS-100 and Stress–TS-100 groups show that, similarly to what occurs in other pathways projecting to the BLA (e.g. the entorhinal cortex–BLA pathway; Vouimba *et al*., 2004), exposure to inescapable stress prior to HFS promoted the induction of LTP in the vmPFC–BLA pathway.

In the LFS group, we found that depression levels significantly differed from 100% at all time points post-LFS [*t*-tests for difference from baseline (100%): +1 min, $t_8 = -4.32$, $P < 0.003$ (25.2 ± 5.7%); +10 min, $t_8 = -4.37$, $P < 0.005$ (28.65 ± 6.5%); +20 min, $t_8 = -5.450$, $P < 0.02$ (29.21 ± 5.3); +30 min, $t_8 = -3.64$, $P < 0.01$ (29.74 ± 7.6); +60 min, $t_8 = 4.29$ $P < 0.05$ (29.22 ± 6.3%); see Fig. 3].

Further analysing the post-LFS results from the LFS group compared to those from the Stress–LFS group revealed a significant difference between the groups at all the time points tested (+2 min, $F_{1,15} = 12.64$, $P < 0.005$; +10 min, $F_{1,15} = 8.47$, $P < 0.05$; +20 min, $F_{1,15} = 7.40$, $P > 0.05$; +30 min, $F_{1,15} = 7.34$, $P > 0.05$; +60 min, $F_{1,15} = 9.42$, $P < 0.01$; Fig. 3).

These results for the LFS and Stress–LFS groups show that the vmPFC–BLA pathway was amenable to the induction of LTD under normal and nonstressful conditions. By contrast, exposure to behavioural stress completely blocked the induction of LTD in the BLA in the Stress–LFS group [*t*-test for difference from baseline (100%): $t_7 < 1$; NS for all time-points; see Fig. 3].

Discussion

In this study, we examined activity-dependent changes in the BLA in response to vmPFC stimulation. Single electrical pulse stimulation of

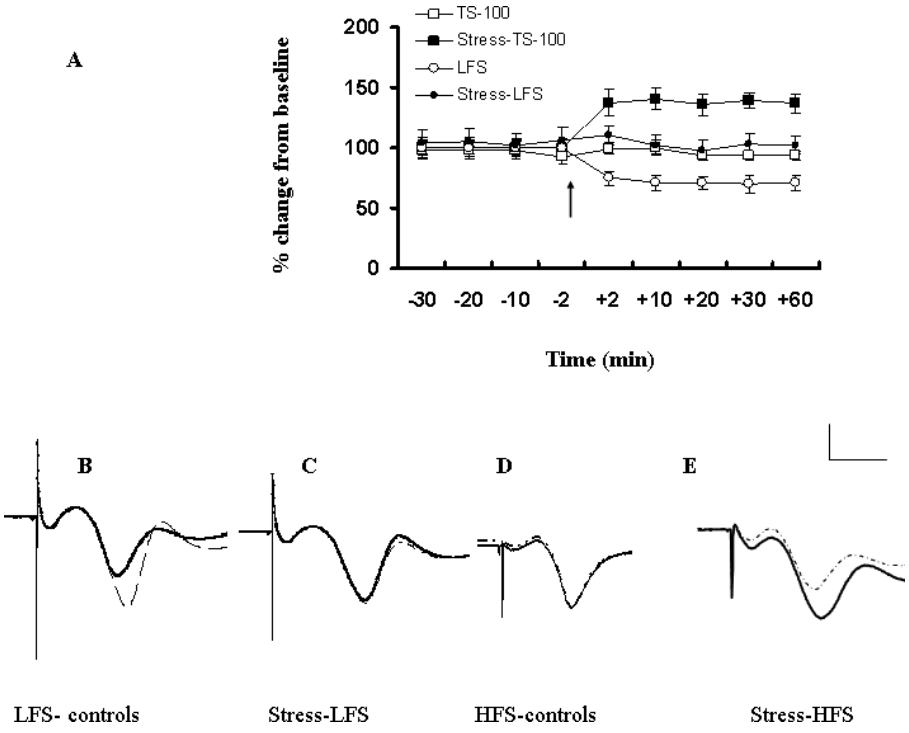

FIG. 3. (A) Four groups were tested: TS-100 (HFS using a theta-like pattern at 100 Hz); Stress–TS-100 (TS-100 following exposure to an elevated platform stressor); LFS (low frequency stimulation at 1 Hz); and Stress–LFS (LFS following exposure to an elevated platform stressor). Following electrical stimulation, a significant difference in the amplitude of the fPSP was found between the TS-100 group and the Stress–TS-100 group ($P < 0.05$), as well as between the LFS and the Stress–LFS group ($P < 0.001$). Thus, while stress promoted the induction of LTP in the vmPFC–BLA pathway, it inhibited the induction of LTD. Bottom (B–E), representative evoked field potentials in the BLA immediately before and 60 min after TS-100 or LFS stimulation of the vmPFC. The baseline (dashed line) and the response (thick line) traces following TS-100 or LFS are superimposed and are averages of 20 evoked responses each. The arrow in A denotes the time of the application of TS-100 or LFS. (B) Control rats + LFS; representative evoked field potentials in the BLA taken from control rats pre- and post-LFS of the vmPFC. (C) Stressed rats + LFS; representative evoked field potentials in the BLA taken from stressed rats pre- and post-LFS of the vmPFC. (D) Control rats + TS-100; representative evoked field potentials in the BLA taken from control rats pre- and post-TS-100 of the vmPFC. (E) Stressed rats + TS-100; representative evoked field potentials in the BLA taken from stressed rats pre- and post TS-100 of the vmPFC. Calibration bars, 0.2 mV, 10 ms.

the vmPFC evoked consistent fPSPs in the BLA, suggesting that stimulation of the vmPFC excites neuronal firing in the BLA. Nevertheless, the same protocols of HFS, which are routinely applied to induce robust and long-lasting LTP in the hippocampus and in the vmPFC (e.g. Maroun & Richter-Levin, 2003), failed to induce LTP in the BLA, suggesting that this pathway is not amenable to the induction of excitatory synaptic plasticity.

LTP has been induced in several pathways that transmit input from cortical areas to the amygdala *in vivo* (Racine *et al*., 1983; Yaniv *et al*., 2001; Doyere *et al*., 2003). Our findings are the first to report resistance to the induction of LTP in the BLA *in vivo*. It should be noted that *in vitro* studies showed that HFS to the external capsule induced short-term, but not long-term, synaptic enhancement in the BLA (Li *et al*., 1998) and in the lateral amygdala (Watanabe *et al*., 1995, 1996).

Conversely, under the same conditions, the induction of LTD in the vmPFC–BLA pathway is favoured over the induction of LTP. The induction of LTD has been previously reported *in vitro* in the lateral BLA synapses (Wang & Gean, 1999; Rammes *et al*., 2000; Lin *et al*., 2003). However, to the best of our knowledge, this study is the first to report LTD in the BLA *in vivo*. Thus, our study shows for the first time that the vmPFC–BLA pathway is resistant to the induction of LTP and amenable to the induction of LTD.

A central finding of this study is that 30 min of exposure to inescapable stress effectively reversed plasticity in the vmPFC–BLA pathway. Exposure to stress promoted the induction of LTP in the BLA as a response to vmPFC stimulation, but completely inhibited the induction of LTD. The stress protocol used, namely the elevated platform stressor, has previously been shown to impede the induction of LTP and facilitate the induction of LTD in the hippocampus (Foy *et al*., 1987; Bennett *et al*., 1991; Diamond *et al*., 1992; Diamond & Rose, 1994; Kim *et al*., 1996, 1998; Pavlides *et al*., 1996; Garcia *et al*., 1997; Xu *et al*., 1997, 1998; Kim & Yoon, 1998; Akirav & Richter-Levin, 1999; Manahan-Vaughan, 2000; Wang *et al*., 2000; Maroun & Richter-Levin, 2003; Vouimba *et al*., 2004; Yang *et al*., 2004, 2005). Moreover, exposure to the elevated platform stressor has been shown to impair the induction of LTP in the BLA–vmPFC pathway (Maroun & Richter-Levin, 2003) and in the hippocampus–vmPFC pathway (Rocher *et al*., 2004).

We find the opposite result, at least with respect to the hippocampus, regarding alterations in LTP–LTD following exposure to acute stress. Thus, this study supports the stance that stress may differentially affect synaptic plasticity in the amygdala and the hippocampus and related areas (including the vmPFC) and, as a consequence, alter the way memory is processed.

The emotional state generated by stress can act as a filter to determine which information is retained and the accuracy with which that retention occurs (Rodríguez Manzanares *et al*., 2005). The amygdala is responsible for fear learning and memory (Brambilla *et al*., 1997; Rogan *et al*., 1997; Fanselow & LeDoux, 1999; Maren, 1999; LeDoux, 2000; but see Cahill *et al*., 1999); hence, increased emotionality should be sustained by corresponding changes in the plasticity in the amygdala. In support of this, it has been shown that heightened emotionality, as occurs during fear-provoking experiences, enhances the induction of synaptic plasticity in the amygdala (McKernan & Shinnick-Gallagher, 1997; Rogan *et al*., 1997; Vouimba *et al*., 2004; Rodríguez Manzanares *et al*., 2005). It has also been shown that exposure to both acute and chronic stressful events can positively affect classical conditioning of tasks, including fear conditioning (Shors *et al*., 1992, 2001; Beylin & Shors, 1998; Cordero *et al*., 2003; Rodríguez Manzanares *et al*., 2005). Accordingly, our data show that arousal, or the motivational state induced by an acutely stressful situation, modifies activity in vmPFC–BLA synapses and makes them amenable to the induction of LTP, presumably to promote information storage about danger and fear. These results corroborate previous *in vitro* studies showing that LTP in restrained rats was generated by a stimulation paradigm that was insufficient in control animals (Rodríguez Manzanares *et al*., 2005). Moreover, it has been reported that platform stress also facilitates induction of LTP in the entorhinal cortex–basal amygaloid nucleus pathway *in vivo* (Vouimba *et al*., 2004; but see Kavushansky *et al*., 2006).

It should be noted that, in contrast to previously reported data (e.g. Vouimba *et al*., 2004; Kavushansky *et al*., 2006), we did not observe enhanced amygdala-evoked field potentials in the baseline readings from the stressed groups. Thus, changes in LTP following exposure to stress could be attributed not to alterations in the basal transmission but rather to a specific facilitation of activity-dependent plasticity in the vmPFC-to-BLA pathway.

Based on the functional role of the vmPFC in promoting extinction rather than preservation of fear memories, it seems reasonable that LTP in the BLA, as a response to vmPFC stimulation, is unlikely to be induced under normal conditions. Ultimately, the lack of these excitatory plastic events may prevent the augmentation of BLA-dependent affective behaviour and the persistence of fear and anxiety (Morgan & LeDoux, 1995; Jinks & McGregor, 1997). This regulation of the vmPFC over the BLA is reduced following stress and fear. In support of this, Correll *et al*. (2005) have shown that a lesion to the PFC afferents resulted in enhanced responsiveness of central amygdala neurons to footshock, whereas this same lesion blunted the further augmentation of the response to footshock after chronic cold exposure when compared with nonlesioned animals. The authors concluded that the PFC usually regulates central amygdala neuronal responsiveness and that this regulation is reduced after chronic stress. Furthermore, extinction of fear, a task that is dependent on an intact vmPFC, is impaired following exposure to behavioural stress (Izquierdo *et al*., 2006; Akirav & Maroun, unpublished observation). Taken together, these results show that stress reduces vmPFC control over amygdala-mediated responses.

Our present work on the vmPFC–BLA pathway, together with previously reported findings on the reverse BLA–vmPFC pathway (Maroun & Richter-Levin, 2003), are evidence as to how plasticity in a circuit could be differentially modified following exposure to stress. Taken together, we propose that, while LTP of the vmPFC is a mechanism for fear extinction, LTD in the vmPFC could be a mechanism for resistance to extinction. This hypothesis is supported by recent work by Herry & Garcia (2002), who reported that prefrontal cortex LTP in response to thalamic HFS is associated with maintenance of extinction. In contrast, the persistence of LTD is associated with the return of learned fear.

Our finding that LTD is favoured over the induction of LTP in the vmPFC–BLA pathway suggests that, under nonstressful conditions, LTD in the BLA encodes the memories of safety and absence of danger whereas, when exposed to an aversive emotional experience, LTD in the BLA is inhibited to promote LTP induction, which encodes the memory of fear (Maren & Fanselow, 1996). It has been suggested recently by Rogan *et al*. (2005) that learned safety involves a reduction in the information flow to the amygdala by an LTD-like mechanism. This hypothesis is supported by previous findings that LTD of the amygdala is implicated in the reduction of conditioned fear responses. The same LFS that induces LTD in the amygdala has been shown to attenuate conditioned fear responses (Lin *et al*., 2003). It has been proposed that post-traumatic stress disorder may represent a form of conditioned fear in which there is a failure of extinction mechanisms (Charney *et al*., 1993). Thus, strategies that promote enduring synaptic depression could be used therapeutically (Li *et al*., 1998).

In support of these hypotheses, Marsicano *et al*. (2002) have shown that mice lacking cannabinoid receptor 1 exhibited impaired fear extinction consolidation, enhanced excitatory LTP in the BLA as a result of HFS to the external capsule, and inhibition of the induction of $GABA_A$ receptor-mediated inhibitory postsynaptic currents.

Our findings constitute the first evidence for bi-directional plasticity (LTD–LTP) in the vmPFC–BLA pathway, which is altered following exposure to an emotional behavioural stress. Our findings for the vmPFC–BLA pathway reverse those reported for the hippocampus. The relevance of this bi-directional mechanism is of crucial importance to extinction of fear, and alterations in LTP–LTD could be associated with inappropriate expression of aversive memories.

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Abbreviations

BLA, basolateral amygdala; fPSP, field postsynaptic potential; HFS, high-frequency stimulation; HFS-100, HFS at 100 Hz; LFS, low-frequency stimulation; LTP, long-term potentiation; NS, not significant; TS-100, theta-like HFS at 100 Hz; TS-400, theta-like HFS at 400 Hz; vmPFC, ventromedial prefrontal cortex.

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