Medial prefrontal cortex activation facilitates re-extinction of fear in rats

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It has been suggested that reduced infralimbic (IL) cortical activity contributes to impairments of fear extinction. We therefore explored whether pharmacological activation of the IL would facilitate extinction under conditions it normally fails (i.e., immediate extinction). Rats received auditory fear conditioning 1 h before extinction training. Immediately prior to extinction, rats received microinfusions into the IL of the GABA_A receptor antagonist, picrotoxin, or the NMDA receptor partial agonist, D-cycloserine. Although neither drug facilitated extinction, they both facilitated the subsequent re-extinction of fear when animals were trained in a drug-free state, suggesting that activating the IL primes behavioral extinction.

In recent years, there has been a growing interest in the behavioral and neural mechanisms of fear extinction (Maren 2005; Quirk and Mueller 2008; Herry et al. 2010). Notably, impairments in this form of learning are associated with several anxiety disorders (Rasmusson and Charney 1997; Rosen and Schulkin 1998; Myers and Davis 2002; Wessa and Flor 2007; Mutigg et al. 2008). In rats and humans, extinction learning occurs when a conditioned stimulus (CS) that has been previously paired with an aversive unconditioned stimulus (US) is presented repeatedly in the absence of the US (LeDoux 2000; Pare et al. 2004; Maren 2005). Although repeated CS presentations lead to a loss of the conditioned fear response, this loss of fear is fragile and recovers with the passage of time and with changes in context (Pavlov 1927; Bouton et al. 2006; Myers and Davis 2007). Hence, extinction procedures do not erase the original fear memory, but yield a new safety memory that inhibits fear under certain conditions.

Considerable work indicates that fear extinction requires a distributed neural circuit in the brain including the amygdala, medial prefrontal cortex (mPFC), and hippocampus (LeDoux 2000; Maren and Quirk 2004; Pare et al. 2004). The hippocampus has a critical role in the contextual specificity of extinction (Corcoran and Maren 2001; Corcoran et al. 2005; Bouton et al. 2006), whereas the mPFC and amygdala are involved in the acquisition, consolidation, and recall of extinction memories (Fall et al. 1992; Santini et al. 2001; Milad and Quirk 2002; Santini et al. 2004; Burgos-Robles et al. 2007; Milad et al. 2007; Quirk and Mueller 2008). Within the mPFC, two regions in particular have been implicated in the expression of fear (Sierra-Mercado et al. 2010). The infralimbic division (IL) of the mPFC projects to inhibitory neurons in the amygdala involved in suppressing fear after extinction (Rosenkranz and Grace 2002; Pare et al. 2004; Liukhtik et al. 2008), whereas the prelimbic division projects to excitatory projection neurons involved in fear expression (McDonald et al. 1996; Liukhtik et al. 2005; Burgos-Robles et al. 2009). Within the mPFC, both GABAergic and glutamatergic synaptic transmission have been implicated in extinction learning. Specifically, microinfusions of GABA_A receptor agonists or NMDA receptor antagonists impair (Laurent and Westbrook 2008; Sotres-Bayon et al. 2009), whereas GABA_A receptor antagonists facilitate (Thompson et al. 2010), extinction memory in rats.

Despite these advances in understanding the neural mechanisms of extinction learning, less progress has been made in understanding the nature and causes of the extinction impairments that contribute to psychopathology in humans. In a recent human study (Milad et al. 2009), Milad and colleagues reported that patients with post-traumatic stress disorder exhibit extinction impairments that correlate with hypoactivity in the mPFC during extinction learning and recall. Interestingly, it has also been reported that extinction impairments in rats are associated with reduced neuronal function in the mPFC, particularly in IL (Milad and Quirk 2002; Izquierdo et al. 2006; Burgos-Robles et al. 2007; Chang et al. 2010). Indeed, we have recently found reduced spike bursting in IL neurons when extinction is conducted immediately after fear conditioning (Chang et al. 2010), a procedure that yields an “immediate extinction deficit” whereby CS-alone trials yield little to no long-term fear reduction (Maren and Chang 2006; Chang and Maren 2009; Kim et al. 2010).

Collectively, work in both rats and humans suggest that impaired extinction may be due to reduced neuronal activity in the mPFC during extinction learning. The present study aimed to test this hypothesis by examining whether pharmacologically facilitating mPFC function with either picrotoxin (a GABA_A receptor antagonist) or D-cycloserine (an NMDA receptor partial agonist) prior to an extinction session would rescue the immediate extinction deficit.

The subjects were 72 adult male Long-Evans rats (250–300 g) obtained from a commercial supplier (Harlan Sprague-Dawley), singly housed, and handled before the experiments. All experiments were carried out in accordance with guidelines approved by the University of Michigan University Committee on Use and Care of Animals. Eight identical observation chambers (MED-Associates) were used in the experiments. The floor of each chamber consisted of rods wired to a shock source and solid-state grid scrambler (MED-Associates) for the delivery of footshock US (0.5 sec; 1 mA). A speaker mounted outside a grating in one wall of the chamber was used for the delivery of acoustic CS (2 sec; 80 dB; 2 kHz). Illumination, odor, and ambient noise were manipulated to create two distinct contexts for the experiments. Each conditioning chamber rested on a load-cell platform that was used to record chamber displacement in response to each rat’s motor activity. Freezing was measured during the 1-min intertrial intervals after CS offset during conditioning, extinction,
and the retention test, and during the minutes preceding the first CS presentation of each session.

One week prior to fear conditioning, rats were implanted with a 26-gauge stainless-steel guide cannulae (Plastic On) aimed at the IL (AP +2.8 mm, ML +1.0 mm, DV −4.1 mm relative to bregma) with an 11° angle toward the midline in the coronal plane. Rats were then submitted to three phases of behavioral training: fear conditioning and extinction on Day 1, and retention testing on Day 2. On Day 1, rats received five CS–US trials (60-sec intertrial interval) in a novel context. One hour after conditioning they were transported to another room for micro-infusions, where they received infusions of picrotoxin (100 ng; Sigma; PIC), D-cycloserine (10 μg; Sigma; DCS) or sterile saline (0.9%; SAL-E and SAL-NE for extinction and no-extinction control, respectively). The doses of picrotoxin (Weinberg et al. 2010) and DCS (Botreau et al. 2006; Walker et al. 2002) were chosen based on previously published reports indicating their efficacy in facilitating neuronal activity. All drugs were delivered in 0.5 μL of sterile saline (0.1 μL/min), and another minute was allowed for diffusion of the drug before the internal cannulae were removed. Immediately after the infusions, the rats received an extinction session consisting of 45 CS-alone presentations in a context different from that used for conditioning. Animals in the no-extinction control condition were placed in the extinction context but did not receive extinction trials. On Day 2, all rats were returned to the extinction context and exposed to another 45 CS-alone presentations to assess fear to the extinguished CS, as well as re-extinction of fear to that CS. The experimental contexts were counterbalanced among the groups.

At the completion of all behavior tests, rats were perfused (0.9% saline followed by a 10% formalin solution) and their brains were extracted and post-fixed (10% formalin solution for 2 d followed by 10% formalin and 30% sucrose solution, sectioned (45 μm), and stained (0.25% thionin). All behavioral data are expressed as means and standard errors of the means and were submitted to analysis of variance (ANOVA). Post hoc comparisons in the form of Fisher’s LSD tests were performed after a significant F ratio. For the picrotoxin experiment, four of 36 rats were excluded because their cannula missed the IL. This yielded the following group sizes: PIC (n = 10), SAL-E (n = 10), and SAL-NE (n = 12). For the D-cycloserine experiment, two of 36 rats were excluded due to failed shock delivery during conditioning. This yielded the following group sizes: DCS (n = 12), SAL-E (n = 10), and SAL-NE (n = 12). IL cannula placements for rats included in the data analyses are depicted in Figure 1.

Conditioned freezing in the two experiments is shown in Figure 2 (PIC, upper panels; DCS, lower panels). For both experiments, freezing behavior was low before the first conditioning trial and increased in frequency thereafter (Fig. 2A,D). There was an equivalent increase in freezing across trials in all groups (group × trial, F10,145 < 1 and F10,155 < 1; PIC and DCS, respectively). One hour after conditioning, rats received extinction training (Fig. 2B,E). Picrotoxin infusions into the IL completely eliminated the expression of freezing during extinction training (Fig. 2B). During the extinction session, an ANOVA revealed significant main effects of group (F2,29 = 9.8, P < 0.001) and trial block (F9,261 = 6.7, P < 0.0001), and a significant interaction between the two (F18,261 = 11.9, P < 0.0001). A post hoc comparison revealed that freezing in SAL-E rats was significantly higher than that in both SAL-NE and PIC rats (both P < 0.05), which did not differ from one another. During the test session, animals treated with picrotoxin the previous day exhibited a return of fear early in the test session, but nonetheless exhibited a facilitated rate of re-extinction (Fig. 2C). An ANOVA revealed significant main effects of group (F2,29 = 4.8, P = 0.02) and trial block (F9,261 = 23.4, P < 0.0001), and a significant interaction between the two (F18,261 = 2.3, P < 0.005). Post hoc comparisons revealed that freezing in PIC rats was significantly lower than their SAL-E and SAL-NE controls (both P < 0.05), which did not differ from one another. Planned comparisons revealed that the freezing levels were equivalent among groups during the first five-trial block (F2,29 < 1), but freezing in PIC rats dropped more rapidly compared to their saline controls during the remaining trials. Hence, although PIC infusions into the IL before extinction did not overcome the immediate extinction deficit, they facilitated the re-extinction of fear.

Similar to picrotoxin infusions, DCS infusions also facilitated the re-extinction of fear, but did so without any effect on the expression of fear during the extinction session itself (Fig. 2E). During the extinction session, an ANOVA revealed significant main effects of group (F2,31 = 6.5, P < 0.005) and trial block (F9,279 = 19.6, P < 0.0001), and a significant interaction between the two (F18,279 = 4.0, P < 0.0001). In this case, post hoc comparisons revealed that freezing among SAL-NE rats was significantly lower than both SAL-E and DCS rats (both P < 0.05), which did not differ from one another. During the test (Fig. 2H), an ANOVA revealed significant main effects of group (F2,31 = 4.8, P < 0.05) and trial block (F9,279 = 23.0, P < 0.0001), and a significant interaction between the two (F18,279 = 2.4, P < 0.005). Post hoc comparisons revealed that freezing levels in DCS rats were significantly lower than their SAL-NE and SAL-E controls (both P < 0.05), which did not differ from one another. Planned comparisons revealed that the freezing levels were equivalent among groups during the first five-trial block (F2,31 = 1.7, P = 0.20), but DCS rats extinguished at a faster rate than their saline controls during the remaining trials. Thus, picrotoxin and DCS did not eliminate the immediate extinction deficit, but facilitated the re-learning of extinction.

The present results reveal that augmenting excitatory transmission in the mPFC can facilitate some aspects of extinction, including fostering the encoding of an extinction memory that is more easily reacquired. This outcome was independent of the effect of the drugs on the expression of conditioned extinction.
fear during extinction, suggesting that facilitated re-extinction was not due to a nonspecific anxiolytic effect of the drugs. Collectively, these data are consistent with recent data revealing that the mPFC is critical not only for extinction (Quirk and Mueller 2008), but also for re-extinction (Laurent and Westbrook 2008; Thompson et al. 2010). For example, Thompson et al. (2010) have recently reported that picrotoxin infusions into IL facilitate the re-extinction of contextual fear under conditions that produced little initial extinction. Picrotoxin infusions alone in the absence of extinction training did not facilitate re-extinction. Interestingly, the present results together with the work by Thompson et al. (2010) indicate that neither picrotoxin nor DCS infusions into the mPFC enhance original extinction. In both studies, drug-treated rats exhibited a complete recovery of fear 24 h after extinction and were no different from nonextinguished controls. This is surprising insofar as it has recently been reported that BDNF infusions in the mPFC are sufficient to produce extinction (even in the absence of extinction training) under some conditions (Peters et al. 2010).

It is worth noting that in the study by Thompson et al. (2010) picrotoxin infusions in the IL facilitated later extinction of contextual fear even when delivered during extinction of another distinct context. The authors suggested that activating the IL primed the extinction circuitry nonassociatively, thereby augmenting subsequent extinction learning. It is possible that the facilitation of re-extinction in our experiments was also a consequence of IL metaplasticity induced by picrotoxin. Indeed, the Thompson et al. (2010) data raise the interesting possibility that IL activation would facilitate not only subsequent learning about the specific stimuli present during extinction training, but any stimulus with a previous conditioning history. Rather than selectively enhancing the encoding of a specific extinction memory, IL activation might prospectively prime extinction learning to any aversive stimulus that occurs within some window of time after activation. Further experiments examining the effects of IL picrotoxin on context extinction prior to cue extinction in a novel context, for example, would be important to address this possibility.

Our finding that pharmacological activation of the IL ameliorates the immediate extinction extends a recent study that found electrical stimulation of the IL also ameliorates the immediate extinction deficit in rats (Kim et al. 2010). In this report, electrical activation of the IL reduced the expression of conditioned freezing during the earliest trials of the retention test the following day, whereas pharmacological activation of IL in the present study and the Thompson et al. (2010) report appears to result in more rapid re-extinction. One possibility is that we did not infuse sufficient quantities of picrotoxin and DCS into IL to achieve optimal facilitation of extinction learning. However, picrotoxin totally eliminated the freezing behavior during extinction training, and both drugs have previously been reported to be effective at equivalent or lower doses (Walker et al. 2002; Beretta et al. 2005; Boteau et al. 2006; Thompson et al. 2010; Weinberg et al. 2010). It is possible that the electrical stimulation of the PFC produces a greater reduction of conditioned fear because it activates both PFC neurons, as well as backfiring amygdaloid neurons involved in extinction learning.

The fact that we only observed an effect of IL activation on the re-extinction of fear may not be surprising when one considers that the neural circuit for extinction learning is likely to be quite distributed. In addition to the mPFC, other brain structures, including the amygdala and hippocampus, contribute to the encoding and retrieval of extinction memories (Falls et al. 1992; Walker et al. 2002; Hobin et al. 2003). Indeed, rats can acquire fear extinction without the mPFC under some conditions (Gewirtz et al. 1997; Garcia et al. 2006; Chang and Maren 2010). Hence, the mPFC may have a largely modulatory role in the acquisition and retrieval of extinction memory (rather than serving as the locus for the storage of that memory). By this view, the immediate extinction deficit may result from dysfunction amongst numerous brain areas in the extinction circuit, in addition to the mPFC. If so, rescuing mPFC function might facilitate some aspects of extinction, such as re-extinction, without necessarily eliminating the immediate extinction deficit. Systemic manipulations that more broadly influence activity in the various brain structures involved in extinction learning might be particularly effective in ameliorating the immediate extinction deficit (Langton and Richardson 2010).

Although picrotoxin and DCS target different neurotransmitter receptors in the mPFC, their effects on extinction may be mediated by a common mechanism. Picrotoxin is a GABA_A receptor antagonist that reduces inhibitory synaptic transmission, thereby releasing IL principal neurons from local inhibition (Connors 1984; Chagnac-Amitai and Connors 1989; Metherate and Cruikshank 1999). Disinhibition of the IL allows for greater excitation of amygdala interneurons (Beretta et al. 2005; Akirav and Maroun 2007), and this may be the mechanism accounting for the dramatic reduction in conditional freezing in rats receiving picrotoxin prior to extinction training. On the other hand, DCS may influence extinction by directly augmenting excitatory synaptic transmission in IL. NMDA receptors are involved in spike bursting in IL, and NMDA antagonists in IL impair extinction (Burgos-Robles et al. 2007; Sotres-Bayon et al. 2009). DCS infusions in the IL may promote bursting and thereby augment the
activation of inhibitory interneurons in the amygdala involved in extinction. Alternatively, DCS may have augmented local synaptic plasticity in the mPFC that has been implicated in extinction and re-extinction (Hugues et al. 2004; Santini et al. 2004; Peters et al. 2010). In either case, the facilitation of re-extinction by intra-IL DCS infusions is particularly exciting insofar as systemic DCS administration facilitated extinction in rats (Langton and Richardson 2010) and has been used successfully in humans as an adjunct to exposure-based therapies (Ressler et al. 2004; Hofmann et al. 2006).

There is considerable debate in the clinical literature about when therapeutic interventions should be attempted after psychological trauma (Bisson et al. 1997; Evely and Mitchell 1999; Campfield and Hills 2001; McNally et al. 2003; Rothbaum and bursting in the ventromedial prefrontal cortex. Neuron 53: 871–880). Burgos-Robles A, Vidal-Gonzalez I, Quirk GJ. 2000. Normal conditioned inhibition and extinction of freezing and fear-potentiated startle following electrolytic lesions of medical prefrontal cortex in rats. Behav Neurosci 114: 712–726. Burgos-Robles A, Vidal-Gonzalez I, Quirk GJ. 2000. Normal conditioned inhibition and extinction of freezing and fear-potentiated startle following electrolytic lesions of medical prefrontal cortex in rats. Behav Neurosci 114: 712–726. Burgos-Robles A, Vidal-Gonzalez I, Quirk GJ. 2000. Normal conditioned inhibition and extinction of freezing and fear-potentiated startle following electrolytic lesions of medical prefrontal cortex in rats. Behav Neurosci 114: 712–726.

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