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Abstract

Obsessive-compulsive disorder (OCD) is characterized by compulsive urges that can resemble avoidance of perceived danger. It is treated with exposure-with-response-prevention (ERP) therapy, in which patients are prevented from carrying out compulsions in response to triggers. Due to their repetitive nature, OCD compulsions are thought to resemble habit formation (Gillan et al., 2015), but little is known about the effects of repetitive avoidance on subsequent extinction. Using a platform-mediated avoidance task (Bravo-Rivera et al., 2014), we recently reported that a minority of rats persist in their avoidance following several days of extinction with a barrier that prevents access to the platform (extinction with response prevention, Ext-RP) (Rodríguez-Romaguera et al., 2016). A possible factor contributing to persistent avoidance after extinction is the development of habits over extended periods of training. Therefore, we trained two groups of rats with either 8 days (8d) or 20 days (20d) of avoidance conditioning, followed by 4 days of Ext-RP and a subsequent test with the barrier removed. Both groups showed similar avoidance conditioning. During Ext-RP, however, the 20d group showed impaired extinction of freezing (RM-ANOVA; $F_{(1, 28)} = 57.37$, $p<0.001$), ending with elevated freezing levels. The following day, 20d rats showed increased avoidance at test compared to the 8d group (t-test; $t_{76} = 4.03$, $p<0.001$), but did not display differences in freezing. Thus, the ability to re-access the platform eliminated the excessive fear in this group. To assess whether 20d group interpreted the barrier as a safety signal, an additional test session was run with the barrier placed opposite to the platform. Under these conditions, avoidance was reduced in the 20d group (t-test; $t_{29} = 4.05$, $p<0.001$), suggesting the barrier signaled safety to these rats. We are currently using cFos to compare activity in prefrontal-striatal-amygdala circuits in the 8d and 20d groups. Our results suggest that repeated expression of avoidance-like compulsions may reduce the effectiveness of extinction-based therapies, and increase subjects' reliance on apparent safety cues.

Authors

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Abstract

Memories are not static in the brain, but shift with the passage of time (Frankland and Bontempi 2005). Previously, we showed that the prelimbic - amygdalar projection (PL-BLA) is necessary to retrieve a 6-hour fear memory, whereas the prelimbic - thalamic projection (PL-PVT) is necessary to retrieve a 7-day fear memory (Do-Monte, et al., 2015). The somas of PL-BLA and PL-PVT neurons are in different layers of PL. What characterizes the activity of both neuronal populations in early vs. late fear retrieval? To address this, we infused separate retrograde tracers into BLA and PVT, exposed rats to auditory fear conditioning, and then assessed early (2 h) fear retrieval. One hour after test, rats were sacrificed and brains were processed for fluorescent labeling of the retrograde tracers, as well as the activity marker c-Fos. Compared to unconditioned controls, early fear retrieval increased activity in PL-BLA neurons (21% vs 5% of PL-BLA neurons expressing c-Fos, p=0.03) but not in PL-PVT neurons (4% vs 5% of PL-PVT neurons expressing c-Fos, p=0.47). To characterize the timing of PL neuronal responses during early and late timepoint, we recorded from 216 individual neurons in different PL layers, using 32 channel silicon probes (NeuroNexus). Neurons in layers 2-5 of PL, which project to BLA but not to PVT, showed conditioned excitatory tone responses during early retrieval (2, 24 h), but not during late retrieval (4 d). In contrast, neurons in layer 6, which project to PVT but not to BLA, showed no excitatory conditioned responses in early or late retrieval, but showed pronounced and long-lasting inhibitory responses during late retrieval. Our findings suggest that, following fear conditioning, the conditioned output of PL shifts with time from increased activity in projections to BLA to decreased activity in projections to PVT. We previously showed that PVT neurons develop excitatory tone responses with the passage of time after conditioning, and optogenetic silencing of PL-PVT fibers induces both excitation and inhibition of PVT neurons (Do-Monte et al., 2015). Thus, PL-PVT inhibition could indirectly increase PVT activity, through disinhibitory circuits.

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Abstract

The infralimbic prefrontal cortex (IL) is necessary for both extinction of conditioned fear (Do-Monte et al., 2015) and extinction of platform-mediated active avoidance (Bravo-Rivera et al., 2014). Brain-derived neurotrophic factor (BDNF) is critical for learning and memory processes. Blocking extracellular BDNF in IL, but not PL, during extinction of conditioned fear impairs its acquisition and recall (Rosas-Vidal et al., 2014). Here we examined the role of BDNF in extinction of active avoidance. We found that blocking extracellular BDNF in either IL ($p< 0.05$) or PL ($p<0.01$) during extinction of avoidance impaired its recall but not its acquisition. To determine the possible source of extinction-related BDNF, we combined retrograde tracers in IL or PL with immunohistochemistry. Interestingly, we found that extinction of avoidance increased BDNF expression in ventral-hippocampal (vHPC) neurons projecting to IL or PL ($p=0.004$ and $p=0.010$ respectively), but not amygdala or mediodorsal thalamic neurons projecting to IL or PL. To determine whether BDNF produced in vHPC is necessary for extinction of avoidance, we injected lentiviri expressing the CRISPR/Cas9 system targeting the *bdnf* gene. CRISPR-Cas9 was sufficient to impair BDNF expression in vHPC ($p= 0.014$). Furthermore, BDNF knock-down in vHPC neurons impaired recall of extinction of avoidance ($p=0.047$ and $p=0.019$ respectively). Post-traumatic stress disorder is associated with reduced hippocampal volumes (Bremner et al., 2002, Bremner et al., 1995, Chao et al., 2013) and with decreased hippocampal-prefrontal connectivity Admon et al., 2012). Our results suggest that reduced BDNF release by an impaired hippocampal-prefrontal pathway may be associated with increased avoidance behaviors seen in post-traumatic stress disorder.