Erasure of traumatic fear memory in mice by a combination of fluoxetine and fear extinction training

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Purpose of the study

❑Chronic treatment with antidepressant fluoxetine reactivates developmental-like plasticity in the adult visual cortex after the end of a critical period (Maya Vetencourt et al., 2008, Science, 320, 385-388).

❑It is likely that antidepressant drugs can also enhance neuronal plasticity and reorganize neuronal network in the brain areas involved in the regulation of mood.

❑Traumatic fear memories can be completely erased by extinction during a postnatal critical period (Gogolla et al., 2009, Science, 325, 1258-61).

❑May chronic fluoxetine lead to erasure of fear memory in adulthood?

Conclusions

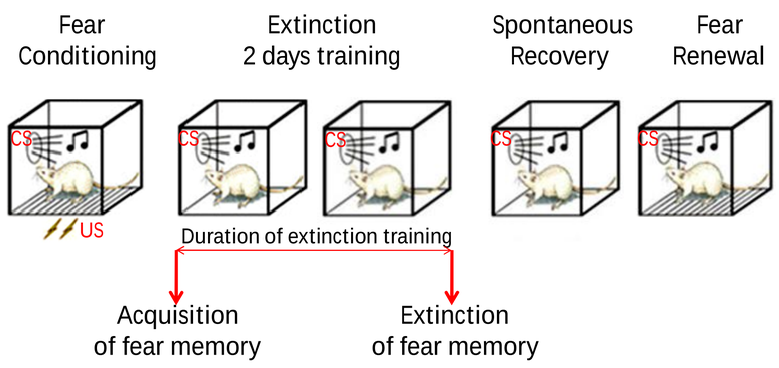
❑In adult Bl6C57/Rcc male mice treated with chronic fluoxetine either before or after fear conditioning, extinction training induced permanent loss of conditioned fear memory

❑In contrast, antidepressant treatment did not affect fear memory in those mice, which were not subjected to extinction training

❑Behavioral changes induced by fluoxetine were associated with the BDNF levels, in the amygdala and hippocampus, the brain regions crucial in the processes of contextual fear memories

❑Our results suggest that antidepressant fluoxetine can reactivate early-life pattern of conditioned fear memory in adult mice and lead to a long-term erasure of traumatic experiences when combined with extinction training.

Animal model: Fear Conditioning (FC)



CS, conditioned stimulus (sound); US, unconditioned stimulus (electric footshock)

❑Adult male mice C57Bl/6JRcc were housed individually 7 days prior to fear conditioning

❑Fear conditioning and extinction took place in two different contexts, conditioned context and extinction context, respectively. Freezing behavior was the measure of fear memory

❑In our study, two antidepressant treatment – paradigms were used:
(A) Antidepressant treatment prior to fear conditioning. Fluoxetine was given to the mice in drinking water at the dose of 0.08 mg/ml (Rantamäki et al., 2007, Neuropsychopharmacology, 32, 2152-62)

(B) Antidepressant treatment after fear conditioning. After the successful acquisition of fear conditioning, the mice were divided into two groups. One received fluoxetine in drinking water and the other received tap water

❑No potential conflict of interest

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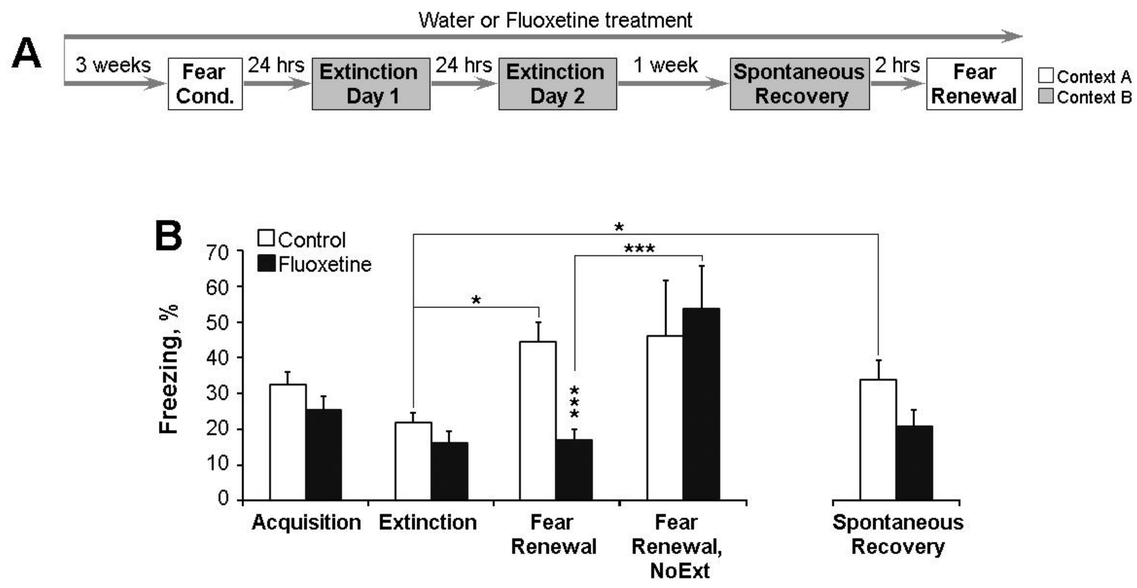
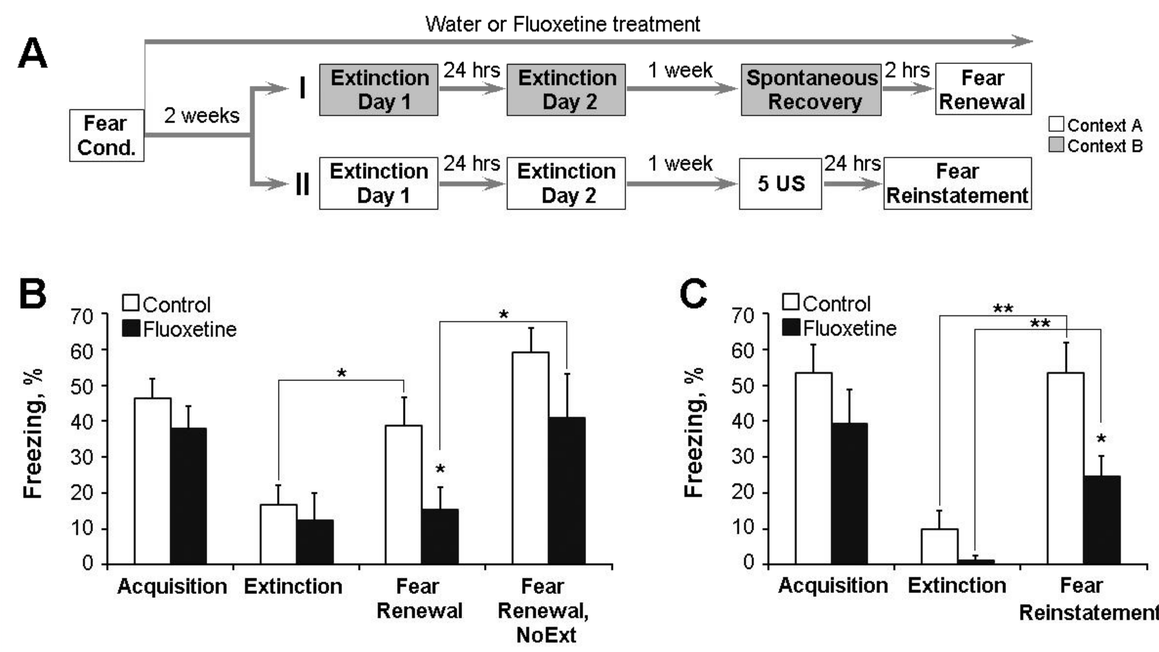
1 Chronic fluoxetine treatment prior fear conditioning leads to fear erasure when combined with extinction training



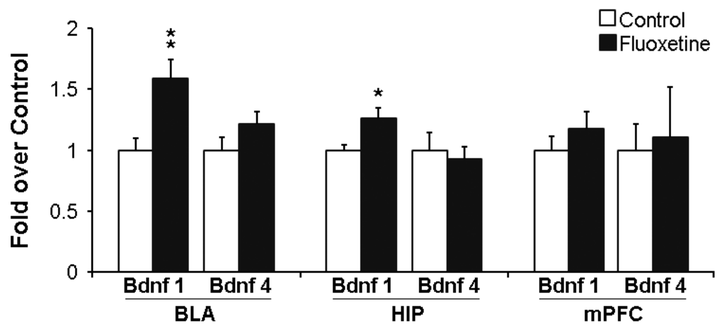
(A) Experimental protocol. (B) Both Control and Fluoxetine groups exhibited similar levels of fear acquisition and extinction. One week after extinction training, Control group, but not Fluoxetine group, showed spontaneous recovery ($P<0.05$) and fear renewal ($P<0.05$) when compared to the extinguished level of freezing. In the fear renewal test, Fluoxetine+Extinction group froze less than either Control+Extinction group ($P<0.001$) or Fluoxetine group without extinction training (NoExt) ($P<0.001$). *$P<0.05$, ***$P<0.001$.

2 Extinction training is effective in combination with chronic fluoxetine treatment given after fear conditioning



(A) Experimental protocols. Protocol I – "Fear Renewal" experiment; protocol II – "Fear Reinstatement" experiment, 5 US, 5 unsignaled electric footshocks. (B) "Fear Renewal" experiment: Both Control and Fluoxetine groups exhibited similar levels of fear acquisition and extinction. One week after extinction training, Control group, but not Fluoxetine group, showed fear renewal ($P<0.05$) when compared to the extinguished level of freezing. In the fear renewal test, Fluoxetine+Extinction group froze less than either Control+Extinction group ($P<0.05$) or Fluoxetine group without extinction training (NoExt) ($P<0.05$). (C) "Fear Reinstatement" experiment: One week after successful acquisition and extinction of fear memory, mice received 5 USs, and next day, were tested for fear reinstatement. Both Control (**$P<0.01$) and Fluoxetine (**$P<0.01$) groups exhibited increased level of freezing when compared to the extinguished level, but Fluoxetine group showed reduced level of fear reinstatement ($P<0.05$). *P<0.05, **$P<0.01$.

3 Chronic fluoxetine following the fear conditioning increases the mRNA level of activity-dependent regulated BDNF transcript 1 in the basolateral amygdala and hippocampus



Fluoxetine treatment significantly enhanced the mRNA levels of activity-dependent regulated brain-derived neurotrophic factor (BDNF) transcript 1 in the basolateral amygdala (BLA) and hippocampus (HIP), but not in the medial prefrontal cortex (mPFC), whereas BDNF transcript 4 was not regulated in any of the brain areas investigated. *P<0.05, **$P<0.01$.