

Brief Communication

Activation of BDNF signaling prevents the return of fear in female mice

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There are significant sex differences in vulnerability to develop fear-related anxiety disorders. Females exhibit twice the rate of post-traumatic stress disorder (PTSD) as males and sex differences have been observed in fear extinction learning in both humans and rodents, with a failure to inhibit fear emerging as a precipitating factor in the development of PTSD. Here we report that female mice are resistant to fear extinction, and exhibit increased DNA methylation of *Bdnf* exon IV and a concomitant decrease in mRNA expression within the medial prefrontal cortex. Activation of BDNF signaling by the trkB agonist 7,8-dihydroxyflavone blocks the return of fear in female mice after extinction training, and thus represents a novel approach to treating fear-related anxiety disorders that are characterized by a resistance to extinction and increased propensity for renewal.

There are significant sex differences in terms of vulnerability to develop fear-related anxiety disorders. Females exhibit twice the rate of post-traumatic stress disorder (PTSD) as males (Olff et al. 2007), which cannot be explained by the severity of the experienced trauma or comorbidity with other affective disorders (Tolin and Foa 2006). Furthermore, sex differences have been observed in fear extinction learning in humans and rodents, with a failure to inhibit fear emerging as a precipitating factor in the development of PTSD (Lebron-Milad et al. 2012; Ter Horst et al. 2012). In accordance with previous observations we have found that there are significant sex differences in the extinction of conditioned fear in mice. Male and naturally cycling female C57BL/6 mice ($n = 15\text{--}16/\text{group}$, 9 wk of age) were first trained on a cued-fear-conditioning task in which a 70-dB white noise (conditioned stimulus [CS], 2 min) coterminated with mild foot shock (unconditioned stimulus [US] 0.7 mA, 1 sec) on three occasions. Twenty-hours later, mice were extinction trained in a new context (30 nonreinforced, 2-min, 5-sec inter-trial interval, tone (CS) exposures in context B). On Day 3, all mice were returned to context B and tested (two CS presentations) for retention of memory for fear extinction. There was no difference between male and female mice in the acquisition of cued fear (data not shown). However, there was a significant sex difference in memory for the extinction of conditioned fear ($F_{(3,59)} = 11.41$, $P < 0.0001$; Tukey's post hoc test: fear conditioned without extinction training (FC-No EXT) male vs. extinction trained (EXT) male, $P < 0.0001$; EXT male vs. EXT female, $P < 0.05$), with male mice exhibiting significantly lower levels of freezing than females (Fig. 1). These data suggest that female mice are resistant to the extinction of conditioned fear; however, the neural mechanisms underpinning this effect are not known.

Epigenetic mechanisms influence cognition and memory by regulating learning-induced gene expression (Day and Sweatt 2011). One such epigenetic mechanism is DNA methylation, which has been implicated in experience-dependent plasticity and in the formation and maintenance of fear-related memories (Miller et al. 2010; Baker-Andresen et al. 2012). Activity-dependent brain-derived neurotrophic factor (BDNF) signaling enhances neural plasticity and is necessary for the formation of

fear-related memories (Peters et al. 2010; Andero and Ressler 2012) with the epigenetic regulation of *Bdnf* expression being shown to be critical for the acquisition and extinction of conditioned fear (Bredy et al. 2007). Furthermore, dysregulation of BDNF has been implicated in many neuropsychiatric disorders (Bouille et al. 2012). Recently, significant sex differences in BDNF signaling have been observed within the prefrontal cortex (Hill and van den Buuse 2011), a region of the brain in which sexual dimorphism in epigenomic function has also been reported (Xu et al. 2008). However, it is not yet known whether there are sex differences in the epigenetic regulation of *Bdnf*, which would subsequently contribute to the observed differences in fear-related learning and memory. To address this issue, we measured the level of DNA methylation surrounding the transcription start site (TSS) of exon IV of the gene encoding BDNF by methylated DNA immunoprecipitation (MeDIP) followed by quantitative PCR (qPCR) (Fig. 2A). Briefly, genomic DNA was isolated from tissue samples encompassing the prefrontal cortex by overnight proteinase K treatment, phenol–chloroform extraction, ethanol precipitation, and RNase digestion. Prior to MeDIP, genomic DNA was randomly fragmented by sonication into fragments of ~ 500 bp in length, with 1 μg fragmented DNA used for each MeDIP assay. MeDIP was performed using a MeDIP assay kit (Active Motif) as per the manufacturer's instructions. Methylated DNA fragments were recovered by reverse cross-link followed by ethanol precipitation and then quantified by qPCR using MeDIP-qPCR primers for *Bdnf* exon IV (forward, 5'-GTGGACTCCCACCCACTTT-3'; reverse, 5'-TATTACCTCCGCCATGCAAT-3').

In response to the extinction of conditioned fear, *Bdnf* expression is altered in an isoform-specific manner; *Bdnf* exon IV expression increases in response to fear extinction and is marked by learning-induced epigenetic modifications surrounding its promoter (Bredy et al. 2007). Furthermore, reduced BDNF exon IV expression is associated with deficits in inhibitory neurotransmission in the prefrontal cortex (Sakata et al. 2009), thus adversely affecting the formation and maintenance of extinction memories when occurring in the medial prefrontal cortex (ILPFC) (Akirav et al. 2006), an area of the brain that is critically involved in fear extinction. As opposed to examining the well-characterized promoter region of *Bdnf* exon IV, we selected a locus immediately downstream of TSS due to the presence of several binding motifs for transcription factors, including Sp1, YY1, and CTCF, all of which are known to interact with DNA methylation in regulating

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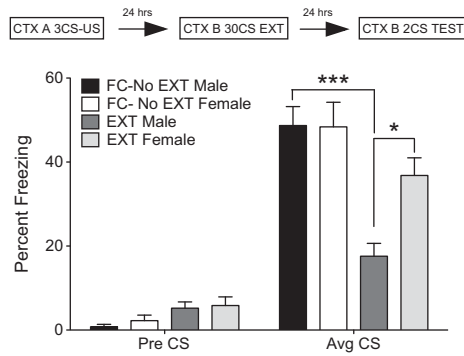


Figure 1. Female mice exhibit impaired retention of fear extinction memory compared to males. Twenty-four hours after a 30 CS extinction session in context B, male mice (EXT male) freeze significantly less than no-extinction controls (FC-No EXT male) when presented with two CS in the extinction context, suggesting retention of the memory for extinction training. While no difference in the retention of fear is observed between sexes (FC-No EXT male vs. FC-No EXT female), female mice (EXT female) display a significant extinction impairment compared to extinguished males. (***) $P < 0.0001$, (*) $P < 0.05$.

transcriptional activity. As an indirect measure of the functional relevance of variations in DNA methylation, we also measured *Bdnf* exon IV mRNA expression within the ILPFC of naive male and female mice. Briefly, RNA was isolated from samples encompassing the ILPFC of naive male and female mice using the Trizol extraction method (Invitrogen). Total RNA (1 μ g) was used for cDNA synthesis using the Omniscript RT kit (Qiagen). PCR was then performed using primers for *Bdnf* exon IV (forward, 5'-GCAGCTGCCTTGATGTTAC-3'; reverse, 5'-CCGTGGA CGTTTACTTCTTTC-3') and for phosphoglycerate kinase (*Pgk*) as an internal control (forward, 5'-TGC ACGCTTCAAAAGCGCACG-3'; reverse, 5'-AAGTCCACCCTCATCACGACCC-3'). qPCR was performed using a RotorGeneQ (Qiagen) cycler using SYBR-green (Qiagen). The threshold cycle for each sample was chosen from the linear range and converted to a starting quantity by interpolation from a standard curve run on the same plate for each set of primers. *Bdnf* exon IV mRNA levels were normalized for each well to *Pgk* mRNA using the $\Delta\Delta$ CT method, and each qPCR was run in duplicate for each sample and repeated at least two times. mRNA levels were analyzed by unpaired *t*-tests.

Our results revealed a significant sex difference in DNA methylation and mRNA expression. Naive female mice exhibited significantly greater methylation (unpaired *t*-test, $t = 2.75$, $df = 7$, $P < 0.05$) (Fig. 2C) relative to naive males, which was accompanied by decreased levels of *Bdnf* exon IV mRNA expression (unpaired *t*-test, $t = 2.04$, $df = 6$, $P < 0.05$) (Fig. 2B). Together, these data suggest a potential relationship between sex differences in the epigenetic regulation of *Bdnf* exon IV within the medial prefrontal cortex and fear extinction in mice. Therefore, we next asked whether these differences could collectively be

overcome to promote the extinction of conditioned fear in female mice.

A brief reminder CS after fear conditioning renders the memory for that fear temporarily labile and sensitive to modification, requiring re-stabilization or updating of the memory trace through a process known as reconsolidation (Przybylski and Sara 1997; Przybylski et al. 1999; Nader et al. 2000). Monfils et al. (2009) capitalized on the labile nature of memory to introduce a retrieval-extinction procedure to interfere with reconsolidation and strengthen the formation of fear extinction memory in rats. They observed a significant reduction in the fear response that did not return as a function of spontaneous recovery, renewal, or reinstatement. These findings were subsequently replicated in humans (Schiller et al. 2010), and in mice in which a single nonreinforced CS prior to extinction training diminished the renewal of conditioned fear (Clem and Haganir 2010). However, not all studies have demonstrated beneficial effects using this approach, and an exaggerated return of fear, dependent on the context in which the fear memory is retrieved, has also been reported (Chan et al. 2010). Based on these observations, we reasoned that a retrieval-extinction protocol might be useful in promoting fear extinction in females, which are otherwise resistant when examined in a standard fear extinction training protocol. Moreover, as there are sex differences in the epigenetic regulation of cortical BDNF expression and in basal levels of BDNF expression in other structures of the fear extinction-related circuitry (Zhu et al. 2006), we hypothesized that fear extinction would be facilitated through direct systemic activation of the downstream signaling target of BDNF, the *trkB* receptor. 7,8-Dihydroxyflavone (7,8-DHF) is a small molecule activator that binds to the *trkB* receptor (Jang et al. 2010), thereby mimicking the effect of BDNF in the brain. Systemic administration of 7,8-DHF has been shown to activate *trkB* receptors, enhance learning and memory (Liu et al. 2010; Andero et al. 2011, 2012), and reverse memory deficits in

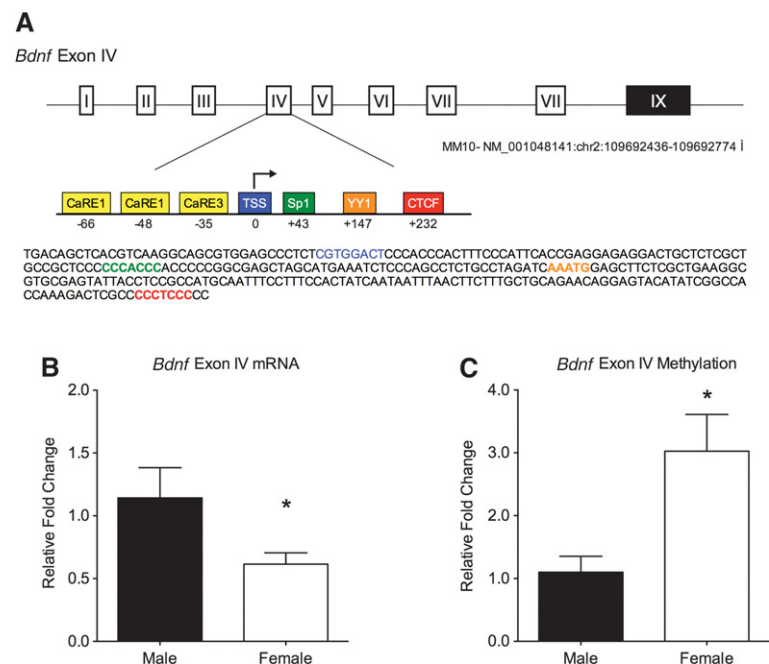


Figure 2. Expression of *Bdnf* exon IV mRNA differs in naive males and female C57BL/6 mice and is accompanied by differences in DNA methylation surrounding TSS. (A) DNA methylation levels were measured at the TSS of exon IV of the gene encoding BDNF. A significant increase in methylation was observed in females (C), along with a concurrent decrease in *Bdnf* exon IV expression (B), compared to males. (*) $P < 0.05$

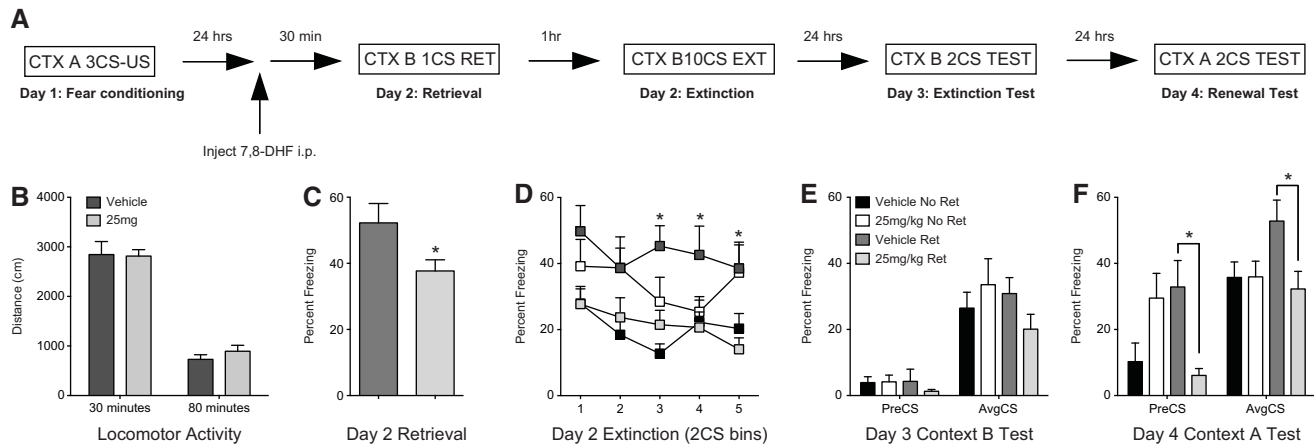


Figure 3. 7,8-Dihydroxyflavone prevents retrieval-induced renewal of fear. (A) Schematic representation of experimental protocol. (B) Analysis of distance traveled 30 and 80 min post-injection with either vehicle (10% DMSO in PBS) or 25 mg/kg 7,8-DHF reveals no effect of drug on locomotor activity. (C) Treatment with 7,8-DHF 30 min prior to retrieval significantly decreased the expression of fear in female mice. (D) Vehicle-treated animals subjected to a retrieval cue (Vehicle Ret) demonstrate a resistance to extinction compared to drug-treated (25 mg/kg 7,8-DHF Ret) and nonretrieval groups (Vehicle No Ret and 25 mg/kg 7,8-DHF No Ret). (E) No significant differences were observed at test in context B. (F) A significant retrieval-induced renewal of fear was observed in the vehicle retrieval group compared to nonretrieval groups, an effect which was blocked in the 7,8-DHF Ret group. (*) $P < 0.05$.

a preclinical model of age-related cognitive decline (Devi and Ohno 2012; Zeng et al. 2012a, b). We therefore investigated whether administration of 7,8-DHF, in combination with a modified version of the retrieval-extinction protocol, could aid in further promoting extinction in female mice.

Female mice ($n = 8/\text{group}$) were trained on a cued-fear-conditioning task and 24 h later were exposed to a single retrieval cue prior to extinction training in a new context (10 or 11 non-reinforced tone exposures in context B, balanced for CS exposure on retrieval). All mice were then returned to context B and tested for retention of memory for fear extinction on Day 3 before being tested for renewal of fear memory 24 h later in context A (Fig. 3A). We found that a single exposure to a retrieval cue, prior to fear extinction training, led to significantly higher levels of within-session freezing, and an exaggerated return of fear when the mice were tested in the context in which fear was initially learned (Fig. 3F), similar to the findings of Chan et al. (2010). In contrast, there were no differences when tested in the extinction context B (Fig. 3E). A single injection of 7,8-DHF (25 mg/kg, i.p., dissolved in 10% DMSO in sterile saline), administered systemically 30 min prior to retrieval, led to a significant reduction in freezing upon retrieval (unpaired t -test, $t = 2.88$, $df = 14$, $P < 0.05$) (Fig. 3C) and completely prevented the return of fear in context A ($F_{(3,31)} = 3.03$, $P < 0.05$; Tukey's post hoc test; Vehicle Ret vs. 25 mg/kg 7,8-DHF Ret, $P < 0.05$) (Fig. 3F). This effect on renewal was due in large part to the very strong effect of 7,8-DHF on contextual memory, as indicated by the pre-CS freezing levels in drug-treated mice ($F_{(3,31)} = 4.66$, $P < 0.01$; Tukey's post hoc test; Vehicle Ret vs. 25 mg/kg 7,8-DHF Ret, $P < 0.05$) (Fig. 3F). Furthermore, this reduction in freezing was not due to a generalized increase in activity as there were no significant differences in locomotion (distance traveled) either 30 min or 80 min post-injection (Fig. 3B). Together these data suggest that 7,8-DHF promotes a reduction in fear-related responding during and following extinction training in female mice, consistent with results suggesting that activation of BDNF signaling can induce extinction in the absence of training (Peters et al. 2010).

This study generated three main findings: (1) female mice are resistant to the extinction of conditioned fear; (2) there are sex differences in the epigenetic regulation of *Bdnf* expression in the medial prefrontal cortex; and (3) female mice exhibit a significant

return of fear after extinction training in a retrieval-extinction paradigm, effects that are completely blocked by targeted activation of BDNF signaling prior to memory retrieval and extinction training. It is important to note that there is evidence to suggest that sex differences in fear extinction are dependent on circulating gonadal hormone levels (Zeidan et al. 2011; Merz et al. 2012); however, naturally cycling mice were examined in this study to closely mimic what occurs in the general population. Moreover, regardless of cycle, we observed a significant sex difference in fear extinction that is associated with basal differences in epigenetic regulation of *Bdnf* within the medial prefrontal cortex. We cannot exclude the possibility that stage of estrous contributed to these effects (Spencer et al. 2010); however, our data on the return of fear after exposure to a retrieval cue in female mice represent a third replication of this effect, making it unlikely that these differences are strictly due to a hormonal influence on fear extinction learning.

Few studies have considered whether there are sex differences in the epigenetic regulation of gene expression, although this is an emerging concept (McCarthy et al. 2009). Using a mouse model that separates hormonal effects from sex chromosome-linked gene effects, Xu et al. (2008) were the first to examine how genes specifically encoded on sex chromosomes influence the way in which the epigenome exerts an effect on gene expression. They found that, regardless of gonadal phenotype, the expression pattern of the H3K27^{me3} histone demethylase ubiquitously transcribed tetratricopeptide repeat gene on X chromosome (*Utx*) was highest in the cortex of female mice. We have observed a similar pattern of *Utx* expression specifically in the medial prefrontal cortex in male and female mice (data not shown). Given the tight association between H3K27^{me3} and DNA methylation, it is likely that sex differences in the epigenome are broadly distributed and contribute to the function of many genes and related behaviors. Our data on DNA methylation status of *Bdnf* exon IV give but one prototypical example of how sex differences in the epigenetic regulation of gene expression may influence fear-related learning and memory. With respect to the influence of 7,8-DHF on the return of fear, previous studies have indicated beneficial effects of 7,8-DHF on fear extinction in paradigms where diminished capacities for extinction are observed, such as following exposure to an acute stressor (Andero et al. 2011). These

observations were later extended by the demonstration of a beneficial effect of 7,8-DHF on stress-induced spatial memory impairments (Andero et al. 2012). Thus, exposure to a retrieval cue prior to fear extinction training may represent an acute stressor, which leads to a significant increase in the return of fear in female mice, an effect that can be completely prevented by activation of BDNF signaling.

In summary, female mice are resistant to fear extinction, and exhibit increased DNA methylation of *Bdnf* exon IV and a concomitant decrease in mRNA expression within the medial prefrontal cortex. Together these findings suggest the intriguing possibility that sex differences in epigenetic regulation of gene expression may represent a general distinction between the male and female brain that will impact a variety of behaviors. In the case of BDNF signaling, targeting downstream trkB receptors to block renewal in female mice offers a novel approach to treating fear-related anxiety disorders characterized by a significant return of fear.

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