Reducing fear extinction deficits in a 5-HT2C receptor editing model of Post-Traumatic Stress Disorder (PTSD)

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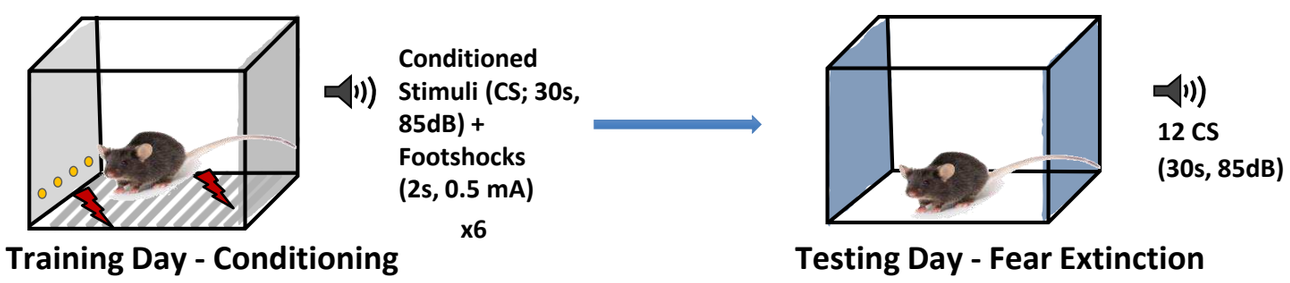
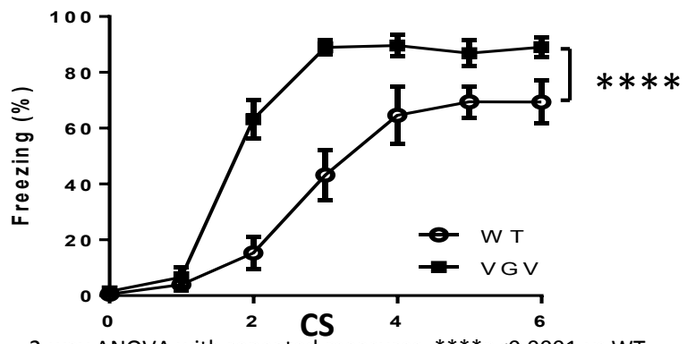
PTSD is a stress-related disorder caused by exposure to a severe psychological trauma, involving fear extinction and fear generalization deficits [1]. Serotonin 2C receptor (5-HT2CR) editing impacts anxiety-like behaviors [2].
We previously demonstrated that mice expressing only the fully edited VGV isoform of 5-HT2CR (VGV mice) display PTSD-like fear memory dysregulations, including fear generalization and fear extinction deficits, as well as biological markers consistent with PTSD (see below). The exposure therapy, commonly used to treat PTSD is based on fear extinction. There are controversies as to whether an antidepressant treatment during exposure therapy is beneficial [3]. Chronic paroxetine prevented many of VGV mice behavioral and biological deficits, but not fear extinction [4].

Goal: Studying the effects of acute treatments with serotonergic antidepressant drugs on VGV mice fear-related behaviors, to determine whether these treatments could restore fear extinction.

Mice: Wild-type (WT) or VGV (10 week-old) male mice raised on C57BL6/J strain.
Acute treatment: Paroxetine (16 mg/kg i.p.) or agomelatine (50 mg/kg i.p.) injected 30 min before the test on day 1.

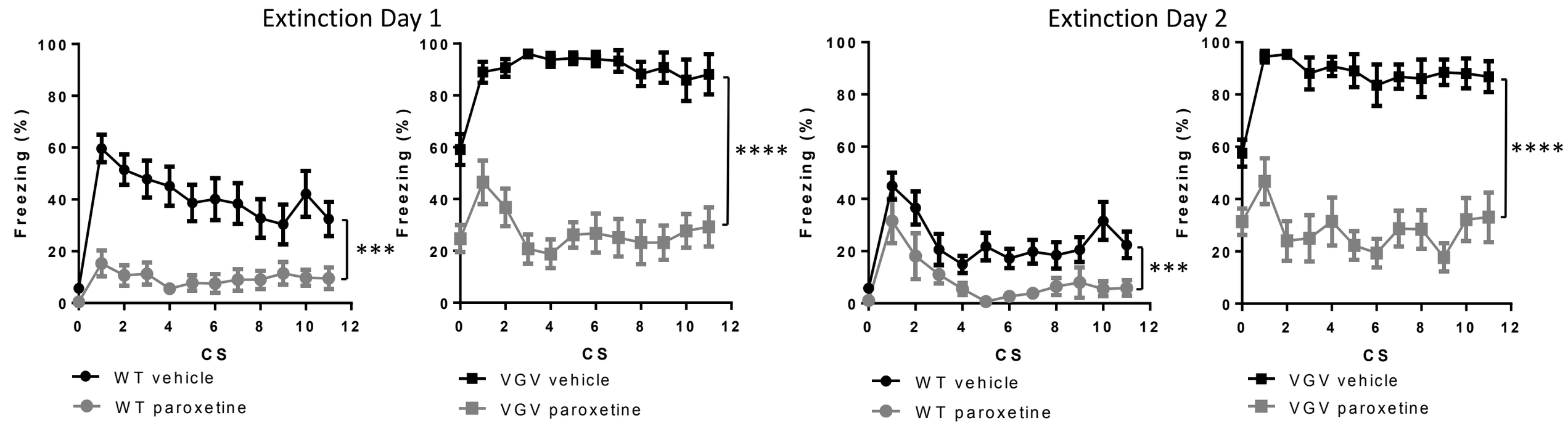


A VGV mice exhibited faster fear acquisition



2-way ANOVA with repeated measures, ****p<0.0001 vs WT.

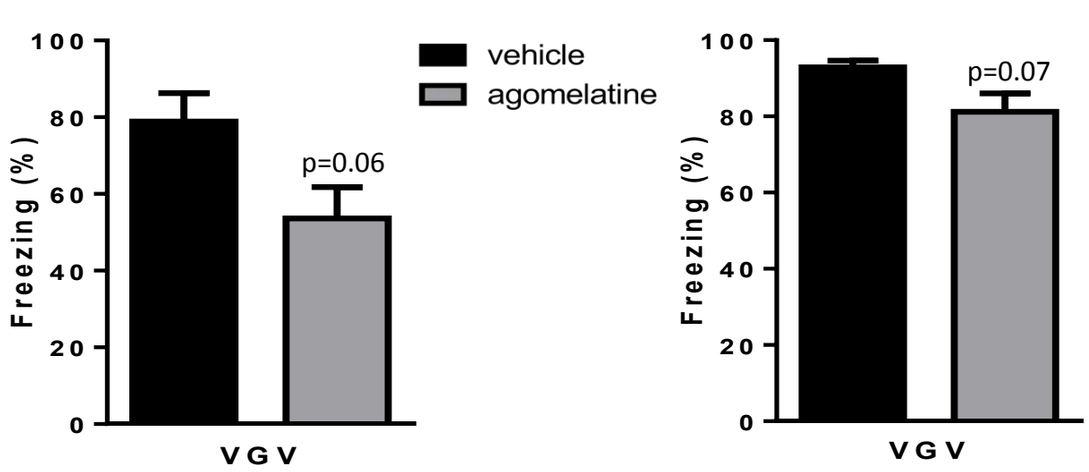
B Acute paroxetine facilitated fear extinction and reduced fear generalization in VGV mice



2-way ANOVA with repeated measures, ***p<0.001, ****p<0.0001 vs Vehicule.

-> Acute paroxetine decreased freezing during extinction in WT mice while inducing an apparent extinction process in VGV mice.
-> Extinction appears consolidated in VGV mice that were administered with paroxetine 24 hours before.
-> Fear generalization is reduced by acute paroxetine in VGV mice on both after the injection, on day 1, and the day after, on day 2.

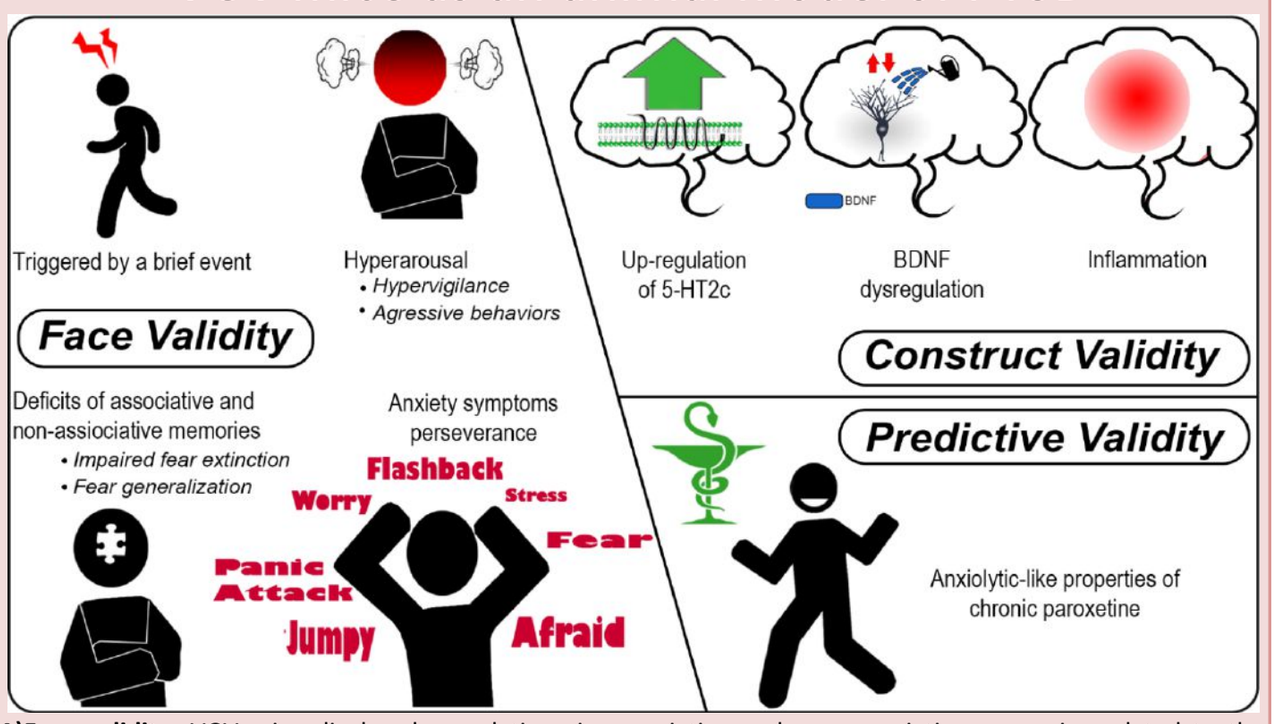
C Agomelatine tended to decrease PTSD-like behaviors



Student's t-test, ****p<0.0001 vs Vehicule.

-> Agomelatine, an antidepressant with weak 5-HT2CR antagonist property, tended to decrease both the total amount of freezing during the extinction session and fear generalization.

VGV mice as an animal model of PTSD



A)Face validity: VGV mice display dysregulations in associative and non-associative memories related to the trauma and exhibit symptom perseverance, as fear dysregulations persisted for weeks.
B)Construct validity: *Bdnf* mRNA exons dysregulations are found in hippocampus, amygdala and frontal cortex of VGV mice. It had been suggested to account for memory processes, synaptic plasticity and neuronal activity impairments in patients. Increased pro-inflammatory cytokines mRNA level is also found in both their hippocampus and amygdala.
C)Predictive validity: Paroxetine is the first-line pharmacological treatment of PTSD. Chronic paroxetine produces anxiolytic effects in human PTSD as well as in VGV mice.

Acute paroxetine reinstates fear extinction in VGV mice.
Initiating a SSRI treatment during exposure therapy may thus facilitate fear extinction in PTSD patients.

Authors declare no conflict of interest. [1] Van Der Kolk, 2001, *Hum. Psychopharmacol.* [2] Martin et al., 2013, *Mol. Psychiatry* [3]Bowers & Ressler, 2015 [4] Regue et al., 2015, *Eur J Pharmacol.*