Pharmacological and Deep Brain Stimulation Treatments in a Rodent Model of Post-Traumatic Stress Disorder

Eric Janezic[1], Ryan LaHood[2], David A. Stidd[3], Jean-Philippe Langevin[4], Edward French[5], and Jean-Marc Fellous[6]

1: Program in Neuroscience, University of Arizona, Tucson AZ - **2:** Program in Molecular and Cellular Biology, University of Arizona, Tucson AZ - **3:** Division of Neurosurgery, University of Arizona, Tucson AZ - **4:** Department of Neurosurgery, University of California, Los Angeles CA - **5:** Department of Pharmacology, University of Arizona, Tucson AZ - **6:** Department of Psychology and Program in Applied Mathematics, University of Arizona , Tucson AZ

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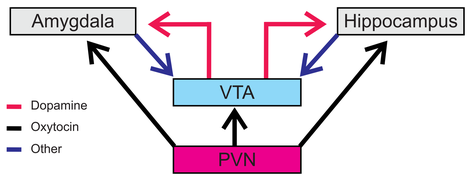
1. Introduction

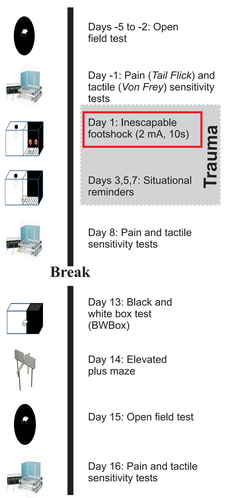
- Post-Traumatic Stress Disorder (PTSD) has a lifetime prevalence of about 7.8% (Kessler et. al., 1995).
- SSRIs are the most commonly prescribed drug treatments for PTSD with a full remission rate of 20-30% (Berger et. al., 2009).
- Deregulation of the amygdala (Liberzon and Sripada, 2007) and decreases in baseline dopamine (Corral-Frias et. al., 2013) have been identified as neurophysiological changes in animal models of PTSD.
- Oxytocin (OXT) has been shown to reduce baseline anxiety in fear-potentiated startle paradigms (Missig e.t al., 2010).
- Nicotine (NIC) and OXT are known to interact with the dopaminergic system (Yin and French, 2000; Baskerville et. al., 2010).
- Deep Brain Stimulation (DBS) has emerged as a viable treatment for diseases such as depression in humans and has been shown effective in a rodent model of PTSD (Langevin, et. al., 2010).

Oxytocin and Dopamine Pathways



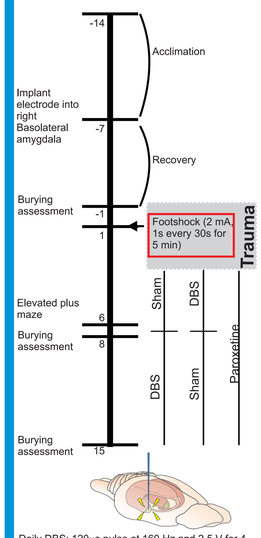
2. Methods

Pharmacological experiments



Sprague Dawley 3-4 month old male rats.
Oxytocin SC injections: 0.2 mg/kg in saline.
Oxytocin SC pumps: 7-Day & 14-Day osmotic pumps (4.2 μg/hr).
Nicotine SC pumps: 28-Day osmotic pumps (0.02μl/hour).
All controls were the Saline (Sal) equivalent.

DBS experiments

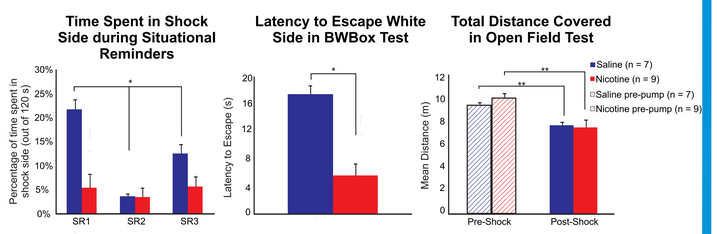


Daily DBS: 120μs pulse at 160 Hz and 2.5 V for 4 hours
Paroxetine (PRX): 5 mg/kg IP

3. Results

A. Effect of Nicotine

Chronic Nicotine Increases Long Term Anxiety

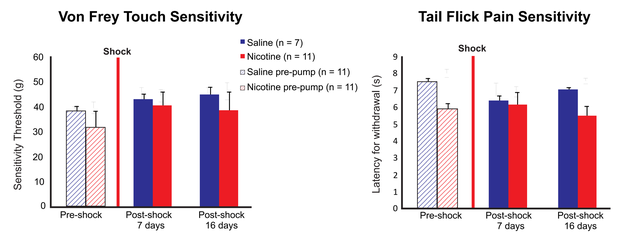


Nicotine brings the animals to maximal avoidance on SR1. This suggests that nicotine increases sensitivity to context (* = p < 0.05).

Nicotine animals are more anxious than controls 13 days after shock (* = p < 0.05).

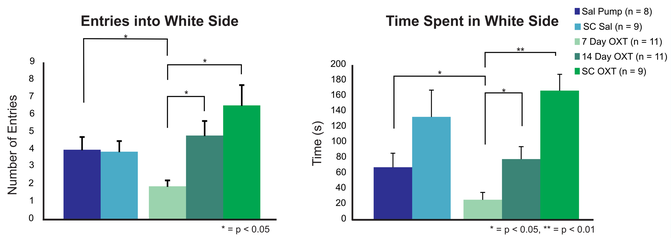
Both groups are more anxious after trauma (** = p < 0.01). There is no difference between the two groups.

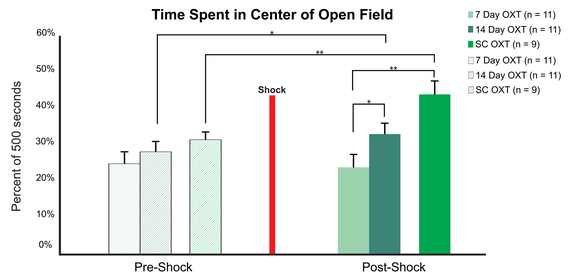
Chronic Nicotine Does Not Affect Touch and Pain Sensitivity



B. Effect of Oxytocin

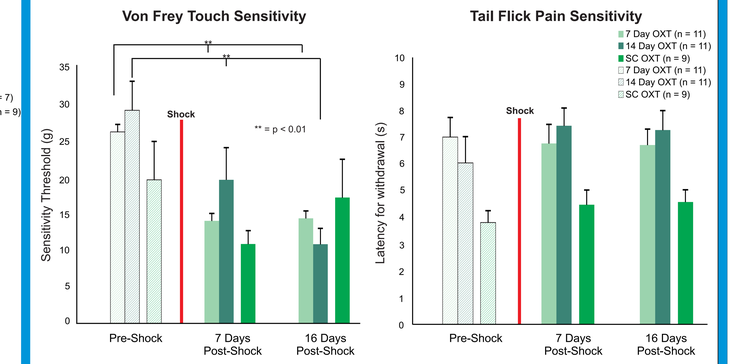
7-Day Chronic Oxytocin Administration Increases Anxiety in BWBox Test





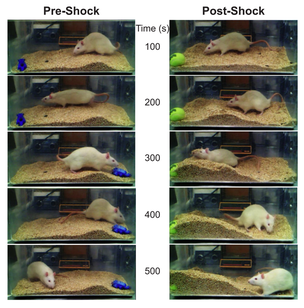
Acute administration of OXT immediately after reactivation of the traumatic context may block memory consolidation and decrease long term anxiety. Chronic OXT post trauma but not during trauma reduces anxiety (* = p < 0.05, ** = p < 0.01).

Chronic Oxytocin Increases Touch Sensitivity, But Not Pain Sensitivity



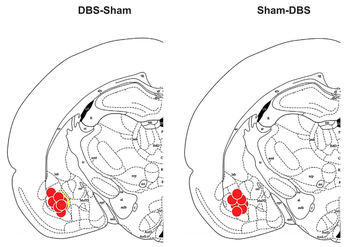
C. Effect of DBS of the Amygdala

Time-lapse of Ball-Burying Behavior



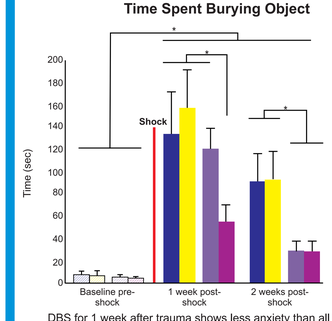
Left: In control conditions, rats do not bury a novel object. Right: After shock, rats bury the item that was present during trauma (Stidd et. al., 2013).

Placement of DBS Electrodes



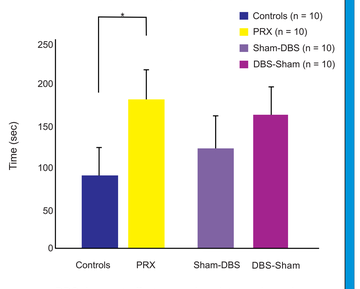
Histology shows that the electrodes were correctly placed in the right basolateral amygdala (Stidd et. al., 2013).

Time Spent Burying Object



DBS for 1 week after trauma shows less anxiety than all other groups, which persists up to 2 weeks after shock even when DBS has stopped. DBS also reduces anxiety even when started one week after initial trauma (* = p < 0.05). Paroxetine is uneffective (Adapted from Stidd et. al., 2013).

Time in Open Arm of Elevated Plus Maze



DBS does not affect general anxiety as shown by the elevated plus maze, but paroxetine does (* = p < 0.05, adapted from Stidd et. al. 2013).

4. Conclusions

- Avoidance of the shock compartment is increased by chronic nicotine suggesting its possible role in memory consolidation.
- Chronic nicotine increases long term anxiety in the BWBox test but not in the open field test.
- Acute administration of OXT immediately after reactivation of the traumatic context may block memory consolidation, and decrease long term anxiety. Chronic OXT post trauma but not during trauma reduces anxiety.
- Chronic Oxytocin affects touch but not pain sensitivity.
- DBS immediately after trauma causes a lasting reduction in anxiety, even after DBS has ceased.
- The DBS effect can be delayed and still cause reduction in anxiety.
- DBS affects cue-related anxiety, while paroxetine affects general anxiety.

5. References

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6. Acknowledgements

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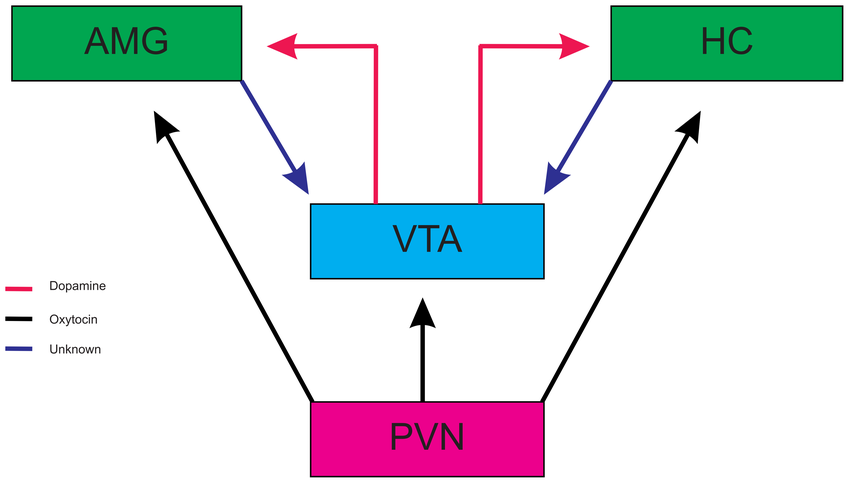
Contact Information: ejanezic@email.arizona.edu


AMG
HC
VTA
PVN
Dopamine
Oxytocin
Unknown