# Oxytocin and Social Bonding as Treatments in a Rodent Model of Post-Traumatic Stress Disorder

Eric Janezic[2], Stephanie Nagl[2], Swetha Uppalapati[1], Edward French[3], and Jean-Marc Fellous[2,4]

**1:** Neuroscience Undergraduate Program, **2:** Computational and Experimental Neuroscience Laboratory, **3:** Department of Pharmacology and **4:** Department of Psychology and Applied Mathematics

## 1. Introduction

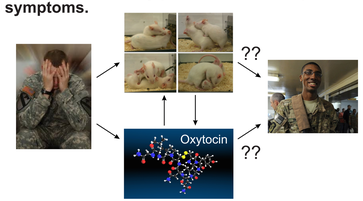
- Post-traumatic Stress Disorder (PTSD) is often caused by the experience of an extreme stressor. Symptoms manifest after 6 months and include re-experiencing of the traumatic event (DSM-5).

- Oxytocin (OXT) is an amino-acid peptide that has been linked to social bonding and stress reduction in rats and humans (Neumann, 2008).

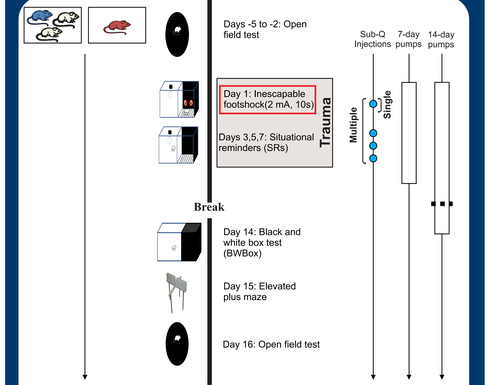
- Previous studies have shown that peripheral, but not central, administration of OXT leads to a reduction in stress response (Ayers et al., 2011).

- OXT and/or social bonding and support may also be beneficial in reducing the probability of developing PTSD (Olff et al., 2010; Olff 2012).

- **We hypothesize that peripheral OXT administration immediately after trauma and continuous social bonding are interventions that may prevent the development of PTSD symptoms.**




## 2. Methods

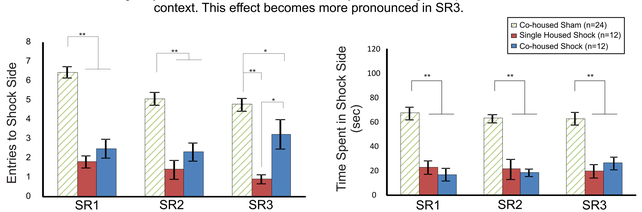



- Sprague Dawley 2-4 months old male rats (Corral-Frias et al. 2013).
- Oxytocin SC injections: 0.2 mg/kg in saline. Oxytocin SC pumps: 7-Day & 14-Day osmotic pumps (0.2 mg/kg/day post shock). All controls were Saline (Sal).
- Co-housed animals consisted of 1 shock and 2 sham animals. Single housed animals were in the shock group.
- *= p<0.05, **= p<0.01

## 3.A. Effect of Social Bonding

### Situational Reminders

Social bonding may have a beneficial effect on anxiety level during re-exposure to a stressful context. This effect becomes more pronounced in SR3.

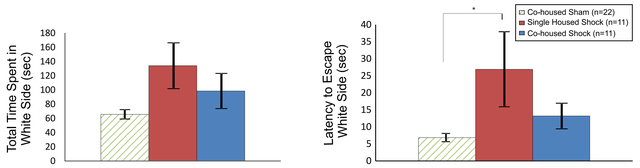



Shock groups had significantly fewer entries to the shock compartment than shams in SR1. The co-housed shock animals made significantly more entries into the shock compartment by SR3 than the single-housed shock rats. The single-housed shock rats showed no significant change in avoidance.

The shocked rats spent significantly less time in the shock compartment than shams in each situational reminder, with no significant differences between the co-housed and single-housed shock groups.

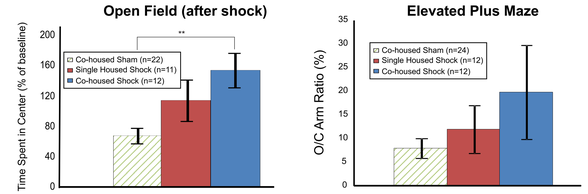
### Black and White Box

The single-housed shock group showed a trend toward avoiding the black side of the BW Box, which is reminiscent of the shock compartment. They also showed a significantly greater latency to escape the white compartment than the co-housed shams.




### General Anxiety Tests

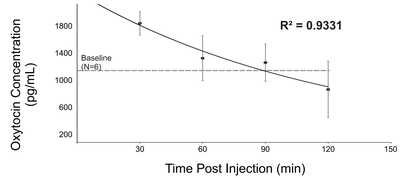
The co-housed shock group displays a trend of lower anxiety in the open field and in the elevated plus maze tests, but the results are not significantly different from the single housed shock group.




The co-housed shock group spent significantly more time in the center of the open field than the co-housed shams. Therefore, social bonding may have decreased anxiety in animals that have experienced trauma compared to shams, or may have induced hypervigilance in shocked animals. There was no significant difference between groups in the EPM, although the same trend can be seen.

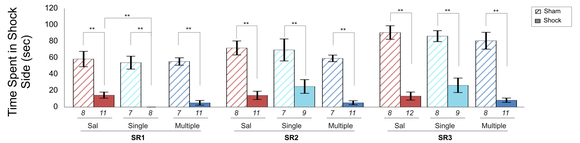
## 3.B. Effect of Oxytocin

Plasma levels of OXT return to baseline 60 minutes after subcutaneous injection.

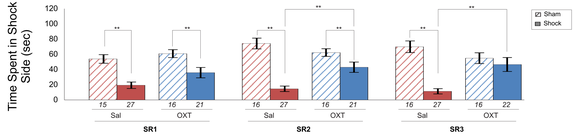



### Situational Reminders

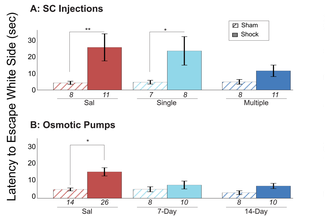
A single OXT injection after shock did not interfere with the consolidation of the traumatic memory at SR1, and did not prevent the consolidation of the other re-exposures to the context without shock (light blue). These subsequent consolidations were prevented in the multiple-injection group (dark blue).




Chronic administration of OXT (pumps) decreased anxiety to the level of sham rats during SR3. These results demonstrate differential effects of OXT when administered acutely and chronically.

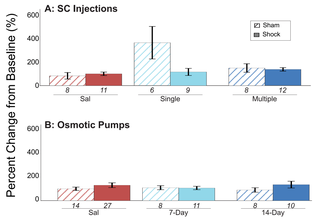



### Black and White Box




The saline and single injection groups showed greater avoidance of the black side (more reminiscent of the shock box) than sham animals. In the multiple injections and chronic OXT groups, the avoidance to the black side was the same as shams. This effect was not seen in the single injection group, suggesting that OXT during SRs was successful in decreasing long term anxiety.

### Open Field




Rats did not show changes in Open Field behavior after shock and drug administration when compared to before shock. General anxiety was unaffected by the shock or the presence of OXT, which may demonstrate the context-specific anxiety induced by the shock paradigm, and relief of trauma-specific anxiety after OXT administration.

## 4. Conclusions

- Social bonding may prevent short term anxiety and the development of certain forms of long-term anxiety.

- Social bonding is mediated by multiple systems, in addition to OXT. Social-bonding induced OXT levels could be less than the ones we administered.

- Social bonding may help prevent certain forms of PTSD-induced long term anxieties. Chronic administration of OXT during contextual reminders can prevent the development of long-term anxiety by reducing context-associated fear.

- Chronic, but not acute OXT is effective at reducing avoidance to the shock compartment.

- Findings in the OXT pump group suggest that OXT affects the consolidation of emotionally salient memories differently than that of neutral memories, or that the emotional memory is unable to be suppressed during re-exposures if the OXT is brief and the system has not had time to adjust.

- OXT may enhance the consolidation of non-emotional memories.

- Another interpretation is that the effect of OXT on consolidation may be strengthened during sleep (when most consolidation occurs).

- SC OXT may have a central effect via receptors in the hindbrain (Ho et al., 2014) but may be acting via peripheral OXT receptors in the body first before acting on the brain (Ring et al., 2006).

- **Future directions** include examination of the effects of vasopressin on traumatic stress, sex differences in OXT effectiveness, and the combination of social bonding and exogenous OXT as a potential treatment for early PTSD intervention.

- More studies may be done to elucidate the mechanism by which systemic OXT is acting to produce behavioral results.

- Recently, Frijling et al.(2014) has proposed similar research to our study using human subjects.

## 5. References

Ayers, Luke W., et al. "Oxytocin reduces background anxiety in a fear-potentiated startle paradigm: peripheral vs central administration." Neuropsychopharmacology 36.12 (2011): 2488-2497.

Corral-Frias NS, LaHood R, Vogelsang K, French ED, Fellous JM. Involvement of the ventral tegmental area in a rodent model of post-traumatic stress disorder. NeuroPsychoPharmacology 38(2): 350-63, 2013.

Frijling, Jessie L., et al. "Efficacy of oxytocin administration early after psychotrauma in preventing the development of PTSD: study protocol of a randomized controlled trial." BMC psychiatry 14.1 (2014): 92.

Ho, Jacqueline M., et al. "Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats." Endocrinology (2014).

Neumann, Inga D. "Brain oxytocin: a key regulator of emotional and social behaviours in both females and males." Journal of neuroendocrinology 20.6 (2008): 858-865.

Olff, Miranda, et al. "A psychobiological rationale for oxytocin in the treatment of posttraumatic stress disorder." CNS Spectr 15.8 (2010): 522-530.

Olff, Miranda. "Bonding after trauma: On the role of social support and the oxytocin system in traumatic stress." European Journal of Psychotraumatology 3 (2012).

Ring, Robert H., et al. "Anxiolytic-like activity of oxytocin in male mice: behavioral and autonomic evidence, therapeutic implications." Psychopharmacology 185.2 (2006): 218-225.

## 6. Acknowledgements

Supported in part by NSF grant CRCNS 1010172 and ONR grant N000141310672 to JMF, a departmental travel award to SN and an ASUA Student Government travel award to SU.
EJ new affiliation: Graduate Neuroscience Program, Delaware State University.

**Contact Information: emjanezic14@students.desu.edu, fellous@email.arizona.edu**