A novel Post Traumatic Stress Disorder (PTSD) model in the rat

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SCAN ME

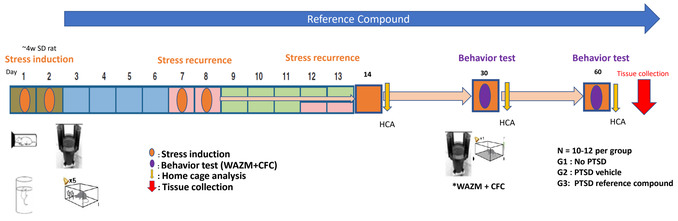
BACKGROUND

PTSD is a serious condition that can lead to intense fear, anxiety and depression, resulting in social distancing and other behavioral disorders. Childhood exposure to highly stressful events increases the likelihood that the adult will be more prone to suffer from PTSD. Current medication, usually antidepressants or anxiolytics, is unspecific, ineffective and has a number of side effects (e.g. sedation, sexual dysfunction). As a result, many people continue to suffer from PTSD in spite of current treatment options, indicating a critical need for new treatments.

A limiting factor in the development of treatment for PTSD is the lack of valid translational models. Naason Science has been developing models of PTSD in the rat and the minipig based on a multi-faceted, prolonged stress paradigm so as to test the efficacy of new compounds. Animals are stressed as juveniles in order to increase their susceptibility to PTSD as adults.

METHODS

PTSD Multiple Stressor Model Design



PTSD-stress induction

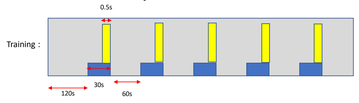
WAZM

Restraint : 2 h

Forced swim: 1 min (swim) + 30 sec Underwater Stress

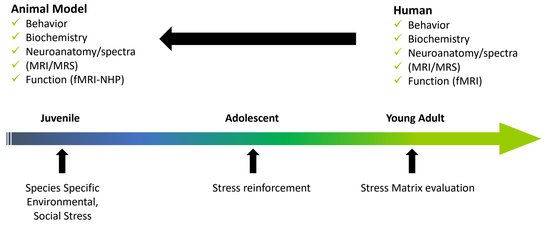
Electric shock with cue (5 times)

CFC experimental scheme



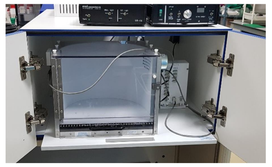
Studies are performed in a blinded manner

Underlying Model Development Philosophy

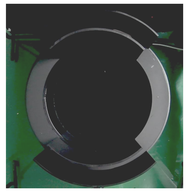


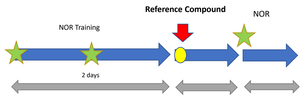
Behavioral Tests

Cued Fear Conditioning

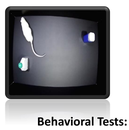


Water Associated Zero Maze





HCA
WAZM
NOR
Cortisol

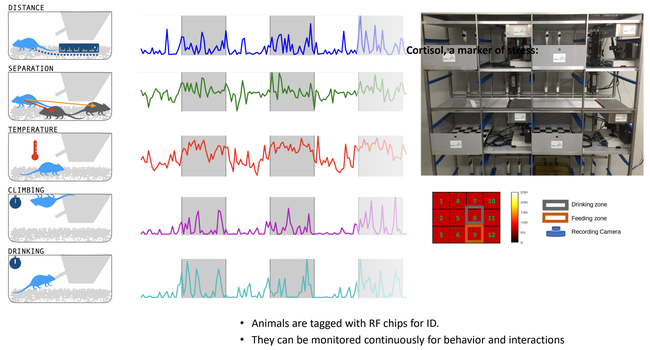


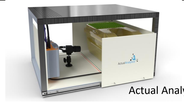
Behavioral Tests:
Novel Object Recognition
Water Associated Zero Maze
Cued Fear Conditioning
24h Home Cage Activity observation

Core HCA Data – showing individual behaviors and locomotion

★ HCA–behavior Index

1. Zone Occupancy (s)
2. Total Moving Distance (mm)
3. Separation/Isolation Distance (mm)
4. Total Moving Time (s)
5. Drinking Time (s)
6. Thigmotactic Time (s); moving time limited to a cage wall
7. Isolated Time (s)
8. In Center Zone Time (s)
9. Rearing Time (s)
10. Core body temperature





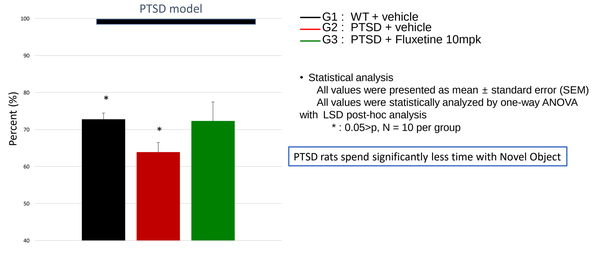
Actual Analytics

Cortisol, a marker of stress:

- Animals are tagged with RF chips for ID.
- They can be monitored continuously for behavior and interactions

RESULTS

Novel Objective Recognition

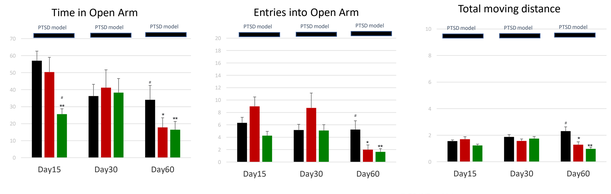


- Statistical analysis
  All values were presented as mean ± standard error (SEM)
  All values were statistically analyzed by one-way ANOVA with LSD post-hoc analysis
  * : 0.05>p, N = 10 per group

PTSD rats spend significantly less time with Novel Object

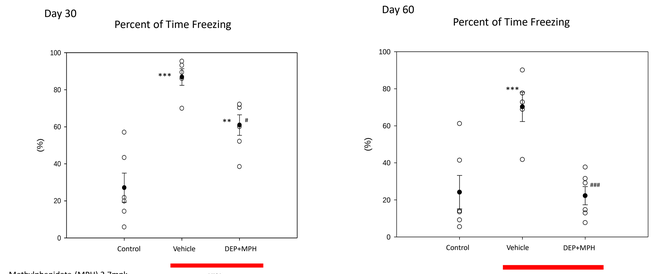
WAZM

After 60 days PTSD rats are less prone to enter open areas of WAZM



- Statistical analysis
  All values were presented as mean ± standard error (SEM)
  All values were statistically analyzed by one-way ANOVA with LSD post-hoc analysis
  - * : 0.05>p, ** : 0.01>p; G1 vs All group
  - # : 0.05>p; G2 vs All group. G1 (n=12), G2 (n=12), G3(n=12)

Exposure to Stress as Juveniles results in increased freezing time in CFC test



Methylphenidate (MPH) 2.7mpk
Desipramine (DES) 10mpk

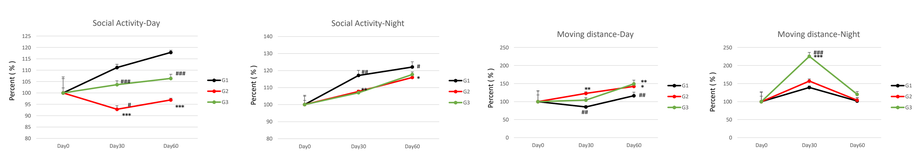
NB. Diazepam was not effective in this model

N=6 animals/group
Testing Time = 180 sec
Mean ± SEM

Stats: one-way ANOVA followed by post-hoc LSD;
*p<0.05, **p<0.01, ***p<0.001 compared to Control (no PTSD)
#p<0.05, ##p<0.01 ###p<0.001 compared to vehicle (PTSD)

PTSD animals demonstrate less social activity than do their cage mates

standardized to day 0



Stats: one-way ANOVA followed by post-hoc LSD;
*p<0.05, **p<0.01, ***p<0.001 compared to G1
#p<0.05, ##p<0.01 ###p<0.001 compared to G2

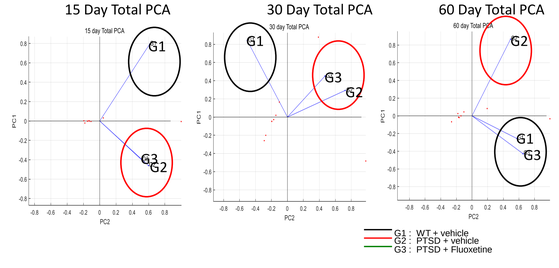
MPH-methylphenidate 2.7mpk
DES-Desipramine 10mpk

Total moving distance

PTSD animals move significantly more during the day

standardized to day 0

Principal Component Analysis
(99.8%)



Cortisol, a marker of stress:		
Treatment	Cortisol (pg/ml)	
	Day 30	Day 60
Control	344.64±65	460.65±39
PTSD/Vehicle	423.59±32	683.76±66*

SUMMARY AND CONCLUSIONS

Rats exposed to multiple stresses as juveniles experience latent behavior similar to that of PTSD sufferers, including: **social distancing**, **enhanced anxiety** and **elevated cortisol levels**.

Naason has established a robust rodent model of PTSD.
This model contains elements of both anxiety and depression, as per the human condition.

Studies are ongoing using MRI, MRS and blood markers.
Naason is also developing a large animal model using the minipig (**see Poster 560.18**)

The model presented here is a simple, robust model of PTSD that should facilitate dissecting out various aspects of this disorder and provides a screening paradigm for new medical treatments.

References

Model developed with the help of Prof. Gal Richter-Levin, Dept. Psychology, U. Haifa.
Richter-Levin, G., et al. "**Animal models of PTSD: a challenge to be met**." Mol Psychiatry. 2019 Aug;24(8):1135-1156.

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Front. Behav Neurosci 2014 Jan 17;8:1. **Water associated zero maze: a novel rat test for long term traumatic re-experiencing. Gilad Ritov, Gal Richter-Levin**

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