A Translational Approach to a Therapeutic Intervention with Physical Activity for Neurological/Cognitive Dysfunction

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Bass Connections in Brain & Society

MOUSE: Alzheimer's Disease ← **Can physical fitness ameliorate cognitive impairment and neuroinflammation in neurological/cognitive dysfunctions?** → **HUMAN: Post-Traumatic Stress Disorder**

Background

Alzheimer's Disease

- AD is an age-related, neurodegenerative disease that causes neuronal damage and death and leads to cognitive impairment
- High incident rate in women may be explained by loss of ovarian function during menopause

Neuroprotective Effects of Exercise

- Physical exercise has been associated with reduction in rates of cognitive decline

Aims/Research Questions

Aims

- Demonstrate how exercise can delay cognitive decline in AD
- Determine how progressive neuroinflammation in an AD mouse model is influenced by exercise

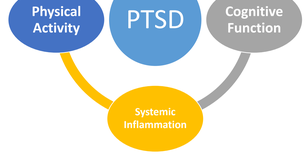
Research Question

- Does 12 weeks of exercise begun just after ovarian failure (Transitional Menopause) protect against memory loss and neuroinflammation in a mouse model of AD?

Background

Post-Traumatic Stress Disorder

- PTSD is a mental health condition that is caused by an experienced traumatic event



Aims/Research Questions

Aims

- To explore the relationship between PTSD, Inflammatory Markers, Physical Activity, and Cognitive Function

Research Questions

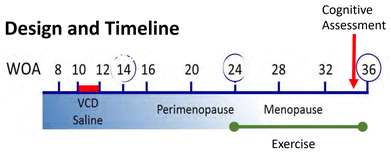
- How do changes in physical activity levels affect aerobic endurance and inflammatory biomarker concentrations among patients with PTSD following a 12-month physical activity intervention?
- How do differing baseline physical activity levels affect the presence of inflammatory biomarkers and cognitive function in PTSD patients prior to a 12-month physical activity intervention?

Methodology

Female Alzheimer's Mouse Model – CVN-AD

- develops human AD-like pathogenesis
- transitional menopause induced by ovotoxin VCD which kills ovarian follicles

Design and Timeline



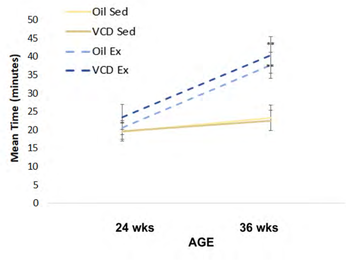
Exercise

- From 24-36 WOA mice ran on wheels for 6-8 hours/day, 5 days/week and underwent forced treadmill training for 45 minutes, 2 days/week

Exercise increased fitness of CVN-AD mice on a treadmill endurance test

Time to Exhaustion Endurance Test

- For every 2 minutes, the speed of the treadmill increases by the same factor until mice are no longer able to run



Methodology

Sample

- 302 older patients with pre-diabetes (67 with PTSD)

Enhanced Fitness Intervention

- 12 month telephone physical activity counseling
- Measures Collected at baseline and at 12 mos.

Cognitive Function - AD8 (baseline only)

- Scores: 0-1 = normal cognition, ≥ 2 = cognitive impairment

Systemic Inflammation

- 9 serum cytokines collected for each individual

Aerobic Fitness – 6 Minute Walk Test (6MWT)

- Participants instructed to walk as far as they can in 6 minutes

Statistics

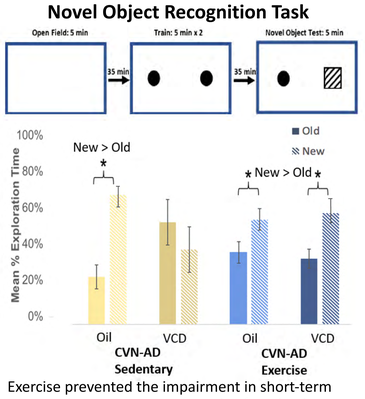
- Between-group comparisons (PTSD vs. No PTSD): t-tests
- Associations between variables: bivariate correlations

Table 1. Participant Characteristics at Baseline by PTSD Status

Variable	Without PTSD (n= 235)	With PTSD (n = 67)	With vs. Without PTSD (p-value)
Age (yr)	68.6 ± 6.2	62.9 ± 3.9	< 0.01
Race (%)			< 0.01
African-American	21.8	47.8	--
Caucasian	76.5	49.3	--
No. of Comorbidities	3.9 ± 2.4	4.5 ± 2.3	0.11
Body Mass Index (kg/m²)	31.2 ± 3.6	31.3 ± 3.7	0.85
AD8 Scores	1.10 ± 1.67	3.40 ± 2.64	< 0.01
6-Minute Walk Task (m)	1621.2 ± 385.9	1675 ± 354.4	0.30
Physical Activity (min)	118.2 ± 184.8	89.8 ± 127.5	0.24

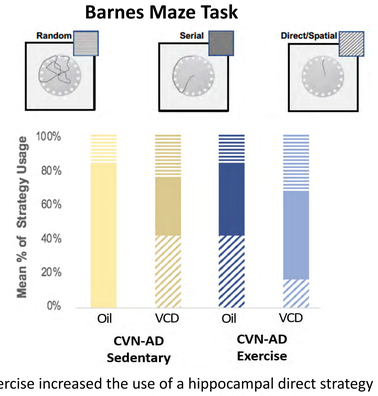
Exercise improved short term episodic memory and increased use of a hippocampal strategy

Novel Object Recognition Task



Exercise prevented the impairment in short-term memory induced by loss of ovarian function in CVN-AD

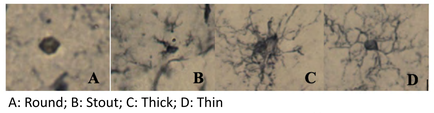
Barnes Maze Task



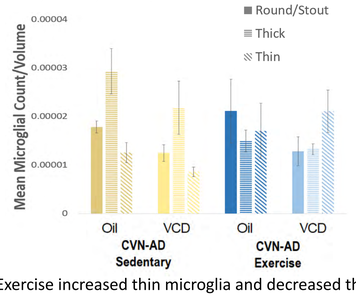
Exercise increased the use of a hippocampal direct strategy to locate the escape hole in cycling CVN –AD mice, but was unable to provide similar neuroprotective effects in menopaused CVN-AD mice

Exercise decreased neuroinflammation

IBA-1 Stain (Microglia marker)



A: Round; B: Stout; C: Thick; D: Thin



Exercise increased thin microglia and decreased thick microglia, suggesting decreased neuroinflammation

Relationships with Cognitive Function

Results:

Cross-Sectional Associations

- PTSD vs. Non on AD8
  - PTSD ∝ sig. worse cognitive function (p<.01)
- AD8 w/ 6MWT, PA (PTSD only)
  - N.S.

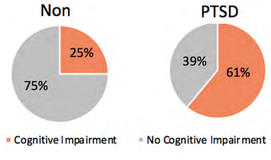
Longitudinal Associations

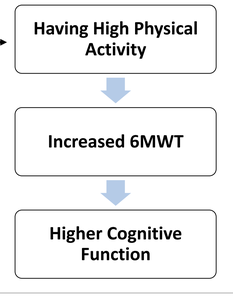
- AD8 w/ changes in PA, 6MWT
  - ΔPA (r=-.33, p<.05)

Conclusion:

In PTSD vs. non-PTSD patients:

Limitations: AD8 only at baseline





Relationships with Inflammatory Biomarkers

Results:

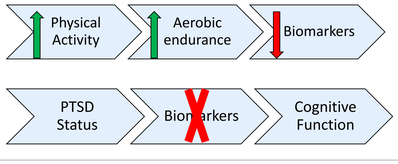
Cross-Sectional Associations

- PTSD vs. Non on Inflammatory markers (BM)
  - PTSD ∝ ↓ BM levels (D-Dimer, HA, TNFR1, VCAM); p<.10
- AD8 and BM (PTSD only)
  - VCAM (r=-.09), IL8 (r=.24), ps<0.05

Longitudinal Associations

- Changes in PA, 6MWT, and changes in BM (PTSD only)
  - ΔPA: IL6 (r=-.13), TNFa (r=-.13), TNFR1 (r=-.11), TNFR2 (r=-.14); ps<.10
  - Δ6MWT: ΔHA (r=-.15), IL6 (r=-.17); ps<.05

Conclusions:



MOUSE: Alzheimer's Disease → **CONCLUSION: Physical activity is a non-invasive intervention to ameliorate cognitive impairment in neurological/cognitive dysfunctions** ← **HUMAN: Post-Traumatic Stress Disorder**