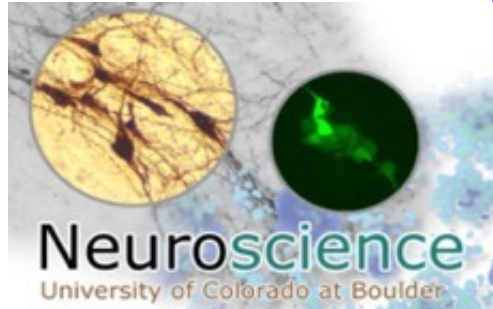




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A Fresh Perspective on Exercise Immunology: It's All in the Brain

Monika Fleshner, PhD

Professor of Integrative Physiology

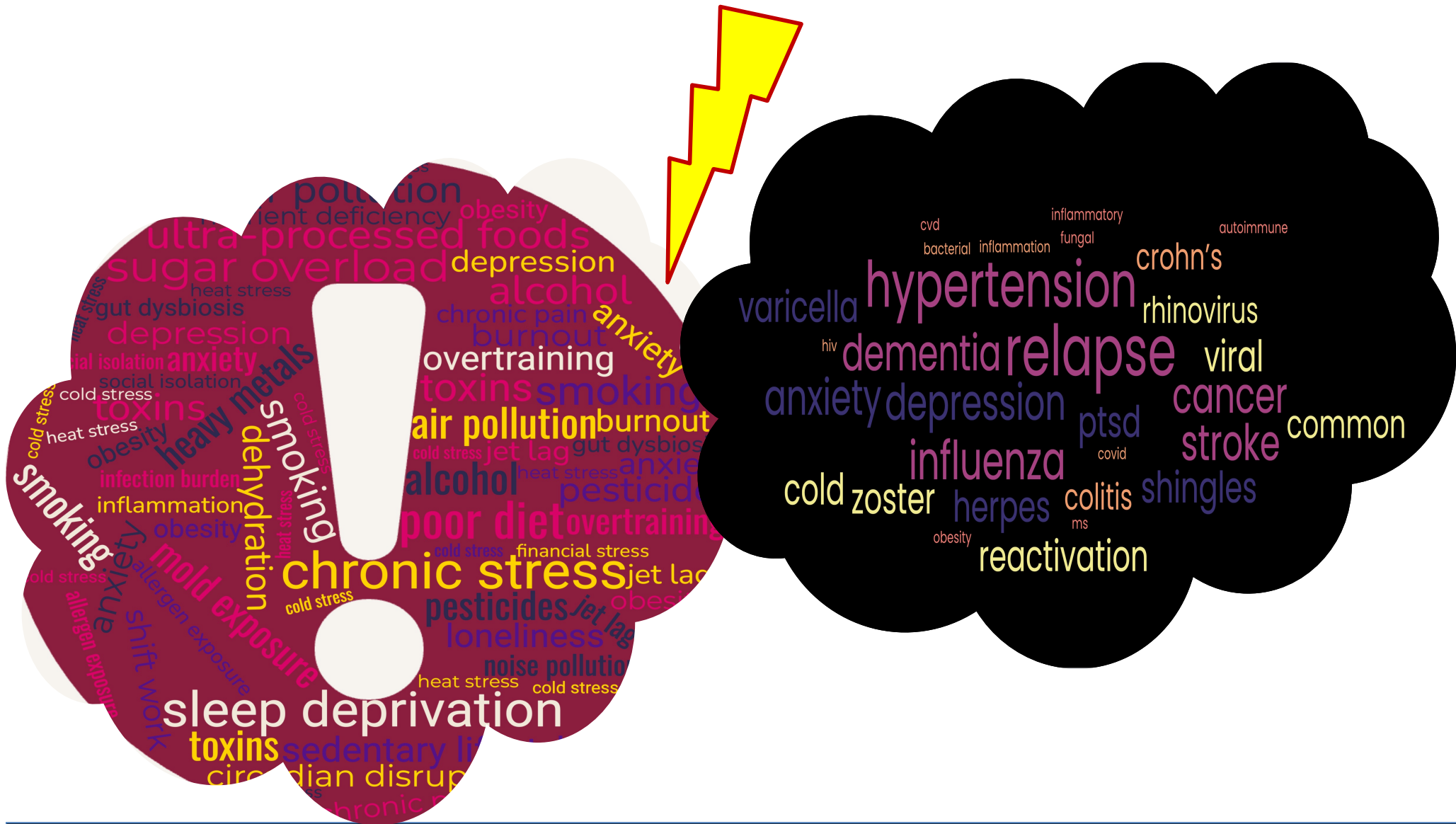
Advancing Neuroscience: From Molecules to Mind

August 13, 2026

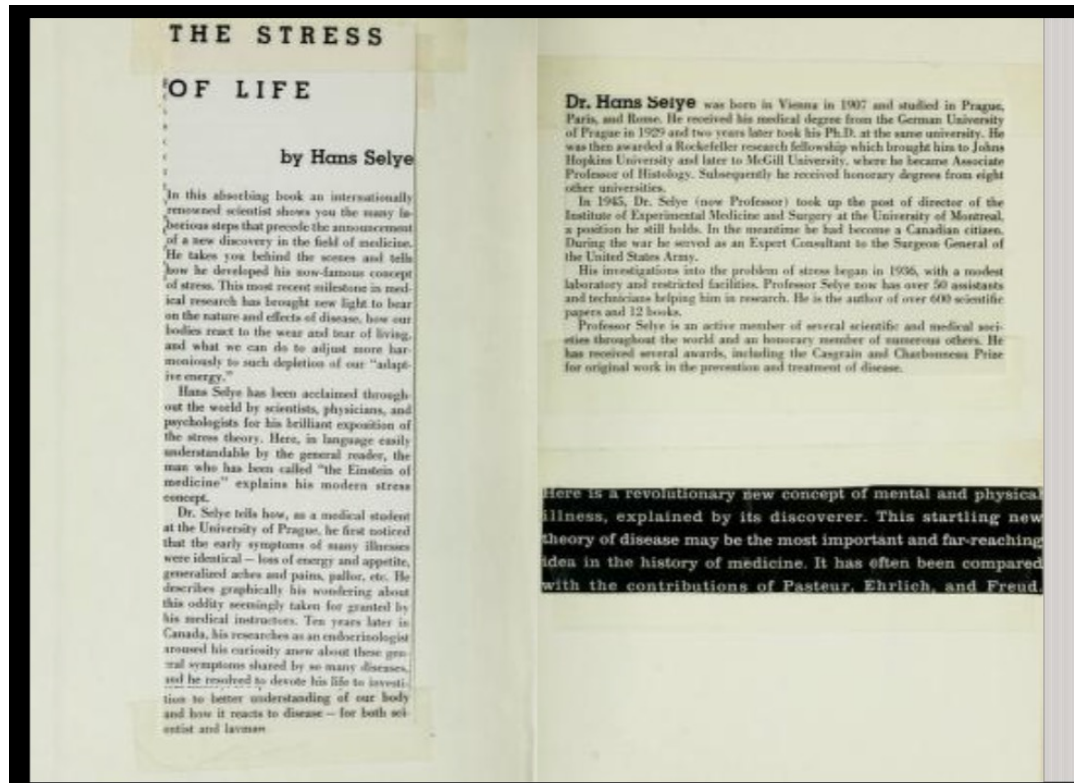


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Stress Increases Disease Risk



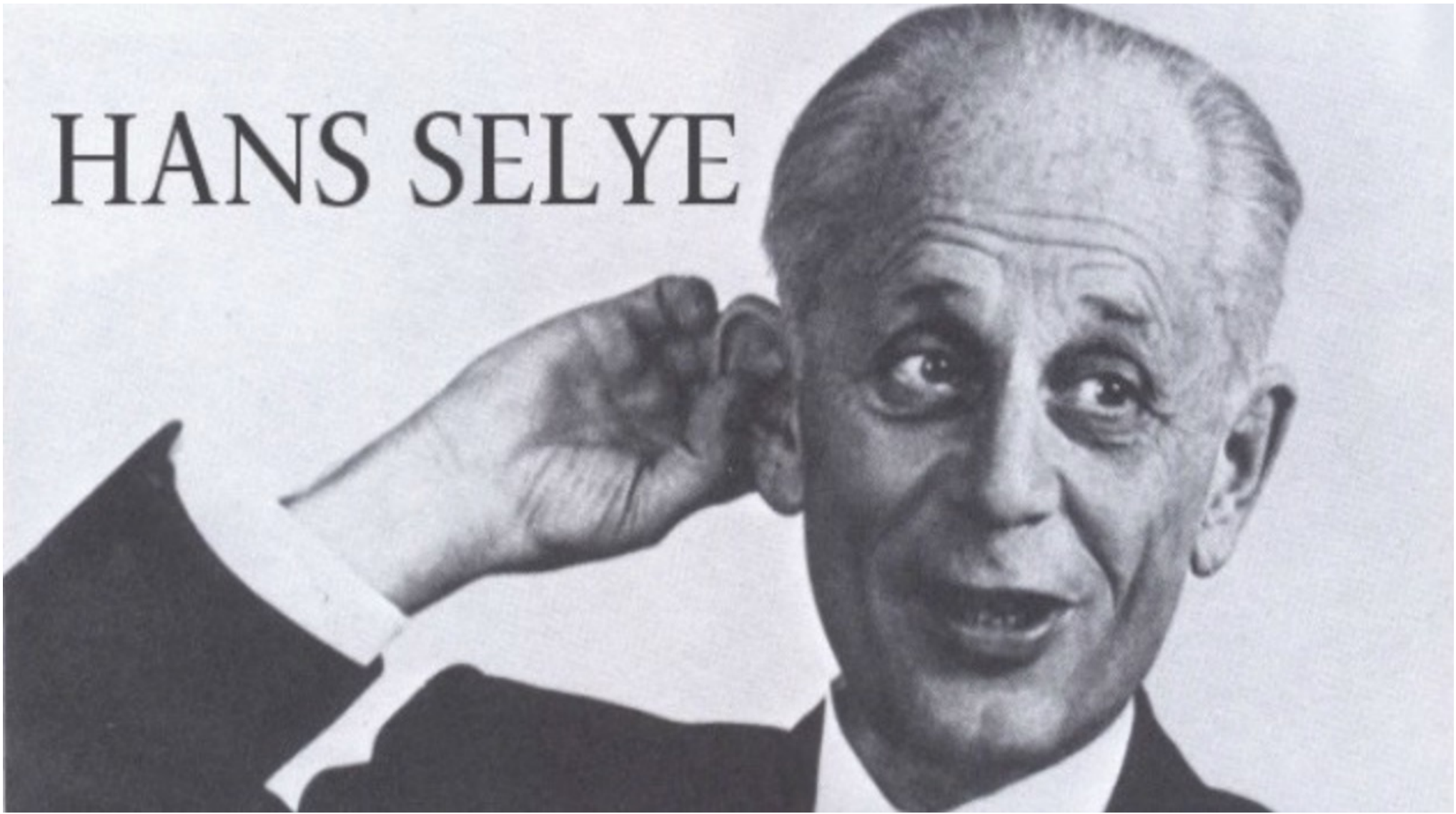
In 1928, Hans Selye published "The Stress of Life," which acknowledged the stress in life.



"Stress in addition to spring itself, is body to the value and placed upon it" of itself"
(Seyle, 1978).



HANS SELYE



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Current Stress Biology

- The **stress response** is generated in response to a **stressor**.
- A **stressor** is an aversive event or substance that the organism would choose to avoid if possible.
- **Stress-resistance** is the capacity to endure more stress before suffering negative consequences.
- **Stress-resilience** is the capacity to bounce back quickly after experiencing negative impacts of stress.

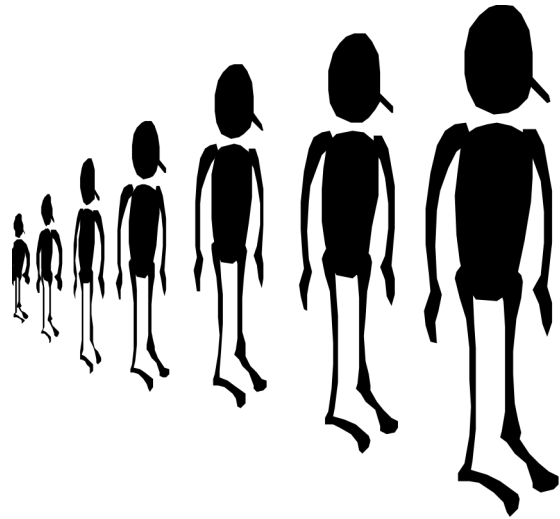


NIH Stress Biology Factoids

- **Males and females respond to stressors differently.** National Institutes of Health in the USA enacted the Revitalization Act of 1993, which led to an uptake in inclusion of males and females in research globally.
- **Stress is not always bad.** The stress response results in a spectrum of changes ranging from adaptive to maladaptive.
- **Stress impacts physiological systems with unique chronologies, and impacted systems influence each other.** e.g., acute traumatic and chronic stressors may initially disturb sleep and contribute to immune dysregulation.

National Institutes of Health 2018





Age, gender, genetics

intensity

controllability

chronicity

**Factors that modulate the impacts
of stress on mind and body**

Physical activity status



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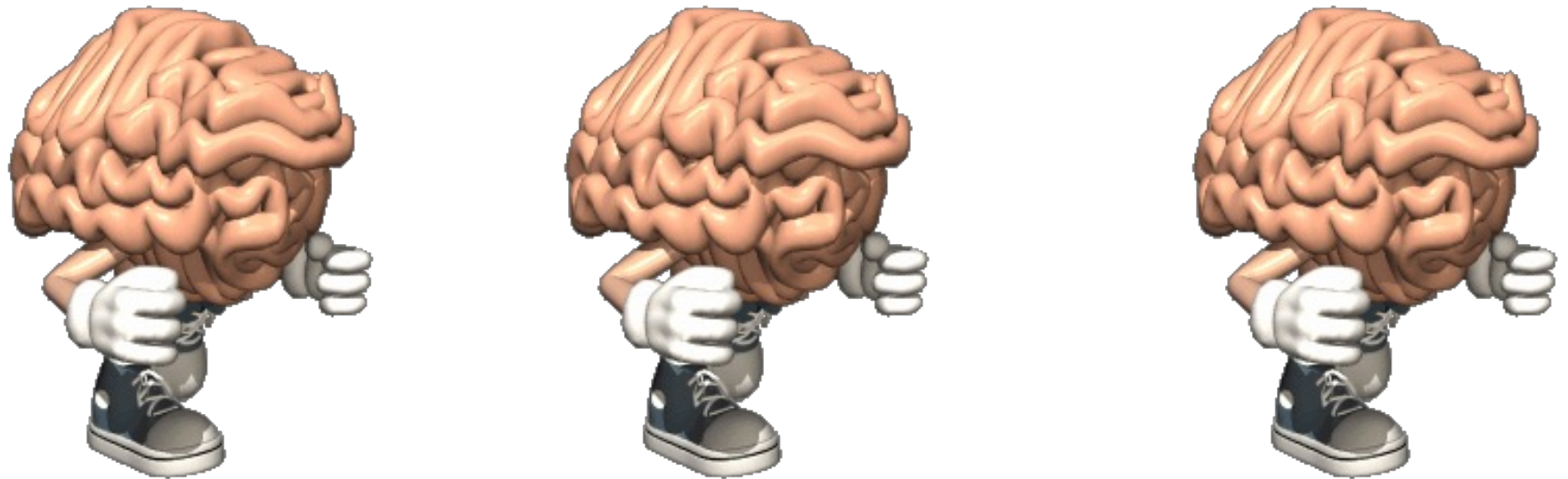


**Physical activity increases
resistance and resilience to
detrimental stressors.**



How does physical activity reduce the negative impacts of stress?

It's all in the brain!

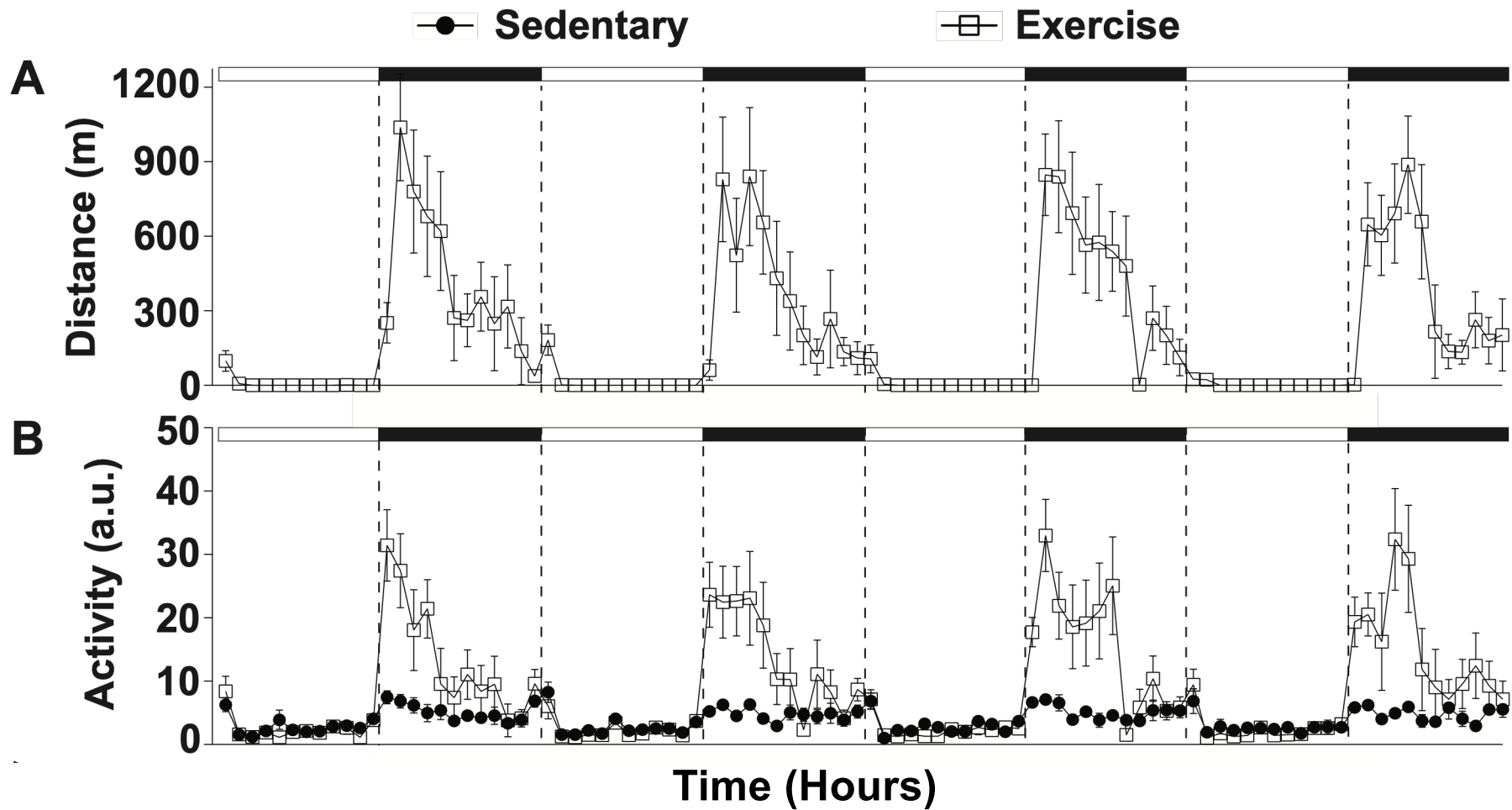


Experimental Approach

- ✓ Use animal models to *avoid the challenges of human stress, immune, and brain studies.*
- ✓ **Modulate physical activity** using voluntary wheel running. It is a naturalistic, inherently rewarding behavior that avoids the **stress associated with forced exercise.**



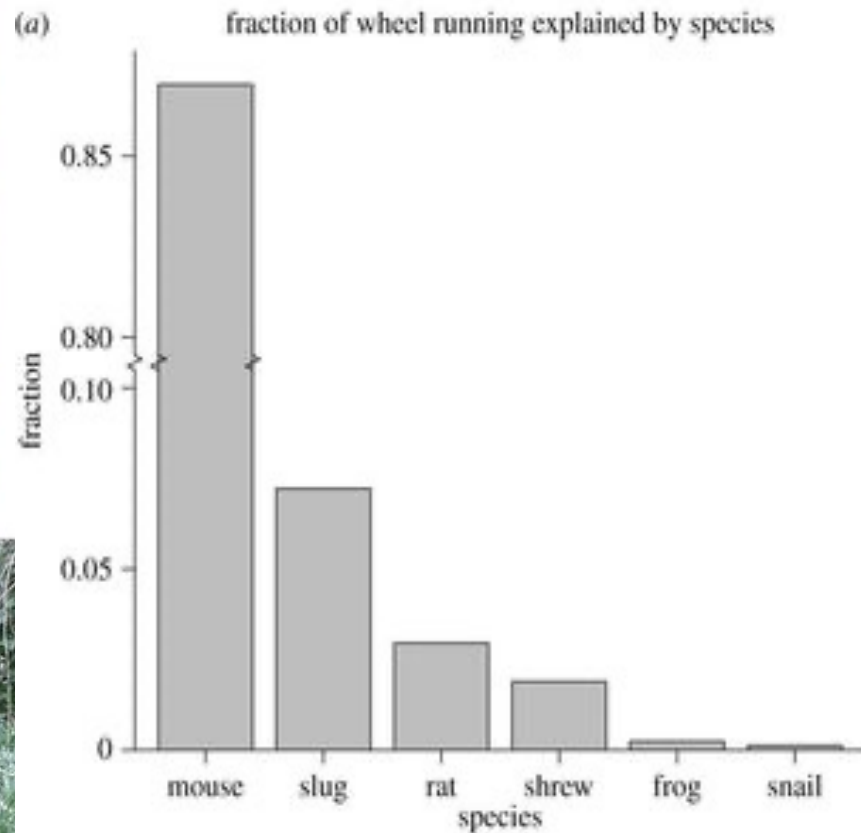
Voluntary Wheel Running



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“Wheel Running in the Wild” by Meijer and Robbers (2014) *Proceedings of the Royal Academy of Science.*



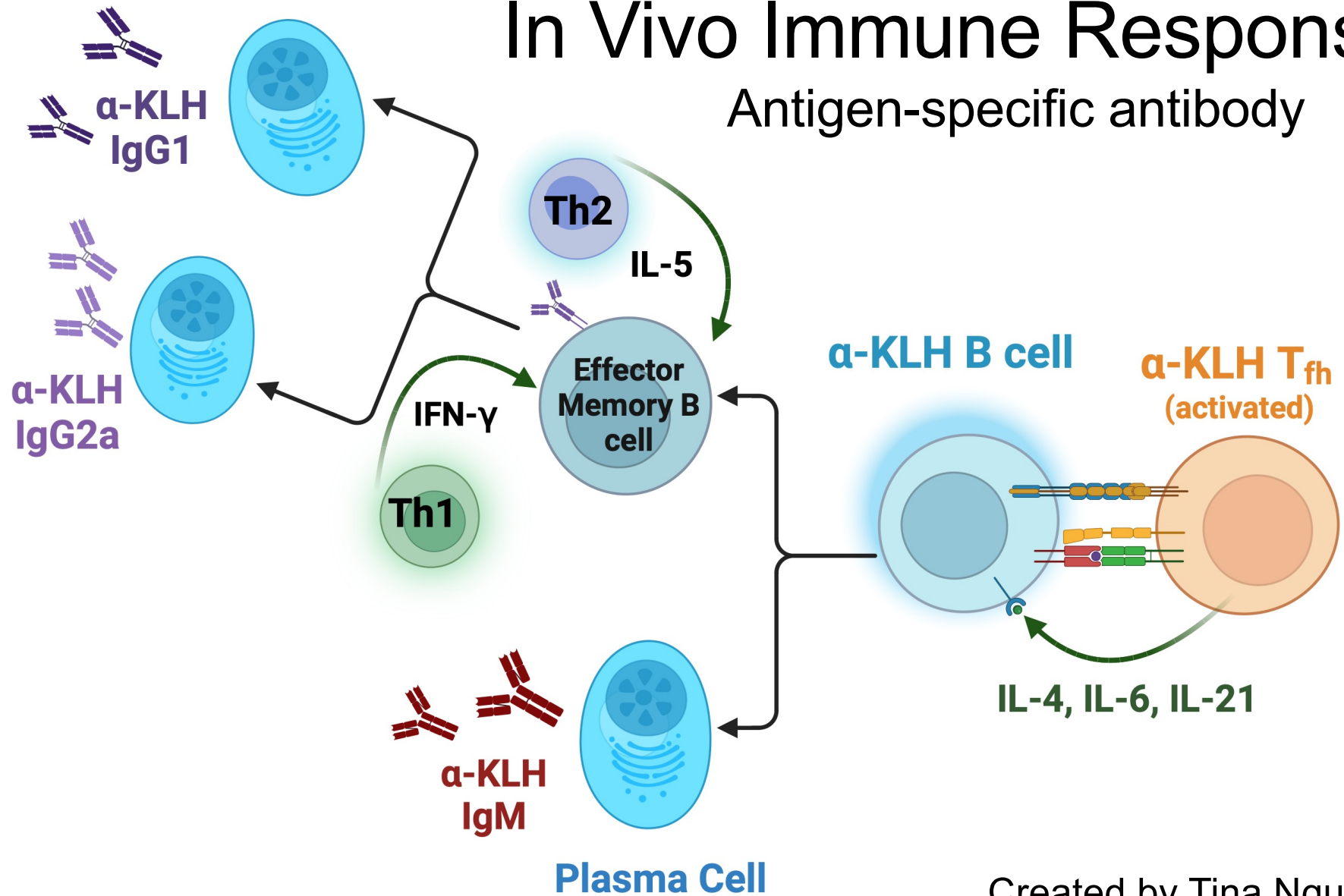
Experimental Approach

- ✓ Use animal models to **avoid the challenges of human stress, immune, and brain studies.**
- ✓ **Modulate physical activity** using voluntary wheel running. It is a naturalistic, inherently rewarding behavior that avoids the **stress associated with forced exercise.**
- ✓ Assess a **health-relevant** measure of immunity that is **stress-sensitive**, with a **known mechanism: *In vivo antibody response.***



In Vivo Immune Response:

Antigen-specific antibody

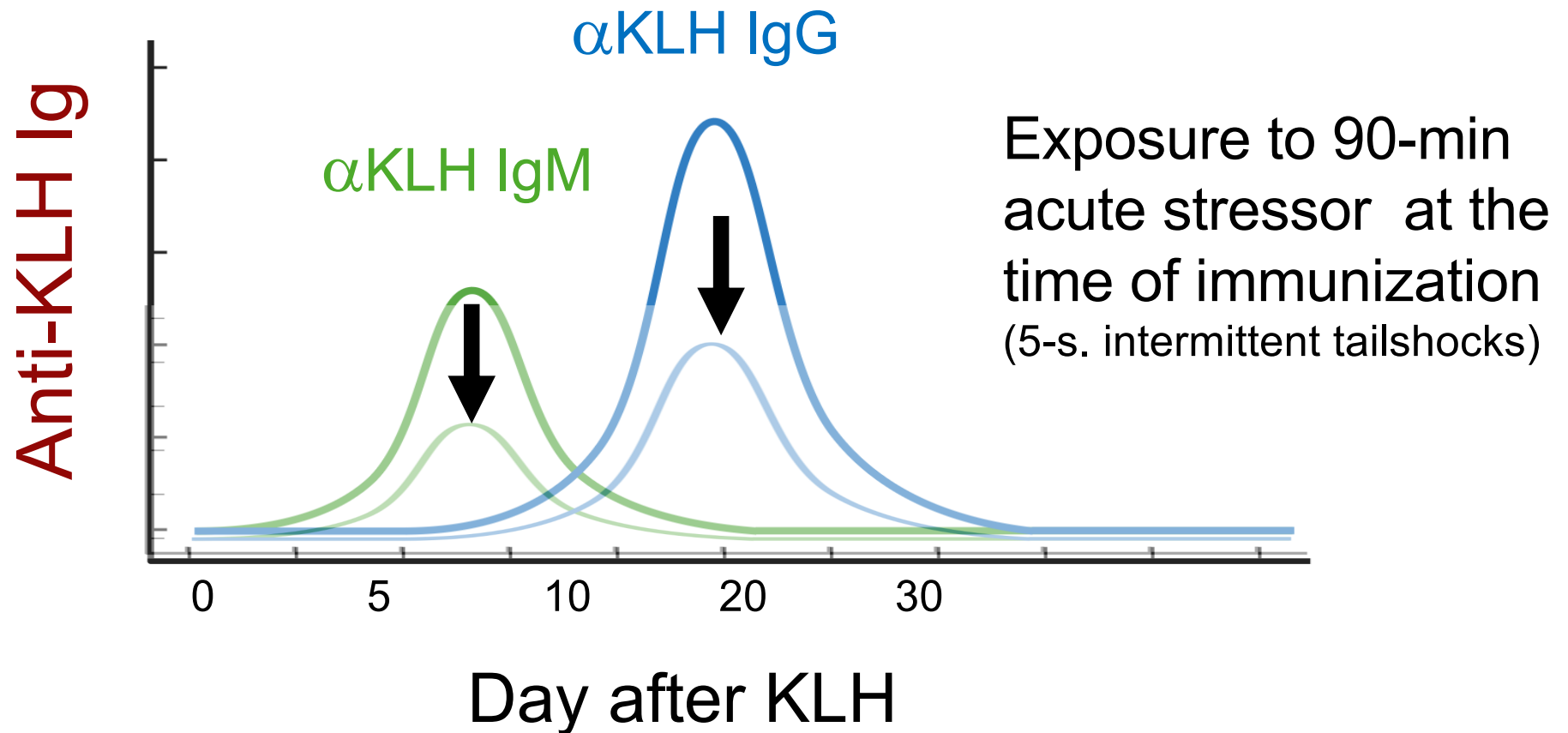


Created by Tina Nguyen

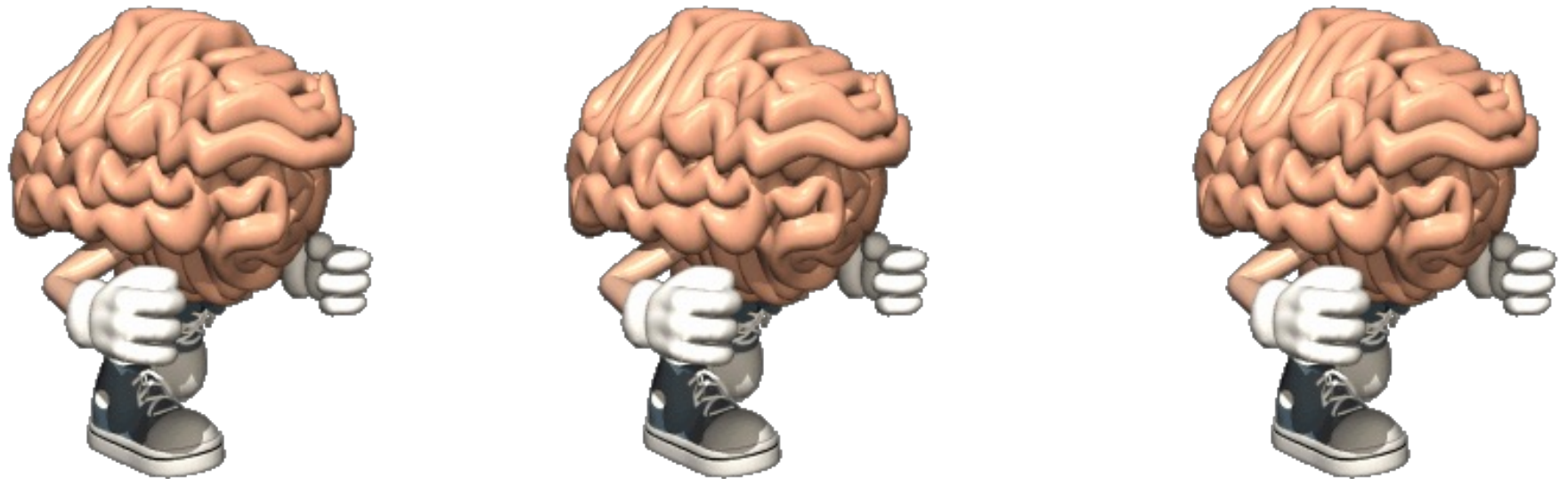


In Vivo Immune Response:

Antigen-specific antibody



Does physical activity prevent stress-induced suppression of the anti-KLH antibody response?



Subjects and General Procedures

Subjects:
Male F344 rats
8 weeks of age

Procedures:



No Stress Stress

Sed

6-10

6-10

Run

6-10

6-10

6 weeks

Sedentary
or
Wheel running

Stressor

100, 5-s, 1.6mA

KLH

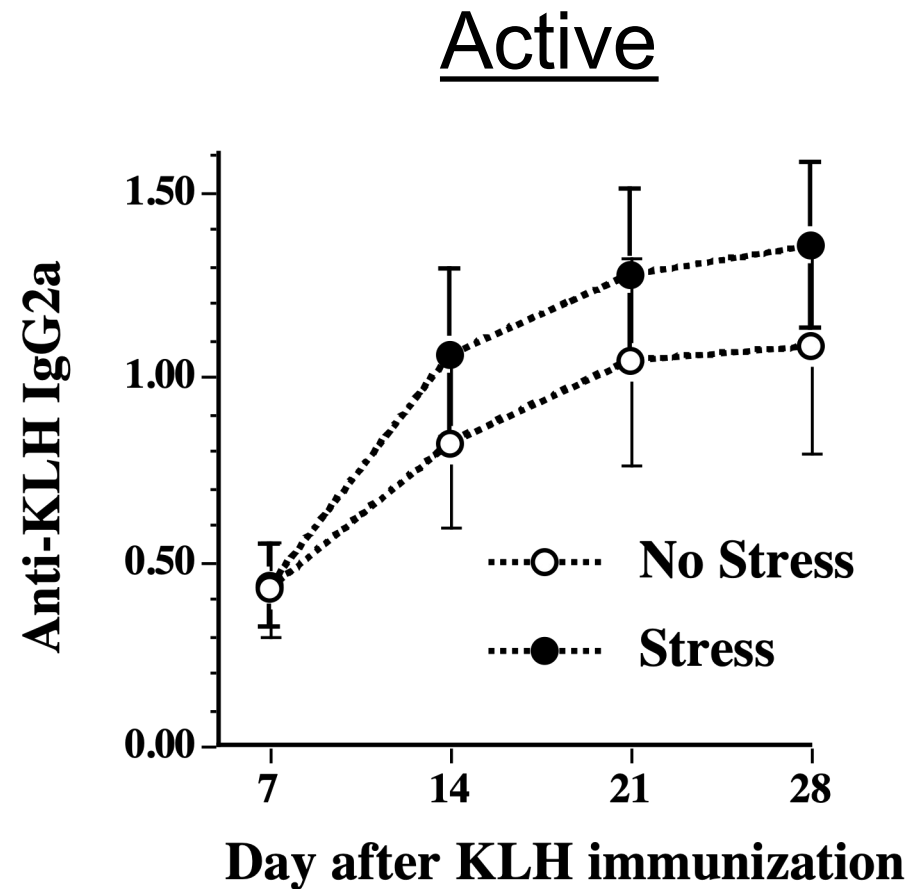
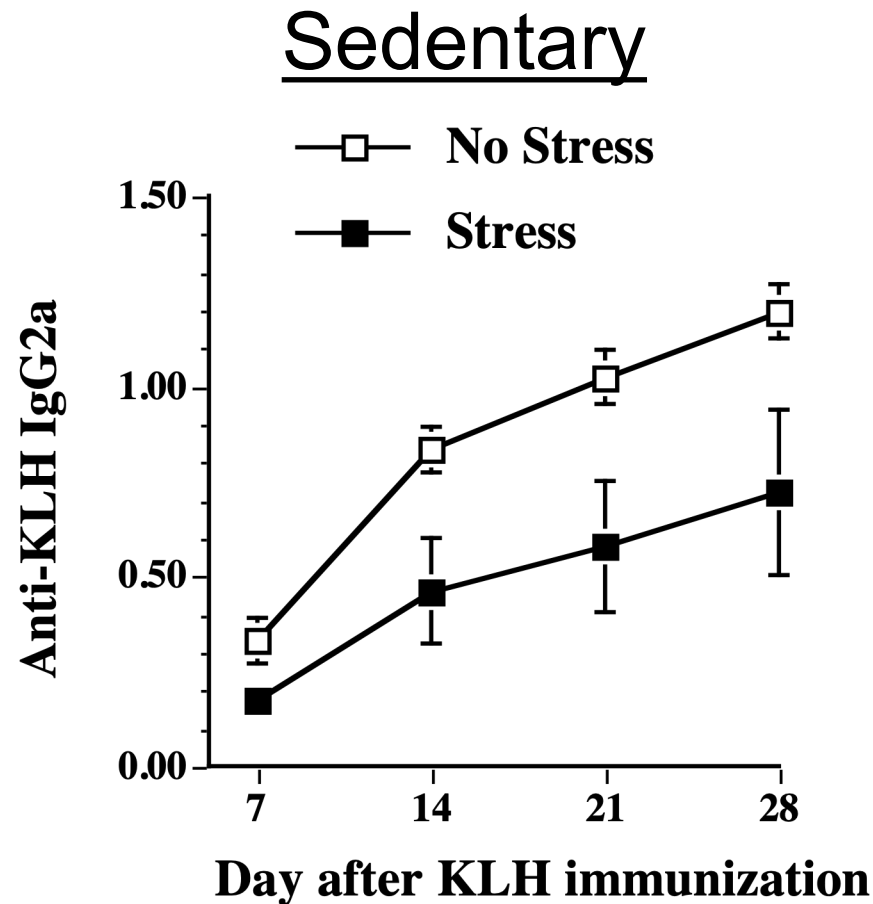
Dependent Measures

Brain, Endocrine
anti-KLH Ig



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Physical Activity Prevents Stress-Induced Immunosuppression.

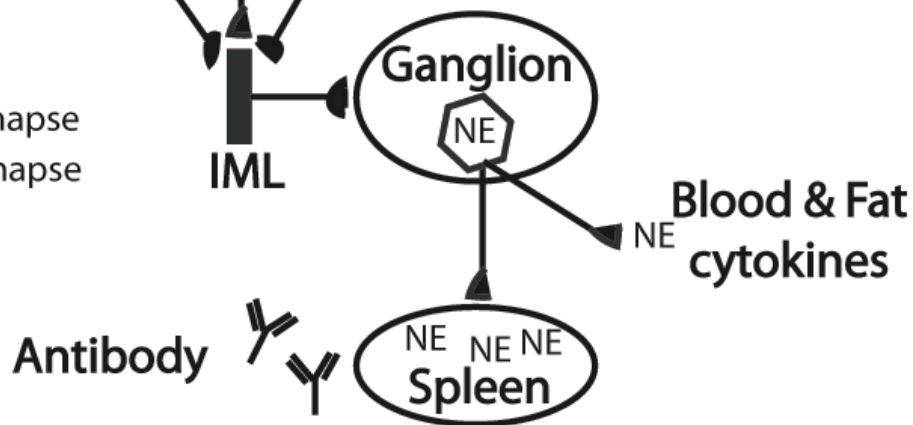


Stressor exposure

How does physical activity
prevent suppression of
KLH Ig?

It's all in the brain!

△ inhibitory synapse
▲ excitatory synapse

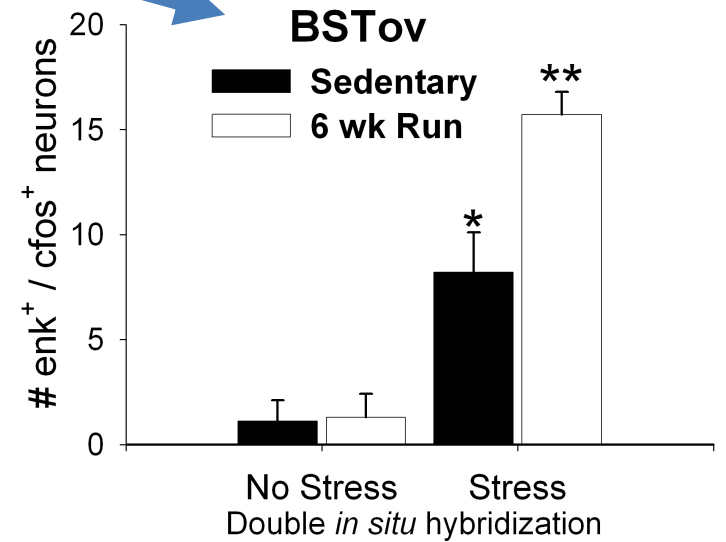
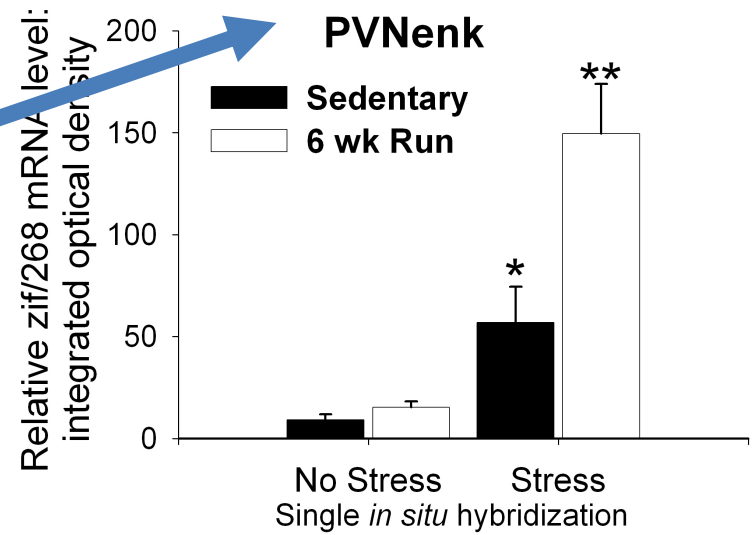
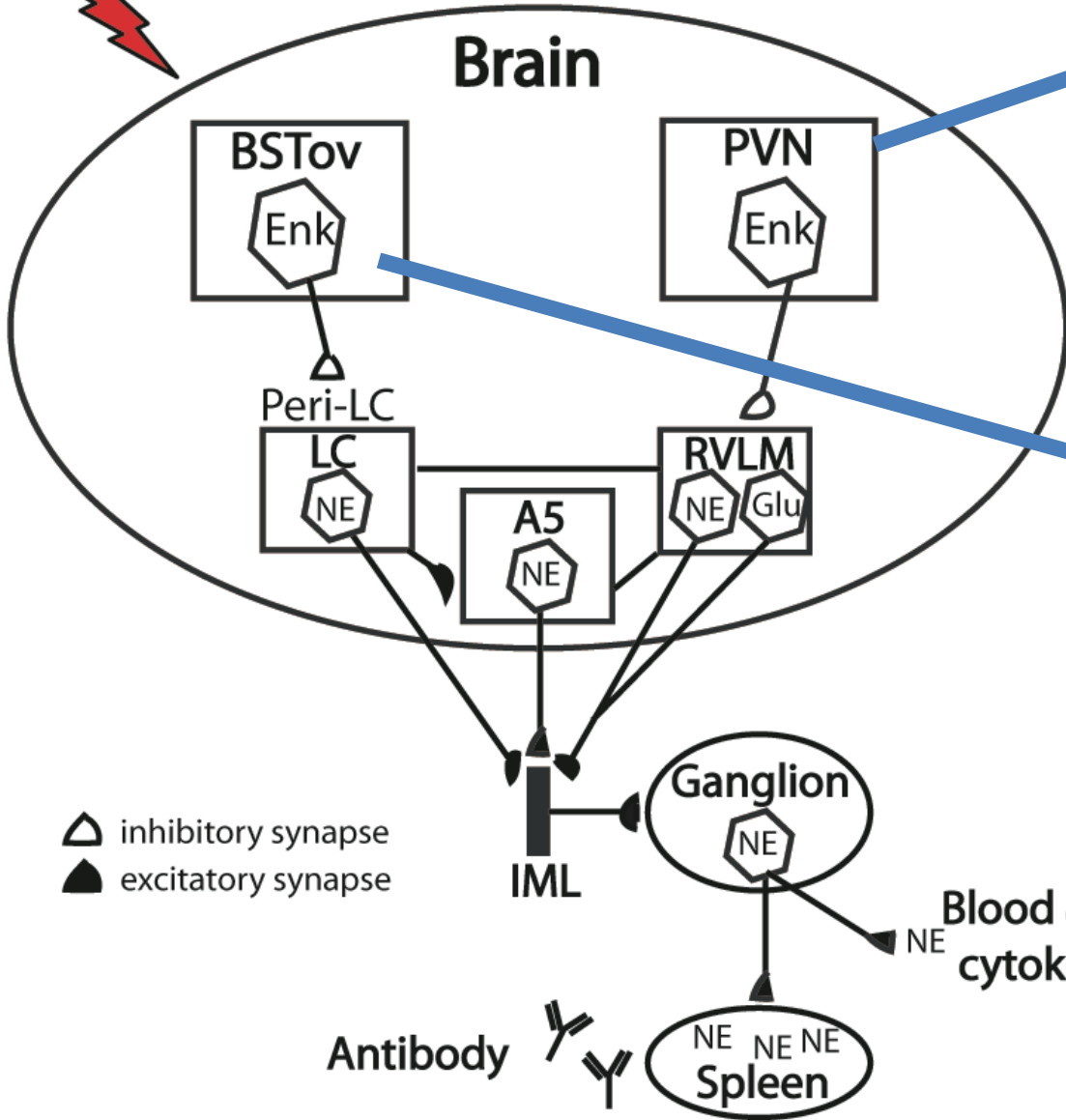


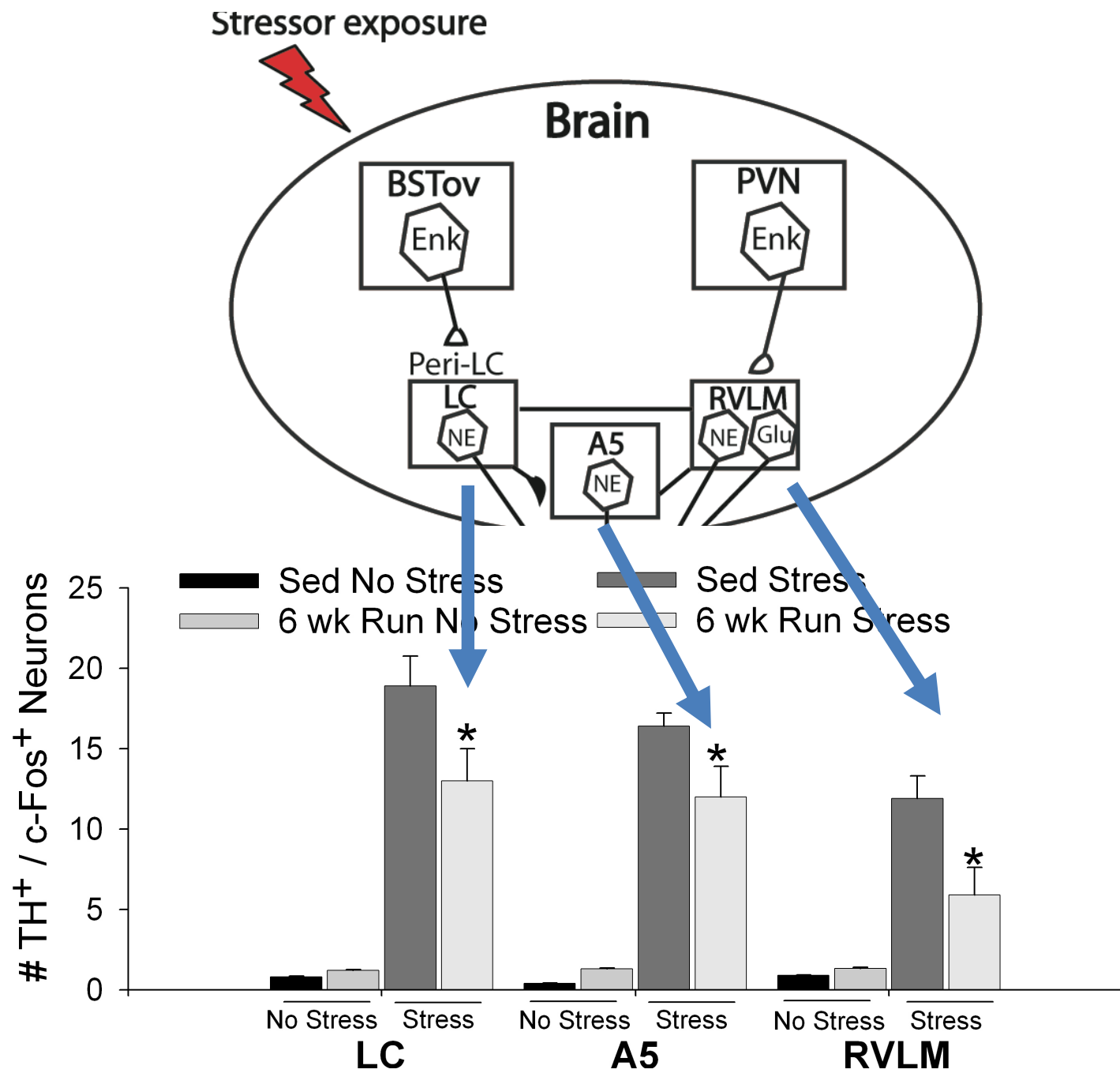
**Sympathetic
Nervous System
Neurocircuitry**



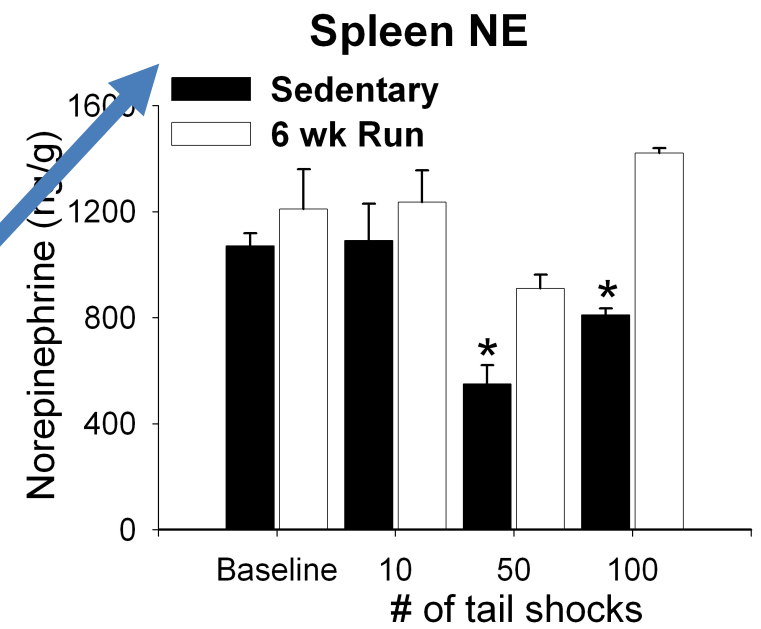
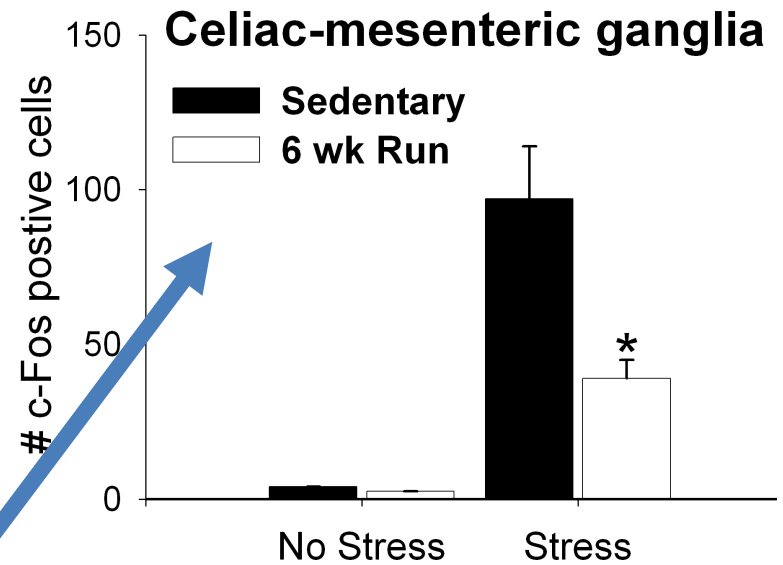
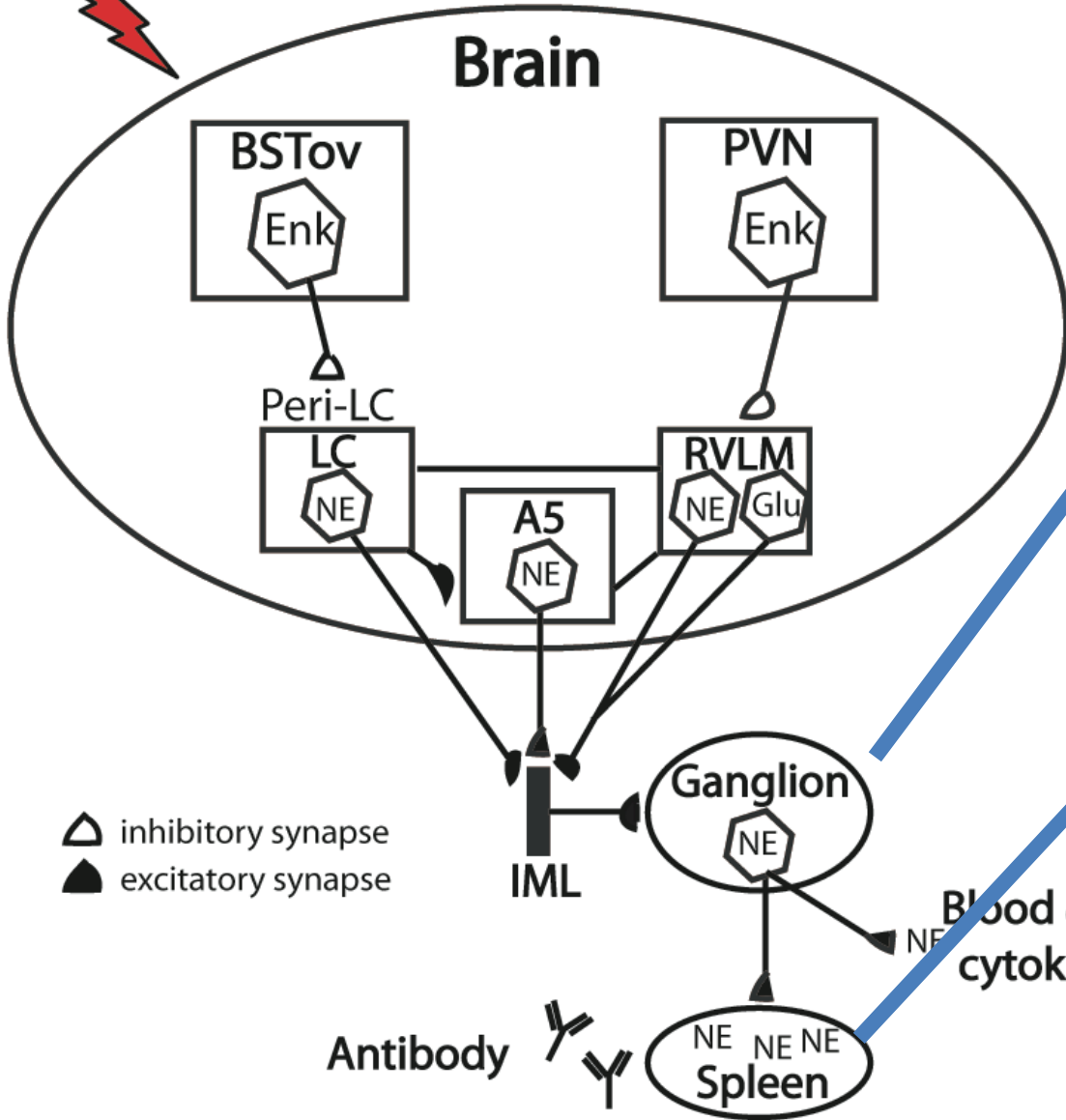
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Stressor exposure





Stressor exposure



Physical Activity Prevented Stress-Induced Immunosuppression.



Smith, TP, Kennedy, S and **Fleshner, M (2004)**. *Influence of age and physical activity on the **primary in vivo antibody** and T cell-mediated responses in men.*

Journal of Applied Physiology 97(2): 491-498.

Grant, RW; Mariani, RA; Vieira, VJ; **Fleshner, M**; Smith, TP; Keylock, KT; Lowder, TW; McAuley, E; Hu, L; Chapman-Novakofski, K; **Woods, JA. (2008)**. *Cardiovascular Exercise Intervention Improves the **Primary Antibody Response to Keyhole Limpet Hemocyanin (KLH)** in Previously Sedentary Older Adults.*

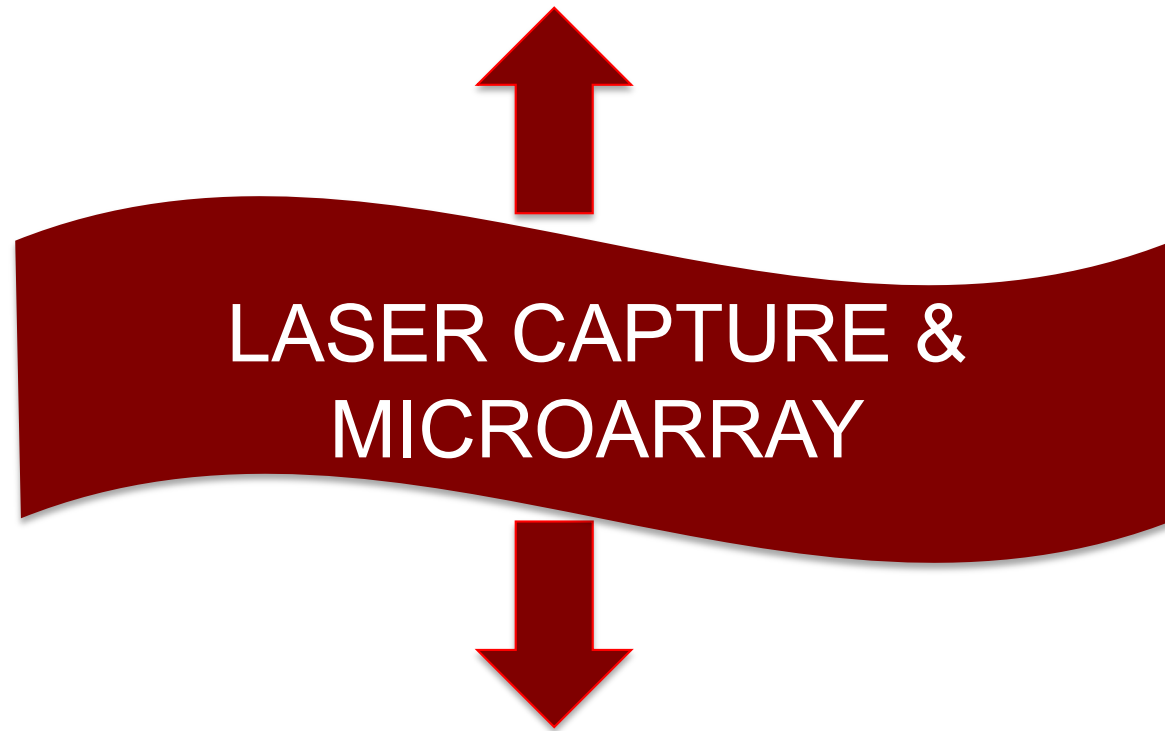
Brain Behavior Immunity 22(6): p. 923-32.10.1016/j.bbi.2008.01.006.



Microarray analyses reveal novel targets of exercise-induced stress resistance in the dorsal raphe nucleus. A. B.

Loughridge, B. N. Greenwood, H. E. Day, M. B. McQueen and M. Fleshner.

<https://www.ncbi.nlm.nih.gov/pubmed/23717271>

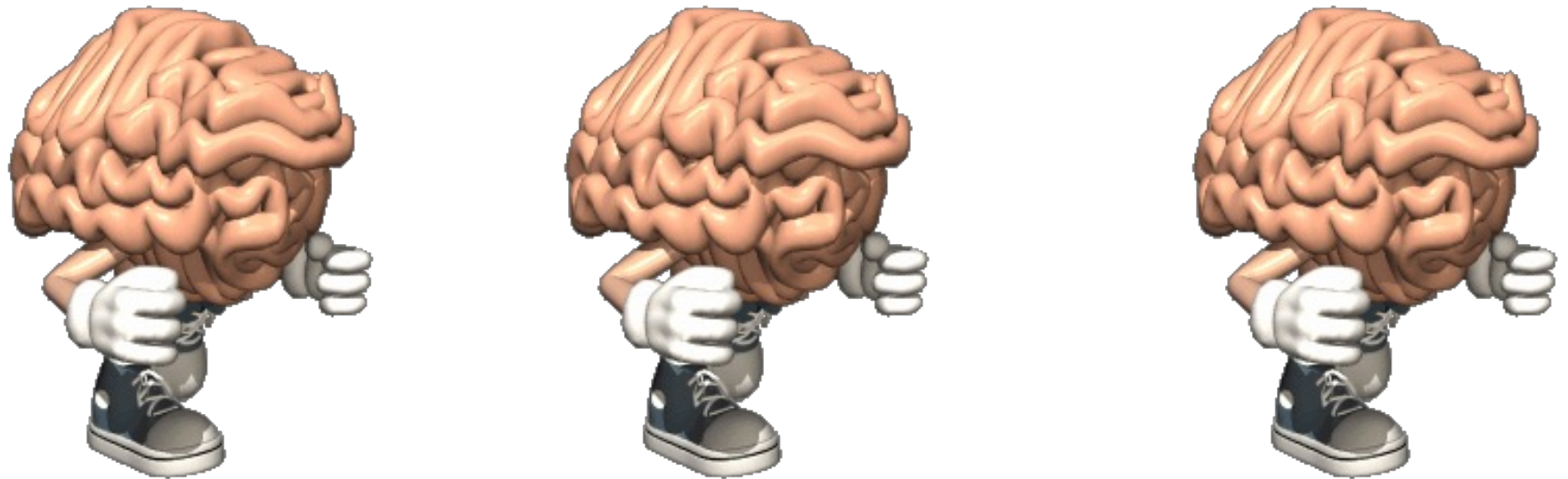


Explore patterns of gene expression differences in the brain due to 6 weeks of voluntary wheel running.



How does physical activity reduce the negative impacts of stress?

It's all in the brain!





The 17th ISEI Symposium

HOME

GREETINGS

OVERVIEW

SCHEDULE

REGISTRATION

PROGRAM

INSTRUCTIONS

VENUE

August 27-30, 2026
Waseda University, Tokyo, Japan



WASEDA University
早稲田大学

The 17th ISEI Symposium
- ISEI 2026 Tokyo -

Exercise Immunology: From Scientific Basis to Practical
Applications

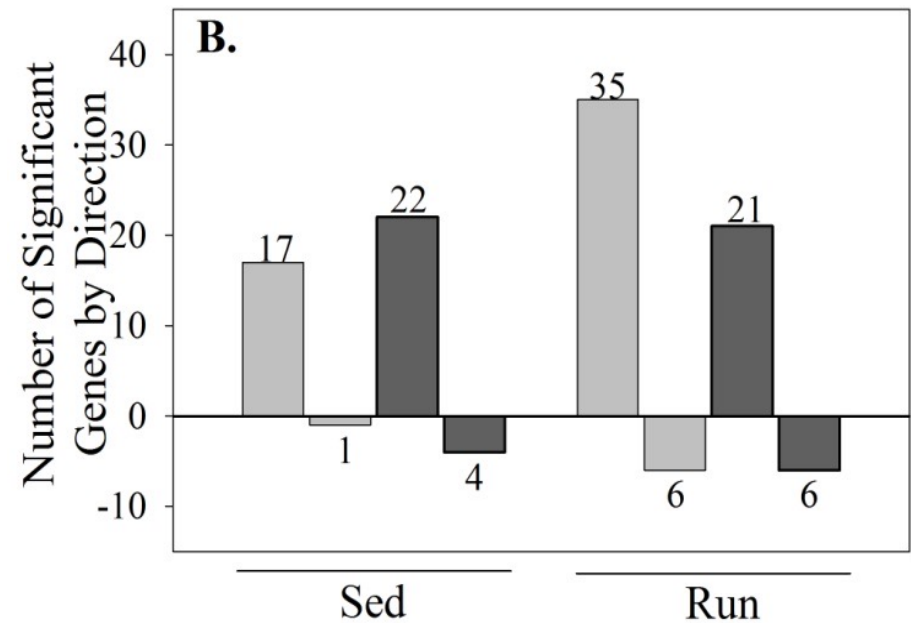
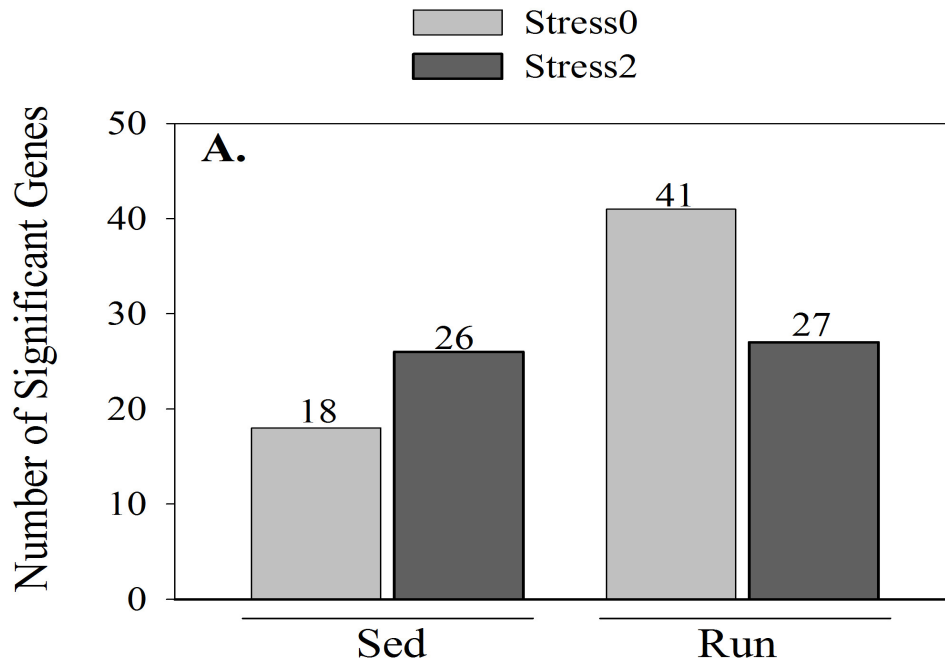
<https://exerciseimmunology.com/>



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Differential Gene Expression

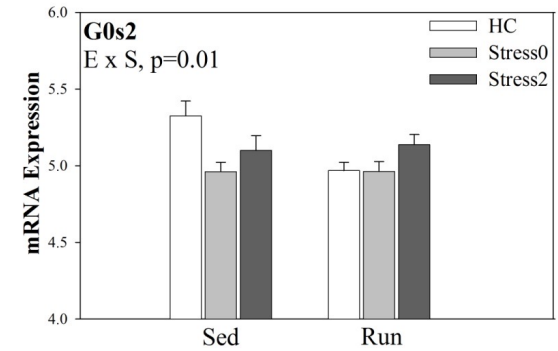
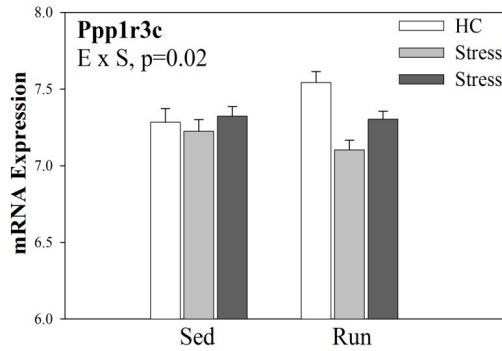
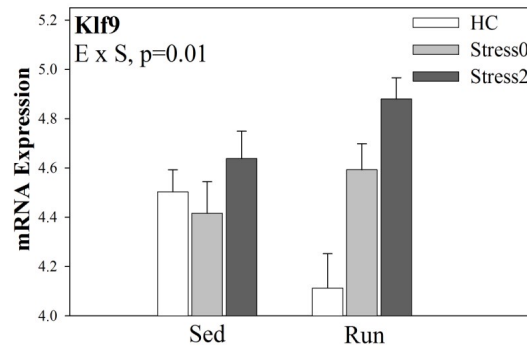
Stress changes the expression of more genes in physically active rats than sedentary rats



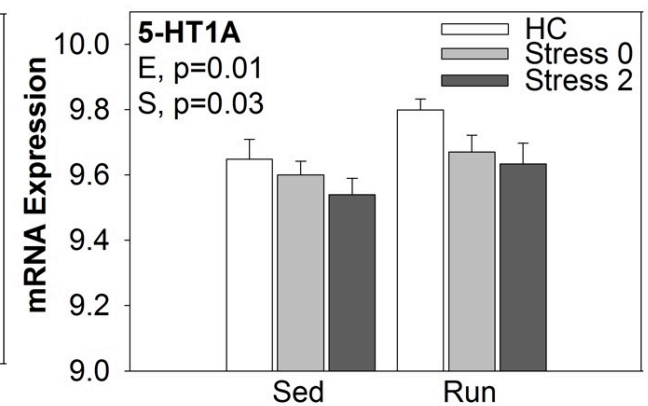
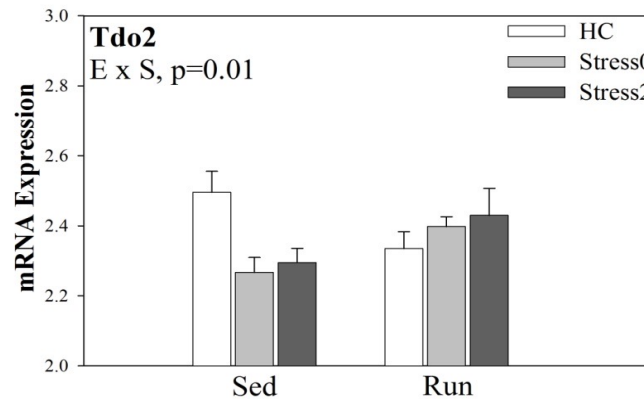
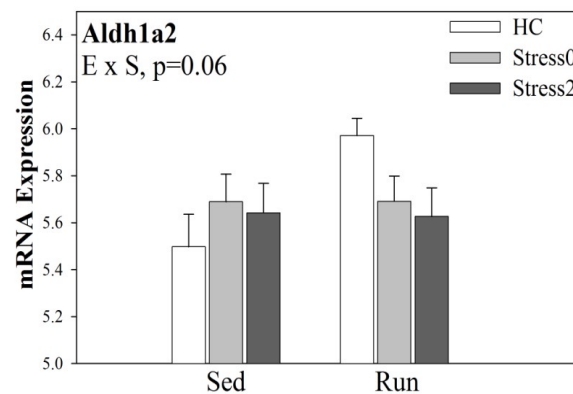
Log Fold Change (LFC) of $\geq \pm 1.1$ compared to home cage control



Diurnally Regulated Circadian Orthologs

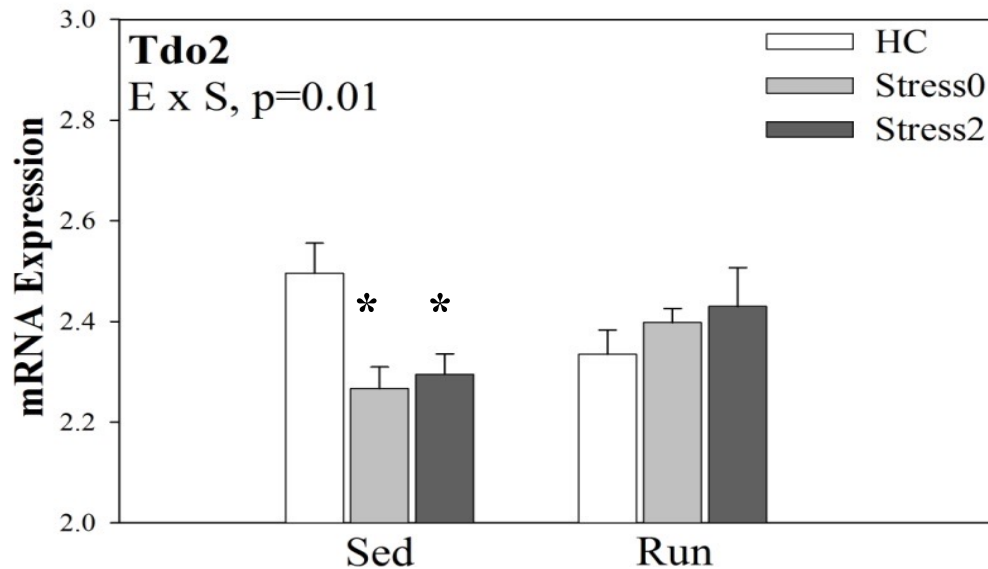


Tryptophan Metabolism & 5HT Transmission

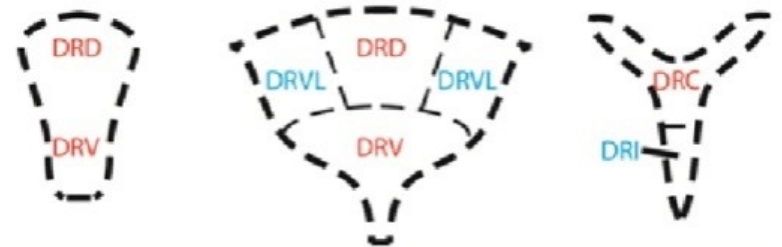


Novel Gene Targets: Tdo2

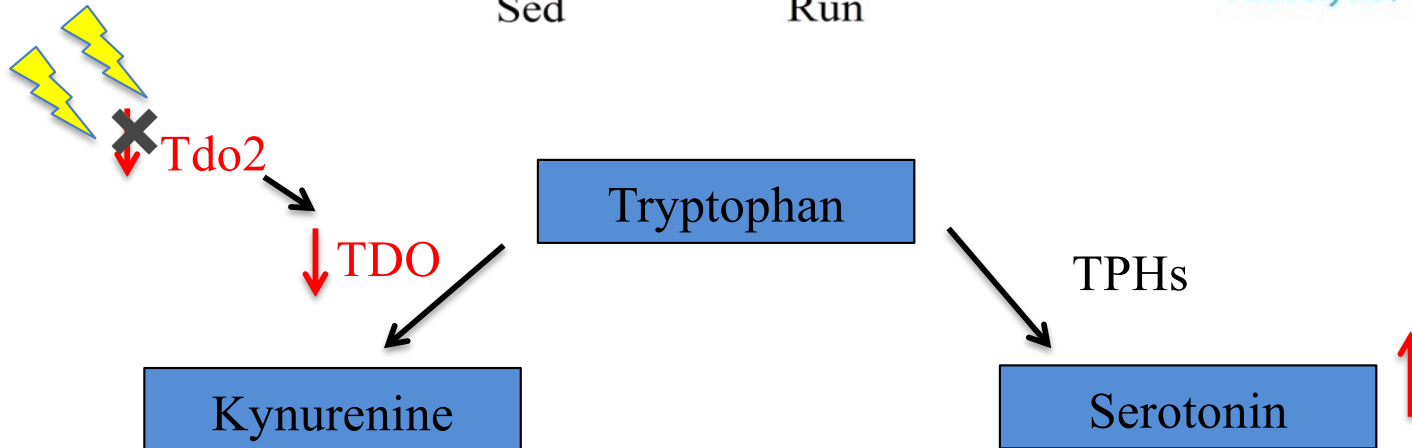
Tryptophan Metabolism & 5HT Transmission



*Exercise may increase 5HT in
anxiolytic DRN*



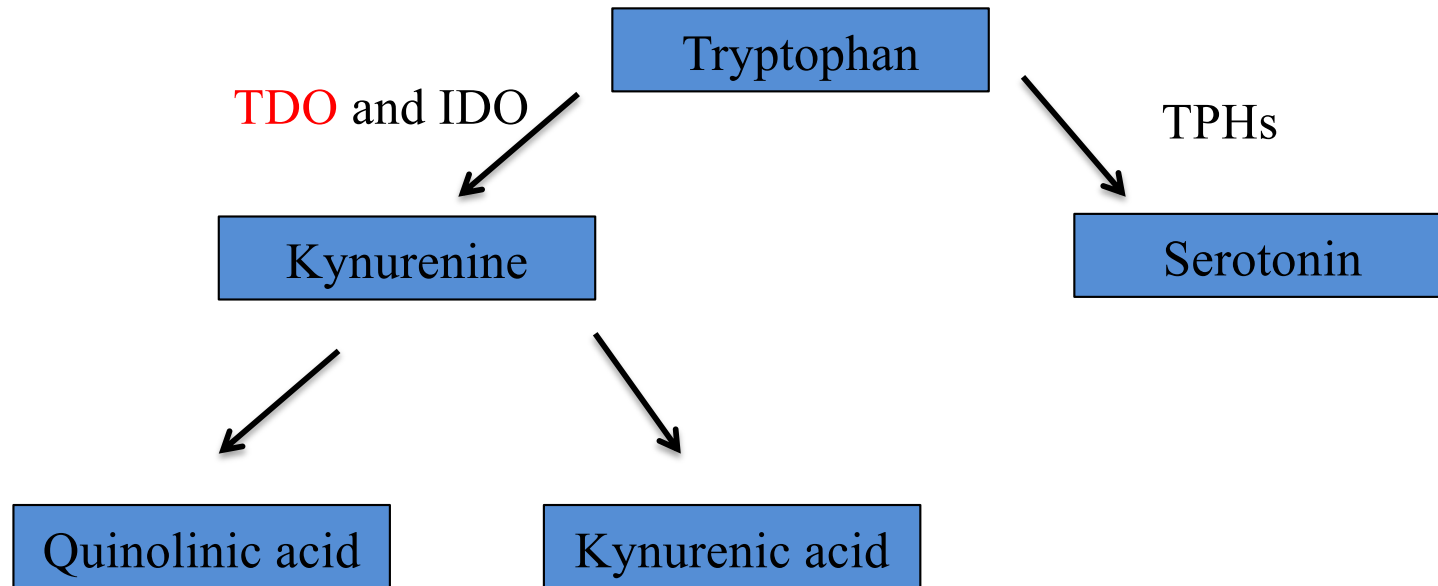
Anxiety/stress-promoting DRN (DRD, DRV, DRC)
Anxiolytic / stress resistant DRN (DRVL, DRI)



Novel Gene Target:Tdo2

Tryptophan Metabolism & 5HT Transmission

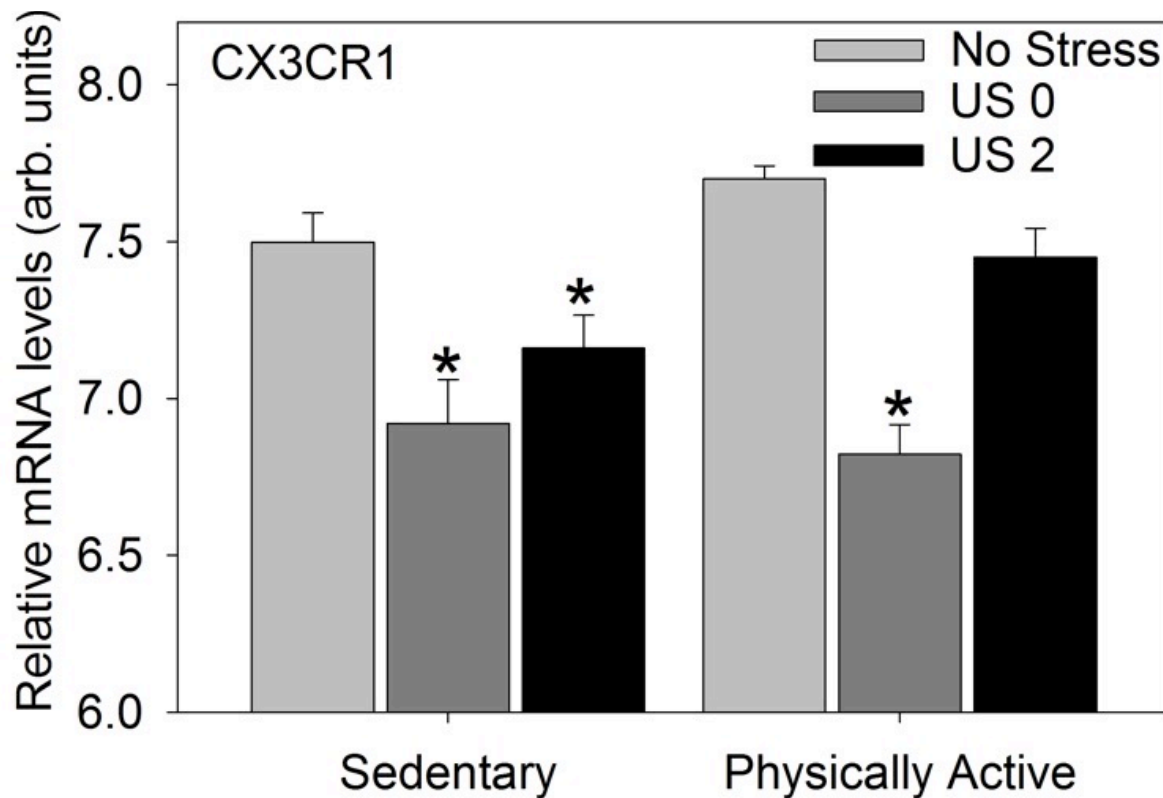
- Tryptophan is the precursor to 5-HT
- Tdo2 gene encodes for TDO, an enzyme involved in tryptophan metabolism



Novel Gene Targets: CX3CR1

Immune Related

- CX3CR gene encodes receptor for the CX3CL (Fraktalkine).
- CX3CR is expressed only on microglia in the brain and inhibits microglia inflammatory/destructive activation.



Exercise may constrain inflammation.

A molecular signature of stress resilience??



Fleshner Supporting Citations

Exercise, Stress & the Brain

Campeau S, Nyhuis TJ, Sasse SK, Kryskow EM, Herlihy L, Masini CV, Babb JA, Greenwood BN, Fleshner M, Day HE. Hypothalamic pituitary adrenal axis responses to low-intensity stressors are reduced after voluntary wheel running in rats. *J Neuroendocrinol.* 2010;22(8):872-88. Epub 20100416. doi: 10.1111/j.1365-2826.2010.02007.x. PubMed PMID: 20406350; PMCID: PMC4469265.

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Fleshner Supporting Citations

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Campisi J, Leem TH, Greenwood BN, Hansen MK, Moraska A, Higgins K, Smith TP, Fleshner M. Habitual physical activity facilitates stress-induced HSP72 induction in brain, peripheral, and immune tissues. *Am J Physiol Regul Integr Comp Physiol*. 2003;284(2):R520-30. Epub 20021024. doi: 10.1152/ajpregu.00513.2002. PubMed PMID: 12399251.

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Fleshner M. Exercise and neuroendocrine regulation of antibody production: protective effect of physical activity on stress-induced suppression of the specific antibody response. *Int J Sports Med.* 2000;21 Suppl 1:S14-9. doi: 10.1055/s-2000-1454. PubMed PMID: 10893019.

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Fleshner Supporting Citations

Mechanisms: Stress & KLH Antibody:

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