Sex Differences in Neurodegeneration: Discovery of Neuroprotective Treatments

Rhonda Voskuhl, M.D.

Jack H. Skirball Chair
Professor, UCLA Department of Neurology, David Geffen School of Medicine
Director, UCLA Multiple Sclerosis Program
Faculty Neurologist, UCLA Comprehensive Menopause Care Program

Disclosures

Dr. Voskuhl is an inventor on University of California, Los Angeles (UCLA) patents for estriol and ER beta ligand treatments for cognitive decline during menopause, multiple sclerosis, Alzheimer's Disease, and other neurodegenerative conditions.

She is a consultant in the company that **licensed UCLA patents (CleopatraRX**) and co-founder of a **nonprofit (The CleopatraRX Foundation**).

Lessons: For MS menopausal women
From otherwise healthy menopausal women

✔ **American Academy of Neurology Annual Meeting**

April 2024, Denver Convention Center

✔ **American Academy of Gynecology Annual Meeting**

May 2024, San Francisco Convention Center

✔ **North American Menopause Society**

September 2024, Chicago Convention Center

Leveraging Known Sex Differences in Diseases to Discover Novel Treatments:

1) Females more susceptible to MS and autoimmune diseases (autoimmunity)

2) Males worse disability progression (neurodegeneration)

Leveraging Sex Differences
Neuroimmunology & Neurodegeneration

1. Sex Chromosomes

Females: XX

Males: XY

2. Sex hormones

Females: Estrogen

Males: Testosterone

Sex Differences

1) Females more susceptible to MS and autoimmune diseases (autoimmunity)

2) Males worse disability progression (neurodegeneration)

Leveraging Sex Differences
Neuroimmunology & Neurodegeneration

1. Sex Chromosomes

Females: XX

Males: XY

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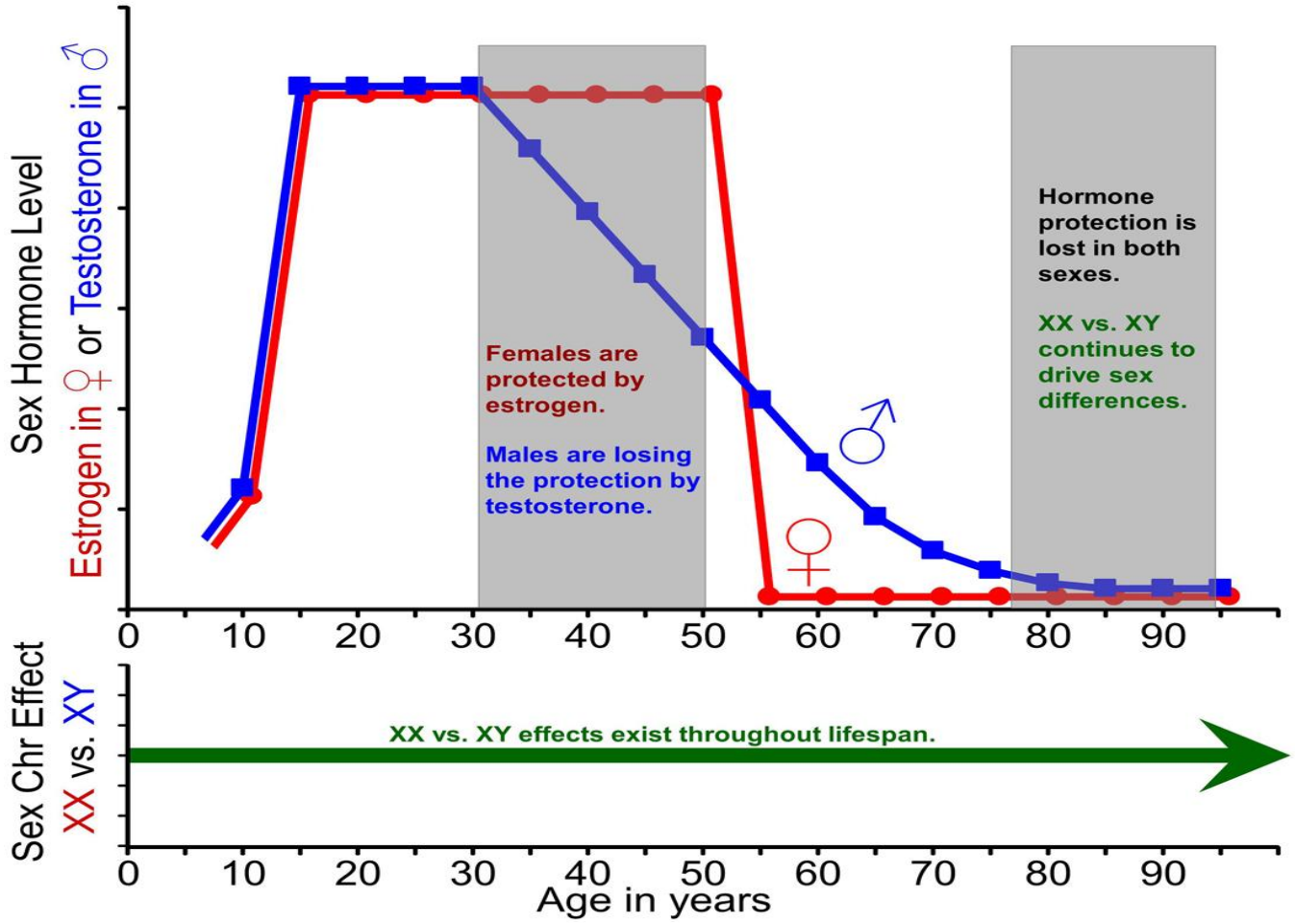
Males: Testosterone

Neurodegeneration with Aging
The Loss of Neuroprotective Sex Hormones



R. Voskuhl & Y. Itoh, *Journal of Experimental Medicine*, 2022

Effect of Aging and Sex: MS

Aging: Neurodegeneration
- Disability worsening & brain atrophy

Sex Differences in Neurodegeneration:
- Male sex is a risk for worse disability progression
- MS men have worse gray matter substructure atrophy
- Mean age in early 40s (18-65 range)

Weinshenker, 1994; Beatty 2002; Confavreux, 2003; Savettieri 2004;
Koch 2010; Schoonheim 2012; Ribbons 2015; MacKenzie-Graham 2019

UCLA & Charite Hospital (Berlin, Germany)
n=134: 89 MS and 45 age, sex-matched healthy controls

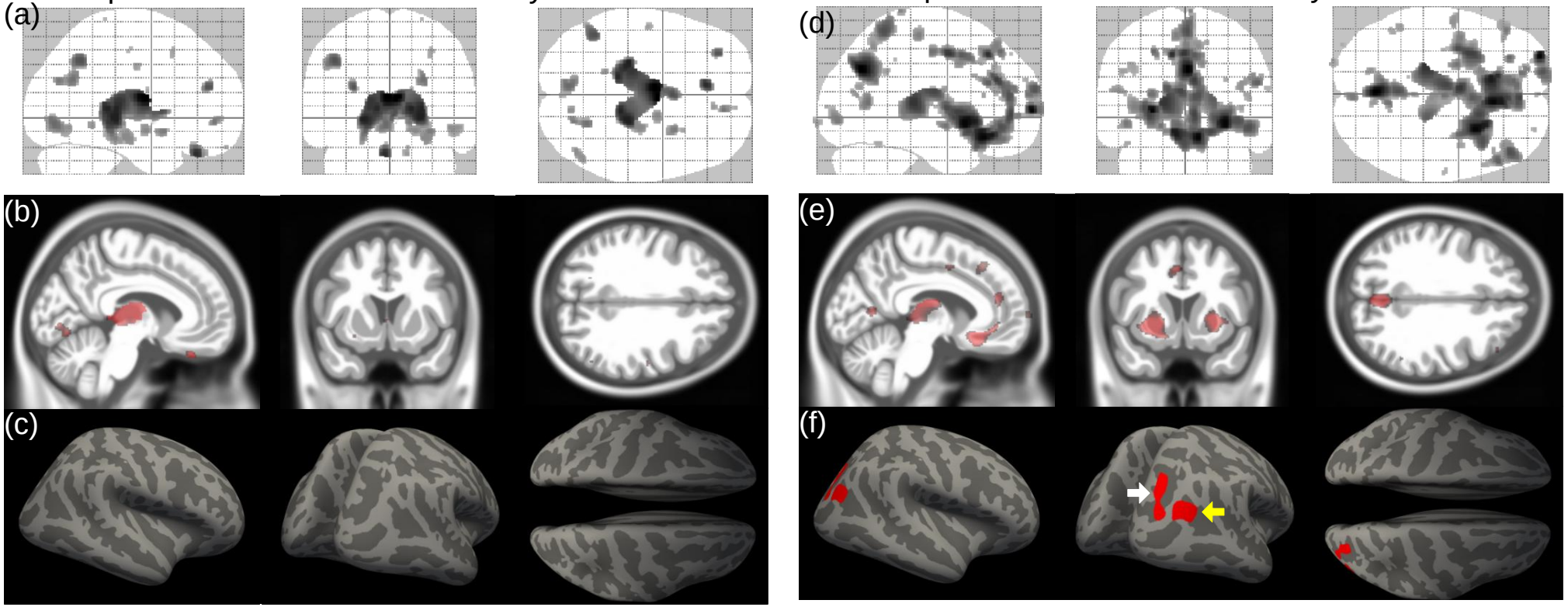
(mean & median ages: 40 & 42 years)

Women

Multiple Sclerosis Female vs. Healthy Control Female

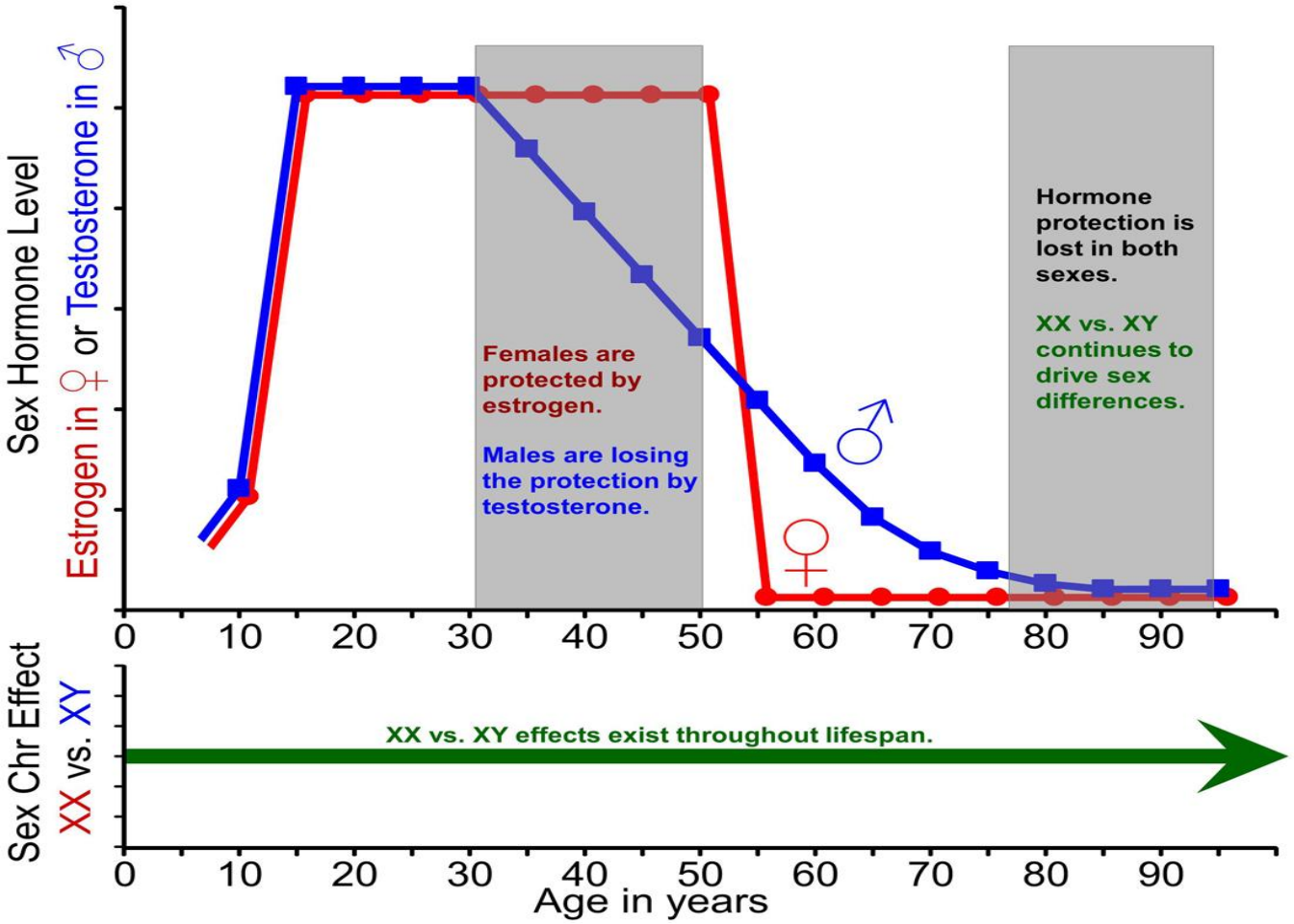
Men

Multiple Sclerosis Male vs. Healthy Control Male



A. MacKenzie-Graham, K. Patel, R. Voskuhl (UCLA) & S. Gold, F. Paul (Charite), Biology of Sex Differences 2020

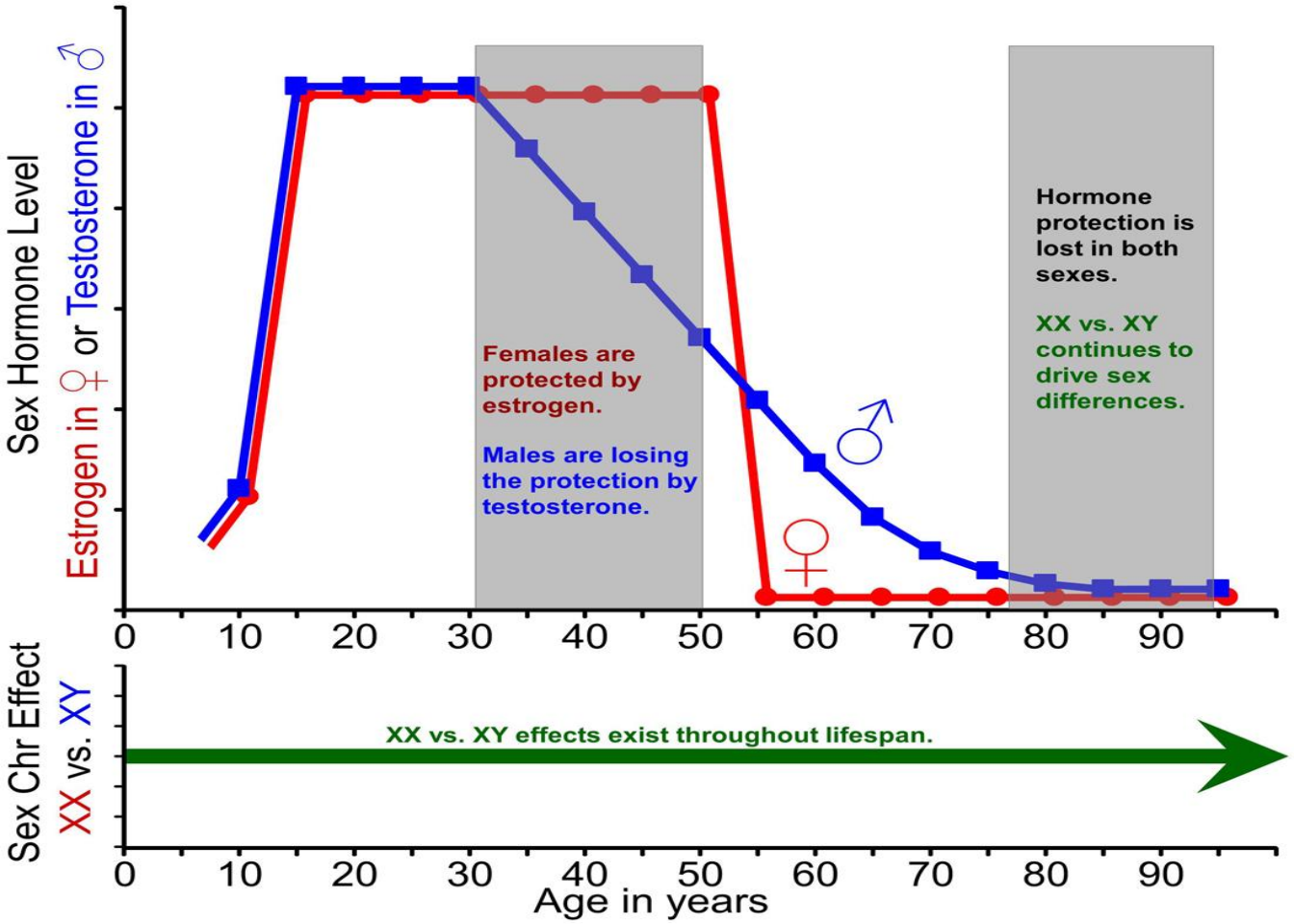
Sex Differences in Neurodegeneration
Timing of the Loss of Sex Hormones



Regional brain atrophy in MS men worse (early 40s).

R. Voskuhl & Y. Itoh, *Journal of Experimental Medicine*, 2022

Sex Differences in Neurodegeneration
Timing of the Loss of Sex Hormones



Regional brain atrophy in MS men worse (early 40s).

What about the abrupt drop in estrogen with menopause?

R. Voskuhl & Y. Itoh, *Journal of Experimental Medicine*, 2022

Menopause during MS

Subjective: Questionnaire, MS symptoms worse

Objective Exams: Longitudinal cohorts, disability worsening menopause.

MRI: Ovarian failure (lower anti-Mullerian hormone, age 42-45)
Lower AMH ∝ worse disability: Lower AMH ∝ cerebral cortex atrophy

Disability worsening & Cortical atrophy

Smith, 1992; Holmqvist, 2006; Bove, 2016; Ladeira, 2018; Baroncini, 2019; Graves, 2018

Sex Differences in MS

1) Females more susceptible to MS and autoimmune diseases (autoimmunity)

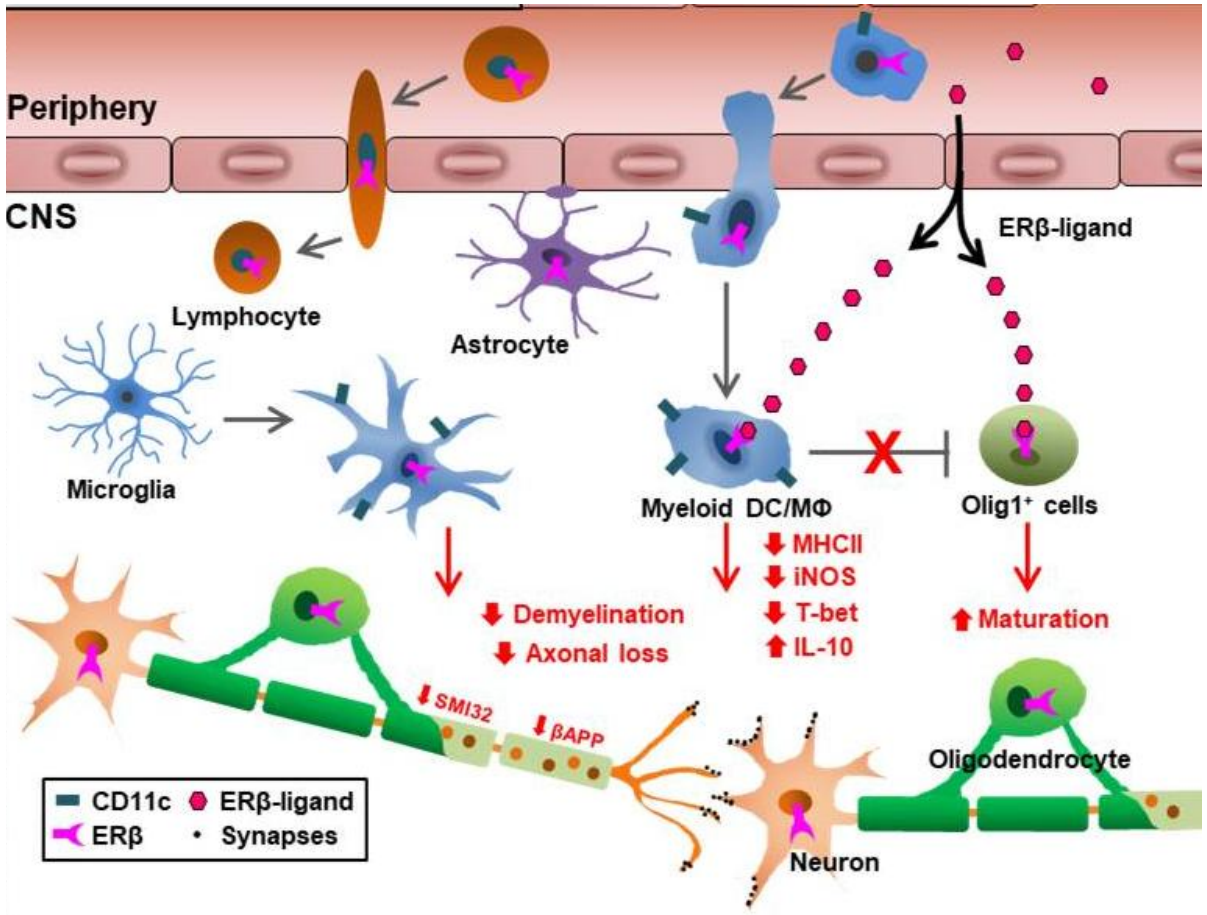
2) Males worse disability progression (neurodegeneration)

3) That is until …

   menopause, disabilities worsen (neurodegeneration): ↓ E

   conversely, late pregnancy is protective (neuroprotection) ↑ E

ERβ Ligand & Estriol MS models (EAE & Cuprizone)



Tx: ERβ / Estriol in Oligodendrocytes & Microglia

Spinal cord
Corpus callosum
Remyelination & Axonal sparing

Cerebral cortex
Hippocampus
↓ Synaptic loss ↓ Atrophy

Kim, *Brain*, 2018, Ziehn, *Lab. Invest.*, 2012; Ziehn, J. *Neurosci.*, 2012; Voskuhl, *PNAS*, 2019; Meyer, *Lab. Invest.*., 2023.

Estriol (ERβ) 8mg vs placebo trial in MS women
12 month treatment duration

- Improvement in cognitive processing speed in Estriol (vs placebo)

- Improvement in cognitive processing speed ∝ Higher estriol blood levels

- Reduced cerebral cortex atrophy in Estriol (vs placebo)

- Reduced serum neurofilament light chain (sNfL) in Estriol (vs placebo)

R. Voskuhl, *Lancet Neurol*. 2016, A. Mackenzie-Graham, *Brain & Behavior* 2018;
J. Kuhle (Basel) & R. Voskuhl (UCLA), *Annals of Clinical & Translational Neurology,* 2022

Menopause in Healthy Women

Subjective clinical: Cognitive difficulties with menopause “Brain Fog”.

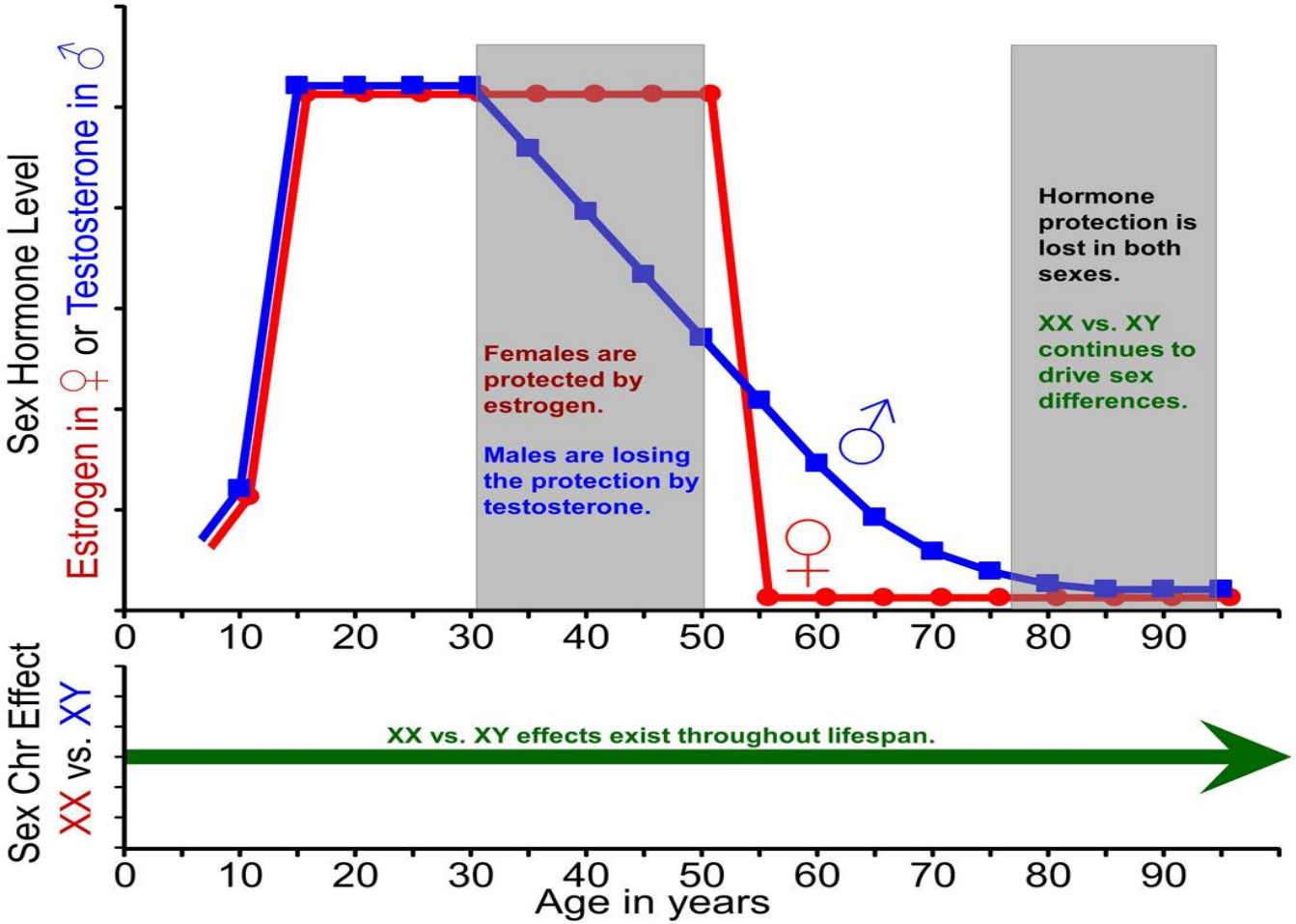
Objective clinical: Quantified using objective, cognitive domain-specific tests.
Verbal memory & processing speed
(not global cognition).

MRI:
Surgical menopause (<age 50) … 15 years later: hippocampal-cortex atrophy.
Natural menopause (age 50-55) … 3 years later: prefrontal cortex atrophy
Natural menopause (age 50-55)… hippocampal - prefrontal connectivity
(Not global brain atrophy)

Cognitive domain-specific & Region-specific

North American Menopause Society 2021, Kantarci, K. 2018, Bookheimer, 2008, 2010, 2011, 2016

Sex Differences in Neurodegeneration
Timing of the Loss of Sex Hormones



Brain Aging: Focus on what is preventable.

How to treat the abrupt drop in estrogen with menopause.

R. Voskuhl & Y. Itoh, *Journal of Experimental Medicine*, 2022

HRT: The Past Approach

Hormone Replacement Trials (HRT) in Menopause: premarin, estradiol

Designed for: Effect on hot flashes, osteoporosis, cardiovascular

Not designed for: Effect on cognition.

Used exploratory outcomes:

- Global cognition (presence or absence of “dementia”, type unclear)
- Global brain atrophy

Primary Outcomes needed:

- Cognition domain-specific (verbal & working memory, processing speed)
- Brain region-specific atrophy (hippocampus and frontal cortex)

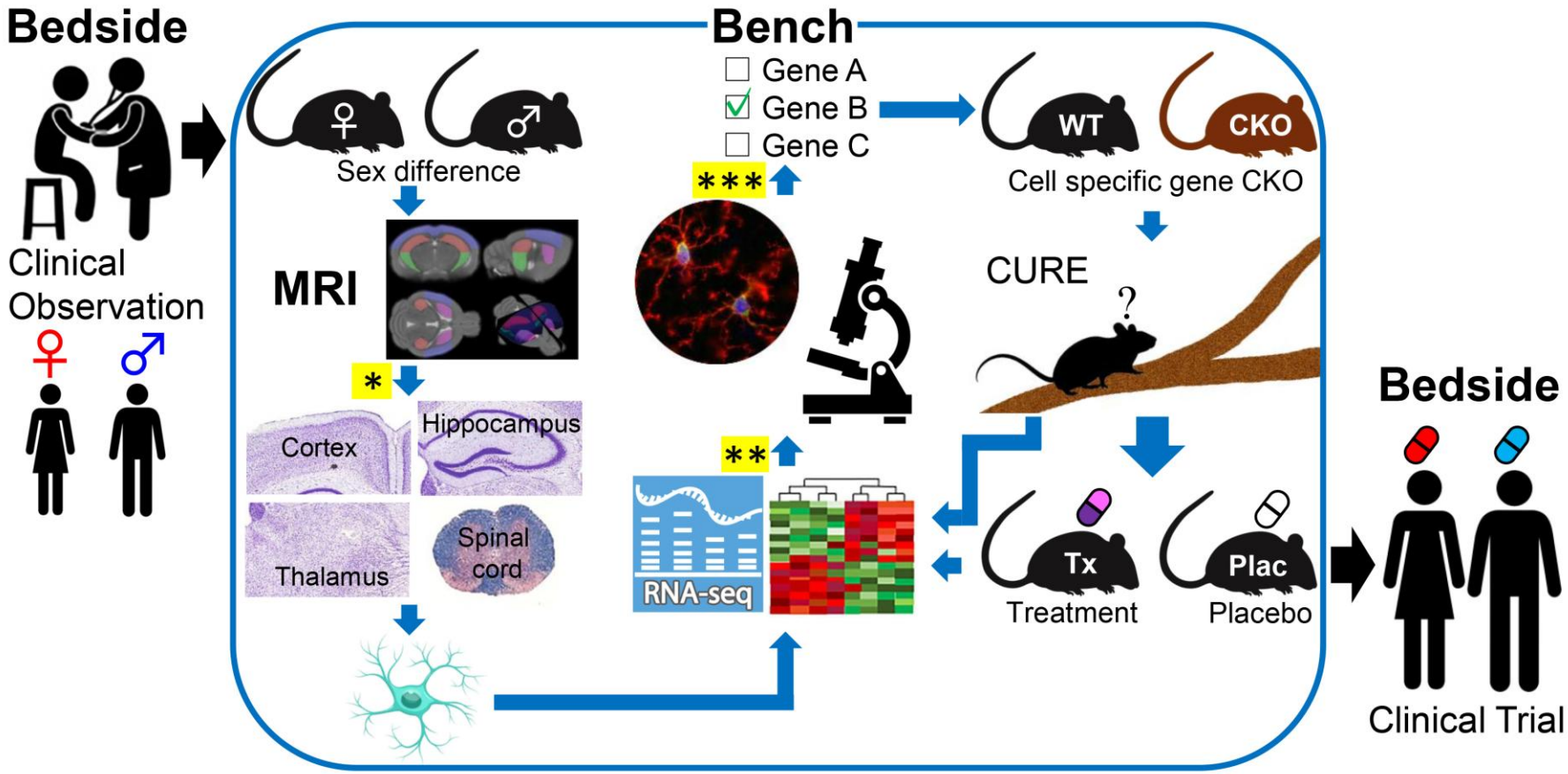
HRT: Estrogens Are Not All Alike

Estrogen Type:
- Premarin: Low dose, mix of various estrogens
- Estradiol: Binds ERα strongly, also ERβ
- Estriol: Binds mainly ERβ (weak for ERα)

Estrogen Efficacy for the Brain:
No evidence that Premarin is neuroprotective
Yes evidence for Estradiol (ERα) and Estriol (ERβ) is neuroprotective

Estrogen Blood Level:
Higher blood level more neuroprotection (dose & compliance)
- Estradiol treatment is limited by strong binding to ERα (breast)
- Estriol ERβ (brain)

Bedside to Bench to Bedside



Cell-specific, Tissue-specific Approach (Female vs Male)

Voskuhl Profile, *Lancet Neurology*, February 2024

R. Voskuhl & Y. Itoh, *Journal of Experimental Medicine*, 2022

nature communications

Article

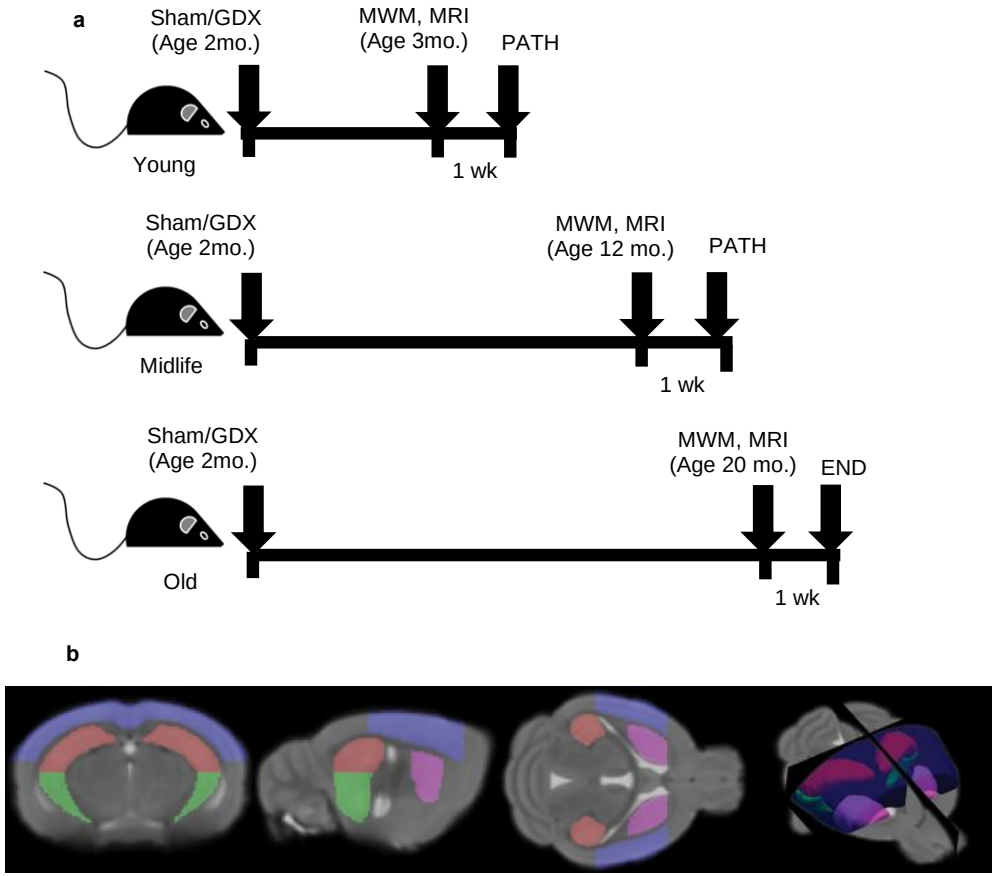
https://doi.org/10.1038/s41467-023-41723-7

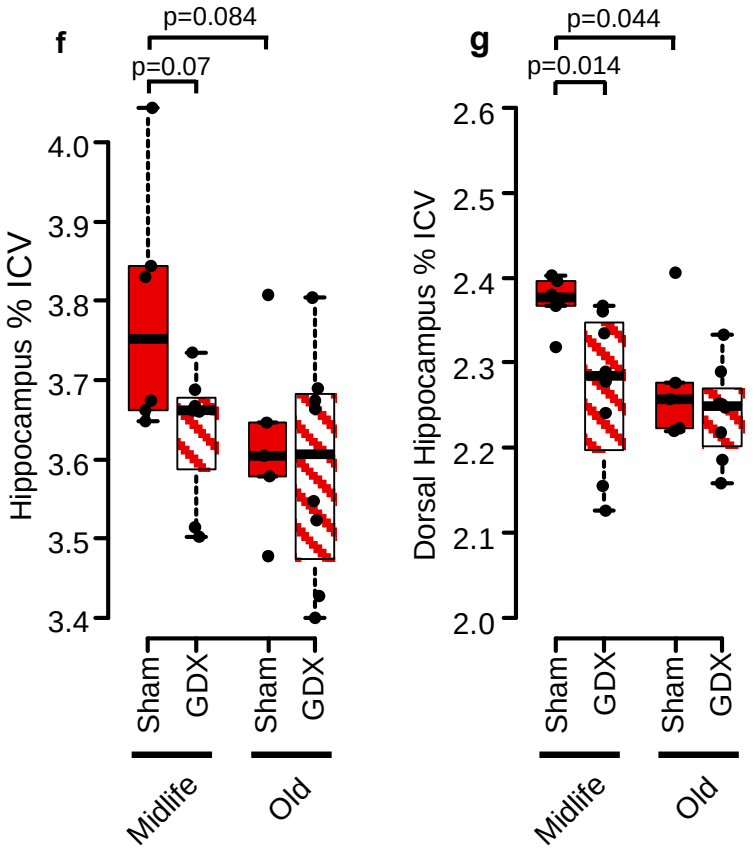
Estrogen receptor beta in astrocytes modulates cognitive function in mid-age female mice

Noriko Itoh[1], Yuichiro Itoh[1], Cassandra E. Meyer[2], Timothy Takazo Suen[1], Diego Cortez-Delgado[1], Michelle Rivera Lomeli[1], Sophia Wendin[1], Sri Sanjana Somepalli[1], Lisa C. Golden[1], Allan MacKenzie-Graham[1,2] & Rhonda R. Voskuhl[1]

N. Itoh, et al. *Nature Communications*, 2023

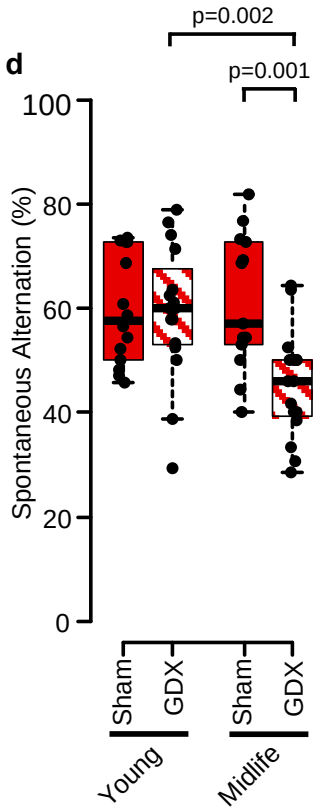
Dorsal Hippocampal Atrophy by MRI

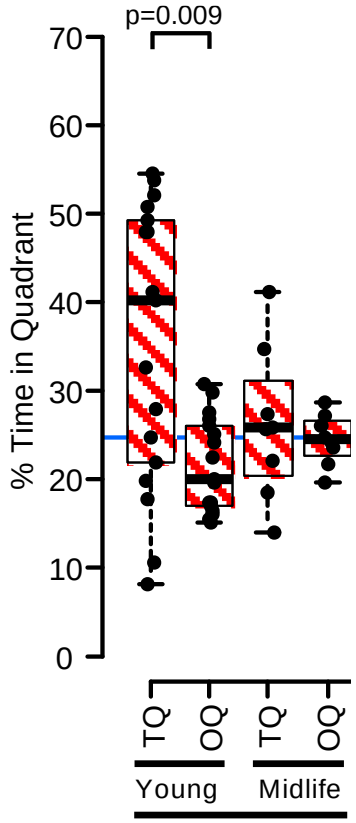


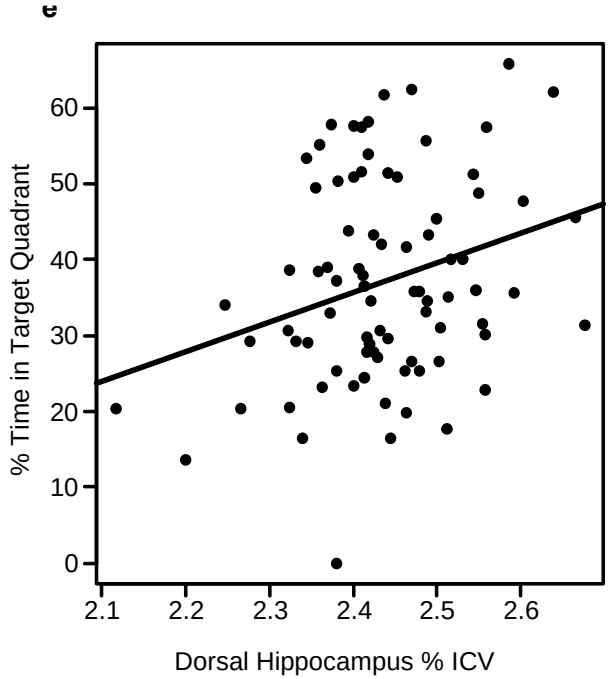


N. Itoh, et al. *Nature Communications*, 2023

Cognitive Deficits
Ovariectomized Females at Midlife



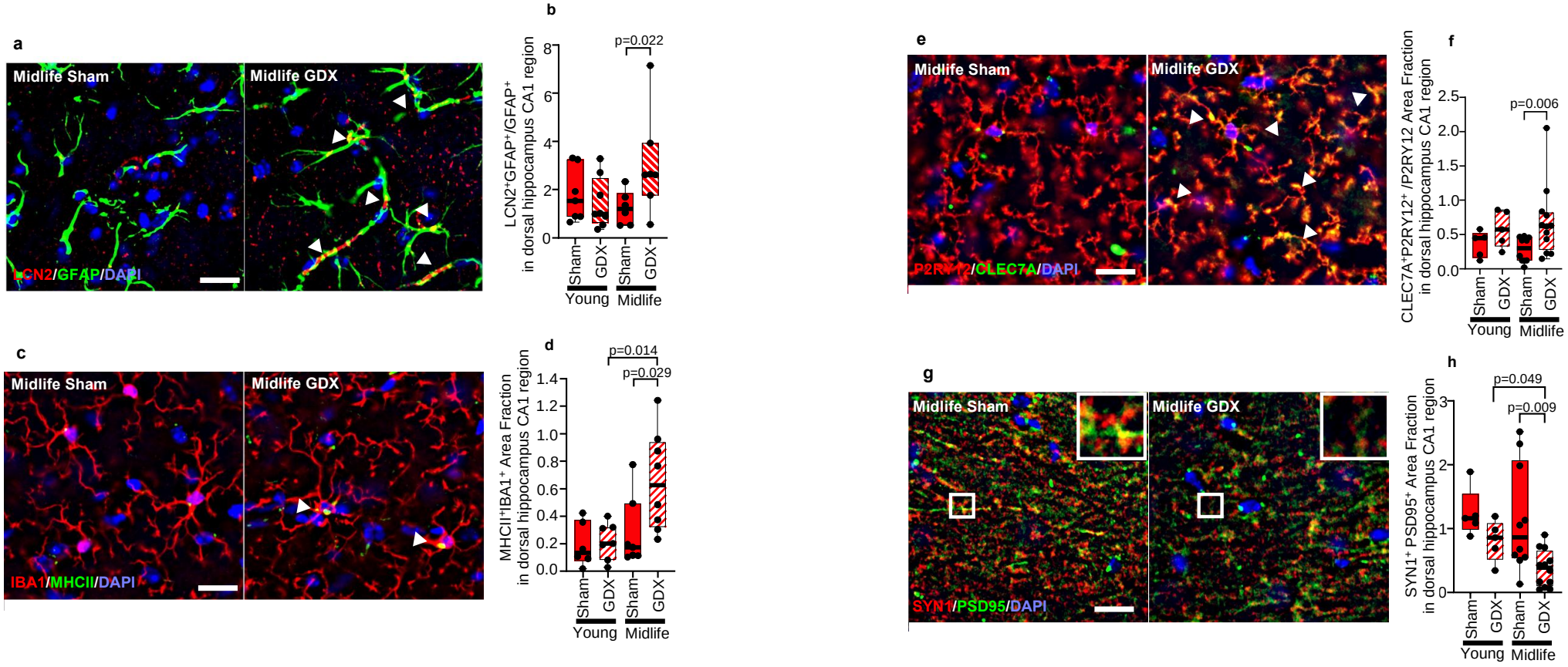




Sex Hormone x Age Interaction

N. Itoh, et al. *Nature Communications*, 2023

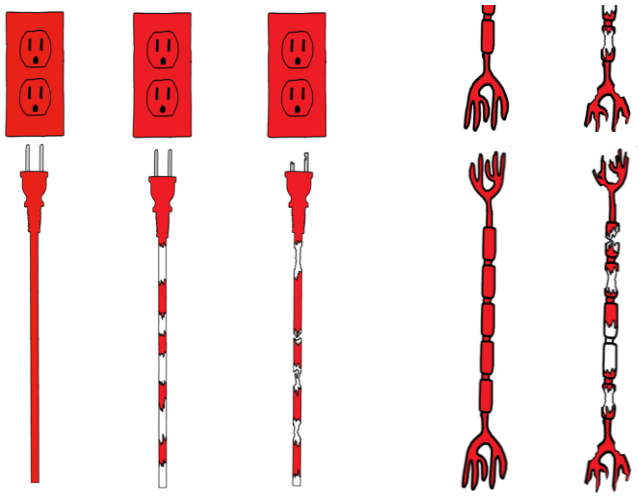
Glial Activation and Synaptic Loss Ovariectomized Females at Midlife



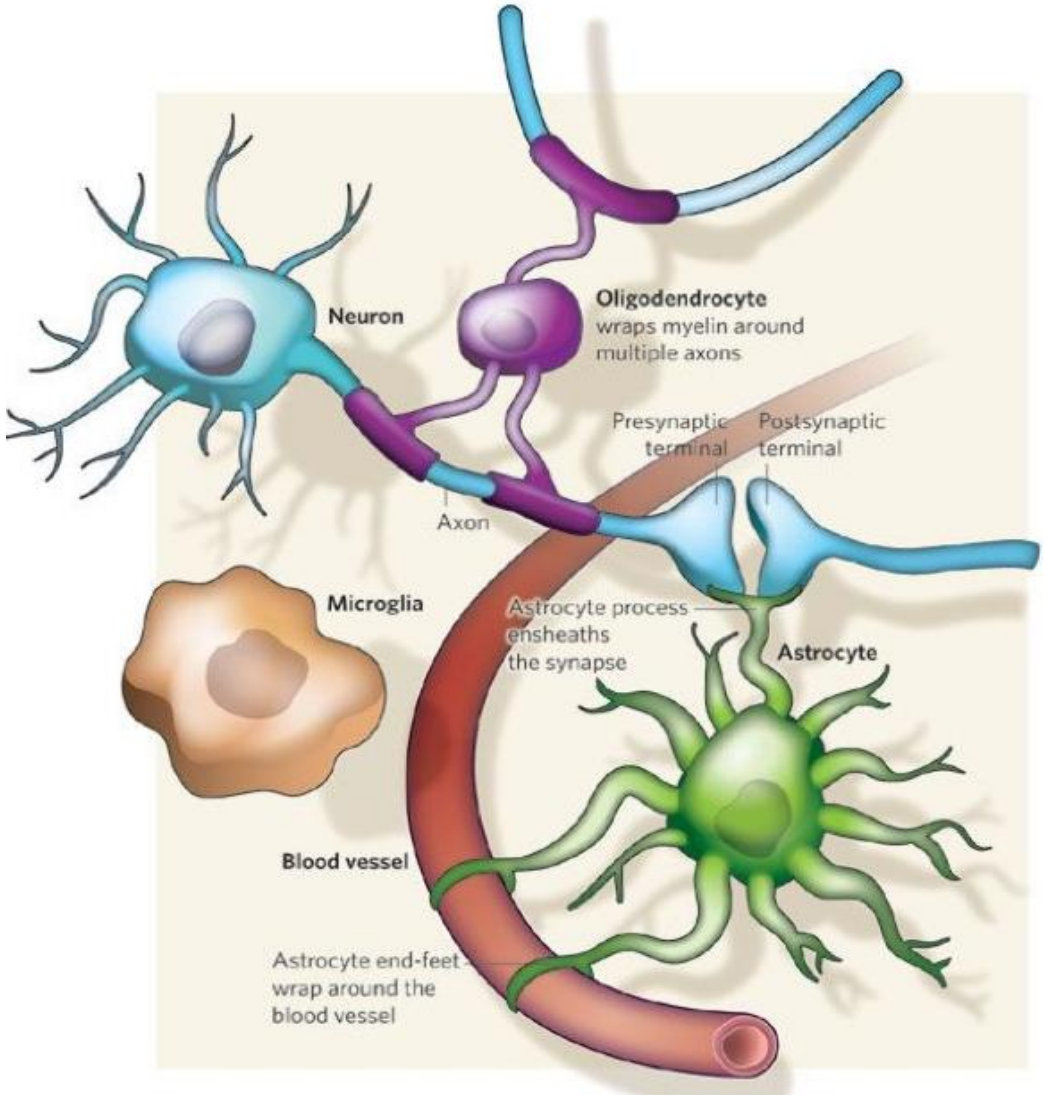
Sex Hormone x Age Interaction

N. Itoh, et al. *Nature Communications*, 2023

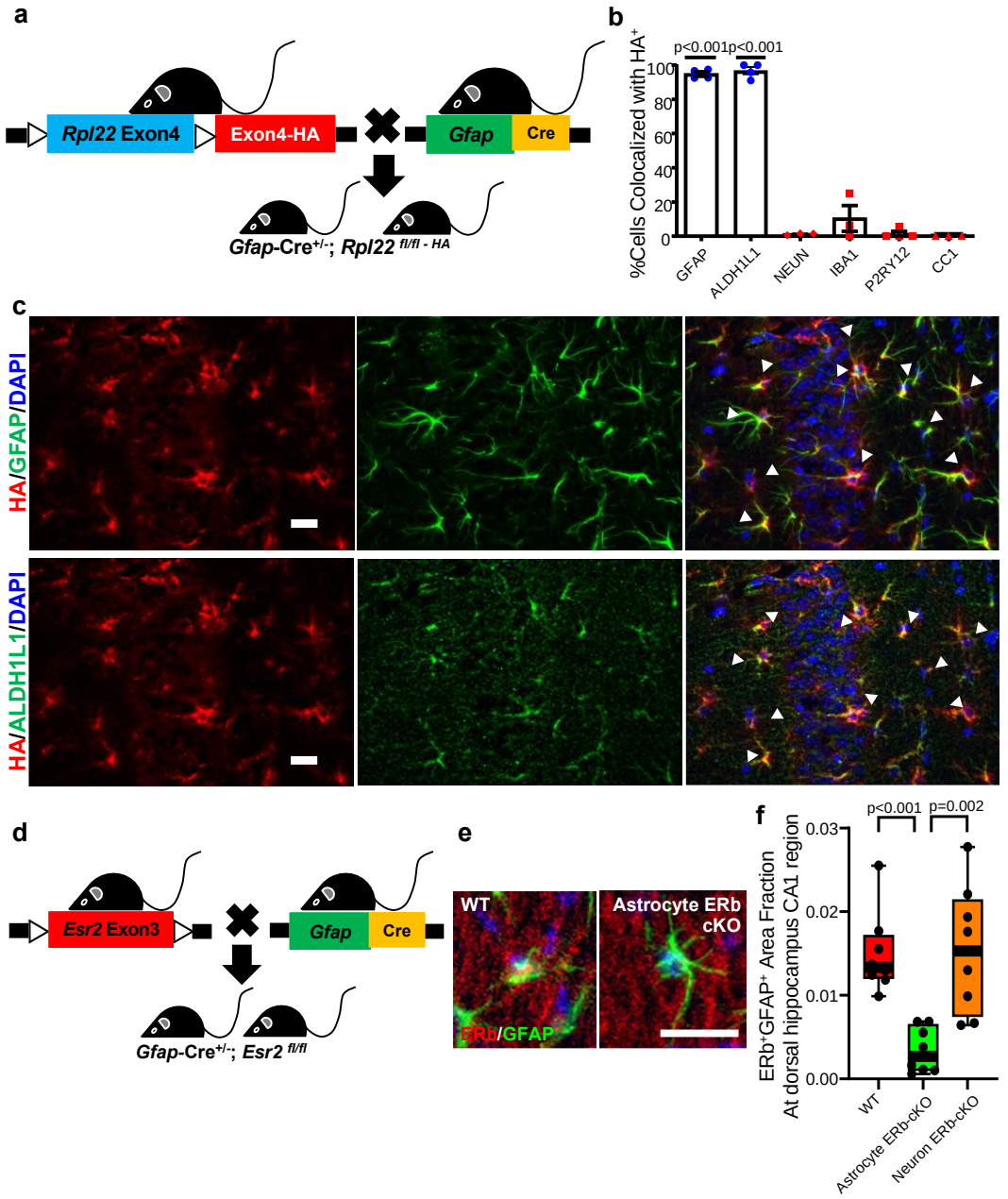
Neuroprotective Treatments:



Myelin, Axons,
Neurons, Synapses
= Functional Conduction

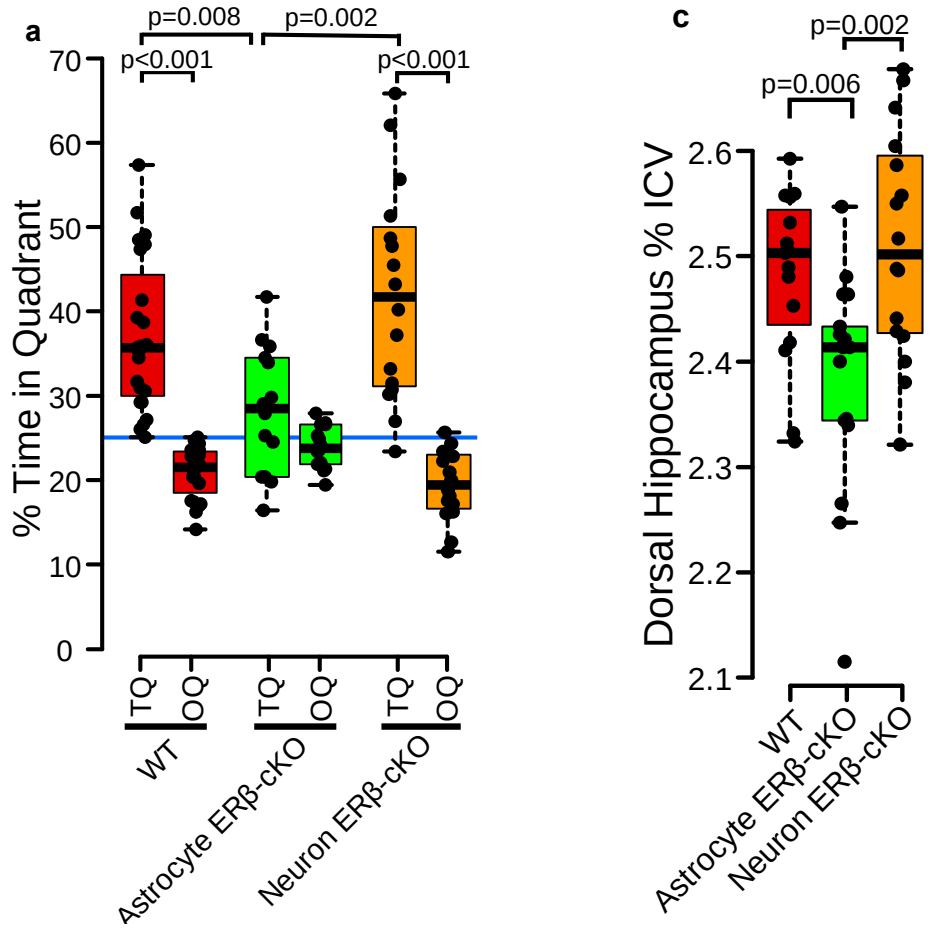


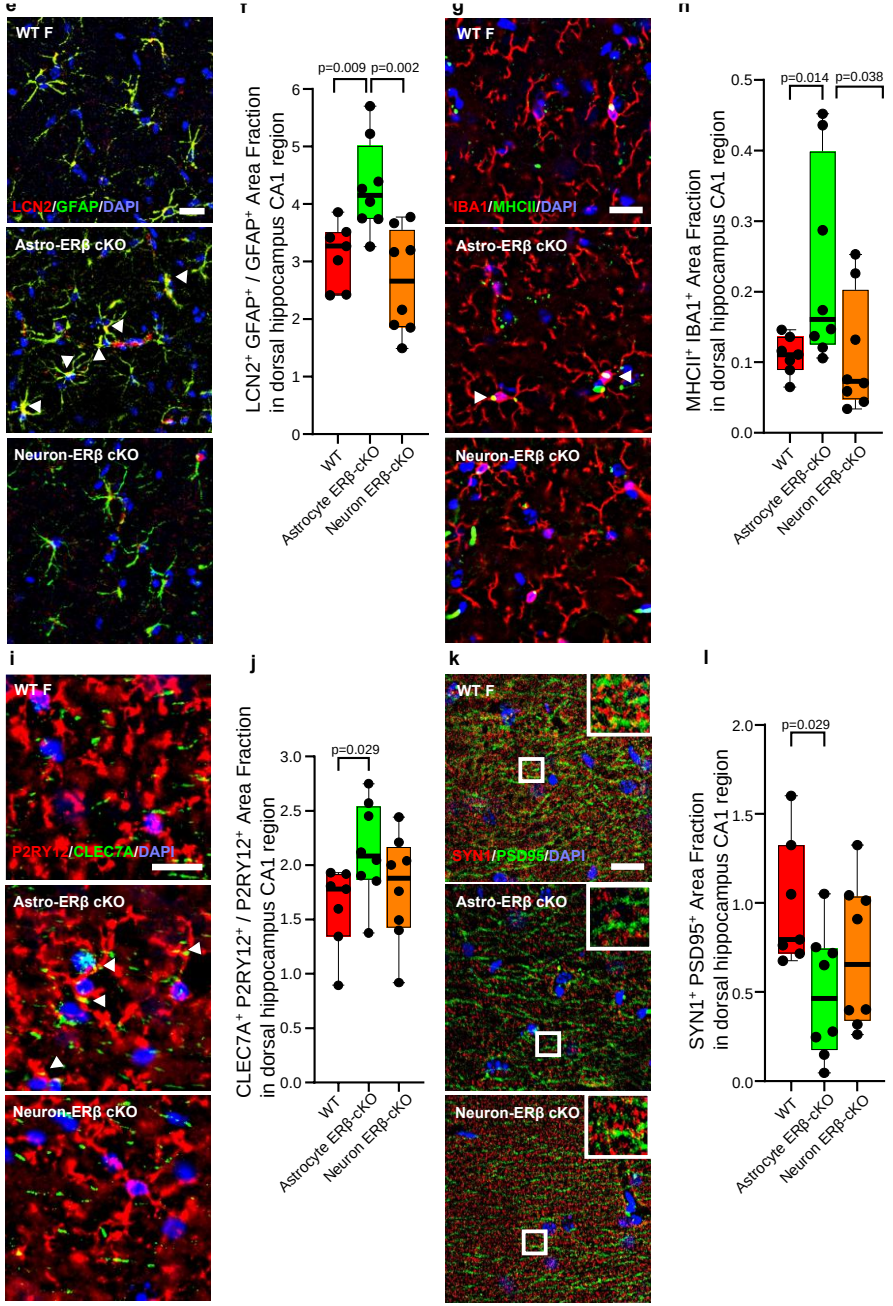
ERbeta (ERβ) CKO Astrocytes or Neurons Midlife Females



N. Itoh, et al. *Nature Communications*, 2023

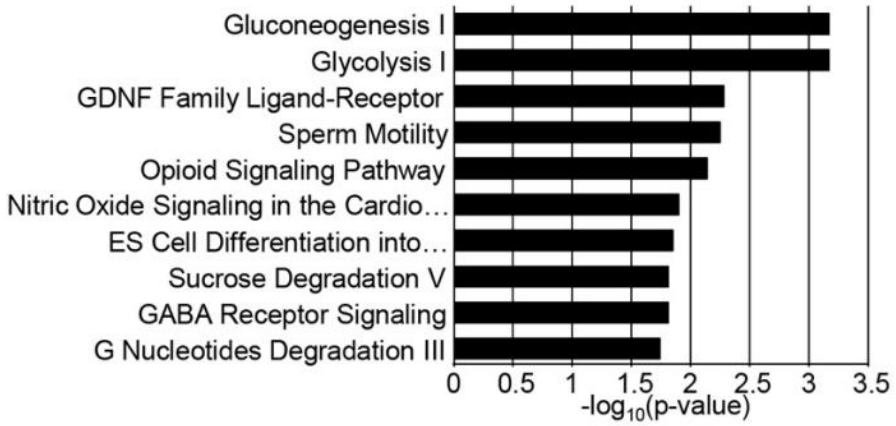
Astrocyte ERβ CKO

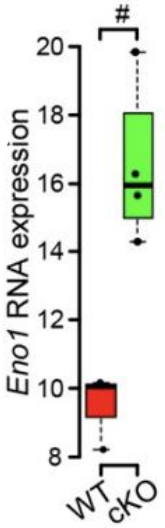


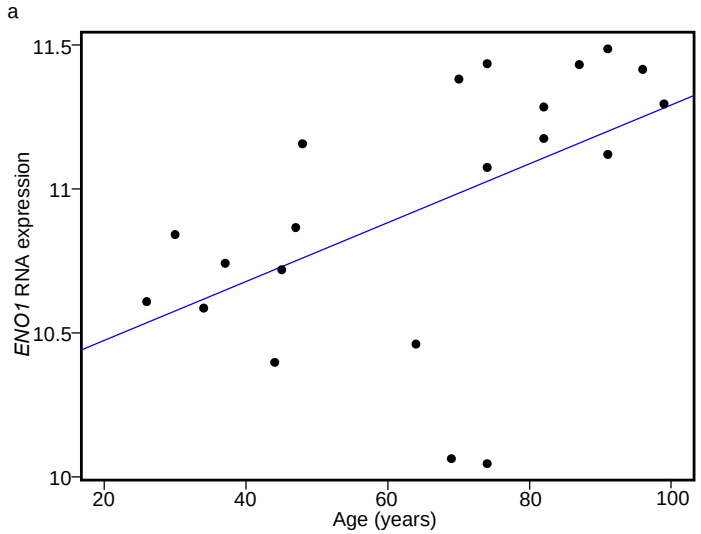


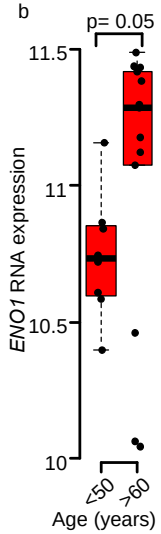
N. Itoh, et al. *Nature Communications*, 2023

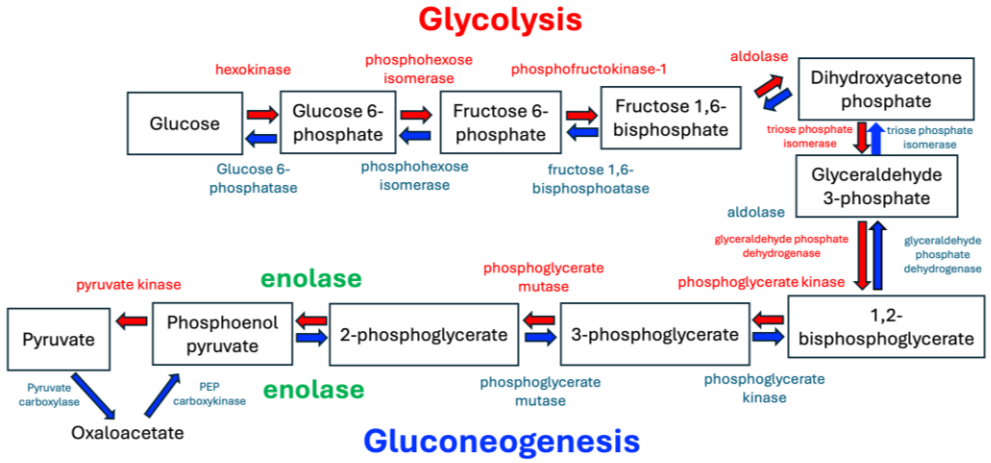
Glucose Metabolism in Astrocytes: Estrogen Deficient





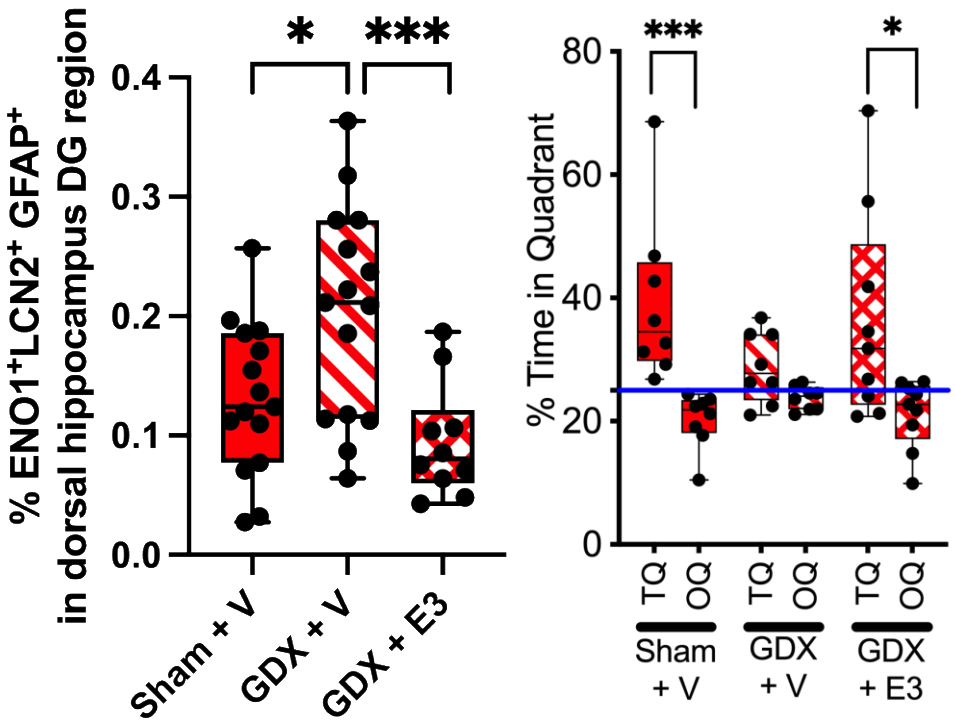




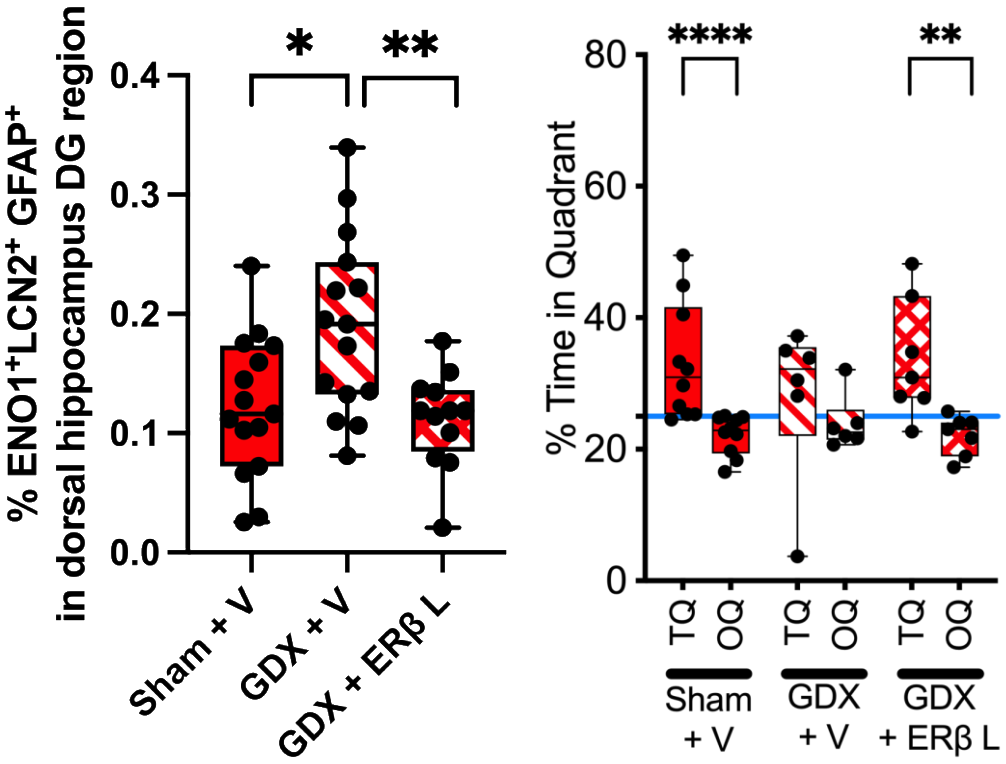


Nature Communications, 2023

Estriol Treatment at Midlife



ERβ Ligand Treatment at Midlife



Novel Estrogen Treatment Designed for the Brain during Menopause

Sex hormone x Age interaction: Estrogen Loss x Midlife Aging

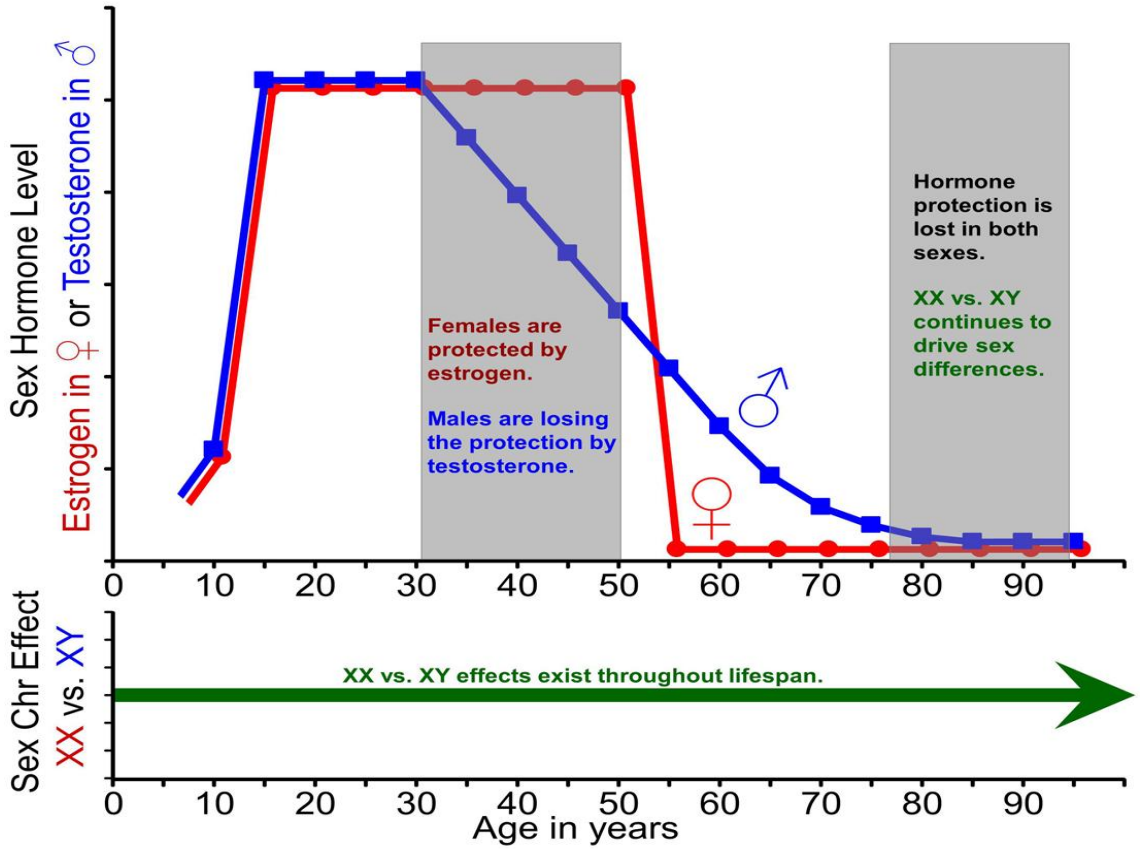
Cognitive deficits, Hippocampal Atrophy, Glial activation, Synaptic Loss

Mediated by ERβ in Astrocytes (altered glucose metabolism in brain)

Prevented by ERβ Ligand and Estriol Treatment

N. Itoh, et al. *Nature Communications*, 2023; American Menopause Society Sept 2024

HRT Designed for Cognition in Menopausal Women
Estriol binds ERβ for Neuroprotection
Weak binding of ERα in breast



Estriol Target:
ERβ in
Astrocytes

Hippocampus
↓ Synaptic loss
↓ Atrophy (MRI)
Improve Cognition

Translation to Clinic
Estriol treatment in clinical practice.

Estriol targets ERβ (brain), weak binding to ERα (breast)
Over four decades of safety data in Europe and Asia
Menopausal ages, no HRT contraindications
HRT safety (annual mammograms, gynecology visits)
No standardization – Not informative
Various U.S. compounding pharmacies
Various doses of estriol
Various progesterone and timing
Not following effect on cognition
Not gaining insights to advance women's cognitive health

Translation to Clinic: Initiatives

UCLA Comprehensive Menopause Care Program
Gynecology Dept. + Experts in bone, heart, brain (etc)

CleopatraRX licensed UCLA patents for optimal estriol & progesterone
Blister pack (PearlPAK) of capsules for convenience & compliance
National pharmacy ships PearlPAK to patient's house
Follows patient's cognition (month 0,12, 24, etc.)

The Cleopatra Foundation nonprofit for those who cannot afford.
Outreach to underserved: Seminars, Website: Effect of menopause on brain

Future Ramifications for All

Alzheimer's Disease (AD):

Aging is a risk factor

Two thirds of AD patients are women

AD begins in same brain regions as those affected in women during menopause

No neuroprotective treatment for Alzheimer's Disease

Mild Cognitive Impairment (MCI) precedes Alzheimer's Disease (AD)

Brain aging precedes Mild Cognitive Impairment (MCI)

Brain aging → MCI → AD

Brain Aging: Some things not reversible, but loss of neuroprotective estrogen is reversible

UCLA Team

Laboratory

Lisa Golden, Ph.D.
Roy Kim, Ph.D.
Cassandra Meyer, Ph.D.
Marina Ziehn, Ph.D.
Rory Spence, Ph.D.
Alessia Tassoni, Ph.D.
Vista Farkhondeh, B.S.
Timothy Suen, B.S.
Jade Vieira, B.S.
Riddhi Duggal, B.S.
Diego Cortez Delgado, B.S.
Michelle Rivera
Sofia Ban
Sophia Wendin
Daron Assatoury
Sanjana Somepalli
Sankino li
Mike Montag, B.S., M.S.

Faculty

Yuichiro Itoh – Neurogenetics (X chromosome, RNA-Seq)
Noriko Itoh – Estrogen Receptor Beta - Menopause
Allan MacKenzie-Graham – Neuroimaging (EAE & MS)
Michael Sofroniew – Astrocyte biology
Arthur Arnold – Sex chromosome biology
Prabha Siddarth – Statistical analyses
Kevin Patel - patient care, trials, & neuroimaging
Callie Momtazee - patient care & trials
Eric Williamson - patient care

DAVID GEFFEN SCHOOL OF MEDICINE
UCLA

Thank you!

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NIH NINDS R35 Research Program Award NS132150

Translation to Clinic (MS): Multicenter, Phase 2, Double-blind, Comparator-Controlled Trial

Estriol (ERβ) treatment (with tailored progesterone)
Menopausal women with MS (ages 45-65)

Primary: MRI (cerebral cortex atrophy, hippocampus)

Secondary: Cognitive (domain-specific) testing; sNfL

Exploratory: Other MRI (thalamus); Other MS disabilities

ECTRIMS/ACTRIMS Hot Debate Stage (2023)
MSJ (2024)

The Underserved: Ethnic Minorities

African American Menopausal women may be more likely to get dementia
African American Menopausal women may be more likely to get breast cancer
Differential response to standard hormone treatment for non-cognitive issues

Impact on Society:
Mothers and grandmothers need cognition preserved
Critical fabric of the family