
# Women and Alzheimer's Disease Risk Begins in Midlife During the Menopausal Transition: Implications for Prevention and Treatment

**60th Advisory Committee on Research on Women's Health NIH**

**Roberta Diaz Brinton, Ph.D.**
**Center for Innovation in Brain Science**
**Health Sciences**
**College of Medicine**
**University of Arizona**
**Tucson, AZ**

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# Disclosures

## Sponsors

National Institute on Aging

Alzheimer's Drug Discovery Foundation

Alzheimer's Association

Women's Alzheimer's Movement

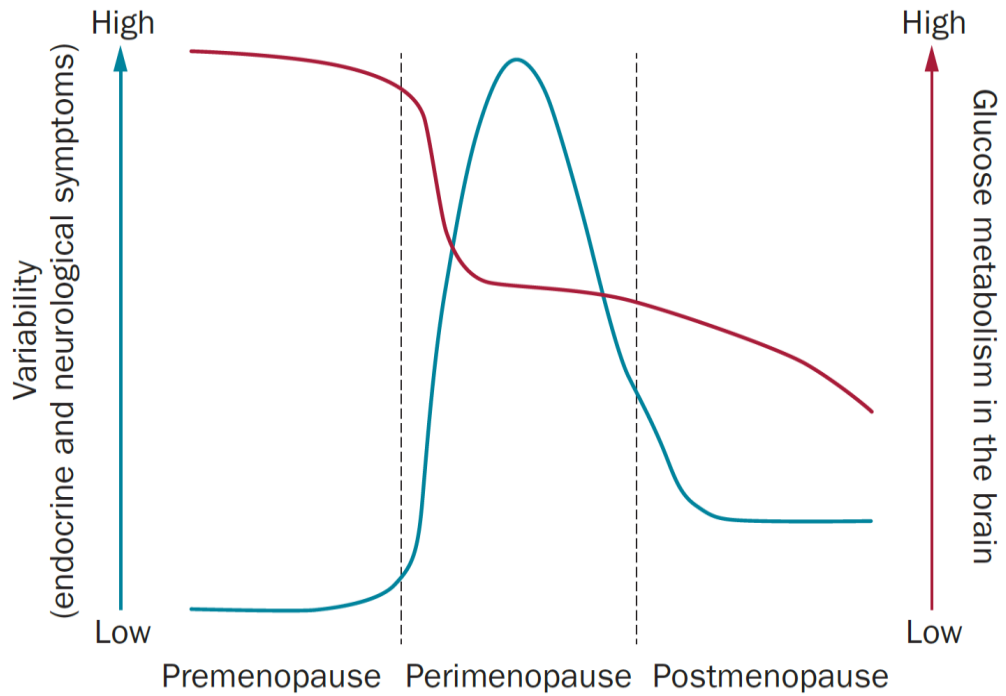
## Patents

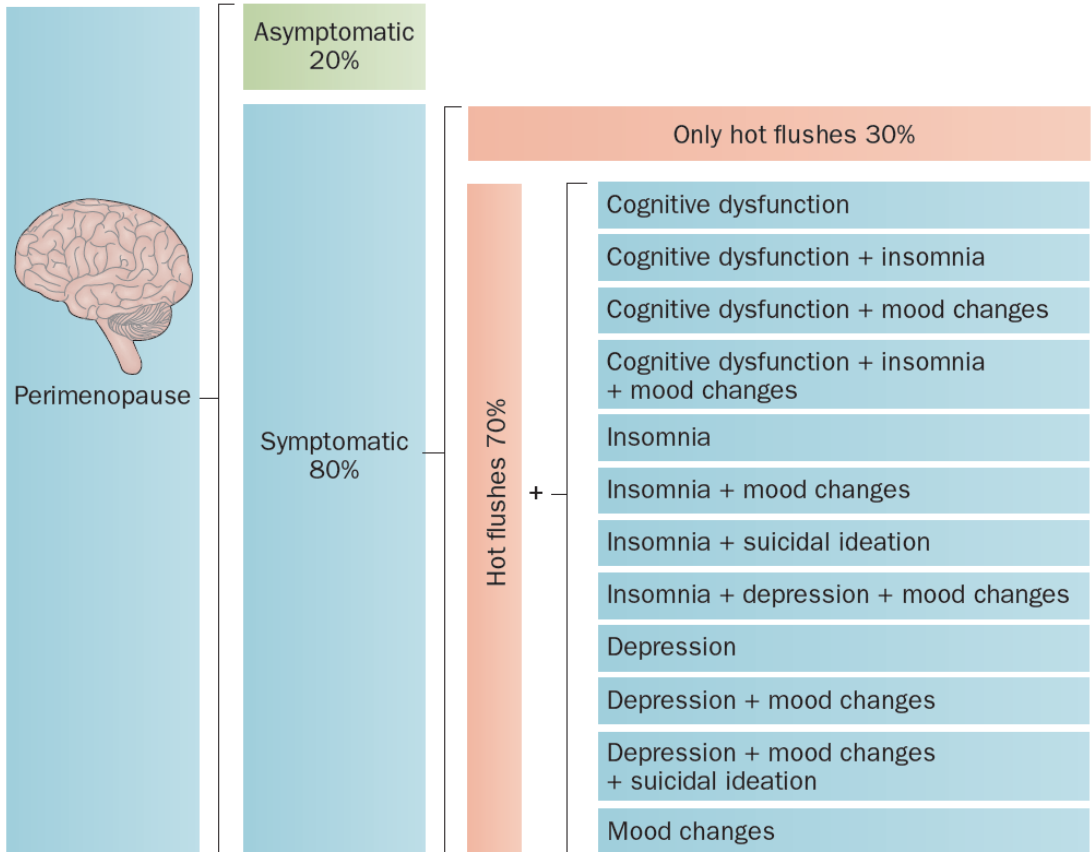
- Allopregnanolone  a method for enhancing neurological function (US8969329B2)
- Agents, compositions and methods for enhancing neurological function (US20170258810A1)
- Agents, compositions and methods for treating and preventing Alzheimer's disease (PCT WO2019/178230)
- Phytoestrogenic formulations for alleviation or prevention of menopausal symptoms (US8680140B2).
- Phytoestrogenic formulations for alleviation or prevention of neurodegenerative diseases (US8552057B2)
- Neuroprotection and myelin repair using nestorone® (US9446051B2)

## BioTech

- NeuTherapeutics, LLC.

# Perimenopause-Menopause Transition of Female Brain is a Mid-Life Neurological Transition

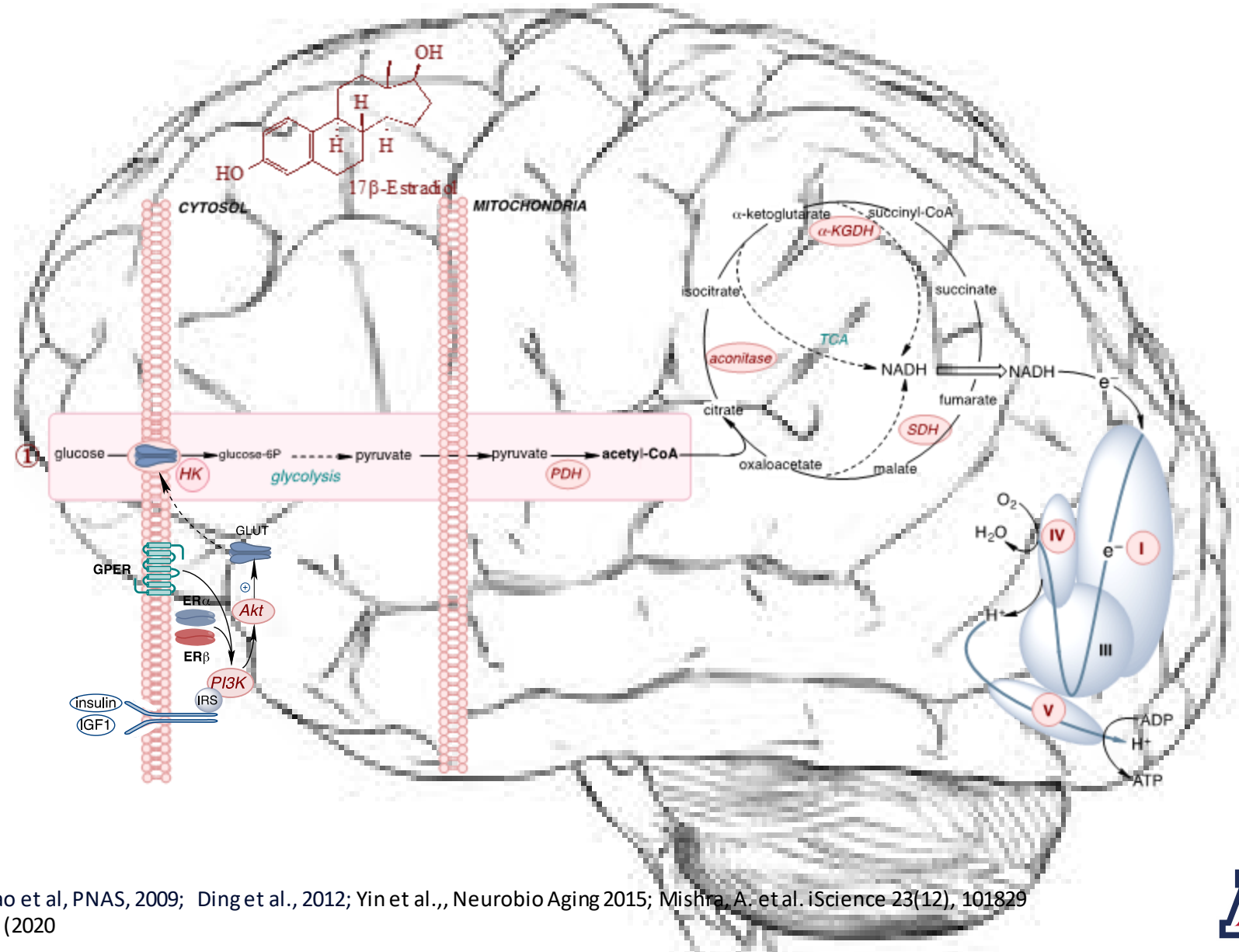



P01AG026572

*Brinton et al., Nature Rev Endo 2015*

# Early Midlife Bioenergetic Transition in Female Brain: Implications for Risk of Alzheimer's in Later Life




Brinton et al., Nature Rev Endo 2015; Yao et al, PNAS, 2009; Ding et al., 2012; Yin et al.,, Neurobio Aging 2015; Mishra, A. et al. iScience 23(12), 101829 (2020); Wang, Y. et al., Sci Rep 10, 8528 (2020

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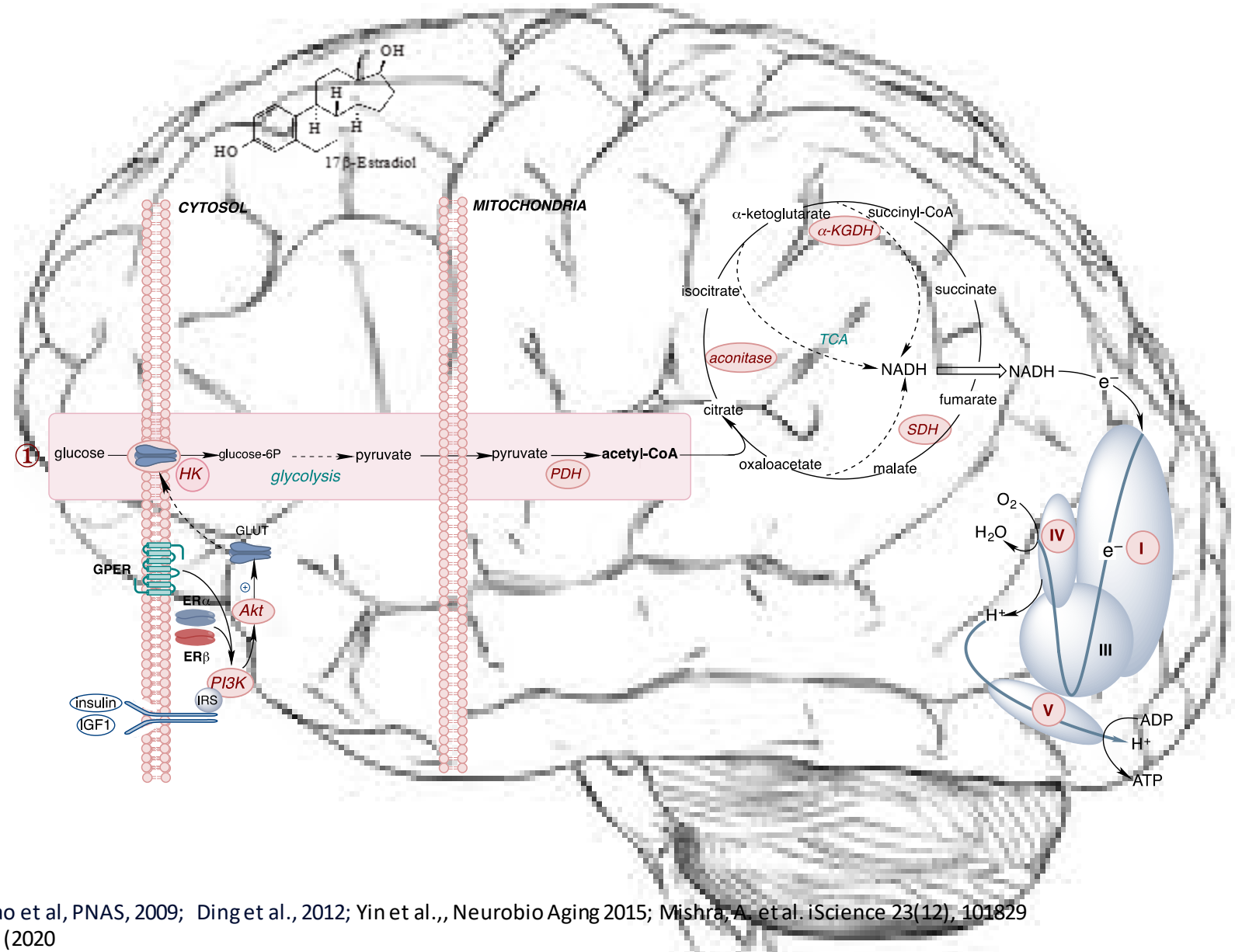
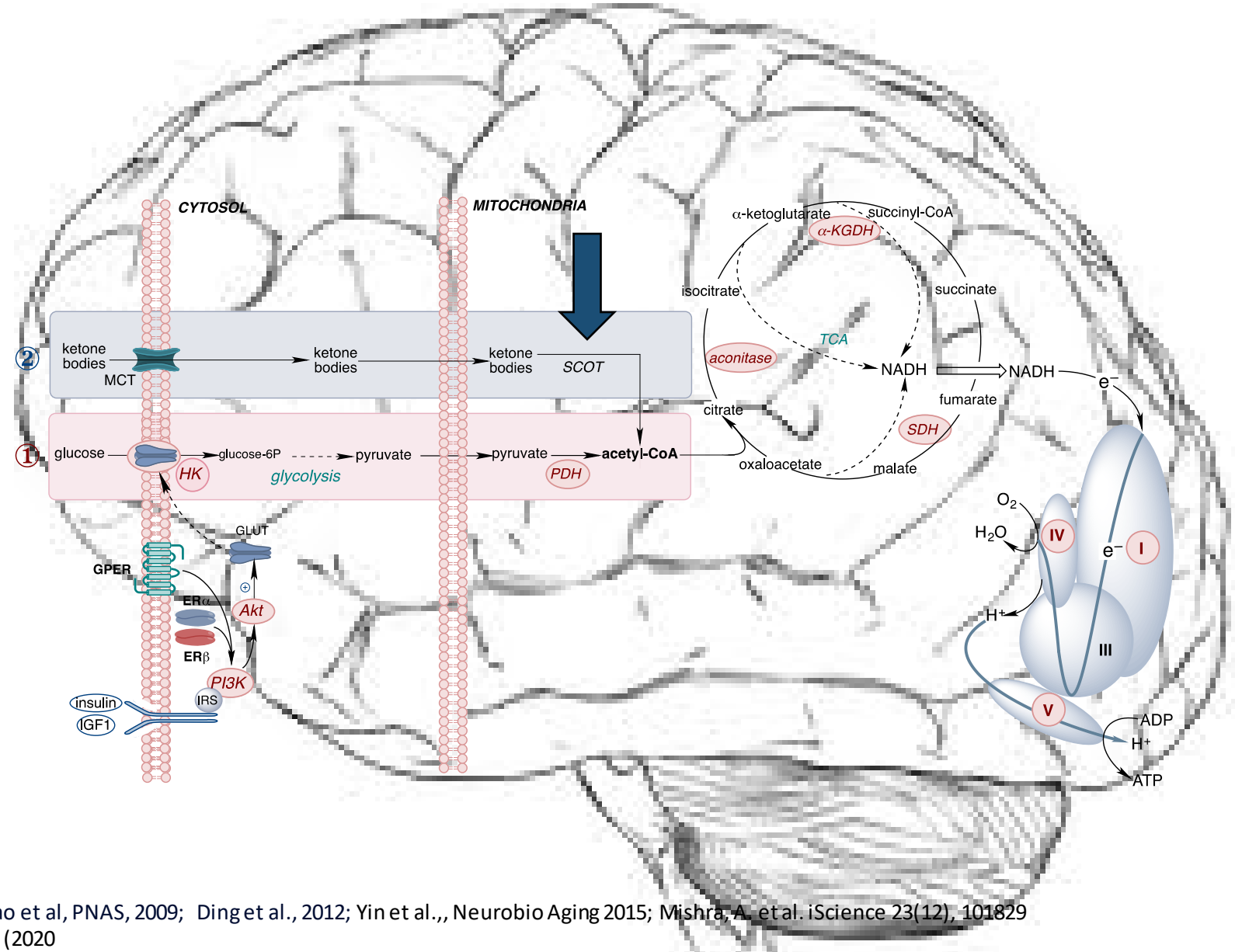
# Early Midlife Bioenergetic Transition in Female Brain: Implications for Risk of Alzheimer's in Later Life




Brinton et al., Nature Rev Endo 2015; Yao et al, PNAS, 2009; Ding et al., 2012; Yin et al.,, Neurobio Aging 2015; Mishra, A. et al. iScience 23(12), 101829 (2020); Wang, Y. et al., Sci Rep 10, 8528 (2020

# Early Midlife Bioenergetic Transition in Female Brain: Implications for Risk of Alzheimer's in Later Life

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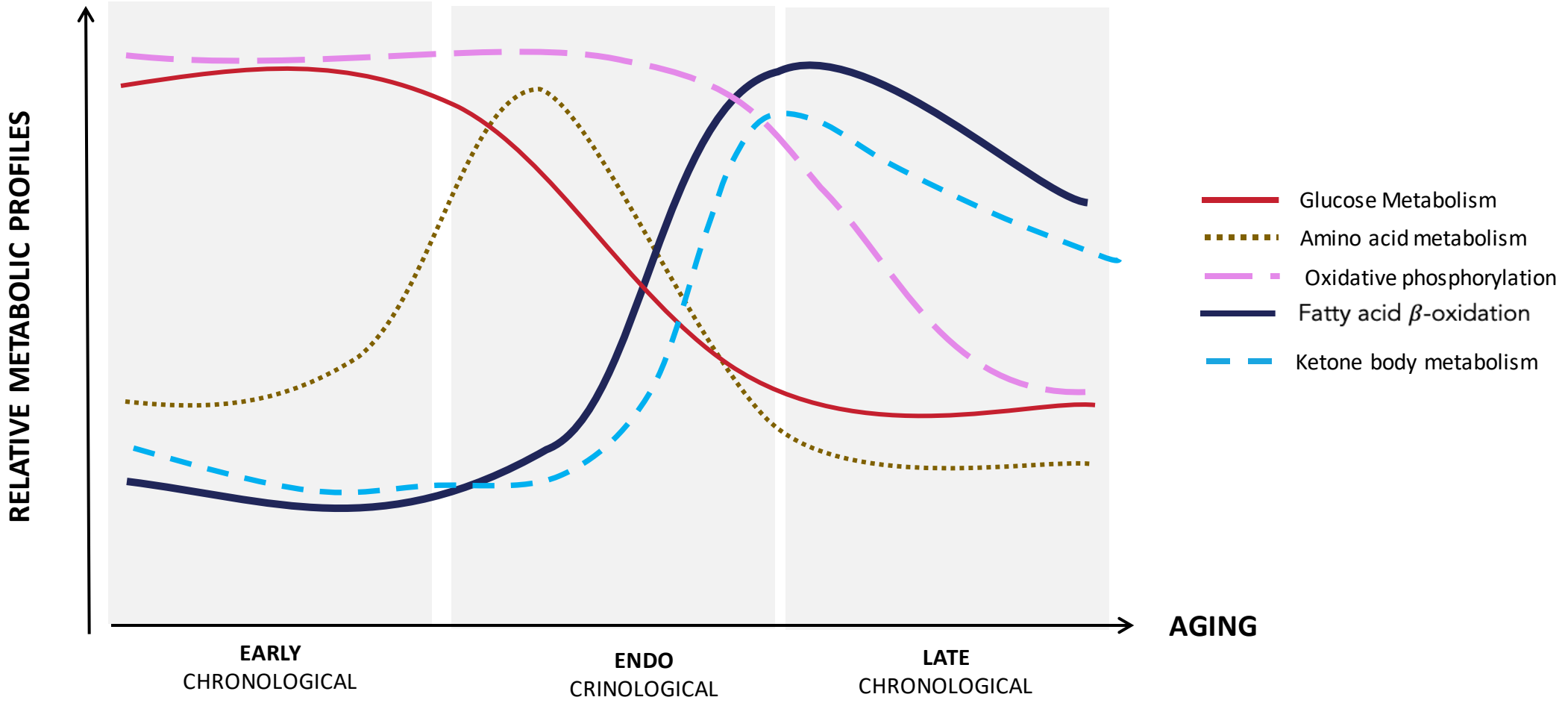
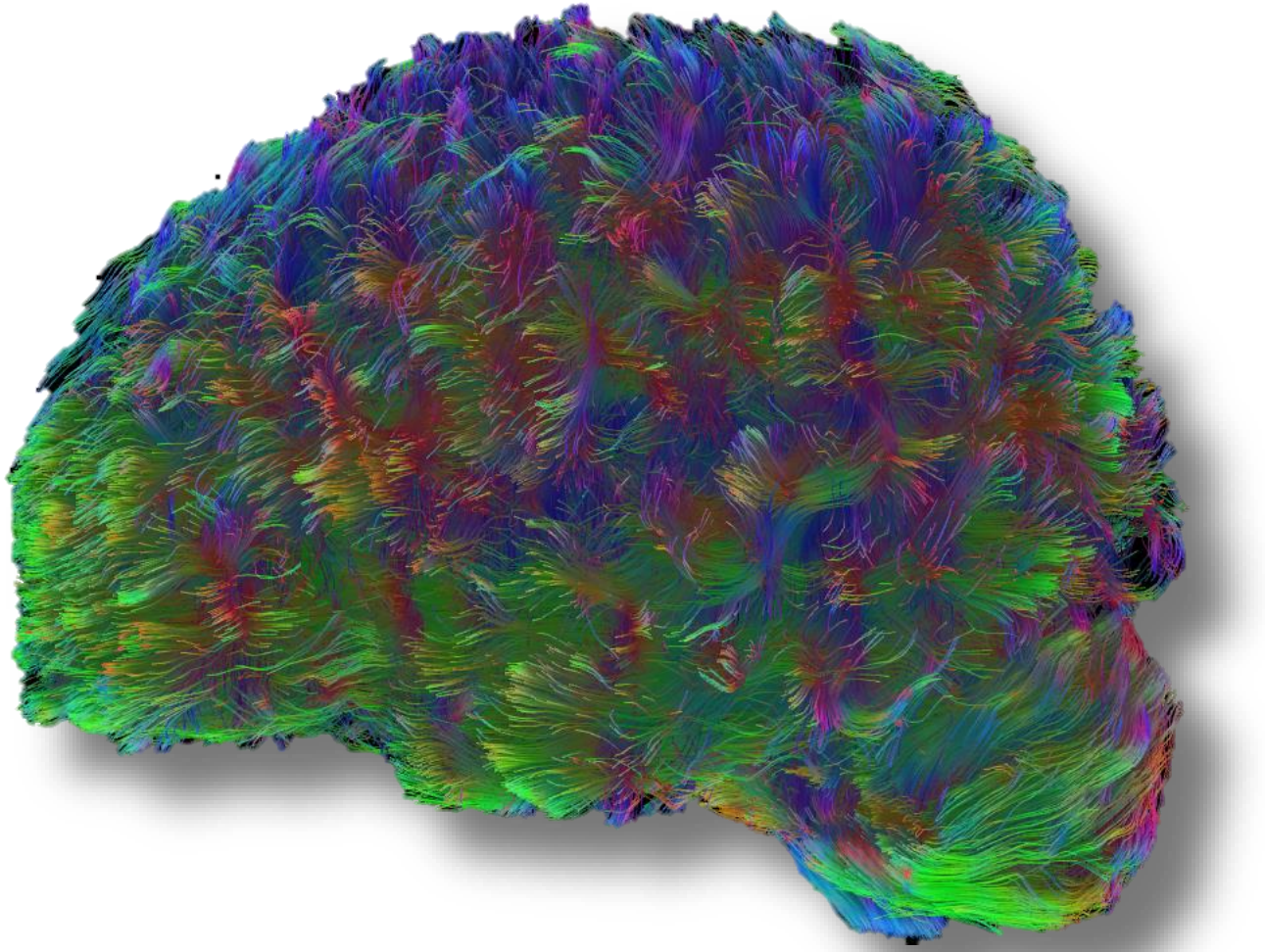
# Metabolic Reprogramming Transitions in Mid-Life Female Brain




Brinton et al., *Nature Rev Endo* (2015); Mishra, A. et al. *iScience* 23(12), (2020); Wang, Y. et al., *Sci Rep* **10**, 8528 2020 ; Ding et al.,*PLoS One*, 2012; Yin et al., *Neurobio Aging* 2015; Klosniski et.,al , *EBioMedicine 2015;* Mishra, A. et al., *Front Aging Neurosci* 2018; Yao J et al., Proc Natl Acad Sci USA. 2009 Aug 25;106(34)

What is the source of ketone bodies to fuel a starving brain?

# The Brain is the Most Lipidated Organ of the Body: 60% of Brain Matter is White Matter



Surface of the left hemisphere with 50,000 tracts visualized. Colors indicate fiber direction (red = left-right; blue = superior-inferior; green = anterior-posterior (Raikes & Brinton, 2021)

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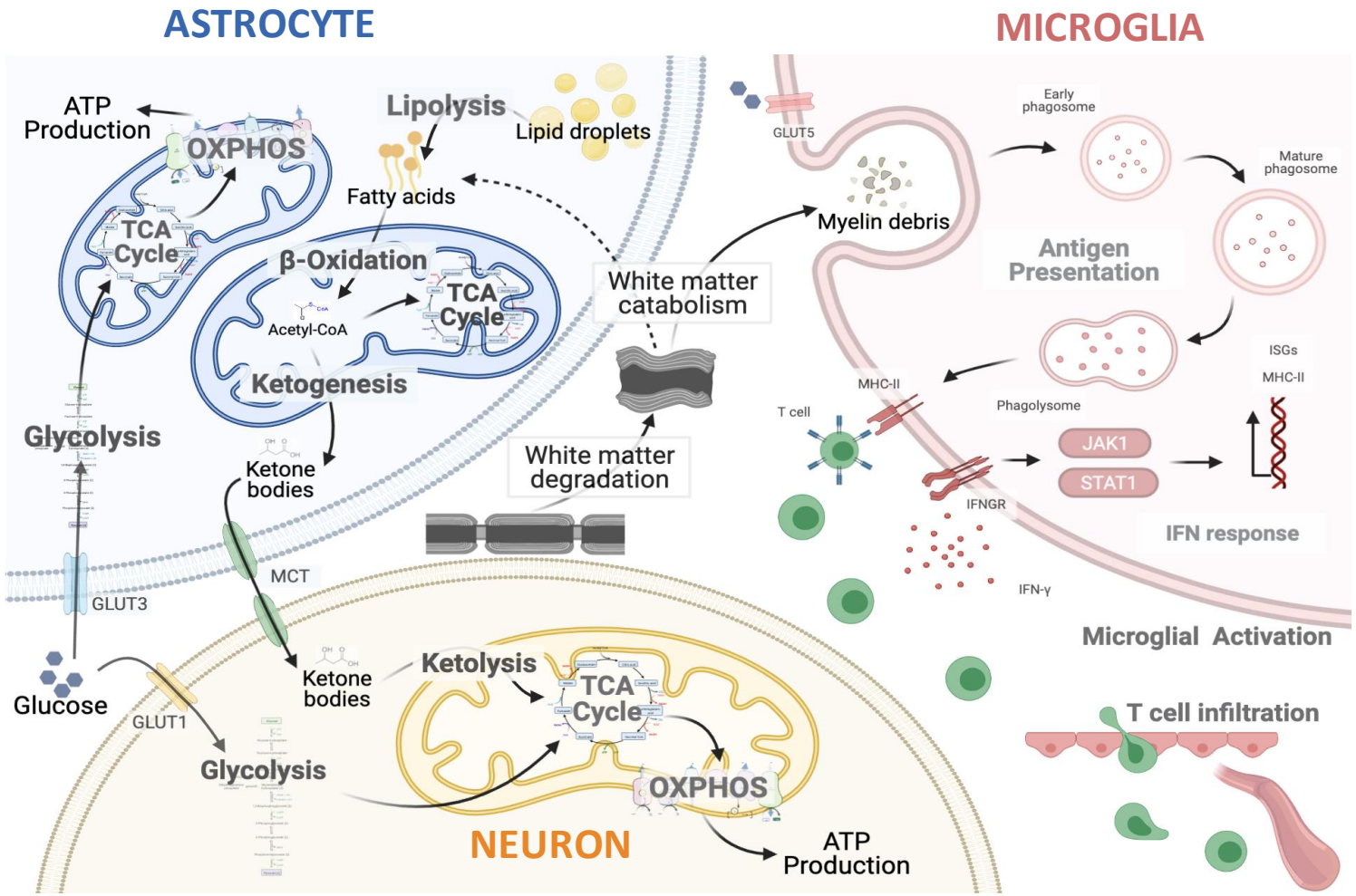
# Coordinated Systems of Biology Between Immune and Metabolic Systems to Sustain Neuronal Survival Through Utilization of White Matter Lipids

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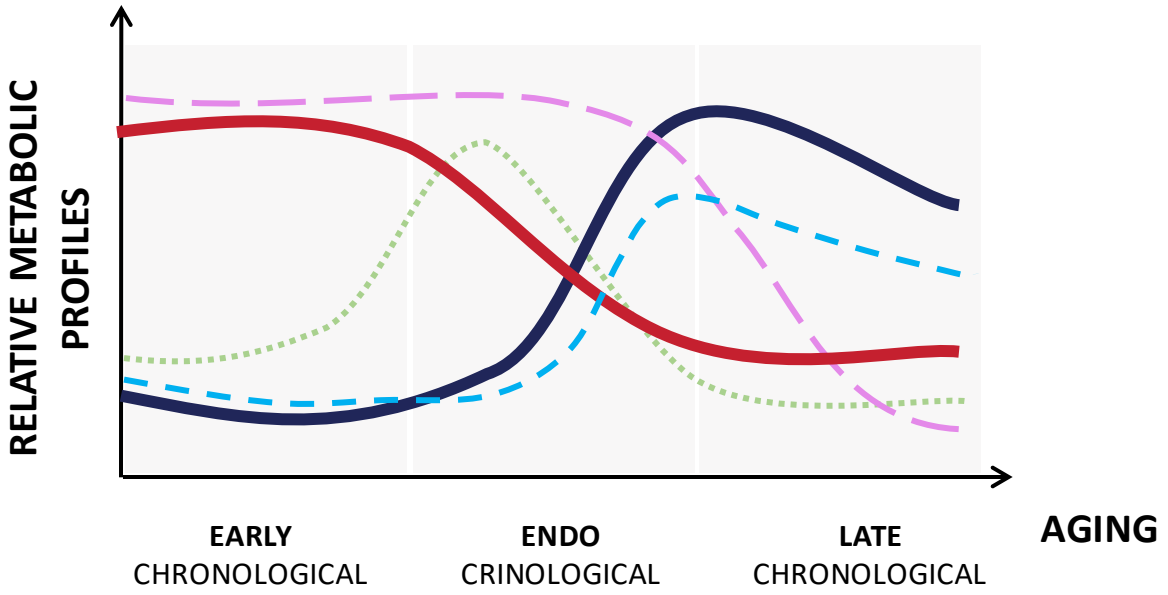
Brinton et al., *Nature Rev Endo* (2015); Mishra, A. et al. *iScience* 23(12), (2020); Wang, Y. et al., *Sci Rep* **10**, 8528 (2020 ; Ding et al.,*PLoS One*, (2012); Yin et al., *Neurobio Aging* (2015); Klosniski et.,al , *EBioMedicine (2015);* Mishra, A. et al., *Front Aging Neurosci* (2018); Yao et al, *PNAS* (2009);

# Metabolic Reprogramming of Brain: Coordinated Metabolic and Immune System Activation

## METABOLISM




Glucose Metabolism

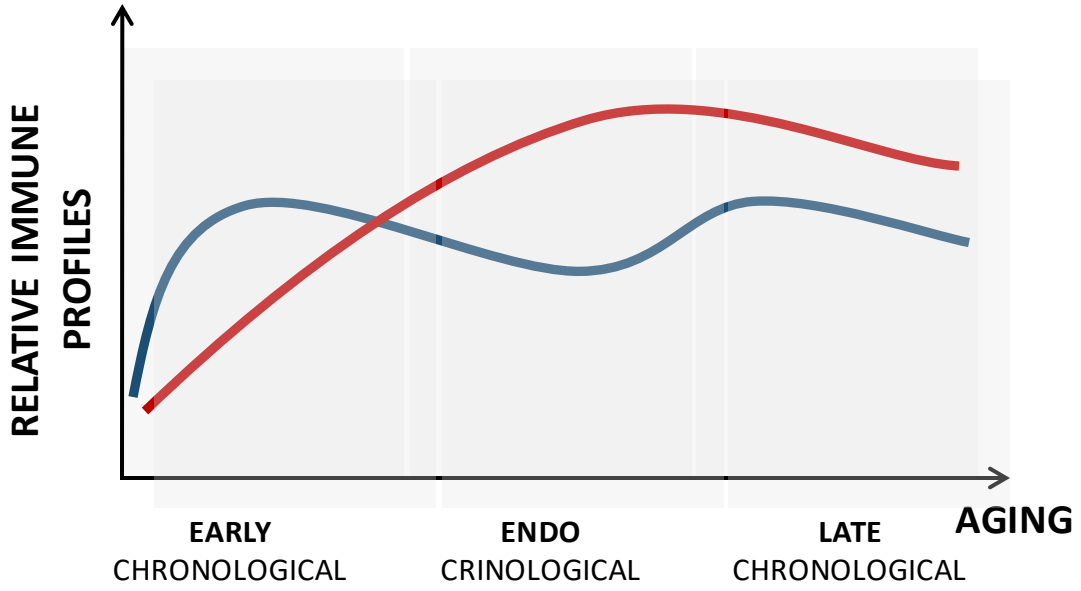
Fatty acid $\beta$-oxidation

Amino acid metabolism

Ketone body metabolism

Oxidative phosphorylation

## IMMUNE

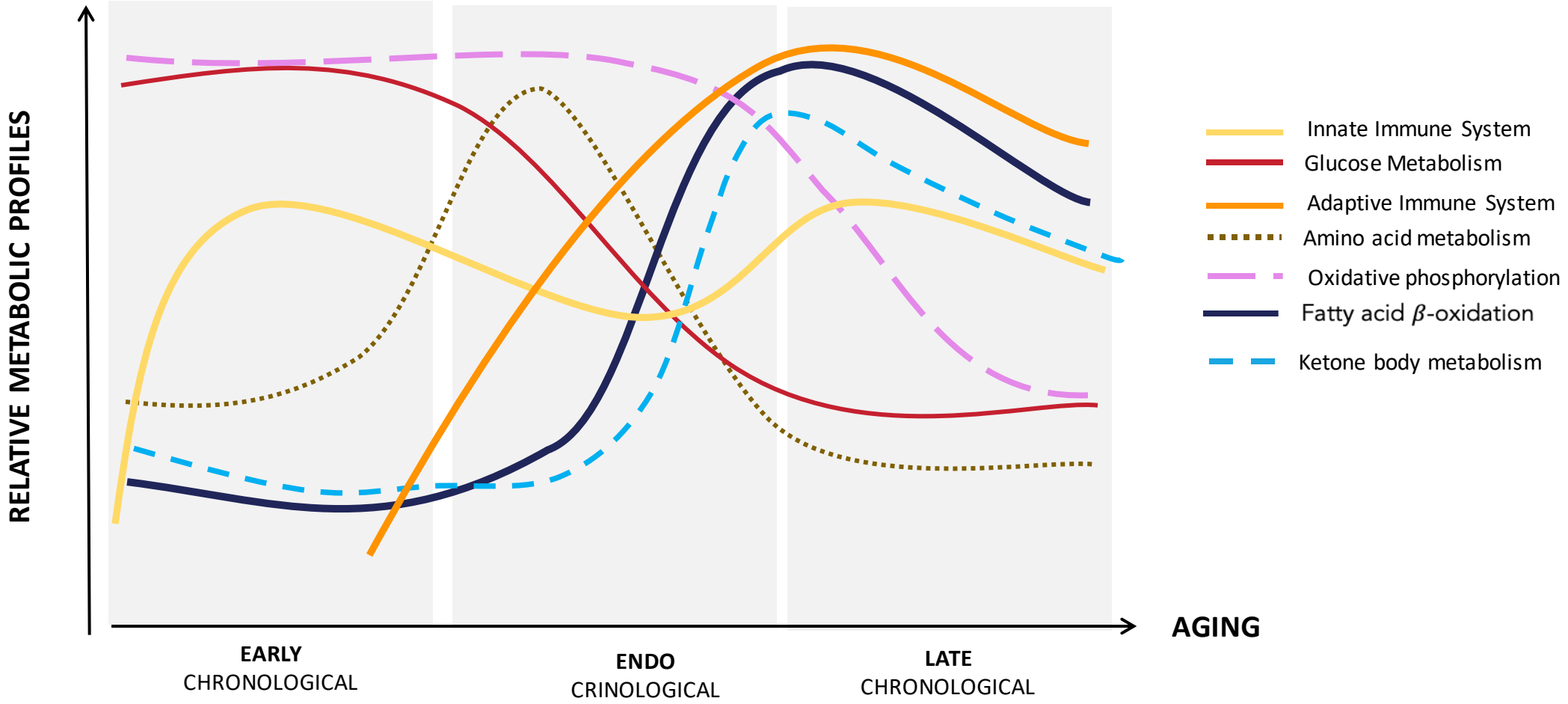



Innate Immune Response

Adaptive Immune Response

Brinton et al., *Nature Rev Endo* (2015); Yao et al, *PNAS* (2009); Ding et al.,*PLoS One*, (2012); Yin et al., *Neurobio Aging* (2015); Klosniski et.,al , *EBioMedicine (2015);* Mishra, A. et al., *Front Aging Neurosci* (2018). Mishra, A. et al. *iScience* 23(12), 101829 (2020); Wang, Y. et al., *Sci Rep* **10**, 8528 (2020);

# Neuro-Immune and Metabolic Reprogramming Transitions in Mid-Life Female Brain

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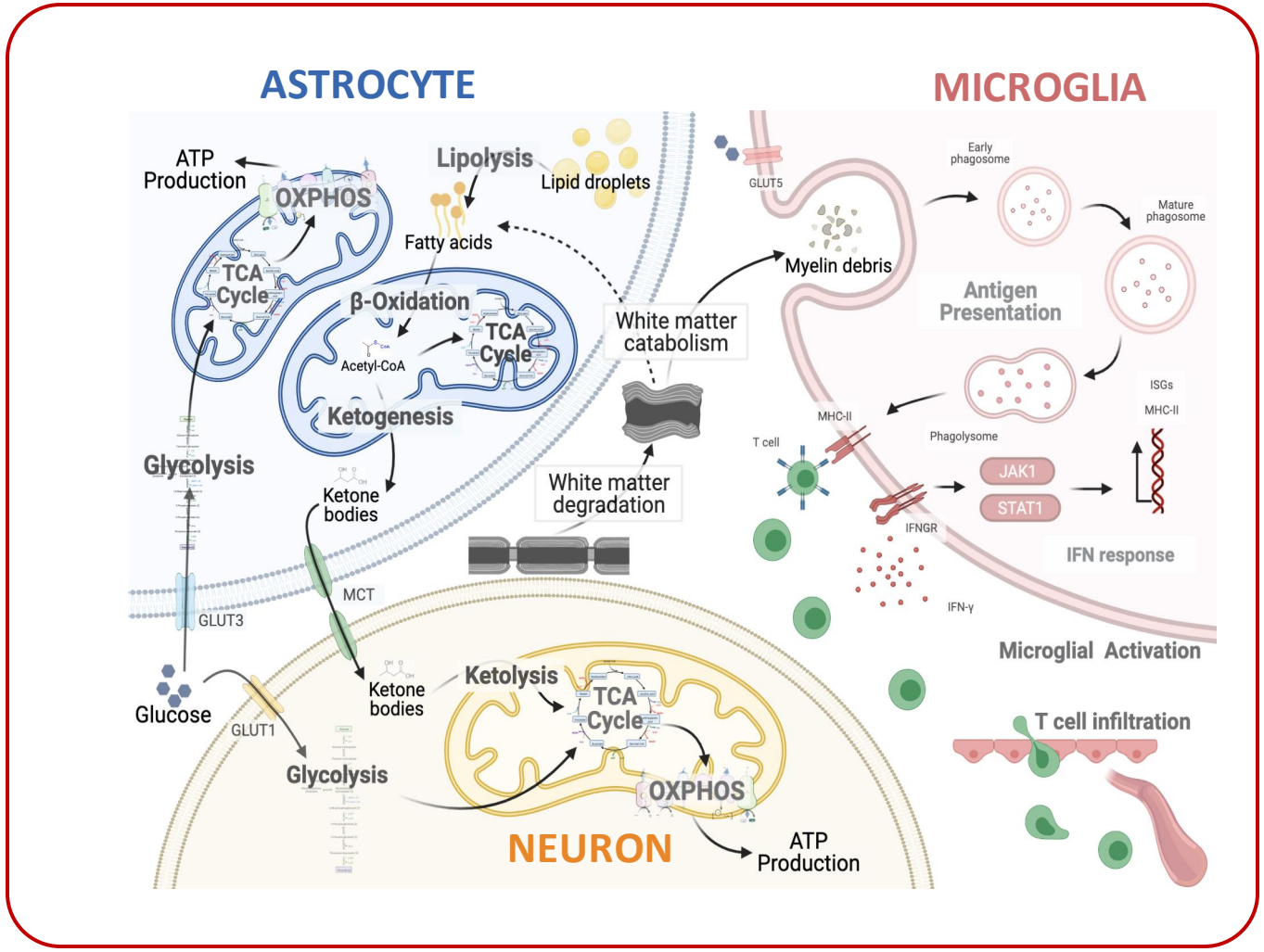
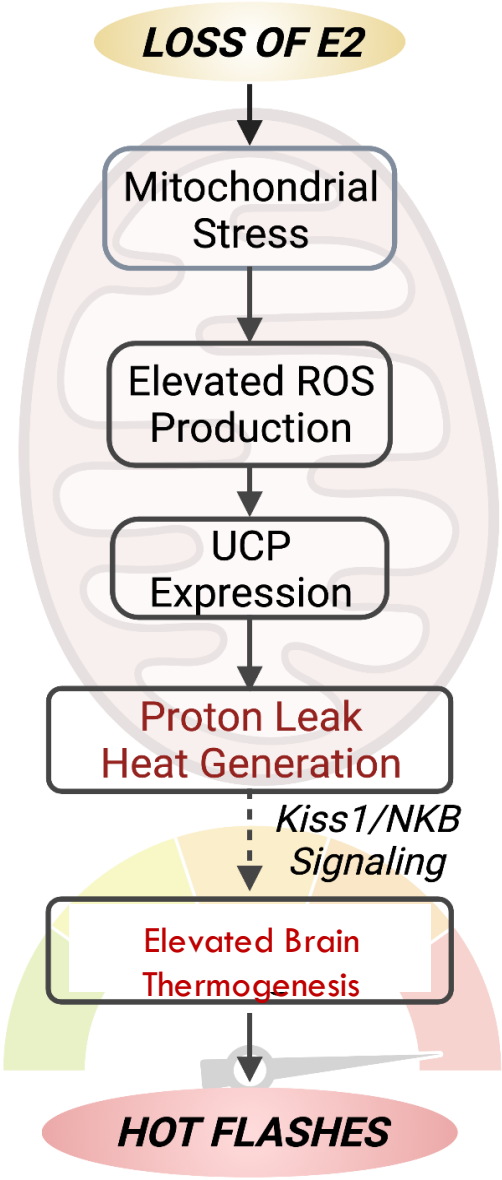
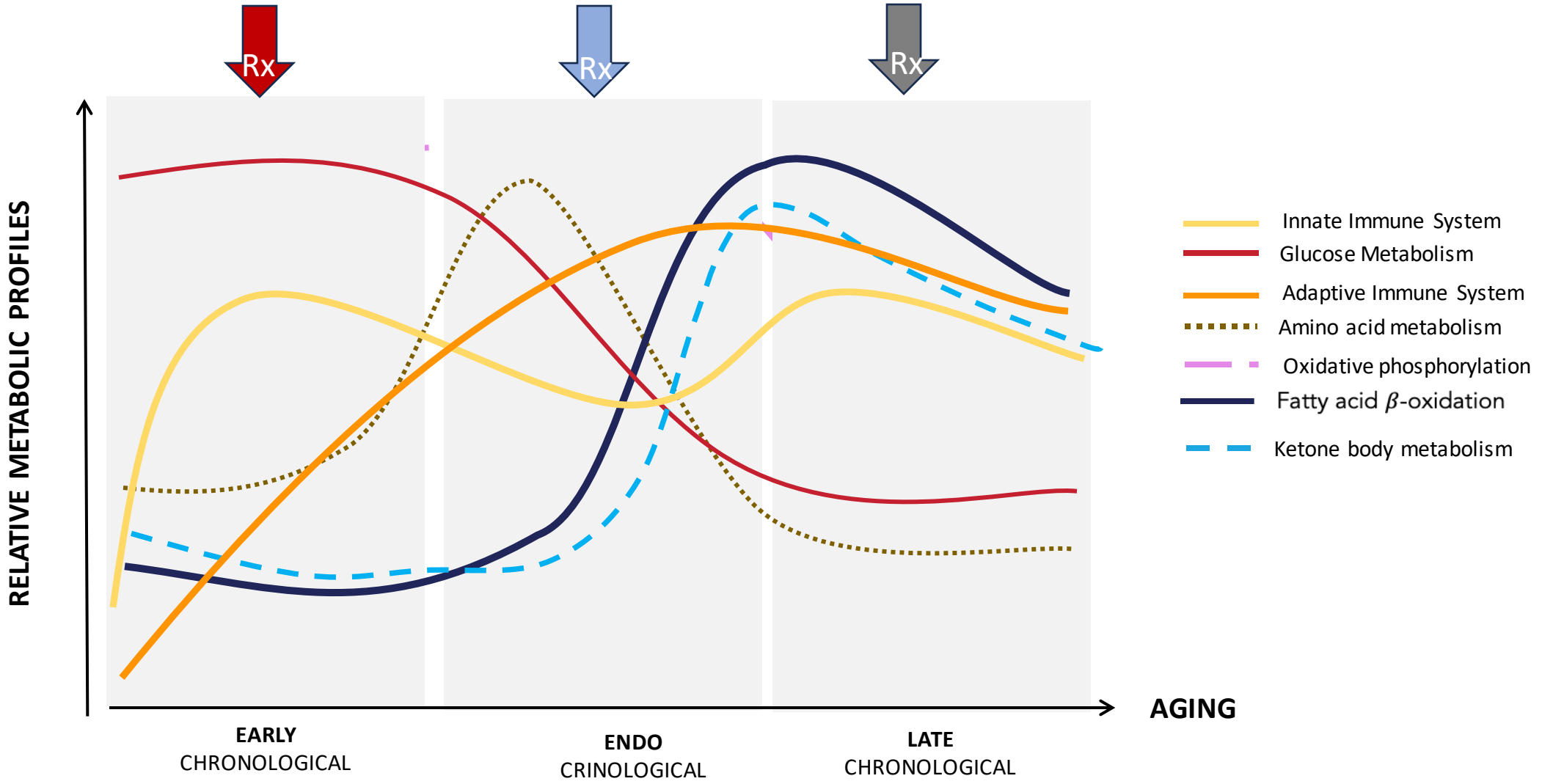
# Utilization of White Matter Lipids: Link to Menopausal Hot Flashes




Yin F and Brinton RD in preparation 2024

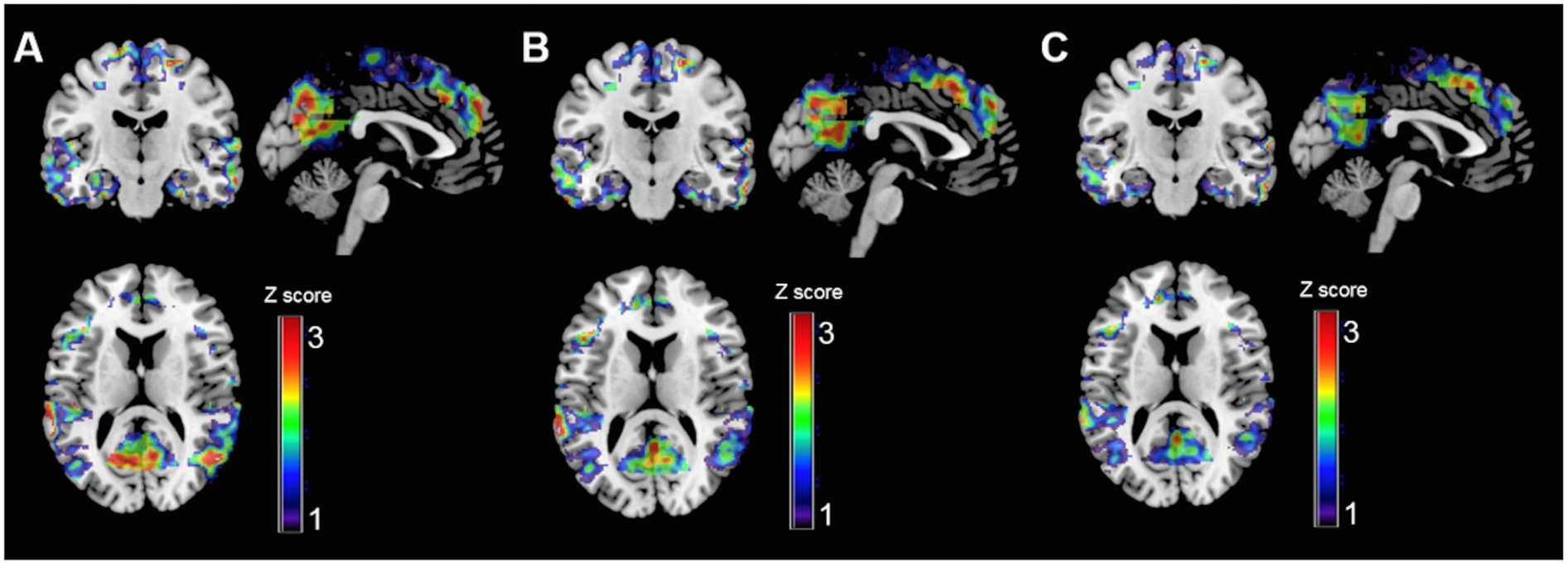
# Precision Menopausal Hormone Therapy: Timing Matters
# Estrogen Sustains Brain Health Does Not Reverse Disease

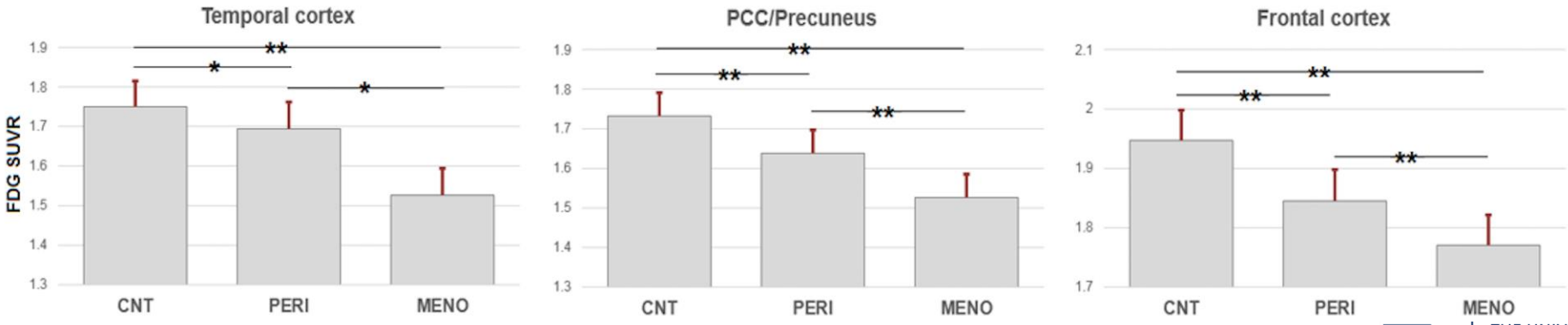



Brinton et al., *Nature Rev Endo* (2015); Mishra, A. et al. *iScience* 23(12), (2020); Wang, Y. et al., *Sci Rep* **10**, 8528 2020 ; Ding et al.,*PLoS One*, 2012; Yin et al., *Neurobio Aging* 2015; Klosniski et.,al , *EBioMedicine 2015;* Mishra, A. et al., *Front Aging Neurosci* 2018; Yao J et al., Proc Natl Acad Sci USA. 2009 Aug 25;106(34)

# Is There Evidence for Metabolic Reprogramming in the Human Brain?

# Discovery to Clinical Translation:
# Human Brain Glucose Uptake Declines in Endocrinological Aging




Mosconi, L. et al. *PloS one*, 12(10), (2017)

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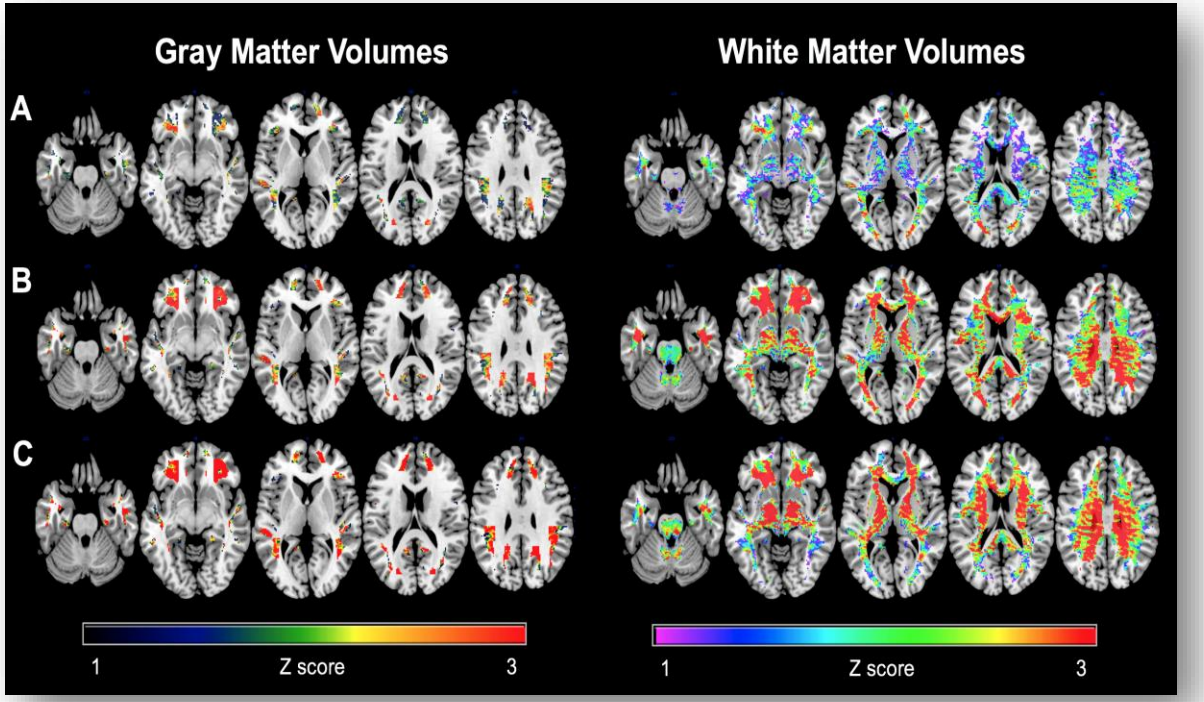
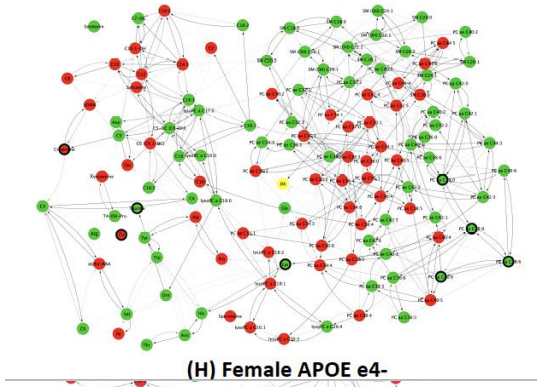
# White Matter Loss is Consistent with Myelin Profile of Plasma Metabolome




Mosconi et al., Neurology. 2017

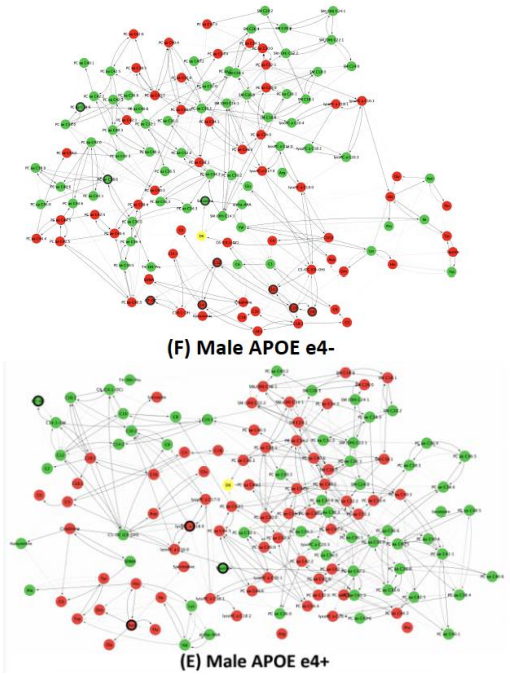
## Metabolomic Auxiliary Fuel Phenotype

**FEMALE**




**Female Elevated Sphingomyelins and Phosphatidylcholines**

**MALE**




**Male Elevated Branched Amino Acids and Amines**

Chang et al. Alzheimer's Dement. 2022

Arnold et al.,.Nat Commun. 2020 Mar 2;11(1):1148.

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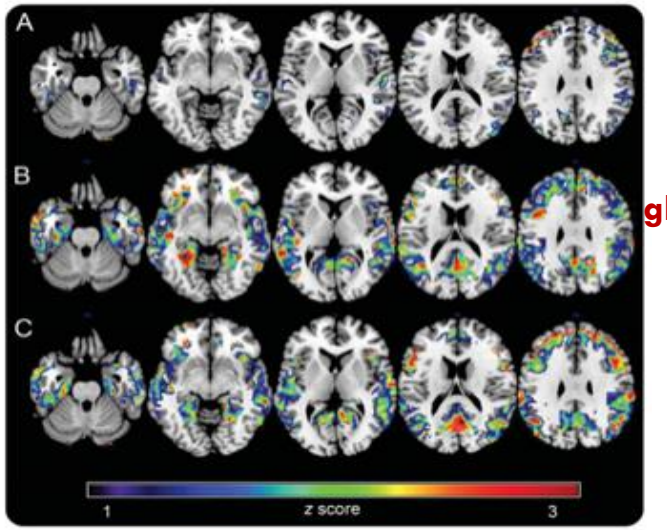
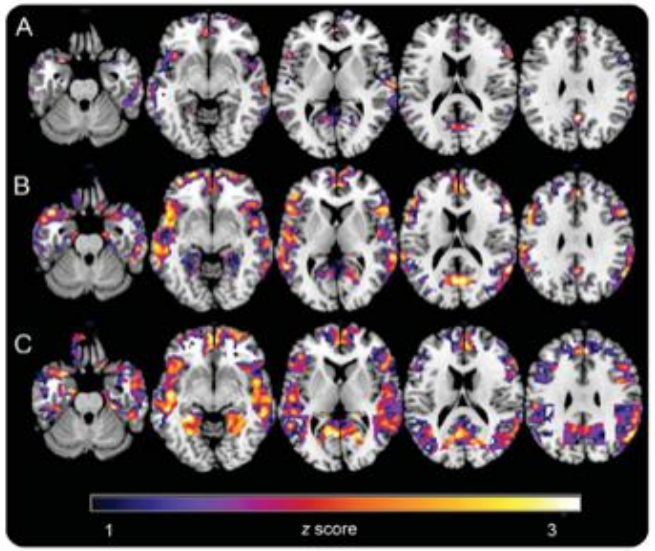
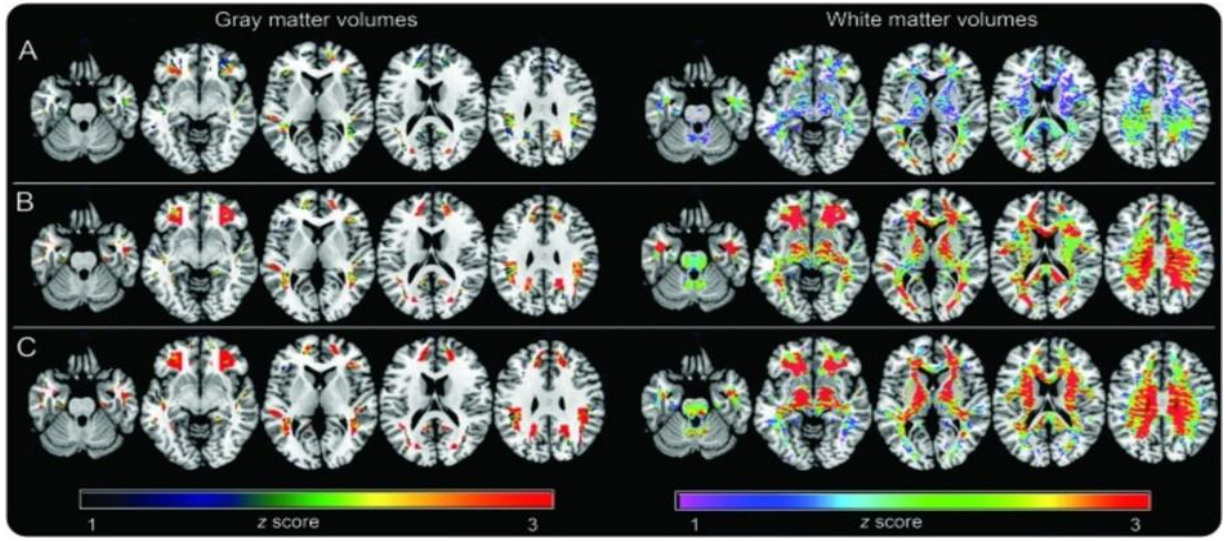
# Decline in Brain Glucose Metabolism is Coincident with Decline in White Matter Volume and Emergence of Beta Amyloid Plaque During Menopausal Transition




18F-fluoro-2-deoxyglucose (FDG)–PET brain glucose metabolism as a function of chronologic vs endocrine aging

PiB–PET β-amyloid deposition as a function of chronologic vs endocrine aging




Mosconi et al, Neurology. 2017 Sep 26; 89(13): 1382–1390.

If Loss of Estrogen Initiates MidLife Trajectory of Vulnerability,

Does Menopausal Hormone Therapy Impact Risk of Alzheimer's?

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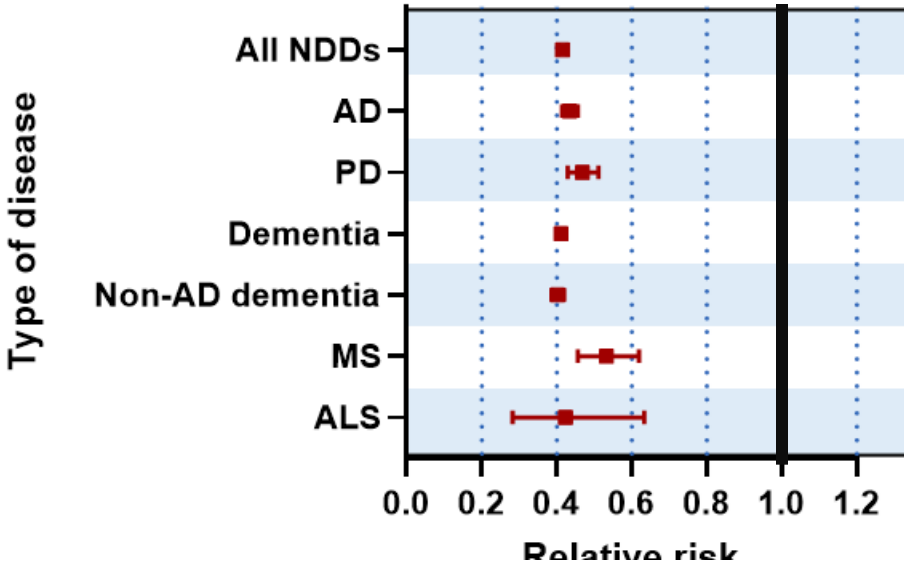
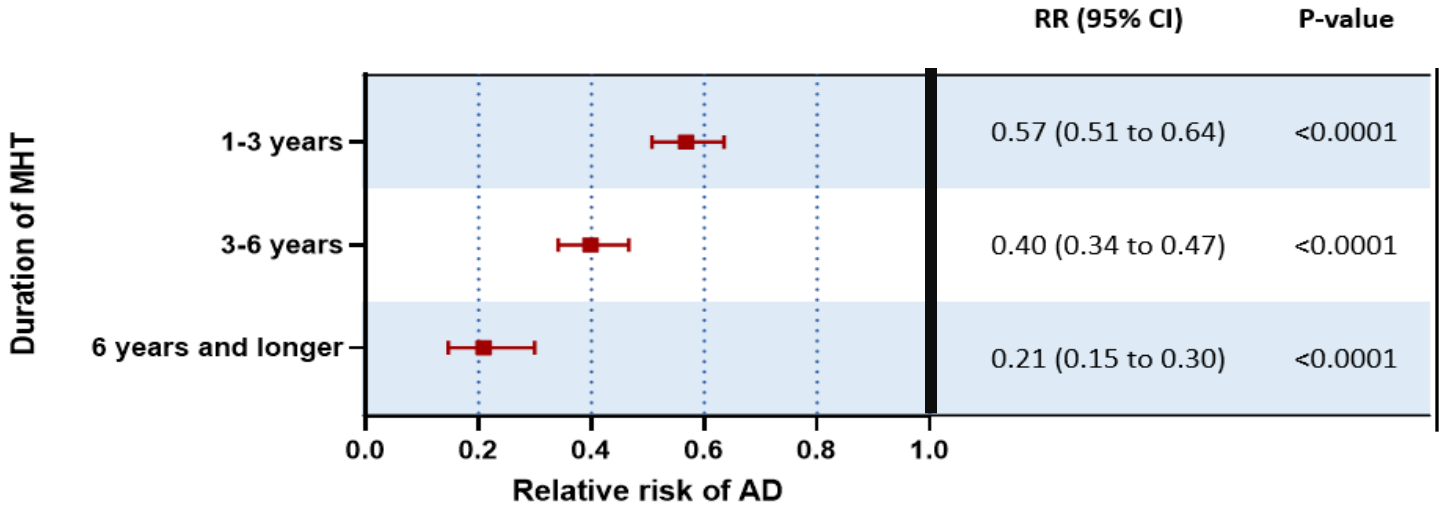
# Menopausal Hormone Therapy (MHT) and Neurodegenerative Diseases (NDD): A Retrospective Analysis in 379,352 Women




| Type of disease | Control, No. (%) (N=189,676) | Treatment, No. (%) (N=189,676) | RR (95% CI) | P-value |
|---|---|---|---|---|
| All NDDs | 14,920 (7.87) | 6,260 (3.30) | 0.42 (0.40 to 0.43) | <0.0001 |
| AD | 5,414 (2.85) | 2,361 (1.24) | 0.43 (0.41 to 0.46) | <0.0001 |
| PD | 1,574 (0.83) | 739 (0.39) | 0.47 (0.43 to 0.51) | <0.0001 |
| Dementia | 12,711 (6.70) | 5,263 (2.77) | 0.41 (0.40 to 0.43) | <0.0001 |
| Non-AD dementia | 7,896 (4.16) | 3,192 (1.68) | 0.40 (0.39 to 0.42) | <0.0001 |
| MS | 473 (0.25) | 252 (0.13) | 0.53 (0.46 to 0.62) | <0.0001 |
| ALS | 78 (0.04) | 33 (0.02) | 0.42 (0.28 to 0.63) | <0.0001 |




| Duration of MHT | RR (95% CI) | P-value |
|---|---|---|
| 1-3 years | 0.57 (0.51 to 0.64) | <0.0001 |
| 3-6 years | 0.40 (0.34 to 0.47) | <0.0001 |
| 6 years and longer | 0.21 (0.15 to 0.30) | <0.0001 |

Kim, YU.. Brinton RD Alzheimers Dementia 2021 May 13;7(1)

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# If Estrogen is Beneficial for the Brain…….

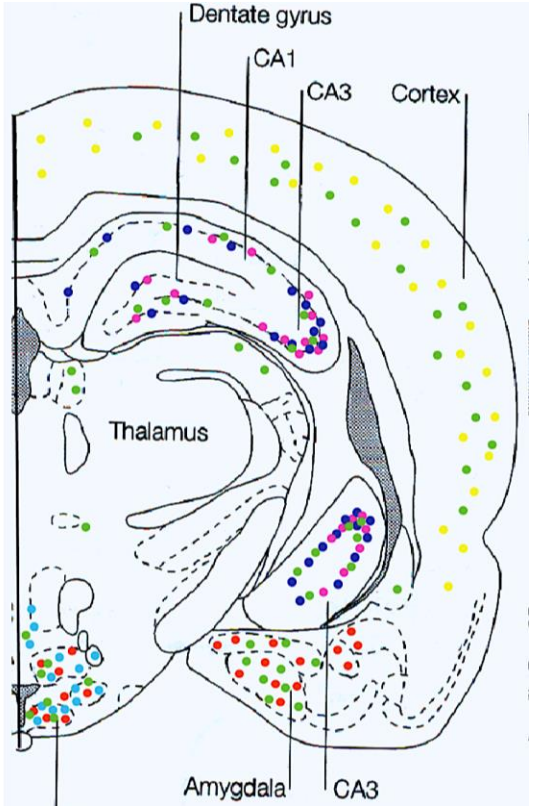
Why do 80% of women elect not receive hormone therapy for menopausal symptoms?

Fear of Breast Cancer

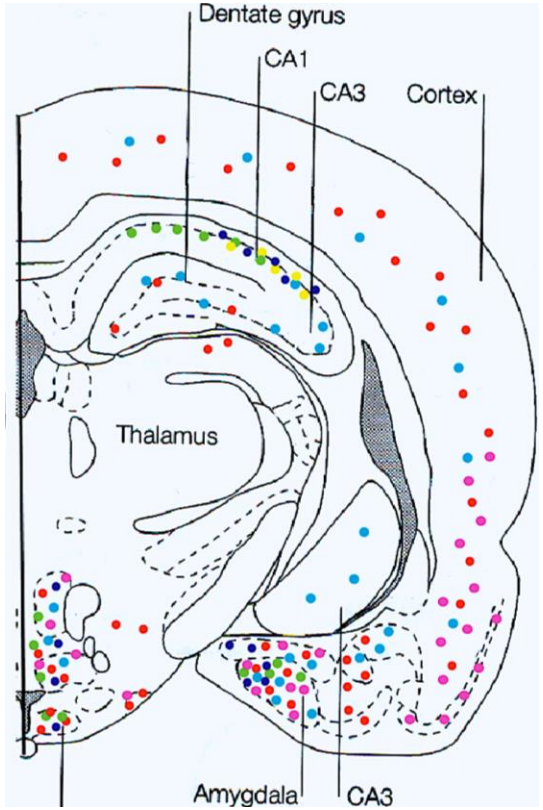
To sustain brain health, had to address breast health

# Distribution of Estrogen Receptor α & β in Brain: ERβ Estrogenic Mechanisms

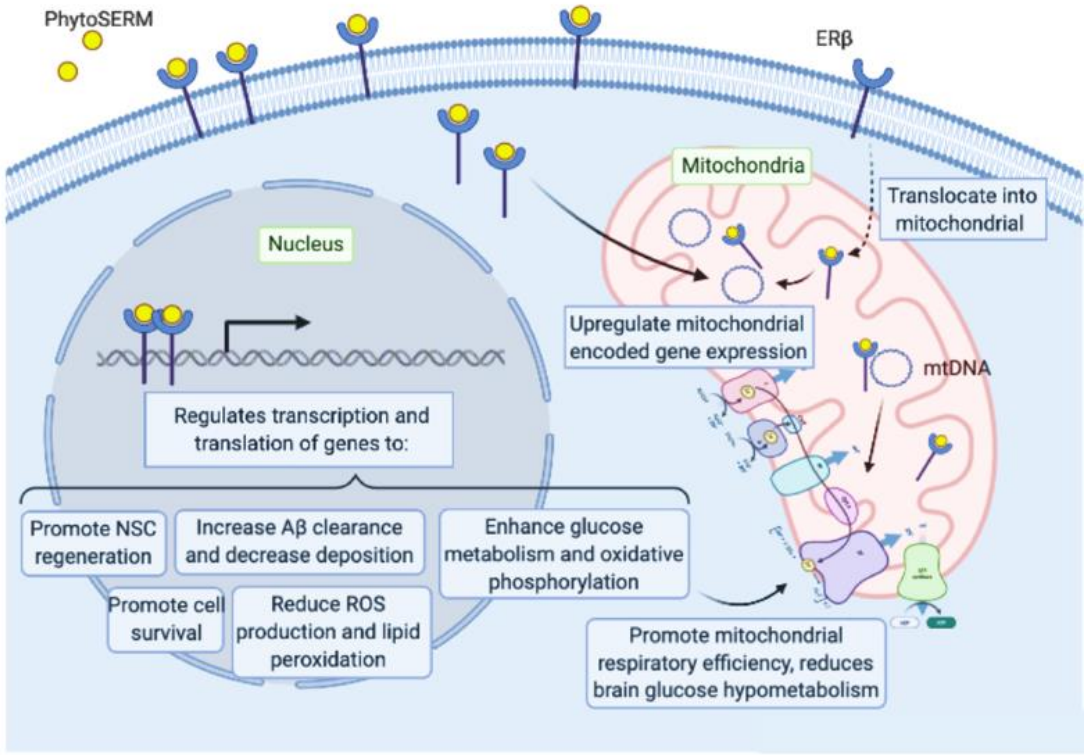
## ERα Distribution in Brain




## ERβ Distribution in Brain




## ERβ Mechanism of Action in Brain

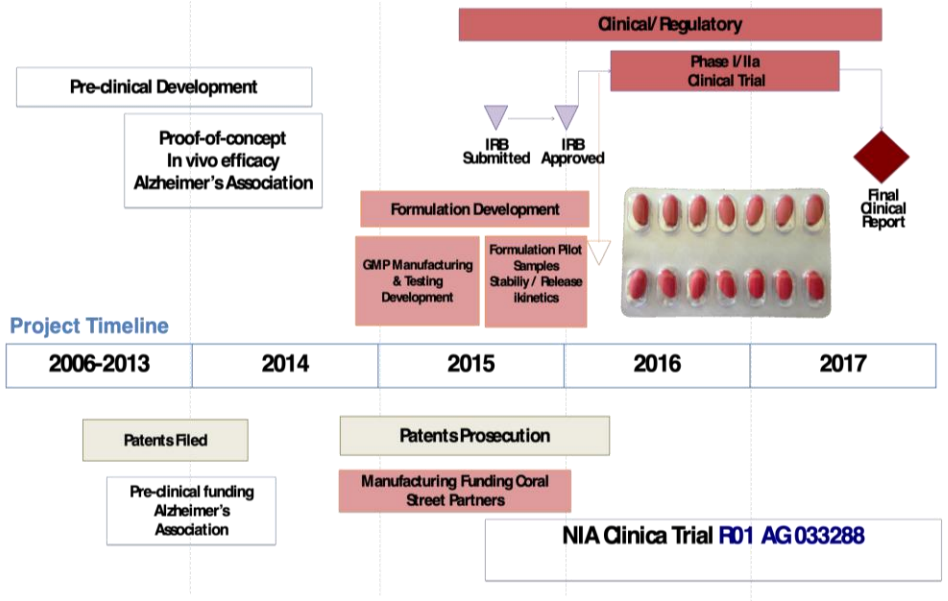



Zhao et al., 2004; Zhao and Brinton, 2005; Zhao and Brinton, 2007; Wang et al., 2008; Irwin et al., 2012, Wang et al., 2008; Zhao et al., 2009, Yao et al., 2013

# Estrogen Receptor β Inhibits Breast Cancer Cell Proliferation and Migration

- Estrogen receptor β inhibits 17β-estradiol-stimulated proliferation of the breast cancer cell line T47D, PNAS, 2004, Jan 26, 2004, 101 (6) 1566-1571
- Estrogen receptor β inhibits human breast cancer cell proliferation and tumor formation by causing a G2 cell cycle arrest. Cancer Res 2004 Jan 1;64(1):423-8.
- Estrogen receptor β inhibits breast cancer cells migration and invasion through CLDN6-mediated autophagy, J Exp Clin Cancer Res 2019 Aug 14;38(1):354.
- Estrogen receptor beta repurposes EZH2 to suppress oncogenic NFκB/p65 signaling in triple negative breast cancer. *Nature* Breast Cancer, (2022) 8:20

# Estrogen Receptor β Targeted PhytoSERMs for Menopausal Symptoms: Phase 1b/2a Clinical Trial for Safety and Feasibility




**NIA 5R01AG033288**

Clinicaltrials.gov NCT01723917

## PHASE 1b/2a: RCT

PARTICIPANTS
- 70 Peri-Post Menopausal Women
- Vasomotor Symptoms
- Subjective Cognitive Complaint

TREATMENT
- Placebo
- 50 mg
- 100 mg

1/day for 3 months

PRIMARY OUTCOMES
- Safety
- Pharmacokinetics

EXPLORATORY OUTCOMES
- Hot Flash
- Cognitive Function

### PRIMARY OUTCOMES

- ✓ No indicators of toxicity
- ✓ Predictive pharmacokinetics
- ✓ Effective dose: 50 mg/daily
- ✓ Detection of change in hot flash frequency feasible
- ✓ Biomarker of responder feasible


Hernandez et al., Menopause, 2018, 2:191-196
Schneider et al., Menopause: 2019, 26, No. 8, pp. 874-884

# PhytoSERM Development:
# Pharmaceutical Rigor for PhytoSERM Nutraceutical

| Preclinical Development | Phase I Safety and Feasibility Clinical Trial | Safety and Chronic Toxicity Profile | Phase 2 Proof of Concept Clinical Trial |
|---|---|---|---|
| Established: | Established: | Established: | Established: |

**NIA R01AG075122 / NCT05664477**

PhytoSERM Efficacy to Prevent Menopause Associated Decline in Brain Metabolism and Cognition: A Double-Blind, Randomized, Placebo-Controlled Phase 2 Clinical Trial

HFrelief

**NIA R44AG07802 / NCT06186531**

PhytoSERM for Menopausal Hot Flashes and Sustained Brain Health

https://www.hfrelief.org/

# Key Concepts

- **Menopause is a Neurological Transition that can unmask vulnerability to age-associated neurodegenerative disease.**
- **Menopausal Transition involves both the Metabolic and Immune Systems of the Brain**
- **Menopausal Hormone Therapy Sustains and Promotes Healthy Brain Aging –**

  ***Does Not Reverse Disease***

- **Promoting Brain *and* Breast Health is Feasible through ERβ selective formulation**

# Gaps and Opportunities in Women's Brain Health

- **Precision Hormone Therapy to Prevent Neurological Risks**
- **Biomarkers of Transition Stage beyond Clinical Symptoms that Determine Reflect Neurological Health or Vulnerability**

# Brinton Research Team, Sponsors & Collaborators

## TEAM

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- John McLean
- Georgina Torrandell, PharmD
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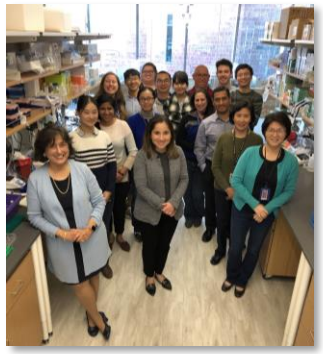
## SPONSORS

- National Institute on Aging
- Alzheimer's Drug Discovery Fd
- Alzheimer's Association
- Womens Alzheimer's Movement
- Robins Trust



### National Institute on Aging

- P01AG026572
- R01AG057931
- RF1AG059093
- R37AG053589
- R01 AG063826
- R43 AG063674
- 5R25NS107185
- T32AG061897

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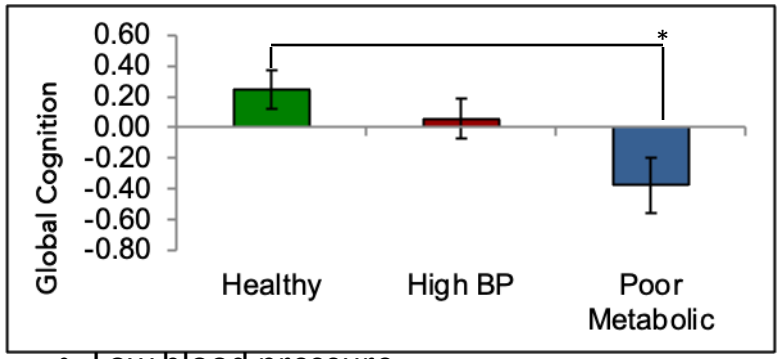
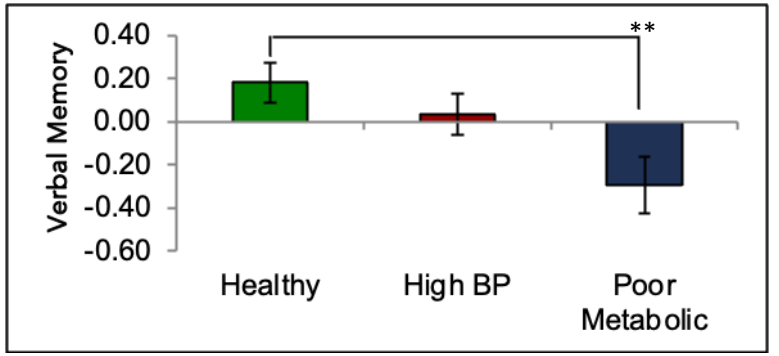
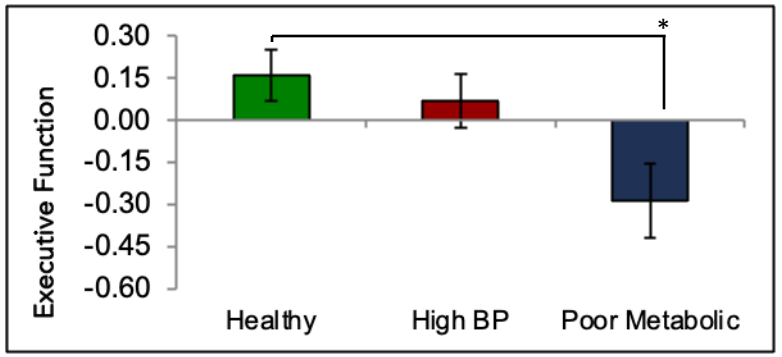
# Detecting Cognitive Resilience vs Vulnerability *in Healthy Women*




- Low blood pressure

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Rettberg et al., Neurobiol Aging. 2016; 40:155-63; Karim et al., Menopause, 26(1):2019.