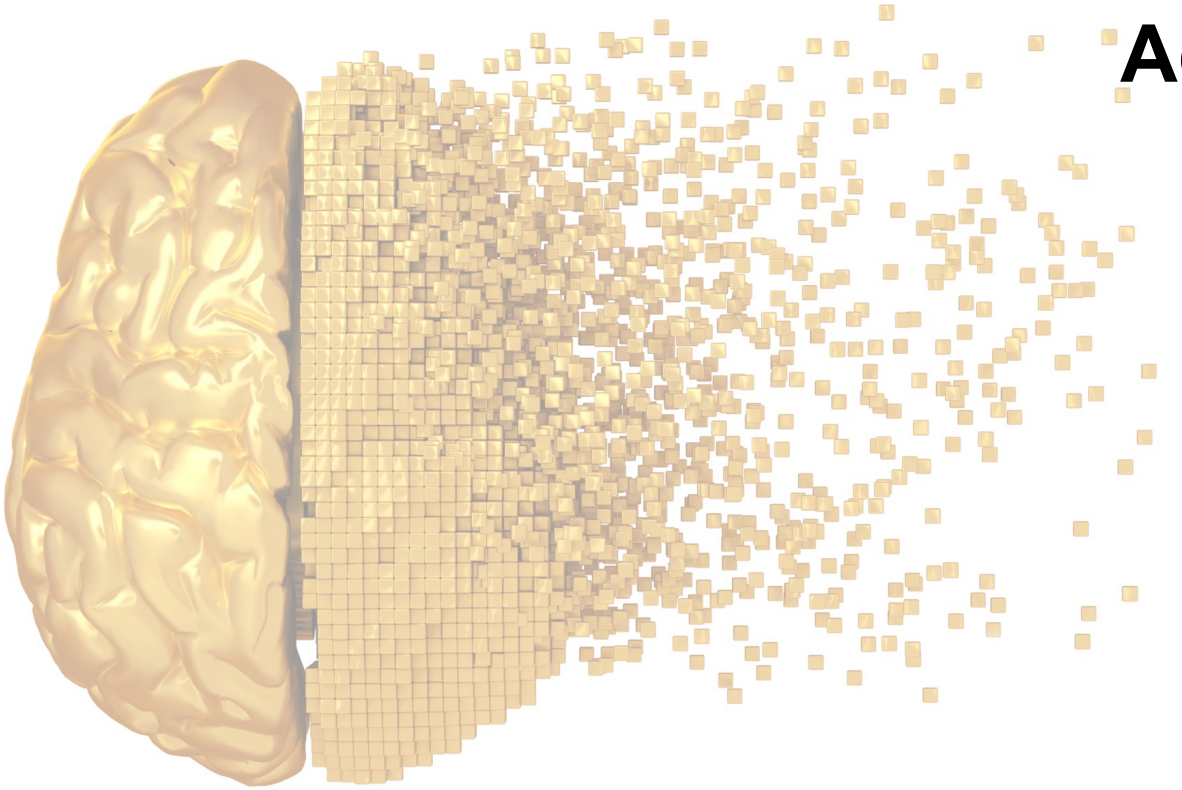
Neuromuscular junction in Alzheimer's disease



Agenor Limon, PhD

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Mitchell Center for Neurodegenerative Diseases

utmb Health

BBC

Why just two hours of exercise a week can be life-changing

7 January 2025

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Trends in Neurosciences

Review

Physical exercise, cognition, and brain health in aging

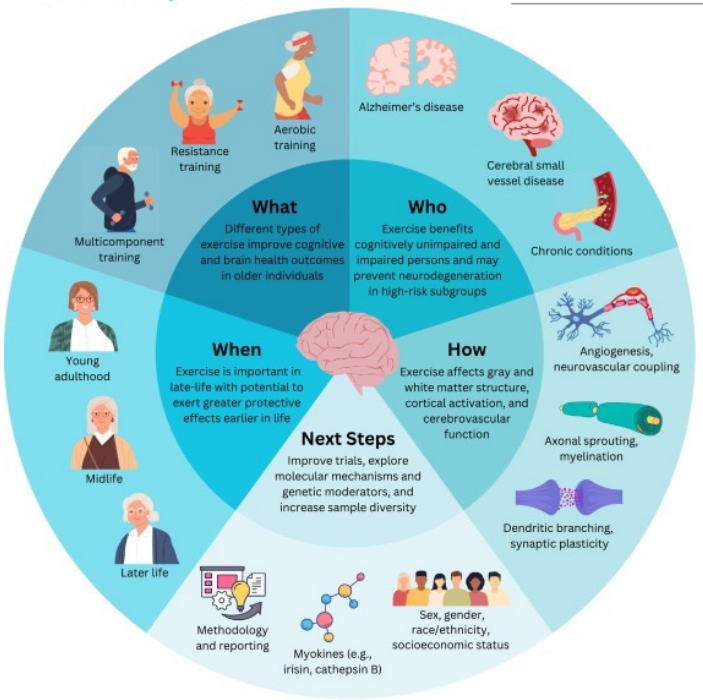
Nárlon C. Boa Sorte Silva[1,2,3], Cindy K. Barha[4,5], Kirk I. Erickson[6,7], Arthur F. Kramer[8,9], and Teresa Liu-Ambrose[1,2,3,*]

Exercise training is an important strategy to counteract cognitive and brain health decline during aging. Evidence from systematic reviews and meta-analyses supports the notion of beneficial eff
impaired older individuals. Howeve
fluenced by moderators such as exe

Highlights

frontiers in Psychology

REVIEW
published: 27 April 2018
doi: 10.3389/fpsyg.2018.00509

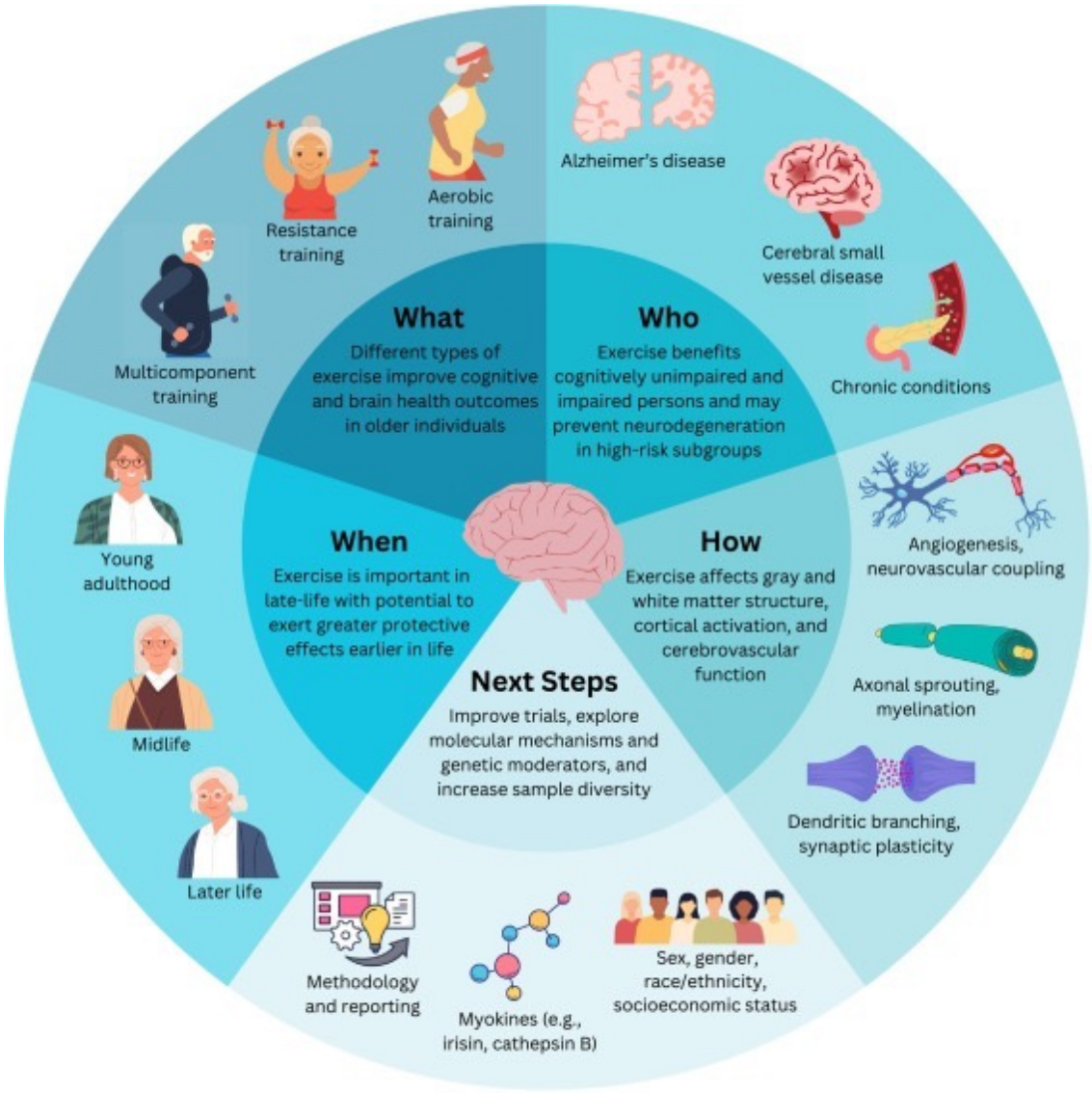


Trends in Neurosciences

Effects of Physical Exercise on Cognitive Functioning and Wellbeing: Biological and Psychological Benefits

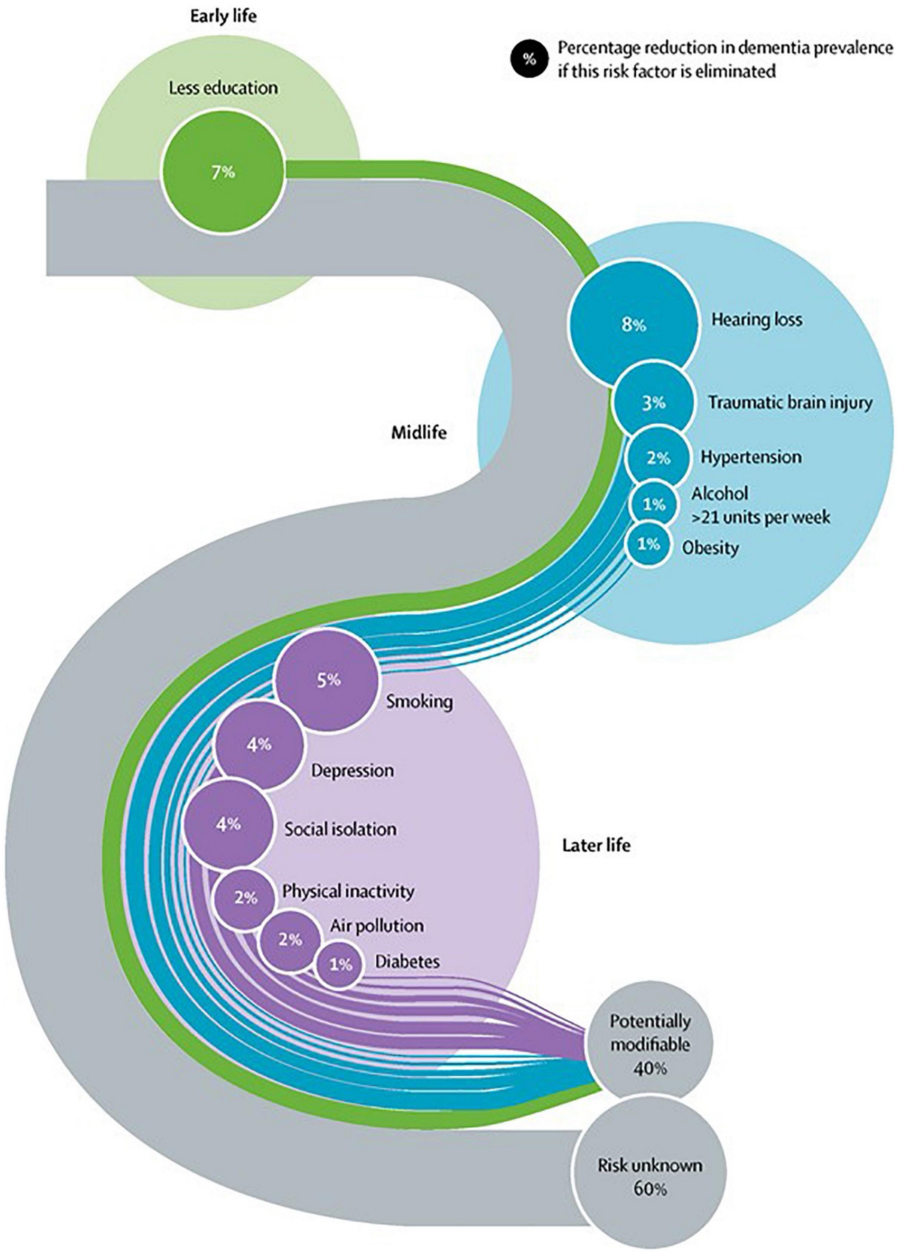
Laura Mandolesi[1,2], Arianna Polverino[1,3], Simone Montuori[1], Francesca Foti[2,4], Giampaolo Ferraioli[5], Pierpaolo Sorrentino[6] and Giuseppe Sorrentino[1,3,7]*

[1] Department of Movement Sciences and Wellbeing, Parthenope University of Naples, Naples, Italy, [2] IRCCS Fondazione Santa Lucia, Rome, Italy, [3] Istituto di Diagnosi e Cura Hermitage Capodimonte, Naples, Italy, [4] Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy, [5] Department of Science and Technology, Parthenope University of Naples, Naples, Italy, [6] Department of Engineering, Parthenope University of Naples, Naples, Italy, [7] Institute of Applied Sciences and Intelligent Systems, CNR, Pozzuoli, Italy

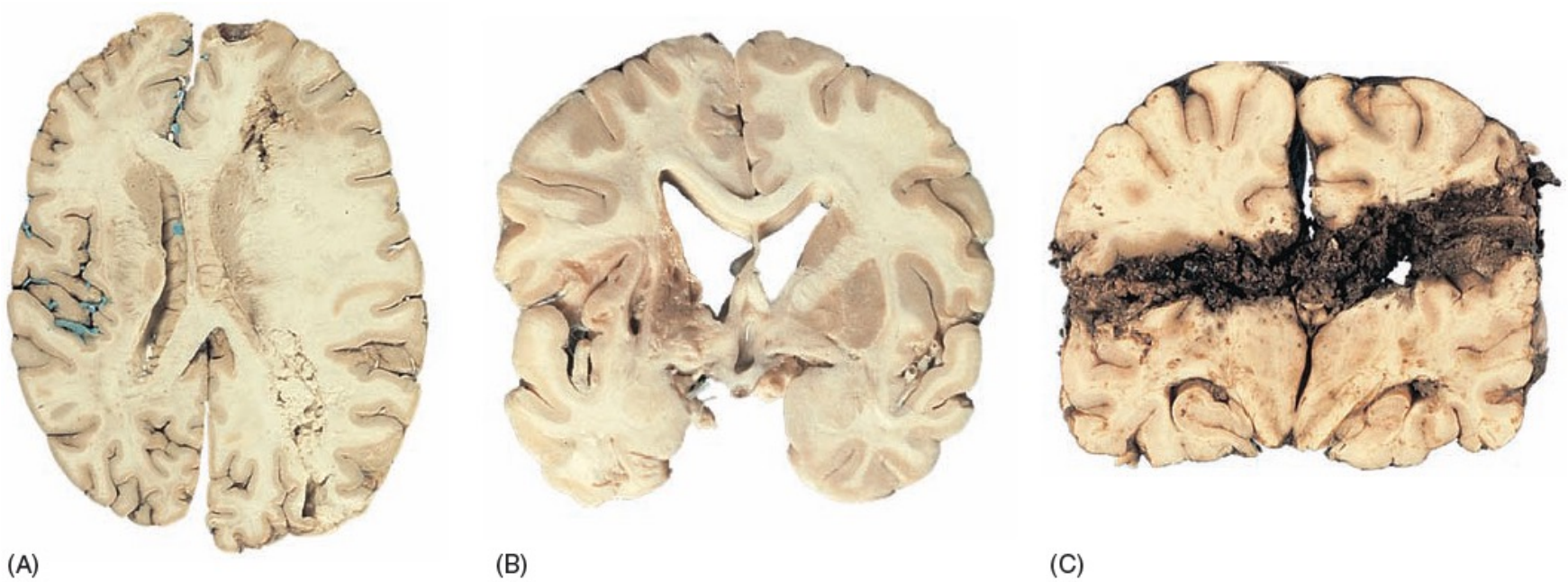


Trends in Neurosciences

40% risk of AD is modifiable



What is AD/ADRD?

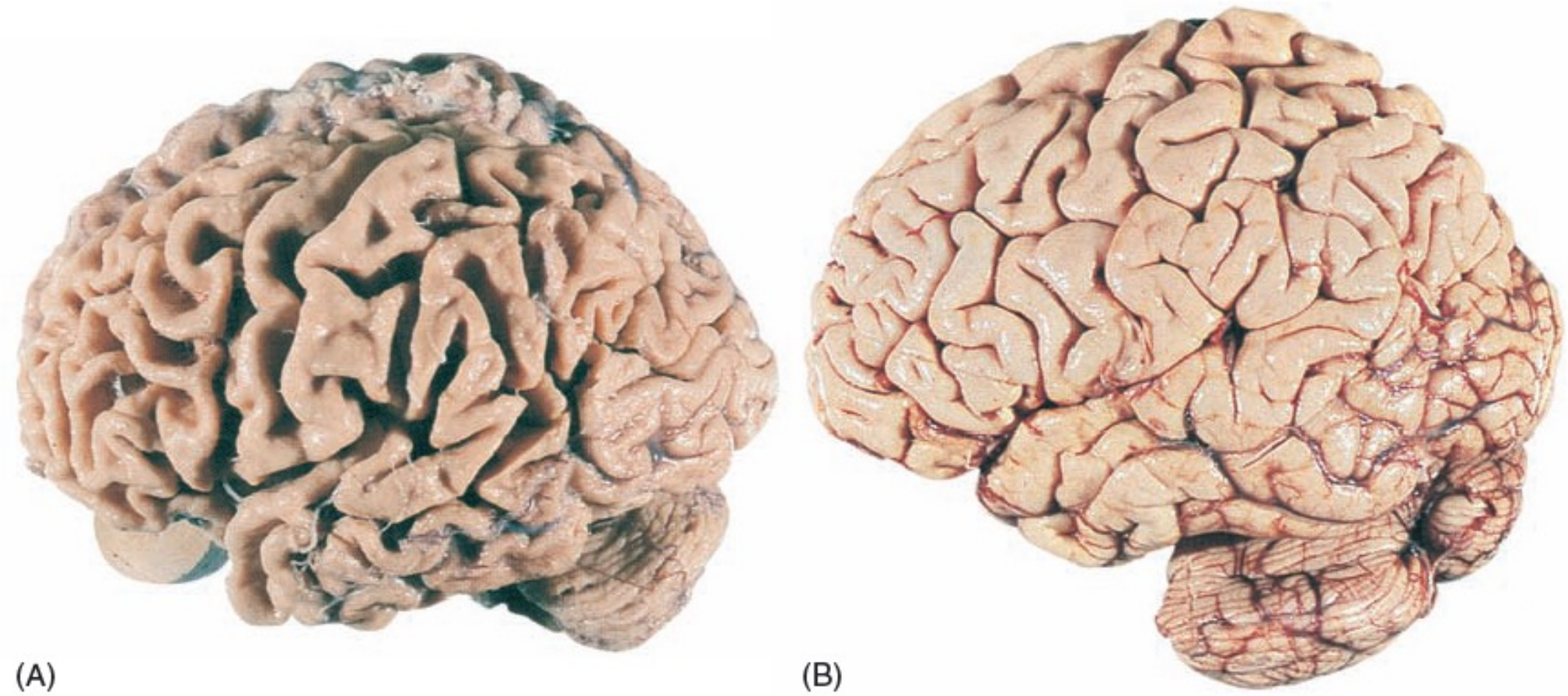


Damage to the human brain

- Stroke caused severe swelling of the right hemisphere
- Stroke caused cell loss in left hemisphere
- Gunshot wound

Brain with Alzheimer’s diseases

Normal Brain



(A)

(B)

Type of brain disorders

- **<u>Specific disorders (focal damage)</u>:** The disorder depends on the area of the brain affected (bullet wounds, strokes).

- **<u>Generalized disorders (widespread damage)</u>:** The disorder affect multiple cognitive abilities (closed head injury, dementing disorders, demyelinating diseases, toxic substances)

Dementing diseases

Loss of cognitive function, sometimes accompanied by personality changes, which interferes significantly with the individual's daily activities work and social activities

Stages: Mild, Moderate, Severe

Mild: Person retains judgment and can sustain daily activities on her/his own (personal hygiene, etc) but work and social activities are impaired.

Moderate: Independent living becomes hazardous (e.g., subject forgets to turn off the stove) and requires some degree of supervision.

Severe: Cognitive abilities are so compromised that the person requires constant supervision.

Types of dementias

- Dementias are divided in 3 varieties: Cortical, subcortical and mixed variety.

- **Cortical**: co-occurrence of many cognitive deficits including aphasia, apraxia, agnosia, acalculia, visuospatial deficits and memory problems (e.g. Alzheimer's, Frontotemporal dementias, Creutzfeldt-Jakob (prion diseases)

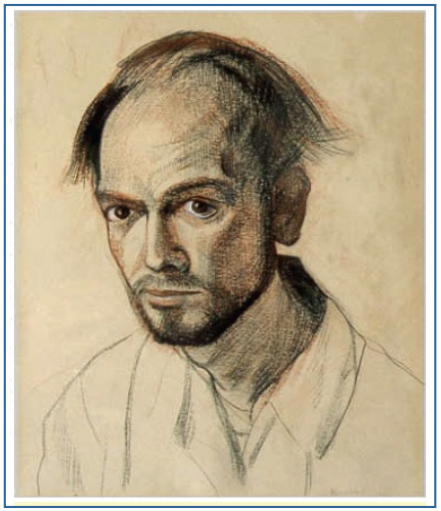
- **Subcortical:** more likely to manifest first as personality changes, attention deficits, slowness in cognitive processing, difficulties with tasks requiring strategy (e.g. Parkinson's, Huntington's).

- **Mixed**: Both cortical and subcortical involvement, patterns of cognitive performance midway between cortical and subcortical types (e.g. Vascular dementia, Lewy body dementia.)

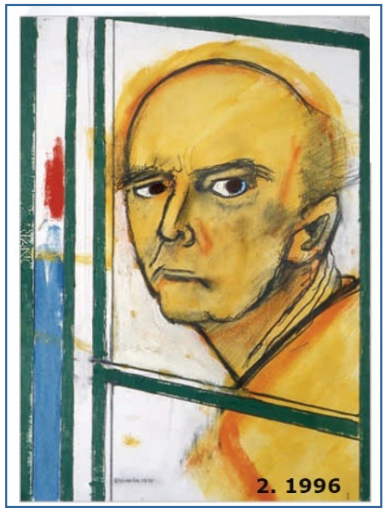
Alzheimer's Disease

What is Alzheimer's disease?

*An **irreversible** and **progressive** neurodegenerative disorder characterized by gradual loss of memory and other cognitive functions, deficits in activities of daily living, behavior, personality and judgment. Accounts for the majority of dementia cases among people age 65 and older.*



William Utermohlen 1967



1 year later of diagnose Alzheimer's Disease

5 years later

Alzheimer's disease numbers

- More than 5 million Americans have Alzheimer's Diseases today.
- Someone develops AD every 68 seconds
- By 2050, the number of people living with AD could triple.
- It is the 6th cause of death in the United States. Right now, 1 in 3 seniors dies with Alzheimer's or another dementia.

Alzheimer's Disease Progression

Mild Cognitive Impairment

AD Progression

Death from pneumonia and/or other comorbidities

Mild

- Loss of recent memory
- Faculty judgment
- Personality changes

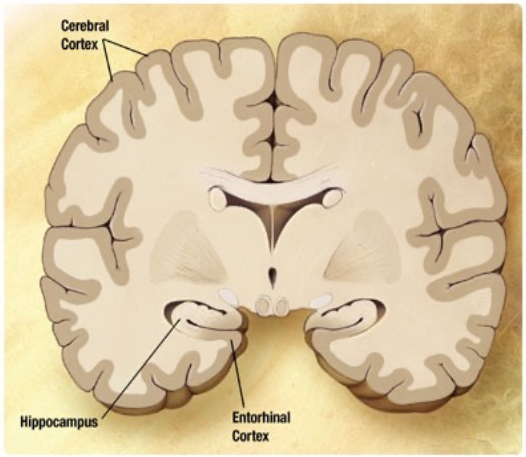
Moderate

- Verbal and physical aggression
- Agitation
- Wandering
- Sleep disturbances
- Delusions

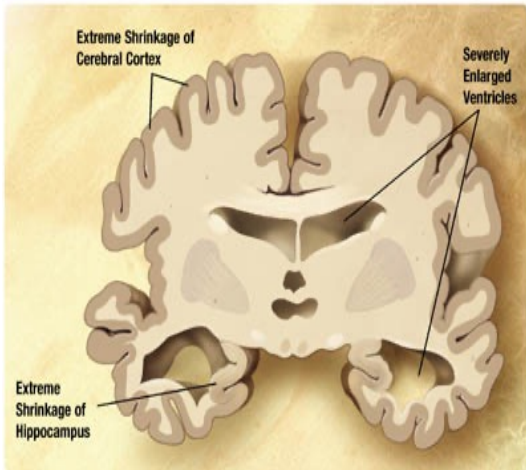
Severe

- Loss of all reasoning
- Bedridden
- Communication disability

Preclinical AD

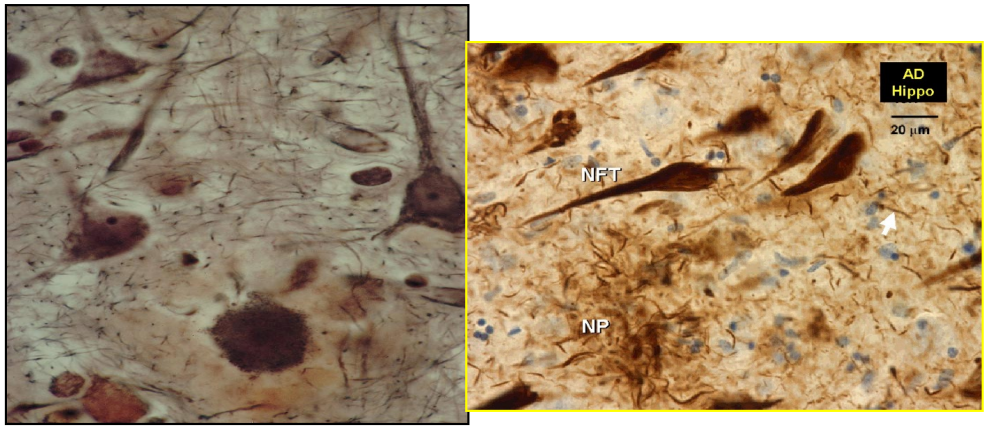


Severe AD

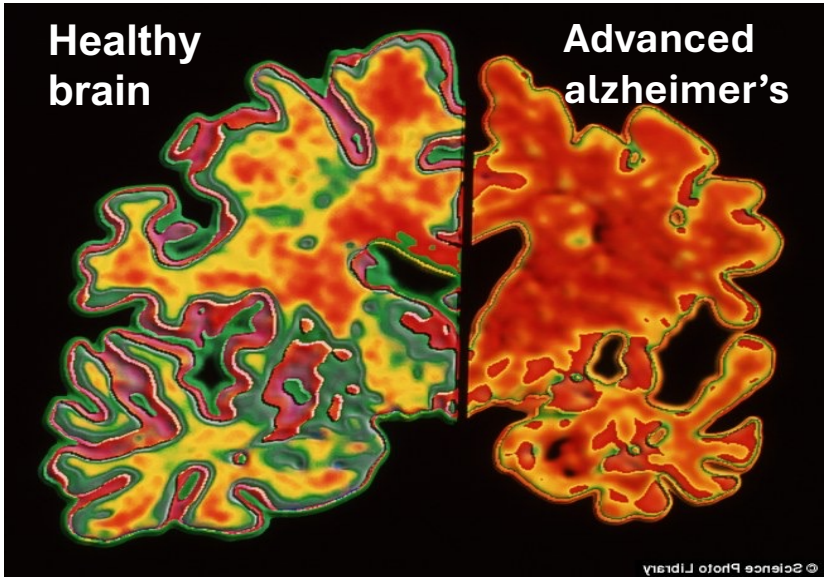


Alzheimer's Disease Pathology

- **Amyloid plaques**
  Insoluble extracellular deposits which accumulate in the cortex and hippocampus.
  Composed of amyloid – beta (Aß) protein fragments: Aß40 and Aß42.



- **Neurofibrillary tangles**
  Bundles of insoluble helical fibers within neurons.
  Composed of hyperphosphorylated tau proteins that are normally associated with microtubules.



- **Intensive loss of synaptic contacts and neurons. Cortical atrophy: loss of 1/3 of brain mass**
- **Other effects may contribute such as inflammation**

Alzheimer's Disease Risk Factors

Scientists don't yet fully understand what causes Alzheimer's disease (AD), but it is clear that it develops as the result of a complex series of events that take place in the brain over a long period of time. It is likely that the causes include genetic, environmental, and lifestyle factors. Because people differ in their genetic make-up and lifestyle, the importance of these factors for preventing or delaying AD differs from person to person.

Aging

- Progressive increase in the amounts of oxidatively modified DNA bases, lipids and proteins in the brain
- Alteration in multiple neurotransmitters and neurotrophic factor signaling pathway
- Increase expression of pre-apoptotic proteins

Family history of dementia

- Susceptibility/risk genes

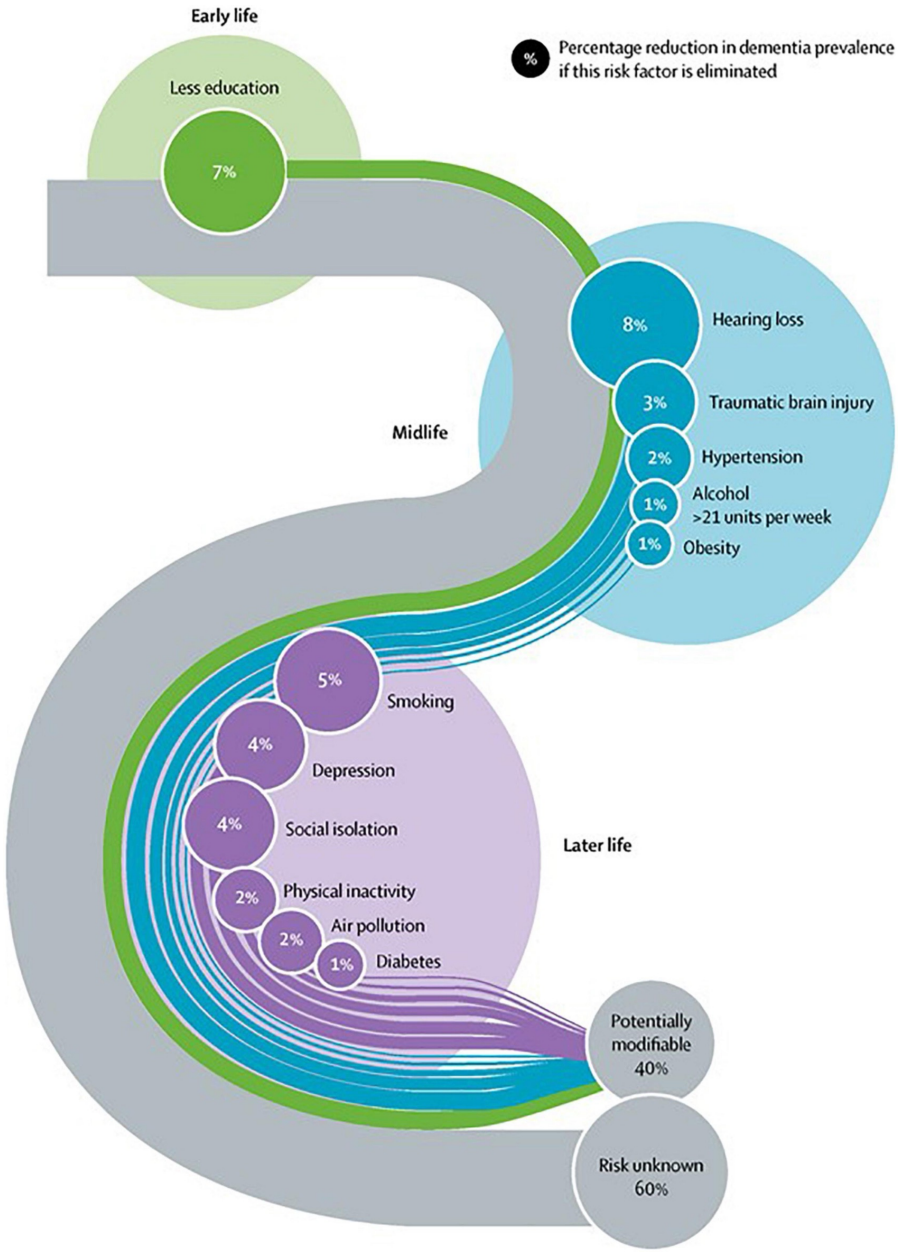
Cardiovascular Disease

- High blood pressure and high cholesterol levels
- Stroke, Ischemia.

Gender

Lower educational level

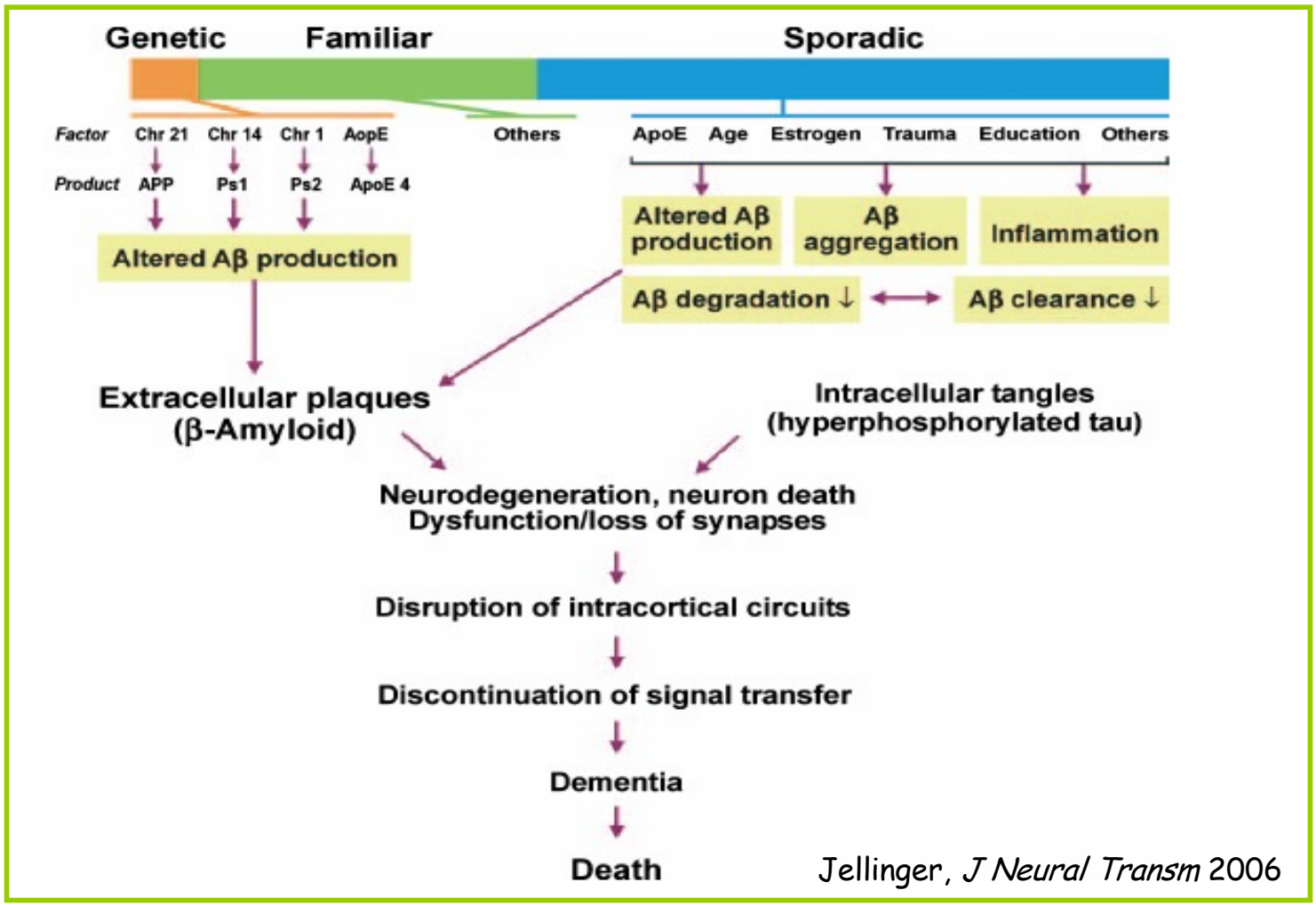
Life style


Early life
Less education
7%
% Percentage reduction in dementia prevalence if this risk factor is eliminated
Midlife
8% Hearing loss
3% Traumatic brain injury
2% Hypertension
1% Alcohol >21 units per week
1% Obesity
5% Smoking
4% Depression
4% Social isolation
Later life
2% Physical inactivity
2% Air pollution
1% Diabetes
Potentially modifiable 40%
Risk unknown 60%

Types of Alzheimer

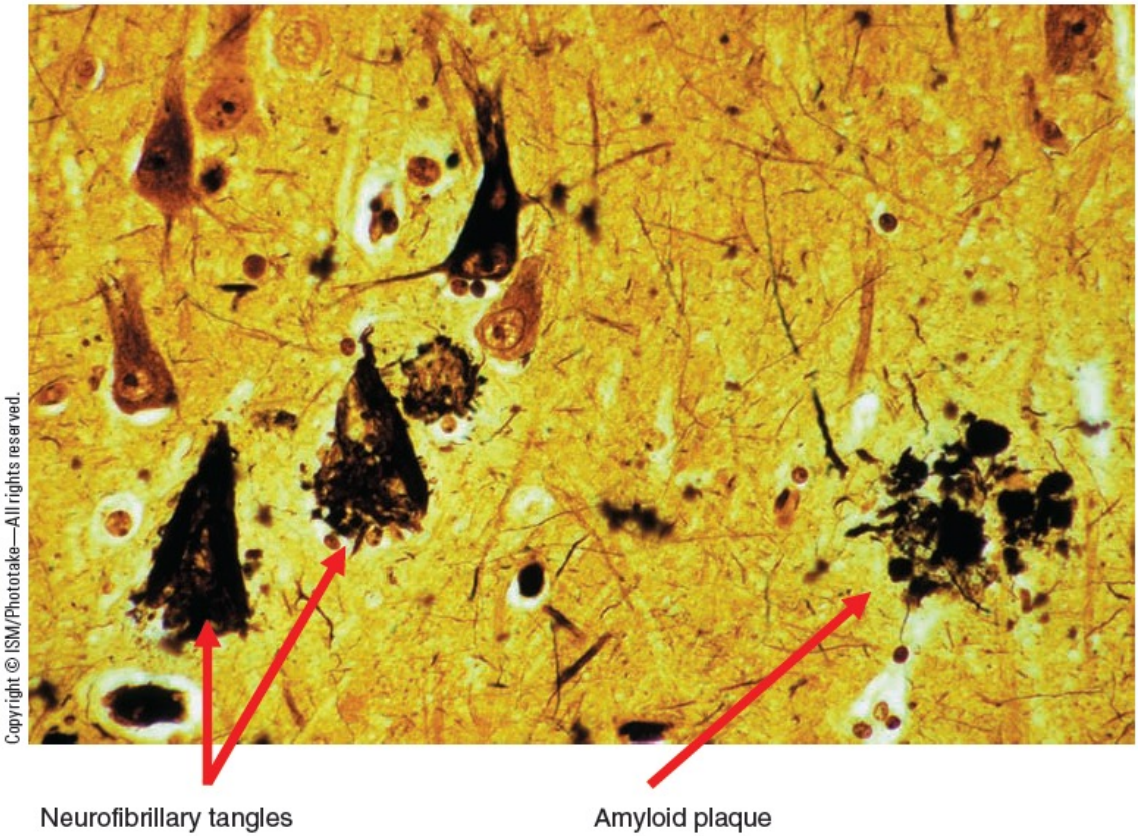
Early-Onset AD
(Familiar)

Late-Onset AD
(Sporadic)

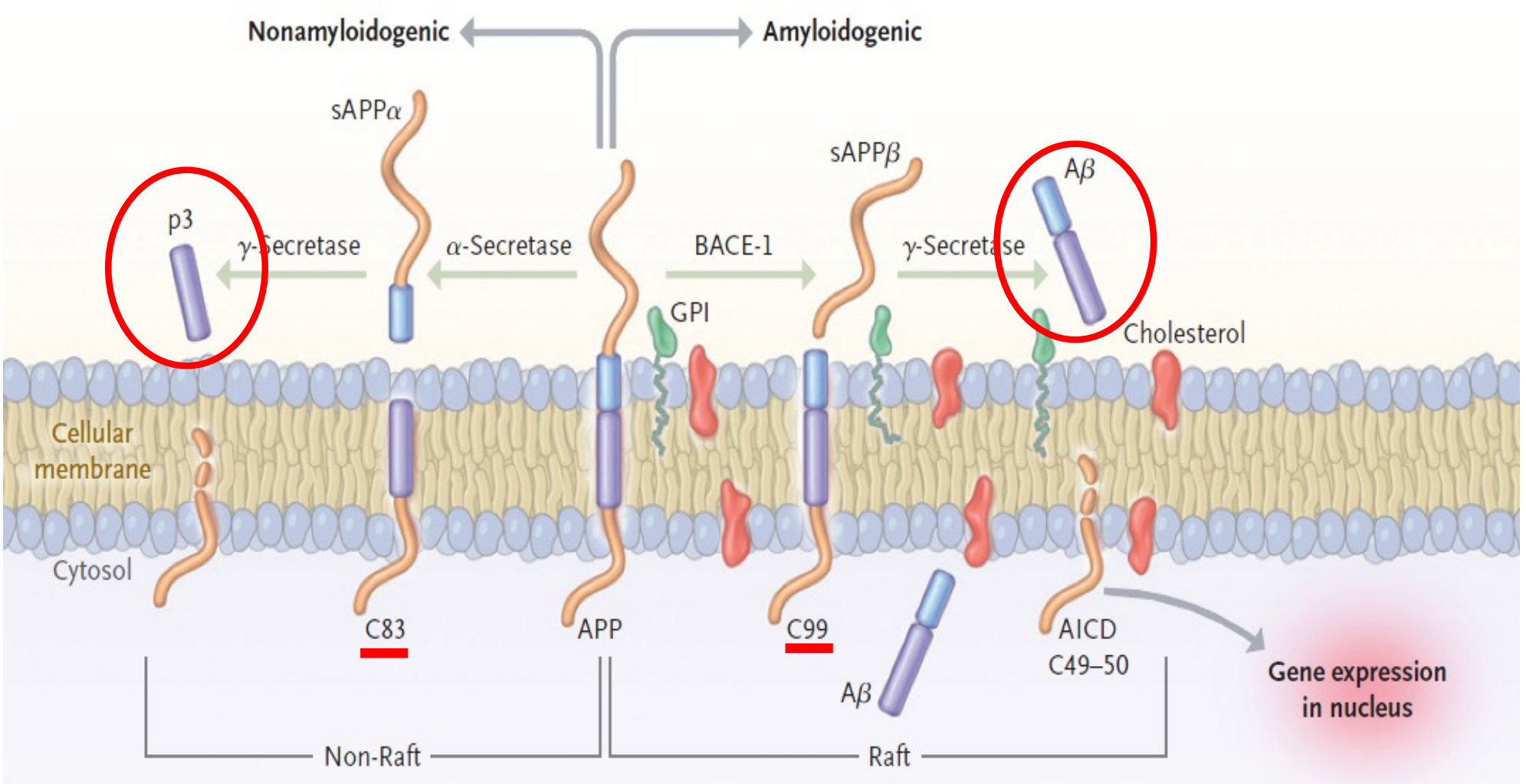


Jellinger, *J Neural Transm* 2006

Neurofibrillary tangles and senile plaques in Alzheimer's disease.

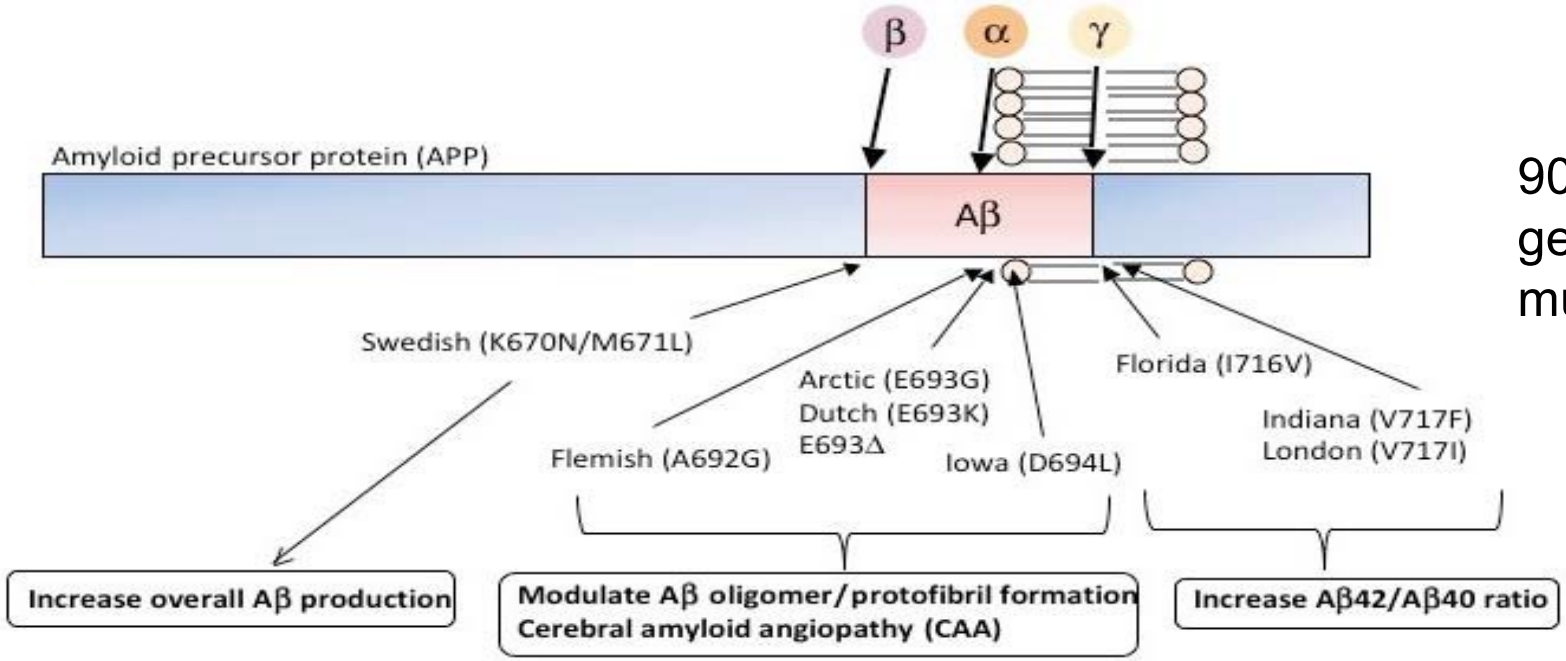


Processing of Amyloid Precursor Protein



(Querfurth and LaFerla . The New. England J of Mediciene 2010)

Amyloid Precursor Protein (APP) mutations



90 known genetic mutations

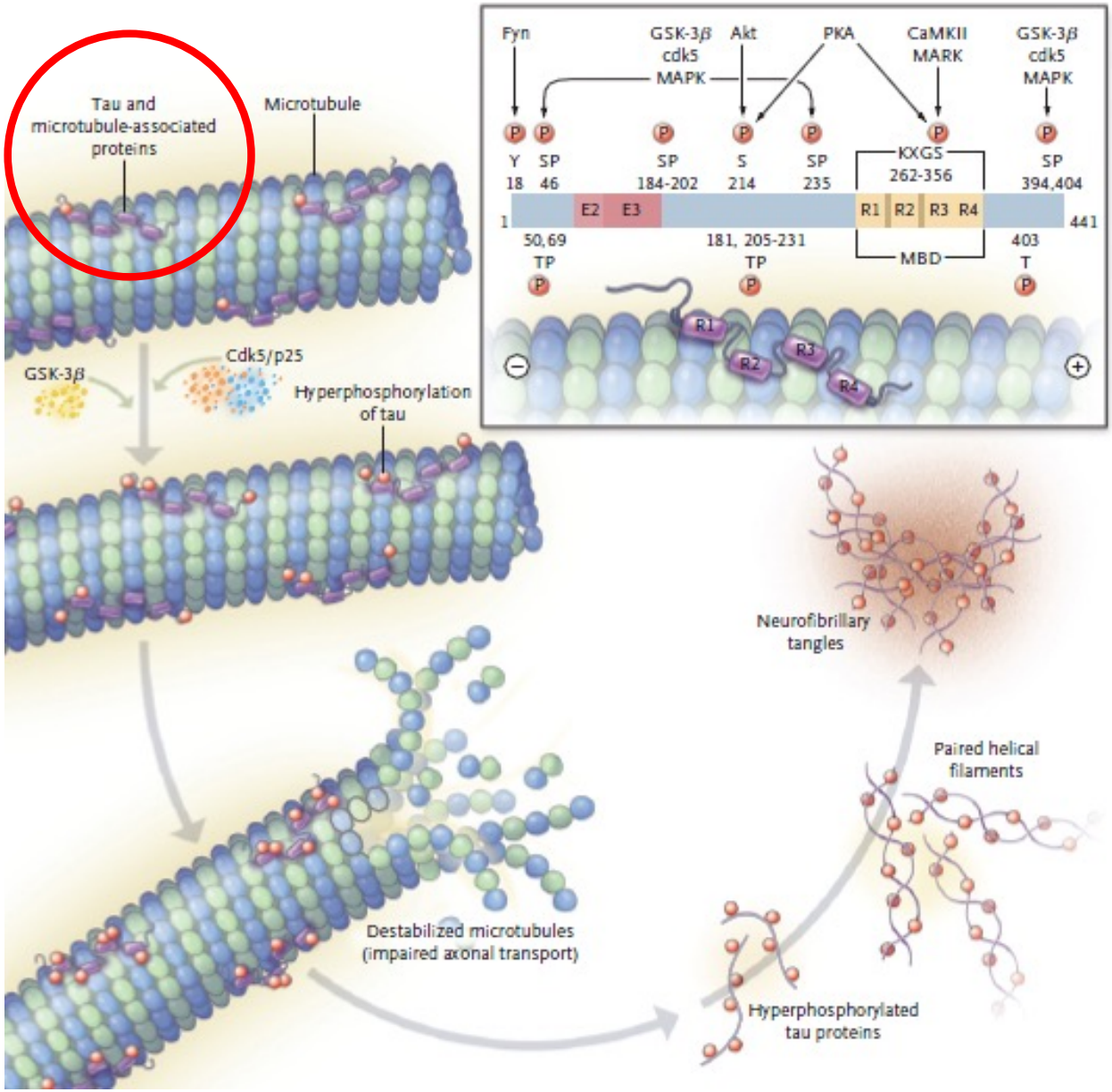
(http://www.alzforum.org/res/com/tra/app/default.asp)

(Kitazawa et al., 2012. Curr Pharm Des)

https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002270

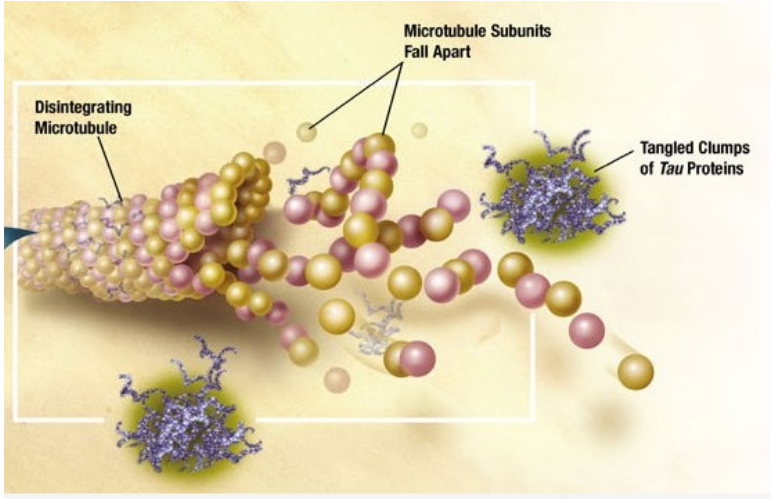
Tau Structure and Function

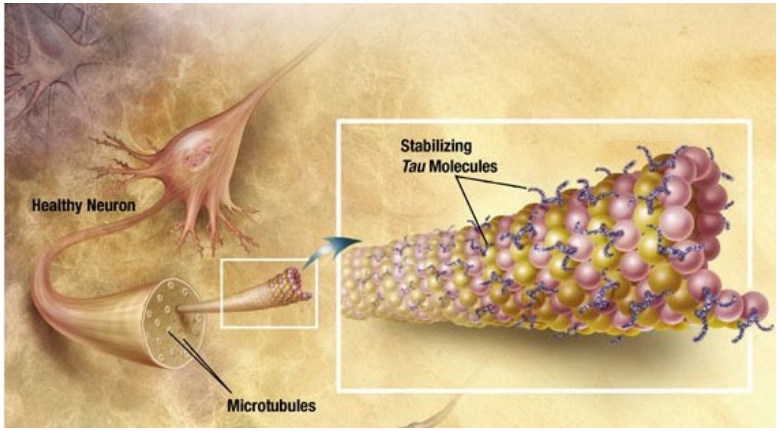
Tau proteins stabilize microtubules (MT) in neurons, particularly in axonal processes.
MT main functions are to provide structure, organize the cytoplasm of the cell, and serve as tracks for the transport of cellular elements form the cell body to the axonal terminals (synapses) --



(Querfurth and LaFerla . The New. England J of Mediciene 2010)

Tau protein

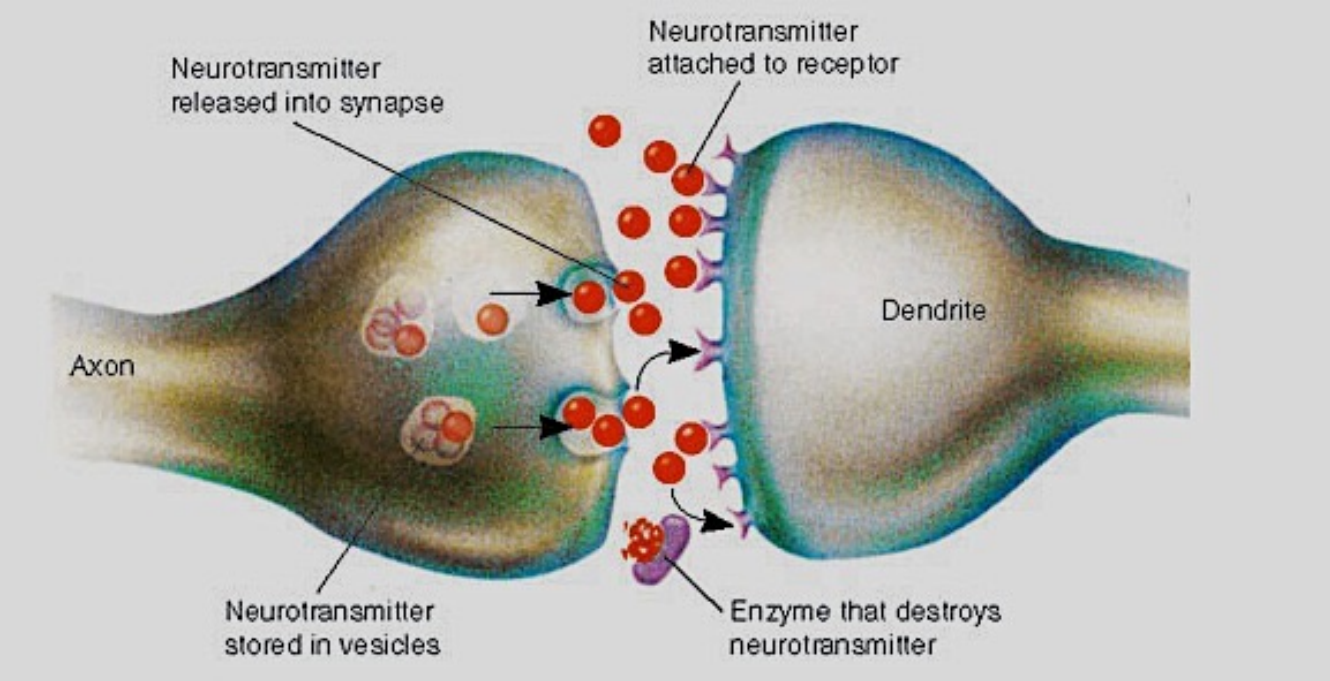


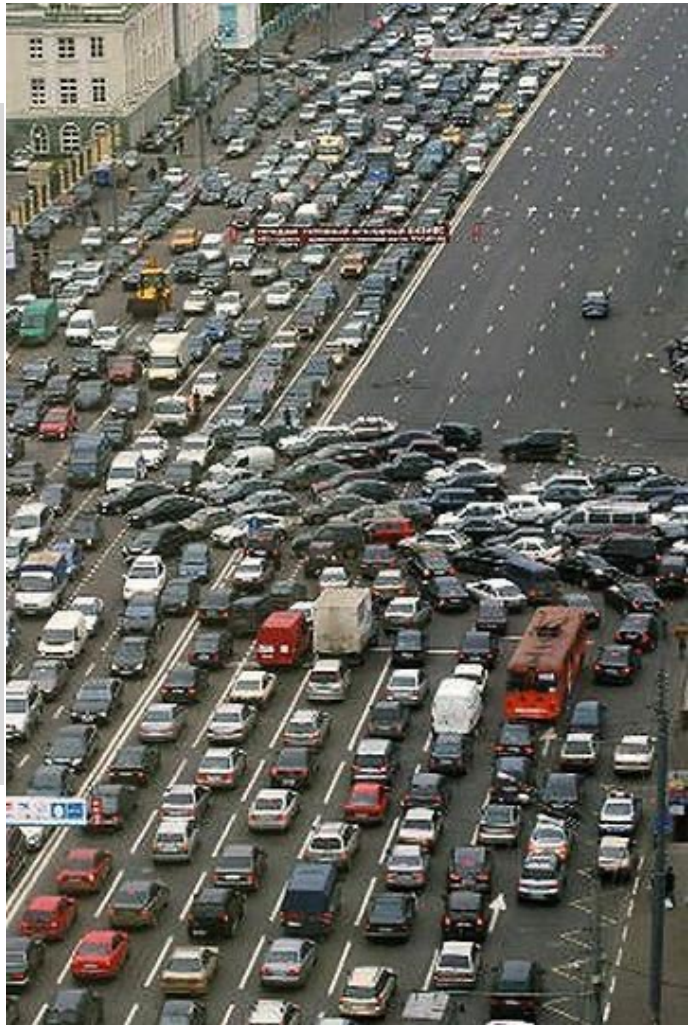


- In AD and other tauopathies, for unknown reasons, tau protein becomes hyperphosphorylated, dettaches from MTs, and form paired helical filaments (PHF) that clump inside neurons forming neurofibrillary tangles (NFT), which eventually occupy most of the cytoplasm of the affected neurons.
- The release of tau destabilizes the MTs leading to their disintegration.
- The loss of MTs will affect axonal transport and neuronal morphology, which is also sustained by the microtubular network.

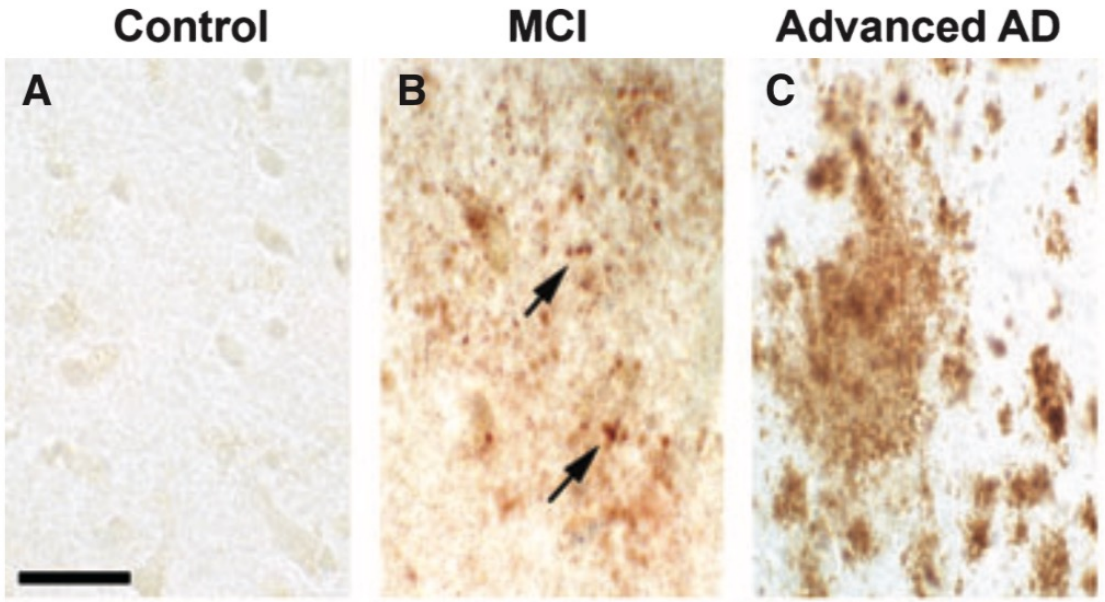
Tau protein

Neurons have a unique shape and depend on the cytoskeleton, particularly MTs, to keep axonal transport running from the cell body to synaptic terminals – the loss or the alteration of axonal transport caused by tau pathology can be compared to a bad traffic jam in neuronal processes



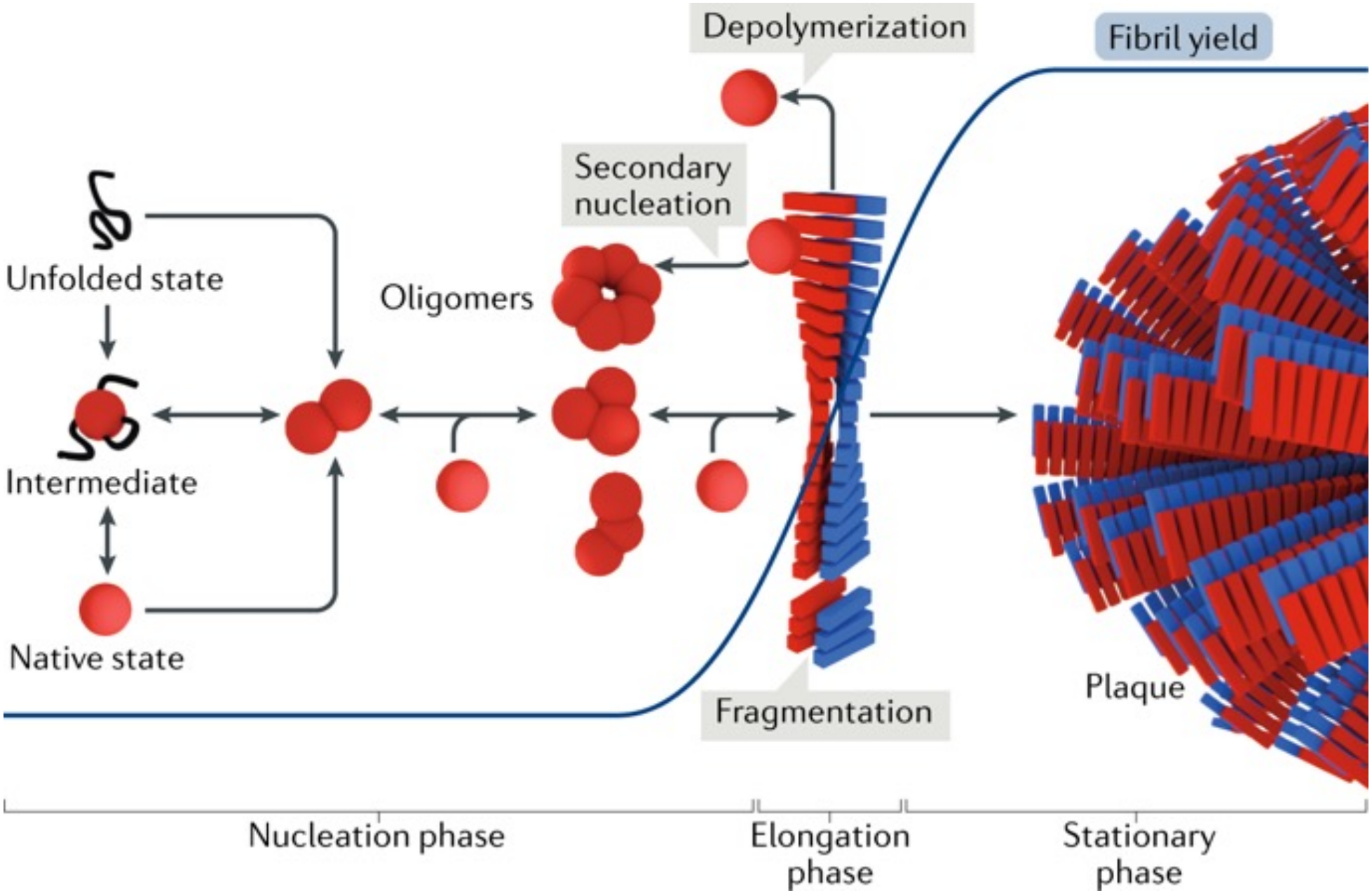


20 years before the symptoms appear there are already changes in the brain

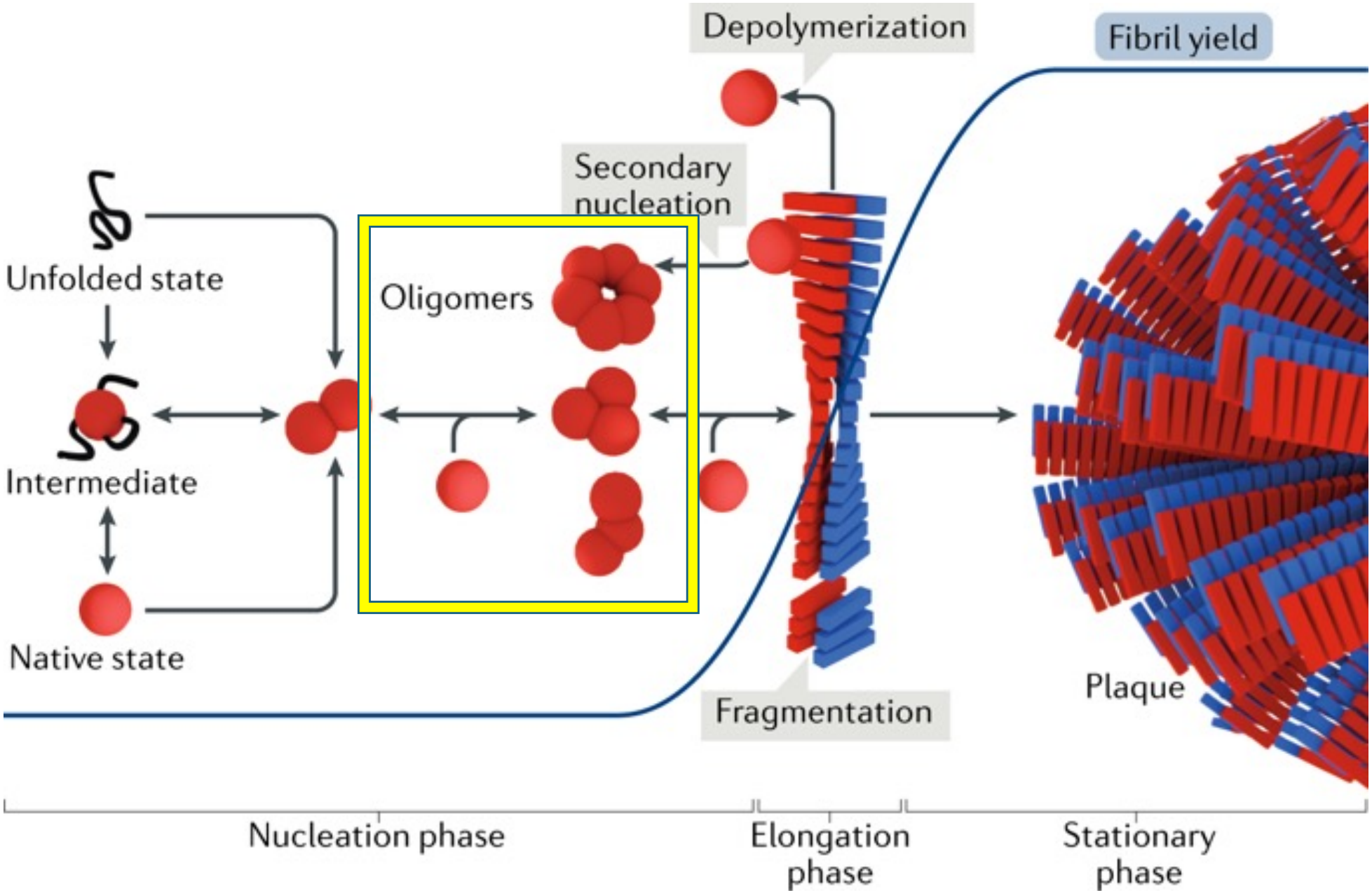


Pham et al., 2010

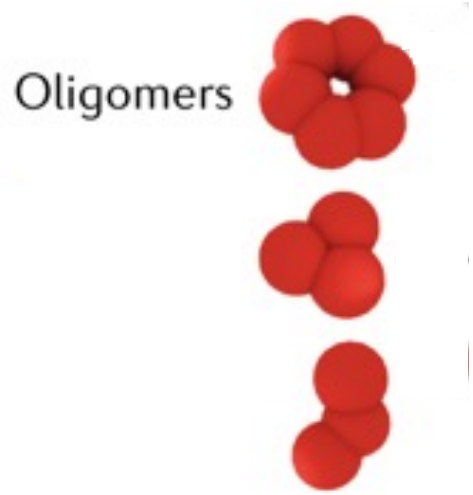
Toxic effects of Aβ starts before plaque formation



Toxic effects of Aβ starts before plaque formation



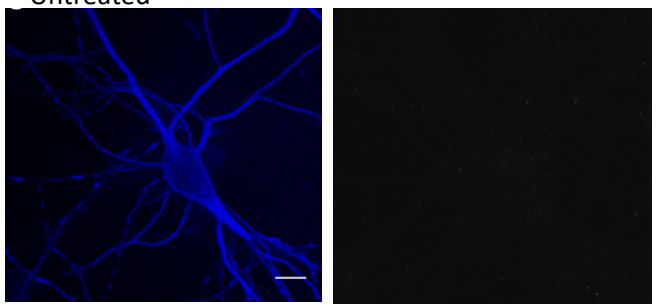
Toxic effects of Aβ starts before plaque formation



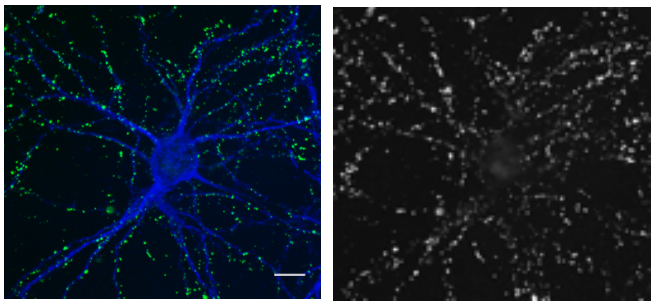
Most evidence indicate that oligomers are responsible for cognitive impairment.

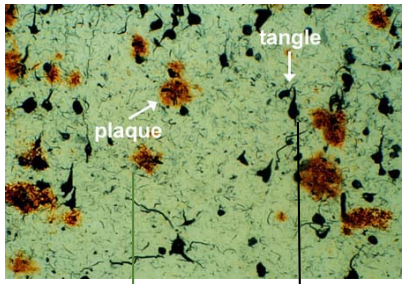
Oligomeric species of Aβ and Tau target synapses and disrupt their function

Untreated



500 nM Aβ oligomers



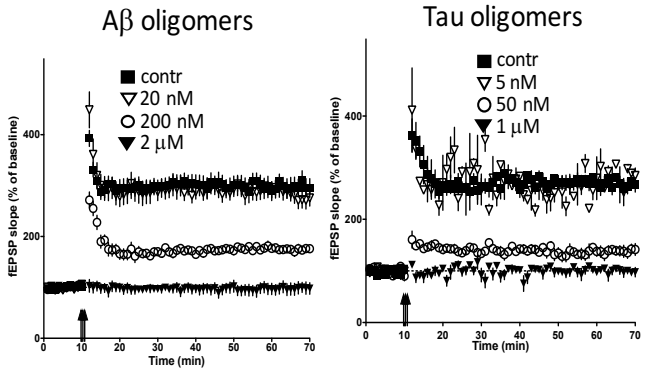


Aβ oligomers

Tau oligomers

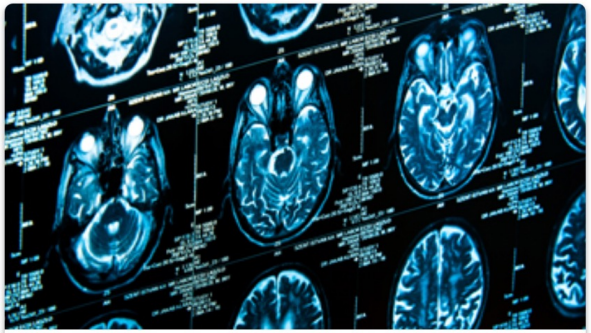
Synaptic spine

LTP expression in hippocampal slices (Schaffer collateral)



Navigating Treatment Options

Progress in Alzheimer's research has created promising new treatments. Learn about the different drugs so you can discuss the options with a doctor.

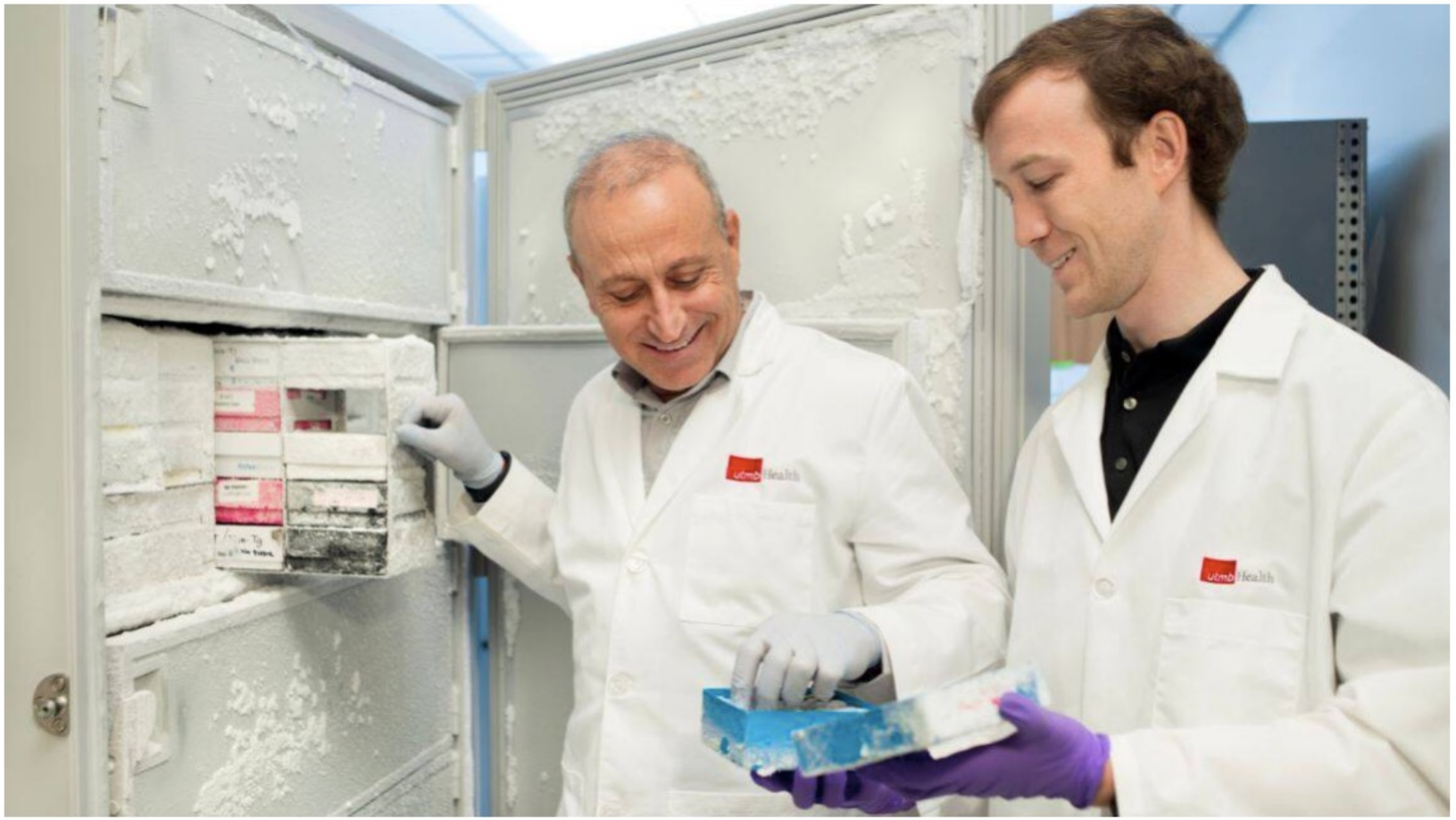


Donanemab Approved for Treatment of Early Alzheimer's Disease

Donanemab (Kisunla™) has received traditional approval from the FDA for the treatment of early Alzheimer's disease.

Lecanemab Approved for Treatment of Early Alzheimer's Disease

Lecanemab (Leqembi®) has received traditional approval from the FDA for the treatment of early Alzheimer's disease.



Dr. Rakez Kayed: Leading the Fight against Neurodegenerative Diseases One Protein at a Time

While the search for more treatments for AD/ADRD continue, current therapies have strengthened the efforts to detect the earliest possible AD for therapeutical intervention and prevention

FUNCTION, 2023, 5(1): zqad066

https://doi.org/10.1093/function/zqad066
Advance Access Publication Date: 4 December 2023
Original Research

RESEARCH ARTICLE

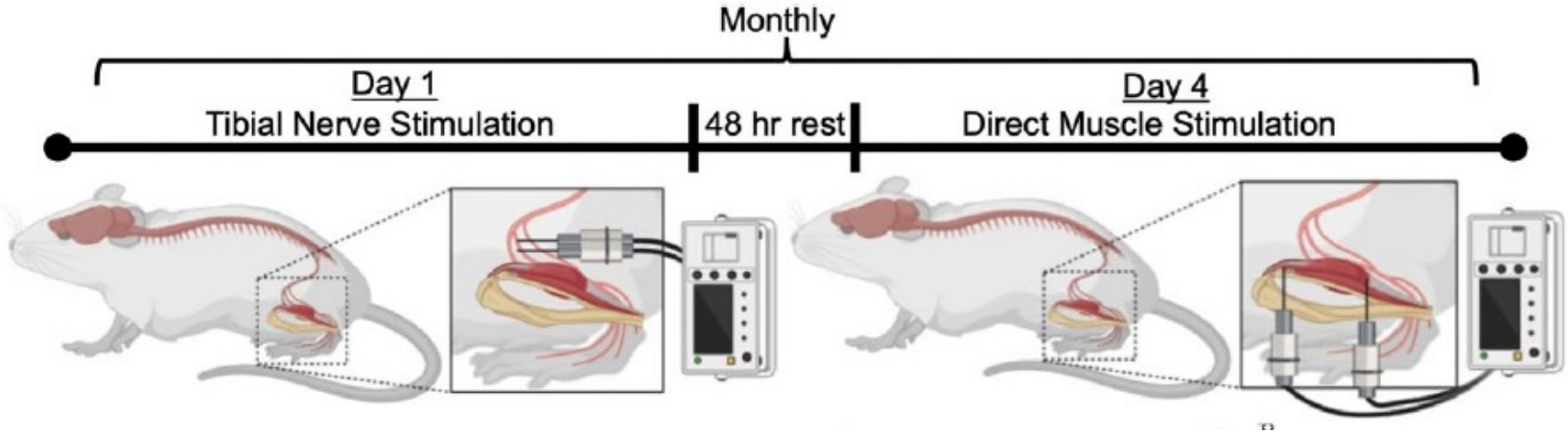
Neuromuscular Dysfunction Precedes Cognitive Impairment in a Mouse Model of Alzheimer's Disease

Matthew H. Brisendine[1], Anna S. Nichenko[1], Aloka B. Bandara[1], Orion S. Willoughby[1], Niloufar Amiri[1], Zach Weingrad[2], Kalyn S. Specht[1], Jacob M. Bond[3], Adele Addington[1], Ronald G. Jones, III[4], Kevin A. Murach[4], Steven Poelzing[3], Siobhan M. Craige[1,3], Robert W. Grange[1], Joshua C. Drake[1,3,*]

[1]Department of Human Nutrition, Foods, and Exercise, Virginia Tech, Blacksburg, VA 24061, USA, [2]Department of Biological Sciences, Virginia Tech, Blacksburg, VA 24061, USA, [3]Translational Biology, Medicine, and Health Program, Virginia Tech, Roanoke, VA 24016, USA and [4]Department of Health, Human Performance, and Recreation, University of Arkansas, Fayetteville, AR 72701, USA

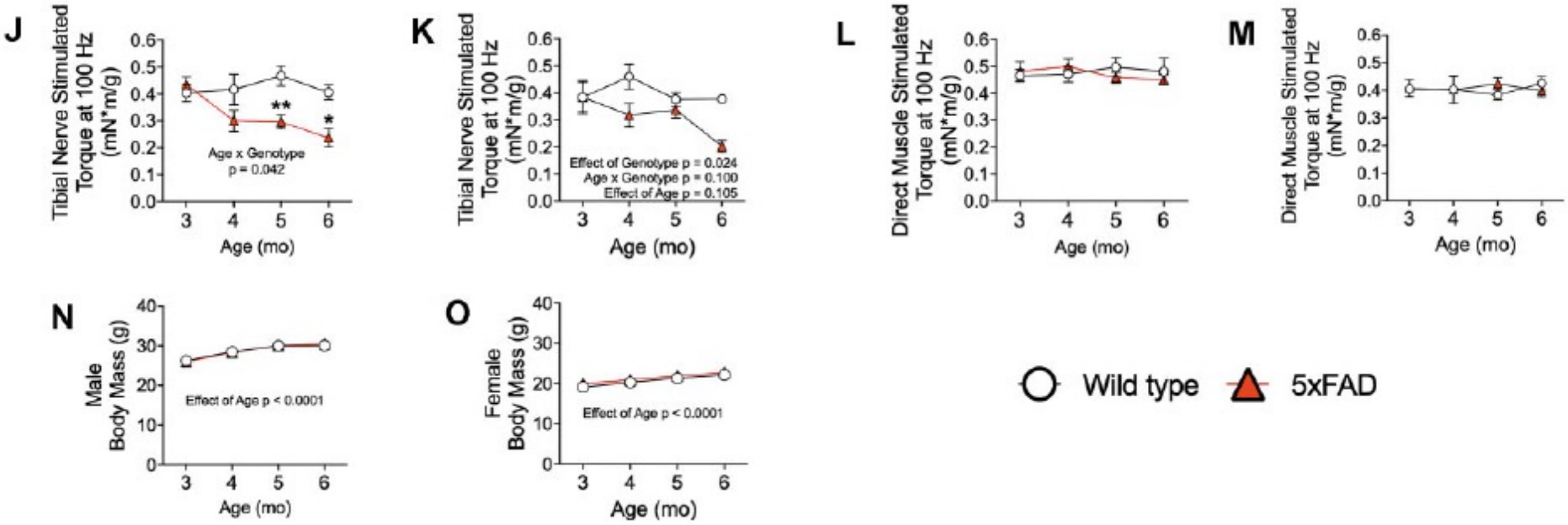
*Address correspondence to J.C.D. (e-mail: joshuacd@vt.edu)

Alterations in NMJ transmission on animal models of AD



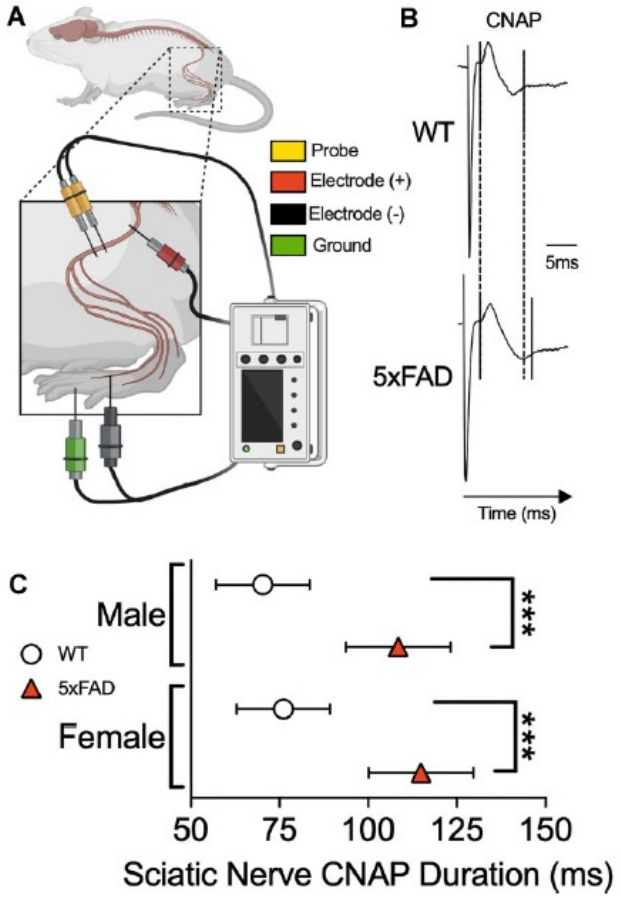
Male

Female



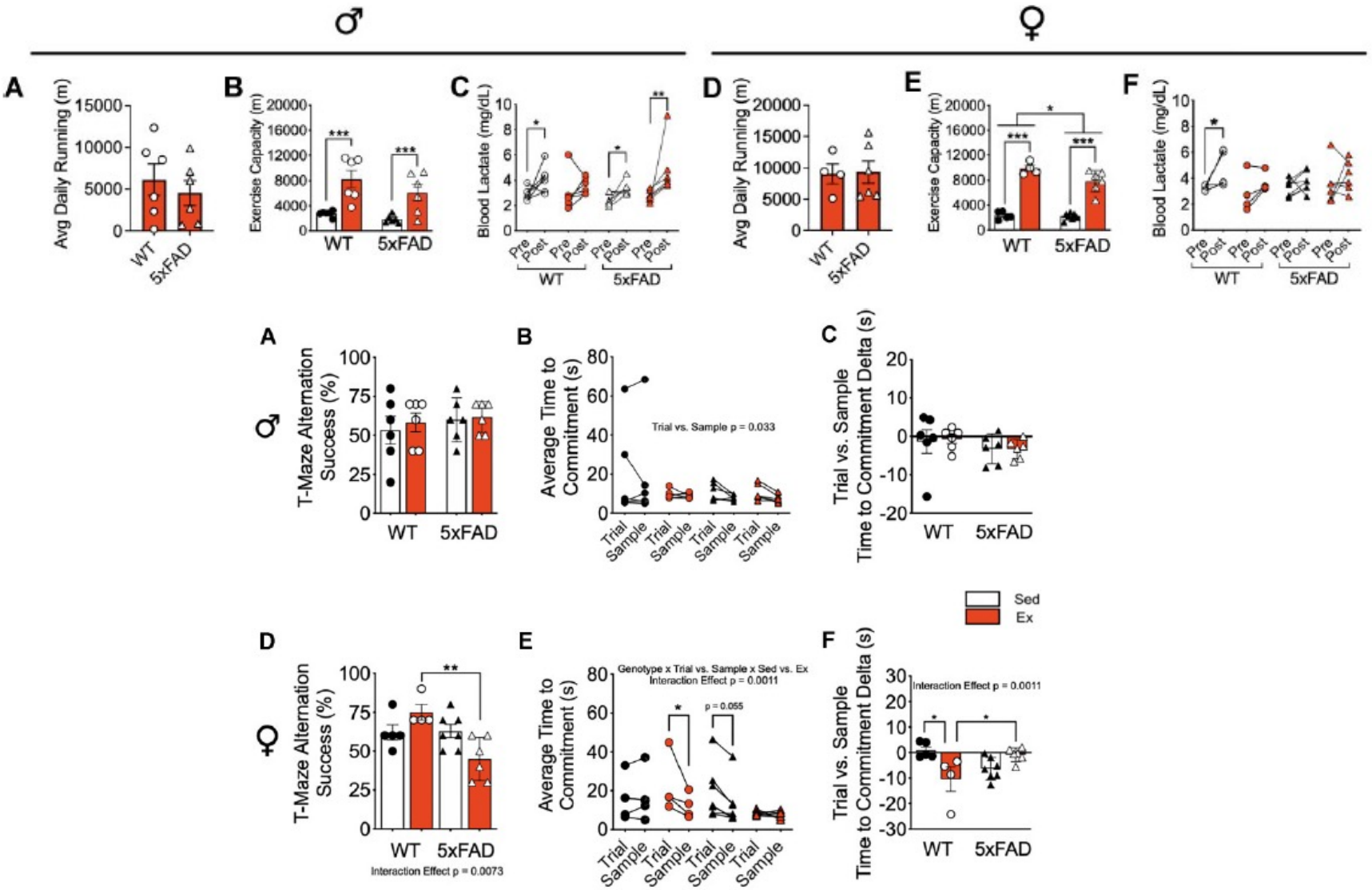
Brisendine et al., 2023

Alterations in NMJ transmission on animal models of AD



Brisendine et al., 2023

Effects of exercise on hearth capacity and cognition



Brisendine et al., 2023

OPEN

Sarcopenia is a predictor for Alzheimer's continuum and related clinical outcomes

Jeonghun Kim[1,7], Sang-Il Suh[2,7], Yu Jeong Park[3], Minwoong Kang[4], Su Jin Chung[5], Eun Seong Lee[6], Hye Na Jung[2], Jae Seon Eo[6], Seong-Beom Koh[3], Kyungmi Oh[3,8]✉ & Sung Hoon Kang[3,8]✉

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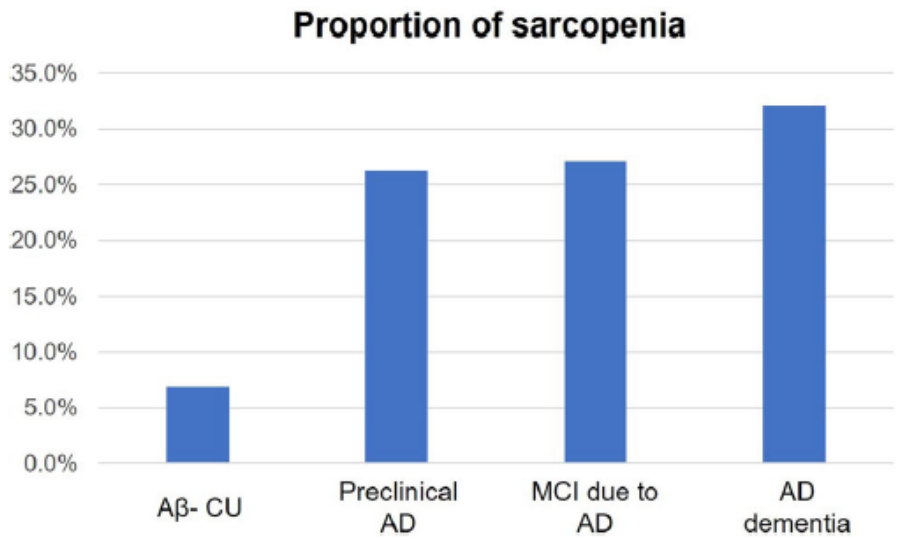
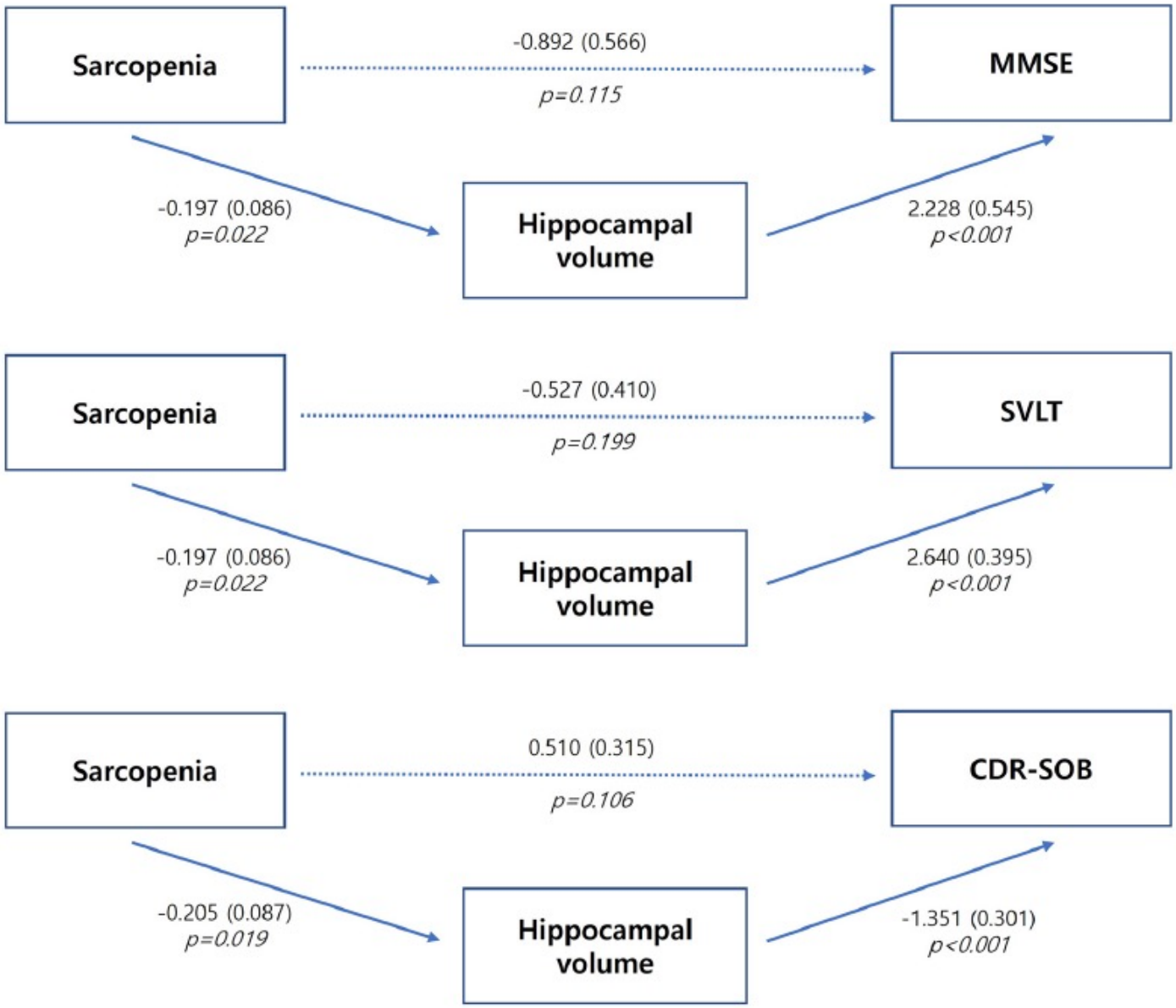
	Total (n = 200)	With sarcopenia (n = 44)	Without sarcopenia (n = 156)	*p* value
Disease stage				0.010
Aβ-CU	58 (29.0%)	4 (9.1%)	54 (34.6%)	
Preclinical AD	19 (9.5%)	5 (11.4%)	14 (9.0%)	
MCI due to AD	96 (48.0%)	26 (59.1%)	70 (44.9%)	
AD dementia	27 (13.5%)	9 (20.5%)	18 (11.5%)	
Demographics				
Age, years	72.3 ± 6.6	73.8 ± 5.7	71.8 ± 6.8	0.078
Sex, female	146 (73.0%)	33 (75.0%)	113 (72.4%)	0.884
Education, years	9.2 ± 4.4	8.2 ± 3.1	9.4 ± 4.7	0.052
Hypertension	95 (47.5%)	27 (61.4%)	68 (43.6%)	0.056
Diabetes	45 (22.5%)	15 (34.1%)	30 (19.2%)	0.511
APOE4, carriers	90 (45.0%)	25 (56.8%)	65 (41.7%)	0.107
Clinical implication				
HV, mL	3.50 ± 0.51	3.27 ± 0.45	3.57 ± 0.51	0.001
MMSE	25.5 ± 3.6	23.7 ± 4.1	26.0 ± 3.4	< 0.001
SVLT	3.5 ± 3.3	1.9 ± 3.0	3.9 ± 3.3	< 0.001
CDR-SOB	1.6 ± 1.8	2.5 ± 2.3	1.4 ± 1.5	0.009

	Hippocampal volume	
	*β (SE)	*p* value
Sarcopenia	−0.206 (0.087)	0.020
Age	−0.013 (0.007)	0.053
Sex	0.238 (0.017)	0.028
Education years	0.001 (0.009)	0.885
Hypertension	0.048 (0.081)	0.554
Diabetes	−0.091 (0.091)	0.920



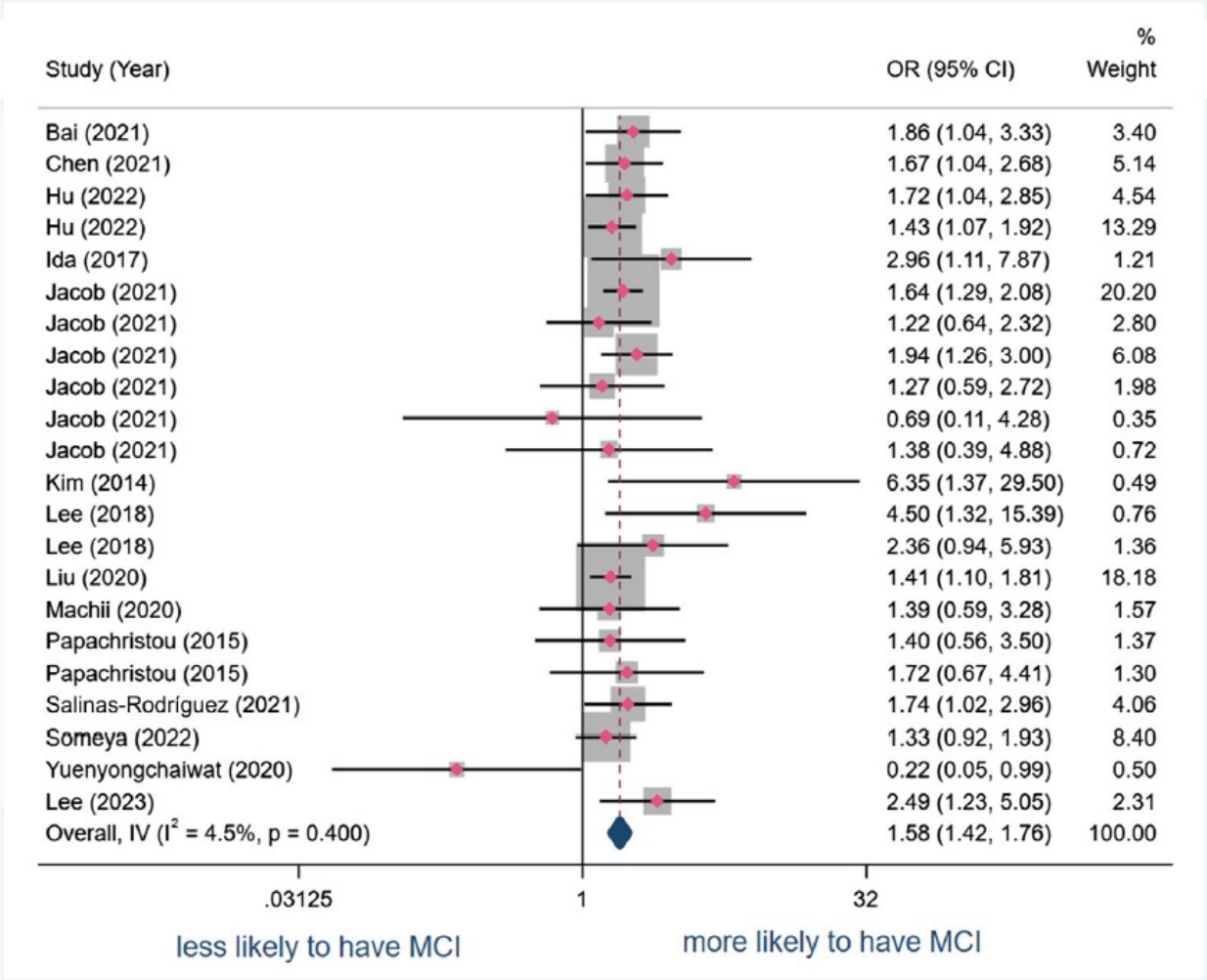

Sarcopenia
-0.892 (0.566)
p=0.115
MMSE
-0.197 (0.086)
p=0.022
Hippocampal volume
2.228 (0.545)
p<0.001
Sarcopenia
-0.527 (0.410)
p=0.199
SVLT
-0.197 (0.086)
p=0.022
Hippocampal volume
2.640 (0.395)
p<0.001
Sarcopenia
0.510 (0.315)
p=0.106
CDR-SOB
-0.205 (0.087)
p=0.019
Hippocampal volume
-1.351 (0.301)
p<0.001

Journal of Cachexia, Sarcopenia and Muscle 2024; **15**: 1240–1253
Published online 7 May 2024 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.13485

REVIEW

Meta-analysis on the interrelationship between sarcopenia and mild cognitive impairment, Alzheimer's disease and other forms of dementia

Nadjia Amini[1]*, Mounir Ibn Hach[2], Laurence Lapauw[1], Jolan Dupont[1,3], Laura Vercauteren[1], Sabine Verschueren[4], Jos Tournoy[1,3] & Evelien Gielen[1,3]



Functional Alterations in AD

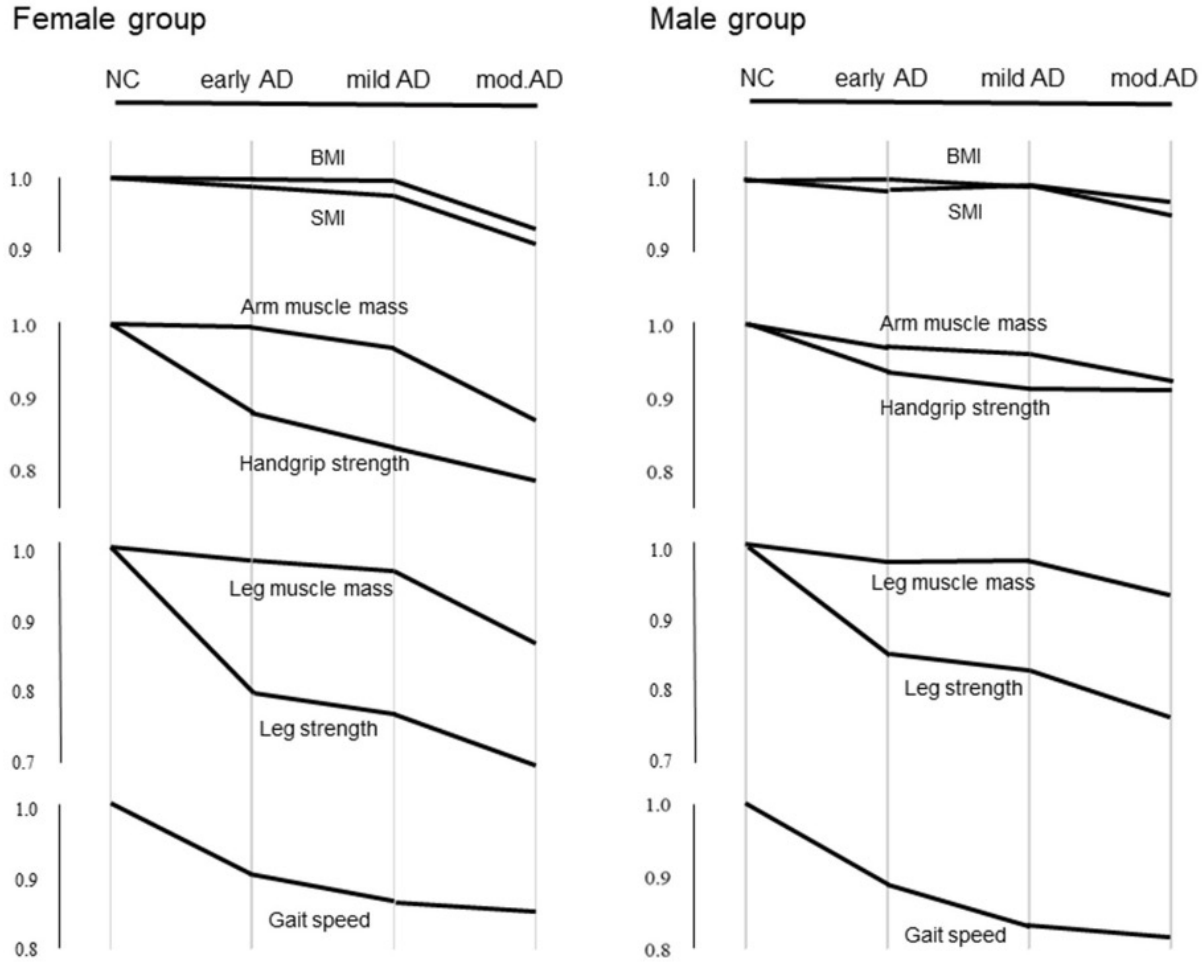


FIGURE 1 | Differences in average values of BMI, SMI, muscle strengths and masses in the upper and lower extremities, and gait speed at various stages of AD compared with the NC. The Y axis indicates reduction from the mean values of the parameters in the NC group. Values in early, mild, and moderate AD groups are normalized to the mean of the NC group.

Owaga et al., 2018; Frontier in Neurology

International Journal of
Molecular Sciences

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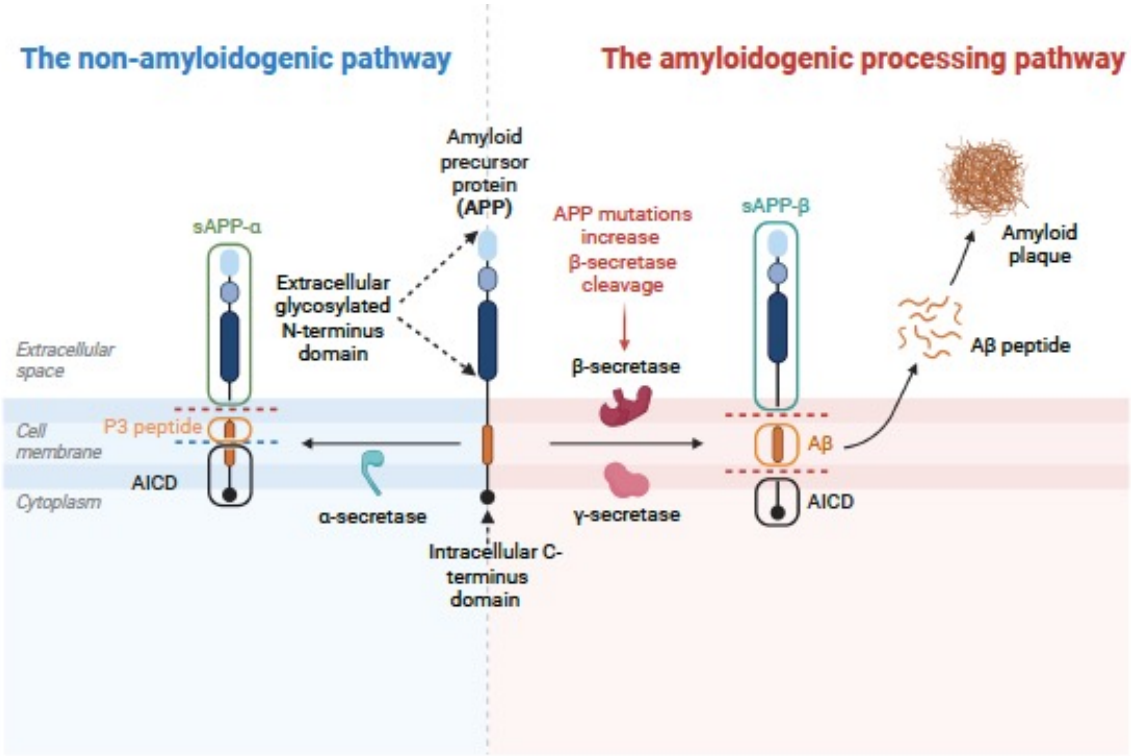
Review

APP in the Neuromuscular Junction for the Development of Sarcopenia and Alzheimer's Disease

Min-Yi Wu [1], Wen-Jun Zou [1], Daehoon Lee [1,2], Lin Mei [1,*] and Wen-Cheng Xiong [1,2,*]



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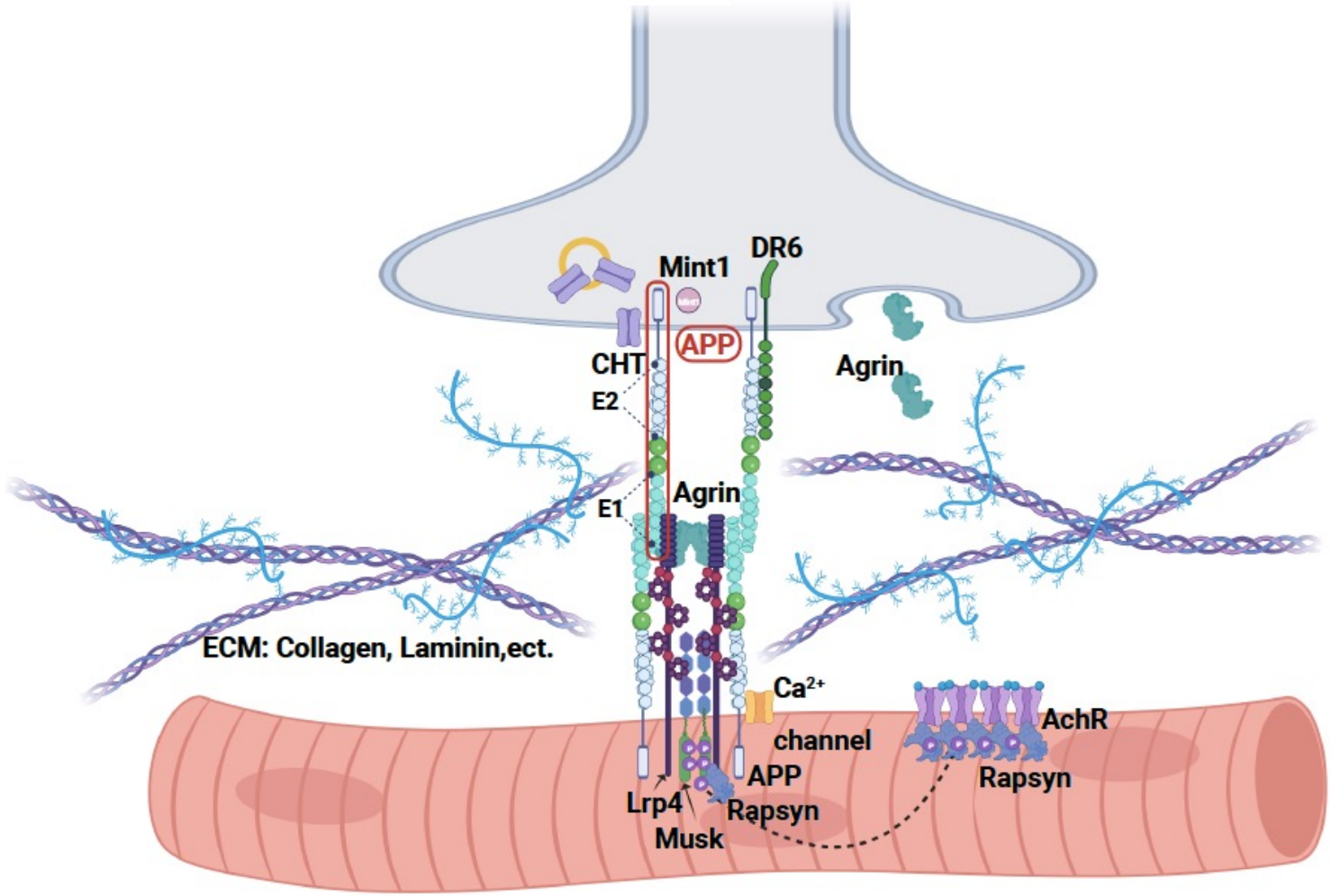

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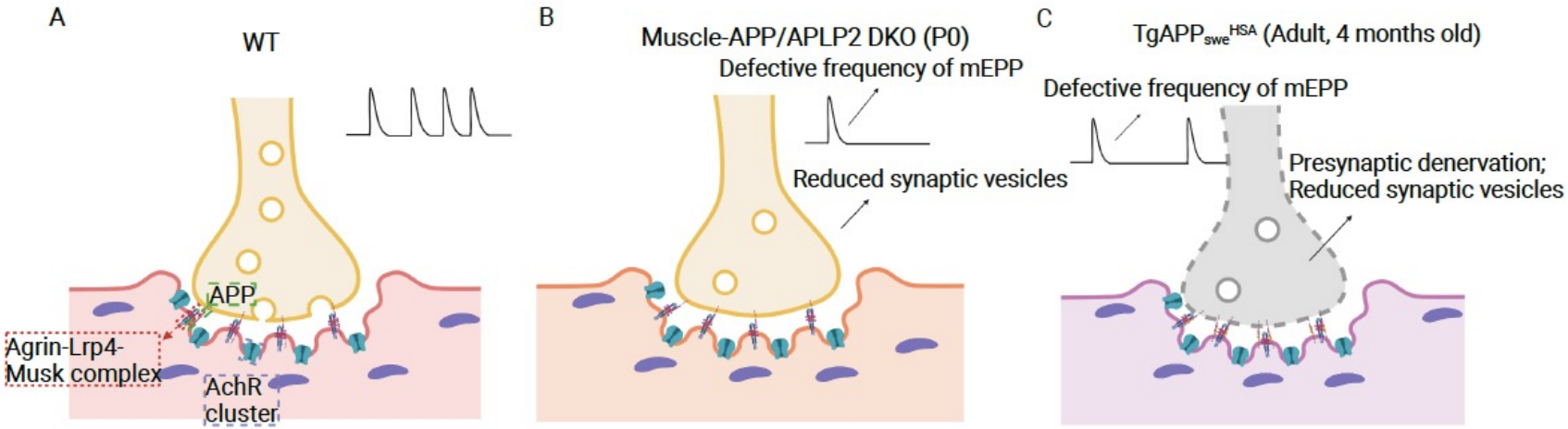

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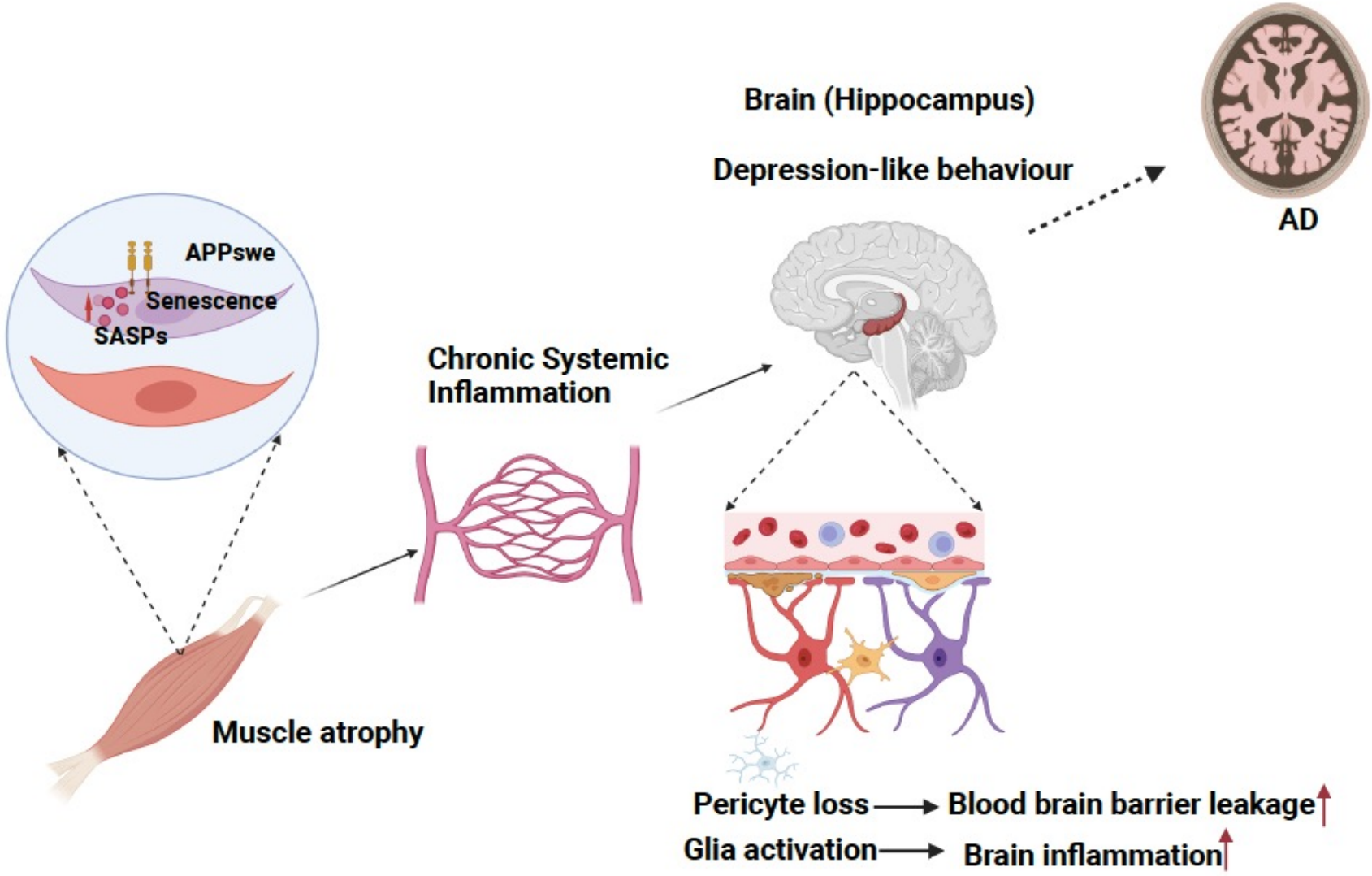

ORIGINAL ARTICLE

Journal of Cachexia, Sarcopenia and Muscle 2024; **15**: 1358–1375
Published online 22 April 2024 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.13482

Accelerated sarcopenia precedes learning and memory impairments in the P301S mouse model of tauopathies and Alzheimer's disease

Savannah Longo, María Laura Messi, Zhong-Min Wang, William Meeker & Osvaldo Delbono*

Department of Internal Medicine, Sections on Gerontology and Geriatric Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA

P301S *tau* gene mutation causes rapidly lethal and early-onset FTDP-17

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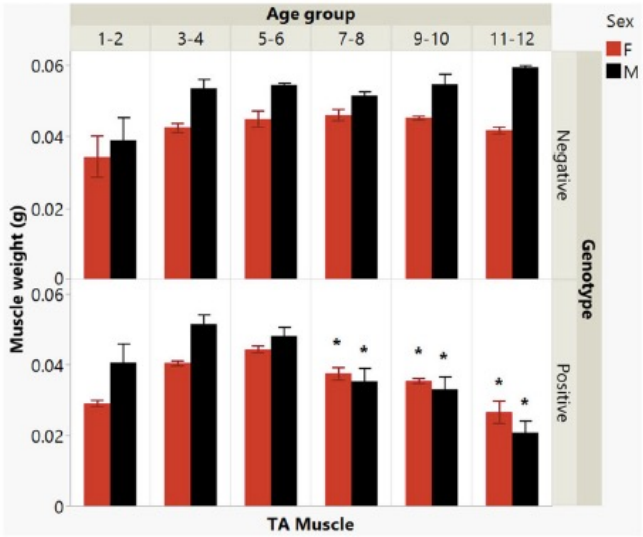

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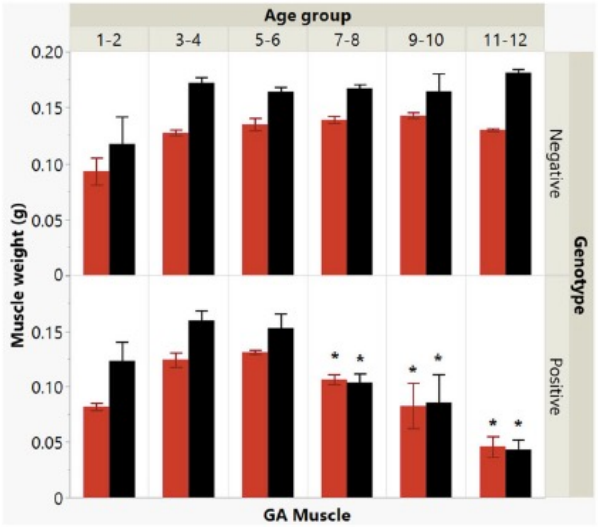

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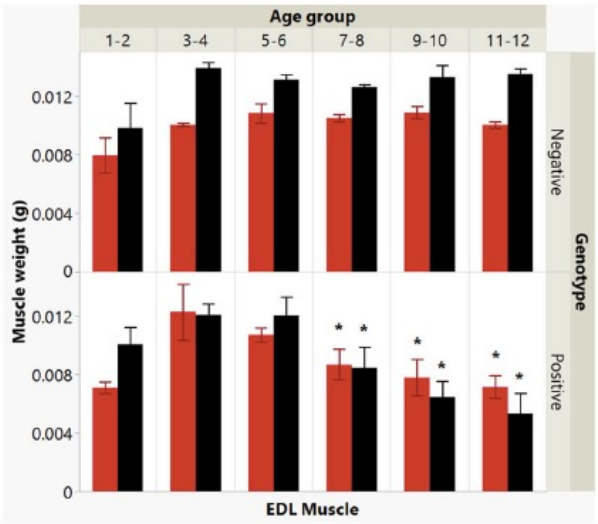

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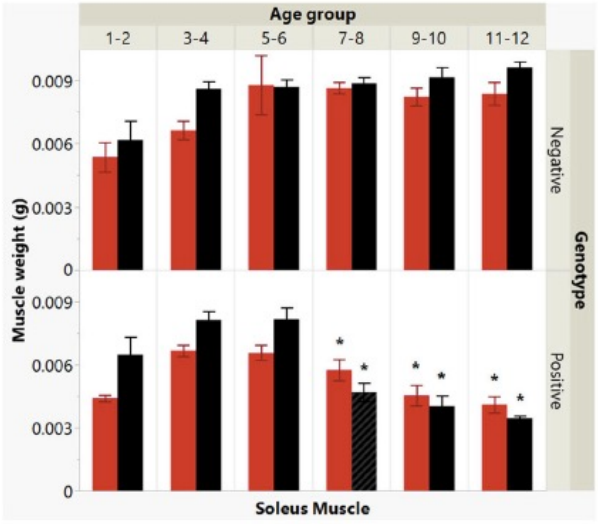

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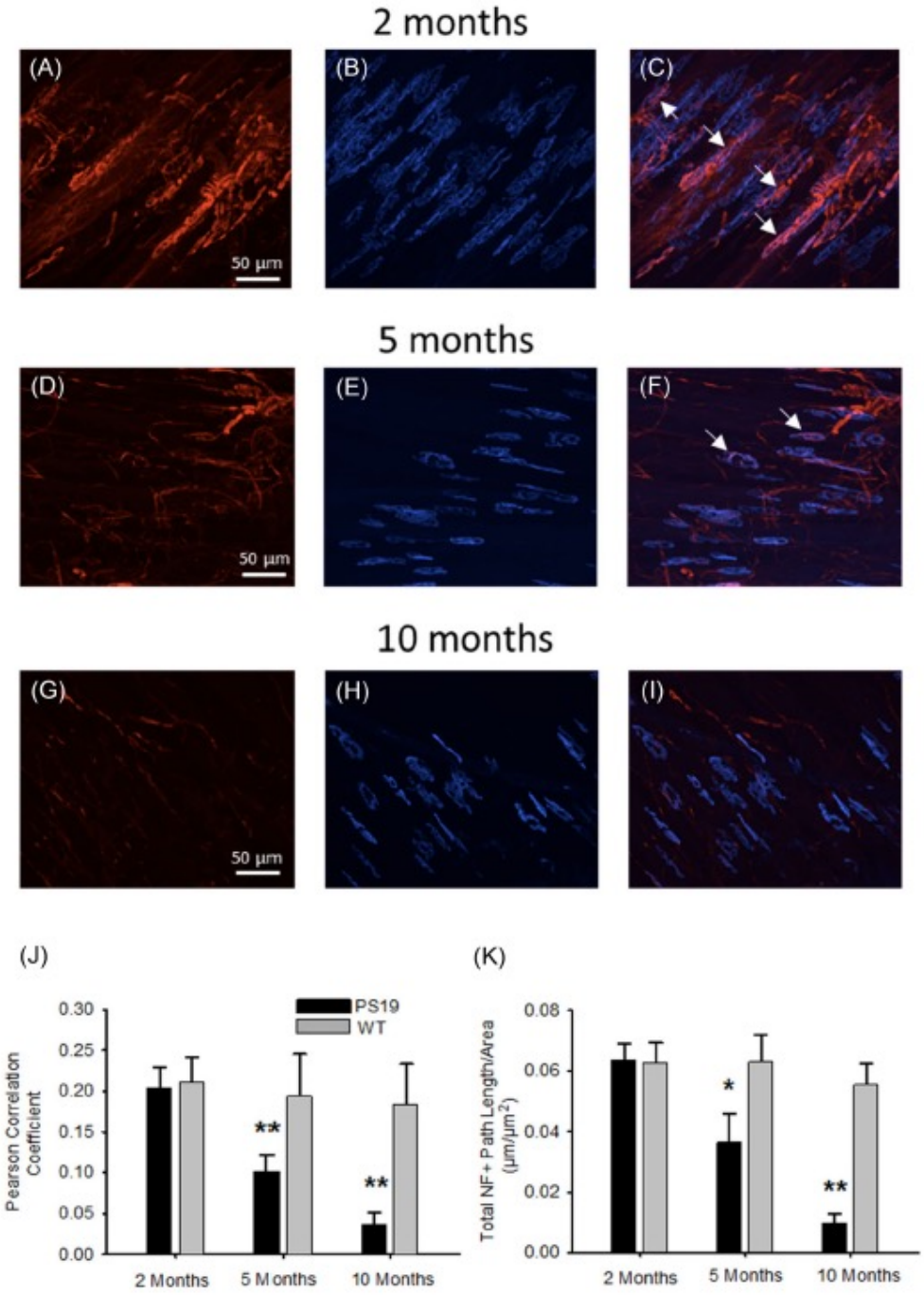
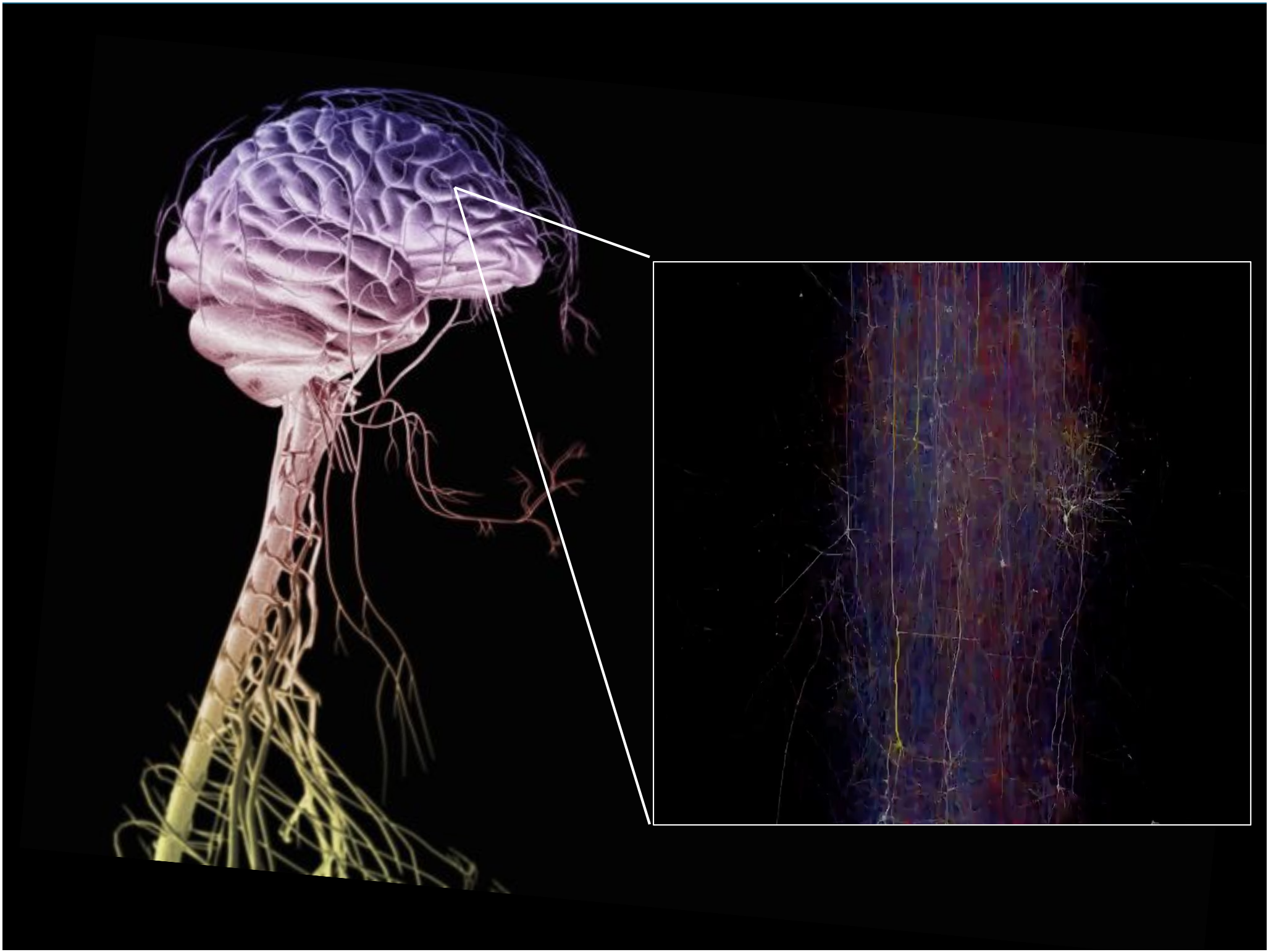
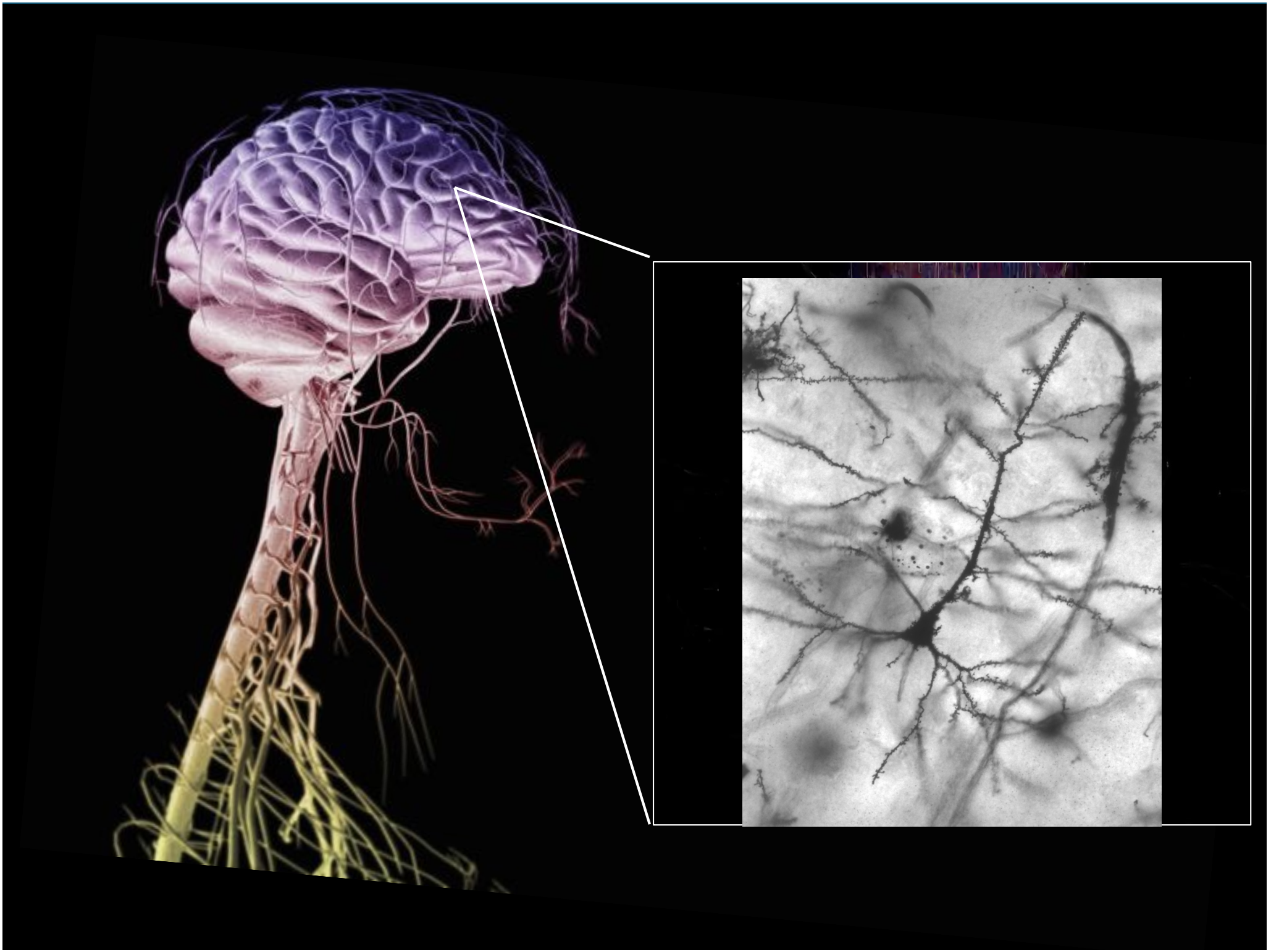
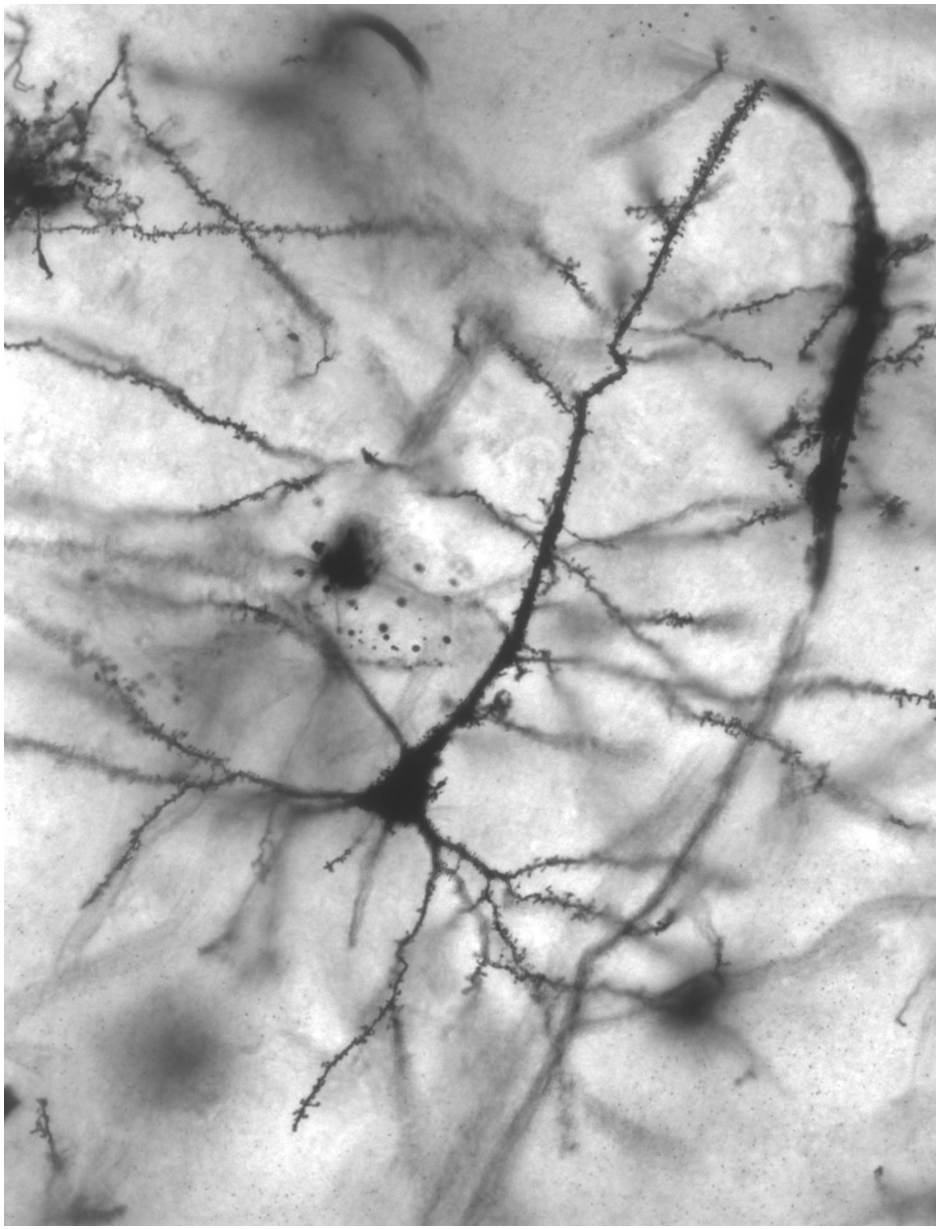


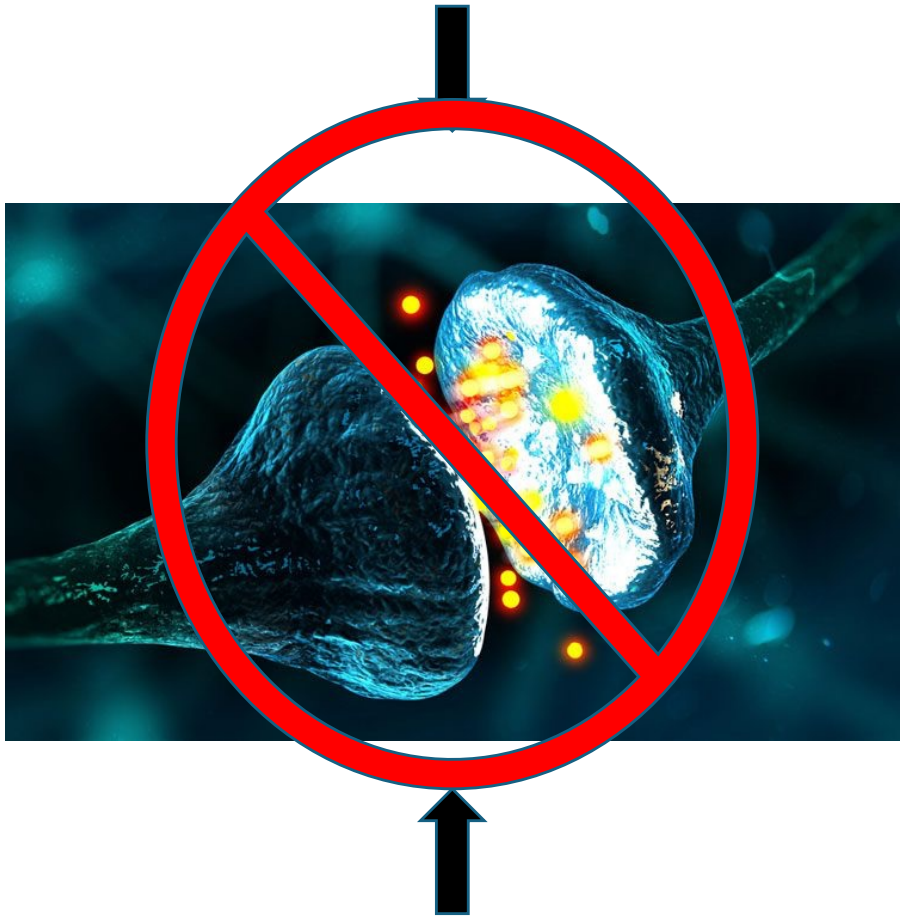
How oligomers can lead to Alzheimer’s disease?



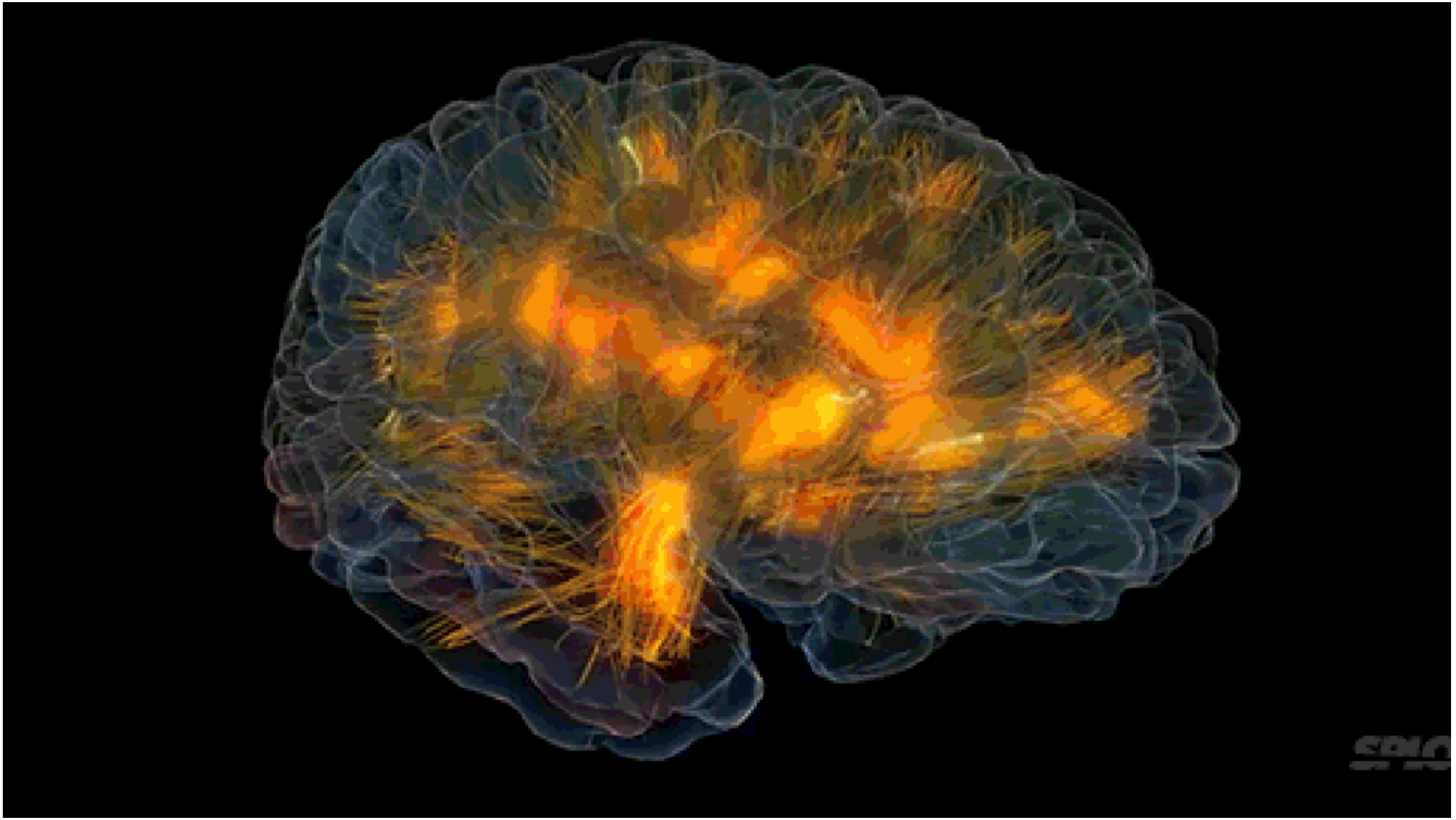




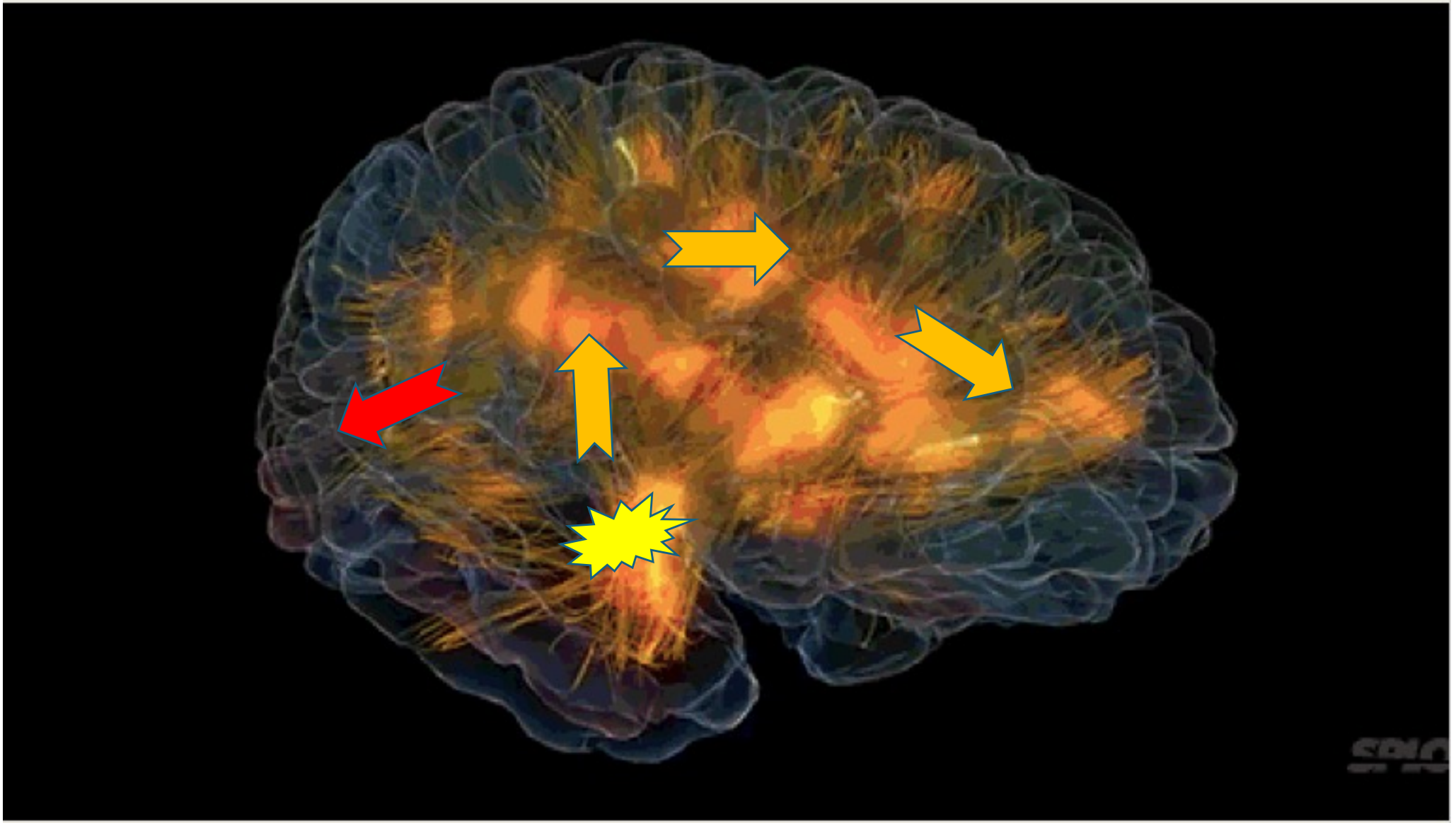
β-amyloid oligomers



Tau oligomers

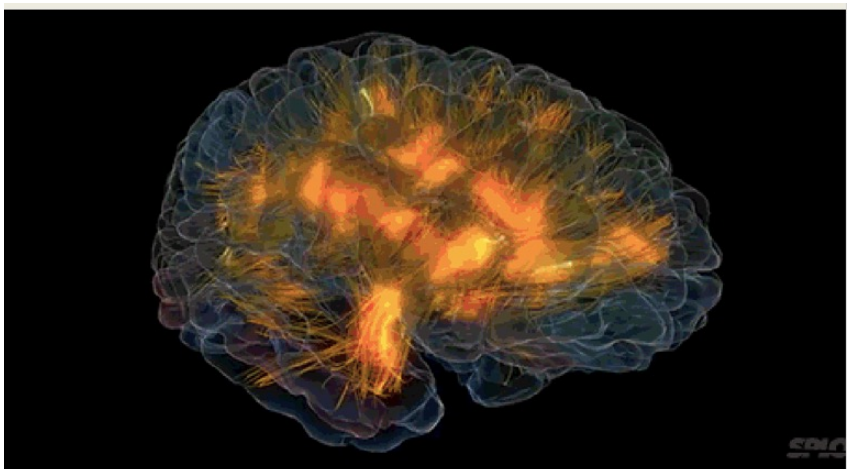


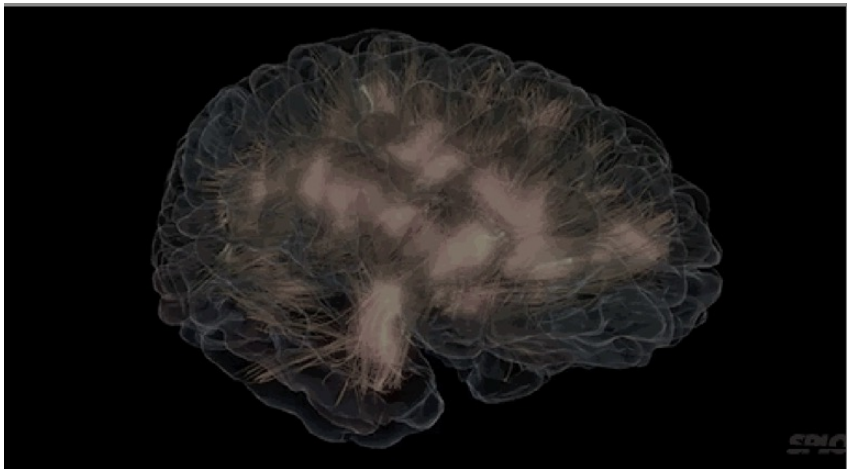
β-amyloid oligomers

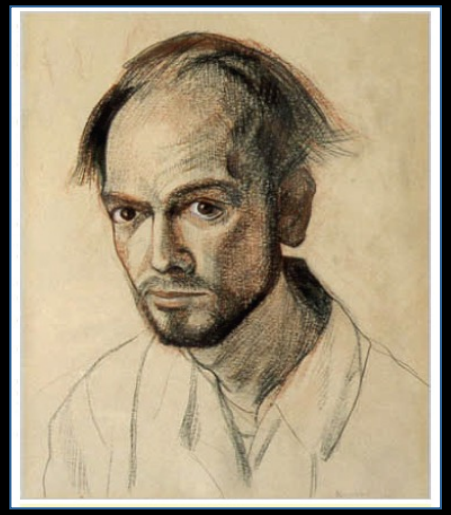


Tau oligomers

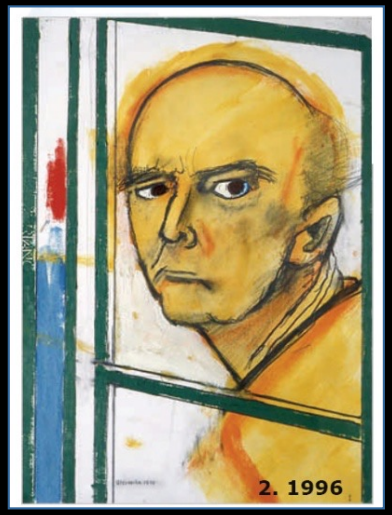
AD Progression







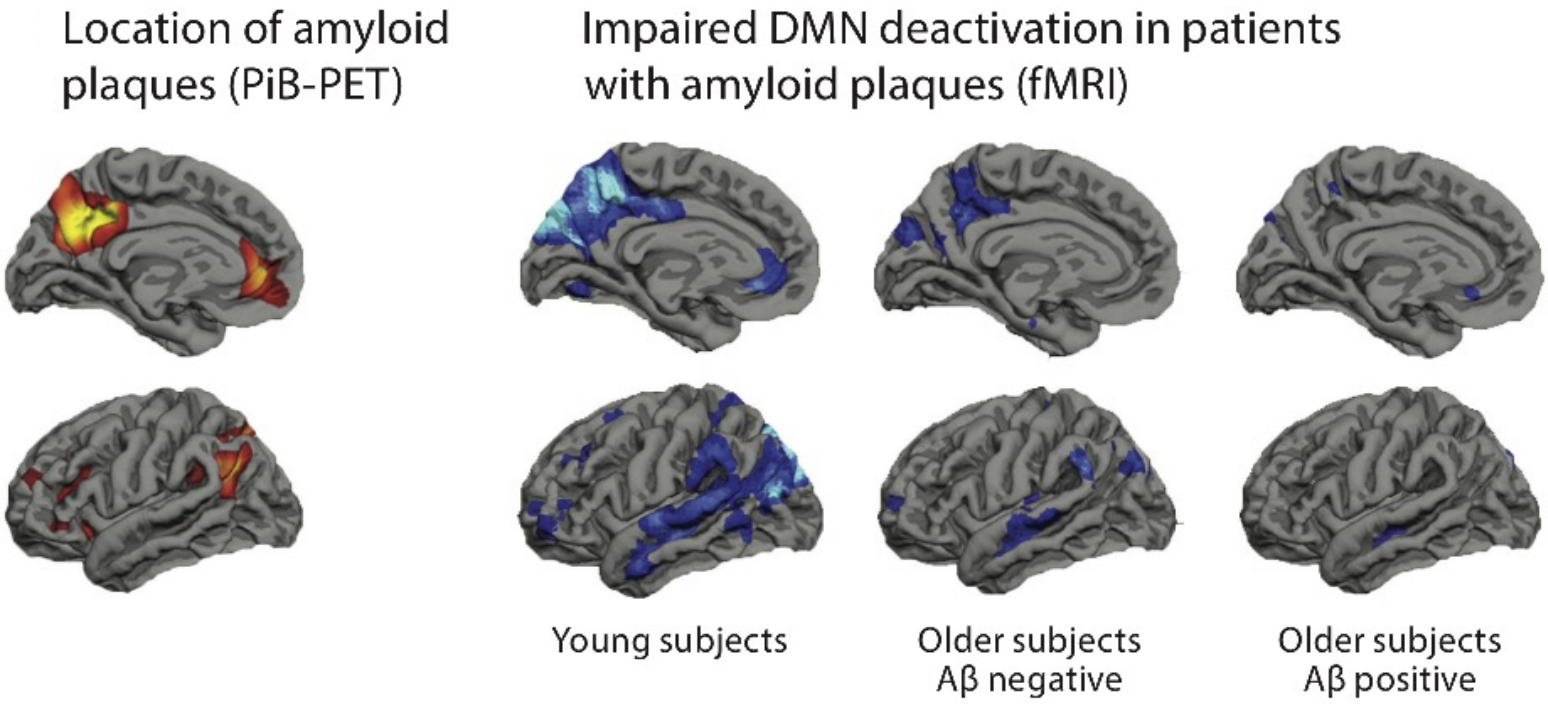
William Utermohlen 1967



1 year later of diagnose Alzheimer's Disease

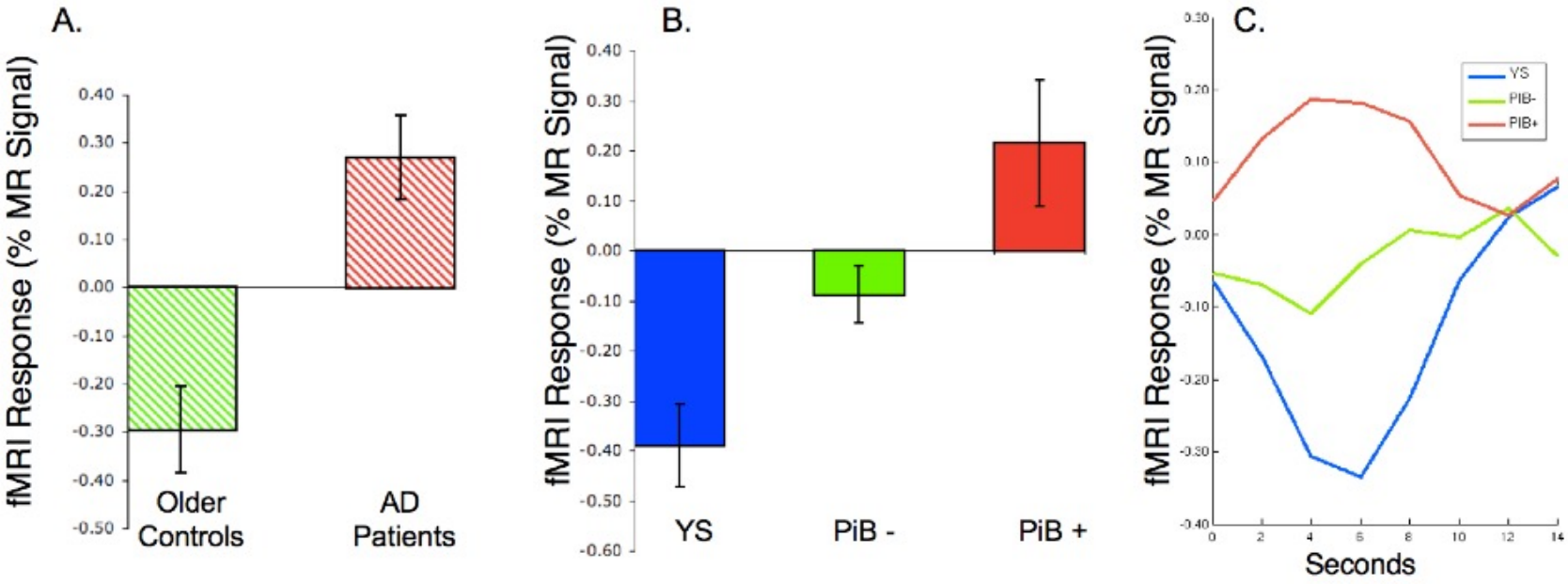
5 years later

Reduced deactivation of the DMN is observed in old individuals with no Aβ burden



Sperling et al., 2009

Paradoxical increase of the DMN is observed in old individuals with high Aβ burden



Celone et al, 2006,
Pihlajamaki et al., 2008

Sperling et al., 2009

Loss of functional $GABA_A$ receptors in the Alzheimer diseased brain

Agenor Limon[1], Jorge Mauricio Reyes-Ruiz, and Ricardo Miledi[1]

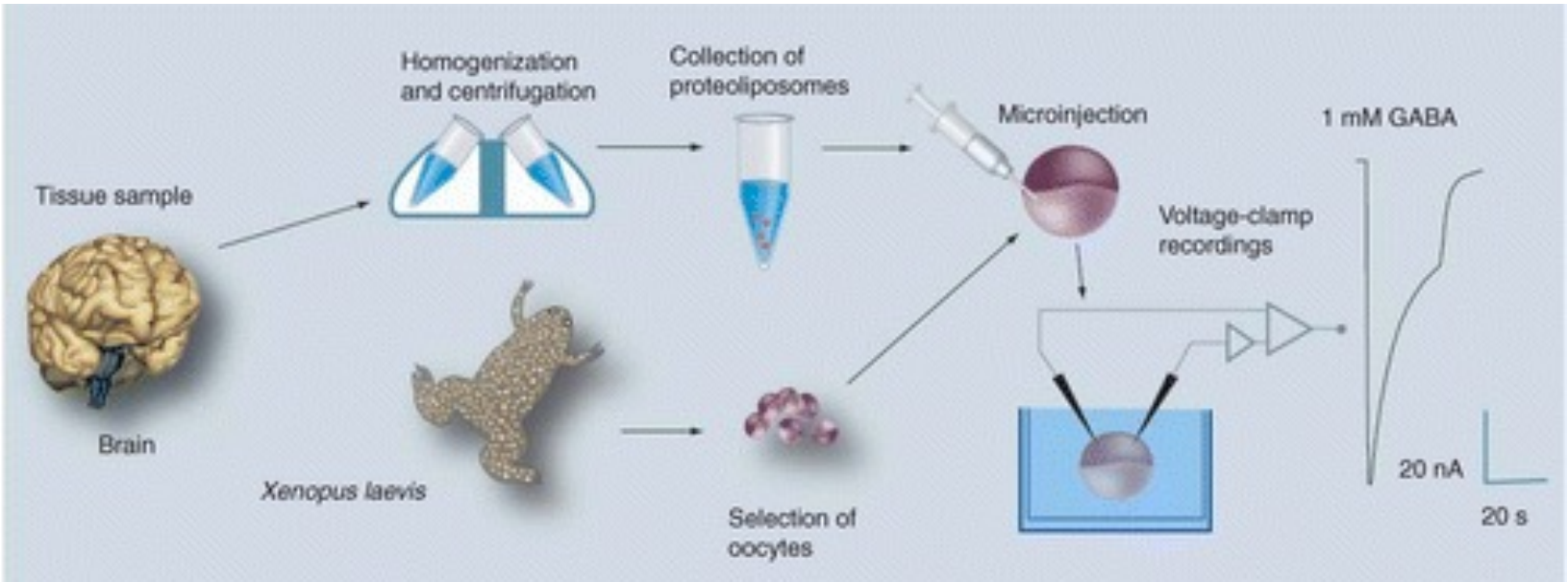
Laboratory of Cellular and Molecular Neurobiology, Department of Neurobiology and Behavior, University of California, Irvine, CA 92697

Contributed by Ricardo Miledi, March 21, 2012 (sent for review February 21, 2012)

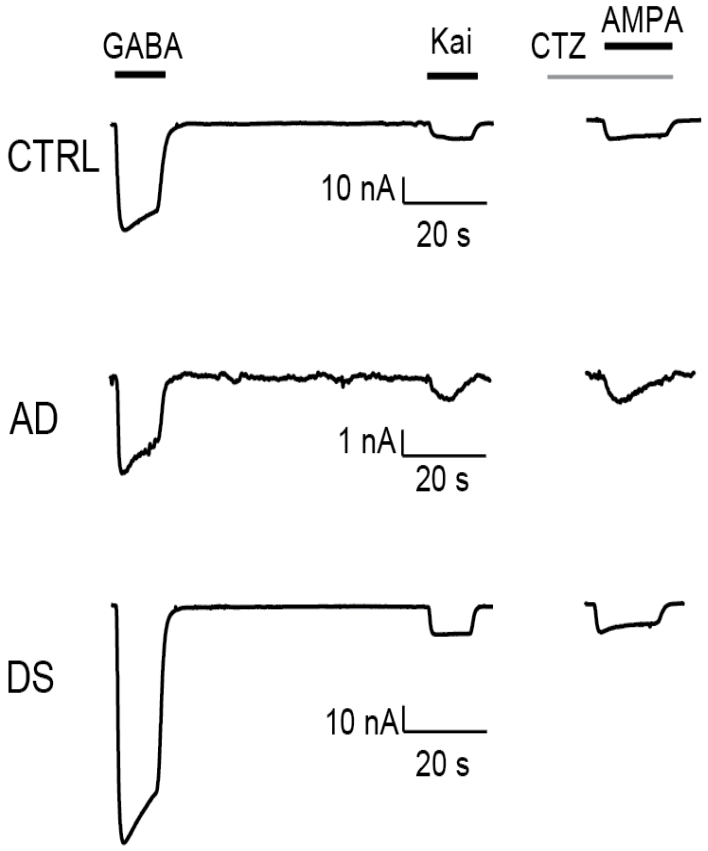
The cholinergic and glutamatergic neurotransmission systems are known to be severely disrupted in Alzheimer's disease (AD). GABAergic neurotransmission, in contrast, is generally thought to be well preserved. Evidence from animal models and human postmortem tissue suggest GABAergic remodeling in the AD brain. Nevertheless, there is no information on changes, if any, in the electrophysiological properties of human native GABA receptors as a consequence of AD. To gain such information, we have microtransplanted cell membranes, isolated from temporal cortices of control and AD brains, into *Xenopus* oocytes, and recorded the

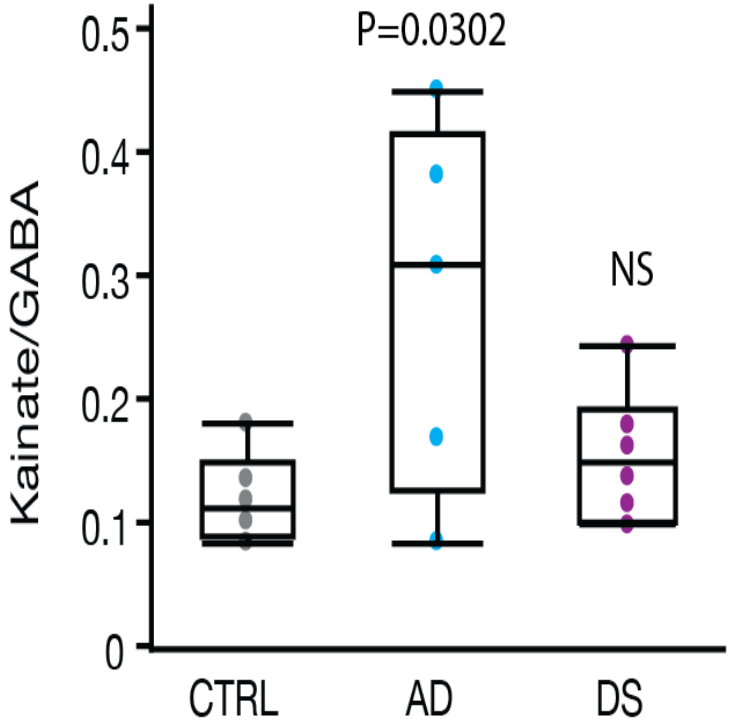
it remains to be determined how those reductions affected the function of $GABA_AR$s in cellular membranes. This lack of information is a critical void, considering the correlation between cortical hyperexcitability, the pathological state of patients with AD (12, 13), and the protective effects of $GABA_AR$ agonists against Aβ-induced injury (14). In the present study, we have extended our previous observations and report clear evidence of functional remodeling of native human $GABA_AR$s in AD.

Results



Increased electrophysiological E/I in AD





Lauterborn et al, Nat Comm, 2021

Global E/I balance in AD

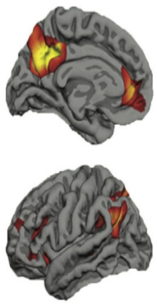
Parietal Cortex

Frontal Cortex

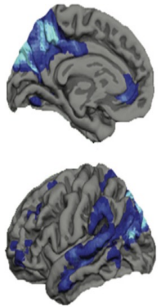
Medial Temporal Cortex

Hippocampus

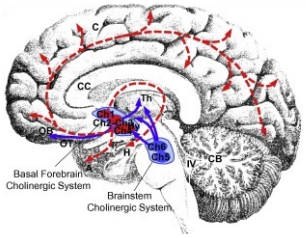
Aβ accumulation



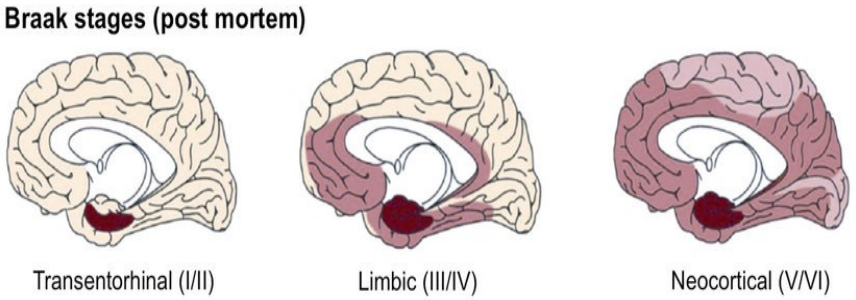
Hyperactivation



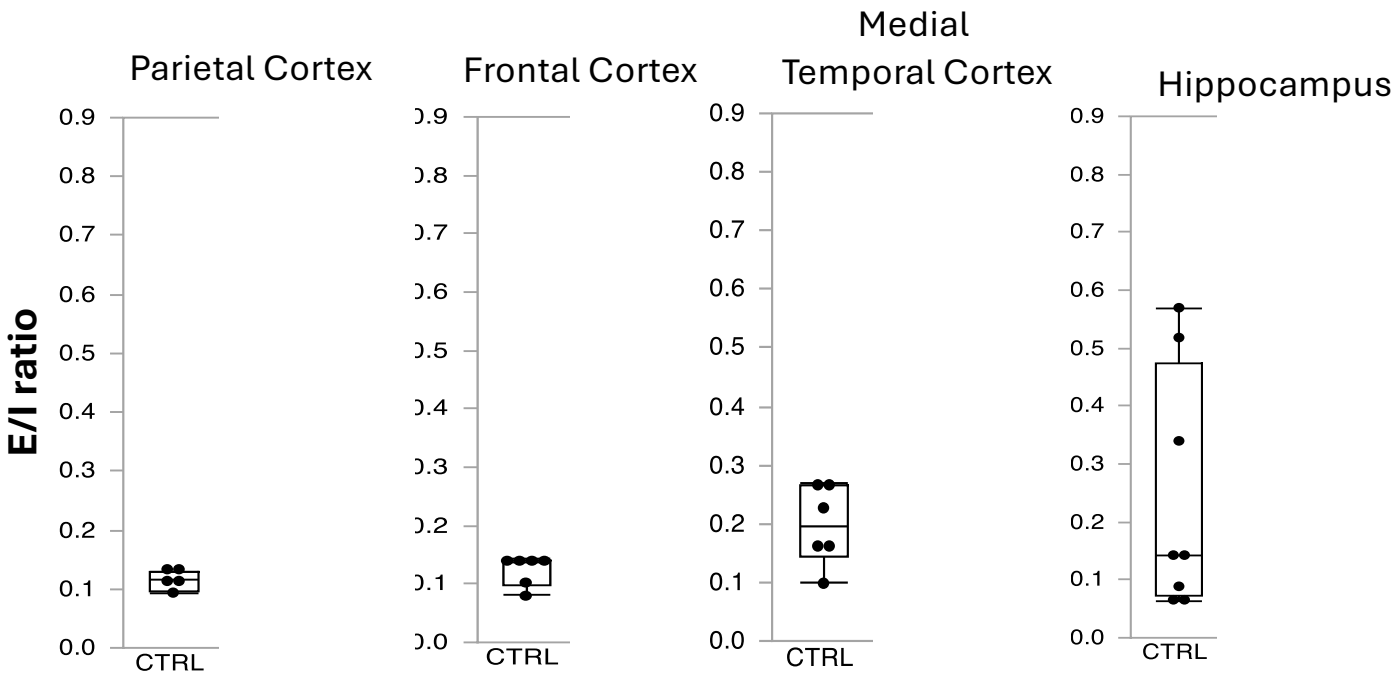
Reduction of Glu activity



First areas affected by the pathology



Global *e*E/I balance in Health

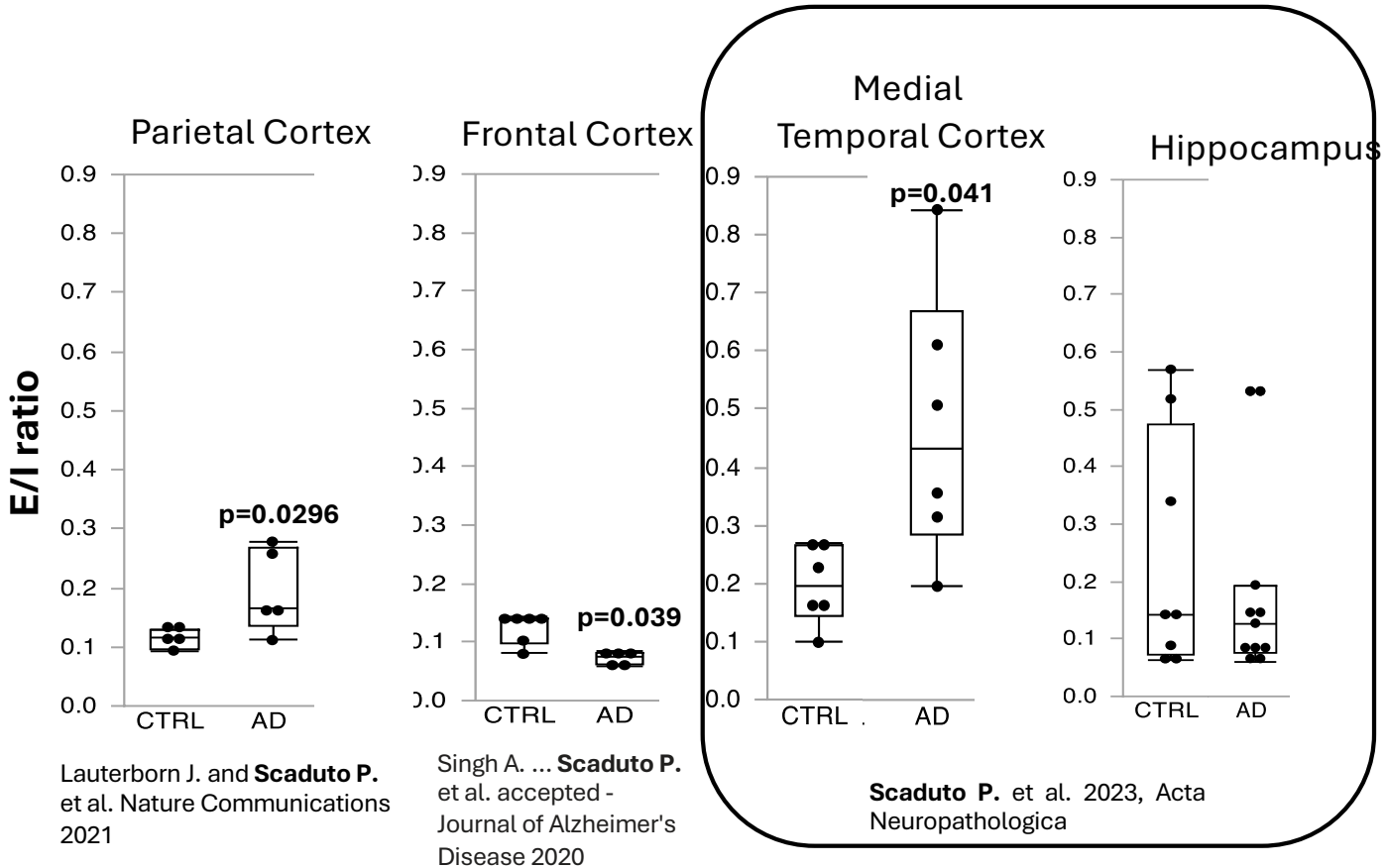


Lauterborn J. and **Scaduto P.** et al. Nature Communications 2021

Singh A. … **Scaduto P.** et al. accepted - Journal of Alzheimer's Disease 2020

Scaduto P. et al. 2023, Acta Neuropathologica

*e*E/I imbalance in AD



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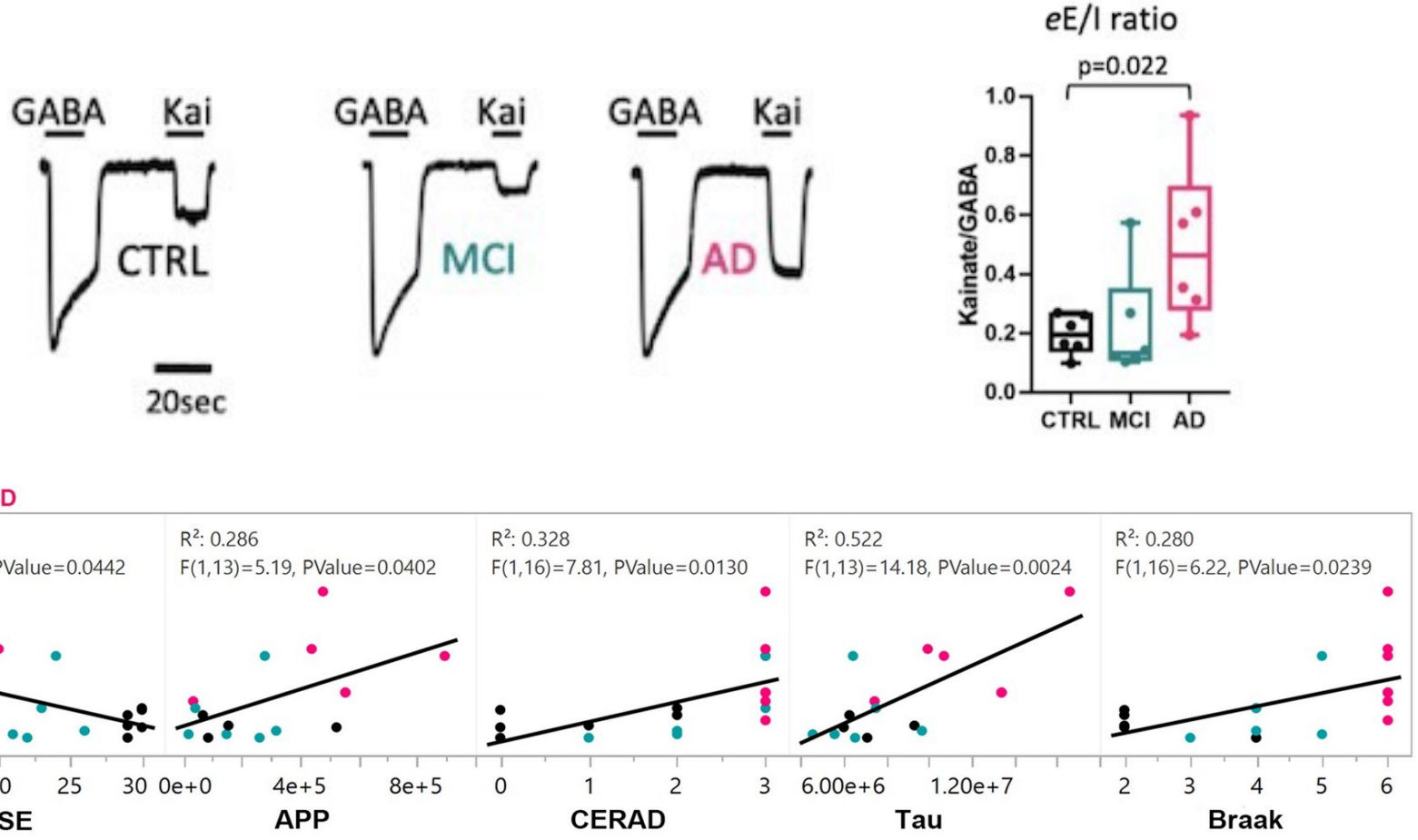
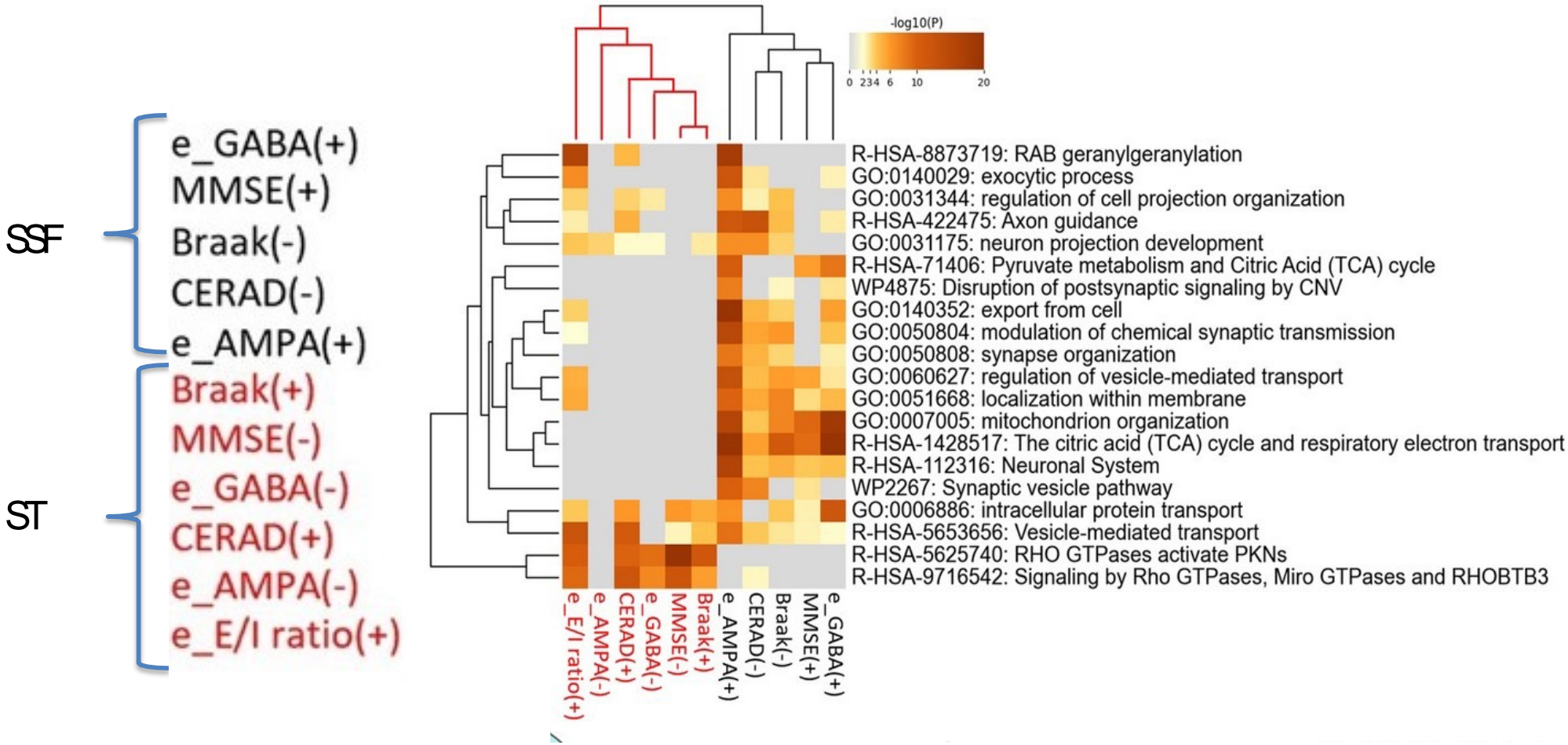
TCx *e*E/I ratio correlates with cognitive decline and neuropathological hallmarks



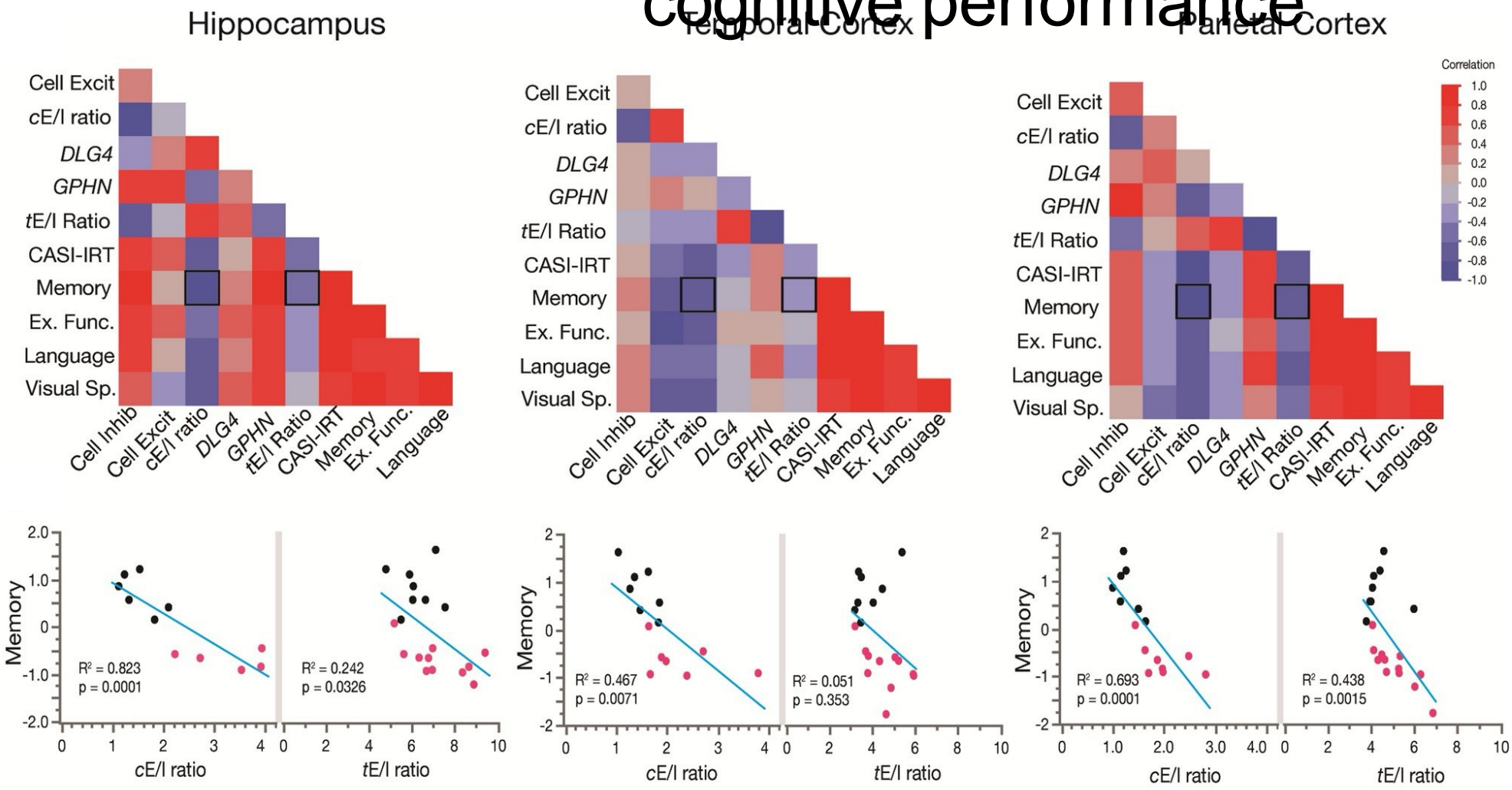
Scaduto et al, 2023. Acta Neuropathologica

Multidimensional analysis of electrophysiology, synapto-proteome, and neuropathological change



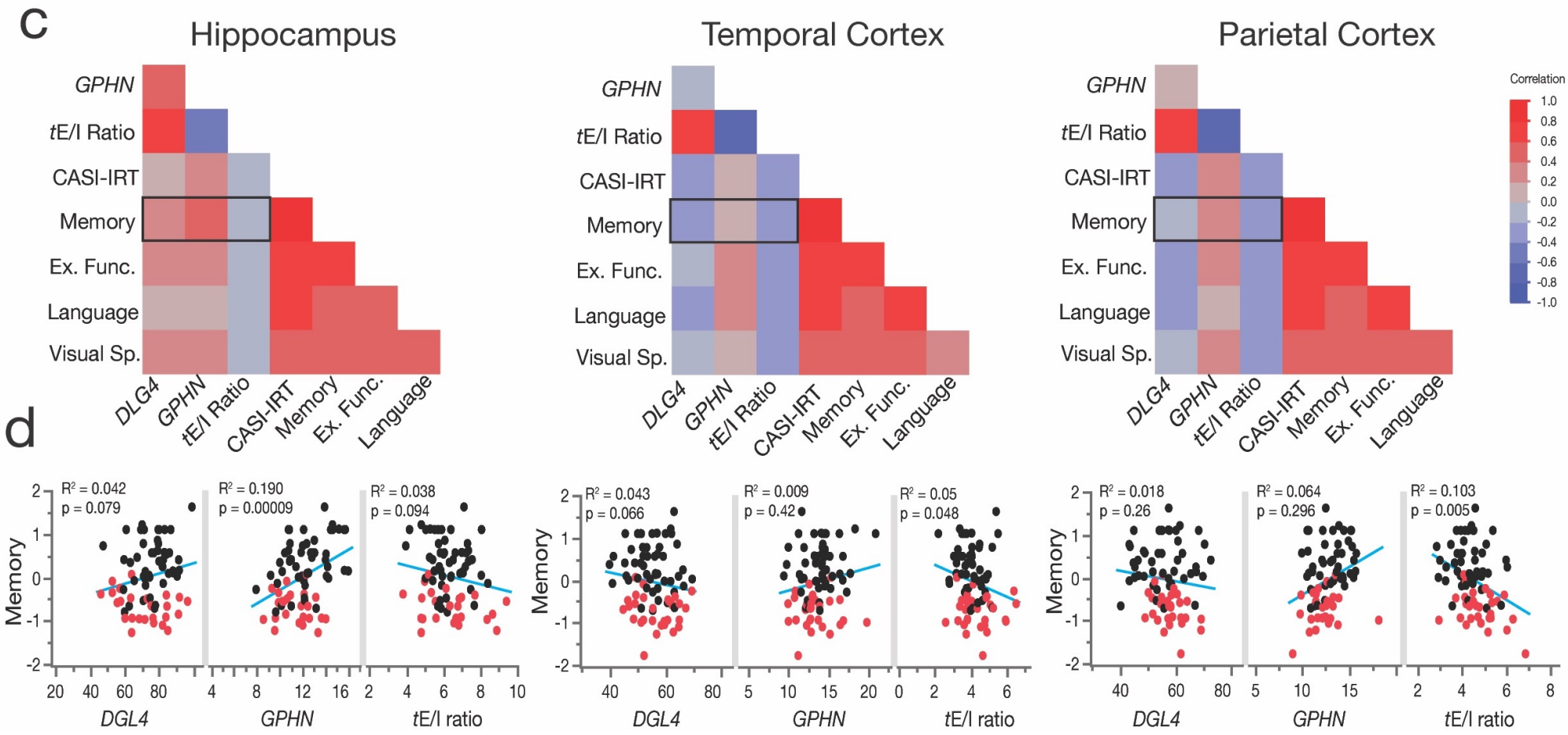
Scaduto et al, 2023, Acta Neuropathologica

Cellular and transcriptomic E/I ratio and cognitive performance



Scaduto et al, 2023, Acta Neuropathologica

Multivariate correlation with Cognitive Performance all cohort



Scaduto et al, 2023, Acta Neuropathologica

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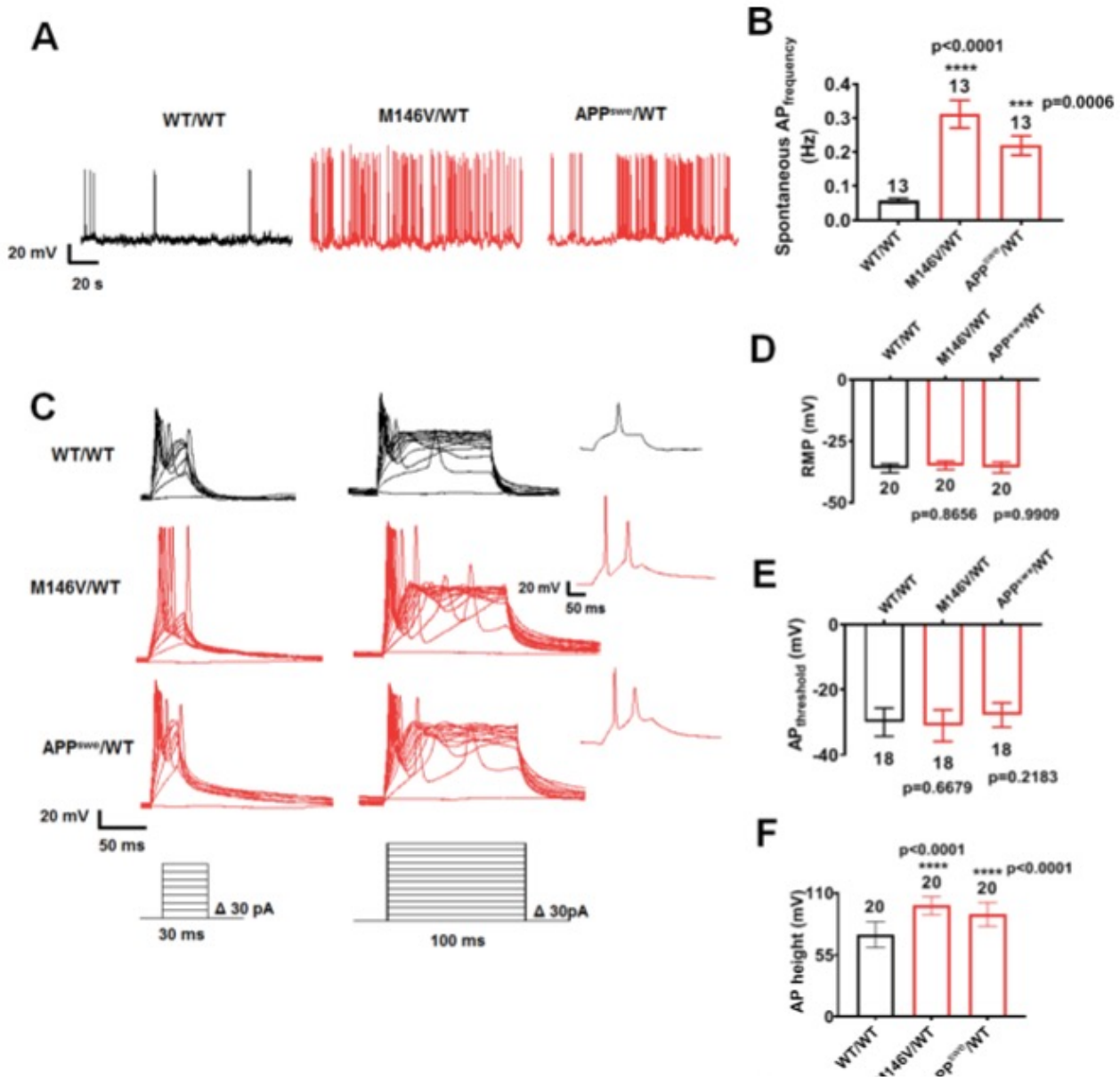
RESEARCH ARTICLE

Mechanisms of hyperexcitability in Alzheimer's disease hiPSC-derived neurons and cerebral organoids vs isogenic controls

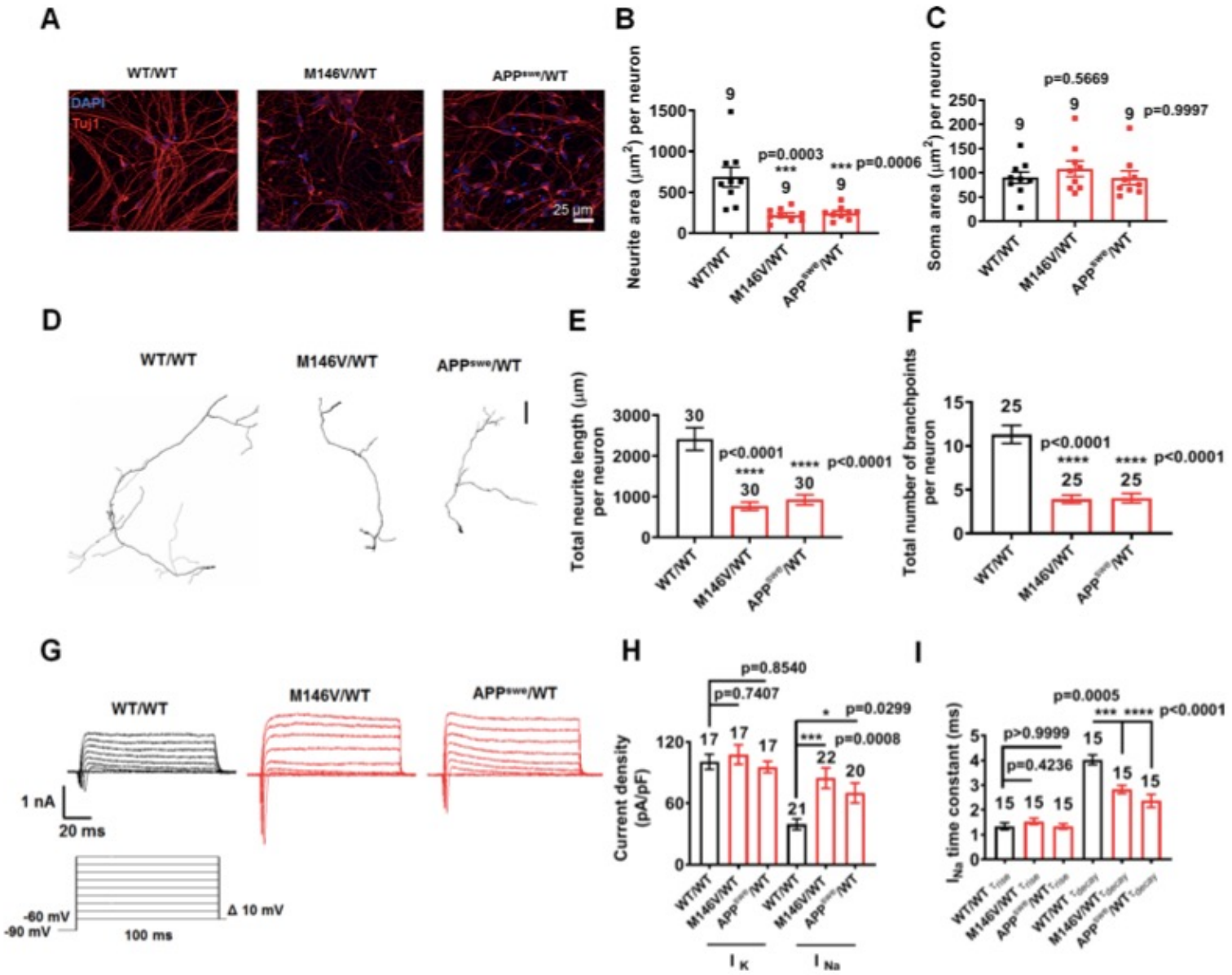
Swagata Ghatak[1†], Nima Dolatabadi[1†], Dorit Trudler[1], XiaoTong Zhang[1], Yin Wu[1], Madhav Mohata[1], Rajesh Ambasudhan[2], Maria Talantova[1], Stuart A Lipton[1,2,3,4,5*]

[1]Department of Molecular Medicine, The Scripps Research Institute, La Jolla, United States; [2]Neurodegenerative Disease Center, Scintillon Institute, San Diego, United States; [3]Department of Neuroscience, The Scripps Research Institute, La Jolla, United States; [4]Neuroscience Translational Center, The Scripps Research Institute, La Jolla, United States; [5]Department of Neurosciences, School of Medicine, University of California, San Diego, San Diego, United States

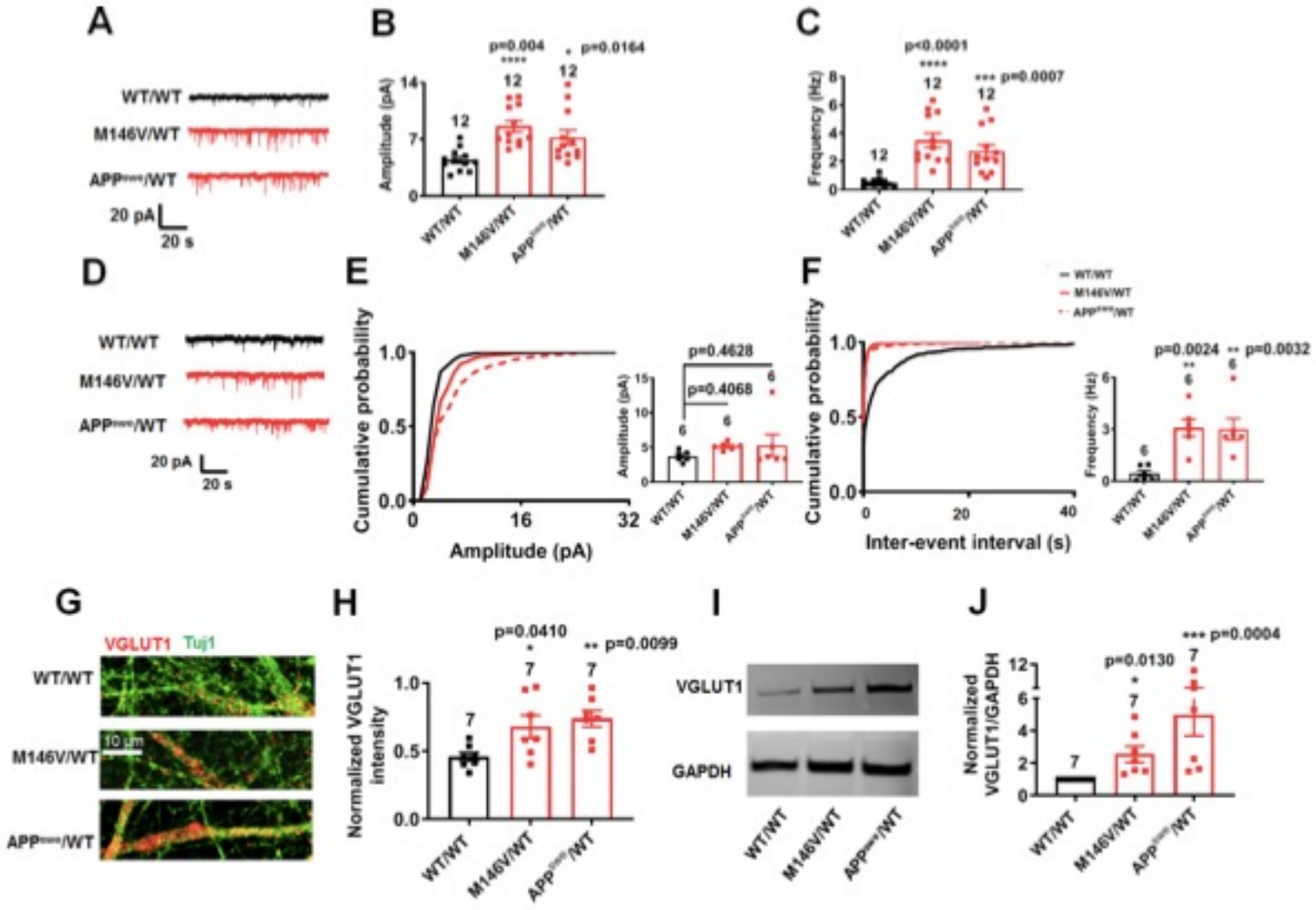
Hyperexcitability in AD



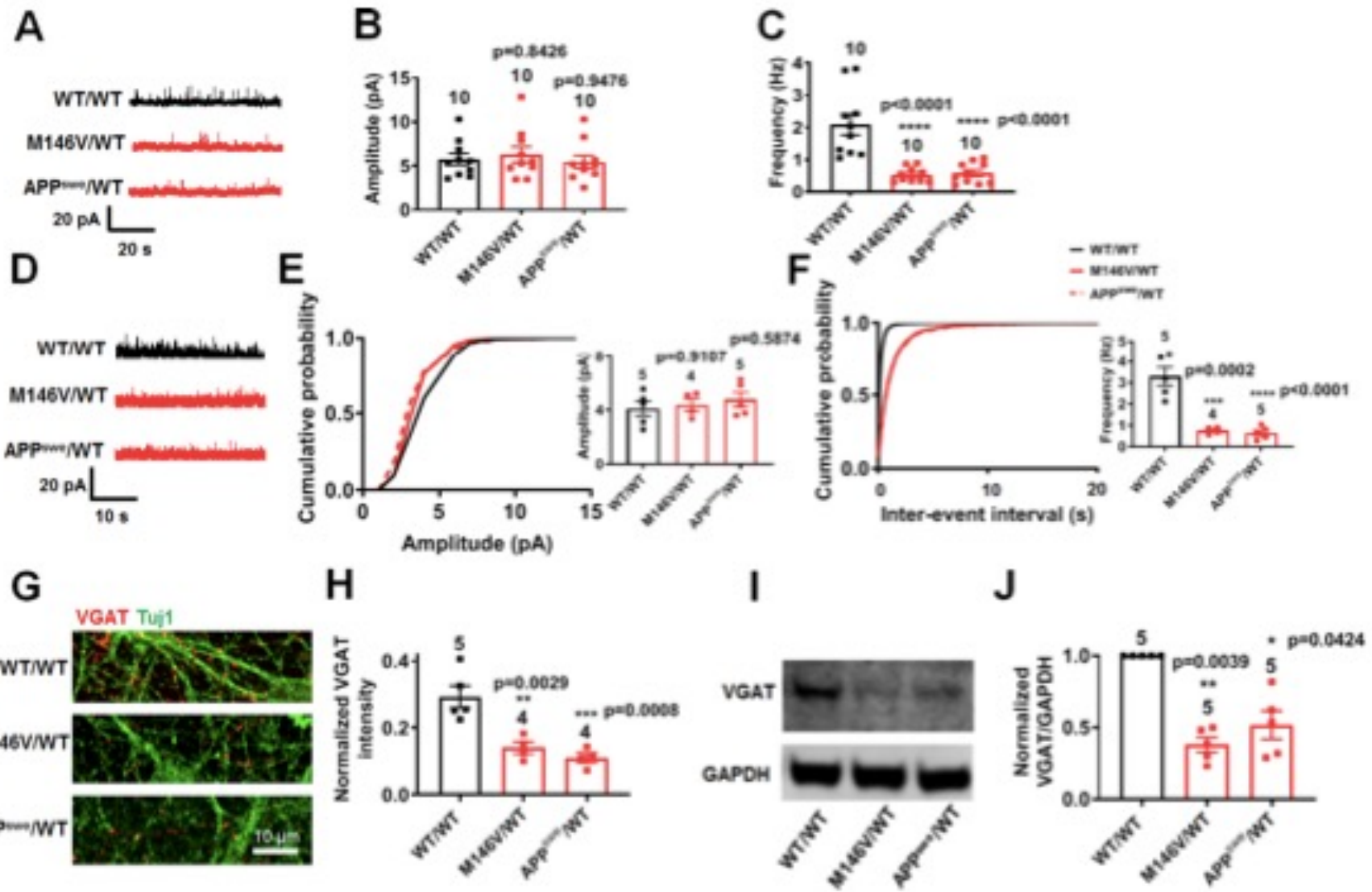
Ion channel alterations

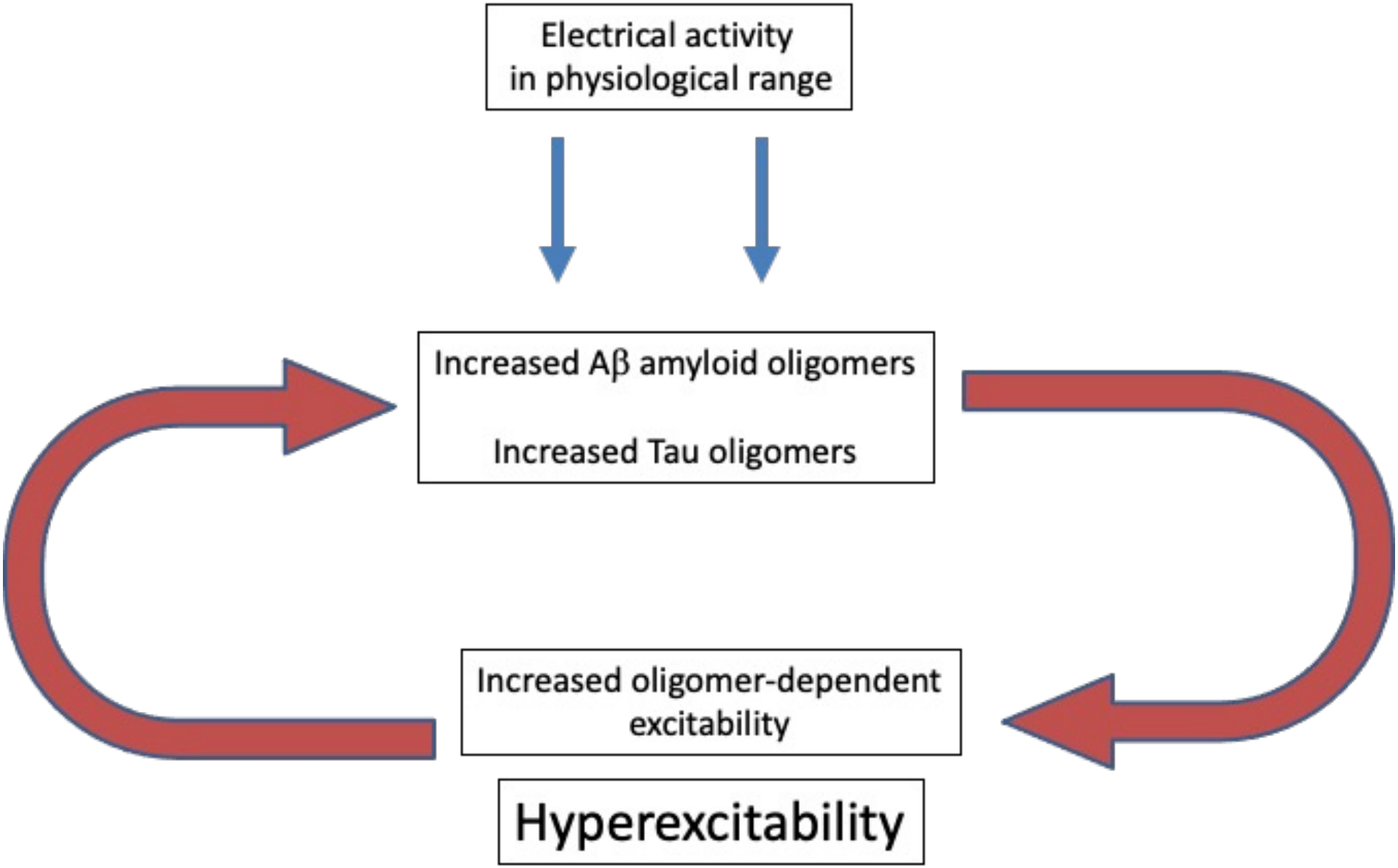


Enhanced excitability



Reduced inhibition

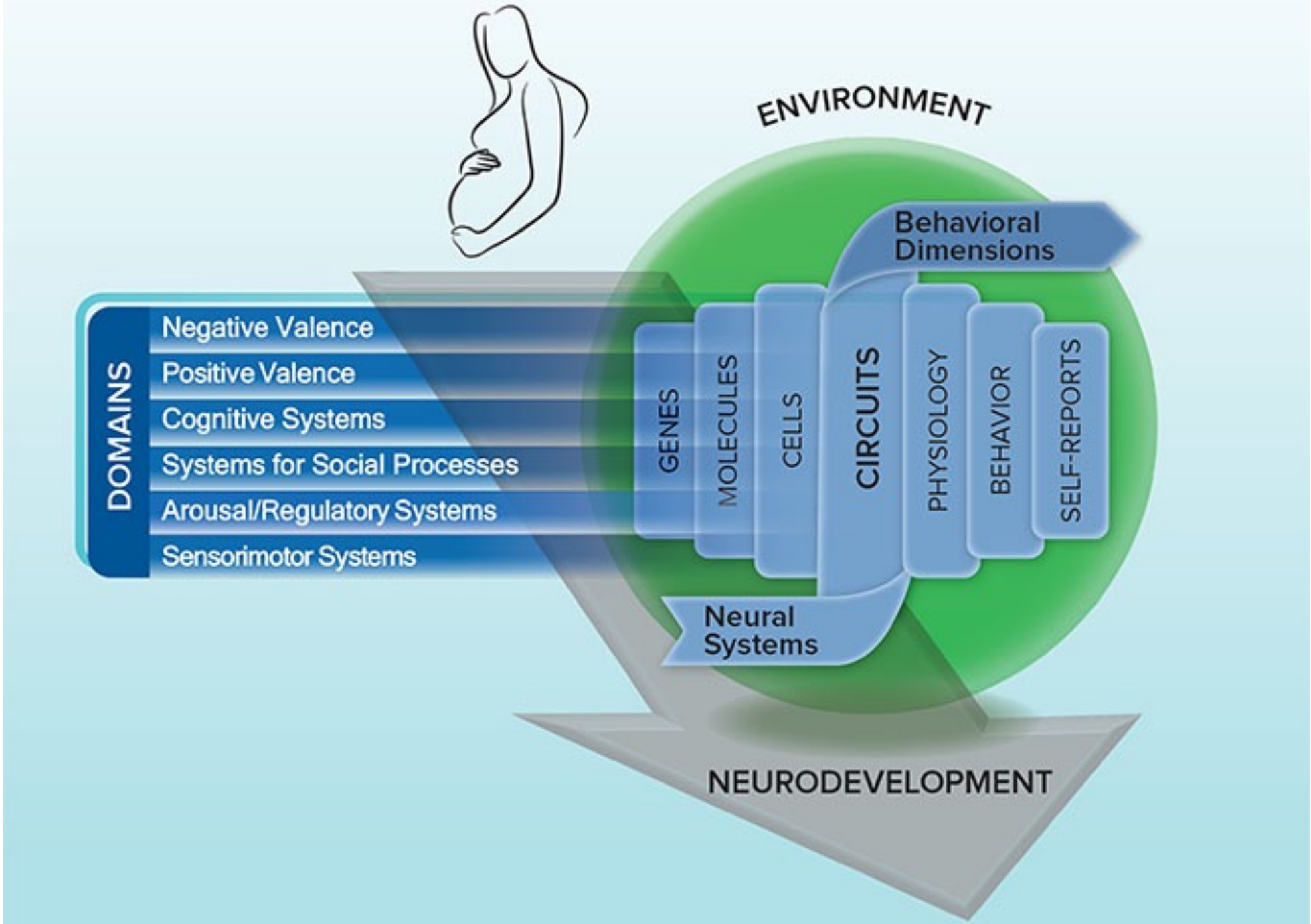



Electrical activity
in physiological range
Increased Aβ amyloid oligomers
Increased Tau oligomers
Increased oligomer-dependent
excitability
Hyperexcitability

Heterogeneity of Dementia

- Alzheimer's disease
- Amyotrophic Lateral Sclerosis (20% also show Frontotemporal dementia)
- Chronic Traumatic Encephalopathy
- Corticobasal Syndrome
- Frontotemporal Dementia (Diagnostic challenge and confused with psychiatric disorders)
- HIV-related cognitive Impairment
- Huntington's Disease
- Parkinson's Dementias
- Posterior Cortical Atrophy
- Primary Progressive Aphasia
- Non fluent Variant Primary Progressive Aphasia
- Progressive Supranuclear Palsy
- Rapidly Progressive Dementias
- Vascular Dementia

https://memory.ucsf.edu/what-dementia


ENVIRONMENT
Behavioral Dimensions
DOMAINS
Negative Valence
Positive Valence
Cognitive Systems
Systems for Social Processes
Arousal/Regulatory Systems
Sensorimotor Systems
GENES
MOLECULES
CELLS
CIRCUITS
PHYSIOLOGY
BEHAVIOR
SELF-REPORTS
Neural Systems
NEURODEVELOPMENT