DONALD G. STEIN, PHD.
PROFESSOR EMERITUS
EMORY UNIVERSITY
ATLANTA, GEORGIA

- Don retired in 2021 from Emory University School of Medicine, Atlanta, as Emeritus Asa G. Candler Professor and Distinguished Professor in Emergency Medicine, and professor in the Neuroscience and Behavioral Biology Program.
- His team's early findings on sex differences in recovery from brain injury led to decades of research on the role of neurosteroids in the plasticity and repair of CNS injury.
- Dr. Stein is the author of 450 articles, book chapters, reviews and papers on the subject of repair and recovery from brain injury.

A DISCUSSION ON WHAT WE BELIEVE WE KNOW ABOUT DEMENTIA AND ALZHEIMER'S DISEASE TREATMENTS

Is Aging A Disease?

- It has been widely found that the volume of the brain and/or its weight declines with age at a rate of around 5% per decade after age 40[1] with the actual rate of decline possibly increasing with age particularly over age 70.

- The rate of reduction in brain volume may increase with age particularly over 70 although numbers studied are very small.

- Because of the individual differences seen in brain development and ageing mapping structure to function and change because of ageing is a complex task.

- In recent years, it has seemed increasingly likely that there is an overlap between vascular and AD dementias and there have been calls for AD to be reclassified as a vascular disorder or for dementia to become a multifactorial disorder.

- There are many influences on the ageing brain, genetics, biological, and environmental influences all of which contribute to the physiological and cognitive changes.

- **The characteristic neurofibrilliary tangles and plaques found in AD are also evident to some degree in most elderly brains at postmortem examination even those without symptoms, as are white matter lesions.**

ALHZHEIMERS

TOP 10 EARLY SIGNS

MEMORY LOSS

CHANGES IN MOOD

MISPLACING BELONGINGS

HARD TO COMPLETE FAMILIAR TASK

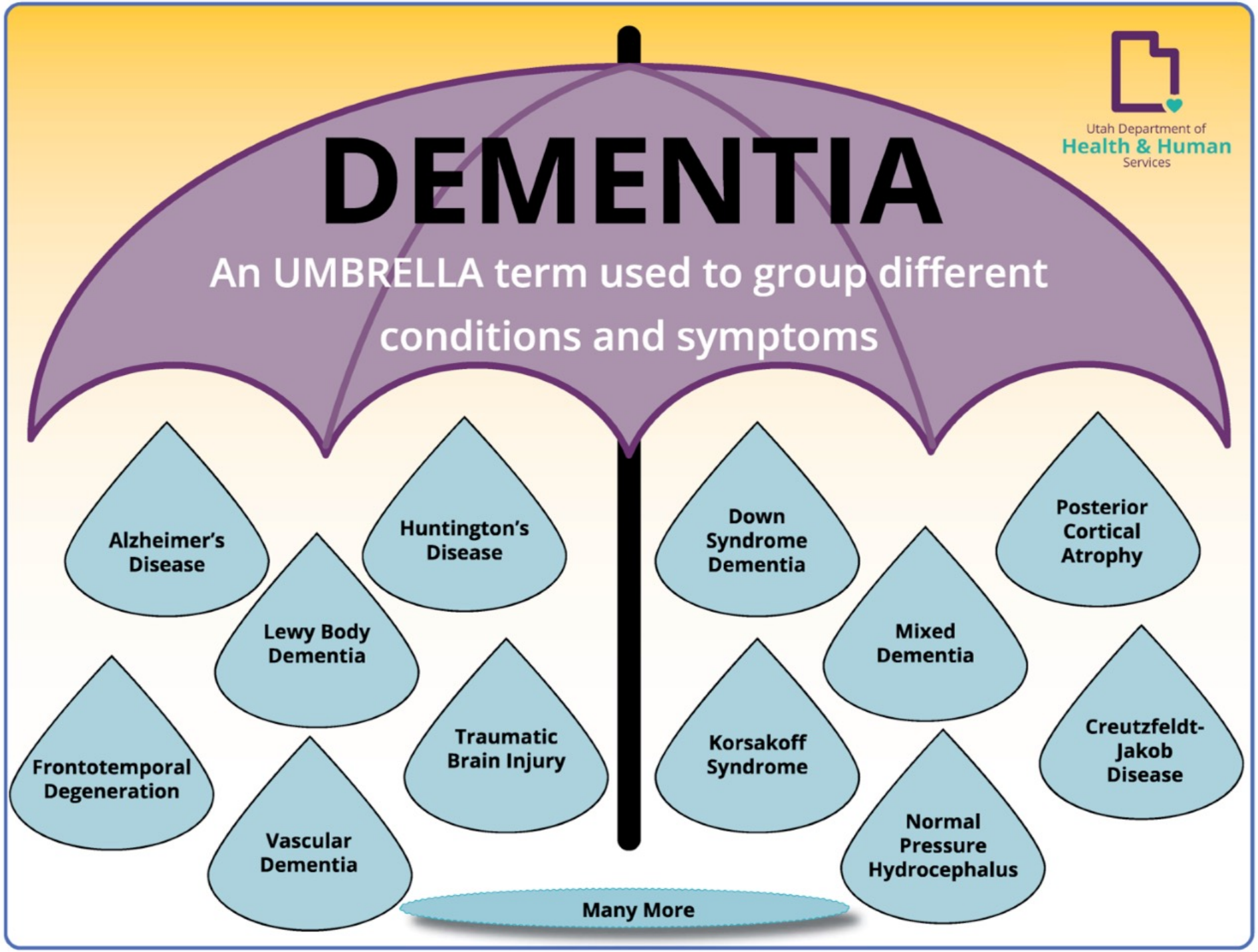
CONFUSION OF TIME AND PLACE

SOCIAL WITHDRAWAL

POOR JUDGEMENT

STRUGGLING TO COMMUNICATE

CHANGES IN VISION

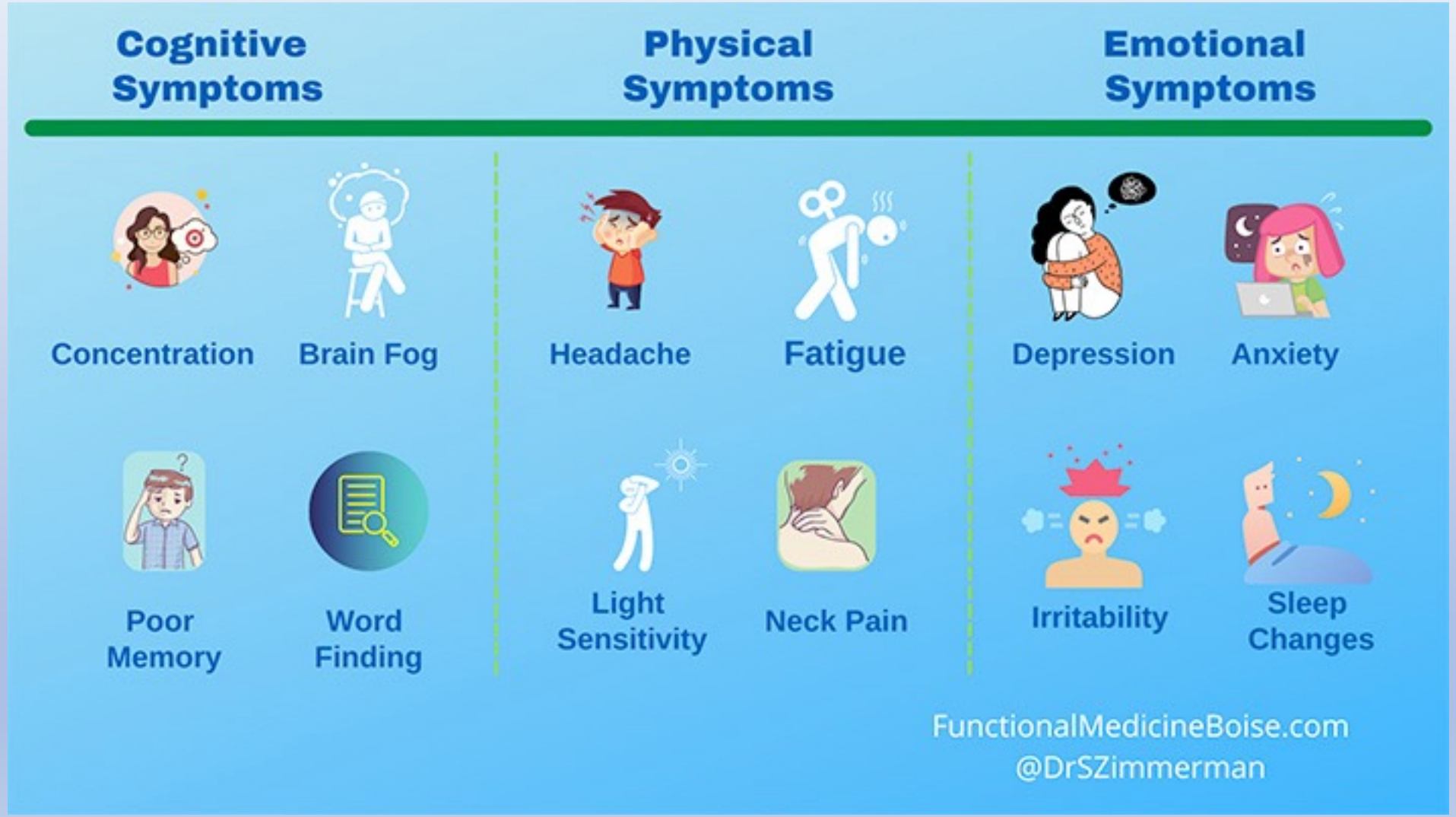

DEMENTIA
An UMBRELLA term used to group different conditions and symptoms
Utah Department of Health & Human Services
Alzheimer's Disease
Huntington's Disease
Down Syndrome Dementia
Posterior Cortical Atrophy
Lewy Body Dementia
Mixed Dementia
Frontotemporal Degeneration
Traumatic Brain Injury
Korsakoff Syndrome
Creutzfeldt-Jakob Disease
Vascular Dementia
Normal Pressure Hydrocephalus
Many More

The Problem Of Defining Dementia

- Who defines what dementia is.
- There are thought to be over 80 different ‘forms’ of dementia.
- AD is but one form of dementia.
- Is dementia just a disease of the brain or a more systemic disorder?
- The definition of dementia is the gradual reduction of cognitive skills, memory, language usage and
- Problem-solving ability.
- Caused by ‘physical changes’ in the brain.
- What are we supposed to be treating?
- What is ‘the best’ treatment for dementia? Do we need different treatments for each of the different ‘forms’ of dementia?

Other CNS Diseases Have Symptoms that Overlap With Dementia and AD

SOME SYMPTOMS OF CONCUSSION



Signs and Symptoms of Depression

Persistent feelings of sadness

Loss of interests In activities

Trouble sleeping or oversleeping

Appetite or weight changes

Fatigue or decreased energy

Difficulty thinking clearly or quickly

Irritability, frustration, or pessimism

Physical aches and pains

Recurrent thoughts of death or suicide

What's Normal Aging and What's Not?

- " Functional decline that is part of aging sometimes seems similar to functional decline that is part of a disorder. For example, with advanced age, a mild decline in mental function is nearly universal and is considered normal aging. This decline includes increased difficulty learning new things such as languages, decreased attention span, and increased forgetfulness."

- "Sometimes the distinction between functional decline that is part of aging and functional decline that is part of a disorder seems arbitrary. For example, as people age, blood sugar levels increase more after eating carbohydrates than they do in younger people. This increase is considered normal aging. However, if the increase exceeds a certain level, diabetes, a disorder, is diagnosed. In this case, the difference is one of degree only."

- Other disorders affect people of all ages but may cause different symptoms or complications in older people. The following are some examples:

- **Underactive thyroid gland (hypothyroidism):** Usually, younger people gain weight and feel sluggish. In older people, the first or main symptom may be confusion.

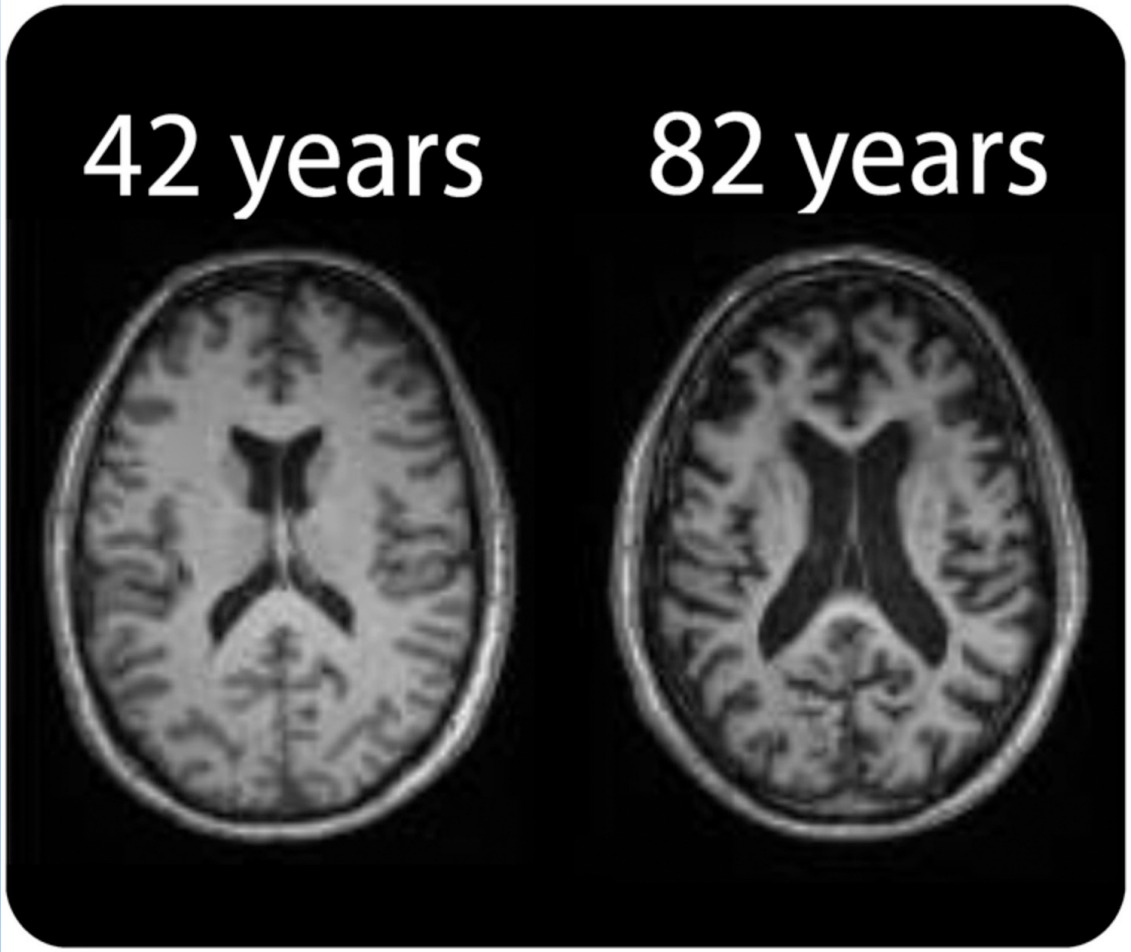
- **Overactive thyroid gland (hyperthyroidism):** Usually, younger people become agitated and lose weight. In contrast, older people may become sleepy, withdrawn, depressed, and confused.

- **Depression:** Usually, younger people become tearful, withdrawn, and noticeably unhappy. Sometimes older people do not seem unhappy. Instead, they become confused, forgetful, and listless, lose interest in their usual activities, or seem lonely.

- **Heart attack:** Usually, younger people have chest pain. Older people may not have chest pain but may have difficulty breathing or abdominal pain. They may sweat profusely, suddenly feel tired, pass out, or become confused.

- *Quoted from Steffanci R, (2022) Merck Manual: Disorders in older people.*

“Normal Aging” Results In Substantial Brain Changes



A Brief Overview Of What Are Thought To Be The Causes Of Dementia

Current Thinking on the Causes of Alzheimer's Disease and Dementia from the National Health Service UK

- Alzheimer's disease is the most common type of dementia.
- *Alzheimer's disease is thought to be caused by the abnormal build-up of 2 proteins called amyloid and tau.*
- Deposits of amyloid, called plaques, build up around brain cells. Deposits of tau form "tangles" within brain cells.
- Researchers do not yet fully understand how amyloid and tau are involved in the loss of brain cells.
- Vascular dementia is caused by reduced blood flow to the brain, which damages and eventually kills brain cells.
- Frontal lobe dementia. *Thought to be caused by an abnormal clumping of proteins, including tau, in the frontal and temporal lobes at the front and sides of the brain.*

Plaques and Tangles. Cause Or A Product Of The Disease?

- People with Alzheimer's disease have plaques and tangles in their brains.
- Plaques are clumps of a protein called beta-amyloid.
- Tangles are fibrous masses made up of tau protein. It's thought that these clumps damage healthy brain cells and the fibers connecting them.
- People who die of other causes but with plaques and tangles in their brain may not always show signs of dementia.
- Do plaques and tangles (*bAmyloid, tau protein*) ‘cause’ dementia or are they by-products of the disease?
- What do we need to treat in this situation?

Is Dementia A Brain Or Systemic Disease?

- In some cases, genetic factors explain AD risk, but a high percentage of late-onset AD is unexplained.
- AD is associated with a number of physical and systemic problems; suggesting that AD is a multifactorial, inflammatory disease that affects both the CNS and periphery.
- AD modulates whole-body changes and vice versa.
- A common feature of many systemic processes linked to AD is involvement in energy metabolism.
- Despite efforts to strictly define AD as a homogeneous CNS disease, there may be no single cause or pathway leading to the syndrome of AD dementia.

QUESTION: DID THE ASHES CAUSE THIS FIRE?

QUESTION: DID ALL THIS DETRITUS CAUSE A TORNADO?

The Story Gets More Complex: Transposable Elements: Another Potential Cause of AD

- Transposable elements (TEs), also known as "jumping genes," are DNA sequences that move from one location on the genome to another. *These elements were first identified more than 50 years ago by geneticist Barbara McClintock.*

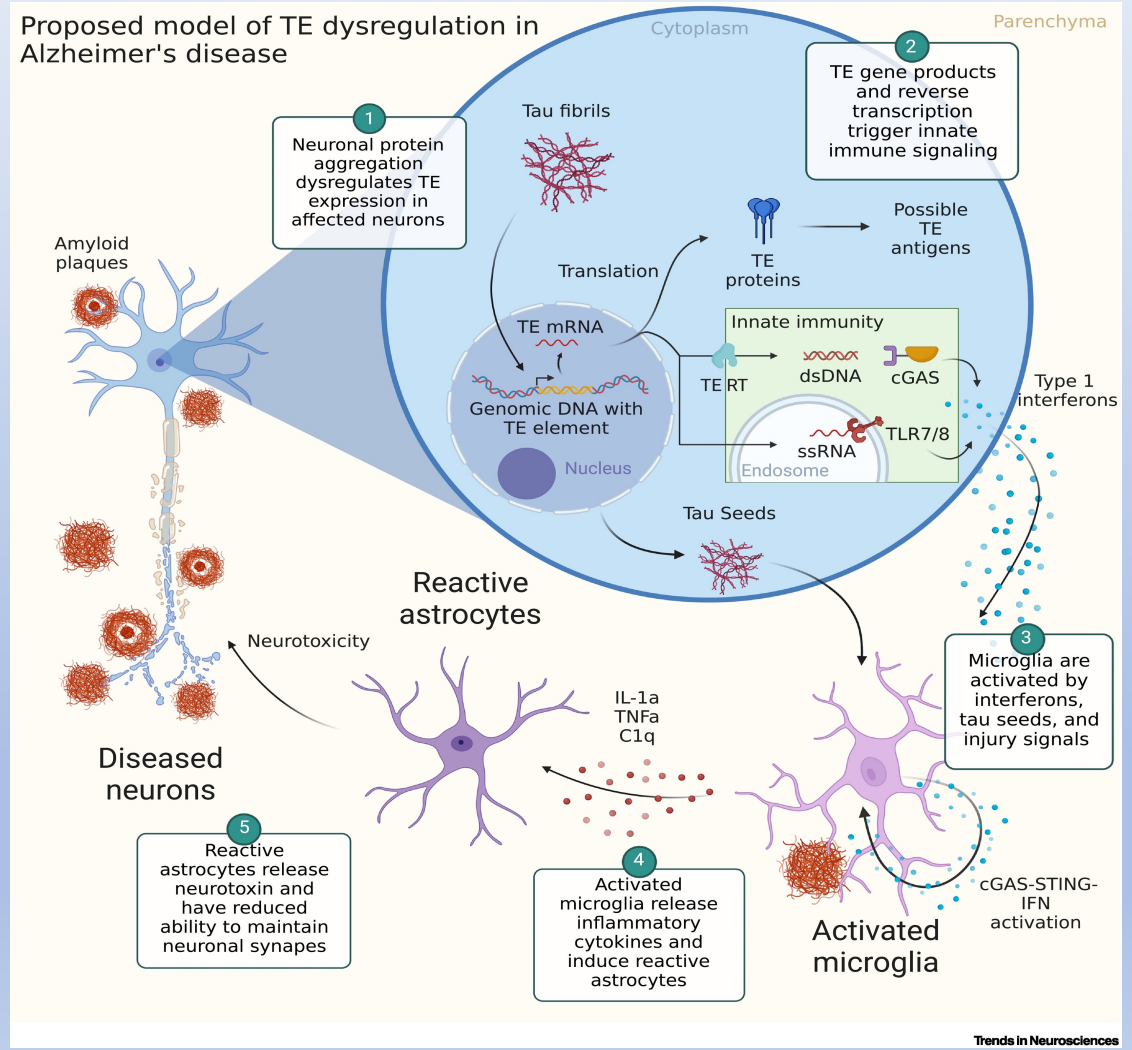
- TE-derived sequences are estimated to account for ~45% of the human genome, the majority are degenerate and incapable of mobilization.

- Autonomous TEs can move on their own, while nonautonomous elements require the presence of other TEs in order to move.

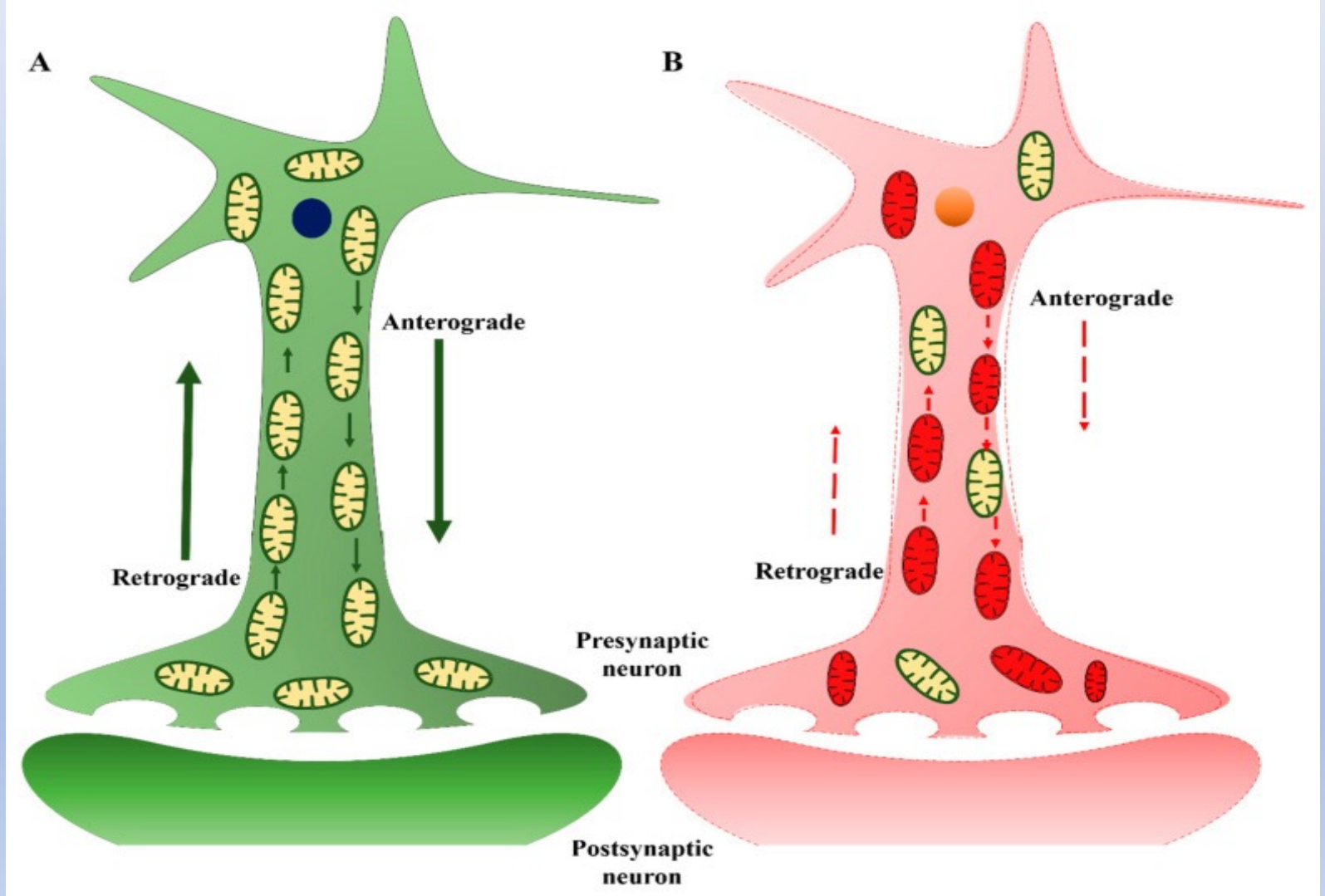
- However, TE surveillance may deteriorate with brain aging, and this can lead to leading to cellular degeneration and the symptoms of AD.

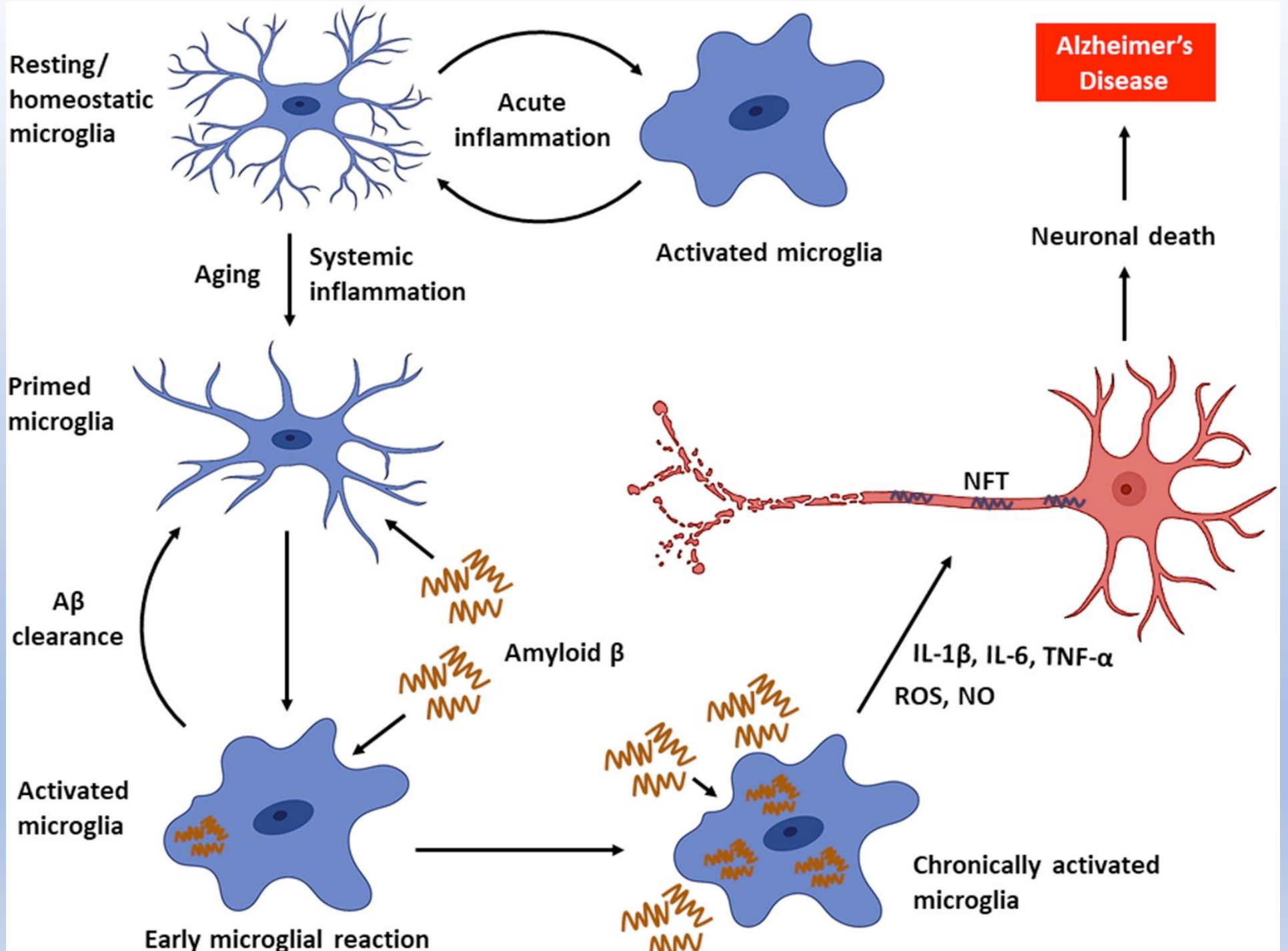
- In humans and animal models, aberrant TE activation has been implicated in many neurologic disorders, including multiple sclerosis Rett syndrome amyotrophic lateral sclerosis (ALS)-frontotemporal degeneration (FTD).

Aging And Neurodegenerative Disease Are Characterized By Genomic Instability In Neurons, Including Aberrant Activation And Mobilization Of Transposable Elements. Guo, et al, Cell Rep, 2018



Other Components Of/In AD: Mitochondrial Transport Is Highly Disrupted But Not Just In The Brain




Resting/
homeostatic
microglia
Acute
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NFT
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IL-1β, IL-6, TNF-α
ROS, NO
Activated
microglia
Chronically activated
microglia
Early microglial reaction

Cures Everything: Currently Available Online For Only $99/bottle

The Marketing Of Brain Plasticity

Plasticity in a Bottle?

Top 10 Brain Supplements

1. Alpha Focus
2. Cerebral Charge
3. Neuro HD
4. MedixSelect Cresceo
5. MRM Neuro-Max II
6. FutureBiotics ThinkFast
7. ProSupps I-Focus
8. TheraBotanics Cebria
9. Vitazen CogniZen
10. Truetoniqs Brain Toniq

The Hard Sell

- Alpha focus has jumped to the top ranking in every category.
- It is specifically designed to boost memory focus, reduce mental focus and support healthy brain function.
- Alpha focus helps your brain naturally increase its potential and immediately improves function.
- Alpha focus jump-starts your mental focus.
- The natural ingredients smooth enural pathway to give razor-sharp focus without negative side effects.

The Promise of Advanced Bionutritionals: All In Just One Capsule

- Each and every one of our cells contains mitochondria. Mitochondria convert oxygen to energy. Optimal mitochondrial function is essential for good health.
- As you age, your mitochondria become less efficient in producing energy. Anti-aging experts believe that maintaining mitochondrial health is important for cellular energy production.
- Now you can support the health of your Mitochondria and support energy production with the essential nutrients found in Advanced Mitochondrial Formula. Including:
- **Niacinamide:**
- This powerful nutrient is a form of Vitamin B3 that directly affects your body's ability to produce energy. Niacinamide is an essential cofactor for ATP (energy) generation in mitochondria. It raises levels of NAD — one of the most crucial molecules for health and energy — which is thought to promote mitochondria performance and energy metabolism.
- **Quercetin:** Research suggests that this potent antioxidant may help increase mitochondrial biogenesis in brain and muscle.
- **Resveratrol:** This superstar polyphenol found in red grapes has powerful antioxidant properties that reduce oxidative stress while promoting a healthy inflammatory response. As a potent antioxidant, resveratrol protects mitochondria from free-radical damage, promotes mitochondrial function, and may encourage the production of new mitochondria.
- **Curcumin:** Curcumin is the main active ingredient in turmeric. As a strong antioxidant it fights oxidative stress while promoting a normal inflammatory response. Curcumin supports stamina, physical performance as well as neurofunction.
- **Acetyl l-Carnitine:** This nutrient is essential to the production of energy since it transports fatty acids into cells' mitochondria. These fats are burned to create usable energy.
- **Alpha Lipoic Acid:** This powerful antioxidant supports mitochondrial function and decreases oxidative stress. Research suggests that Alpha-Lipoic Acid helps protect mitochondria from free radical damage. It is both water- and fat-soluble, which allows it to work in every cell or tissue in the body.
- **Coenzyme Q10:** Not only does CoQ10 support your heart, research has shown that CoQ10 boosts cellular energy output throughout the body. CoQ10 helps mitochondria burn fuel more effectively. By increasing the efficiency of our mitochondria, CoQ10 reduces oxidant damage and provides protection for every cell in the body.

So, Where Do We Stand Now?

ADDRESSING THE PROBLEM OF CLINICAL ENDPOINTS IN BOTH ANIMAL AND HUMAN STUDIES

- In clinical trials:
  - Is the right drug being used for the specific condition?
  - Are doses and duration of treatments appropriate for the condition being treated?
- Are the endpoints:
  - Representative of the disease being treated?
  - Providing detailed information?
  - Being measured at the right time? And for the right duration?
  - Reliable? low variability? Measures of daily life?

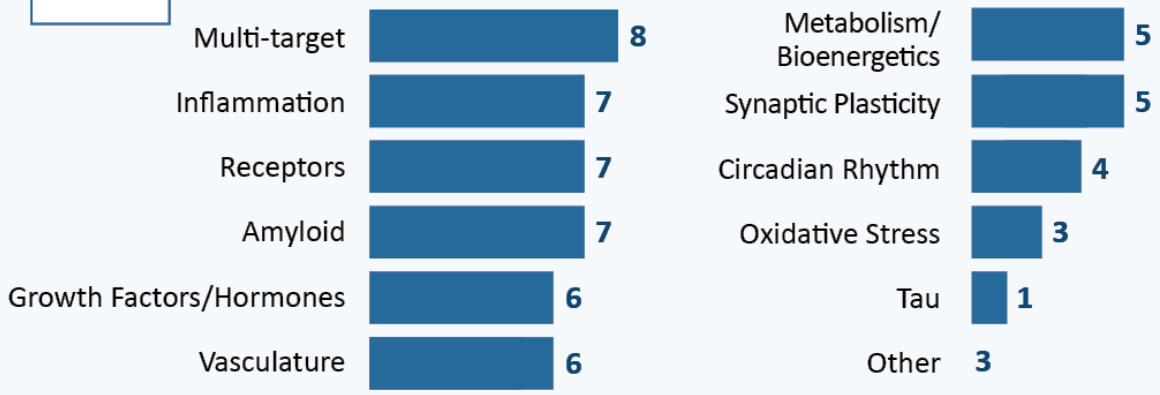
Active NIA AD/ADRD Clinical Trials

Pharmacological — 70 TRIALS

62 trials

Phase I & Phase II

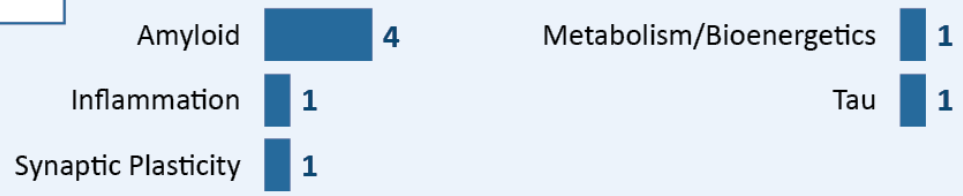
Targeted Disease Process



8 trials

Phase II/III, Phase III, & Phase IV

Targeted Disease Process



Non-Pharmacological — 158 TRIALS

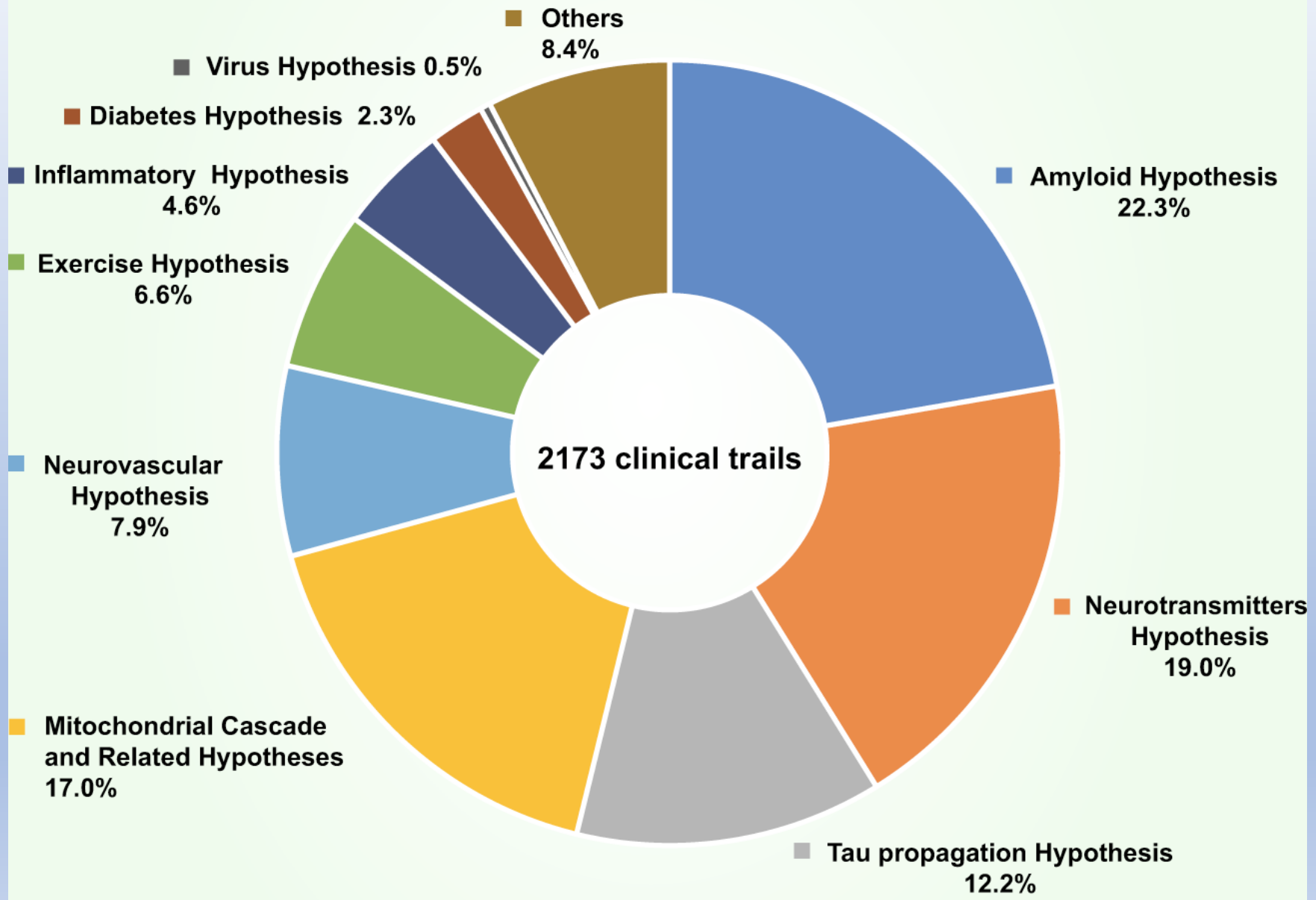
Modality

For more information please visit
www.nia.nih.gov/research/ongoing-AD-trials

NIH National Institute on Aging

Data last updated: March 2023.

Various Hypotheses of Alzheimer's Disease in Clinical Trails up to 2019




Rx Only
NDC 64406-101-01
Aduhelm™
(aducanumab-avwa)
Injection
170 mg/1.7 mL
(100 mg/mL)
For Intravenous Infusion Only
Must be diluted prior to use
Biogen

The Process Of Drug Approval Needs Attention

- “The drug maker Biogen said it would abandon its ownership rights to Aduhelm, an Alzheimer’s drug that had provoked fierce criticism of the company and regulators after it was approved based on weak evidence that it would help patients.

- With an initial sticker price of $56,000 a year, Aduhelm was once projected to be taken by millions of Alzheimer’s patients, strain Medicare’s budget and bring in billions of dollars a year. But Aduhelm failed spectacularly in the marketplace.

- Biogen’s decision closes out a years long saga that generated outrage and eroded trust in the regulatory process for bringing new medicines to market. One F.D.A. adviser called the approval of the drug perhaps “the worst approval decision that the F.D.A. has made that I can remember.”

- A congressional inquiry later found that the F.D.A.’s process for approving Aduhelm had been “rife with irregularities”

- Aduhelm has been supplanted by two Alzheimer’s drugs that have shown evidence that they can *somewhat slow* cognitive decline but that doctors say may not have a significant enough effect to be noticeable to patients or families. (donanebab, leqembi)”
- *Source: NYT, January 21, 2024*

“How Many Clinical Trials Can’t Be Trusted”

R. Van Noorden, Nature 169, July 2023 (review article)

- Over 500 clinical trials were evaluated by *John Carlisle (editor, J Anesthesia).*
- Forty-four percent of the trials contained flawed data, impossible statistics, incorrect calculations, or duplicated numbers or figures.
- Only recently The Dana Farber Cancer Institute of Harvard University had to *retract over 35 published papers which were deemed to be fabricated.*
- *If clinical trials are based on translational studies, and if the studies are fabricated, this can have serious consequences for patients in the trials and beyond.*

The Pitfalls Of Drug Commercialization

- Industry dominates the research agenda.
- Objectivity and careful evaluation of research data suffers.
- Secrecy and obtaining patent rights replace collegiality and collaborations.
- Emphasis on product development and less on the development of new knowledge.
- Far more $$ are spent on marketing than on research needed to develop new drugs.
- Pharmaceutical and health product companies spent a record $372 million into lobbying Congress *and federal agencies last year*, outspending every other industry and making up over half of all health sector lobbying efforts,

What Can We Do (If Anything)To Make Things Better *For Patients?*

- Diet ‘may’ have a part to play in biological ageing and the development of cognitive decline. Does the gut ‘microbiome’ play a role leading to dementia?
- In addition to a healthy diet, low to moderate alcohol intake may reduce cardiovascular risk and may stimulate the hippocampus.
- Exercise is also beneficial and studies have shown increasing executive functioning and even reduction in the ageing expected decline of white and grey tissue density with increased fitness.
- Schooling and occupation ‘may’ contribute to a cognitive reserve that protects against decline despite neuropathology[22,1]

A Different Approach: Exploring The Critical Role Of Systemic Inflammation As A Probable Cause Of Dementias

- Studying the role of progesterone as a potential, ‘pleuripotent’ treatment
- Dementia in females after menopause
- P4 is a potent anti-inflammatory agent
- P4 is a neuroprotective agent after brain injury
- Equally effective in males and females
- No serious side effects after chronic dosing in GBM and other CNS injuries
- Downside: its really cheap.

WATCH TI

Wh

Aging

- **WATCH THE MEMORY HEALTH VIDEO NOW**

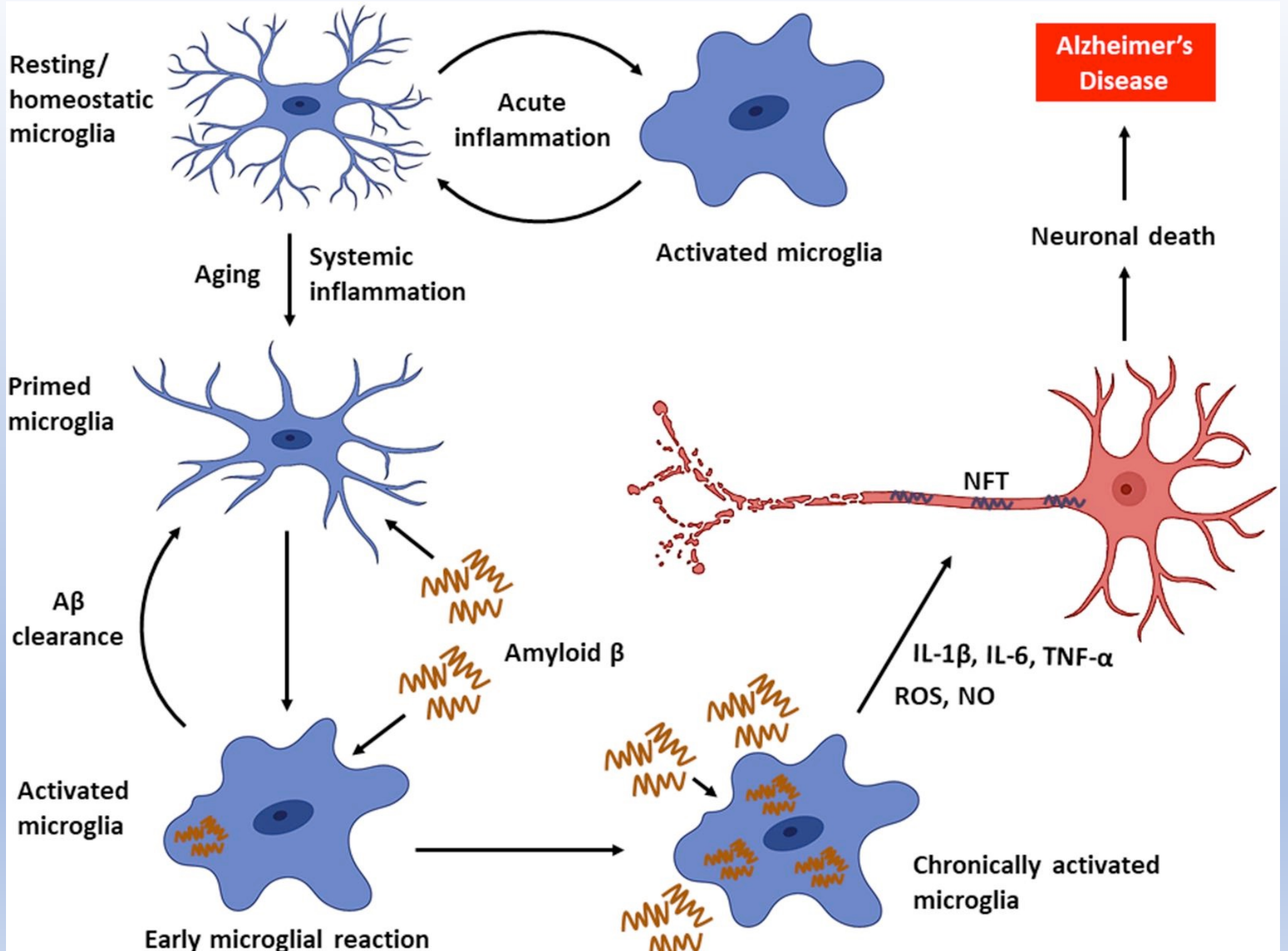
Current ‘Treatments’ For Dementia

- As of October 2021, the FDA has approved several medications for the treatment of Alzheimer's disease. These include:

- 1. Cholinesterase Inhibitors:
- - Donepezil (Aricept)
- - Rivastigmine (Exelon)
- - Galantamine (Razadyne)
- 2. NMDA Receptor Antagonist:
- - Memantine (Namenda)

- These medications are used to help manage symptoms of Alzheimer's disease, such as memory loss, confusion, and changes in behavior.
- It is important to note that these medications do not cure Alzheimer's disease, but they can help improve symptoms and slow down the progression of the disease in some patients.

END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Why Haven't We Done Better? Dogma Is Often The Handmaiden of Contemporary Science

"Normal science, the activity in which most scientists inevitably spend almost all their time, is predicated on the assumption that the scientific community knows what the world is like. Much of the success of the (scientific) enterprise derives from the community's willingness to defend that assumption even at considerable cost. Normal science often suppresses fundamental novelties because they are necessarily subversive of its basic commitments."

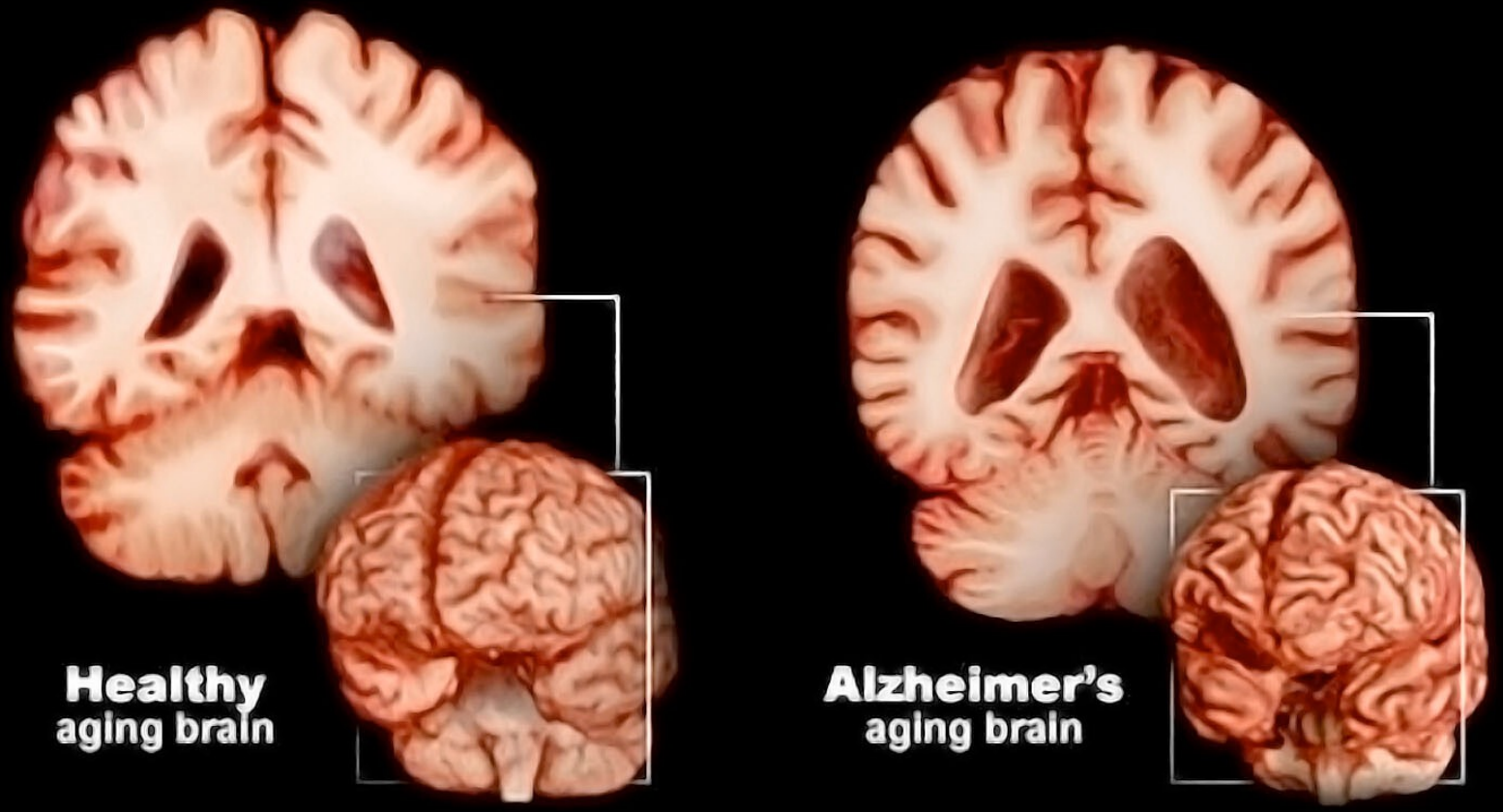
-Kuhn, T.S. "The Structure of Scientific Revolution"
2nd Edition, 1970 Univ. Chicago Press

How Does Science (& Everything Else) Work? Some Basic Assumptions.

- ***"We know that people can maintain an unshakable faith in any proposition, however absurd, when they are sustained by a community of like-minded believers."***
- ***"You will often find that knowing little makes it easier to fit everything you know into a coherent pattern."***
- ***I have yet to meet a successful scientist who lacks the ability to exaggerate the importance of what he or she is doing, and I believe that someone who lacks a delusional sense of significance will wilt in the face of repeated instances of multiple small failures and rare successes, the fate of most researchers.***

- ***D. Kahneman (Nobel Prize in Economic Sciences), Thinking, Fast and Slow,*** Farrar, Straus & Giro

Aging vs Alzheimer's Disease



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- Give a precise definition of dementia
- There are over 80 forms of dementia

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❑ DEFINITION:

- "Dementia is an acquired global impairment of intellect, memory and personality but without impairment of consciousness"

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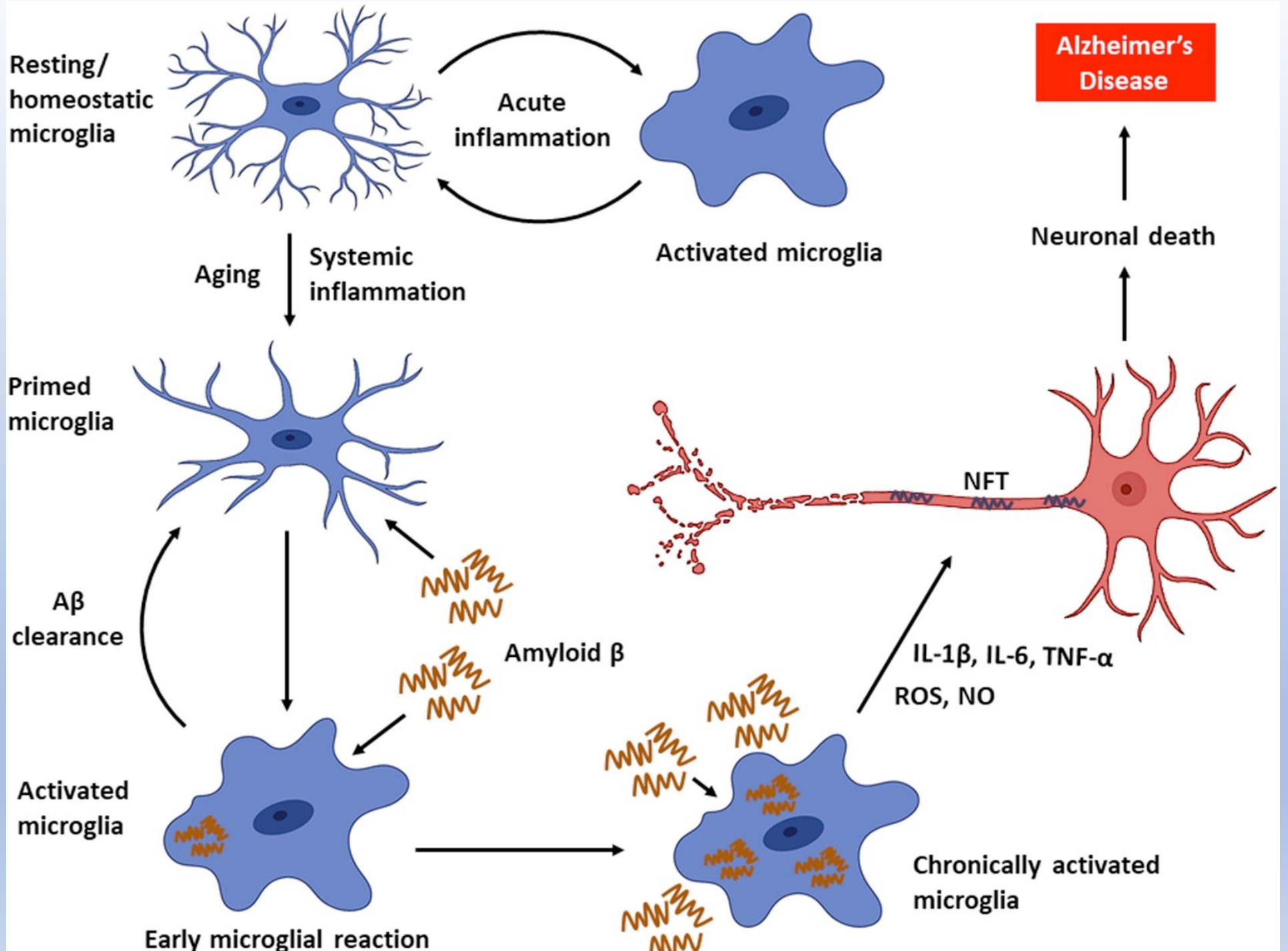
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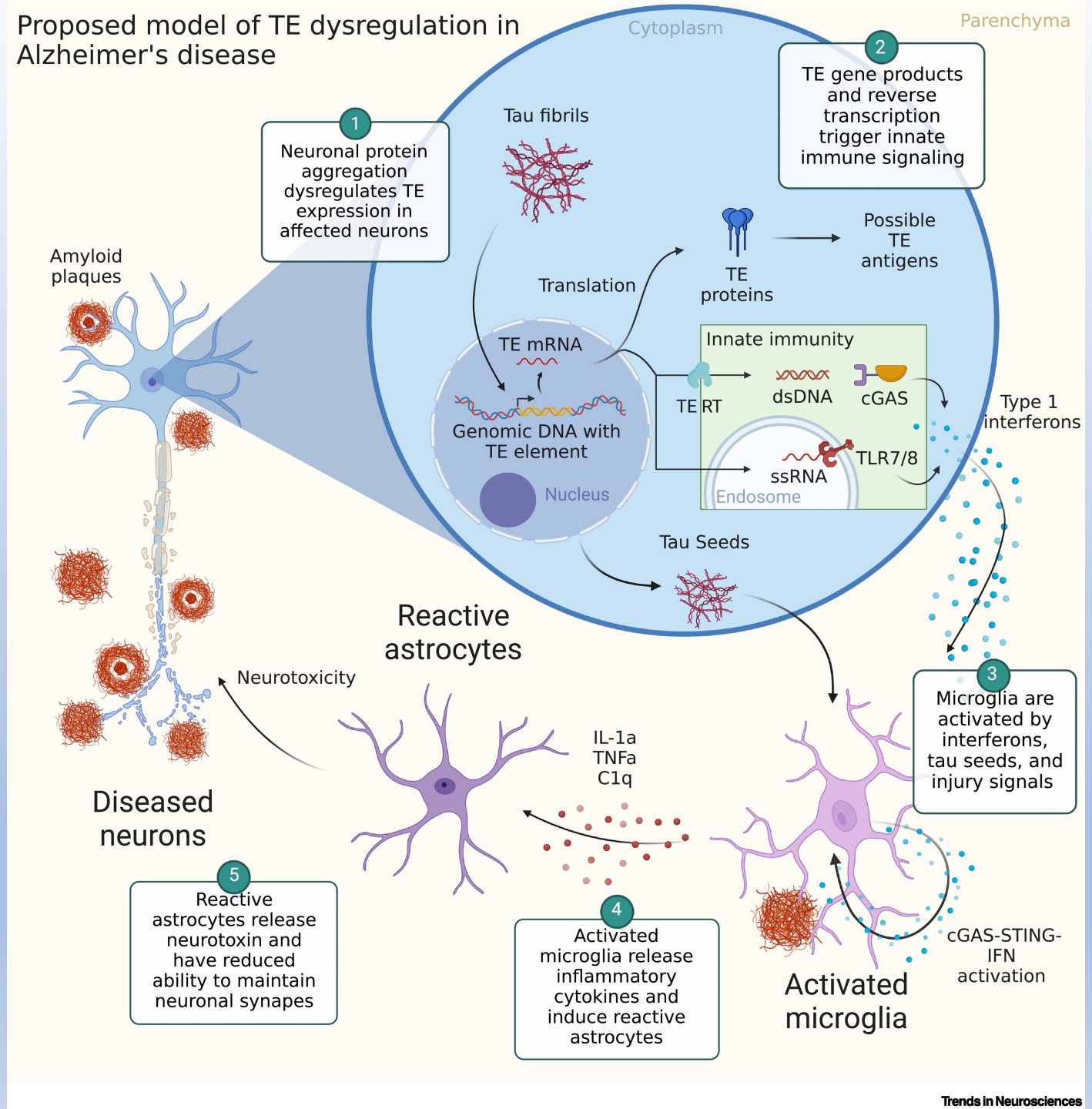
Proposed model of TE dysregulation in Alzheimer's disease
Cytoplasm
Parenchyma
1
Neuronal protein aggregation dysregulates TE expression in affected neurons
Tau fibrils
2
TE gene products and reverse transcription trigger innate immune signaling
Possible TE antigens
TE proteins
Translation
Amyloid plaques
TE mRNA
Genomic DNA with TE element
Nucleus
Innate immunity
TE RT
dsDNA
cGAS
TLR7/8
ssRNA
Endosome
Type 1 interferons
Tau Seeds
Reactive astrocytes
Neurotoxicity
IL-1a
TNFa
C1q
3
Microglia are activated by interferons, tau seeds, and injury signals
Diseased neurons
5
Reactive astrocytes release neurotoxin and have reduced ability to maintain neuronal synapes
4
Activated microglia release inflammatory cytokines and induce reactive astrocytes
cGAS-STING-IFN activation
Activated microglia
Trends in Neurosciences

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