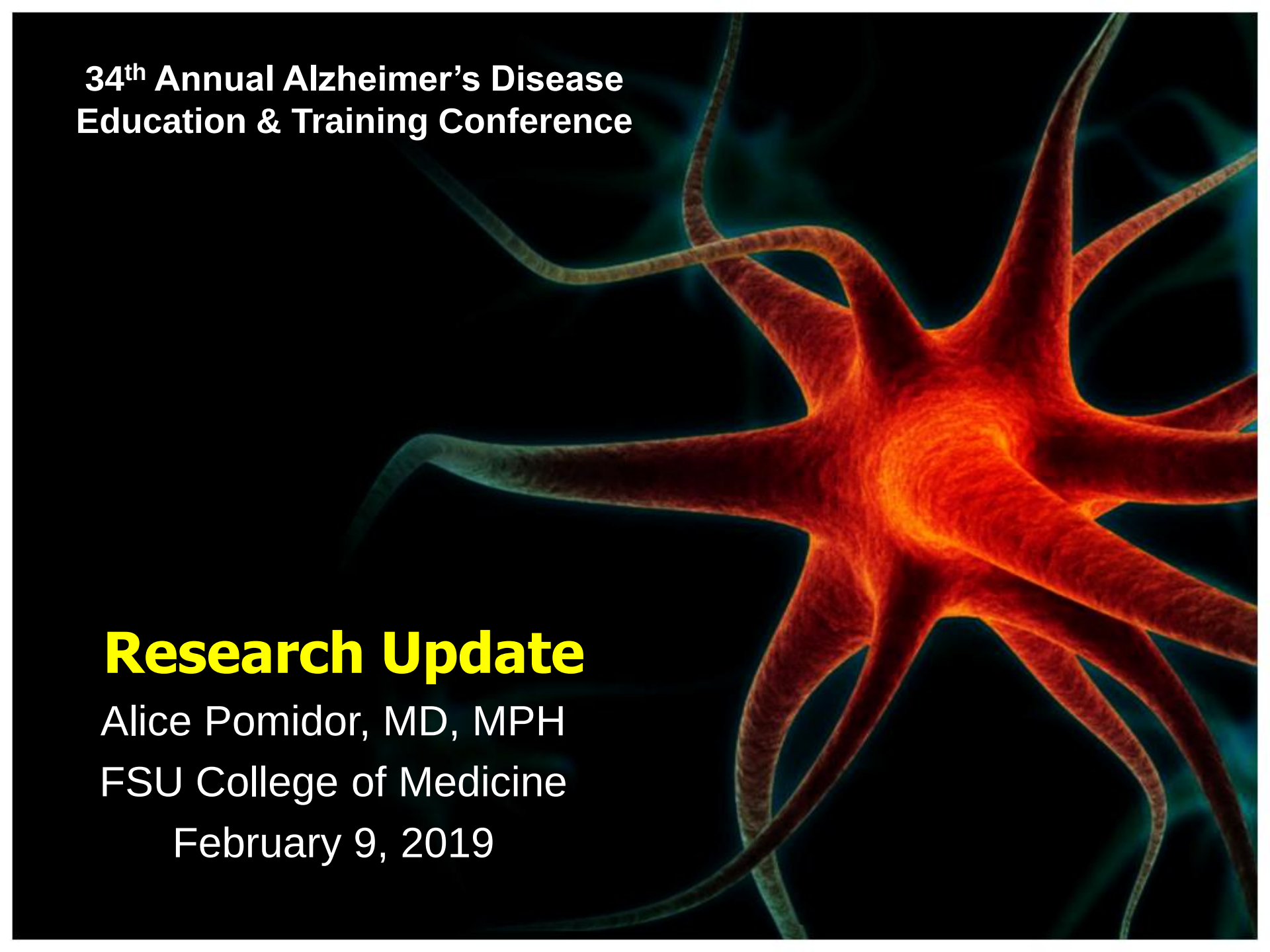
34th Annual Alzheimer's Disease Education & Training Conference



Research Update

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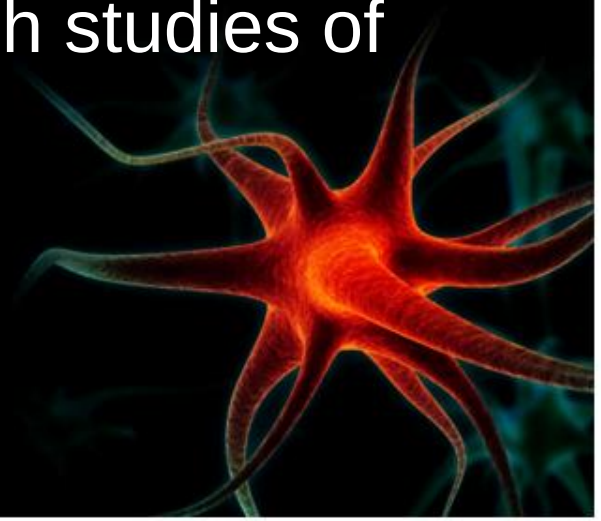
FSU College of Medicine

February 9, 2019

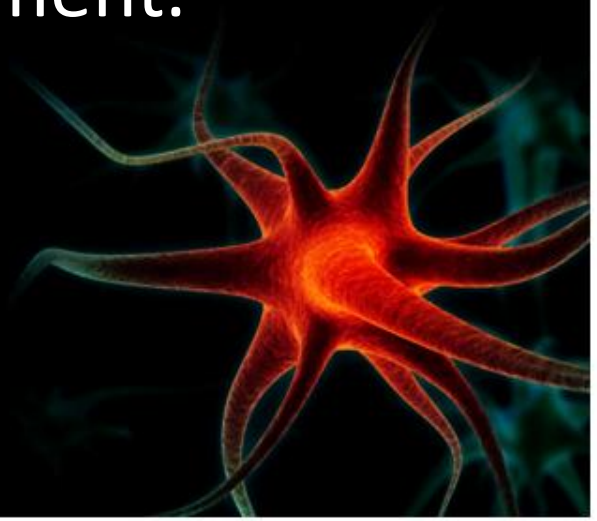
Objectives

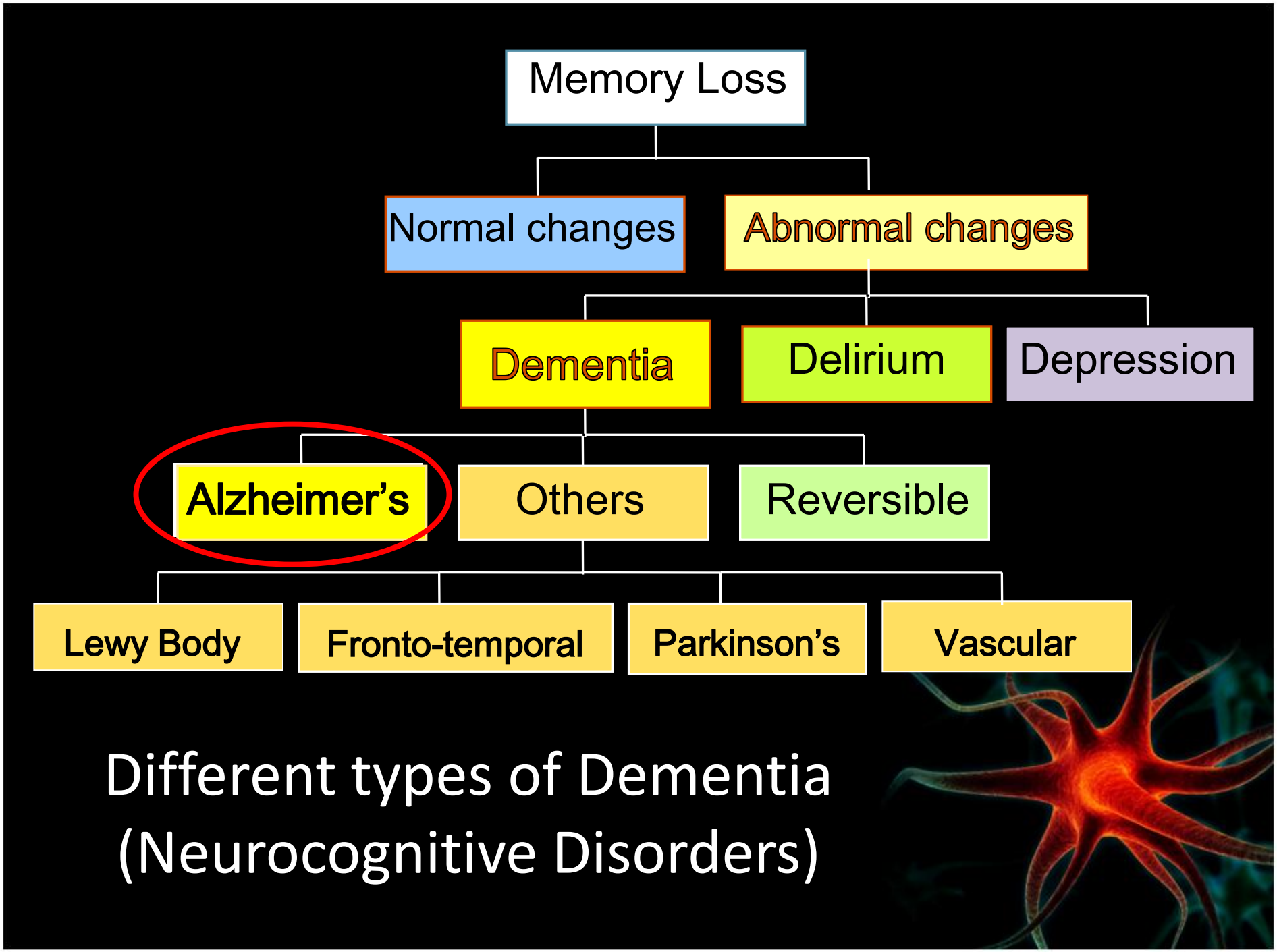
- Review current theories about the causes and risk factors for Alzheimer's-type dementia
- Discuss recent research findings related to Alzheimer's
- Present currently ongoing research studies of Alzheimer's



Dementia: acquired progressive cognitive decline in one or more cognitive areas (memory, planning, language, etc.), which interferes with independence in everyday function and is based on 1) concern of a knowledgeable person and 2) documentation of clinical assessment.

Diagnostic and Statistical Manual 5, 2013

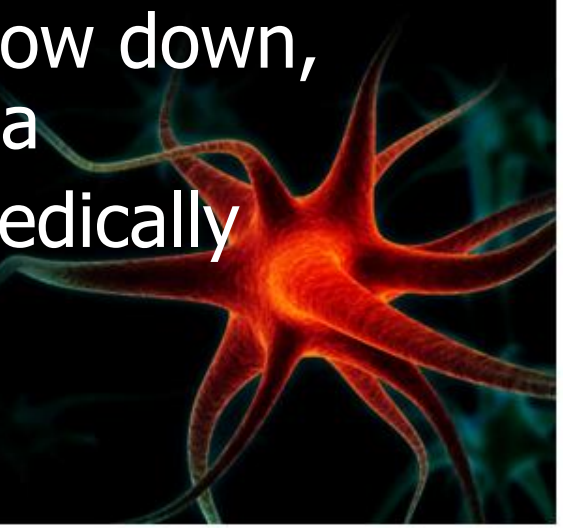




Different types of Dementia (Neurocognitive Disorders)

Research Areas

- National Plan Goal 1: Prevent and Effectively Treat Alzheimer's Disease by 2025
- Understanding the causes and risk factors for developing AD
- Diagnosing AD early, before too much damage has occurred
- Finding ways to delay the onset, slow down, or stop the progression of dementia
- Treating the effects of dementia medically and with effective caregiving

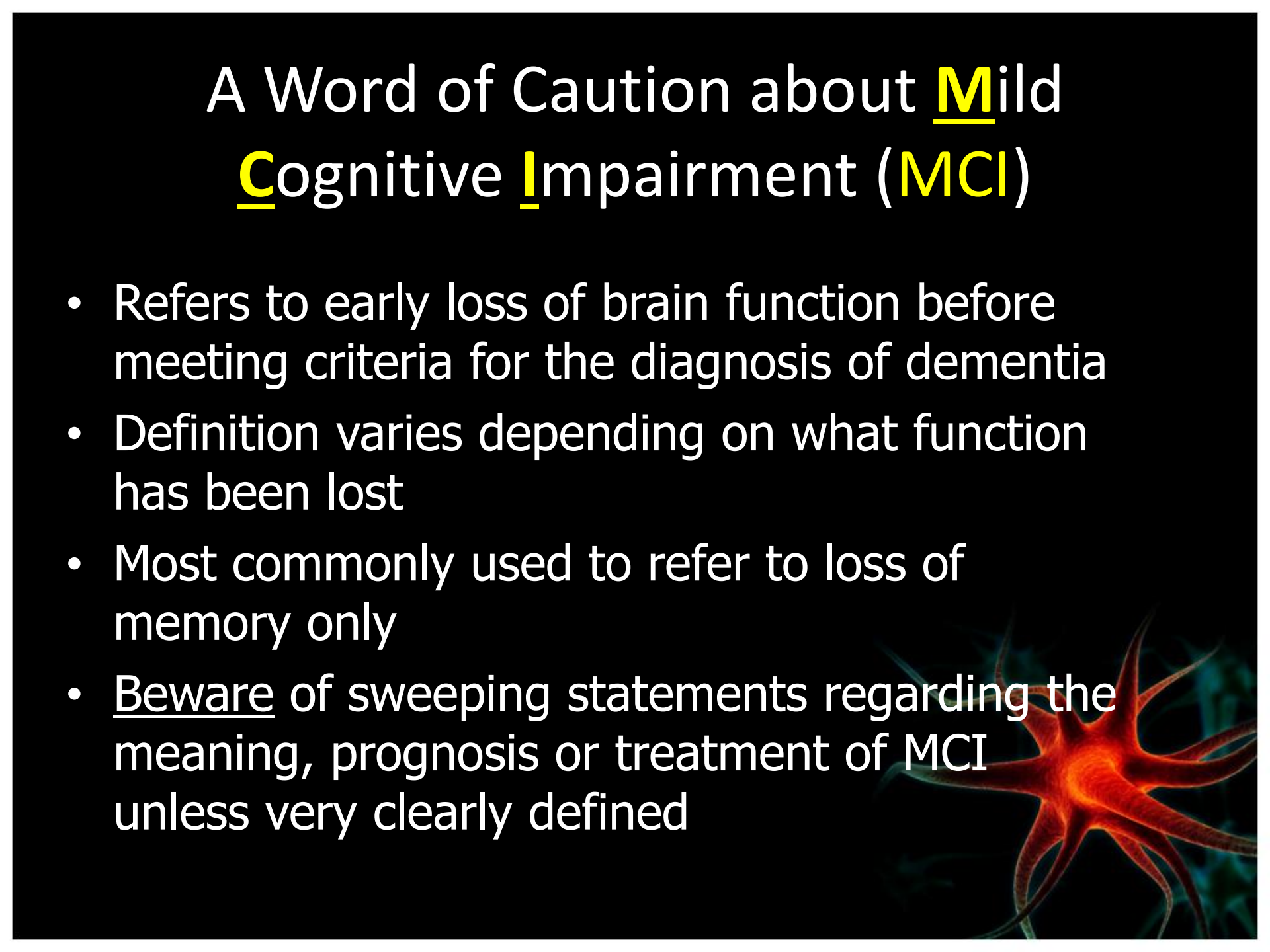


Alzheimer's Disease (AD)

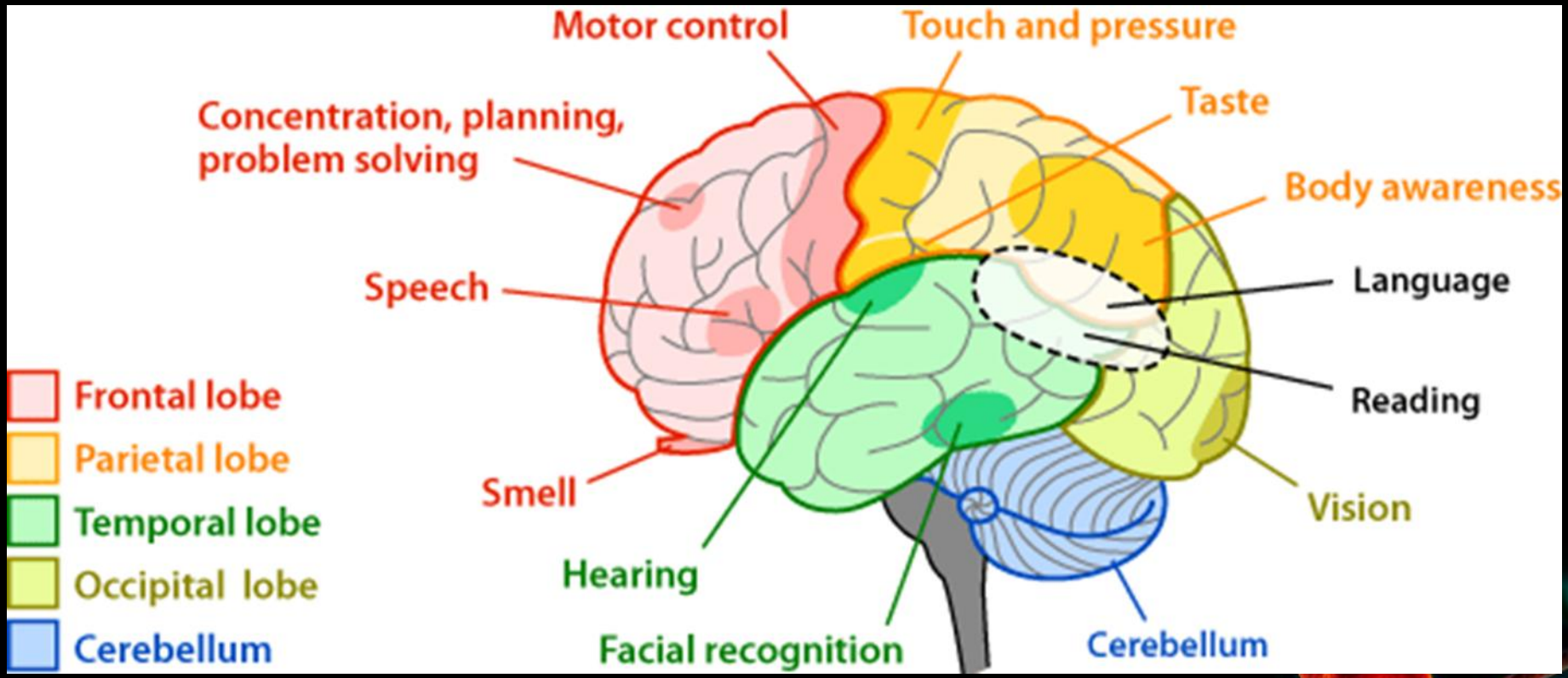
- Causes ongoing brain cell damage which leads to symptoms of:
  - Memory loss
  - Neurologic changes:
    - Language problems
    - Dressing, driving or toileting problems
    - Using objects incorrectly
    - Personality changes
  - Difficulty thinking - judgment, insight, abstract reasoning
  - Affects social functioning

A Word of Caution about Mild Cognitive Impairment (MCI)

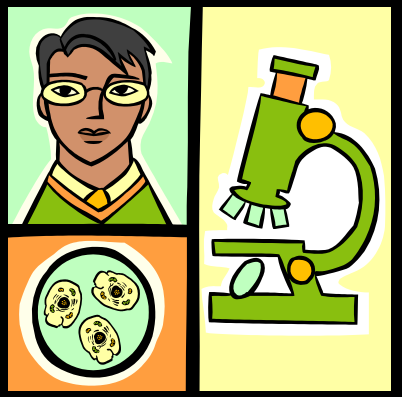
- Refers to early loss of brain function before meeting criteria for the diagnosis of dementia
- Definition varies depending on what function has been lost
- Most commonly used to refer to loss of memory only
- Beware of sweeping statements regarding the meaning, prognosis or treatment of MCI unless very clearly defined



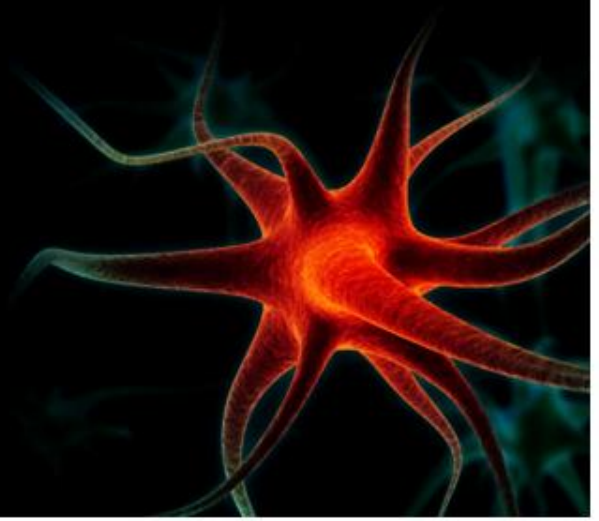
Brain functions



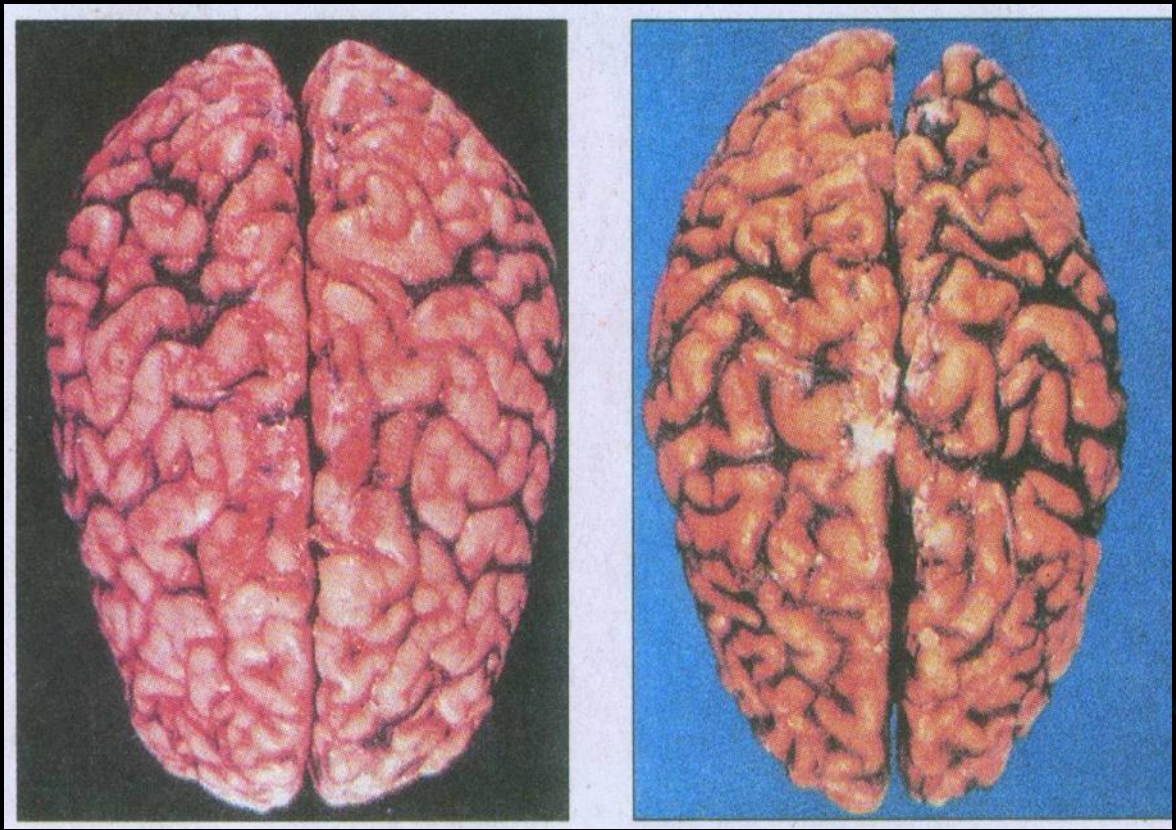
Basic Biology of AD



- Has 3 key features:
  - Amyloid protein **plaques** (toxic substance outside the cell)
  - Neurofibrillary **tangles** (abnormal machinery inside the cell, "tau" protein)
  - Loss of brain cell connections and communication, causing more **cell death**

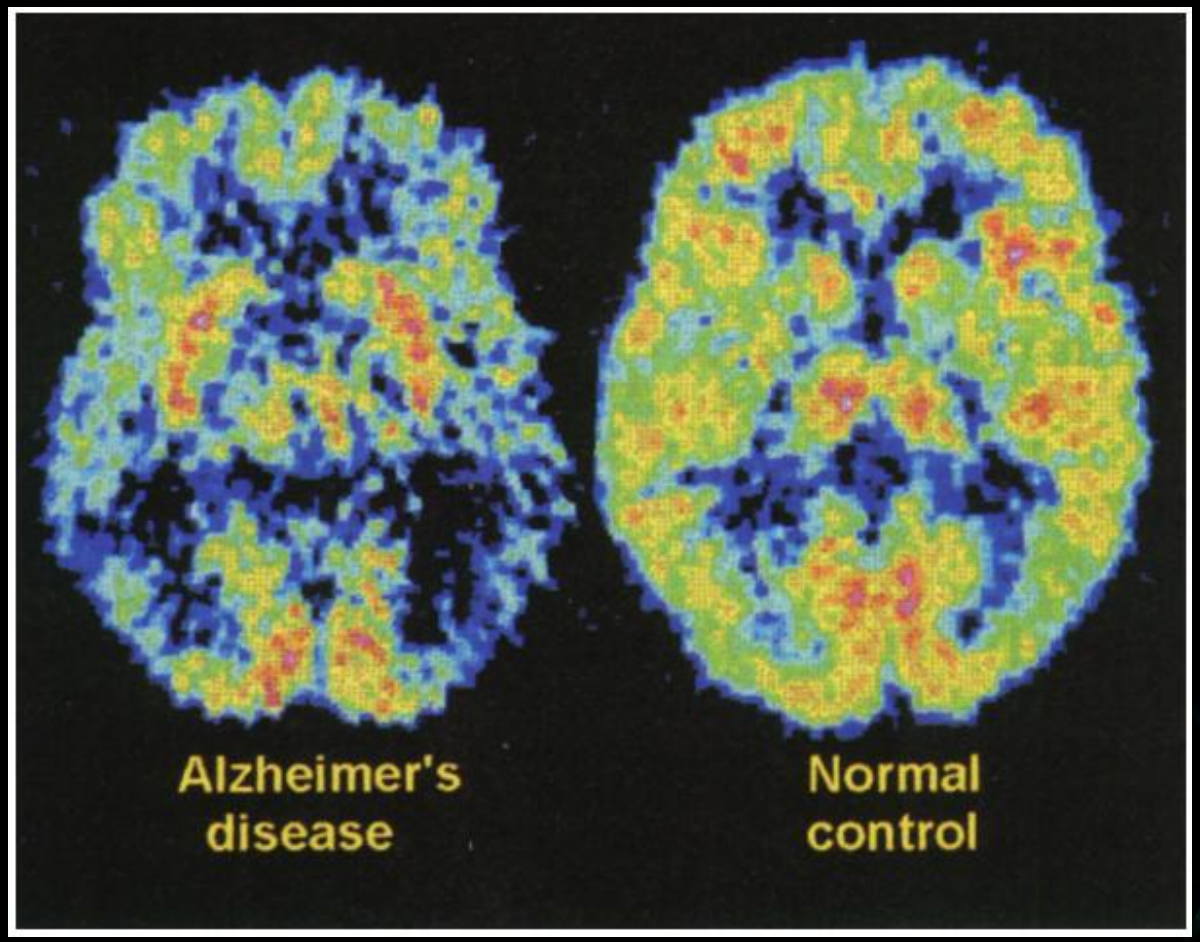


Alzheimer's Disease (AD)

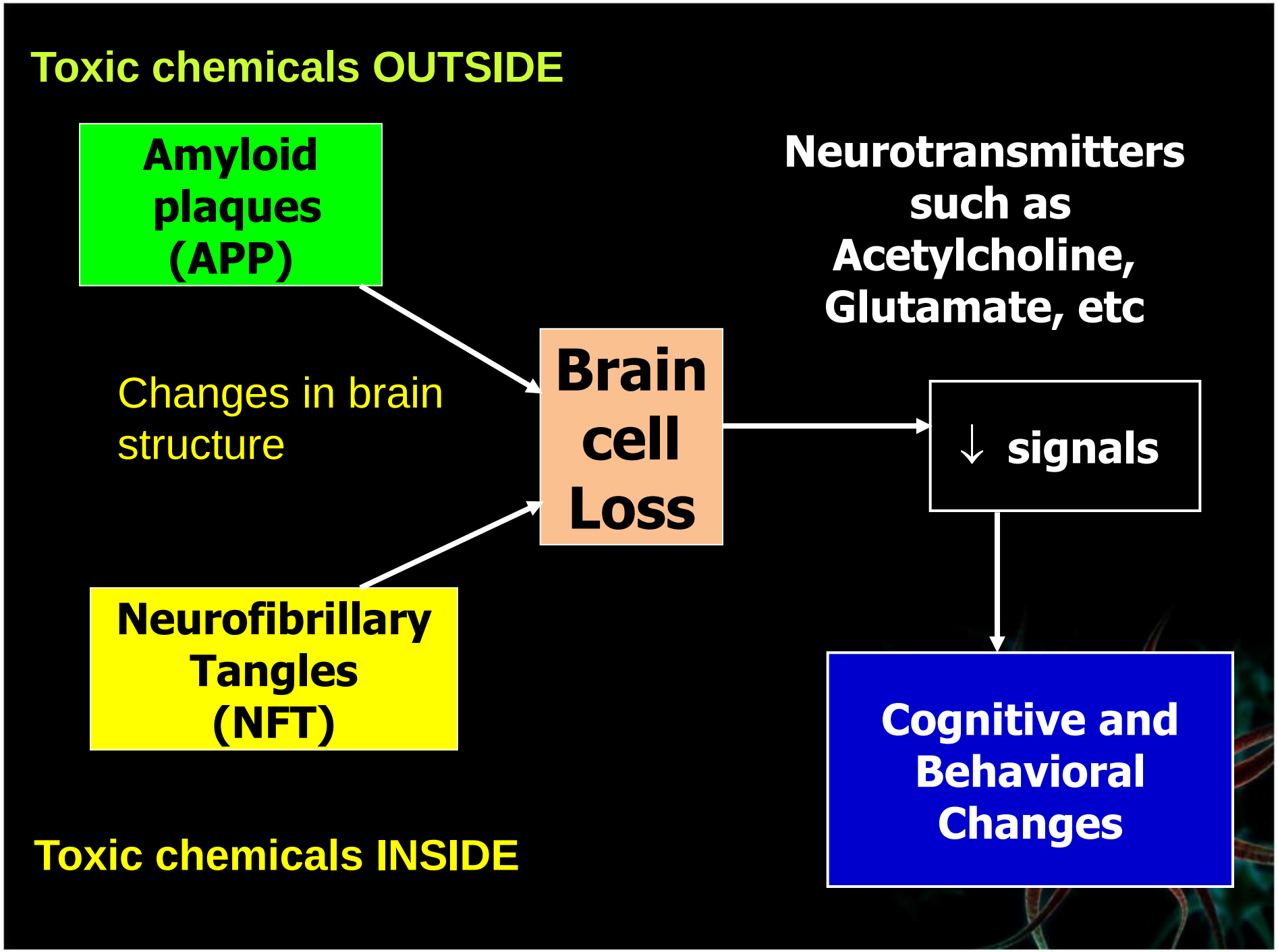


Brain shrinks as the cells die

PET Scan and AD

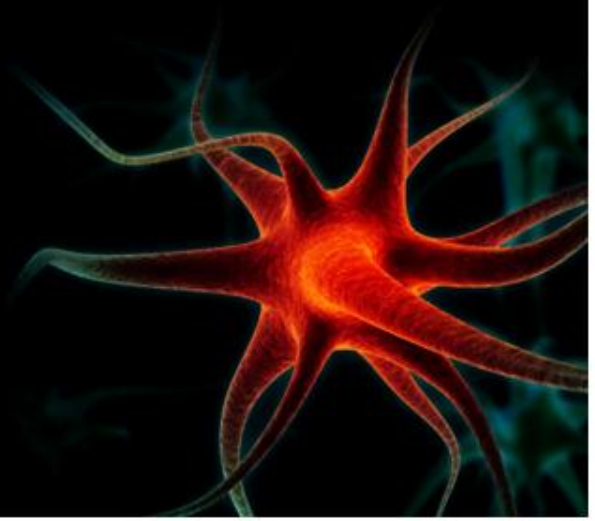


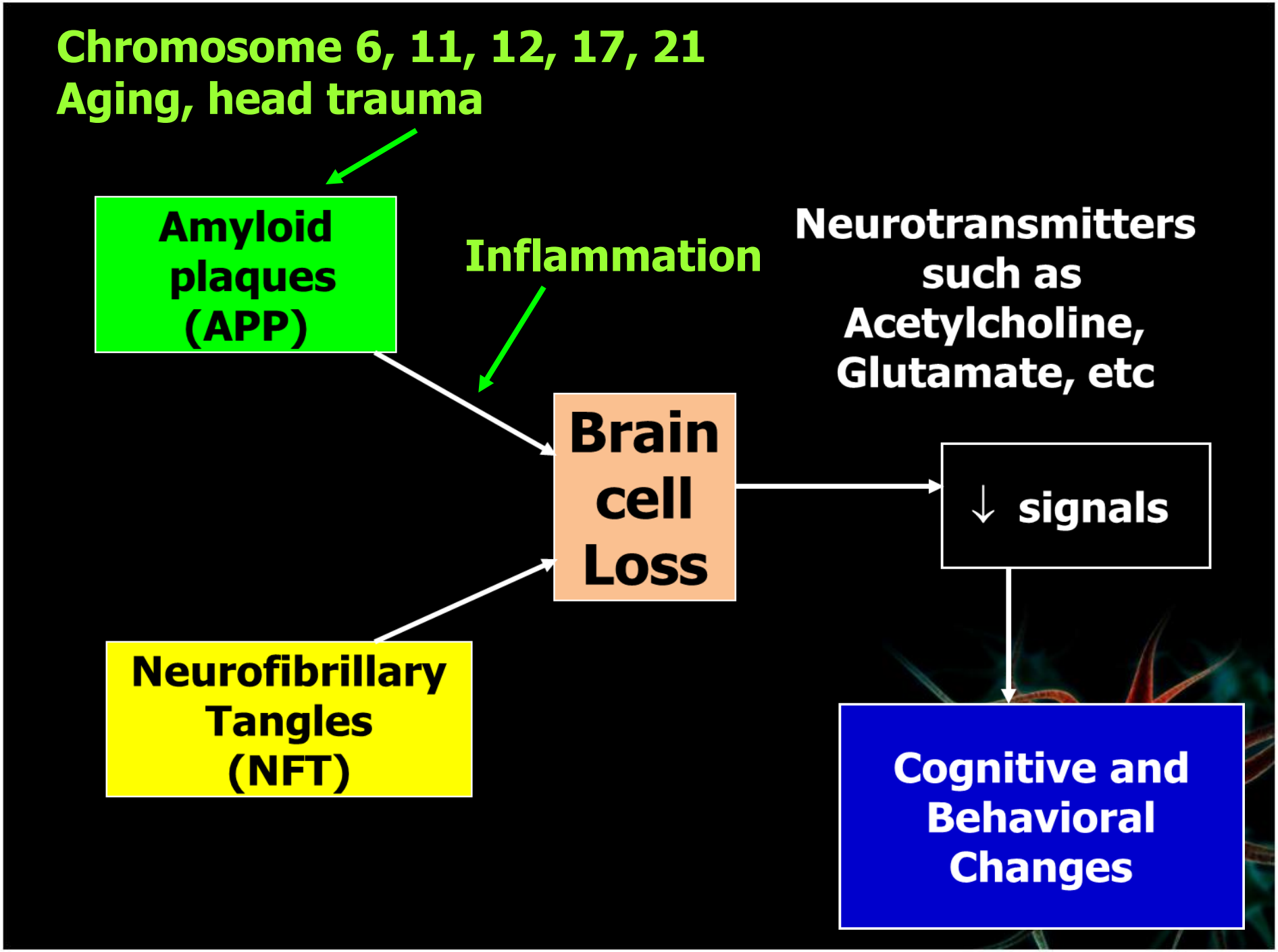
Brain can no longer work properly


Toxic chemicals OUTSIDE
Amyloid plaques (APP)
Neurotransmitters such as Acetylcholine, Glutamate, etc
Changes in brain structure
Brain cell Loss
↓ signals
Neurofibrillary Tangles (NFT)
Cognitive and Behavioral Changes
Toxic chemicals INSIDE

Plaque-related Causes

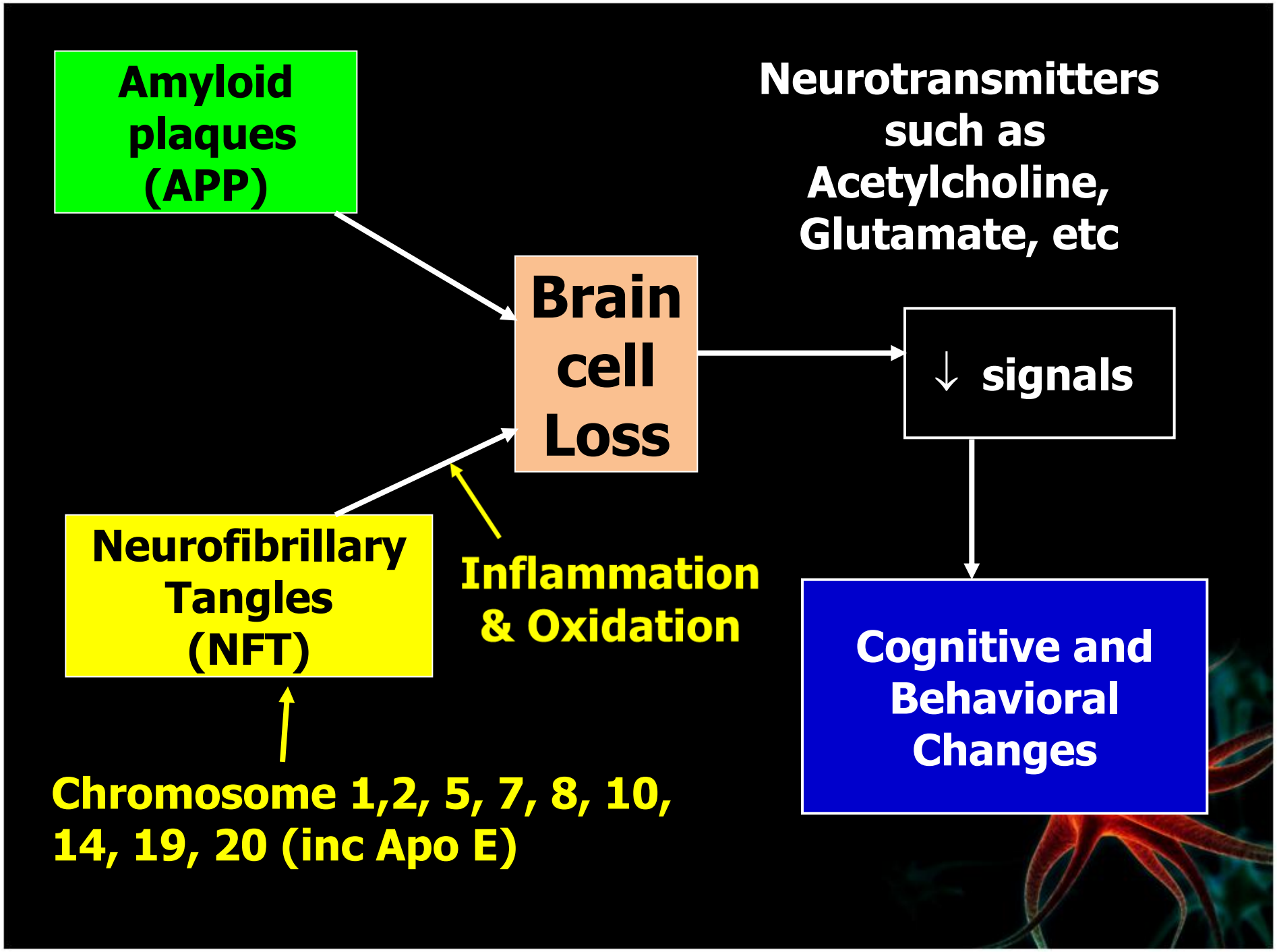
- Genetic predisposition (chromosomes 6,11,12, 17, 21, others)
- Difficulty cleaning up toxic proteins outside the brain cell (low cognitive reserves, aging)
- Increased burden of cell death, such as head trauma
- Possibly triggered by infections?? (periodontal disease theory)




Chromosome 6, 11, 12, 17, 21
Aging, head trauma
Amyloid plaques (APP)
Inflammation
Neurotransmitters such as Acetylcholine, Glutamate, etc
Brain cell Loss
↓ signals
Neurofibrillary Tangles (NFT)
Cognitive and Behavioral Changes

Tangle-related Causes

- Genetic predisposition (chromosomes 1, 2, 5, 7, 8, 10, 14, 19, 20)
- Fat protein changes (apolipoprotein E, cholesterol metabolism)
- Difficulty cleaning up toxic proteins inside the brain cell
- Difficulty supplying energy to the cell connections (free radicals, super oxide dismutase = SOD)

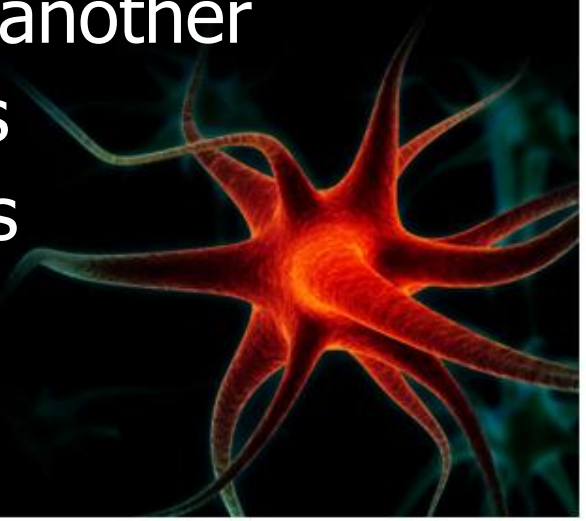

Amyloid plaques (APP)
Neurotransmitters such as Acetylcholine, Glutamate, etc
Brain cell Loss
↓ signals
Neurofibrillary Tangles (NFT)
Inflammation & Oxidation
Cognitive and Behavioral Changes
Chromosome 1,2, 5, 7, 8, 10, 14, 19, 20 (inc Apo E)

Brain Cell: More Problems

- Brain cell (neuron):
  - Unable to make chemical signals the brain uses to communicate (called neurotransmitters) such as Acetylcholine
  - Overexcited neurons confuses messages, blocks effective messages (static)
  - Unable to talk to other cells because reception is blocked, so it dies

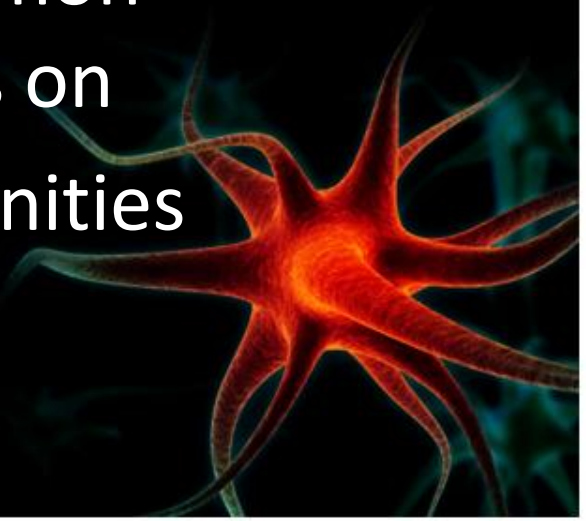
Summary of Causes of AD

- Family inheritance of a genetic tendency to develop AD
- Making too much toxic material inside and/or outside brain cells, and/or unable to clean it up
- Problems making energy and getting it to the connections from one cell to another
- Problems making brain chemicals
- Blocked reception of brain signals



If there are so many causes, is it really one disease?

- Probably not—most likely a combination of many related factors
- May partly explain why different people behave differently
- AD persons tend to share a common pattern of behavior as time goes on
- Gives us many different opportunities to try to help the problem



So what can Research do?

Phases of Clinical Trials

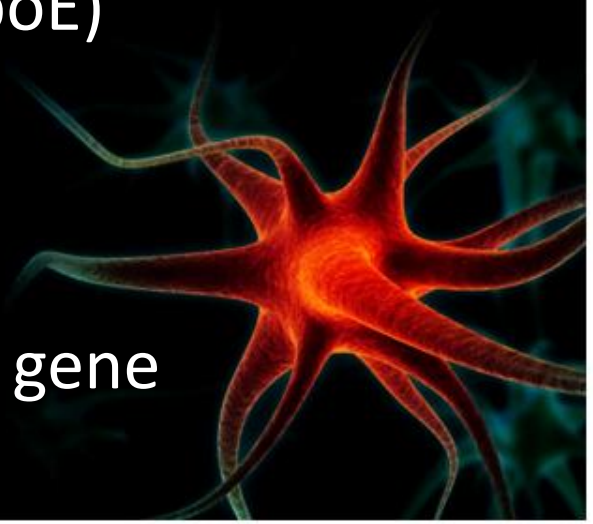
- Phase 1- Small number of people (10-100) tested to check safety, how the treatment affects the body in humans, and how high the dose can go
- Phase 2 – Larger numbers of people (100s), see if the treatment changes symptoms or change the disease. Uses placebos for comparison, often establishes what dose will be used.
- Phase 3 – Big studies (1000s), compare treatment with a known treatment or placebo to see if it is safe and actually works (efficacy)
- Phase 4 – After the treatment has been released to the public, monitoring the (side) effects

Early detection blood test

- Neurofilament blood test
- Developed using registry of families with strong inheritance
- Detected whenever there is damage to the nervous system
- Does not tell you what is causing the damage
- Normal vs. levels in dementia still need to be established *(Buchman 2019)*

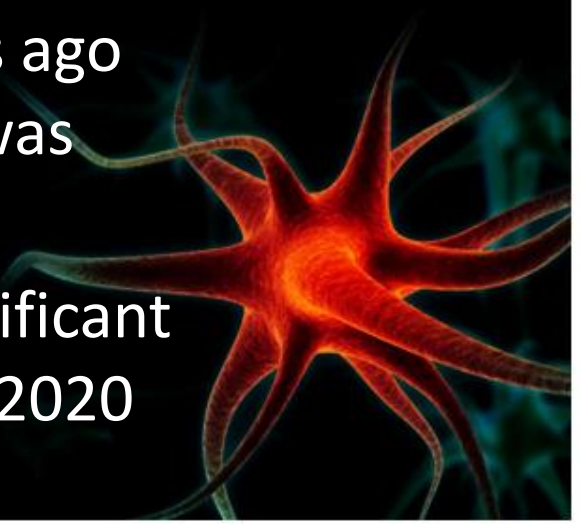
Family/Genetic Research

- Registries of families with early and late-onset disease and their unaffected family members for ongoing lab study & DNA sequencing *(Genetics Initiative)*
- Research with families who have known kinds of problems to develop interventions (ApoE)
- Gene therapy far in the future
- Protein/vaccine therapies started
- Ethics of genetic screening?
- Overlap with vascular diseases, ApoE4 gene



Protein Therapy

- CERE-110 uses a virus to transfer a gene that makes Nerve Growth Factor (NGF), a protein that may make nerve cells in the brain healthier and protect them from dying
- Half of 50 patients with mild-mod Alzheimer's had CERE-110 surgically injected into the brain, while the other half had a "placebo" surgery where no medication was injected.
- Phase 1 study on 10 patients tested 2 years ago showed it was safe, the NGF worked, and was tolerated well.
- Enrollment finished in March 2013, no significant changes after 2 years, final study to end in 2020



Prevention vaccine

- Patients receive an antibody protein which clears beta amyloid and eliminates the need for the patient to make their own (crenezumab, gantenerumab)
- 100 young family members from 26 families carrying mutation receiving shots to see if it will prevent Alzheimer's
- In Phase 3 trials; ending 2018-2021
- Separate gantenerumab study of 797 persons with/without APOE 4

  no benefit in 2 years but may need higher dosage

Risk Factor/Lifestyle: Brain Training

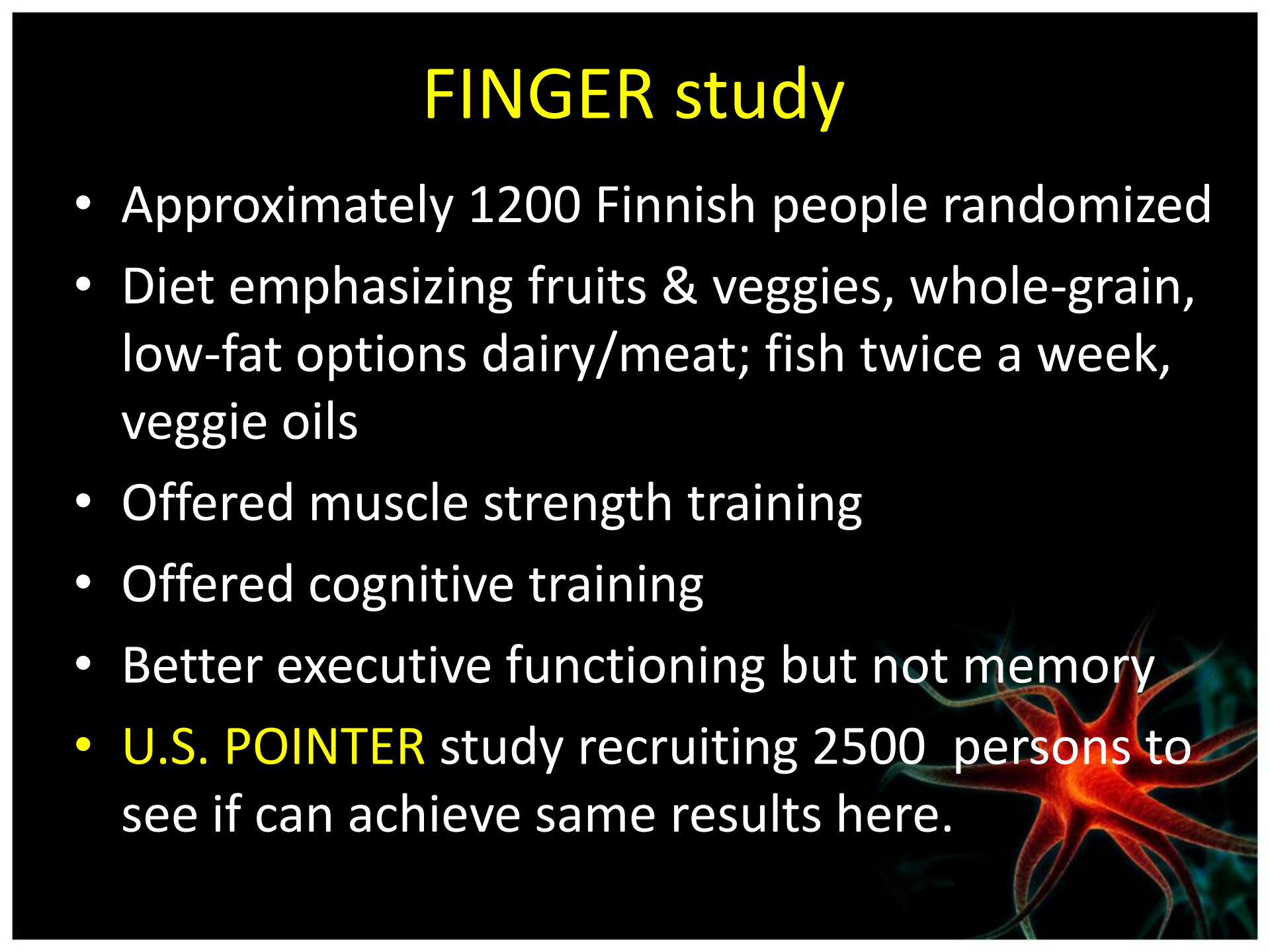
- 2000+ older adults randomly trained on improving memory, reasoning, or speed-of-processing
- After 10 years, the reasoning- and speed-trained groups kept some improvements but did not change risk of dementia. *Rebok, et al J Am Ger Soc Jan 2014*
- Currently 3 studies involving computer training using games, practice exercises underway
- One includes whether daily functioning improves
- Results due out starting next year

Risk Factor/Lifestyle: Exercise

- 45 minutes, 3 times a week helps to delay severity
- ACT –cycling and/or cognitive training, recruiting now
- EXERT-Older adults with MCI ,year-long program at local YMCAs, one group high-intensity aerobics, other will do stretching, still recruiting
- Exercise/Posit Science module training for 12 wks, finishes in 2020
- Aerobic exercise studies—3 ongoing

FINGER study

- Approximately 1200 Finnish people randomized
- Diet emphasizing fruits & veggies, whole-grain, low-fat options dairy/meat; fish twice a week, veggie oils
- Offered muscle strength training
- Offered cognitive training
- Better executive functioning but not memory
- U.S. POINTER study recruiting 2500 persons to see if can achieve same results here.



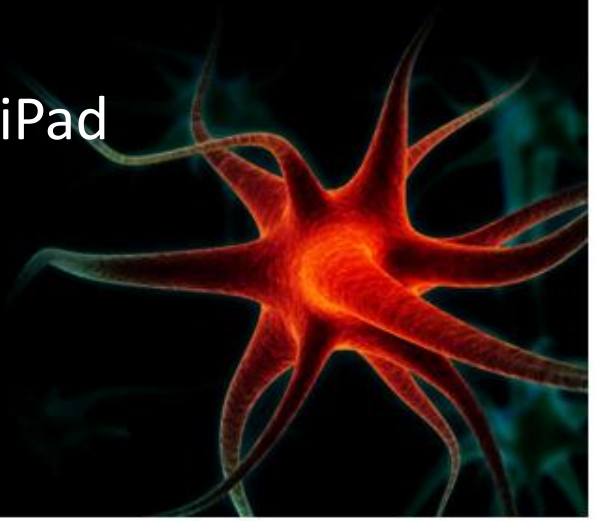
Antioxidants/Nutrients

- Vitamin E- supplements in veterans with mild-mod AD slowed functional decline about 20% per year, or 6 months over about 2-1/2 years. *(Dysken et al, JAMA Jan 2014)* PREADVISE trial completed and no benefit found (*Kryscio, et al, JAMA Neurology May 2017*)
- Resveratrol—basic actions studied in mice. Found in grapes, red wine. Safety established in Phase 2 trial published Sept 2015 for 1000mg dose. 119 persons studied, might imitate anti-aging chemical process *(Sawda et al Ann NY Acad Sci Sept 2017.)*

New BDPP Phase I trial still recruiting.

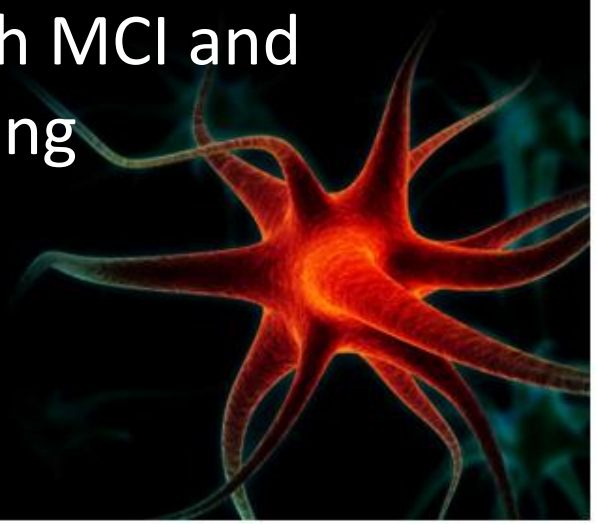
Symptom or alternative treatments-10

- Piromelatine (melatonin relative)—improve sleep & memory
- DHA nutrient supplementation in APOE 4 carriers
- Strawberry powder
- Keto, Atkins diets
- Glutathione (N-acetylcycteine & glycine) to delay progression
- Omega 3 oil supplementation
- Light therapy while playing video games on iPad
- Stem cell infusion
- Transcranial direct current stimulation
- Transcranial magnetic stimulation



Sleep Apnea
(sleep-disordered breathing)

- Frequent pauses in breathing during sleep
- Reduces oxygen levels, causing damage
- Older women with sleep apnea twice as likely to develop MCI or dementia *(Yaffe 2014)*
- Pilot study to see if oxygen supplementation can delay cognitive loss in people with MCI and sleep apnea completed, results pending

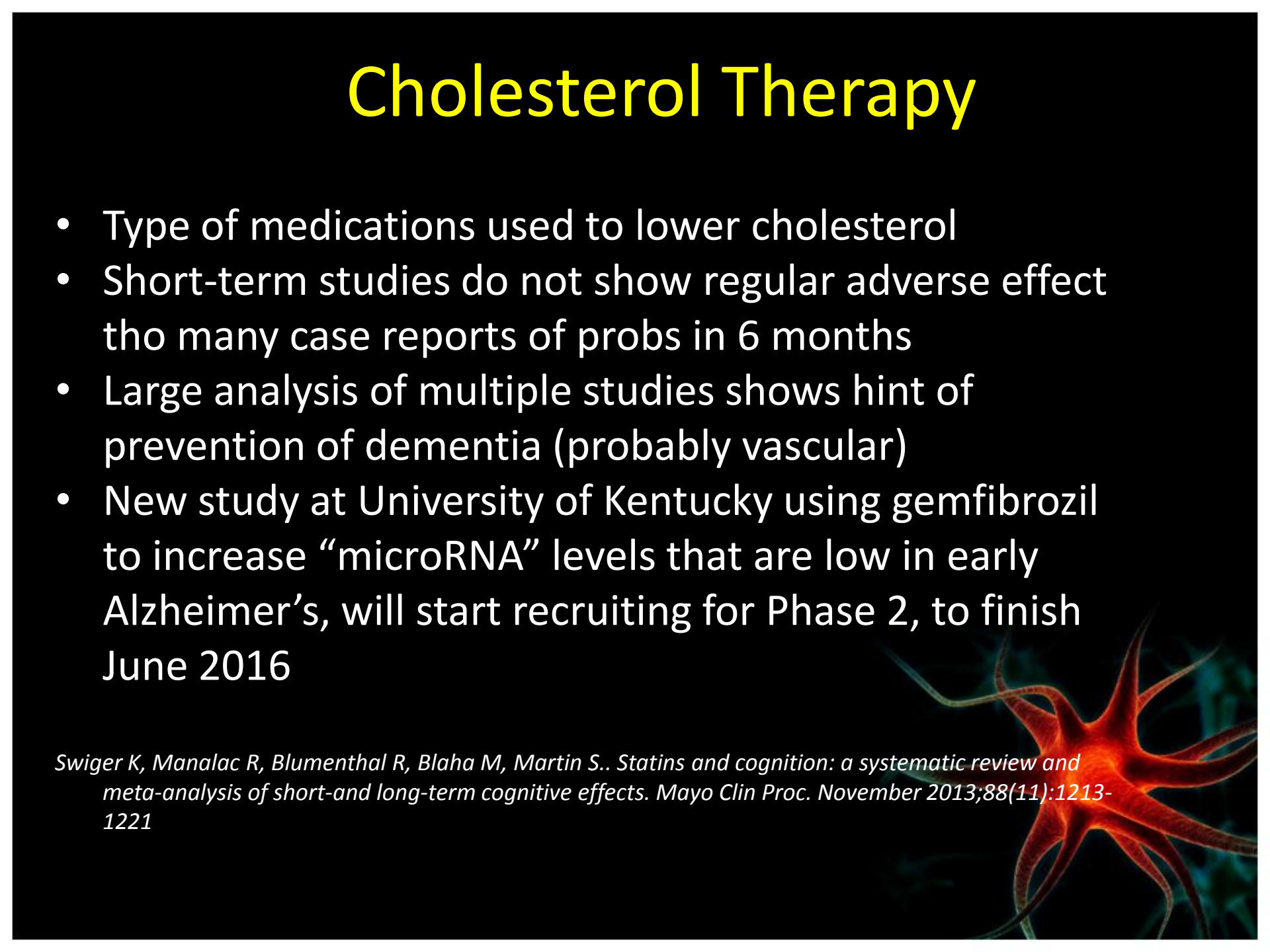


Diabetes medications

- Intranasal insulin-Pilot study showed improvement in memory, slowed decline in function and memory (*Craft 2012*). Current study (SNIFF) in persons with MCI and mild Alzheimer's with 4 months of treatment showed some improvement in memory (*Craft 2017*).
- Exenatide-May be able to protect neurons from death, study still recruiting people with MCI or early Alzheimer's. Helpful in mod Parkinson's, Phase 2.
- Metformin- No effect
- Glitazones not effective in 2012 trial *(Imfeld)*

Cholesterol Therapy

- Type of medications used to lower cholesterol
- Short-term studies do not show regular adverse effect tho many case reports of probs in 6 months
- Large analysis of multiple studies shows hint of prevention of dementia (probably vascular)
- New study at University of Kentucky using gemfibrozil to increase “microRNA” levels that are low in early Alzheimer’s, will start recruiting for Phase 2, to finish June 2016



Swiger K, Manalac R, Blumenthal R, Blaha M, Martin S.. Statins and cognition: a systematic review and meta-analysis of short-and long-term cognitive effects. Mayo Clin Proc. November 2013;88(11):1213-1221

Deep Brain Stimulation

- Implanted electrodes used to simulate portions of brain to improve function in Parkinson's patients, reduce seizures
- Found to also improve memory
- Study begun last fall,

  to conclude 2017

Stem cell drug

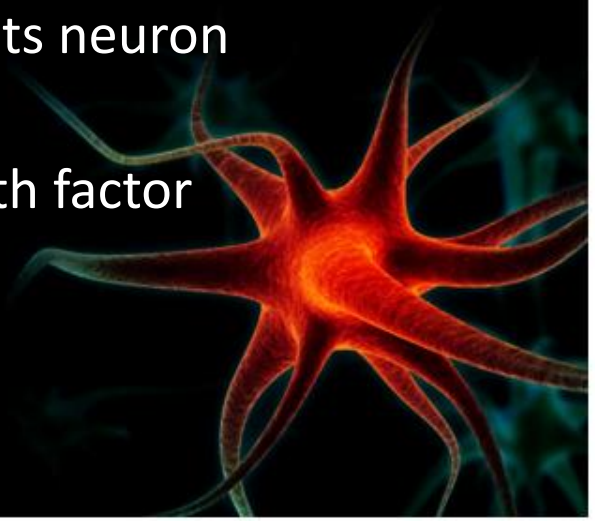
- AstroStem is investigational, derived from own fat tissue stem cells
- Presently used to help cancer patients with leukemias keep their body defenses going
- Noticed that people had less “chemo brain” during treatment if on this medication
- 3 year, Phase 2 study, still recruiting, will give medication to people with MCI to see if it prevents progression; results 2017

Hormone therapy

- Allopregnanolone is a metabolite of the hormone progesterone made in the brain and spinal cord, and occurs at high levels in the blood of pregnant women
- Found in mice to promote the birth of new neurons, lower amyloid and dampen inflammation
- Phase 1 trial at USC in 16 men and 16 women with (MCI) or early AD will give IV drug in different doses once/wk for 3 months, target to boost blood levels to those seen during pregnancy, still recruiting

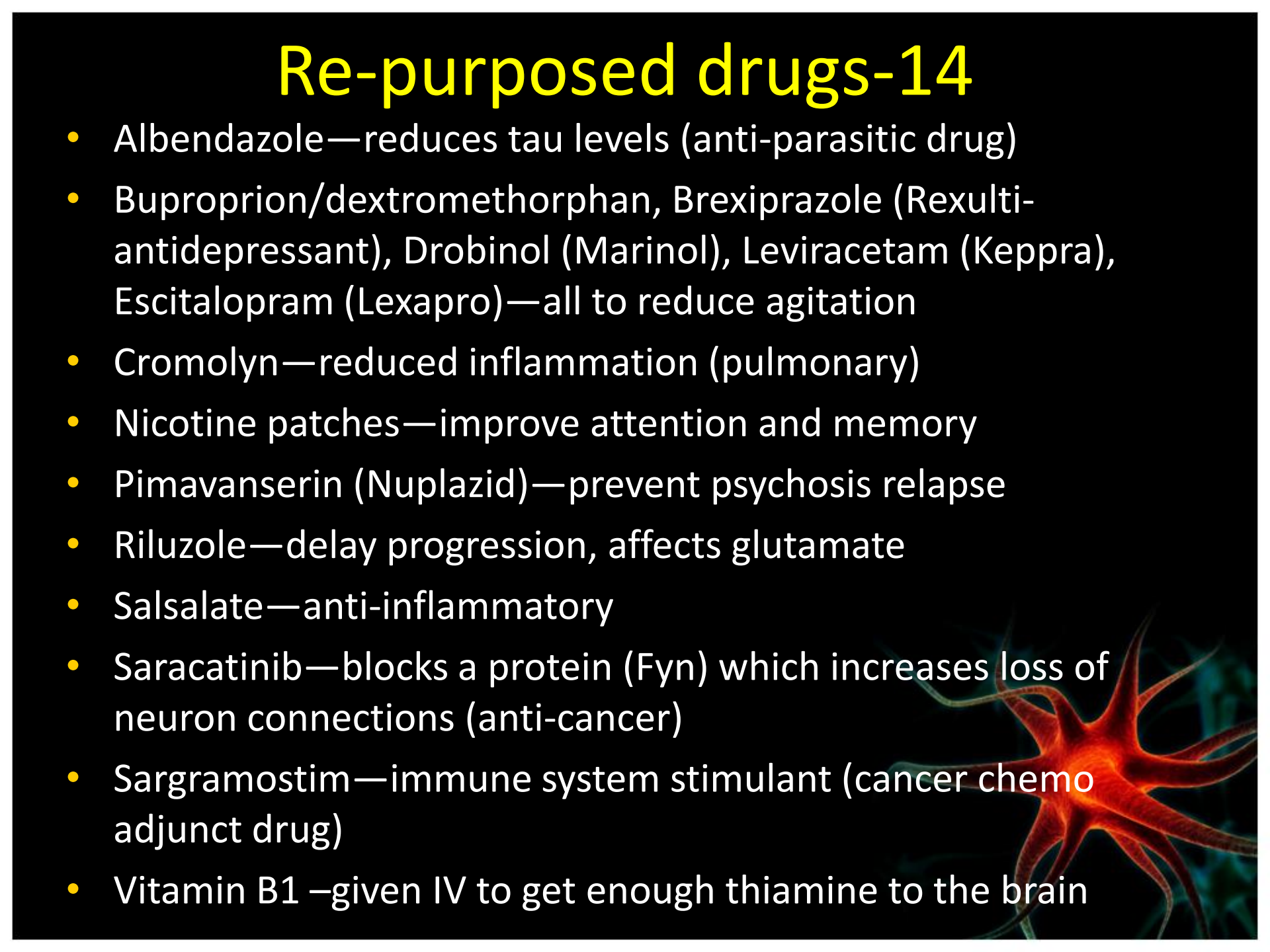
New Drug Research-21

- BAN2401—monoclonal antibody
- ABBV8E12, BIIB076, BIIB092, LY3303560, R07105705, TRX0237—all anti-tau antibodies/drugs
- AMX0035—drug to block cell death pathways, phase 2 trial
- BHV-4157 (troriluzole)—affects glutamate
- CAD106 and CNP520, LY3002813 and LY3202626—anti-amyloid antibodies
- E2609, Posiphen—reduce amyloid production
- GRF6019—plasma-derived product to delay progression
- Bryostatin-1—protein kinase C activator, prevents neuron death
- NDX-1017—restore function by activating growth factor
- Neflamapimod—supports synapses
- S-Equol—estrogen-like compound
- VU319—acetylcholine receptor activator



Re-purposed drugs-14

- Albendazole—reduces tau levels (anti-parasitic drug)
- Buproprion/dextromethorphan, Brexiprazole (Rexulti-antidepressant), Drobinol (Marinol), Leviracetam (Keppra), Escitalopram (Lexapro)—all to reduce agitation
- Cromolyn—reduced inflammation (pulmonary)
- Nicotine patches—improve attention and memory
- Pimavanserin (Nuplazid)—prevent psychosis relapse
- Riluzole—delay progression, affects glutamate
- Salsalate—anti-inflammatory
- Saracatinib—blocks a protein (Fyn) which increases loss of neuron connections (anti-cancer)
- Sargramostim—immune system stimulant (cancer chemo adjunct drug)
- Vitamin B1 –given IV to get enough thiamine to the brain



Conclusions

- Most hopeful avenues for therapy in near future probably those related to glucose and cholesterol management.
- Long-term, the new protein therapies being developed to stop or clear formation of toxic amyloid & tau products in the brain most promising.
- In the meantime, effective caregiving strategies the most important for care of the Alzheimer's patient

World Alzheimer Report

https://www.alz.co.uk/research/WorldAlzheimerReport2018.pdf

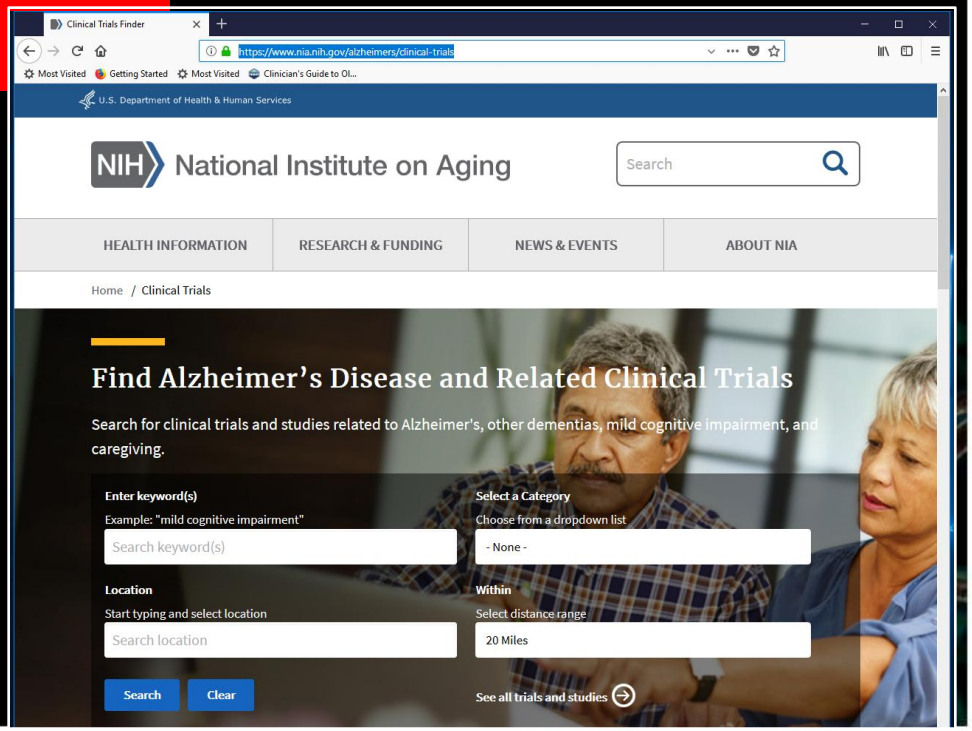
Alzheimer's Disease International

World Alzheimer Report 2018

The state of the art of dementia research: New frontiers

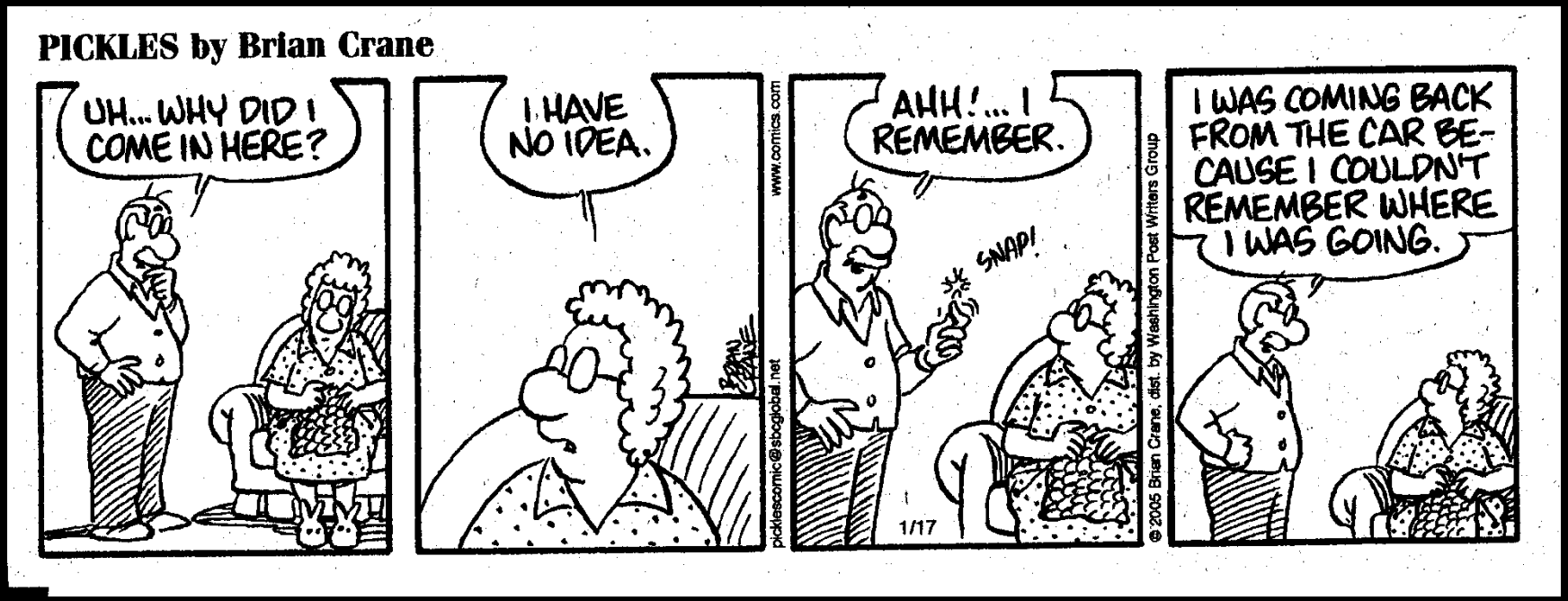
Clinical Trials Finder

https://www.nia.nih.gov/alzheimers/clinical-trials



Further Information

- Alzheimer's Disease Education and Referral Center, 1-800-438-4380, http://www.nia.nih.gov/alzheimers
- Alzheimer's Foundation of America, 1-866-232-8484, https://alzfdn.org/
- Alzheimer's Association, 1-800-272-9300, https://www.alz.org/
- Alzheimer's Disease International https://www.alz.co.uk /



Questions?

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