

# Dementia Update 2016

Frustration, Progress, and Hope

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Disorders



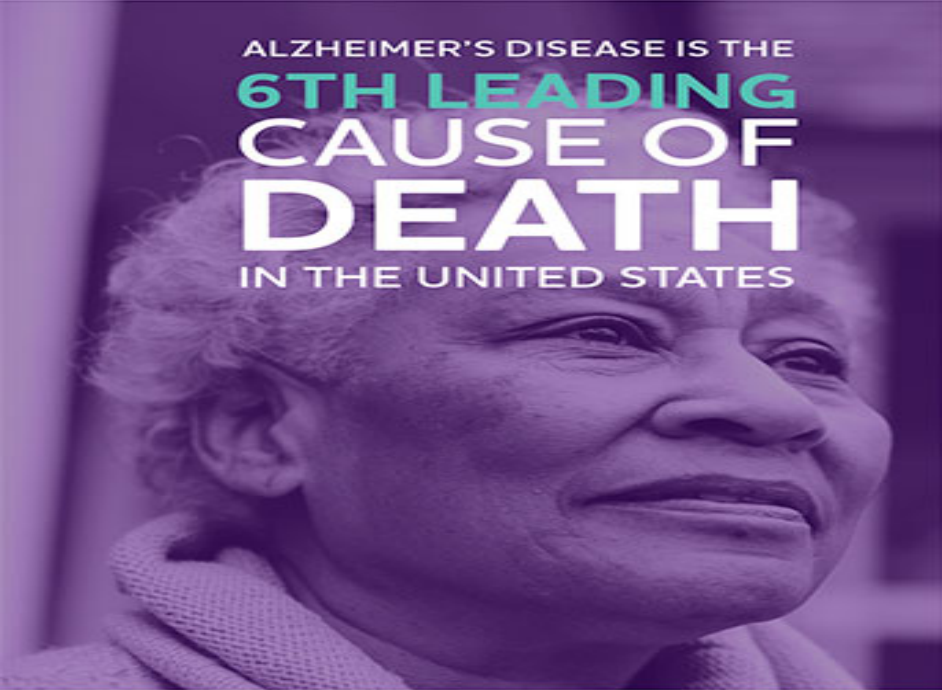






- Facts and figures
- Types and definitions
- Pathophysiology
- Treatment failures
- Risk factors
- Hope
- Preventative strategies
- Early detection
- Biomarkers
- Treatment
- Future

ALZHEIMER'S DISEASE IS THE  
**6TH LEADING**  
CAUSE OF  
**DEATH**  
IN THE UNITED STATES



**MORE THAN**  
**5 MILLION**

AMERICANS ARE LIVING WITH ALZHEIMER'S

**1 IN 3 SENIORS**  
DIES WITH ALZHEIMER'S  
OR ANOTHER DEMENTIA



IN 2015, MORE  
THAN 15 MILLION  
CAREGIVERS  
PROVIDED AN  
ESTIMATED

**18.1 BILLION**  
HOURS OF  
UNPAID CARE

ALZHEIMER'S COSTS CAREGIVERS  
MORE THAN THEIR TIME

FAMILY CAREGIVERS SPEND MORE THAN  
**\$5,000 A YEAR**  
CARING FOR SOMEONE WITH ALZHEIMER'S

FOR SOME FAMILIES THIS MEANS  
**MISSING A VACATION**

BUT FOR OTHERS, IT MAY MEAN  
**GOING HUNGRY**

**EVERY**  
**66 SECONDS**

SOMEONE IN THE UNITED STATES  
DEVELOPS THE DISEASE



IN 2016, ALZHEIMER'S AND OTHER  
DEMENTIAS WILL COST THE NATION

**\$236 BILLION**

IT  
KILLS  
MORE  
THAN

BREAST AND  
PROSTATE CANCER  
COMBINED

In fact...

## Women are at the epicenter of the AD crisis

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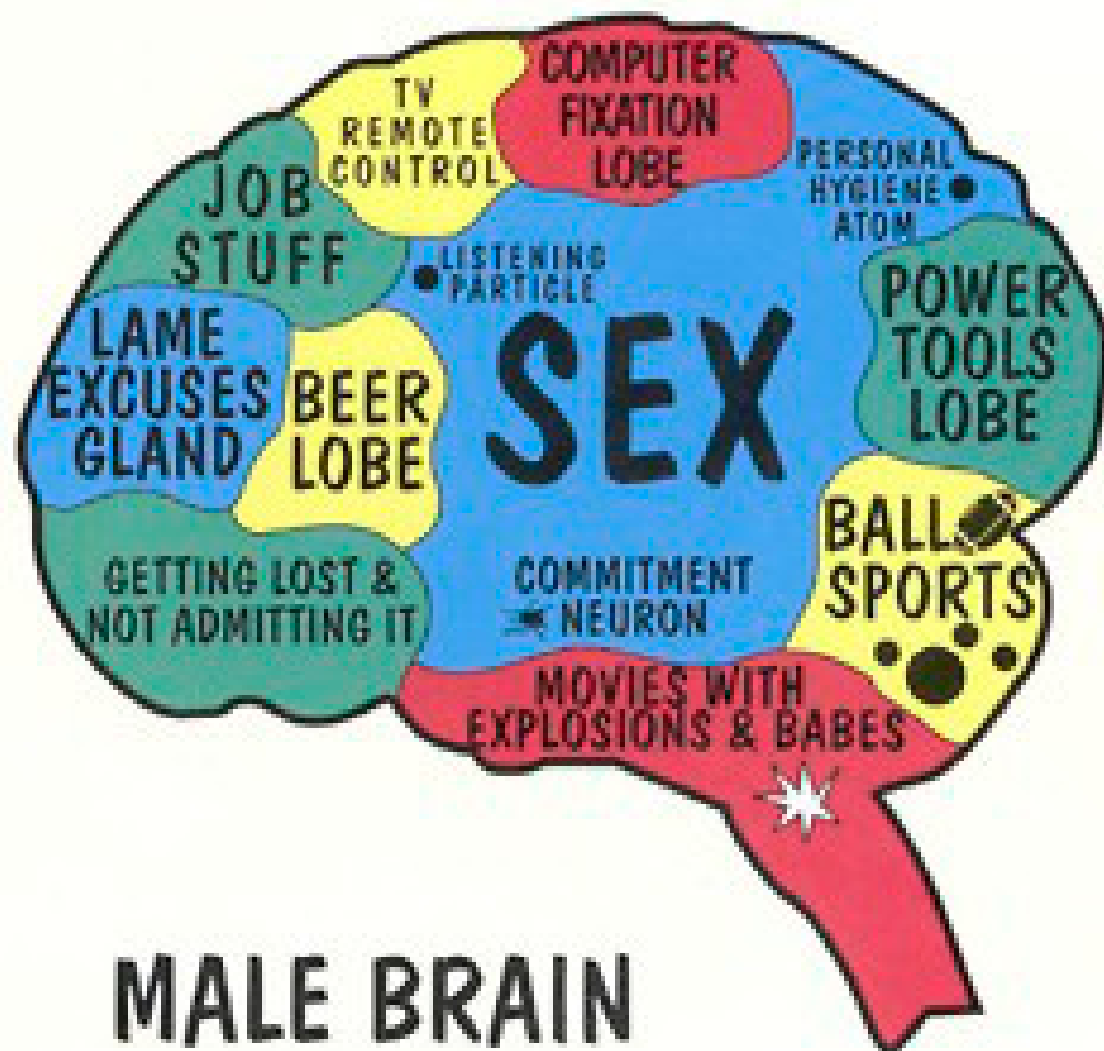
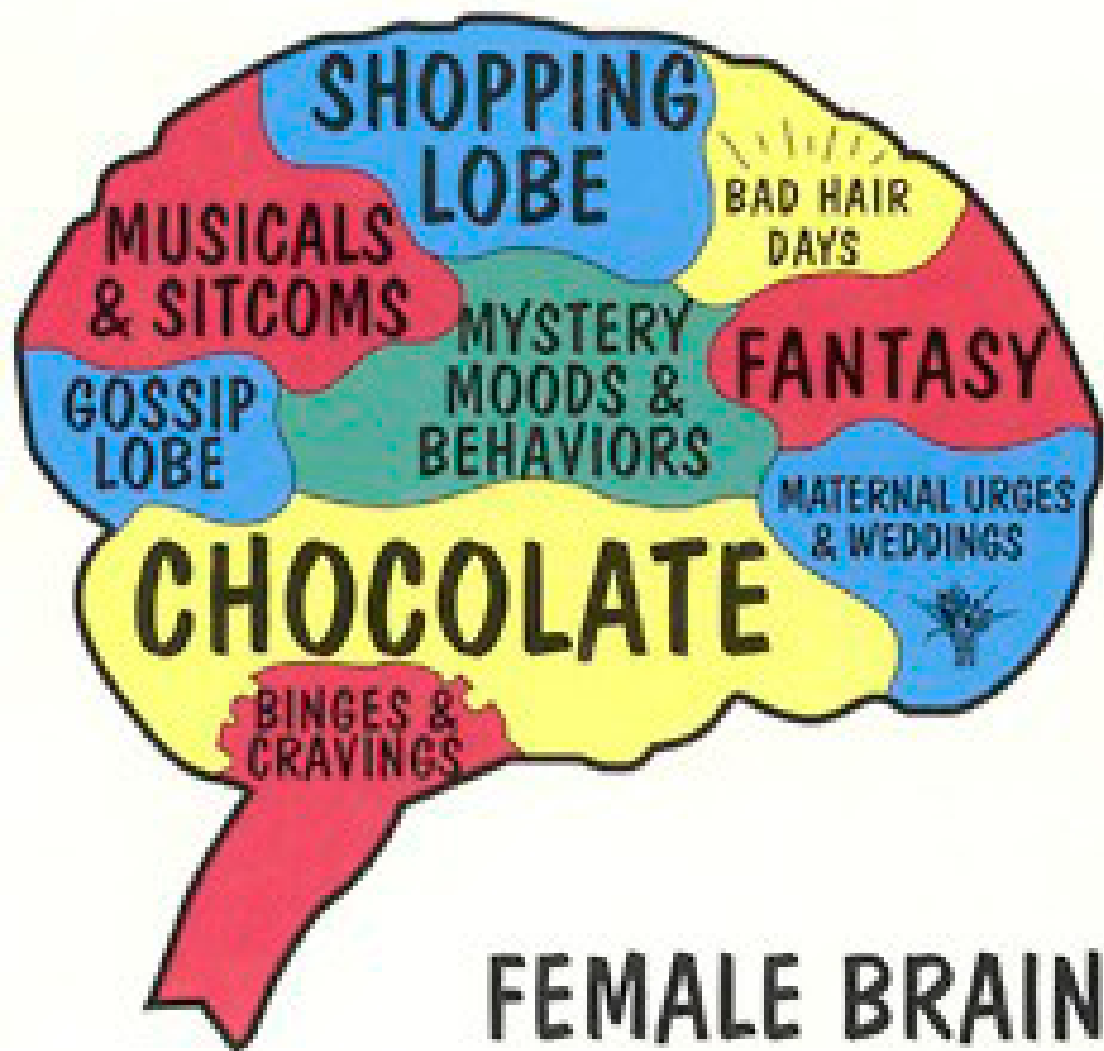
- **2/3 of the 5 million seniors with AD are women**
- In all people > 71yo...
  - 16% of the women have AD
  - 11% of the men have AD
- At age 65, women without AD have a 1 in 6 chance of developing AD during the remainder of their lives, compared with a 1 in 11 chance in men



# Why?

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- Women have a higher life expectancy (81 vs 76)
- After the age of 80, the risk of developing AD is the same between the 2 sexes
- But in the 70-79 age group, the risk for women is 2 times that of men
  - Men are more likely to die earlier of heart disease, hypertension, or diabetes, before they develop AD.
  - Those that survive are assumed to have a more robust cardiovascular system, and that has been shown to be protective against dementia
- Women have a 70% higher risk of depression
- In the pre-feminist era, women had less education and less stimulating jobs; perhaps less social interactions
- APOe4 allele seems to carry a greater risk for women than men. There is some evidence to suggest it may interact with estrogen.



Reported at 2016 AAIC from a Mayo Clinic – Jacksonville study of 1,600 pts in a brain bank review:

Men are more likely to be:

- Misdiagnosed
- Underdiagnosed
- Affected at a younger age
- Have a shorter disease duration
- More likely to have symptoms involving speech and movement
- Less affected with memory symptoms early in the course of their disease



# Dementia: Criteria

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- DSM IV Criteria for dementia:
  - Development of multiple cognitive deficit including memory impairment and at least one of the following:
    - aphasia
    - apraxia
    - agnosia
    - executive functioning disturbance
  - The cognitive deficit must,
    - be sufficiently severe to cause impairment in occupational and social functioning.
    - represent a decline from a previous higher level of functioning.

# Dementia Types

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## Cortical

- AD
- FTD
- PCA

## Vascular

- Small vessel ischemic
- Multi infarct

## Lewy Body

- PDD
- DLB

## Mixed

## Other

- CJD
- NPH
- HD
- WKS
- CTE



# Alzheimer's: DSM IV Criteria

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- Development of multiple cognitive deficits manifest by both
  - memory impairment
  - 1 or more of following
    - aphasia
    - apraxia (inability to perform learned purposeful movements)
    - agnosia
    - disturbance in executive function
- These cause significant impairment in social or occupational function & represent a decline
- Onset is gradual

# Definitions

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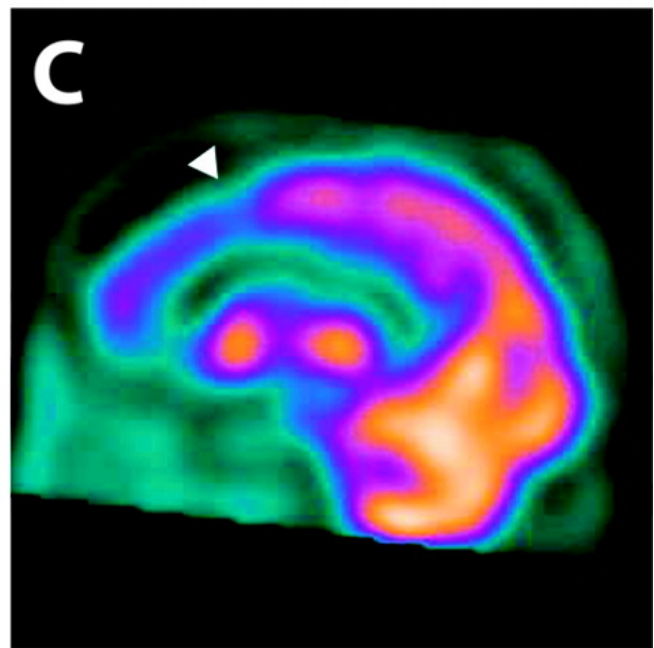
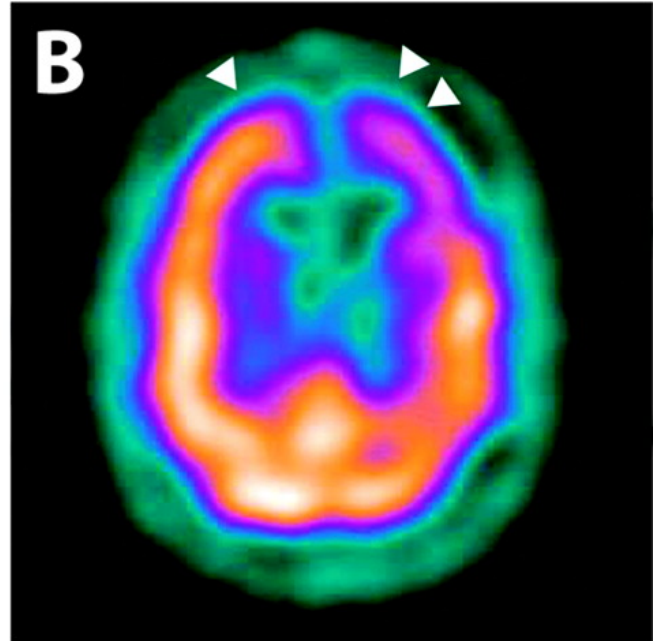
- Alzheimer's Disease
  - A new definition, proposed by a group of international experts
  - The aim is to achieve earlier diagnosis, even before the onset of proven dementia
  - Is now considered a disease of a “continuum of stages” involving degenerative and regressive or retrogressive stages of mental capacity

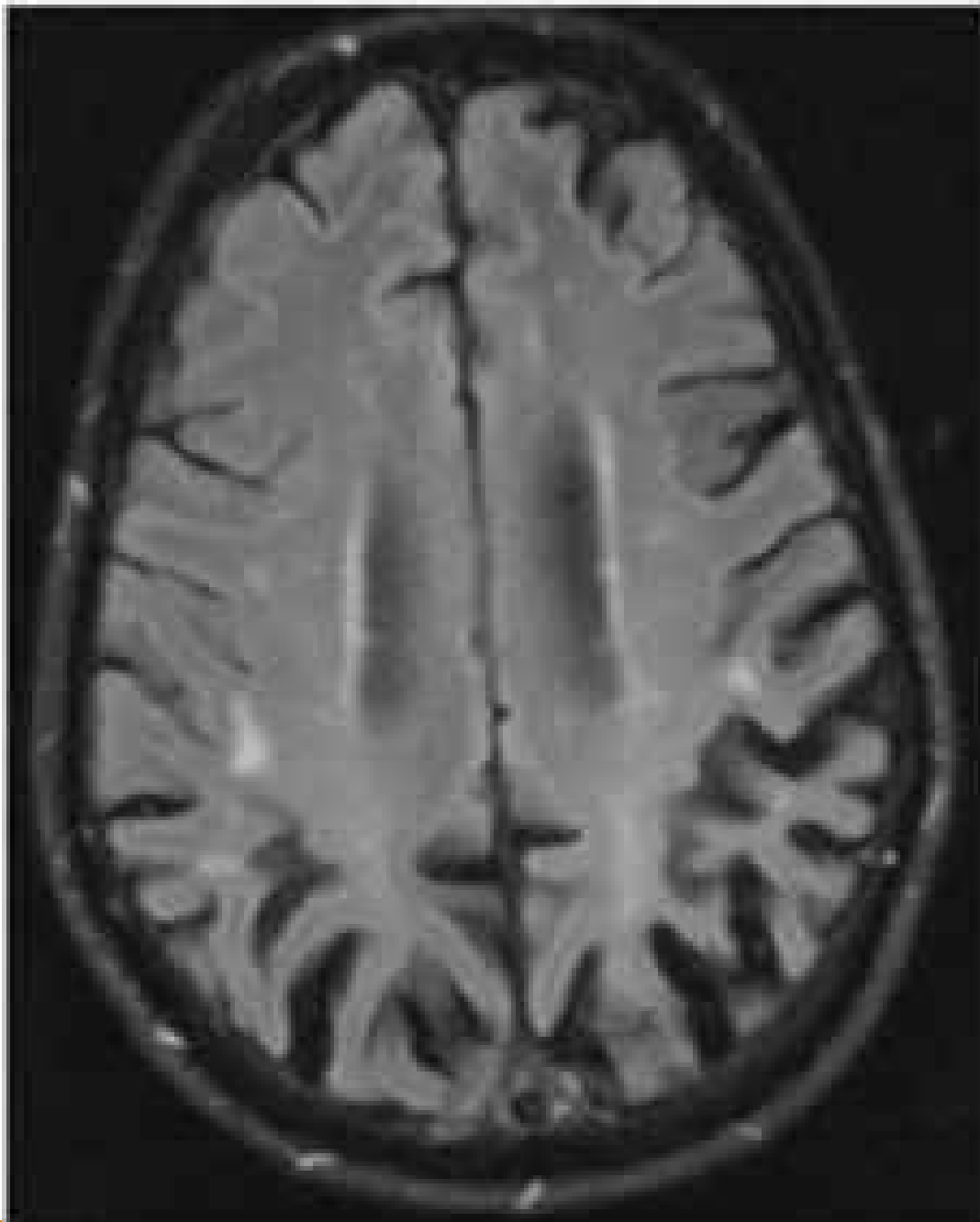
# The progression of AD is separated into 3 phases:

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- 1. Preclinical Stage** – The patient has no outward symptoms but imaging and biomarker tests identify changes that are occurring within the brain
- 2. Mild Cognitive Impairment** – Some outward signs of change begin to occur. There is some memory loss but patient is still capable of independent living.
- 3. Alzheimer's Disease** – These patients meet the established criteria for dementia
  - Mild
  - Moderate
  - Severe







Lewy Body



# DLB

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- Affects 1.3 million Americans – is the most misdiagnosed dementia
- Early and accurate Dx can be life saving; i.e. avoid Rx that can:
  - Exacerbate psychosis
  - Precipitate NMS
- Needs to be distinguished from idiopathic PD
  - Less response to dopaminergics
  - More dopaminergic side-effects

# DLB Diagnostic Criteria

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## PROBABLE:

- Dementia (1 year rule)
- At least one of the following:
  - Fluctuating attention and concentration
  - Recurrent, well-formed visual hallucinations
  - Spontaneous parkinsonian motor signs

## SUGGESTIVE:

- REM sleep behavioral disorder
- Severe neuroleptic sensitivity
- Low dopamine transport uptake in the basal ganglia (SPECT or PET)

# PDD

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- An accurate prior Dx of PD
- Dementia causing a decline in function severe enough to impair the patient in daily activities involving at least one of the following cognitive domains:
  - Attention
  - Executive function
  - Visual-spatial ability
  - Memory
  - Language
  - Apathy
  - Personality change
  - Hallucinations
  - Delusions
  - Excessive sleepiness

# VASCULAR DEMENTIA



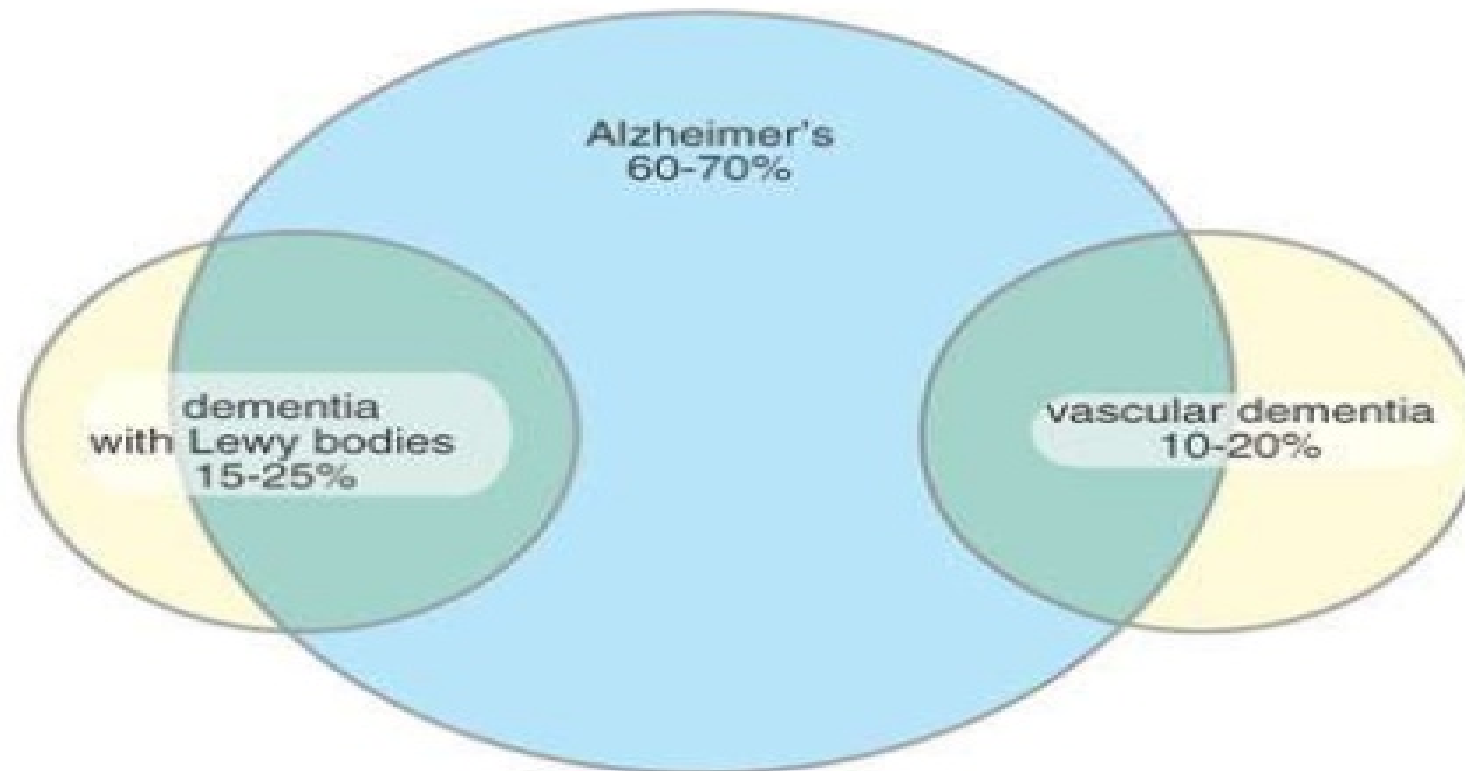
VASCULAR DEMENTIA CAN CAUSE THE FOLLOWING SYMPTOMS:

- CONFUSION
- THE LACK OF ATTENTION AND CONCENTRATION
- DECREASED ABILITY TO ORGANIZE THOUGHTS OR ACTIONS
- DECREASED ABILITY TO ANALYZE SITUATIONS, EFFECTIVE PLANNING AND COOPERATION
- PROBLEMS WITH MEMORY
- RESTLESSNESS AND ANXIETY
- UNSTEADY GAIT
- THE SUDDEN AND FREQUENT URGE TO URINATE OR URINARY INCONTINENCE
- WANDERING AT NIGHT
- DEPRESSION

# Mixed Dementias

- It is possible to have more than one dementia, and in fact many patients have both Alzheimer's disease and either dementia with Lewy bodies or vascular dementia.

## Mixed Dementia: Overlap of Alzheimer Disease with Other Dementias





# Mixed Dementia

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- Are very common
- Specific proteinopathies predispose an individual to other protein misfoldings
- Vascular disease is a risk factor for the propagation of other known dementia pathologies

# Mixed Dementia

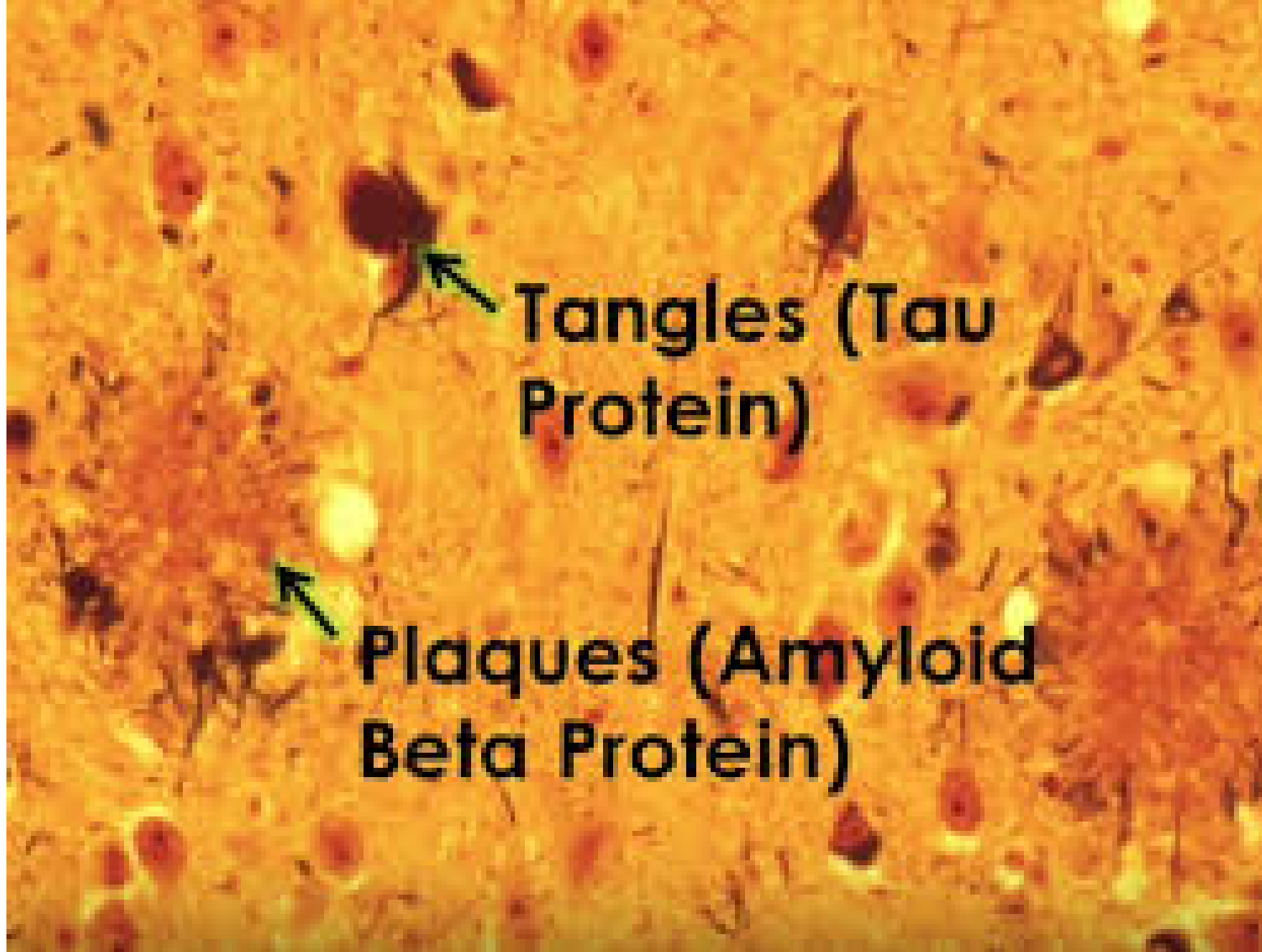
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- Lancet June 13, 2016
  - A post mortem study of 478 pts with AD showed:
    - 39% had moderate to severe atherosclerosis
    - 35% had arteriosclerosis
- Many pts with DLB were also found to have plaques and tangles
- Most pts with vascular dementia also had plaques and tangles
- Many pts with AD also were found to have Lewy Bodies

# Pathologic Processes and Targets

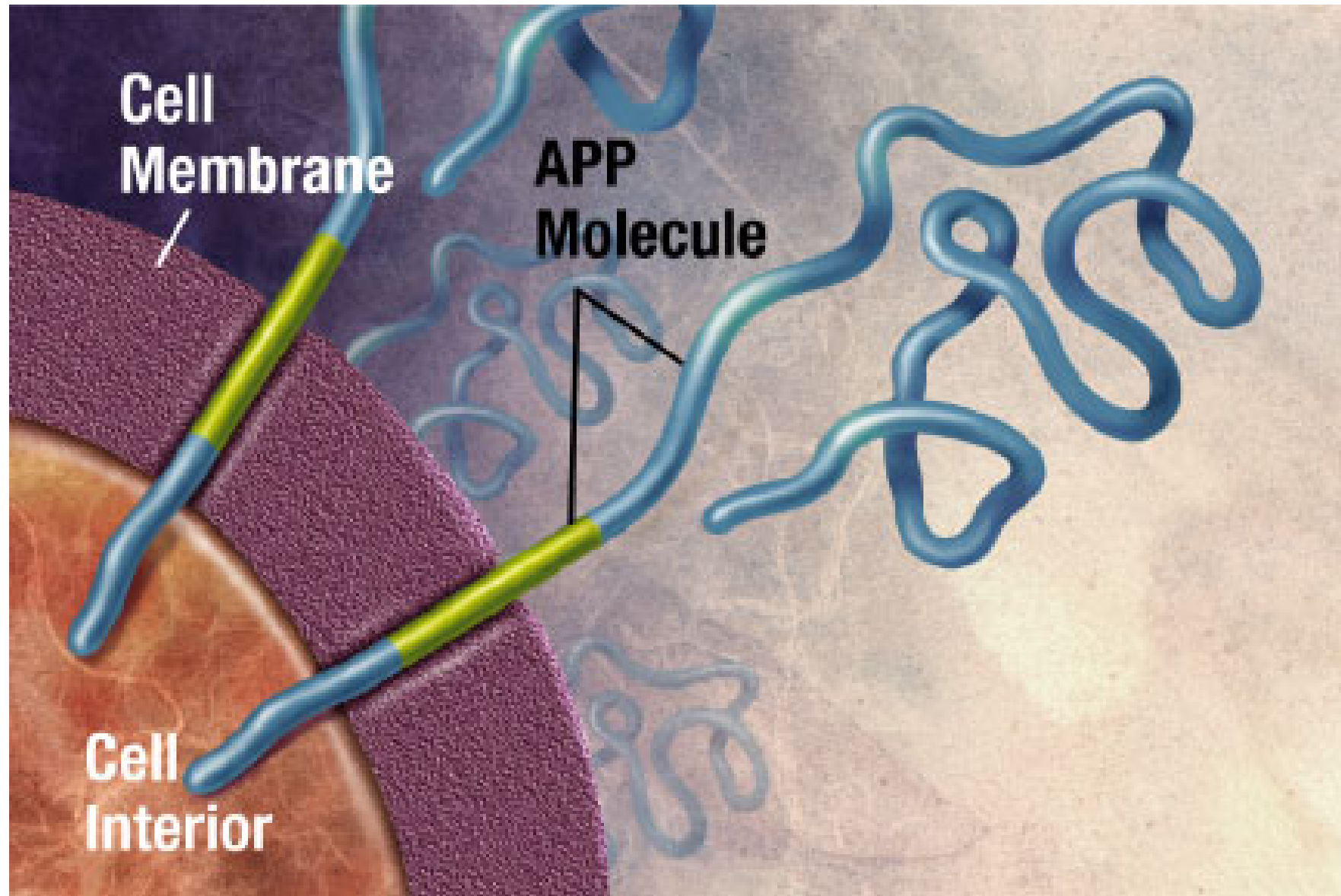
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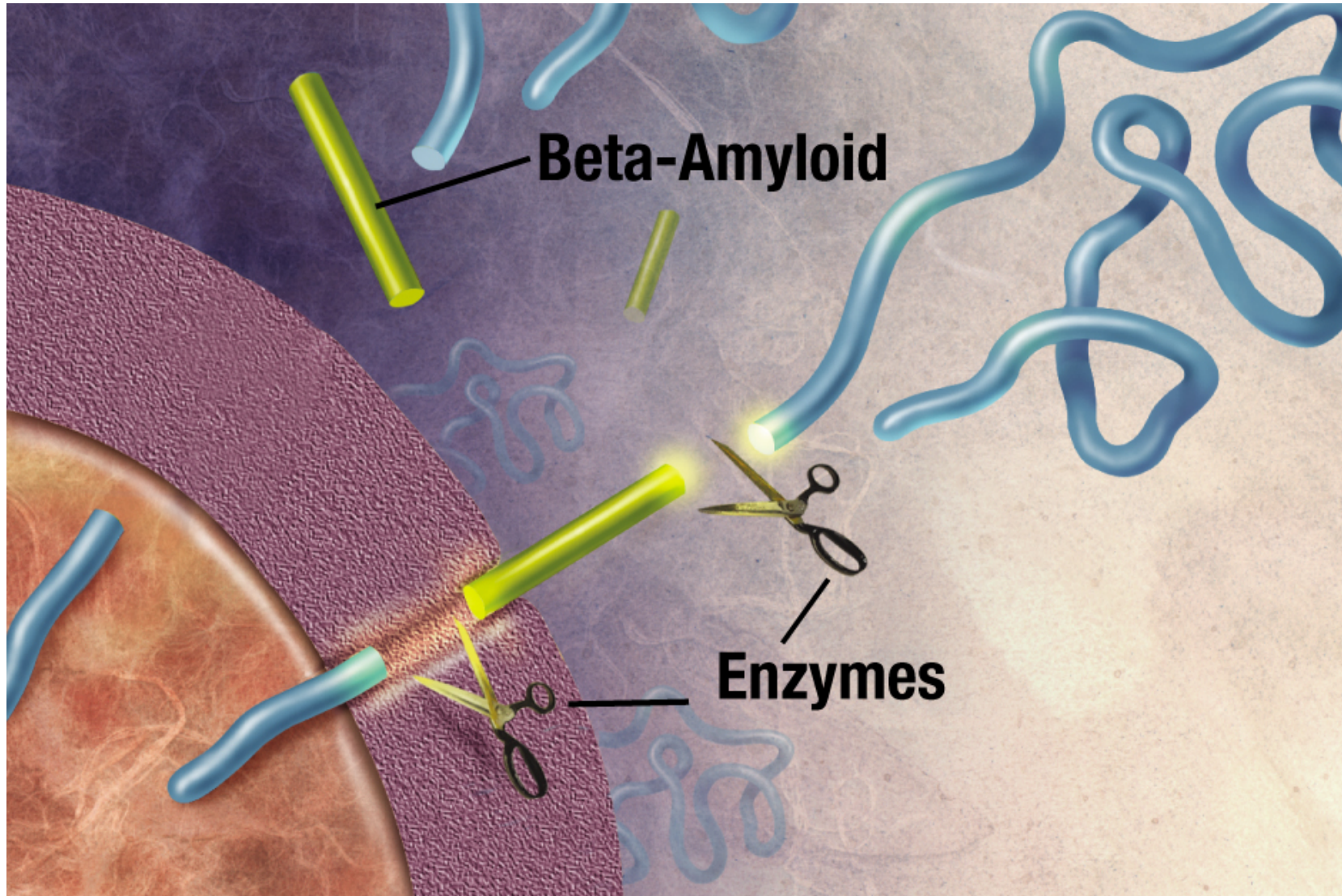
- Beta Amyloid
- Tau
- Inflammation
- Immunological dysfunction
- Insulin resistance
- Mitochondrial dysfunction
- Autophagy

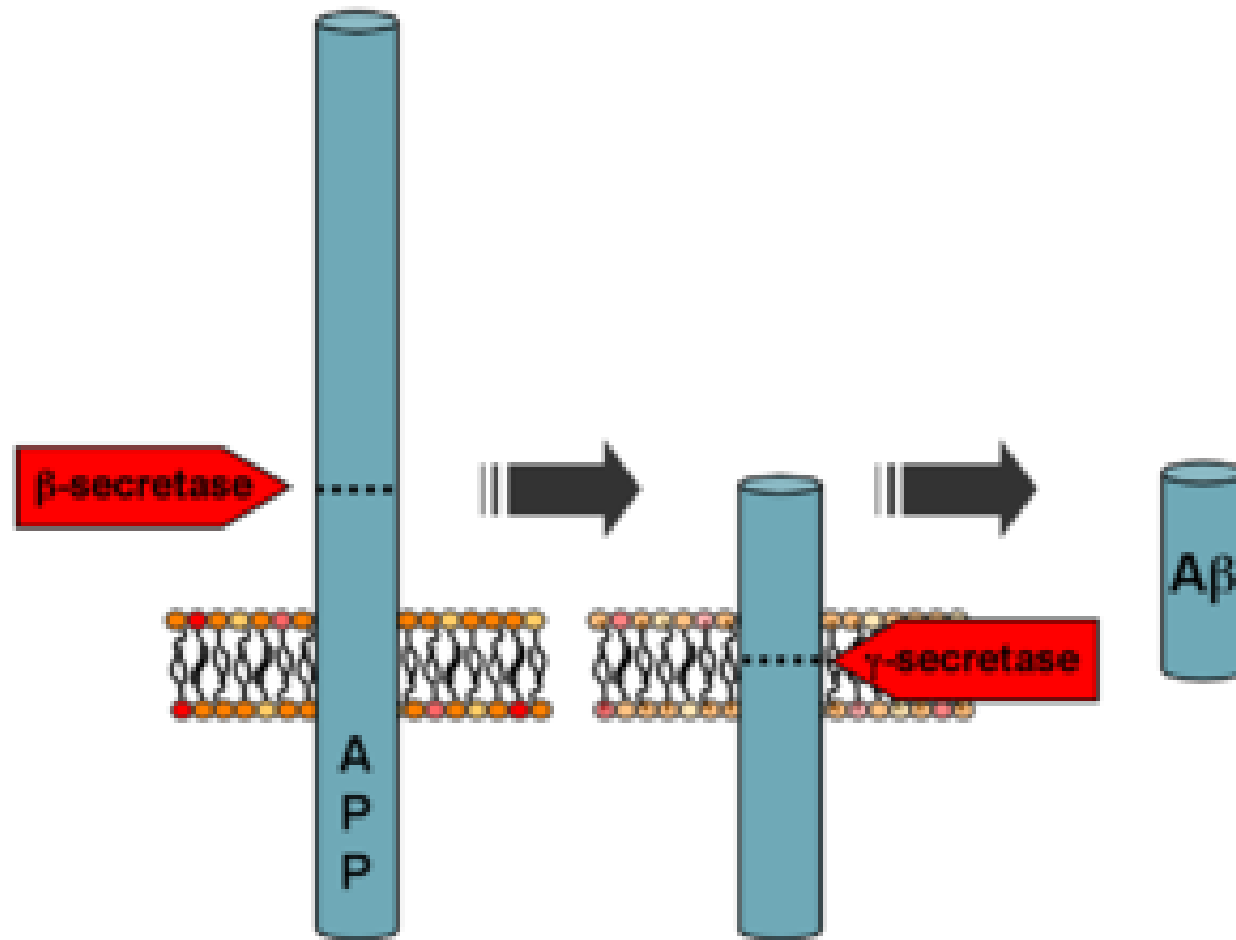


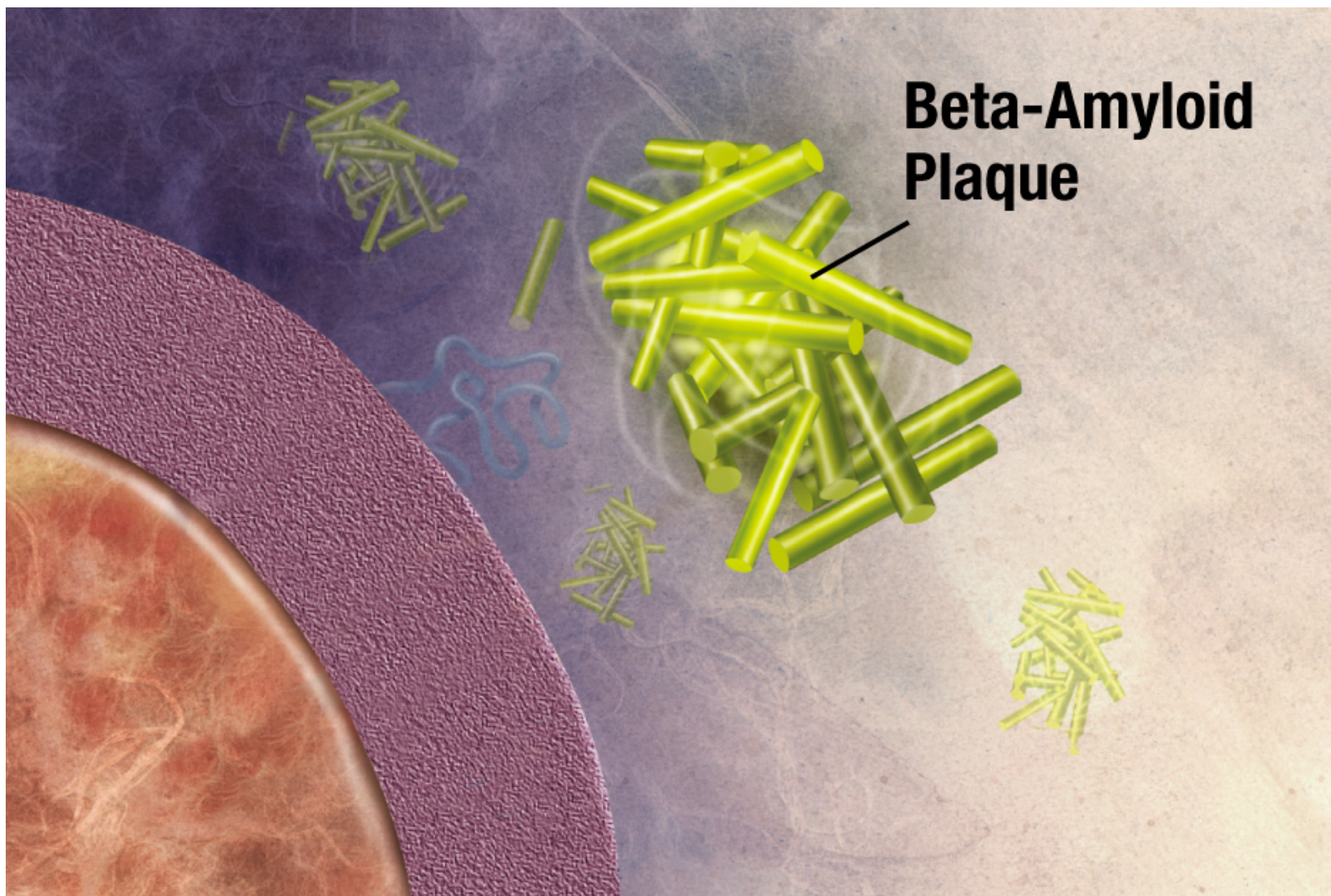
**Tangles (Tau Protein)**

**Plaques (Amyloid Beta Protein)**











# Flaws in the Amyloid Theory

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- Some individuals have large amounts of amyloid loads but no AD
- There is a poor correlation between the amount of AB and the severity of the AD
- Numerous interventions have demonstrated amyloid removal:
  - Vaccines
  - Monoclonal antibodies that attack amyloid (Solanezumab) (Aducanumab)
  - Beta secretase inhibitors
  - Gamma secretase inhibitors
  - \*ALL OF THESE AGENTS FAILED IN CLINICAL TRIALS

# Newest Research

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A soluble, 2-molecule aggregate (dimer) of beta-amyloid protein fragments may initiate the disease

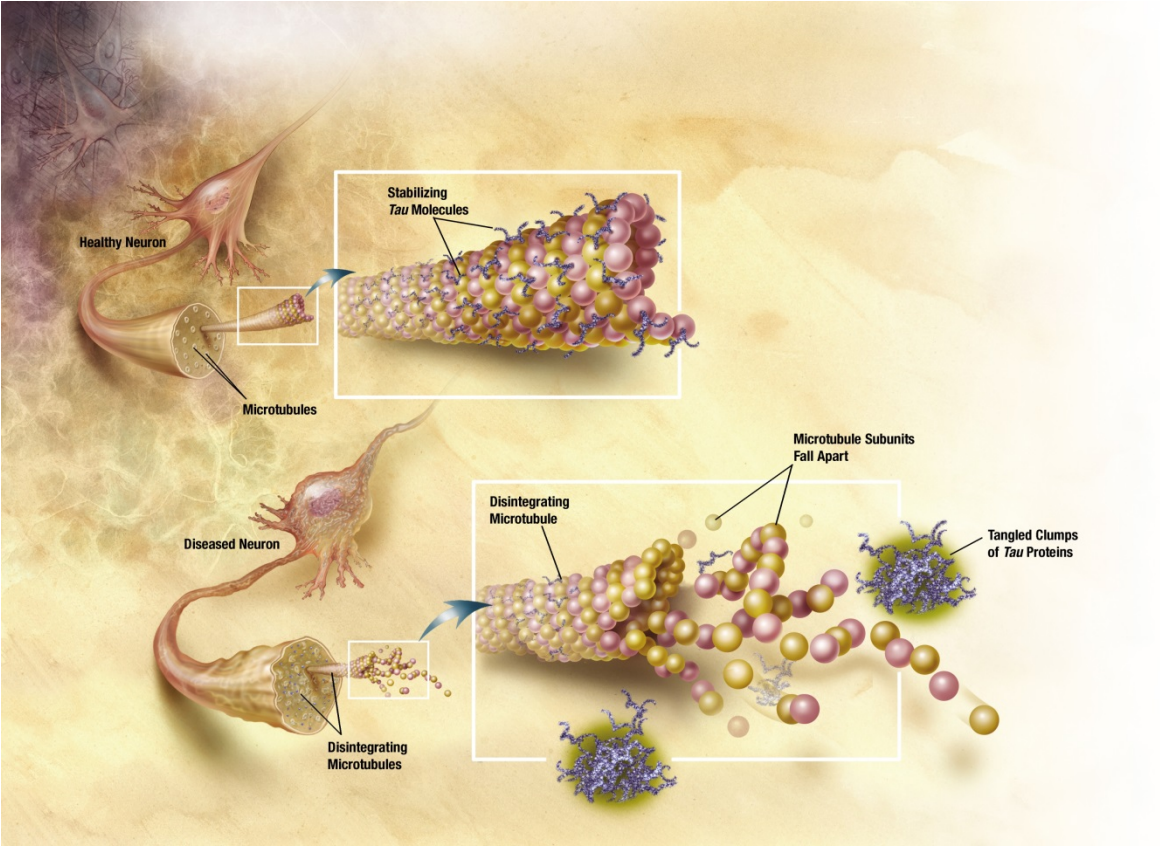
- The soluble monomers and the insoluble plaque cores had no effect
- The dimers impaired memories of newly learned behaviors
- The dimers reduced the density of dendritic spines by 47%, thus directly altering synapses

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Small, diffusible amyloid beta oligomers (amyloid derived diffusible ligands) are now thought to be highly toxic to neurons

Neurological dysfunction evoked by ADDL's occurred well in advance of cellular degeneration. They seem to have an immediate effect on hippocampal signal transduction.

# Tau



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Tau is a collection of microtubule associated proteins (MAP) expressed from a single gene on chromosome 17

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Tau is the basic component of neurofibrillary degeneration. Tau aggregation, in the form of filaments (either helical, twisted, or straight) have been implicated in more than 20 neurodegenerative disorders, including; AD, PSP, CBD, \*FTD, and \*FTDP-17.

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NFT's are the result of degeneration of microtubules. Tangles occur when tau protein, which normally stabilizes microtubules, converts from a soluble to an insoluble form – a process known as hyperphosphorylation.

# Tau and Prions

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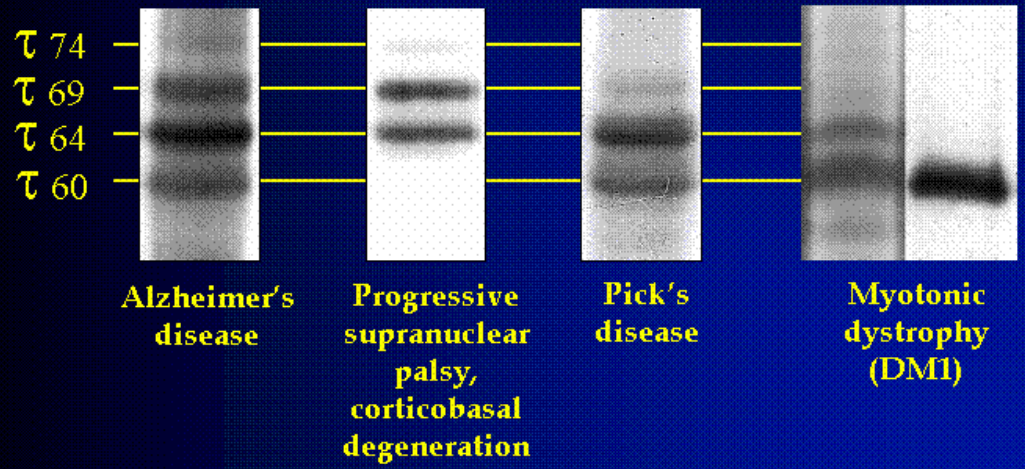
- The tau protein is located on chromosome 17
- This protein can be “corrupted” by strains of misfolded proteins that act very similarly to prions
- Prions are composed of normal proteins that are misfolded
- In the CNS, different misfoldings (prion strains) have been identified – these can be transmitted – like a virus – and are strain specific
- Scientists took 28 patients with known tauopathies to post. Clinically, they had one of 5 forms that were identified by a unique tau-prion strand. In every patient with AD, the exact same tau-prion strand was identified. The same held true in other clinical tauopathies.
- Treatment options
  - Antibodies to remove the prions
  - Block prion movement between cells
  - Stop cells from making new copies of the prion protein





## Tau pathology

### The different biochemical signatures



# UNFORTUNATELY...

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- A recently completed phase 3 trial of a potent tau aggregation inhibitor (LMTM) was negative.
- LMTM, (a derivative of methylene blue) failed to slow the rate of decline in cognition or in daily functioning

# So...

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- Is amyloid beta:
  - A culprit?
  - A conspirator?
  - A bystander?
  
- And where does tau fit in?

# So...

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- It is now apparent, that removing amyloid from a clinically affected brain seems to offer no benefit
  - Yet, there are many studies that show that amyloid deposition is a predictor of, and possibly a prerequisite for, future disease
- Recent studies have shown that neurodegeneration alone did not confer a significantly different risk of developing AD than the control group
  - Yet, some studies suggest that levels of tau more closely coordinate with cognitive decline than do levels of amyloid

# Lancet Neurology: 15: 10, Sept 2016

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$A+ N+ > A+ N- > SNAP = A-N+$

- The presence of both amyloid and neurodegeneration confers the highest risk
- Neurodegeneration seems to act as a compounding factor
- Neurodegeneration alone did not confer a significantly different risk from the control group

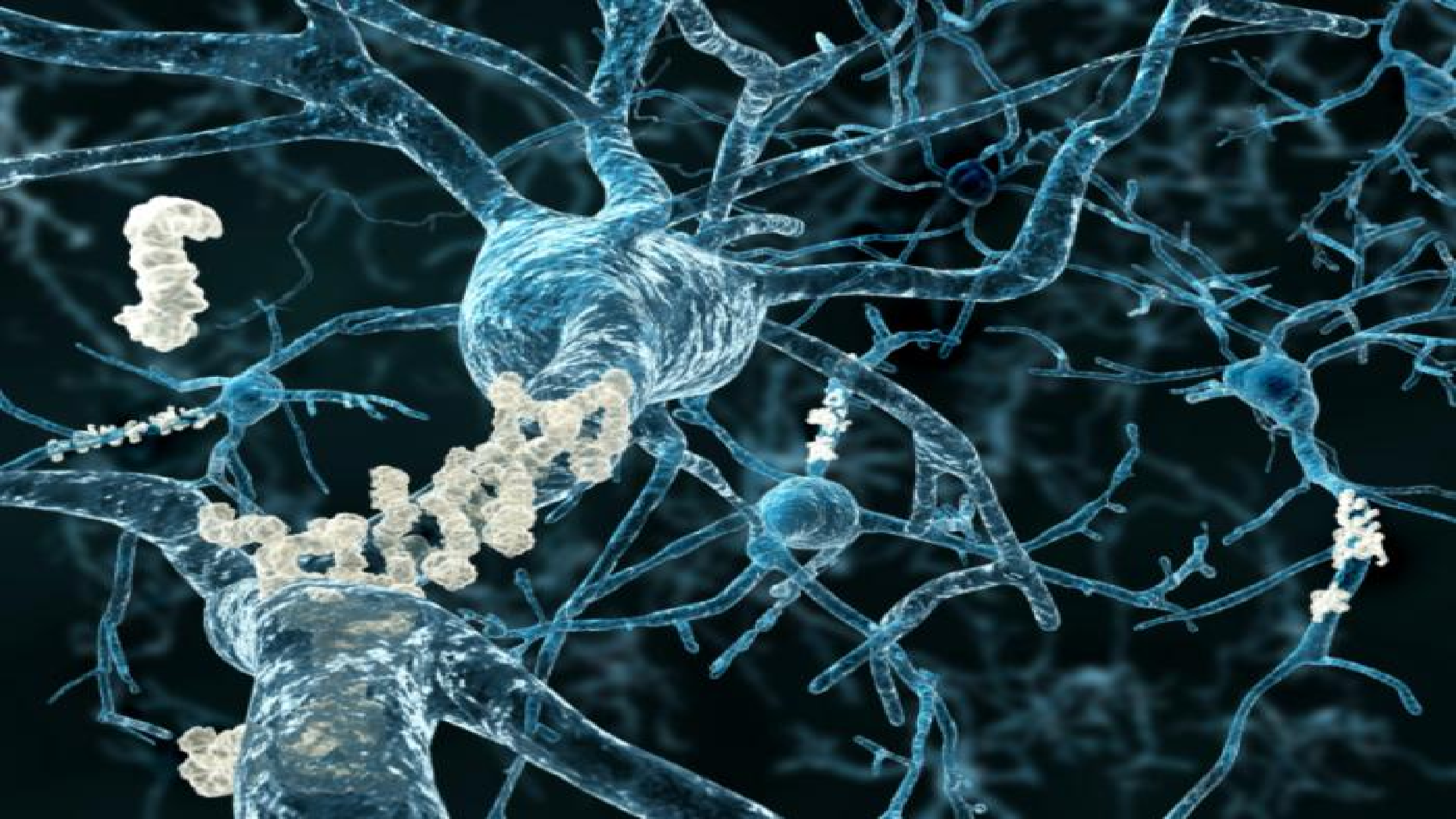
SNAP: Suspected Non-Alzheimer's Pathology



# It Takes 2 to Tango

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- Tau and amyloid in combination seems to show a strong connection with the burdens of AD and declining function
- These misfolded proteins are thought to independently coexist... with preferences in different parts of the brain



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The brain does not exist in a vacuum. It dwells in our bodies where it is in constant conversation with our body's other great communicator, i.e. the immune system.



# LilrB2

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- A molecule found to be important in the immune system has now been found to play an important role in the brain
- This molecule works at the synapse – acting like a brake to slow the ferocity of the immune response
- Amyloid-beta has a high affinity for LilrB2 at the synapse – thus, “taking off the brake,” allowing the immune response to deteriorate the synapse
- Therefore, blocking amyloid-beta from binding to LilbR2 may be a viable treatment strategy to prevent cognitive decline

# C1q

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- A protein typically associated with immune function was found to have a 300 fold uptick in prevalence in old brains compared to young
- This is seen especially at the synapses, and especially in the hippocampus
- Microglia produce C1q in the brain, and this protein is essential in initiating the complement system
- Astrocytes produce numerous other proteins that join C1q in the formation of the complement cascade as part of our immune response
- Buildup of C1q at the synapse may not be directly toxic, but it is thought to leave the brain vulnerable. When any number of stresses occur, the astrocytes can be triggered to release the other components and initiate the destructive cascade that injures/destroys the synapse.
- Work is ongoing to develop drugs that block this complement cascade
- ADDL's promote C1q deposition at the synapse

# Solanezumab

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- A humanized monoclonal antibody that preferentially binds to soluble forms of amyloid
- In preclinical studies it dramatically promoted amyloid clearance from the brain
- Recently released data from a phase 3 clinical trial showed that this agent **FAILED** to improve cognition or functional ability

# Aducanumab

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- Biogen monoclonal antibody that was just granted fast track designation
- Like previously studied monoclonals, it is thought to help clear the brain of beta-amyloid plaques
- Currently being studied in patients with early and mild forms of AD

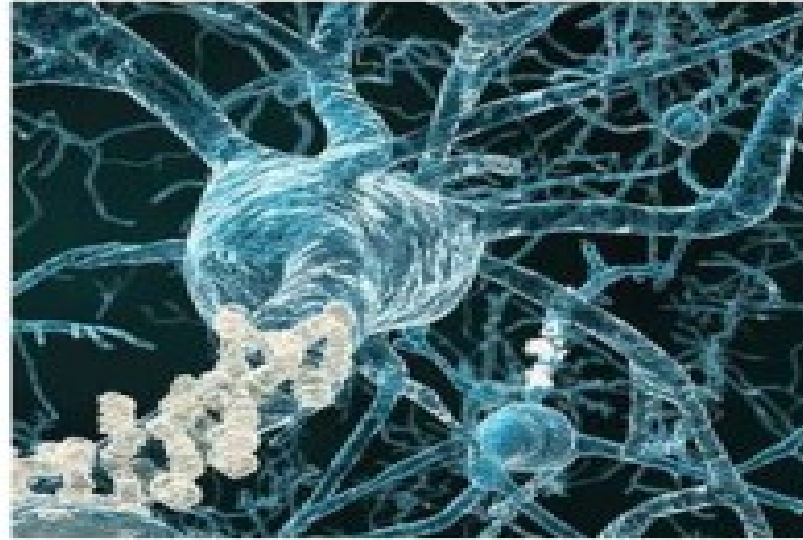
# IVIg

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- 18 month GAP trial (gammaglobulin Alzheimer's partnership)
- Showed no significant difference in the rates of cognitive or functional decline compared to placebo (this in contrast to the highly favorable results suggested in the phase 2 trials)



# Could Alzheimer Disease be Diabetes Type 3?



# Insulin Resistance

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- Diabetes

- Doubles the risk for AD
- A meta-analysis of 19 longitudinal studies looked at the association of DM with relative risk for AD, vascular dementia, any dementia, and MCI. Their conclusion:
  - AD – 1.46
  - Vascular dementia – 2.48
  - Any dementia – 1.51
  - MCI – 1.21



# Insulin Resistance

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- In pts > 65 years old
  - Prevalence of DM: 8.5%
  - Prevalence of Dementia: 6.4%
- It is estimated that Type II DM or abnormal fasting blood glucose may be present in up to 80% of patients with a diagnosis of AD
- It has been clearly demonstrated that patients with AD have decreased ability to metabolize glucose in the hippocampus and other areas of the brain

# Insulin Resistance

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Ties back into the ADDL (amyloid-derived diffusible ligand) hypothesis

- ADDL's bind at the synapse and lead to a dramatic loss in the number of available insulin receptors
- High brain insulin levels also lead to insulin resistance
- Up to 30% of all adults > 60 years old may have insulin resistance and most are unaware
- Brain insulin levels may be 300x normal – this can lead to insulin resistance, even with normal blood glucose levels

# IDE (Insulin Degrading Enzyme)

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- Is a protease that not only degrades insulin but also beta amyloid – in fact, it appears to be the only protease involved in beta amyloid degradation.
- Beta-amyloid competes with insulin to be degraded by IDE.
- An increase in CNS insulin levels may inhibit beta amyloid degradation by IDE

Therefore, optimized brain insulin levels promote beta amyloid clearance and thus may have a protective role in AD.

# Strategies to Treat Insulin Resistance

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- Diet – low fat, low sugar, Mediterranean diet
  - High fat, high sugar diets led to increased amyloid production
- Aerobic exercise
- Lower visceral (belly) fat
  - Subcutaneous fat may actually be beneficial

# Nasal Insulin

## - SNIFF study: NIA, USC, Wake Forest

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The Study of Nasal Insulin and the Fight Against Forgetfulness

- The results from a small preliminary study looked promising
- This ongoing study is investigating the effects that nasal insulin has on:
  - Cognition, memory, and ADLs
  - Entorhinal cortex and hippocampal atrophy
  - CSF biomarkers

Could inducing ketosis to address brain glucose hypometabolism offer any benefit?

# Revisiting Brain Inflammation in Alzheimer's Disease

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*Induction by autophagy enhancers*

Phagophore

Mutant aggregate-prone proteins



*Neurodegeneration*

Lysosome

*Degradation of mutant aggregate-prone proteins*

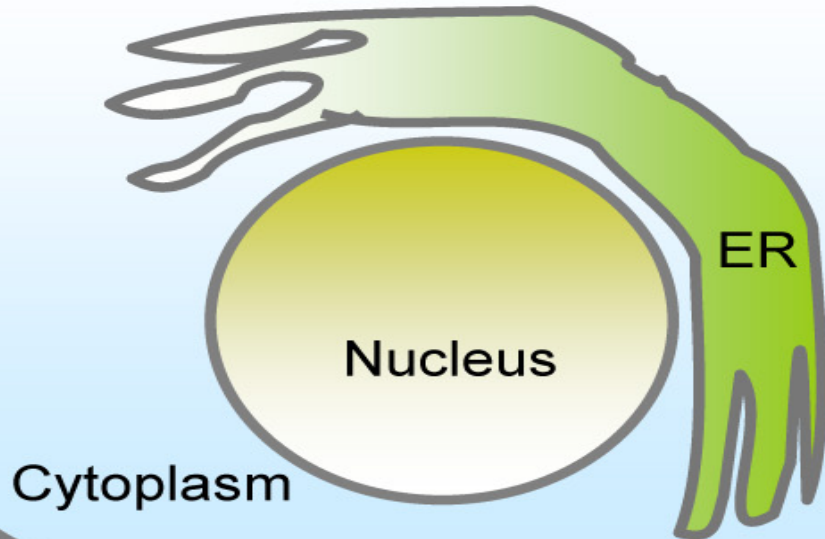
Autophagosome

Autolysosome

**Autophagy**

*Reduction of mutant protein-associated aggregates and toxicity*

*Protection in various models of neurodegenerative diseases*





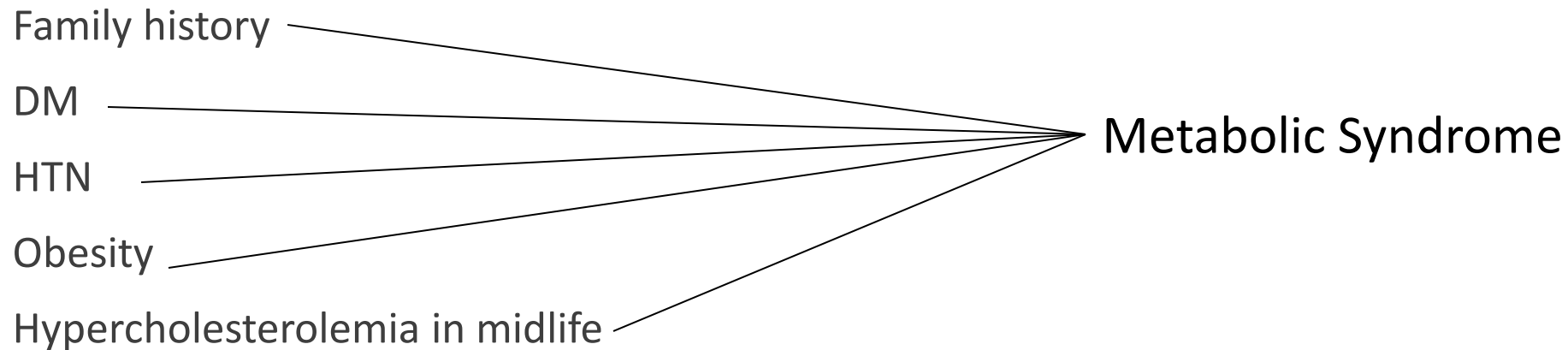
- Autophagy is the neuron's recycling system and it has been shown to be impaired in AD
- This can lead to inflammation and cell destruction
- In cerebral inflammation, microglia, (close cousins of pathogen eating macrophages), swarm around plaques and tangles
- This is thought to be helpful in gobbling up amyloid and damaged cells and cellular debris
- But, can this immunologic enthusiasm also cause harm to healthy cells?
- Conditions that are known to accelerate dementia such as head trauma and systemic infections are also known to cause inflammation

- Most NSAID studies have shown no benefit in the treatment or prevention of AD, and one study actually suggested harm
- There is however a more recent study that suggested that naproxen showed benefit
- TREM 2 agents which suppress inflammatory responses by repression of microglia mediated cytokine production, are currently under investigation
- Specific IL-12 and IL-23 blockers are currently being investigated

# Risk Factors

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Advancing age – for every 5-year age group beyond 65, the percentage of patients with AD doubles



- Pts in their 40s with total cholesterol 249-500 were 1.5 times more likely to develop AD than those with cholesterol less than 198

# Risk Factors (cont)

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- Down's Syndrome
- Head injury
- Decrease in exercise
- Heavy drinkers (more than 2 drinks per day) developed AD 4.8 years sooner
- Heavy smokers (more than 1 pack per day) developed AD 2.3 years sooner
- A cognitive complaint
- Unmarried in midlife
- Depression

# Education

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Less than 12 years of education:

- ➡ 15% increased risk compared to those with 12-15 years of education
- ➡ 35% increased risk compared to those with more than 15 years of education

Is this due to an increase in cognitive reserve or due to social cofactors?

- Even when cofactors are taken into account, fewer years of education does increase the risk of developing AD.

African Americans > Caucasians

- But this seems to be due to cofactors, particularly years of education,



# Genetic Factors in the Development of Alzheimer's Disease

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- Chromosome 1 – mutations on the presenilin-2 gene
- Chromosome 14 – mutations on the presenilin-1 (gamma secretase) gene
- Chromosome 19 – ApoE allele
- Chromosome 21 – mutations on the APP gene

# Reasons for Optimism?

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- Are we seeing less dementia than expected?
- Studies now suggest that the dementia rate is decreasing in some wealthy countries
- CFAS II (Cognitive Function in Aging Study) suggested that the dementia prevalence in the UK was lower than previously expected – *Lancet*, July 11, 2013
- David Green published research in *Legacy* that showed similar declines in England, Sweden, Germany, and the Netherlands



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In the US, a multi-year study funded by the federal government followed up on new dementia cases, in people over the age of 60, in 5-year blocks of time.

- **1978-1982** - Baseline rate for comparison
- **1986-1993** - 22% drop in new cases
- **1996-2000** - 38% drop in new cases
- **2006-2009** - 44% drop in new cases

**\* In addition, the average age for dementia diagnosis rose from 80yo in the first group to 85yo in the last one.**

# Prevention

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- AD is not a fate without the possibility of change
- We have now identified modifiable risk factors. If behavior can be altered or actions be taken early enough, some targeted interventions can have a major impact on delaying or preventing AD symptoms in vulnerable individuals.
- **Since age is the #1 risk factor for AD, it is thought that delaying the onset of AD by 5 years may prevent 50% of all cases**

# Exercise and Diet

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- FINGER study: a 2-year study of 1,260 participants aged 60-77 randomized into 2 groups. The control group received regular medical attention and the study group had...
  - Nutritional guidance
  - Management of heart health risk factors
  - Regular exercise (cardiovascular and weight training)
  - Diet heavy in fruits, vegetables, and fish and low in saturated fats
- Conclusion: after 2 years the intervention group scored significantly better on a comprehensive cognitive exam and on specific tests of memory, executive function, planning, judgment, problem-solving, and cognitive processing speed
- A 7-year extended follow-up is ongoing and will measure the incidence of AD in both groups

# Exercise and Diet

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- Another recent study published in the *Annals of Internal Medicine*, Feb 2013: 20,000 pts enrolled in their 40's and 50's were followed into their 70's and 80's.
  - Conclusion: patients who were physically fit / physically active in mid-life were 40% less likely to develop dementia or AD compared to their counterparts who were not
- *Annals of Internal Medicine*, 2006, Volume 134, pp 73-81: Looked at 1,740 participants over the age of 65.
  - Conclusion: Those who exercised vigorously (3-4 times per week) had a 34% reduction in the development of dementia in elderly persons compared with those who didn't

# AAIC 2016 Data

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- A Study of 3536 Patients Concluded:

“Vascular intervention does not appear to affect dementia incidence in patients who are cognitively healthy”

# On the Other Hand...

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Neurology 86:20 May 17, 2016

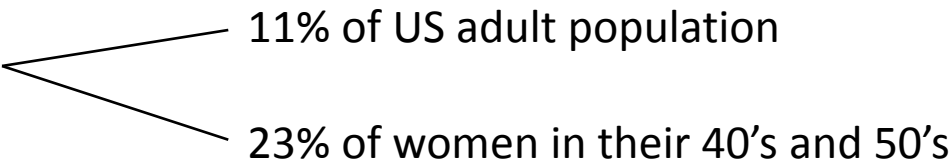
LTPA – Leisure Time Physical Activity

- Was shown in this study of 1228 pts to be protective against decline in cognitive performance
- Low level LTPA was associated with a greater level of cognitive performance decline especially in processing speed and episodic memory



# Downstream Benefits?

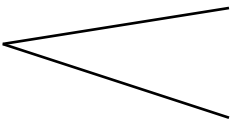
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- SSRIs 
  - 11% of US adult population
  - 23% of women in their 40's and 50's
- Can reduce the amyloid-beta burden in key regions of the brain (*Science*, May 2014)
  - Specifically, citalopram (which is the most selective for increasing serotonin)
- Patients who have used SSRIs during a 5-year period have fewer amyloid deposits compared to a control group. Activation of serotonin receptors reduces amyloid-beta production and activates intracellular signaling pathways. (*Proceedings of the National Academy of Science*, 2011)



# Statins

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- Statins 
  - Over 15 million Americans are currently on statins
  - NIH guidelines indicate that 35 million Americans should be
- In February 2012, the FDA issued a statement – based on anecdotal reports – warning of possible adverse mental affects associated with statin use. \* BUT... *Annals of Internal Medicine*, Nov 19, 2013 concluded in a well designed study that statins are NOT linked to memory loss or dementia.
- Moreover...
  - Rotterdam study, 2008 – Prospective study of almost 7,000pts followed for 12-15 years showed that statins are associated with a reduced risk of AD, regardless of lipophilicity. Non-statin cholesterol lowering agents were not.
  - A Johns Hopkins study, published in *Mayo Clinic Proceedings*, Oct 2013 – Concluded that the long-term use of statins reduced dementia risk by 29%. High potency (artorvastatin and rosuvastatin) seems to be more important than solubility.
  - The conclusion from an article published in *Circulation* were that the benefits of statins largely outweighed the risks

# Metformin

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- The most commonly prescribed drug for the treatment of type-2 DM
- Presentation to the Alzheimer's Association International Conference, 2013
  - Compared to people taking sulfonylureas, those taking metformin has a 20% reduced risk of developing AD over the 5 year study period
    - This was an observational, retrospective, population-based study. It showed an association, NOT cause and effect.
  - On the other hand, another study showed that metformin use overactivates AMPK (adenosine monophosphate activated protein kinase), and enzyme that promotes Alzheimer changes (*Neuron*, 2013)
  - J. Alzheimer's Dis 2014; 41(1): 61-8 – Controlling for age, education, diabetes duration FBS, and vascular and nonvascular risk factors metformin use showed a significant inverse association with cognitive impairment in longitudinal analysis, with use for more than 6 years showing the lowest incidents of cognitive impairment

# The Importance of Early Detection

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- More and more data is consistent with the paradigm that interventions aimed at preventing cognitive decline need to occur before symptoms manifest
- Amyloid begins its neural stranglehold up to 30 years prior to symptom onset
- If the pathologic substrates of AD can be removed early in the process, can Alzheimer's be delayed? Be prevented?

Perhaps combination therapies with early pharmacologic interventions to remove or prevent amyloid, tau, and inflammation... along with lifestyle modifications and other preventative strategies can make a difference.

# Biomarkers

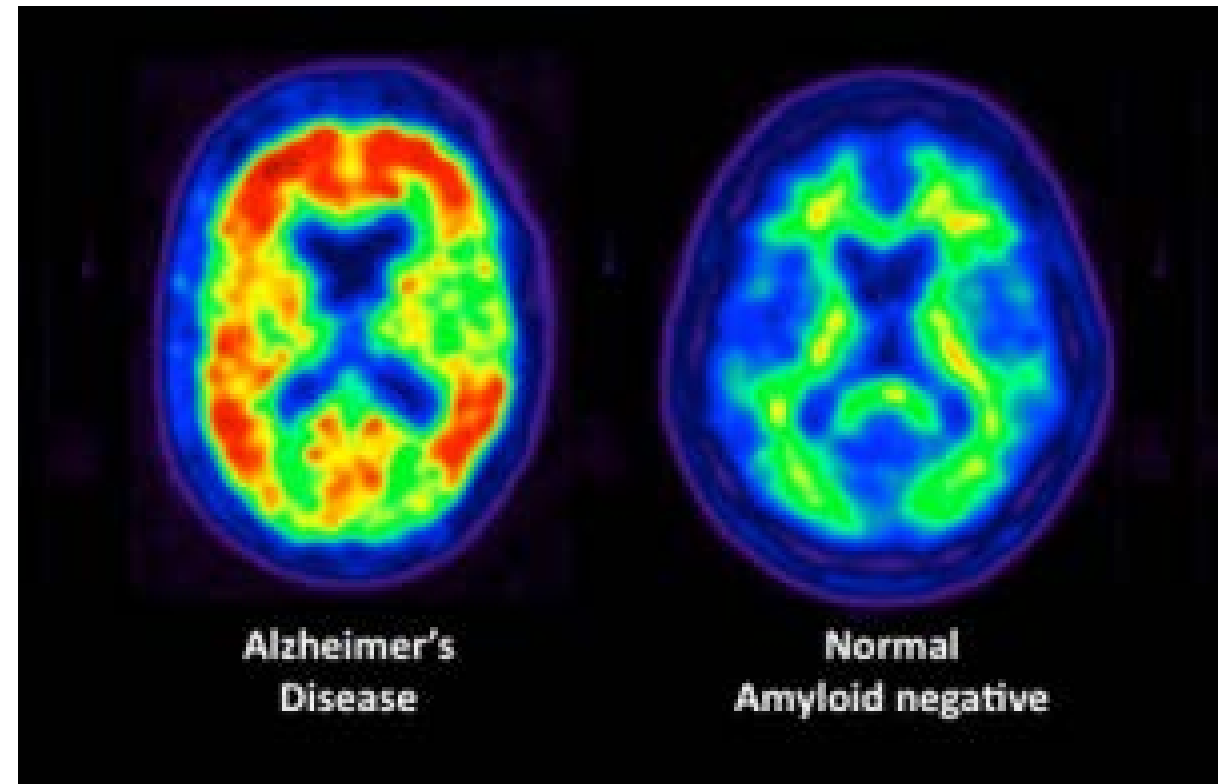
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- Amyloid Measures
- Neuronal Injury Measures
- Other Preclinical Screens

# Amyloid PET Brain Imaging

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- PIB (Pittsburgh Compound B)
- Florbetapir (Amyvid)



# Amyloid PET

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- If a person with dementia does not have amyloid buildup, then the cause is very unlikely to be AD
- If amyloid buildup is seen in a patient with memory impairment, then the likelihood that this symptom is secondary to AD is significantly increased
- If a person without memory complaints has amyloid buildup, it does NOT mean that they will develop AD

## Amyloid Measures

# CSF Analysis

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Decrease amyloid beta 42

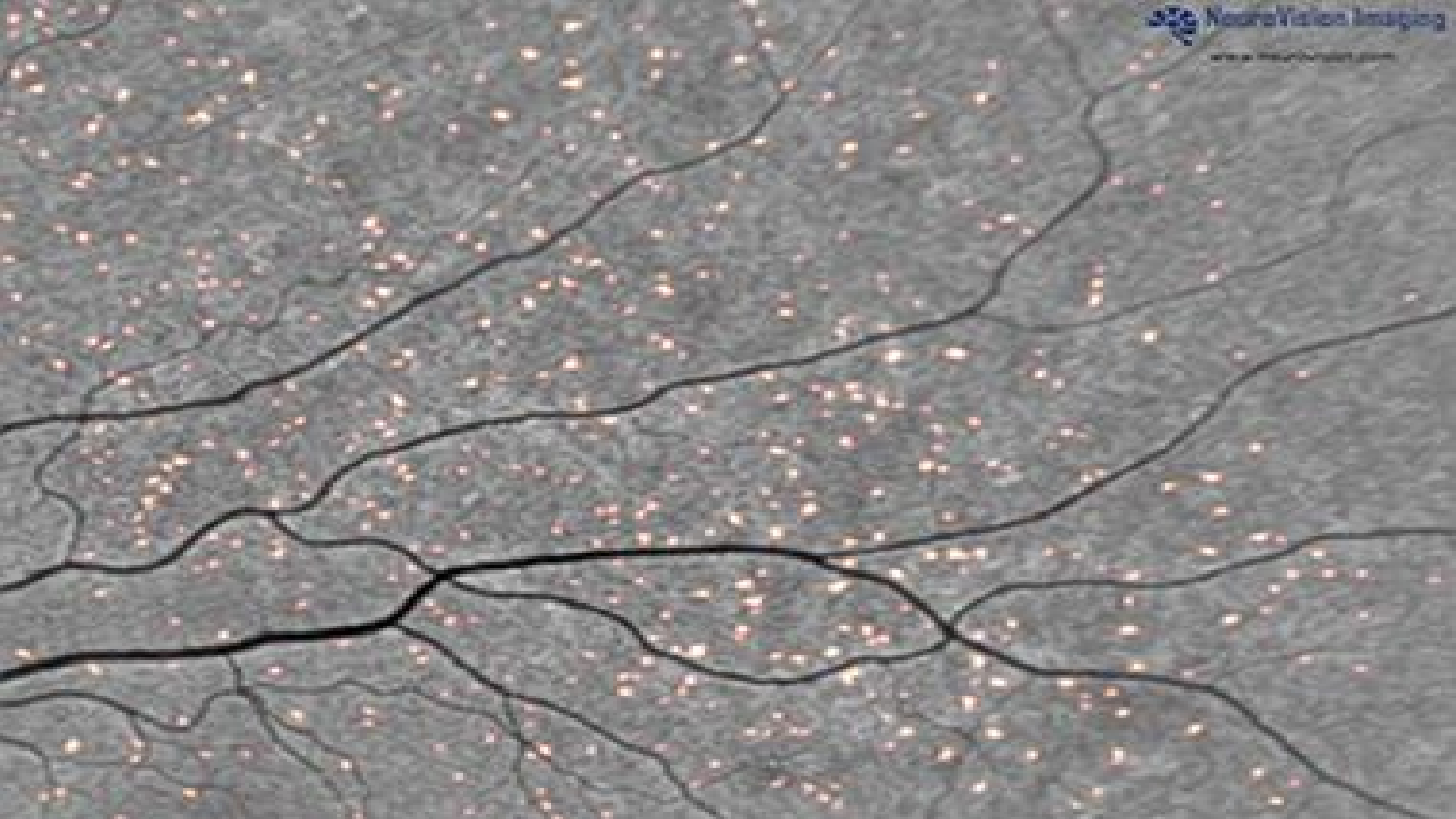
# Non-Invasive Detection of Beta-Amyloid in the Retina

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A very promising development presented at last year's AAIC by the Australian National Science Agency

- In preliminary published results in 40 patients, the test could differentiate between AD and non-AD with 100% sensitivity and 80.6% specificity
- This optical imaging exam appears to detect changes that occur 15-20 years prior to clinical diagnosis
- The process involves “staining” amyloid plaques in the retina with curcumin (a component of the spice turmeric)





## Amyloid Measures

# ADx Imaging

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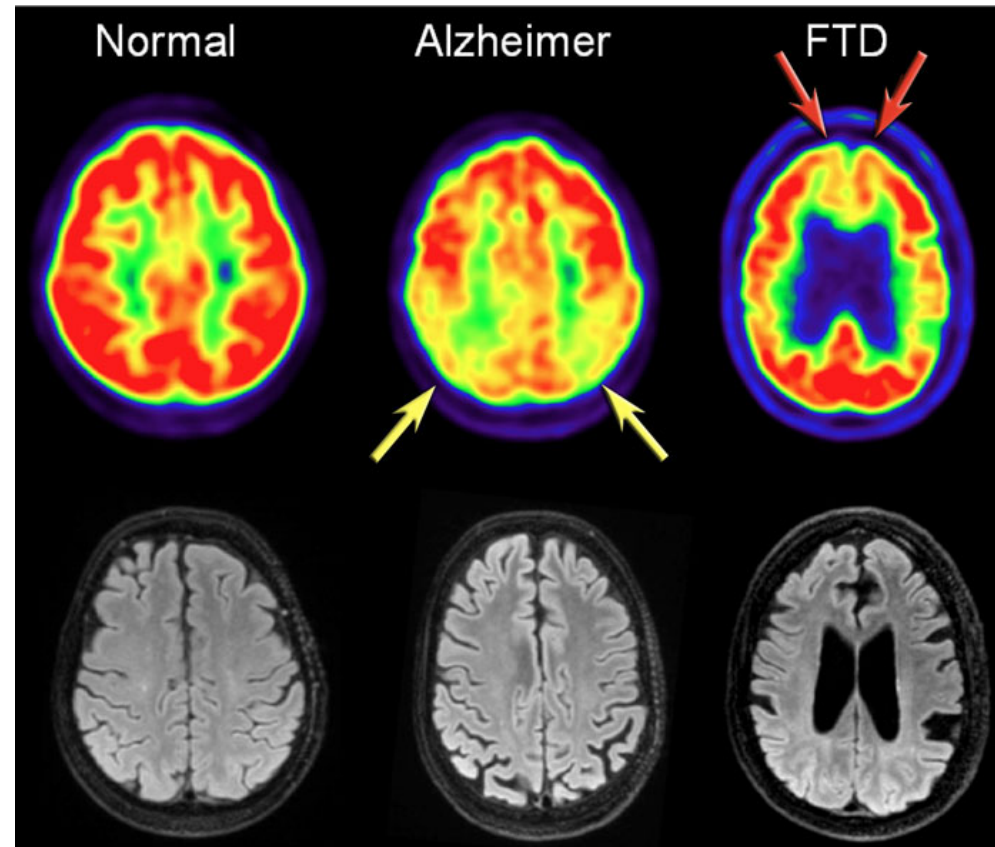
## Alzeca Biosciences – study published in Journal of Alz Disease

- ADx is a nanoparticle that can be given IV that can carry an encapsulated agent across the BBB to bind precisely to amyloid plaques
- Researches were able to obtain precise, high resolution images of amyloid plaques using conventional MRI
- If substantiated in larger studies, this would result in amyloid detection being more available and affordable

# Neuronal Injury Measures

## FDG-PET

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## Neuronal Injury Measures

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Increase CSF phosphorylated tau

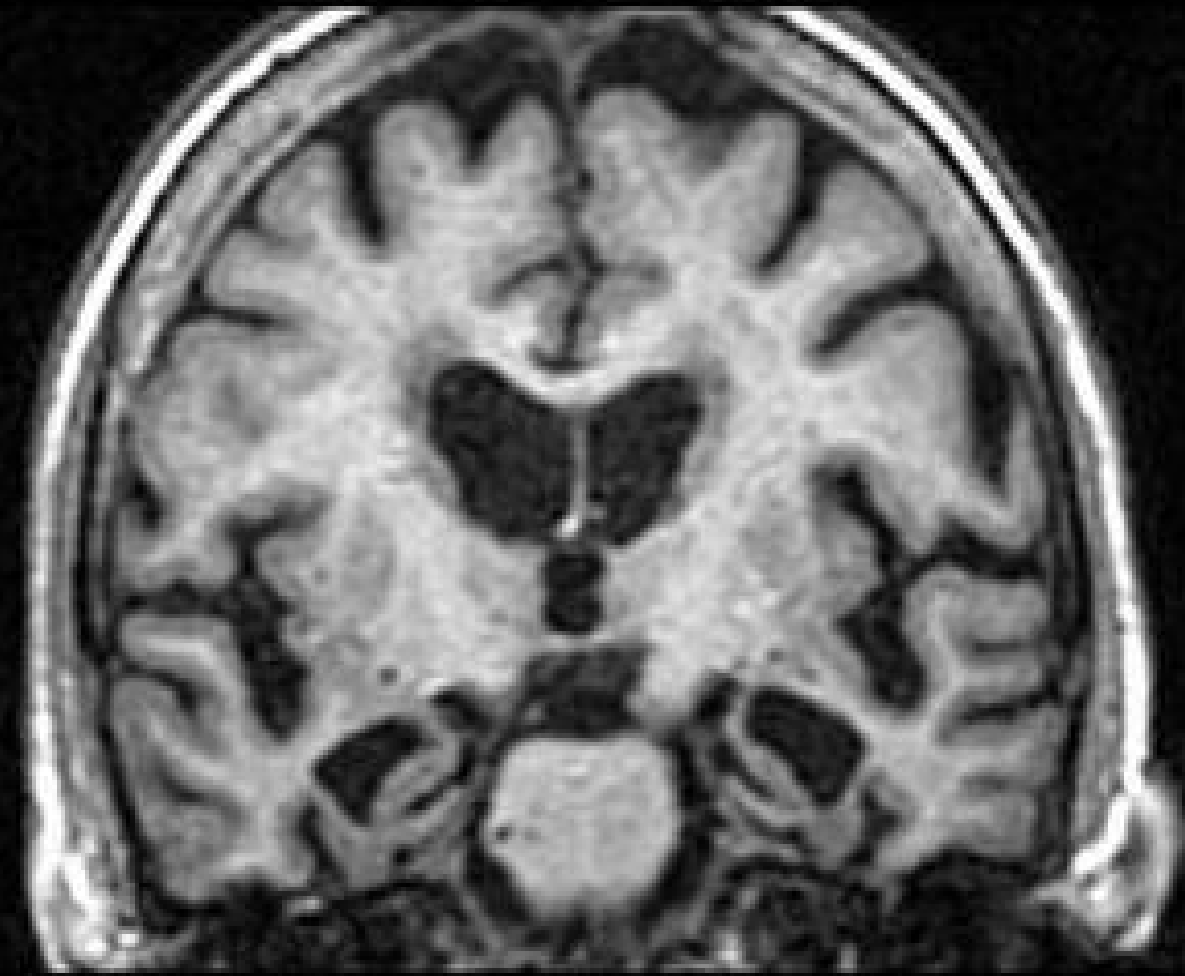
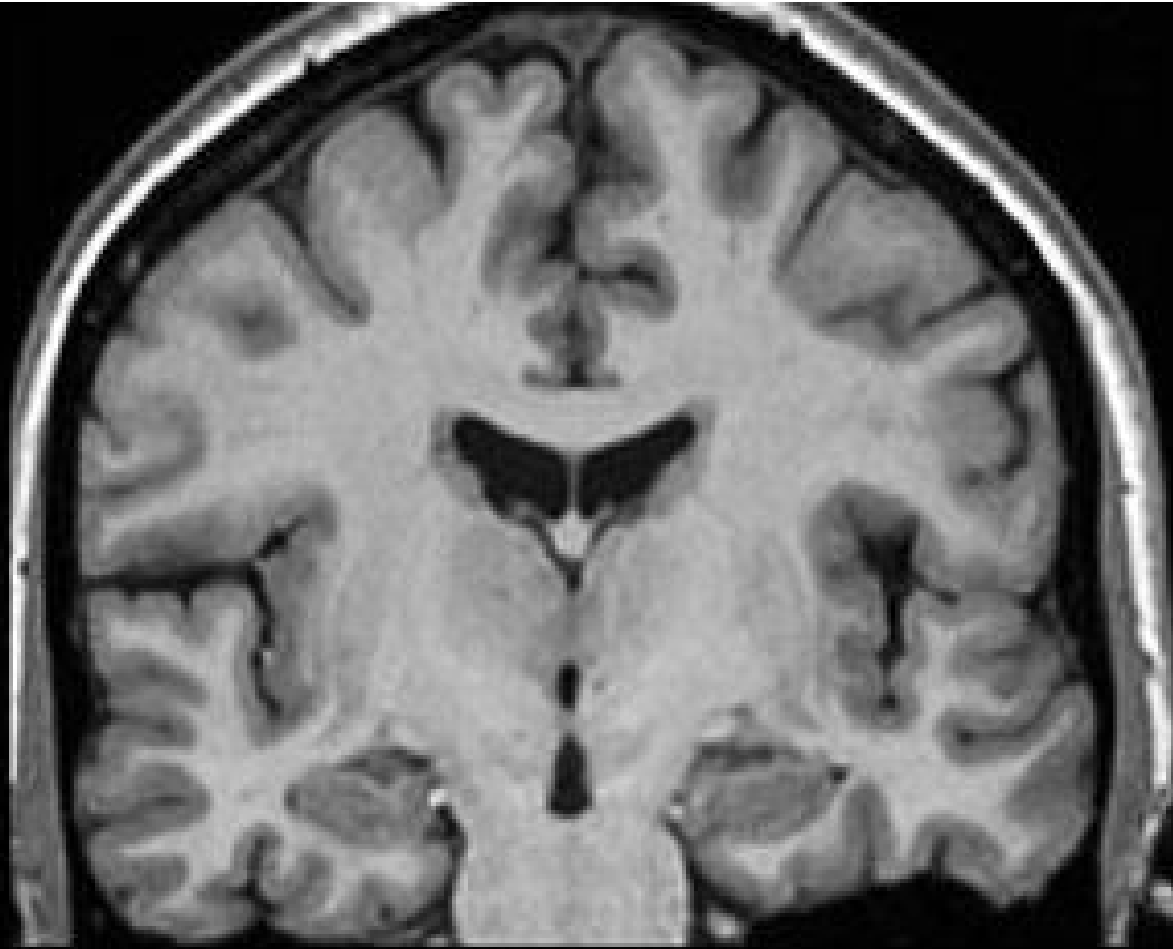
# Specific Lipid Panels

## - Another Promising Biomarker

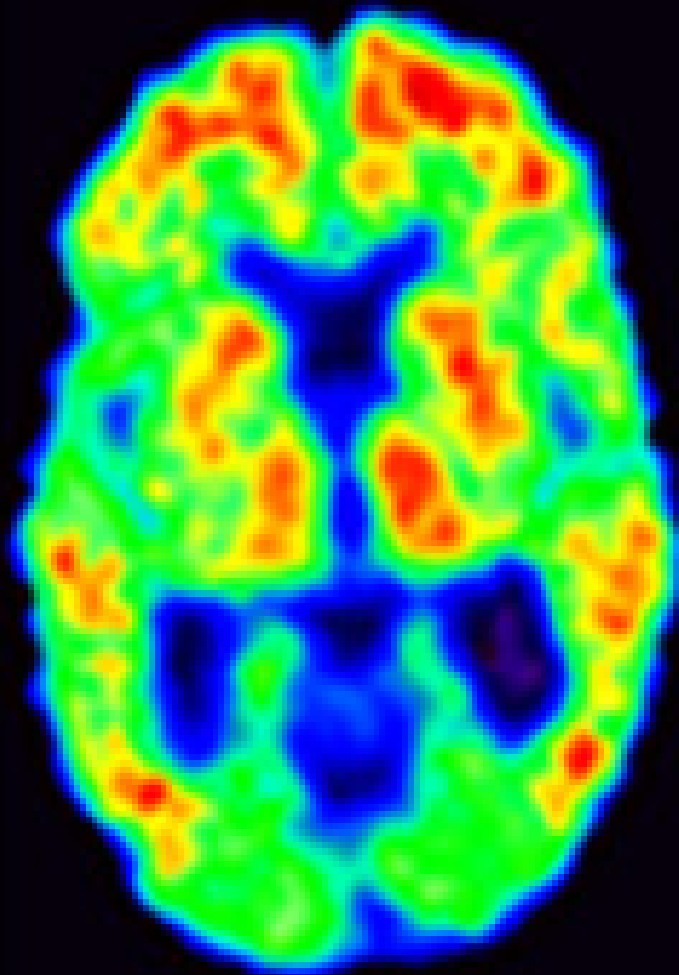
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- Researchers looked at 4,600 potential metabolites of CNS cell breakdown
- They discovered that 10 lipids were significantly altered in the plasma of cognitively normal adults who would then go on to develop the clinical symptoms of AD
- It is thought that this 10-lipid phospholipid biomarker panel reflects the breakdown of neural cell membranes in those individuals destined to develop advanced MCI or AD
- Interestingly, APOe4 was not one of these lipids
- This panel predicted clinical AD based on the patient's performance on cognitive skills tests, rather than distinguishing among causes of impairment such as vascular dementia vs AD
- This is based on work being done at the Rochester Medical Center

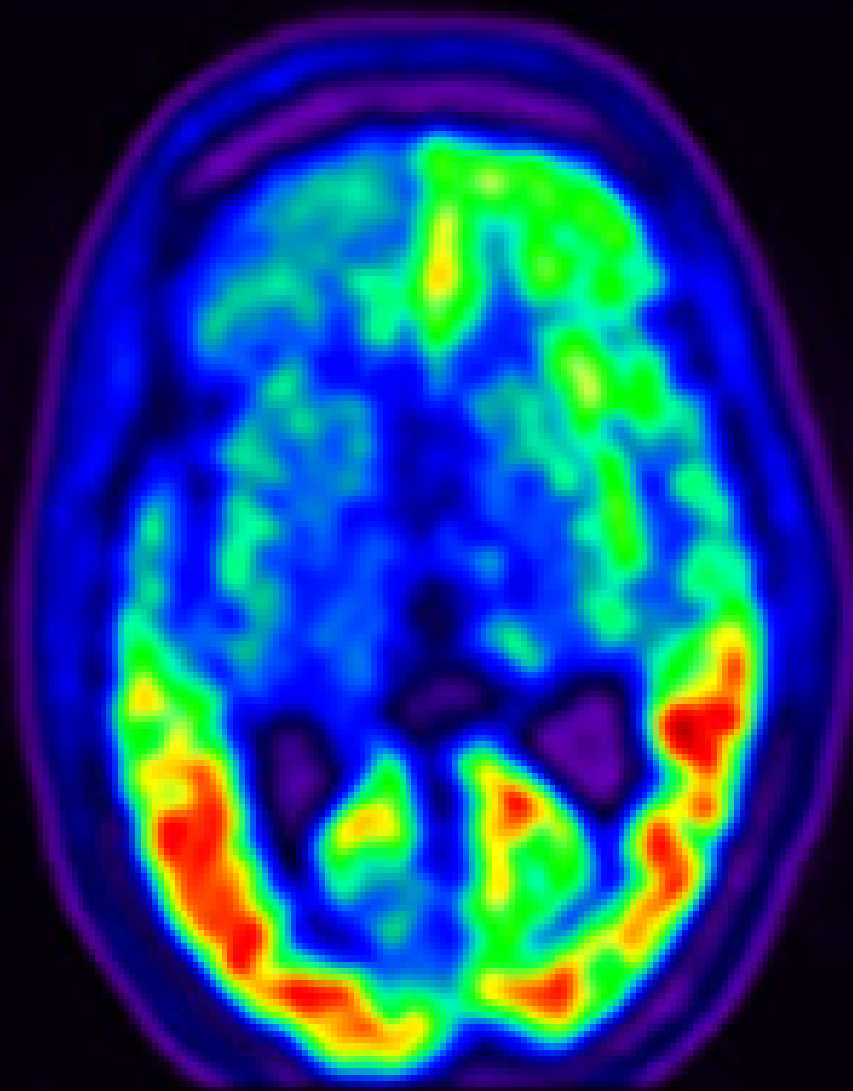
## Neuronal Injury Measures



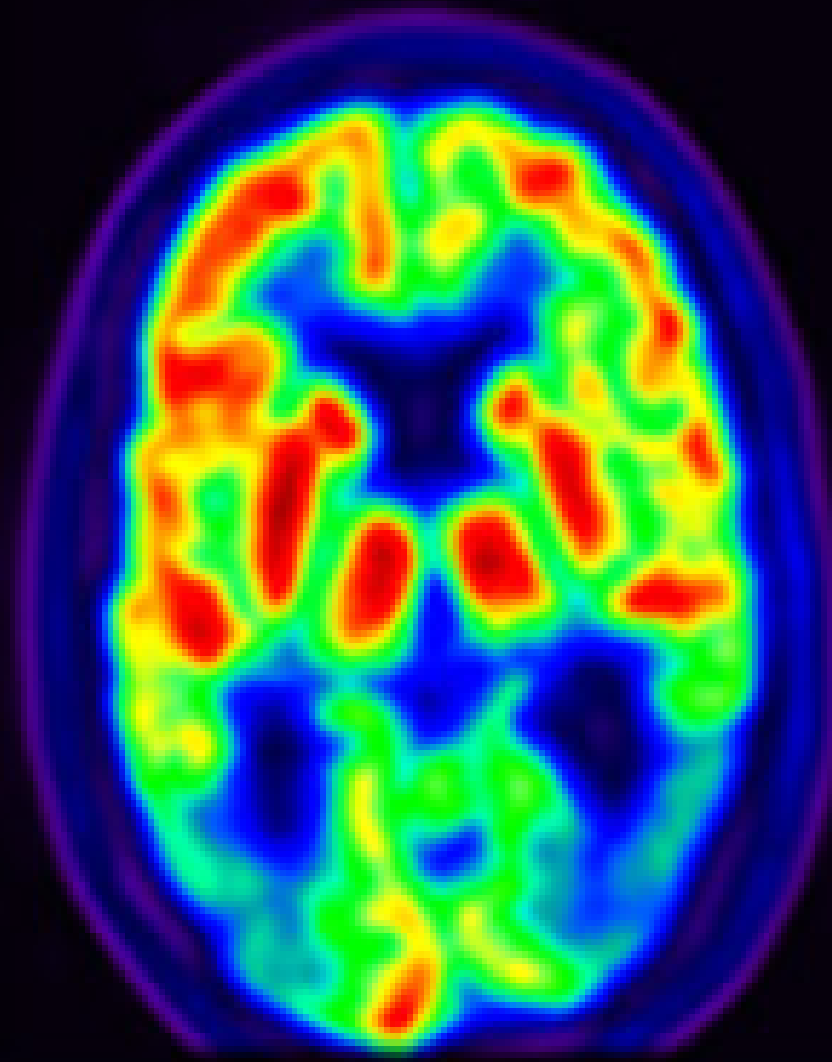
amyloid protein  
PET scan



tau protein  
PET scan



metabolic activity  
PET scan



# Other Preclinical Screens

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- UPSIT (University of Pennsylvania Smell Identification Test)
  - Recent research from Harvard was presented at the 2014 AAIC in Denmark
    - Inexpensive and easy to administer
    - Poor UPSIT scores correlated with lower cognitive scores and was confirmed by other physical markers of AD, including atrophy (which represents neurodegeneration) and amyloid deposits
  - A second study from the UFCOM found that among 757 participants, lower scores on UPSIT were associated with the transition to dementia and AD



## Other Preclinical Screens

# Mild Behavioral Impairment (MBI)

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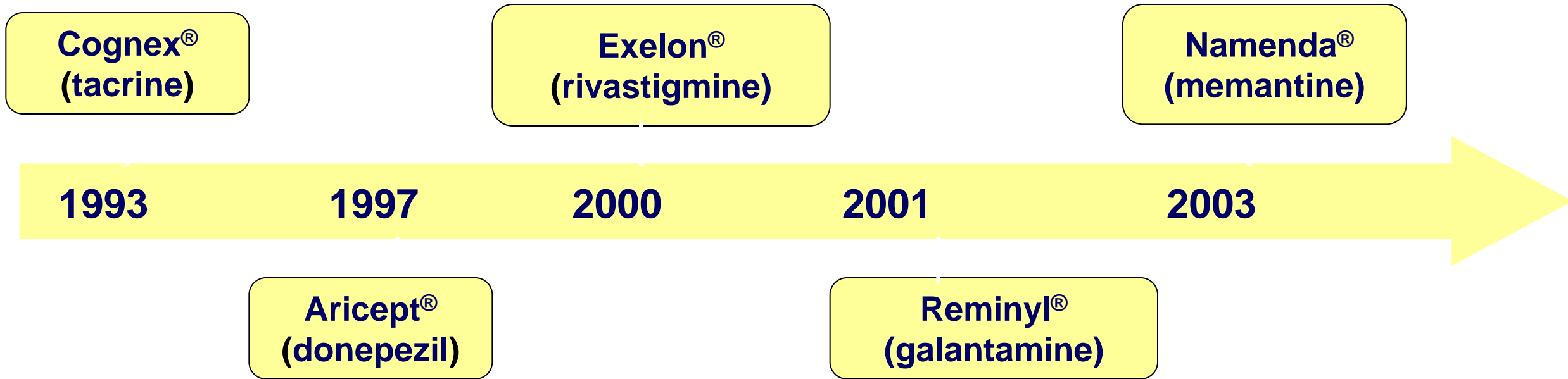
- Is a predictor of neurodegeneration and progression to dementia
- AMJ Psychiatry 2014 171 [5] showed:
  - Agitation > apathy > anxiety > irritability > depression
  - Predicted future dementia

# WILL YOU GET ALZHEIMER'S? ANSWER THESE QUESTIONS TO FIND OUT

QUESTION	YES	NO	SEVERITY
<b>This domain describes interest, motivation, and drive</b>			
Has the person lost interest in friends, family, or home activities?	YES	NO	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	YES	NO	1 2 3
Has the person become less spontaneous and active for example, is she/he less likely to initiate or maintain conversation?	YES	NO	1 2 3
Has the person lost the motivation to act on their obligations or interests?	YES	NO	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	YES	NO	1 2 3
Does she/he no longer care about anything?	YES	NO	1 2 3
<b>This domain describes mood or anxiety symptoms</b>			
Has the person developed sadness or appear to be in low spirits? Does he/she have episodes of tearfulness?	YES	NO	1 2 3
Has the person become less able to experience pleasure?	YES	NO	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	YES	NO	1 2 3
Does the person view herself/himself as a burden to family?	YES	NO	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	YES	NO	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	YES	NO	1 2 3
<b>This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward</b>			
Has the person become agitated, aggressive, irritable, or temperamental?	YES	NO	1 2 3
Has she/he become unreasonably or uncharacteristically argumentative?	YES	NO	1 2 3
Has the person become more impulsive, seeming to act without considering things?	YES	NO	1 2 3
Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?	YES	NO	1 2 3
Has the person become more easily frustrated or impatient? Does she/he have troubles coping with delays, or waiting for events or for their turn?	YES	NO	1 2 3
Does the person display a new recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.)?	YES	NO	1 2 3

Has the person become more stubborn or rigid, i.e., uncharacteristically insistent on having their way, or unwilling/unable to see/hear other views?	YES	NO	1 2 3
Is there a change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order)?	YES	NO	1 2 3
Does the person no longer find food tasteful or enjoyable? Are they eating less?	YES	NO	1 2 3
Does the person hoard objects when she/he did not do so before?	YES	NO	1 2 3
Has the person developed simple repetitive behaviors or compulsions?	YES	NO	1 2 3
Has the person recently developed trouble regulating smoking, alcohol, drug intake or gambling, or started shoplifting?	YES	NO	1 2 3
<b>This domain describes following societal norms and having social graces, tact, and empathy</b>			
Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others feelings?	YES	NO	1 2 3
Has the person started talking openly about very personal or private matters not usually discussed in public?	YES	NO	1 2 3
Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?	YES	NO	1 2 3
Does the person seem to lack the social judgement she/he previously had about what to say or how to behave in public or private?	YES	NO	1 2 3
Does the person now talk to strangers as if familiar, or intrude on their activities?	YES	NO	1 2 3
<b>This domain describes strongly held beliefs and sensory experiences</b>			
Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?	YES	NO	1 2 3
Has the person developed suspiciousness about the intentions or motives of other people?	YES	NO	1 2 3
Does she/he have unrealistic beliefs about her/his power, wealth or skills?	YES	NO	1 2 3
Does the person describe hearing voices or does she/he talk to imaginary people or spirits?	YES	NO	1 2 3
Does the person report or complain about, or act as if seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?	YES	NO	1 2 3

# Current Treatments



Cognex is a registered trademark of Warner-Lambert Company.

Aricept is a registered trademark of Eisai Company Ltd.

Exelon is a registered trademark of Novartis AG.

Reminyl is a registered trademark of Janssen Pharmaceutica.

Namenda is a registered trademark of Forest Laboratories Inc.

# Benefits of Combined Cholinesterase Inhibitor and Memantine Treatment in Moderate-Severe AD

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- *Alzheimer's Dementia*, May 2013
  - Conclusion: Treatment with combination therapy produces consistent benefits that appear to increase over time and that are beyond those of cholinesterase treatment alone
- *JAMA*
  - Conclusion: Combination therapy showed positive results in all measures, i.e. cognition, global status, function, and behavior

# The Future...

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- Nasal insulin
  - SNIFF study: utilizing intranasal insulin did seem to improve glucose metabolism in the hippocampus and frontal lobes without affecting blood glucose levels
- Anti-APOe monoclonal antibodies – Is APOe a therapeutic target?
- Blood transfusions
  - Blood from young mice transfused into older mice seems to lead to better cognitive performance (*Science*, Sept 2014)
- Brain derived neurotropic factor
- Neural stem cells
  - Can up-regulate neprilysin (a protein that breaks down beta-amyloid)
- TC-2153 (*Journal of Alzheimer's Disease*, May 2014)
  - Reversed AD symptoms in mice
  - Blocks the effects of STEP (striatal enriched tyrosine phosphate); STEP prevents synaptic strengthening in the brain

