The 900 lb Gorilla in our Midst

AlzD = Alzheimer's Disease
EOAD = Early Onset AlzD

PART-2: Chaps 12 & 13
Alzheimer's Pathology:
EOAD and AlzD

.

Spring 2021

From my personal Top 50 List:

- why selective vulnerability?
- why no tau mutants in AlzD?
- is AlzD possible w/out A-beta?
- why is atrophy "undefined"?
- why is familial AlzD accelerated?
- why is Semantic D lateralized?
- why have all α-amyloid trials failed?

behind schedule: two choices

Option A: go faster, excerpt chapter highlights

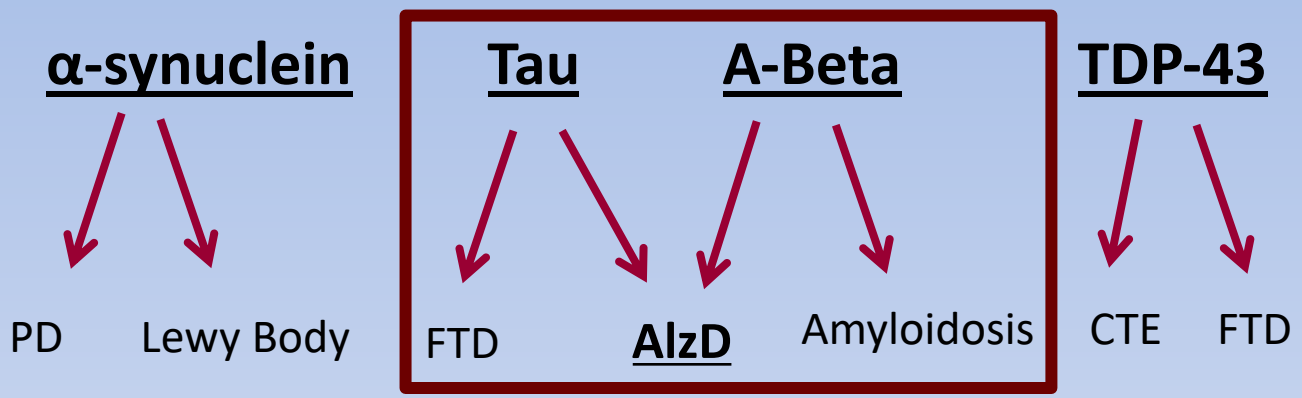
Option B: cover fewer chapters

A bit about **Chapter 14** .... Cognitive Reserve

+ see Chapters 12, 13, 18, 19, 20 -- SNCD

The Big Four
α-synuclein
TDP-43
beta-amyloid
tau
+ fus/bvFTD

Primary connections are shown!



The Cast of Bad Actors

- **Tau, A-Beta** mentioned already; much more below on AlzD, EOAD
- **LBD / *alpha synuclein*** including Parkinson's, LB dementia
- **FTD:** includes behav. variants, semantic dementia, primary progressive aphasia
- **TDP-43** = TAR DNA-binding protein 43, transcription factor; also *fus*

Which of the above are IDPs?

fus: what about MY contributions???

EOAD: Please review Glossary and make suggestions

Table 13.1 for Dementias**: note that AlzD, EOAD** *are not* **included**

Categories of FTD Dementia. Delving into neurodegeneration leads us into the *fog of dementia* with all its overlapping, fuzzy and contradictory reports. **Table 13.1** attempts to parse the major variants of FTD along with guesstimates of how much different pathologies contribute to each variant. Not that this will help, but, for a given FTD variant (e.g. bvFTD) the next 3 columns show approximate contributions of different pathologies—each of which is considered a different "FTLD"! We said it wouldn't help, but please do note that *only the far right column concerns familial cases*: we welcome contributions to help us flesh out and refine this table.

if you have Amyloid you don't get on this FTD table!

Table 13.1	% tau-Picks	% TDP	% fus	useful resource	-- % familial
bvFTD	55%	25%	20%	Bang et al. 2015	-- 35% *MAPT,GRN C9ORF72*
SemD	20%	80%	???	Landin-Romero 2016	-- 5% [all non-TDP?]
PPA	88%	50%	???	Bang et al. 2015	-- family history ~ 25%
CBD/PSP	50%	25% - 50%	???	Kertesz et al., 2000; Bang	--

Table 13.1: Pathology underlying FTP Variants. This table attempts to provide rough / best estimates of the contributions of pathology to different FTD variants, as well as the fraction of each variant that is familial (genetically inherited). The percentages given for different pathologies concern the sporadic cases; the familial cases are a separate category and the familial % shown, for each FTD variant, is a guess as to what % of the total number of sporadic + familial cases is familial. Of the total FTD population, bvFTD is the most common variant, while SemD makes up about 1/3rd of FTD cases per Landin-Romero et al. (2016); who also note some associations between tau mutations and TDP pathology subtypes). Yokota et al. (2009) provides pathology estimates that overlap table values: all SemD cases had TDP; bvFTD was 64% "Picks" (tau); 28% TDP-43. In those bvFTD and PPA cases that showed strong motor (ALS-like) symptoms, which some classify as FTD-MND (motoneuron disease), predominantly TDP-43 pathology was reported by Vinceti et al. (2019), but see further details below. Tee and Gorno-Tempini (2019) summarize family history data for PPA and SemD.

The 900 lb Gorilla in our Midst

AlzD = Alzheimer's Disease
EOAD = Early Onset AlzD

Is it Tau or Amyloid?
Neither or Both?
Is it purely SVD (small vessel disease)?
Is it inflammation and Type 3 diabetes?
What does Craig Ferris think?
[big Pharma has lost their minds]

much more to come: Chap. 18, 19, 20 in SNCD
biomarkers, adv. AlzD, treatments

Faculty Candidate Seminar: 3/16/21 Zhuzhu Zhang, Salk Institute

Investigate DNA methylation in postmortem brain samples from Alzheimer's disease (AD) patients

Her AlzD data is unpublished but Methods are methinks (w/ Ed Callaway)

3 control & 5 Alzheimer's prefrontal cortex (PFC) human postmortem samples

In collaboration with

Rudolf Jaenisch (MIT)

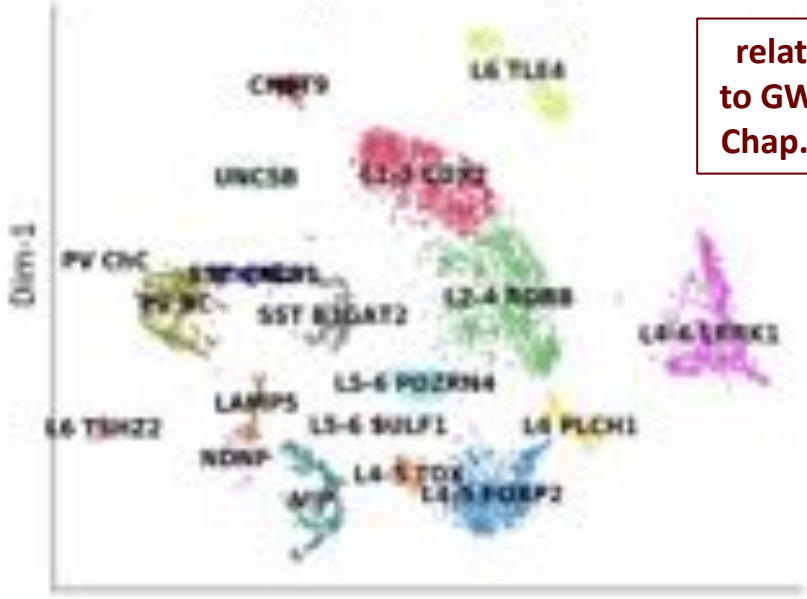
Brad Hyman (Mass General)

Derek Oakley

Anthony Filamor

publishes thousands of papers

Single nucleus DNA methylome sequencing identifies cell types in human prefrontal cortex



relates to GWAS Chap. 19

← this was never explained ☹

EPIGENETICS: the "methylome" is a historical record (of sorts) of which genes are shut down (and thus which are active). ZZZ was able to study neuronal diversity and connectivity of human brains [post-mortems] with this method, but also saw a cell phenotype assoc. with AlzD. Asked if she could track the spread of AlzD pathology, she said not yet ***and that*** these are **Braak Stage 5!**

nature REVIEWS NEUROSCIENCE

Brain Banking is Best!

BRAAK STAGES

widely used in AlzD literature for staging

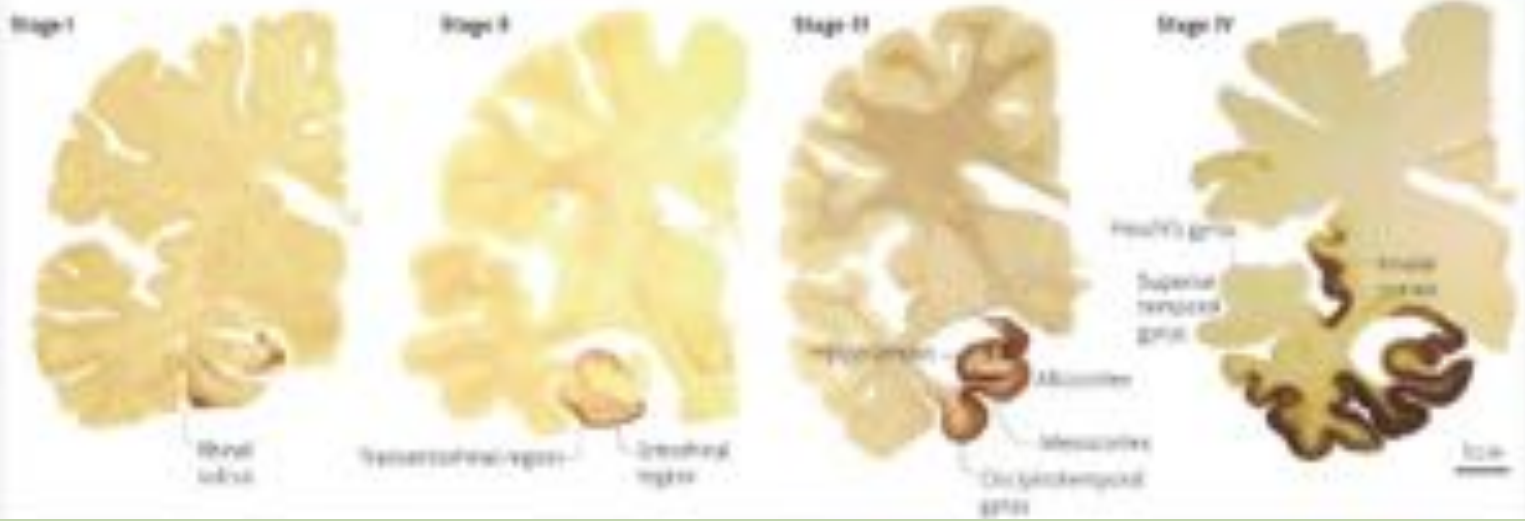
SEE FIGURE LEGEND IN NOTES

FIGURE 2 | Brain banking and longitudinal studies of disease progression.

FROM THE FOLLOWING ARTICLE:

Brain banking: opportunities, challenges and meaning for the future

anyone feeling Ghoulish this week?



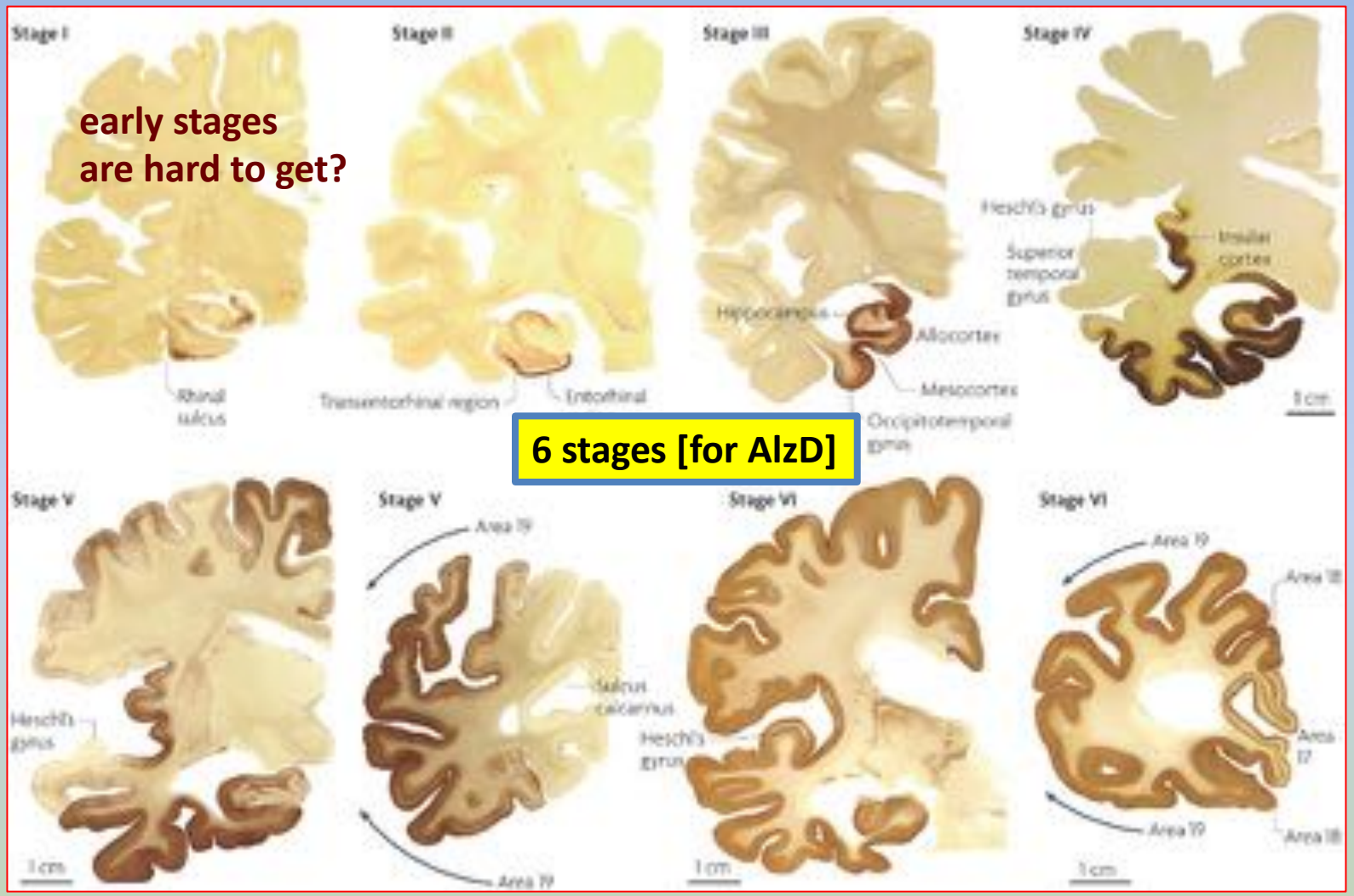
post-mortem pathology staged by Heiko Braak, born 1937

notice the SPREAD of pathology

isocortex = neocortex. allocortex = not 6 layers

mesocortex is transitional (btw neo and allo)

Progression of Hyper-Phosphorylated Tau protein: pioneered by Braak



Tau proteins (or τ **proteins**, after the Greek letter by that name) are **proteins** that stabilize microtubules. They are abundant in neurons of the central nervous system and are less common elsewhere, but are also expressed at very low levels in CNS astrocytes and oligodendrocytes.

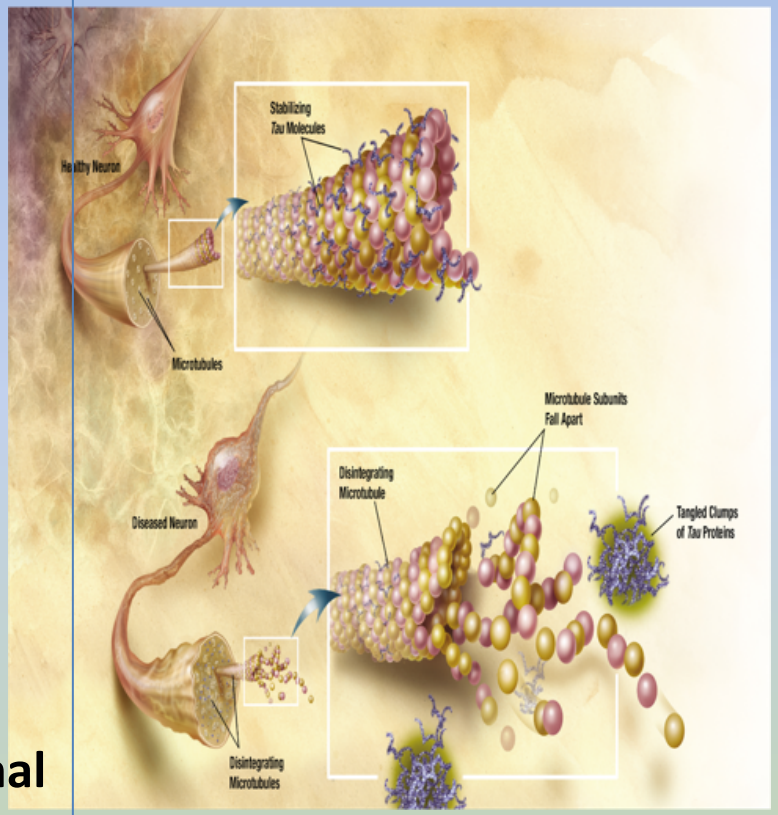
GENERAL: Protein Tau & Neurofibrillary Tangles

In Healthy Cells: TAU

- **promotes self assembly of axonal microtubules** and helps to stabilize them
- a certain number of **phosphate molecules** are attached which enables Tau to bind to microtubules

In Alzheimer's

- an abnormally large number of additional phosphates attach to tau. This hyper-phosphorylation of tau disengages it from microtubules
- disengaged tau proteins aggregate to form **paired helical filaments,** which in turn can combine with neurofilaments to create **neurofibrillary tangles**
  .
- these aggregates **MIGHT collapse the internal transport network within neurons** and alter intracellular physiology, as well as the ability of neurons to communicate with each other



← PHFs and NFTs!

Interim Summary

Tau pathology seen in both FTD (some cases) and AlzD (all cases)

Amyloid appears first (or maybe not)

Amyloid Cascade: plaques or ABO's trigger/enhance Tau pathology

ABO (Amyloid Beta Oligomers) are popular villains these days
but we have to see what Lady Christchurch says (Chap. 18)

Once Tau pathology is entrenched in ERC, it spreads across neocortex
selective vulnerability of ERC neurons has no explanation

Tau Ignition: momentary "spark" of amyloid can set AlzD in motion
vs. "cascade" where **ongoing** Amyloid toxicity is the culprit
Big Pharma has bet on Cascade...and lost many, many billions $$

Pick's, FTD and AlzD

PICK'S: once was a disease, now its a pathology (sorta)

Google pick's disease

People also ask

- What are the signs of Pick's disease?
- What is the life expectancy of someone with Pick's disease?
- Is Pick's disease hereditary?
- How does Pick's disease progress?
- What are the 10 warning signs of dementia?
- How do you get Niemann Pick disease?
- What are the final stages of FTD?
- What is the 30 question cognitive test?
- Is Niemann-Pick disease curable?
- What are the first signs of FTD?
- What are the 3 stages of dementia?
- Is Huntington's disease a form of dementia?
- What is Niemann Pick Disease Type A symptoms?
- Is Wilson disease genetic?
- What causes Niemann-Pick Type C?

Alzheimers.Net seems good

This list of answers is riddled with really bad information!

egregiously incorrect...AND you should spot it!

recent usage of Pick's Disease

might get added to Chapter 18

Neuron 2021

High-Contrast *In Vivo* Imaging of Tau Pathologies in Alzheimer's and Non-Alzheimer's Disease Tauopathies

Highlights

- A new probe, PM-PBB3, captures pathological tau deposits *in vivo* with high contrast
- PM-PBB3 allows an individual-based identification of AD and non-AD tauopathies
- Autopsy assays of PET-scanned patients supported the *in vivo* performance of PM-PBB3

Authors

Kenji Tagai, Maiko Ono, Manabu Kubota, ..., Naruhiko Sahara, Makoto Higuchi, Hitoshi Shimada

Correspondence

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In Brief

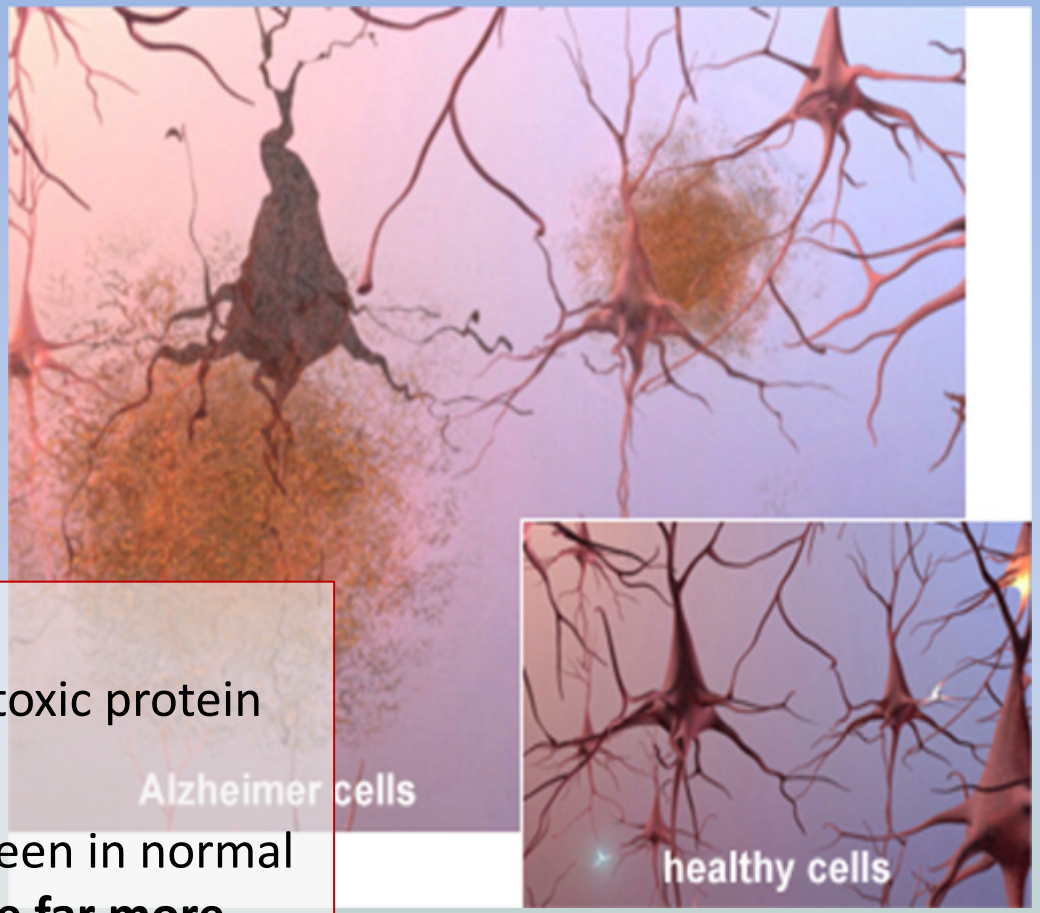
Tagai et al. developed a positron emission tomography probe, ^{18}F-PM-PBB3, for tau deposits in Alzheimer's and non-Alzheimer's disease tauopathies. This probe was demonstrated to enable individual- and pathology-based diagnosis, differentiation, and staging of these disorders in addition to translational research and development on tauopathies from mouse models to humans.

In this case they use Pick's to refer to FTD cases w/ Tau pathology: this is a pathology category, not a clinical diagnosis! [even though they refer to it as "Pick's Disease"; that is fine!]. Tau isoforms are either of the 3-repeat or 4-repeat variety and the "Pick's" autopsies are of the 3-repeat variety, whereas 4-repeat pathology is associated with PSP and CBD!

CBD = corticobulbar degeneration

PSP = progressive supranuclear palsy

Amyloid Plaques



Found in extracellular space

- largely insoluble deposits of toxic protein beta amyloid
- formation of these plaques seen in normal aging but in **Alz D plaques are far more numerous in particular brain regions**
- **still unclear whether or not these plaques cause Alzheimer's or are the result of the disease progression**...possibly a compensatory response**...BUT...EOAD!**

← more on EOAD and amyloid story in Chap 18

Amyloid Precursor Protein (APP)

- source material / beginning of **path to amyloid plaques**
- **APP is transmembrane protein**
- APP can be processed in different ways by different sets of enzymes: normally, about 90% APP enters non-plaque forming pathway **while 10% enters amyloidogenic pathway** [***normally***]
- formation of plaques is dependent on how APP is cleaved
- mutations in APP and cleavage enzymes lead to **EOAD**
- abnormal cleavage of APP into **AB peptides** might occur only at specific and predetermined sites and only in select nerve cells
- **Recent discovery: a different type of mutation in APP, one that reduces AB levels, protects carriers from getting the disease**

AB = A-beta = Aβ these are all the same thing

Greek Letters are not used in SNCD

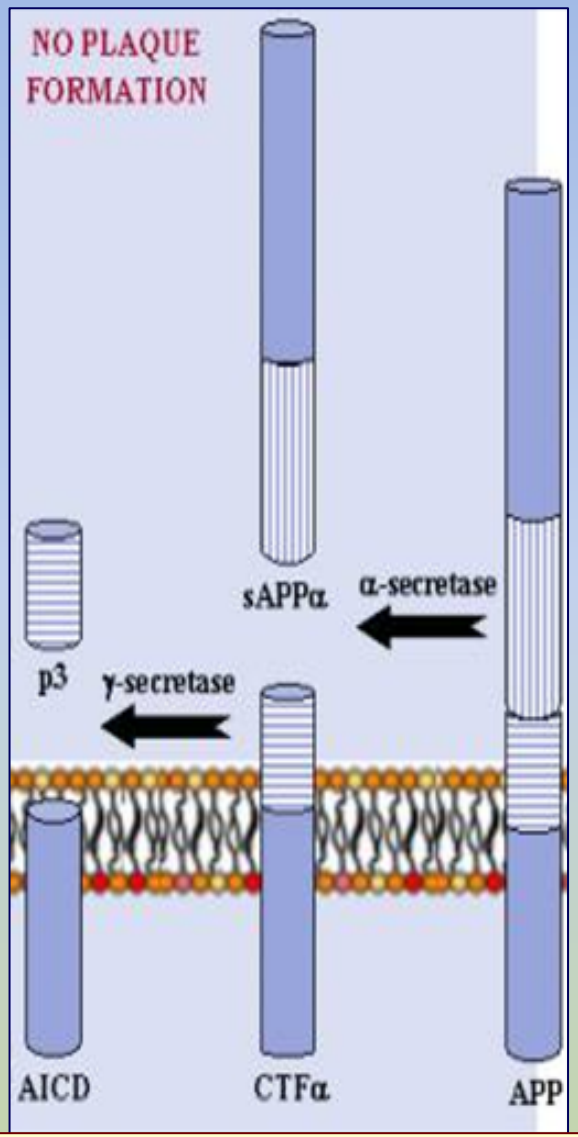
EOAD = Early Onset Alzheimers Disease

APP Processing: Non-Amyloidogenic

KEEP!

Non-amyloidogenic pathway

- **alpha-secretase** first cleaves APP to give an N-terminal fragment (sAPPa) and a C-terminal fragment (CTFa)
  - sAPPa → neuroprotective
  - CTFa remains in the membrane
- **y- secretase then cleaves CTFa** into a N-terminal fragment (P3) and a membrane bound C-terminal fragment (AICD or APP intracellular domain)
  - AICD is involved in nuclear signaling via transcriptional regulation and axonal transport via its association w/ diff proteins



KEY DIFF:

← β cut

← α cut

← γ cut

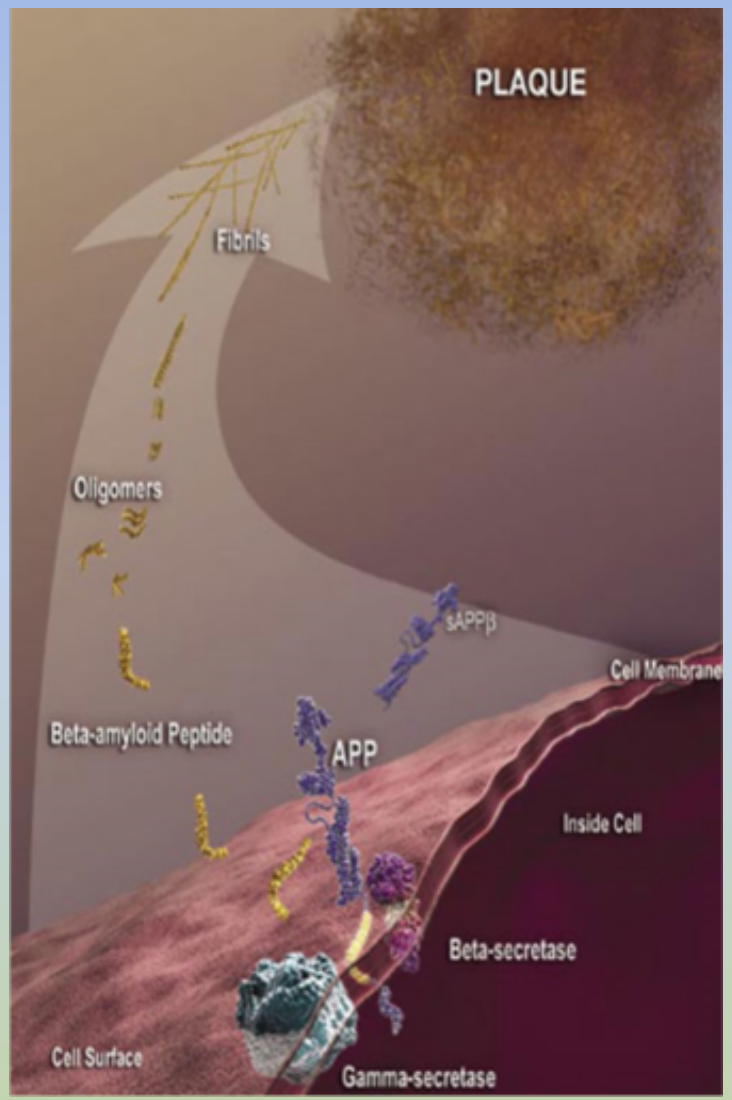
but Beta Secretase → Aβ pathology!
β leaves longer C-terminal (next slide)
next, cleavage by ɣ secretase → Aβ
[beta amyloid and Aβ are the same thing]

Key difference is alpha vs. beta cut: alpha is literally cutting the **A-beta** peptide in half: ***before*** it can be created! But if beta cuts first, alpha cannot cut. See notes & next slide.

APP Processing: Amyloidogenic

Amyloidogenic Pathway (plaque formation)

- APP is first cleaved by **beta secretase**
- **gamma secretase** then cleaves the C-terminal protein which results in the formation of beta amyloid peptide
- **A-beta can accumulate in extracellular space** and because it is stickier than other fragments, it can aggregate to form amyloid plaques **[it seems to fight off infections]**
- binding of A-beta monomers together to forms soluble aggregates known as ABOs **(A-beta oligomers).** if not naturally cleared from the brain they might trigger toxic pathways and/or accumulate to produce larger, insoluble fibrils and eventually (with other debris) start to form plaques, also potentially toxic and neuroinflammatory.

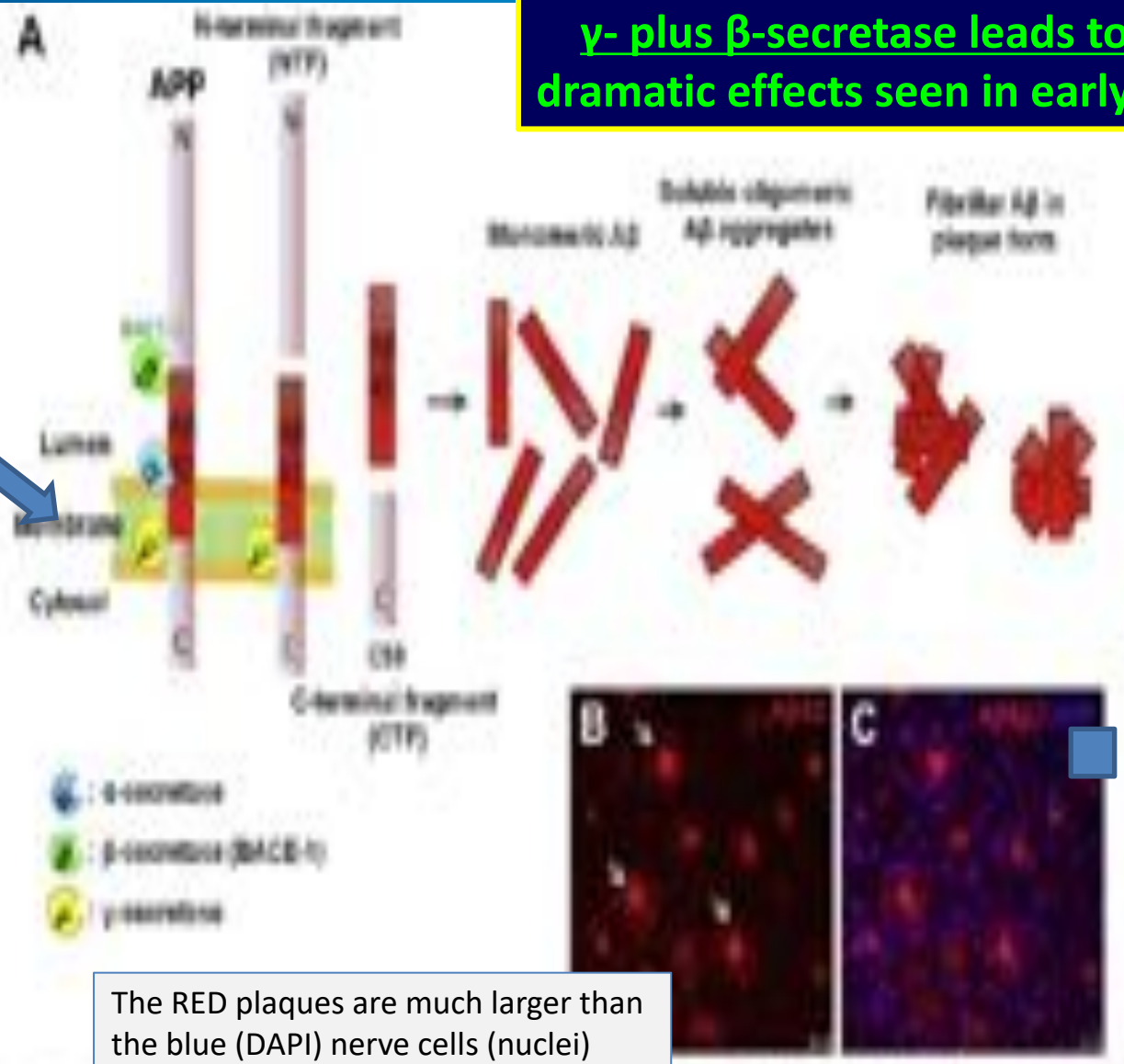


Is this "extracellular lipofuscin", so to speak?

Actually, amyloid is MUCH WORSE because it often leads to inexorable and massive cognitive decline (i.e. AlzD)

γ- plus β-secretase leads to AlzD: dramatic effects seen in early-onset AlzD

actions of secretases



The RED plaques are much larger than the blue (DAPI) nerve cells (nuclei)

Figure 1. (A) Schematic representation of APP processing by various secretases under physiological and pathological conditions. (B-C) Cortex of a 9-months-old AD model mouse (5XFAD) with APP and PS1 mutations stained with antibody against $A\beta_{1-42}$ (in red) and nuclear stain DAPI (in blue). Arrows indicate the presence of amyloid plaques. Bar = 20 μm.

more from Shukla 2012 paper below …

Potentials Consequences of AB & plaques

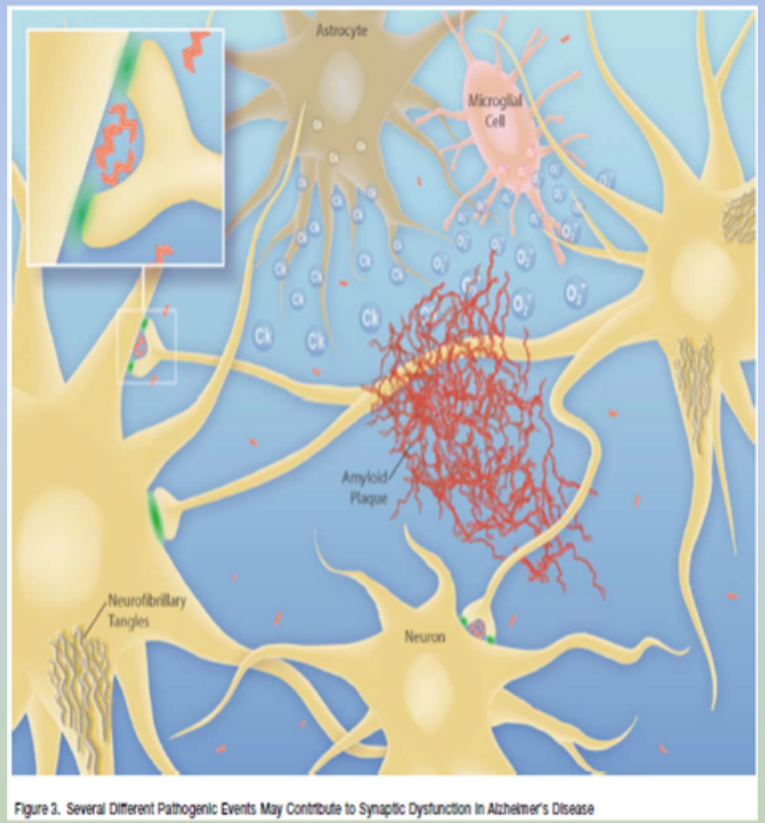


Figure 3. Several Different Pathogenic Events May Contribute to Synaptic Dysfunction in Alzheimer's Disease

- disrupt brain cells by blocking synapses
- spread APP undergoes vesicular anterograde transport within axons; axon terminals might therefore secrete AB
  - might account for spread of amyloid pathology from ERC into other cortical regions.
- as debris accumulates microglia and astrocytes may become reactive i.e. inflamed (neuroinflammation)
- *oxidative damage* to cells may also ensue due to metabolic stresses on neurons and glia, possibly contributing to an SASP response

Have *claims* on this slide been validated?

EOAD: TBA

[addressed at greater length in Chapter 18, biomarkers]

What IF, EOAD and Sporadic AlzD (i.e. "AlzD") are two *very different* things?

note that:

Early Onset ABSOLUTELY involves APP/A-beta mutations

see *Norm* in our Course Intro slide set

2015

Amyloid β oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis

Kirsten L. Viola · William L. Klein

cited 393x

ABOs are THE BEST (i.e. the worst) iaw NU's Viola and Klein, Cognitive Neurology Center

A tremendous amount of work has been done on ABOs, thus propelling them into the AlzD spot-light.

NOTES:

- ABO's may behave like prions
- may also induce tau responses

RLA Questions

1. Why might ABOs be more toxic than other amyloid species?
2. Paper Claims Slide: Which highlighted claim is *least likely* to be true?
3. Has Immuno-Staining advanced our understanding of AlzD Pathology?
4. Is Measuring ABOs in CSF a good diagnostic test for AlzD?
5. Regarding Receptor Candidates (Fig. 7) assume that "any 5" of the 16 listed receptors is essential for AlzD. *How would you proceed*?
6. "Beginning of 3rd Decade" *update*: Is the Cascade Hypothesis over?
7. How might the process in FIGURE-6 affect associative learning?
8. How likely is insulin/diabetes to play a role in AlzD pathology?

Each chat-room composes an answer [ideally: aggregated opinions]

When ready, return to main room for Discussion

FRIDAY-RLA: paste tidbit or Q. about sumting from Chap. 12, 13 *that we did not talk about*** eof

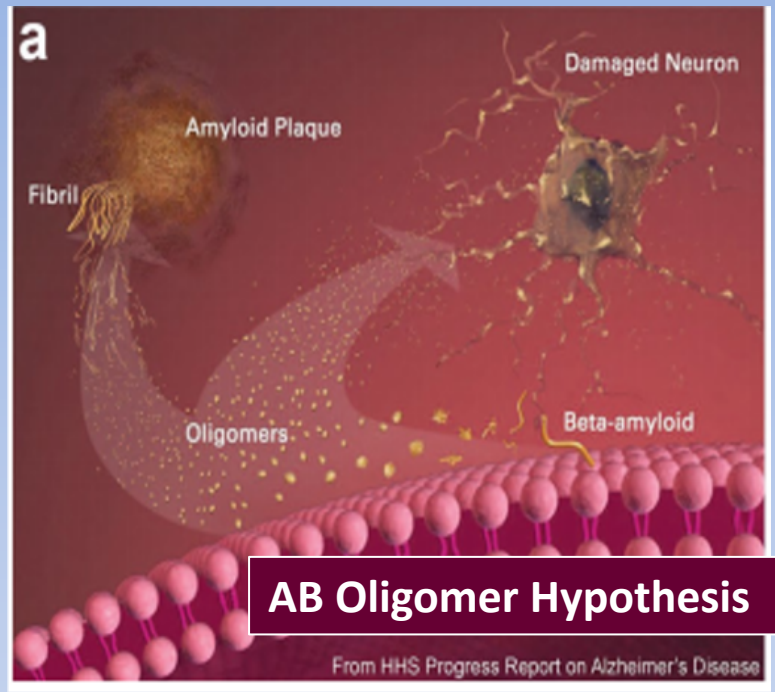
**or that I did not explain very well

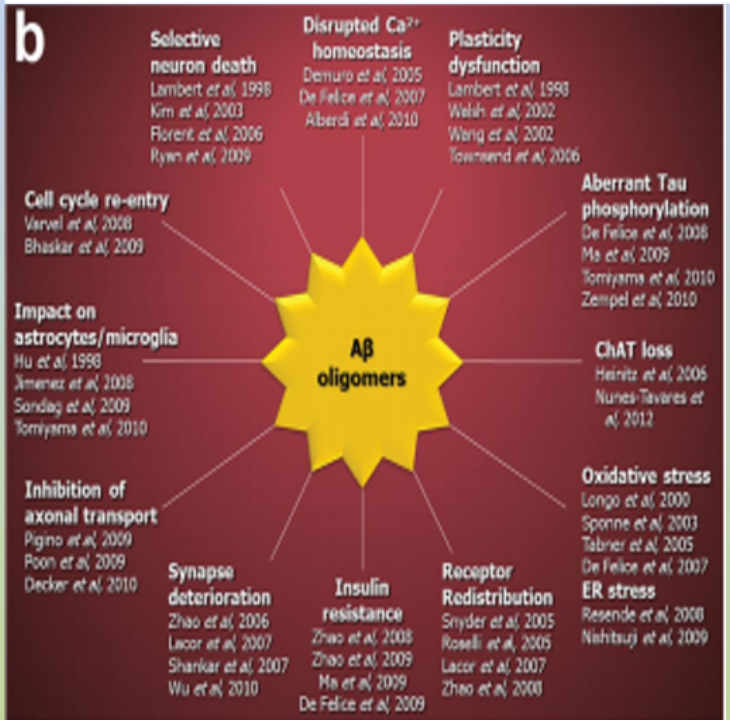
Main ABO Claims iaw Students

Nerve cell damage leading to Alzheimer's dementia is instigated by toxic amyloid beta oligomers (ABOs)

- Soluble oligomeric AB species detected in AD brain tissue more than 20 years ago, presence **was regarded only as evidence of ongoing fibrillogensis** i.e. not relevant to nerve cell damage, onset of dementia
- ABO's now thought to act like **pathogenic gain of function ligands**, targeting certain cells and synapses on those cells
- cellular damage instigated by toxic ABOs extend to the major aspects of AD neuropathology
- **Not much is known about the mechanism and etiology of ABO build up in sporadic AD**
  - At early pathological stages, in a field of hundreds of neurons, only about a dozen show the presence of ABOs

ala Mozart: too many hypotheses! ➔





Amyloid β oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis

ABOs REVIEW, cited 350x

Kirsten L. Viola · William L. Klein

from Northwestern Univ. – the Other NU, 2015

chat your nomination for: *Worst Claim in Abstract*

Abstract Protein aggregation is common to dozens of diseases including prionoses, diabetes, Parkinson's and Alzheimer's. Over the past 15 years, there has been a paradigm shift in understanding the structural basis for these proteinopathies. Precedent for this shift has come from investigation of soluble Aβ oligomers (AβOs), toxins now widely regarded as instigating neuron damage leading to Alzheimer's dementia. Toxic AβOs accumulate in AD brain and constitute long-lived alternatives to the disease-defining Aβ fibrils deposited in amyloid plaques. Key experiments using fibril-free AβO solutions demonstrated that while Aβ is essential for memory loss, the fibrillar Aβ in amyloid deposits is not the agent. The AD-like cellular pathologies induced by AβOs suggest their impact provides a unifying mechanism for AD pathogenesis, explaining why early stage disease is specific for memory and accounting for major facets of AD neuropathology. Alternative ideas for triggering mechanisms are being actively investigated. Some research favors insertion of AβOs into membrane, while other evidence supports ligand-like accumulation at **particular synapses** [abstract continues in notes below]

Paper CLAIMS: ABO's on the Job!

- trigger redistribution of spine proteins
- ↑'s NMDA, mGluR receptor activity
- causes Phospho-tau, insulin resistance, synapse loss and oxidative stress
- associated w/ hypercholesterolemia & diabetes (co-morbidities)
- rapidly inhibits LTP in brain slices
- kills cells via FYN signaling mechanism
- distinct build-up mech ≠ plaque mech.
- failure to target ABOs might explain most poor clinical results in AlzD to date **AND**
- ABO antibodies rescue memory in transgenic mouse strains
- early presence means ABOs might be good for diagnostics and drug-targeting

[stay tuned for biomarkers & brain imaging]

↑↑ Which highlighted claim is *least likely* to be true?

Has Immuno-Staining advanced our understanding of AlzD Pathology?

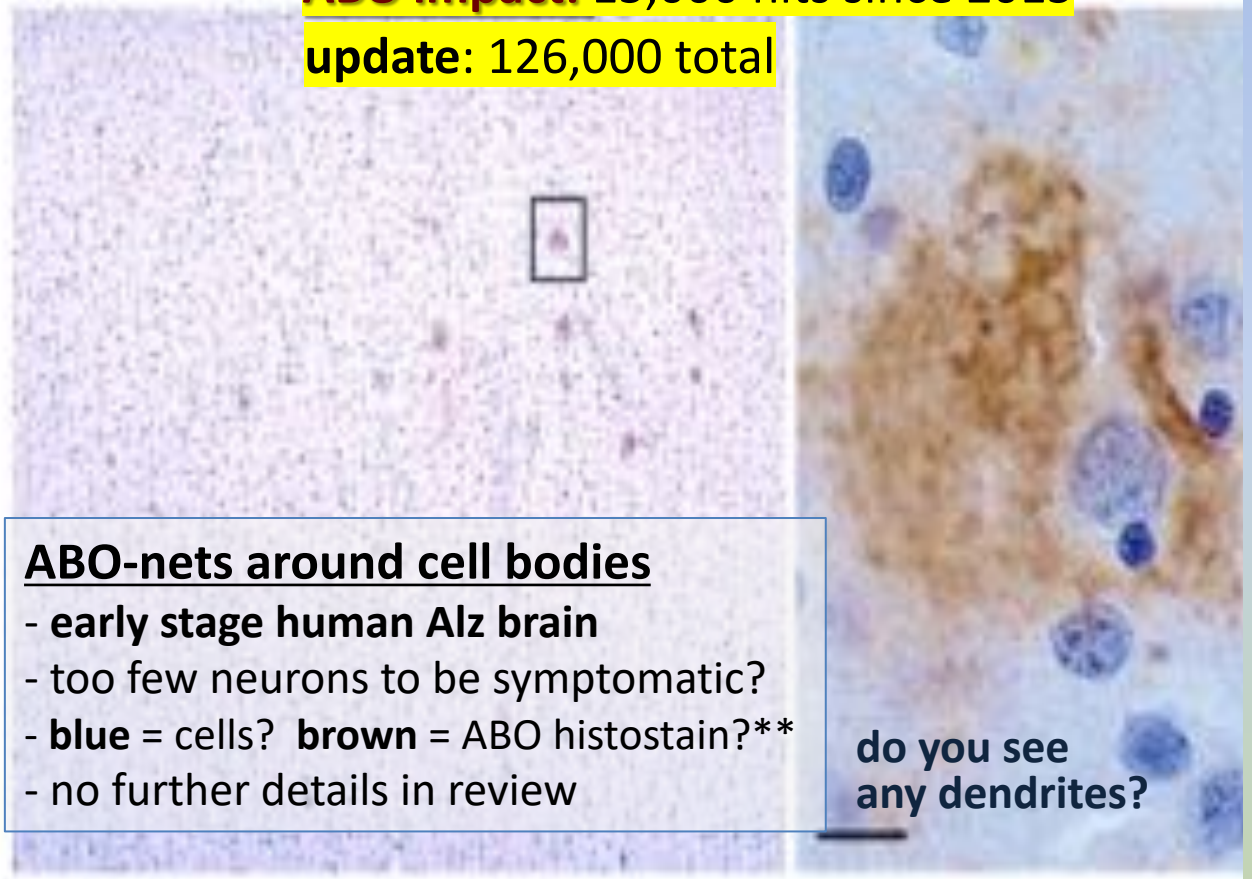
basic immuno and counter-stains here; poorly defined in review article

Acta Neuropathol (2015) 129:183–206

Fig. 2 Perisomatic AβOs consistent with synapse binding are present early in human neuropathology. *Left* Low magnification of human cortical brain section stained with an anti-oligomer antibody. Scattered individual neurons are surrounded by AβOs in early AD, before the appearance of amyloid plaques. The perineuronal distribution of these AβOs (*right*) is consistent with a binding site within the dendritic arbor. *Scale bar* 10 μm. Adapted from Lacor et al. [91]

ABO impact: 15,000 hits since 2015

update: 126,000 total



ABO-nets around cell bodies

- **early stage human Alz brain**
- too few neurons to be symptomatic?
- **blue** = cells? **brown** = ABO histostain?**
- no further details in review

do you see any dendrites?

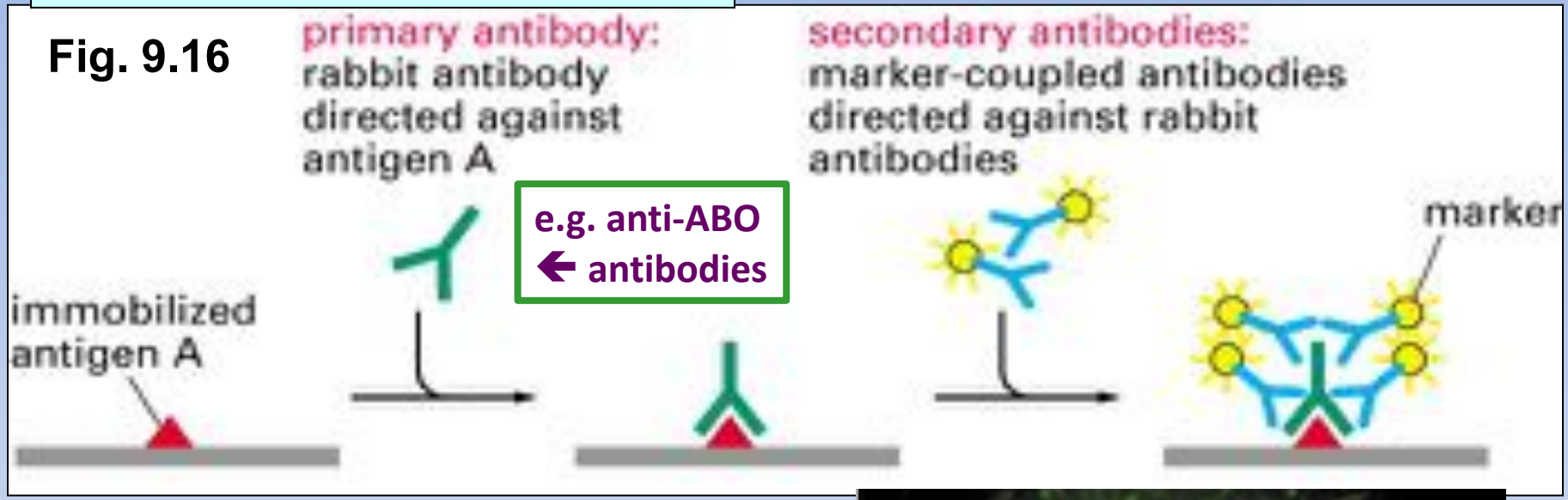
Autopsy Material
aka: post-mortem

***the variegated blue structures seem unlikely to *all be* neurons**
the diffuse brown labeling fits with a regular HRP-reaction product

Imaging Subcellular Structure with Great Specificity

Crash Course: indirect immunofluorescence aka "**immunostaining**"

Fig. 9.16



1. **Repeat 3x** for Triple Label Immuno!
2. **Genetic Version:** In Situ Hybridization or "Go FISH" !!!
3. **Molecular Imaging Version**: **GFP** (the imaging gods have awoken)

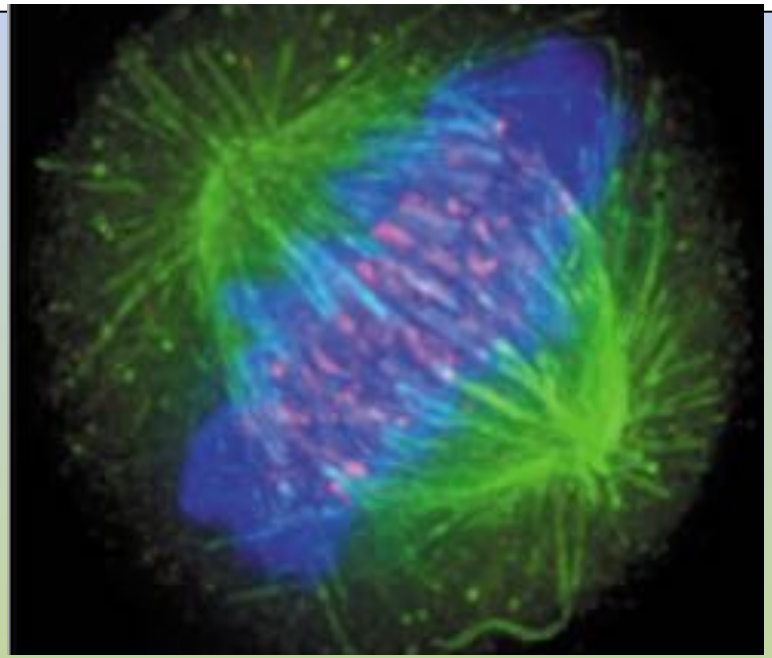
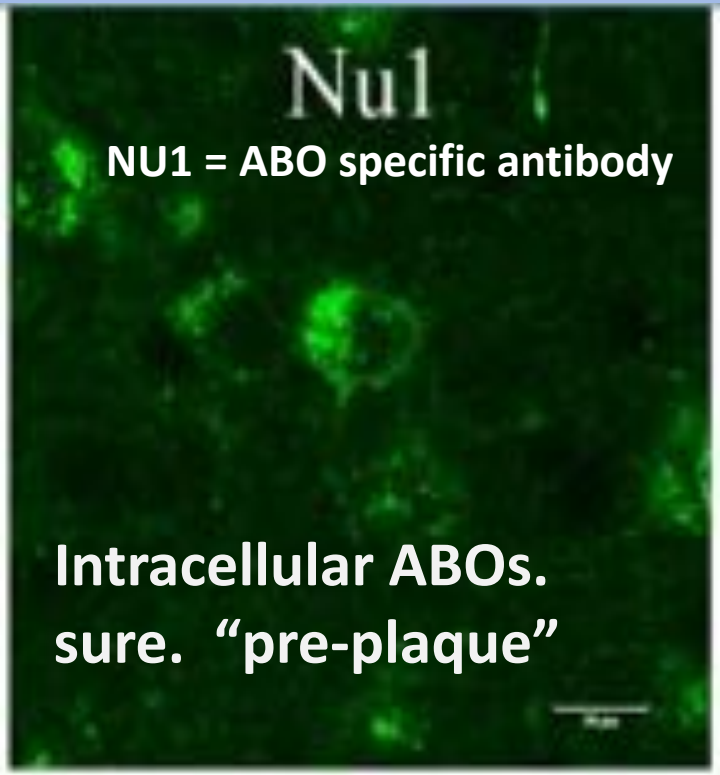


Fig. 9-14 MBOC --Triple Label
green – anti-microtubules, spindle
red – anti-centromeres
blue – DAPI, UV-excited DNA stain

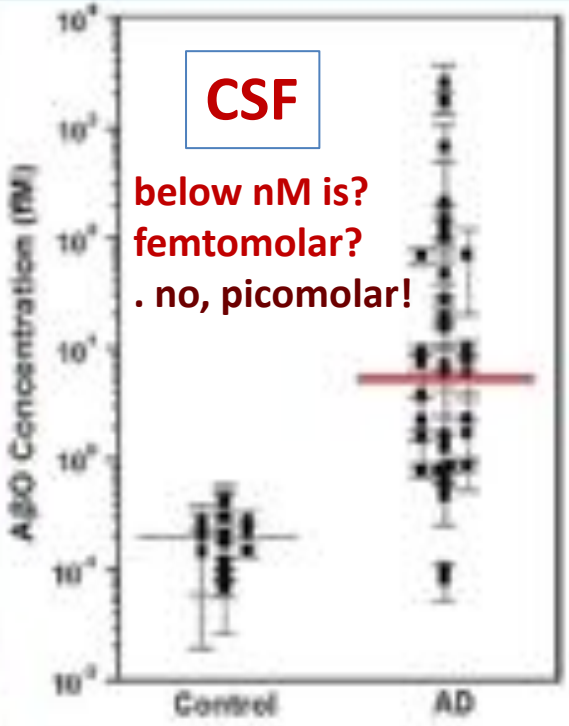
since 2014: immunofluor=21,000; GFP=29,000; FM was great, cfocal made it fantastic

Confocal Brain Section, Transgenic Mouse



w/ APP, AB “overproduction”

Human CSF conc. of ABO’s



precision matters!

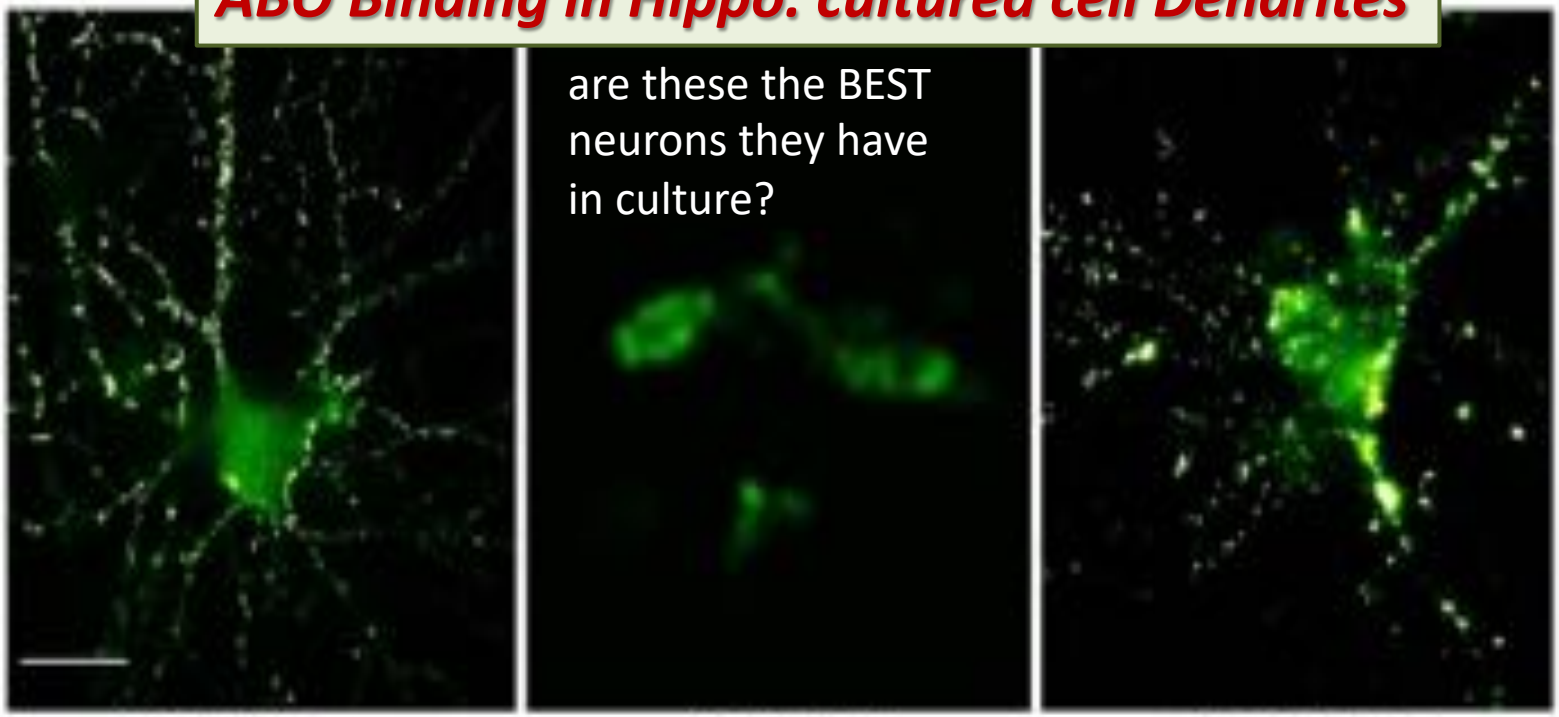
in HUMANS?

Fig. 4 AβOs can accumulate in intracellular and extracellular pools. Intracellular AβOs are detectable in animal models overproducing APP and Aβ; however, the presence of extracellular AβOs on dendrites and in CSF suggests they are also important in AD. *Left* A representative micrograph of confocal fluorescence labeling of amyloid-β peptide (Aβ)-oligomer-specific antibody NU1 immunoreaction in young, pre-plaque Tg mice shows intracellular localization of AβOs. Adapted from Ferreira et al. [140]. *Right* A scatter plot from the ultrasensitive scanometric detection of AβOs in cerebrospinal fluid. Adapted from Georganopoulou et al. [45]. The response for the negative human control subject (brain extract) was similar to that observed for the chip control. The data points are averages of several separate experiments normalized for each assay based on the highest response in a series of runs. The mean values for ADDL concentrations (*solid lines*) are estimated for each group based on a calibration curve

maybe… presumably more compelling in original article.

ABOs ala Viola and Klein, 2015

ABO Binding in Hippo. cultured cell Dendrites



Similar pattern in "extract": some non-specific gunk (maybe auto-Fluor.) **DIC imaging would be great here.**

Fig. 5 Synthetic and brain-derived AβOs are ligands that target synapses. AβOs extracted from AD brain or prepared in vitro show punctate binding to neuronal cell surface proteins. Cultured hippocampal neurons were incubated with synthetic AβOs or soluble extracts of human brain. Binding was visualized by immunofluorescence microscopy by using a polyclonal anti-Aβ oligomer antibody, M93. Synthetic AβOs (*Left*), soluble extracts of non-AD control brains (*Center*), and soluble AD-brain extracts (*Right*) are shown. Small puncta, bound largely along neurites, are evident for AD extracts and synthetic AβOs but not for control extracts. *Bar* 10 μm. Adapted from Gong et al. [47]

Synthetic ABOs intrigue!

Image here does not confirm "synaptic" targeting, but does look "**dendritic**" at left.
Middle Panel control looks "too good": most IHC images show *some background*.
AlzD Extract is messier than "synthetic ABOs" but is dendritic, looks reasonable.

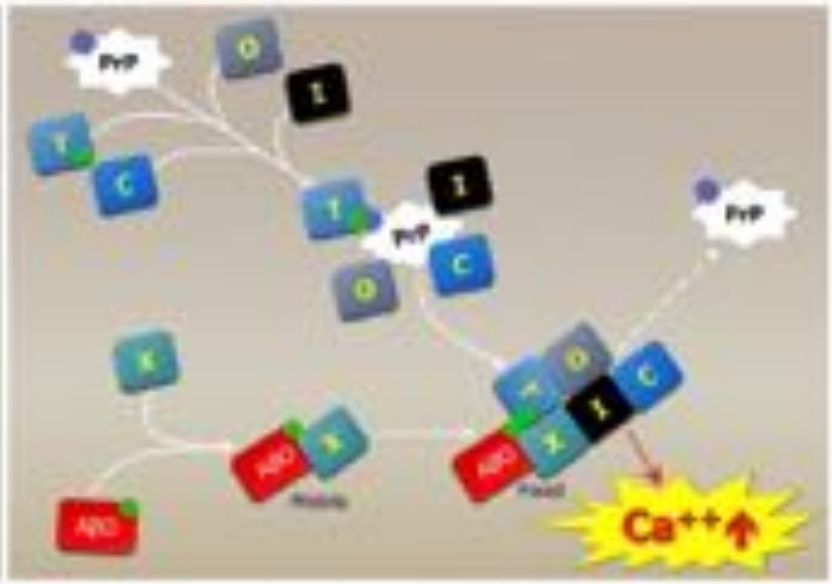
Single-Particle Tracking is a cool technique!

Claim Here is that ABO's can stop movement of mGluRs and cause Ca++ damage

This can be visualized only in cultured cells; significance unclear, but:

Neuron (Renner, 2010) is a very selective journal = #1 Neuro Journal

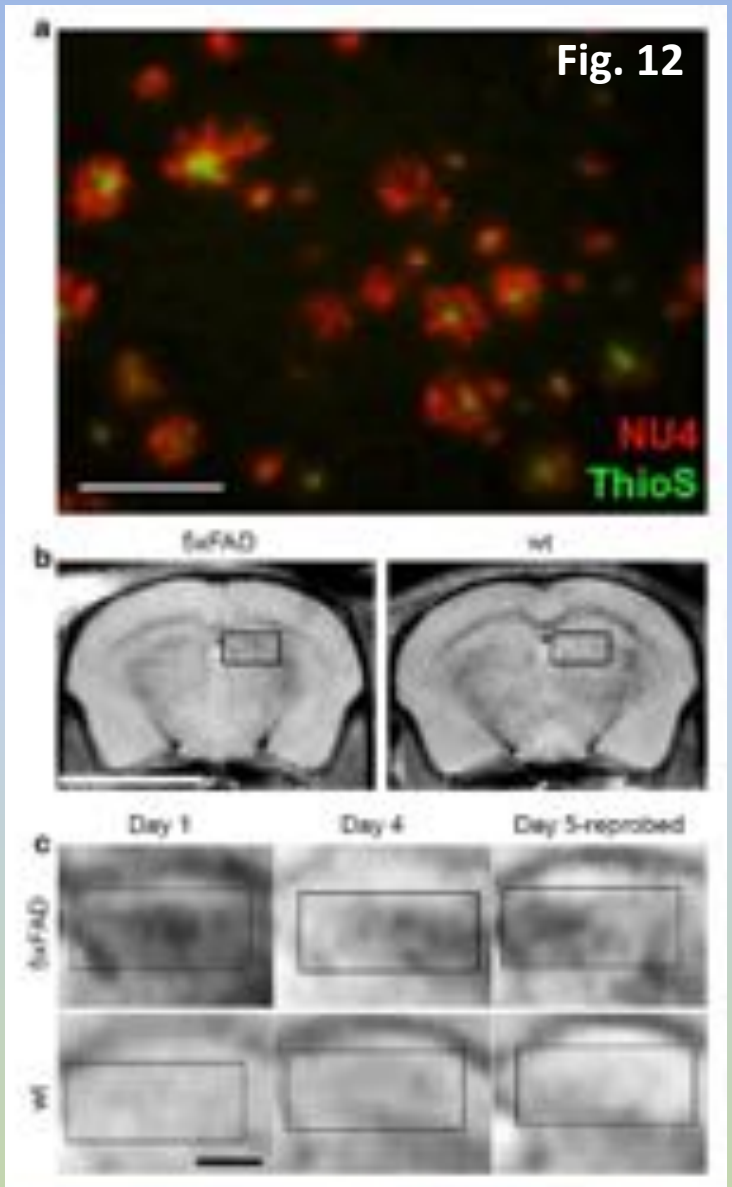
Right Panel suggests role for Prion Protein (aka PrP) in toxic damage to cell.



Viola and Klein, 2015

Fig. 8 Single molecule trafficking shows AβOs stop diffusion of mGluR5 and "highjack" membrane proteins that can lead to elevated Ca^{2+}. *Left panels* Dual-color single-particle tracking was used to monitor mGluR5 (*red*) and biotin-AβO (*green*) diffusion at synapses over time. Following the tracings of mGluR5, mGluR5 diffuses together with an AβO (5 min) outside synapses before both become stabilized at a synaptic site (60 min). Adapted from Renner et al. [143]. *Right* Clustering of membrane proteins, possibly involving PrPc, leads to AβO binding recruitment and membrane receptor reorganization that instigates toxic signaling. AβO binding to an unidentified receptor, X, and the recruitment of effector protein co-receptors leads to hyperactive Ca^{2+} signaling and downstream toxicity

this is what they said 30 years ago about calcium and stroke…



5xFAD is transgenic AlzD mouse model [see notes]
ABOs are indicated by antibody staining in (a).
green is **ThioflavinS** plaque staining [good for PET?]
red / NU4 is anti-AB oligomers antibody

(Fig. 12b) How to make an MRI Probe
[also see next slide]
- conjugate antibody to magnetic particles
- deliver to CNS via olfactory nerve
- show label in transgenic mouse
- publish in *Nature*
- ignore all the WT dark spots

(Fig. 12c) shows re-probing of hippocampus
on day 5; labels different region.

Etiology aka The Root Causes:
"remarkably little is known about the etiology of ABO accumulation in sporadic AlzD" p. 185

ABOs ala Viola and Klein, 2015

cited 123x, a bit light for Nature, Topic

nature nanotechnology

vs. 350 cites for 2015 niche journal

ARTICLES

PUBLISHED ONLINE: 22 DECEMBER 2014 | DOI: 10.1038/NNANO.2014.254

← will this MRI distinguish *normals* from early AlzD? it's the **best!

Towards non-invasive diagnostic imaging of early-stage Alzheimer's disease

2015

Kirsten L. Viola[1†], James Sbarboro[1†], Ruchi Sureka[1†], Mrinmoy De[2], Maira A. Bicca[1,3], Jane Wang[1], Shaleen Vasavada[1], Sreyesh Satpathy[4], Summer Wu[4], Hrushikesh Joshi[2], Pauline T. Velasco[1], Keith MacRenaris[5], E. Alex Waters[5], Chang Lu[1], Joseph Phan[1], Pascale Lacor[1], Pottumarthi Prasad[6], Vinayak P. Dravid[2,7]* and William L. Klein[1,7]*

One way to image the molecular pathology in Alzheimer's disease is by positron emission tomography using probes that target amyloid fibrils. However, these fibrils are not closely linked to the development of the disease. It is now thought that early-stage biomarkers that instigate memory loss are composed of Aβ oligomers. Here, we report a sensitive molecular magnetic resonance imaging contrast probe that is specific for Aβ oligomers. We attach oligomer-specific antibodies onto magnetic nanostructures and show that the complex is stable and binds to Aβ oligomers on cells and brain tissues to give a magnetic resonance imaging signal. When intranasally administered to an Alzheimer's disease mouse model, the probe readily reached hippocampal Aβ oligomers. In isolated samples of human brain tissue, we observed a magnetic resonance imaging signal that distinguished Alzheimer's disease from controls. Such nanostructures that target neurotoxic Aβ oligomers are potentially useful for evaluating the efficacy of new drugs and ultimately for early-stage Alzheimer's disease diagnosis and disease management.

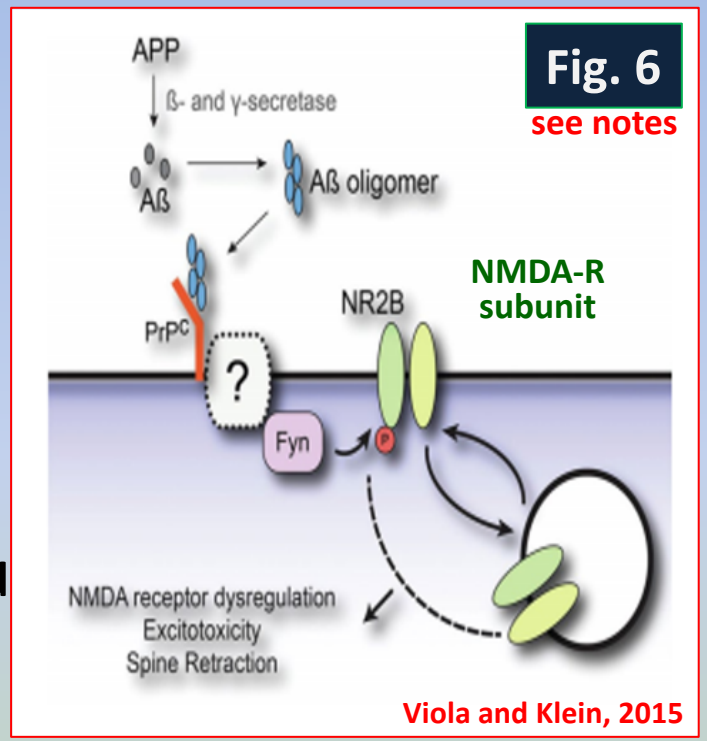
Ref. #174 from ABO article

**i.e. the BEST image they have—all the others are worse, typically.

More on Mechanisms & Localization

additional ABO details

- ABOs have been seen in cholinergic neurons
  → role in cholinergic deficiency?
- Intraneuronal ABOs are associated with loss of MAP2 in dendrites and postsynaptic terminals
- Evidence suggests that ABOs accumulate intracellularly **[HOW?]** and are secreted down-stream to the extracellular space
  - Extracellular prion-like spread → cell to cell transfer & self replication
  - ABOs act as template to promote formation of larger aggregates in a self-propagating manner
  - inside cells: promotes tau toxicity
- **Binding of ABOs to membranes might be mediated by cell surface proteins acting as *toxin receptors***
  - ***Membrane proteins → PrP as toxic receptor***
    PrP coupled to tyrosine kinase Fyn which is consistent with studies claiming:
    Fyn claimed to be essential for ABO induced toxicity



DQ: how might this affect associative learning?

PrP = Prion Protein aka Protease Resistant Protein aka CD230
associated with: Kuru, CJ-disease, scrapie and BSE (see Wikipedia page)
associated with AlzD? note: Prion Deniers are still active online

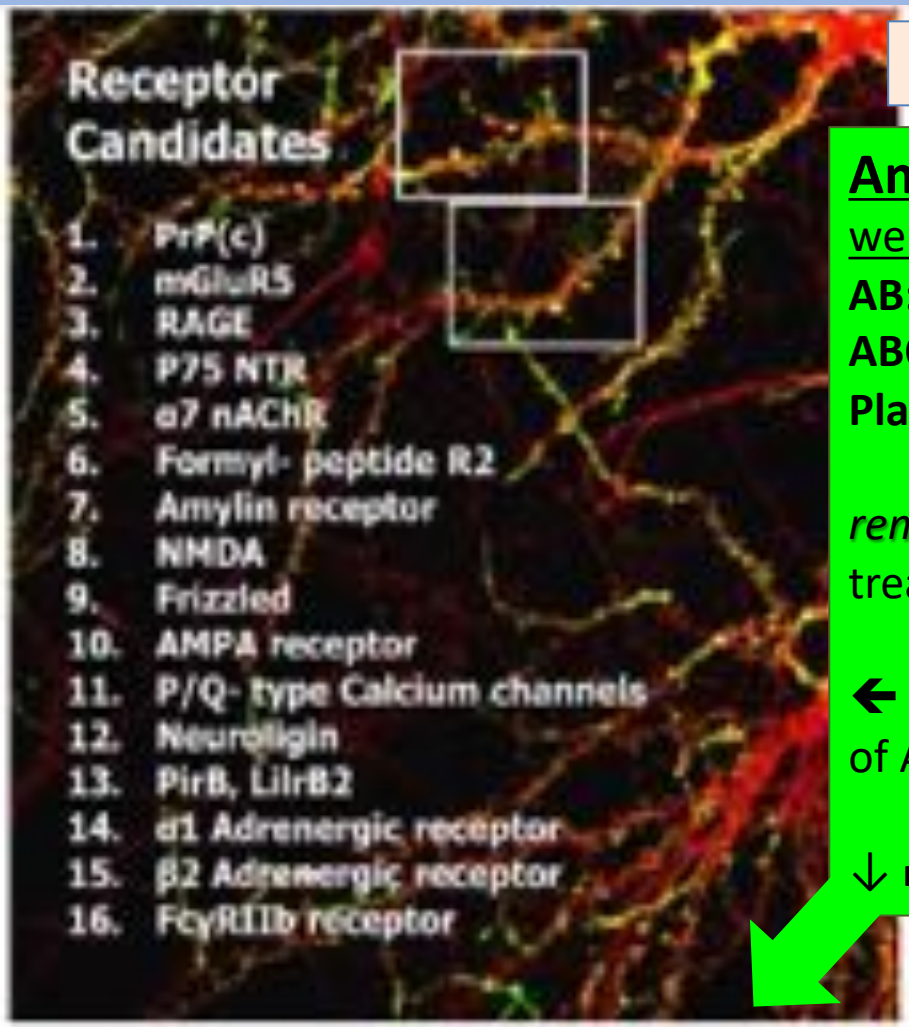


Fig. 7 A surfeit of toxin receptor candidates. Provided is a current list of candidate Aβ/Aβ oligomer receptors that have been proposed over the last 20 years. No single candidate has been shown to be necessary and sufficient to account for all aspects of AβO binding and toxicity

N&S logic is ideal, but not quite relevant here: notes!

← *ala Mozart*: too many receptors!

Amyloid Hypothesis

we do not know what the Toxic Component is!

AB: might induce Tau hyperphosphorylation

ABOs: might be toxic themselves

Plaques: might be inflammatory sites

removing AB (plaques only?) does not help

treatment might be needed years earlier

← I don't know if this list of possible receptors of ABO binding is meaningful or not!

↓ **note caveat -** but N&S logic only good in theory

ABOs ala Viola and Klein, 2015

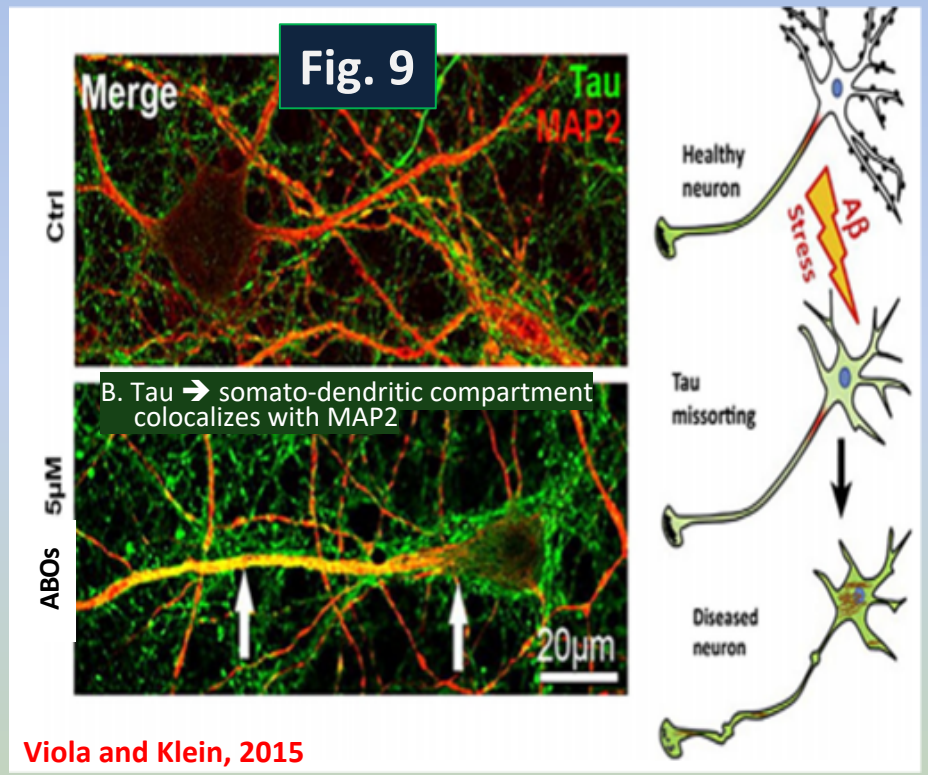
How does binding of ABOs to neuronal membranes instigate a toxic cascade?

- ABO's may be **intrinsically toxic**
  - Capable of creating neurotoxic pores within membranes...*allegedly*...
  - Intracellular ABOs acting through glutamate receptors **might elevate calcium levels leading to ROS**
- ABO binding to toxin "receptors" might **perturb** vital signaling
- Toxic High-Jacking
  - ABO's could act as **receptor agonists:** glutamate receptor hyperactivity ➔ **excessive calcium levels**
- Downstream Events
  - **ABOs instigate tau pathology**
  - Tau hyperphosphorylation, **plus** mis-sorting induced by ABOs, perhaps a significant factor in damaging neurons

ABO Transduction Possible Mechanisms

Pathological Tau/MAP2 redistribution

MAP2 is another Microtubule Associated Protein



Viola and Klein, 2015

sounds pretty awful! …

…but there is just one tiny problem…

see MAP notes

ALL AMYLOID TRIALS FAIL

…and will continue to fail…

this is the word of Don

Tau Ignition?

amyloid (in sporadic AlzD) is perhaps not toxic?

"A-Beta initiates tau pathway": claim maybe wrong?

even if AlzD-trending brains send ABOs to tau…

… the A-Beta to tau pathway maybe can't be blocked?

only by halting tau actions/damage can we block AlzD?

is it:
Tau
or tau

some nice grist here for "cumulative" final exam questions-general rule: make connections

Some Additional Notes on Tau Damage/Pathology: covered in later slides

1. forward & retro transport of Tau impaired + *gating* at axon might go bad.
2. Tau cross-links actin affecting dendritic spines and organelle transport (e.g. mitoch.)
3. Tau elongates mitochondria, might impair electron transport chain (and ↑ ROS)
4. CNS uses O2 & lacks antioxidants; 02 damages lipids, proteins, DNA, RNA
5. protective peroxisomes and "REST" proteins function less well b/c of Tau [see notes]
6. epigenetic suppression of heterochromatin is undone by DNA, protein damage
   nuclear Tau MIGHT also contribute to *deregulation*, but "nuclear" status is uncertain
7. ectopic reactivation of neuronal cyclin genes might lead to apoptosis. **Qs? *PING ME***

MODERN SAMPLING: ABOs associated with exosomes, synaptic and clinical failures, metal transport, APP-interactions, calcium dyshomeostasis.

ABO's: released by large aggregates, visualized in living mice, visualized sub-synaptically with Super-Resolution microscopy

since 2015

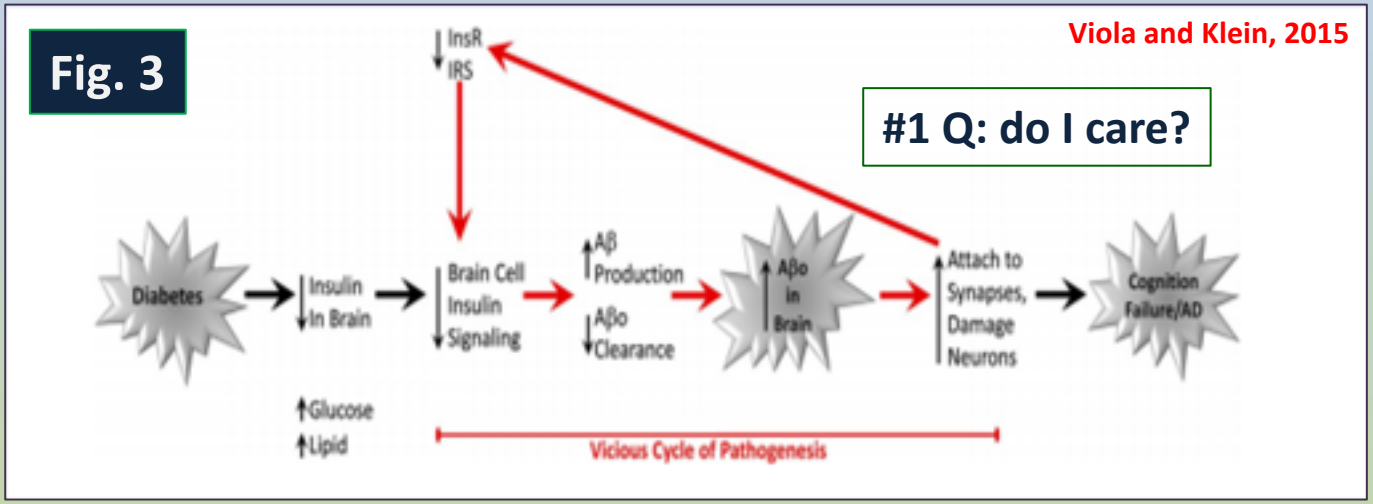
The ABO story is ALIVE and WELL much more to explore

HELP WANTED!

ABO Etiology

Insulin Signaling: CHAPTER 19! (stay tuned)

- **Claim cited on p. 185: CNS insulin signaling** helps prevent ABO buildup ***and also blocks*** neurotoxic ABO binding.
- **Conversely: ABOs can (*allegedly*) impair insulin signal transduction**
  - ABOs might block trafficking of insulin receptors on dendritic membranes thus rendering neurons insulin resistant.
  - **Consistent with claim that AlzD **IS** Type 3 Diabetes***
    BOLD CLAIM: In normal aging, there is a decrease
    in CNS insulin signaling → toxic ABO buildup → AD
  - **Some Evidence:** animals given IVC injections of ABOs showed impaired brain insulin signaling and memory loss [**more in SNCD Chapter 19**]



***G-scholar citations**: *Type2* = 1330 thousands *Type3* = 3 thousands

Amyloid-β and tau — a toxic *pas de deux* in Alzheimer's disease

Lars M. Ittner and Jürgen Götz

Nature Neuro - 2011

Abstract | Amyloid-β and tau are the two hallmark proteins in Alzheimer's disease. Although both amyloid-β and tau have been extensively studied individually with regard to their separate modes of toxicity, more recently new light has been shed on their possible interactions and synergistic effects in Alzheimer's disease. Here, we review novel findings that have shifted our understanding of the role of tau in the pathogenesis of Alzheimer's disease towards being a crucial partner of amyloid-β. As we gain a deeper understanding of the different cellular functions of tau, the focus shifts from the axon, where tau has a principal role as a microtubule-associated protein, to the dendrite, where it mediates amyloid-β toxicity.

Reflecting an aging population, for most societies dementia is becoming a major health burden. In 2009, 35.6 million cases of Alzheimer's disease were recorded worldwide, a number that is estimated to be more than doubled by 2050. A cure for Alzheimer's disease and related forms of dementia is lacking, and current treatments are limited to modest symptomatic relief (reviewed in REFS 1,2).

The brains of patients with Alzheimer's disease, in addition to showing nerve and synapse loss, are histopathologically characterized by two hallmark lesions — amyloid-β-containing plaques and neurofibrillary tangles (NFTs), which are composed of hyperphosphorylated forms of the microtubule-associated protein tau[3].

early onset AlzD, FTD genes:

identified in genes that encode the amyloid precursor protein (APP), presenilin-1 (PS1) or PS2 (REF. 7). The tau-encoding microtubule-associated protein tau (*MAPT*; also known as *tau*) gene carries mutations in a subset of familial forms of FTD[8], establishing a prominent role for tau in neurodegenerative disease[9]. In sporadic Alzheimer's disease (SAD), polymorphisms of apolipoprotein E4 (*APOE4*) and other genes have been associated with an increased risk of developing the disease[7]. The identification of these pathogenic mutations in people with Alzheimer's disease and FTD has assisted in the generation of a plethora of transgenic animal models (reviewed in REF. 9). However, it is important to keep in mind that the vast majority of Alzheimer's disease

Ittner and Gotz INTRO

"direct link" AB => Tau. yet molecular nature of interaction is "unresolved"?

amyloid toxic species is:
AB, dimers, oligomers or fibrils?

targets and mechanisms:
synapses, post-synaptic compartment
NMDAr, mGluR, α7-nAChR, prionR
acting via direct or indirect interactions
dx receptors => spine loss, LTD. forgetting?

more details on tau:
mostly in axons, some in dendrites.
role in microtubule stabilization/transport
toxic when aggregated in soma
excess (P) => decreased binding to tubules
soluble Tau affects mitochondria

DQ: any evidence in AlzD for tau-based pathology, independent of amyloid?
difficult to establish b/c amyloid is so prevalent

Nature Neuro - 2011

FYN = tyrosine kinase
NMDAr = NMDA receptor (Ca++ channel)
PSD95 = spine-organizing protein
*tau = hyper-phosphorylated tau
APP = amyloid precursor protein
FAD = familial AlzD = EOAD

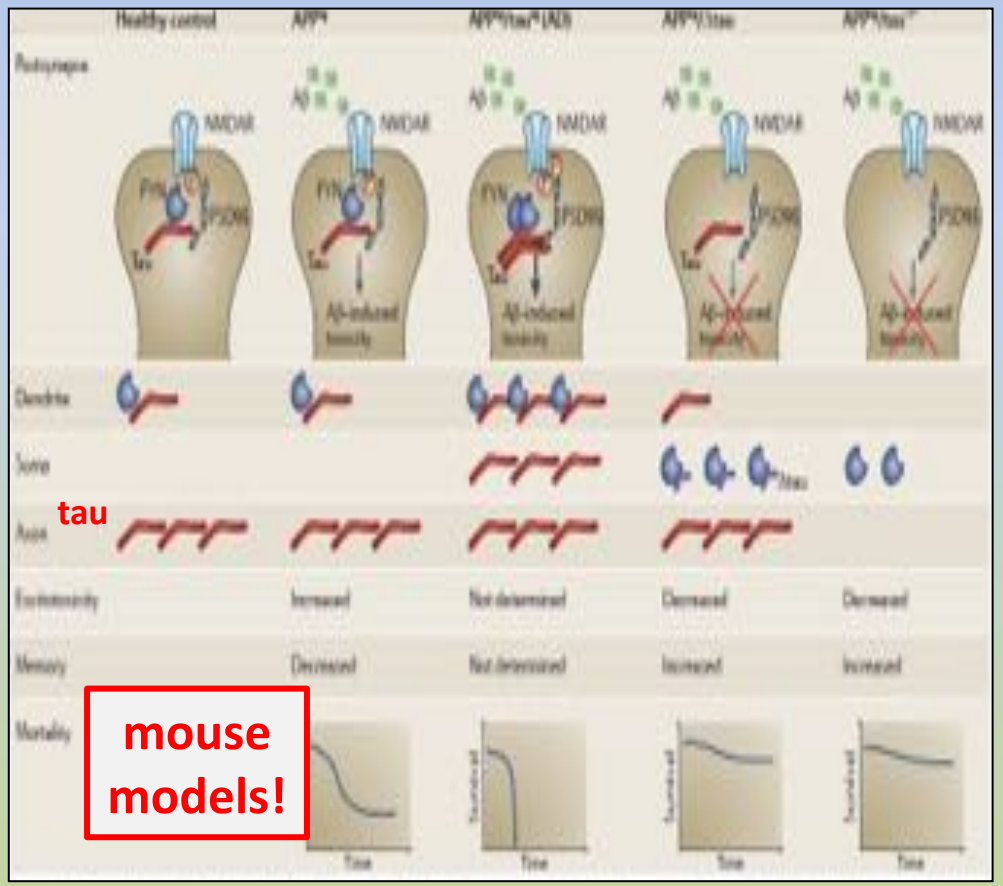
***nuances* of normal tau functioning:**
binds to microtubules via "MTB repeats"
tau-dynactin facilitates intracell. transport
and links actin to microtubules
tau-FYN: moves FYN to dendritic spines
FYN => NMDAr-PSD95 scaffolding
BUT: hyperphosphorylated Tau*
Tau* => FYN* => NMDAr* => excitotoxicity

beta-amyloid cascade hypothesis:
Amyloid-B drives Tau Pathology
EOAD patients have mutations that affect Amyloid
APP transgenic mice => *tau [in tau strains]
but tau mice show no amyloid plaques
Aβ injection => makes Tau-mice worse
BUT Tau-/- mice are fine w/out Aβ [← ?? need to fix]

synergistic effect:
both impair mitochondrial function
tau impairs Complex I
Aβ blocks Complex IV

tau mediates Aβ toxicity
tau-/- have no FYN localiz, NMDA damage
and also spared mitochondrial damage?
effect mimicked by peptide drug?

overlaps w/ ABO, earlier papers



tau/A-beta
3-possible MODES of interaction

TRIGGER **MEDIATOR** **CONVERGING**

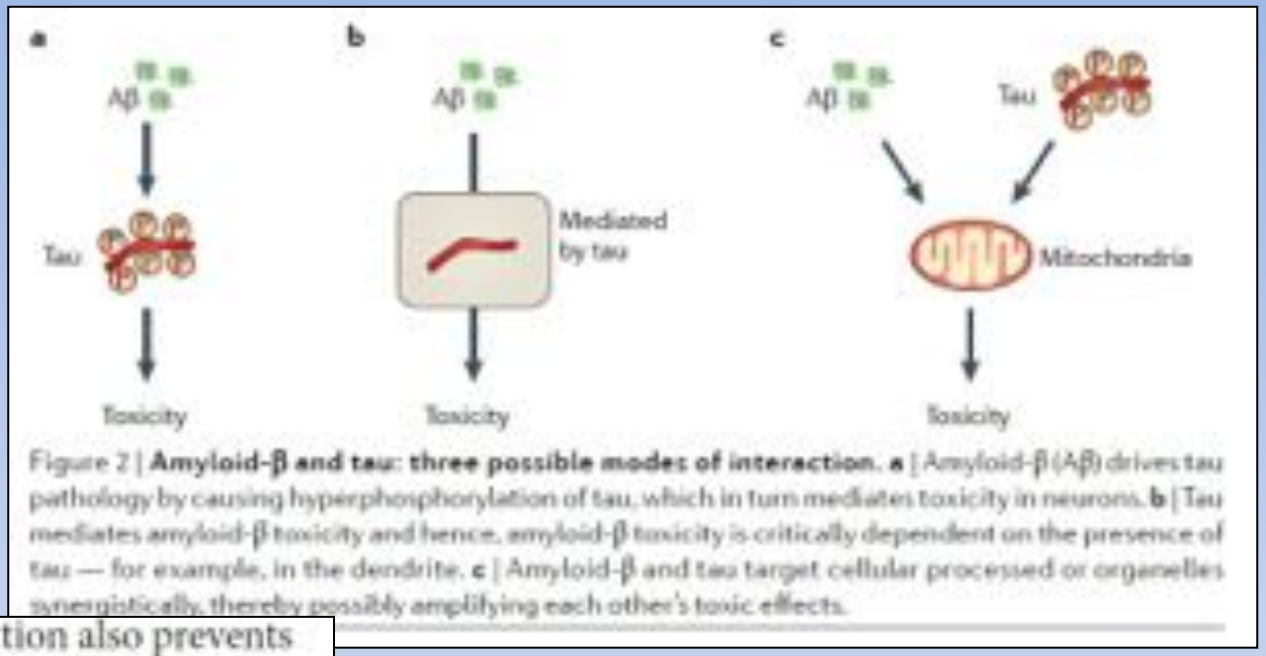


Figure 2 | **Amyloid-β and tau: three possible modes of interaction. a** | Amyloid-β (Aβ) drives tau pathology by causing hyperphosphorylation of tau, which in turn mediates toxicity in neurons. **b** | Tau mediates amyloid-β toxicity and hence, amyloid-β toxicity is critically dependent on the presence of tau — for example, in the dendrite. **c** | Amyloid-β and tau target cellular processes or organelles synergistically, thereby possibly amplifying each other's toxic effects.

Interesting Tie Ins

Interestingly, tau reduction also prevents amyloid-β-induced defects in axonal transport of mitochondria[47], which may link the 'tau axis hypothesis' to two additional hypotheses in the field: the 'axonal transport impairment' hypothesis, according to which tau induces failure of axonal transport[53,54]; and the 'oxidative stress' hypothesis, according to which mitochondria — being an essential axonal transport cargo — are functionally impaired, resulting in the production of reactive oxygen species[55].

← as the renowned Lawrence Smith said a long time ago:
everything keeps getting the same

Ittner and Gotz
Nature Neuro - 2011

student of SNCD note: Gotz is co-author of the 2015 Frost 1FF model, stay tuned…Chapter 19

cited 14,008 times iaw GScholar
4,200 times since 2017

Acta Neuropathologica

Review

Neuropathological staging of Alzheimer-related changes

H. Braak and E. Braak*

Summary. Eighty-three brains obtained at autopsy from nondemented and demented individuals were examined for extracellular amyloid deposits and intraneuronal neurofibrillary changes. The distribution pattern and packing density of amyloid deposits turned out to be of limited significance for differentiation of neuropathological stages. Neurofibrillary changes occurred in the form of neuritic plaques, neurofibrillary tangles and neuropil threads. The distribution of neuritic plaques varied widely not only within architectonic units but also from one individual to another. Neurofibrillary tangles and neuropil threads, in contrast, exhibited a characteristic distribution pattern permitting the differentiation of six stages. The first two stages were characterized by an either mild or severe alteration of the transentorhinal layer [Pre-α (transentorhinal) stages I–II]. The two levels of limbic stages (stages III–IV) were marked by a conspicuous alteration of layer Pre-α in both transentorhinal region and proper entorhinal cortex. In addition, there was mild involvement of the first Ammon's horn sector. The hallmark of the two isocortical stages (stages V–VI) was the destruction of virtually all isocortical association areas. The investigations showed that recognition of the six stages required qualitative evaluations of only a few key preparations.

but shows substantial variability [3, 5, 18, 34, 35, 37, 38, 44, 56].

End-stages of AD are easily recognized at neuropathological examination. Evaluation of cases with mild to moderate affection, in contrast, is fraught with difficulties. Currently, quantitative analyses of particular areas are required for distinction of fully developed AD from cases with insufficiently dense changes [32, 35]. Little effort has as yet been made to further differentiate cases which do not meet the conventional diagnostic criteria [5]. Upon evaluation of a large number of cases with various degrees of involvement the existence of characteristic changes in the distribution pattern of neurofibrillary tangles (NFT) and neuropil threads (NT) became apparent (Tables 1, 2). It is tempting to assume that this sequence of involvement also reflects – in a still unknown manner – the clinical course of AD. This study, however, is not aimed at correlating morphological changes with clinical symptoms but tries to show differences in the pattern of NFT and NT rendering morphological staging of AD-related changes possible.

Materials and methods

re: "**seriously**?" – I went back and forth on this a lot, after my initial hackles response.

Tangle Formation in AD (Tau and Neurofilament)

PREVIEW of pdf/slides to come

Seriously???

How do we know that TAU is not first?

nice *tau* summary

see anything integrative here

The event that follows plaque formation in AD is the formation of NFTs. In contrast to Aβ plaques, NFTs so far have not been associated with mutations but are due to modulations of kinase and phosphatase activities. NFTs are composed of aberrantly hyperphosphorylated cytoskeletal components like tau and neurofilament proteins.

Normally, tau functions to regulate microtubule (MT) assembly and transport. There are six tau isoforms in human brain produced from a single gene through alternative mRNA splicing (38). Based on the number of microtubule-binding repeats, tau can be categorized into two groups, one with three repeats (3R) and the other with four repeats (4R) as shown in Figure 2. In the tau filaments obtained from AD brain, similar to normal human brain, all six isoforms are found. Tau, an abundant soluble protein in axons, normally promotes assembly and stability of microtubules and vesicle transport but, when hyperphosphorylated, becomes insoluble, lacks affinity for microtubules and forms paired helical structures. Like Aβ oligomers, intermediate aggregates of abnormal tau molecules are cytotoxic and impair cognition (39–41). Filamentous tau is also found in other neurodegenerative disorders like corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Pick's disease and Parkinson-dementia complex of Guam (42). None of these diseases, unlike AD, lack Aβ pathology. When tau becomes hyperphosphorylated in AD, it dissociates from MT assembly, resulting in destabilizing MTs and impairment of axonal transport. The phospho-tau aggregates form filamentous structures called paired helical filaments (PHFs), which further combine to form the aggregates of insoluble NFTs (43). Under physiological conditions, proteasome assembly cleans up any aggregate that may be potentially toxic to the system. Inhibition of this clean-up process by the proteasome is sufficient to induce neuronal degeneration and death (44). Also, various reports suggest that, at least in some part, formation of highly insoluble NFT is associated with oxidative stress (45,46). Due to hyperphosphorylation of tau, not only the normal function of stabilizing microtubules is hampered, but a gain of toxic function is exhibited due to sequestering of normal tau. Reports have shown that the absence of normal tau results in the disru

Shukla 2012, p.2

is their "no more cascade" claim true?
does it make sense based on their ABO data?

"amyloid cascade" 17,700 hits since 2017

what does "supplanted" mean?

Review

The Amyloid-β Oligomer Hypothesis: Beginning of the Third Decade

An UPDATE by
~ Viola & Klein

Erika N. Cline, Maira Assunção Bicca, Kirsten L. Viola and William L. Klein*
Department of Neurobiology, Cognitive Neurology and Alzheimer's Disease Center, International Institute for Nanotechnology, and Chemistry of Life Processes Institute, Northwestern University, Evanston, IL, USA

Abstract The amyloid-β oligomer (AβO) hypothesis was introduced in 1998. It proposed that the brain damage leading to Alzheimer's disease (AD) was instigated by soluble, ligand-like AβOs. This hypothesis was based on the discovery that fibril-free synthetic preparations of AβOs were potent CNS neurotoxins that rapidly inhibited long-term potentiation and, with time, caused selective nerve cell death (Lambert et al., 1998). The mechanism was attributed to disrupted signaling involving the tyrosine-protein kinase Fyn, mediated by an unknown brain receptor. Over 4,000 articles concerning AβOs have been published since then, including more than 400 reviews. AβOs have been shown to accumulate in an AD-dependent manner in human and animal model brain tissue and, experimentally, to impair learning and memory and instigate major facets of AD neuropathology including tau pathology, synapse deterioration and loss, inflammation, and oxidative damage. As reviewed by Haydon and Teplow in 2013, the AβO hypothesis "has all but supplanted the amyloid cascade." Despite the emerging understanding of the role played by AβOs in AD pathogenesis, AβOs have not yet received the clinical attention given to amyloid plaques, which have been at the core of major attempts at therapeutics and diagnostics but are no longer regarded as the most pathogenic form of Aβ. However, if the momentum of AβO research continues, particularly efforts to elucidate key aspects of structure, a clear path to a successful disease modifying therapy can be envisioned. Ensuring that lessons learned from recent, late-stage clinical failures are applied appropriately throughout therapeutic development will further enable the likelihood of a successful therapy in the near-term.

At the core of the ACH is the idea that amyloid, in some fashion, triggers pathological processes associated with Tau and the progression of AlzD. ONE of the assaults on ACH stems from failures (to date) of amyloid removal. But is this sufficient to dispense with the ACH?

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926 *Current Neuropharmacology, 2017, 15, 926-935*

REVIEW ARTICLE

The Amyloid Cascade Hypothesis in Alzheimer's Disease: It's Time to Change Our Mind

ACH = Amyloid Cascade Hypothesis

Roberta Ricciarelli[1,*] and Ernesto Fedele[2,3,*]

[1]*Department of Experimental Medicine, Section of General Pathology, University of Genova, Genova, Italy;* [2]*Department of Pharmacy, Section of Pharmacology and Toxicology, University of Genova, Genova, Italy;* [3]*Center of Excellence for Biomedical Research, University of Genova, Genova, Italy*

ARTICLE HISTORY

Received: November 03, 2016
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DOI:

Abstract: Since its discovery in 1984, the beta amyloid peptide has headed the boards of neurosciences as the star molecule in Alzheimer's disease pathogenesis. In the last decade, however, this vision has been challenged by evidence-based medicine showing the almost complete failure of clinical trials that experimented anti-amyloid therapies with great hopes. Moreover, data have accumulated which clearly indicate that this small peptide plays a key role in the physiological processes of memory formation. In the present review, we will discuss the different aspects of the amyloid cascade hypothesis, highlighting its pros and cons, and we will analyse the results of the therapeutic approaches attempted to date that should change the direction of Alzheimer's disease research in the future.

Keywords: Alzheimer's disease, beta amyloid, clinical trials, LTP, memory, anti-amyloid therapy.

frontiers in Cellular Neuroscience

REVIEW

Senescence as an Amyloid Cascade: The Amyloid Senescence Hypothesis

Chaska C. Walton*, David Begelman, Wynnie Nguyen and Julie K. Andersen*

OPEN ACCESS

Due to their postmitotic status, the potential for neurons to undergo senescence has historically received little attention. This lack of attention has extended to some non-postmitotic cells as well. Recently the study of senescence within the central nervous system (CNS) has begun to emerge as a new etiological framework for neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). The presence of senescent cells is known to be deleterious to non-senescent neighboring cells via development of a senescence-associated secretory phenotype (SASP) which includes the release of inflammatory, oxidative, mitogenic, and matrix-degrading factors. Senescence and the SASP have recently been hailed as an alternative to the amyloid cascade hypothesis and the selective killing of senescence cells by senolytic drugs as a substitute for amyloid beta (Aβ) targeting antibodies. Here we call for caution in rejecting the amyloid cascade hypothesis and/or the dismissal of Aβ antibody intervention at least in early disease stages, as Aβ oligomers (AβOs) and cellular senescence may be inextricably linked. We will review literature that portrays AβO as a stressor capable of inducing senescence. We will discuss research on the potential role of secondary senescence, a process by which senescent cells induce senescence in neighboring cells, in disease progression. Once this seed of senescent cells is present, the elimination of senescence-inducing stressors like Aβ would likely be ineffective in abrogating the spread of senescence. This has potential implications for when and why AβO clearance may or may not be effective as a therapeutic for AD. The selective killing of senescent cells by the immune system via immune surveillance naturally curtails the SASP and secondary senescence outside the CNS. Immune privilege restricts the access of peripheral immune cells to the brain parenchyma, making the brain a safe harbor for the spread of senescence and the SASP. However, an increasingly leaky blood brain barrier (BBB) compromises immune privilege in aging AD patients, potentially enabling immune infiltration that could have detrimental consequences in later AD stages. Rather than an alternative etiology, senescence itself may constitute an essential component of the cascade in the amyloid cascade hypothesis.

We will revisit this topic in Chapter 19.

In what sense are there 2 dia
reasons to dismiss the ACH hy
refers to pharm vs. ABOs.

What evidence is there to SU

This abstract is nicely INTEGRATIVE in that it combines early semester concepts with new materials.

Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years

Journal Neuropathol., 2011

Heiko Braak, MD, Dietmar R. Thal, MD, Estifanos Ghebremedhin, M

highlights *Locus Coeruleus*
2011, cited by 726

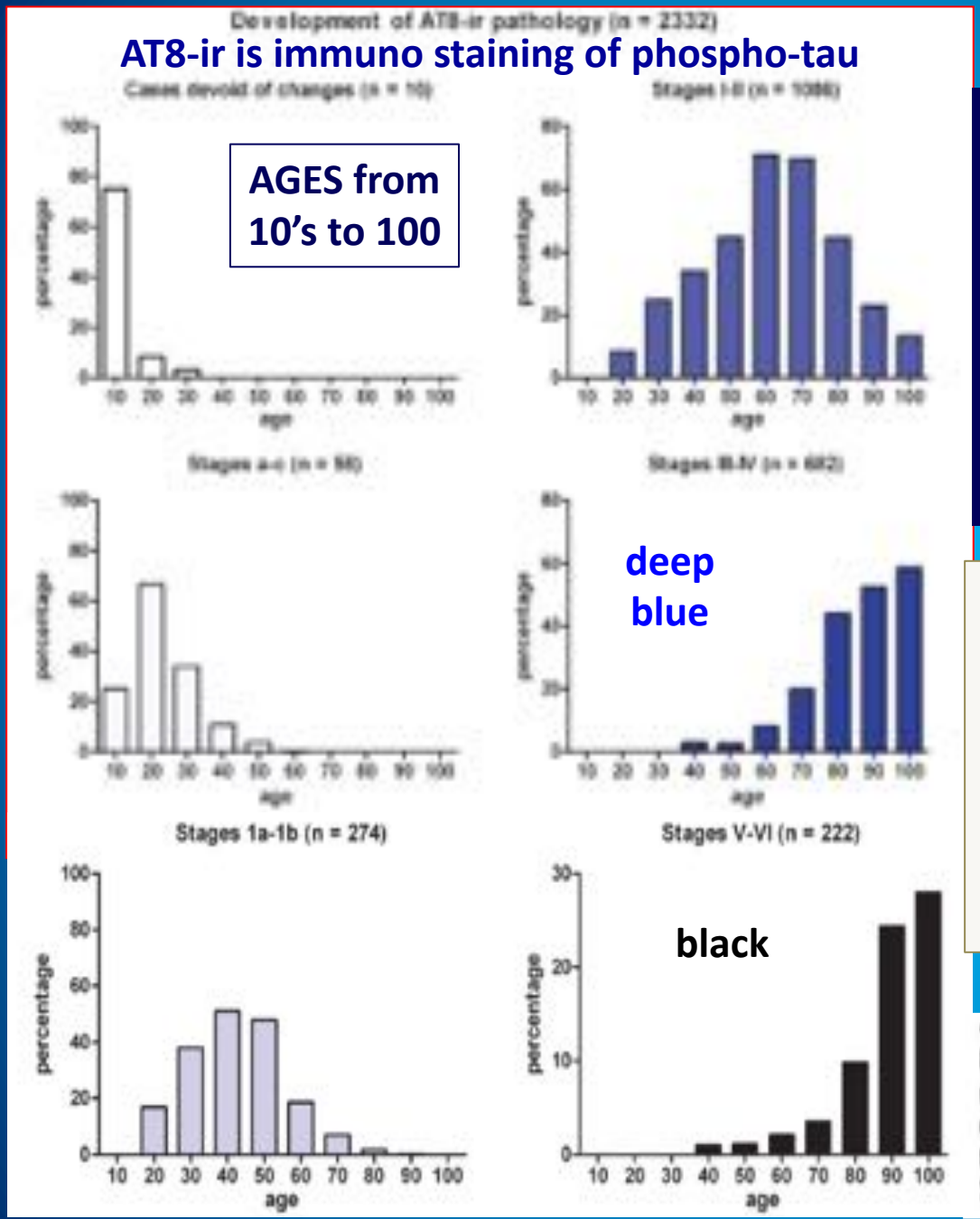
Abstract

Two thousand three hundred and thirty two nonselected brains from 1- to 100-year-old individuals were examined using immunocytochemistry (AT8) and Gallyas silver staining for abnormal tau; immunocytochemistry (4G8) and Campbell-Switzer staining were used for the detection of β-amyloid. A total of 342 cases was negative in the Gallyas stain but when restaged for AT8 only 10 were immunonegative. Fifty-eight cases had subcortical tau predominantly in the locus coeruleus, but there was no abnormal cortical tau (subcortical Stages a–c). Cortical involvement (abnormal tau in neurites) was identified first in the transentorhinal region (Stage Ia, 38 cases). Transentorhinal pyramidal cells displayed pretangle material (Stage Ib, 236 cases). Pretangles gradually became argyrophilic neurofibrillary tangles (NFTs) that progressed in parallel with NFT Stages I to VI. Pretangles restricted to subcortical sites were seen chiefly at younger ages. Of the total cases, 1,031 (44.2%) had β-amyloid plaques. The first plaques occurred in the neocortex after the onset of tauopathy in the brainstem. Plaques generally developed in the 40s in 4% of all cases, culminating in their tenth decade (75%). β-amyloid plaques and NFTs were significantly correlated ($p < 0.0001$). These data suggest that tauopathy associated with sporadic Alzheimer disease may begin earlier than previously thought and possibly in the lower brainstem rather than in the transentorhinal region.

confined to the human CNS and chiefly include intraneuronal formation of abnormal tau protein and extracellular deposition of β-amyloid protein (1). Alzheimer disease–related lesions develop at given predilection sites within the brain and progress according to a predictable sequence from there to hitherto uninvolved areas (2–7).

Once initiated, the process progresses for decades without remission until it crosses a threshold to clinically recognizable dysfunction (6). Recently, we found that intraneuronal lesions associated with AD occur before puberty or in early young adulthood and most often affect noradrenergic projection neurons of the locus coeruleus, one of several subcortical nuclei that generate diffuse projections to the cerebral cortex (8). Abnormal tau can be visualized by immunohistochemistry with the antibody AT8, which recognizes a phosphate-dependent epitope at serine 202 and threonine 205 (9). Alzheimer disease may begin with misfolded and abnormally phosphorylated tau protein in the proximal axon of caeruleus projection neurons (8). Thereafter, similar material fills the somatodendritic compartment of involved cells. This soluble and nonargyrophilic "pretangle" material gradually aggregates into insoluble fibrillary and argyrophilic neuropil threads (NTs) in dendritic processes and into neurofibrillary tangles (NFTs) in neuronal somata. These inert neurofibrillary changes of the Alzheimer

Braak et al., 2011



Some tau pathology is **evident in 20's** in subcortical locations, espec. Locus Coeruleus (Stages I-II, left). With age, more substantial pathology emerges, extending well into neocortex (III-IV), **especially at age 70** and older. Dense pathology is seen most often in folks at **age 80 or more**.

Pathological Spread of p-Tau

white = cases devoid of tau deposits
pale blue = subtle subcortical lesions
[but not "true" pathology"]
deep blue = neocortical pathology; more extensive in stages III-IV
black = stage V – VI pathology

FIGURE 1. Development of abnormal intraneuronal tau deposits in 2,332 nonselected autopsy cases. White columns represent the relative frequency of cases devoid of any tau deposits. Pale blue columns show the development of subtle subcortical lesions in cases with Stages a to c pathology. Columns in medium blue show an extension of these nonargyrophilic lesions into portions of the cerebral cortex (Stages 1a and 1b). Development of the pretangle material into argyrophilic neurofibrillary lesions characterizes Stages I to VI as follows: deep blue for Stage I and II cases, dark blue for Stage III and IV cases, and black for Stage V and VI cases.

note: stained for lipofuscin, apparently with negative results

Braak et al., 2011
Figure 2

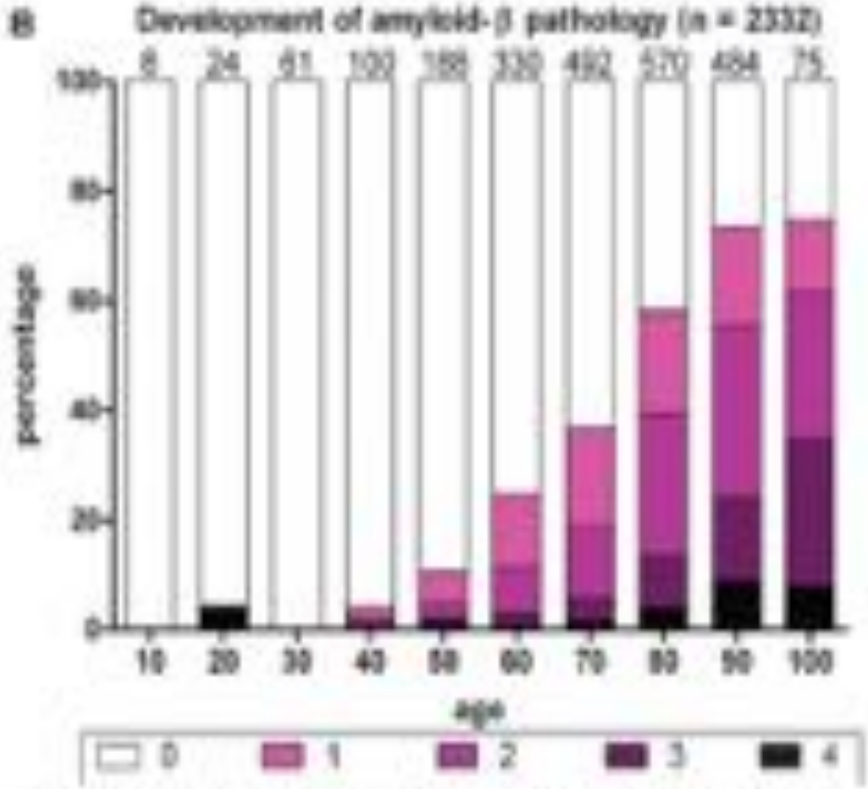
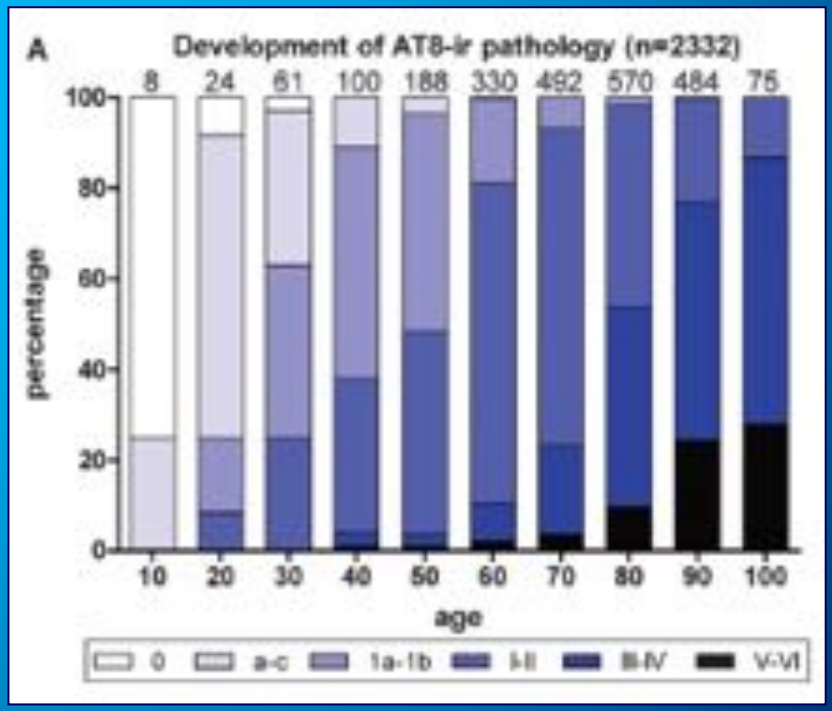


FIGURE 2. Development of AT8-immunoreactivity (ir) versus β-amyloid pathologic findings. **(A)** White columns indicate the relative frequency of 2,332 nonselected autopsy cases devoid of any abnormal intraneuronal tau deposits. Columns in shades of blue indicate the relative frequency of cases with all types of intraneuronal lesions. **(B)** Development of extracellular β-amyloid deposits. Purple areas within the columns indicate subgroups of cases showing plaque-like β-amyloid deposits in temporal neocortex (Phase 1, light purple), allocortex and neocortical association areas (Phases 2 and 3, middle purple and dark purple), or in virtually all cerebral cortical regions (Phase 4, black). Note the relatively late appearance of β-amyloid plaques.

← The purple bars show *amyloid* pathology emerging in the 60's and 70's, while ***tau***, **blue bars below**, is widely present by the 30's and 40's.

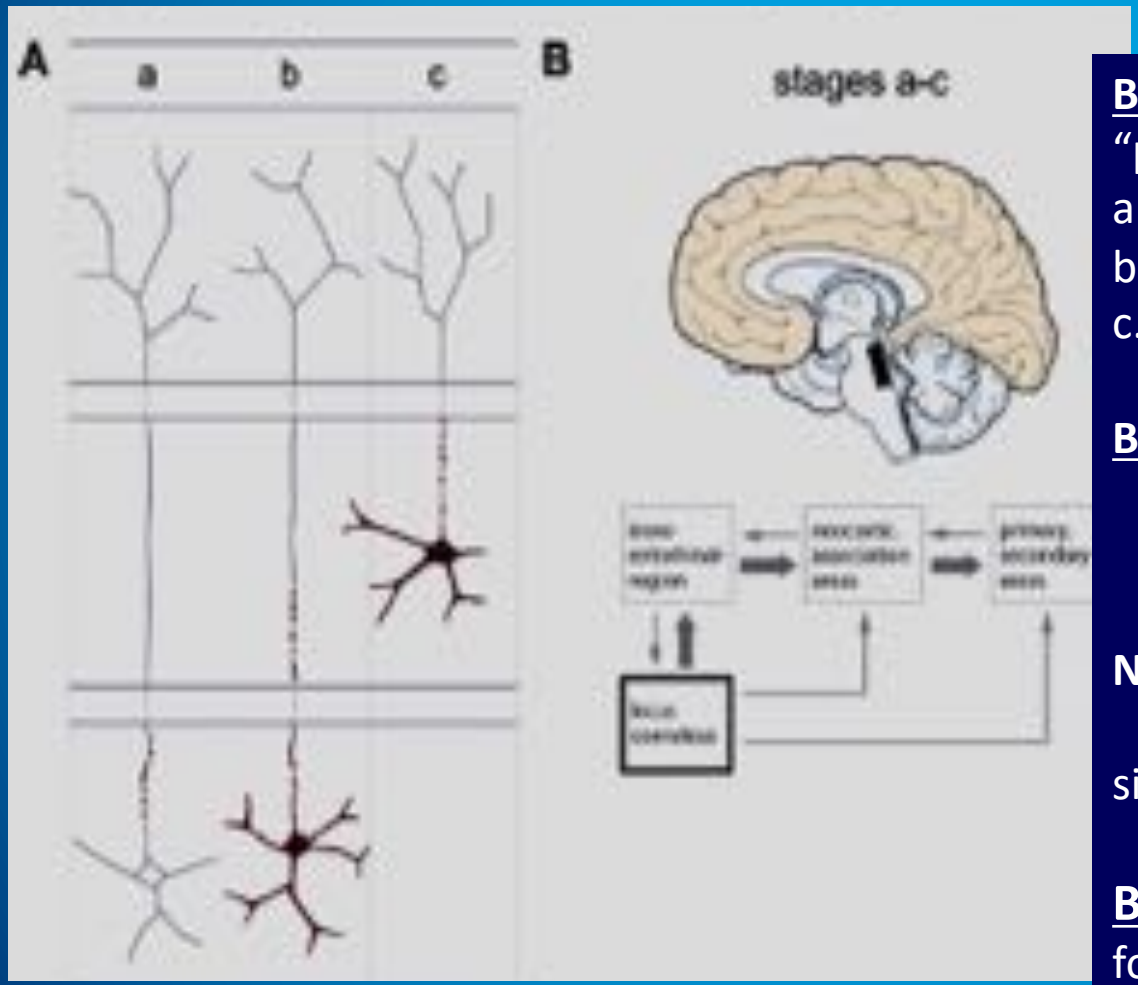
Braak suggests that sporadic AlzD ensues from a **"tauopathy…beginning in childhood".**

is there a subset that won't get AlzD even if they live to be 200?



Braak et al., 2011

Pre-tangle Tau protein aggregates seen in children advance over time both locally in Locus Coeruleus and in terms of projections into neocortex



<u>Braak has two staging systems #1:</u>
"pretangle" phospho-tau is seen:
a. in small amounts in prox. axon
b. more robust later in LC neurons
c. eventually is seen in other brain-stem neurons

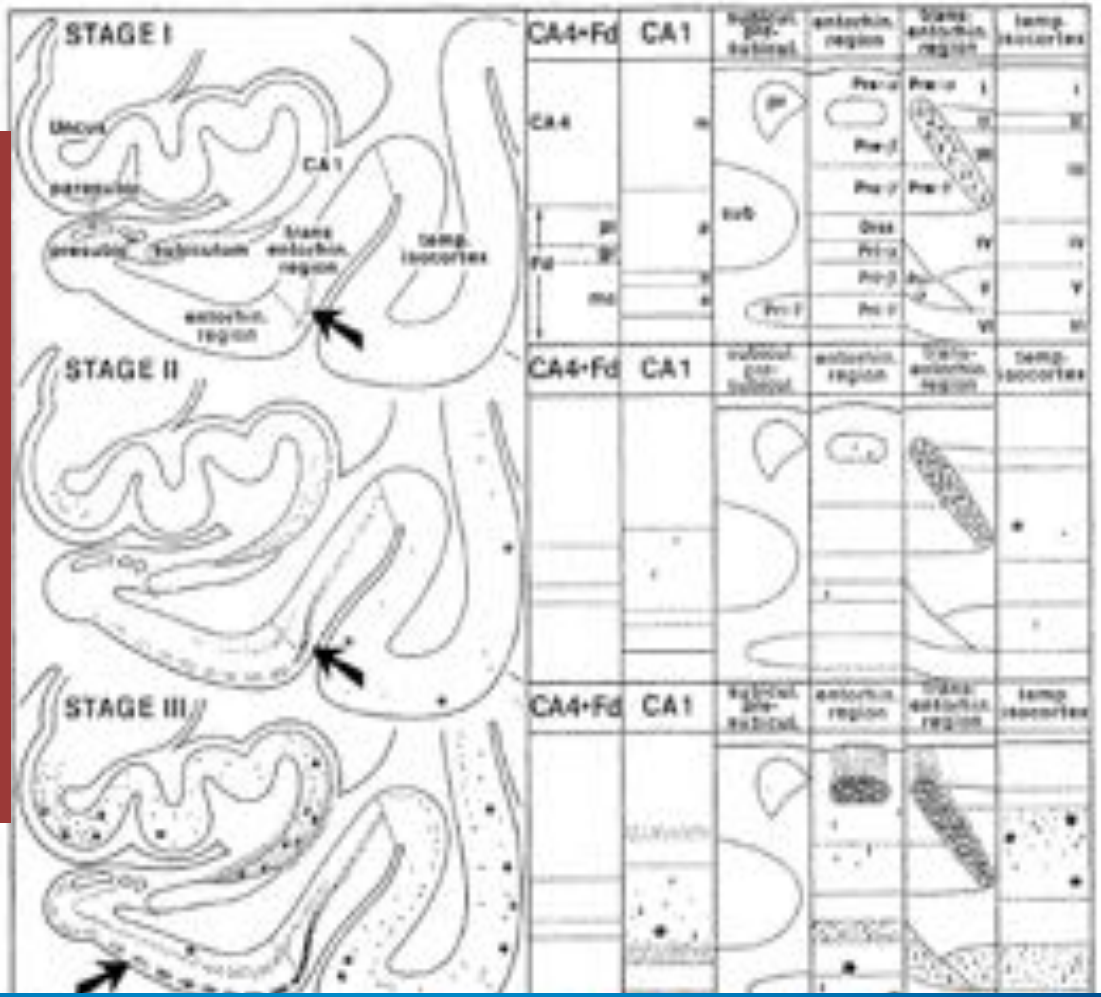
<u>Brain Diagram (B)</u> shows projection targets of cells in a-c with more cortical spread with age

Next slide show "pathological" tau stages w/ Roman Numerals similar to earlier Braak and Braak.

<u>BIG NEED</u>: better BIOMARKERS for early tau pathology.

for personal use:
transentorhinal

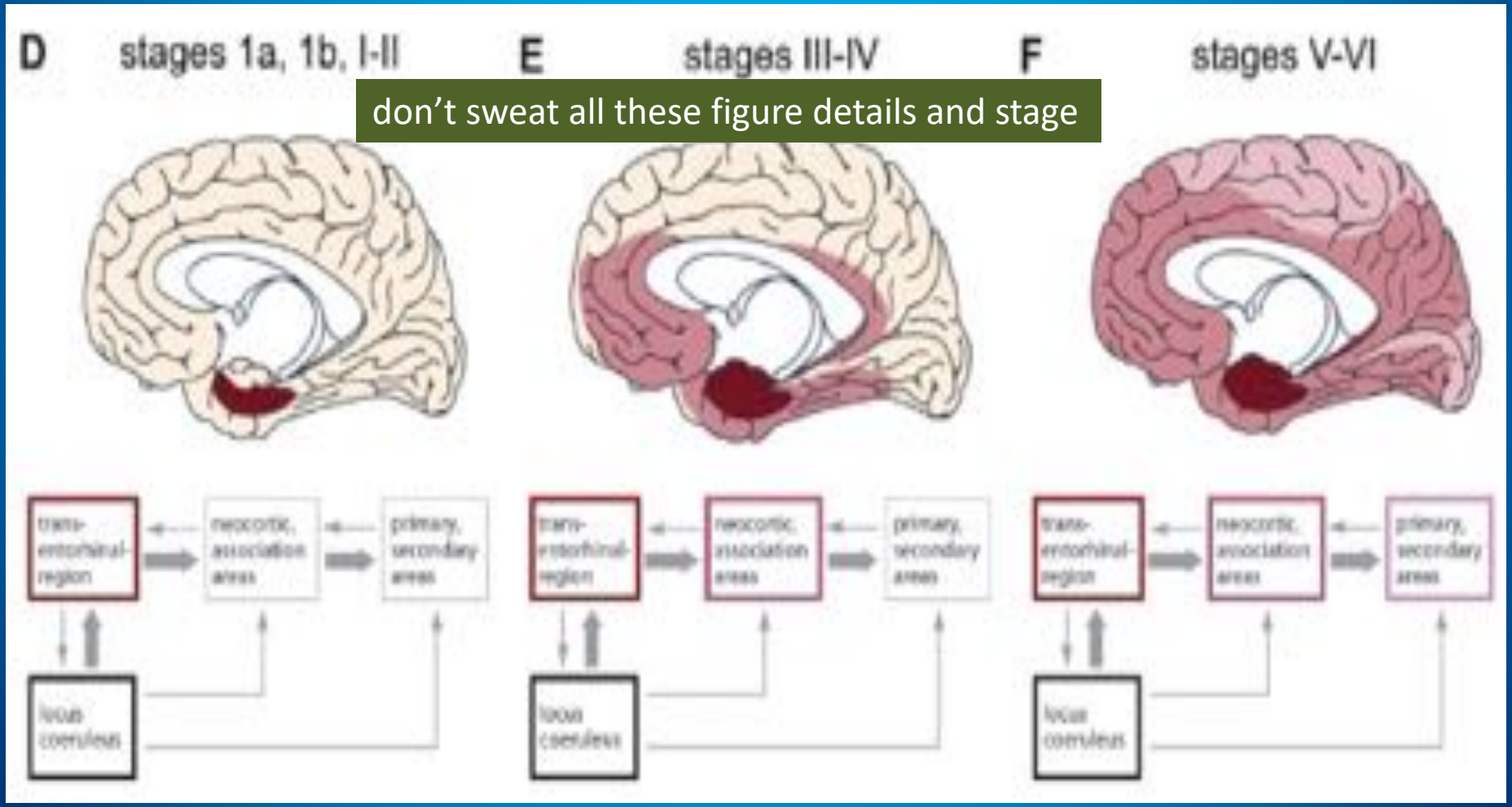
i pasted this for personal use b/c this is a nice depiction of the trans-entorhinal region ➔ of which B&B speak, which is transitional from ERC/hippo to neocortex (6 layers, aka isocortex). This figure shows tau pathology spread thru the hippocampus (beyond our objectives), but you should note that hippo/ERC involvement precedes substantial emergence in neocortex.



Braak et al., 2011

Figure 4

<u>Pathological Tau</u> stages seen in neocortex are subsequent to the "pre-tangle Tau" seen in Locus Coeruleus. By age 40, a very large majority of individuals are early stages (II or less) but increasing number of stage III-IV are seen in the 60's and especially 70's (see Figure 2)



While LC is a locus of early Tau pathology, noradrenergic innervation of neocortex is sustained at least in early AlzD. But system impairments might contribute to cognitive decline. + Nor-Epi boost might offer some relief. perhaps

ELSEVIER

Brain Research

2019

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Research report

Complex noradrenergic dysfunction in Alzheimer's disease: Low norepinephrine input is not always to blame

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ABSTRACT

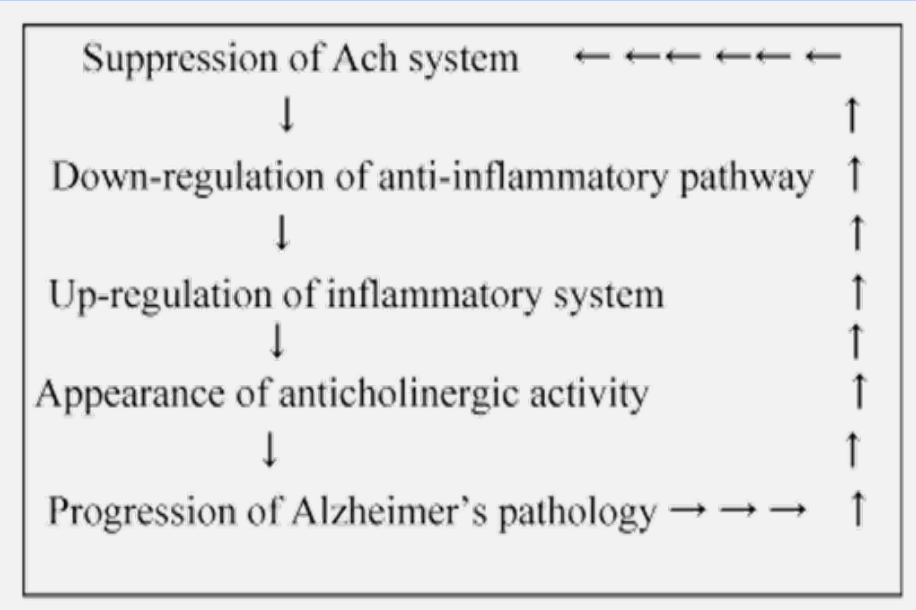
The locus coeruleus-noradrenergic (LC-NA) system supplies the cerebral cortex with norepinephrine, a key modulator of cognition. Neurodegeneration of the LC is an early hallmark of Alzheimer's disease (AD). In this article, we analyze current literature to understand whether NA degeneration in AD simply leads to a loss of norepinephrine input to the cortex. With reported adaptive changes in the LC-NA system at the anatomical, cellular, and molecular levels in AD, existing evidence support a seemingly sustained level of extracellular NE in the cortex, at least at early stages of the long course of AD. We postulate that loss of the integrity of the NA system, rather than mere loss of NE input, is a key contributor to AD pathogenesis. A thorough understanding of NA dysfunction in AD has a large impact on both our comprehension and treatment of this devastating disease.

Cholinergic Hypothesis: *reprised!*

Oldest hypothesis for the cause of Alzheimer's

- was proposed that AlzD is caused by reduced synthesis of acetylcholine
- majority of therapeutic treatments were based on this hypothesis, however therapies boosting ACh showed marginal results

- early "version" of slide: Cholinergic cells found in the "hippocampus, cerebral cortex". ***TRUE***???
- Essential neurotransmitter for forming memories
- ACh levels are reduced as much as 90% in Alzheimer's
- Acetylcholinesterase Inhibitor: take it w/ your coffee?**
- Cholinergic deficit also proposed to initiate aggregates, neuroinflammation



** aka Pesticides, Nerve Agents [Sarun. Soman, VX]

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Basal forebrain degeneration precedes and predicts the cortical spread of Alzheimer's pathology

2016

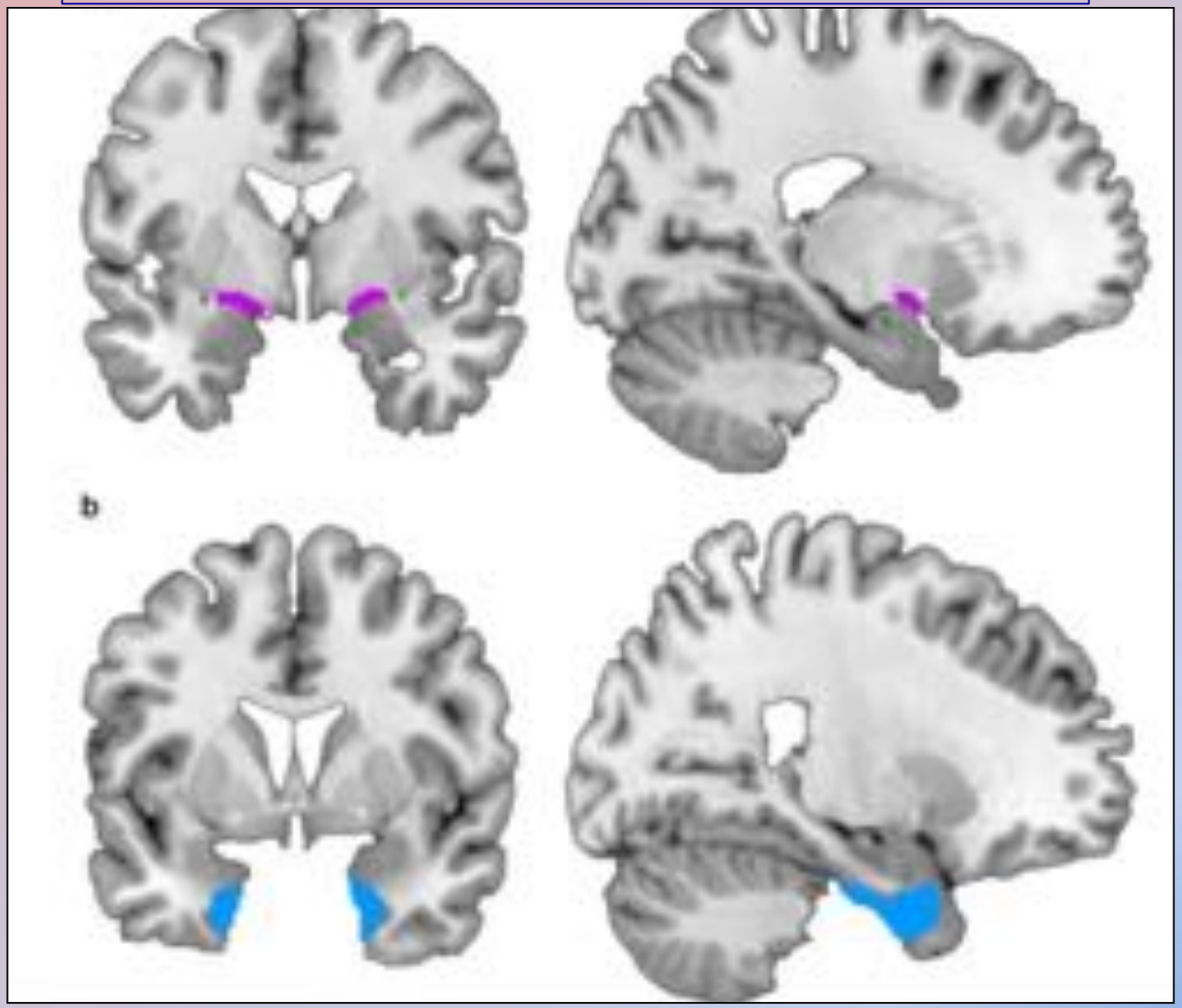
Taylor Schmitz, Nathan Spreng and ADNI.

claims that (i) pathology begins in basal forebrain (BFB) and (ii) that BFB pathology predicts subsequent ERC pathology and CSF AB42-positive individuals.

BFB and ERC are among the first to show both plaques and NFTs, but BFB is first whereas "parallel" BFB/ERC degeneration is not supported by their data.

There is considerable debate whether Alzheimer's disease (AD) originates in basal forebrain or entorhinal cortex. Here we examined whether longitudinal decreases in basal forebrain and entorhinal cortex grey matter volume were interdependent and sequential. In a large cohort of age-matched older adults ranging from cognitively normal to AD, we demonstrate that basal forebrain volume predicts longitudinal entorhinal degeneration. Models of parallel degeneration or entorhinal origin received negligible support. We then integrated volumetric measures with an amyloid biomarker sensitive to pre-symptomatic AD pathology. Comparison between cognitively matched normal adult subgroups, delineated according to the amyloid biomarker, revealed abnormal degeneration in basal forebrain, but not entorhinal cortex. Abnormal degeneration in both basal forebrain and entorhinal cortex was only observed among prodromal (mildly amnestic) individuals. We provide evidence that basal forebrain pathology precedes and predicts both entorhinal pathology and memory impairment, challenging the widely held belief that AD has a cortical origin.

Purple = basal forebrain / ACh. Blue = ERC



Schmitz & Spreng, 2016

"Ch4" = basal forebrain

2. Volume Declines

1. Baseline Volumes

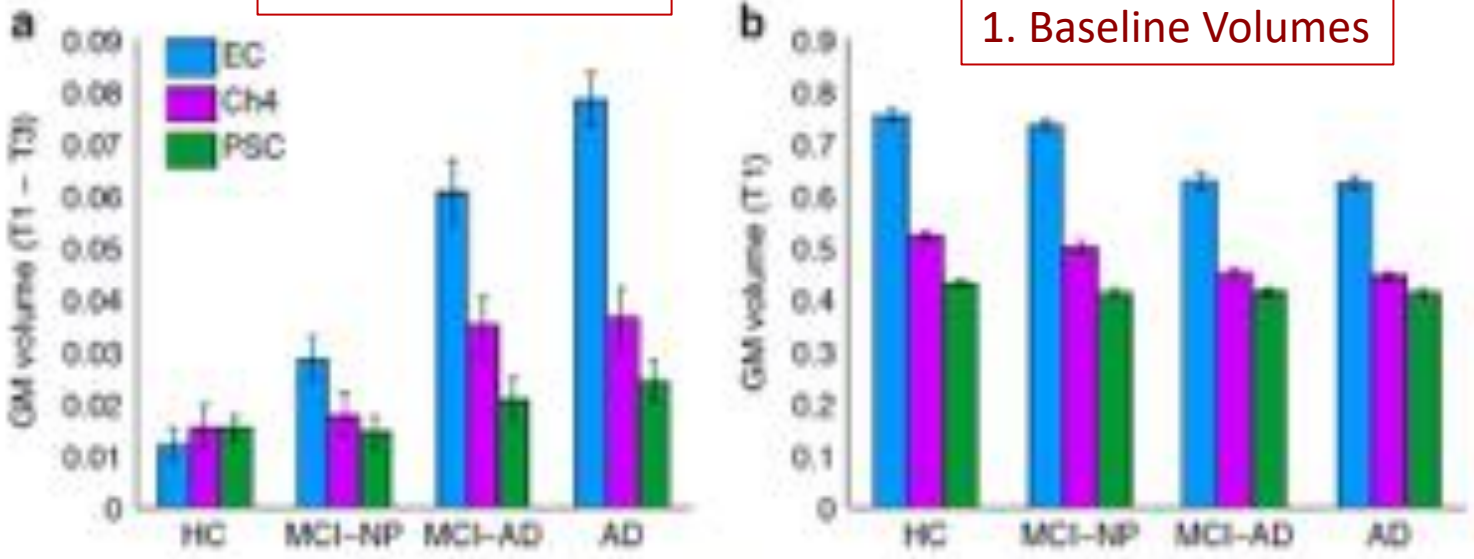


Figure 2 | Volumetric group differences. Volumetric group differences (diagnosis) in *a priori* ROIs for the EC (blue), basal forebrain NbM (Ch4; magenta) and PSC (green). (**a**) Magnitudes of GM degeneration from baseline (T1) to 2 years post baseline (T3) in each diagnostic group: HCs ($n = 150$), MCI-NP ($n = 103$), MCI-AD ($n = 84$) and probable AD individuals (AD; $n = 97$). (**b**) GM volume at baseline in each diagnostic group.

PSC= primary somatosensory cortex HC = healthy controls EC = ERC
MCI-AD (MCI progressing to AlzD) MCI-NP (MCI not-progressing)

Schmitz & Spreng, 2016

BACK TO BASICS: OD reprised …

Oxidative Damage Is the Earliest Event in Alzheimer Disease

and then declines!

AKIHIKO NUNOMURA, MD, PHD, GEORGE PERRY, PHD, GUMBRAECH ALIEV, MD, PHD, KEISUKE HIRAI, PHD, ATSUSHI TAKEDA, MD, PHD, ELIZABETH K. BALRAJ, MD, PAUL K. JONES, PHD, HOSSEIN GHANBARI, PHD, TAKAFUMI WATAYA, MD, SHUN SHIMOHAMA, MD, PHD, SHIGERU CHIBA, MD, PHD, CRAIG S. ATWOOD, PHD, ROBERT B. PETERSEN, PHD, AND MARK A. SMITH, PHD

Abstract. Recently, we demonstrated a significant increase of an oxidized nucleoside derived from RNA, 8-hydroxyguanosine (8OHG), and an oxidized amino acid, nitrotyrosine in vulnerable neurons of patients with Alzheimer disease (AD). To determine whether oxidative damage is an early- or end-stage event in the process of neurodegeneration in AD, we investigated the relationship between neuronal 8OHG and nitrotyrosine and histological and clinical variables, i.e. amyloid-β (Aβ) plaques and neurofibrillary tangles (NFT), as well as duration of dementia and apolipoprotein E (ApoE) genotype. Our findings show that oxidative damage is quantitatively greatest early in the disease and reduces with disease progression. Surprisingly, we found that increases in Aβ deposition are associated with decreased oxidative damage. These relationships are more significant in ApoE ε4 carriers. Moreover, neurons with NFT show a 40%–50% decrease in relative 8OHG levels compared with neurons free of NFT. Our observations indicate that increased oxidative damage is an early event in AD that decreases with disease progression and lesion formation. These findings suggest that AD is associated with compensatory changes that reduce damage from reactive oxygen.

Post-mortems from AlzD patients revealed ***less*** oxidized nucleoside and amino acid as NFTs, amyloid increased.

2001, 1690 cites
[that's more than 5]

INTRODUCTION

Several studies have now established the association of neuronal oxidative stress with Alzheimer disease (AD) (1, 2). This stress is manifested by damage to proteins (3–5), lipids (6, 7), and nucleic acids, i.e. nuclear and mitochondrial DNA (8, 9) as well as RNA (10). Apoli-

16), while others argue Aβ is the result (17–19) of oxidative stress.

In this study, we address the chronological issue of oxidative stress in a series of cases of AD with different duration of disease by examining the levels of 8-hydroxyguanosine (8OHG), an oxidized nucleoside derived from

Journal of Neuropathology and Experimental Neurology, 2001, Vol. 60, pp. 759-767

select abstracts

Evidence of increased oxidative damage in subjects with mild cognitive impairment

2005

J.N. Keller, PhD; F.A. Schmitt, PhD; S.W. Scheff, PhD; Q. Ding, PhD; Q. Chen, PhD; D.A. Butterfield, PhD; and W.R. Markesbery, MD

Abstract—*Objective:* To determine if increased levels of oxidative damage are present in the brains of persons with mild cognitive impairment (MCI), a condition that often precedes Alzheimer disease (AD). *Methods:* The authors assessed the amount of protein carbonyls, thiobarbituric acid-reactive substances (TBARS), and malondialdehyde in the superior and middle temporal gyri (SMTG) and cerebellum of short postmortem interval and longitudinally evaluated normal subjects and those with MCI and early AD. *Results:* Elevated levels of protein carbonyls (~25%), malondialdehyde (~60%), and TBARS (~220%) were observed in the SMTG of individuals with MCI and early AD vs normal control subjects. The elevation in TBARS was associated with the numbers of neuritic but not diffuse plaques. Levels of protein carbonyls increased as delayed verbal memory performance declined. *Conclusion:* Oxidative damage occurs in the brain of subjects with mild cognitive impairment, suggesting that oxidative damage may be one of the earliest events in the onset and progression of Alzheimer disease.

NEUROLOGY 2005;64:1152–1156

Oxidative damage is present in a number of neurodegenerative conditions including Alzheimer disease (AD).[1-3] Evidence for oxidative damage in the AD brain includes the presence of elevated levels of oxidized lipids, nucleic acids, and proteins.[1-6] While the precise role that increased levels of oxidative damage play in mediating the onset and progression of AD

MCI may be one of the earliest phases in the development of AD.[9,10] The neuropathologic changes and neuron degeneration in MCI show some overlap with the autopsy findings in older cognitively intact individuals,[11,12] suggesting that MCI may provide an opportunity to clarify whether increased oxidative damage is an important factor in the pathogenesis of