Summa Health Senior Health Symposium: **Session 7A**

Complex Care Institute

Palliative Care | Senior Health | Pastoral Care | Complex Care Clinic | Pain Stewardship

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Breakout 1:
Advanced Diagnostics, Imaging and Therapeutics for Dementia

In-person attendees:
Breakout session is located next door at Juve Family Behavioral Health Pavilion.

Virtual attendees:
Click on Breakout Room #1

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Advanced diagnostics, imaging and therapeutics for dementia

Dr. James Bavis

Joseph Marchiano, PharmD, BCPS, BCGP

Objectives

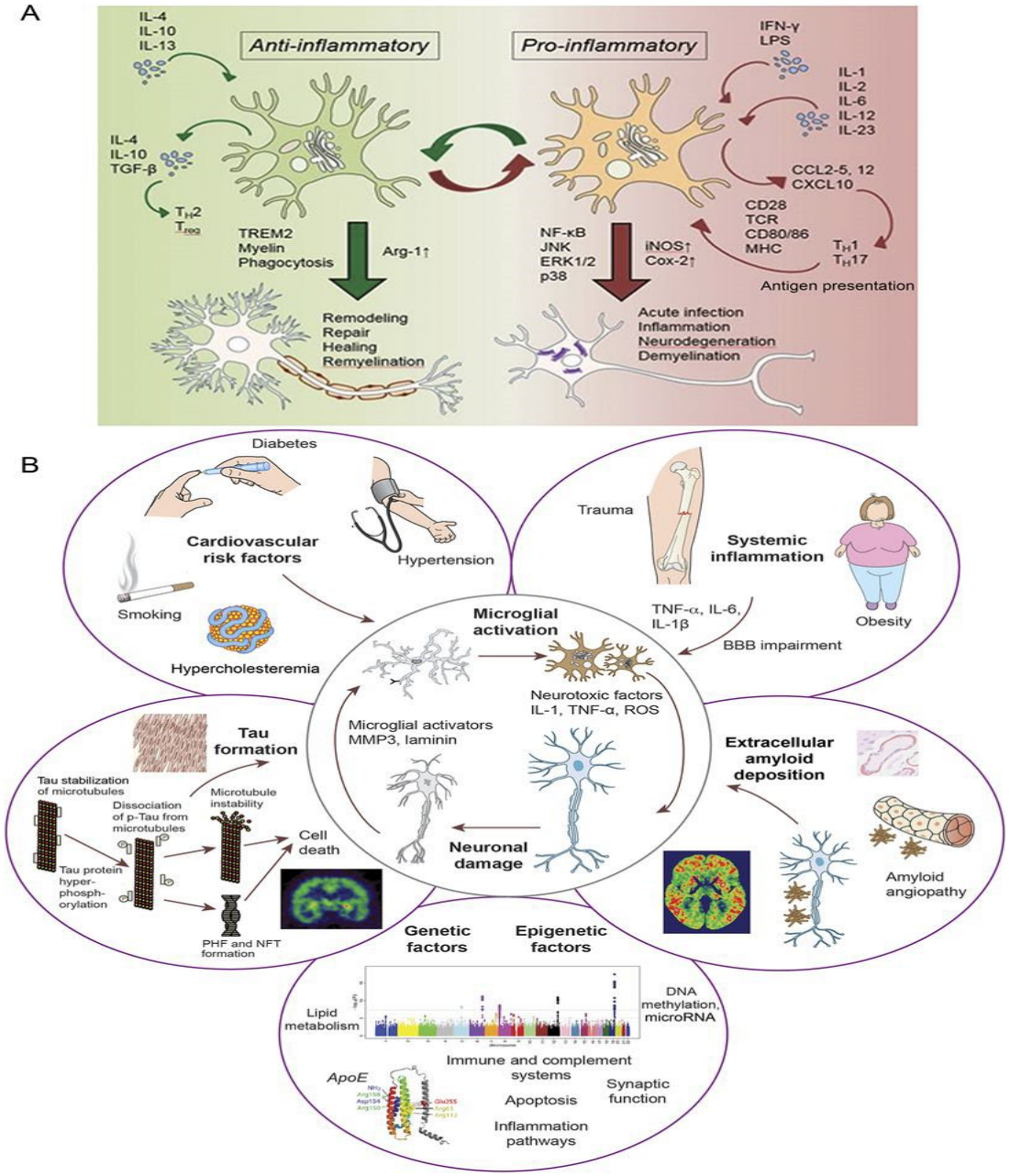
1. Evaluate the latest advancements in diagnostic tools and imaging techniques for assessing dementia patients
2. Explore emerging therapeutic interventions and treatment modalities for dementia, including pharmacological and non-pharmacological approaches

Advances in Dementia Diagnostics

Pathology of Alzheimer's Dementia

- The disease pathology is marked by the build up of insoluble aggregate, amyloid β and phosphorylated tau.
- The amyloid β and phosphorylated tau engender the formation of neurofibrillary tangles.
- The presence and production of amyloid β and phosphorylated tau are very closely tied to Alzheimer's disease and not to other neurodegenerative processes
- Therefore, measuring the presence and production of amyloid β and phosphorylated tau in fluid leads to better identification of Alzheimer's dementia over other causes of memory loss.

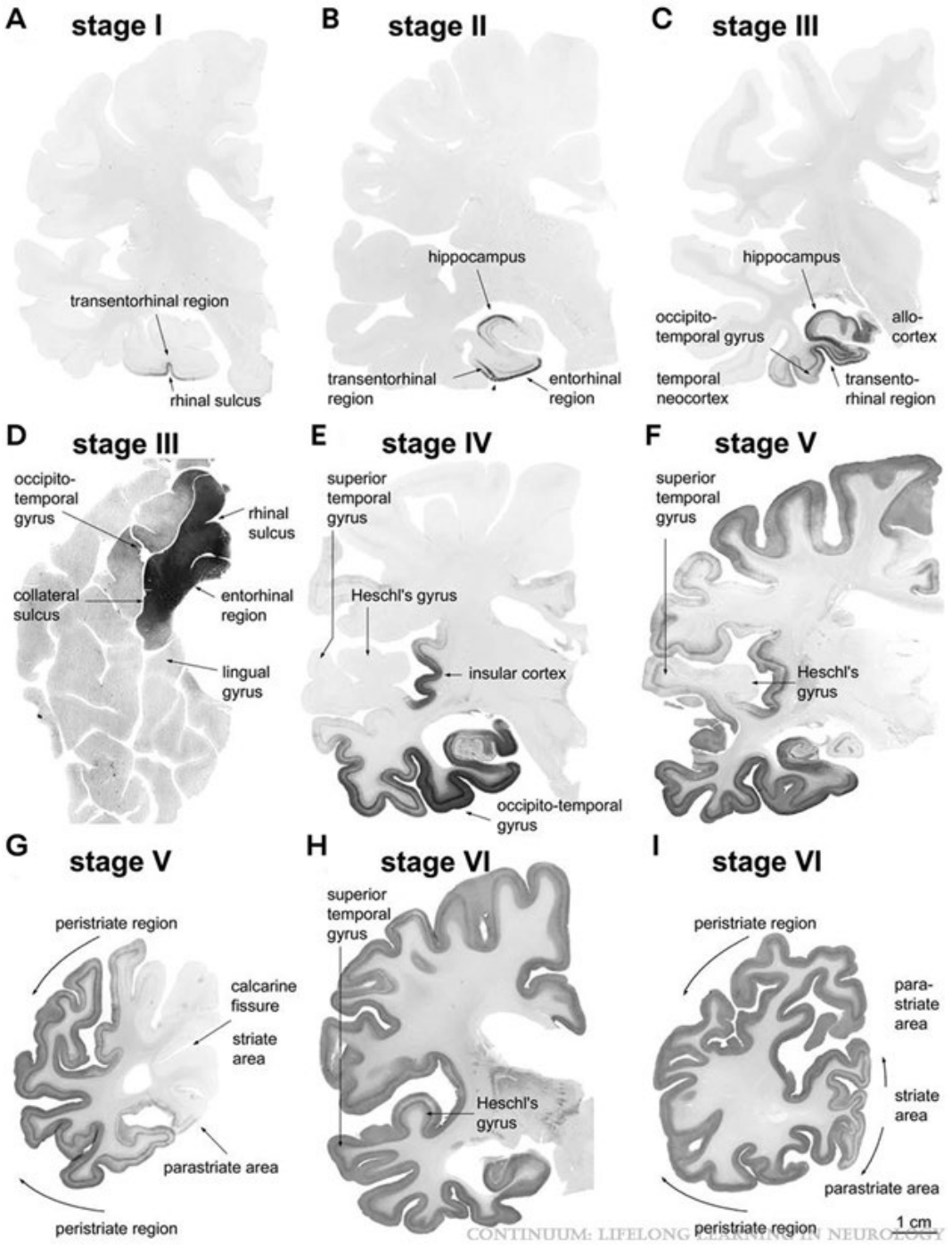
Pathology of Alzheimer's Dementia



(A) Microglia can be activated by either anti-inflammatory stimuli (IL-4, IL-10, or IL-13) or proinflammatory cytokines (IFN-, LPS) that determine the polarization status of the cell. The anti- and proinflammatory responses involve the activation of different intracellular pathways and result in opposite effects on neuronal cells. (B) Systemic (cardiovascular risk factors and systemic inflammation), local (amyloid deposition and tangle formation), and genetic factors contribute to microglial activation. BBB = blood-brain barrier; COX-2 = cyclooxygenase-2; IFN = interferon; IL = interleukin; iNOS = inducible nitric oxide synthase; LPS = lipopolysaccharide; MHC = major histocompatibility complex; NF-κB = nuclear factor κB; NFT = neurofibrillary tangles; PHF = paired helical filaments; p-tau = phosphorylated tau; ROS = reactive oxygen species; TCR = T cell receptor; TGF-β = transforming growth factor β.

Microglial activation in early Alzheimer trajectory is associated with higher gray matter volume
Grazia Daniela Femminella, MD,
PhD, Melanie Dani, MD, Melanie Wood, MD, Zhen Fan, MSc, Valeria Calsolaro, MD, Rebecca Atkinson, MSc, Tru di Edginton, PhD, Rainer Hinz, PhD https://orcid.org/0000-0002-7808-9207, David J. Brooks, MD, FMedSci, and Paul Edison, MD, PhD, FRCPAuthors Info & Affiliations
March 19, 2019 issue
92 (12) e1331-e1343
https://doi.org/10.1212/WNL.0000000000007

Pathology of Alzheimer's Dementia



Braak staging of neurofibrillary tangles. Stages 1 through 4 are largely restricted to the mesial temporal lobe, whereas stages 5 and 6 are widespread in the neocortex.Reprinted with permission from Braak H, et al, Acta Neuropathol.[14] © 2006 Springer-Verlag.

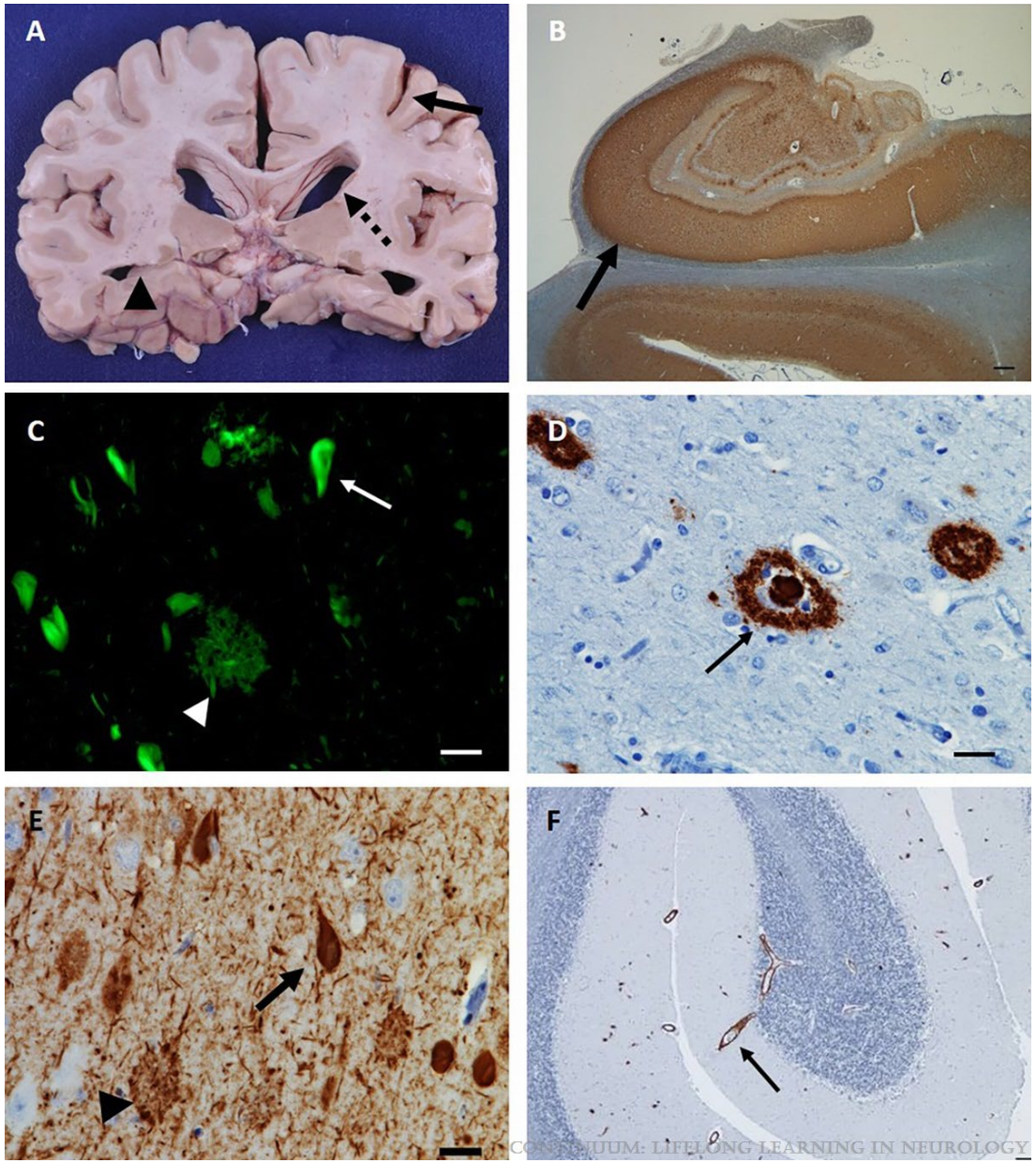
Neuropathology of Dementia Disorders

Schneider, Julie A.

CONTINUUM: Lifelong Learning in Neurology28(3):834-851, June 2022.

doi: 10.1212/CON.0000000000001137

Alzheimer's Disease Pathology



A. Gross neuropathologic features of AD include cortical atrophy (arrow), ventricular enlargement (dashed arrow) and hippocampal atrophy (arrowhead).

B. Low-power photomicrograph (1x) of hippocampus stained demonstrating an abundance of p-tau deposition, most prominent in CA1 (arrow).

C, Thioflavin S staining identifies senile amyloid plaques (arrowhead) and tau neurofibrillary tangles (arrow), the pathologic hallmarks of AD.

D. High-power photomicrographs (40x) of senile plaques (arrow)

E. High-power photomicrograph (40x) of neurofibrillary tangles (arrow) and dystrophic neurites (arrowhead).

F. Low-power photomicrograph reveals amyloid deposition in blood vessel walls (arrow), the pathologic hallmark of cerebral amyloid angiopathy.

Late-onset Alzheimer Disease Rabinovici, Gil D.CONTINUUM: Lifelong Learning in Neurology25(1):14-33, February 2019.

Target Therapy: Blocking Tau Phosphorylation

- A major component of neurofibrillary tangles are paired helical filaments made from hyperphosphorylated tau and neurofilaments from the cytoskeleton of nerve cells.
- Inhibiting hyperphosphorylation of tau can slow the development of neurofibrillary tangles
- Memantine, a medication FDA approved for moderate to severe Alzheimer's, is a medication that works in part by attenuating the hyperphosphorylation of tau.
- Memantine has other important pathways to neuron cell death through its antagonist blockade glutamatergic NMDA receptor on nerves which we will go over later.

Fluid Biomarkers: Phosphorylated Tau (P-tau)

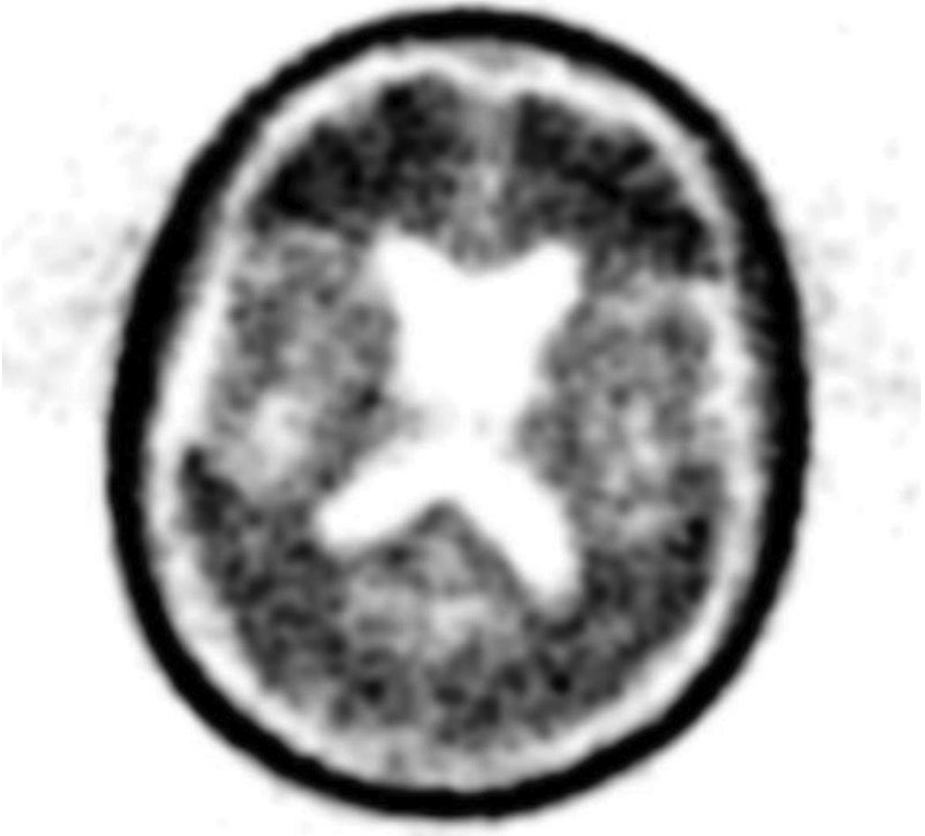
- P-tau refers to (hyper)phosphorylated tau protein variants including p-tau 217, 181, and 231) which are produced in Alzheimer's after amyloid β deposition
  - These hyperphosphorylated tau proteins are not able to do their job of maintaining the cytoskeleton of the neuron leading to cell breakdown.
  - Other neurodegenerative diseases have increased tau protein levels, but this P-tau form is found in Alzheimer's and not in other tau-opathies.
- In autopsy and biopsy studies there is a correlation between CSF P-tau and AD-type neurodegeneration
- Studies of blood P-tau levels are highly correlated with amyloid PET results.

Fluid Biomarkers: Amyloid β (Aβ)

- Peptides Aβ42 and Aβ40 can be measured in CSF and plasma using multiple different assays.
- The recommended use of these peptide measurements is the Aβ42 / Aβ40 ratio
  - Plasma Aβ42 assays have weaker correlation to Aβ42 measured in CSF
  - The differences in the raw quantities of the peptides in plasma in AD patients compared to controls was smaller
  - The Aβ42 / Aβ40 ratio has been shown to better correlate to CSF measures and to amyloid burden on amyloid PET scans
- CSF Aβ42 / Aβ40 ratio is considered one of the Core 1 diagnostic test based on its correlation with amyloid burden found on amyloid PET and brain tissue pathology studies
- CSF Aβ42 / Aβ40 may also be more sensitive at picking up early Alzheimer's in patients who clinically are just in mild cognitive impairment

Amyloid PET

- This diagnostic tool uses compounds based on thioflavin T, a stain for amyloid on pathology slides, are used to detect amyloid β in the brain
  - ^{18}F-florbetapir (Amyvid)
  - ^{18}F-flutemetamol (Vizamyl)
  - ^{18}F-flutafuranol (NAV4684)
- These compounds have a high affinity for Amyloid β in the brain
- 96% sensitivity and 100% specificity
- High percentage agreement of interpretation among
- This procedure is diagnostic and is a Core 1 recommended test for Alzheimer's diagnostics
- Limited availability
- Insurances coverage for this new procedure has been difficult to obtain.



Amyloid positron emission tomography (PET) shows reduced gray-white matter differentiation of the bilateral frontal, parietal, and posterior-lateral temporal areas on florbetapir PET scan suggestive of moderate to severe amyloid-β neuritic plaques. Dark (black) regions in frontal and parietal cortices indicate retention of florbetapir tracer to amyloid plaques.

Alzheimer Disease. McDade, Eric M. CONTINUUM: Lifelong Learning in Neurology28(3):648-675, June 2022.

Amyloid PET

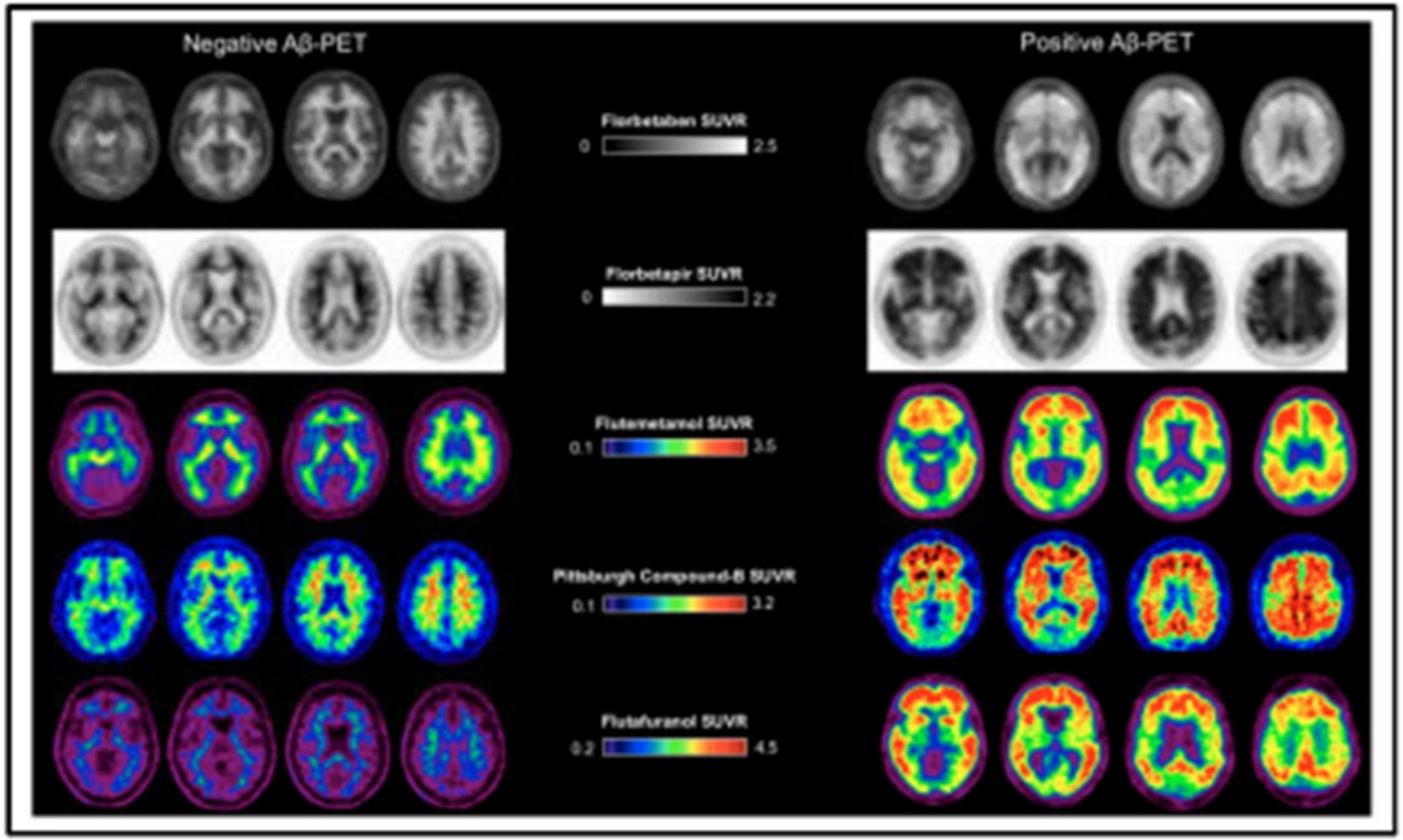


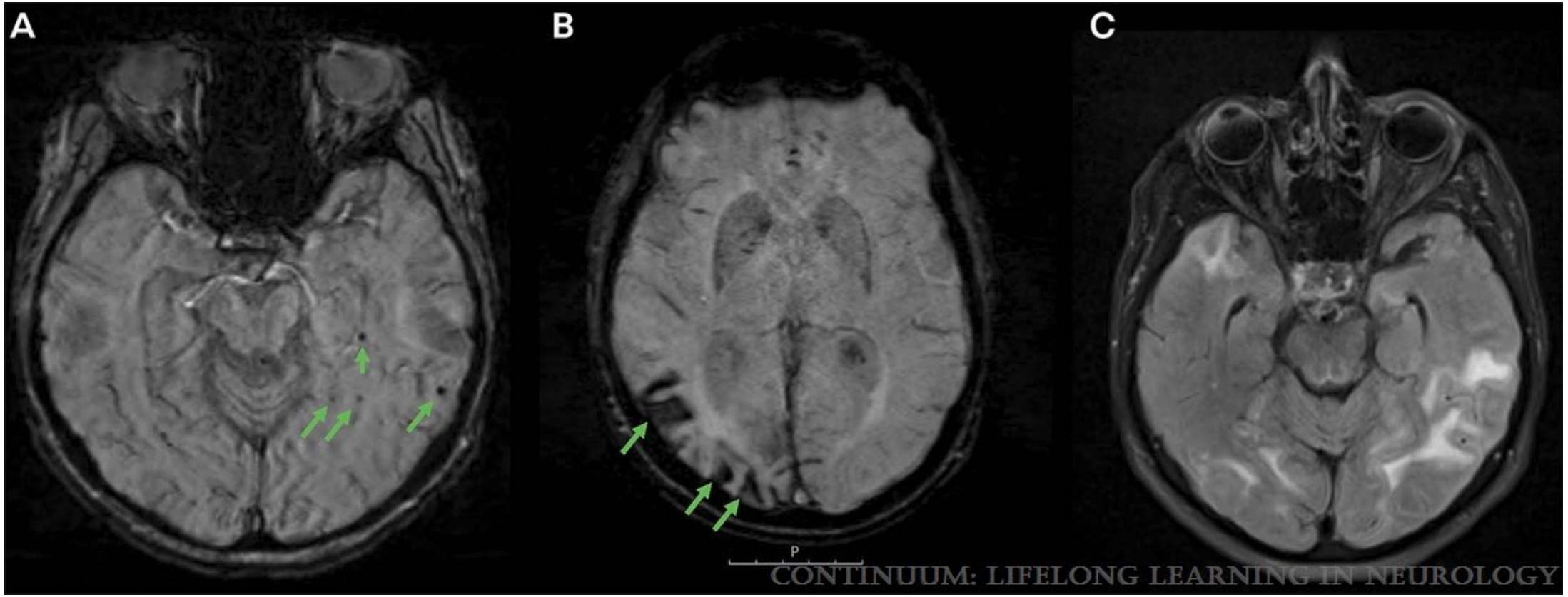
FIGURE 3. Examples of negative and positive Aβ PET findings using different tracers. (^{18}F-flutafuranol images are courtesy of Victor Villemagne and Christopher C. Rowe.)

Image from Chapleau and others, THE JOURNAL OF NUCLEAR MEDICINE Vol. 63 No. 6 (Suppl. 1) June 2022

Amyloid As a Therapeutic Target

- Later we will review new monoclonal antibody therapies that target the removal of Amyloid β.
  - Aducanemab
  - Lecanemab
  - Donanemab
- These therapies carry with them a risk of a potentially severe adverse reaction labeled ARIA (Amyloid-Related Imaging Abnormalities)
  - ARIA-E: vasogenic edema
  - ARIA-H: cerebral hemorrhage.
- As a result of these potential side effects, it is required that the Alzheimer's diagnosis be confirmed with CSF biomarkers or Amyloid PET imaging.

ARIA from anti-amyloid monoclonal antibody treatments



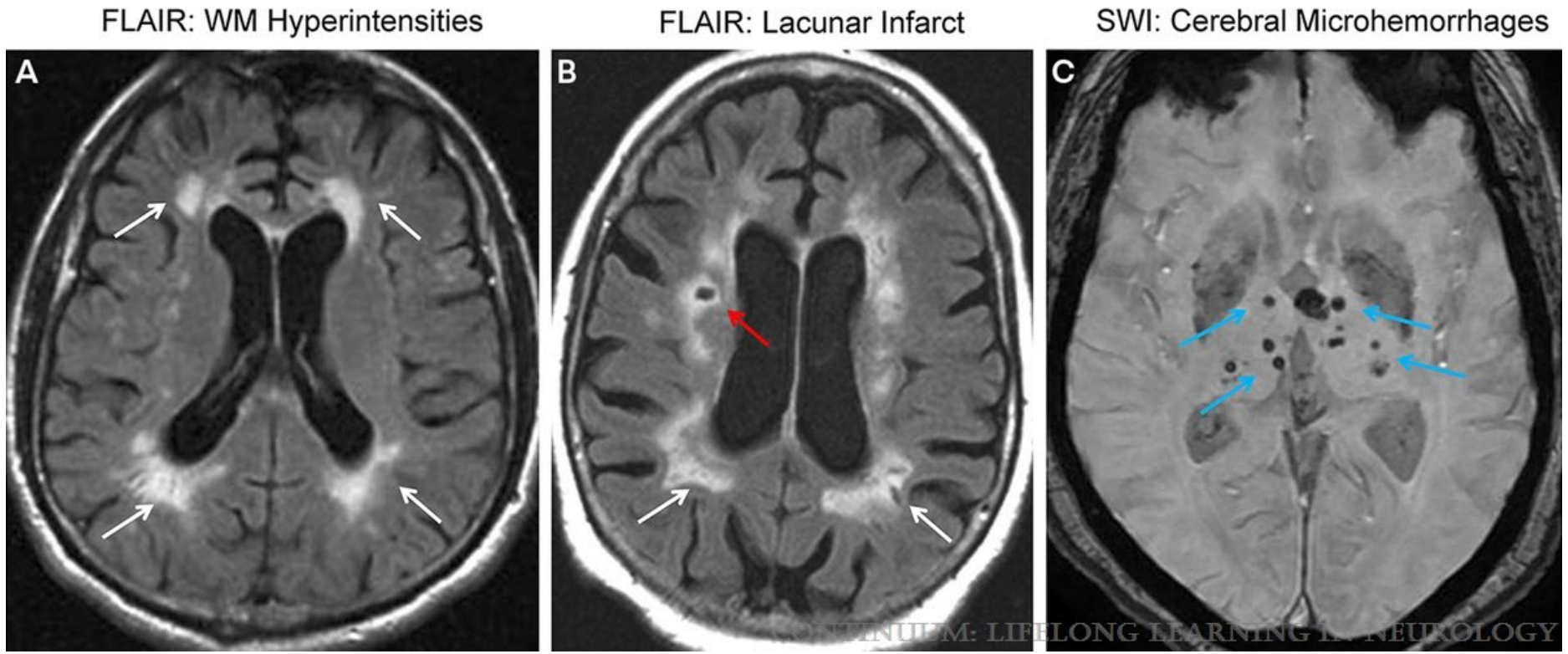
Examples of amyloid-related imaging abnormalities (ARIA). A, Axial susceptibility-weighted imaging (SWI) shows ARIA-H with cerebral microhemorrhages (arrows); B, Axial SWI shows the superficial siderosis that can be seen in ARIA-H and indicates hemosiderin staining on the pial surface of the brain (arrows); C, Axial imaging fluid-attenuated inversion recovery (FLAIR) image shows ARIA-E with multiple areas of edema.

The Value of Neuroimaging in Dementia Diagnosis Raji, Cyrus A.; Benzinger, Tammie L. S.CONTINUUM: Lifelong Learning in Neurology28(3):800-821, June 2022.

Neuroimaging in Dementia

- More traditional imaging for a dementia workup has included: CT head, MRI brain, and FDG-PET
- CT head and MRI brain are primarily used to determine if there is an anatomical cause for a person's memory loss
  - Stroke
  - Small vessel vascular disease
  - Cerebral hemorrhages
  - Tumors of the brain
  - Infections of the brain
- MRI brain offers greater resolution than CT and therefore is the preferred modality between the two.
- FDG –PET is primarily used to assist with differentiating between Alzheimer's and Frontotemporal Dementia.

Neuroimaging in Dementia: MRI brain



Neuroimaging in Dementia; Risacher, Shannon L.; Apostolova, Liana G. CONTINUUM: Lifelong Learning in Neurology29(1):219-254, February 2023.
doi: 10.1212/CON.0000000000001248. Modified with permission from Razek A and Elsebaie N, Clin Imaging.

Common findings on MRI's of the brain of patient's being evaluated for memory loss.

A. Small vessel disease causing hyperintensities in the periventricular and subcortical WM regions
B. Old lacunar (small) strokes
C. Cerebral microhemorrhages, which rule out the use of anti-amyloid monoclonal antibody treatments

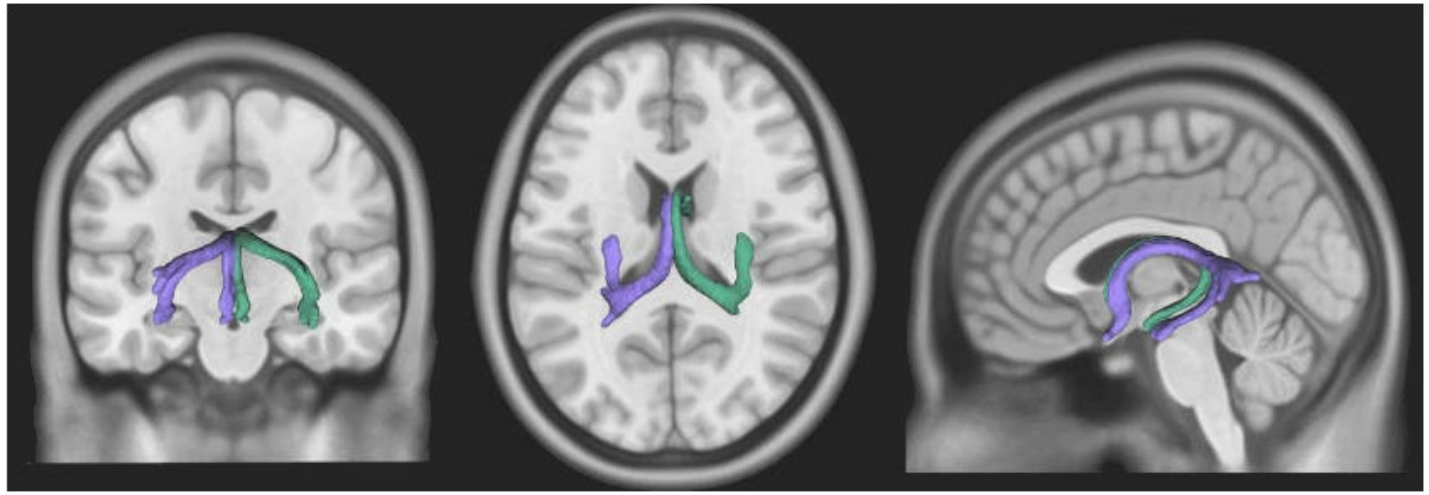


Fig. 1. Three-dimensional representation of the fornix of a healthy adult subject. Coronal (left), axial (center) and sagittal (right) views, overlapped on a T1-weighted magnetic resonance image. DSI studio software was used for visualization (dsi-studio.labsolver.org).

MRI Volumetric Measurement: Fornix

- One helpful feature of MRI as a diagnostic tool is the ability to accurately measure volumes of areas of the brain.
- Different dementias preferentially attack different areas of the brain
- In Alzheimer's, the fornix is a primary area of attack.

Fornix Degeneration in Alzheimer's

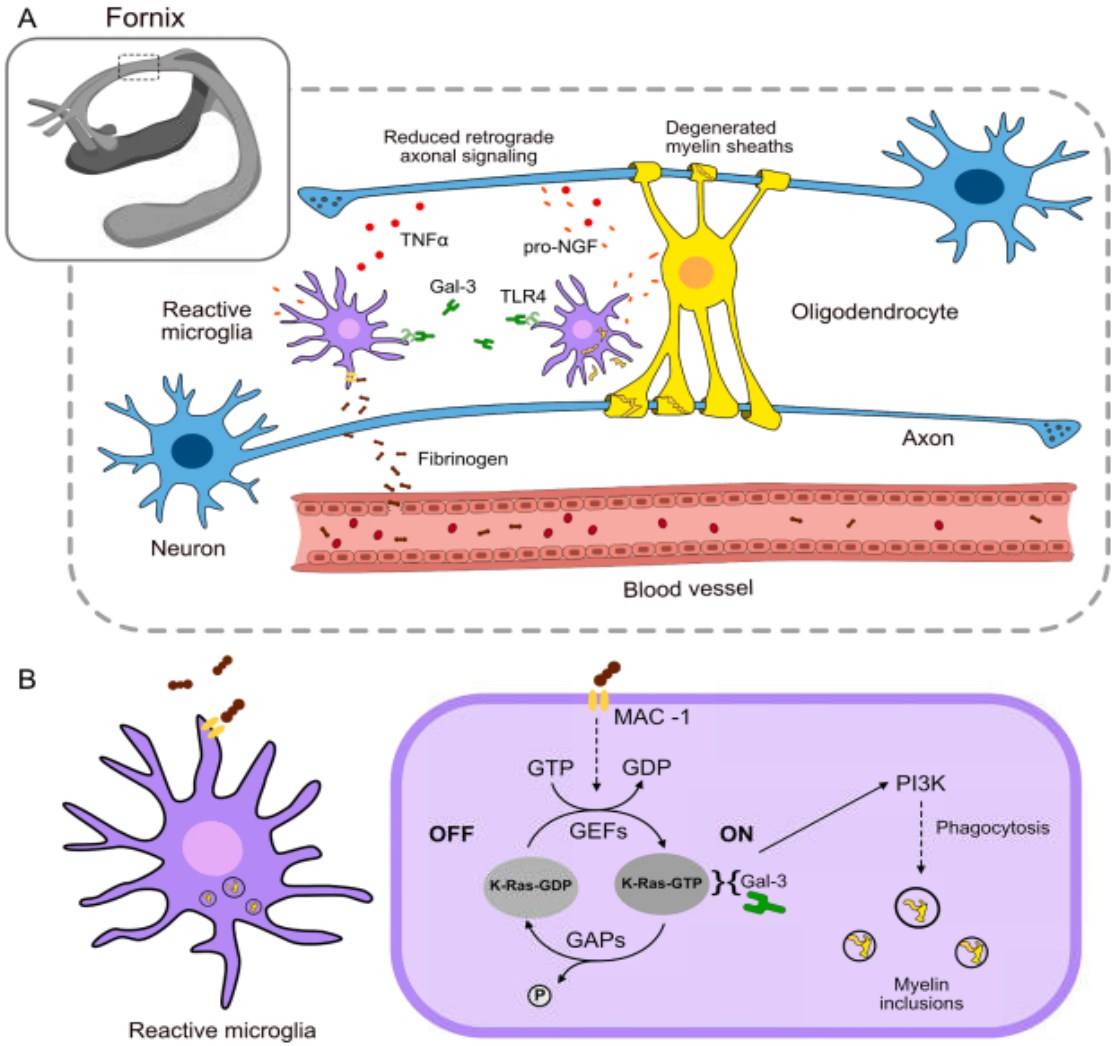


Fig. 2. Schematic representation of a hypothetical model of fornix degeneration due to risk factors of Alzheimer's disease. A) Blood-brain barrier permeability induces inflammation of the white matter. The readjustment of endothelial tight junctions in response to a compromised blood microcirculation facilitates the extravasation of fibrinogen, capable of activating microglia. Reactive microglia can maintain and extend inflammation by releasing Gal-3 acting through TLR4. Reactive microglia phagocyte degenerated myeline and releases pro-NGF and TNFα that may impact oligodendrocytes viability and reduce retrograde axonal transport, thus, neuronal survival. B) Phagocytic phenotype in microglia is sustained by Gal-3 expression. Fibrinogen promotes microglia activation through binding the MAC-1 surface receptor. Gal-3 acts as a molecular switch that up-regulates and prolongs PI3K activity maintaining a phagocytic phenotype in microglia. Gal-3; galectin-3, TLR4; toll-like receptor 4, TNFα; tumor necrosis factor alpha; I3K; phosphatidylinositol 3-kinase; NGF, nerve growth factor; GTP, guanosine triphosphate; GDP, guanosine diphosphate; GEFs, guanine nucleotide exchange factors; GAPs, GTPase-activating proteins.

Fornix degeneration in risk factors of Alzheimer's disease, possible trigger of cognitive decline.
María Lacalle-Aurioles, Yasser Iturria-Medina

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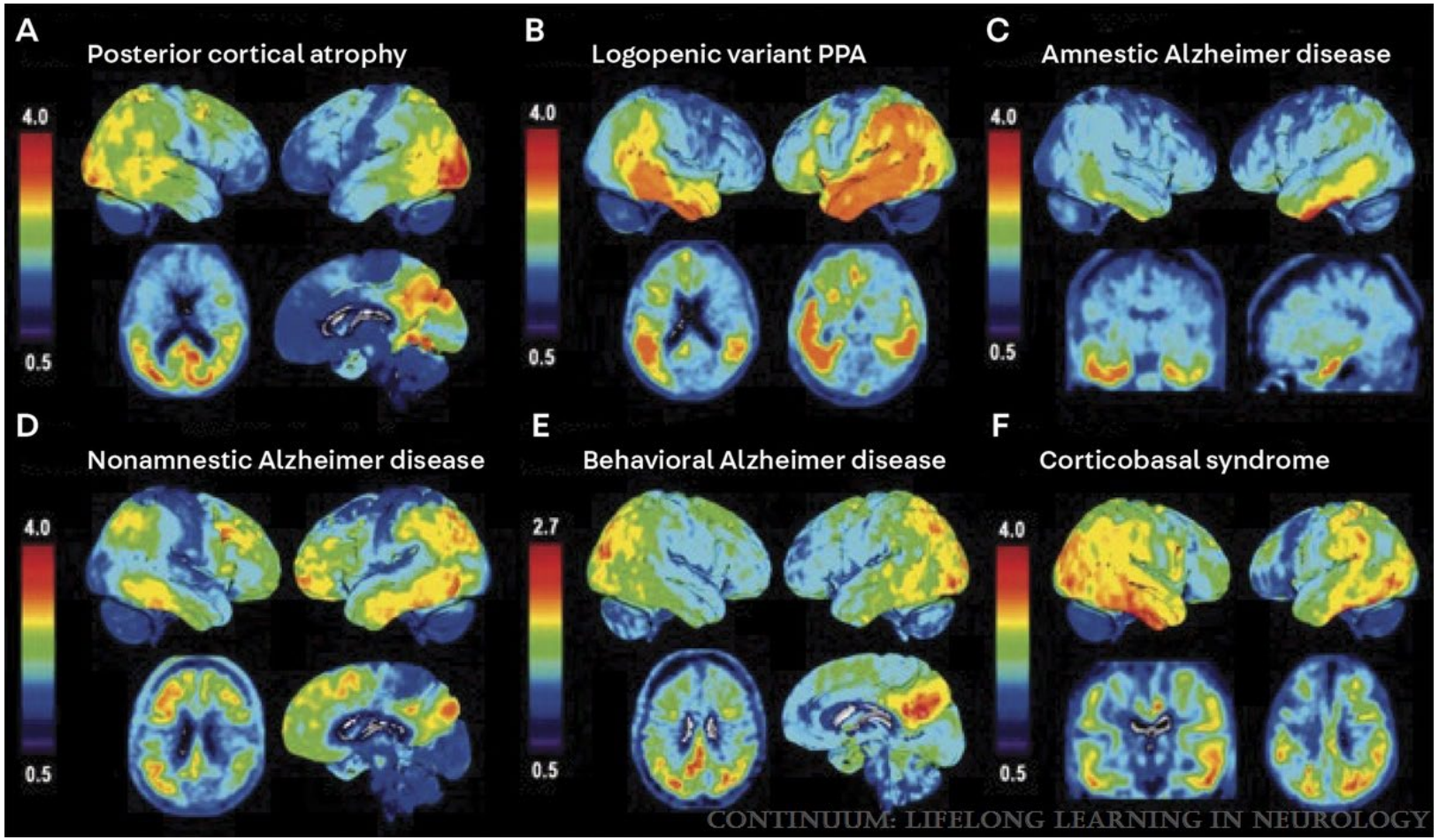
Anatomical Distribution of Alzheimer's Disease

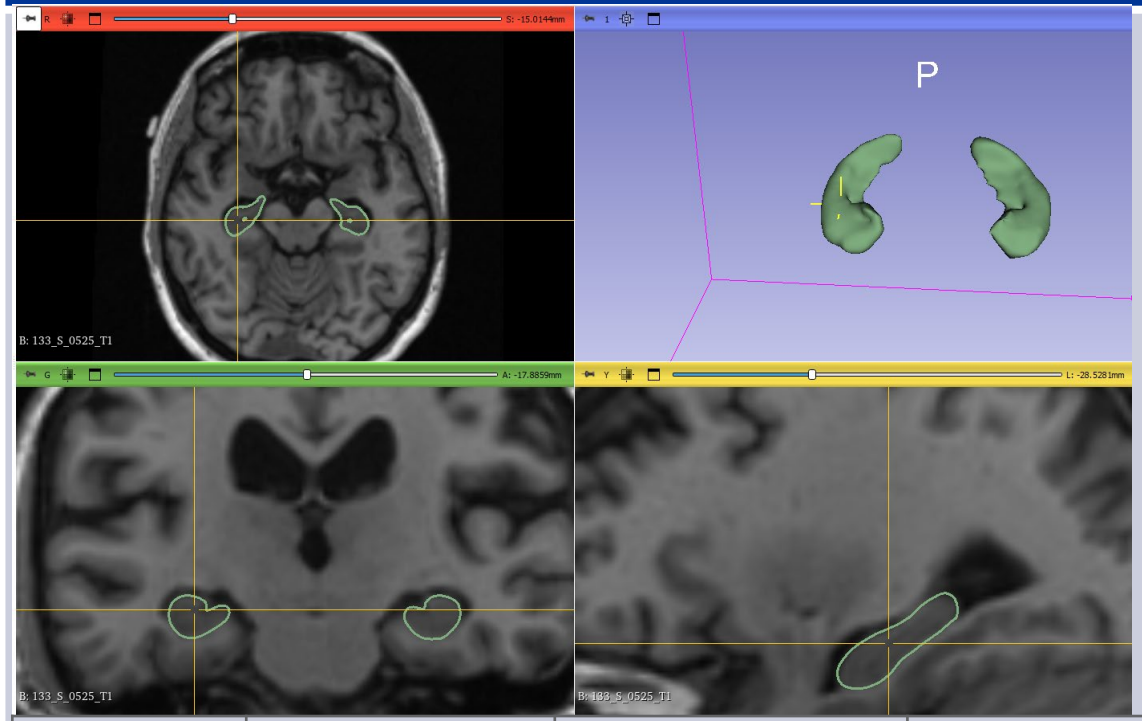


Regional tau positron emission tomography (PET) correlates with Alzheimer disease clinical phenotypes. Tau PET binding in Alzheimer disease highlights the differences in the pattern of neurofibrillary tau burden that reflects differences between amnestic and nonamnestic-predominant phenotypes. Color scale represents standardized uptake value ratio (SUVR), with yellow-red representing regions of higher retention of tau PET tracer.PPA = primary progressive aphasia.Reprinted with permission from Ossenkoppele R, et al, Brain.76 © 2016 Oxford University Press.

Alzheimer Disease_McDade, Eric M. CONTINUUM: Lifelong Learning in Neurology28(3):648-675, June 2022.

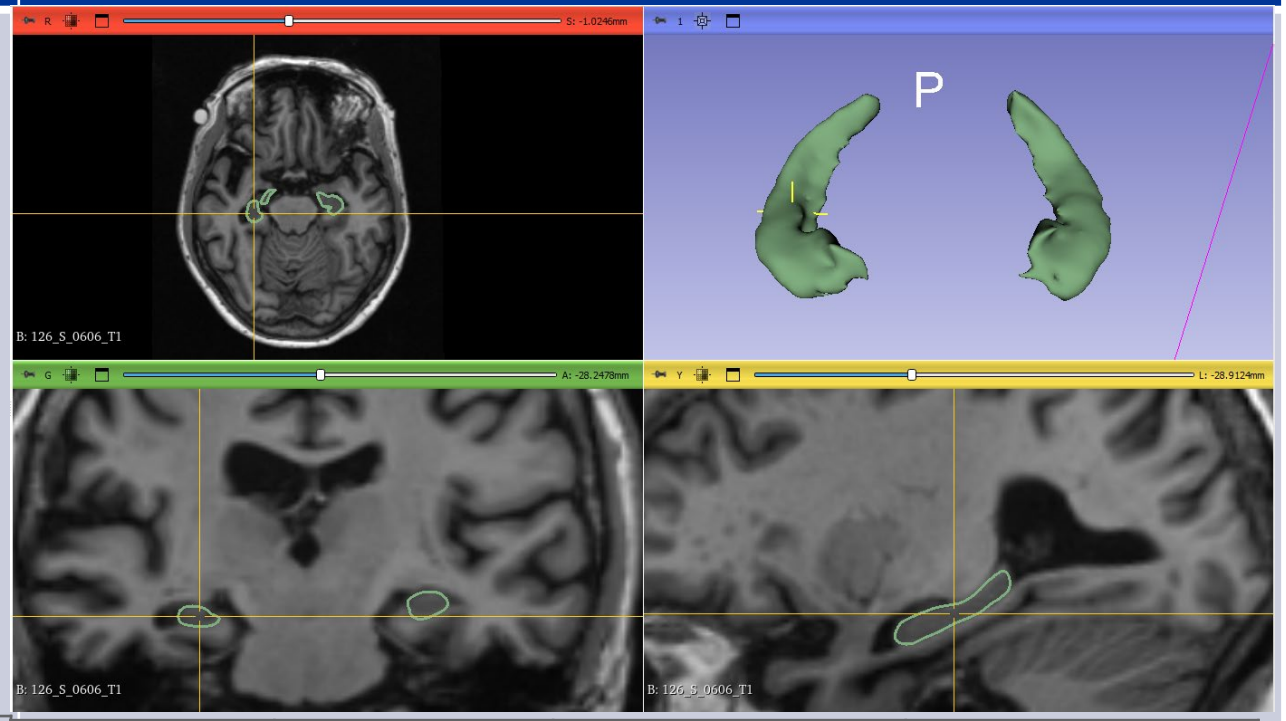
Hippocampal Volumetrics in two patients

Normal control (Female, 70 y.o.)



	Raw Volume [mm3]	Volume normalized by eTIV*	Normal lower limit (normalized by eTIV) (from a population 25-35 y.o)
Left hippocampus	2878	2132	1664
Right hippocampus	2966	2197	1927

Patient with AD (Female, 69 y.o.) Volumetrics reveals bilateral hippocampal atrophy



	Volume [mm3]	Volume normalized by eTIV*	Normal lower limit (normalized by eTIV) (from a population 25-35 y.o)
Left hippocampus	2139	**1584**	1664
Right hippocampus	1824	**1351**	1927

Slide 1: Manual segmentation and hippocampal volumetrics in two patients with similar age and estimated intracranial volume (ICV). Patient 1 is a control with normal hippocampal volumes, while Patient 2 has been diagnosed with Alzheimer's Disease (AD), exhibiting bilateral hippocampal atrophy. Volumes are normalized to ICV to account for differences in head size.

ADNI-Harmonized Protocol For Manual Hippocampal Segmentation

Tracer #	Scheltens 0		Scheltens 2		Scheltens 4	
	Local	Harmonized	Local	Harmonized	Local	Harmonized
6						
10						
13						
14						
16						
20						

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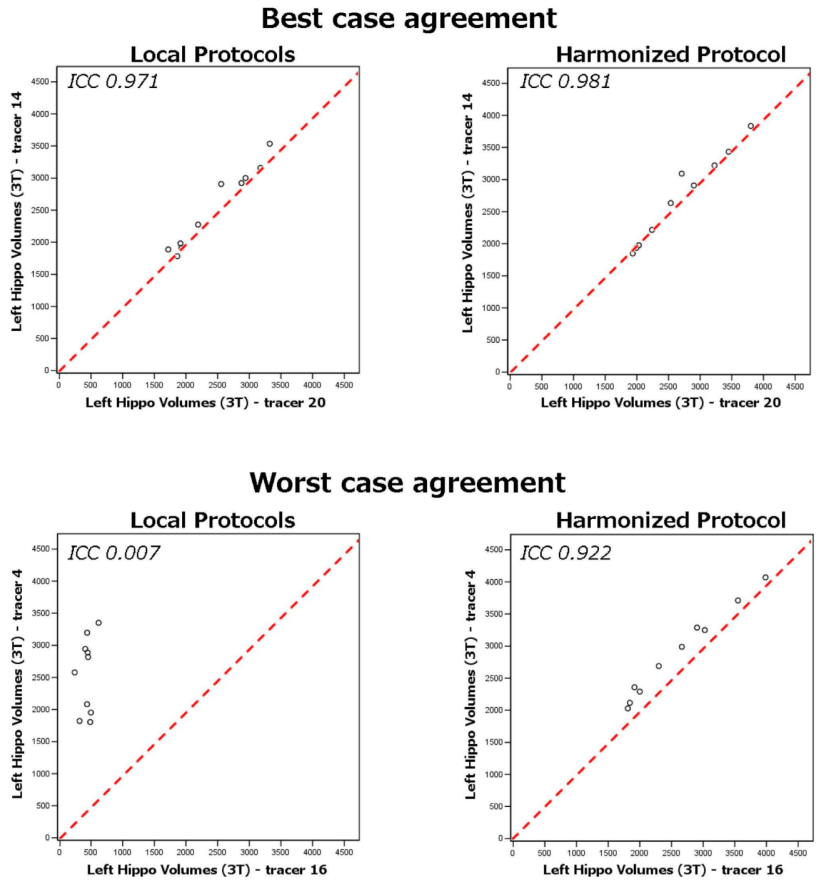

Validation of the ADNI-Harmonized protocol for manual hippocampal segmentation. This includes a 3D rendering of three hippocampi, representing varying degrees of atrophy (Scheltens score). The comparison shows the variability when expert tracers used their own local protocols versus the Harmonized protocol (HarP), with HarP greatly reducing this variability.

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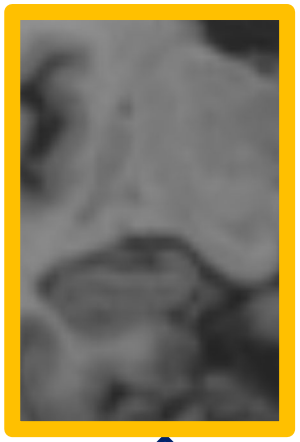
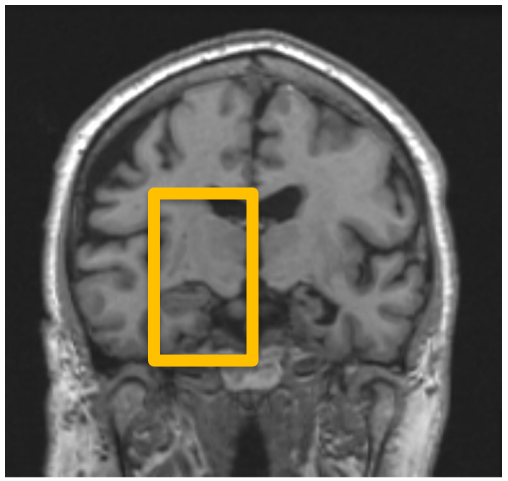
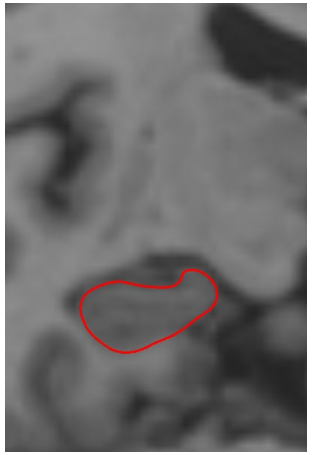
Hippocampal Volumetrics: AI

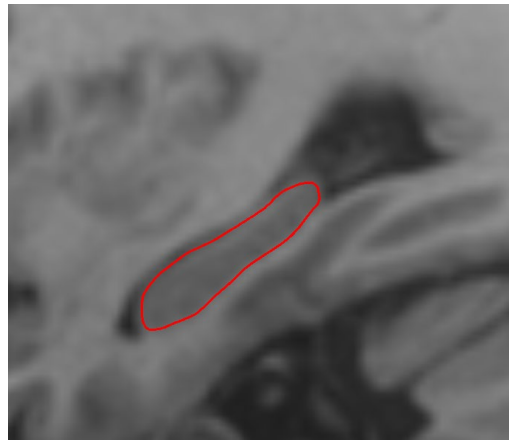


Attention step: Hippocampal ROI extraction



Neural network (Black box)



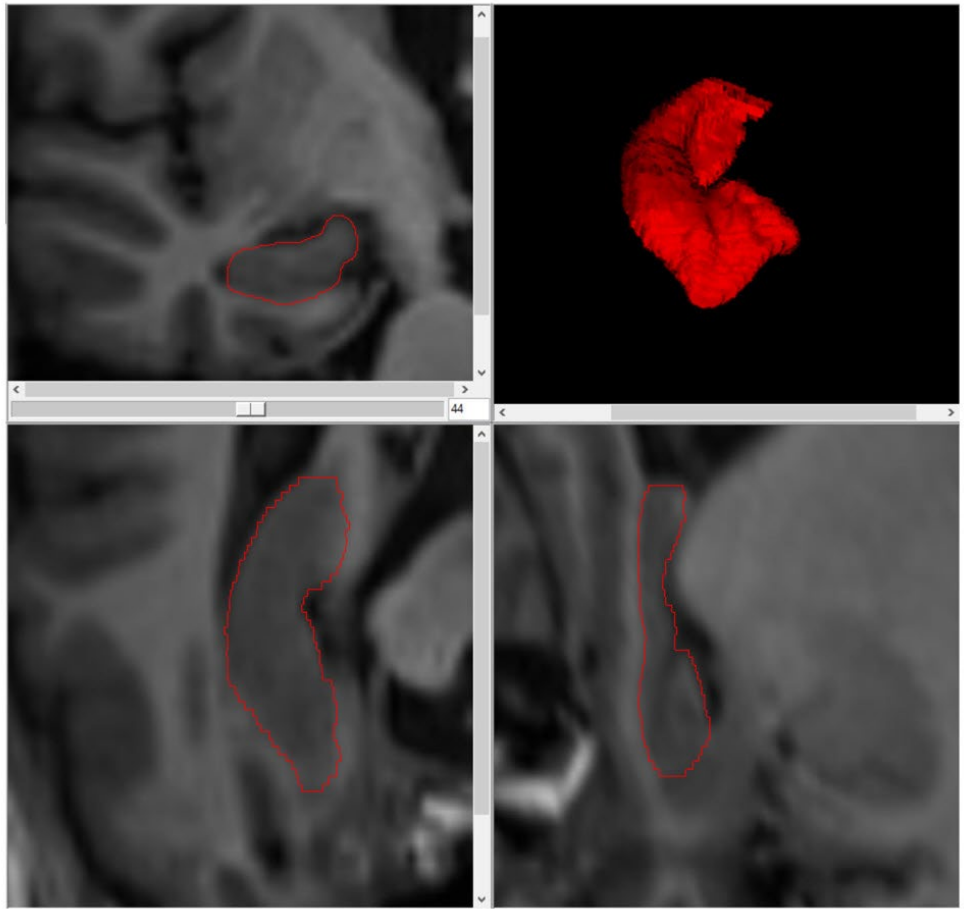


Cendejas-Zaragoza L, et al (2021). COVID-19 Volumetric Pulmonary Lesion Estimation on CT Images using a U-NET and Probabilistic Active Contour Segmentation. In: *2021 43rd Annual International Conference of the IEEE Engineering in Medicine Biology Society (EMBC)*. Nov:2021:3850-3853.

Hippocampal Volume Evolution

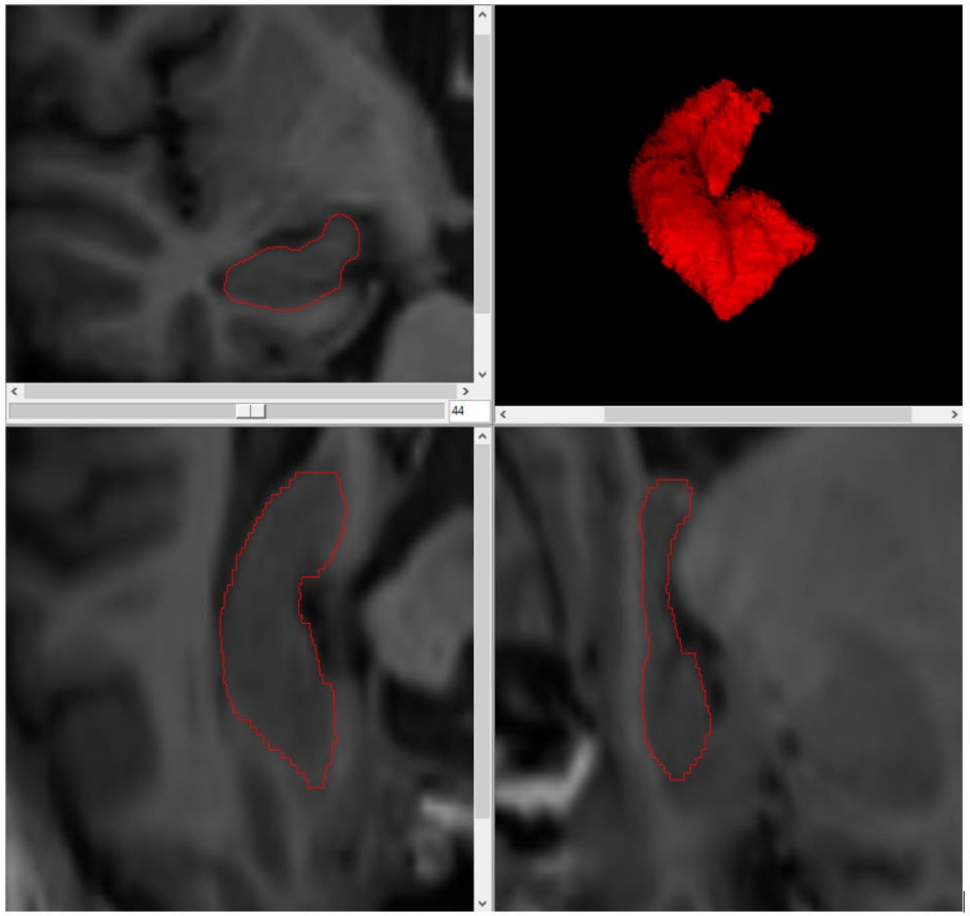
Right Hippocampus

Date of MRI: 12/11/2023



Right Hippocampus

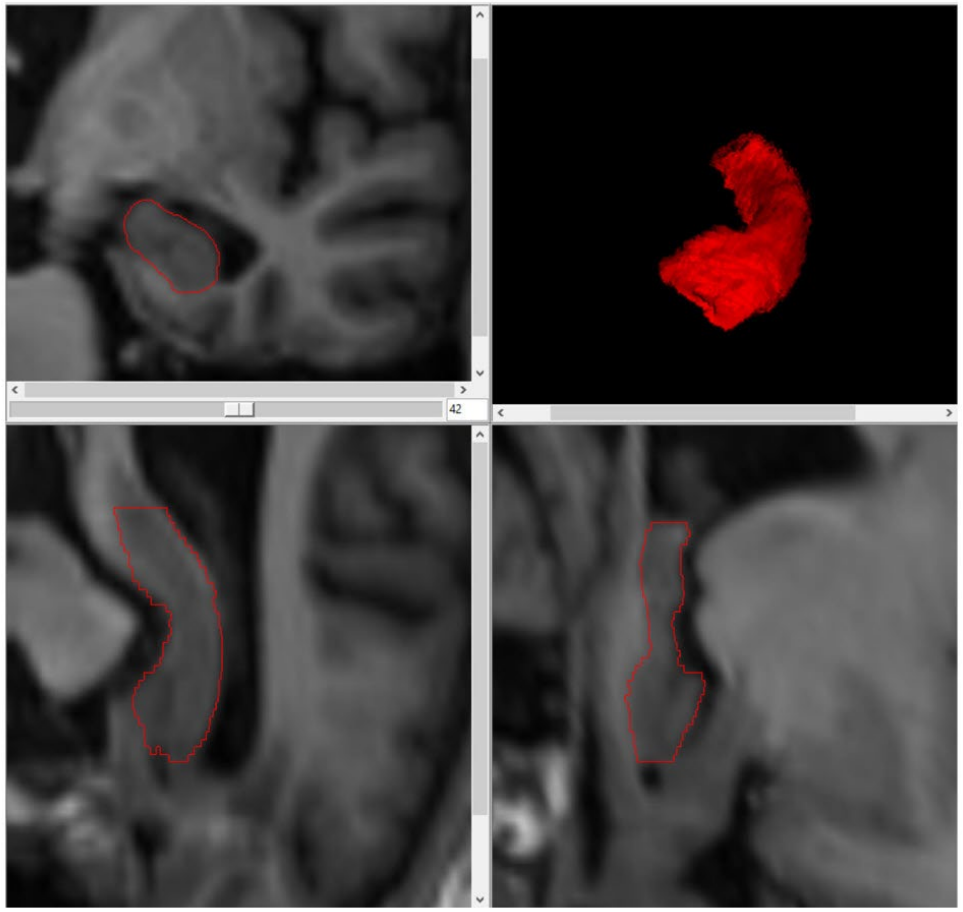
Date of MRI: 06/03/2024



Hippocampal Volume Evolution

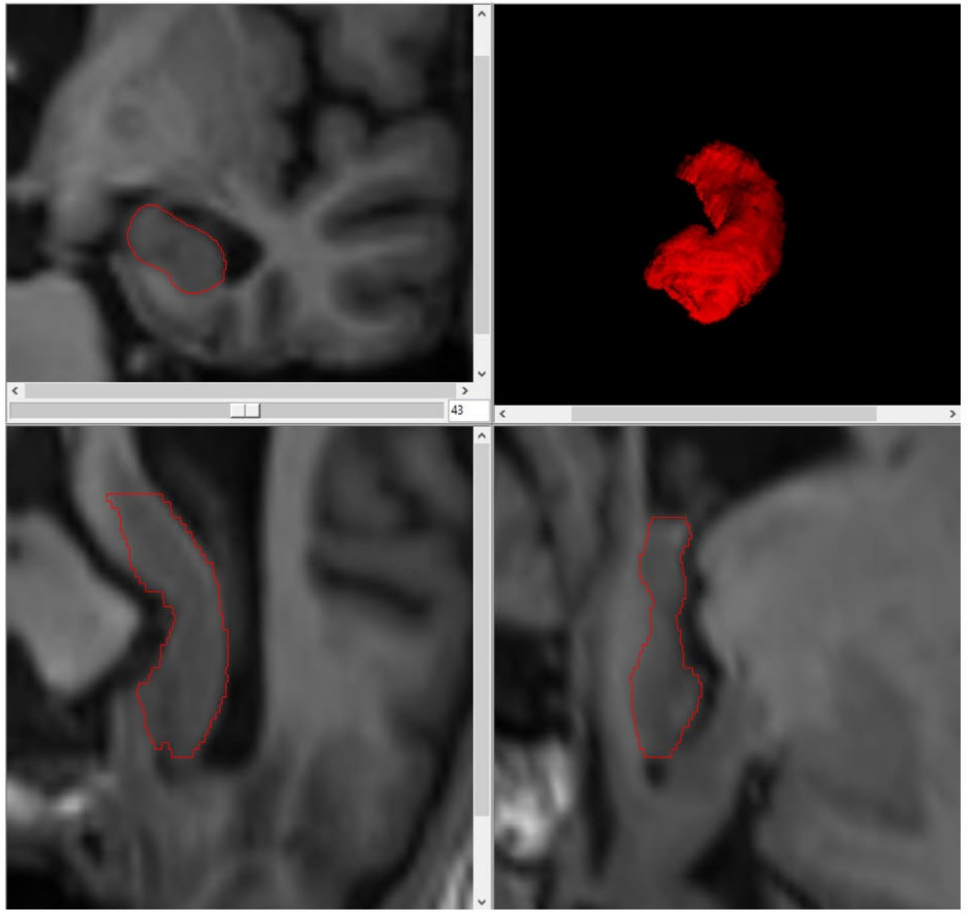
Left Hippocampus

Date of MRI: 12/11/2023



Left Hippocampus

Date of MRI: 06/03/2024



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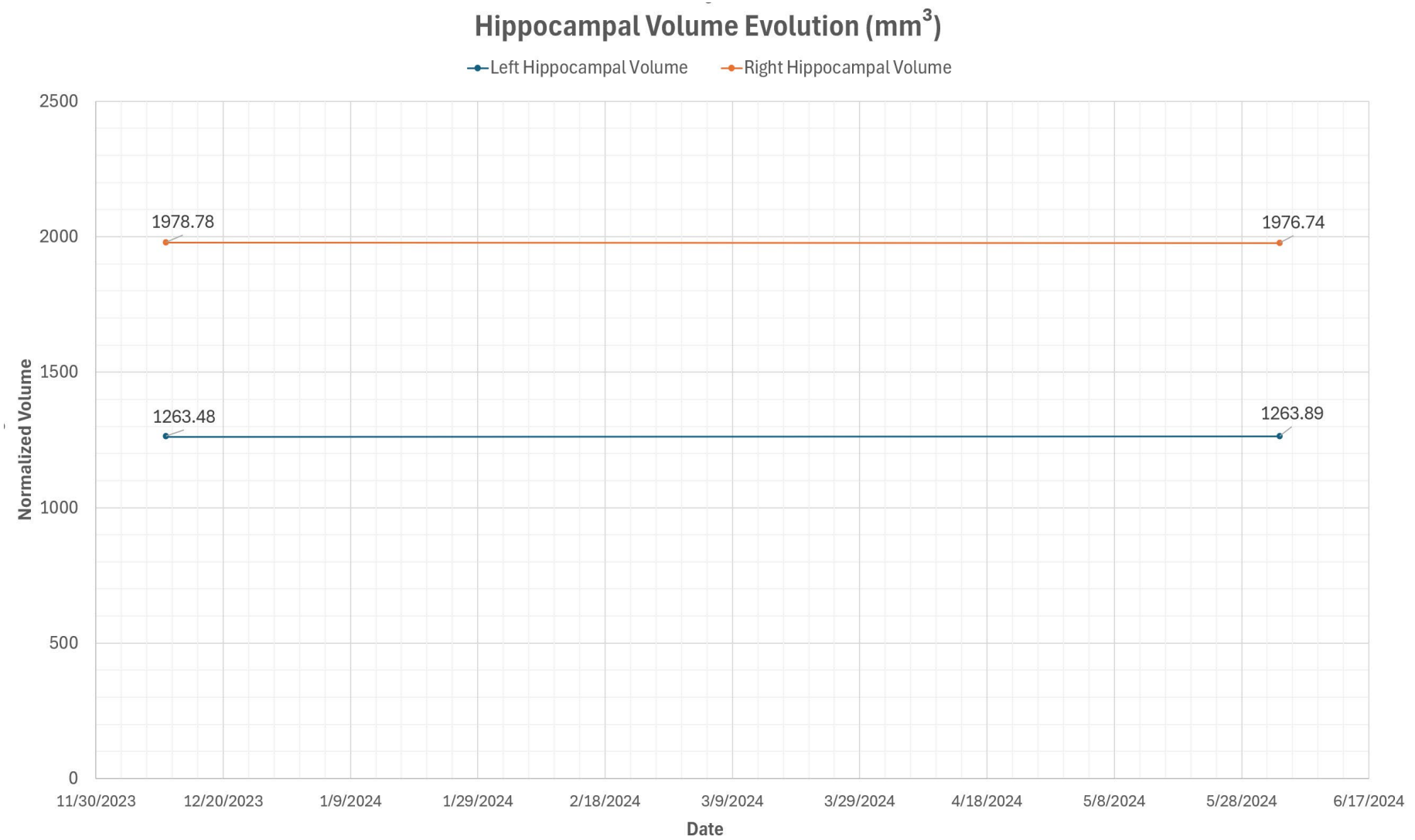

	MRI 12/11/2023	MRI 06/03/2024
Normalized RH Volume (mm^3)	1978.78	1976.74
Normalized LH Volume (mm^3)	1263.48	1263.89
Raw RH Volume (mm^3)	3016.76	3013.60
Raw LH Volume (mm^3)	1926.24	1925.84

Findings:

The hippocampal quantitative volumetric analysis consistent with unilateral left hippocampal atrophy. The right hippocampal volume is within normal limits.

No significant interval changes in right and left hippocampal volume since prior MRI of 12/11/2023.

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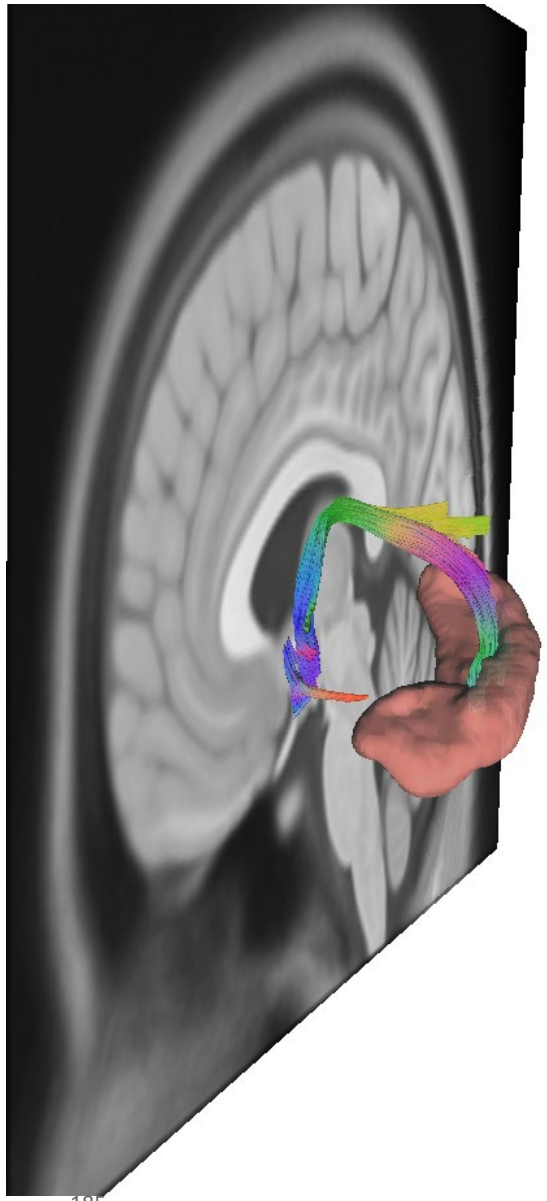
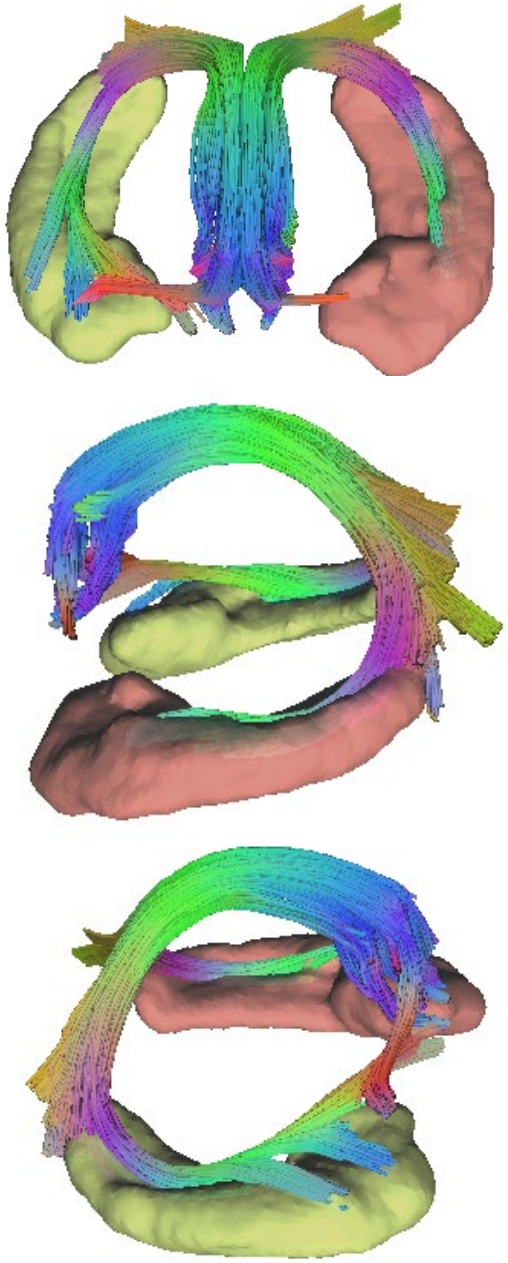
Normal average subject.
Hippocampus + Fornix





3D volume rendering of hippocampal formations alongside tractography of the fornix via diffusion sequences. The data presented is based on an average normal subject.

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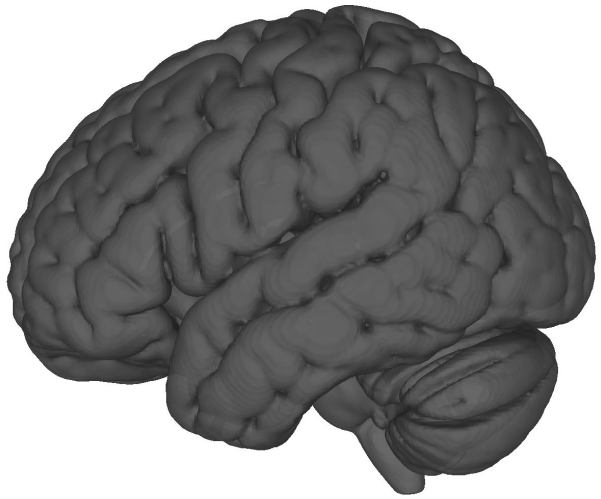
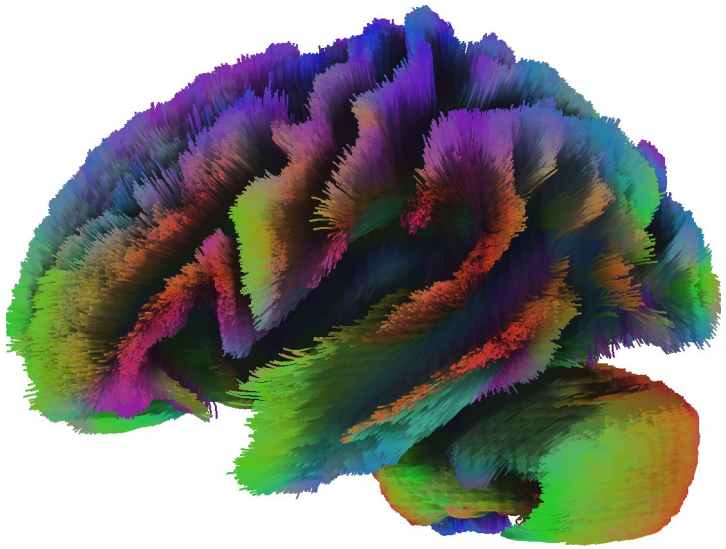
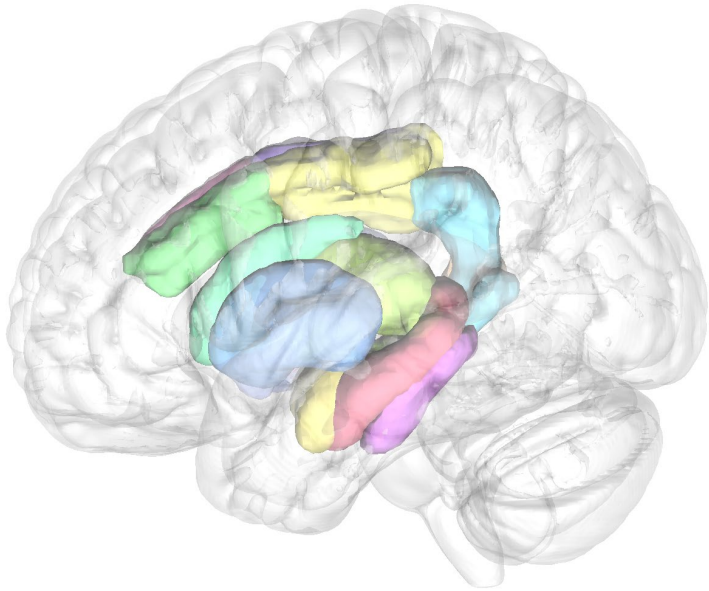
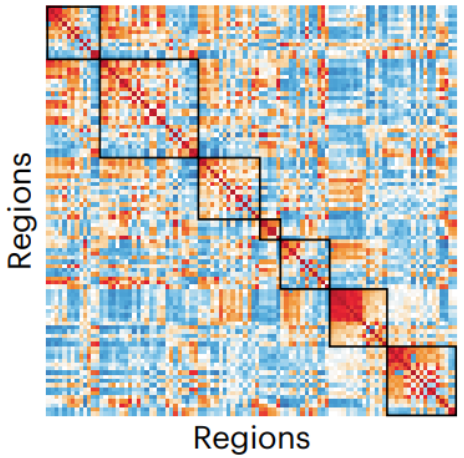
Quantifying the structural connections -> Creating a connectome







How many tracts are connected with each relevant structure?



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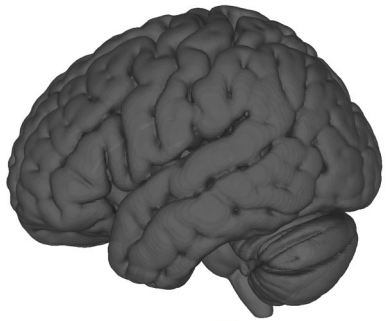
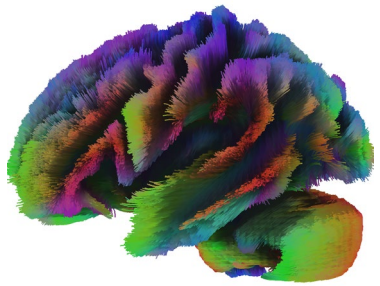
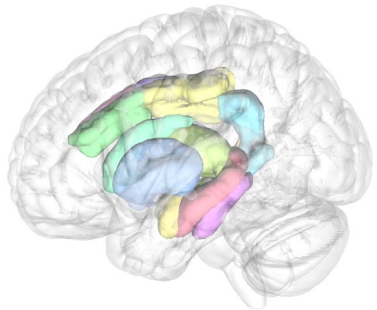
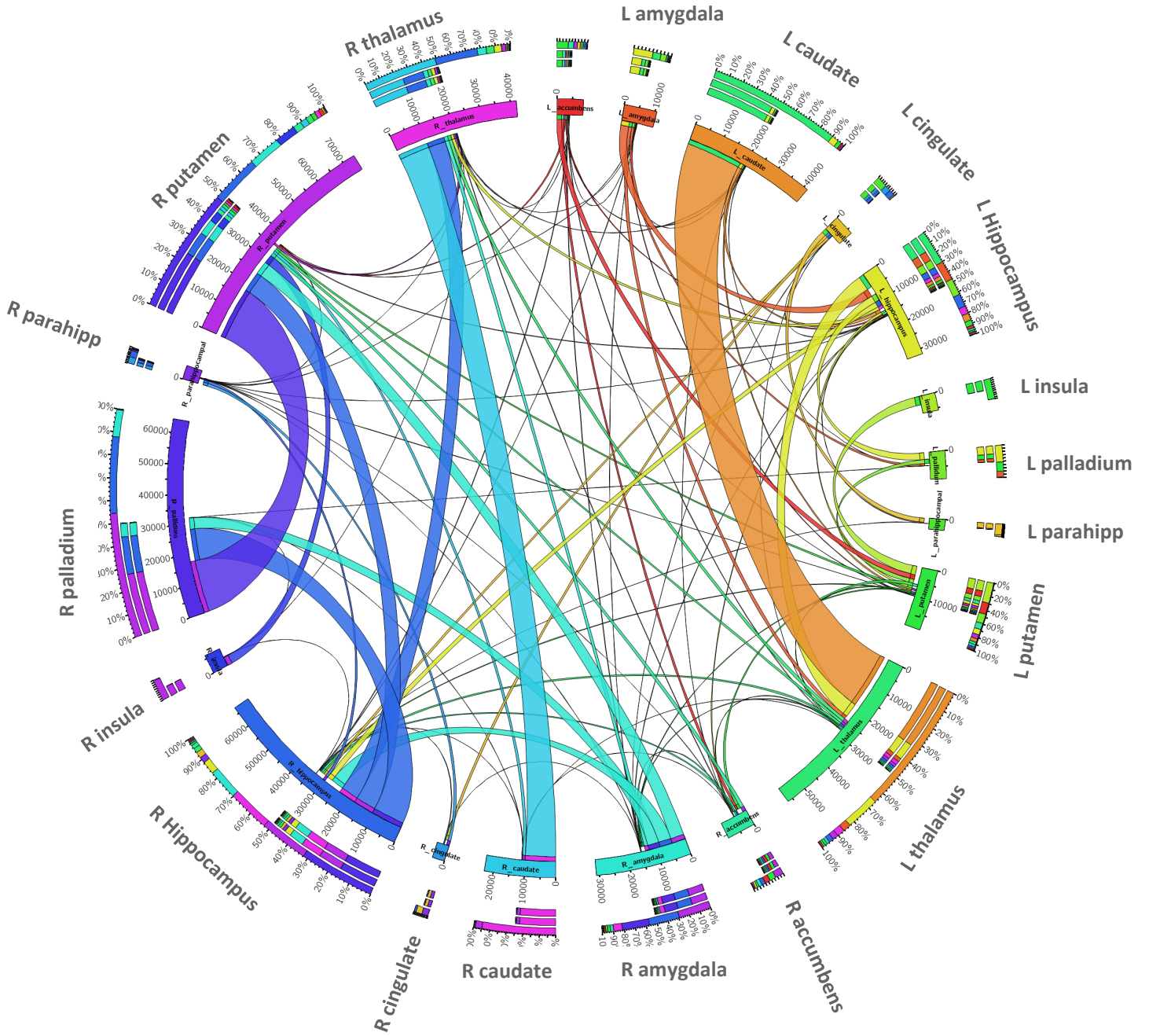
Quantifying the structural connections -> Creating a connectome









Robust WM connectivity between ipsilateral structures

Direct/Indirect connectivity between contralateral structures

Connectivity asymmetry between L and R structures

e.g. R/L hippocampus
R/L caudate

Summa Health

Cholinergic Tracts and Cholinergic Therapies

- Loss of acetylcholine producing neurons has long been noticed in Alzheimer's and other dementias
- Donepezil, Rivastigmine, and galantamine inhibit acetylcholinesterase and thereby increase the acetylcholine activity
- The increase in acetylcholine activity helps with short term memory and attention

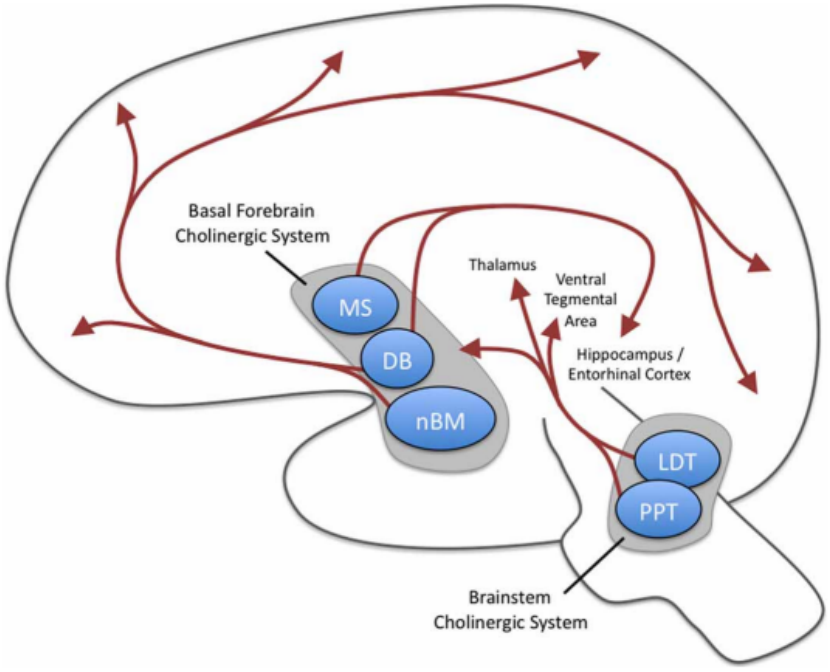
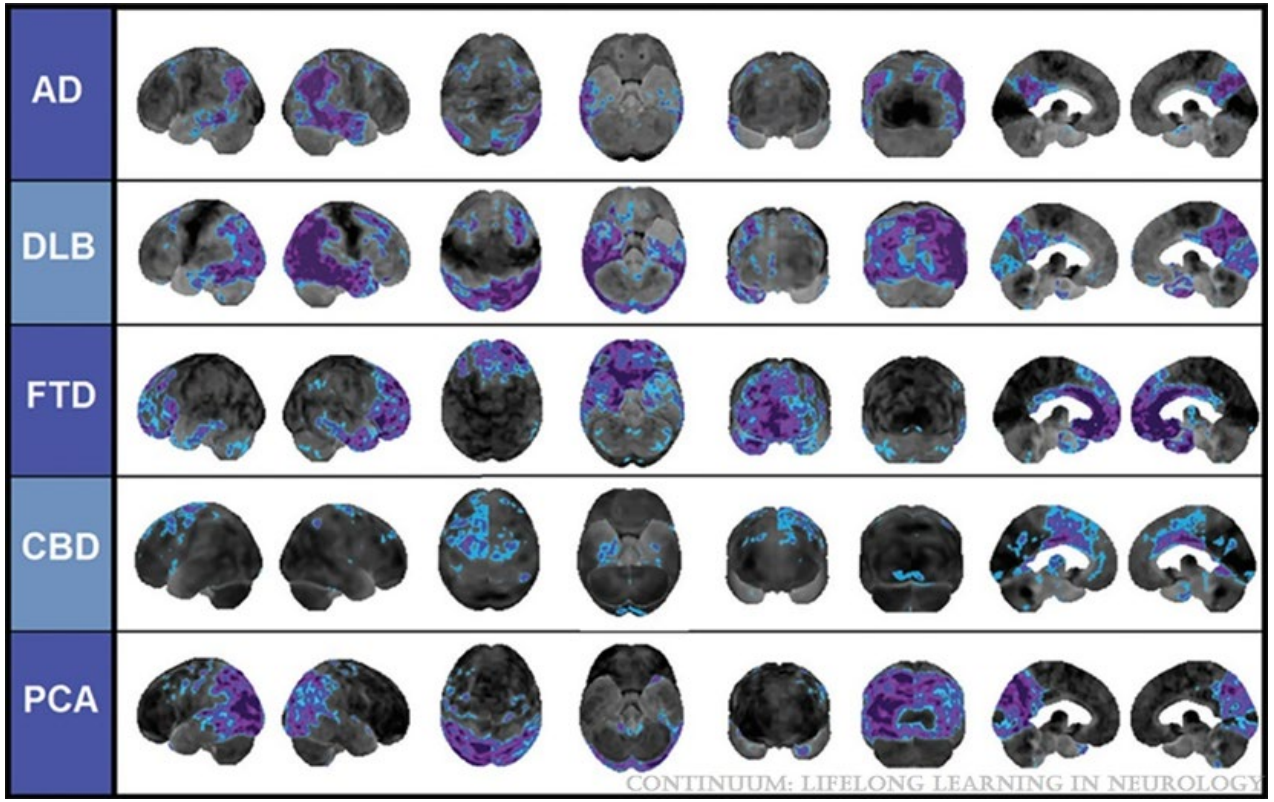


FIGURE 1 | Major cholinergic projections of the central nervous system. Two groups of projections exist: the magnocellular basal forebrain cholinergic system and the brainstem cholinergic system. The magnocellular basal forebrain cholinergic system includes the medial septal nucleus (MS), the vertical and horizontal limbs of the diagonal band of Broca (DB), and the nucleus basalis magnocellularis (nBM). The horizontal limb of the DB and nBM has extensive diffuse projections to neocortex as well as projections to basolateral amygdala and olfactory bulb (these latter two are not shown here). The MS and vertical limb of the DB project to hippocampus and entorhinal cortices. The brainstem cholinergic system includes the pedunculopontine tegmental nucleus (PPT) and laterodorsal pontine tegmentum (LDT) and projects predominantly to the thalamus but also to the basal forebrain region.

Frontiers in Behavioral Neuroscience **www.frontiersin.org** June 2012 | Volume 6 | Article 24 | **2**

FDG-PET



Differential patterns of hypometabolism on fludeoxyglucose positron emission tomography (FDG-PET) z score maps in neurodegenerative disease with temporal parietal hypometabolism in Alzheimer disease (AD), increased occipital hypometabolism in dementia with Lewy bodies (DLB), frontal dominant hypometabolism in frontotemporal dementia (FTD), asymmetry in corticobasal degeneration (CBD), and posterior dominant cortical hypometabolism in posterior cortical atrophy (PCA). The blue and purple colors denote areas of the FDG-PET scan that are lower than -2 standard deviations from the mean of the control comparison population.Reprinted with permission from Brown RKJ, et al, RadioGraphics.67 © 2014 Radiological Society of North America.

- Shows glucose hypo-metabolism in the brain
- Regions of the brain effected by dementias will have decreased glucose metabolism.
- It is primarily used for distinguishing Alzheimer's from frontal temporal dementia (FTD)
- 86% sensitivity and 97.6% specificity when distinguishing AD from FTD.
- Because there is overlap in regions effected by the different forms of dementia, FDG-PET's usefulness for diagnosis of dementia is limited.

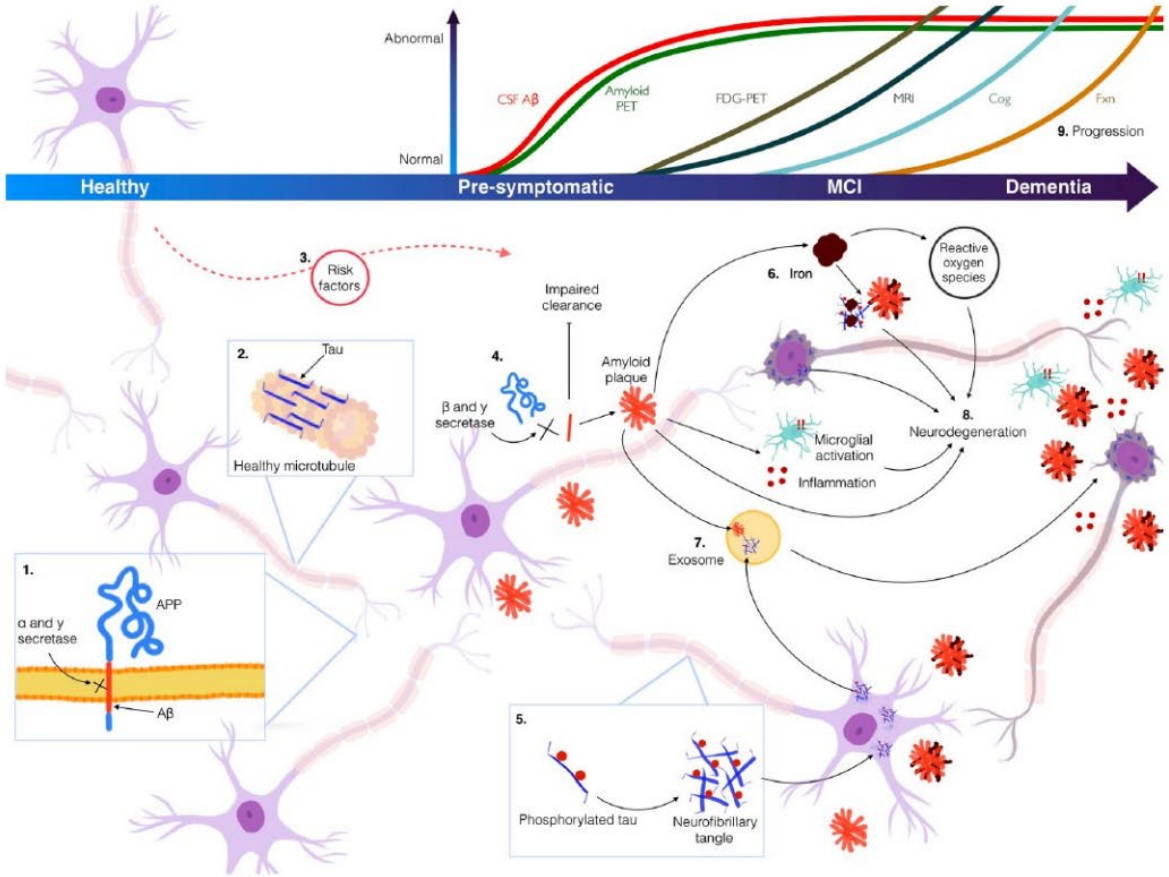
The Value of Neuroimaging in Dementia DiagnosisRaji, Cyrus A.; Benzinger, Tammie L. S.
CONTINUUM: Lifelong Learning in Neurology28(3):800-821, June 2022.

Advances in Dementia Therapeutics

Therapeutics Outline (Alzheimer Disease)

Therapeutics Outline (Alzheimer Disease)

Alzheimer's Disease Dementia: Proposed Pathophysiologic Model



Ertane D. Australas Psychiatry. 2018 Aug;26(4):347-357.
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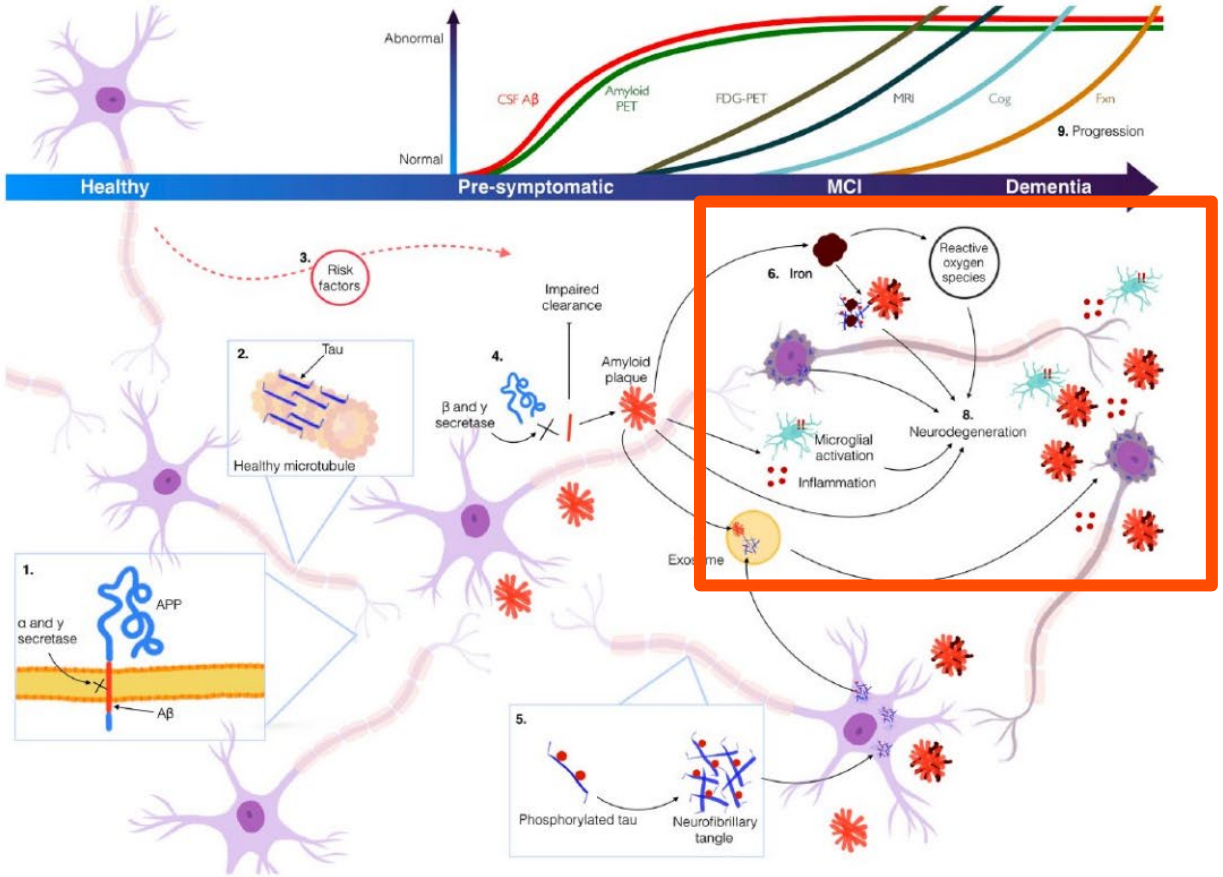

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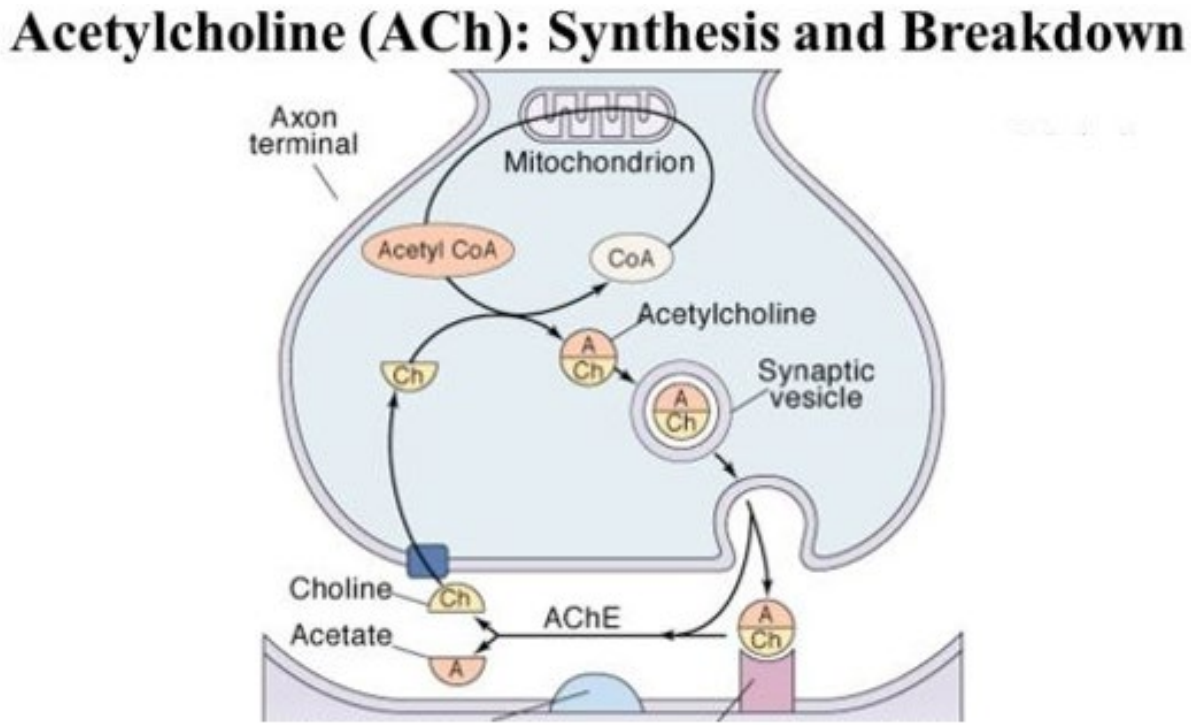
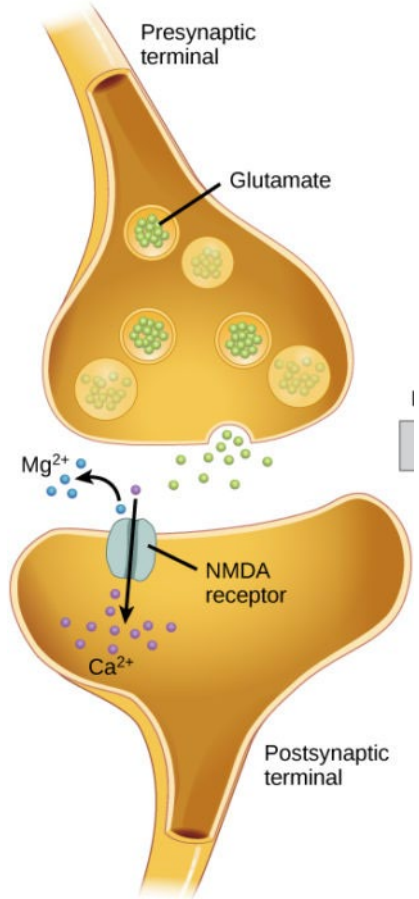
Long-Term Standard



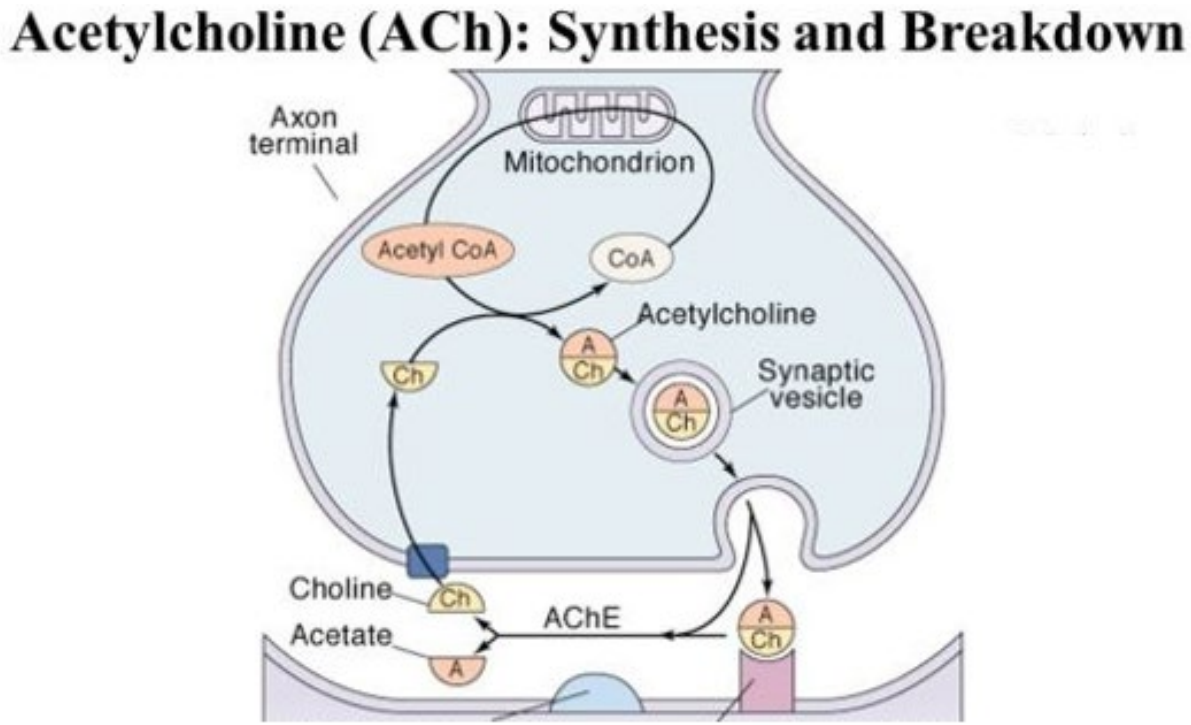


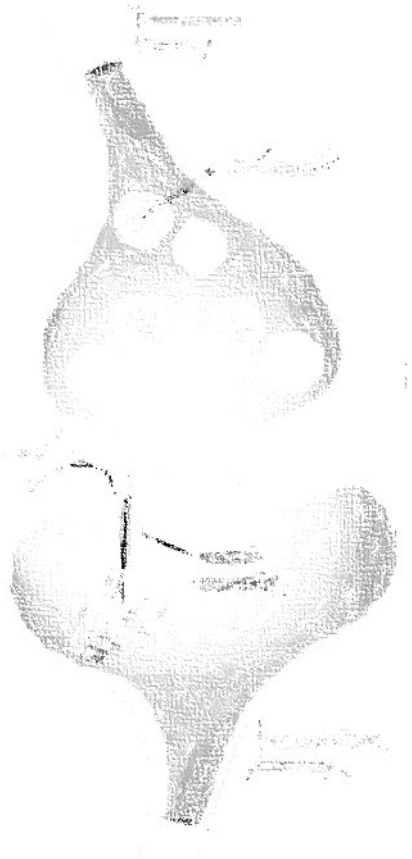
Mild-Severe Disease

Moderate-Severe Disease

Birks JS. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005593.
Joe E. BMJ. 2019 Dec 6;367:l6217.
Lexicomp Online [Internet].
Vyklicky V. Physiol Res. 2014;63(Suppl 1):S191-203.

Long-Term Standard





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AChEI Summary Table

	Donepezil	Rivastigmine	Galantamine
Mechanism	Reversible acetylcholinesterase inhibitor	Pseudo-irreversible acetylcholinesterase and butyrylcholinesterase inhibitor	Reversible acetylcholinesterase inhibitor and nicotinic receptor modulator
Dosage Forms	Tablet Oral disintegrating tablet **Transdermal once weekly patch**	Capsule Transdermal 24 hour patch	24 hour ER capsule Tablet Oral solution
Target Dose and Titration	5 mg PO daily increased to 10 mg PO daily after 4-6 weeks 5 mg/day using donepezil transdermal once weekly patch for 4-6 weeks, then dosage may be increased to 10 mg/day with once weekly patch	1.5 mg PO BID increased by 3 mg PO daily every two weeks to a maximum of 6 mg PO BID *or* 4.6 mg TD daily increased to 9.5 mg TD daily after ≥ four weeks, then increase to 13.3 mg TD daily after ≥ four weeks	4 mg PO BID for four weeks, then 8 mg PO BID for ≥ four weeks, then 12 mg PO BID (all total daily doses given once daily if using ER product)
Notes	23 mg/day dose unlikely to offer advantages with greater risk of several adverse effects Patch efficacy data based on relative bioavailability study Store patches between 2-8° C	Restart titration if therapy interrupted for > 3 days Administer capsules with food Fewer adverse effects with patch Oral formulation may have highest incidence of GI adverse effects	Restart titration if therapy interrupted for ≥ 3 days Administer with food Firm renal / hepatic adjustments
Monitoring	Dizziness (usually transient), syncope, bradycardia (pulse at baseline, monthly during titration, and semiannually thereafter), GI effects (usually transient), insomnia, vivid dreams, serious skin reactions (galantamine)		

Adlarity® (donepezil) transdermal system [package insert]. 2022 Mar.
Birks JS. Cochrane Database Syst Rev. 2015 Apr 10;(4):CD001191.
Birks JS. Cochrane Database Syst Rev. 2018 Jun 18;6(6):CD001190.
Joe E. BMJ. 2019 Dec 6;367:l6217.
Lexicomp Online [Internet].
Pharmacist's Letter. Alzheimer's Dementia Pharmacotherapy [Internet]. c2022.
Zimmerman KM. Pharmacotherapy: A Pathophysiologic Approach, 12e [Internet].

Summa Health

AChEI Summary Table

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Mechanism	Reversible acetylcholinesterase inhibitor	Pseudo-irreversible acetylcholinesterase and butyrylcholinesterase inhibitor	Reversible acetylcholinesterase inhibitor and nicotinic receptor modulator
Dosage Forms	Tablet Oral disintegrating tablet **Transdermal once weekly patch**	Capsule Transdermal 24 hour patch	24 hour ER capsule Tablet Oral solution
Target Dose and Ti	5 mg PO daily increased to 10 mg	1.5 mg PO BID increased by 3 mg PO	4 mg PO BID for four weeks, then 8
Notes	23 mg/day dose unlikely to offer advantages with greater risk of several adverse effects Patch efficacy data based on relative bioavailability study Store patches between 2-8° C	Restart titration if therapy interrupted for > 3 days Administer capsules with food Fewer adverse effects with patch Oral formulation may have highest incidence of GI adverse effects	Restart titration if therapy interrupted for ≥ 3 days Administer with food Firm renal / hepatic adjustments
Monitoring	Dizziness (usually transient), syncope, bradycardia (pulse at baseline, monthly during titration, and semiannually thereafter), GI effects (usually transient), insomnia, vivid dreams, serious skin reactions (galantamine)		

The American Geriatrics Society highlights discussing risks and benefits of these medications prior to initiation and **discontinuing ChEIs after approximately 12 weeks if desired effects are not perceived**

Adlarity® (donepezil) transdermal system [package insert]. 2022 Mar.
Birks JS. Cochrane Database Syst Rev. 2015 Apr 10;(4):CD001191.
Birks JS. Cochrane Database Syst Rev. 2018 Jun 18;6(6):CD001190.
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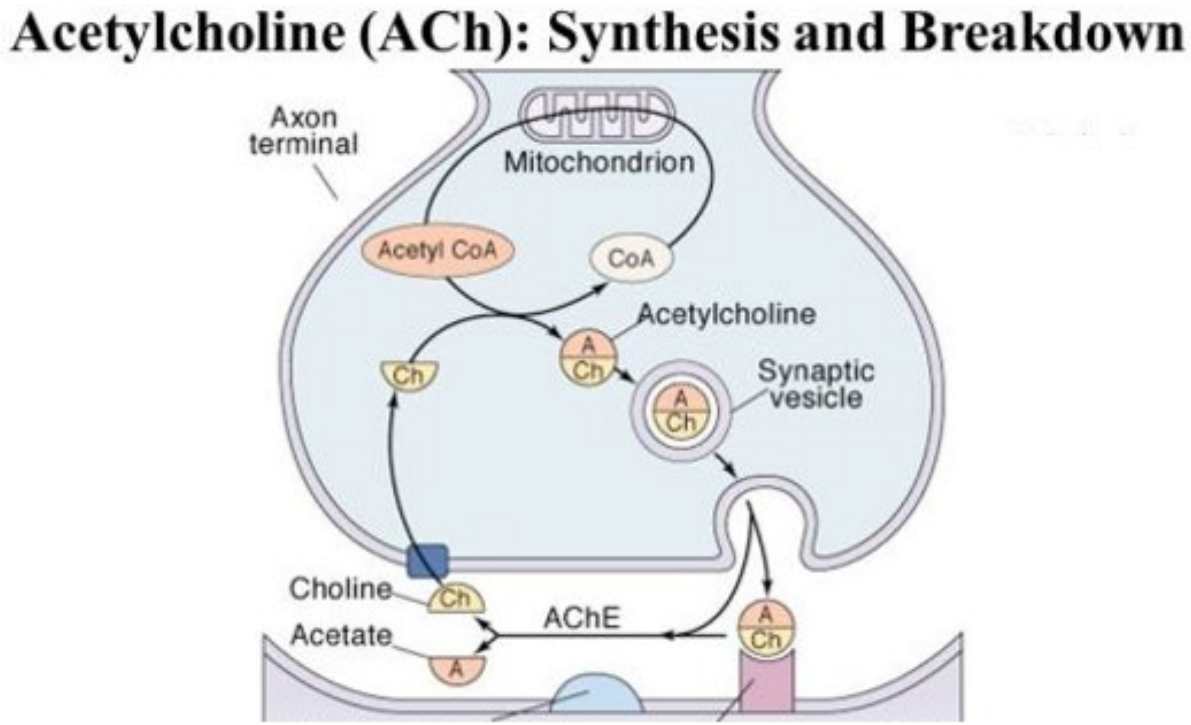
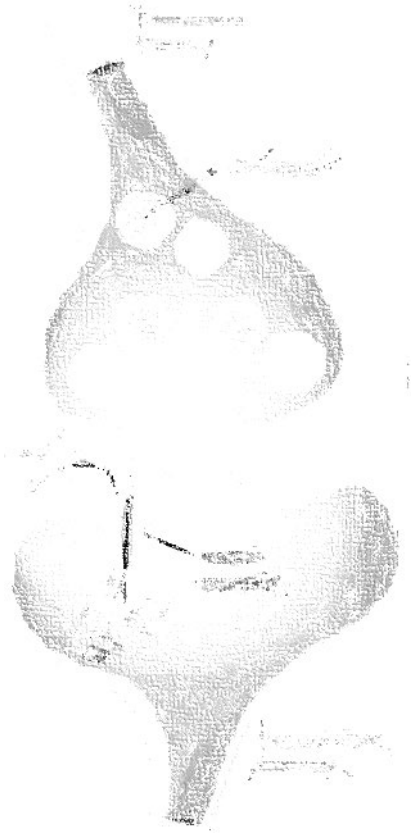
Summa Health

Long-Term Standard





Mild-Severe Disease

Moderate-Severe Disease

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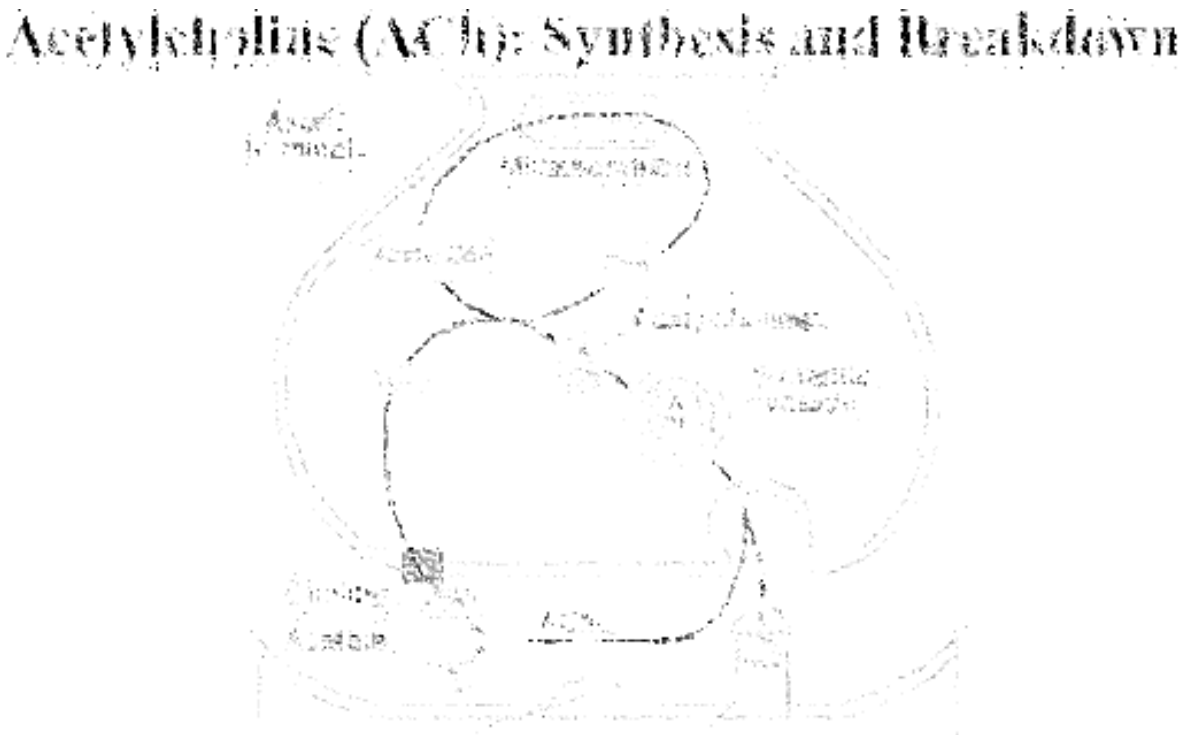
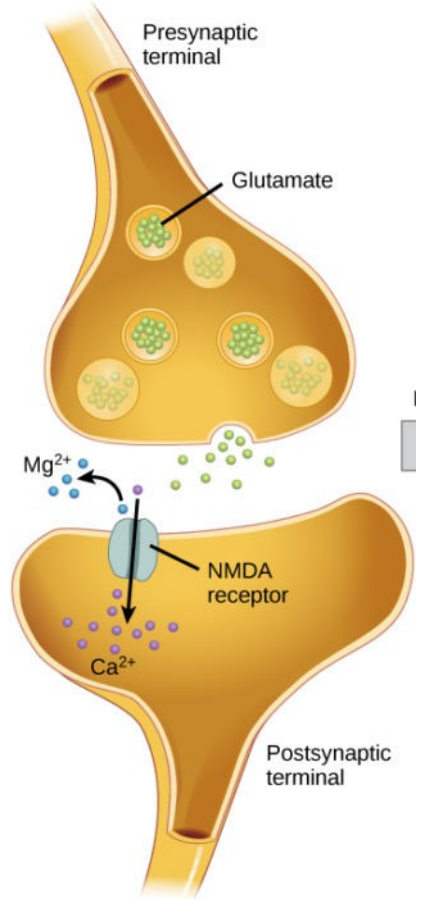
Summa Health

Long-Term Standard



Mild-Severe Disease



Moderate-Severe Disease

Birks JS. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005593.
Joe E. BMJ. 2019 Dec 6;367:l6217.
Lexicomp Online [Internet].
Vyklicky V. Physiol Res. 2014;63(Suppl 1):S191-203.

NMDA Antagonist Summary Table

	Memantine
Mechanism	NMDA Receptor Antagonist
Dosage Forms	Tablet Extended release capsule Oral solution
Target Dose and Titration	IR: 5 mg PO daily increased by 5 mg PO on a weekly basis to 20 mg / day in one-two divided doses ER: 7 mg PO daily increased by 7 mg PO on a weekly basis to 28 mg PO once daily
Notes	Maximum IR dose of 5 mg PO BID and maximum ER dose of 14 mg PO daily recommended with CrCl < 30 mL/min Possible risk of treatment-emergent agitation *Not* effective in mild AD ER capsules may be opened and sprinkled on applesauce for immediate use
Monitoring	Headache, confusion (may be transient), dizziness, hallucinations, constipation

Joe E. BMJ. 2019 Dec 6;367:l6217.
Lexicomp Online [Internet].
Pharmacist's Letter. Alzheimer's Dementia Pharmacotherapy [Internet]. c2022.
Zimmerman KM. Pharmacotherapy: A Pathophysiologic Approach, 12e [Internet].

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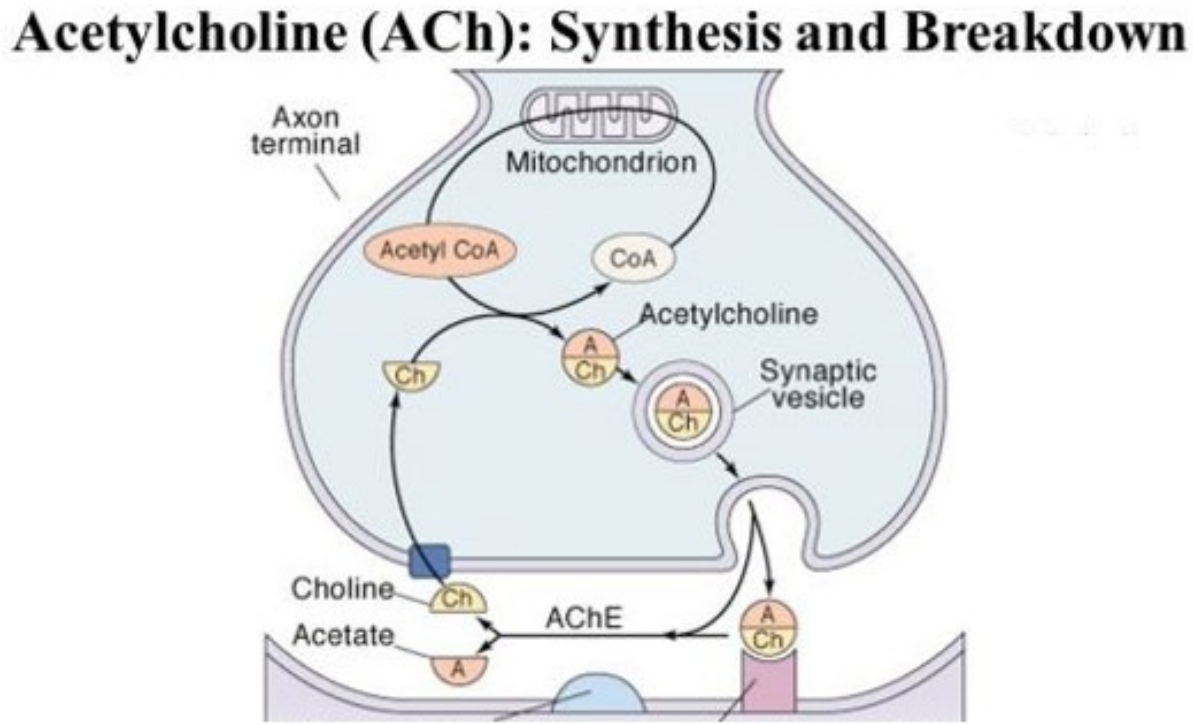

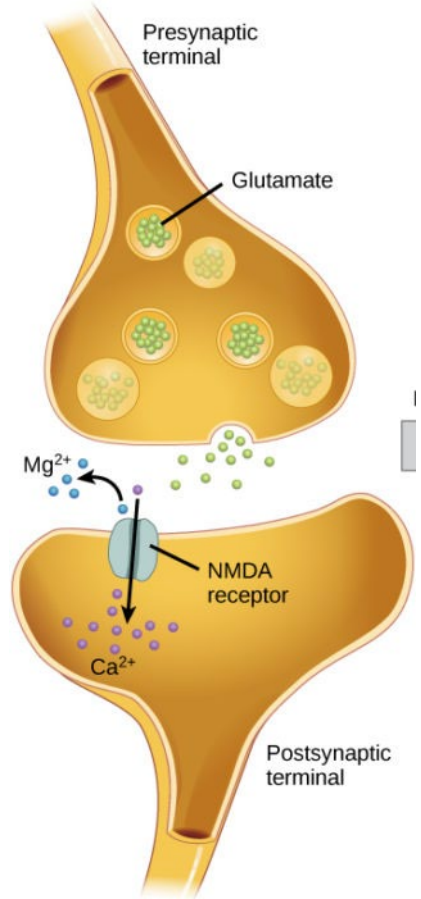

Mild-Severe Disease

Moderate-Severe Disease

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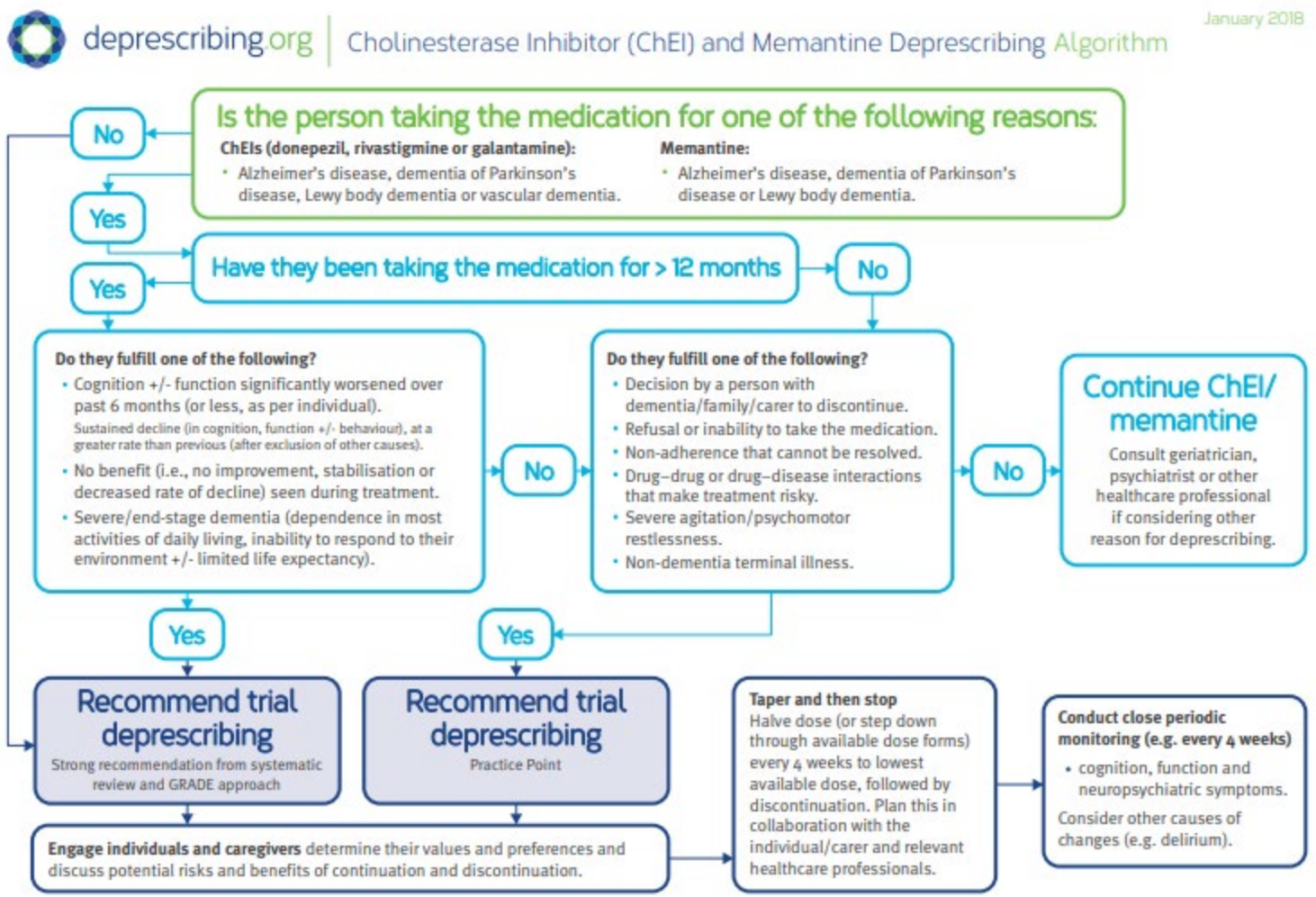
AD Pharmacotherapy: Discontinuation of ChEI or Memantine



Pharmacist's Letter. Alzheimer's Dementia Pharmacotherapy [Internet]. c2022.
Reeve E. Med J Aust. 2019 Mar;210(4):174-179.

Summa Health

AD Pharmacotherapy: Discontinuation of ChEI or Memantine

Monitoring during tapering and after discontinuation

Timing of symptoms after dose reduction/ discontinuation	Types of symptoms	Action to be taken by family/nurses/ care staff	Possible cause*
Less than 1 week	Severe symptoms, including agitation, aggression, hallucinations or reduced consciousness	Restart previous dose immediately and contact responsible healthcare professional as soon as possible	Adverse drug withdrawal reaction
2 to 6 weeks	Worsening of cognition, behavioural or psychological symptoms or function	Contact responsible healthcare professional and consider restarting previous dose and/or make an appointment to see responsible healthcare professional at the next available time	Re-emergence of symptoms that were being treated by ChEI/ memantine
6 weeks to 3 months	Worsening of cognition, behavioural or psychological symptoms or function	Contact responsible healthcare professional at the next available time to make an appointment	Likely progression of condition or possible re-emergence of symptoms that were being treated by ChEI/memantine
> 3 months	Any	As per usual care	Progression of condition

- *Exclude other causes of change in condition (e.g. infection or dehydration) first.
- Discuss monitoring plan with the individual/family/carer and write it down for them (e.g. frequency and type of follow-up). Ensure they have a way to contact a clinician if needed.

Pharmacist's Letter. Alzheimer's Dementia Pharmacotherapy [Internet]. c2022.
Reeve E. Med J Aust. 2019 Mar;210(4):174-179.

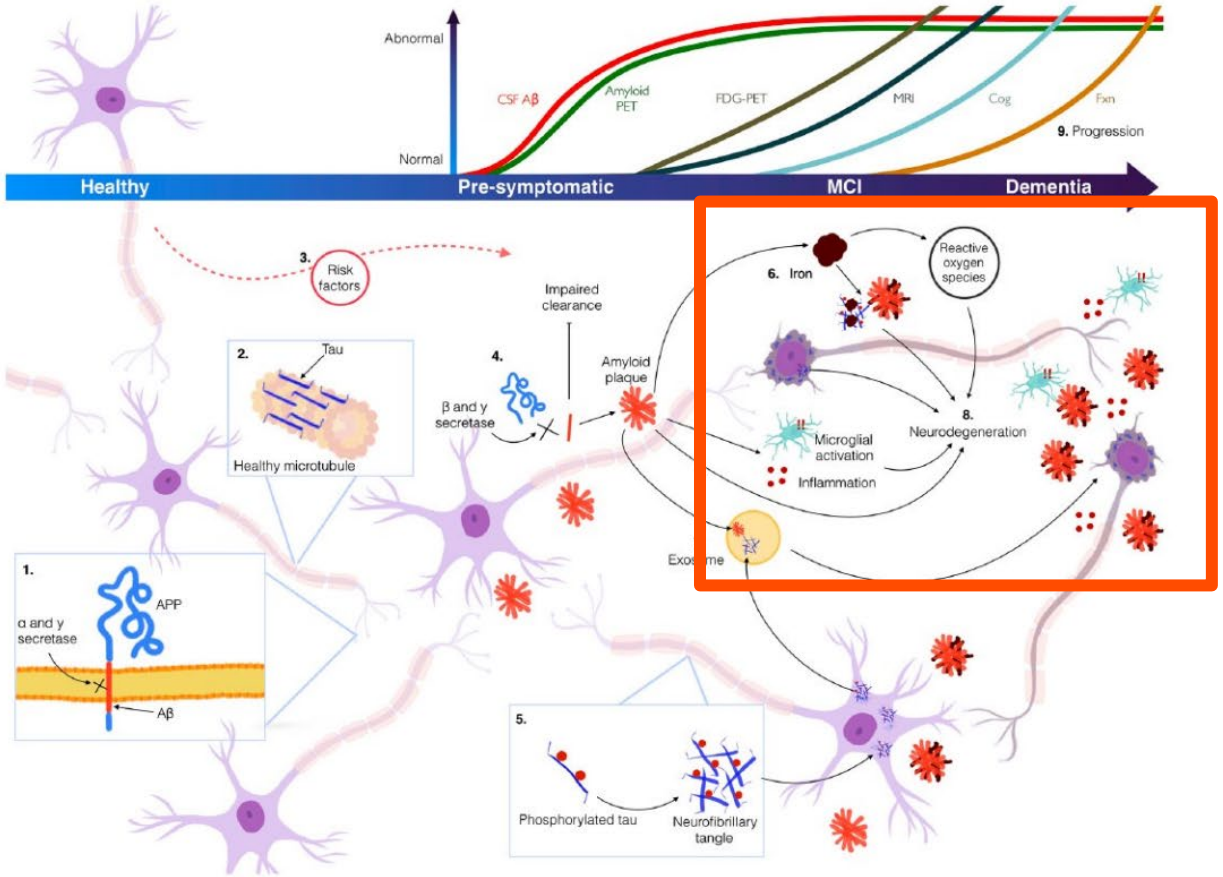
Summa Health

Therapeutics Outline (Alzheimer Disease)

Therapeutics Outline (Alzheimer Disease)

Summa Health

Alzheimer's Disease Dementia: Proposed Pathophysiologic Model



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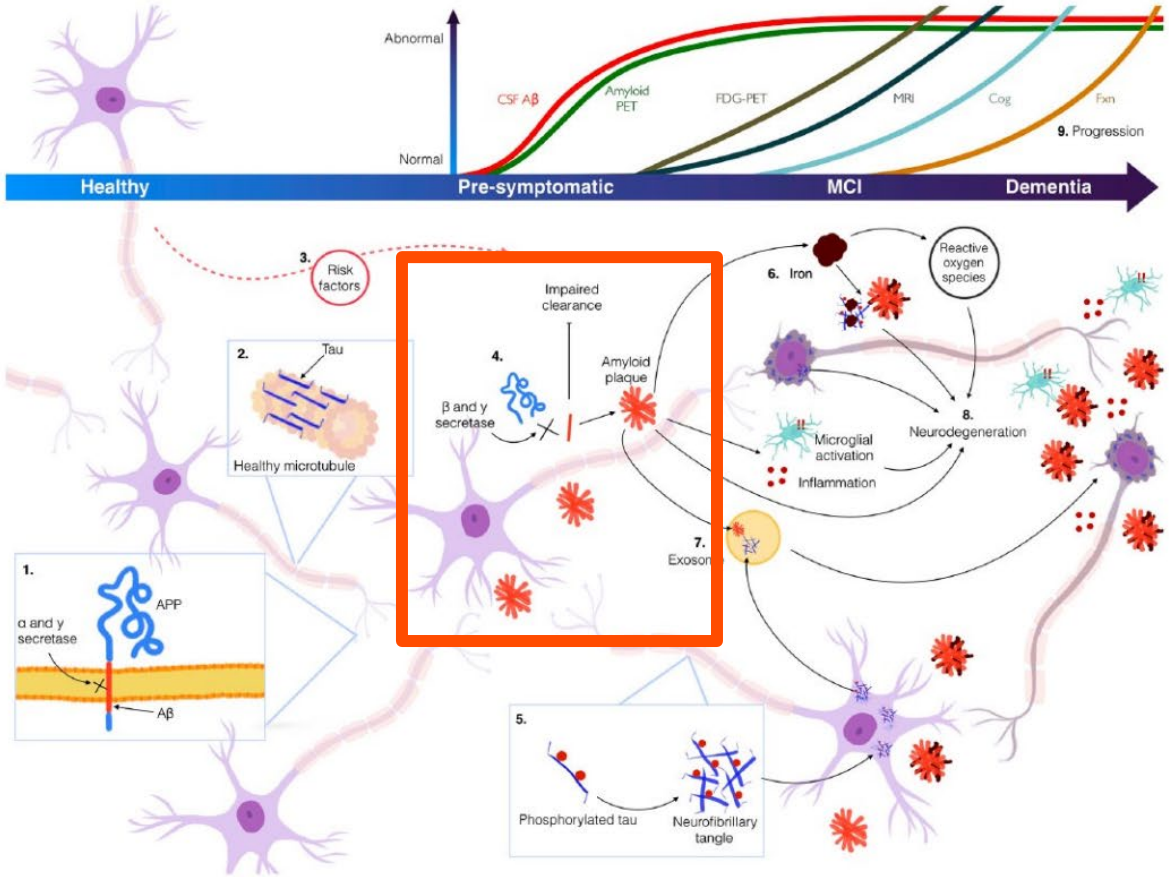

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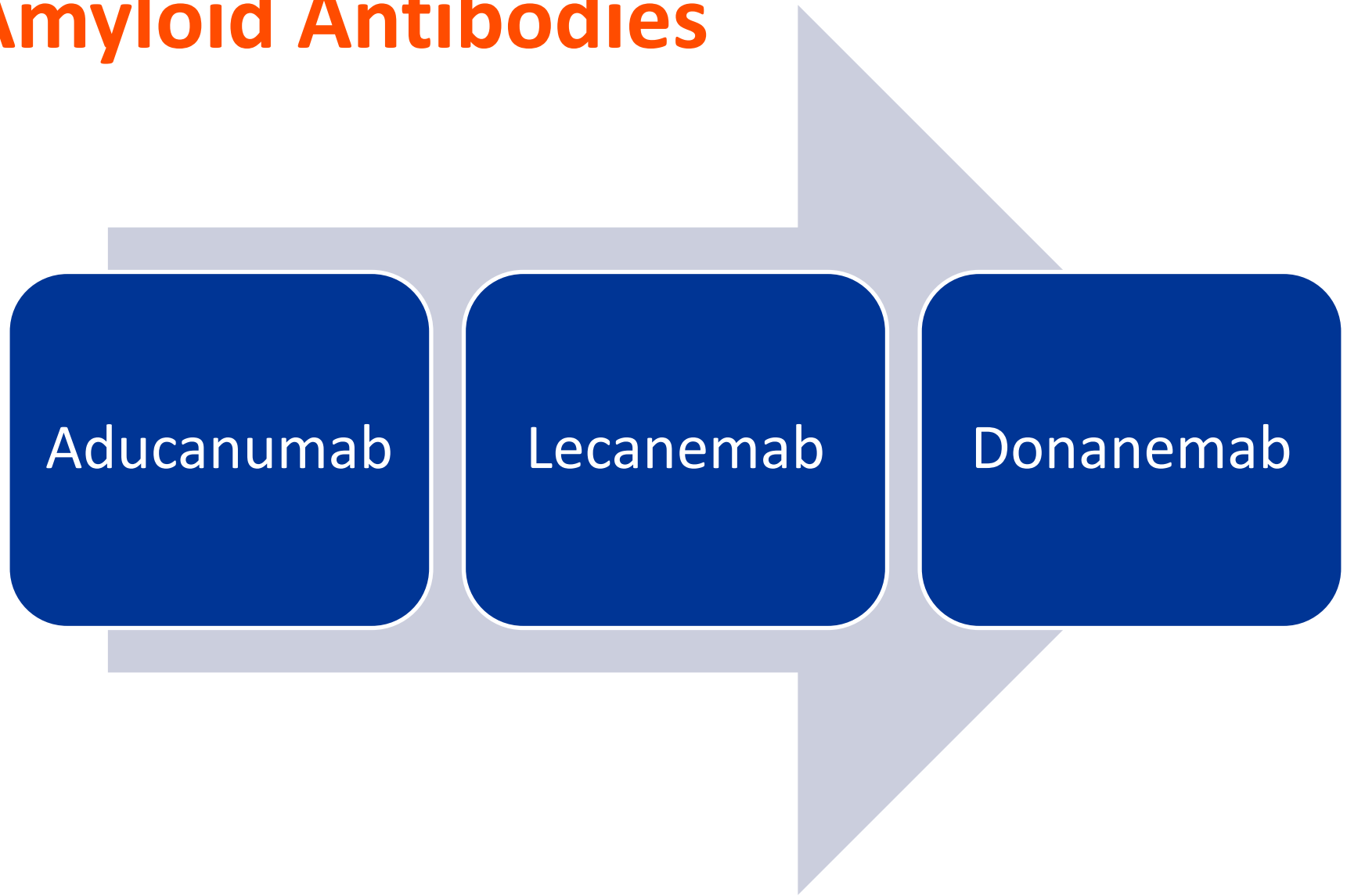
Anti-Amyloid Antibodies



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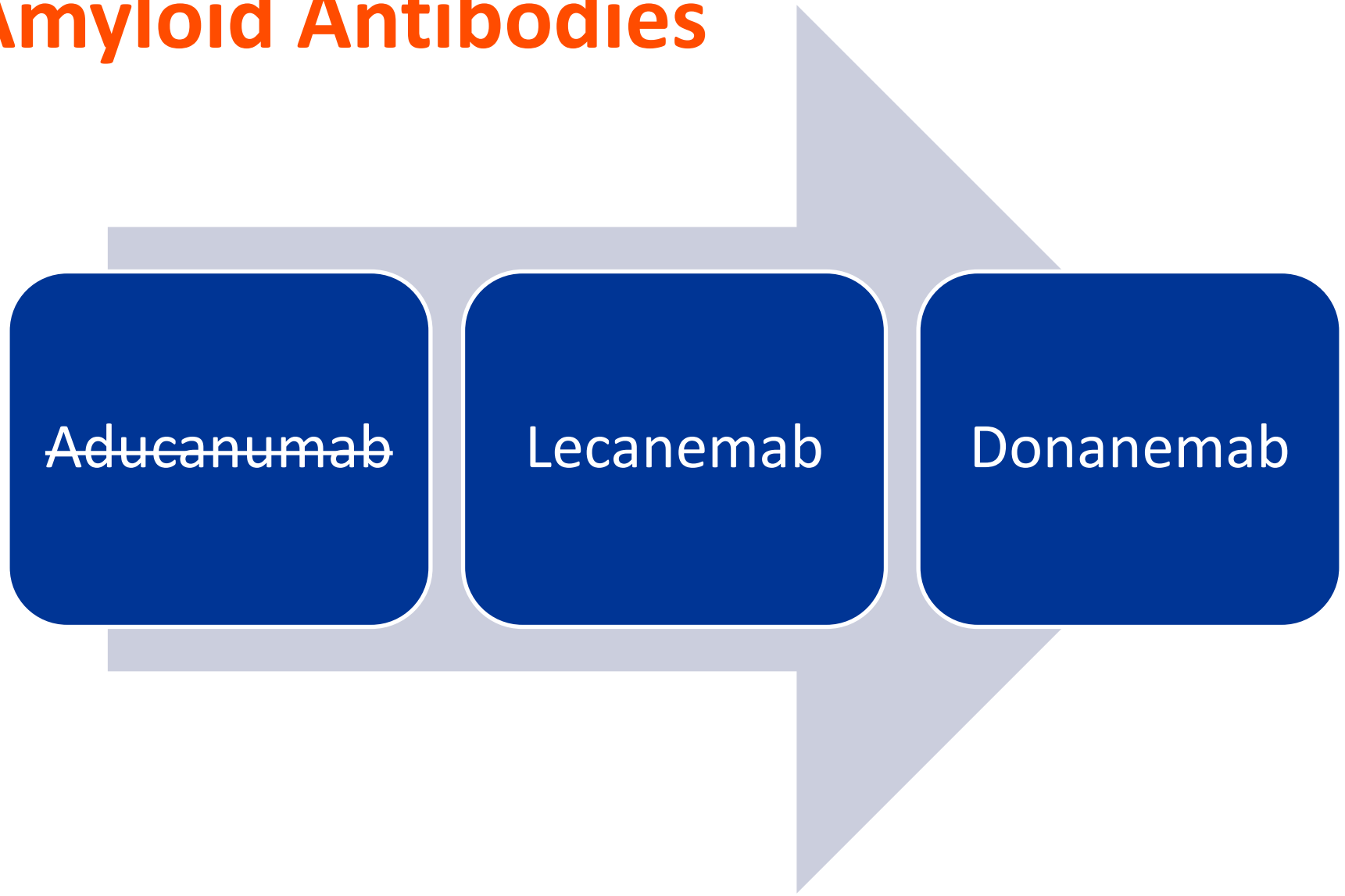


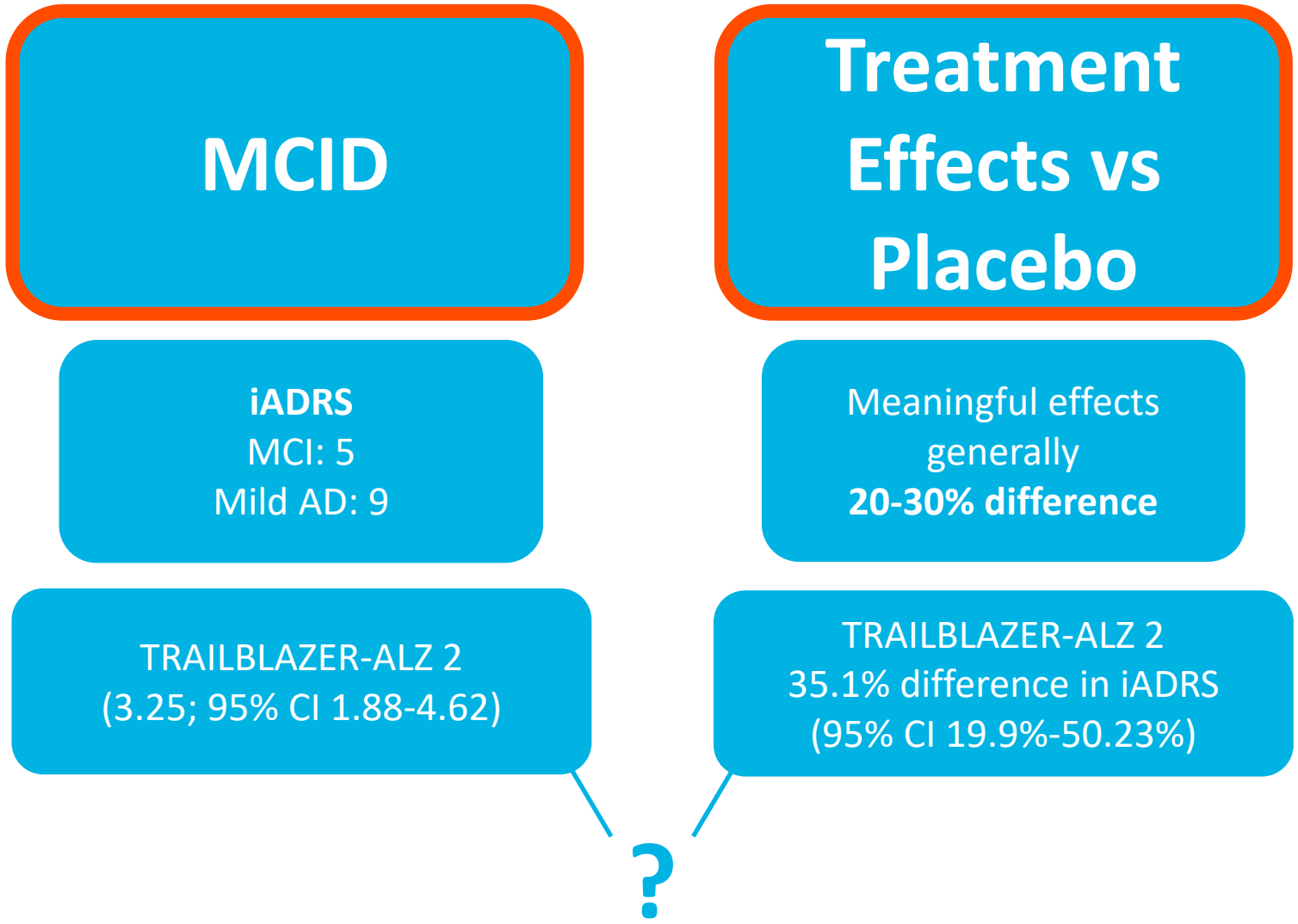
Anti-Amyloid Antibodies

	Clarity AD	*TRAILBLAZER-ALZ 2*
Study Type	Placebo-controlled double-blind randomized trial	Placebo-controlled double-blind randomized trial
Sample Size	1795 patients with mild cognitive impairment due to AD or mild AD-related dementia with confirmed amyloid pathology	1736 patients with mild cognitive impairment due to AD or mild AD-related dementia with confirmed amyloid and tau pathology
Treatment Arms	• Lecanemab 10 mg/kg every 2 weeks for 18 months • Placebo every 2 weeks for 18 months	• Donanemab IV 700 mg for the first 3 doses and 1400 mg thereafter for up to 72 weeks • Placebo IV every 4 weeks for up to 72 weeks

Notable Results	• Mean age of 71 years (SD 7.9)
	• Reduced worsening of CDR-SB compared with placebo (-0.45; 95% CI -0.67, -0.23) at 18 months
	• ARIA-E in 12.6% taking lecanemab vs 1.7% taking placebo
	  • 32.6% in ApoE ε4 homozygotes taking lecanemab vs 3.8% taking placebo
	• ARIA-H in 17.3% taking lecanemab vs 9% taking placebo
	  • 39% in ApoE ε4 homozygotes taking lecanemab vs 21.1% taking placebo
		• Mean age of 73 years
		• Low/medium tau population
		  • Primary: Reduced worsening of iADRS compared with placebo
		  • Difference, 3.25 [95% CI, 1.88-4.62]; $P < 0.001$
		  • Reduced progression on CDR-G
		  • Hazard ratio, 0.61 (95% CI, 0.47-0.8); $P < 0.001$
		  • Death in 2.1% taking donanemab vs 1.3% taking placebo
		• Combined tau population
		  • Primary: Reduced worsening of iADRS compared with placebo
		  • Difference, 2.92 [95% CI, 1.51-4.33]; $P < 0.001$
		  • Reduced progression on CDR-G
		  • Hazard ratio, 0.63 (95% CI, 0.51-0.77): $P < 0.001$
		• ARIA-E in 24% taking donanemab vs 2.1% taking placebo
		  • 40.6% in ApoE ε4 homozygotes taking donanemab vs 3.4% taking placebo
		• ARIA-H in 31.4% taking donanemab vs 13.6% taking placebo

Lexicomp Online [Internet]. Sims JR, et al. JAMA. 2023 Aug 8;330(6):512-527. van Dyck CH, et al. N Engl J Med. 2023 Jan 5;388(1):9-21.

MCID and Clinical Trial Effects



Liu KY, et al. Lancet Psychiatry. 2021 Nov;8(11):1013-1016.
Sims JR, et al. JAMA. 2023 Aug 8;330(6):512-527.
Wessels AM, et al. Alzheimers Dement (N Y). 2022 Jun 6;8(1):e12312.

Summa Health

Anti-Amyloid Antibodies: Additional Clinical Considerations (if used)

	Lecanemab	Donanemab
Mechanism	Anti-Amyloid Monoclonal Antibody	Anti-Amyloid Monoclonal Antibody
Dosage Forms	IV solution	IV solution
Target Dose and Titration	Using actual body weight, 10 mg/kg IV once every two weeks	700 mg IV every four weeks for three doses, then 1,400 mg IV every four weeks until amyloid plaques are reduced to minimal levels on PET imaging
Monitoring	PET/lumbar puncture, ApoE ε4 prior to initiation Brain MRI one year prior to initiation; prior to infusion 5, 7, and 14, and for symptoms of ARIA (eg headache, AMS, visual changes, nausea, dizziness) or monitoring of detected ARIA ARIA-H and ARIA-E may require suspension of treatment	PET/lumbar puncture, ApoE ε4 prior to initiation Brain MRI prior to initiation; prior to infusion 2, 3, 4, and 7, and for symptoms of ARIA or monitoring of detected ARIA ARIA-H and ARIA-E may require suspension of treatment
Notes	Black Box Warning Questionable clinical significance pending effects over time for patients matching trial inclusion criteria Multistep logistical process to arrange successful therapy initiation, monitoring, and cost management Exclusion Criteria Donanemab: tau pathology role (in addition to ApoE ε4)	

Lexicomp Online [Internet].
Sims JR, et al. JAMA. 2023 Aug 8;330(6):512-527.
van Dyck CH, et al. N Engl J Med. 2023 Jan 5;388(1):9-21

Summa Health

Anti-Amyloid Antibodies: Additional Clinical Considerations (if used)

Lecanemab Appropriate Use Recommendations (selected):

Category	Recommendation
AD Medications	Patients may be on AChEis and/or memantine
Immunological Disease	Exclude if any history of immunologic disease or systemic treatment with immunosuppressants, immunoglobulins, monoclonal antibodies, or derivatives
CNS Abnormality	Exclude if >4 microhemorrhages; single macrohemorrhage; superficial sidosis; >2 lacunar infarcts or stroke involving major vascular territory; other specified abnormalities (see works cited)
CVA / Seizure	Exclude if stroke or TIA within 12 months; any history of seizures
Psychiatry	Exclude if mental illness/major depression will interfere with comprehension of treatment
Bleeding	Exclude if uncontrolled bleeding disorder; platelet count < 50,000; IRN > 1.5
Anticoagulant	Exclude if patients taking anticoagulants should not receive lecanemab
“Catch-All”	Exclude if unstable medical conditions that may affect or be affected by lecanemab therapy

Cummings J, et al. J Prev Alzheimers Dis. 2023;10(3):362-377.

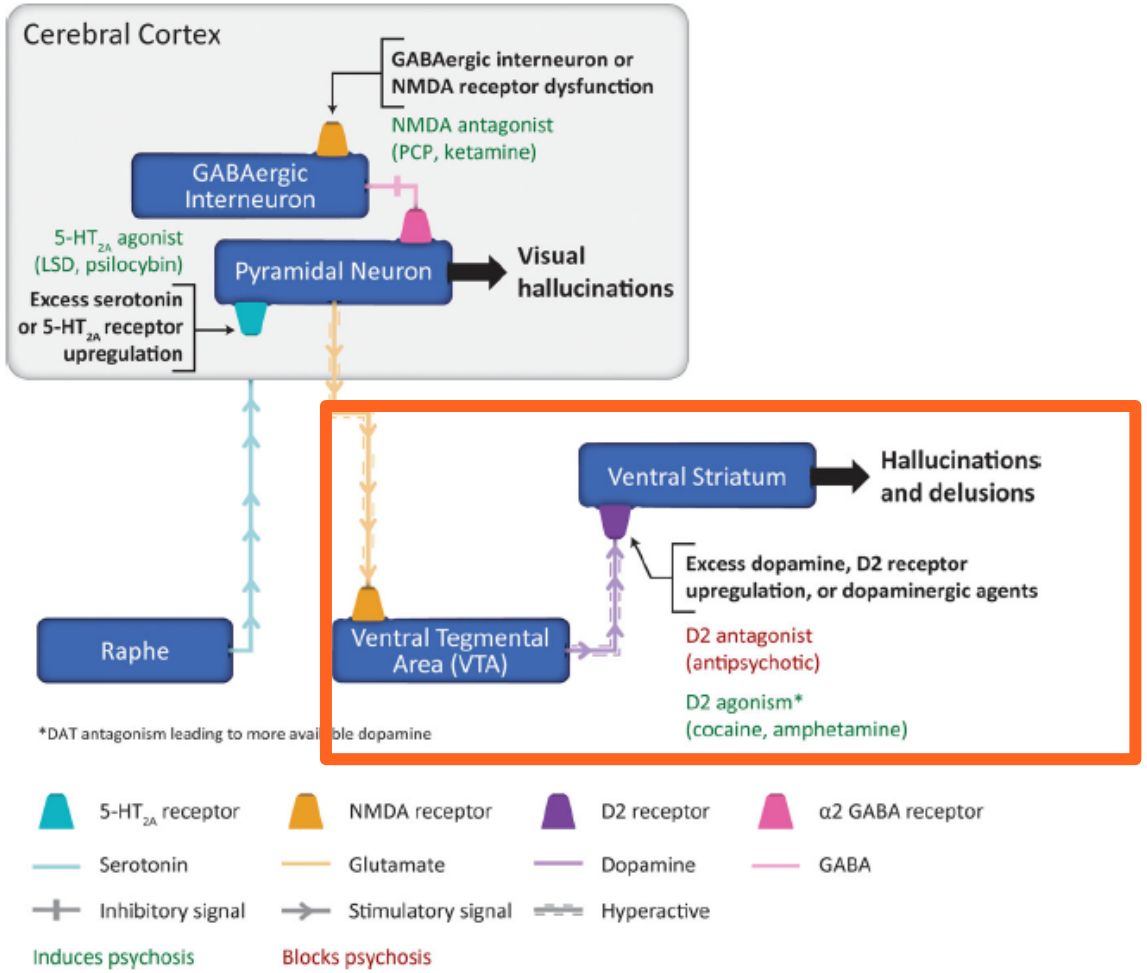
Therapeutics Outline (Alzheimer Disease)

Summa Health

Therapeutics Outline (Alzheimer Disease)

Summa Health

Behavioral and Psychological Symptoms of Dementia (BPSD): Pathophysiology



Cummings JL. CNS Spectr. 2022 Feb;27(1):7-15.

BPSD: Recent News

- Brexpiprazole recently FDA-approved for agitation associated with dementia due to AD
  - 12-week, double-blind, randomized controlled trial
    - Significant agitation at baseline per Cohen-Mansfield Agitation Inventory (CMAI)
    - Brexpiprazole titrated to 2 mg per day or 3 mg per day vs placebo
    - Primary outcome: CMAI change from baseline
      - Difference from placebo: -5.32 (95% CI -8.77, -1.87) with Cohen *d* effect size of 0.35
      - Effects not seen in US region when divided into US / European subgroups
    - Titrate to target dose based on renal/hepatic function
    - Unclear clinical significance and persistence of effects
    - Still follow APA guidance
    - **Black Box Warning still in effect!**

Lee D, et al. JAMA Neurol. 2023 Nov 6:e233810.
Lexicomp Online [Internet].
Reus VI. Washington DC: American Psychiatric Association; c2016.

BPSD and D_2 Blockade: Role in Therapy

2016 American Psychiatric Association Practice Guideline on the Use of Antipsychotics in Patients with Dementia Selected Statements:

Statement 4

- Patients with dementia are recommended to have a comprehensive treatment plan that includes appropriate person-centered **nonpharmacologic** and pharmacologic interventions, as needed

Statement 5

- Nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, dangerous, or cause significant distress to the patient

Statement 6

- Review the clinical response to nonpharmacologic interventions prior to nonemergency use of an antipsychotic medication to treat agitation / psychosis in patients with dementia

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Summa Health

BPSD and D_2 Blockade: Role in Therapy

2016 American Psychiatric Association Practice Guideline on the Use of Antipsychotics in Patients with Dementia Selected Statements:

Statement 7

- Before initiating nonemergency treatment with an antipsychotic, assess and discuss potential risks and benefits of antipsychotic medications with the patient and/or surrogate decision maker

Statement 10

- For those who are started on an atypical antipsychotic for dementia with agitation or psychosis, if there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic medication, the medication should be tapered and withdrawn

Statement 12

- For patients with dementia who show adequate response of behavioral / psychological symptoms to treatment with an antipsychotic medication, attempt to taper and withdraw the medication within 4 months of initiation unless the patient experienced treatment recurrence in previous tapering attempts

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Conclusions

- Imaging techniques, and associated biomarkers, continue to enrich the diagnosis, monitoring, and treatment of dementia.

- Novel therapeutics for both cognitive and behavioral aspects of Alzheimer disease dementia possess questionable clinical significance and are only to be used in highly selected patients after a thorough assessment of individualized risks and benefits.

Advanced diagnostics, imaging and therapeutics for dementia

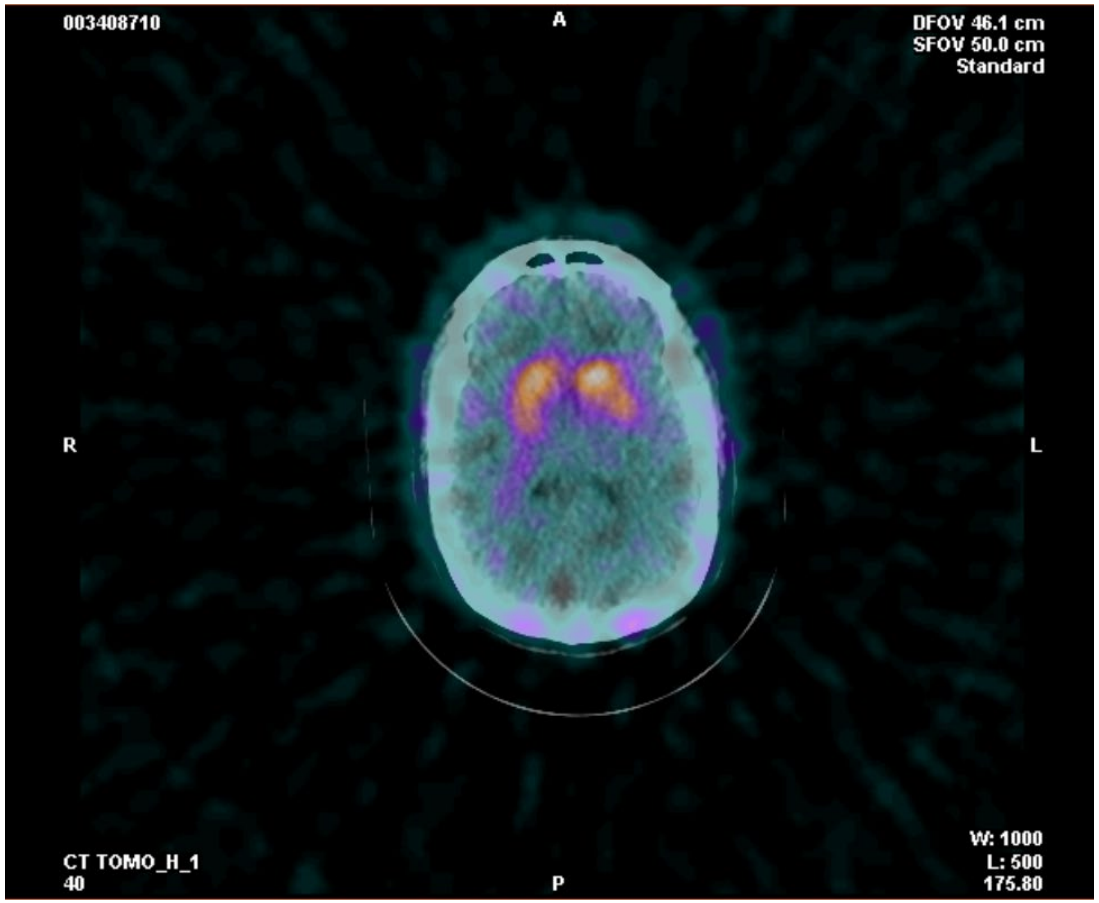
Dr. James Bavis

Joseph Marchiano, PharmD, BCPS, BCGP

Biomarkers for Dementia with Lewy Bodies

- Indicative Biomarkers:
  - Reduced dopamine transporter uptake in basal ganglia on SPECT or PET
  - Low uptake of Iodine-MIBG myocardial scintigraphy
  - Polysomnogram showing REM sleep without atonia
- Supportive Biomarkers
  - Relative preservation of medial temporal lobe structures on CT/MRI
  - Low uptake on SPECT/PET with reduced occipital activity +/- the cingulate island on FDG-PET.
  - Prominent posterior slow wave activity on EEG with periodic fluctuations on pre-alpha/theta range

DaT Scan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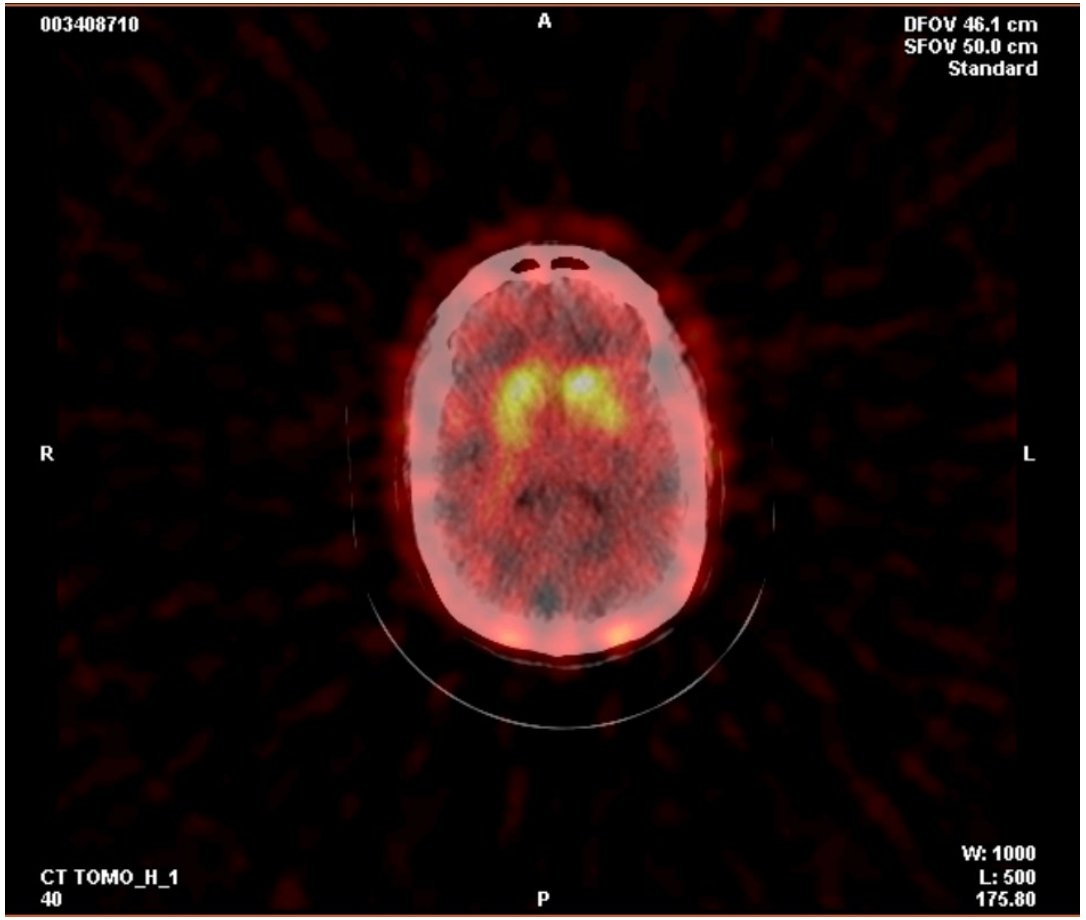
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