Alzheimer's Disease & Cognitive Impairment: Physiology, Chemistry, and Neurotransmitters

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Alzheimer's Disease

Alois Alzheimer
a German physician

- In 1906, Dr. Alzheimer observed a patient with memory loss, language difficulty, strange behaviors, and confusion.
- Brain examination after death showed what is now known as plaques and tangles in the upper cortical layer (published in 1907).

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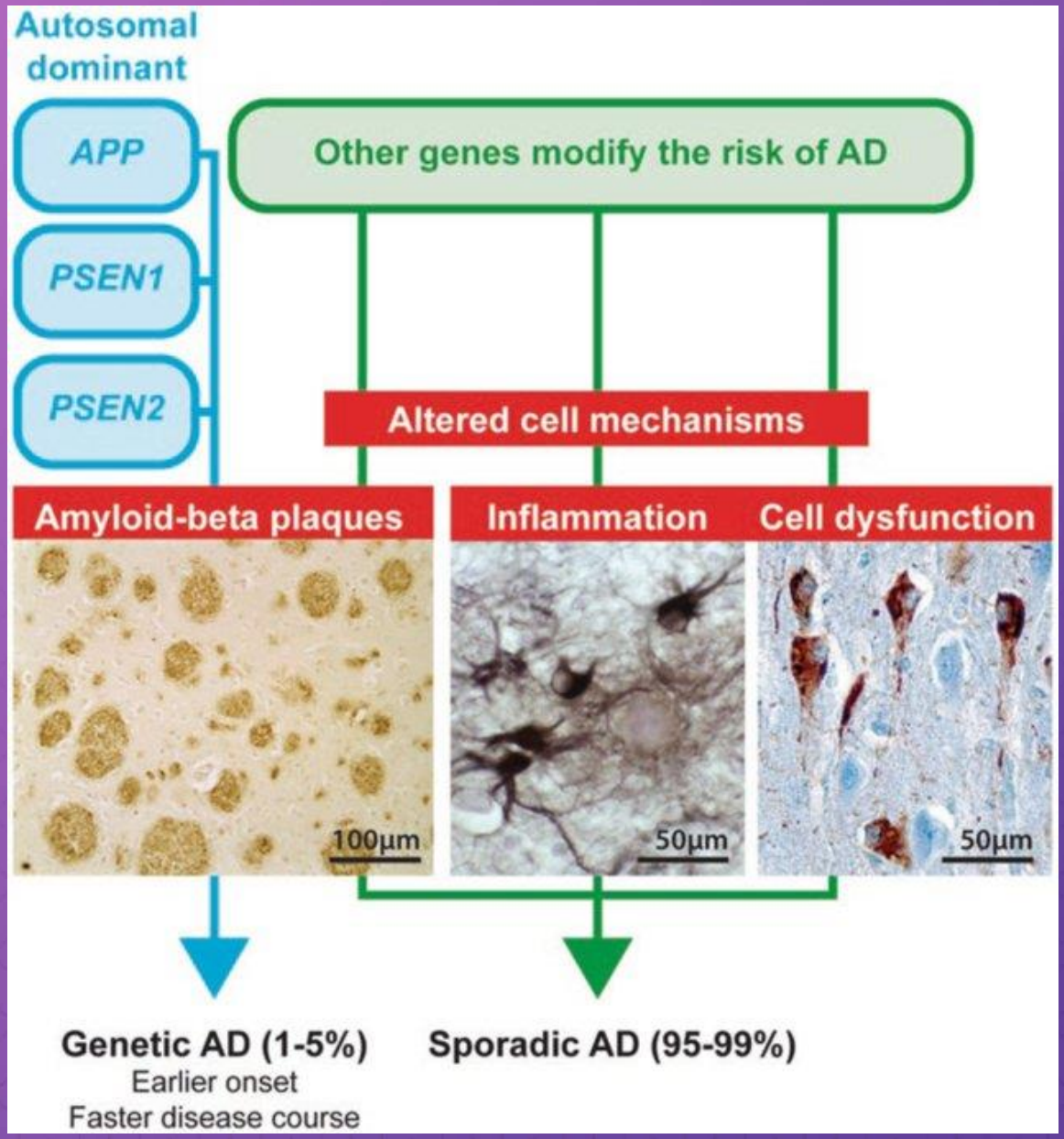
Alzheimer's Disease: Facts

- What is Alzheimer's disease?
  - A currently incurable brain disease that causes progressive and irreversible loss of neurons (neurodegeneration)
- Prevalence?
  - ~ 5.8 Million people in the US
    - ~ 1 person diagnosed every 65 seconds
      - Usually diagnosed ~ 65-85 years of age
  - 6th leading cause of death in the US
- Relevant videos
  - https://www.nia.nih.gov/health/video-how-alzheimers-changes-brain
  - https://www.neuroscientificallychallenged.com/blog/2-minute-neuroscience-alzheimers-disease

Alzheimer's disease is the leading cause of dementia

- Neurodegenerative Disorders
  - Alzheimer's disease (1st)
  - Lewy Body disease (3rd)
  - Parkinson's disease
  - Frontotemporal dementia
- Inflammatory and Immune-Mediated Disorders
- Viral Infection (e.g. HIV, PML)
- Prion Disorders (e.g. CJD)
- Other Conditions (e.g. tumors, traumatic injury, etc.)
- Vascular Diseases (2nd; review article: https://link.springer.com/article/10.1007/s00401-016-1571-z)
  - Large vessel disease
  - Small vessel disease
  - Binswager's disease
  - CADASIL
  - Familial amyloid angiopathies
- Toxic and Metabolic Disorders
  - Alcoholism
  - B12 deficiency



https://www.researchgate.net/publication/318186795_Clinical_Aspects_of_Alzheimer%27s_Disease/figures?lo=1

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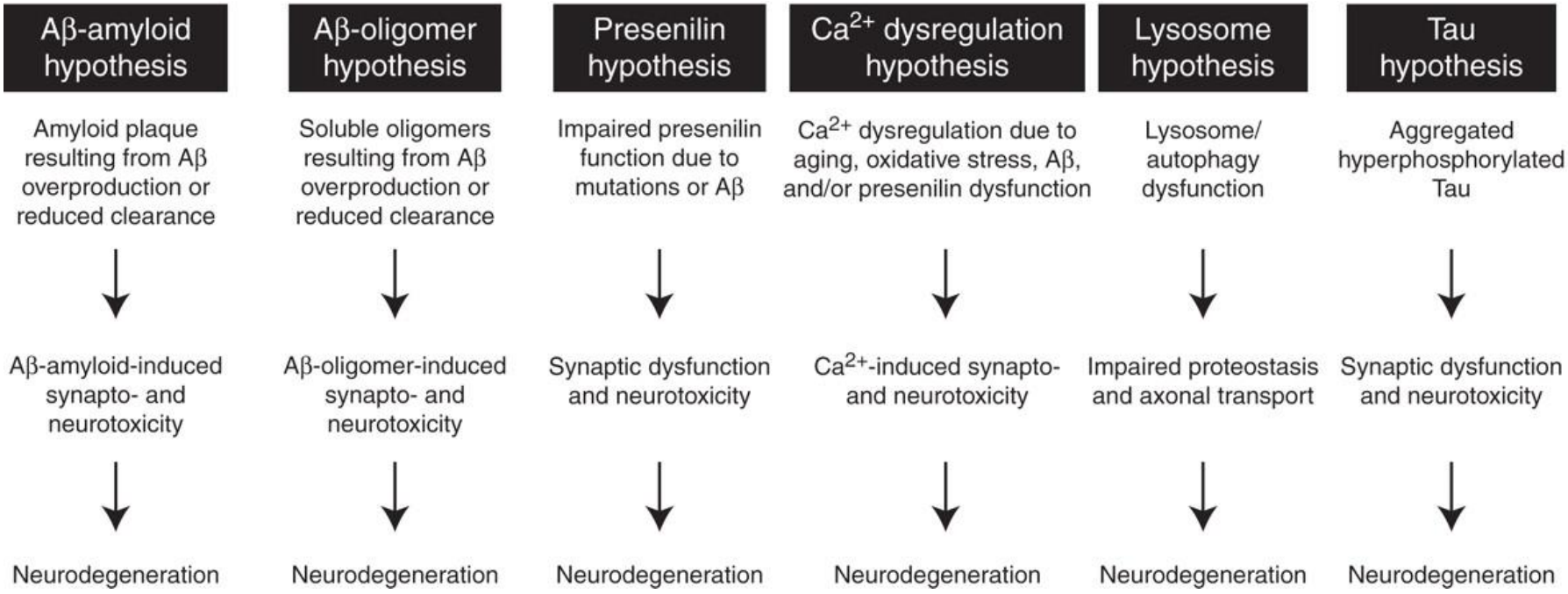
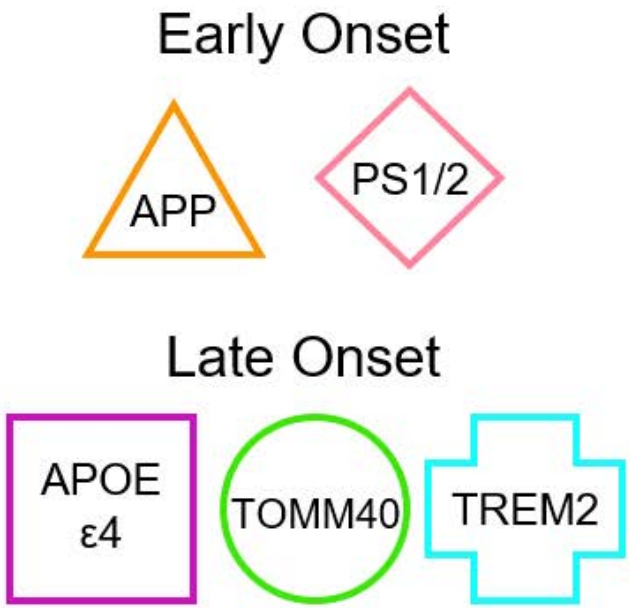
Pathogenic hypotheses for mostly synaptic toxicity in Alzheimer's disease

Loss of synapses correlates better than plaques or tangles with cognitive deficits

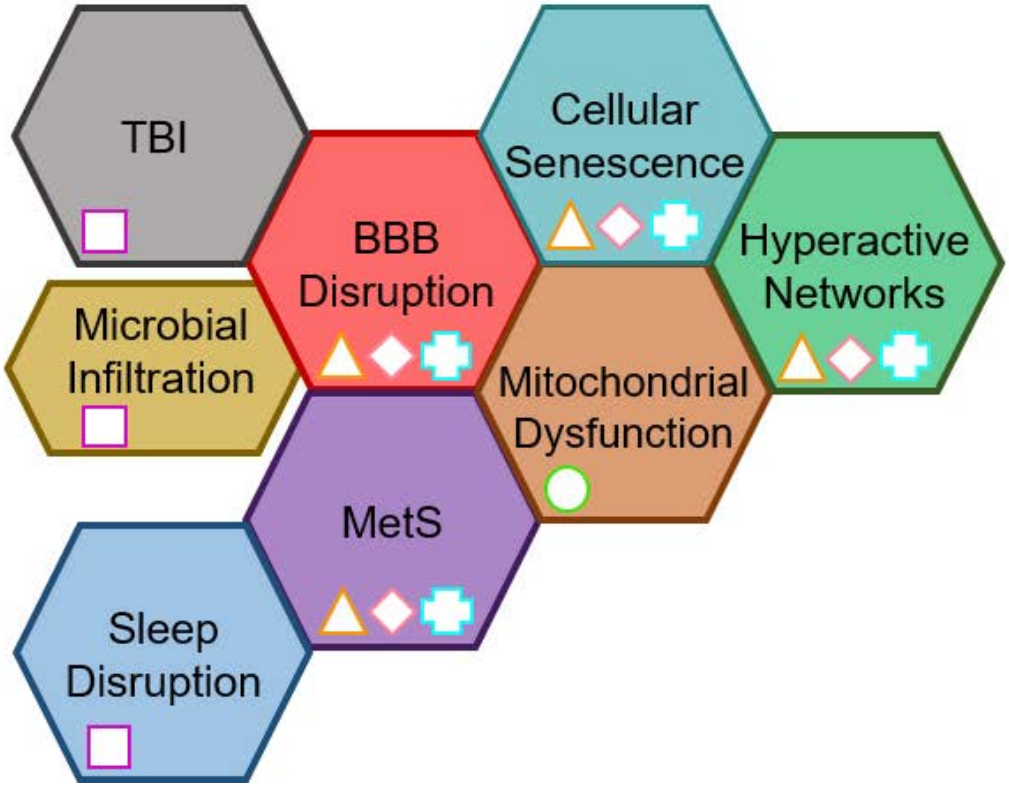


Sheng et al. *Cold Spring Harb Perspect Biol* 2012

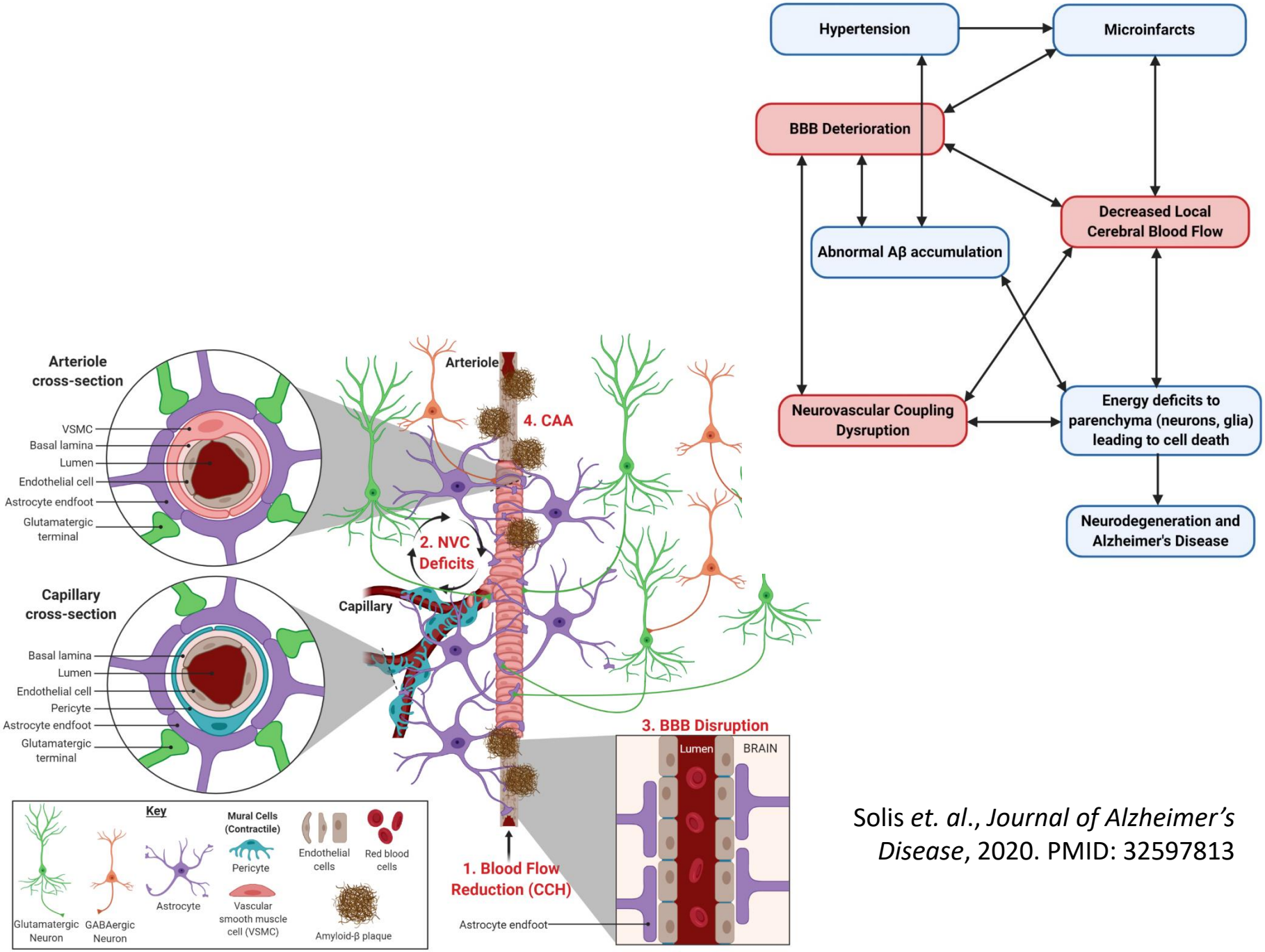
Genetic AD Subgroups



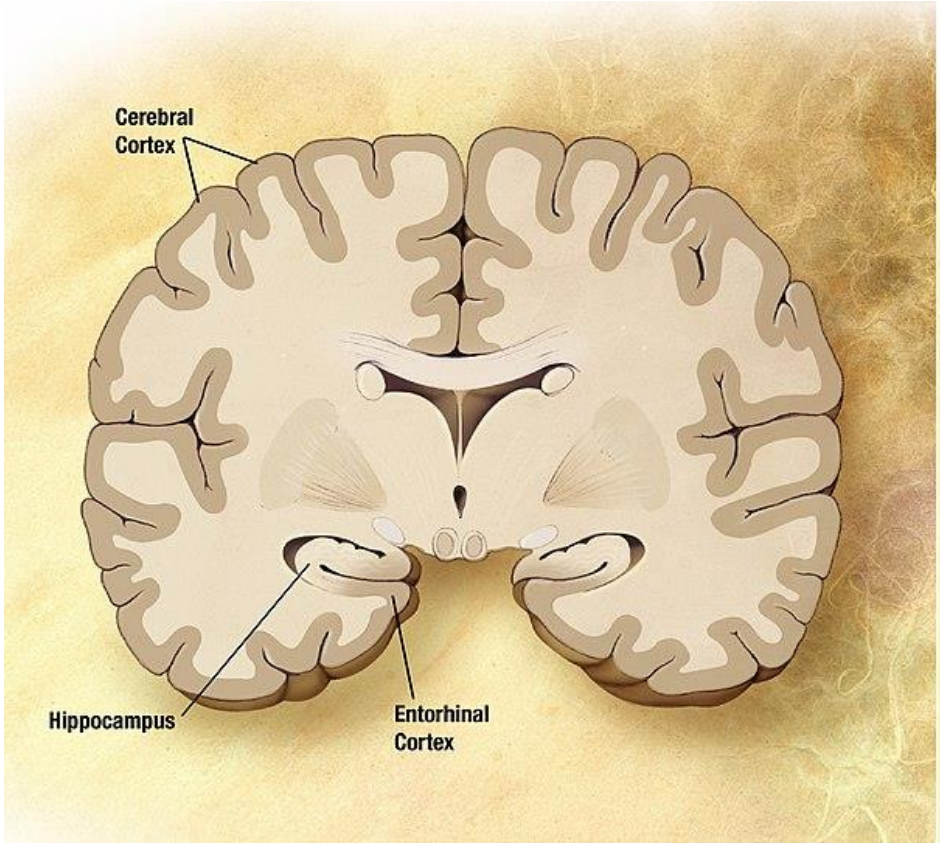
Environmental AD Subgroups

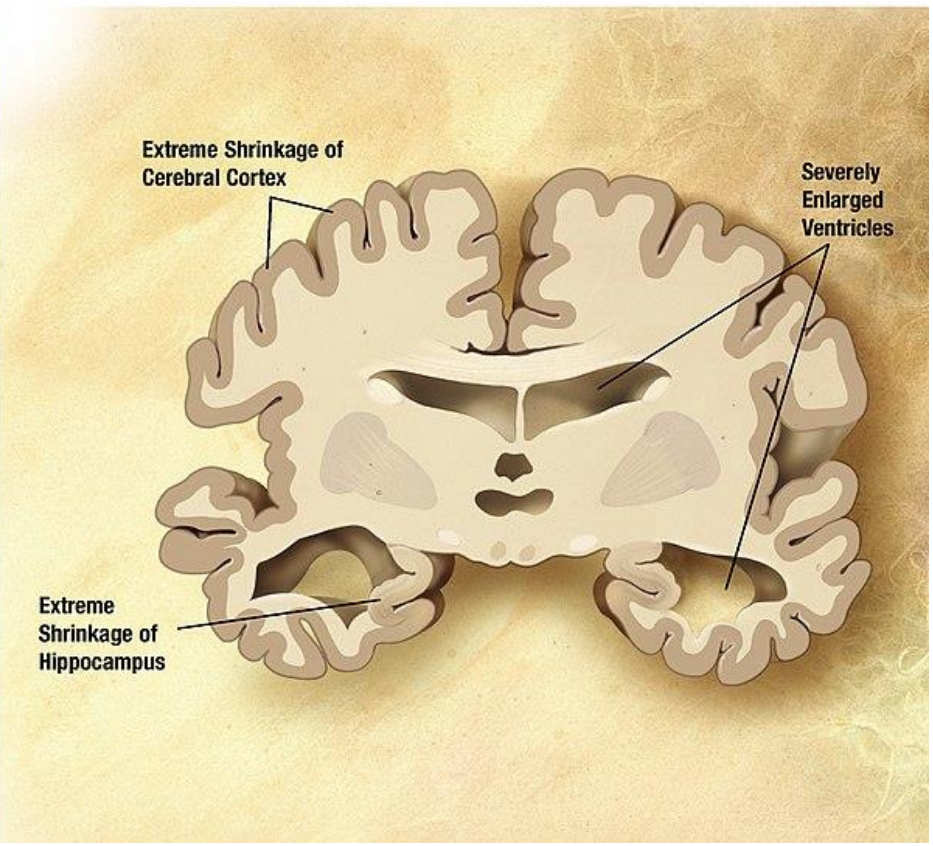


Hascup & *Hascup, Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 2020. PMID: 32885025

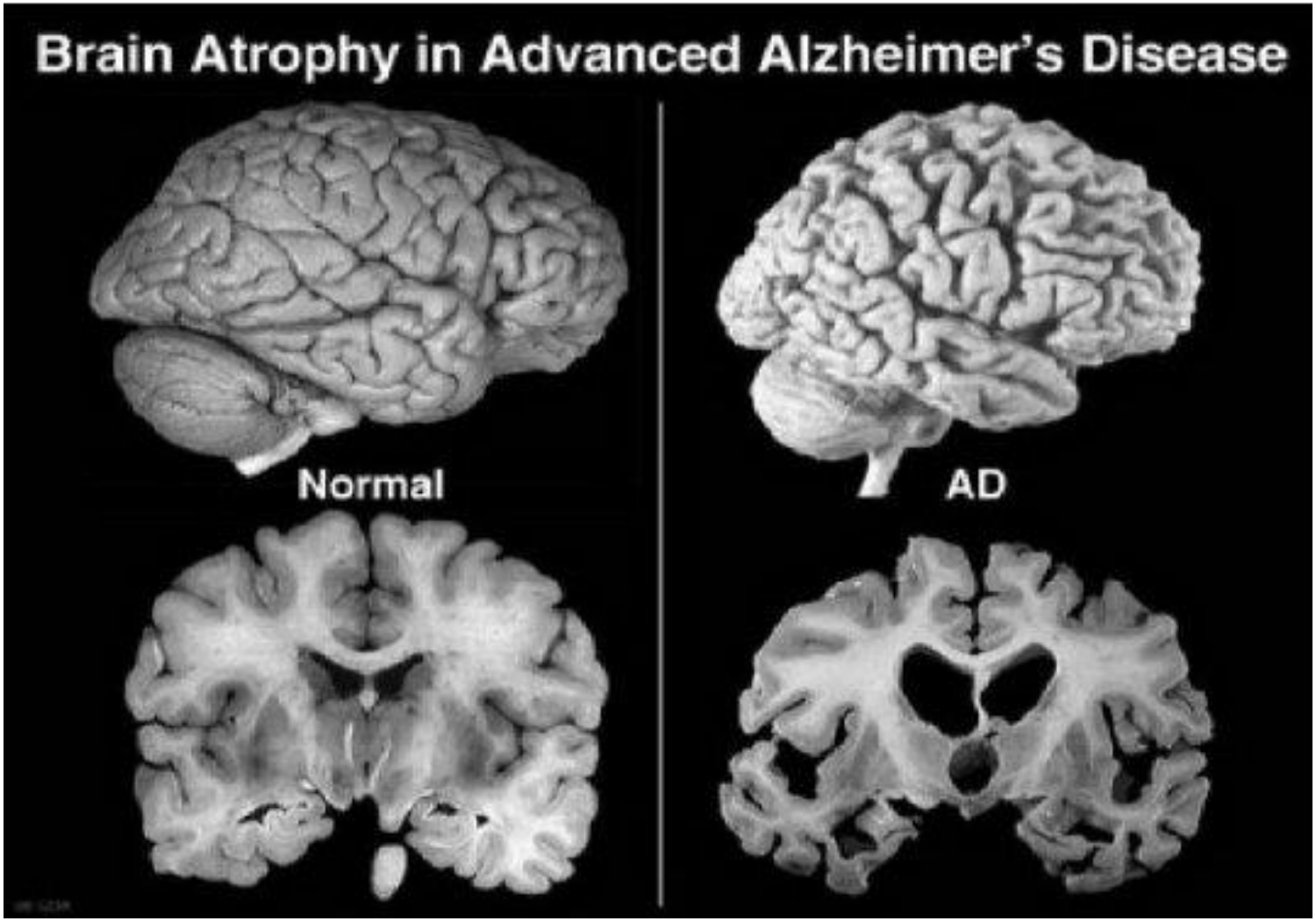


Solis *et. al.*, *Journal of Alzheimer's Disease*, 2020. PMID: 32597813





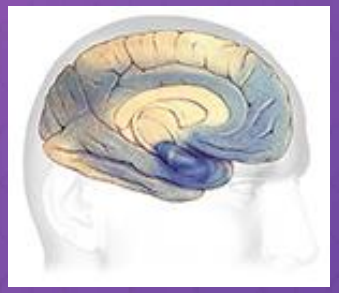
https://www.researchgate.net/publication/308874413_Advances_in_DNA_vaccines_for_Cancer_and_many_other_Diseases/figures?lo=1

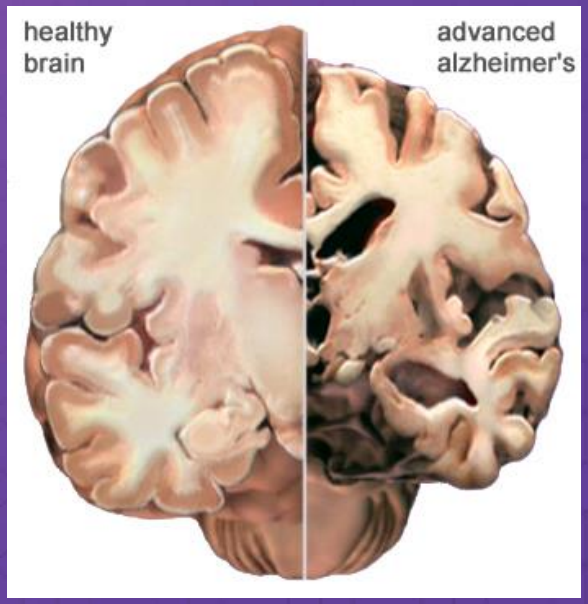


https://www.researchgate.net/publication/273768877_Towards_understanding_Alzheimer%27s_Disease_An_Overview

Alzheimer's disease: Facts & Figures

- 3 hallmarks of AD: β-amyloid plaques, neurofibrillary tangles, and neurodegeneration
  - Specific to AD based on timing, sequence, and location (spreading?)
    - Entorhinal Cortex → Hippocampus →Cortex





Images obtained from: www.alz.org

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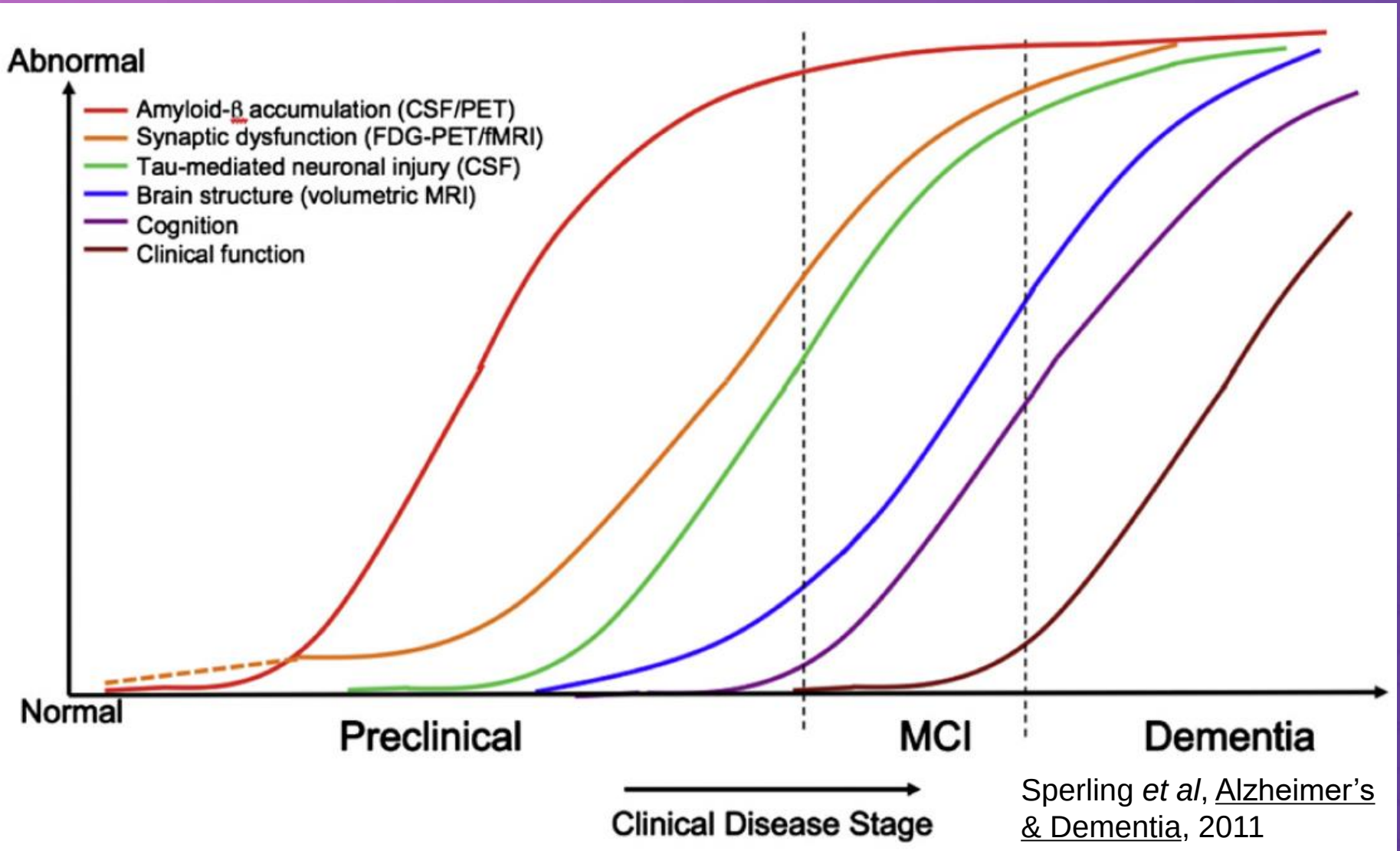
Alzheimer's Disease Progression



Sperling *et al*, Alzheimer's & Dementia, 2011

*Important to note that plaque formation/burden does not necessarily correlate to AD severity.

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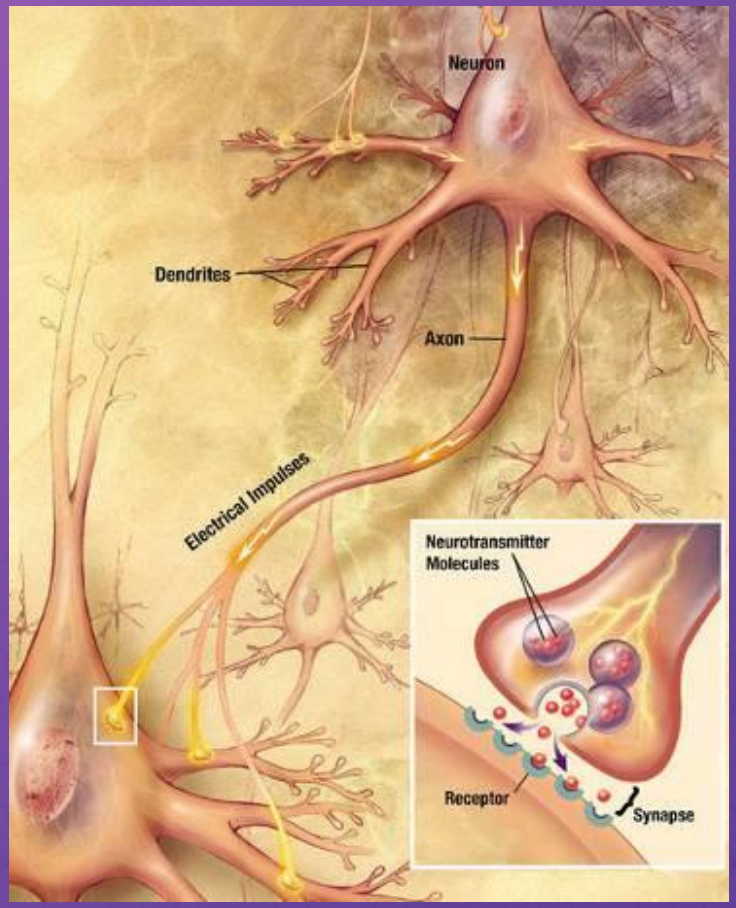
Neurotransmitters

- Implications for treatment
  - Different dementias have different neurochemical profiles (some similarities)
    - Underlie symptoms
  - Pharmacotherapy alters neurotransmission
    - Release, uptake, receptors, etc.
    - Pro-cognitive, antidepressants, antipsychotics, anxiolytic, etc.

Neurotransmitter Types

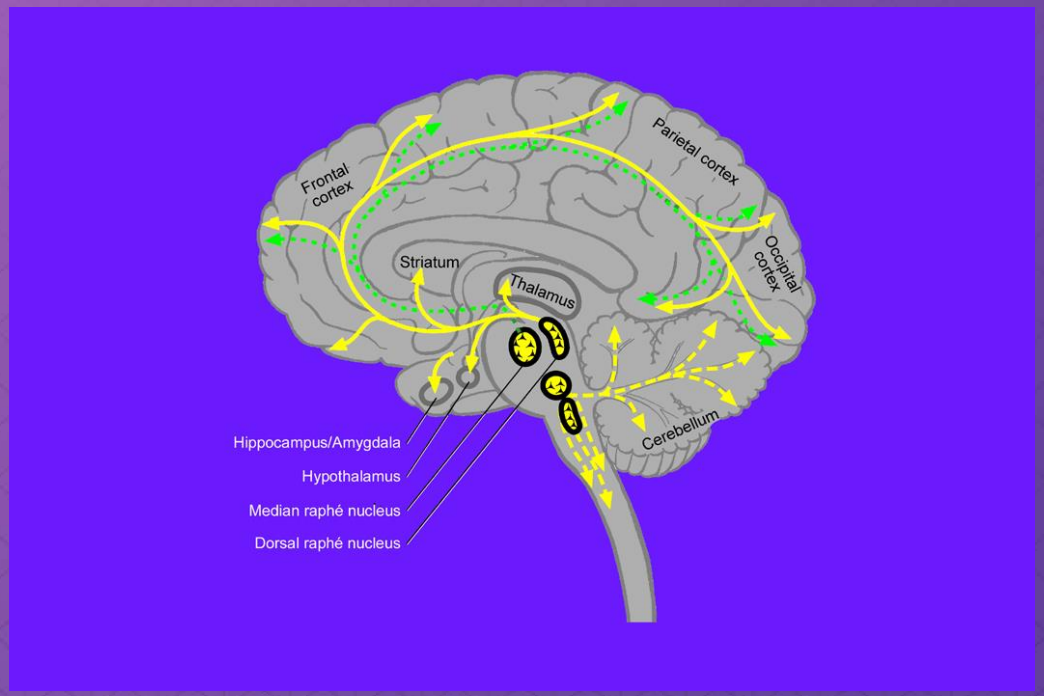
Amino acids	glutamate, aspartate, D-serine, glycine, γ amino butyric acid (GABA)
Biogenic amines	dopamine, serotonin, norepinephrine, epinephrine, histamine
Others	acetylcholine, adenosine, anandamide, nitric oxide
Peptides	over 50 peptide neurotransmitters, somatostatin, substance P, β endorphin



Neurotransmitters activate one or more types of receptors. The effect on the postsynaptic cell depends on the properties of those receptors.

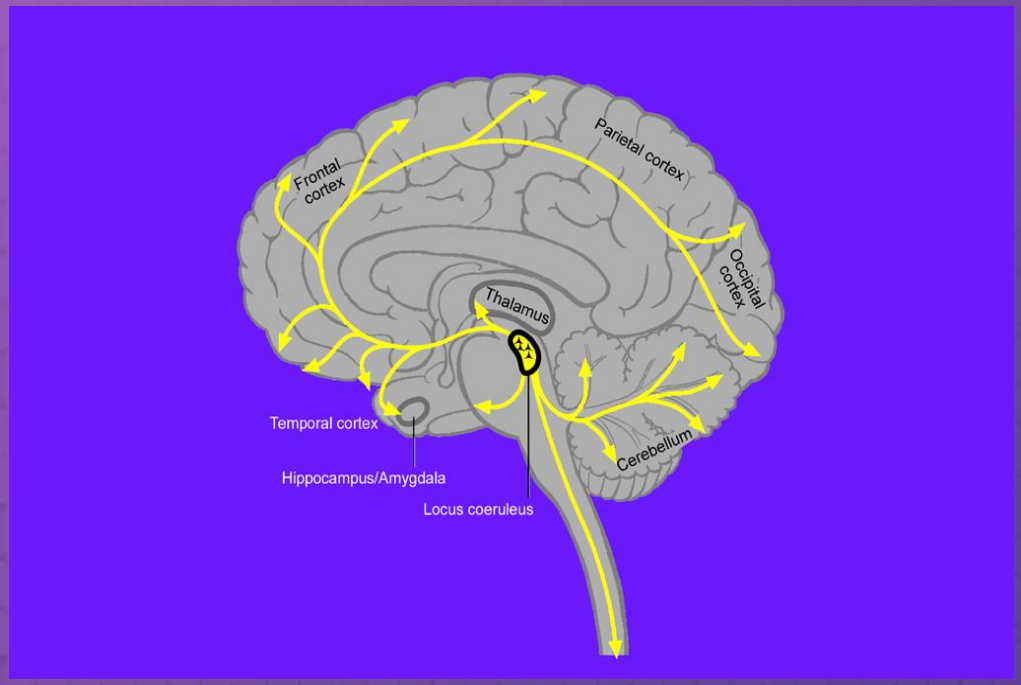
Neurotransmitters and Alzheimer's disease

- Likely involvement of several neurotransmitters
  - Serotonin (5-HT)
    - Abnormalities
      - Raphe: Neuron loss, tangles, reduced 5-HT
      - 5-HT_{2A} receptors reduced with severe dementia
      - Receptor polymorphisms linked to aggression, psychosis, depression, anxiety



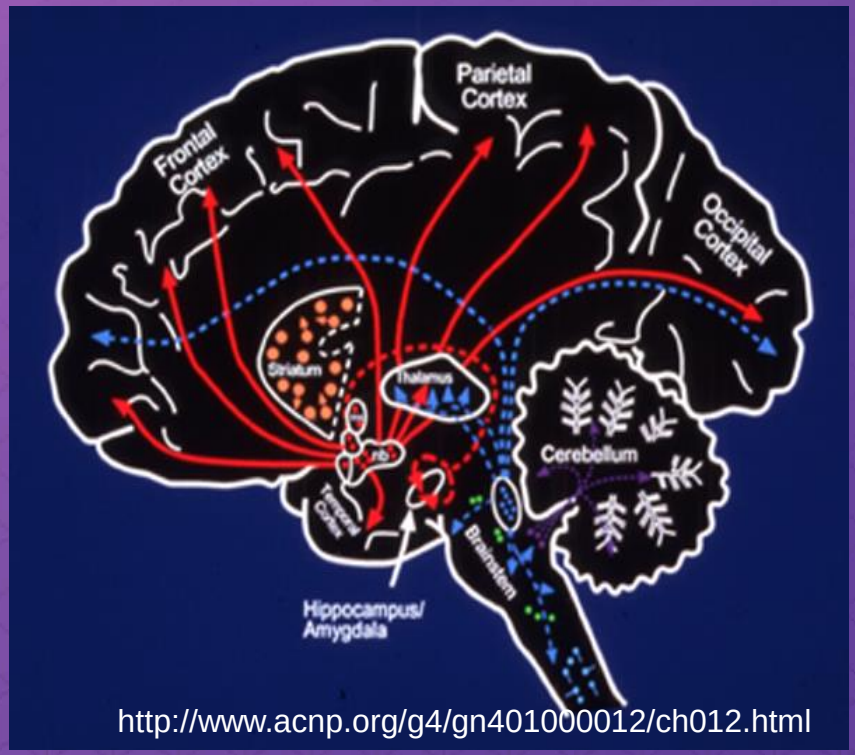
Neurotransmitters and Alzheimer's disease

- Norepinephrine (NE)
  - Abnormalities
    - Locus coeruleus: neuron loss, ↓ NE, ↑ turnover in surviving neurons (transporter upregulation?)
  - May play a role in psychological symptoms of dementia (aggression, agitation, psychosis)



Neurotransmitters and Alzheimer's disease

- Acetylcholine
  - Abnormalities
    - Up to 75% loss of cholinergic neurons in late-stage AD
      - Correlates with some aspects of cognitive impairment
    - ↓ in ChAT activity, choline uptake, AChE activity, nicotine binding (Francis *et al*., 1999)



http://www.acnp.org/g4/gn401000012/ch012.html

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Clinical consequences of cholinergic losses

Memory – hippocampus

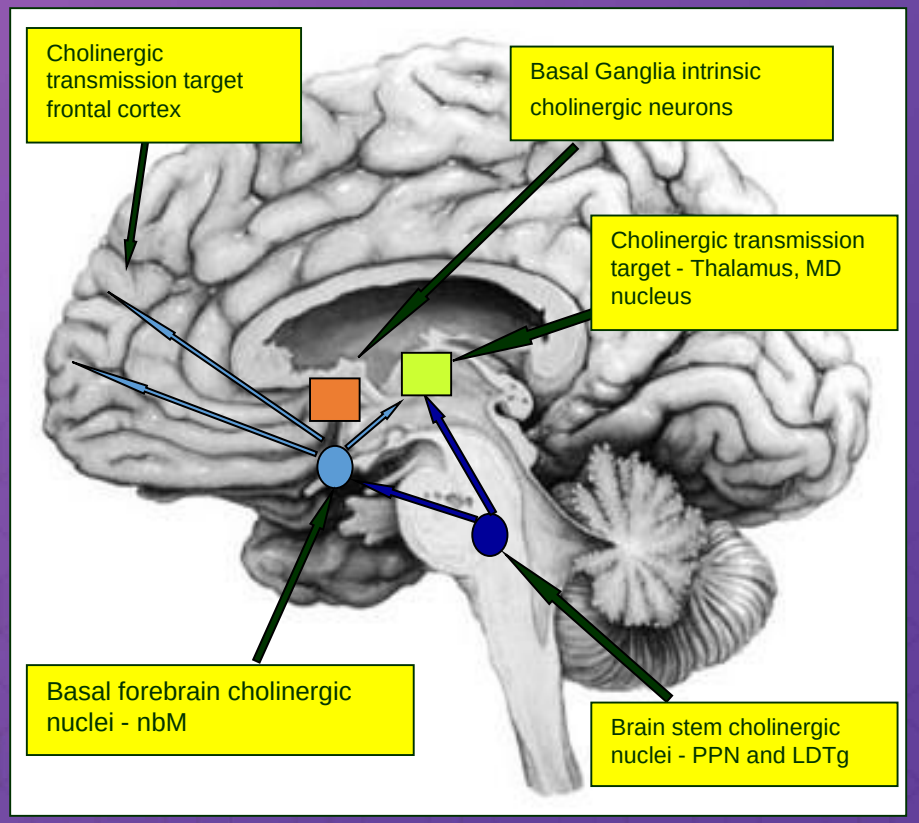
Learning – hippocampus, cortex

Attention – cortex, thalamus

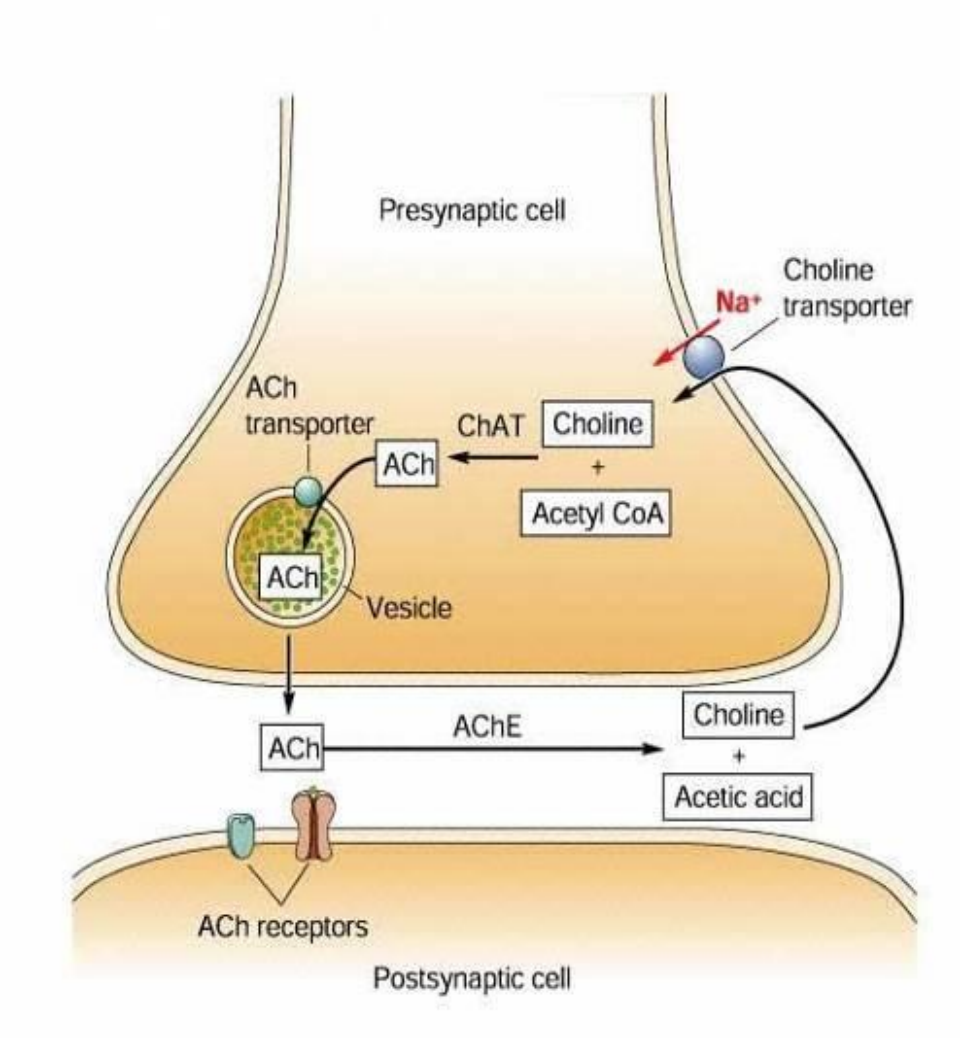
Consciousness, sleep, and dreaming - brainstem, thalamus, cortex

Movement, balance and motor regulation – striatum, brainstem, thalamus

Visual function – cortex, thalamus



Cholinergic terminal



Synthesising enzyme choline acetyltransferase (ChAT)

Acetylcholine released from synaptic vesicles in response to depolarisation

Acetylcholine interacts with receptors (muscarinic and nicotinic) on the pre and postsynaptic membrane

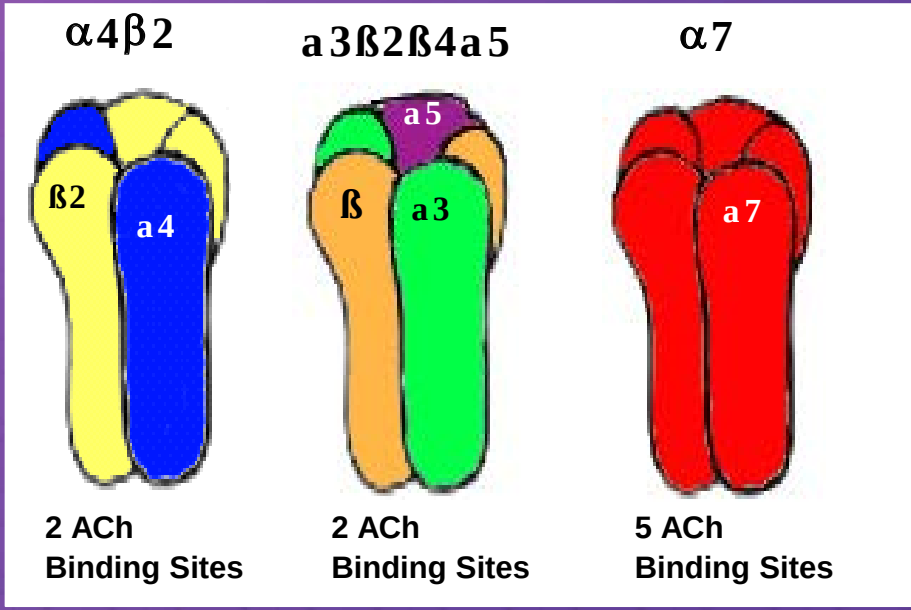
Acetylcholine in the synaptic cleft is removed by degrading enzyme acetylcholinesterase (AChE)

ACh Receptors

- Muscarinic
  - 5 subtypes (M1 – M5)
    - All metabotropic (G-protein coupled)
      - Slow, long lasting changes
    - M1, M3, & M5 stimulate
    - M2 & M4 inhibit
  - Primary locations
    - M1 (postsynaptic): cortex, hippocampus, striatum
    - M2: cortex, hippocampus, thalamus, striatum, cerebellum, brainstem
    - M4: striatum
    - M3 & M5: substantia nigra, thalamus, hippocampus

ACh Receptors

- Nicotinic
  - Ionotropic (ligand-gated ion channels)
    - Ca^{2+}, Na^{+}
    - Fast signaling, local changes
  - Heteroreceptor
    - 11 different subunits
      - α2-α9, β2-β4
  - Presynaptic activation results in neurotransmitter release
    - Dependent on neuron type



Cholinergic Transmission Reduces Alzheimer-type pathology

- Muscarinic M1 Agonists reduce Aβ levels in CSF in AD
- In triple-Tg-AD mouse, M1 agonist AF267B rescued cognitive deficits and reduced Aβ and tau pathology

Fisher A., Neurotherapeutics: 5 2008, 433-442

Caccamo A., Current Alzheimer Research. 6 2009:112-7

(dicyclomine M1 antagonist)

- Cholinesterase inhibitors may reduce amyloid

Several FDA approved drugs to treat AD,
But **NONE** cure, prevent or slow the disease!

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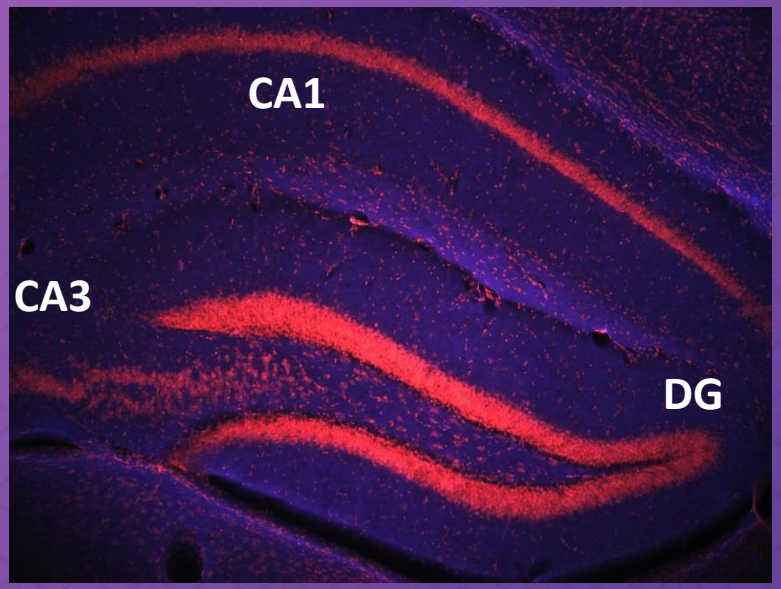
Neurotransmitters and Alzheimer's disease

- Glutamate
  - Small amount required for normal processes
    - Learning and memory
      - Requires neurotransmission in the hippocampus (LTP)
        - Trisynapatic pathway: DG, CA3, CA1



Adapted from Hascup *et. al.*, *Journal of Neurochemistry*, 2019. PMID: 30472734

- Pyramidal neurons (glutamatergic) in entorhinal cortex and hippocampus are particularly vulnerable to damage/cell loss/tangles

Memory Consolidation

Long Term Potentiation

Synaptic Plasticity

Glutamate

Neuronal Dysfunction

Memory Impairment

Neuronal Loss

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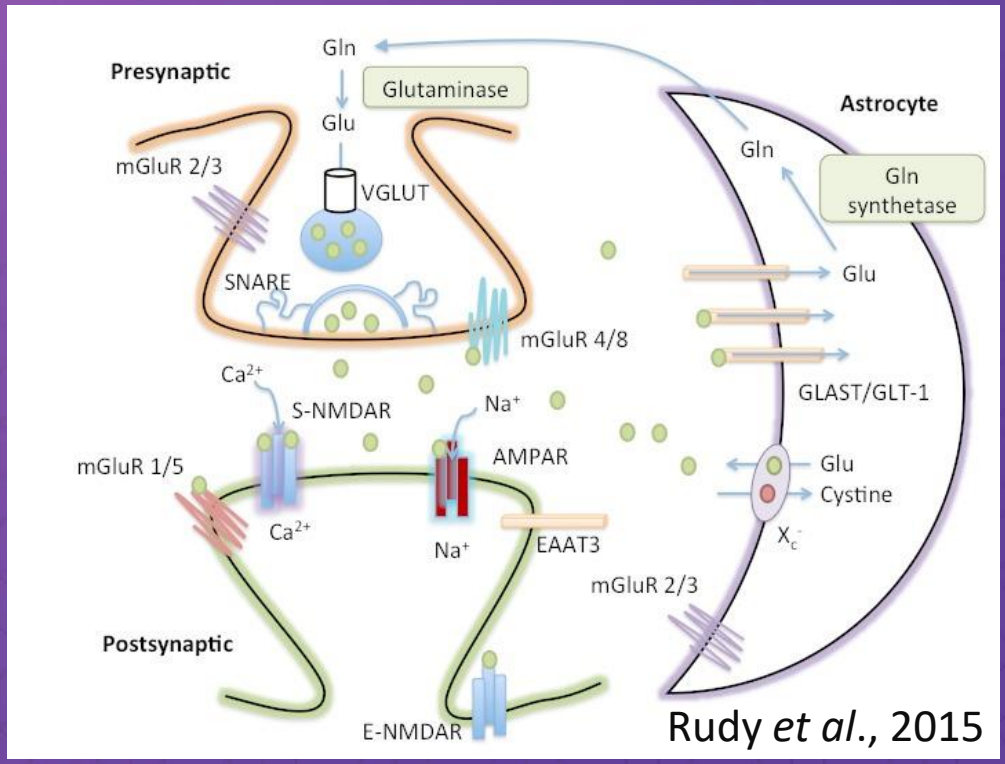
Glutamate

- Regulation of extracellular levels is essential!
  - Excess can erode synaptic regulation (alter learning and memory) and lead to neurodegeneration
    - Through an increase in release or a decrease in clearance
      - Must be cleared via EAATs
    - Excitotoxicity through NMDA receptors / ↑ intracellular Ca^{2+}
- Neurotransmission occurs mainly in tripartite synapse
  - Pre- and post- synaptic neurons, astrocytes



Rudy *et al.*, 2015

Glutamatergic synapse components

Table 1. Brief Overview of Glutamatergic Synapse Components: Localization and Function.

Glutamate synapse components	Localization	Function	References
VGluT	Presynaptic neuron	Packaging glutamate into vesicles	Takamori et al., 2000; Fremeau et al., 2001, 2004
Glutaminase	Presynaptic neuron	Synthesizes glutamate from glutamine	Revett et al., 2013
α7nAChR	Both neurons and glia	Soluble Aβ binding (in low concentrations) triggers Ca^{2+}-dependent release of glutamate from the presynaptic neuron, as well as stimulation of the postsynaptic neuron	Wang et al., 2000b; Gahring et al., 2004; Magdesian et al., 2005; Puzzo et al., 2008; Mura et al., 2012;Hascup and Hascup, 2016
mGluR Group II/III	Pre- and postsynaptic neuron	Gi/o-coupled receptor, inhibition of presynaptic release of glutamate or inhibition of postsynaptic response to stimulation	Ambrosini et al., 1995; Petralia et al., 1996; Ferraguti and Shigemoto, 2006; Rudy et al., 2015
mGluR Group I	Postsynaptic neuron	Gq-coupled receptor, depolarizes neuron upon binding of glutamate and results in Ca^{2+} release from intracellular stores	Petralia et al., 1996; Ferraguti and Shigemoto, 2006; Revett et al., 2013
AMPA	Pre- and postsynaptic neuron	Presynaptically promotes the formation of synapses. Postsynaptically depolarizes the neuron upon glutamate binding	Wisden and Seeburg, 1993; Isaac et al., 2007; Rudy et al., 2015
NMDA	Postsynaptic neuron	Contains a magnesium block that is removed upon depolarization of postsynaptic membrane, allowing for Ca^{2+} influx into the neuron	Calabresi et al., 1992; Wisden and Seeburg, 1993; Pandis et al., 2006; Parsons et al., 2007; Rudy et al., 2015
GLT-1 (EAAT1)/ GLAST (EAAT2)	Astrocytes	Clearance of glutamate from the synapse by uptake into astrocytes	Lehre et al., 1995; Revett et al., 2013
GS	Astrocytes	Conversion of glutamate to glutamine so that it may be transported back to the presynaptic neuron	Norenberg and Martinez-Hernandez, 1979; Parsons et al., 2007; Revett et al., 2013

Note. Outline of glutamate neuronal and astrocytic components and their functions in glutamatergic neurotransmission.
α7nAChR = alpha-7 nicotinic acetylcholine receptor; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAAT = excitatory amino acid transporter; GLAST = glutamate aspartate transporter; GLT-1 = glutamate transporter-1; GS = glutamine synthetase; mGluR = metabotropic glutamate receptor; NMDA = *N*-methyl-*D*-aspartic acid; VGluT = vesicular glutamate transporter.

Findley *et. al.*, *ASN Neuro*, 2019. PMID: 31213067

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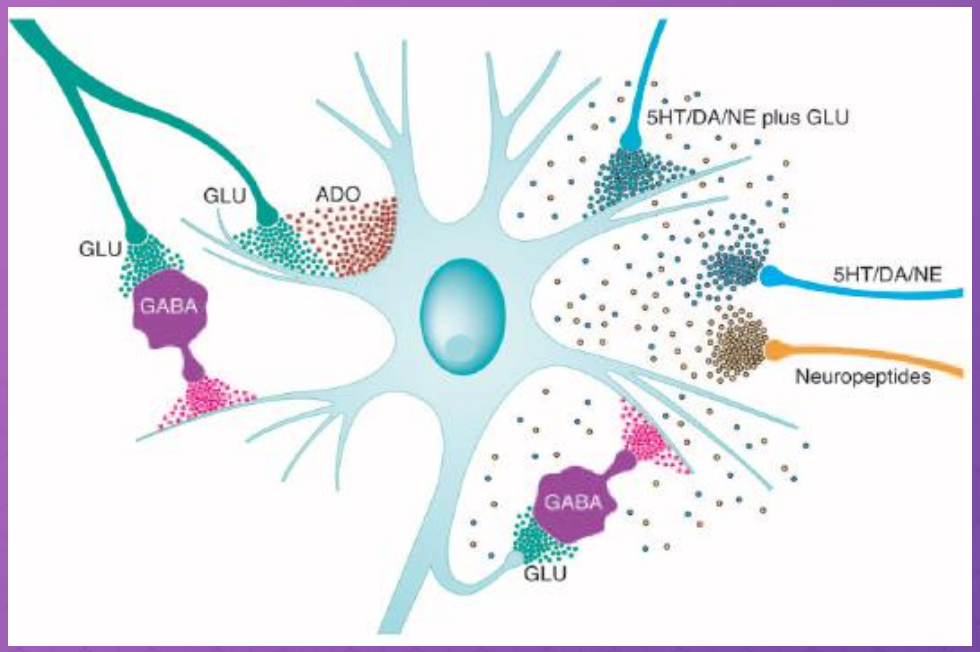
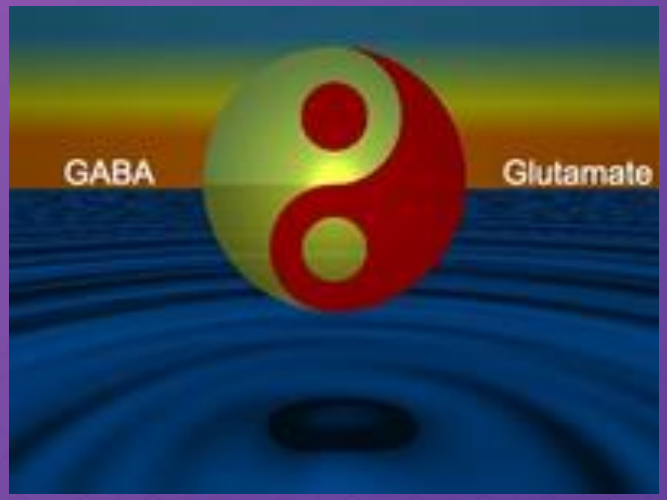
Major transmitters – glutamate (excitatory) and GABA (inhibitory)





- Glutamate and GABA (γ-amino butyric acid) form basis of neurotransmission
- GABA neurons are interneurons in cortex, can be interneurons or projection neurons in subcortical areas (e.g. striatal projection neurons)
- Glutamate neurons are projection neurons
  - corticocortical, thalamocortical, cortical-subcortical (corticofugal)

Alzheimer's pharmacotherapies

- FDA-approved drugs to treat AD
  - Currently 2 classes
    - Cholinesterase inhibitors
    - NMDAR antagonists
  - Approved 1996-2003
    - Combination drug approved in 2014

<u>NONE</u> slow or stop AD progression

Alzheimer's pharmacotherapies

Drug Name	Drug Type and Use	How It Works	Common Side Effects
Aricept® (donepezil)	Cholinesterase inhibitor prescribed to treat symptoms of mild, moderate, and severe Alzheimer's	Prevents the breakdown of acetylcholine in the brain	Nausea, vomiting, diarrhea, muscle cramps, fatigue, weight loss
Exelon® (rivastigmine)	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate Alzheimer's (patch is also for severe Alzheimer's)	Prevents the breakdown of acetylcholine and butyrylcholine (a brain chemical similar to acetylcholine) in the brain	Nausea, vomiting, diarrhea, weight loss, indigestion, muscle weakness
Namenda® (memantine)	N-methyl D-aspartate (NMDA) antagonist prescribed to treat symptoms of moderate to severe Alzheimer's	Blocks the toxic effects associated with excess glutamate and regulates glutamate activation	Dizziness, headache, diarrhea, constipation, confusion
Namzaric® (memantine and donepezil)	NMDA antagonist and cholinesterase inhibitor prescribed to treat symptoms of moderate to severe Alzheimer's	Blocks the toxic effects associated with excess glutamate and prevents the breakdown of acetylcholine in the brain	Headache, nausea, vomiting, diarrhea, dizziness, anorexia
Razadyne® (galantamine)	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate Alzheimer's	Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain	Nausea, vomiting, diarrhea, decreased appetite, dizziness, headache

https://www.nia.nih.gov/health/how-alzheimers-disease-treated

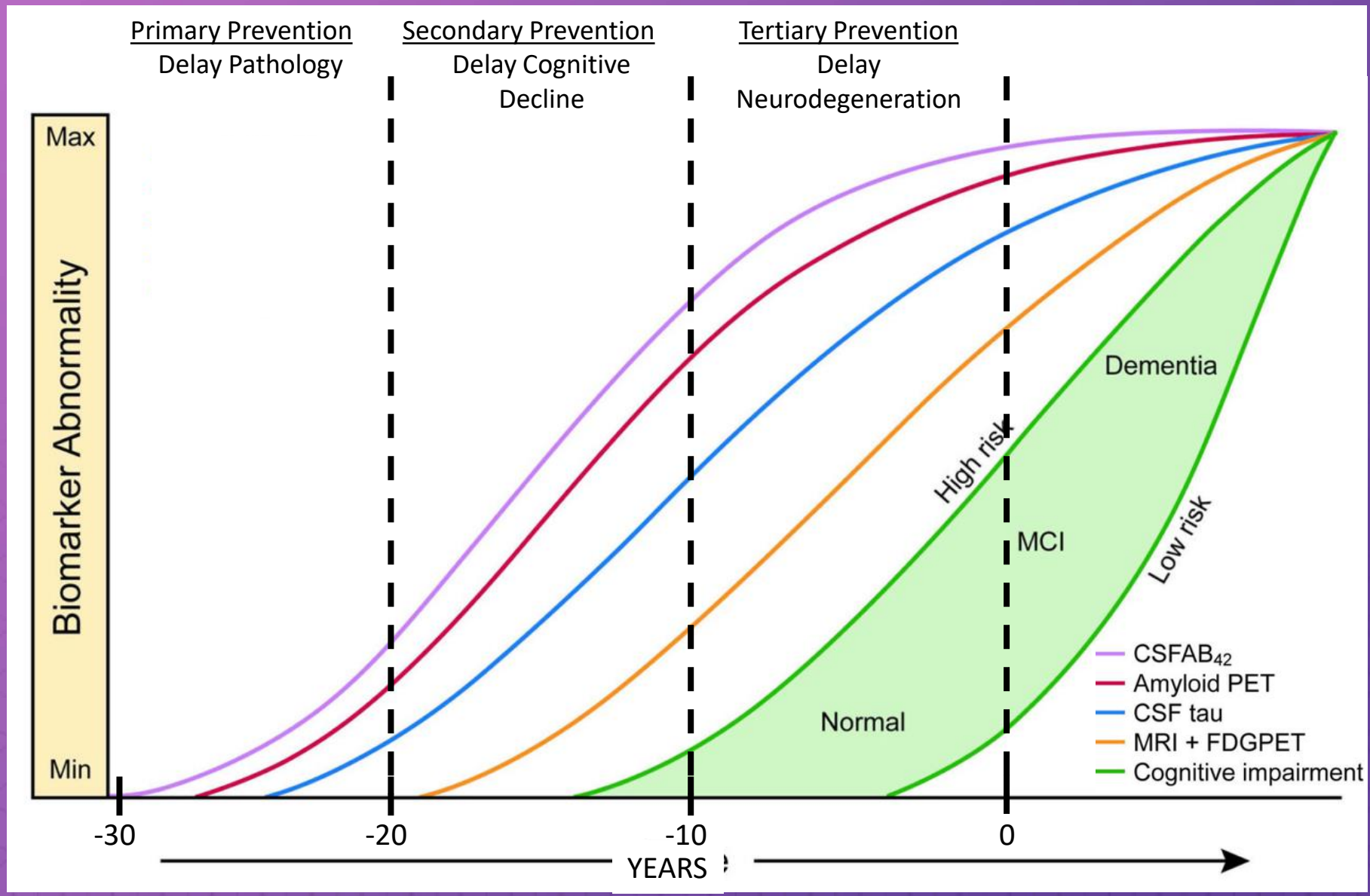
Alzheimer's pharmacotherapies

- Aducanumab to treat early AD
  - Human monoclonal antibody
    - Targets soluble and insoluble amyloid-beta
  - Potential modest benefits
    - Questionable efficacy
  - Under FDA review

So, where does this leave us?

What is the path forward?

What does research tell us?



Modified From: Jack Jr., et al, The Lancet Neurology (2013) &
Sperling, Jack Jr., Aisen; Science Translational Medicine (2011)

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Are there changes in neurotransmission and are they temporally related to the AD continuum?

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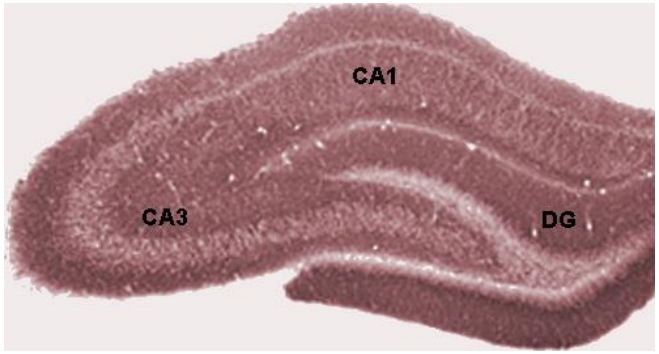
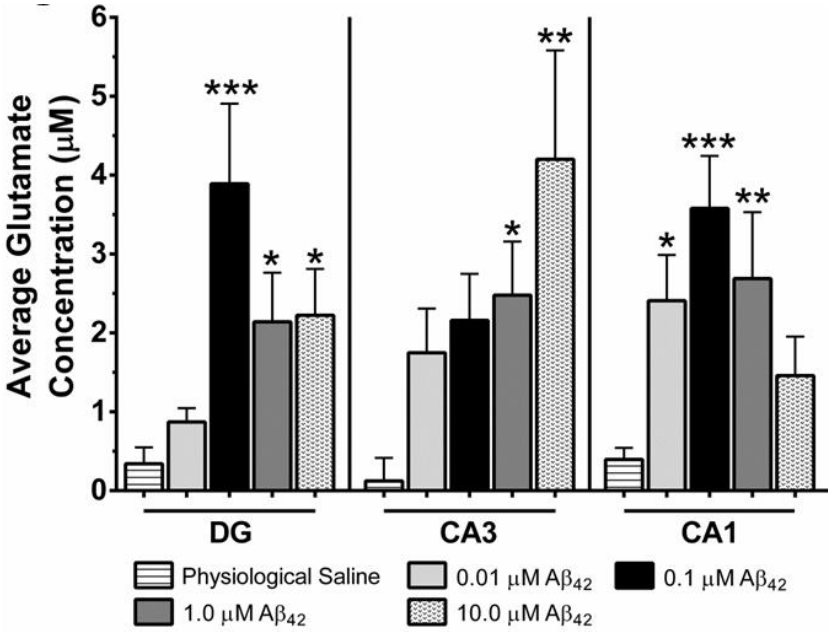
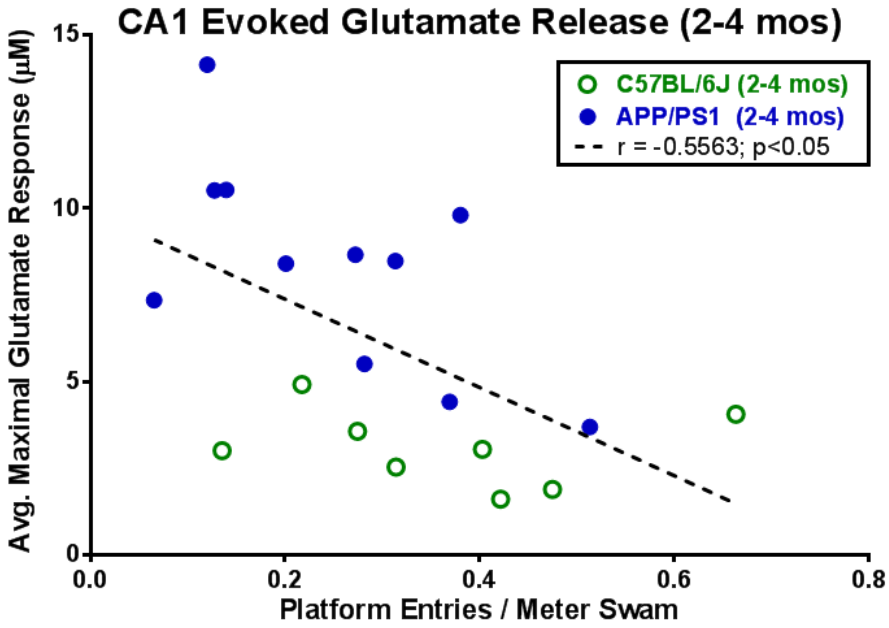
Hippocampal glutamate neurotransmission is required for both learning and memory

- LTP
- Trisynaptic pathway
- Soluble $A\beta_{42}$ elicits glutamate release
- Glutamate release negative correlates with cognition prior to cognitive decline







Adapted from Hascup & Hascup, 2015, 2016. *Journal of Alzheimer's Disease*

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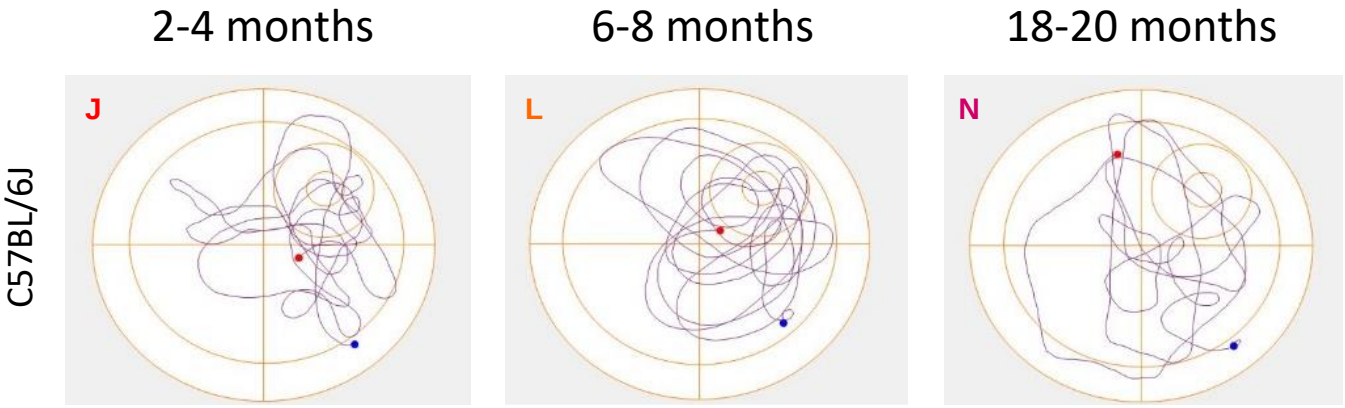

Adapted from Hascup *et. al.*, *Scientific Reports*, 2020. PMID: 32879385

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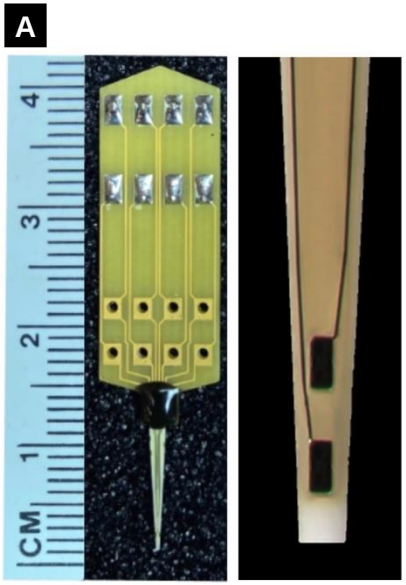

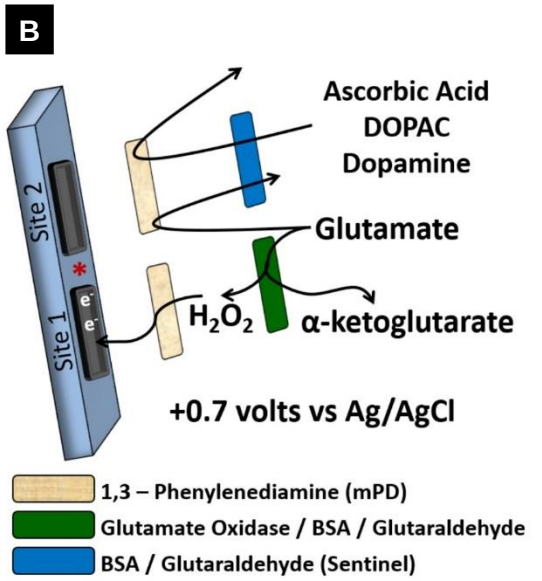

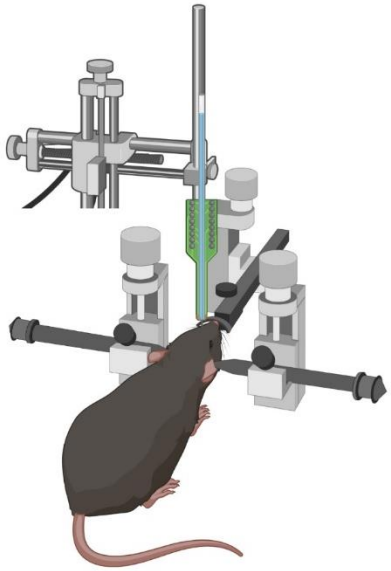

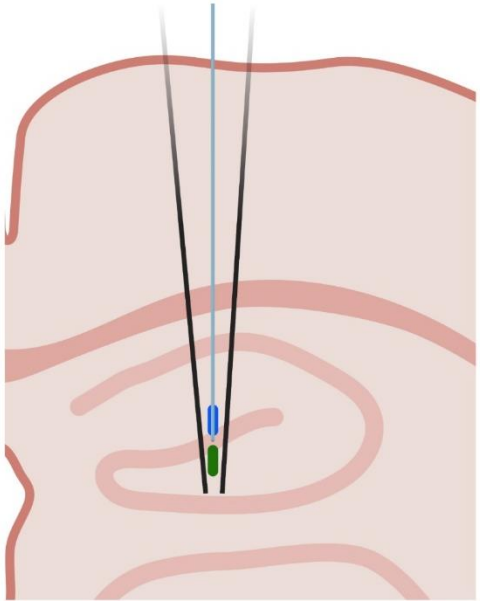

Hascup *et. al.*, *Scientific Reports*, 2020.
PMID: 32879385

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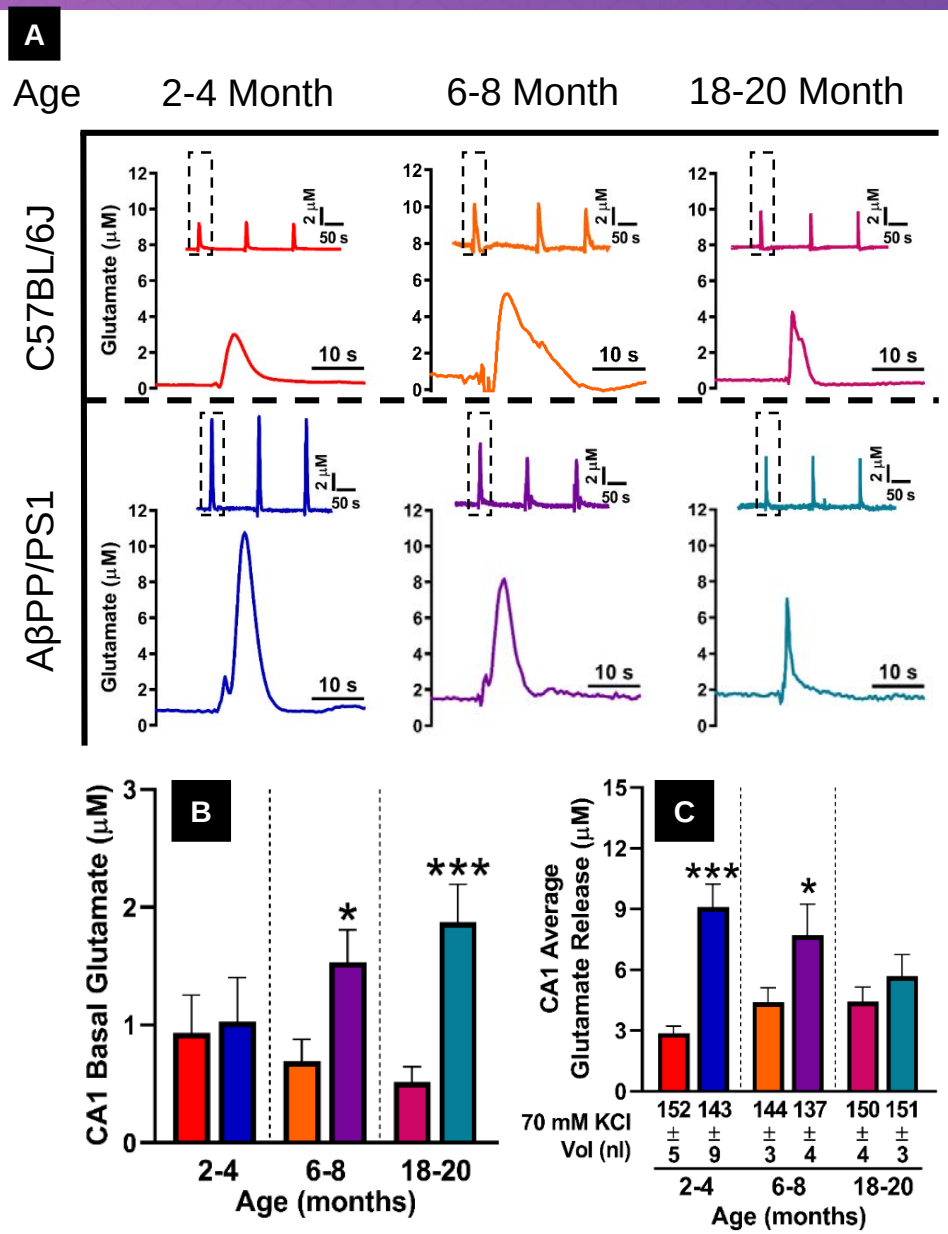

Adapted from Hascup *et. al.*, *Scientific Reports*, 2020. PMID: 32879385

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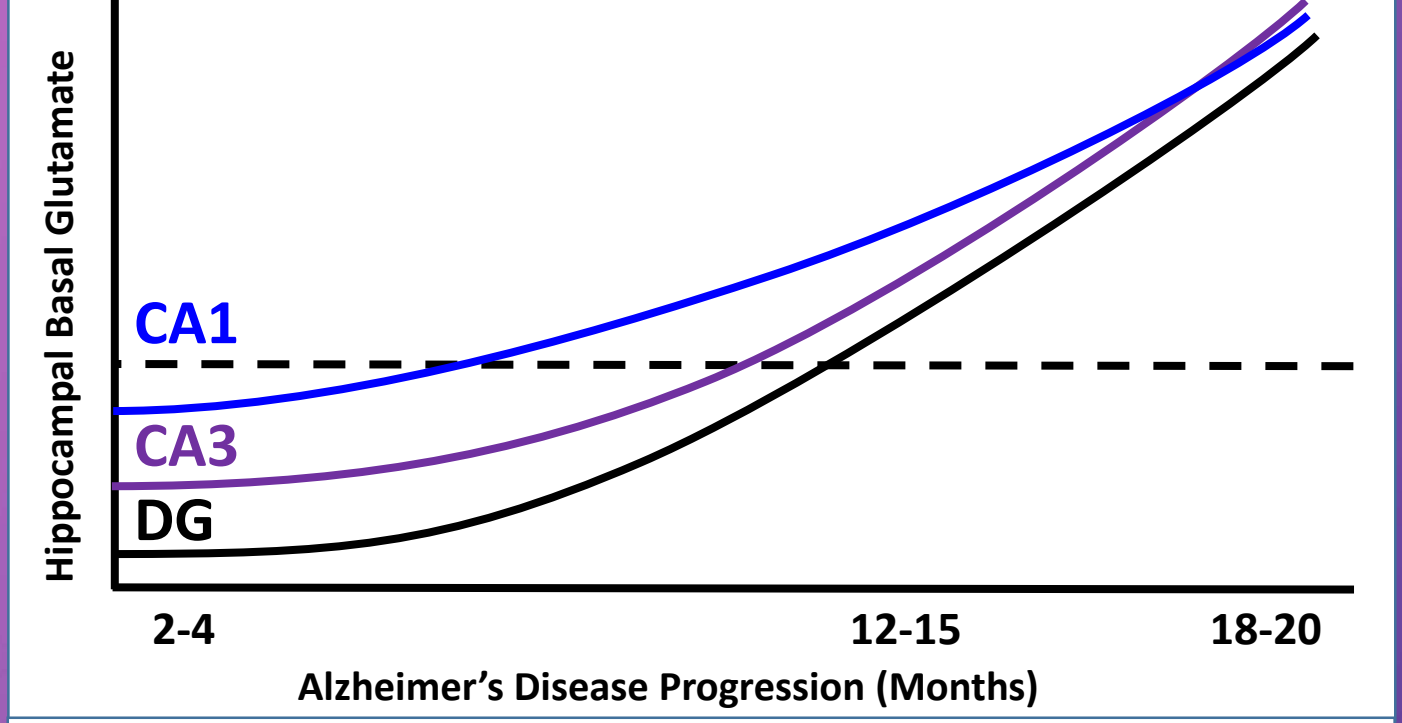
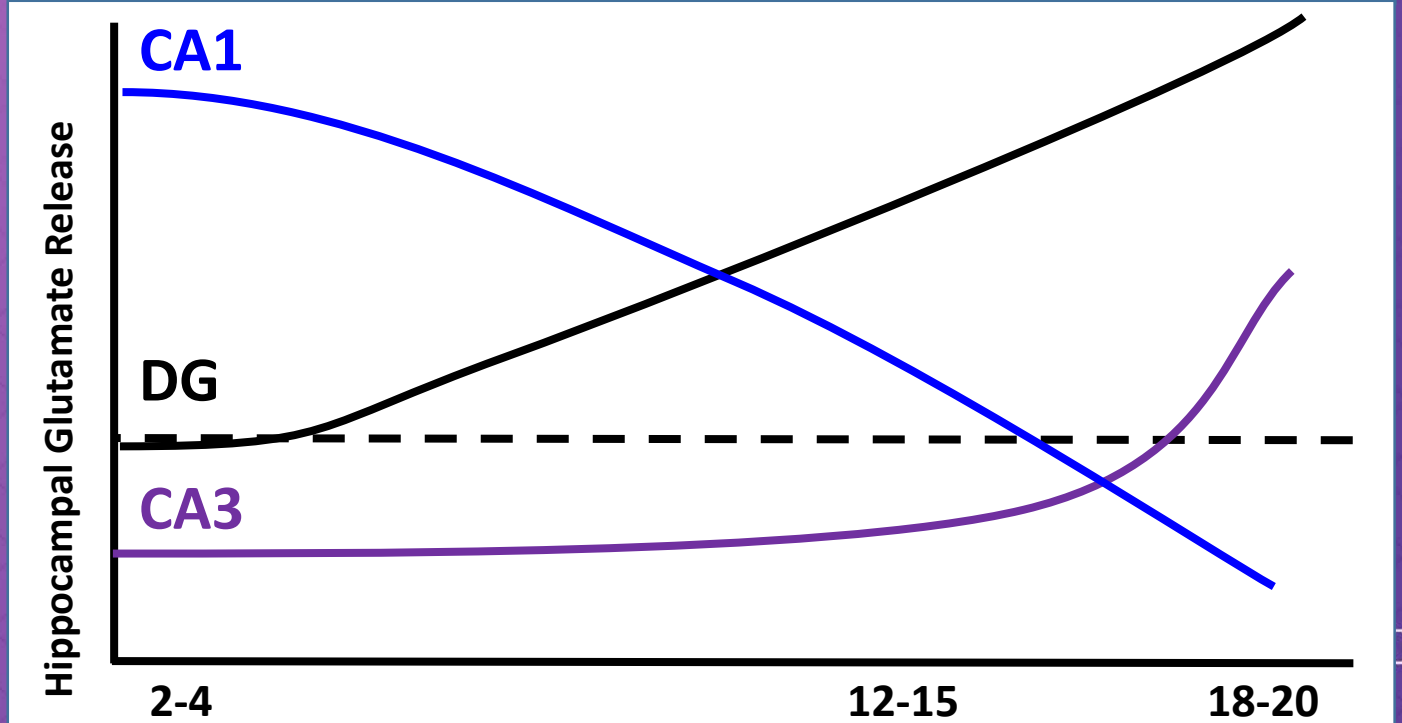
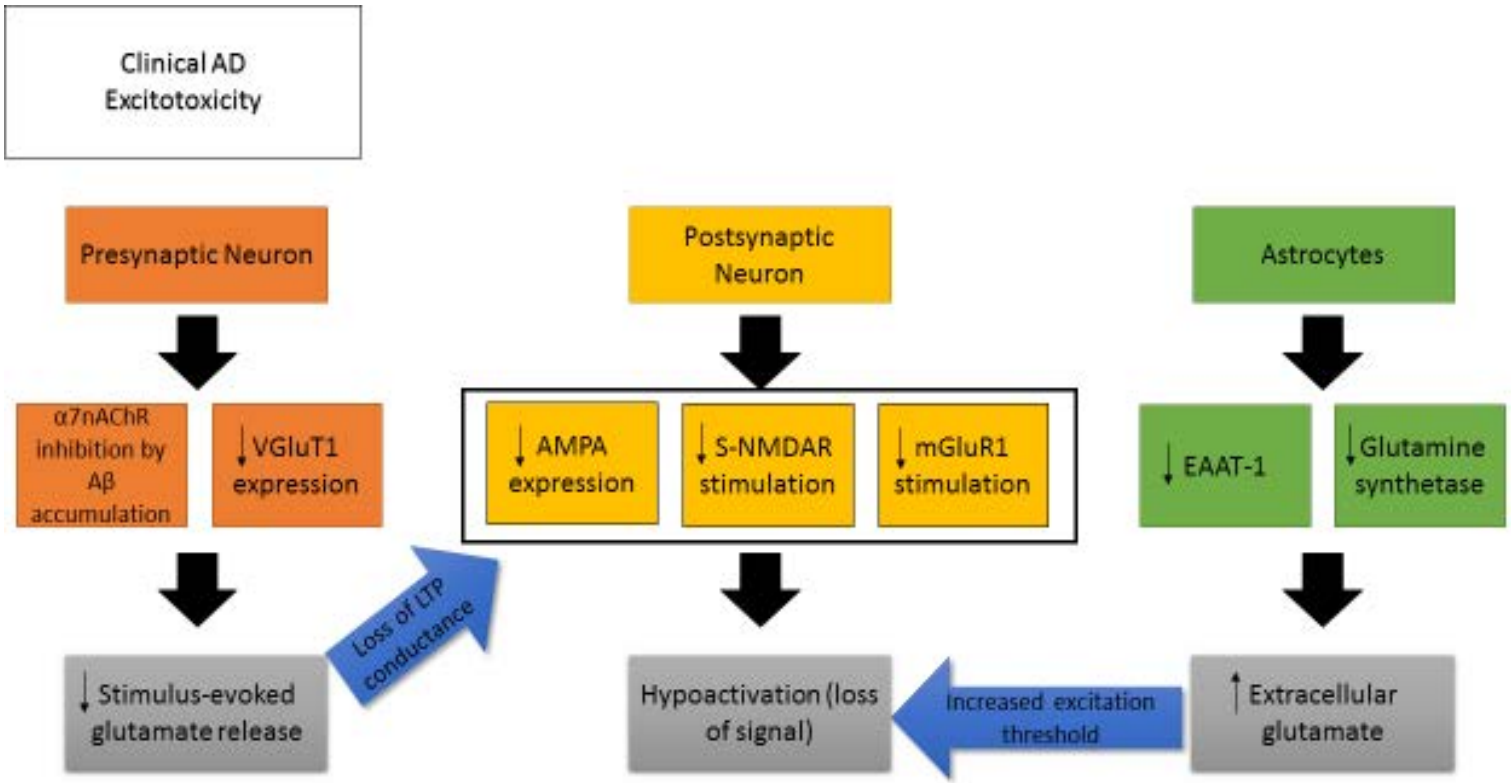




Glutamatergic neurotransmission is altered with disease progression



Vesicular glutamate transporter-1 (VGlut1); α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA); N-methyl-D-aspartate, (NMDA), metabotropic glutamate receptor (mGluR); alpha 7 nicotinic receptor (α7nAChR); excitatory amino acid transporter-1 (EAAT-1).

Adapted from Findley *et. al.*, *ASN Neuro*, 2019. PMID: 31213067

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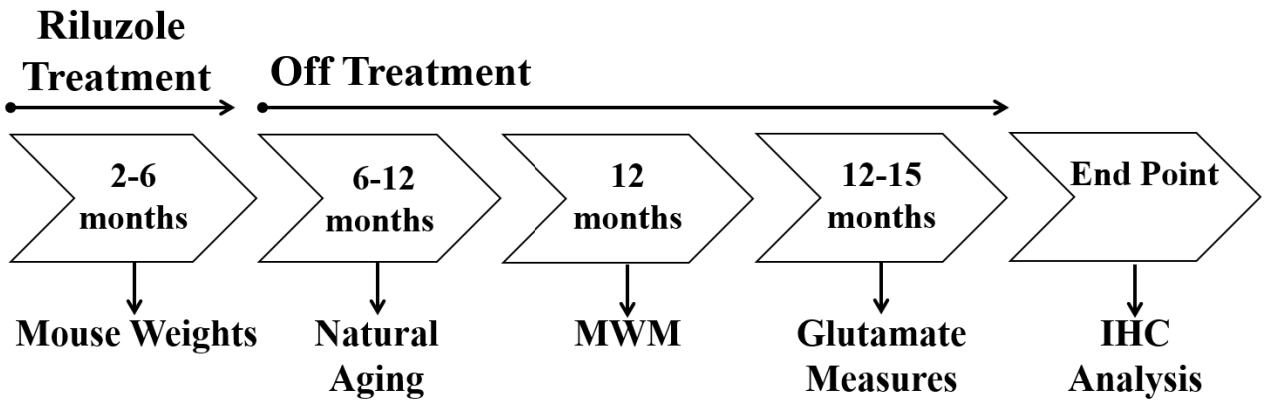
Can these temporally distinct changes in glutamatergic neurotransmission be targeted to improve disease outcome?

Riluzole

- 2-Amino-6-trifluoromethoxybenzothiazole hydrochloride
- FDA / EMA Approved for ALS
- Prevents excitotoxicity by
  1. Inhibiting sodium-dependent presynaptic glutamate release
     - Song J-H et al, 1997 J. Pharmacol. Exp. Ther.
  2. Increasing glutamate uptake
     - Fumagalli et al, 2008; Eur. J. Pharmacol.
  3. Combination of effects?



Animal Number

C57BL/6J Vehicle	14	14	14	13*	12#
AβPP/PS1 Vehicle	12	12	12	12	12
AβPP/PS1 Riluzole	11	11	11	11	9#

Hascup *et. al.*, *Journal of Neurochemistry*, 2020. PMID: 33107040

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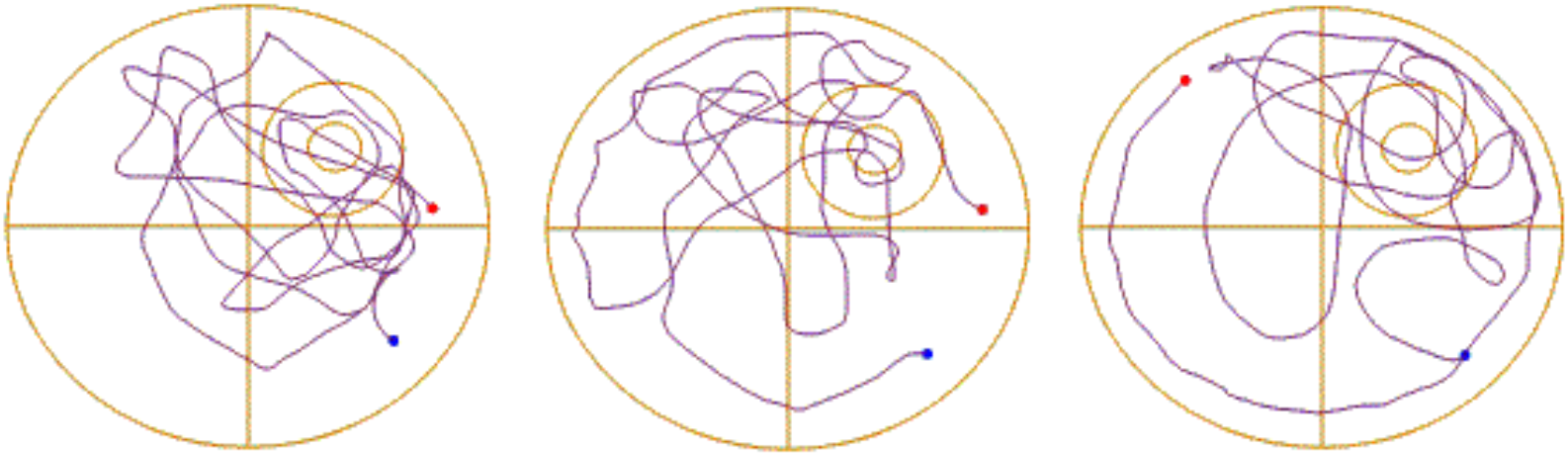
D



C57BL/6J Vehicle **AβPP/PS1 Vehicle** **AβPP/PS1 Riluzole**

Adapted from Hascup *et. al.*, *Journal of Neurochemistry*, 2020. PMID: 33107040

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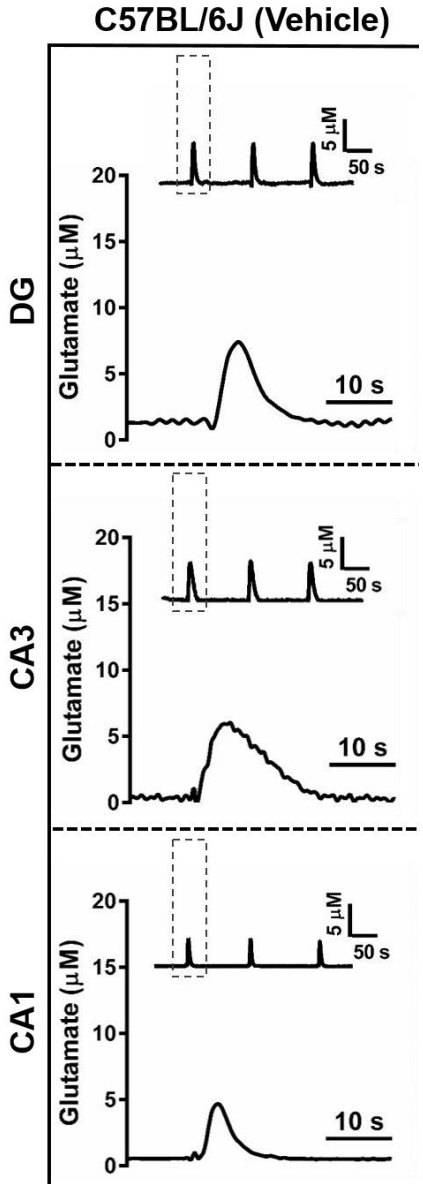

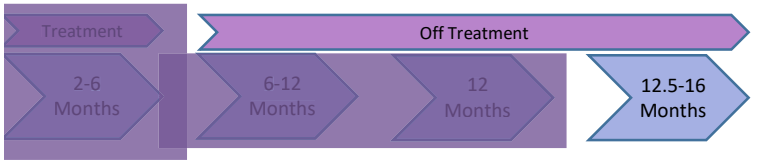

Adapted from Hascup *et. al.*, *Journal of Neurochemistry*, 2020. PMID: 33107040

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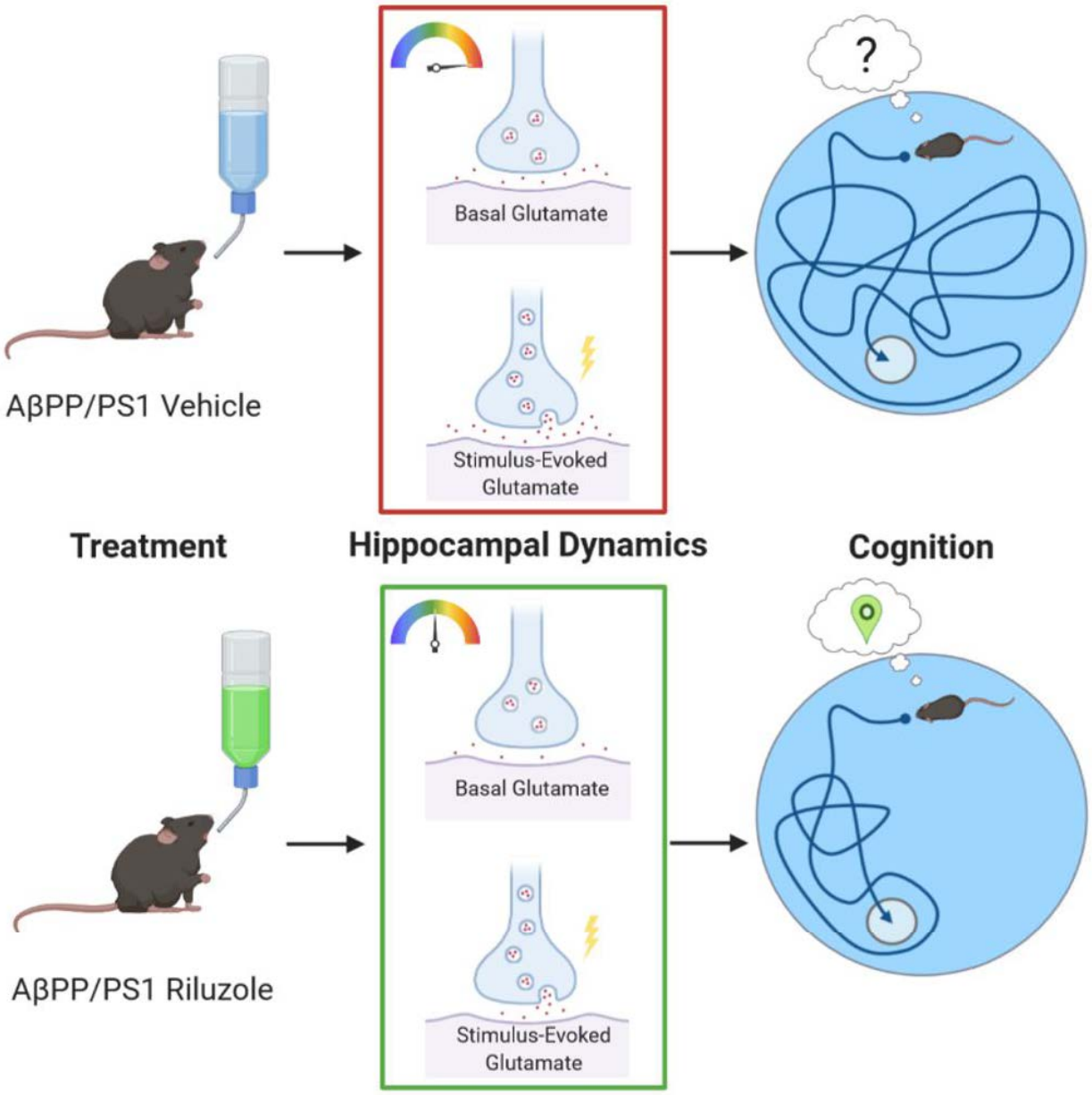

Hascup *et. al.*, *Journal of Neurochemistry*, 2020. PMID: 33107040

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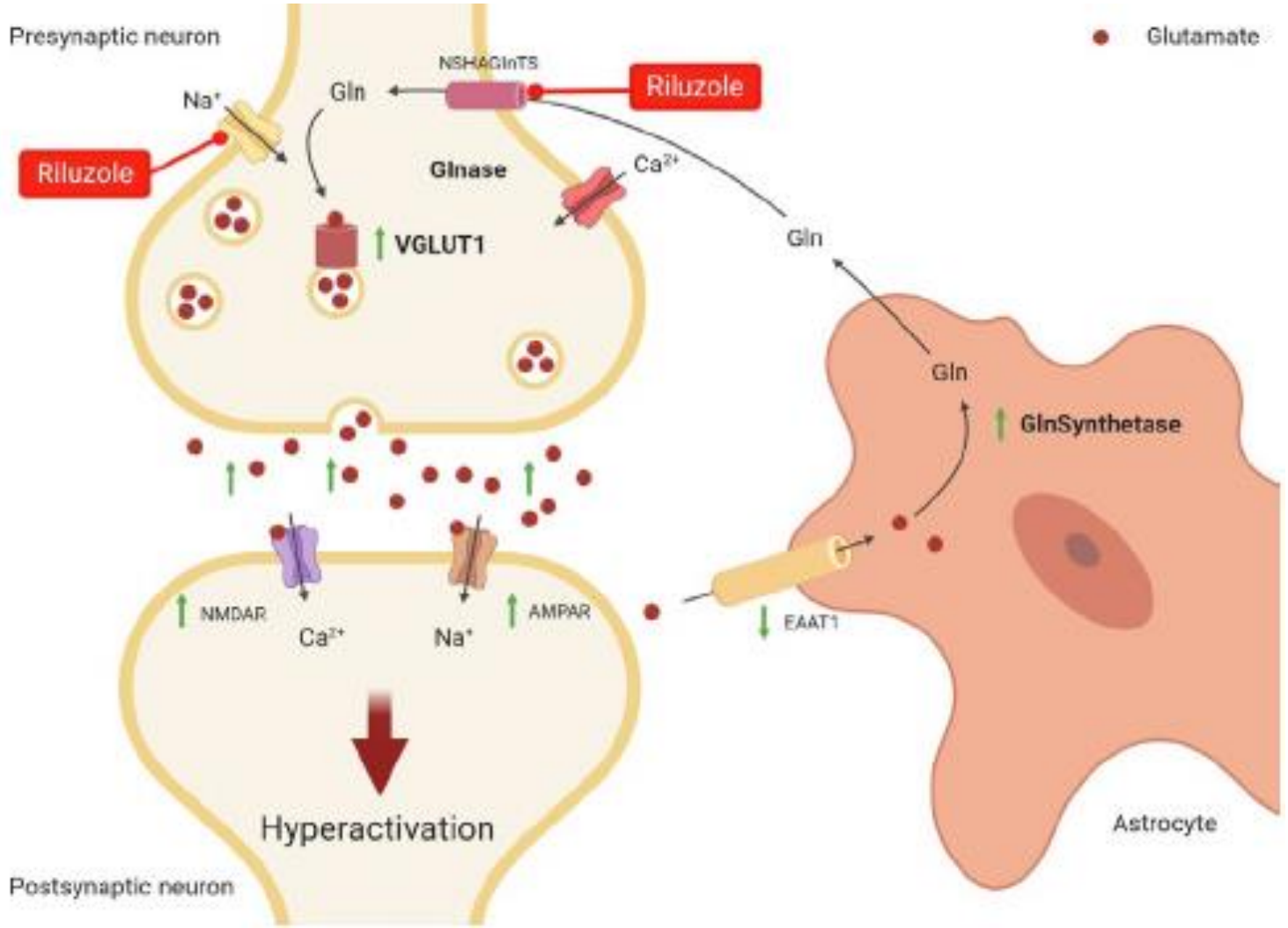

Gulyaeva. *Journal of Neurochemistry*, 2020. PMID: 33276416

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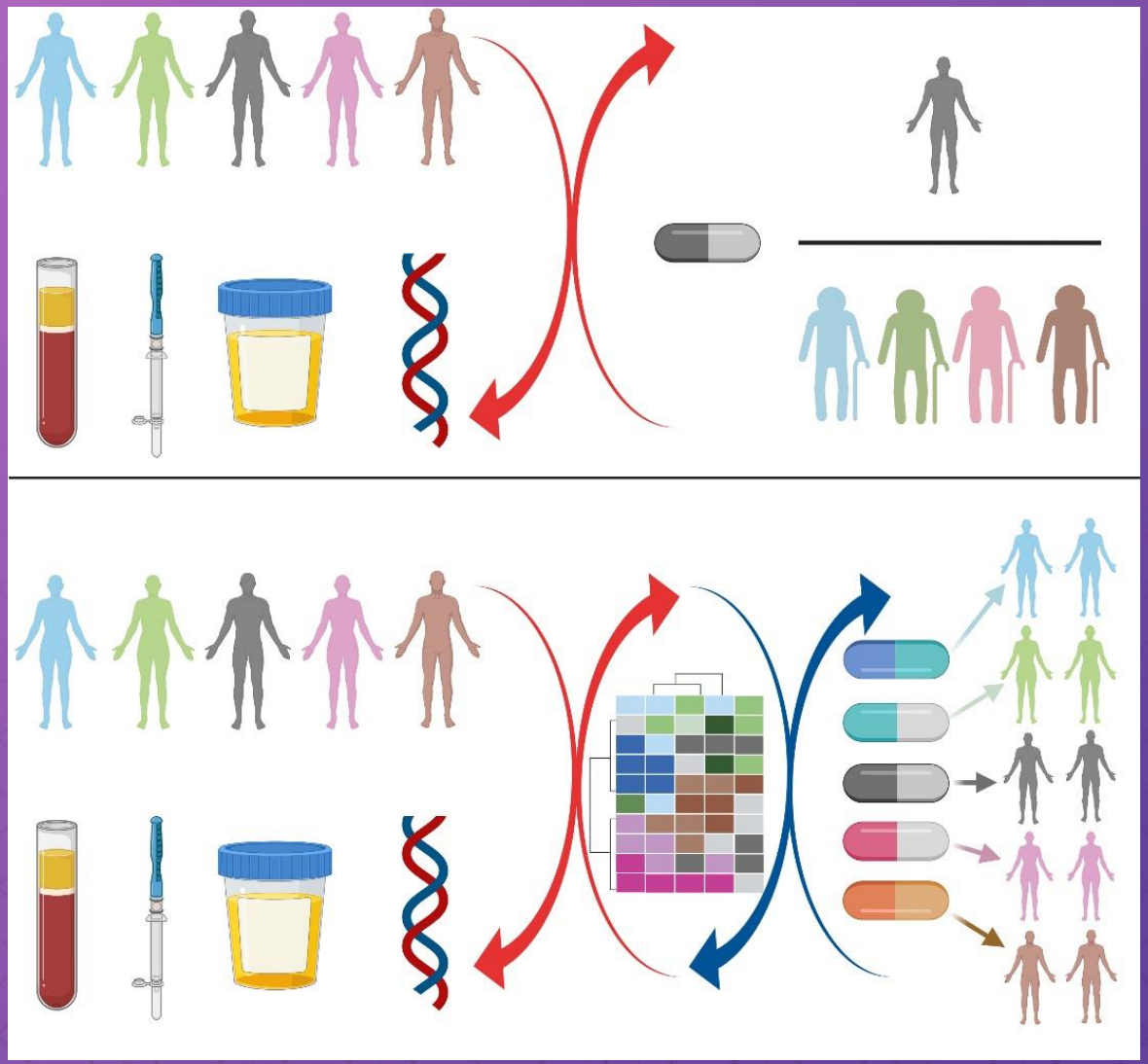
Looking to the future



Questions/Comments?