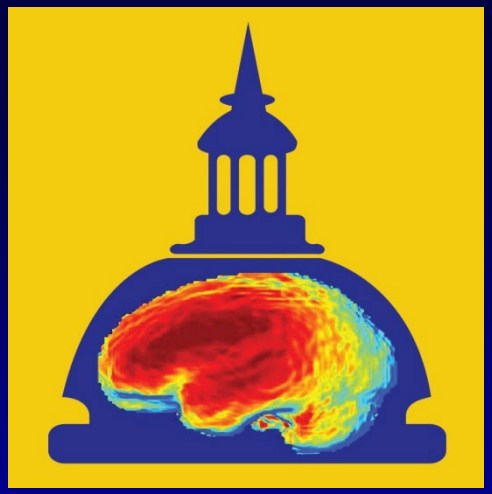

NEURO-PHYSIOLOGICAL VIEW OF LATE-LIFE MENTAL HEALTH AND SUBSTANCE-USE DISORDERS

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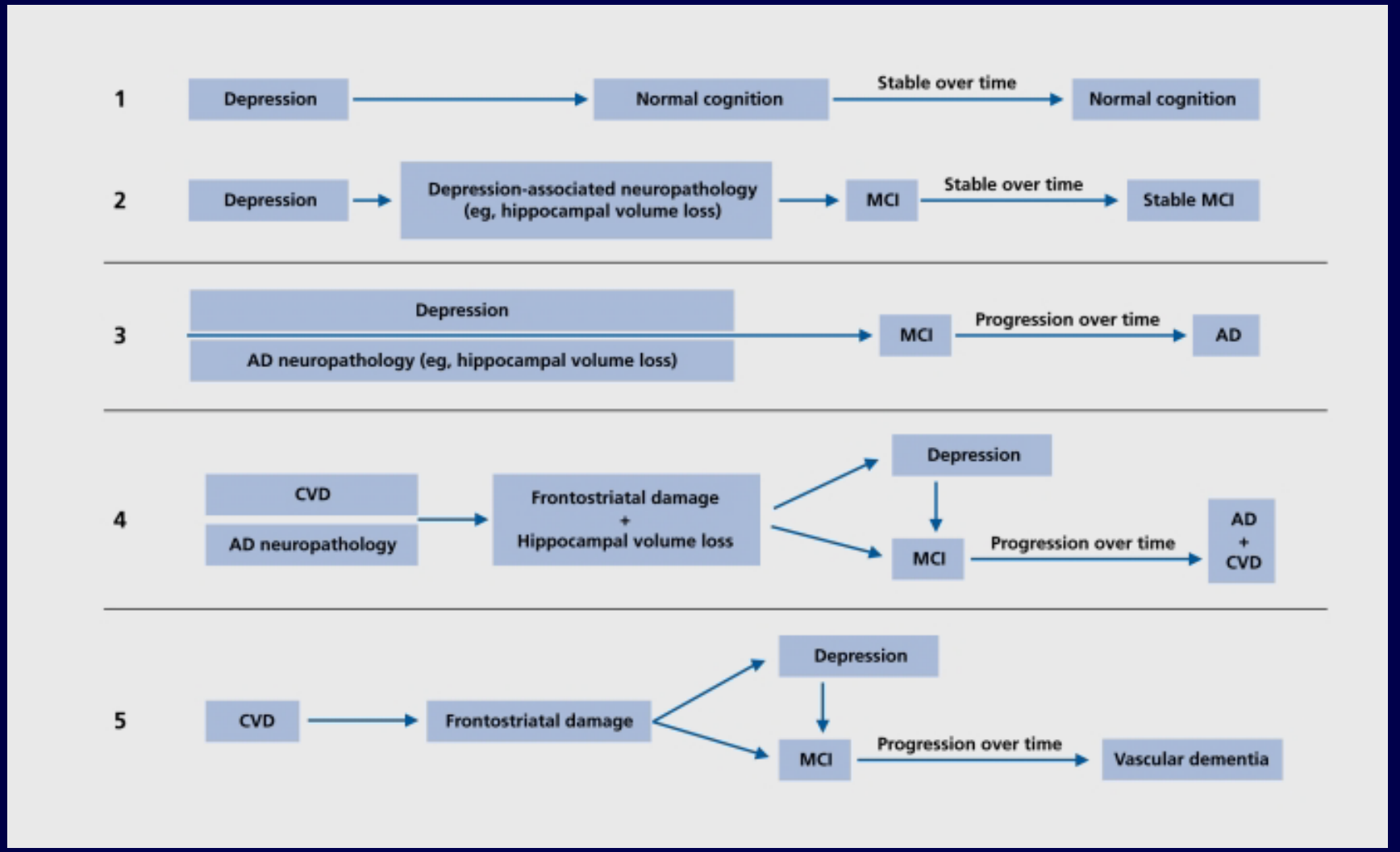
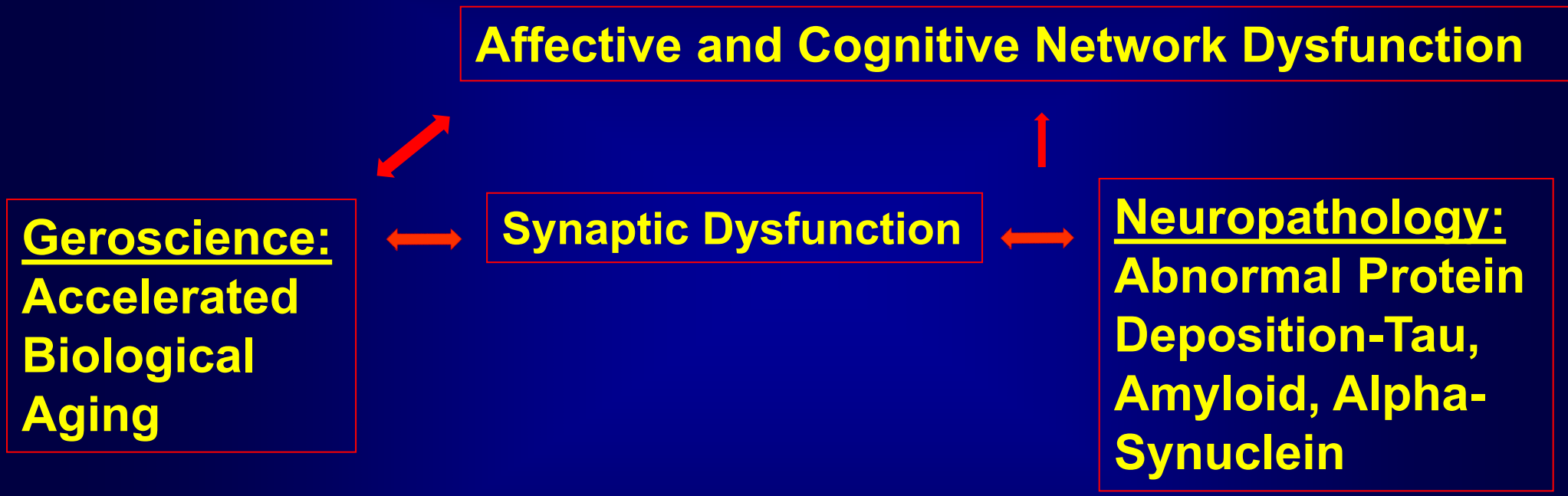
Pathways of Late-Life Depression: Neurobiological Heterogeneity



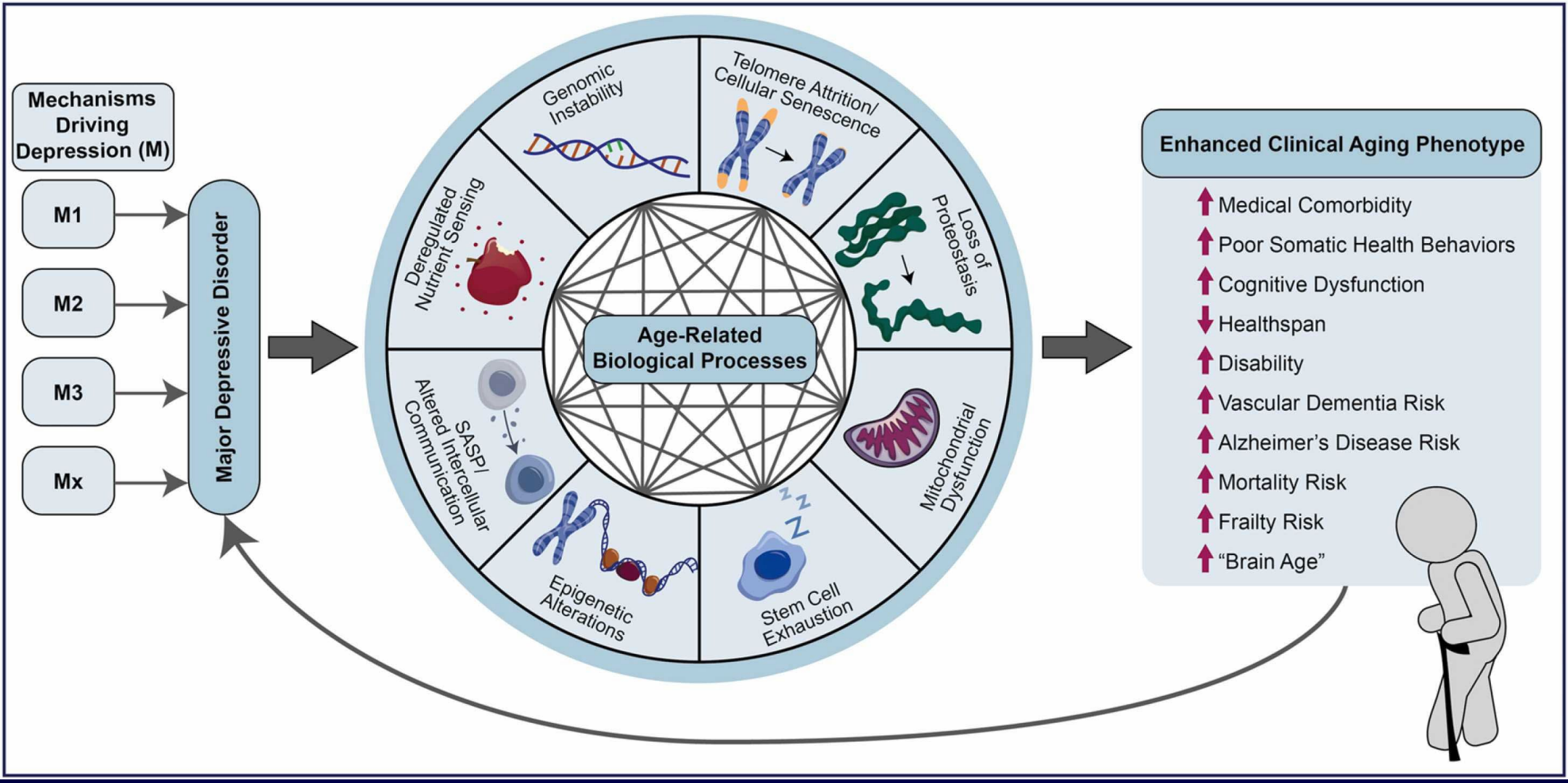
Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds CF 3rd, DeKosky ST, Becker JT.. Dialogues Clin Neurosci. 2008;10(3):345-57.

A Multi-Factorial Model of Late-Life Mental Health and Substance-Use Disorders



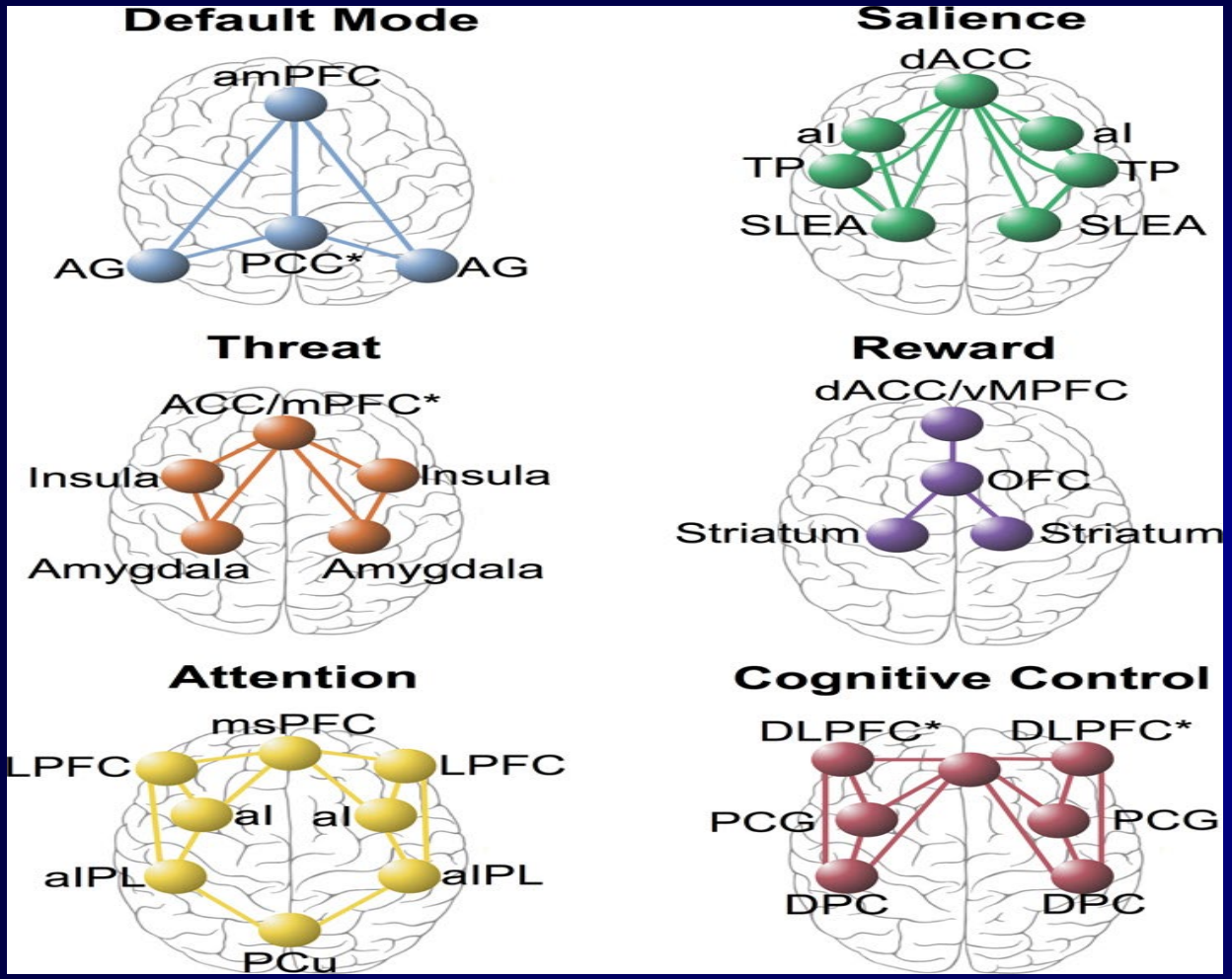
Depression in Late-Life has been the Major Focus of Study

Geroscience Perspective: Accelerated biological aging as a mechanistic link for the elevated risk of adverse health outcomes in Major Depression



Lorenzo EC, Kuchel GA, Kuo CL, Moffitt TE, Diniz BS. Ageing Res Rev. 2023;83:101805.

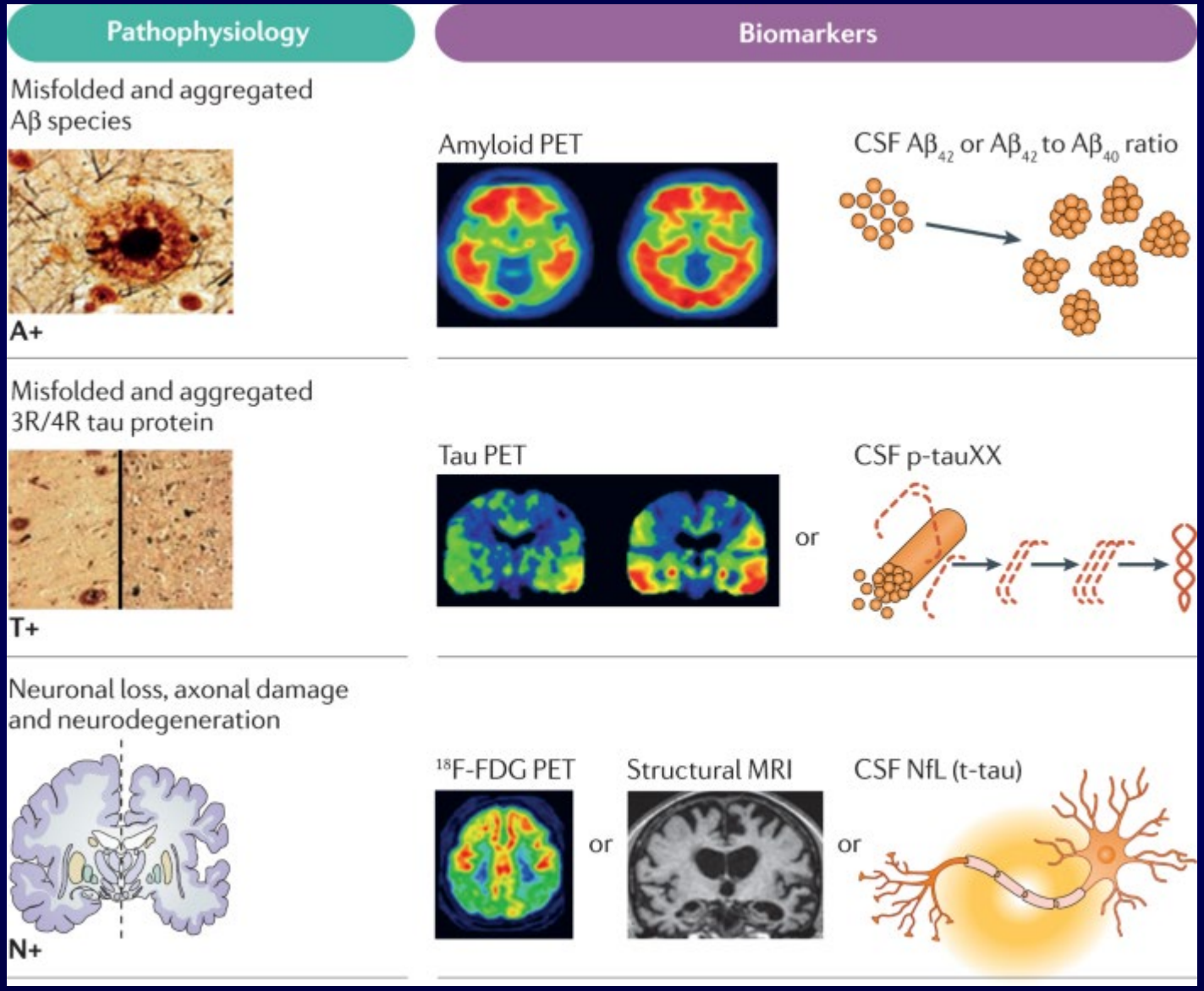
Affective and Cognitive Networks Affected in Mental Health and Substance-Use Disorders



Default mode, salience, reward and cognitive control networks are dysregulated in late-life depression.

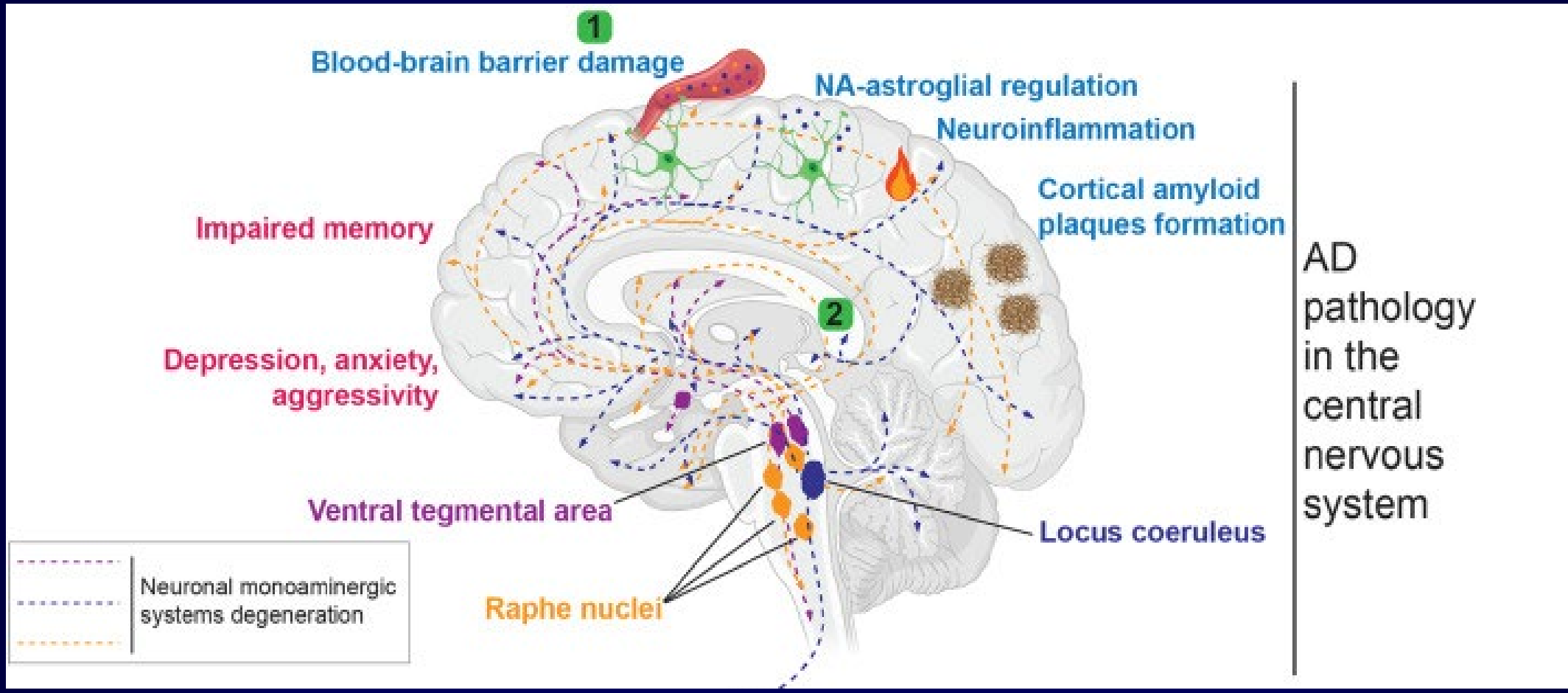
Large-scale intrinsic and task-evoked circuits: ACC, Anterior Cingulate Cortex; AG, Angular Gyrus; aI, Anterior Insula, aIPL, Anterior Inferior Parietal Lobule; amPFC, Anterior Medial Prefrontal Cortex; dACC, Dorsal Anterior Cingulate Cortex; DLPFC, Dorsolateral Prefrontal Cortex; DPC, Dorsal Parietal Cortex; LPFC, Lateral Prefrontal Cortex; mPFC, Medial Prefrontal Cortex; msPFC, Medial Superior Prefrontal Cortex; OFC, Orbitofrontal Cortex; PCC, Posterior Cingulate Cortex; PCG, Precentral Gyrus; PCu, Precuneus; vMPFC, Ventromedial Prefrontal Cortex. Williams, LM Depress Anxiety. 2017 Jan; 34(1): 9–24.

Neuropathology and Synaptic Dysfunction Underlying Cognitive Network Dysfunction Studied with Brain Imaging and Biomarker Methods



Hampel H, et al. Nat Rev Neurol. 2021;17(9):580-589.

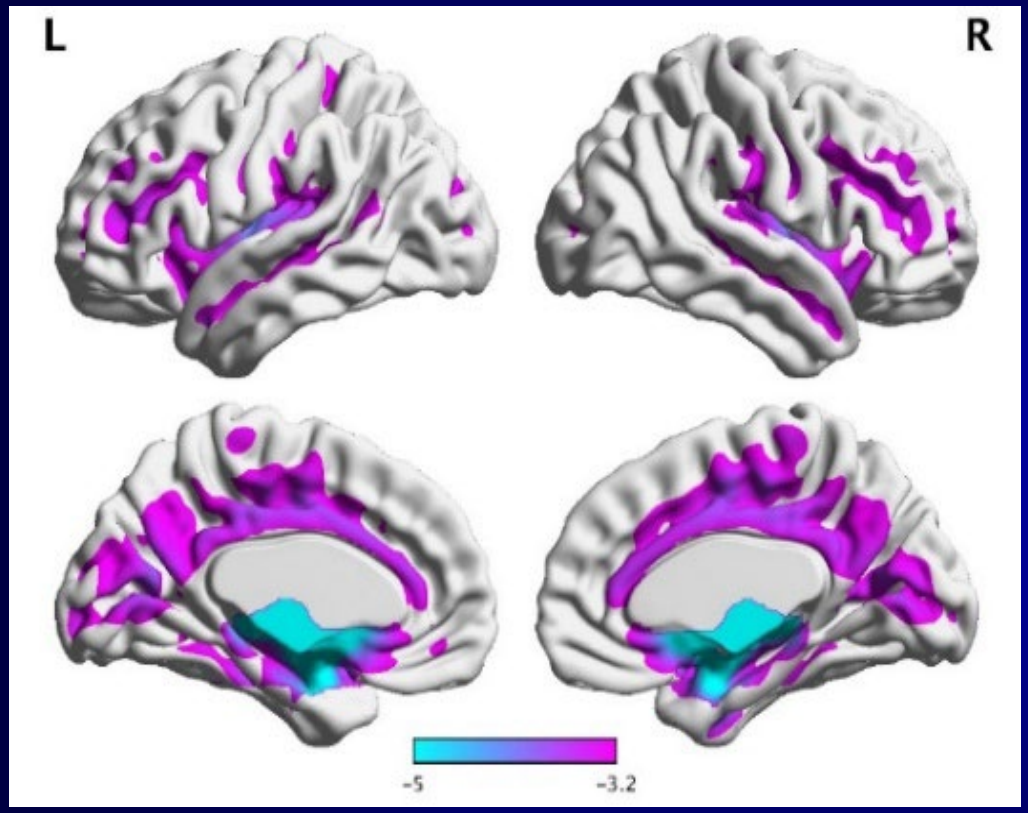
Monoaminergic Neurochemical Pathways are Vulnerable to Synaptic Degeneration in Mental Health and Substance-Use Disorders

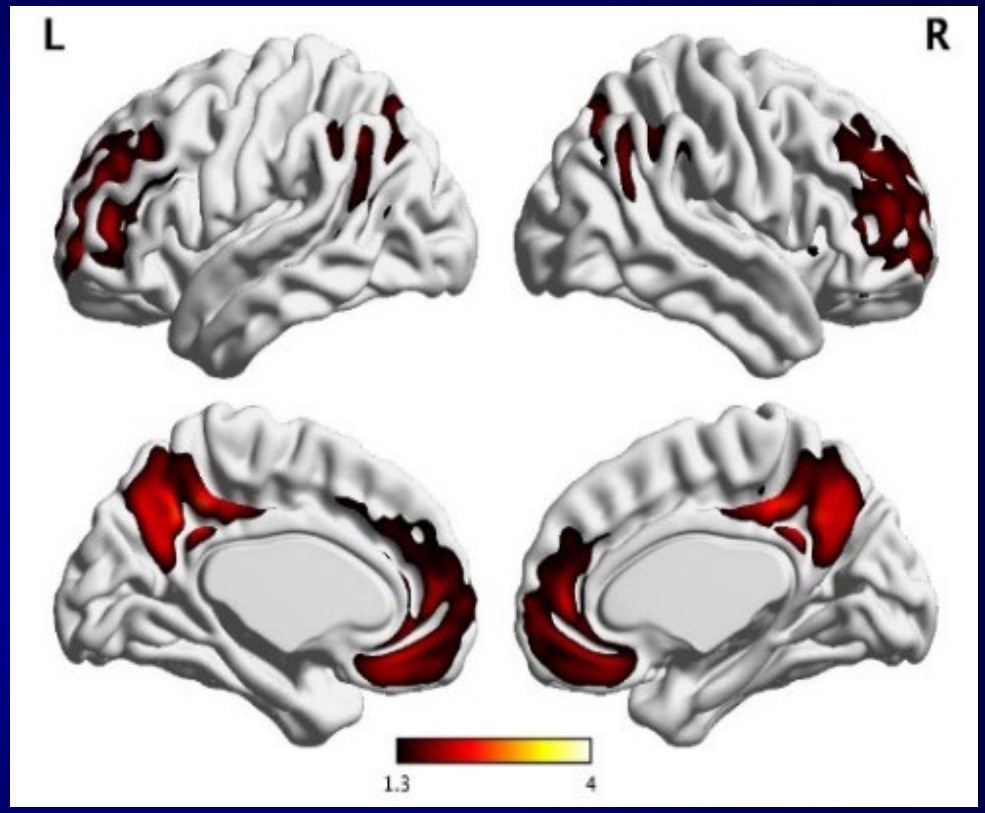


Monoamine system degeneration include the neurotransmitters serotonin (yellow), norepinephrine (blue) and dopamine (purple). Gallo A. et al. Exp Gerontol. 2021;152:111452.

Serotonin Degeneration (5-HTT) is Associated with Neuropathology (Amyloid) in Late-Life Depression and Mild Cognitive Impairment.

5-HTT **Aβ**





mmPLS derived 5-HTT – Aβ spatial covariance pattern superimposed on a 3D brain rendering

Smith GS, Protas H, Kuwabara H, Savonenko A, Nassery N, Gould NF, Kraut M, Avramopoulos D, Holt D, Dannals RF, Nandi A, Su Y, Reiman EM, Chen K. Neuroimage Clin. 2023;37:103322

Understanding Neurobiology Informs Treatment Development

Affective and Cognitive Network Dysfunction:

- *Cognitive Interventions targeting Reward (Engage) and Cognitive Control (nCCR) Networks*

Geroscience:

- *Senolytics*
- *Exercise*

Synaptic Dysfunction:

- *Multi-Modal Antidepressants (Vortioxetine)*
- *Treatments that induce synaptic plasticity (SSRI/SNRIs, Ketamine, Lithium)*

Neuropathology:

- *Amyloid and Tau Immunotherapies*
- *Increase Slow Wave Sleep (Increase Glymphatic Clearance)*

Summary

- Mental heath and substance-use disorders are associated with dysfunction of cognitive networks.
- Multiple mechanisms underlie dysfunction of cognitive networks, including biological aging, synaptic dysfunction and neuropathology.
- Monoamine systems are vulnerable to neurodegeneration and are critically involved in mental heath and substance-use disorders over the lifespan.
- Understanding the heterogeneity of mental heath and substance-use disorders in late-life will inform the development of more effective strategies for individualized treatment and ultimately, prevention.

Priorities for Future Neurobiological Research

- Depression in late-life has been the major focus of study. Other mental health and substance-use disorder, associated with vulnerability to cognitive decline and earlier mortality, require further investigation:
    - Late-life substance-use
    - Chronic schizophrenia and late-onset psychosis
    - Difficult to treat mood disorders, including bipolar disorder and psychotic depression
- Understanding the neurobiology of social disconnection and stress may have an impact on intervention development