



NORMAL AGING OR EARLY DEMENTIA? WHAT TO EXPECT FOR THE NORMAL AGING BRAIN

Emily Morgan, MD
2026

OBJECTIVES

Describe normal age-related changes in the brain

Translate Cellular ---> Functional level

Differentiate normal aging from early dementia

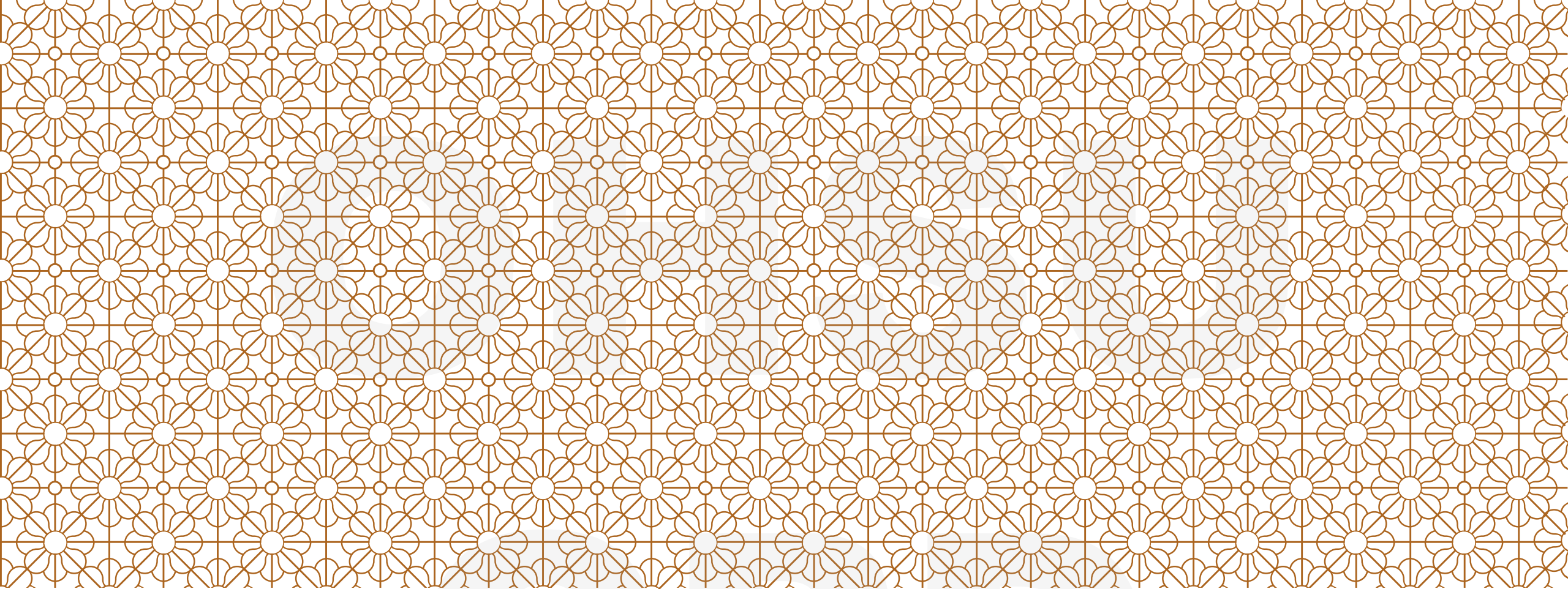
TAKE THIS WITH A GRAIN OF SALT



wiseGEEK

Research on “normal” aging is difficult

- Many studies do not have long term follow-up to look at whether normal subjects develop MCI/dementia
- In longitudinal studies, drop-outs tend to be the least healthy “normal” adults
- Bias – who enrolls in these healthy aging studies? Likely healthier more robust older adults



PHYSIOLOGIC AGING OF THE BRAIN

Cellular Level

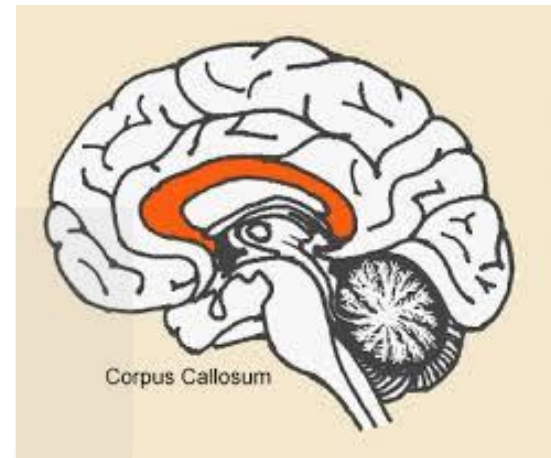
GREY AND WHITE

Grey matter is made up of neurons
Receiving, processing, transmitting
information

White matter is made up of myelinated axons
Forms networks to help different areas of the brain connect



AGE RELATED CHANGES TO WHITE MATTER



Decreased white matter is normal with aging

- Constant volume loss after the age of 40

Largest volume change is in the **corpus callosum**

- Effects ability of hemispheres to communicate
- Decreased nerve signal propagation = slowed retrieval and response times

Minimal change in grey matter volume in comparison

- Neurons do not die with age

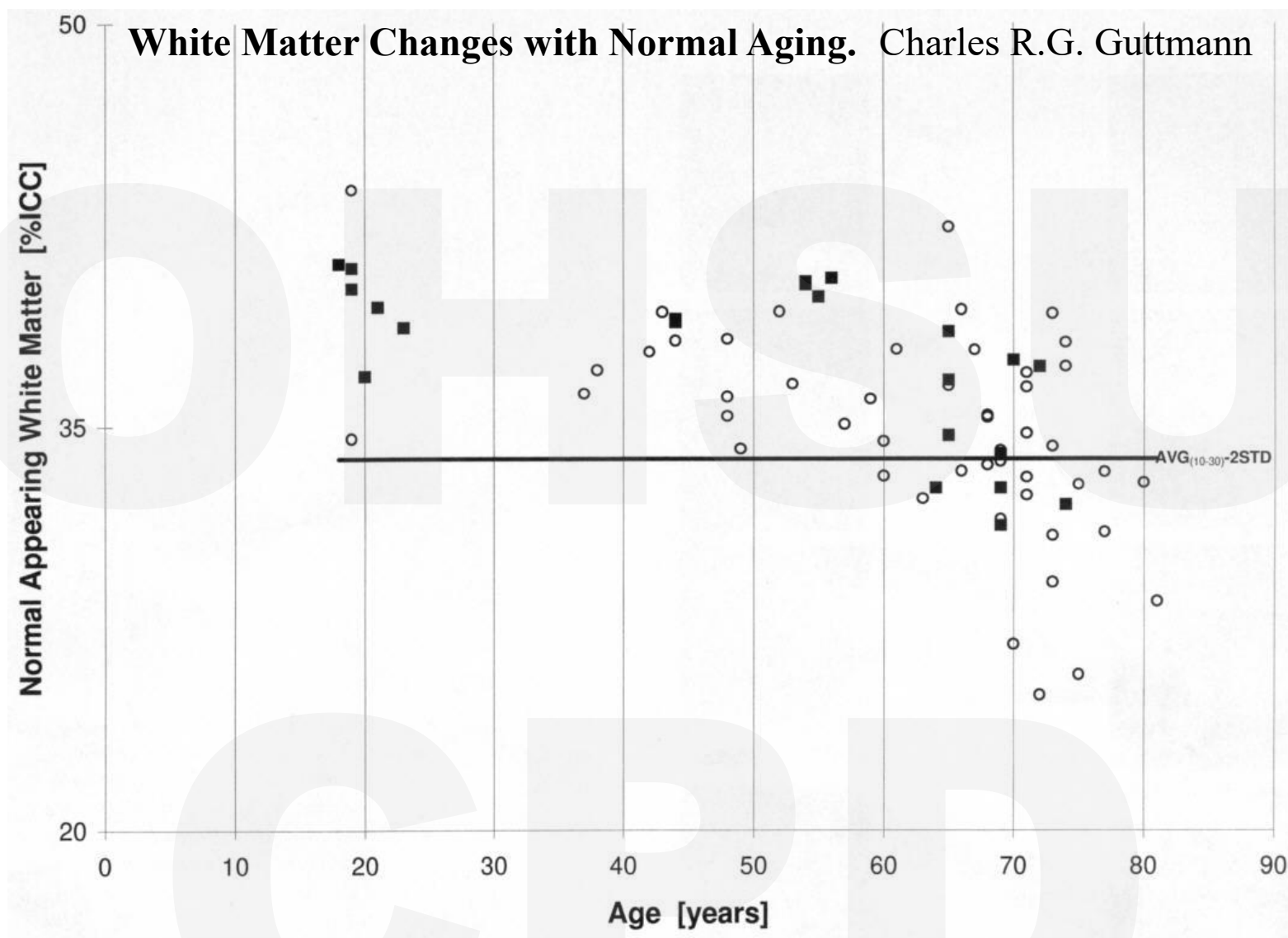


Figure 3: Differences in Volume of White Matter with Advancing Age: This figure presents the white matter volume, as a percent of intracranial cavity volume [%ICC], for each subject (female subjects - open circles; male subjects - filled squares). A horizontal line is drawn two standard deviations below the mean for the 20 year old subjects. Note that only subjects 60 and older fall below the horizontal line.

AGE RELATED CHANGES TO AXONS

Late-differentiating oligodendrocytes produce thinner, more susceptible myelin

Results in “**last in, first out**” deterioration

Frontal and temporal association areas are the last to myelinate → higher cognitive functions such as memory, executive function, and language decline to some degree with normal aging

AGE RELATED CHANGES TO GREY MATTER

CNS signal transmission decreases a few milliseconds/year starting at age 20

Anatomical Change

- Synaptic contacts decrease with age

Functional Change

- Synaptic plasticity decreases with age

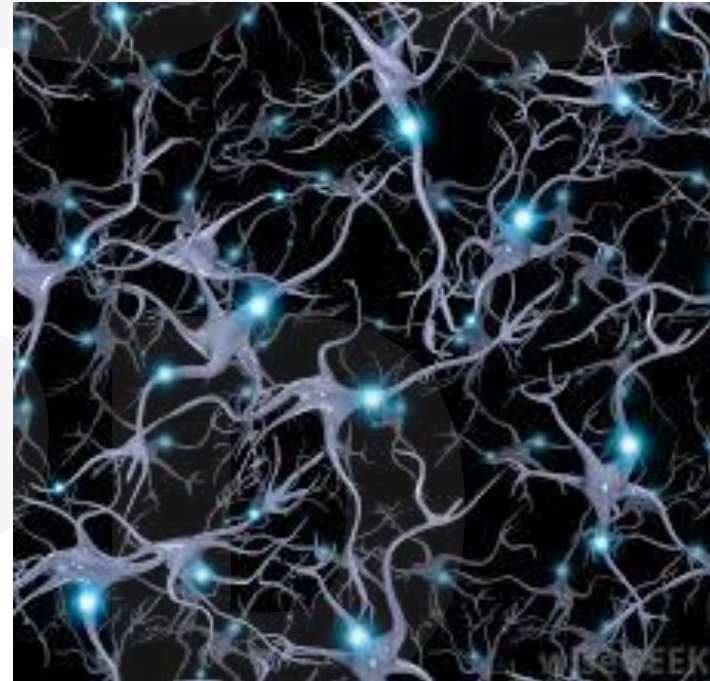
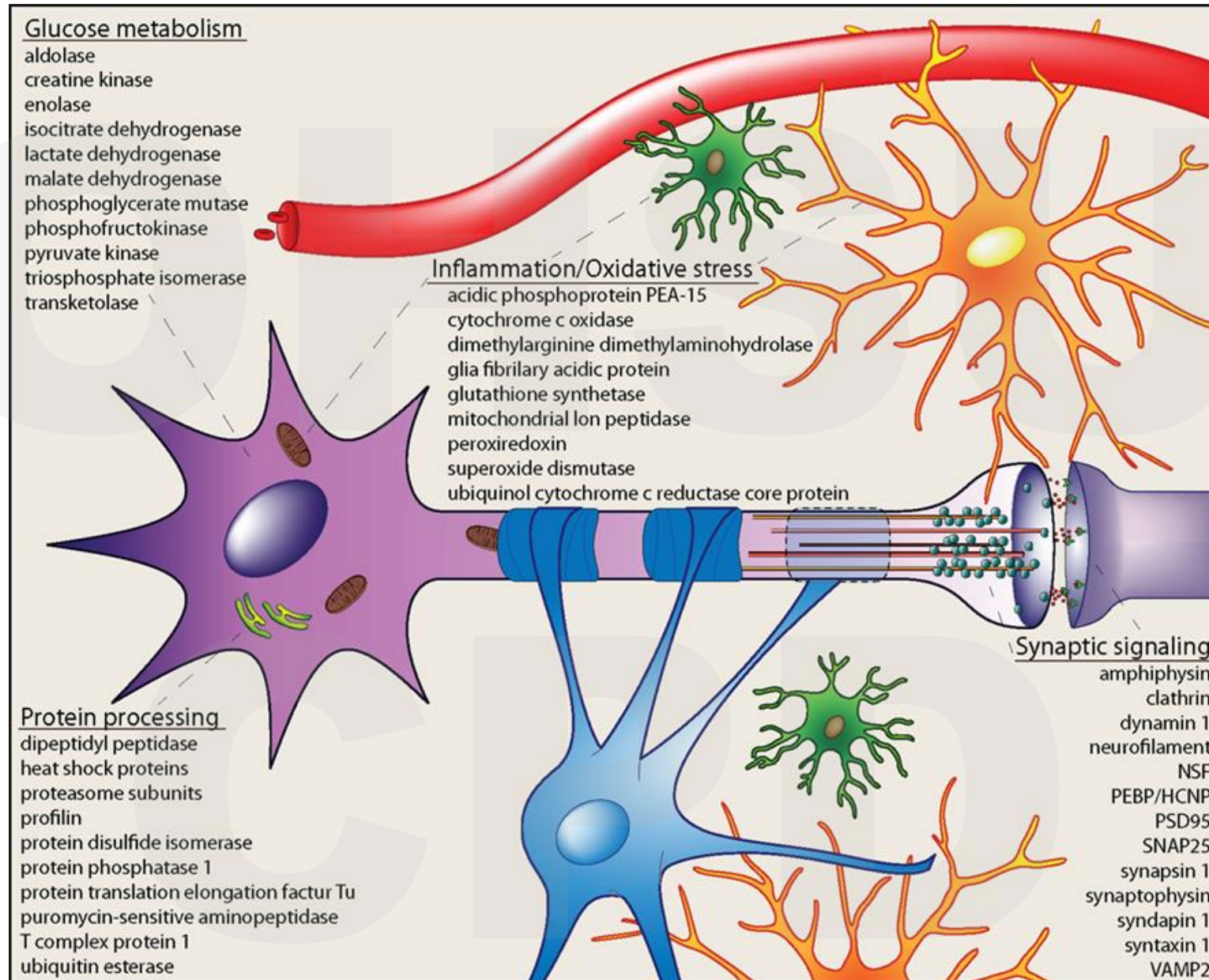


Figure 1. Cellular processes altered in the aging hippocampus.

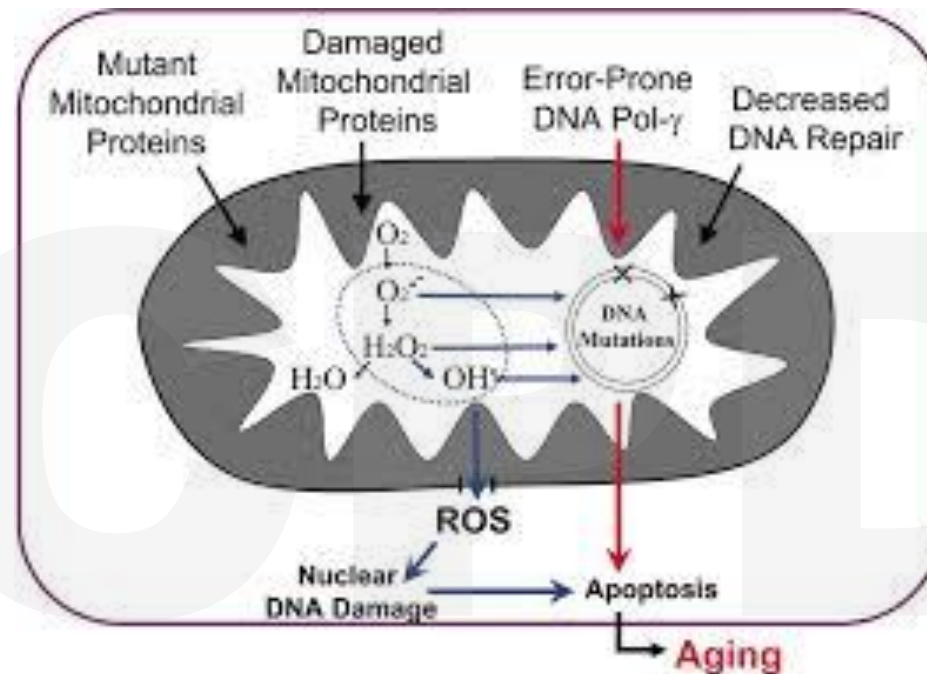


Guilder Heather, et al. The hippocampal neuroproteome with aging and cognitive decline: past progress and future directions. *Frontiers in Aging Neuroscience*. Vol 3 (8), 2011.

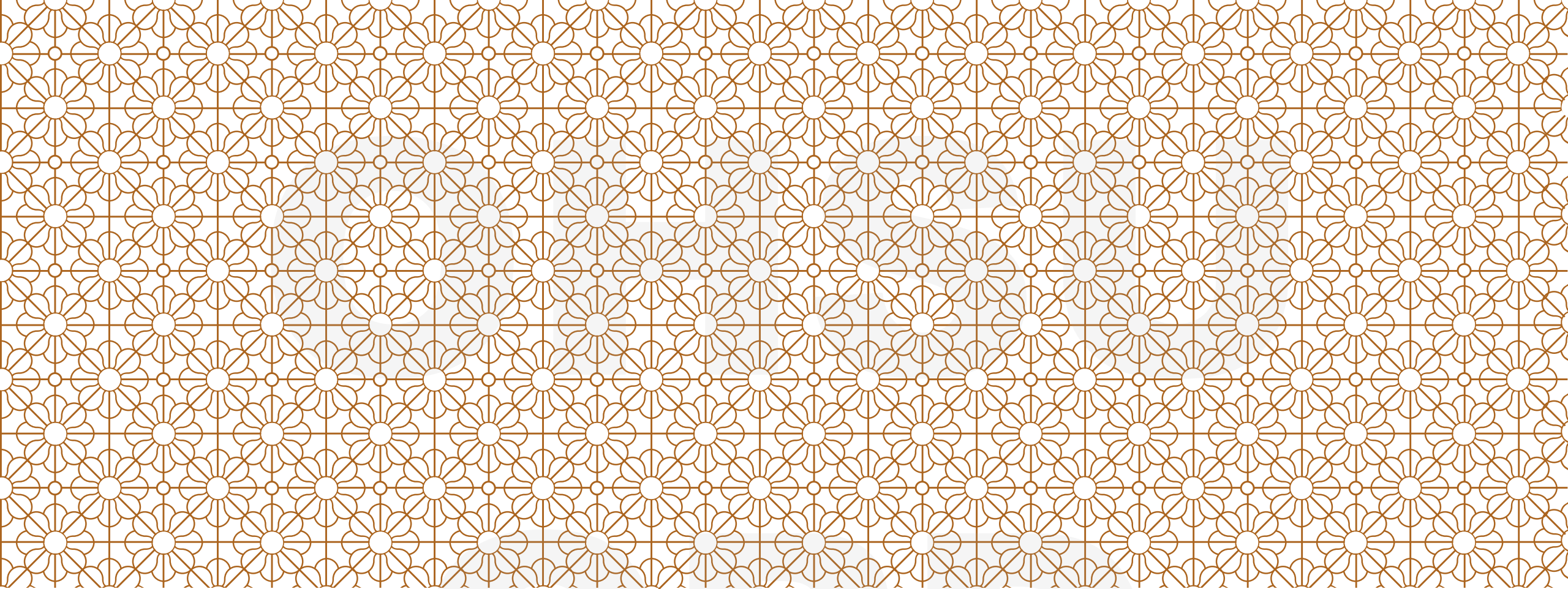
AGE RELATED CHANGE IN MITOCHONDRIA

Change in mitochondrial cells

- Decreased energy stores = decrease in brain's ability to multitask



*PNAS 52 December 19,
200510.1073/pnas.0509776102*



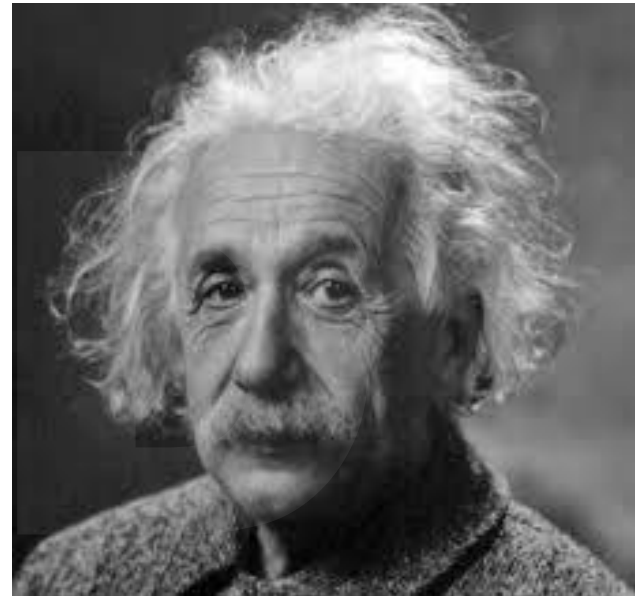
PHYSIOLOGIC AGING OF THE BRAIN

Functional Level

TO QUOTE EINSTEIN...

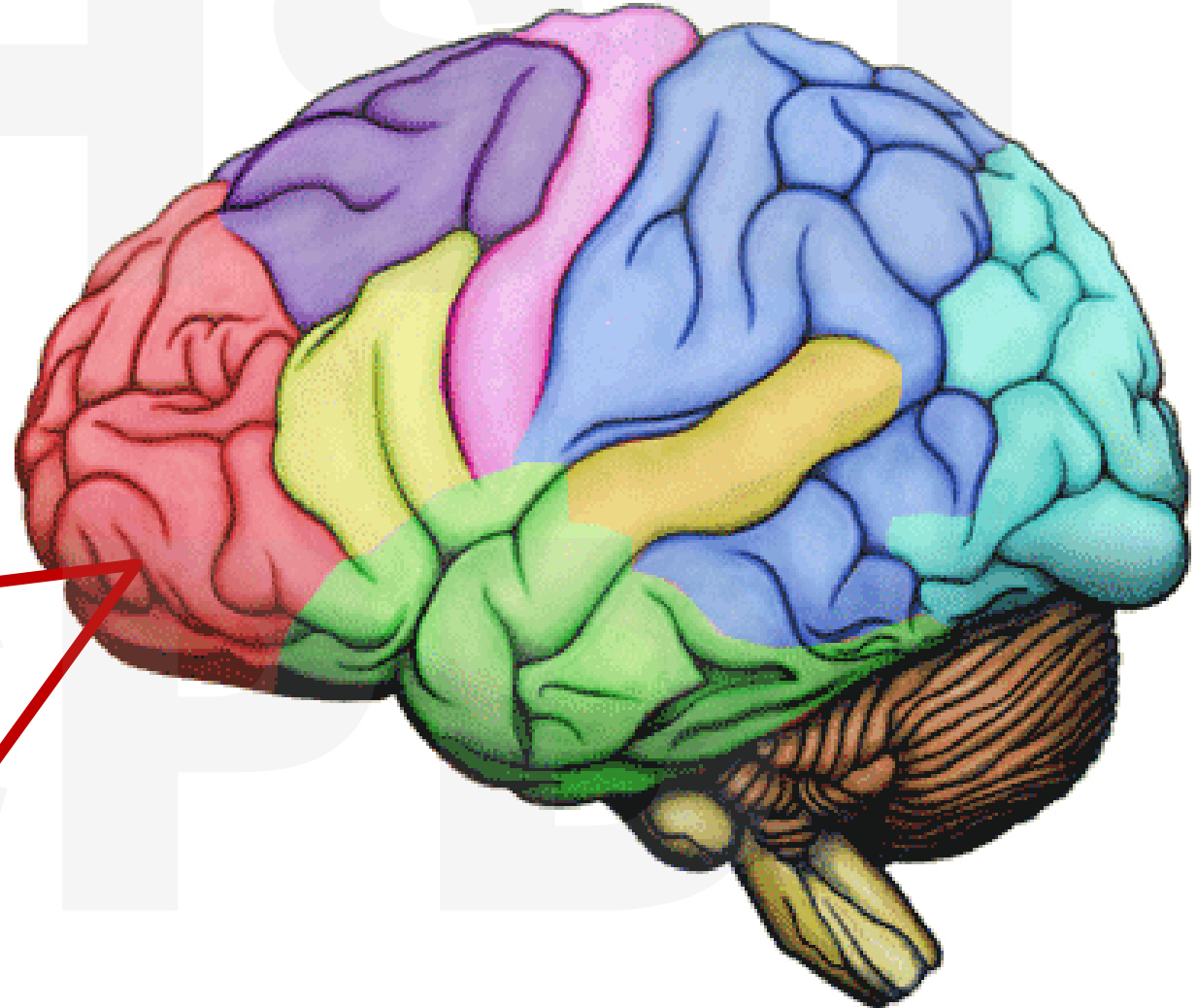
“A person who has not made his great contribution to science before the age of thirty will never do so.”

(Brodetsky, S. Nature 150, 698-699; 1942)



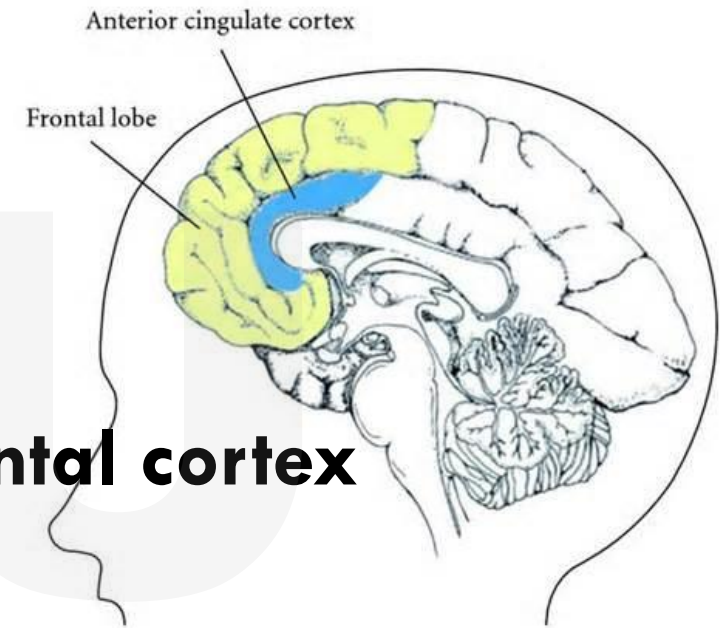
FRONTAL LOBE

Executive function
Problem solving
Organizing
Concentration
Behavior
Personality
Emotion
Impulse control



FRONTAL LOBE HYPOTHESIS

Age-related atrophy most pronounced in **pre-frontal cortex**



PFC is affected by age-related **deficits in dopamine function**

- Reductions in concentration, receptor density, and transporter availability

→ **Cognitive deficits in executive function**

- Filtering, coordinating, and manipulating working memory



FRONTAL LOBE COMPENSATION

Age-related increases in recruitment areas of PFC

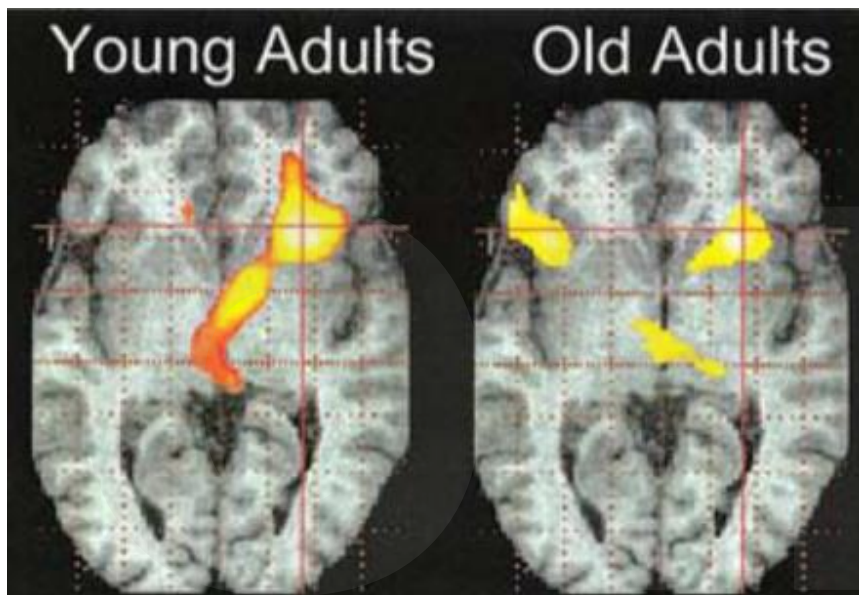
- Attempt to counteract neural decline by reorganizing functions

Hemispheric Asymmetry Reduction in Older Adults (HAROLD)

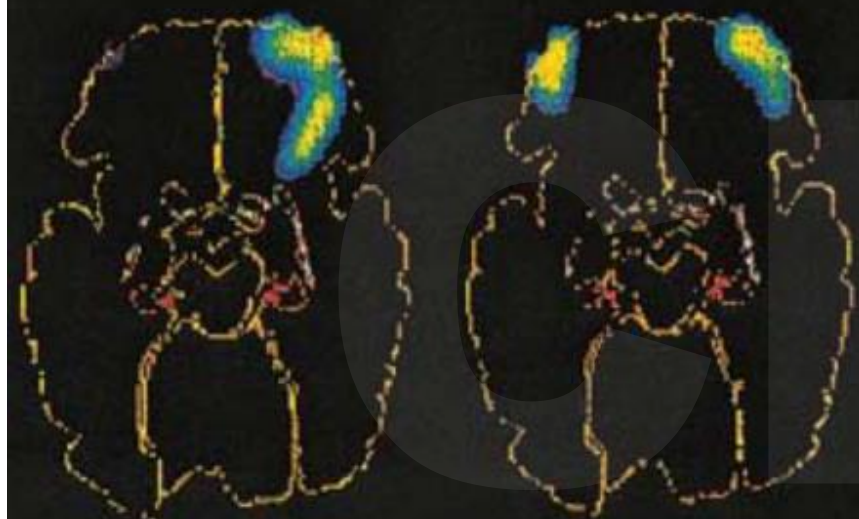
- Increase in bilateral processing

Posterior-Anterior Shift with Aging (PASA)

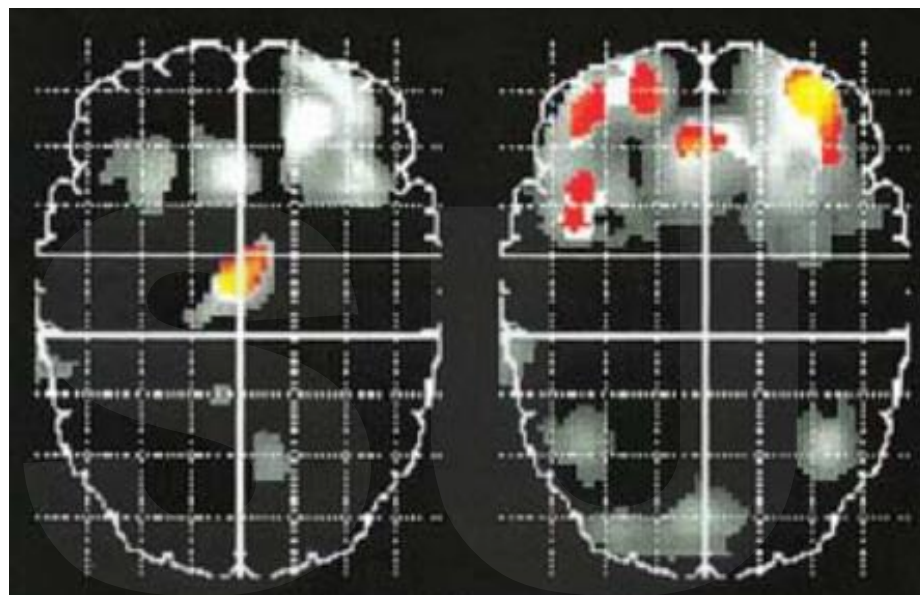
- Across domains: working memory, retrieval, visual processing, problem solving, attention



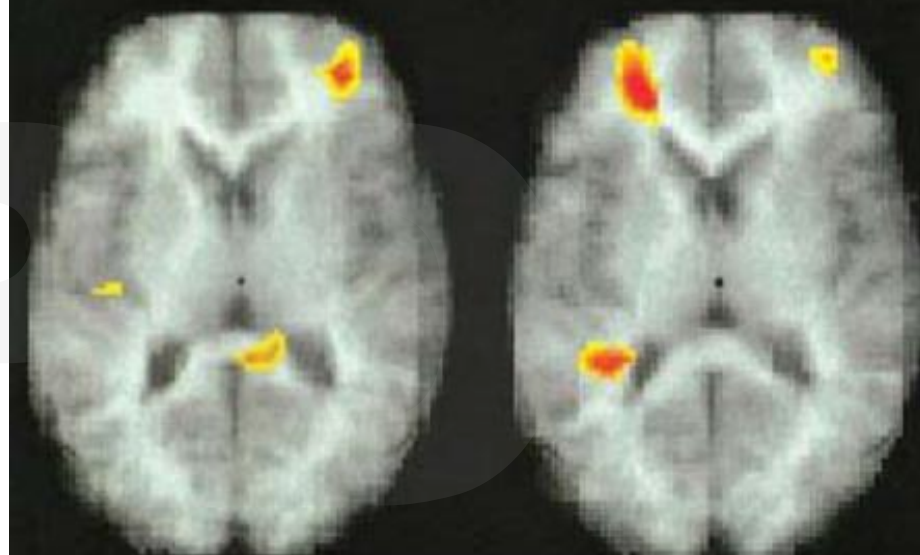
a. Word-Pair Cued-Recall



b. Word-Stem Cued-Recall



c. Word Recognition



d. Face Recognition

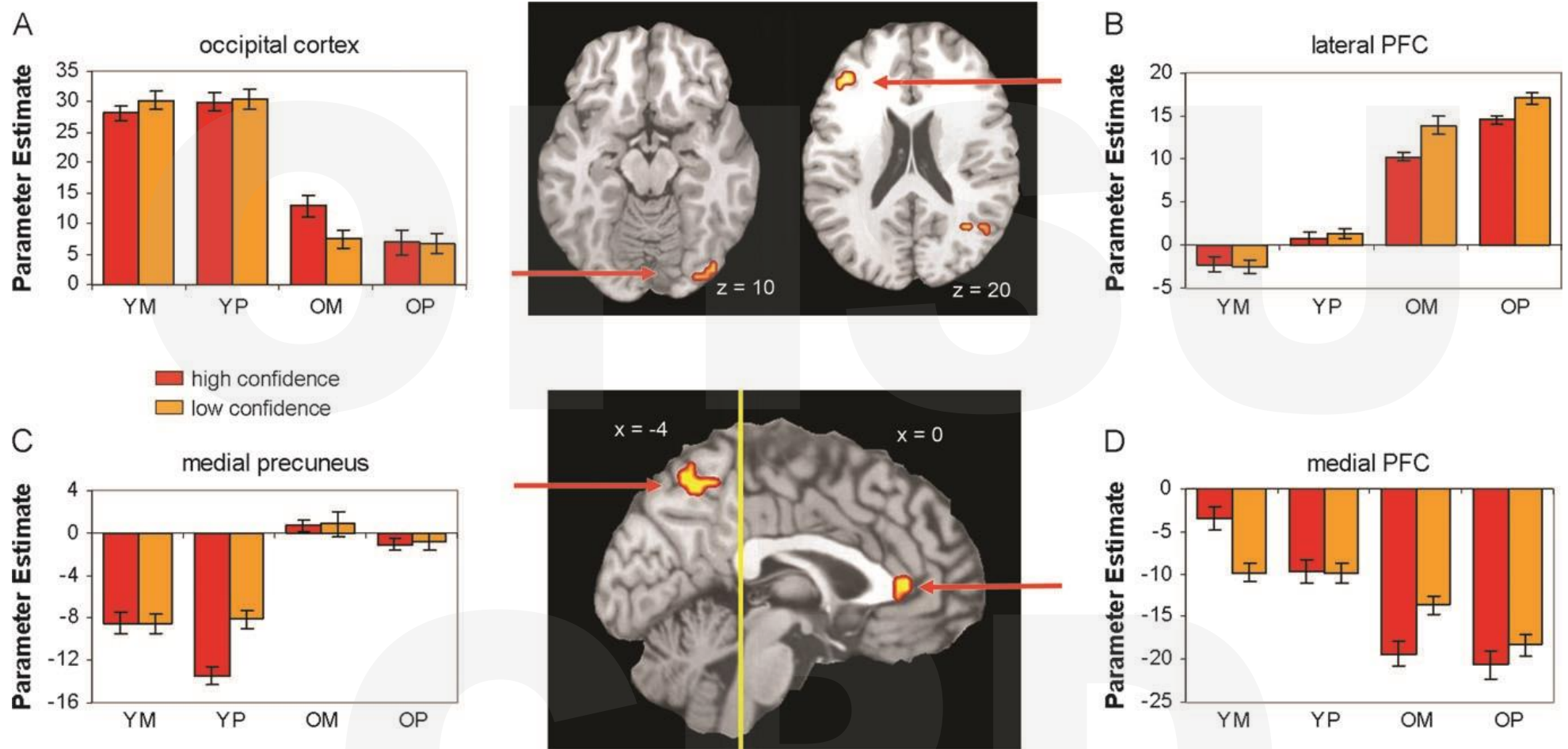


Figure 2. The PASA pattern for activations: across 2 different tasks and 2 levels of confidence, the occipital cortex showed greater activity in younger than in older adults A, whereas PFC showed the opposite pattern (B). The PASA pattern for deactivations: across 2 different tasks and 2 levels of confidence, posterior midline cortex (precuneus, C) showed greater deactivations in younger than older adults, whereas the anterior midline cortex (medial PFC, D) showed the opposite pattern. Davis, et al. Cerebral Cortex May 2008.

FRONTAL LOBE FUNCTIONS

Attention and Multitasking

- Ability to focus on one task at a time is maintained with age
- Ability to shift attention between tasks is impaired with age
- Phenomenon seen across multiple species, indicating biologic basis

Filtering Stimuli

- Developmental skill that increases with age
- With advanced age, this ability starts to decline

Increased distractibility



DRIVING IMPAIRMENT with aging



FRONTAL LOBE FUNCTIONS

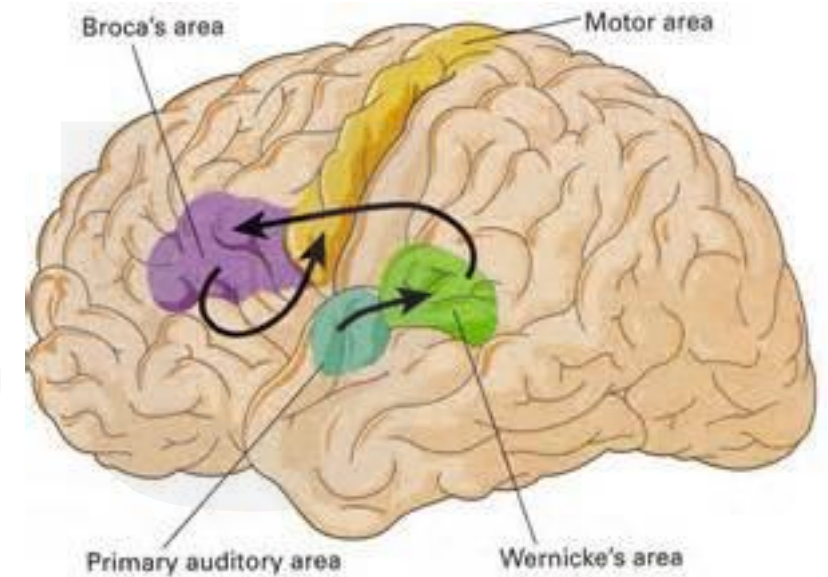
Last in, first out concept:

Ventral and dorsal language processing pathways present at birth

Pathway connecting superior temporal cortex (**Wernicke's area**) to the inferior frontal cortex (**Broca's area**) is NOT present in newborns and develops later

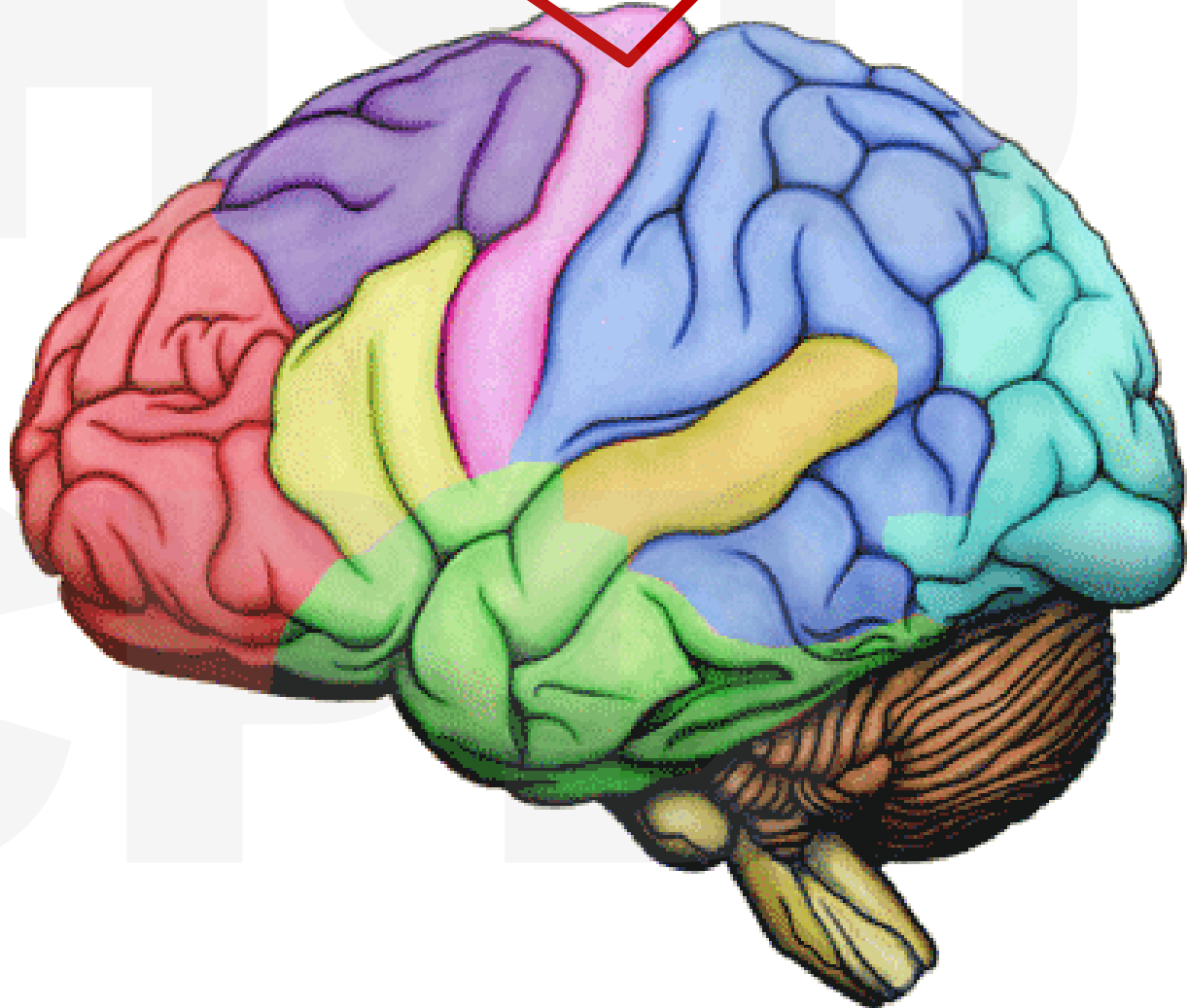
Normal aging impairs language abilities

- Slowed speech
- Impaired word retrieval and naming



MOTOR CORTEX

Voluntary movement



MOTOR CORTEX

Adults >65 years of age exhibit

- 43% volumetric reduction in the premotor cortex neuron cell body size
- Lower glutamate concentrations in the motor cortex
- Increased activation in areas of sensory processing and integration during motor tasks

MOTOR CORTEX

Muscle strength decreases at a rate of $\sim 3\%$ per year after age 70

Coordination difficulty

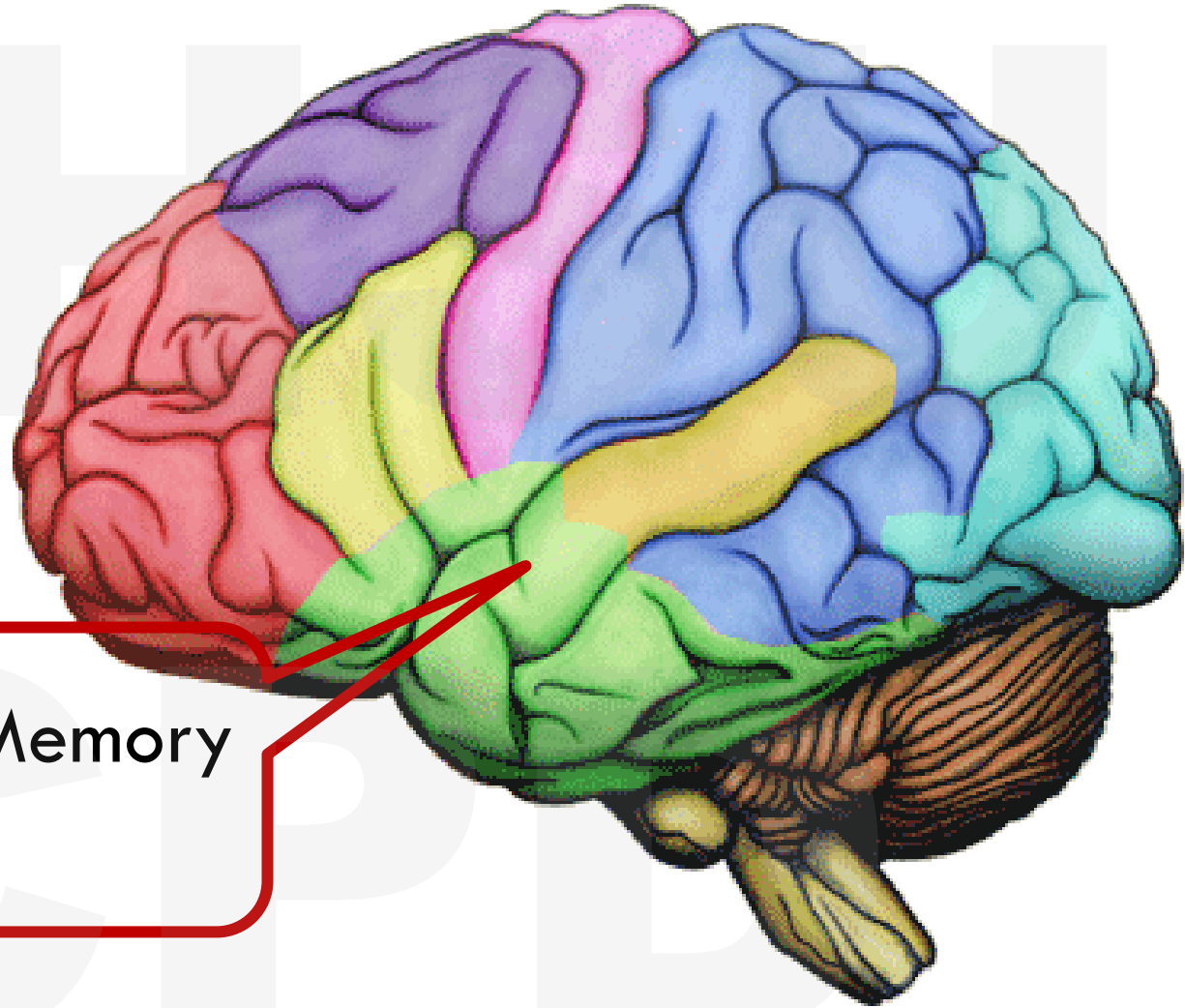
Increased variability of movement

Decreased response times

Difficulties with balance and gait



TEMPORAL LOBE



Navigation, Memory
and Emotion

TEMPORAL LOBE

Navigation and Memory (Hippocampus)

- Annual atrophy rates of 0.79–2.0%

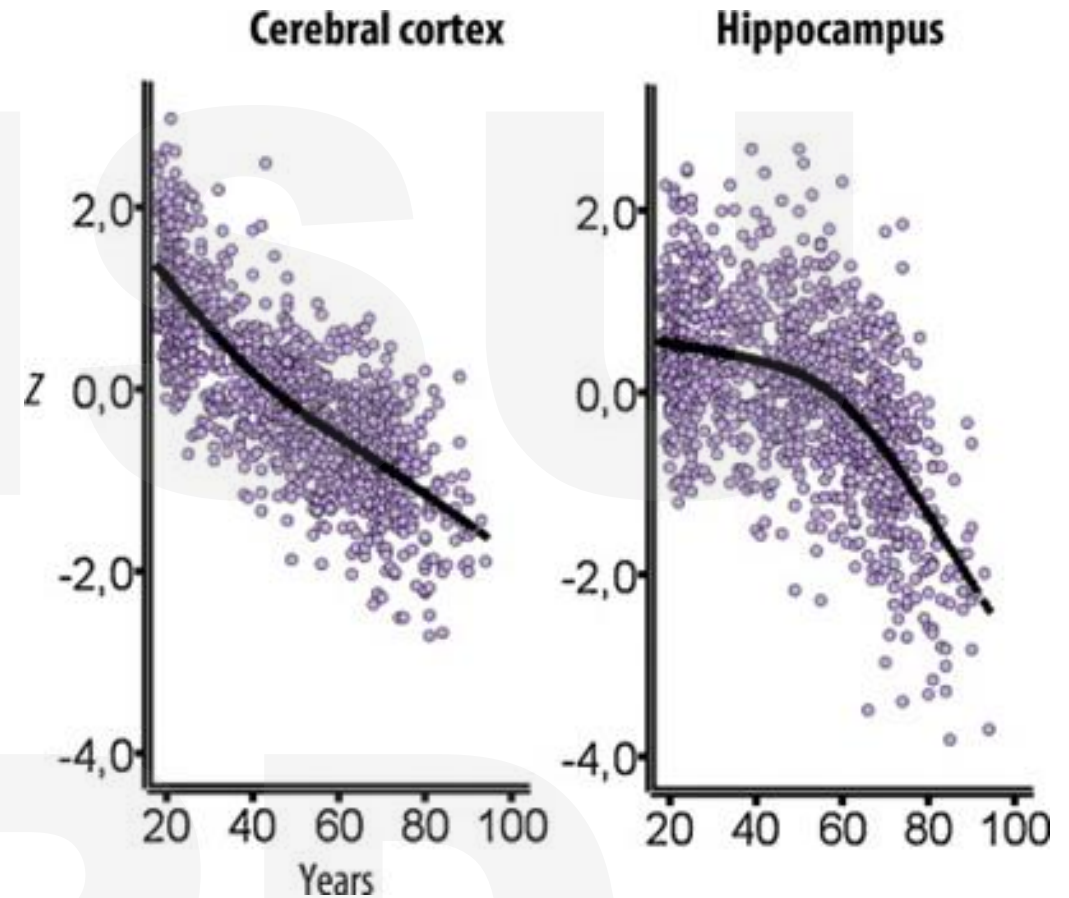


Fig. 5 Life-span trajectories of volumetric reductions. Cross-sectional estimates of adult life-span trajectories of total cerebral cortex volume and total hippocampal volume. Volume is expressed in units of standard deviations. Data from <ce:...

Fjell, Anders, et al. Alzheimer's Disease Neuroimaging Initiative, What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus, Progress in Neurobiology, Volume 117, June 2014, Pages 20-40, ISSN 0301-0082

TEMPORAL LOBE - NAVIGATION

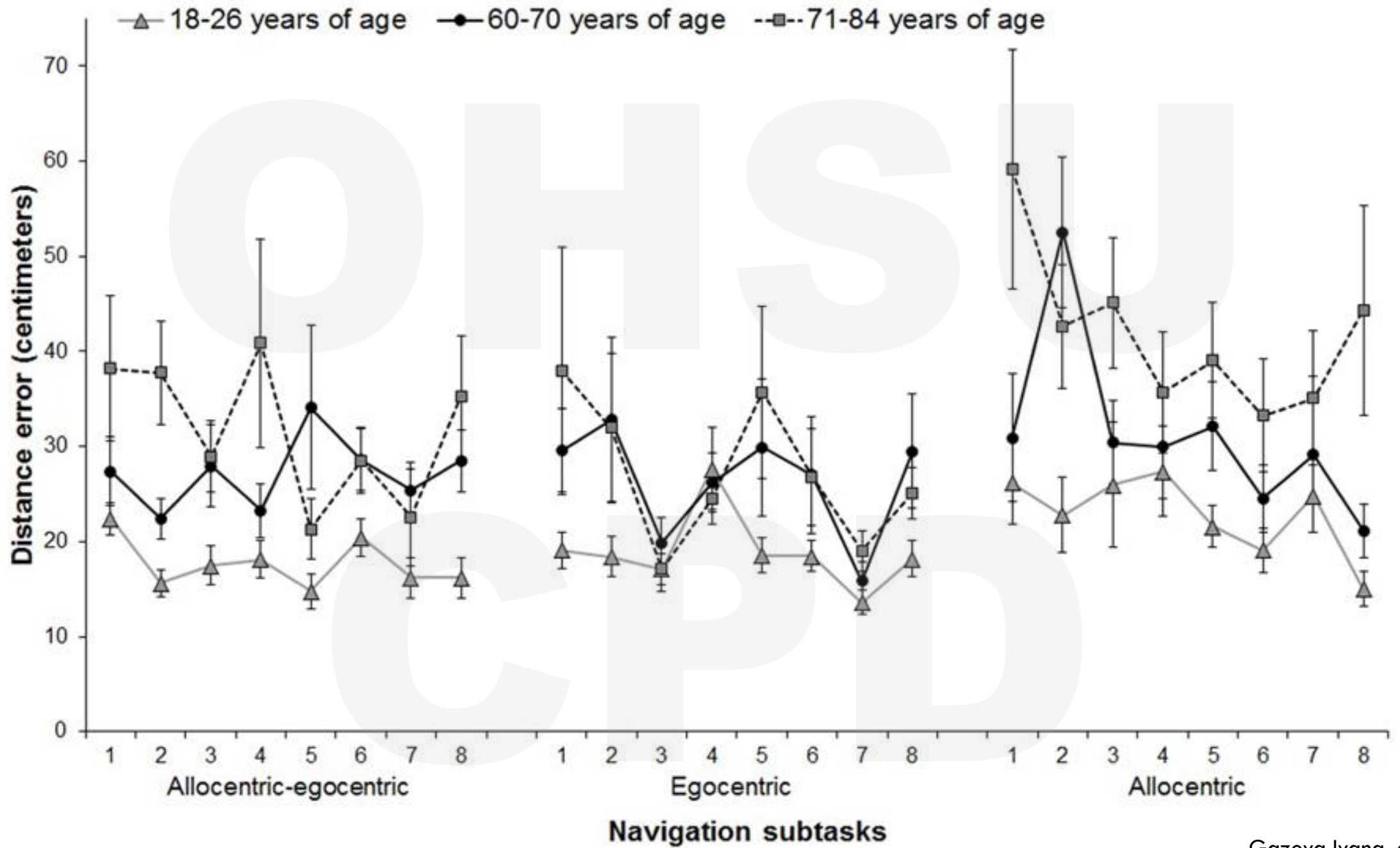
Decline in spatial navigation was shown to be apparent after 60 years of age and further accelerated after 70 years of age (Barrash, 1994).

Allocentric navigation: "world-centered" processing of spatial information

- Individuals have to rely on a "spatial map" using distant landmarks
- Shown to be dependent on medial temporal lobe structures, especially the hippocampus

Egocentric navigation: "body-centered" processing of spatial navigation

- Distance and directions from individuals' body position are used for navigation
- Parietal lobe dependent and was shown not to be affected in older adults



TEMPORAL LOBE - NAVIGATION

Healthy older individuals may avoid new environments and become restricted to well-known familiar places due to impairment in **allocentric** navigation.

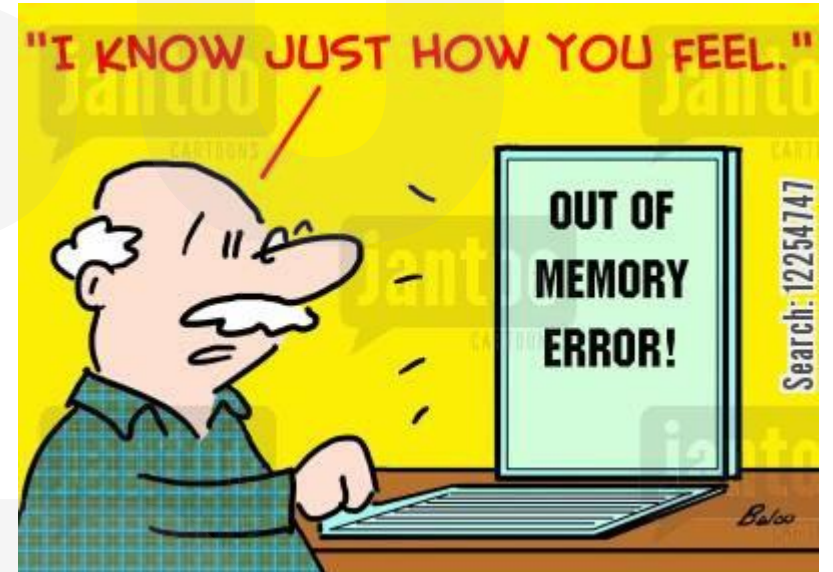
Patients with AD: profound **allocentric AND egocentric** navigation impairments



HIPPOCAMPUS – HOW MEMORIES ARE MADE

Memory is a three step process:

- Forming (coding)
- Storing
- Retrieving



In aging, retrieval of information is affected by the degree to which brain effort is required during processing

HIPPOCAMPUS – HOW MEMORIES ARE MADE

Episodic memory declines most with age

- Conscious recollection of experienced events

Semantic memory shows little age-related decline

- Facts, meanings, concepts, and knowledge

Physical memory is the least affected with age

- Guitar playing, knitting



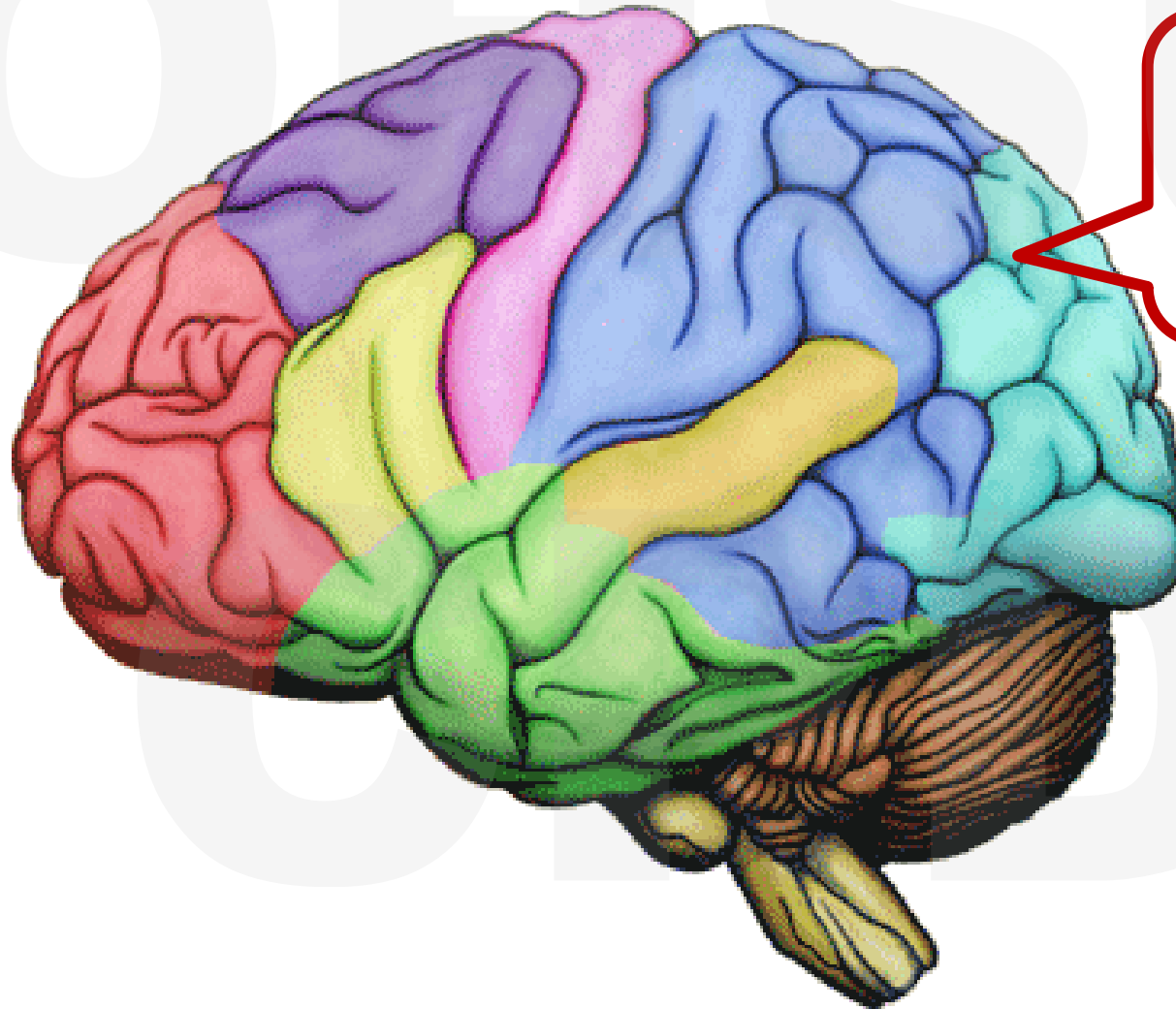
Figure 2. Aging Preferentially Influences Some Cognitive Domains More than Others. In particular, long-term (declarative) memory and working memory decline throughout life and more so in advanced aging, while some abilities, such as knowledge of vocabulary, are relatively maintained into senescence. Priming, a form of nondeclarative memory, can be relatively preserved (data not shown). Plotted data represent a subset of tasks from Park et al., 1996.



GROWING OLD

Sometimes I look back on my life
and I think...um...I think...crap.
Nevermind. I forgot already.

OCCIPITAL LOBE

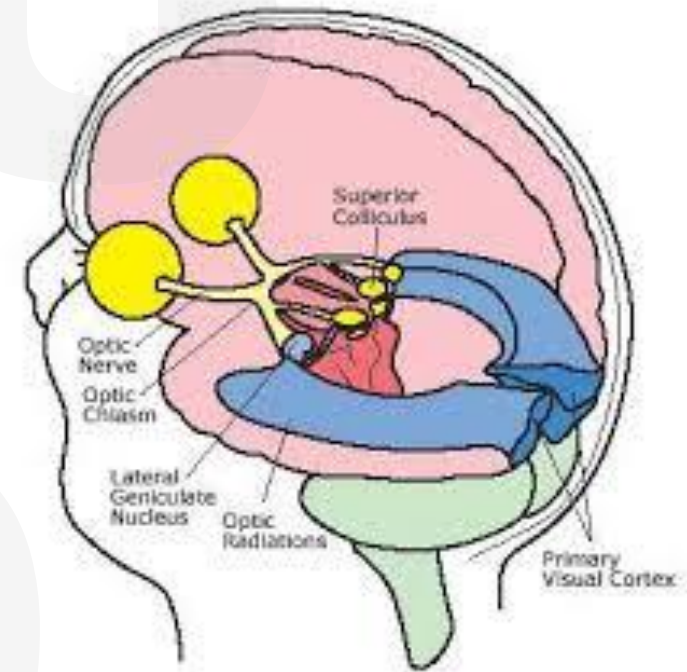


Vision: Image recognition and perception

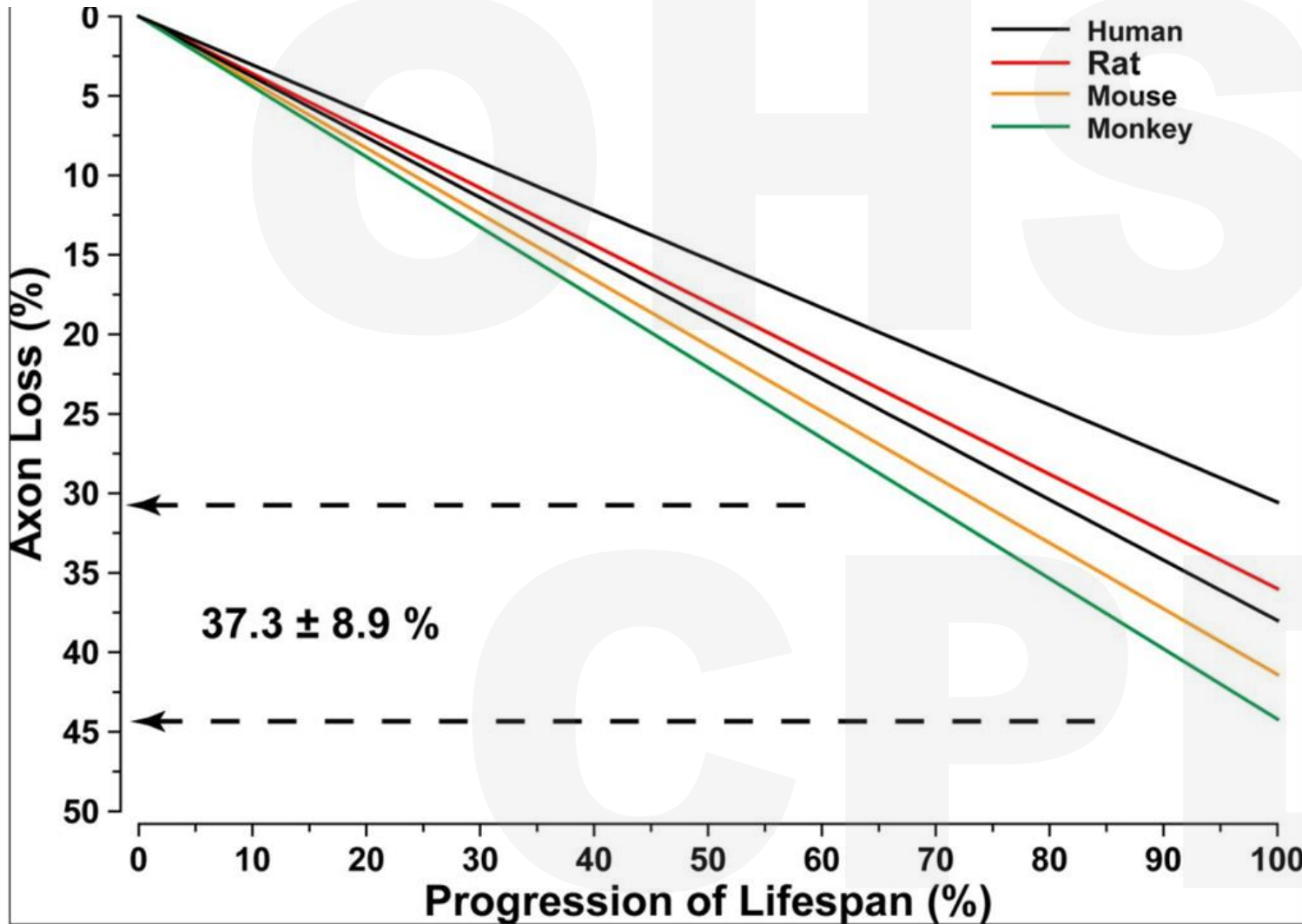
OCCIPITAL LOBE - VISUAL PROCESSING

Little or no age-related change in neuronal density or morphology in the primary visual cortex

Age-related degradation of white matter in the optic nerve, including both loss of axons and abnormalities of myelin sheaths



Axon loss in the aging optic nerve.



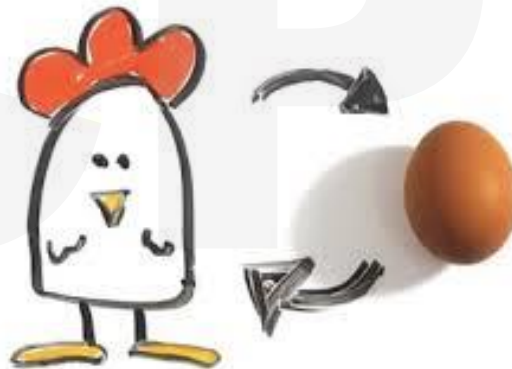
Axon loss in the optic nerve as percent of total population at maturity across progression of lifespan. Regardless of species, decline in the number of axons over a lifetime is approximately 40%.

OCCIPITAL LOBE - VISUAL PROCESSING

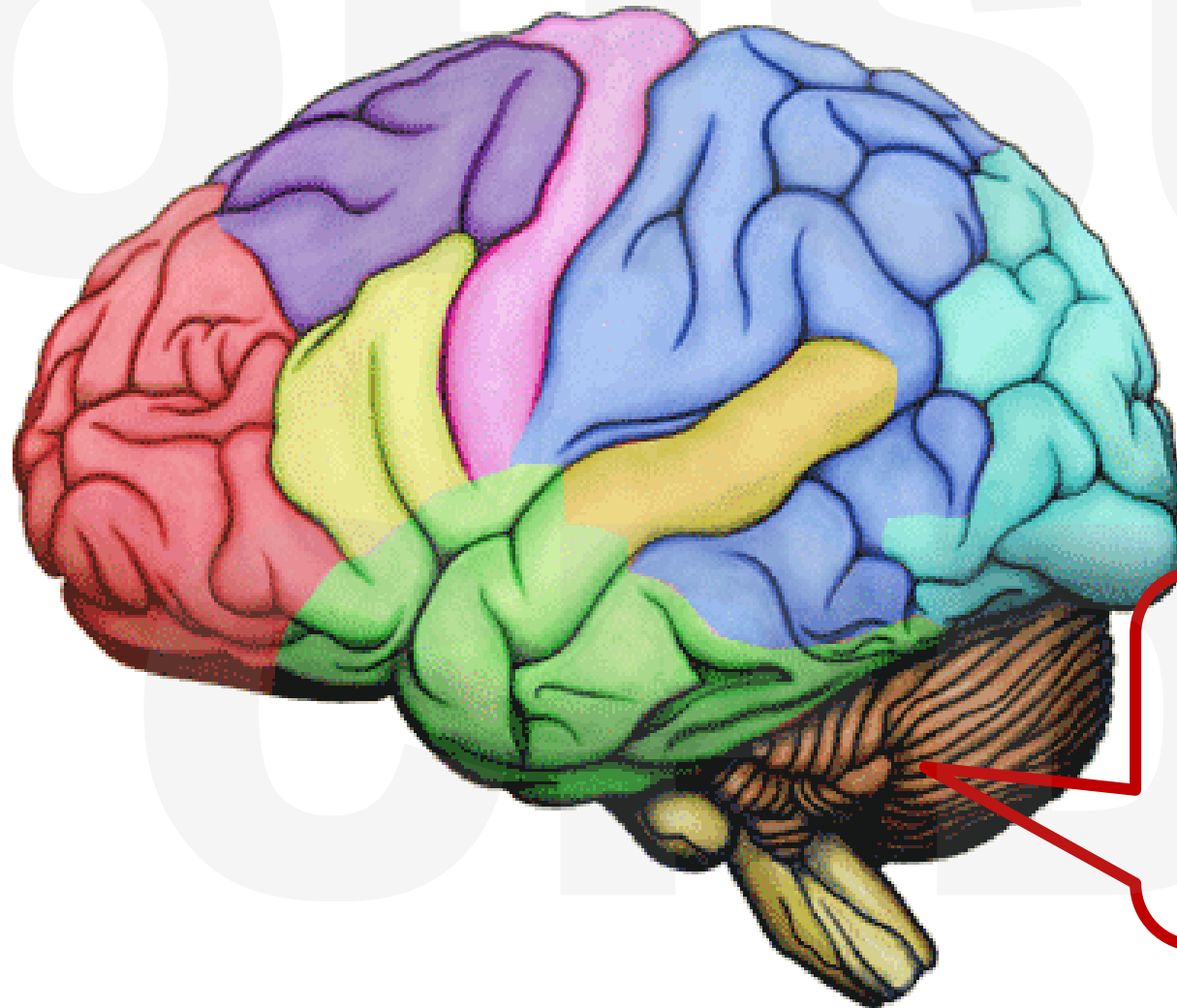
Glaucoma is an ophthalmic disease of aging, historically thought to be secondary to increased intraocular pressure (IOP).

However, a **subset of glaucoma patients have normal IOP**, pointing to pressure-independent factors.

Neuronal degeneration in the lateral geniculate nucleus (LGN) was noted to be increased in all glaucoma subjects.



CEREBELLUM



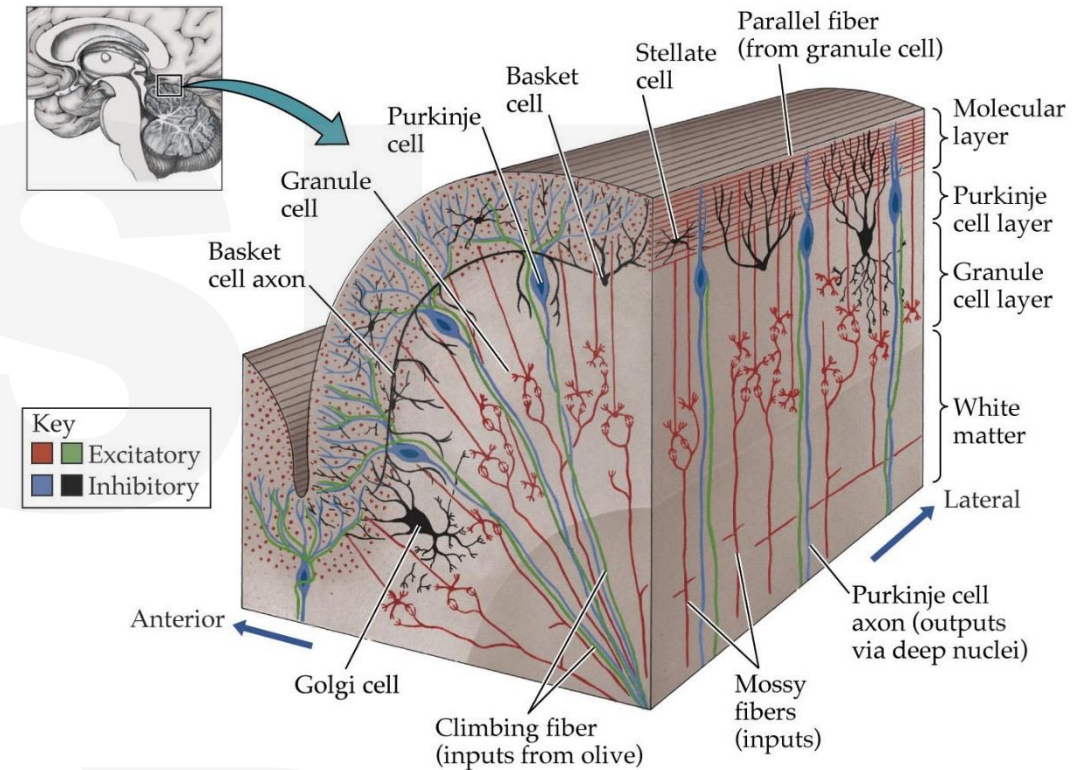
Coordination, Precision,
Balance, Posture,
Cognitive and Emotional
Processing

CEREBELLUM

Healthy aging has been associated with slowing of self-paced movements, reduced coordination, and more variable kinematics.

The number of neurons is stable in numerous **cerebral** areas.

However, the **cerebellum** displays a significant loss of neurons with age.



Significant **Purkinje cell loss of 30–40%**, evenly distributed from the age of 40 to the age of 90.

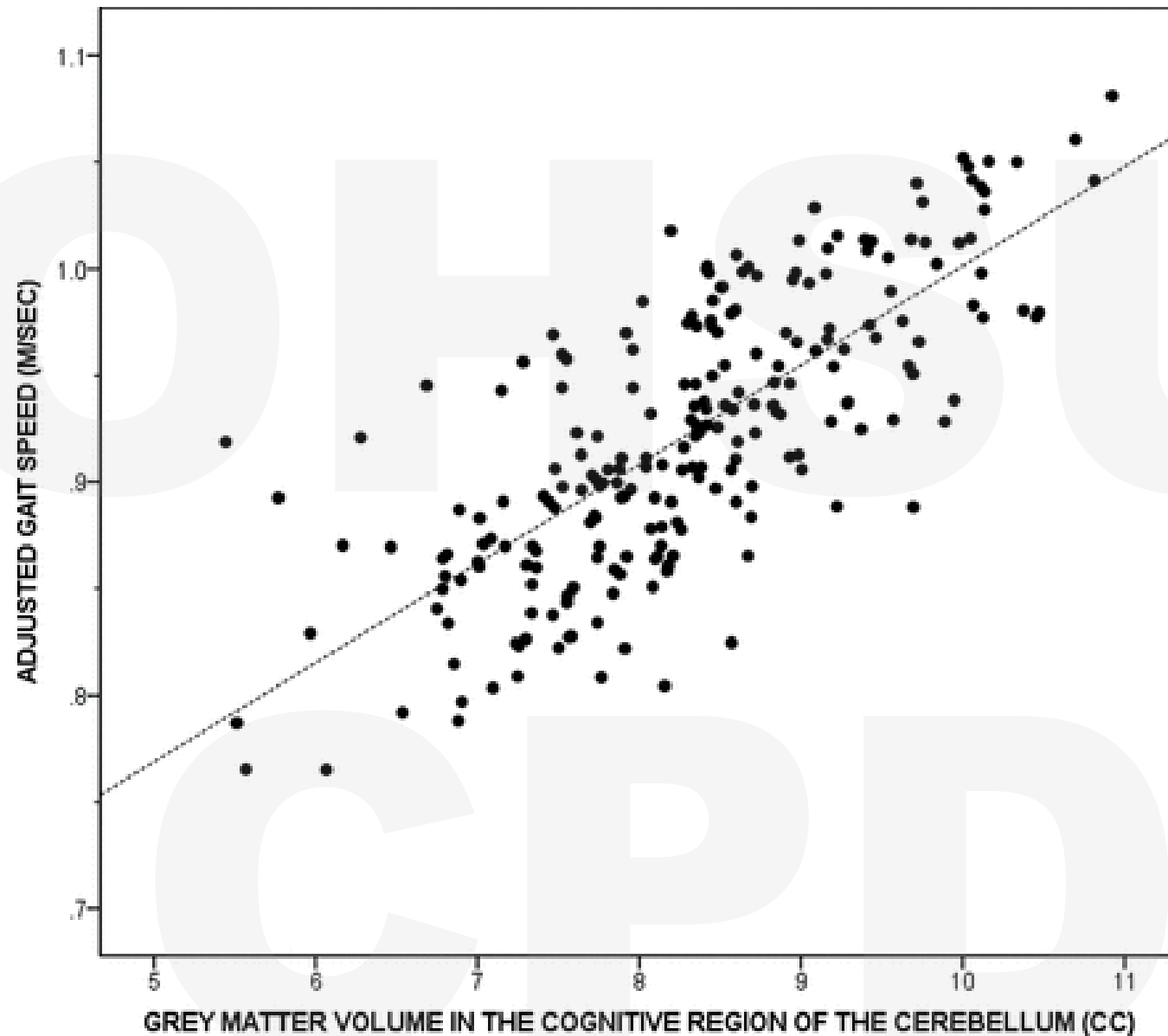


Figure 1. Scatter plot illustrating the association between gray matter volume in the cognitive region of the cerebellum and adjusted gait speed.

CEREBELLUM

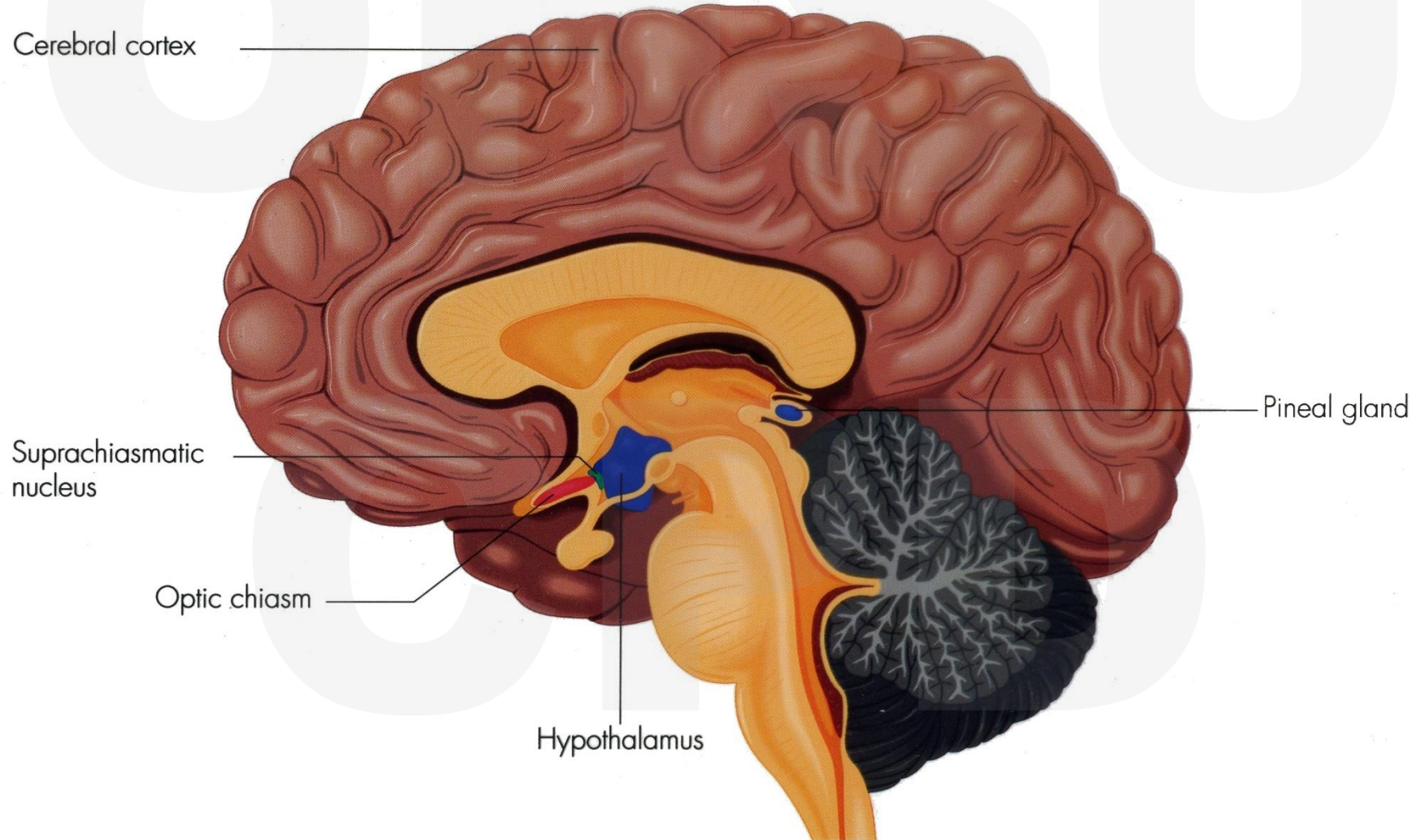
The cognitive region of the cerebellum has the strongest association with gait speed and processing speed.

No known associations between volume measures of the sensorimotor or vestibular region of the cerebellum and gait speed.

Therefore, it appears that the cerebellar role in gait speed control is related to its role in executive function as assessed by speed of mental processing.



SUPRACHIASMATIC NUCLEUS



SLEEP — NORMAL PHYSIOLOGIC CHANGES

SCN = Suprachiasmatic Nucleus

- Principal “time” pacemaker located in the ventral hypothalamus that controls our circadian rhythm
- Entrained by photic stimuli of the daily light-dark cycle, as well as non-photic stimuli such as eating times, exercise, and social interactions
- Rhythmicity is synchronized via humoral and neural signals, through peripheral “oscillators” throughout the body

SCN — CHANGES WITH AGING

Evidence of age-associated changes in SCN:

- Reduced glutamate receptor function and loss of arginine vasopressin neurons in the SCN in people >80 years of age

Regulation of the circadian system by light is affected by aging due to impaired light perception:

- Age-dependent reduction of light transmission of lens and pupil alone can amount to 90% in the elderly
- Light intensity required to achieve comparable entrainment can be 10 times higher in the elderly compared with young subjects

SLEEP — NORMAL PHYSIOLOGIC CHANGES

With aging, the total amount of time asleep shortens:

- Infants and young children sleep 16–20 hours per day
- Adults <60 years of age sleep 7–8 hours per day
- **Older adults >60 years of age sleep 6.5 hours per day**
- Delta sleep (stages 3 and 4), the deepest and most refreshing form of sleep, diminishes with age

Abnormal sleep patterns are also more common with aging, but are NOT considered normal aging:

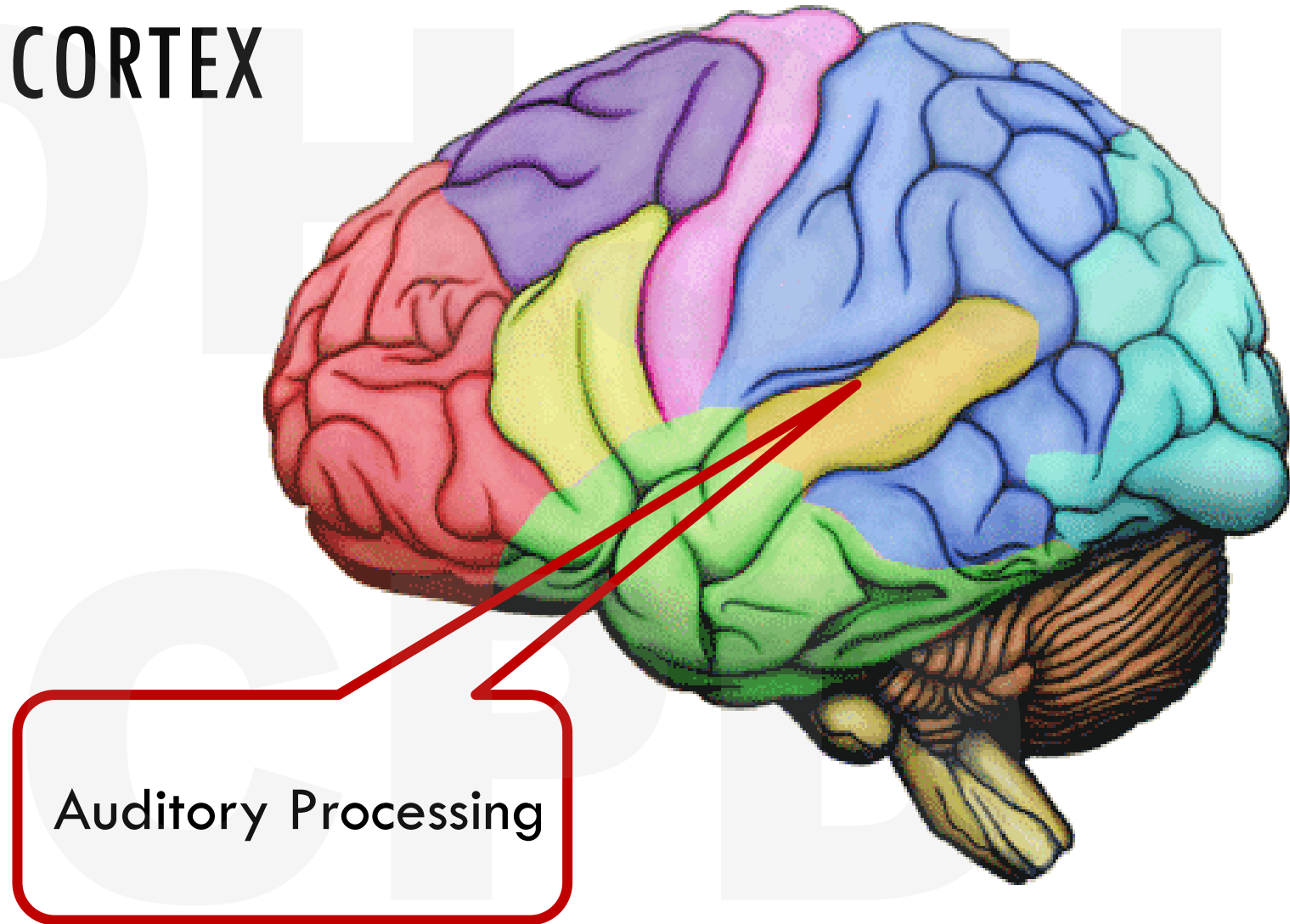
- Insomnia, RLS, OSA, REM sleep behavior disorder

Box 1: Typical sleep changes with aging

- Decreased total nocturnal sleep time
- Delayed onset of sleep
- Advanced circadian phase: early to bed, early to rise
- Reduced slow-wave sleep
- Reduced rapid-eye-movement (REM) sleep
- Reduced threshold for arousal from sleep
- Fragmented sleep with multiple arousals
- Daytime napping

Wolkove N, Elkholy O, Baltzan M, Palayew M. Sleep and aging: 1. Sleep disorders commonly found in older people. *CMAJ : Canadian Medical Association Journal*. 2007;176(9):1299-1304. doi:10.1503/cmaj.060792.

AUDITORY CORTEX



HEARING LOSS — PRESBYCUSIS

Estimated that 40–50% of adults >65 years have some degree of hearing loss

Dominant pathological changes are observed in the auditory periphery, specifically in the cochlea

Temporal cues takes place mainly in the auditory cortex (AC), which points to **central component of presbycusis**

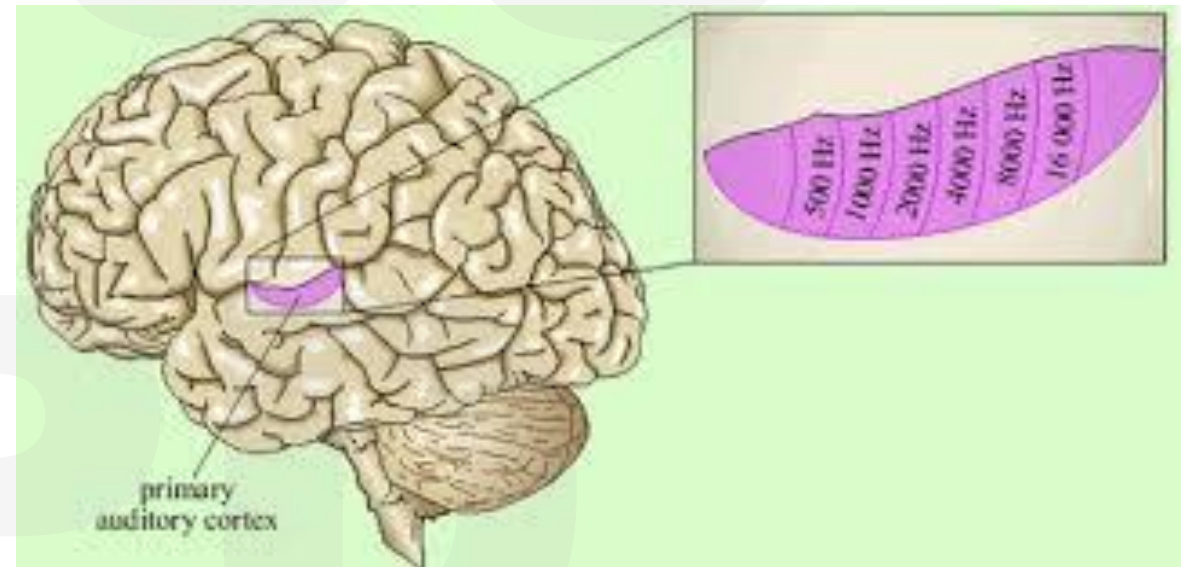
Hearing aids can improve threshold to near the physiologic level, however there is often a persistent deficit in speech understanding; particularly worse with background noise



HEARING LOSS — AUDITORY CORTEX

Speech comprehension in mild-to-moderate hearing loss modifies patterns of neural activation on imaging studies

Structural MRI images have shown that poor hearing acuity is associated with reduced gray matter volume in auditory cortex

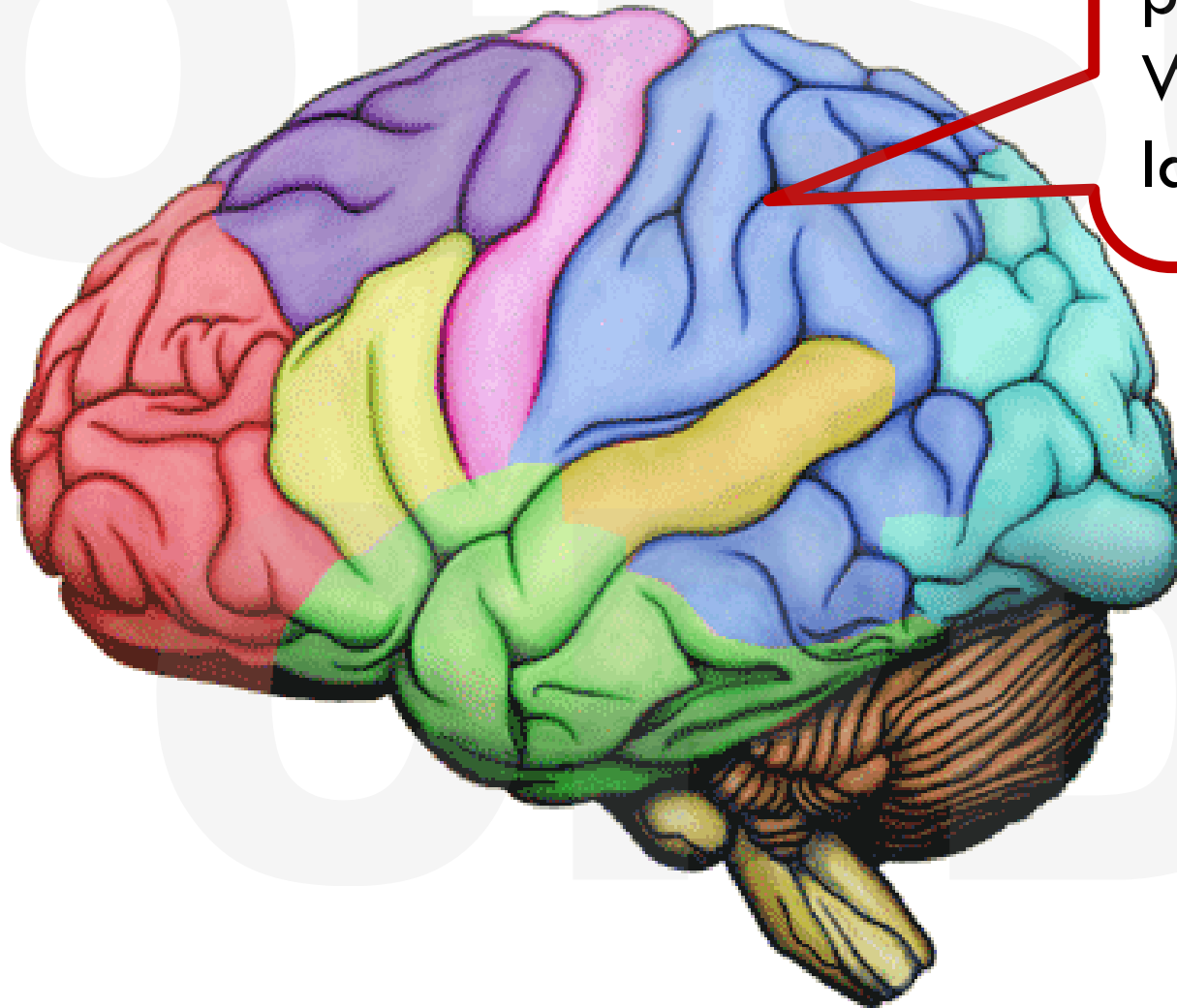


HEARING LOSS — AUDITORY CORTEX

Decreased audibility influences speech processing, especially in complex listening situations (cocktail party problem)



PARIETAL LOBE



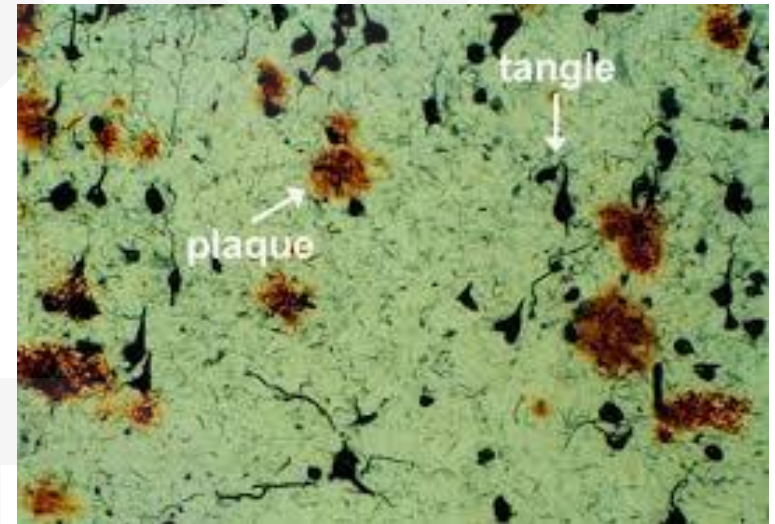
Sensory/somatosensory
perception
Written and spoken
language comprehension

PARIETAL LOBE

Parietal lobe WM disease predicted progression to AD in this large cohort of older, community-dwelling adults, independent of hippocampal volume

Earliest deposition of amyloid plaque pathology occurs in posterior association areas

APOE- ϵ 4, the strongest genetic risk factor for late-onset AD, is differentially associated with increased parietal lobe WM disease in two cohorts



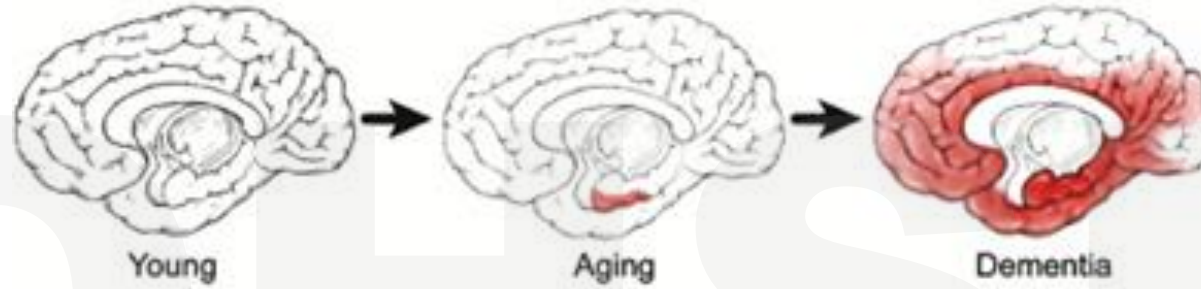
Brickman AM, et al. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiology of Aging*, Volume 36, Issue 1, January 2015, Pages 27-32.

ALZHEIMER'S VS NORMAL AGING

The pattern of atrophy in AD is not random, but usually evolves slowly, following a specific pathway that first involves the entorhinal cortex and the hippocampus, then spreads out to association areas in medial parietal, lateral temporal and frontal regions, eventually affecting all regions of cortex.

Even at the stage of MCI, annual atrophy is several times higher than in normal aging, with further increases in atrophy rate with progression to a full AD diagnosis.

UNITARY FACTOR



MULTIPLE FACTOR

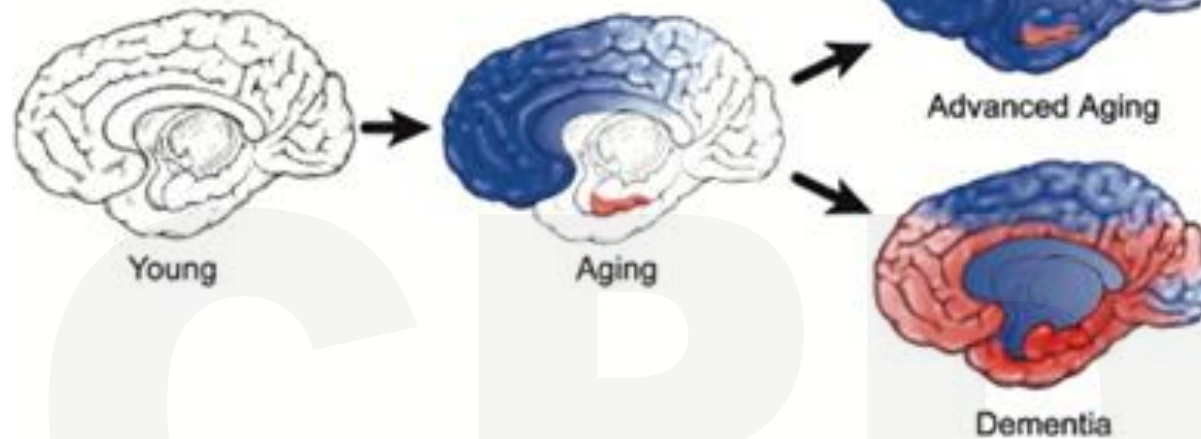


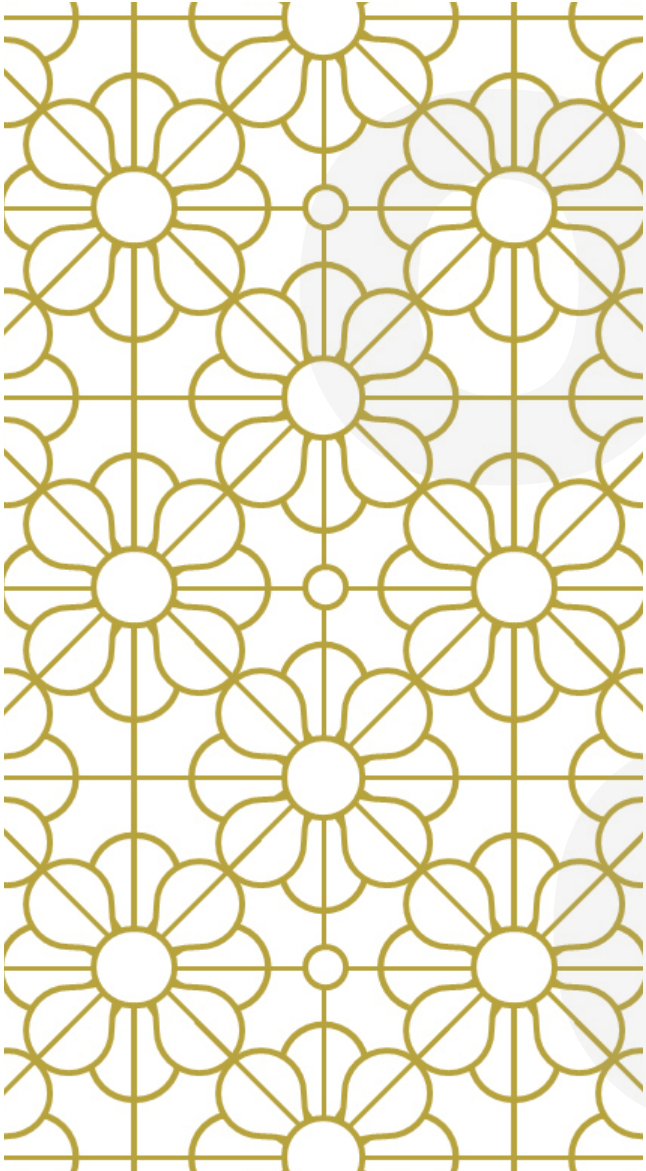
Figure 3. Unitary and Multiple Factor Frameworks of Aging Are Schematically Represented as Heuristics for Discussion. Within a unitary factor framework, mild memory decline common in aging exists along a single continuum with memory impairment associated with dementia. Dementia is considered as an acceleration of the same processes that affect cognition in all individuals. Within a multiple factor framework, separate factors are hypothesized to affect cognition in aging, each with distinct causes, risk factors, anatomic targets, and cognitive sequelae. (Fejell et al)

NORMAL AGING

- Multitasking impaired
- Slowed speech
- Slowed retrieval times
- Decreased episodic memory
- Decreased world navigation
- Less sleep at night, more napping

DEMENTIA

- Difficulty with singular tasks
- Progressive aphasia
- No retrieval (due to no storage)
- Decreased semantic memory
- Decreased personal navigation
- Disrupted day/night cycle

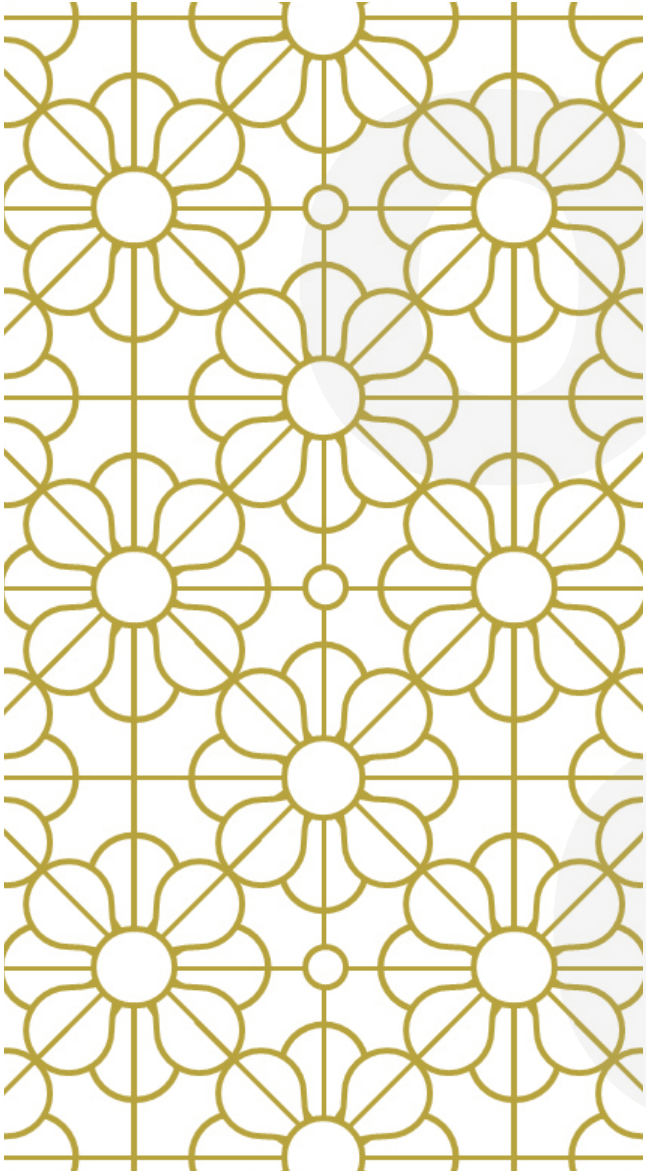


Deficit in at least one objective assessment of:

- **Complex attention**
- **Executive ability**
- **Learning and memory**
- **Language**
- **Visuo-constructional-perceptual ability**
- **Social cognition**

Deficits must interfere with independence (ADLs/IADLs)

**DEMENTIA DEFINED BY DSM-V:
MAJOR NEUROCOGNITIVE DISORDER**



Minor cognitive decline from a previous level of performance in one or more of the stated domains

No interference with function but greater effort and compensatory strategies may be required to maintain independence

**MILD COGNITIVE IMPAIRMENT DEFINED:
MINOR NEUROCOGNITIVE DISORDER**

WHY IS MCI IMPORTANT?

There are interventions that can potential prevent or slow the rate of conversion to dementia

Controlling vascular risk factors

Exercise (Tai chi)

Diet (Mediterranean)

Socialization (avoiding isolation)



REFERENCES

Ackerman, Sandra. The adult brain and normal aging. The Dana Guide. Nov 2007.

Anders M. Fjell, et al. Alzheimer's Disease Neuroimaging Initiative, What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus, *Progress in Neurobiology*, Volume 117, June 2014, Pages 20-40.

Arellanes-Licea E, Caldelas I, De Ita-Pérez D, Díaz-Muñoz M. The Circadian Timing System: A Recent Addition in the Physiological Mechanisms Underlying Pathological and Aging Processes. *Aging and Disease*. 2014;5(6):406-418. doi:10.14336/AD.2014.0500406.

Bernard JA. Rachael D. Seidler, Moving forward: Age effects on the cerebellum underlie cognitive and motor declines, *Neuroscience & Biobehavioral Reviews*, Volume 42, May 2014, Pages 193-207.

Boisgontier MP. Motor aging results from cerebellar neuron death, *Trends in Neurosciences*, Volume 38, Issue 3, March 2015, Pages 127-128.

Brickman AM, et al. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiology of Aging*, Volume 36, Issue 1, January 2015, Pages 27-32.

Buckner Randy L. Memory and Executive Function in Aging and AD: Multiple Factors that Cause Decline and Reserve Factors that Compensate, *Neuron*, Volume 44, Issue 1, 30 September 2004, Pages 195-208, ISSN 0896-6273

Cabeza, Roberto. Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychology & Aging*. 17(1):85-100, March 2002.

REFERENCES

Calkins DJ. Age-Related Changes in the Visual Pathways: Blame It on the Axon. *Investigative Ophthalmology & Visual Science*. 2013;54(14):ORSF37-ORSF41. doi:10.1167/iovs.13-12784.

Clark BC, Taylor JL. Age-Related Changes in Motor Cortical Properties and Voluntary Activation of Skeletal Muscle. *Current Aging Science*. 2011;4(3):192-199.

Davis S, et al. Que ´ PASA? The Posterior--Anterior Shift in Aging. *Cerebral Cortex*. May 2008;18:1201-1209.

Farajnia S, et al. Aging of the suprachiasmatic clock. *Neuroscientist*. 2014 Feb;20(1):44-55. doi:10.1177/1073858413498936.

Fjell, Anders, et al. Alzheimer's Disease Neuroimaging Initiative, What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus, *Progress in Neurobiology*, Volume 117, June 2014, Pages 20-40, ISSN 0301-0082

Gavin M. Bidelman, Joshua W. Villafuerte, Sylvain Moreno, Claude Alain, Age-related changes in the subcortical–cortical encoding and categorical perception of speech, *Neurobiology of Aging*, Volume 35, Issue 11, November 2014, Pages 2526-2540

Gazova Ivana, et al. Spatial navigation in young versus older adults. *Frontiers in Aging Neuroscience*. December 2013, doi: 10.3389/fnagi.2013.00094.

Guilder Heather, et al. The hippocampal neuroproteome with aging and cognitive decline: past progress and future directions. *Frontiers in Aging Neuroscience*. Vol 3 (8), 2011.

Guttmann CRG. White matter changes with normal aging. *Neurology*. April 1998 50:4, 9972-978.

Kemper S, et al. Understanding verbal fluency in healthy aging, Alzheimer's disease, and Parkinson's disease. *Neuropsychology*. Vol. 25, No. 2, 210–225. 2011.

REFERENCES

Matilainen LE, et al. The effects of healthy aging on auditory processing in humans as indexed by transient brain responses. *Clinical Neurophysiology*, Volume 121, Issue 6, 2010, 902 – 911.

Nadkarni NK, et al. Association Between Cerebellar Gray Matter Volumes, Gait Speed, and Information-Processing Ability in Older Adults Enrolled in the Health ABC Study *J Gerontol A Biol Sci Med Sci* (2014) 69 (8): 996-1003.

Ouda L, et al. Age-related changes in the central auditory system. *Tissue Res*. 2015 Jan 29. E-pub ahead of print.

Profant O, et al. Functional Changes in the Human Auditory Cortex in Ageing. Altmann CF, ed. *PLoS ONE*. 2015;10(3).

Reuter-Lorenz Grady PACL, Cabeza R, Dennis NA. Frontal Lobes and Aging: Deterioration and Compensation. In: *Principles of Frontal Lobe Function*. Oxford, UK: Oxford University Press; 2013.

Seidler RD, Bernard JA, Burutolu TB, et al. Motor Control and Aging: Links to Age-Related Brain Structural, Functional, and Biochemical Effects. *Neuroscience and biobehavioral reviews*. 2010;34(5):721-733. doi:10.1016/j.neubiorev.2009.10.005.

Shafto M, Tyler L. Language in the aging brain: the network dynamics of cognitive decline and preservation. *Science*. 346 (6209), 583-587. Oct 31, 2014.

Yang Y, Dai B, Howell P, Wang X, Li K, et al. (2014) White and Grey Matter Changes in the Language Network during Healthy Aging. *PLoS ONE* 9(9): e108077. doi:10.1371/journal.pone.0108077

Zafar U. Khan, et. al. Chapter One - Memory Deficits in Aging and Neurological Diseases, In: Zafar U. Khan and E. Chris Muly, Editor(s), *Progress in Molecular Biology and Translational Science*, Academic Press, 2014, Volume 122, Pages 1-29.