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

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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

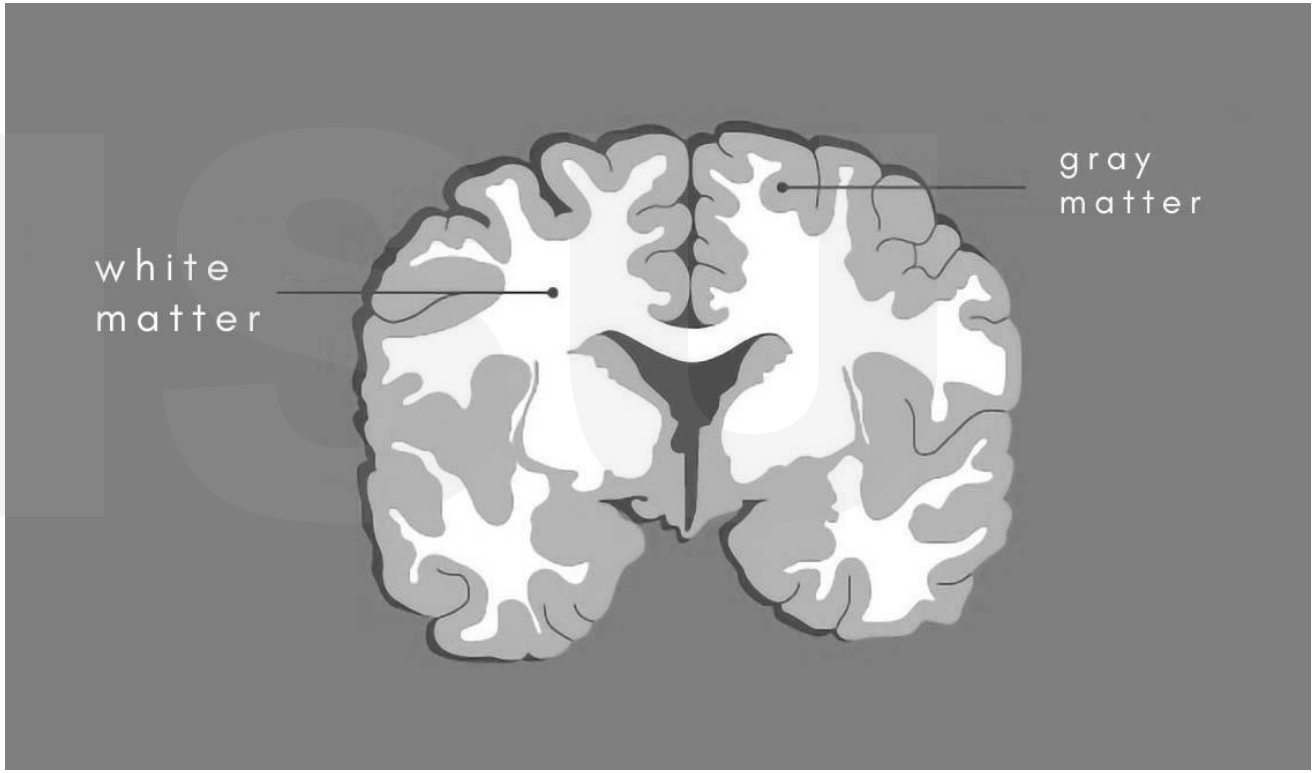
Research on “normal” aging is difficult

- 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



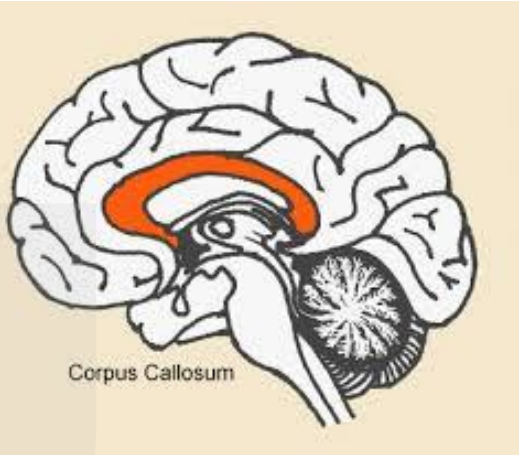
Grey matter is made up of neurons

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

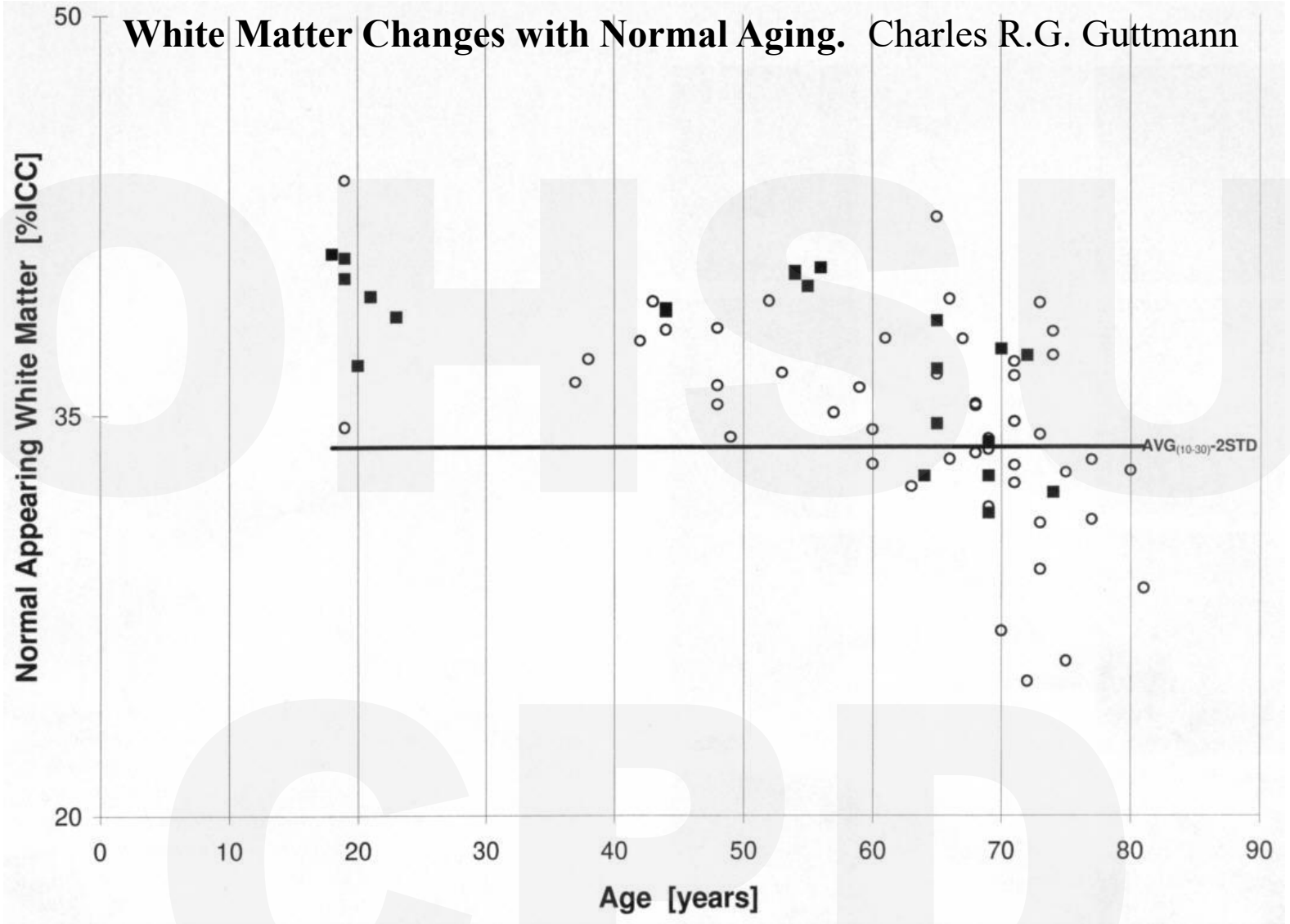


Figure 3: Differences in Volume of White Matter with Advancing Age: This figure presents the white matter volume, as a percent of intracranial cavity volume [%ICC], for each subject (female subjects - open circles; male subjects - filled squares). A horizontal line is drawn two standard deviations below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

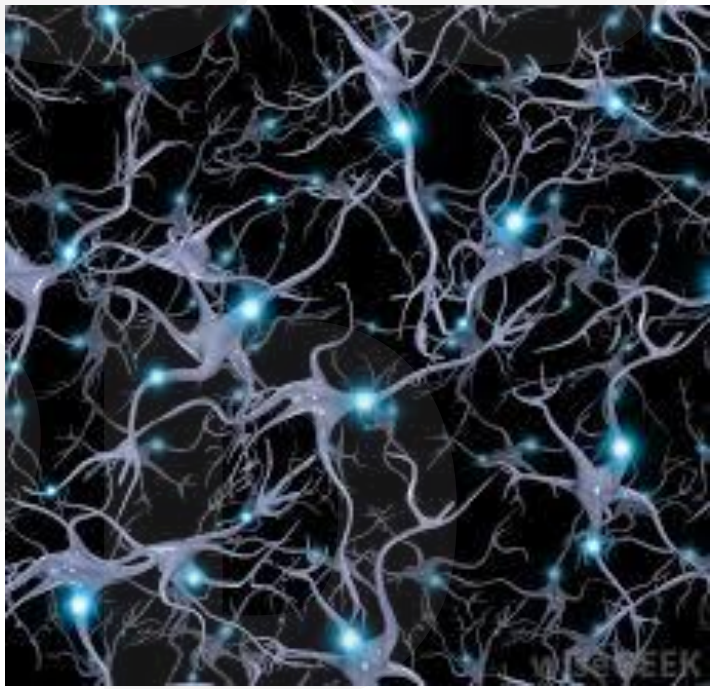
Late-differentiating oligodendrocytes produce thinner, more susceptible myelin

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

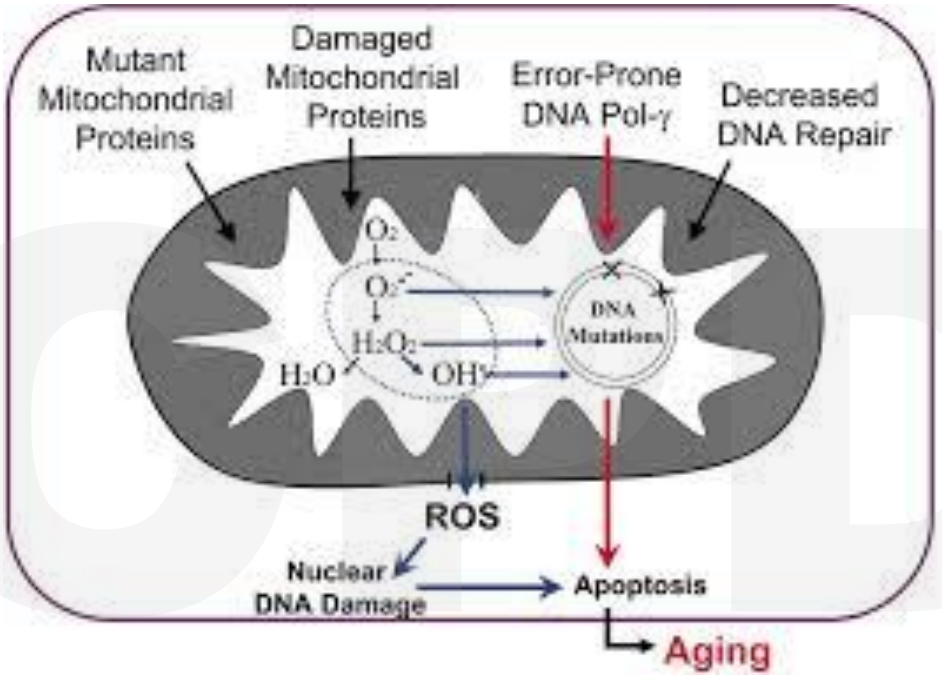
Functional Change

- Synaptic plasticity decreases with age

AGE RELATED CHANGE IN MITOCHONDRIA

Change in mitochondrial cells

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



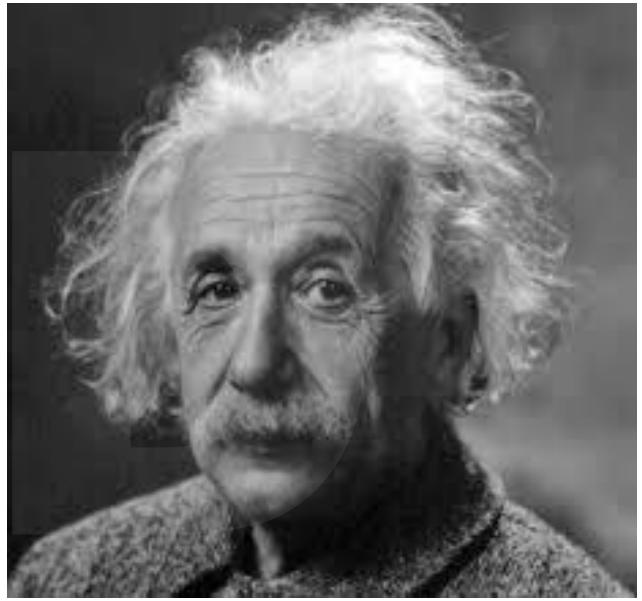
PNAS 52 December 19, 200510.1073/pnas.0509776102

PHYSIOLOGIC AGING OF THE BRAIN | Functional Level

TO QUOTE EINSTEIN…

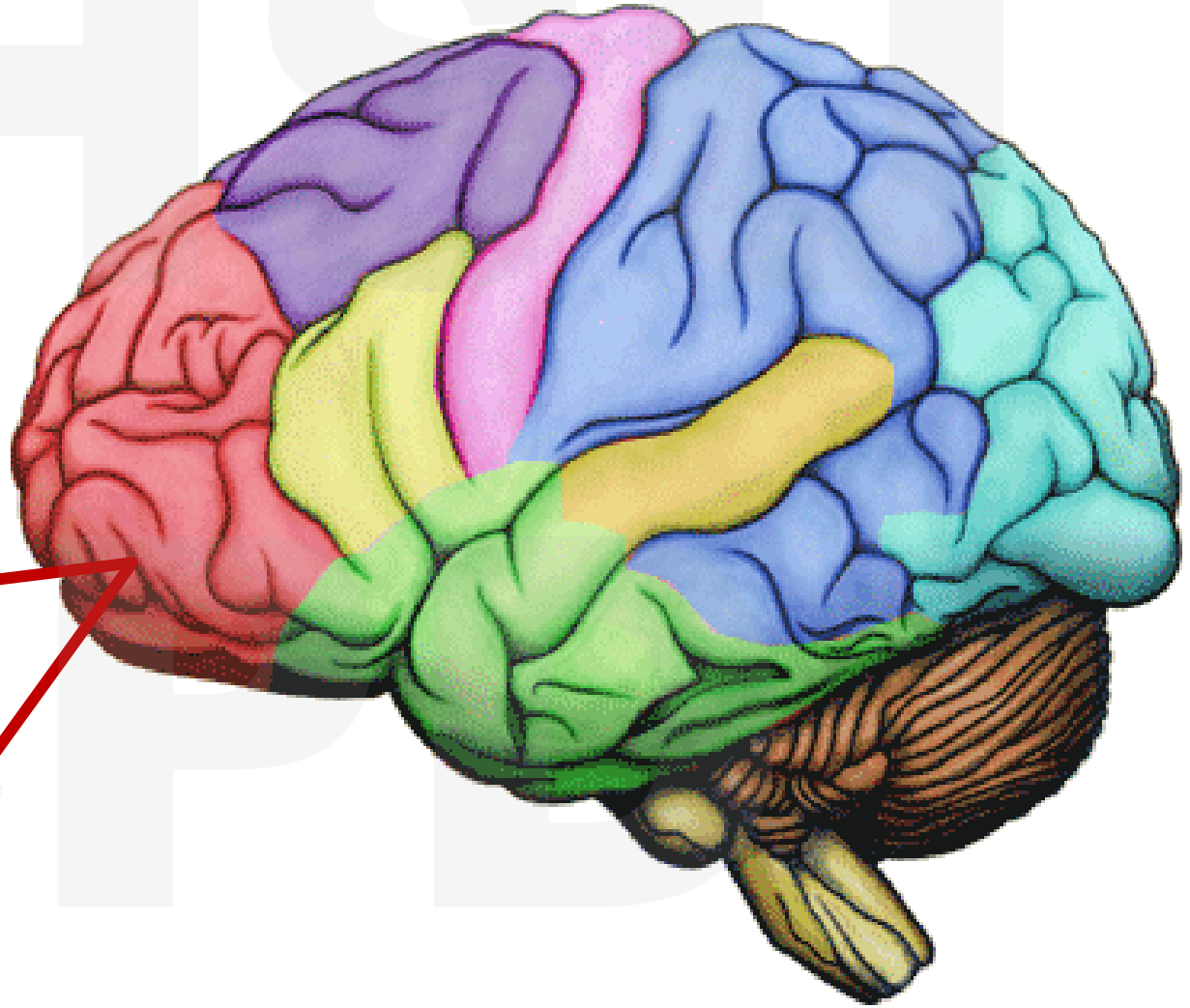
"A person who has not made his great contribution to science before the age of thirty will never do so."

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

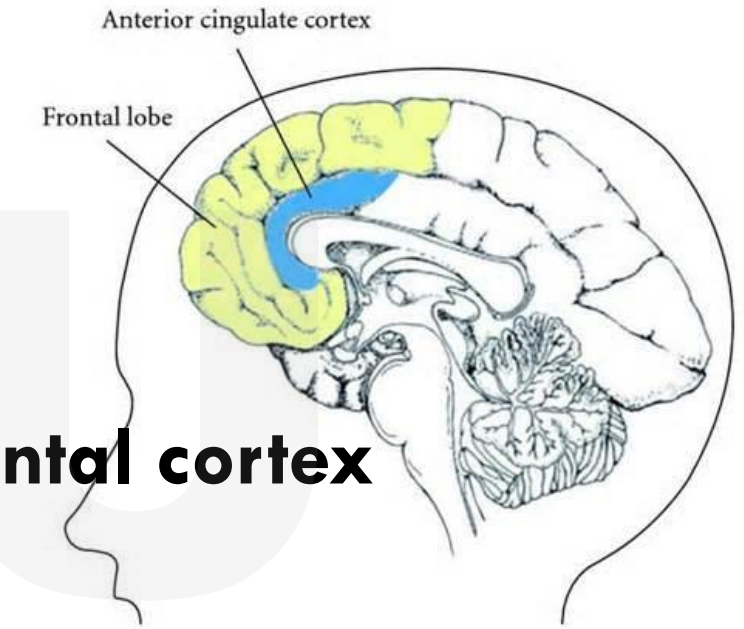


FRONTAL LOBE

Executive function
Problem solving
Organizing
Concentration
Behavior
Personality
Emotion
Impulse control



FRONTAL LOBE HYPOTHESIS



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

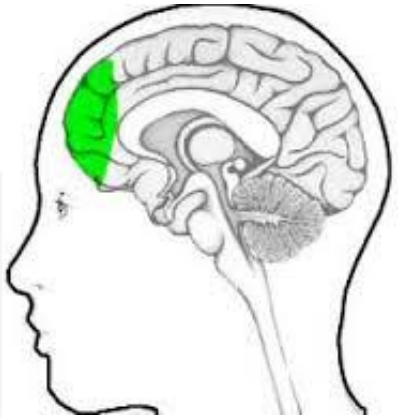
PFC is affected by age-related **deficits in dopamine function**

- 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

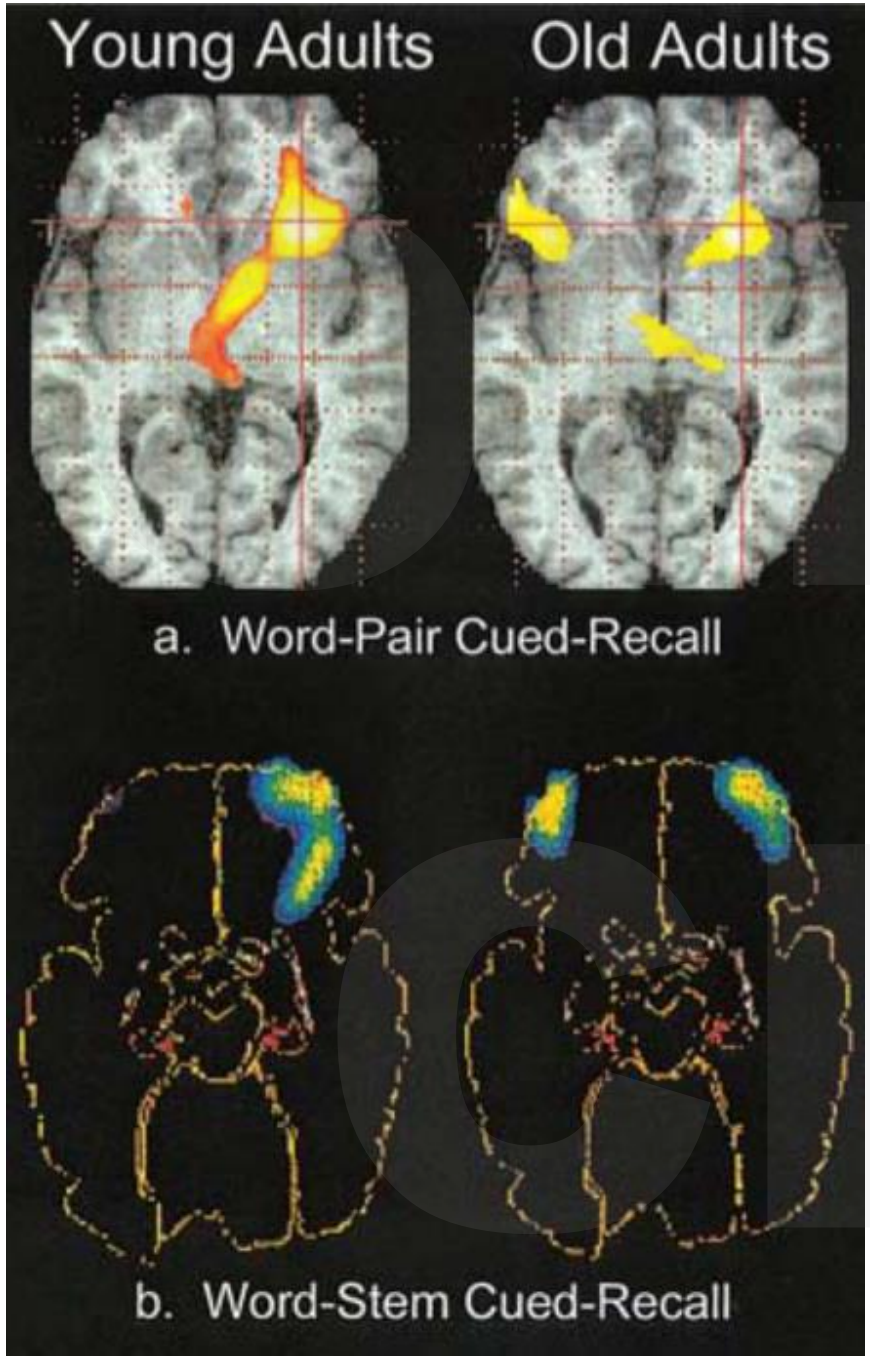
- Attempt to counteract neural decline by reorganizing functions

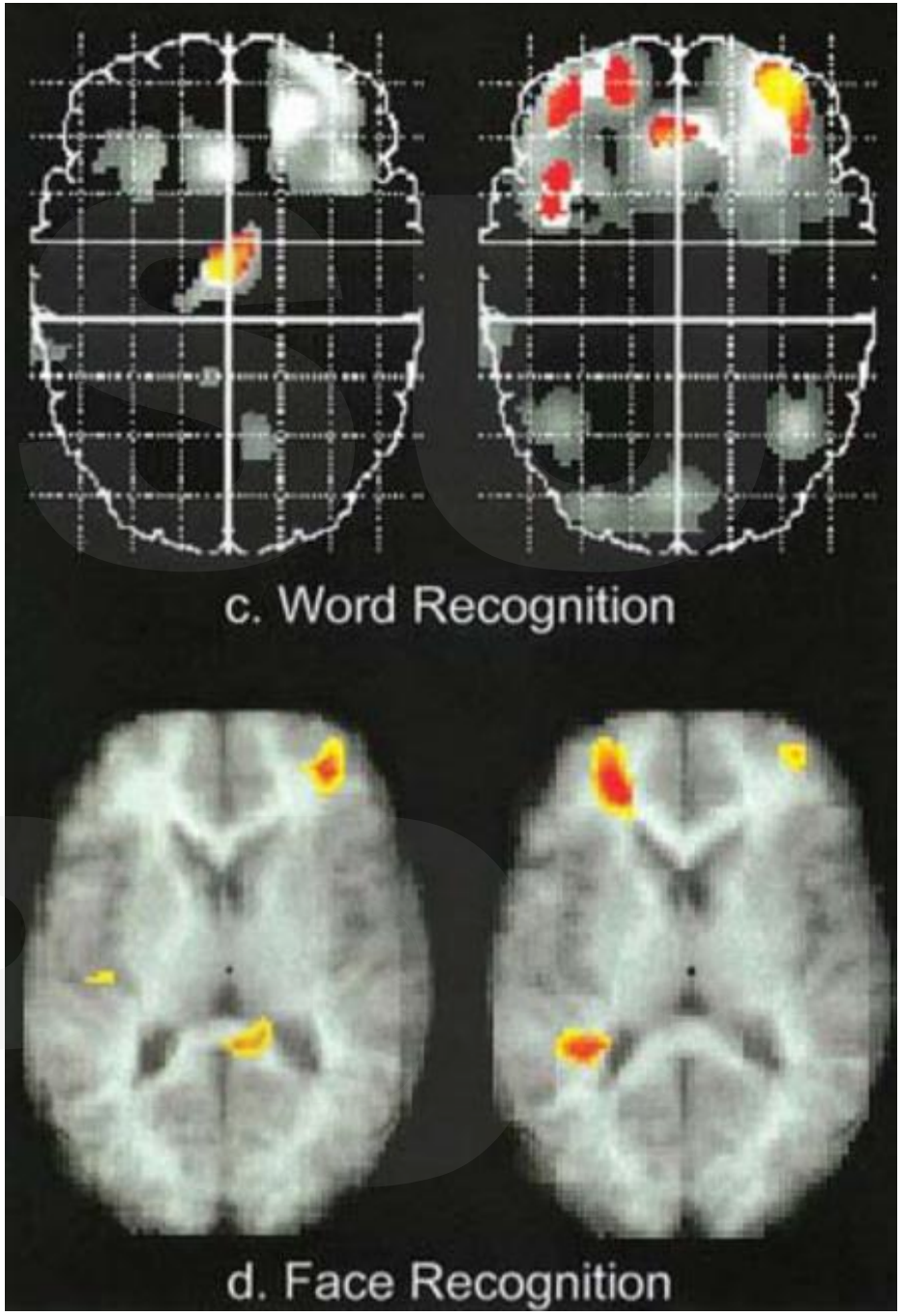
Hemispheric Asymmetry Reduction in Older Adults (HAROLD)

- Increase in bilateral processing

Posterior-Anterior Shift with Aging (PASA)

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





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

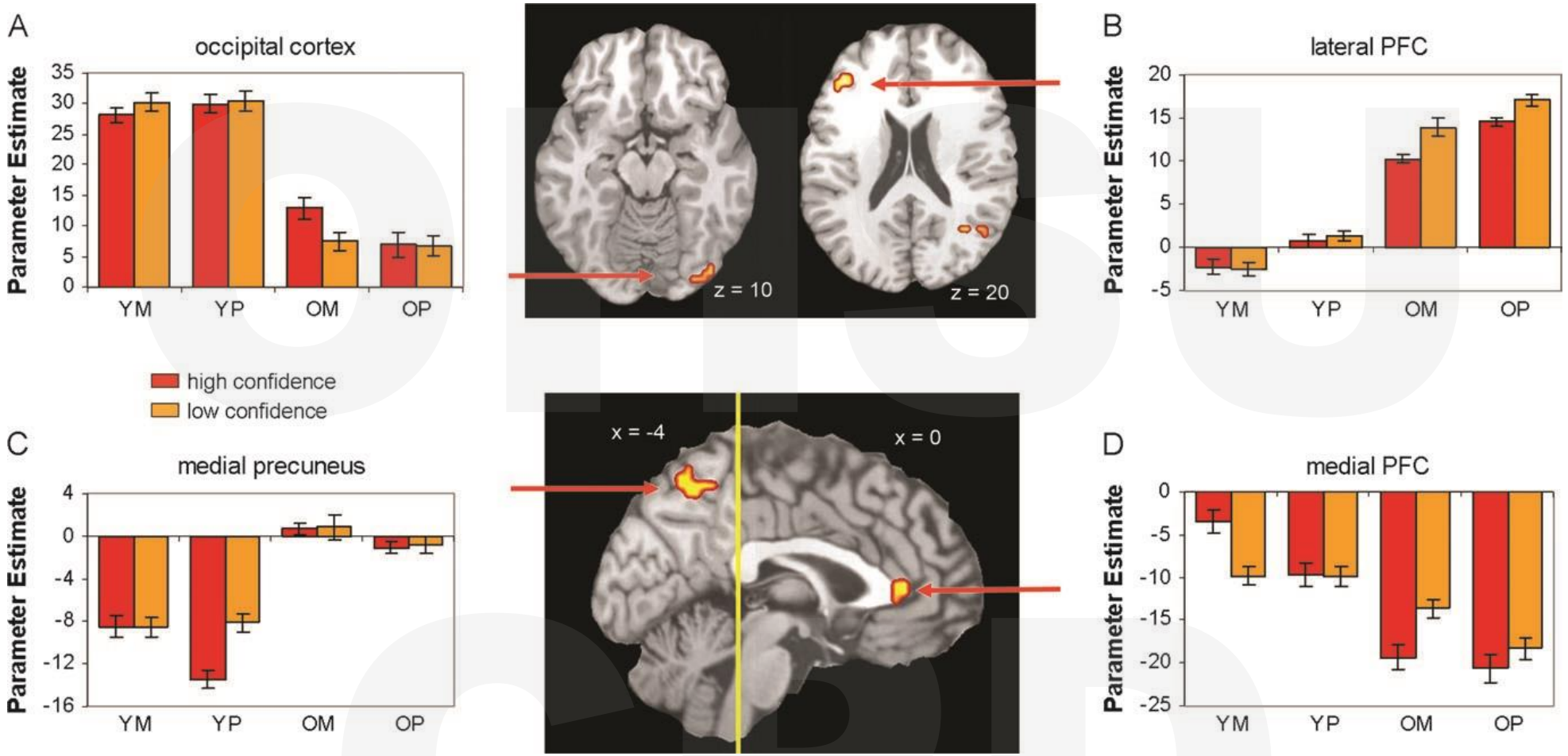


Figure 2. The PASA pattern for activations: across 2 different tasks and 2 levels of confidence, the occipital cortex showed greater activity in younger than in older adults A, whereas PFC showed the opposite pattern (B). The PASA pattern for deactivations: across 2 different tasks and 2 levels of confidence, 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 all. Cerebral Cortex May 2008.

FRONTAL LOBE FUNCTIONS

Attention and Multitasking

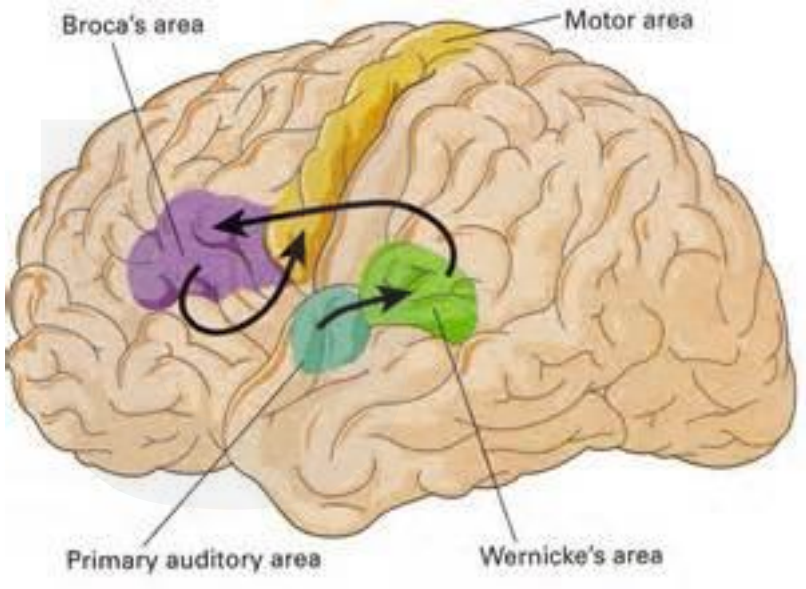
- Ability to focus on one task at a time is maintained with age
- Ability to shift attention between tasks is impaired with age
- Phenomenon seen across multiple species, indicating biologic basis

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:

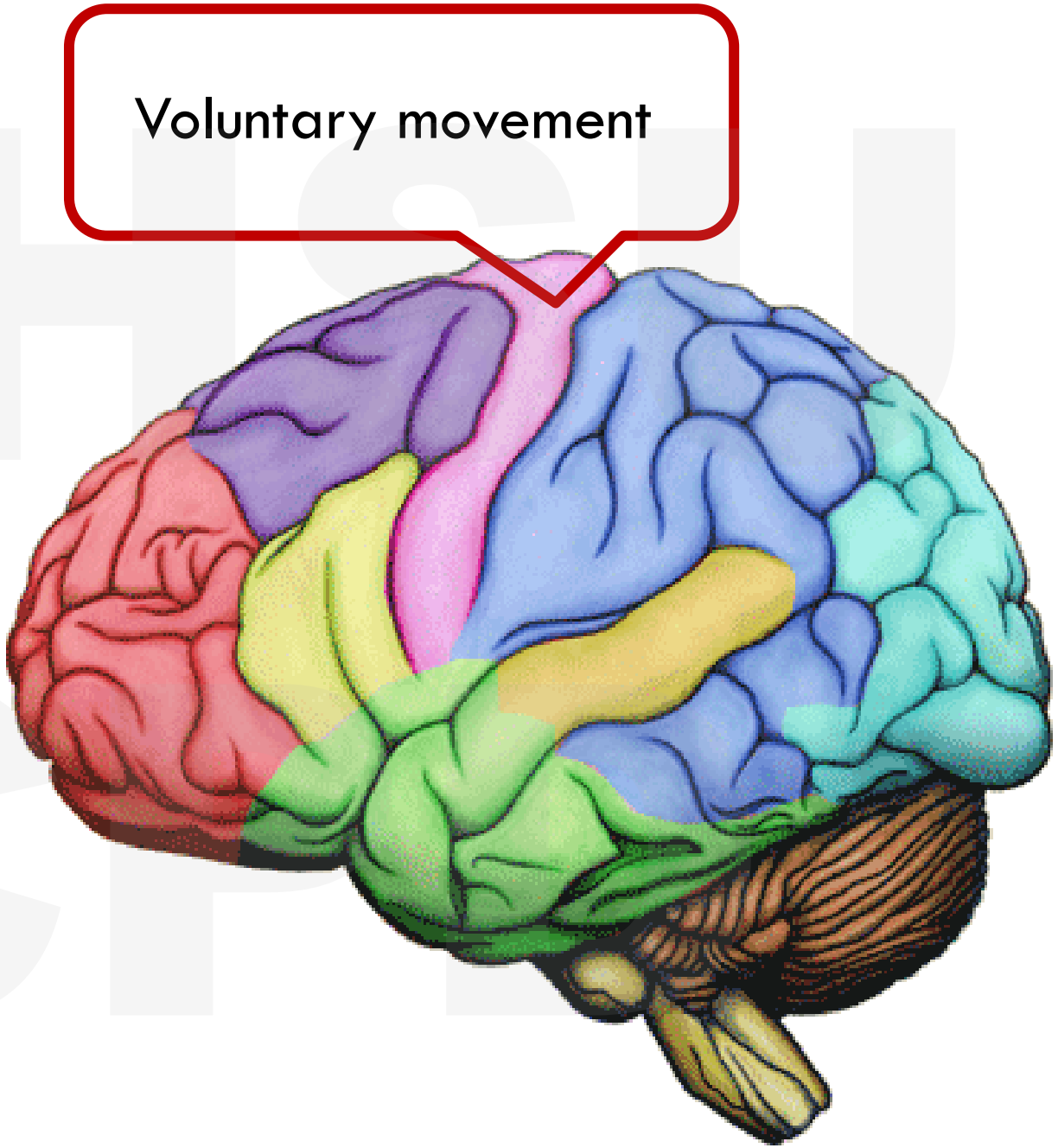
Ventral and dorsal language processing pathways present at birth

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



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 ~ 3% per year after age 70

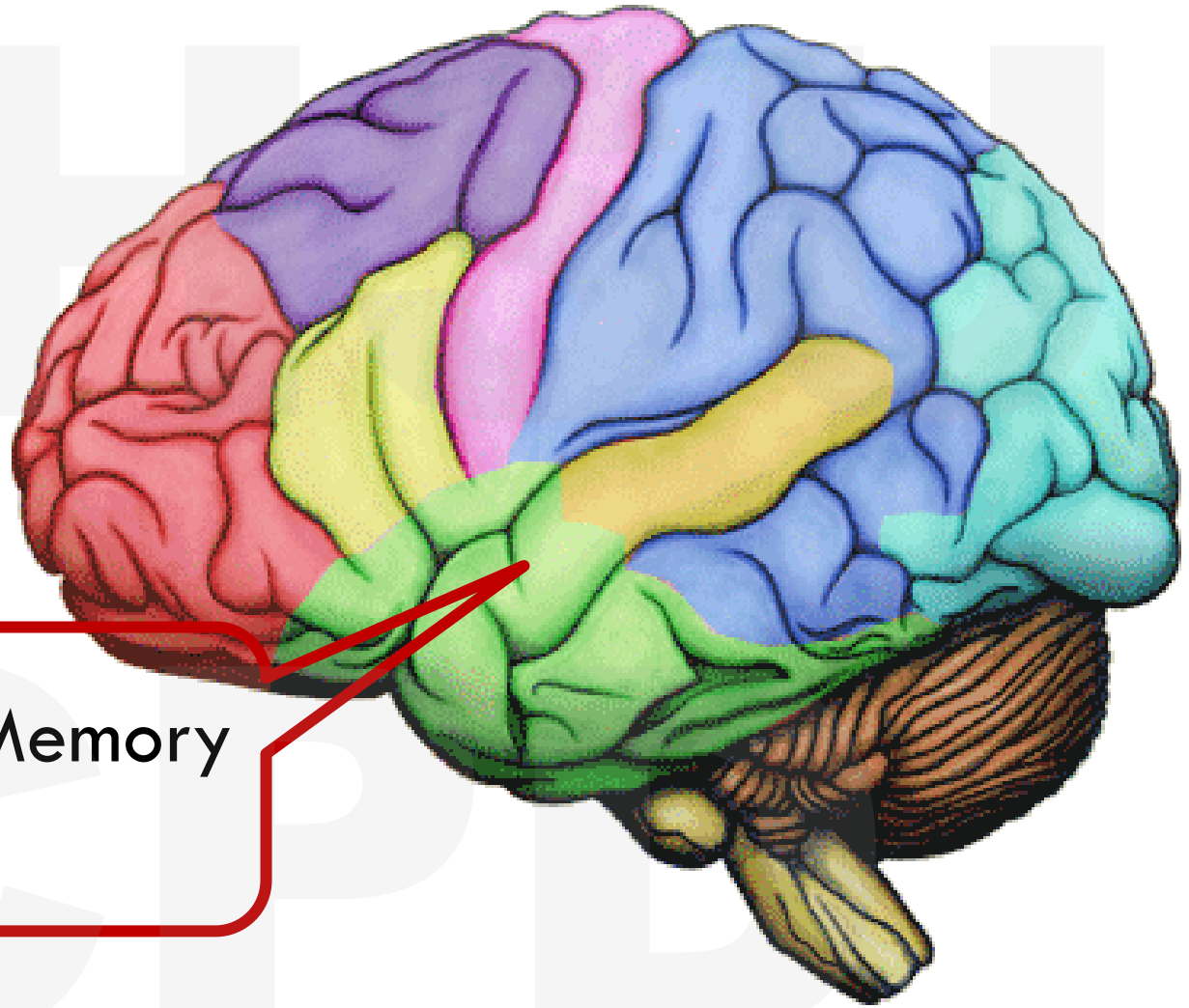
Coordination difficulty

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%

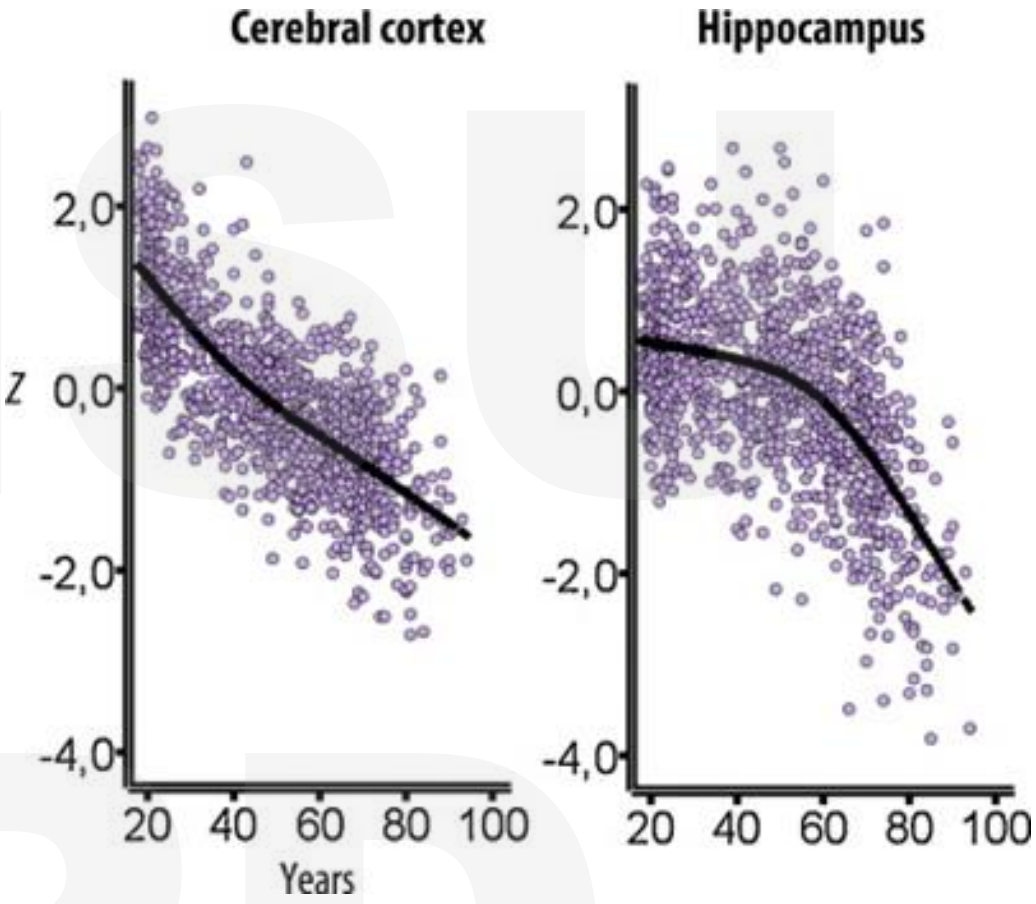


Fig. 5 Life-span trajectories of volumetric reductions. Cross-sectional estimates of adult life-span trajectories of total cerebral cortex volume and total hippocampal volume. Volume is expressed in units of standard deviations. <ce:source> Data from <ce:...

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 - NAVAGATION

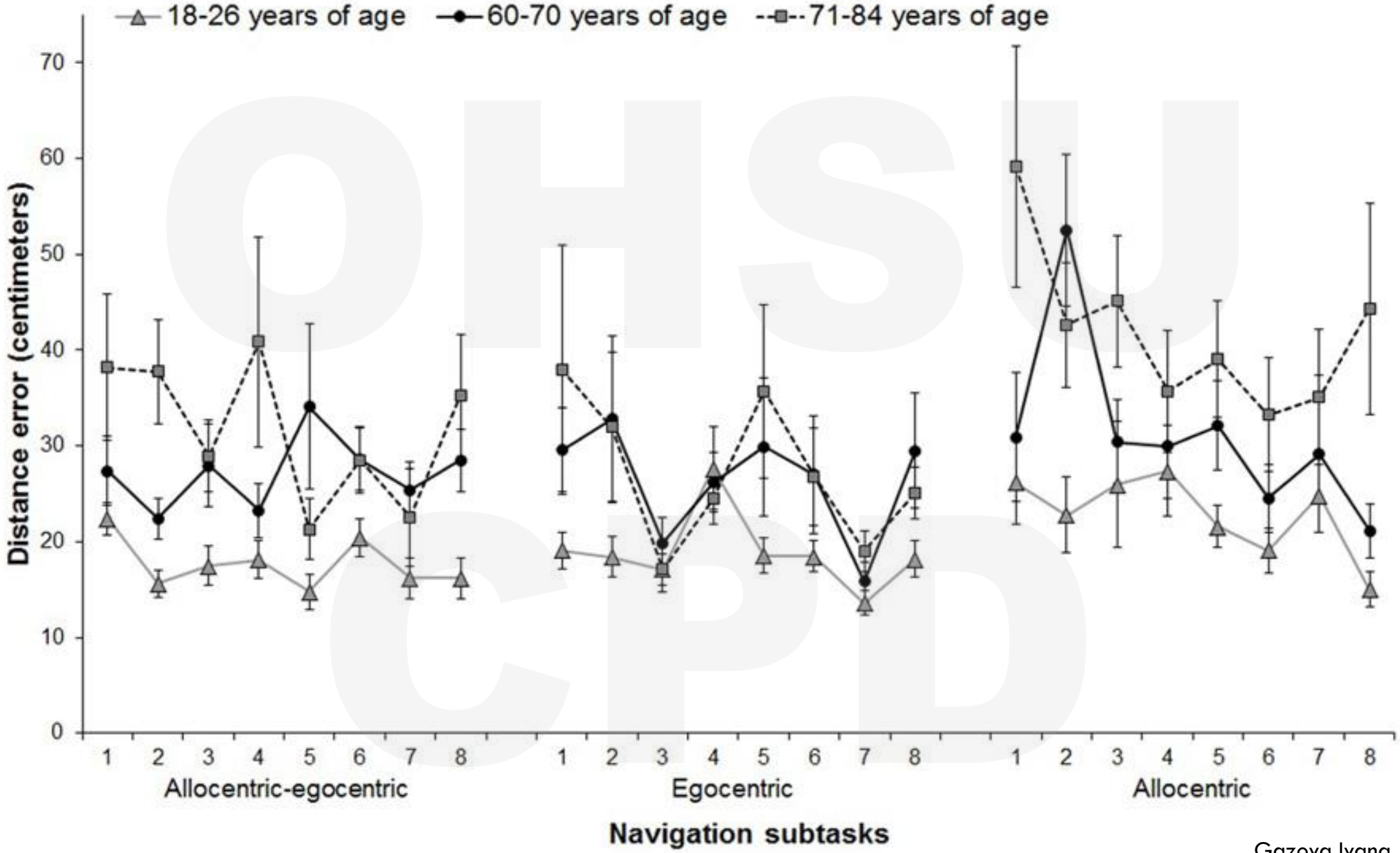
Decline in spatial navigation was shown to be apparent after 60 years of age and further accelerated after 70 years of age (Barrash, 1994).

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



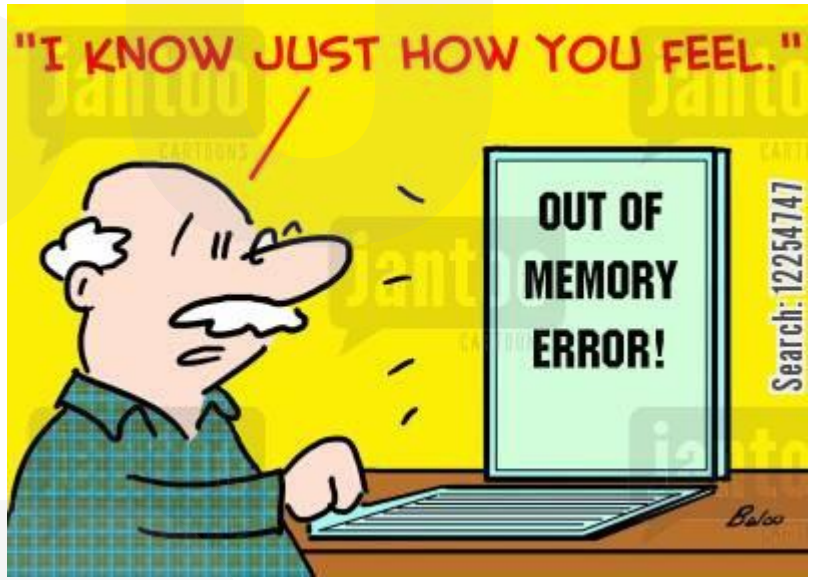
Gazova Ivana, et al. 2013

TEMPORAL LOBE - NAVAGATION

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

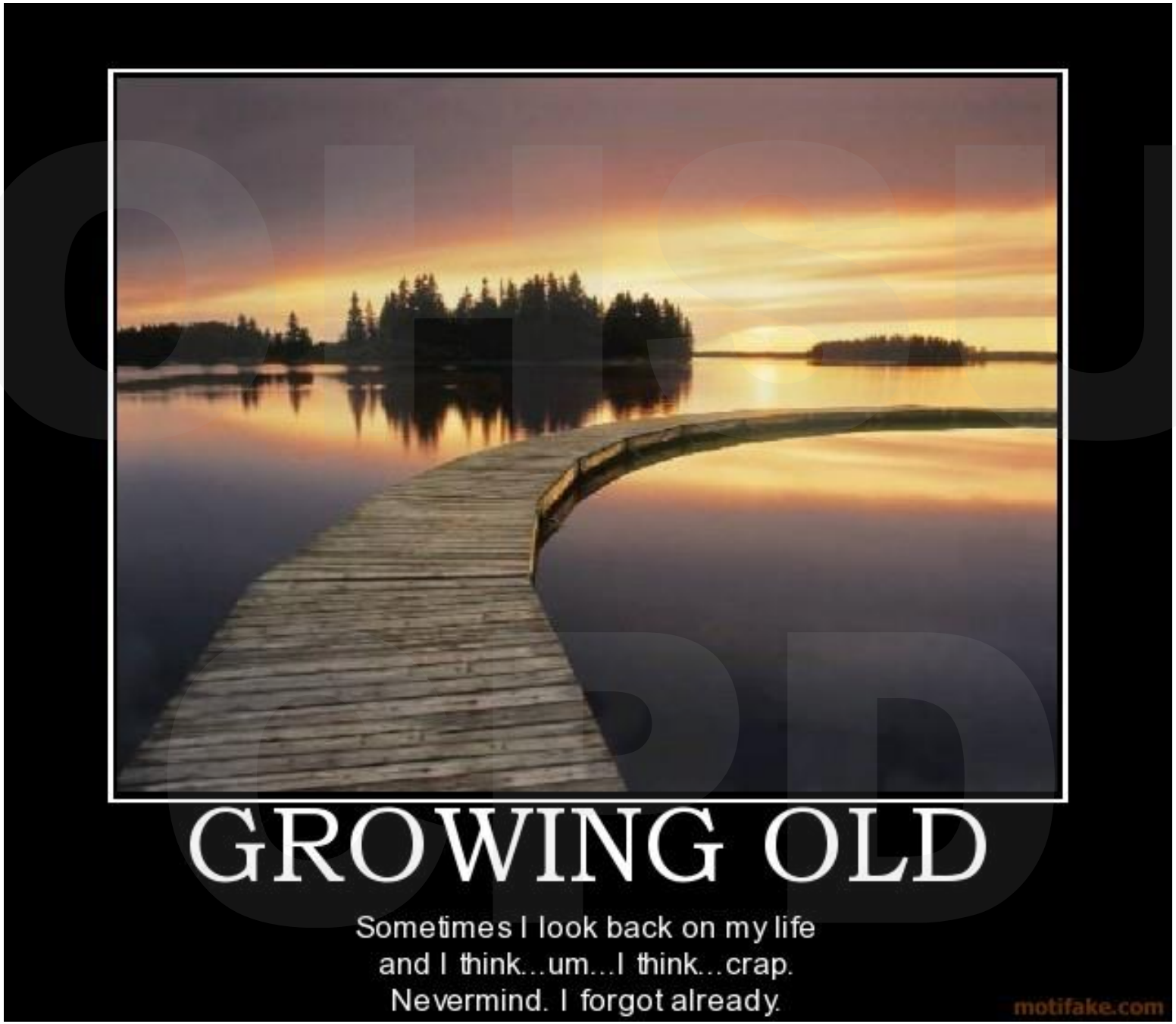
Semantic memory shows little age-related decline

- Facts, meanings, concepts, and knowledge

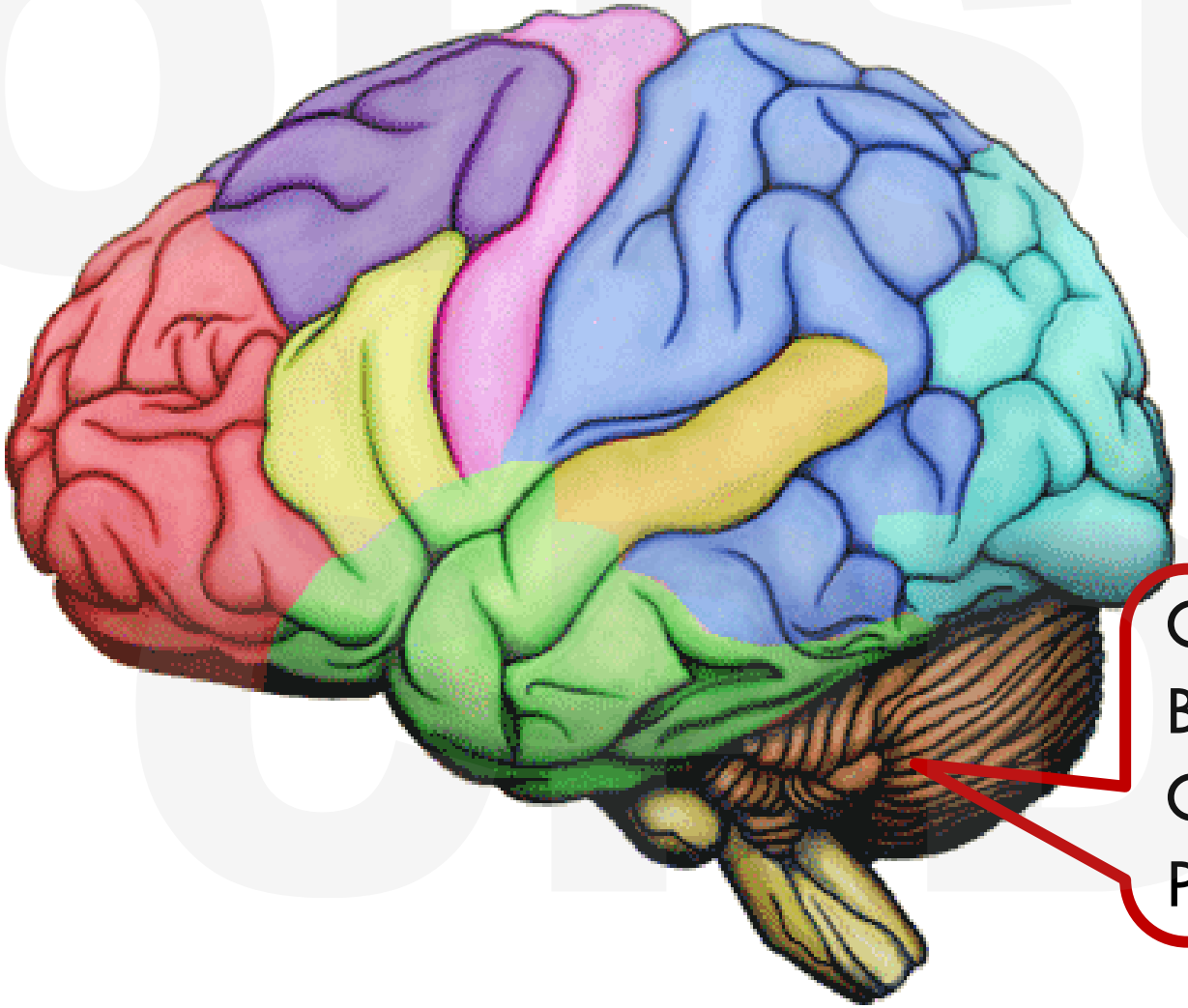
Physical memory is the least affected with age

- 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.
motifake.com

CEREBELLUM



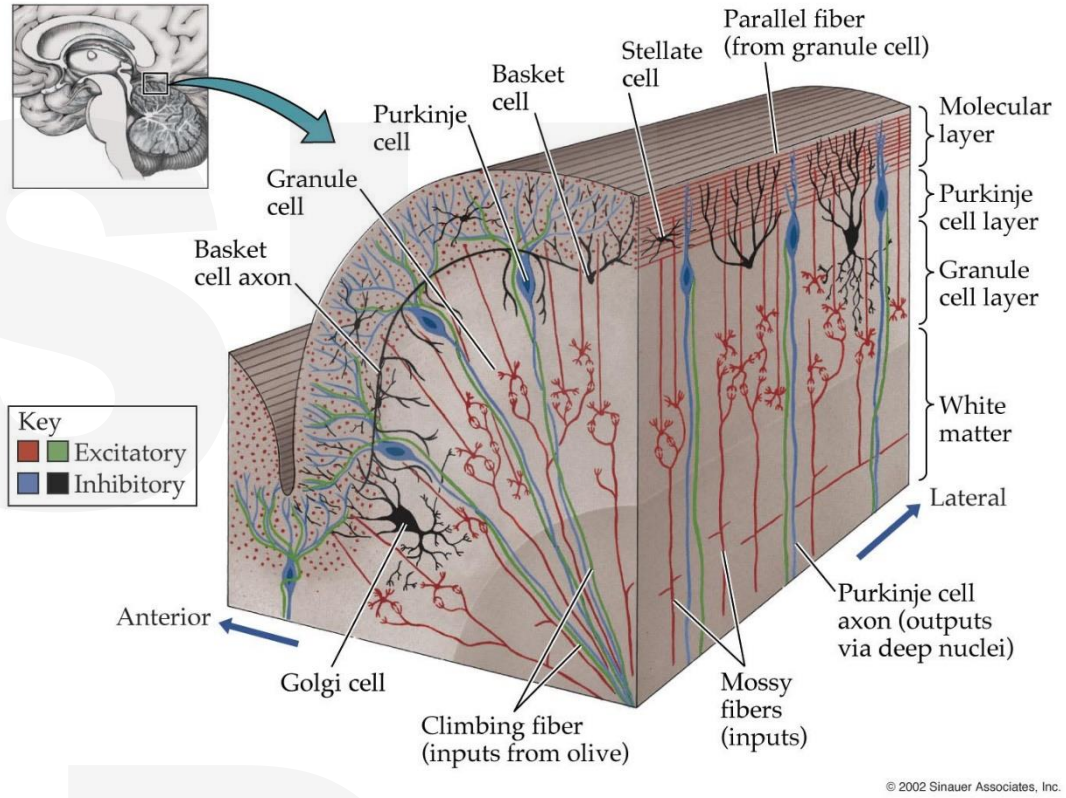
Coordination, Precision, Balance, Posture, Cognitive and Emotional Processing

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.

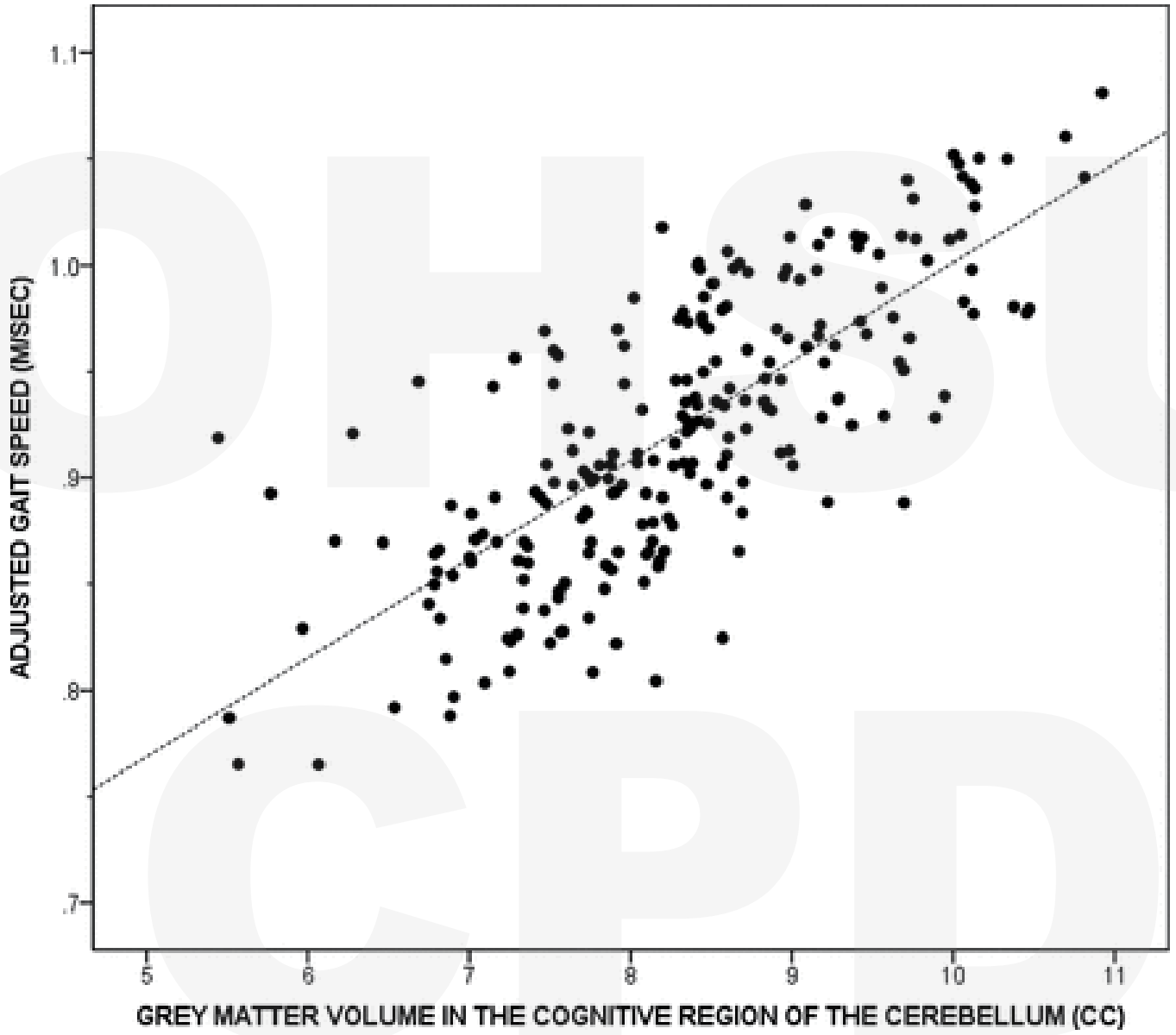
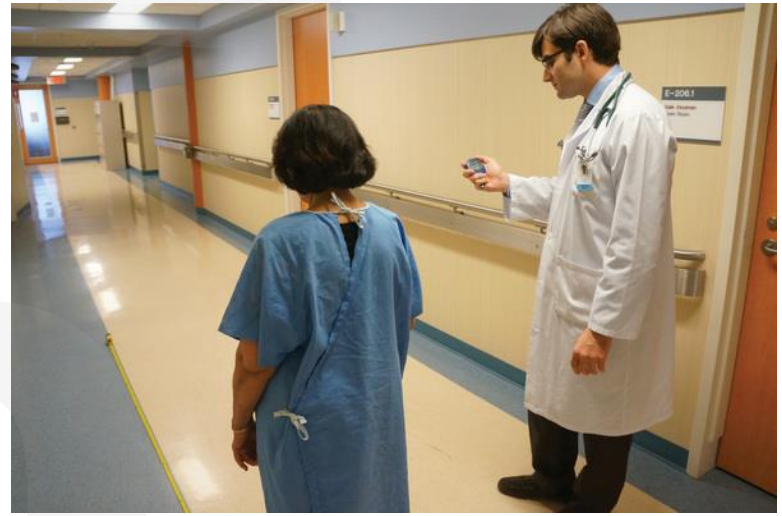


Figure 1. Scatter plot illustrating the association between gray matter volume in the cognitive region of the cerebellum and adjusted gait speed.

CEREBELLUM

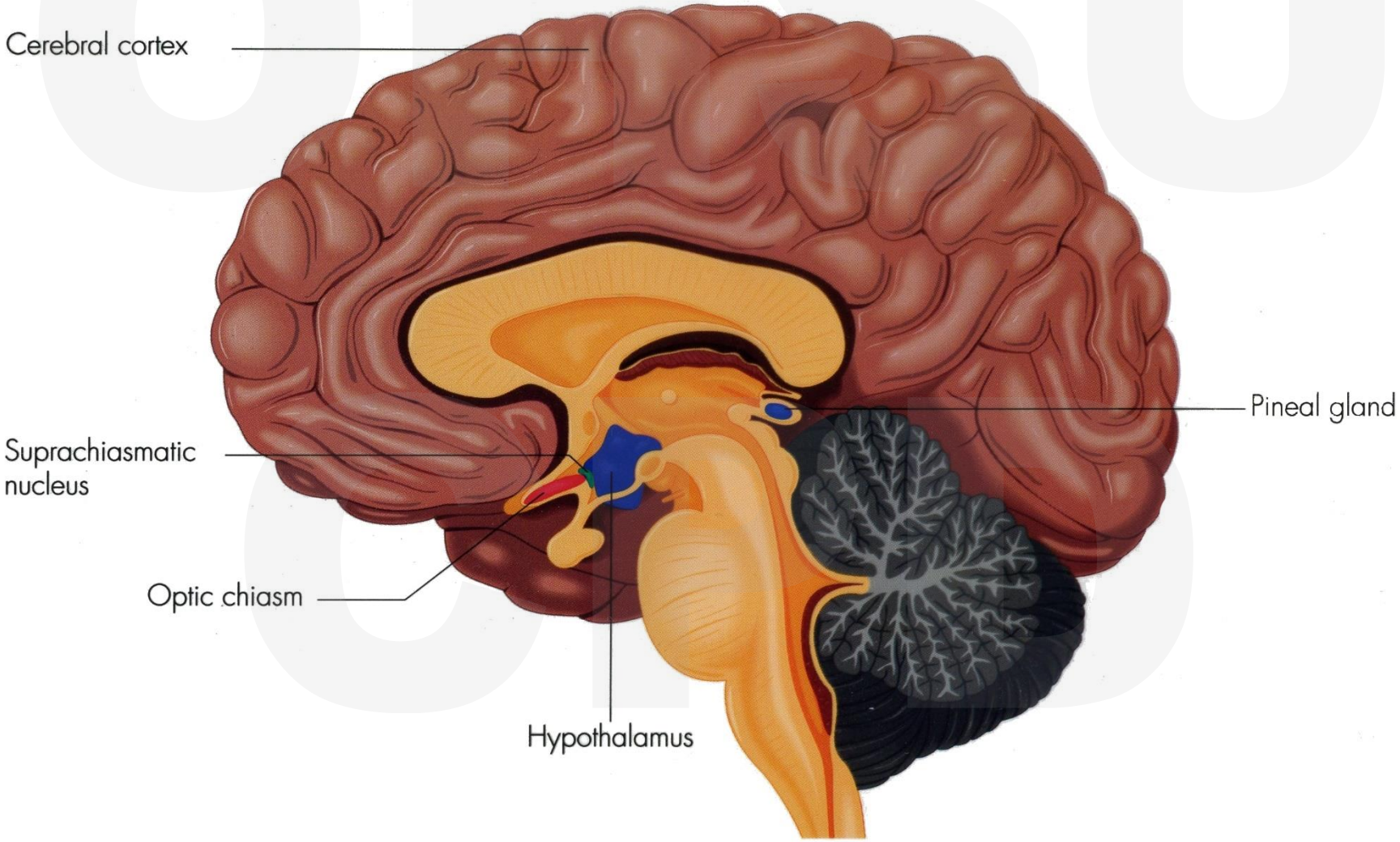
The cognitive region of the cerebellum has the strongest association with gait speed and processing speed.



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

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

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:

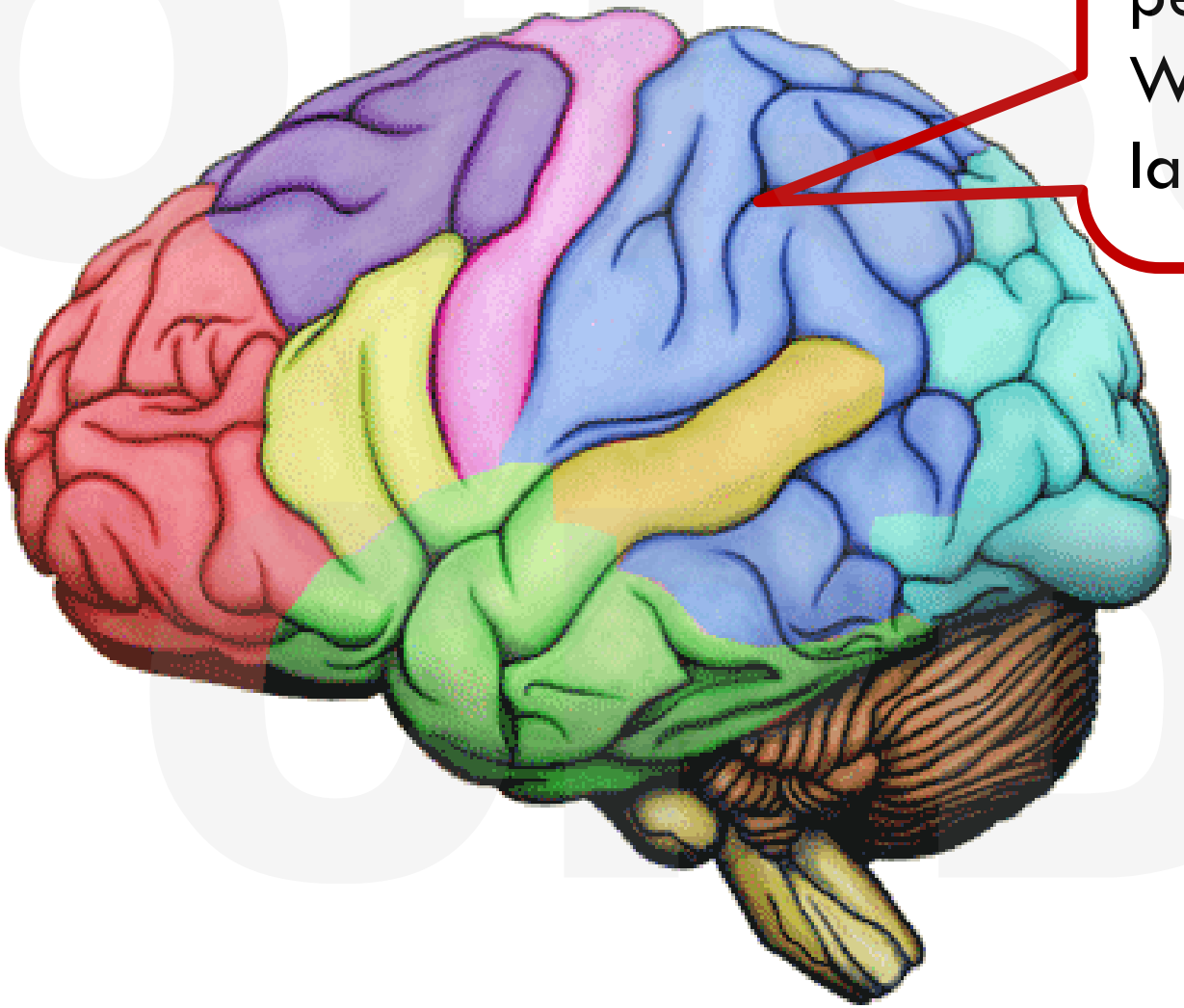
- Insomnia, RLS, OSA, REM sleep behavior disorder

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.

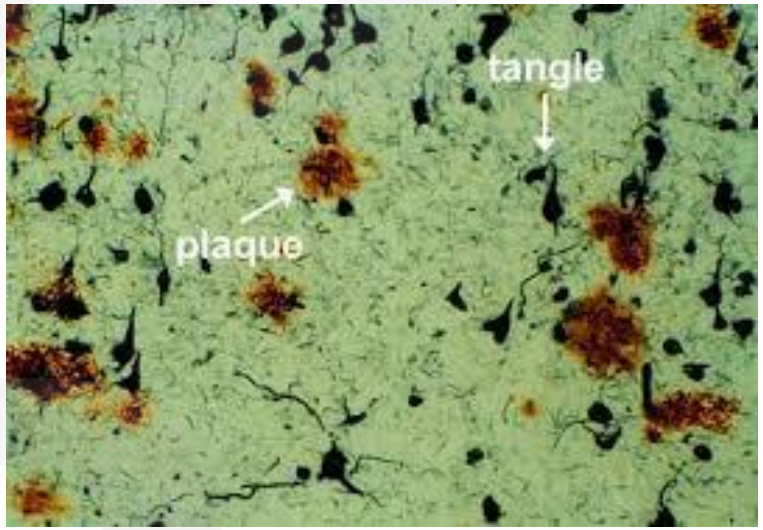
PARIETAL LOBE



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-ε4, 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.

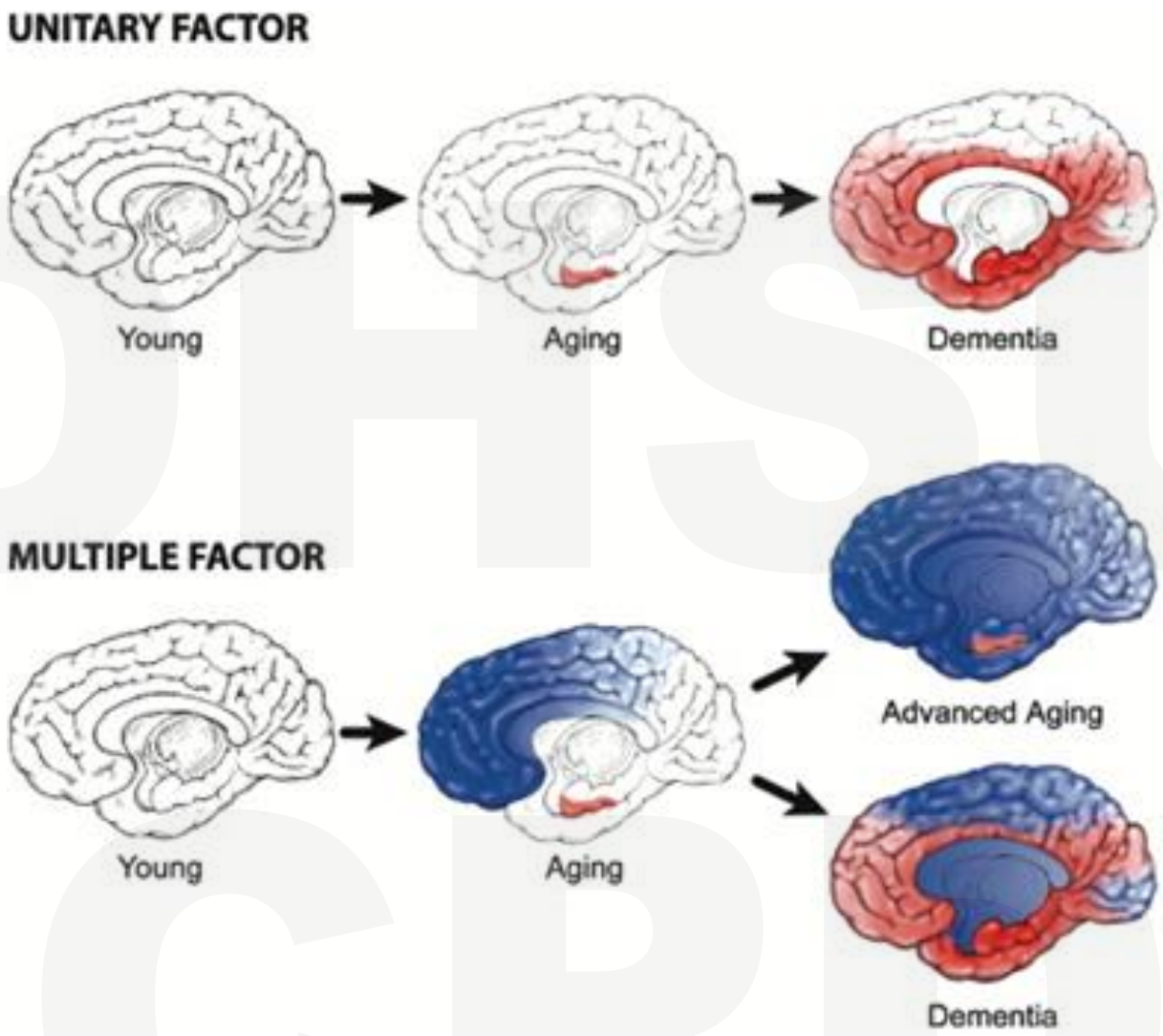


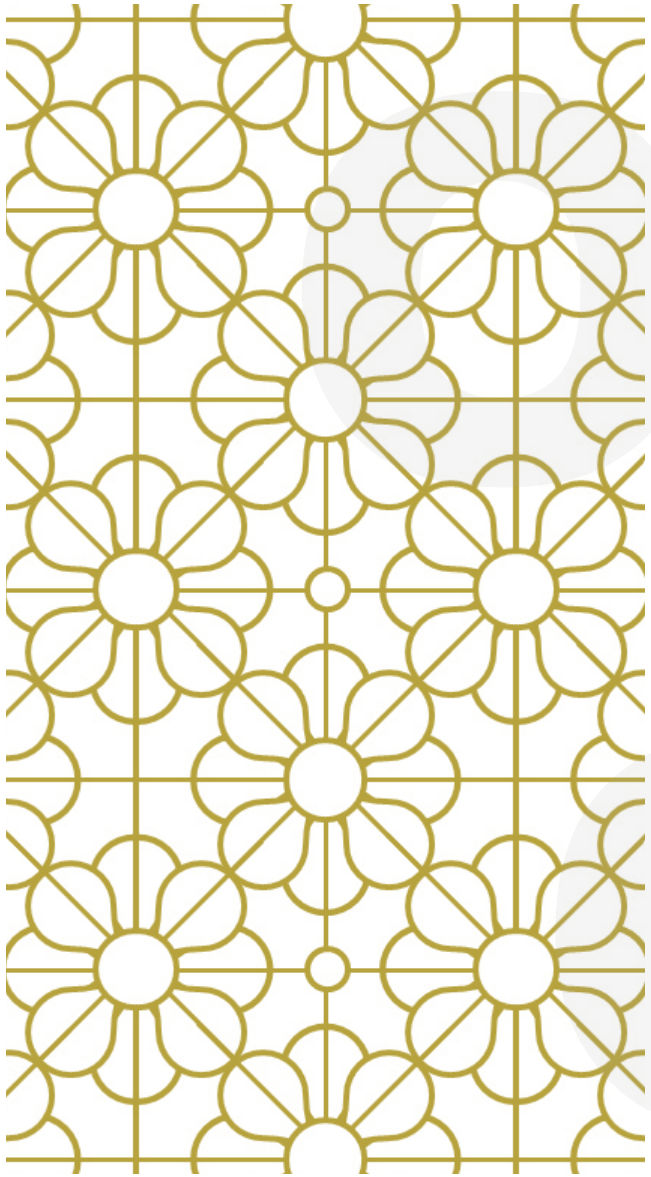
Figure 3. Unitary and Multiple Factor Frameworks of Aging Are Schematically Represented as Heuristics for Discussion. Within a unitary factor framework, mild memory decline common in aging exists along a single continuum with memory impairment associated with dementia. Dementia is considered as an acceleration 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)**

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