

Round 15: Cognitive Decline

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Cognitive Decline

- Why are there age-related deficits in brain function?
 - Lack of (direct) evolutionary pressure
 - Decline occurs after reproductive range, so those with associated genes reproduce -> don't get removed via natural selection
 - Indirect pressure
 - As civilization emerged, there was a benefit of having older people who were still functional to make the village a good place to raise a family
 - More stable villages, with more food, better infrastructure -> more population

Cognitive Decline

- Most cell types renew at various intervals
 - Stomach/intestines – 5 days
 - Skin – 2-4 weeks
 - Red blood cells – 4 months
 - Liver – 150-500 days
 - Bones – 10 years
- Overall, neurons do not renew, they are the age of the person (although there is some neurogenesis)
- Brain maturity & learning occurs by sprouting synaptic connections & synaptic pruning
 - Constant need to grow synaptic connections & synaptic pruning may prove toxic over time
- Regions of the brain that are affected first and more extensively by dementia are those regions with higher baseline plasticity -> memory

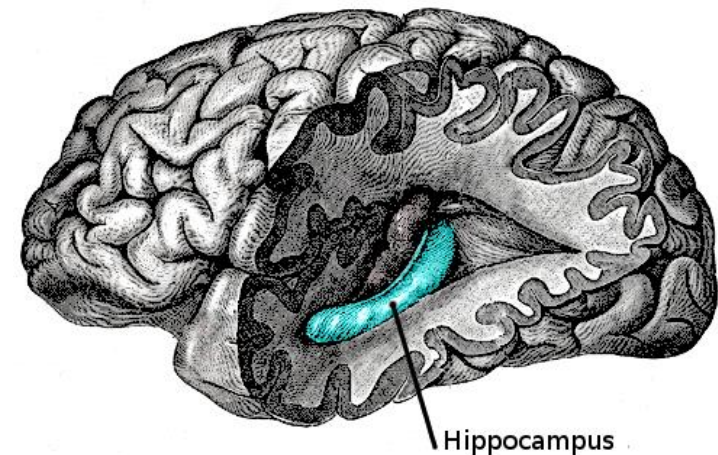
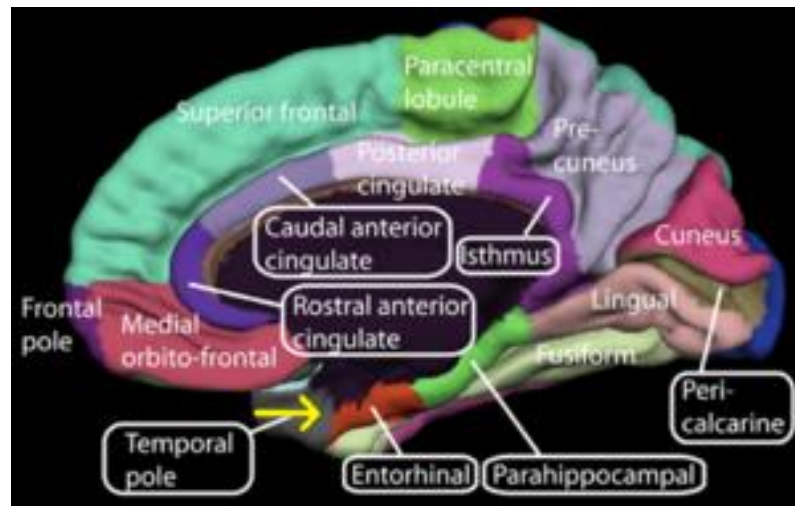
Cognitive Decline

- Typical Ageing
 - Slower gait, shorter stride
 - Sluggish postural reflexes (more prone to falls)
 - Less slow wave and REM sleep
 - Decline in ability to retain large new body of information over long period of time
 - Decreases in rapid word naming & naming as many words as possible that start with a given letter
 - Impaired visuospatial abilities
 - Decline in general intelligence

- Anatomical Changes
 - Decreased brain weight
 - Loss of neurons & myelination
 - Fewer neurons in Substantia Nigra, Locus Coeruleus, Pons
 - Reduction in precursors to Dopamine & Norepinephrine

Mild Cognitive Impairment

- Occurs in 10–20% of people aged 65 and over
- Entorhinal cortex and hippocampus first sites affected
 - Entorhinal Cortex
 - Network hub for memory, navigation, time perception
 - Interfaces between the neocortex & the hippocampus
- Smaller entorhinal cortex and hippocampus than healthy age-matched subjects.
- Diffusion tensor imaging (white matter tracts) abnormalities -> hippocampus & thalamus



Dementia

- Progressive decline in mental function, memory, and acquired intellectual skills
- Usually occurs after 45, mostly over 65
- 11% over 65 show mild to severe mental impairment
- After 75, incidence increases 2% each year

- 70% of all dementia are due to Alzheimer's
 - 15% caused by strokes
 - Thin gyri, enlarged ventricles

- Some genetic component
- Nearly all people who have Down's syndrome linked to chromosome 21 develop Alzheimer's if they live past 35

Depression vs. Dementia

- Preoccupation with mental pain may disrupt pts ability to concentrate -> memory/attention problems
- Physiological processes associated with depression have an affect on memory/attention
- Depressed pts
 - problems are with registering the information and depth of processing
 - Exaggerate difficulties
 - Give up quickly
 - Give false negative “I can’t remember”
- Alzheimer’s pts
 - Retrieving the information
 - Minimize deficits
 - False positives -> confabulation
 - Misspellings are common

Alzheimer's Stages

- Initial stages
 - Repeating themselves, forgetting names, misplacing objects
 - Selectively affects recent declarative knowledge
 - Beginning of detachment from professional, social, recreational activities
 - Become lax & complacent
 - Less interest in eating, drinking, libido
- Intermediate stage
 - Deficits in language, reasoning, spatial orientation, executive functions
 - Interference of recognition memory
 - Failure to store new information for more than a few minutes
 - Attentional deficits -> unable to maintain coherent stream of thought & sequence goal-directed activities
 - Aphasias – spelling, word finding
 - Erosion of hygiene
 - Emergence of delusions & hallucinations
- Late-stage
 - Incontinence
 - Unable to recognize family members
 - Difficulty eating/mobility
 - All cognitive, behavior, psychiatric functions deteriorate
 - Usually die of cardiopulmonary arrest or infection complications

Alzheimer's Causes

- **Amyloid plaques**
 - By-product of the break down of amyloid precursor protein
 - Beta-amyloid 42 especially toxic
 - Levels build up and clump together to form plaques that collect between neurons and disrupt cell function
- **Neurofibrillary Tangles**
 - In healthy cells, tau supports microtubules in neurons -> support the cell and transport nutrients within the cell
 - Tau proteins accumulate inside neurons form tangles which disrupt intracell transport

Alzheimer's Causes

- **Chronic Inflammation**
 - Microglia & astrocytes fail to clear away waste, debris, and protein collections
 - May be due to a failure in a gene TREM2
- **Vascular Contributions**
 - Reduced blood flow & oxygen to brain
 - Breakdown of blood/brain barrier preventing glucose from reaching the brain & the clearing of beta-amyloid & tau -> inflammation

Alzheimer's

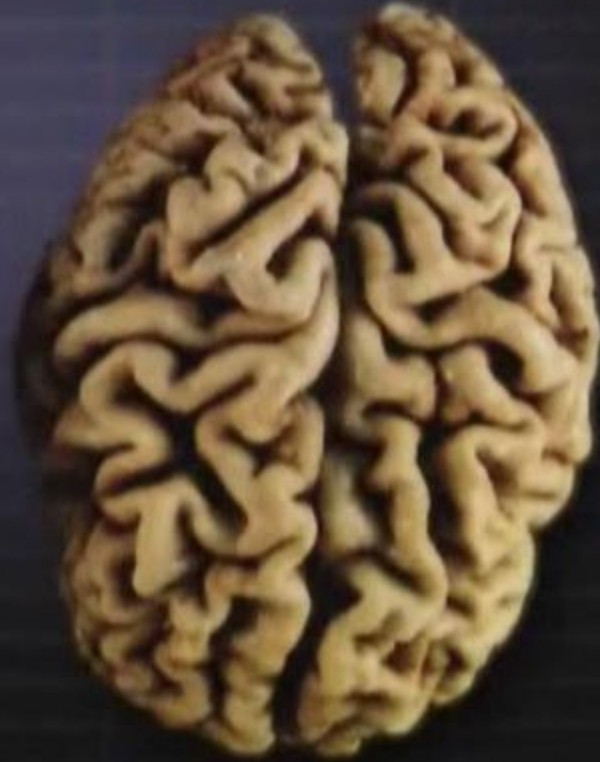
- Candidate biological markers
 - Hypometabolism in parietotemporal region (PET scan)
 - Loss of hippocampal volume (MRI)
 - Presence of e4 alleles
 - Decrease cerebrospinal fluid (CSF) levels of amyloid fragments
 - Increased CSF levels of tau proteins

Alzheimer's

- Entorhinal cortex is typically the earliest site of atrophy, closely followed by the hippocampus, amygdala, and parahippocampus
- Hippocampal volumes reduced by about 10%, 3 years before receiving a diagnosis of dementia
- By the time of clinical diagnosis, whole brain volumes down by ~6%
 - Entorhinal volumes reduced by ~20–30%
 - Hippocampal volumes reduced by ~15–25%
 - Hippocampal atrophy in mild AD are ~3–5% per year
 - 60-90% loss of Choline, precursor to acetylcholine, in hippocampus



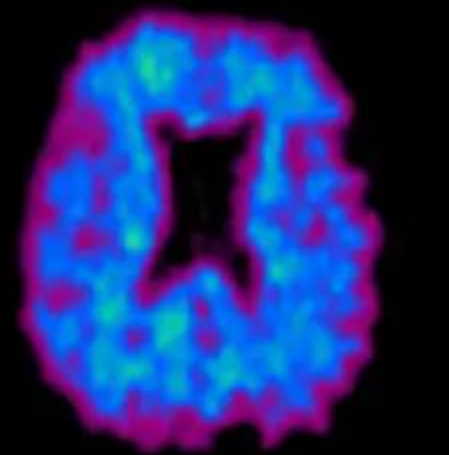
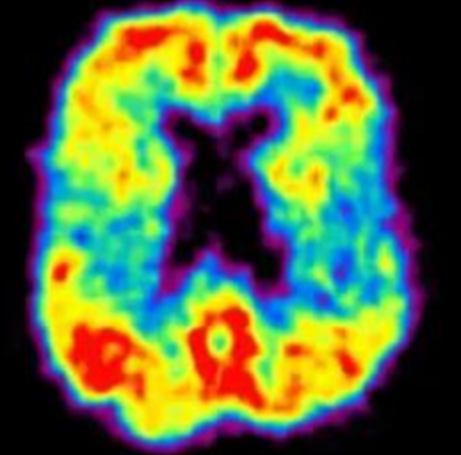
Normal



Alzheimer

AD

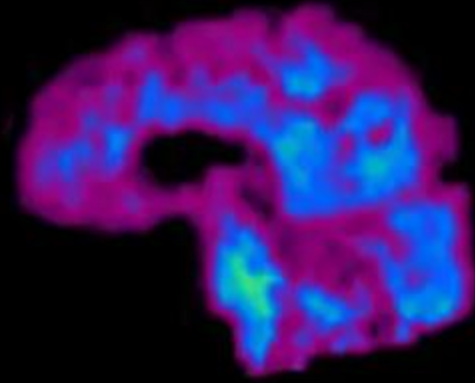
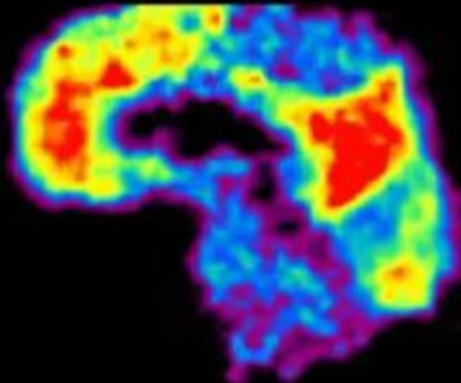
Control



Max

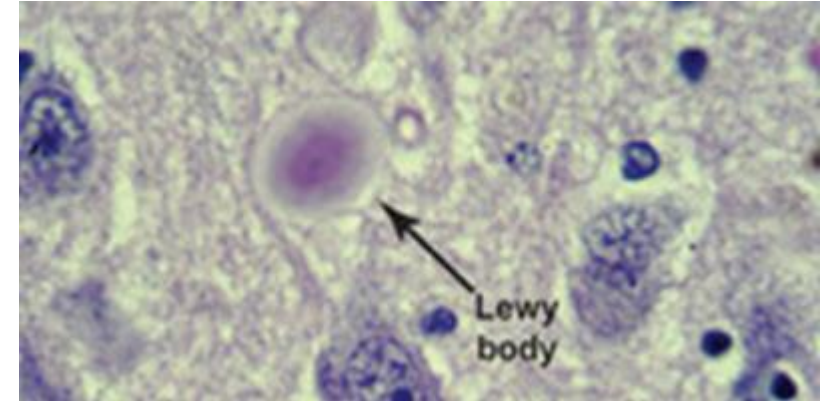


Min



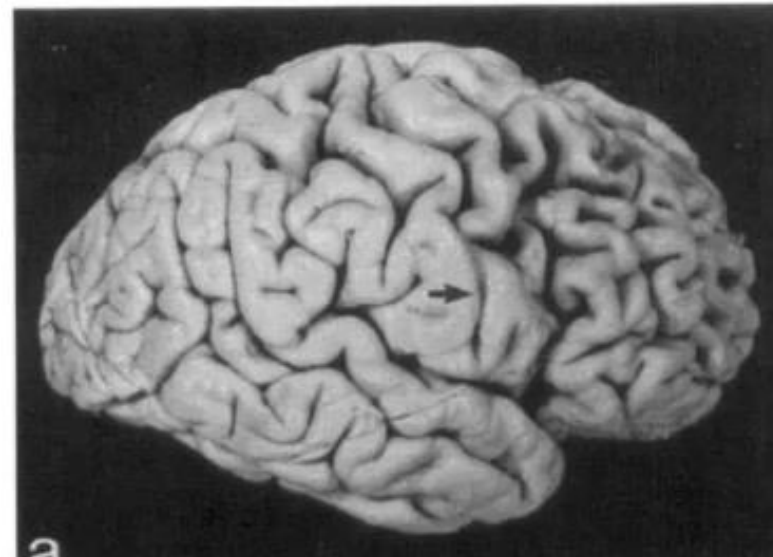
Lewy Body Dementia

- Accounts for 15% of all dementia
 - Robin Williams
- Often comorbid with Parkinson's or has similar symptoms due to dopaminergic cell loss
 - Hunched posture, rigid muscles, a shuffling walk, and trouble initiating movement
- Symptoms
 - Changes in thinking and reasoning
 - Confusion and alertness that varies significantly from one time of day to another or from one day to the next
 - Well-formed visual hallucinations
 - Delusions
 - Sleep disorders – acting out dreams
- LBD distinguished from AD
 - More atrophy of hypothalamus, basal forebrain, midbrain, caudate, and putamen
 - Relative preservation of the medial temporal lobe and the hippocampus
 - Abnormalities in the visual association cortex and posterior putamen in LBD compared with medial temporal lobe and precuneus in AD



Frontotemporal Dementia

- Accounts for 5% of dementias
 - Family history in 50% of cases
- Frontal degeneration -> personality and behavior
 - Fixed mood and behavior, appearing selfish and unable to adapt to new situations
 - Loss of empathy, emotional warmth, and emotional responses
 - Lack of motivation, abandoning hobbies or avoiding social contact
 - Loss of normal inhibitions, talking to strangers or exhibiting embarrassing behavior
 - Difficulty in reasoning, judgement, organization and planning
 - Distractibility and impulsiveness
 - Changes in eating patterns, craving sweet foods, overeating or unusual food preferences
 - A decline in self-care and personal hygiene
- Temporal -> language impairments
 - Ability to assign meaning to words is gradually lost
 - Reading, spelling, comprehension, and expression are usually affected
 - Difficulty finding words and people's names



Other Dementias

- Primary Progressive Aphasia
 - Gradual & isolated degradation of language function
 - Memory, visuospatial, reasoning, behavior all normal
 - May also have acalculia or ideomotor apraxia – cannot mime action associated with a given object



(mirrored image)

Other Dementias

- Progressive Visuospatial Dysfunction

- Balint's syndrome

- Unable to perceive visual field as a whole
 - Difficulty fixating eyes
 - Unable to move hand to a specific object in space

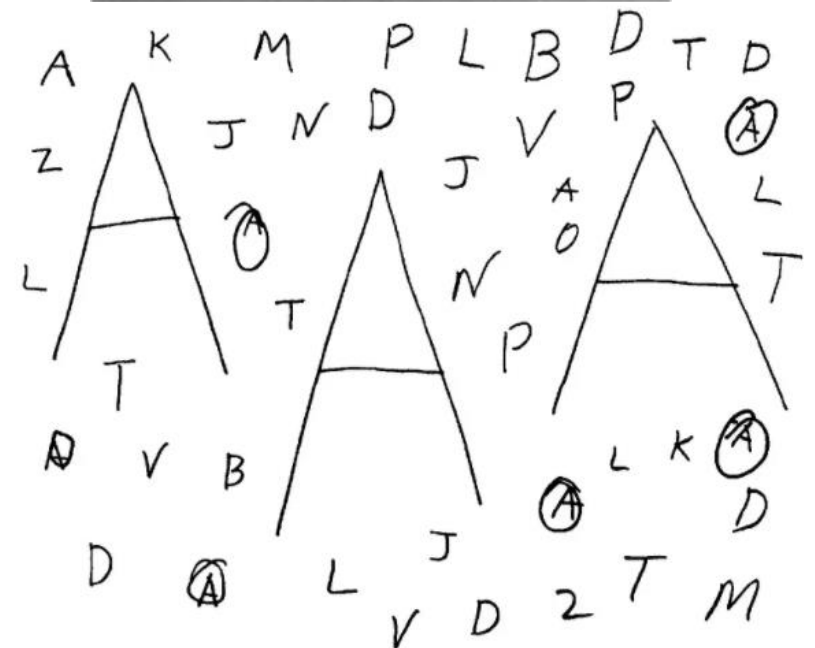
- Gerstmann's syndrome

- Agraphia, acalculia, finger agnosia, left-right disorientation

- Simultanagnosia

- Cannot perceive more than a single object
 - Cannot grasp overall meaning of a scene

- Spatial disorientation, dressing apraxia, hemineglect



Alcohol-related Dementia

- Korsakoff's syndrome
 - Commonly affects men over the age of 45 with a long history of alcohol abuse
 - May be due to lack of thiamine (B1)
- Symptoms
 - Impaired ability to learn things
 - Personality changes
 - Problems with memory
 - Difficulty with clear and logical thinking on tasks which require planning, organizing, common sense judgement, and social skills
 - Problems with balance
 - Decreased initiative and spontaneity

HIV-related Dementia

- ~ 7% of people not taking anti-HIV drugs
- Immune cells that are present in the brain act as HIV reservoirs -> primary source of indirect damage to nerve cell

Early stage:

- Difficulty concentrating
- Impaired memory
- Slowed thinking
- Difficulty keeping track of daily activities
- Irritability
- Unsteady gait, balance
- Poor coordination, changes in handwriting
- Depression

Middle stage:

- Motor dysfunction, muscle weakness
- Slower responses, dropping objects
- Slow motor behavior (e.g., eating and writing)
- Impaired walking, balance, and coordination
- Apathy
- Poor concentration and attention
- Reversing numbers or words

Late stage:

- Loss of bladder or bowel control
- Spastic gait
- Apathy
- Withdrawal
- Psychosis or mania

Treatments

- Acetylcholinesterase Inhibitors
 - Aricept, Exelon
 - Slow the breakdown of Acetylcholine -> involved in memory & judgement
 - Supports communication among nerve cells by keeping acetylcholine high
- Memantine (Namenda)
 - N-methyl D-aspartate (NMDA) antagonist
 - Regulates the activity of glutamate, a chemical involved in information processing, storage and retrieval.
- Clinical trials
 - Aducanumab
 - Antibody derived from healthy aged humans that reduces amyloid plaques
 - FDA did not approve it because of lack of evidence for efficacy
 - Washington University/Denali Therapeutics
 - Antibody HAE-4 -> reduced amyloid plaques in mice

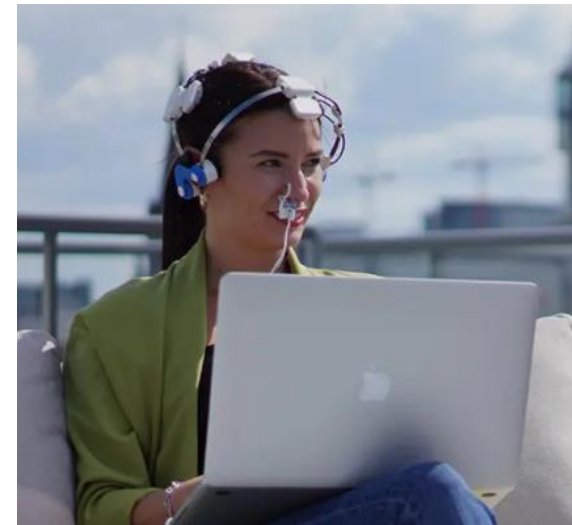
Treatments

- SSRIs
 - Antidepressant helps low mood & irritability
- Anxiolytics
 - (Ativan) Ease anxiety/restlessness
- Antipsychotics
 - (Abilify, Zyprexa, Risperdal) control feelings of aggression, agitation, delusions, hallucinations
- Estrogen hormone replacement
 - Ovarian hormones play a role in promoting synthesis of acetylcholine by the nucleus basalis
 - Menopause -> acute drop in hormones may be why women are more prone to developing AD
 - Risk is lowered when on estrogen replacement

Treatments

Head On! Program at Integrate Brain Health

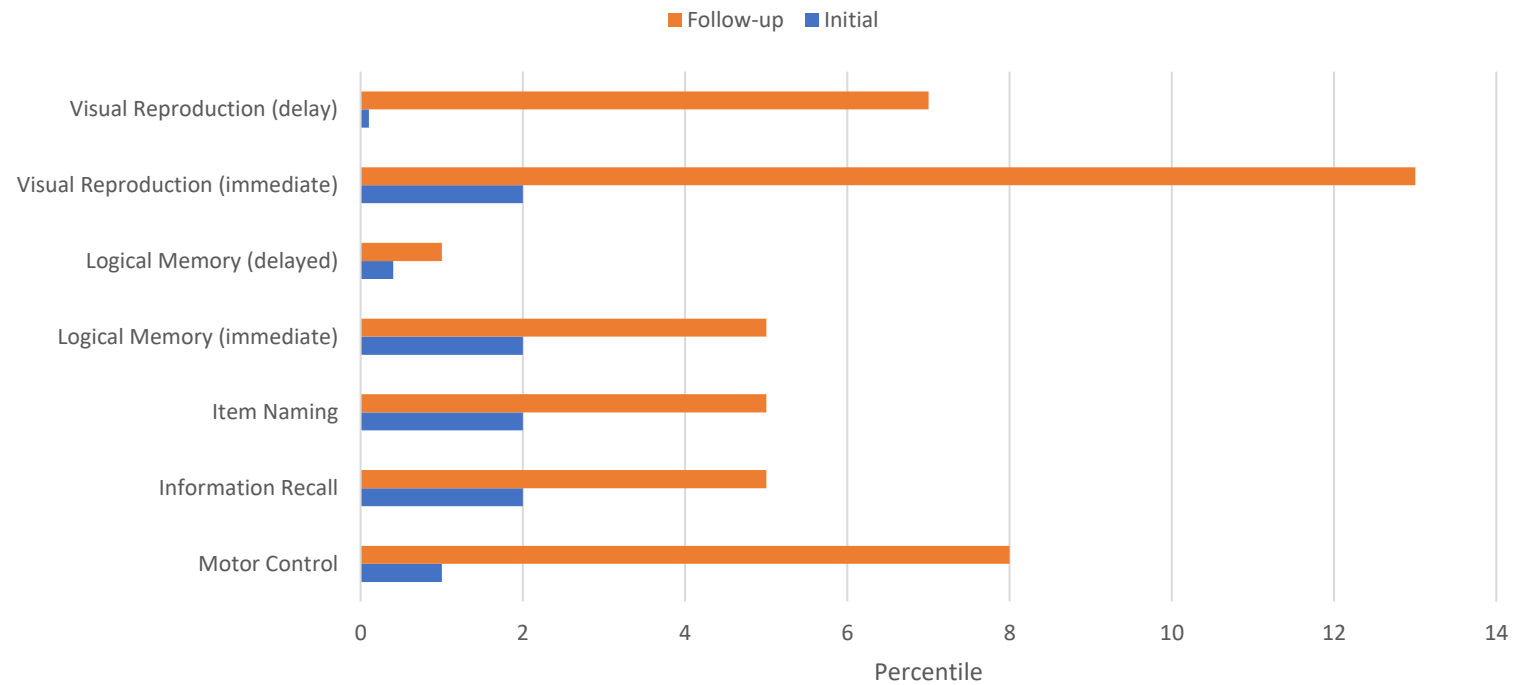
- 74-year-old female presented with memory problems:
 - Remembering past events (i.e., episodic memory) & getting lost while driving to familiar places.
- Battery of neuropsychological tests
 - Deficient verbal processing, item naming, visual reproduction, motor control
- qEEG
 - Regions of concern associated with mental flexibility, memory, symbolic recognition, language processing, self-awareness, visuo-spatial processing, and coordinated motor programming
- Head-On! Program
 - NFB
 - Photobiomodulation
 - Nutrition



Treatments

Head On! Program at Integrate Brain Health

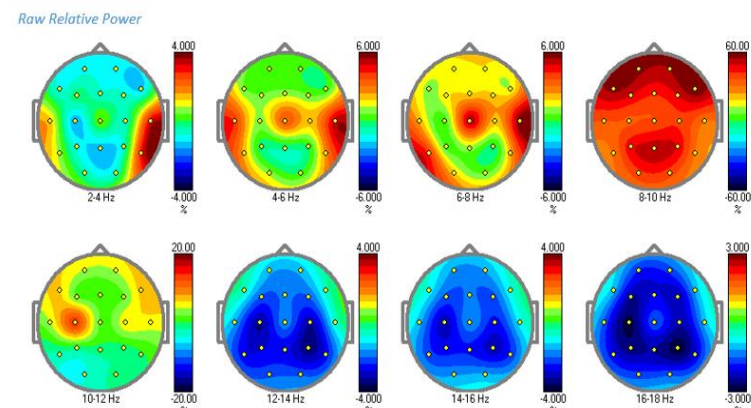
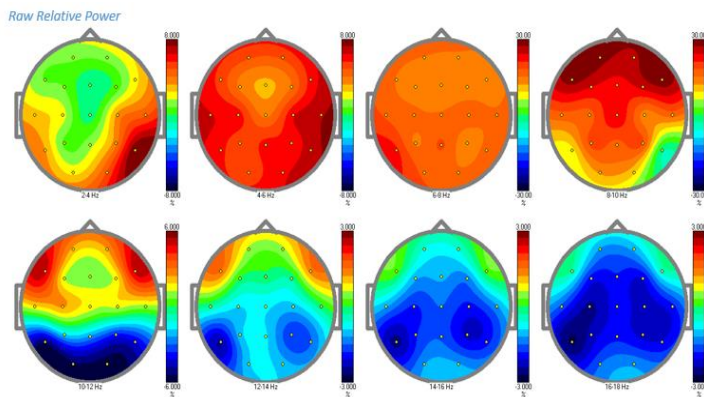
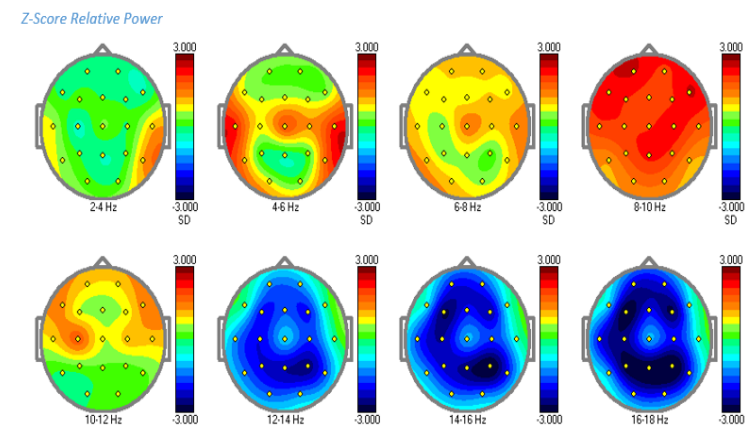
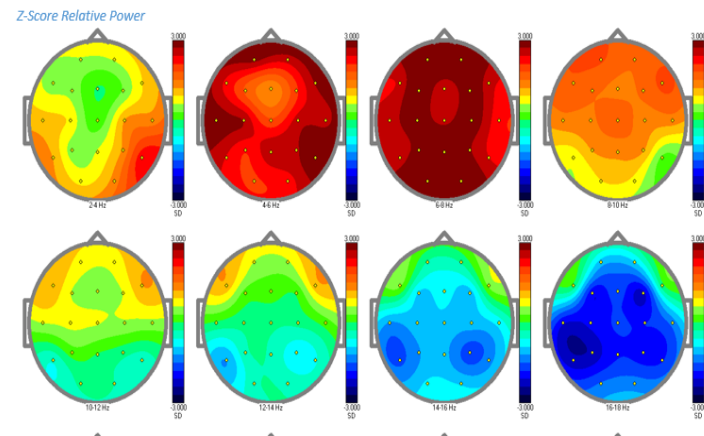
- 3-month follow-up



Treatments

Head On! Program at Integrate Brain Health

- 3-month follow-up



<https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease>

[https://en.wikipedia.org/wiki/Simultanagnosia#:~:text=Simultanagnosia%20\(or%20simultagnosia\)%20is%20a,single%20object%20at%20a%20time.](https://en.wikipedia.org/wiki/Simultanagnosia#:~:text=Simultanagnosia%20(or%20simultagnosia)%20is%20a,single%20object%20at%20a%20time.)

<https://www.dementiacarecentral.com/video/video-brain-changes/>

<https://jnnp.bmj.com/content/85/10/e4.38>

<https://www.businessinsider.com/alzheimers-brain-scans-plaques-tangles-2016-3>

[https://en.wikipedia.org/wiki/B%27s_syndrome#:~:text=B%27s%20syndrome%20is%20an%20uncommon,using%20vision%20\(optic%20ataxia\).](https://en.wikipedia.org/wiki/B%27s_syndrome#:~:text=B%27s%20syndrome%20is%20an%20uncommon,using%20vision%20(optic%20ataxia).)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3312396/>

<https://www.dementia.org.au/information/about-dementia/types-of-dementia/frontotemporal-dementia>

<https://www.dementia.org.au/about-dementia/types-of-dementia/alcohol-related-dementia>

<https://www.dementia.org.au/about-dementia/types-of-dementia/aids-related-dementia>

<https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/lewy-body-dementia>

[Dementia Treatments: Medication, Therapy, Diet, and Exercise \(webmd.com\)](#)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4146132/>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4807333/>

[Medications for Memory Loss | Alzheimer's Association](#)