A *brief* overview of the neurodegenerative diseases of the brain

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UCSF
University of California
San Francisco

GLOBAL
BRAIN HEALTH
INSTITUTE

We will explore three questions today:

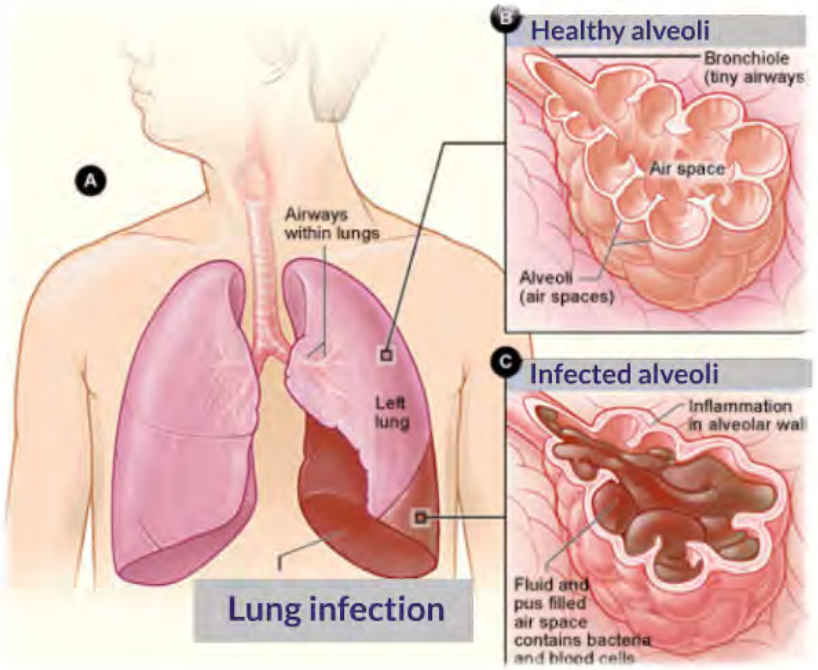
1) What are the neurodegenerative diseases of the brain?
2) What do these diseases have in common?
3) How do they differ?

To answer these questions we must first understand that different diseases of the body produce different **signs** and **symptoms**.

A **sign** is an **objective** manifestation of a disease, whereas a **symptom** is an **subjective** manifestation of a disease.

The group of **signs** and **symptoms** produced by a specific disease process is called a ***clinical syndrome.***

Disease process

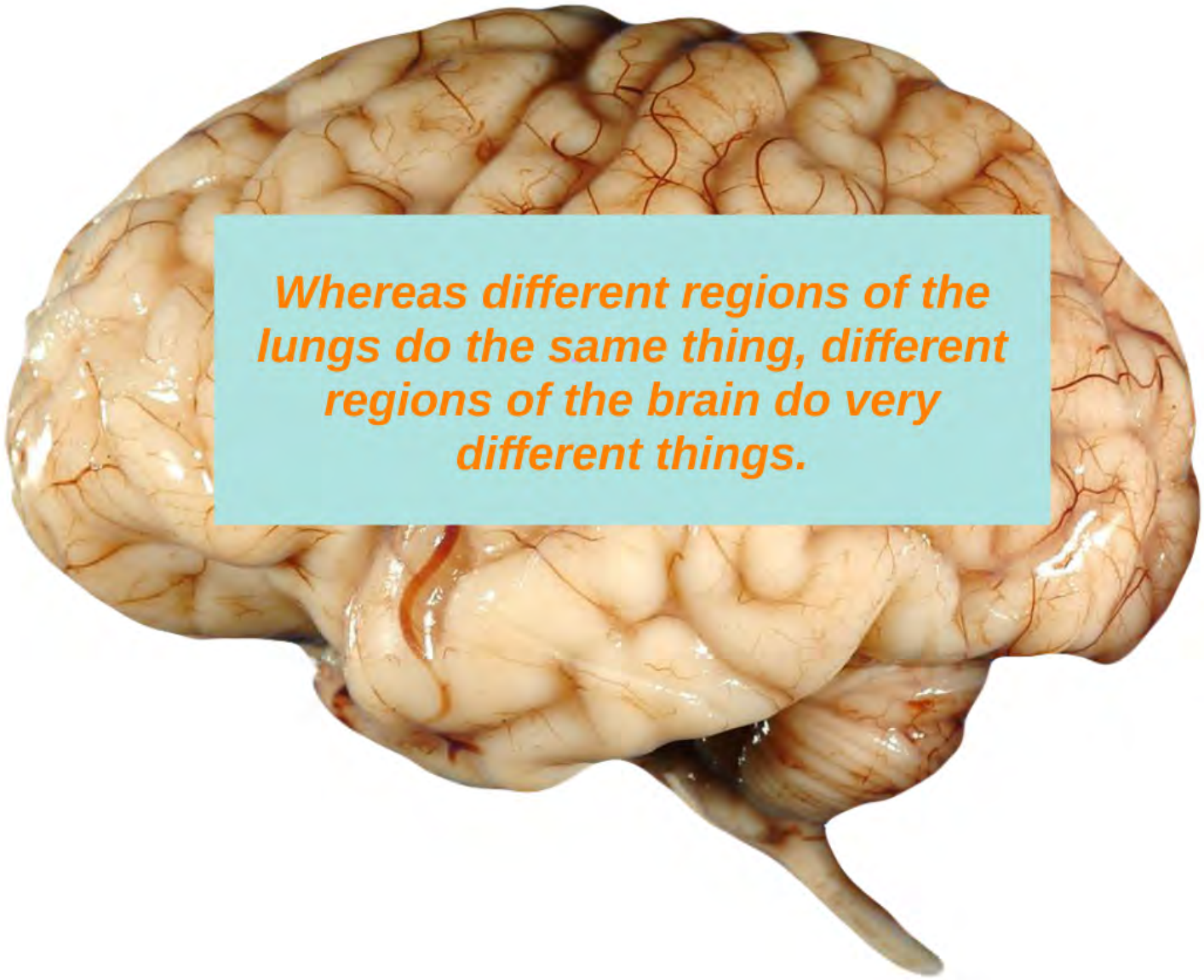


Clinical syndrome

Symptoms of lung infection:
- body aches
- low energy
- shortness of breath
- chills

Signs of lung infection:
- fever
- cough
- wheezing
- difficulty breathing

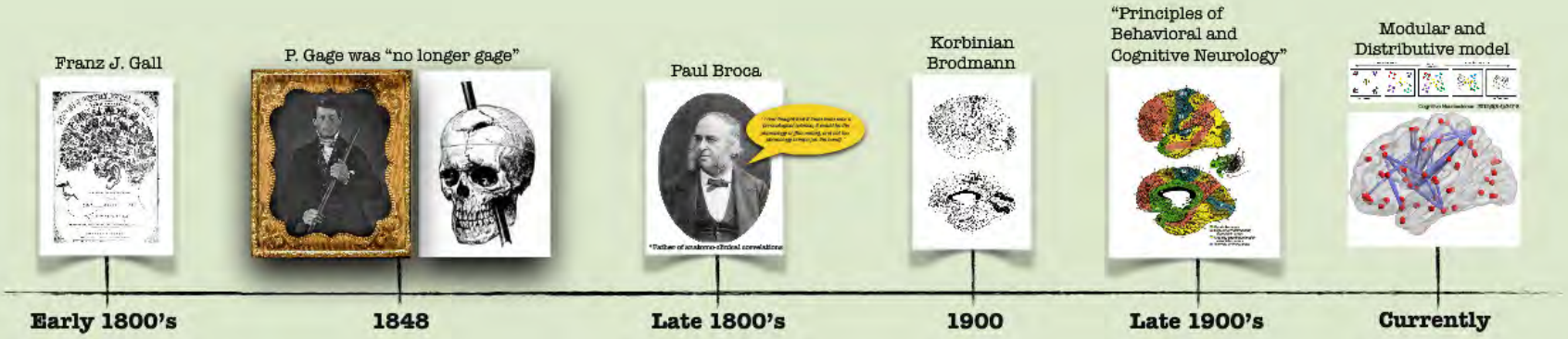
} **"Pneumonia"**


Whereas different regions of the lungs do the same thing, different regions of the brain do very different things.

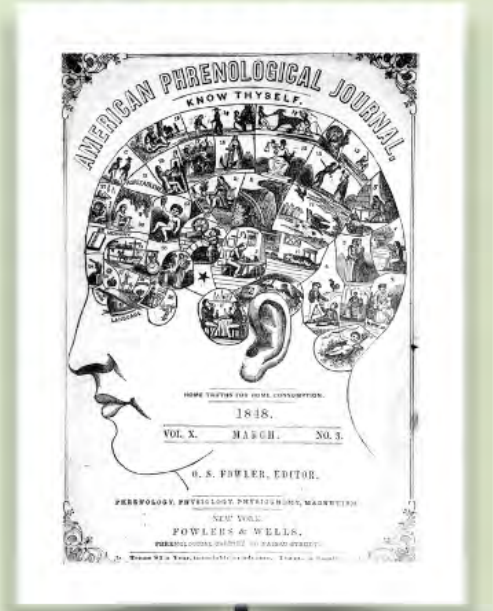
A very brief history of...

CEREBRAL LOCALIZATION *

** The (mostly) precise science of predicting which region/s of the brain are damaged or malfunctioning based on a careful examination of a patient's signs and symptoms (i.e. the clinical syndrome).*



Franz J. Gall



P. Gage was “no longer gage”

Early 1800’s

1848

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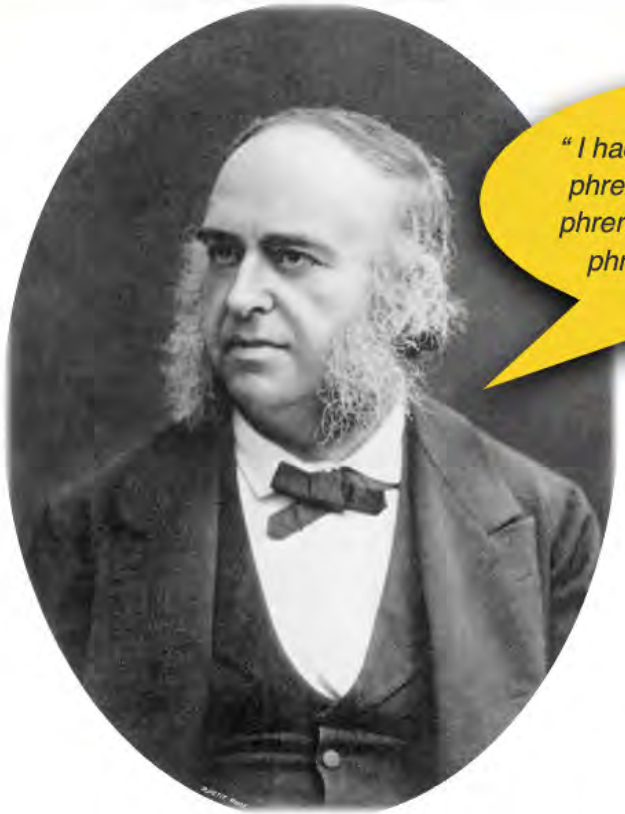
Paul Broca



" I had thought that if there were ever a phrenological science, it would be the phrenology of [the cortex], and not the phrenology bumps [on the head]. "

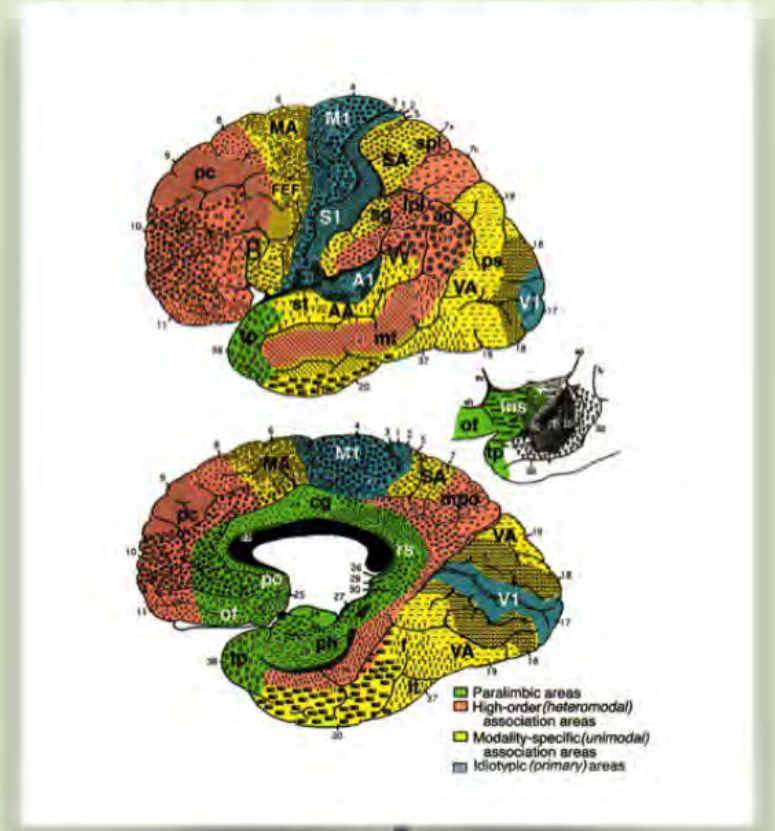
*Father of anatomo-clinical correlations

Late 1800's

Korbinian Brodmann

1900

"Principles of Behavioral and Cognitive Neurology"



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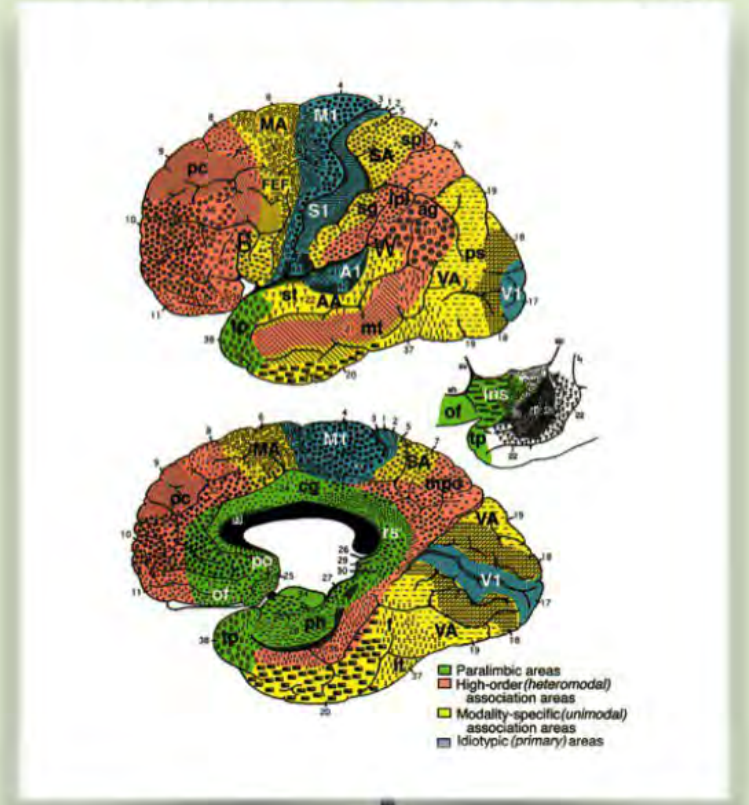
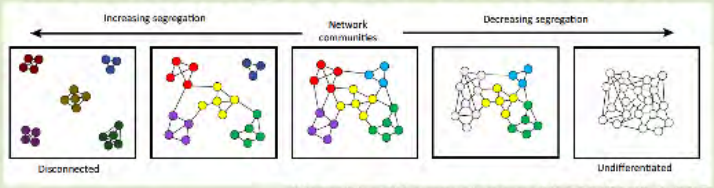
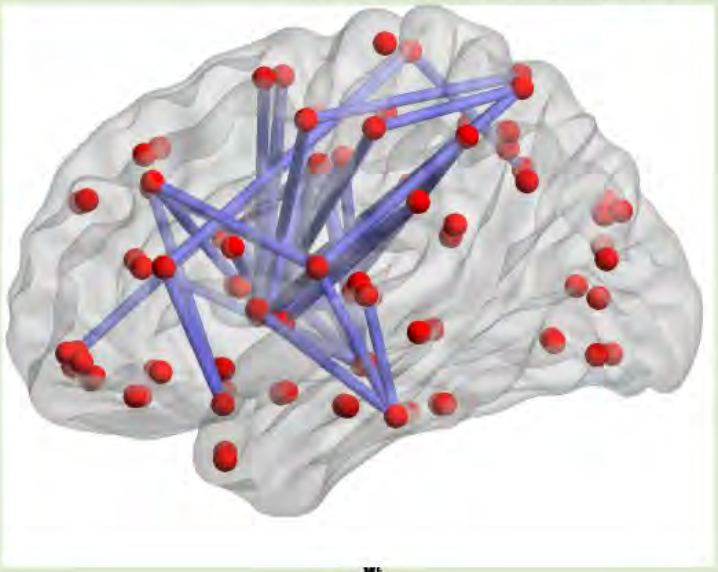


Modular and Distributive model



Cognitive Neuroscience. 2012;3(3-4):247-8



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Currently

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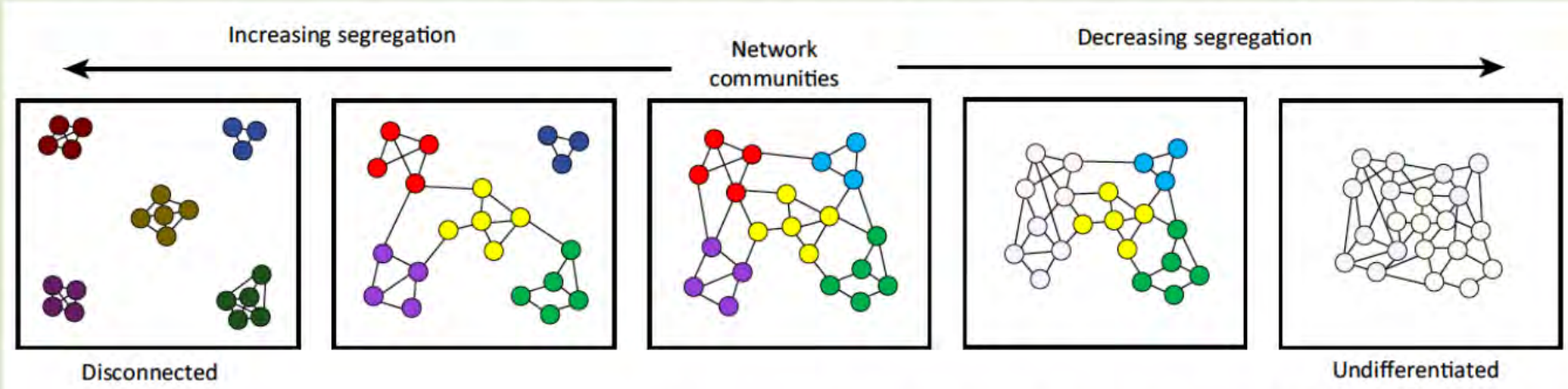

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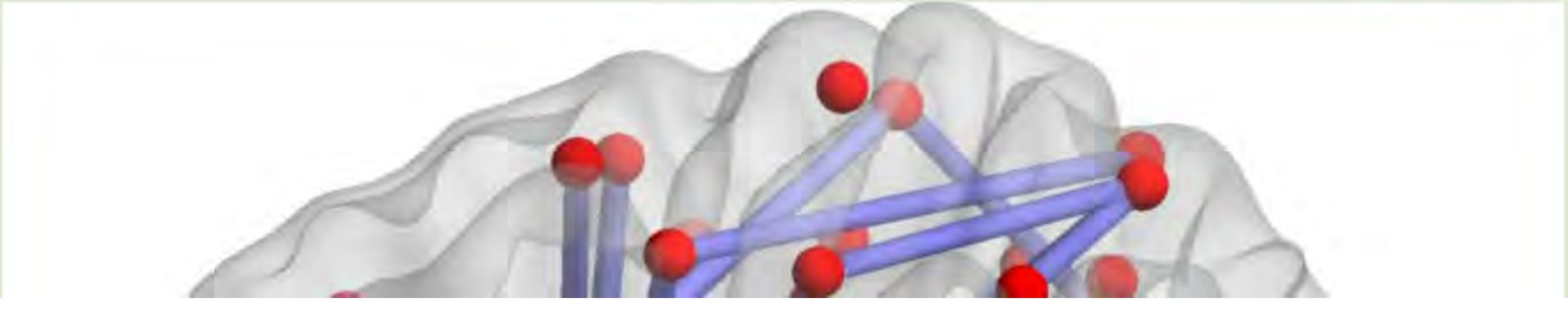
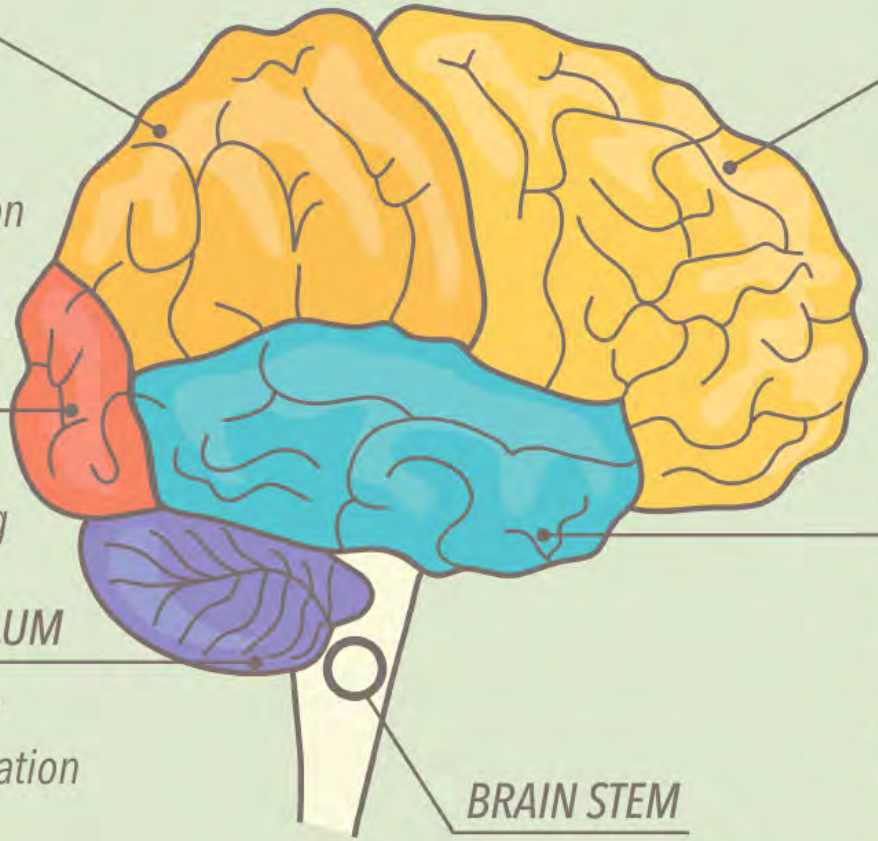


THE BASICS OF CEREBRAL LOCALIZATION



PARIETAL LOBE
- sensation
- language
- spatial navigation
- interpretative

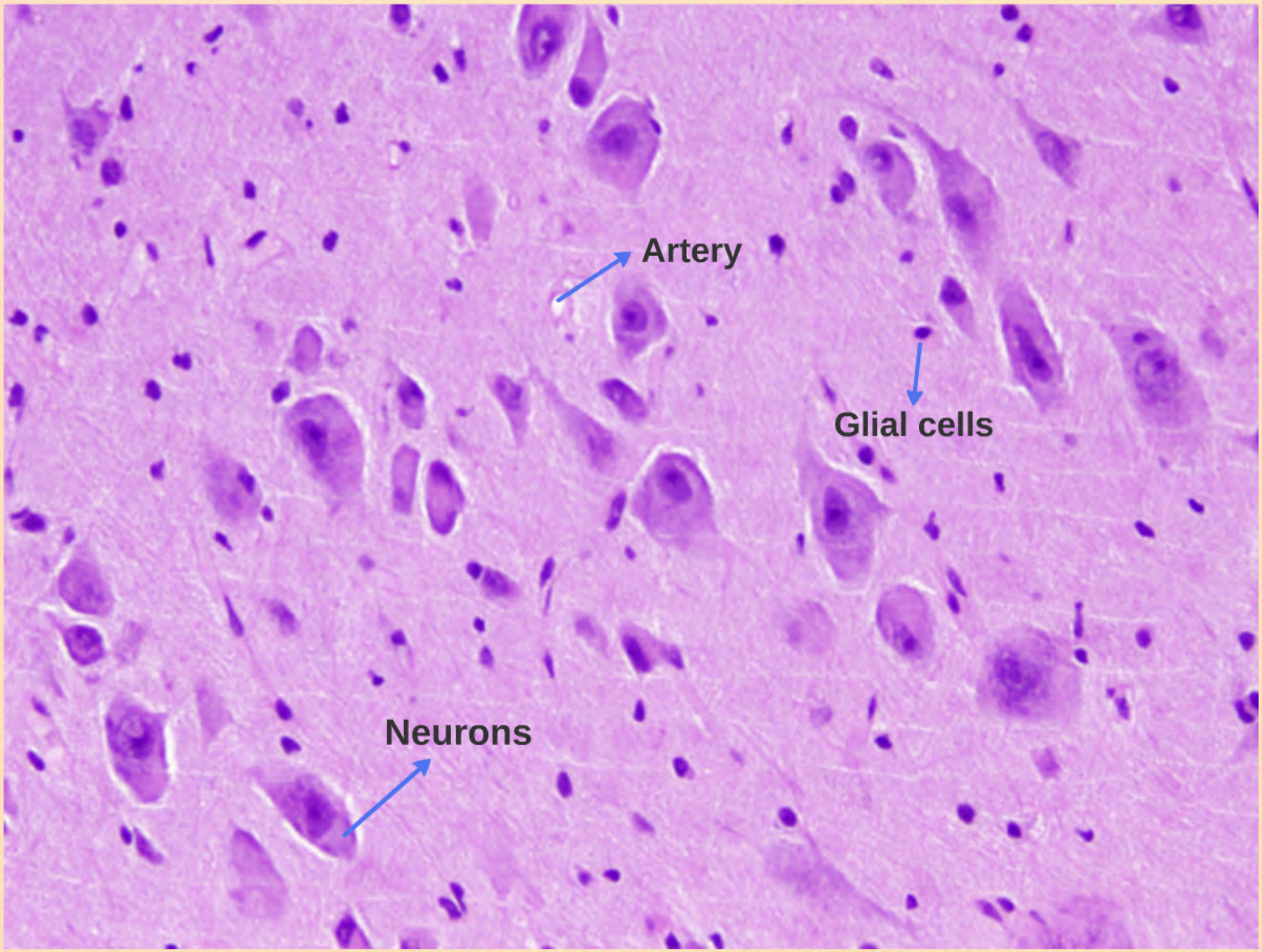
OCCIPITAL LOBE
- "elementary" visual processing

CEREBELLUM
- balance
- coordination

FRONTAL LOBE
- movement
- reasoning
- personality
- multitasking
- language

TEMPORAL LOBE
- langage
- behavior
- vision
- hearing
- memory

BRAIN STEM
- neurotransmitters
- sleep
- movement


Artery
Glial cells
Neurons

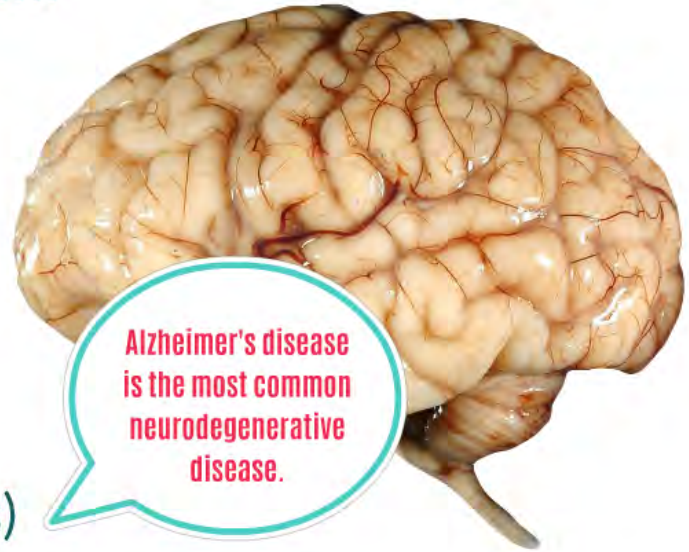
Different brain diseases "attack" different brain substrates and different brain regions:

Cerebrovascular diseases (primarily arteries)

Demyelinating diseases (primarily myelin)

Infectious diseases (various substrates)

Neurodegenerative diseases (primarily neurons)



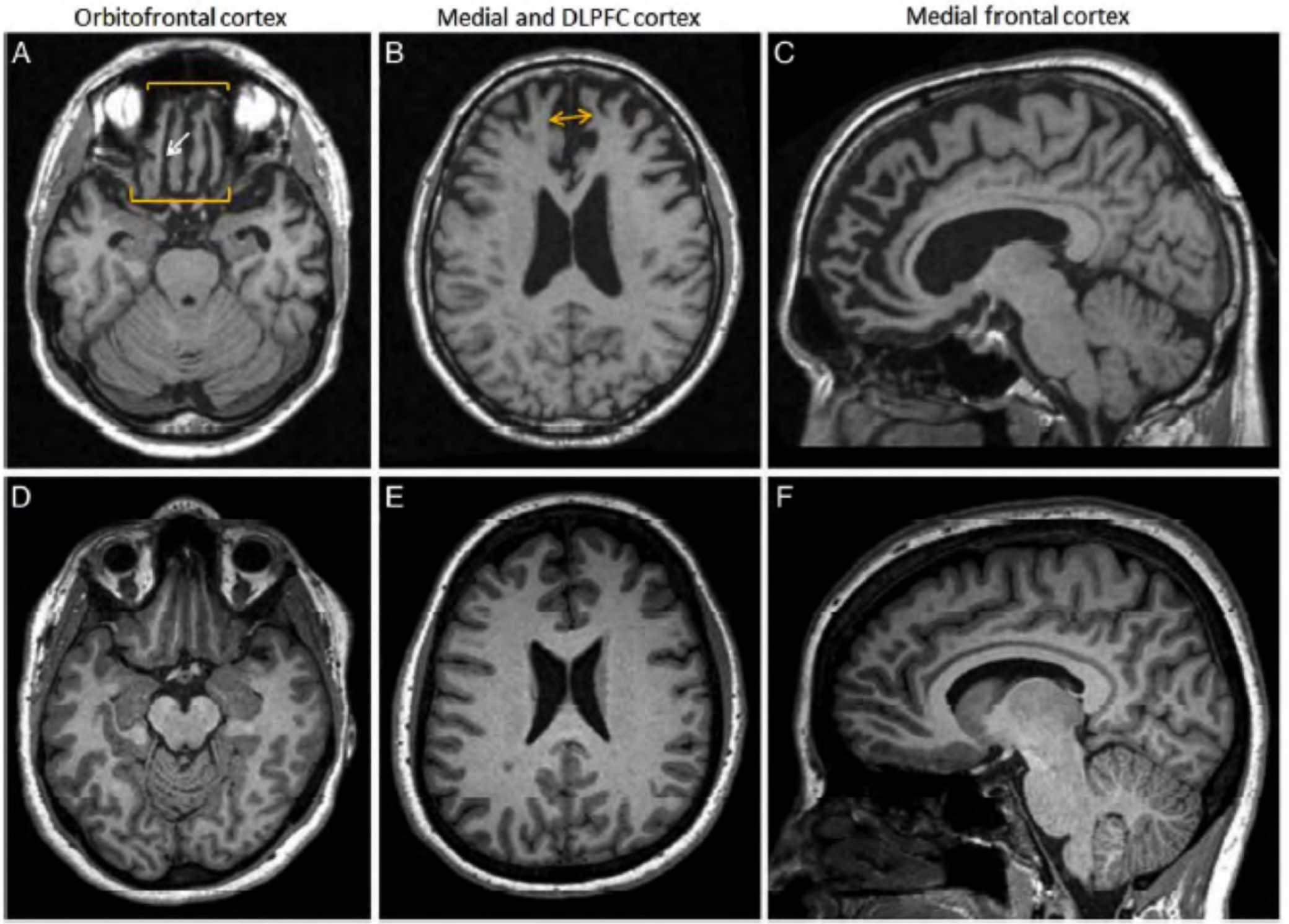
But b
other

But beyond Alzheimer's disease, there are many other neurodegenerative diseases of the brain:

- Frontotemporal lobar degeneration
- Lewy body disease
- Parkinson's disease
- Corticobasal degeneration
- Huntington disease
- Progressive supranuclear palsy
- Creutzfeldt-Jackob disease
- etc.

HEALTHY BRAIN

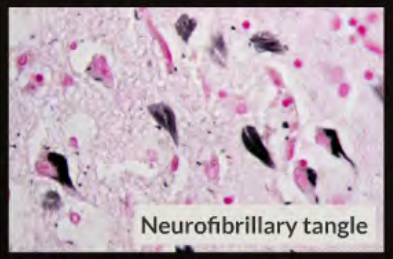
BRAIN WITH A
NEURODEGENERATIVE DISEASE

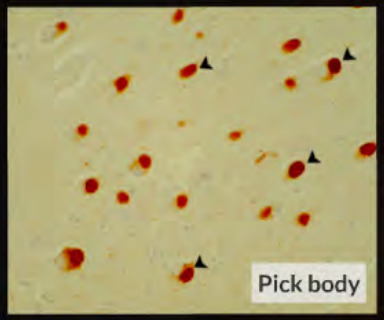

Orbitofrontal cortex
Medial and DLPFC cortex
Medial frontal cortex
A
B
C
D
E
F

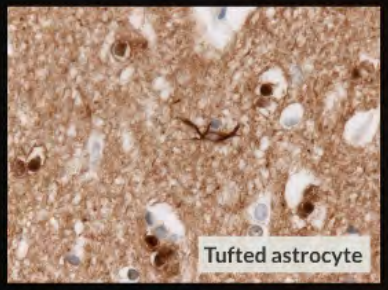
HEALTHY BRAIN

BRAIN WITH A
NEURODEGENERATIVE DISEASE

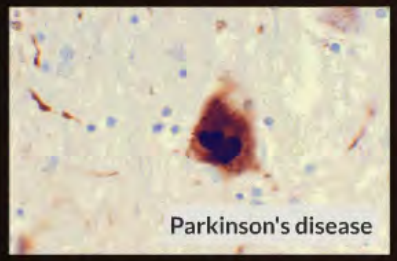
TAU

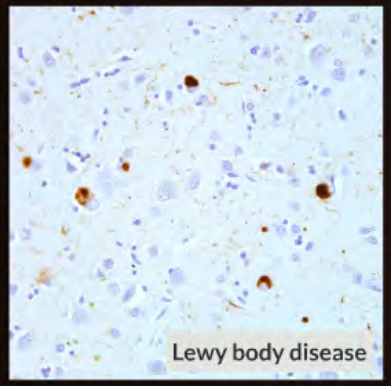




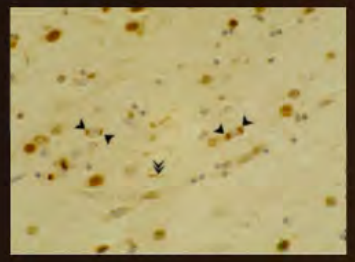


alpha-synuclein

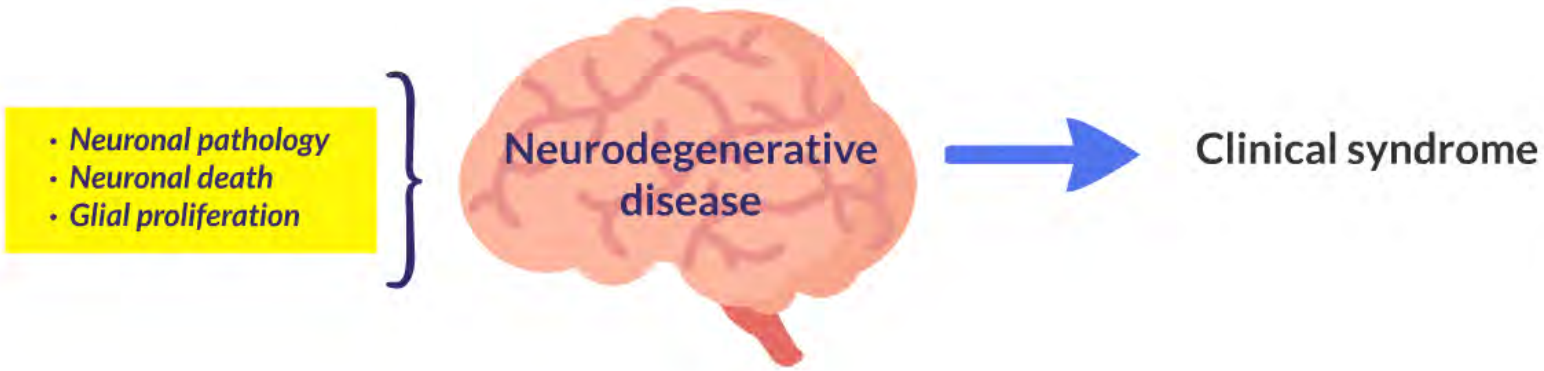




TDP-43



Each neurodegenerative disease of the brain is caused by the progressive accumulation of a specific *pathognomonic* protein inclusion, or proteinopathy. Over time, this accumulation becomes toxic to the brain, leading to irreversible degeneration (death) of neurons and atrophy.


• Neuronal pathology
• Neuronal death
• Glial proliferation
Neurodegenerative disease
Clinical syndrome

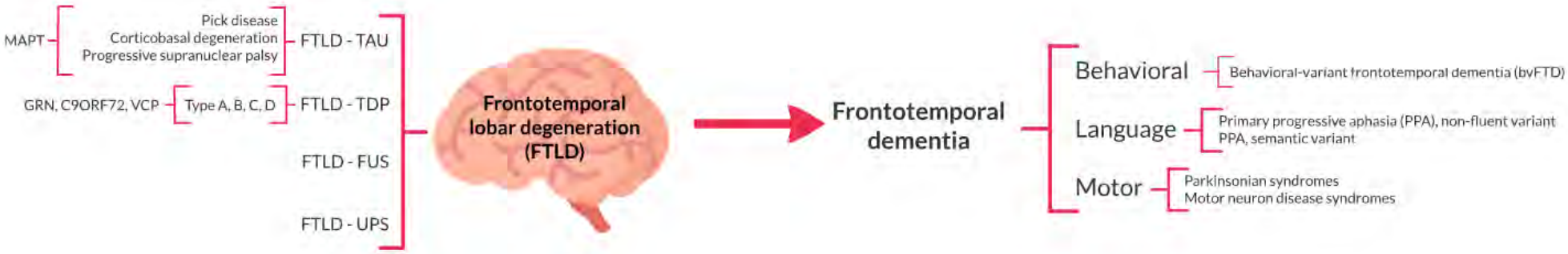
NEURODEGENERATIVE DISEASE

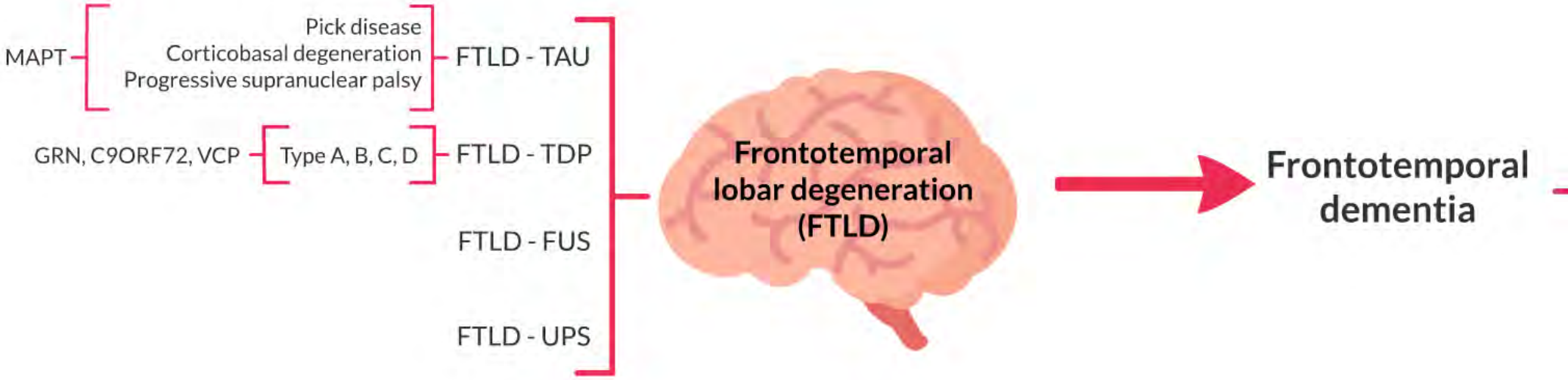
Amyloid beta
amyloid plaques

TAU
neurofibrillary tangles

clinical syndromes

- Memory syndrome → Typical AD
- Language syndrome → Logopenic variant of AD
- Visual syndrome → Posterior variant of AD
- Behavioral syndrome → Frontal variant of AD


MAPT
Pick disease
Corticobasal degeneration
Progressive supranuclear palsy
FTLD - TAU
GRN, C9ORF72, VCP
Type A, B, C, D
FTLD - TDP
FTLD - FUS
FTLD - UPS
Frontotemporal lobar degeneration (FTLD)
Frontotemporal dementia
Behavioral
Behavioral-variant frontotemporal dementia (bvFTD)
Language
Primary progressive aphasia (PPA), non-fluent variant PPA, semantic variant
Motor
Parkinsonian syndromes
Motor neuron disease syndromes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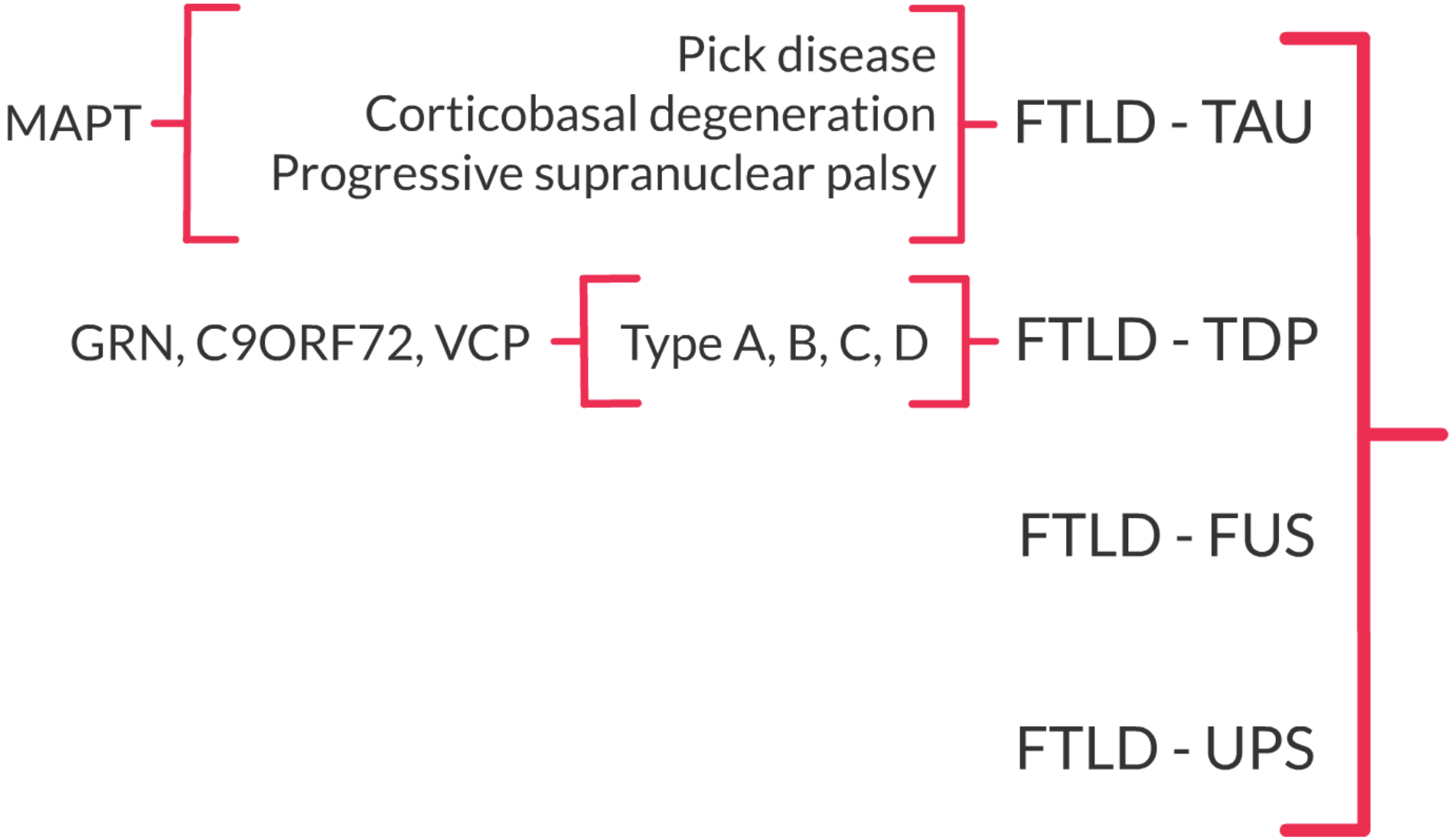
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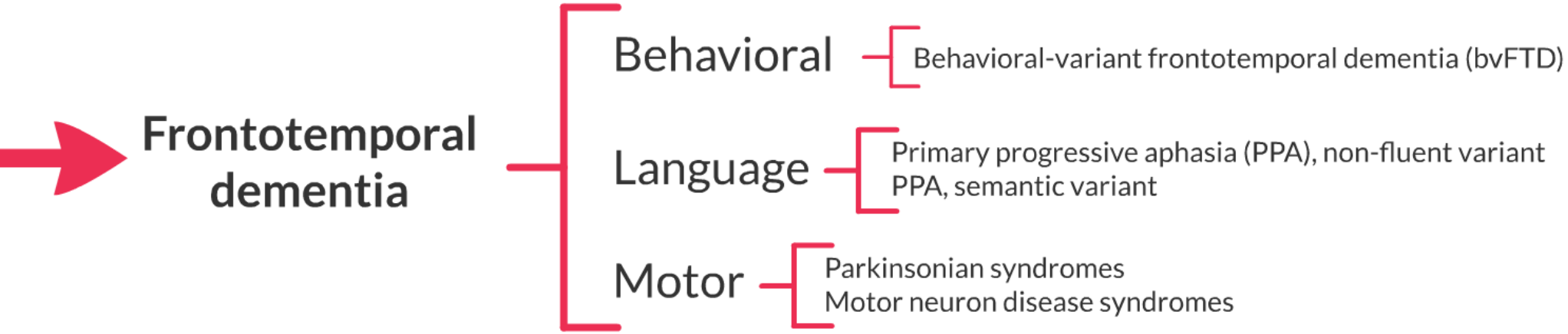
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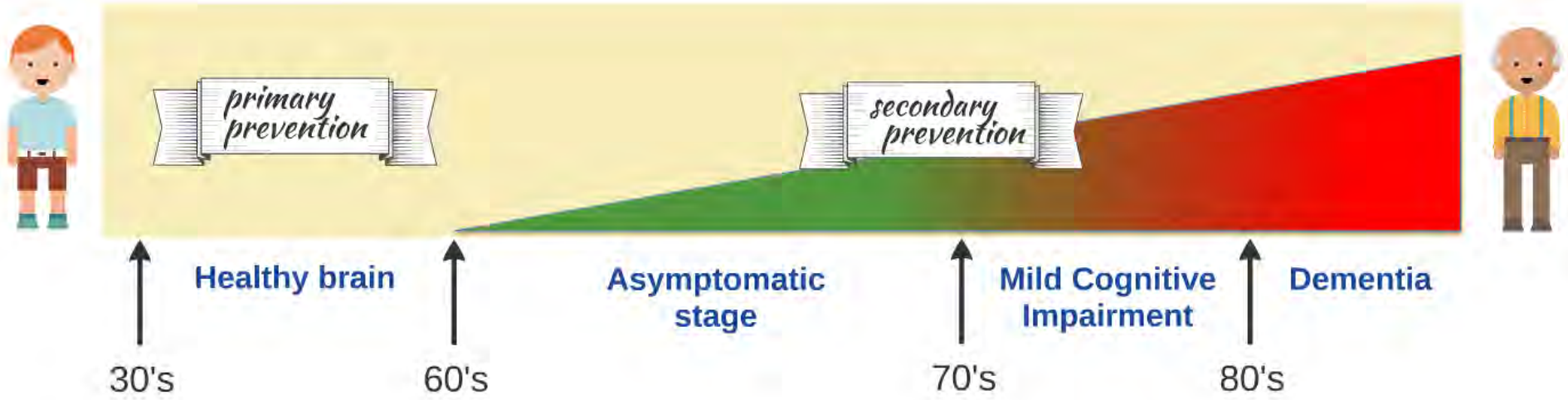


Almost all neurodegenerative diseases of the brain begin insidiously and progress relentlessly over the span of years.

All neurodegenerative diseases lead to disability and death. Although we have symptomatic drug therapies and non-pharmacological therapies and other support strategies available to offer patients and their families, we do not have drug therapies that can cure, stop, or "slow down" these diseases.

2018 ALZHEIMER'S DISEASE FACTS AND FIGURES

AD is the most common cause of dementia in the world.

ALZHEIMER'S DISEASE IS THE

6TH leading cause of death in the United States

16.1 MILLION AMERICANS provide unpaid care for people with Alzheimer's or other dementias

These caregivers provided an estimated **18.4 BILLION HOURS** of care valued at over **$232 BILLION**

Between 2000 and 2015 deaths from heart disease have decreased **11%**

while deaths from Alzheimer's disease have increased **123%**

1 IN 3 seniors dies with Alzheimer's or another dementia

It kills more than breast cancer and prostate cancer **COMBINED**

EARLY AND ACCURATE DIAGNOSIS COULD SAVE UP TO

$7.9 TRILLION in medical and care costs

IN 2018, Alzheimer's and other dementias will cost the nation **$277 BILLION**

BY 2050, these costs could rise as high as **$1.1 TRILLION**

5.7 MILLION Americans are living with Alzheimer's

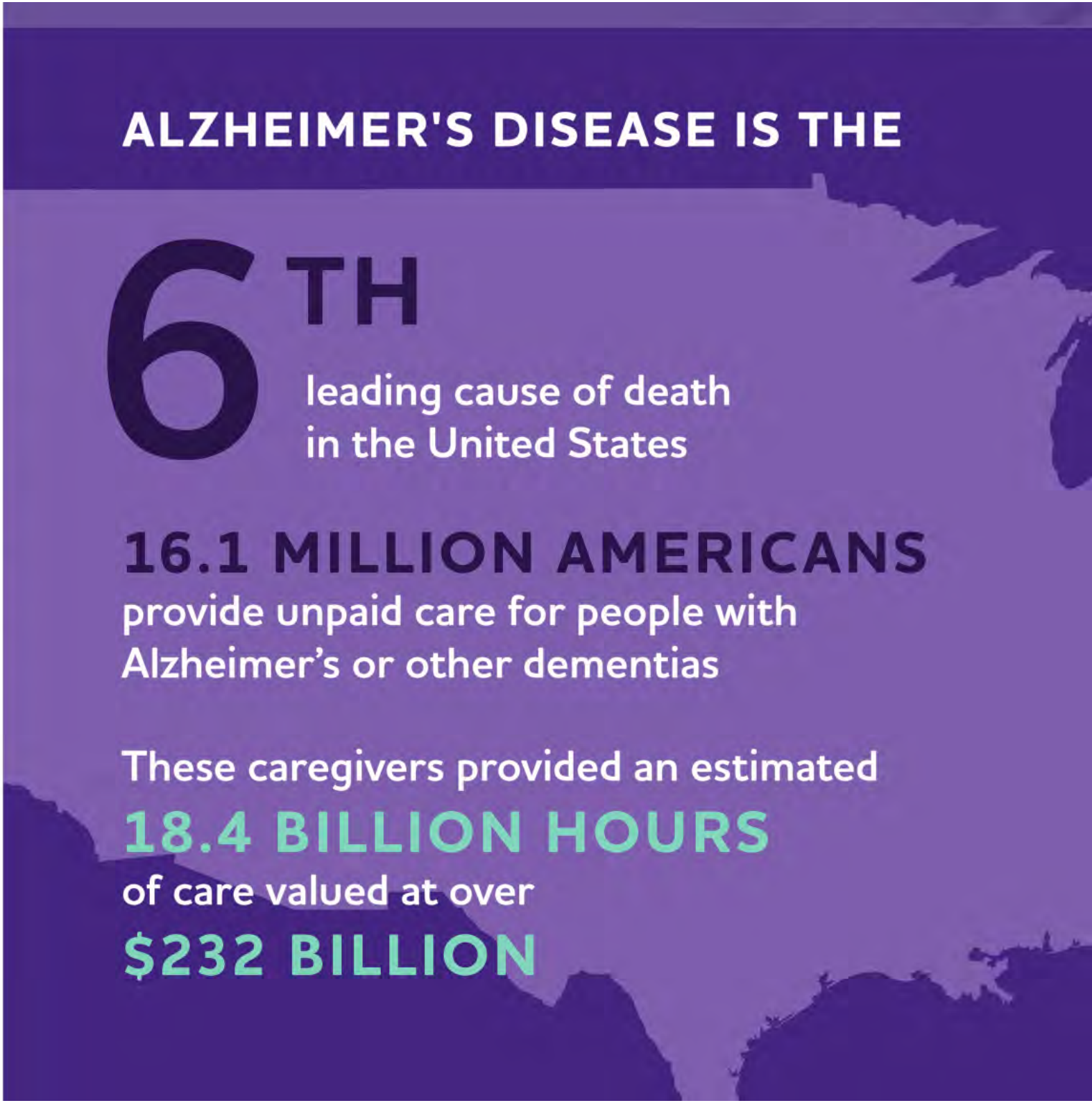
BY 2050, this number is projected to rise to nearly **14 MILLION**

EVERY 65 SECONDS someone in the United States develops the disease

alzheimer's association

THE BRAINS BEHIND SAVING YOURS.

AD is the most common cause of dementia in the world.



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Economists predict:

Preventing or delaying the onset of Alzheimer's by 5 years would cut Medicare spending for Alzheimer's by half.

Neurological evaluation

+ = 1-3hrs

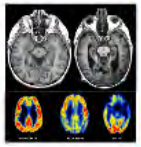
Neuropsychological evaluation

"Paper and pen" examination performed by a neuropsychologist.

The purpose of this examination is to attempt to quantify each patient's cognitive abilities. The provider administers tasks that challenge each of the four main cognitive domains (memory, language, executive, visuospatial). A global mood/psychiatric assessment is also administered.

Scores on each task are graded according to norms that take into account the patient's age and level of education.

Investigations



Blood work:
- *Routine labs*
- *Markers of inflammation*
- *Genetic testing*

Brain imaging: MRI, PET

Cerebrospinal fluid analysis *(lumbar puncture): optional*

Other tests: PET, sleep study, autonomic function testing, etc.

Diagnosis

Neurological evaluation
+
Neuropsychological testing
+
Investigations
+
level of independence
+
Clinical diagnosis

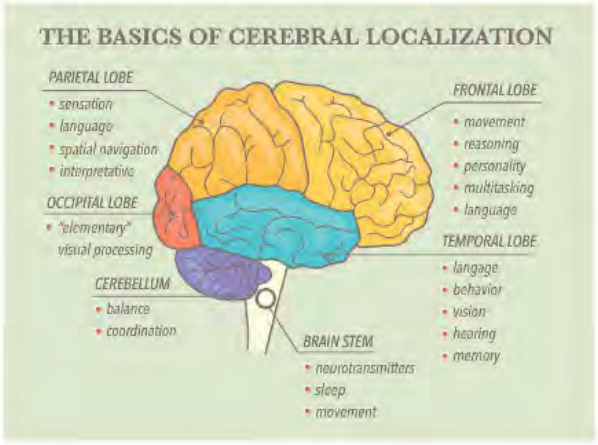
Treatment plan and support

neurologists
neuropsychologists
nurses & social workers

disease-specific treatments
sign/symptom-specific treatments
level of impairment-specific support

PCP → patient & family

Neurological evaluation



History of present illness

Cognitive changes

Memory function:
- *short-term episodic memory*
- *long-term episodic memory*
- *semantic memory*
- *working memory*

Language function:
- *expressive language*
- *receptive language*

Executive function: *difficulty multitasking, concentrating, judgement/problem solving, performing multi-step tasks*

Visuospatial function: *difficulty navigating (getting lost), gauging depth/distance, recognizing faces, recognizing objects*

Motor changes

Problems initiating movement
Problems coordinating movement
Weakness
Rigidity/stiffness
Involuntary movements *(tremor, muscle jerks, twitching, etc.)*
Changes in gait pattern
Imbalance and/or unexplained falls
Asymmetries in movement

Autonomic and sensory changes

Urinary incontinence
Constipation
Positional dizziness
Diminishing sense of smell

Behavior, personality, emotional processing changes

Behavioral disinhibition
- *socially inappropriate behavior*
- *impulsiveness*

Apathy or inertia
Loss of sympathy/empathy
Compulsive/ritualistic behaviors
Altered food preferences
Late-life "psychiatric" changes

Sleep changes

Snoring & apnea
Dream enactment behaviors

\+

Neurological examination

- mental status
- cranial nerves
- motor system
- sensory system
- coordination
- gait

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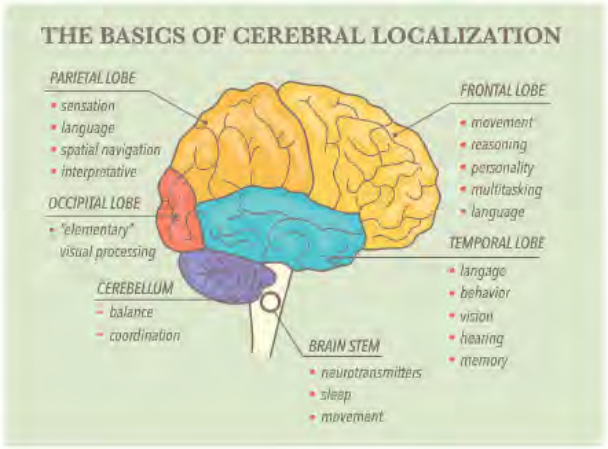

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Investigations

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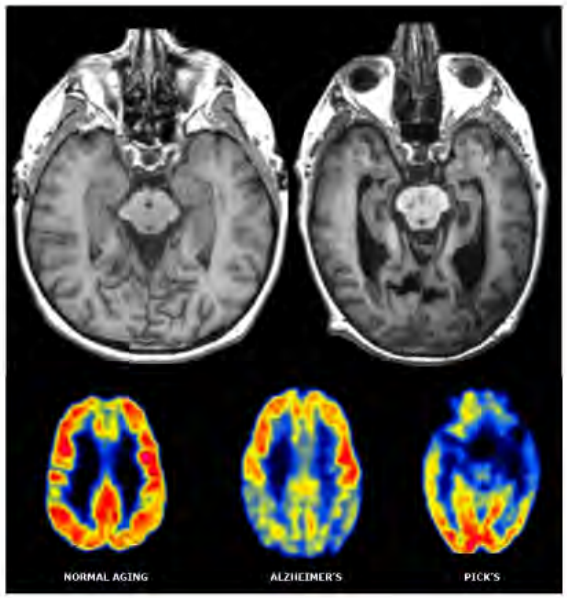

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Neuropsychological testing

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Investigations

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level of independence

=

Clinical diagnosis

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Neuropsychological testing

+

Investigations

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level of independence

=

Clinical diagnosis

Treatment plan and support

neurologists
neuropsychologists
nurses & social workers

disease-specific treatments
sign/symptom-specific treatments
level of impairment-specific support

PCP → patient & family

A *brief* overview of the neurodegenerative diseases of the brain

Serggio Lanata, MD, MS
Assistant Professor
UCSF Department of Neurology
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