The Neuroscience of Human Aging

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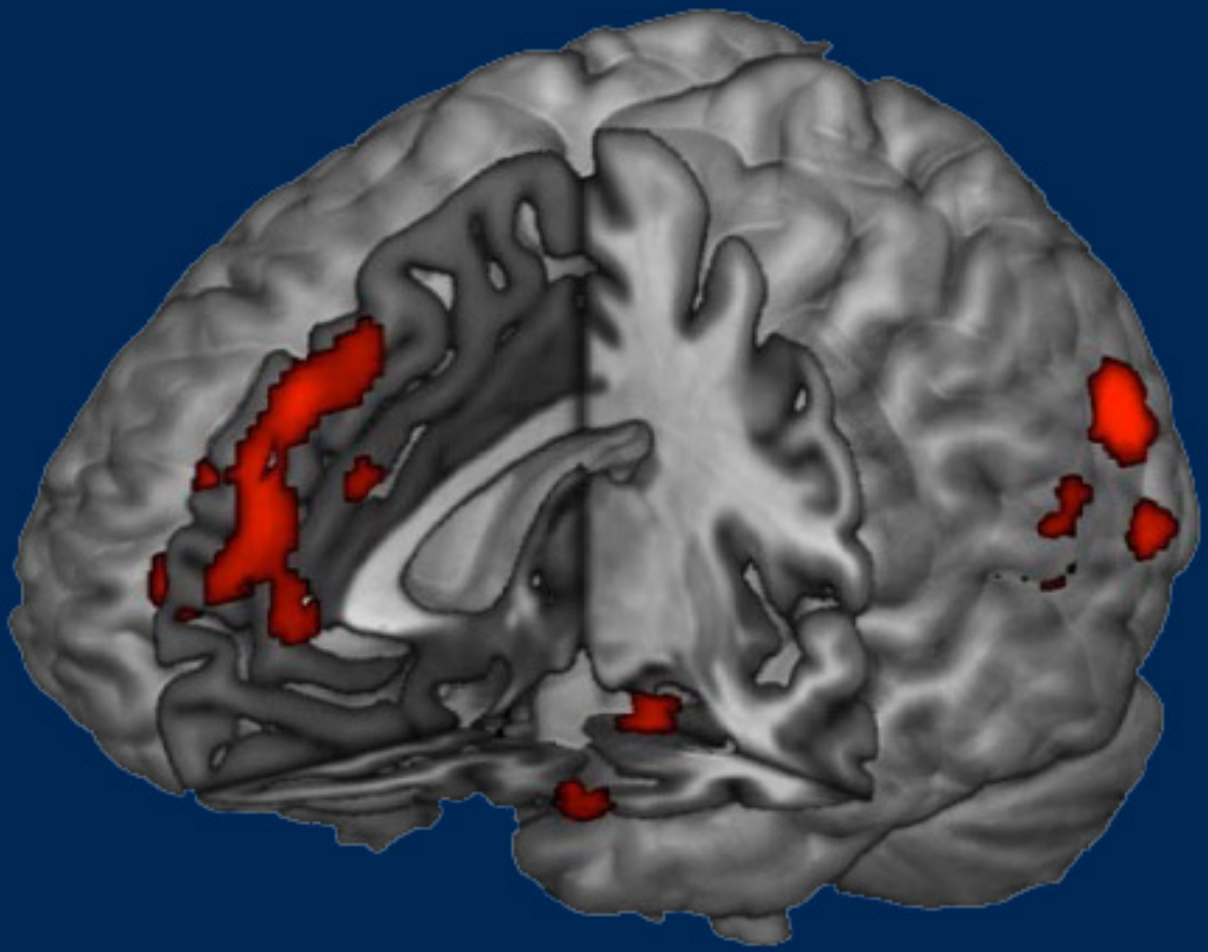


PART I

Development of the Central Nervous System

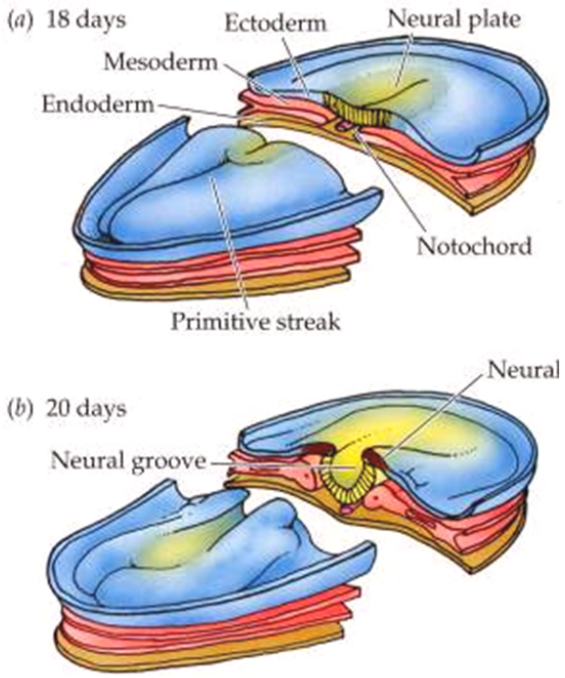
- an ongoing process, through adolescence and maybe even adult hood ?
  - the nervous system is "**plastic**"
- Experience plays a key role
- Dire consequences when something goes wrong
  - "teratogens"
    - Drugs of abuse, industrial chemicals, caffeine?, household chemicals

Stages of Development

Phase	Approximate Age	Highlight
Prenatal	Conception - birth	Rapid physical growth
Infancy	Birth - 2 yrs	Motor development
Childhood	2 - 12 yrs	Abstract reasoning
Adolescence	13 - 20 yrs	Identity creation, "Judgement"

Directly related to maturation of the "Prefrontal Cortex"

At about 18 days after conception the embryo begins to implant in the uterine wall.



a. Consists of 3 layers of cells: endoderm, mesoderm, and ectoderm.

Thickening of the ectoderm leads to the development of the neural plate

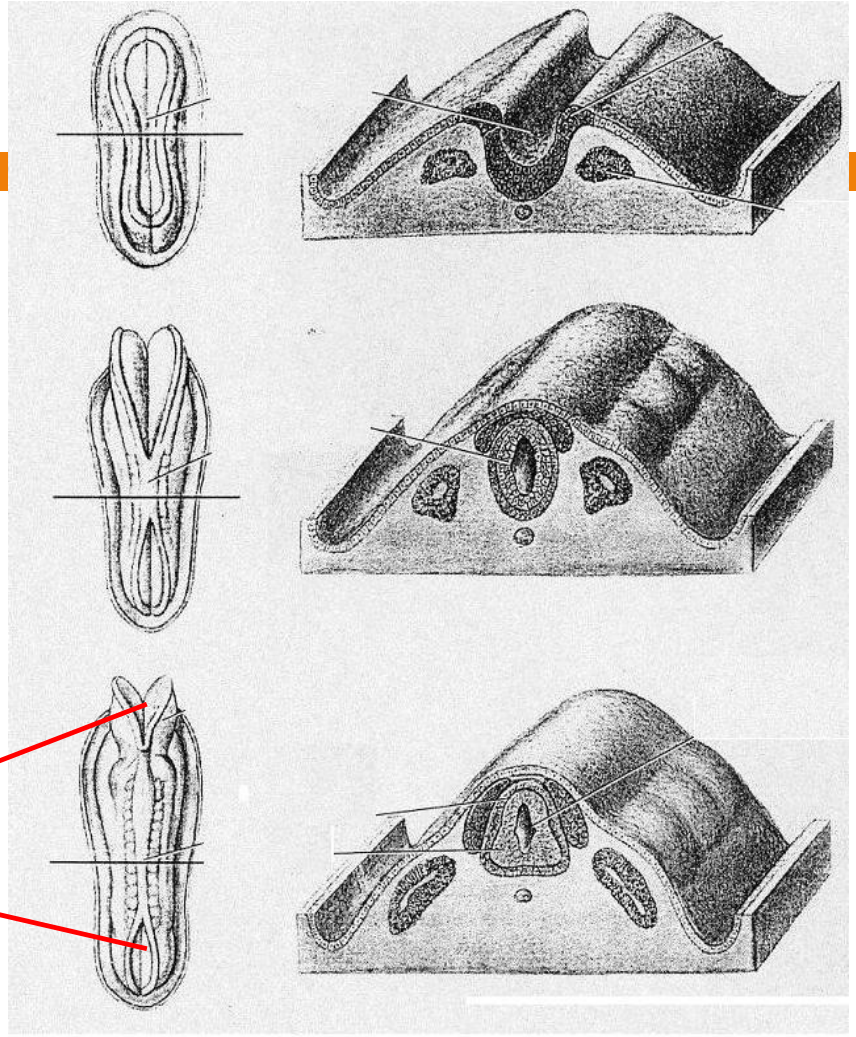
b. The neural groove begins to develop at 20 days.

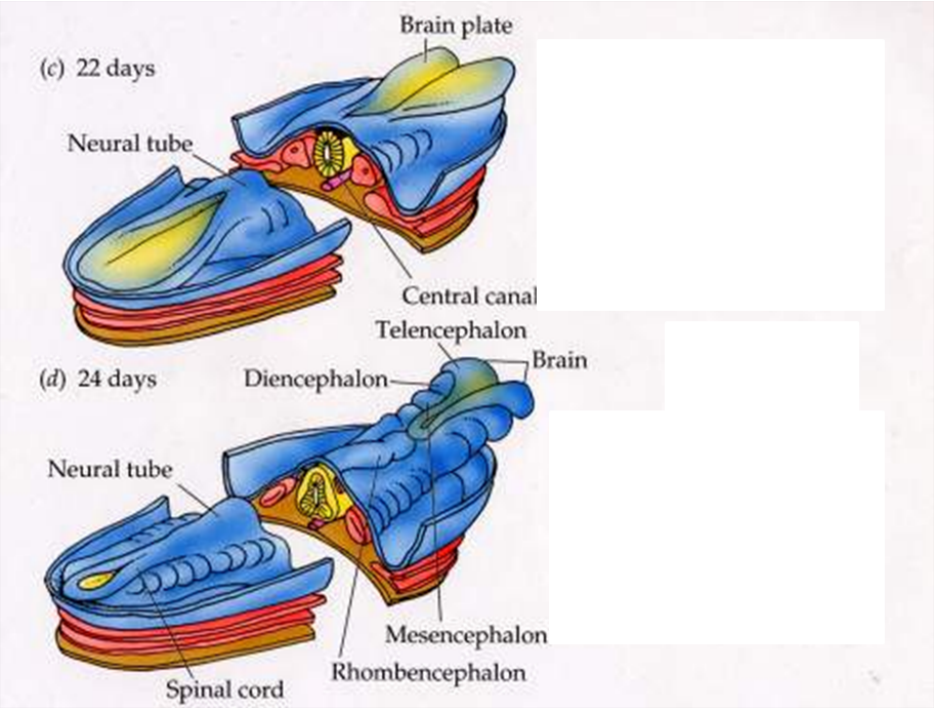
Neural Groove

Neural Tube

Brain

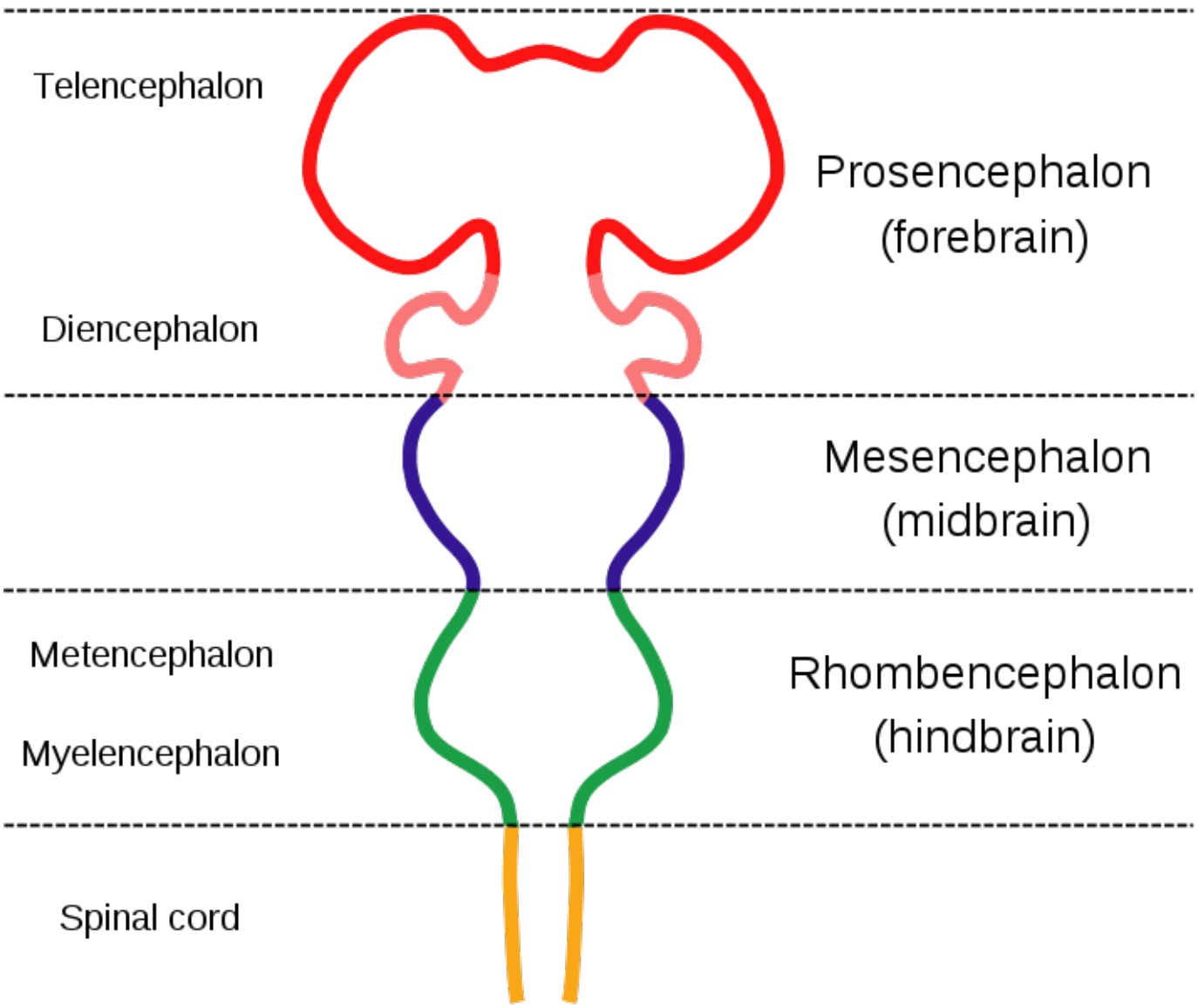
Spinal Chord

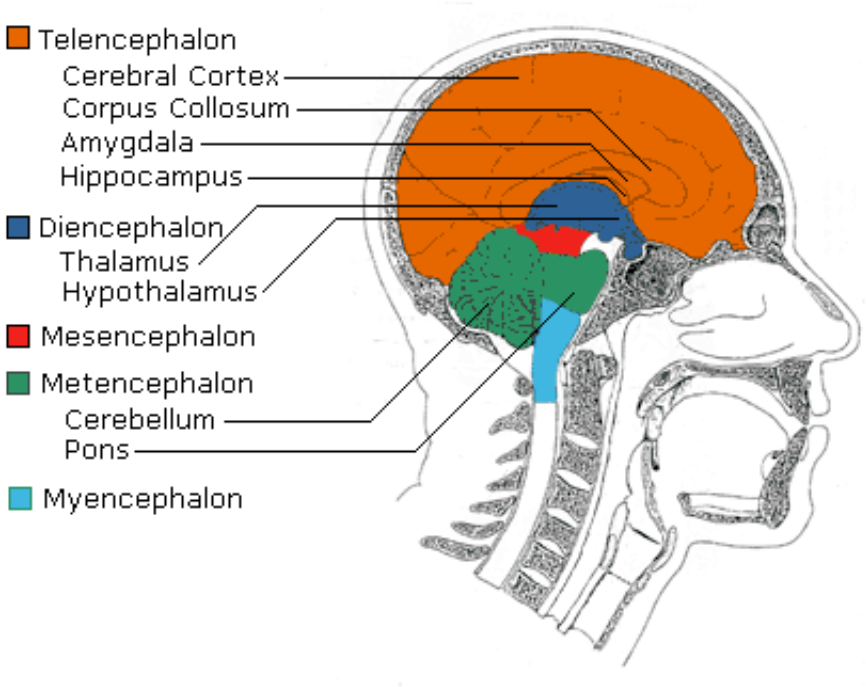


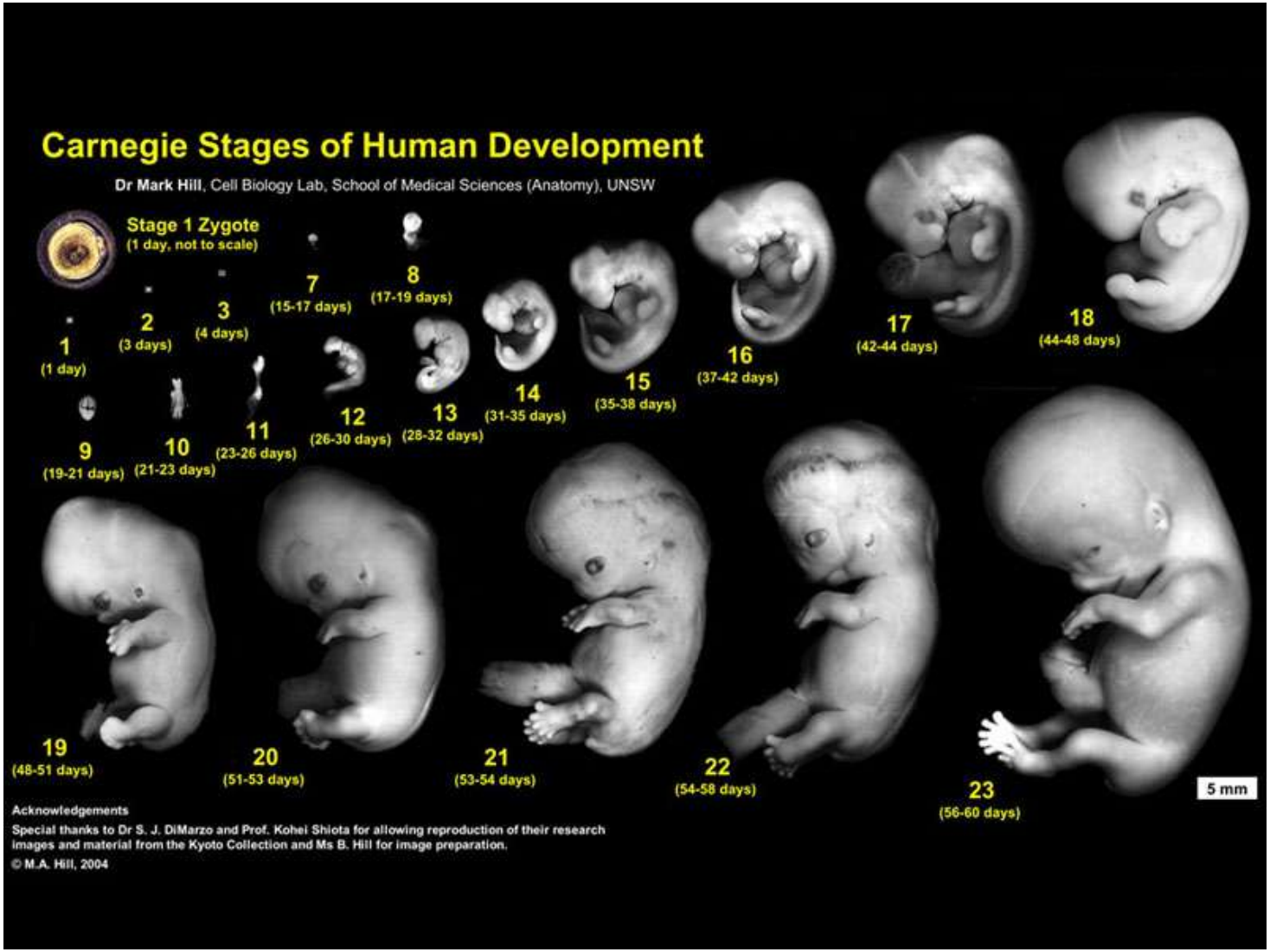


c. At 22 days the neural groove closes along the length of the embryo making the neural tube.

d. A few days later 4 major divisions of the brain are observable – the telencephalon, diencephalon, mesencephalon, and rhombencephalon.


Telencephalon
Diencephalon
Prosencephalon
(forebrain)
Mesencephalon
(midbrain)
Metencephalon
Myelencephalon
Rhombencephalon
(hindbrain)
Spinal cord


Telencephalon
Cerebral Cortex
Corpus Collosum
Amygdala
Hippocampus
Diencephalon
Thalamus
Hypothalamus
Mesencephalon
Metencephalon
Cerebellum
Pons
Myencephalon


Carnegie Stages of Human Development
Dr Mark Hill, Cell Biology Lab, School of Medical Sciences (Anatomy), UNSW
Stage 1 Zygote
(1 day, not to scale)
1
(1 day)
2
(3 days)
3
(4 days)
7
(15-17 days)
8
(17-19 days)
9
(19-21 days)
10
(21-23 days)
11
(23-26 days)
12
(26-30 days)
13
(28-32 days)
14
(31-35 days)
15
(35-38 days)
16
(37-42 days)
17
(42-44 days)
18
(44-48 days)
19
(48-51 days)
20
(51-53 days)
21
(53-54 days)
22
(54-58 days)
23
(56-60 days)
5 mm
Acknowledgements
Special thanks to Dr S. J. DiMarzo and Prof. Kohei Shiota for allowing reproduction of their research images and material from the Kyoto Collection and Ms B. Hill for image preparation.
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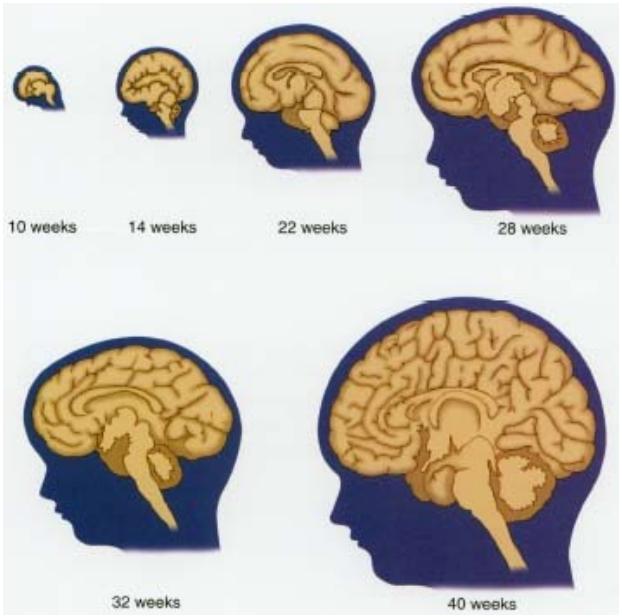
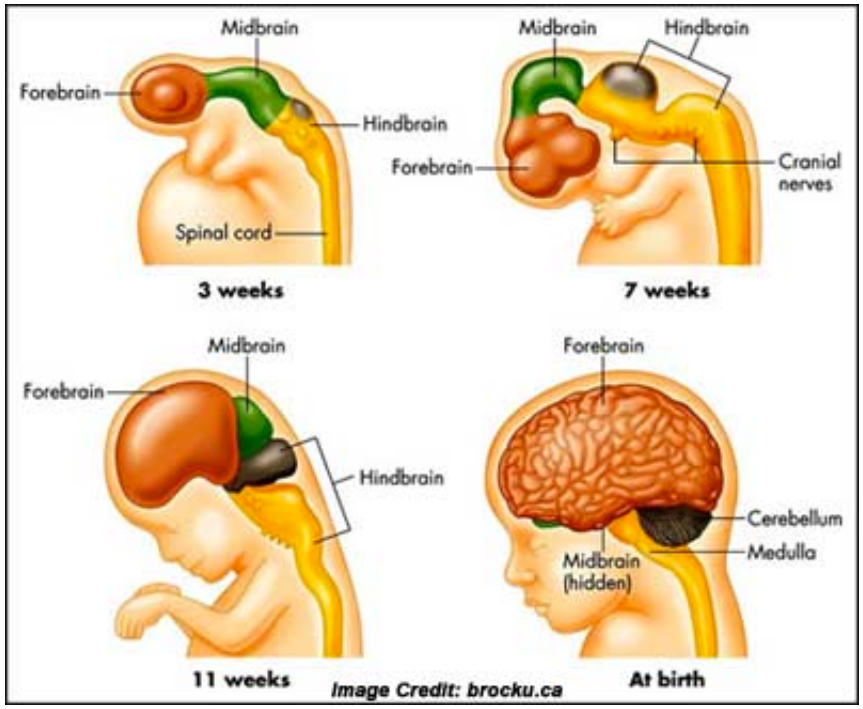
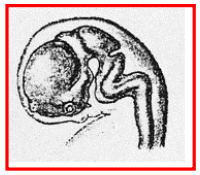

10 weeks
14 weeks
22 weeks
28 weeks
32 weeks
40 weeks

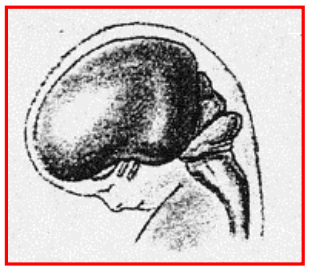

Midbrain
Forebrain
Hindbrain
Spinal cord
3 weeks
Midbrain
Hindbrain
Forebrain
Cranial nerves
7 weeks
Midbrain
Forebrain
Hindbrain
11 weeks
Forebrain
Cerebellum
Medulla
Midbrain (hidden)
At birth
Image Credit: brocku.ca

•Neurons forming rapidly
•1000's per minute

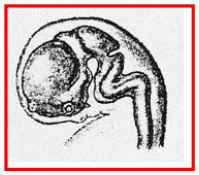


7 Weeks

Division of the halves of the brain visible



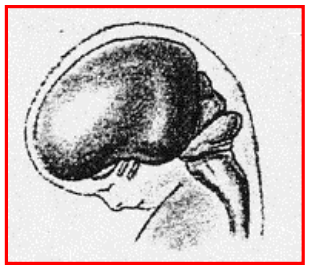
14 Weeks



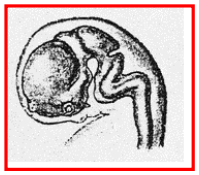
7 Weeks

•Nerve cell generation complete
•Cortex beginning to wrinkle
•Myelinization

6 Months

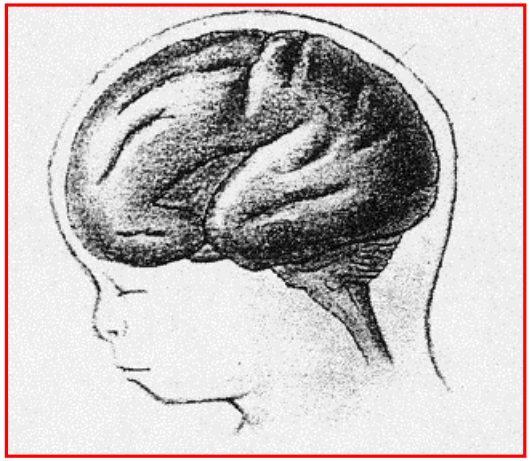


14 Weeks



7 Weeks

9 Months



Before Birth

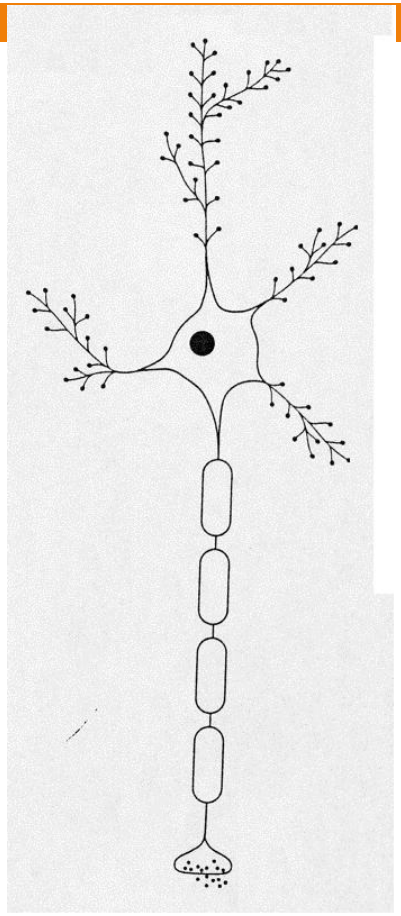
- Tremendous development occurs in utero. Nutrition, maternal emotions, etc. all affect brain development.
- There is no significant growth in the number of brain cells (neurons) following birth.
- What **does** grow after birth are the connections (synapses) between neurons.

Development of the Cortex

- 2 types of cells:
- Neurons
- Glial cells

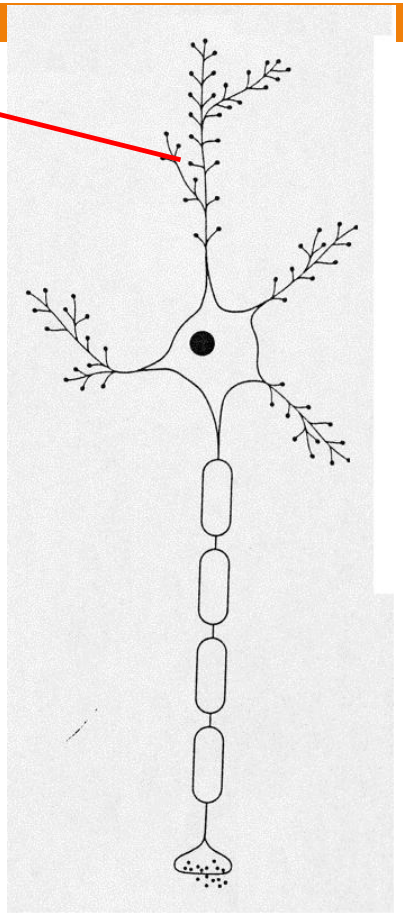
Development of the Cortex

- 2 types of cells:
- Neurons
- Glial cells



Development of the Cortex

- 2 types of ce
- Neurons
- Glial cells



Development of the Cortex

- 2 types of ce
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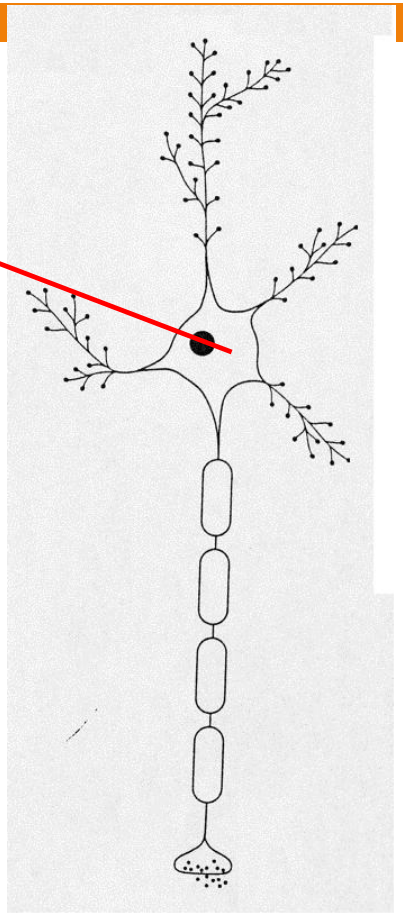
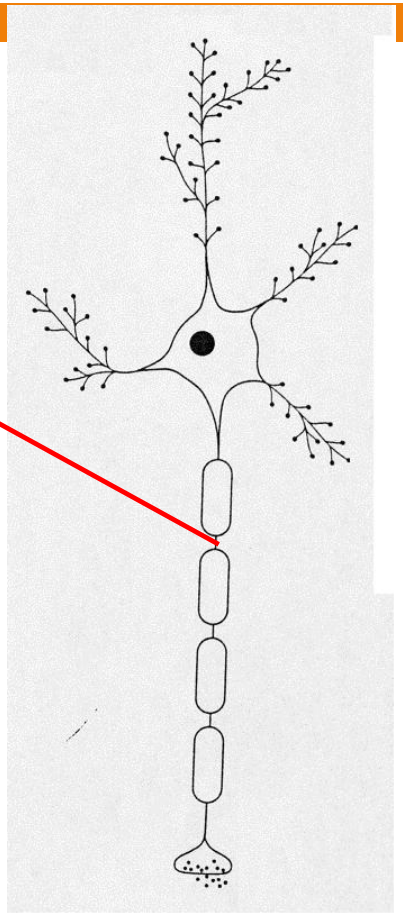


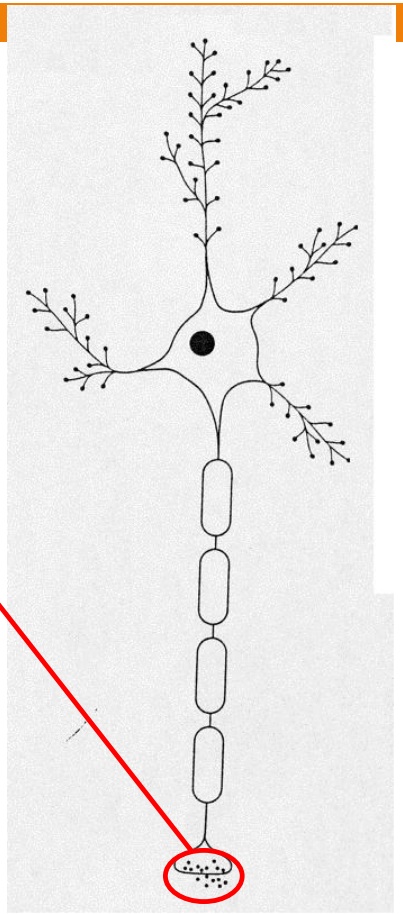
Development of the Cortex

- 2 types of ce
- Neurons
- Glial cells



Development of the Cortex

- 2 types of ce
- Neurons
- Glial cells



Development of the Cortex

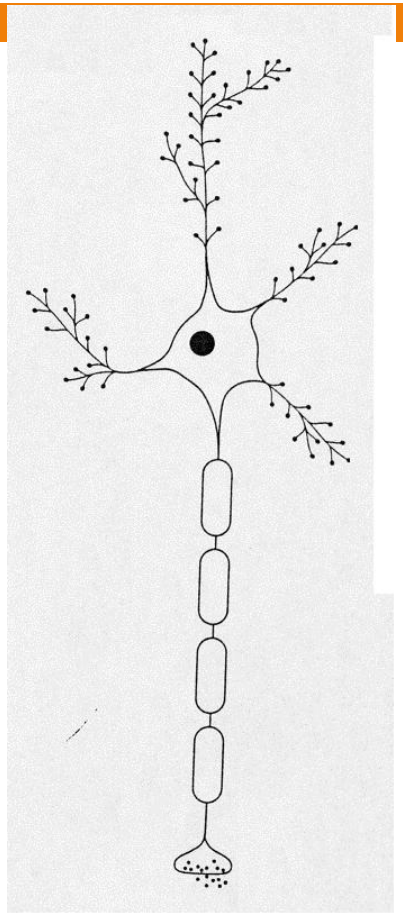
- 2 types of ce
- Neurons
- Glial cells

Dendrite

Cell body

Axon

Synapse



Transmit information through the brain

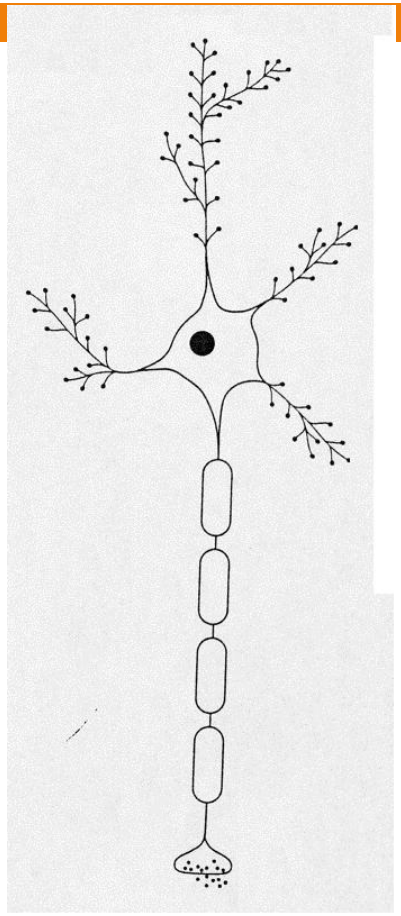
Development of the Cortex

- 2 types of cells:
- Neurons
- Glial cells

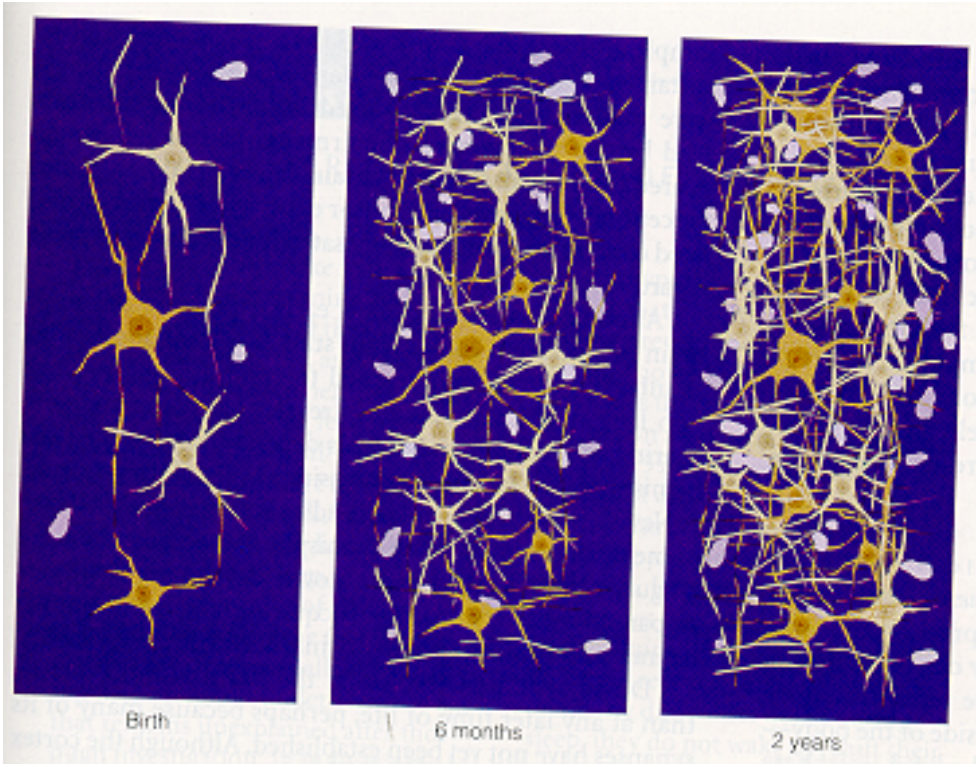
Outnumber neurons 10:1

Nourish, repair, & mylenate neurons

Crucial for development



After birth - development is refinement of neuronal connections, maturity of the neurons, and increasing complexity of dendrite interconnections.



Each cell can form up to 15,000 connections.

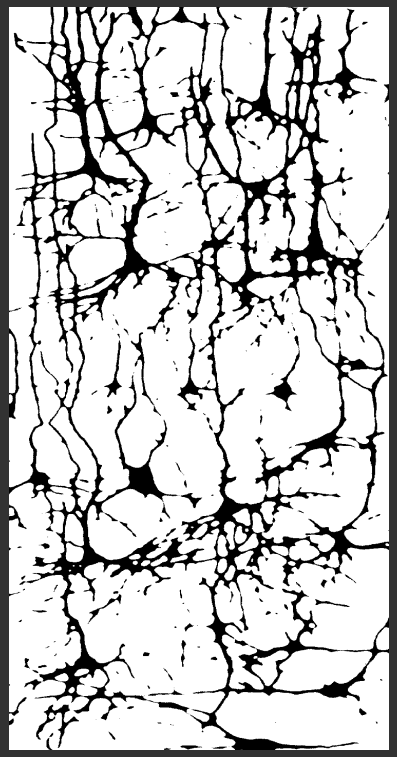
Development of the Brain

- Some theorists refer to the idea of the selection process of neural connections as neural Darwinism.
- In this competition amongst synaptic connections, we initially form more connections than we need.
- The most successful axon connections and combinations survive while the others fail to sustain active synapses.

Human Brain at Birth

6 Years Old

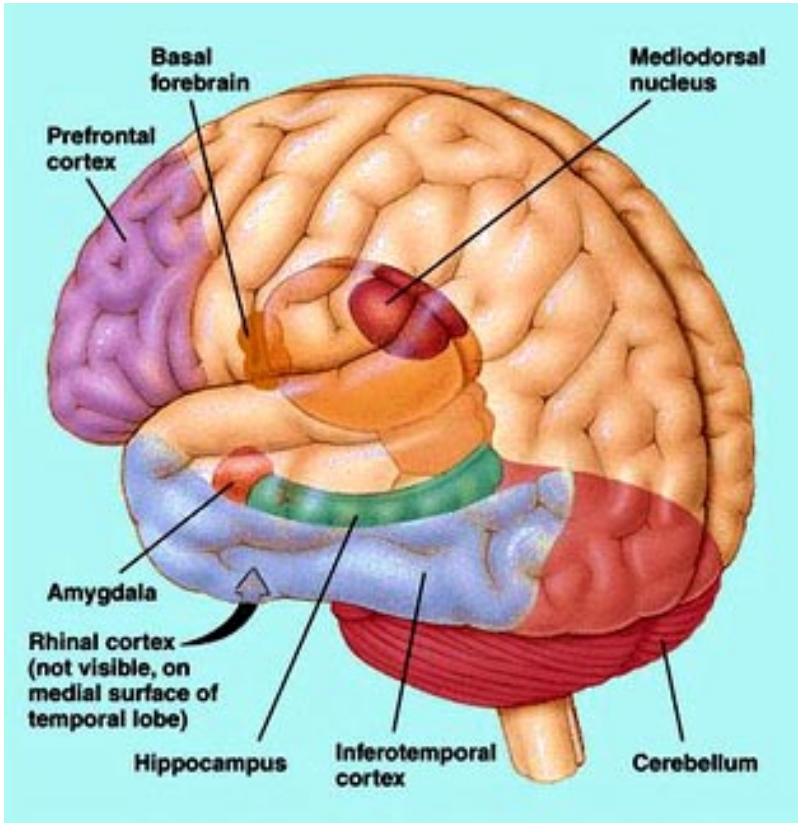
14 Years Old



Development of the Prefrontal Cortex

- Believed to underlie age-related changes in cognitive function, judgement, decision-making
- No single theory explains the function of this area
- Prefrontal cortex plays a role in working memory, planning and carrying out sequences of actions, and inhibiting inappropriate responses

Where is your Prefrontal Cortex ?



The last part of your brain to fully develop

Neuroplasticity in Adults ?

Originally believed that no new neurons were formed after early development. But…

1. Stem cells are undifferentiated cells found in the interior of the brain that generate "daughter cells" which can transform into glia or neurons.

2. New olfactory receptors also continually replace dying ones. Neuronal growth also seen in the hippocampus (memory?)

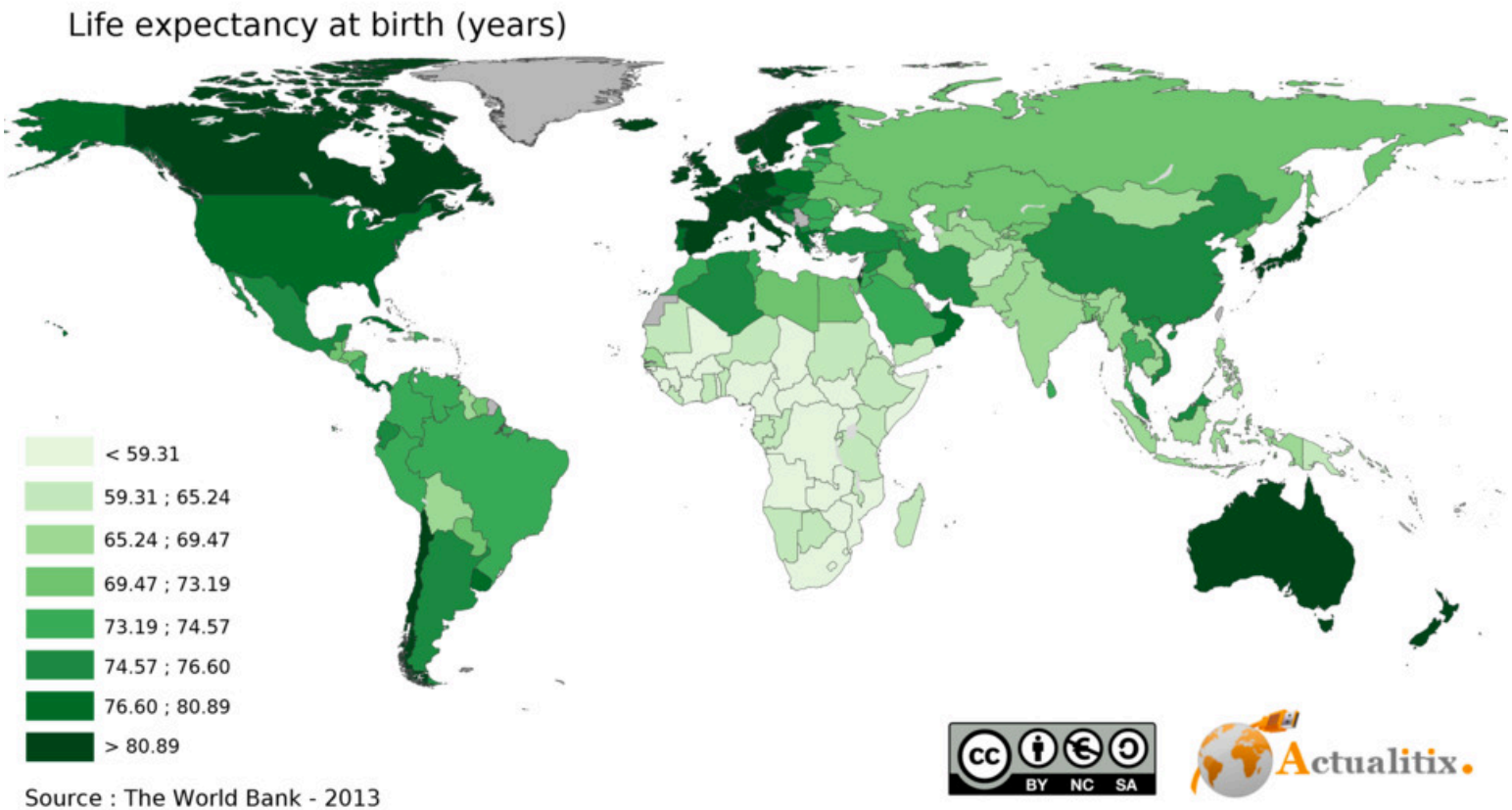
Effects of Experience on the Reorganization of the Adult Cortex

- Skill training leads to reorganization of motor cortex
- Adult musicians who play instruments have an enlarged representation of the hand in somatosensory cortex
- Reorganization is synaptogenesis or pruning of unused synapses…

Development of the Brain

- Extensive practice of a skill changes the brain in a way that improves the ability for that skill.
- For example, MRI studies reveal following:
  - the temporal lobe of professional musicians in the right hemisphere is 30% larger than non-musicians.
  - thicker gray matter in the part of the brain responsible for hand control and vision of professional keyboard players

PART II


Life expectancy at birth (years)
< 59.31
59.31 ; 65.24
65.24 ; 69.47
69.47 ; 73.19
73.19 ; 74.57
74.57 ; 76.60
76.60 ; 80.89
> 80.89
Source : The World Bank - 2013
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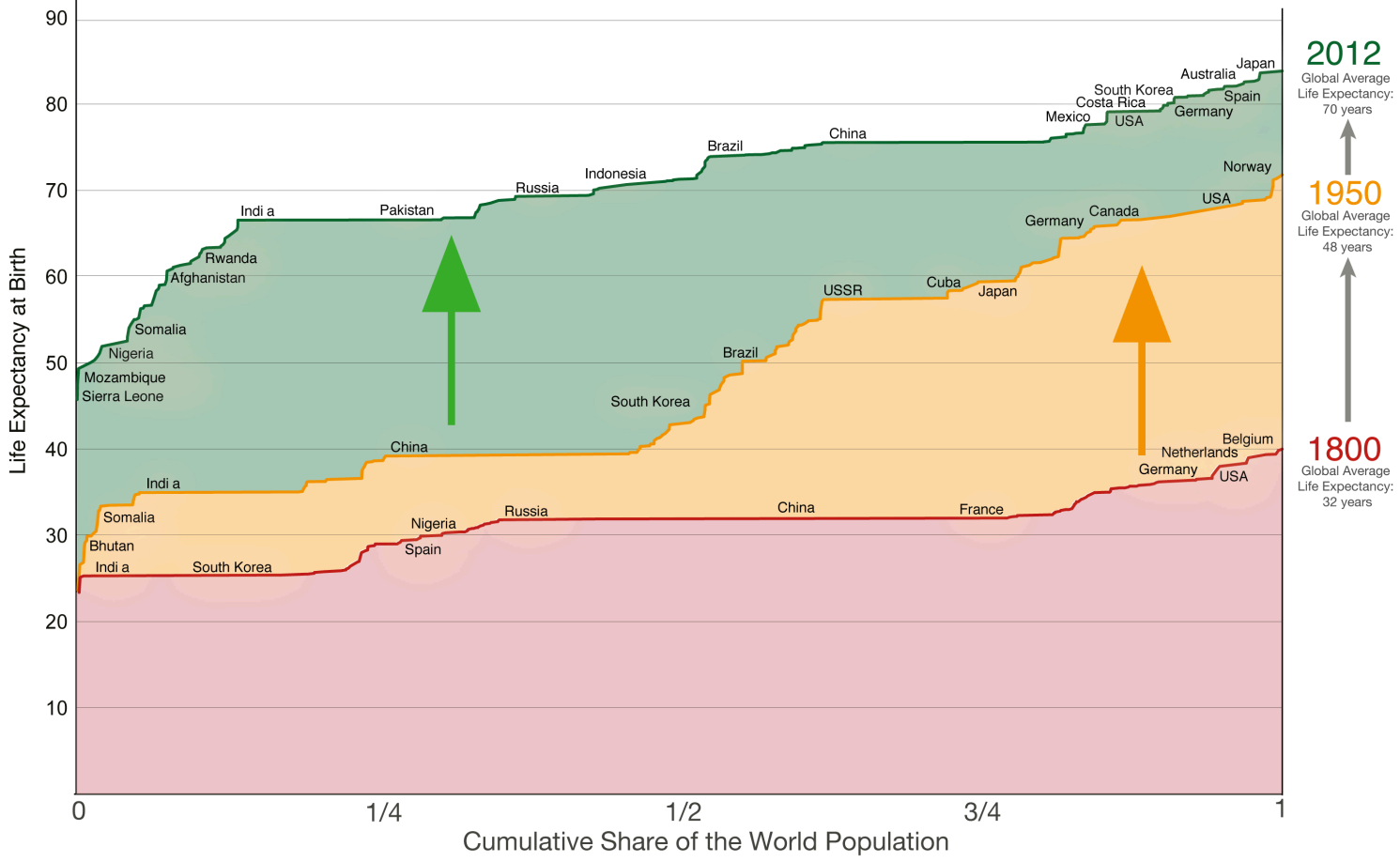
Male		Female	
Country	Years	Country	Years
Highest		**Highest**	
Switzerland	81.3	Japan	86.8
Iceland	81.2	Singapore	86.1
Australia	80.9	Spain	85.5
Sweden	80.7	Republic of Korea	85.5
Israel	80.6	France	85.4
Japan	80.5	Switzerland	85.3
Italy	80.5	Australia	84.8
Canada	80.2	Italy	84.8
Spain	80.1	Israel	84.3
Singapore	80.0	Iceland	84.1
Lowest		**Lowest**	
Lesotho	51.7	Chad	54.5
Chad	51.7	Côte d'Ivoire	54.4
Central African Republic	50.9	Central African Republic	54.1
Angola	50.9	Angola	54.0
Sierra Leone	49.3	Sierra Leone	50.8

Our World in Data

Life Expectancy of the World Population in 1800, 1950 and 2012

Countries are ordered along the x-axis ascending by the life expectancy of the population. Data for almost all countries is shown in this chart, but not all data points are labelled with the country name.

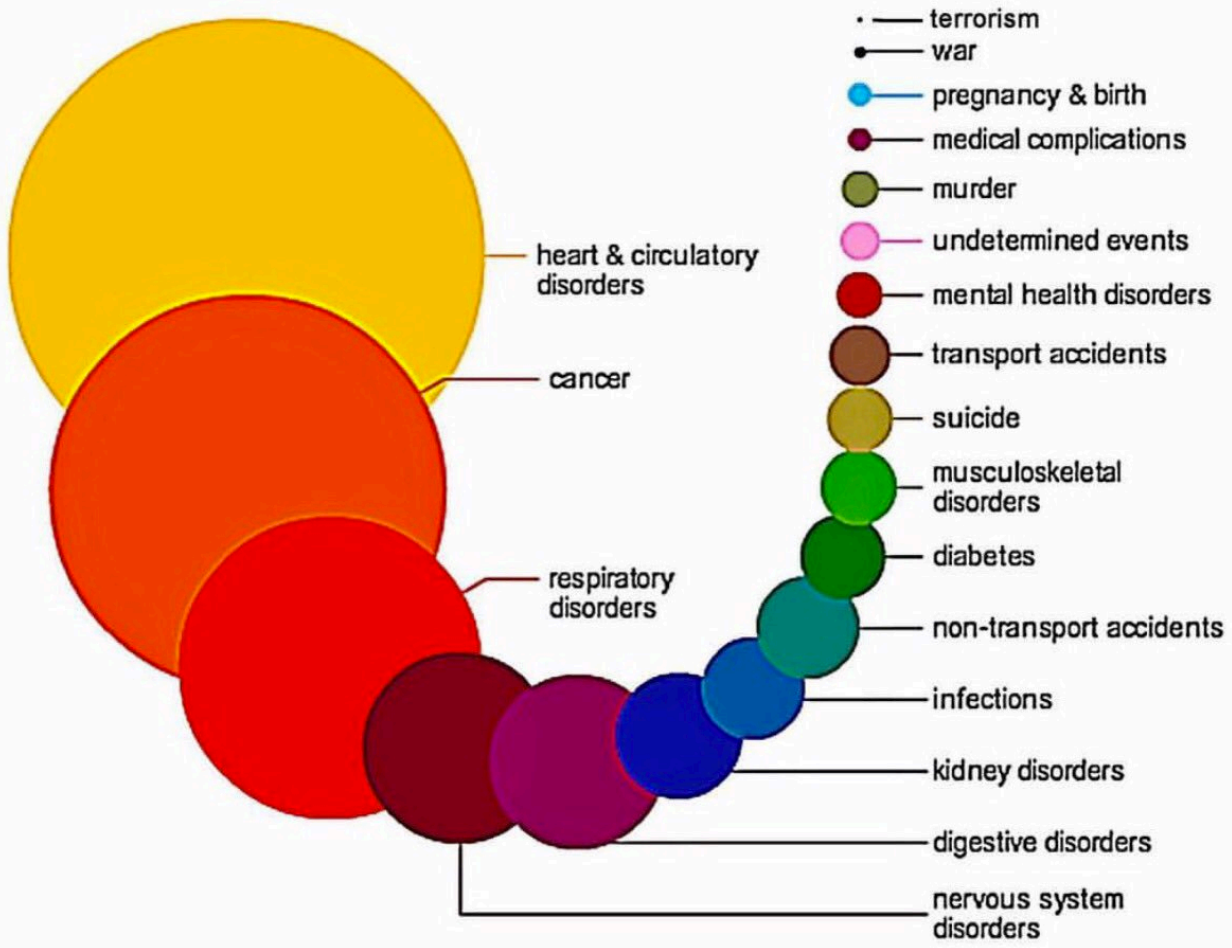


Data source: The data on life expectancy by country and population by country are taken from Gapminder.org.

The interactive data visualisation is available at OurWorldinData.org. There you find the raw data and more visualisations on this topic.

Relatively few people die of old age.

Leading causes of death in perspective



NHS

Definition of Normal Biological Aging

"the decline and deterioration of functional capability at the cellular, tissue, organ, and systems level"

AGING leads to:

1. Loss of ability to maintain homeostasis
2. Decreased ability to adapt to internal and external stress
3. Damage to body systems

Loss of functional properties and decrease in ability to adapt to stress results in increased vulnerability to disease and mortality

1. Loss of ability to maintain homeostasis

Homeostasis

Important functions that must be maintained by body (amongst others)

1. blood sugar levels (glucose)
2. water content (dehydration)
3. pH (gas exchange of CO_2 and O_2)
4. body heat (body temperature)
5. nutrient levels

Examples of Homeostasis:

- Conditions in the body change from time/time
- Every time we alter body conditions, we alter homeostasis

Running or walking:

•body temp (increases) → Lower internal body temp. (sweating)

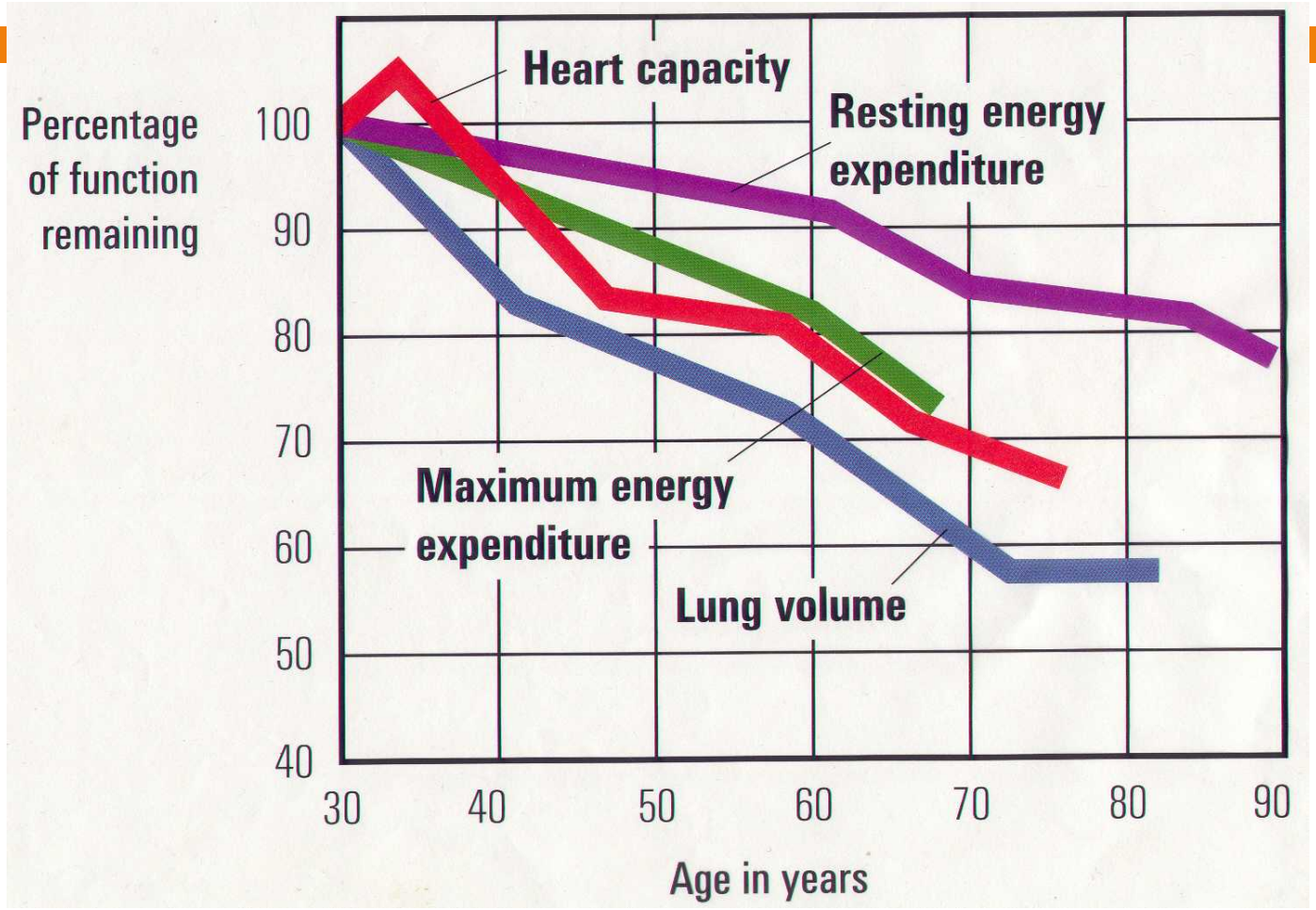
• water loss from cells and tissues (dehydration) → Increased hydration (thirst)

Raises heart rate → Slow heart rate

Utilizes blood glucose → glucose levels restored (appetite, glycogen)

2. Decreased ability to adapt to internal and external stress

Physical Decline with Aging



3. Damage to body systems

Damage to body systems

1. Muscle deterioration and damage
2. Damage to skeletal system (e.g., osteoporosis)
3. Damage to internal organs
4. Damage to nervous system

But why do we age?

1. Error Theories
2. Programmed Theories

Error Theories

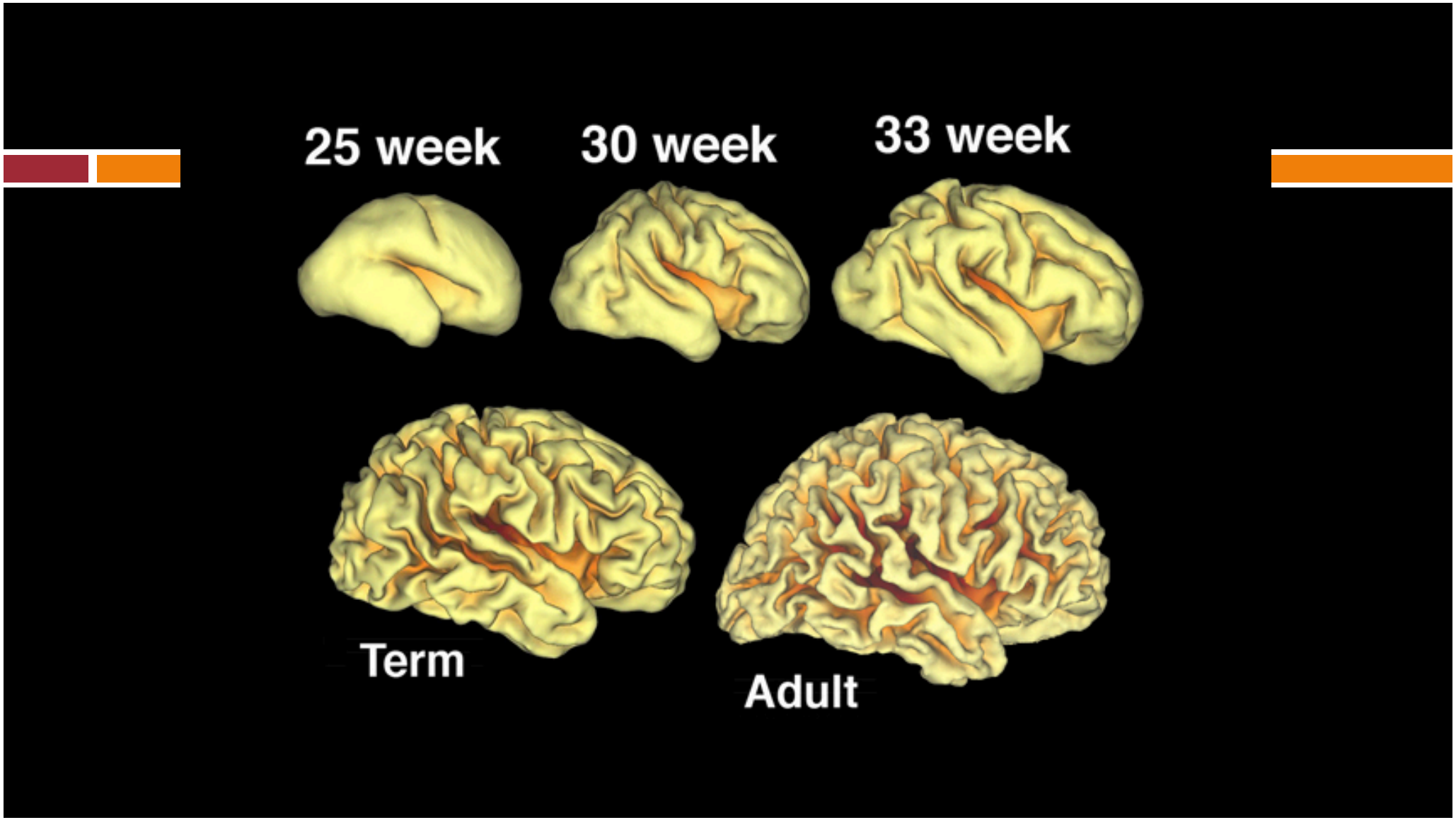
1. Wear and tear theory
2. Rate of living (cells burn out more quickly the more work they do)
3. Cross linking theories (cross linked proteins damage organs)
4. Free radical theories (atoms with unpaired electrons)(do damage to what they encounter)
5. DNA Damage theories

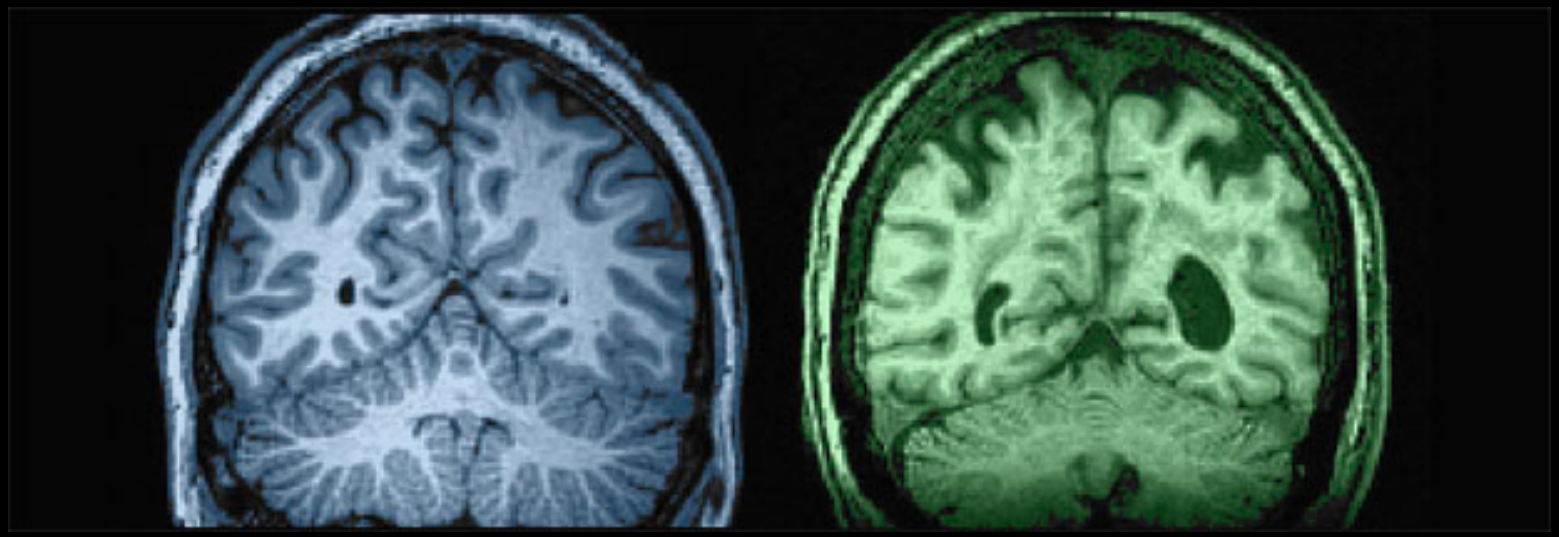
Programmed Theories

1. Programmed Longevity (its in the genetic code)
2. Endocrine Theory (its in the hormones)
3. Immunological Theory (our immune system is programmed to shut down)

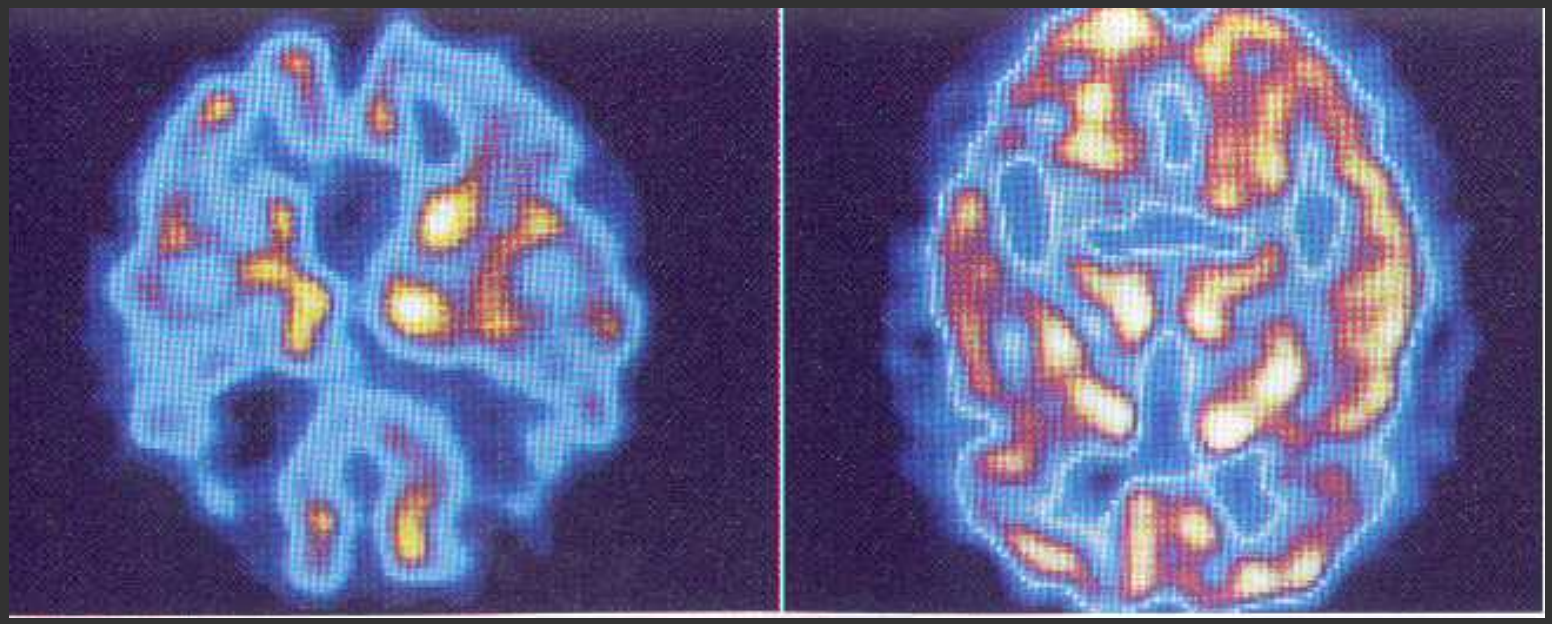
The simple truth is scientists are still not sure why we age

Age-related changes in the nervous system


25 week
30 week
33 week
Term
Adult



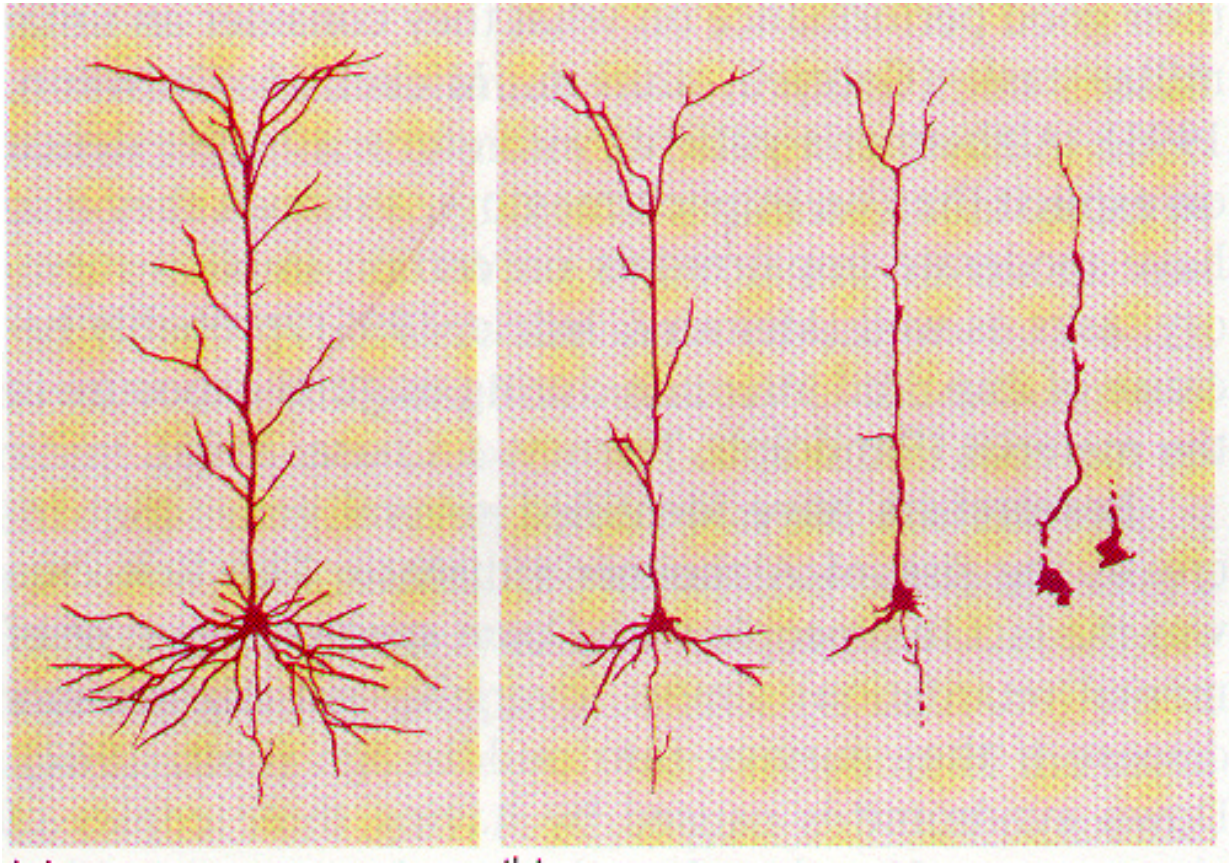
DECREASED CEREBRAL METABOLISM



Alzheimer's

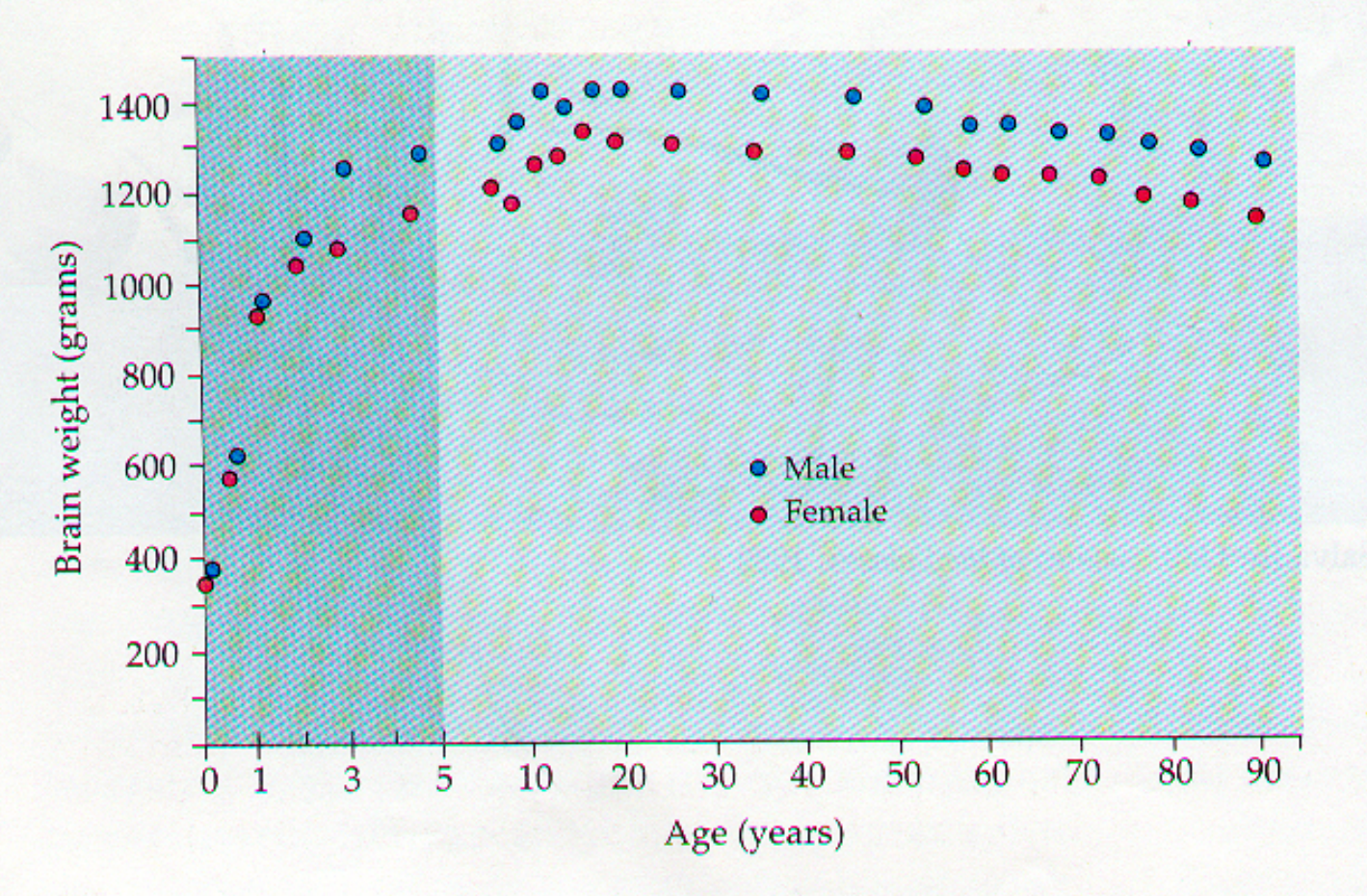
Normal

Neuronal Degeneration



Normal **Alzheimer's**

Brain Weight and Aging



Nerve cells diminish with age

~ 10000 are lost per day

(you start with about 86 billion, so about 23500 years to get to zero)

- lost neurons are not replaced

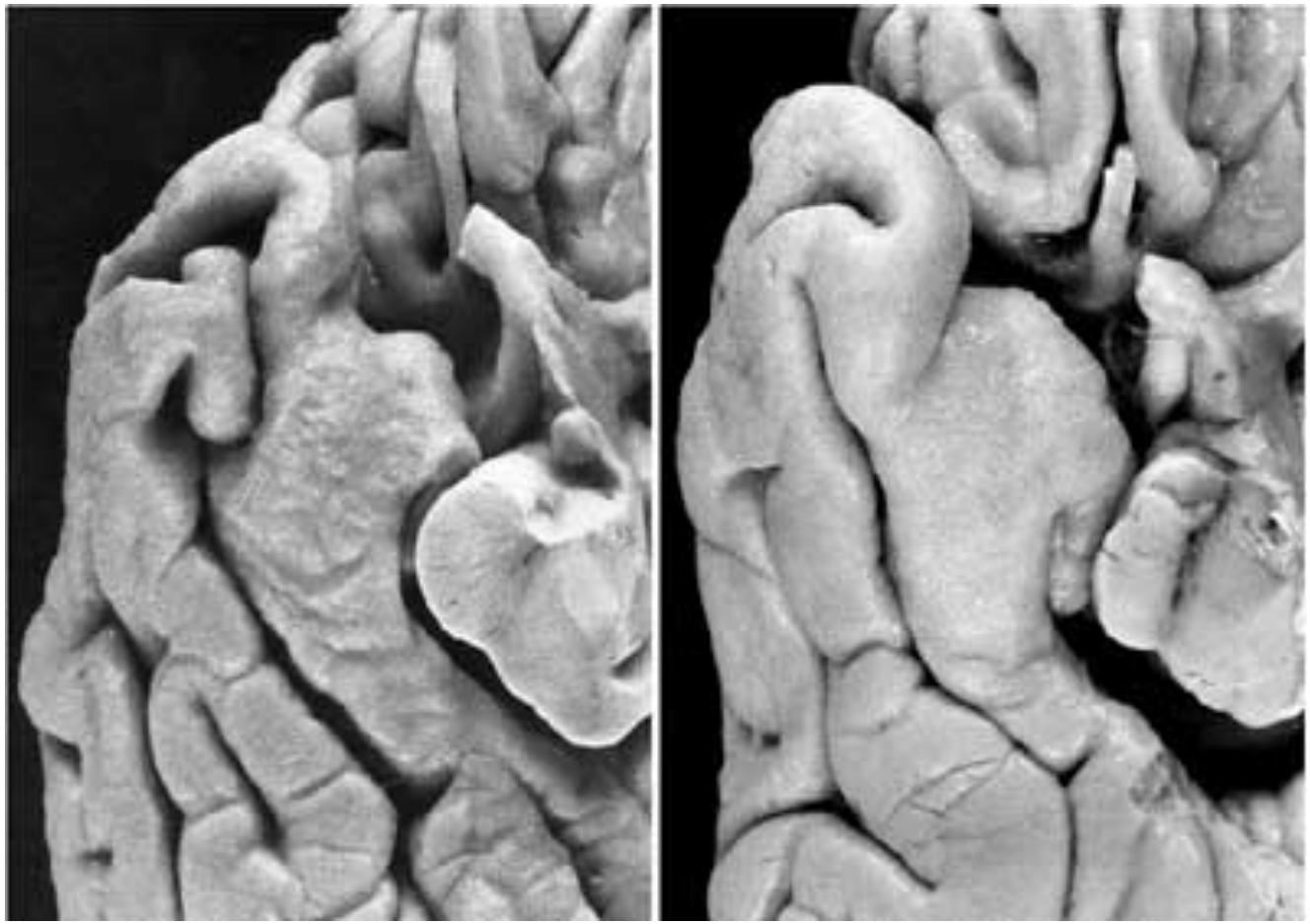
WHY?

- nervous tissue is gradually reduced

But why?

Theories on neuronal death have changed a lot over the past decade. Now, it is believed that most neuronal death is due to non age related factors:

1. damage from external causes
2. neurodegenerative disease

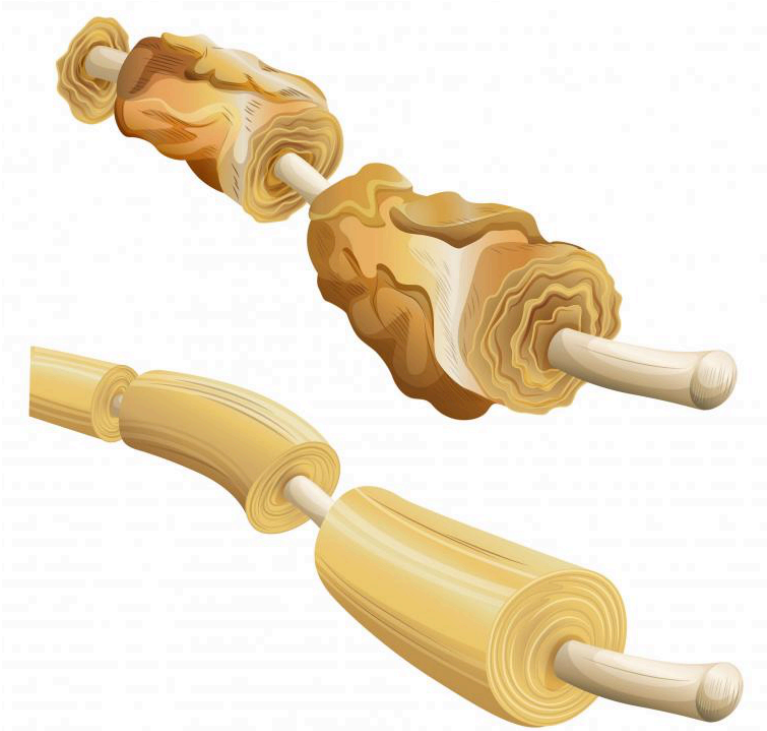


Alzheimer’s

Healthy Senior

However,

Maybe the neurons themselves do change. For example, there may be a loss of myelin which results in a reduction in neural function.



But
“It is suggested that such degenerative changes lead to cognitive decline because they cause changes in conduction velocity, resulting in a disruption of the normal timing in neuronal circuits. Yet as degeneration occurs, other changes, such as the formation of redundant myelin and increasing thickness suggest of sheaths, suggest some myelin formation is continuing during aging.”

Loss of neurons + loss of myelin = decreased brain mass

Note – loss is not uniform across the brain

The Course of Physical Development in Late Adulthood

- The Aging Brain

- The Adapting Brain
  - As the brain ages, it adapts in several ways:
    - Neurogenesis: the generation of new brain cells
    - Dendritic growth can occur in human adults
    - Older brains rewire to compensate for losses
    - Hemispheric lateralization can decrease; may improve cognitive functioning

So, assuming your brain is healthy…

Biological Myths of Aging

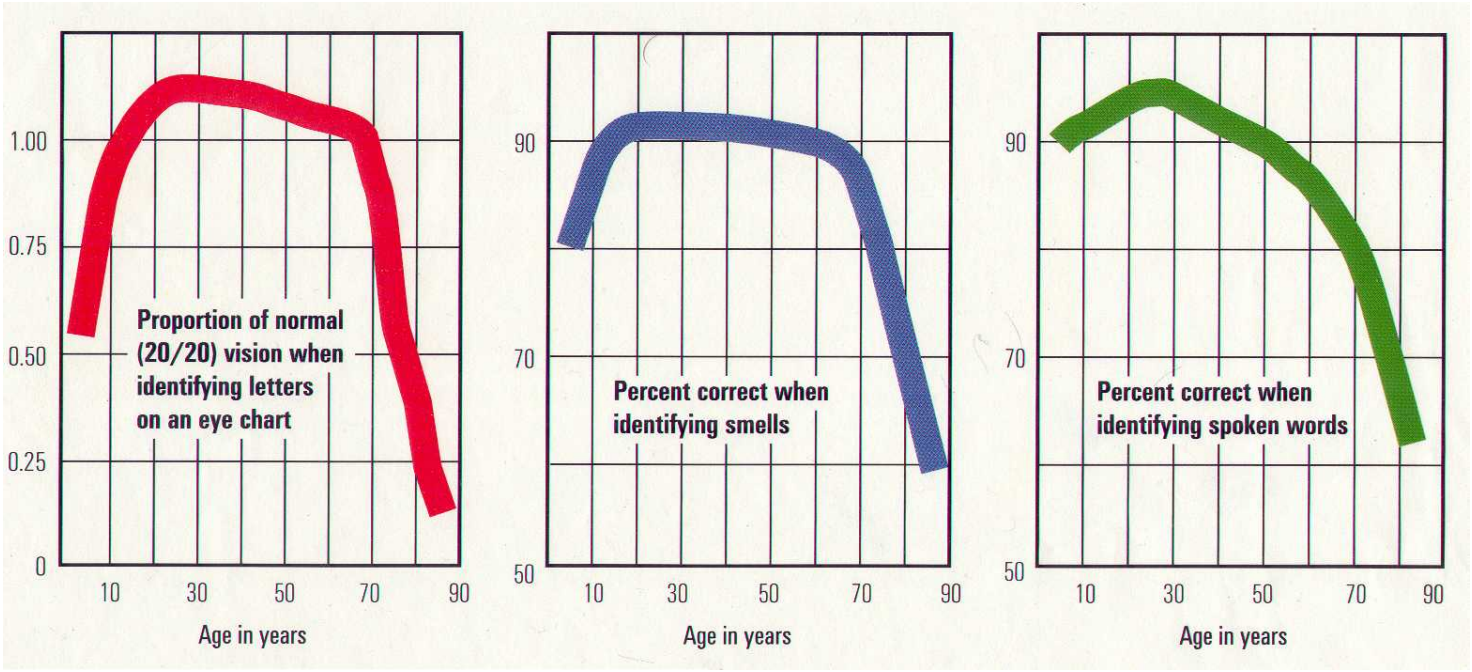
Memory declines drastically with age for all people.

IQ declines drastically with age in all people.

Learning becomes more difficult as we get older.

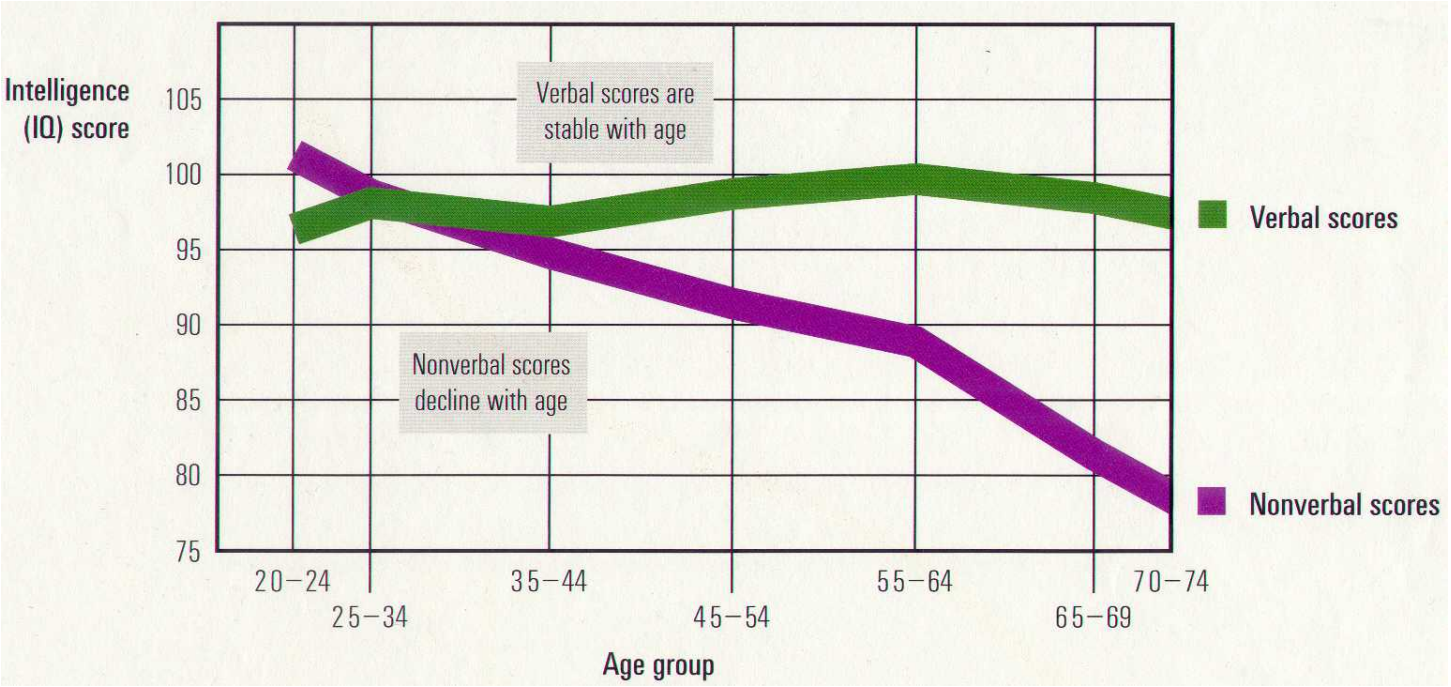
There is nothing you can do counter these aging deficits.

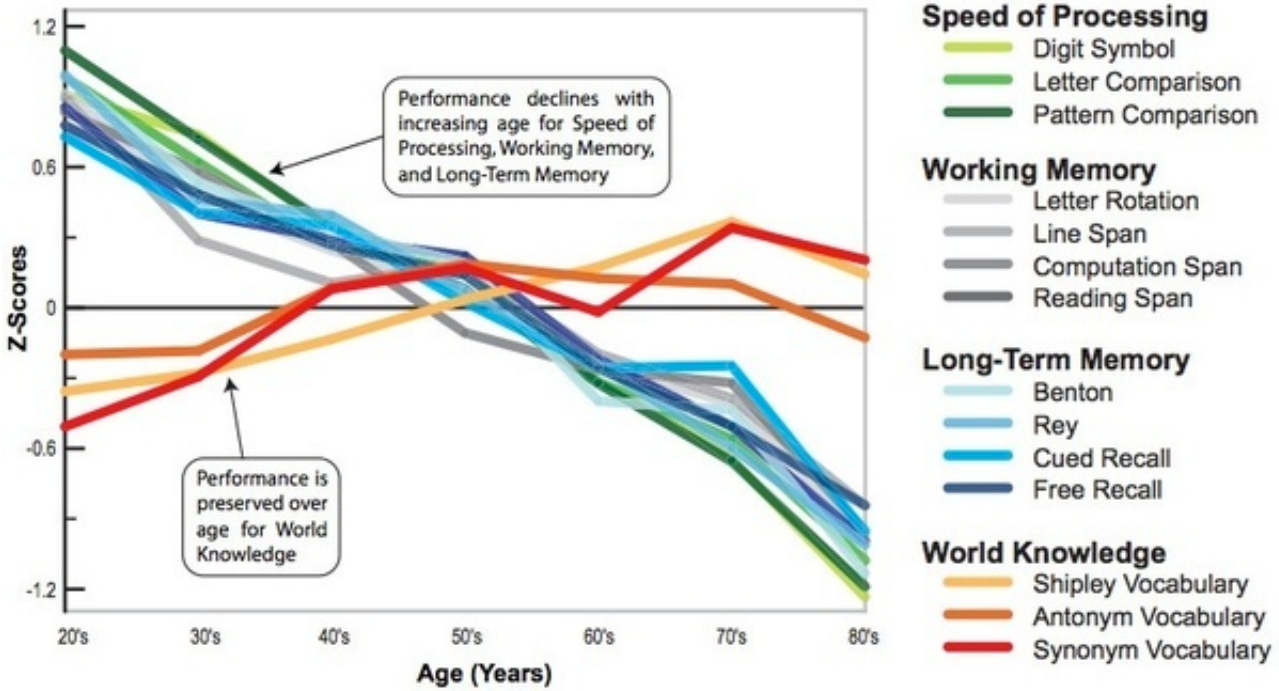
Senses Decline with Aging



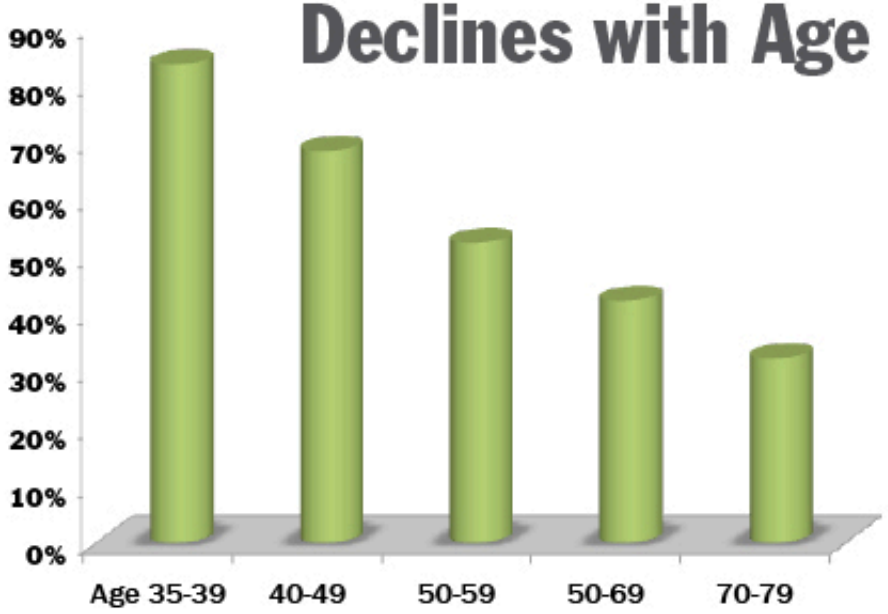
Changes in Cognitive Function

Intelligence and Aging

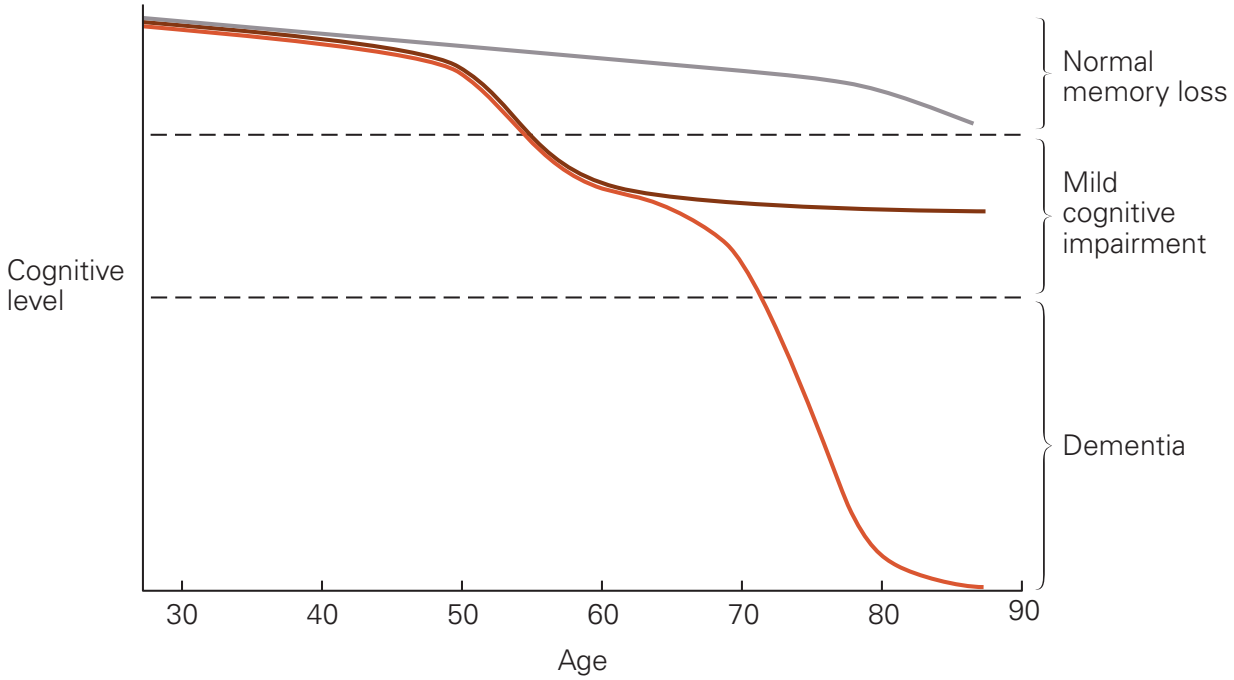



1.2
0.6
0
-0.6
-1.2
Z-Scores
Performance declines with increasing age for Speed of Processing, Working Memory, and Long-Term Memory
Performance is preserved over age for World Knowledge
20's
30's
40's
50's
60's
70's
80's
Age (Years)
Speed of Processing
Digit Symbol
Letter Comparison
Pattern Comparison
Working Memory
Letter Rotation
Line Span
Computation Span
Reading Span
Long-Term Memory
Benton
Rey
Cued Recall
Free Recall
World Knowledge
Shipley Vocabulary
Antonym Vocabulary
Synonym Vocabulary

Normal Memory Recall Declines with Age

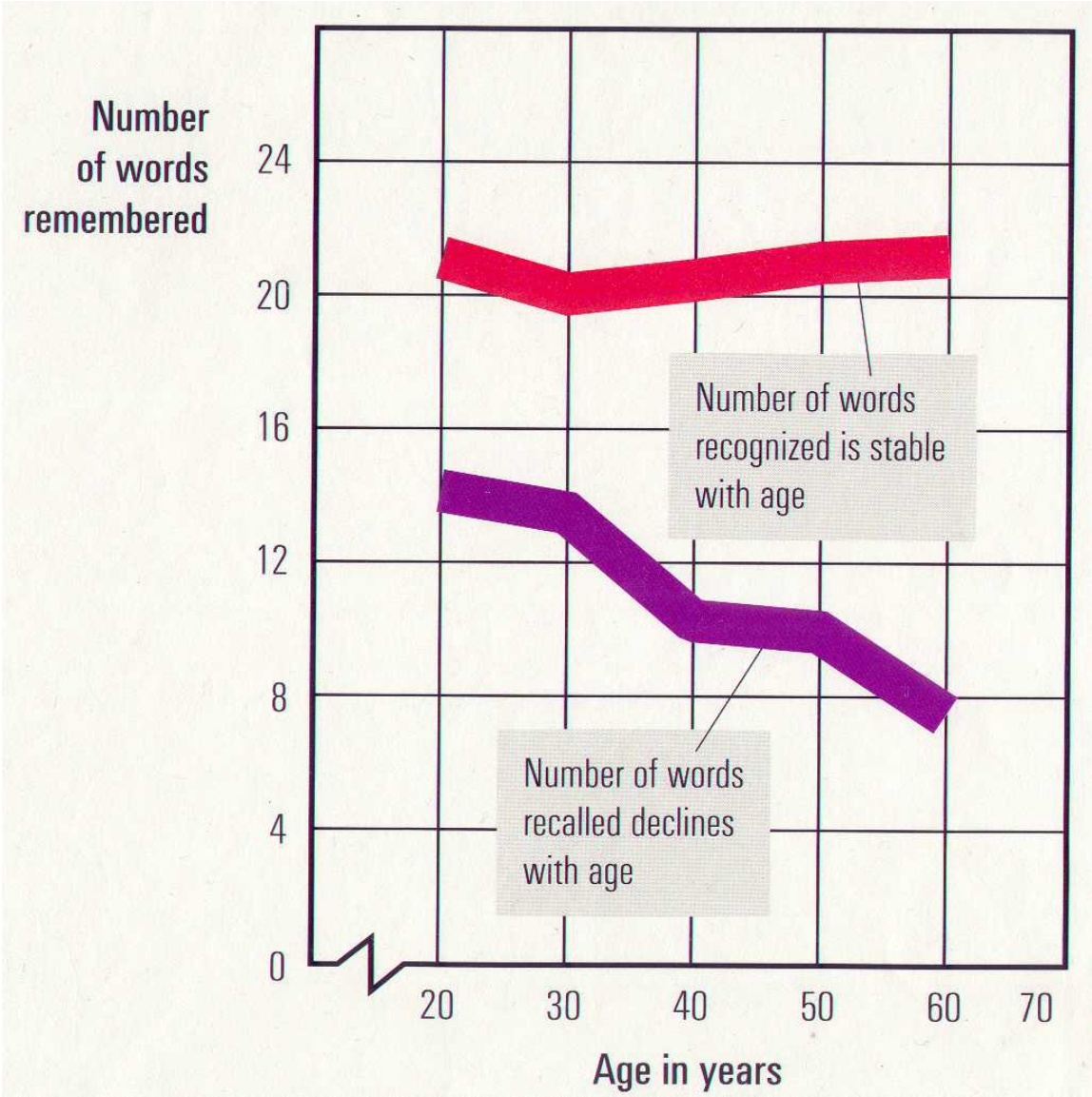


Crook, T.H. et. al. (1993): Recalling names after introduction: Changes across lifespan in two cultures. Developmental Neurospsychology, 9, 103-113.


Normal
memory loss
Mild
cognitive
impairment
Dementia
Cognitive
level
30
40
50
60
70
80
90
Age

Recall and Recognition in Adulthood

- **Recognition**
  - stable
- **Recall**
  - declines



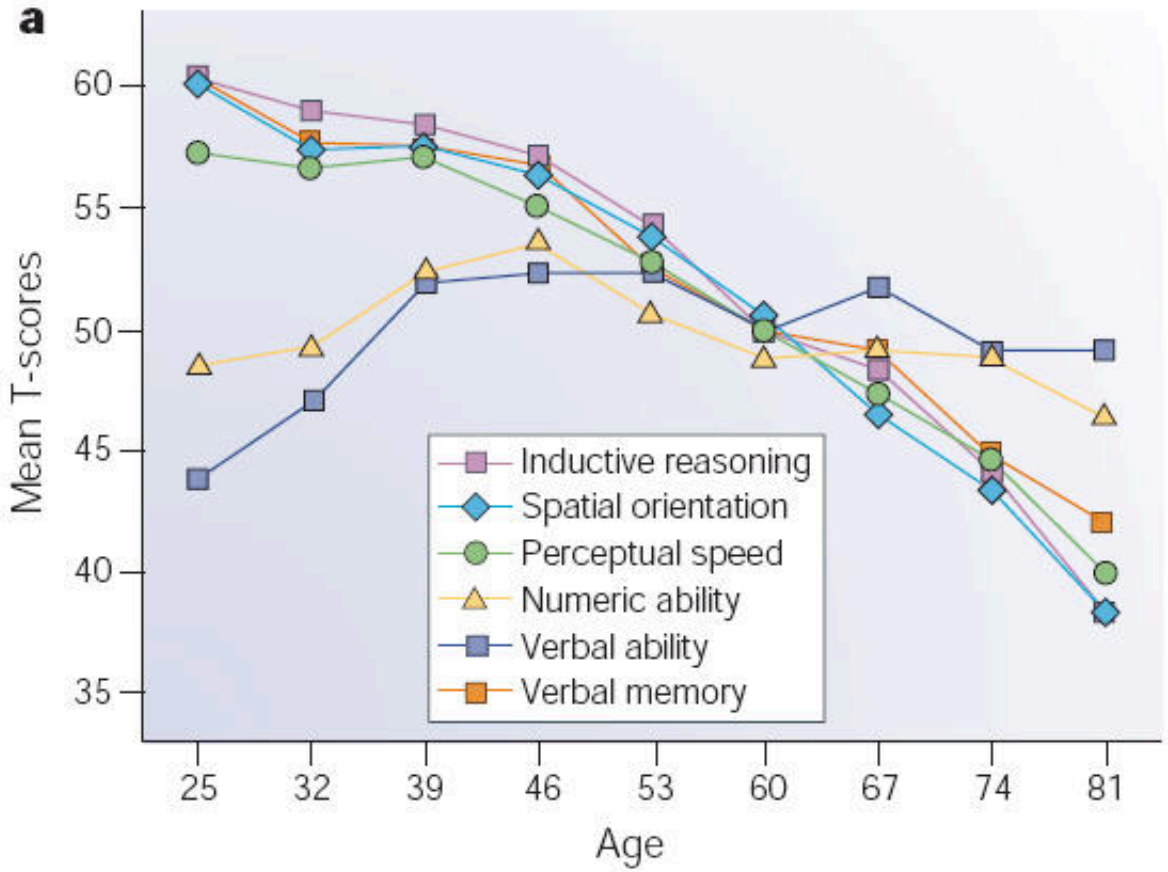
Memory Decline with Aging

Age-Related Deficits:

- •long-term memory
- •physical-motor tasks
- •free recall learning
    - •requiring conscious recollection and effort

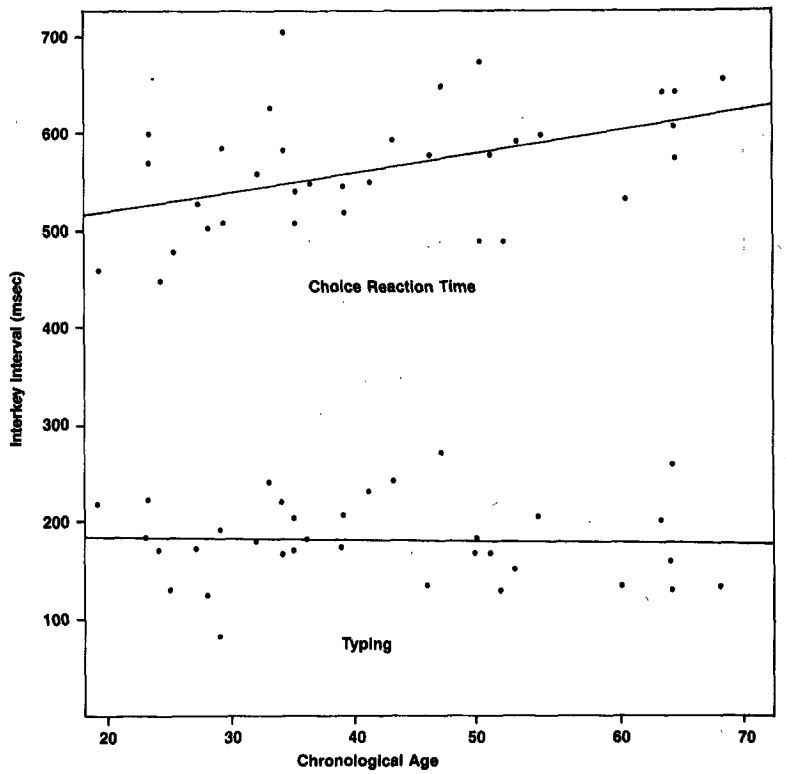
No Age-Related Deficits:

- •short-term memory
- •non physical-motor tasks
- •recognition learning
    - •easily organized task structures or cues


a
Mean T-scores
60
55
50
45
40
35
25
32
39
46
53
60
67
74
81
Age
Inductive reasoning
Spatial orientation
Perceptual speed
Numeric ability
Verbal ability
Verbal memory

Effects of Age and Skill in Typing

Timothy A. Salthouse
Andrus Gerontology Center, University of Southern California and University of Missouri

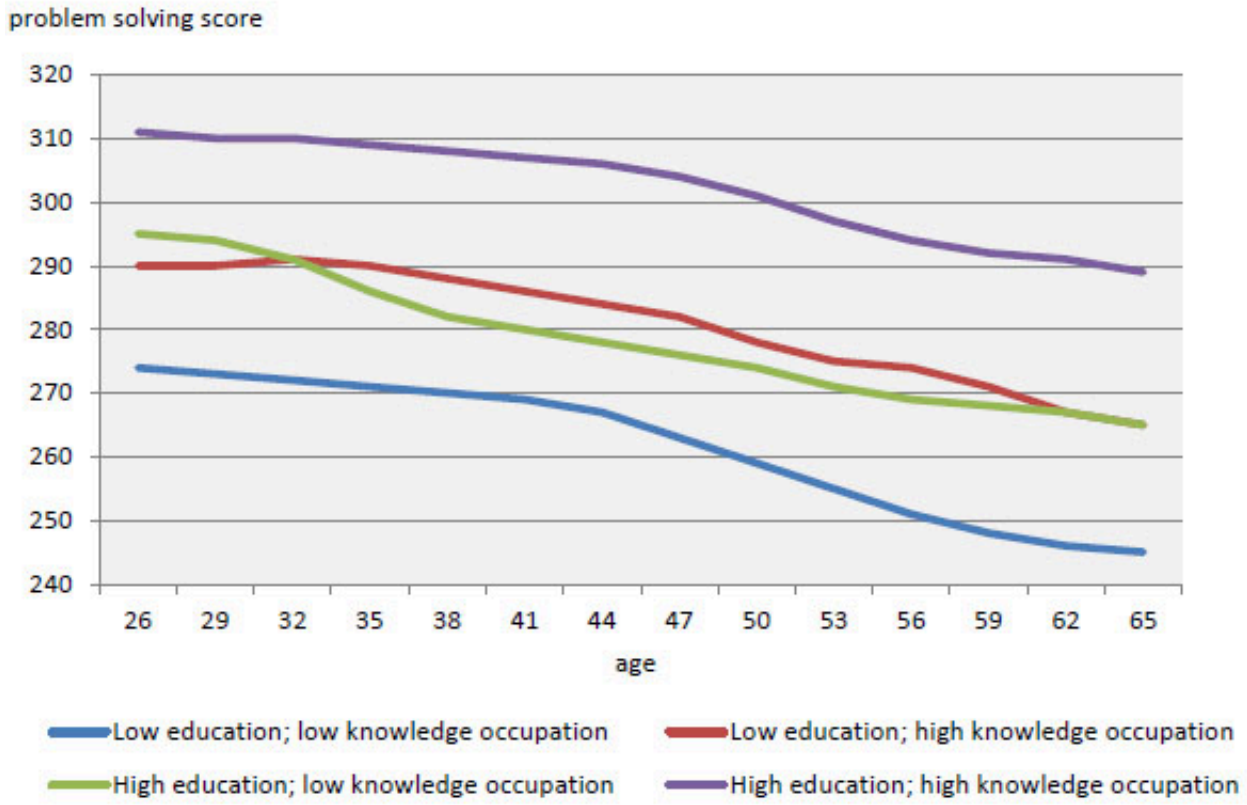


Reducing Cognitive Decline

Reducing Cognitive Decline

1. Live in Favorable Environmental Circumstances

above-average education
high complexity occupations
above-average income
maintaining intact families


problem solving score
320
310
300
290
280
270
260
250
240
26
29
32
35
38
41
44
47
50
53
56
59
62
65
age
Low education; low knowledge occupation
Low education; high knowledge occupation
High education; low knowledge occupation
High education; high knowledge occupation

Reducing Cognitive Decline

2. **Be involved in activities typical of complex and intellectually stimulating environments**
    - extensive reading
    - travel
    - attending cultural events
    - continuing education activities
    - participation in clubs and professional associations

Reducing Cognitive Decline

3. Be married to a spouse with high cognitive status

A few more things…

JNeurosci
THE JOURNAL OF NEUROSCIENCE

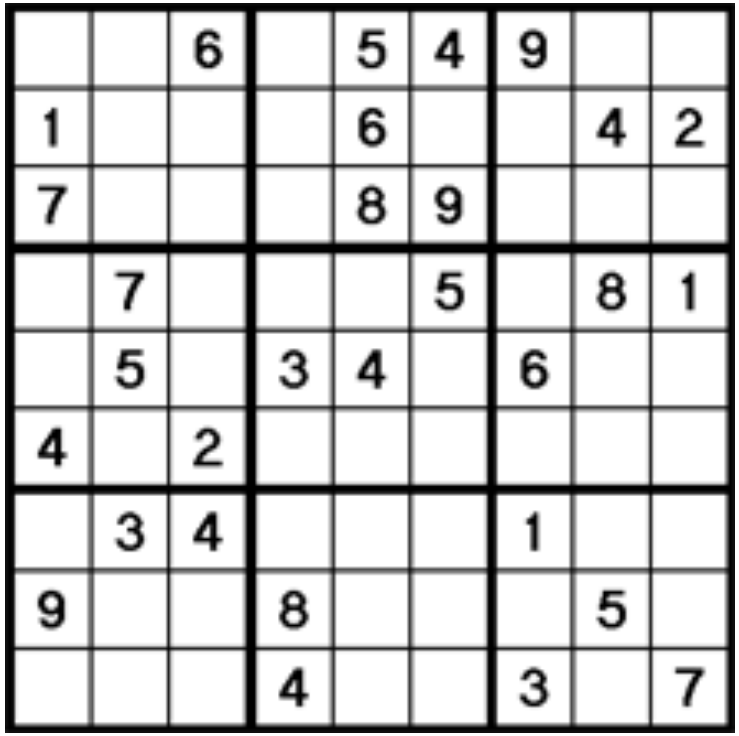
An Official Journal of SfN Society for Neuroscience

Research Articles, Behavioral/Cognitive

No Effect of Commercial Cognitive Training on Brain Activity, Choice Behavior, or Cognitive Performance

Joseph W. Kable, M. Kathleen Caulfield, Mary Falcone, Mairead McConnell, Leah Bernardo, Trishala Parthasarathi, Nicole Cooper, Rebecca Ashare, Janet Audrain-McGovern, Robert Hornik, Paul Diefenbach, Frank J. Lee, and Caryn Lerman

Journal of Neuroscience 2 August 2017, 37 (31) 7390-7402; DOI: https://doi.org/10.1523/JNEUROSCI.2832-16.2017


6 5 4 9
1 6 4 2
7 8 9
7 5 8 1
5 3 4 6
4 2
3 4 1
9 8 5
4 3 7

What is the association between sedentary behaviour and cognitive function? A systematic review

Ryan S Falck,[1] Jennifer C Davis,[1] Teresa Liu-Ambrose[1,2]

Br J Sports Med. 2015 Feb;49(4):248-54. doi: 10.1136/bjsports-2013-093184. Epub 2014 Apr 7.

Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial.

ten Brinke LF[1], Bolandzadeh N[2], Nagamatsu LS[3], Hsu CL[2], Davis JC[4], Miran-Khan K[5], Liu-Ambrose T[6].

⊕ **Author information**

Long-Term Effects of Resistance Exercise Training on Cognition and Brain Volume in Older Women: Results from a Randomized Controlled Trial

Article · June 2015 *with* 336 Reads
DOI: 10.1017/S1355617715000673


1st **John Riley Best**
34.38 · University of British Columbia - Vancouver


2nd **Bryan K. Chiu**


3rd **Chun Liang Hsu**
32.8 · University of British Columbia - Vancouver

+ 1


Last **Teresa Liu-Ambrose**
44.18 · University of British Columbia - Vancouver

Show more authors

Conclusions

•All things being equal, assuming you are healthy, your brain is fine

•IQ does not show a drastic decline with age.

•Only certain types of memory show declines with aging.

•The ability to learn does not deviate much as we get older.

•There is plenty you can do counter aging deficits.

- •Exercise regularly
- •Eat properly
- •Engage in learning activities
- •Stop smoking
- •Stay in touch with friends, families, communities

PART III

Dementia

Normal Aging	Dementia
Not being able to remember details of a conversation or event that took place a year ago	Not being able to recall details of recent events or conversations
Not being able to remember the name of an acquaintance	Not recognizing or knowing the names of family members
Forgetting things and events occasionally	Forgetting things or events more frequently
Occasionally have difficulty finding words	Frequent pauses and substitutions when finding words
You are worried about your memory but your relatives are not	Your relatives are worried about your memory, but you are not aware of any problems

What is Dementia?

- Dementia is characterised by a decline of information processing abilities accompanied by changes in personality and behaviour

- Dementia is an umbrella term for progressive disorder of cognition

Dementia has to be distinguished from *delirium* which is an acute disturbance of cerebral function with impaired conscious level, hallucinations and autonomic overactivity as a consequence of toxic, metabolic or infective conditions.

Depression can mimic the initial phases of dementia and it is termed 'pseudodementia' (which is amenable to antidepressant medication).

Dementia may occur at any age but is **more common in the elderly**, accounting for 40% of long-term psychiatric in-patients over the age of 65 years.

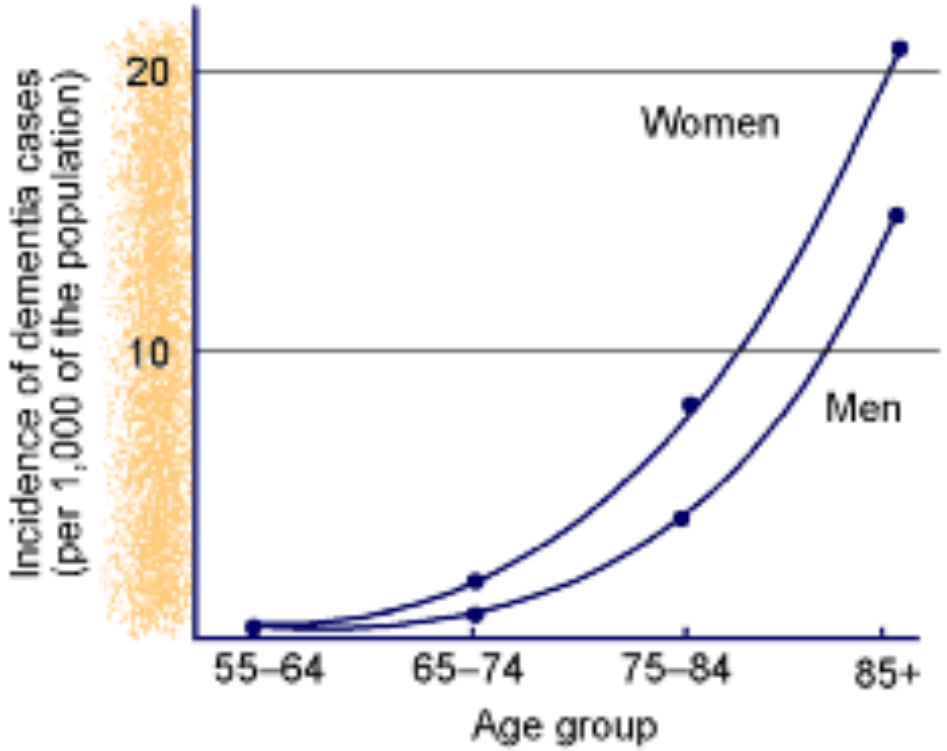
The **prevalence** in persons aged between 50 and 70 years is about 1% and in those approaching 90 years reaches 50%.

An annual incidence rate is 190/100 000 persons.

Mild cognitive impairment (MCI)

- MCI is a relatively recent term, used to describe people who have some **problems with their memory** but do not actually have dementia.
- Some people (80%?) will be in the early stages of Alzheimer's disease or another dementia. Others, however, will have MCI as a result of stress, anxiety, depression, physical illness or just an 'off day'.
- It is estimated that **15% of the population** may be experiencing MCI.
- Currently **extensive research** on MCI is ongoing.
- At the moment there is not enough evidence to recommend any specific treatments.

The exponential increase in the prevalence of dementia by age group in men and women

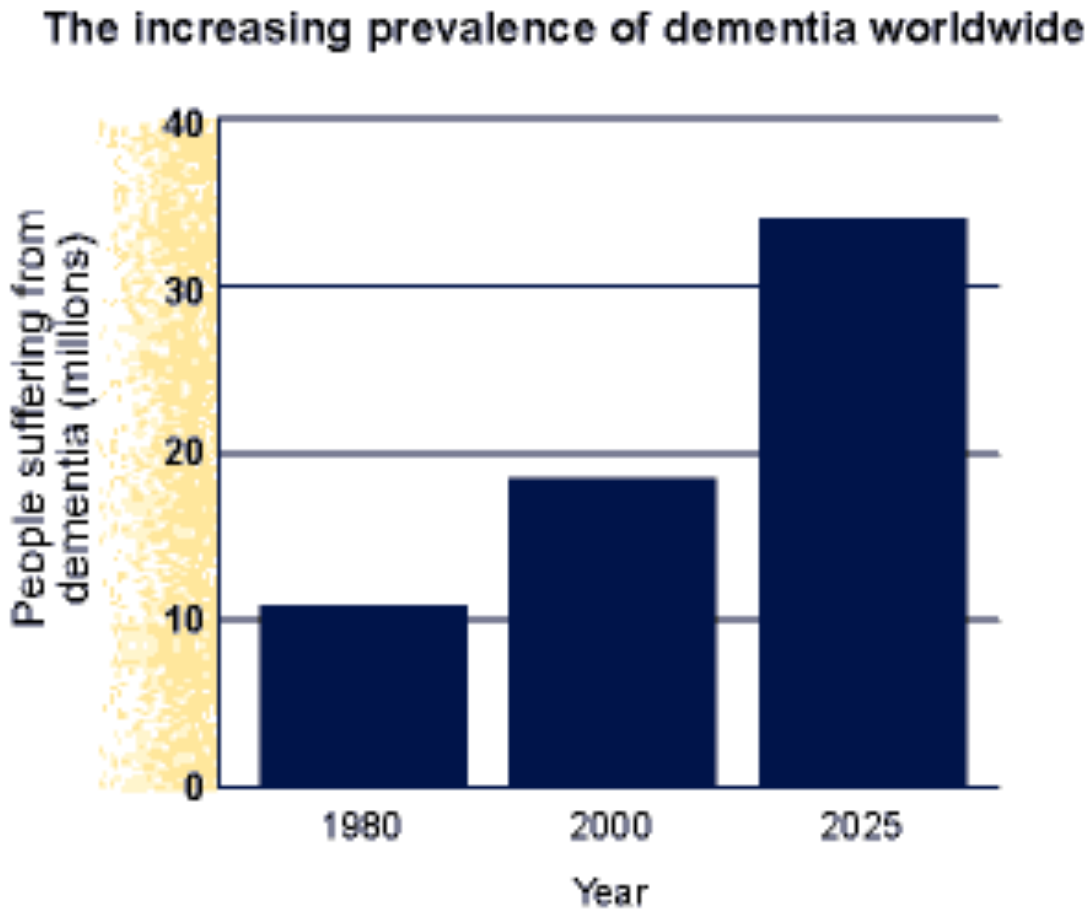


RISK FACTORS FOR DEMENTIA

- **Age**
- **Family history**
- **Head injury**
- **Fewer years of education**

Statistics

- 564,000 people in Canada currently with dementia
- 25,000 new cases diagnosed each year


The increasing prevalence of dementia worldwide
People suffering from dementia (millions)
40
30
20
10
0
1980
2000
2025
Year

Cognitive Symptoms: Changes in Memory

- **Memory is the process of taking in, storing and retrieving information**
- Unable to recall day/ date/ names/ faces
- Repeating questions/ conversations
- Getting lost
- Losing things

Cognitive Symptoms: Changes in Perception

- **Perception is the process of making sense of information you see (external) and information from your body (internal)**
- Unable to recognise objects
- Unable to judge the position/ location of people/ objects.
- Ignoring one side of the world (including oneself, environment)

Cognitive Symptoms: Changes in Executive Functioning

- **Executive functioning involves the processing of information in order to plan, sequence, make decisions, prioritize, problem-solve and self-monitor**
- Difficulties with initiating tasks
- Getting stuck on tasks/ repeating actions
- Not thinking through the consequences of actions

Cognitive Symptoms: Changes in Language

- **Language involves the process of understanding information which is being said by others (receptive language) and the process of expressing information (expressive language)**
- Difficulties understanding (e.g. words, concepts, complex sentences)
- Difficulties finding the word
- Reduced vocabulary

Non cognitive symptoms of Dementia (BPSD)

- Delusions
- Hallucination
- Agitation / wandering
- Depression / dysphoria
- Anxiety
- Euphoria/elation
- Apathy / Indifference
- Disinhibition
- Irritability / lability / aggression
- Aberrant motor behaviour
- Night-time behaviour
- Appetite / Eating change

Most common Types of Dementia

In order of prevalence

- Alzheimer's Disease (~ 60%)
- Vascular Dementia
- Lewy Body Dementia
- Frontotemporal

Rarer forms of Dementia

- Pre-senile Dementia
- Picks Disease
- Korsakov Dementia*
- Pseudo-dementia*
- Endocrine related Dementia*
- Parkinson's Disease
- Huntington's chorea
- Posterior cortical atrophy
- Normal Pressure Hydrocephalus*
- Neurosyphilis*

- **Creutzfeldt-Jakob Disease**
- **Aids-related Dementia**
- **Wernickes**
- **Pernicious anaemia***
- **Subdural haematoma***
- **Subcortical dementias**
- **Progressive supranuclear palsy**
- **Binswangers disease**
- **Semantic dementia**
- **Dementia Pugilistica**

*** Reversible**

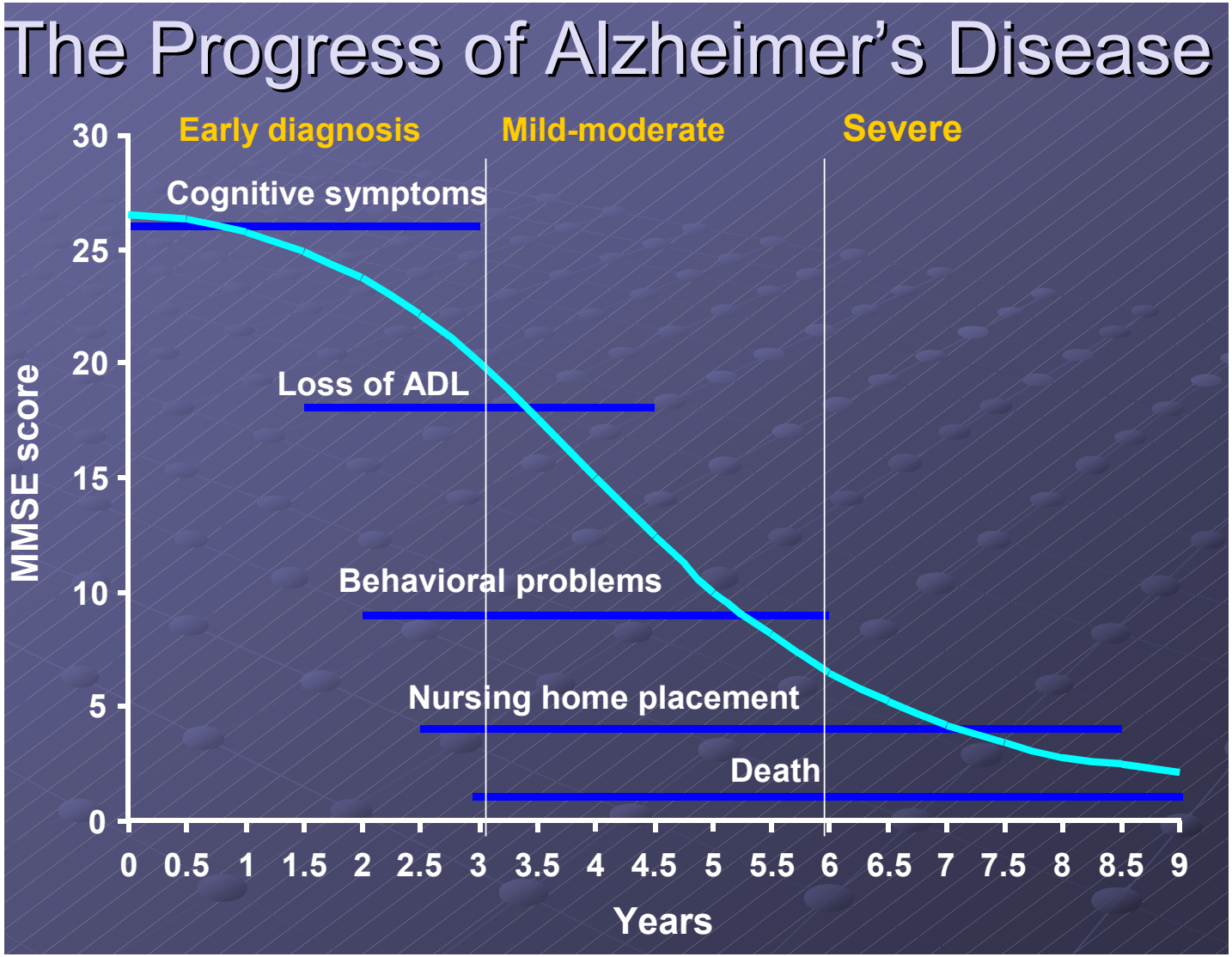
Alzheimer’s Disease

Alzheimer's disease

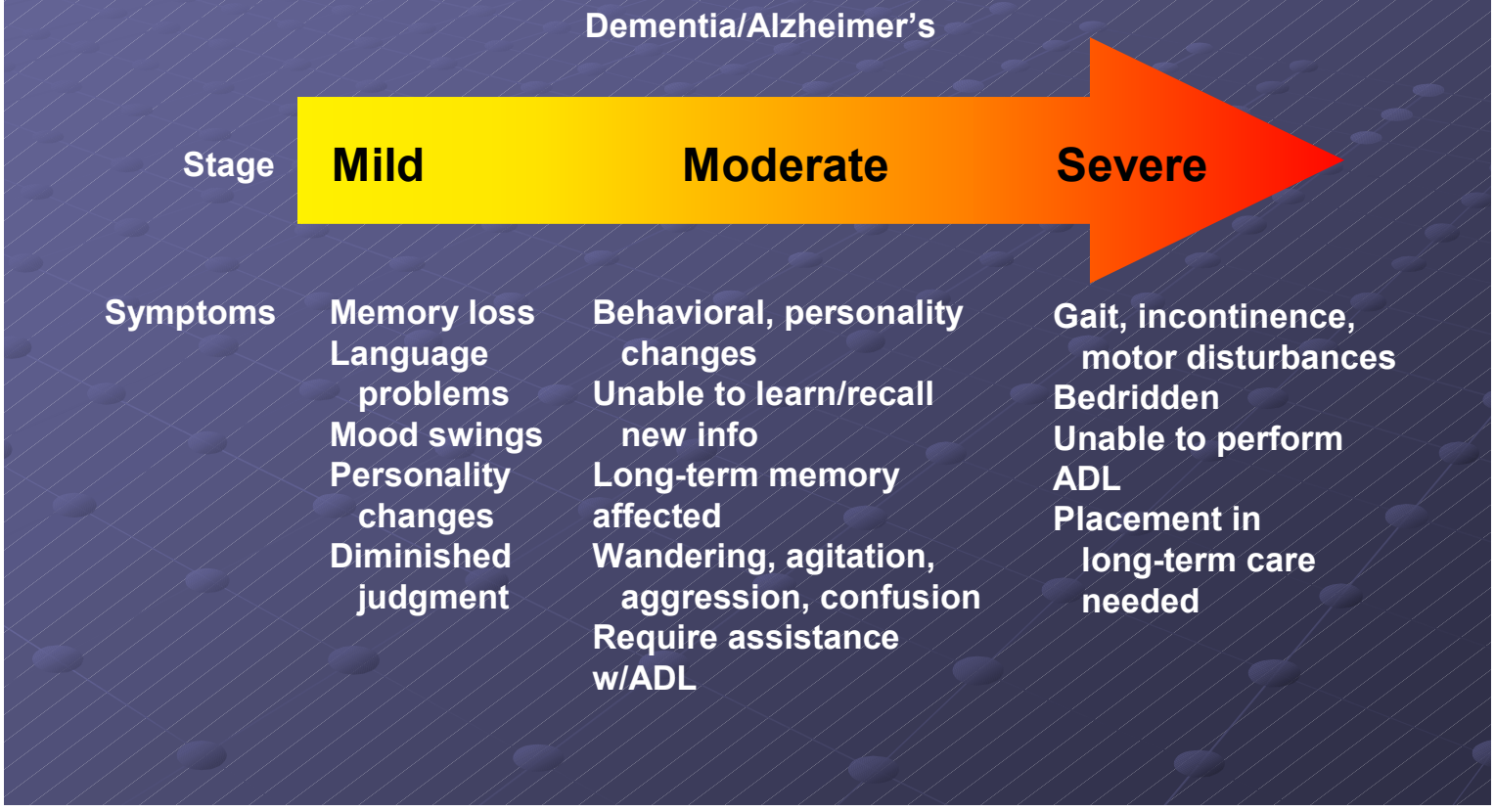
- The commonest cause of dementia.
- The disorder rarely occurs under the age of 45 years.
- The incidence increases with age.
- The cause of AD is not known for sure
- Up to 30% of cases are familial (the loci were found on chromosome 21 and 19).
- Pathology – the presence of senile plaques and neurofibrillary tangles in the brain.
- Diagnosis of AD may be established during life by early memory failure, slow progression and exclusion of other causes.

Signs & Symptoms:

- Memory loss for recent events
- Progresses into dementia → almost total memory loss
- Inability to converse, loss of language ability
- Affective/personality disturbance (fatuous, hostile)
- Death from opportunistic infections, etc.


The Progress of Alzheimer's Disease
Early diagnosis
Mild-moderate
Severe
Cognitive symptoms
Loss of ADL
Behavioral problems
Nursing home placement
Death
MMSE score
30
25
20
15
10
5
0
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9
Years

Alzheimer's Disease Progresses Through Distinct Stages

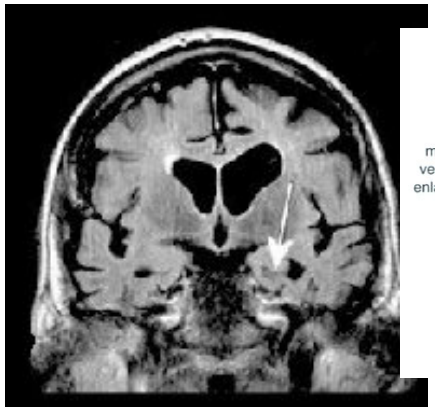


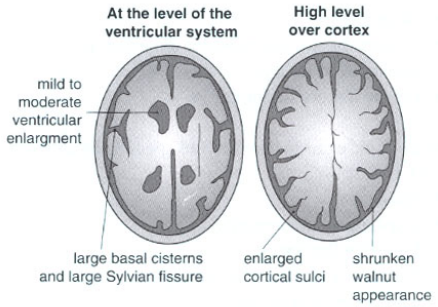
Confirmation of Diagnosis:

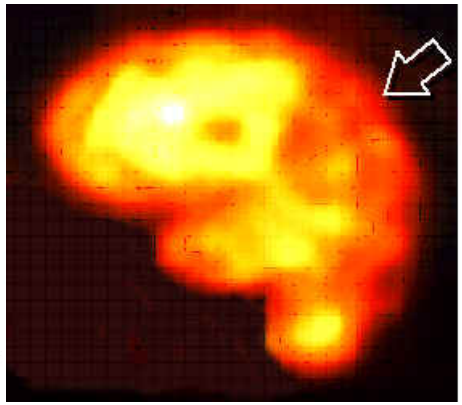
- Neuronal (amyloid, β amyloid, Aβ amyloid) plaques
- Neurofibrillary tangles
- Brain Atrophy

Alzheimer's disease

- **CT scanning** aids diagnosis by excluding multiple infarction or a mass lesion.
- **MRI** shows bilateral temporal lobe atrophy.
- **SPECT** usually shows temporoparietal hypoperfusion.







Stages of Alzheimer's Disease 1

Mild

Primary early symptom is forgetfulness
- names/words
- addresses
- shopping items

Main deficit is in recent memory

Intellectual deficits confirmed by neuropsychological testing

Some awareness of their symptoms, so the person may become anxious, depressed and may be in denial

No distinguishing features on physical examination

Stages of Alzheimer's Disease 2

Moderate

Significant memory loss – close family members / well known routes/places

Personality and behavioural changes

Self-neglect

Disorientation in time and space

Inability to undertake simple tasks i.e. dressing

Reduced range of thinking
(intellectual deficits)

Language problems start

Disinhibition

Stages of Alzheimer's Disease 3

Severe

Dysphasia with disordered and fragmented speech

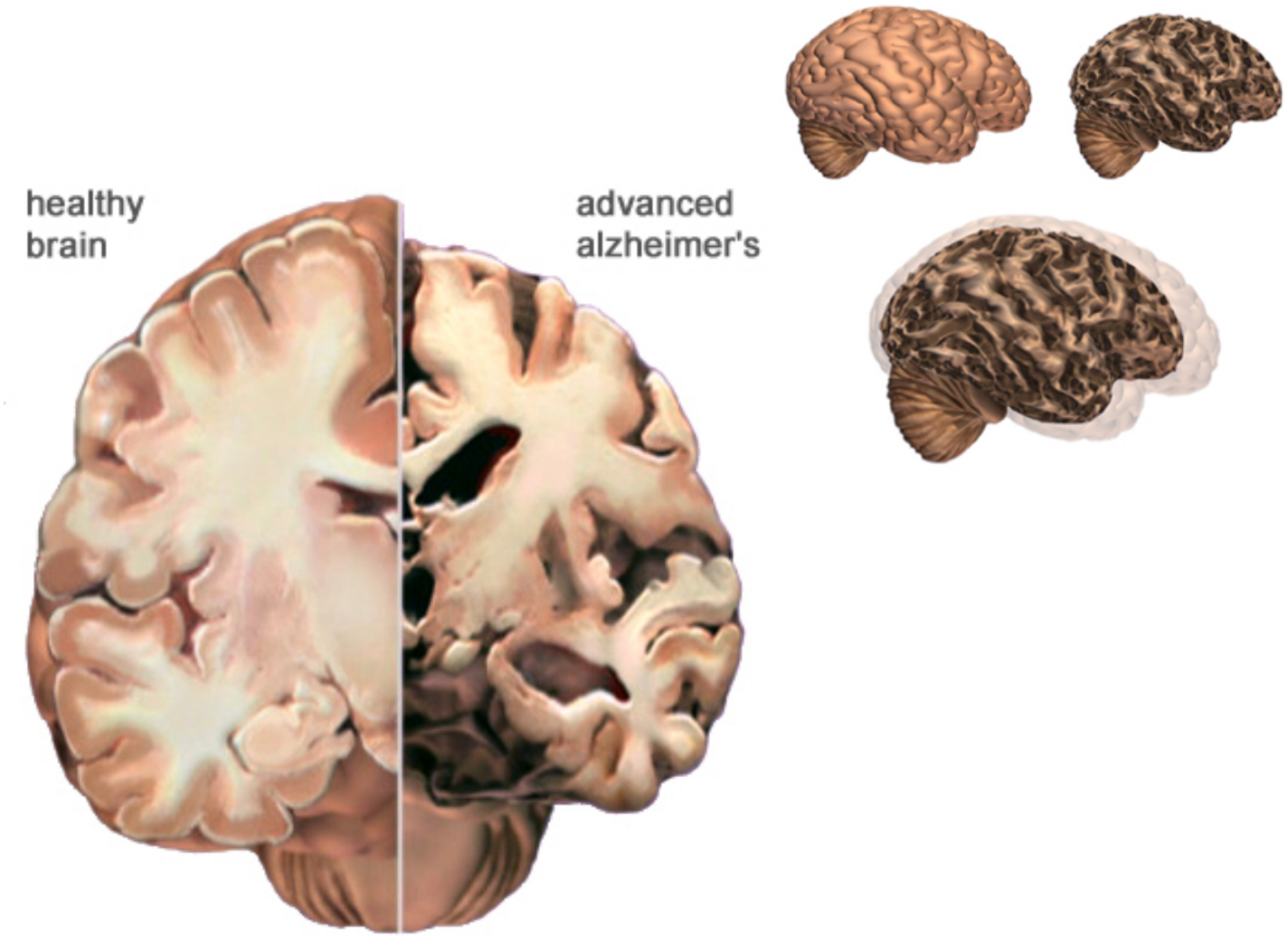
Aggression, restlessness and wandering

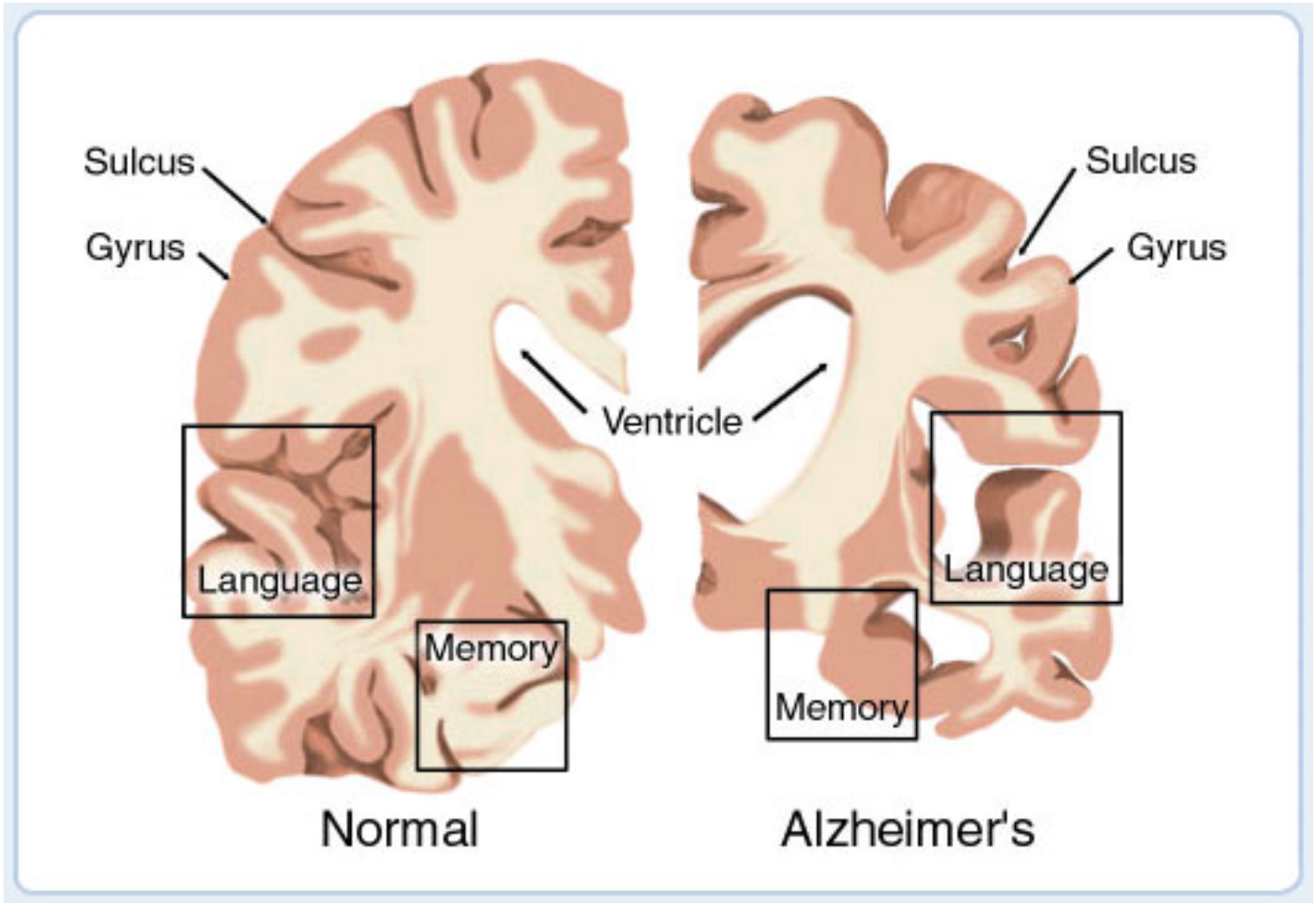
Hallucinations and delusions

Incontinence

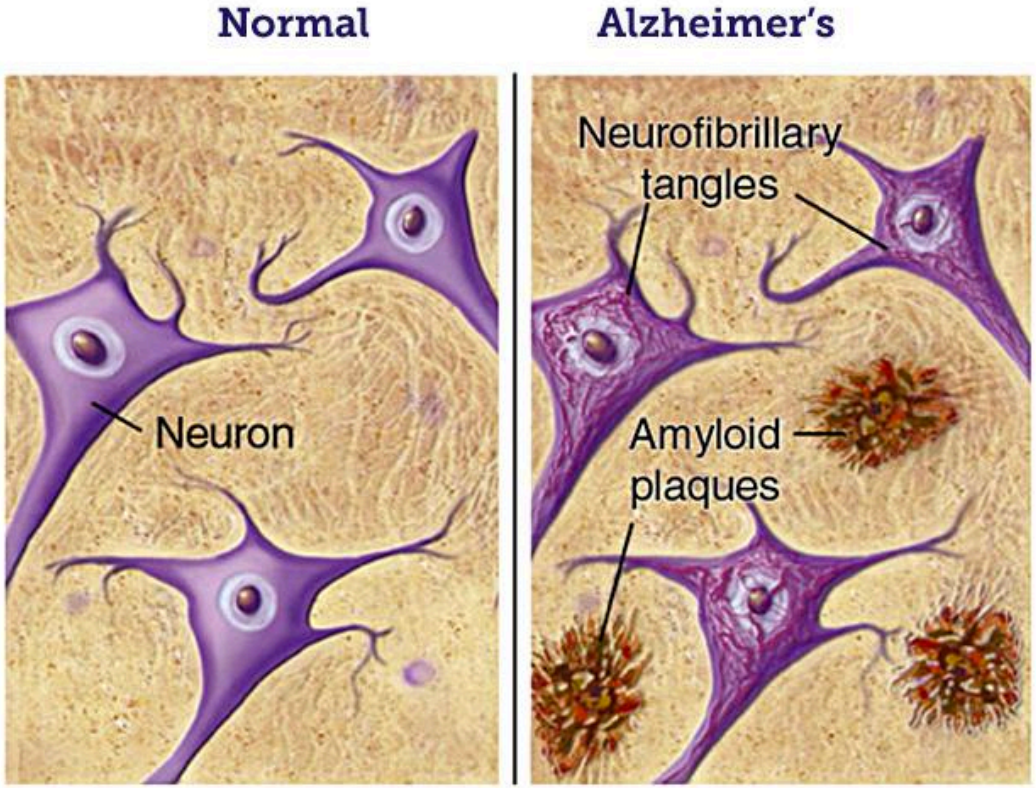
Immobility, rigidity and recurrent falls

General physical deterioration


healthy
brain
advanced
alzheimer's

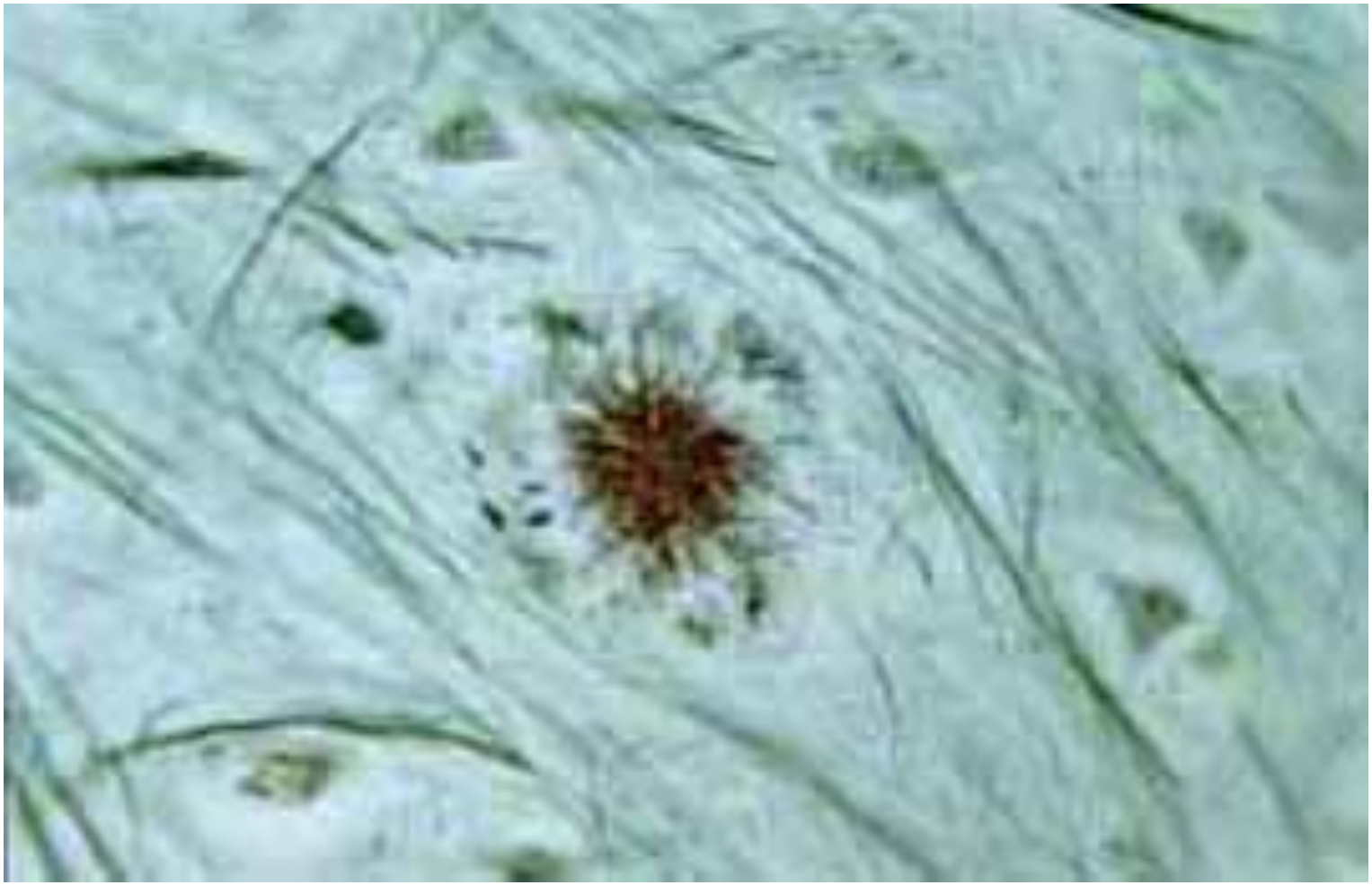

Sulcus
Gyrus
Ventricle
Language
Memory
Sulcus
Gyrus
Language
Memory
Normal
Alzheimer's

Normal vs. Alzheimer's Diseased Brain

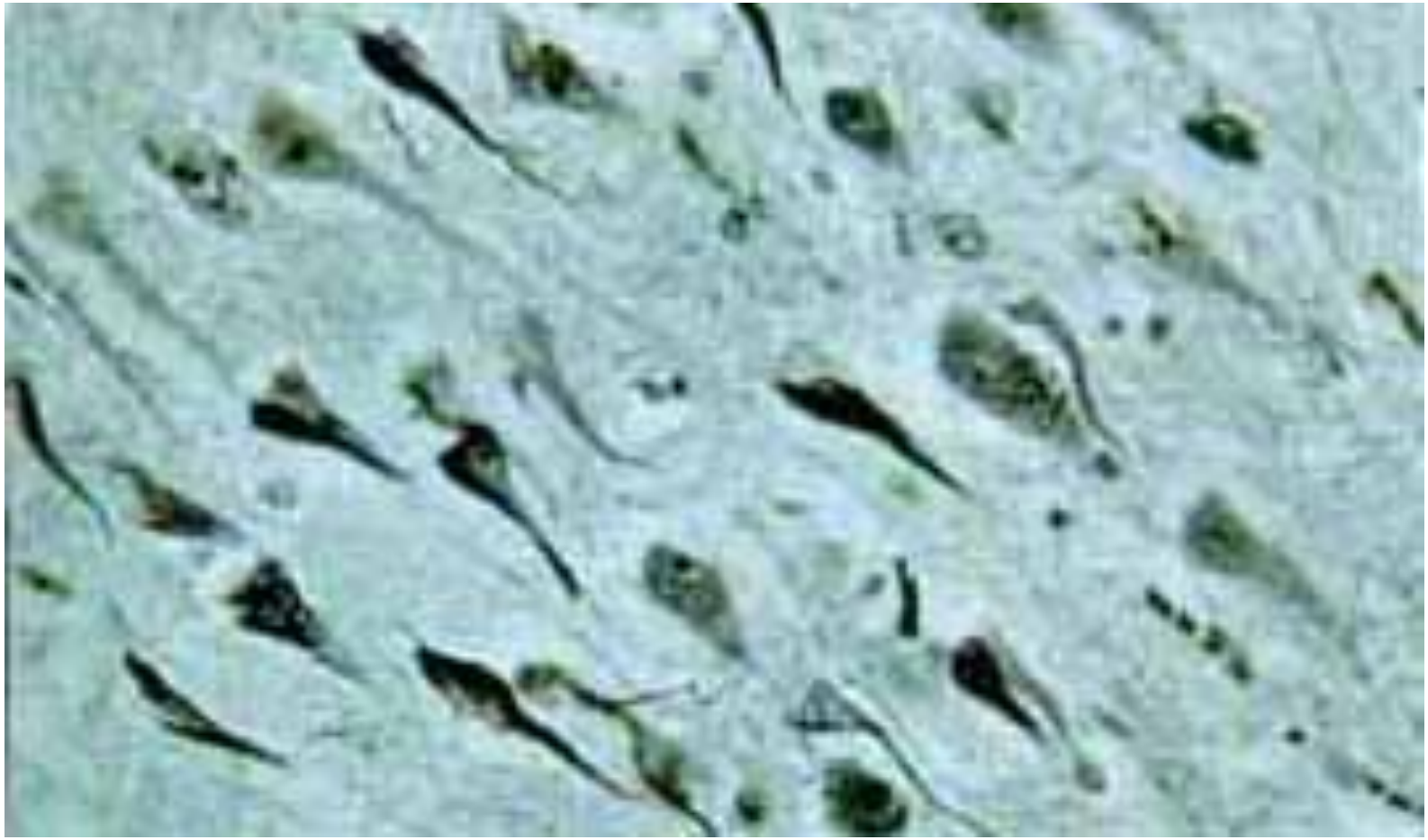


BrightFocus® Foundation
Cure in Mind. Cure in Sight.

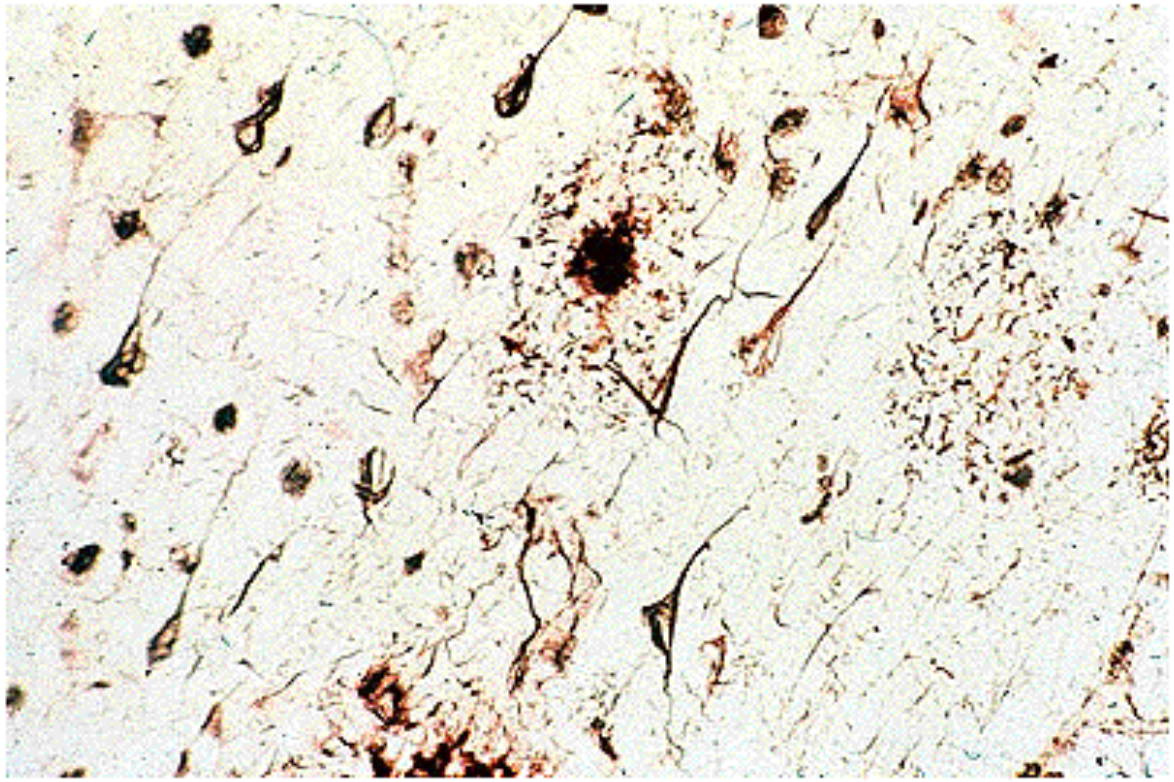
Neuronal Plaques in Alzheimer's Disease

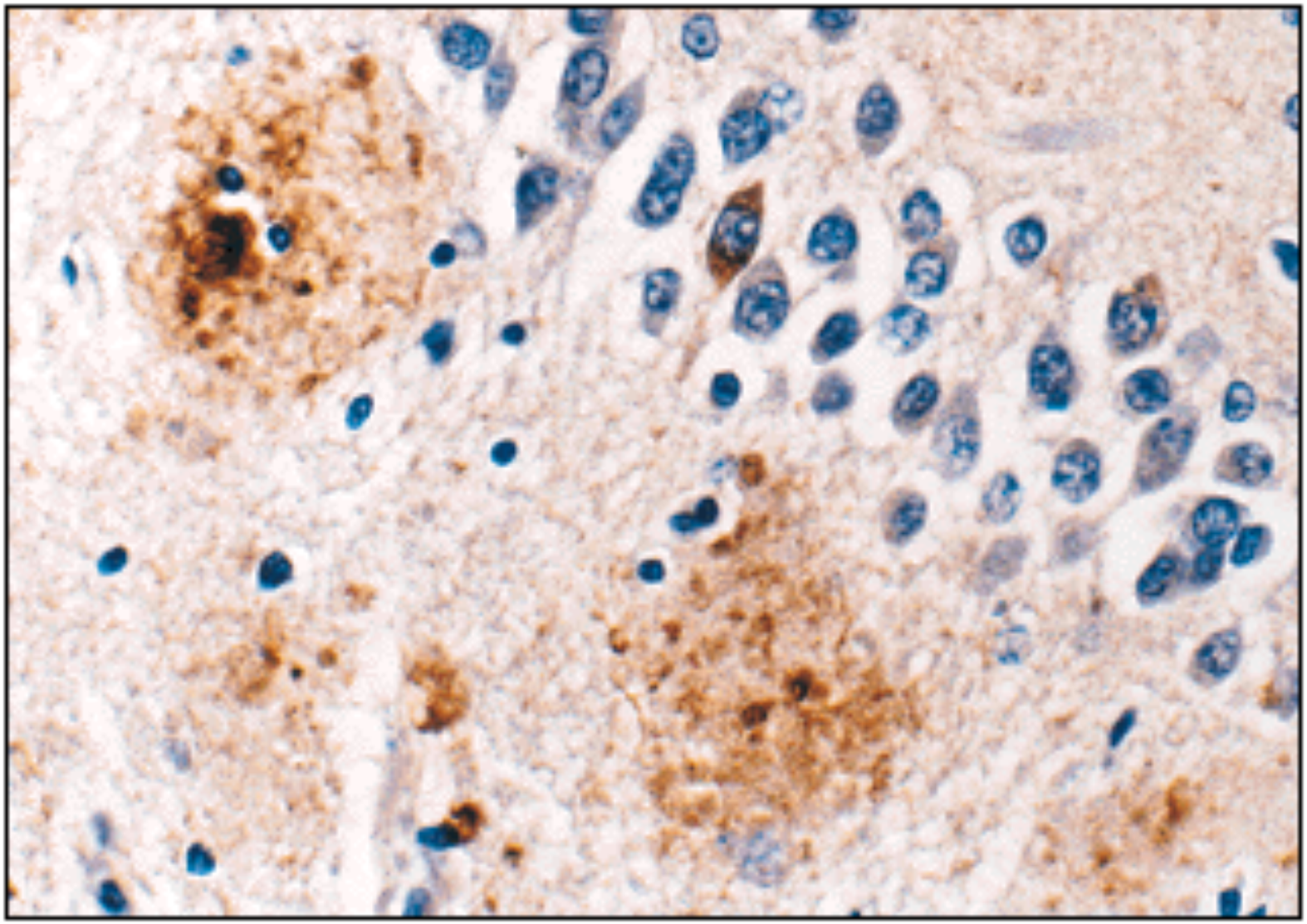


Neurofibrillary Tangles in Alzheimer's Disease



Plaques and neurofibrillary tangles





Alzheimer's Disease, Type 1:

- Several mutations in APP gene on chromosome 21
- Most common = Val717Iso
- Produce abnormal beta amyloid fragment
- 15%-20% of early onset, familial AD
- Autosomal dominant

Alzheimer's Disease, Type 2:

- Epsilon 4 (ε4, AKA E4) allele of the Apolipoprotein E (ApoE) gene on chromosome 19 confers risk

- Epsilon 2 (ε2, AKA E2) allele of the Apolipoprotein E gene on chromosome 19 confers protection

- Mechanism unclear; ApoE is a very low density lipoprotein that transports cholesterol

- Most cases are late onset, familial

- Susceptibility Locus

Alzheimer's Disease, Type 3:

- Mutations (> 130) in the presenilin1 gene on chromosome 14
- Most mutations lead to amino acid substitution
- Overproduction of the beta amyloid fragment
- 30% - 70% of early onset, familial AD
- Autosomal dominant

Alzheimer's Disease, Type 4:

- Mutations in the presenilin2 gene on chromosome 1
- 2 alleles: Asn141Iso and Met239Val
- Overproduction of the beta amyloid fragment
- < 5% of early onset, familial AD (only a few families world wide)
- Autosomal dominant

What causes AD?

Two Major Hypotheses for AD:

β amyloid protein (BAP) v. tau

1. **BAPtists: The accumulation of a fragment of the amyloid precursor protein or APP (the amyloid beta 42 residue fragment or Ab-42) leads to the formation of plaques that someone kill neurons.**

2. **TAUists: Abnormal phosphorylation of tau proteins makes them "sticky," leading to the break up of microtubules. The resulting loss of axonal transport causes cell death.**

Amyloid Hypothesis

(it's the plaques)

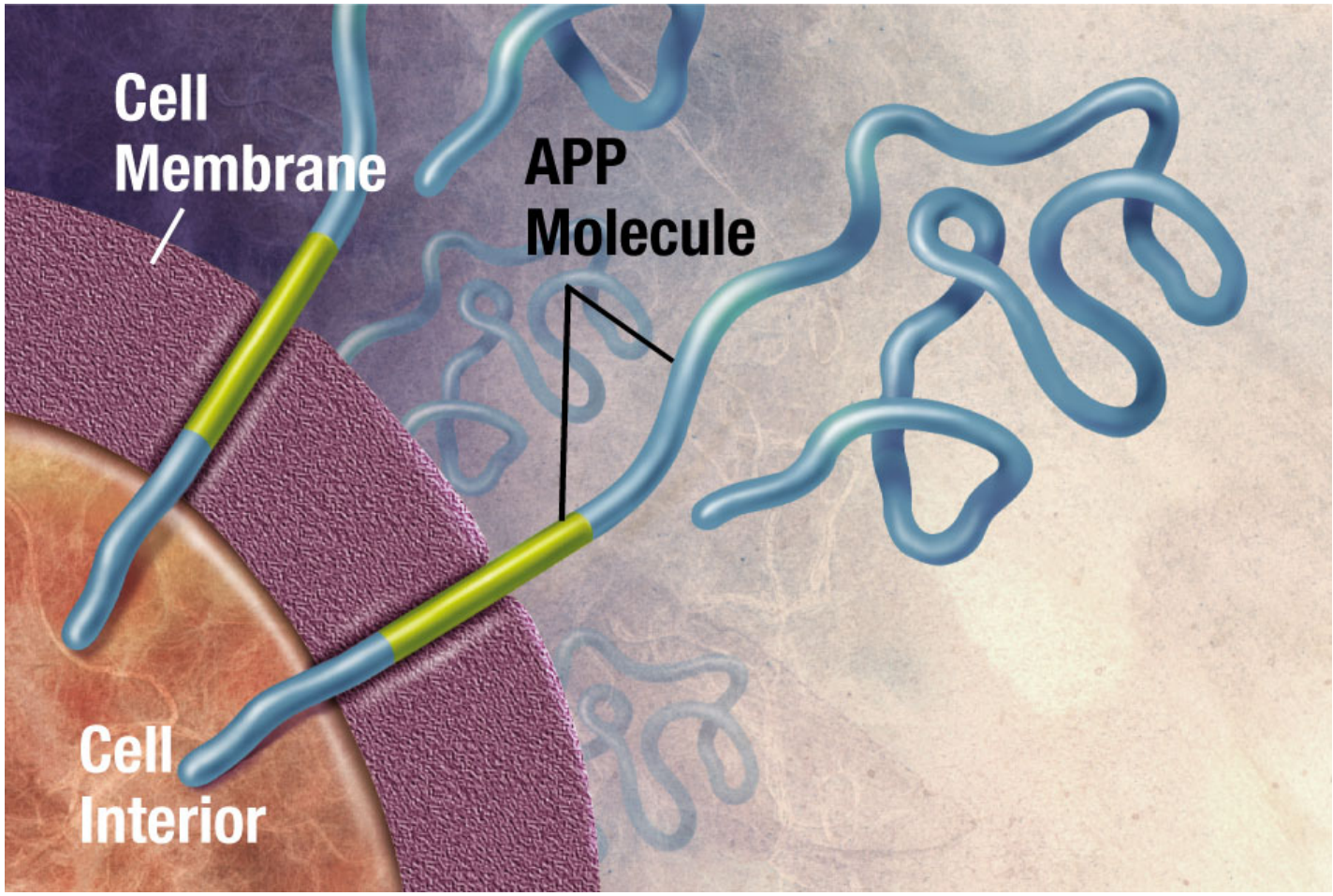
1. The amyloid precursor protein (APP) is broken down by a series of secretases (see next two slides).

2. During this process, a nonsoluble fragment of the APP protein (called Aβ-42) accumulates and is deposited outside the cell.

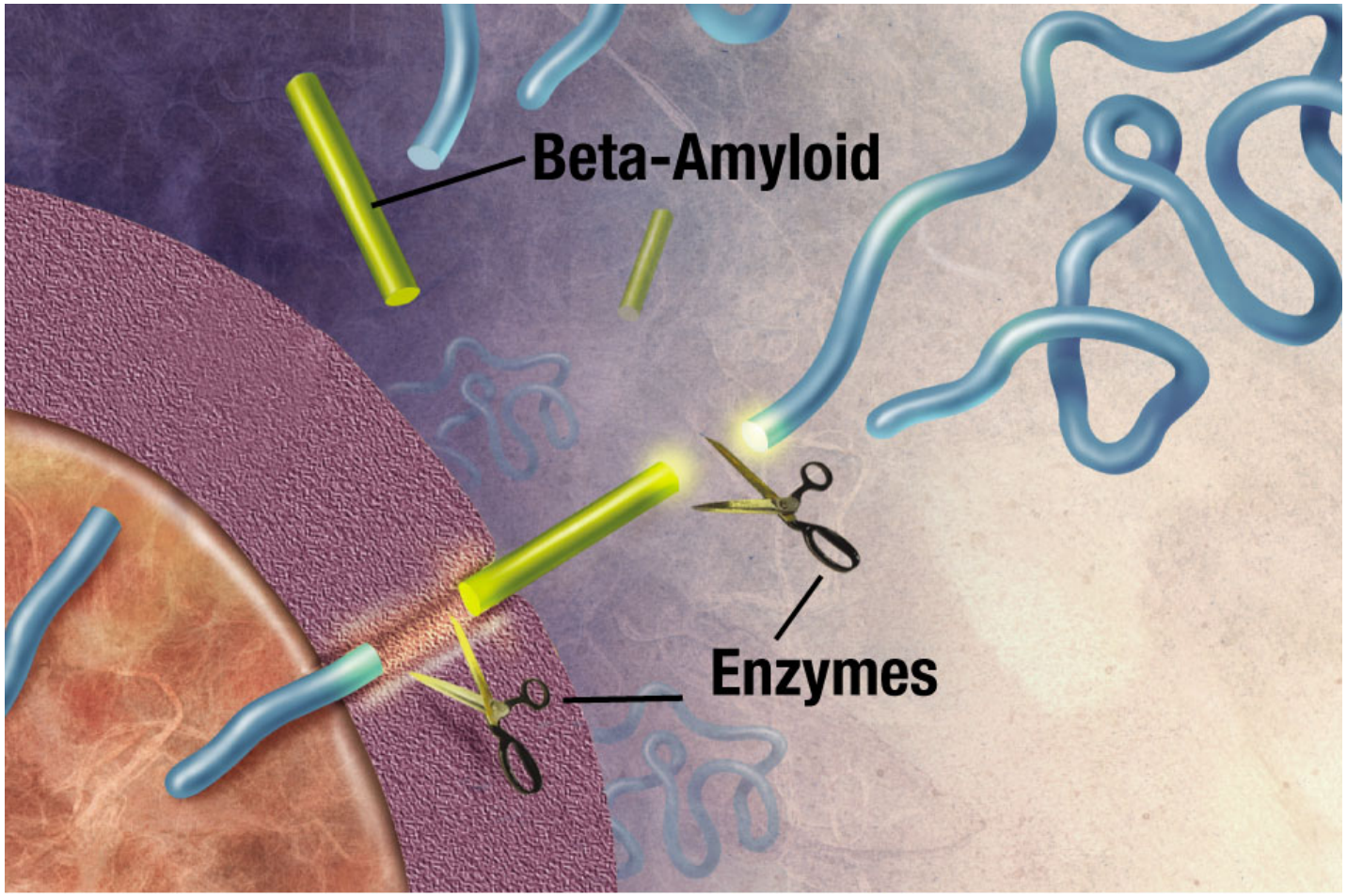
3. The nonsoluble or "sticky" nature of Aβ-42 helps other protein fragments (including apoE) to gather into plaques.

4. Somehow the plaques (or possible the migration of Aβ-42 outside the cell) cause neuronal death.

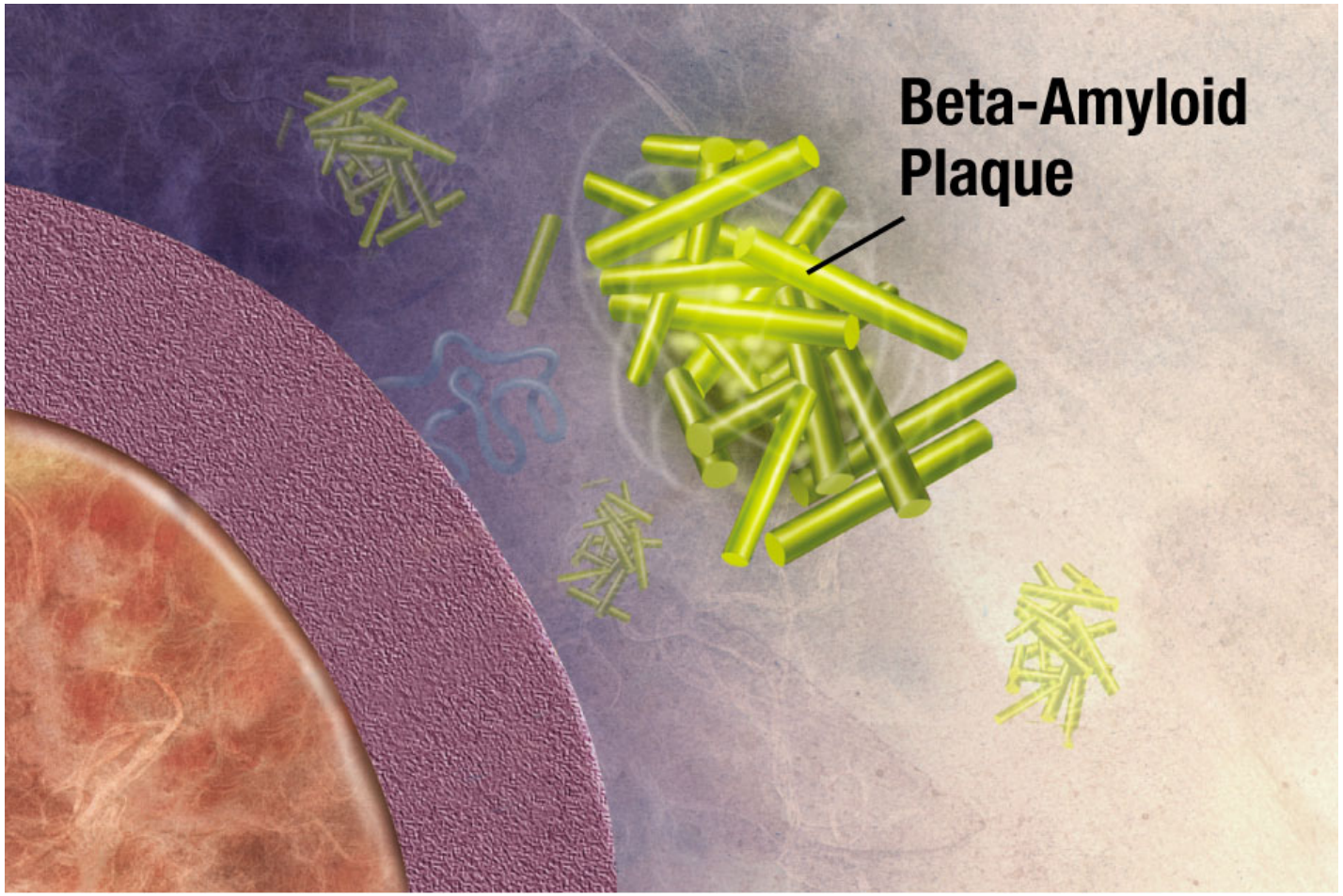
5. May be due to PSEN1 & PSEN2 genes



Amyloid precursor protein (APP) is membrane protein that sits in the membrane and extends outward. It is though to be important for neuronal growth, survival, and repair.



Enzymes cut the APP into fragments, the most important of which for AD is called β-amyloid (beta-amyloid) or Aβ.



Beta-amyloid is “sticky” so the fragments cling together along with other material outside of the cell, forming the plaques seen in the AD brain.

Tau Hypothesis

(it's the tangles)

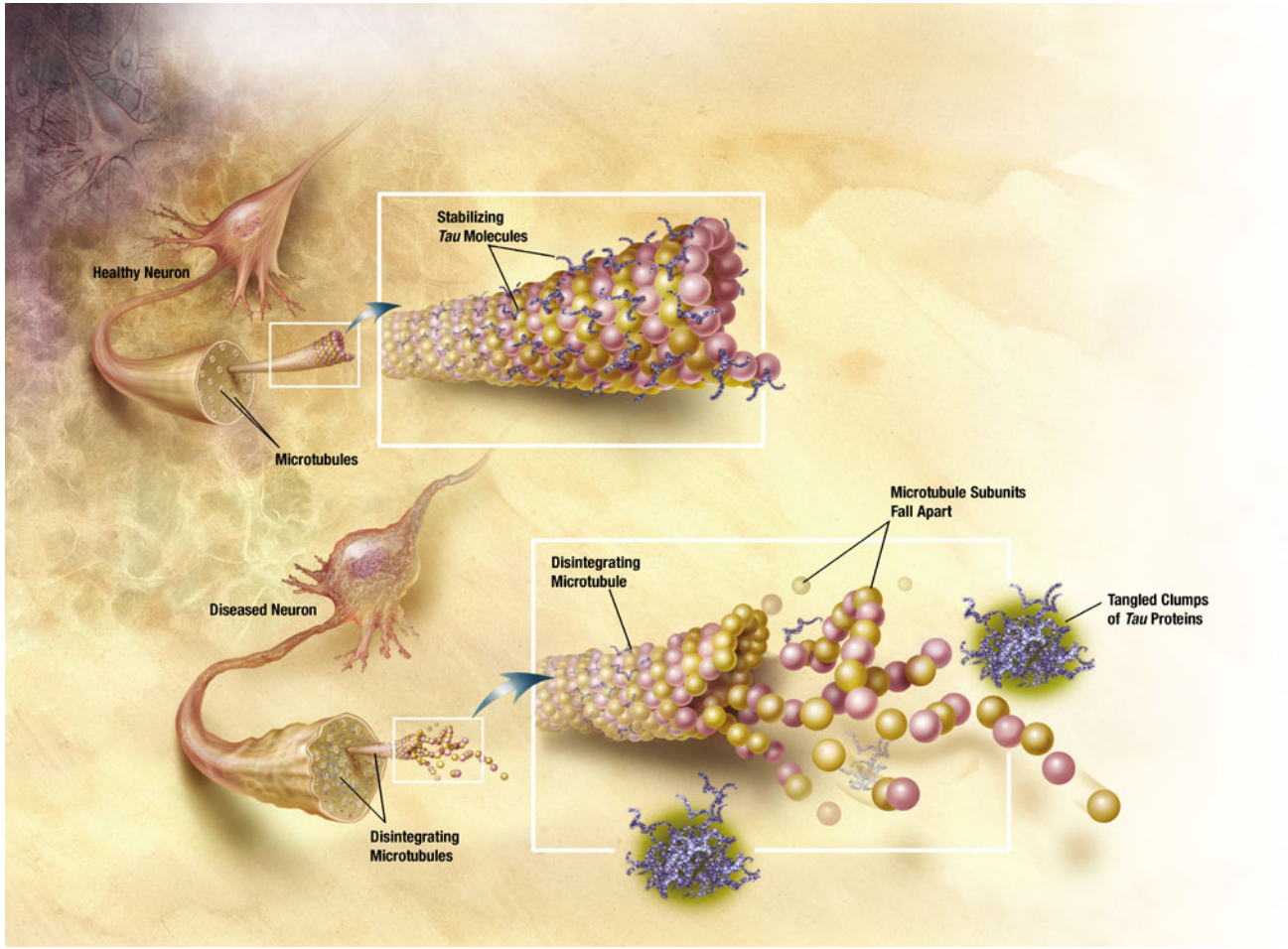
1. Ordinarily, the τ (tau) protein is a microtubule-associated protein that acts as a three-dimensional "railroad tie" for the microtubule. The microtubule is responsible for axonal transport.

2. Accumulation of phosphate on the tau proteins cause "paired helical filaments" or PHFs (like two ropes twisted around each other) that accumulate and lead to the neurofibrillary tangles (NFT). PHFs are the main component in NFTs.

3. Impaired axonal transport is the probable cause of cell death.

4. Focus on MAPT gene (microtubule-associated protein tau)

5. Not as supported as the other hypothesis



Microtubules are like railroad tracks that transport nutrition and other molecules. Tau-proteins act as "ties" that stabilize the structure of the microtubules. In AD, tau proteins become tangled, unstabilizing the structure of the microtubule. Loss of axonal transport results in cell death.

Current theory: Multifactorial, involving several pathways.

- Protein accumulation: → plaques & tangles
- Inflammation: Unregulated activation of glia
- Lipid distribution: Lipid membrane site of APP cleavage.

Current gene candidates for AD:

- Changes too rapidly to keep track of.
- Go to http://Alzgene.org for latest list

Neuroeconomics Lab
University of Victoria
Francisco Colino
Cameron Hassall
Tom Ferguson
Chad Williams
Harvey Howse
AJ Pluta
Angela Norton
Rob McCulloch
Steffanie Fisher
Stephen Luehr
Rob Trska
Jordan Middleton
Taryn Berman
and
Many Undergraduates

Medical Sciences
University of Victoria
Bruce Wright
Ali Walzak
Paul Zehr

Psychology
University of Victoria
Clay Holroyd
Jim Tanaka
Mike Masson

UBC
Gord Binsted
Todd Handy

Dalhousie University
Aaron Newman
Ray Klein
John Christie

University of Calgary
Kent Hecker
Heather Jamniczky
Filomeno Cortese
Sarah Andersen
Pam Hruska

University of Alberta
Kyle Mathewson

Western Ontario
Matt Heath

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Thank you!