Neural structure and function: "How the brain works"

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Understanding normal function

- How does the nervous system work?
- How does the nervous system support movement, perception, action, cognition, emotion, behaviour?
- How does the nervous system develop during childhood?
- How does the nervous system develop/decline during adulthood?

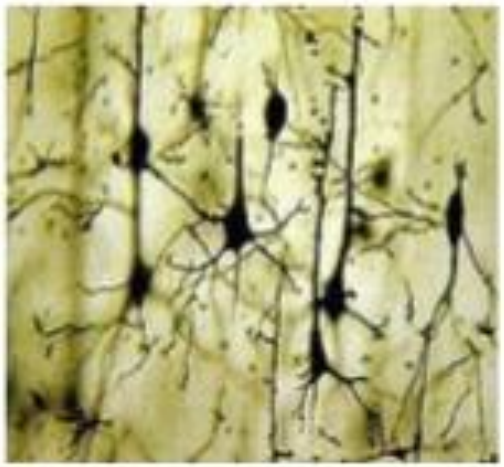
Understanding impaired function

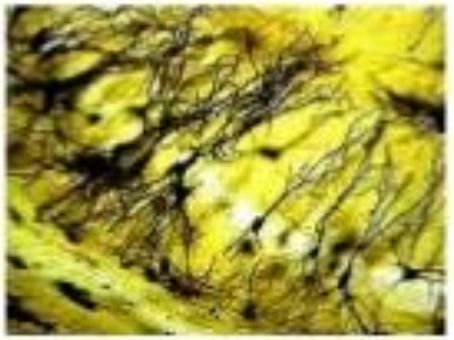
- Effects of traumatic brain/spinal injuries (1 million people in the UK living with effects of brain injury)
- Effects of non-traumatic brain injury – eg stroke (1 stroke every 5 minutes in UK)
- Effects of neurological and neurodegenerative illness: MS (127 000 in UK), MND (5000 in UK, 6 deaths per day) , Parkinson's Disease (130 000 in UK) , dementia (850 000 in UK)
  - Economic impact of dementia more than cancer and heart disease combined
- Effects of neurodevelopmental disorders, including ADHD (1.5% children) and ASD (1.1% of population)
- Effects of psychiatric illness/mental health problems
  - ~1 in 4 people in the UK will experience a mental health problem in their life (16 million people)
  - 10% of 5-16 year olds have a mental health problem
  - Huge economic and social impact

Structure and function of neurons

Brain Cells

- 2 types of cells (glial cells and neurons)
- ~100 billion neurons
- 10^{12} cells in total



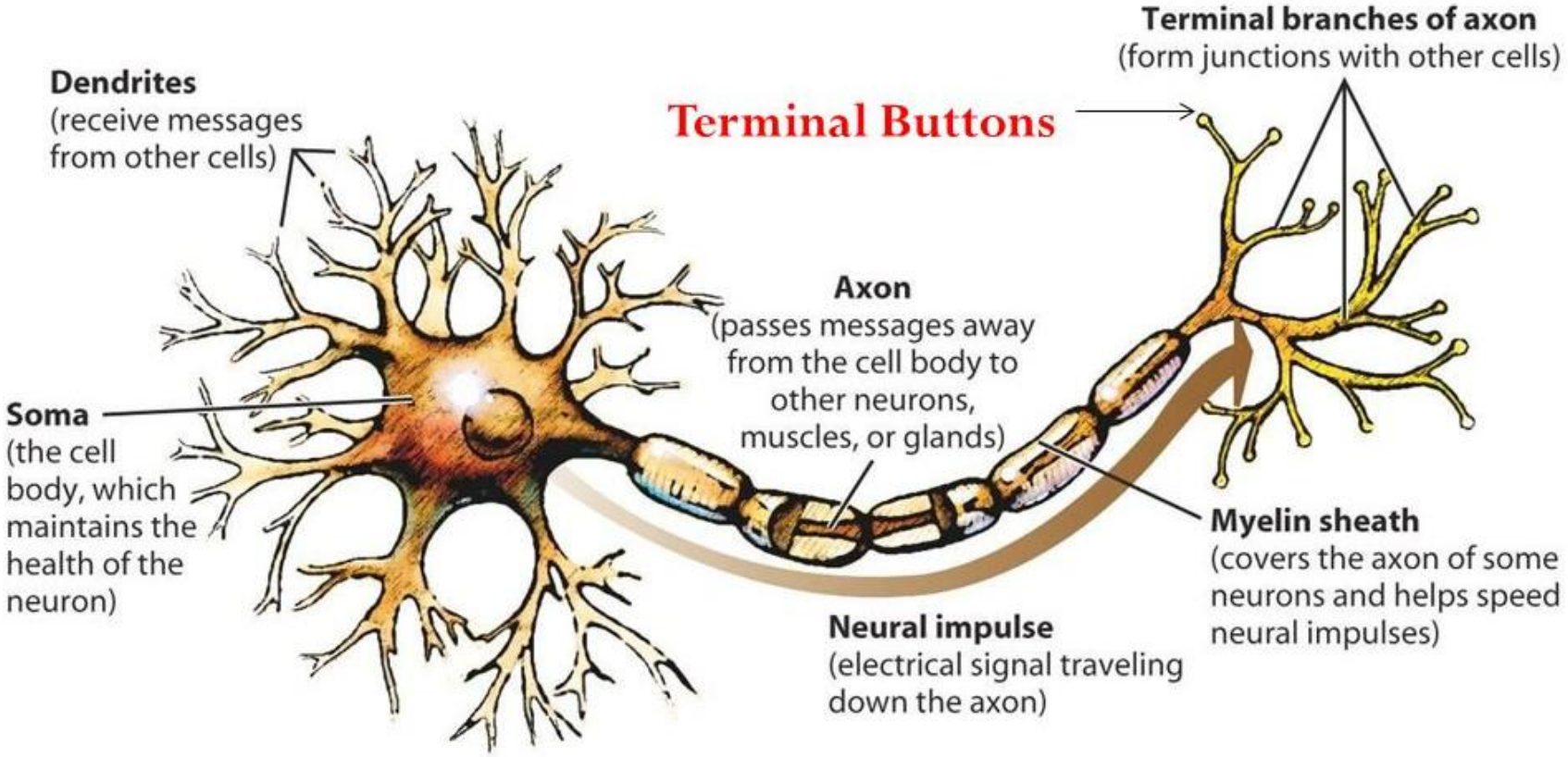


Development

- Neurons formed early in life
- Brain develops during childhood
- Limited regeneration after age 20.

- Glial cells provide structural, metabolic and nutritional support for neurons
- Can replace themselves
- Important in neural development

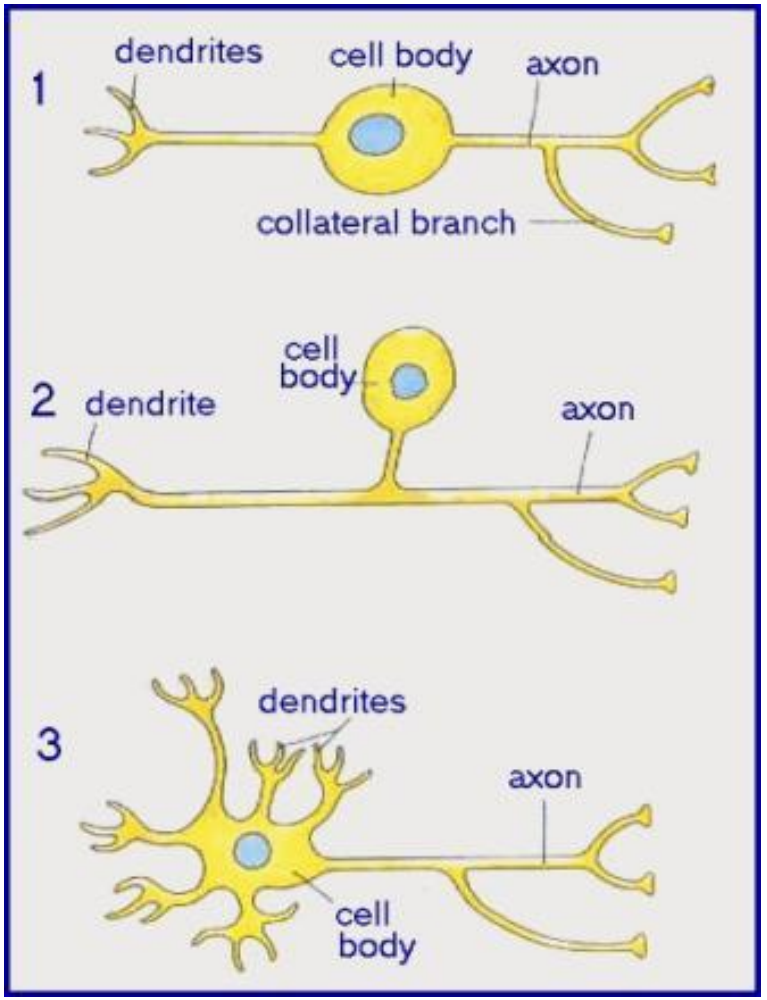
Neurons



Axons can be up to a metre long: longest are in the sciatic nerve

Types of neuron

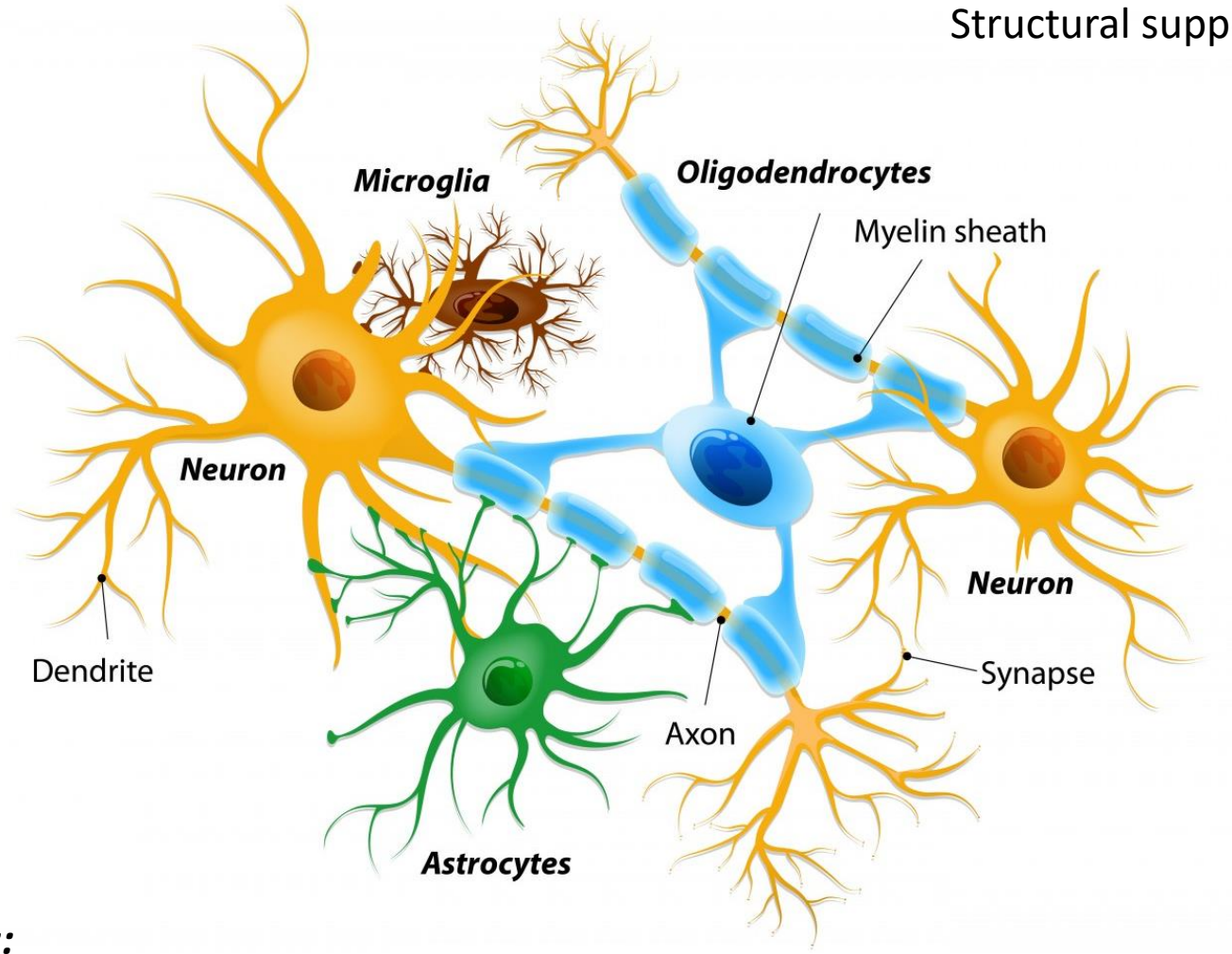
1. Bipolar neuron
2. Monopolar neuron
3. Multipolar neuron



Glial cells

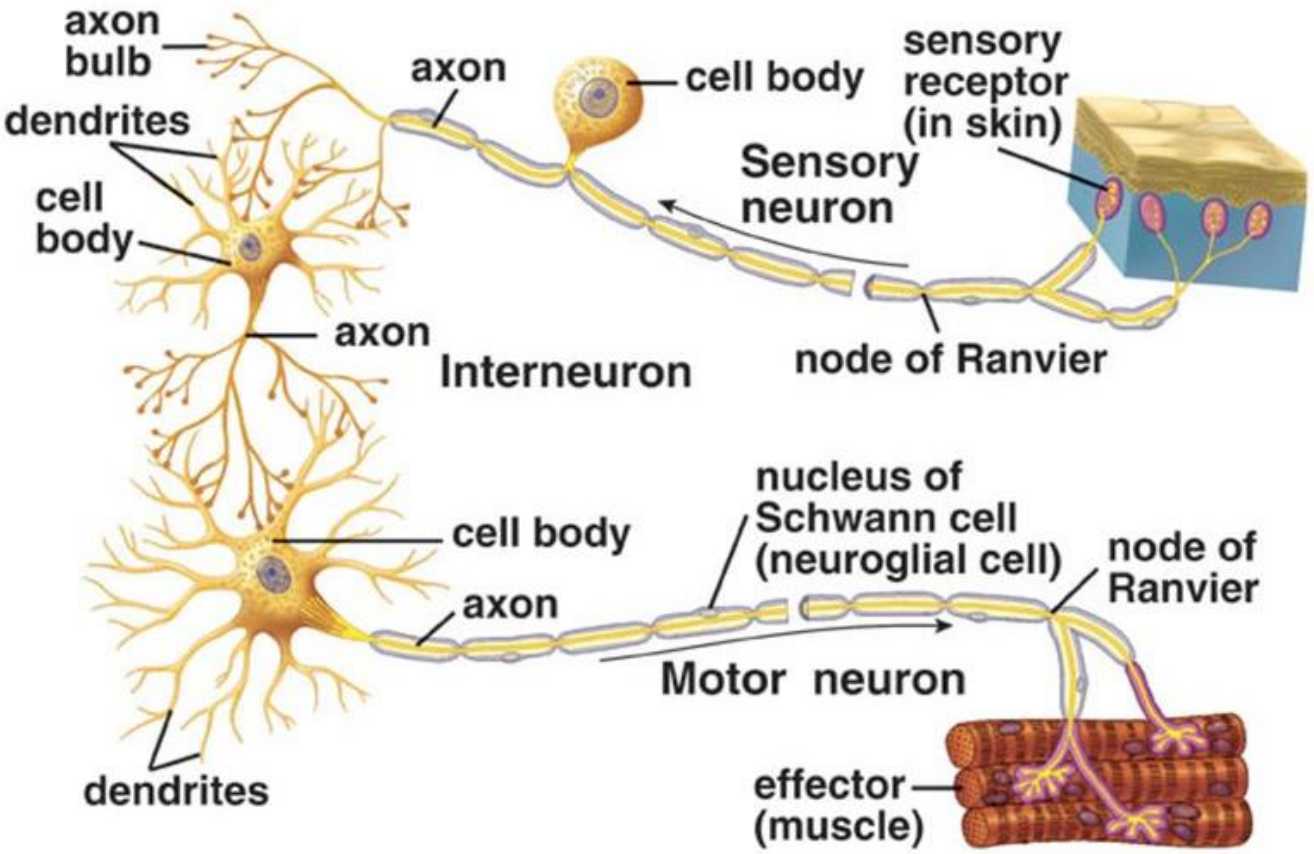
Microglia:
"Scavengers", clean up

Oligodendocytes:
Structural support, myelin



Astrocytes:
Nurtitional and metabolic support

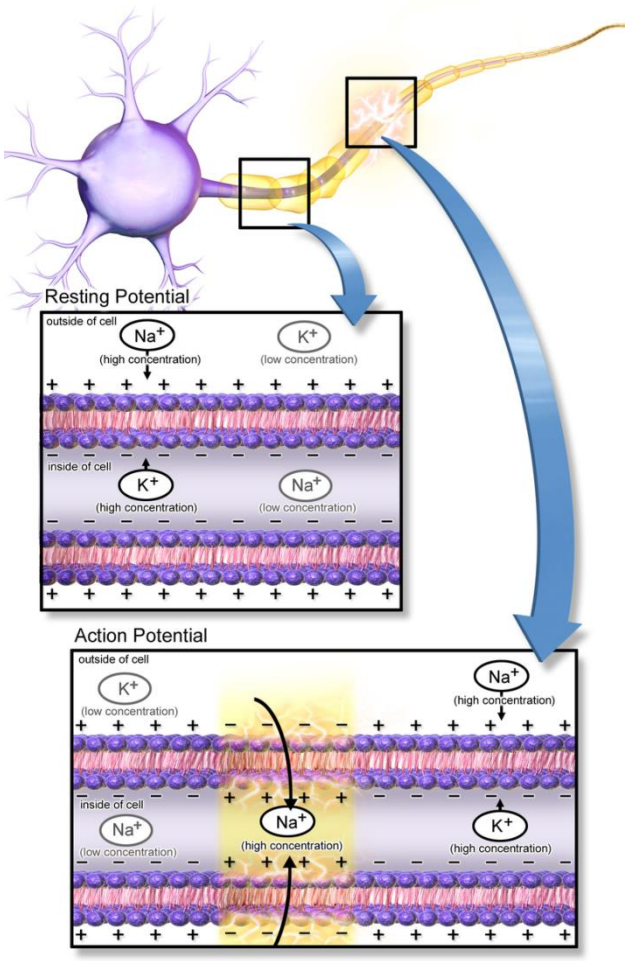
Interconnecting neurons

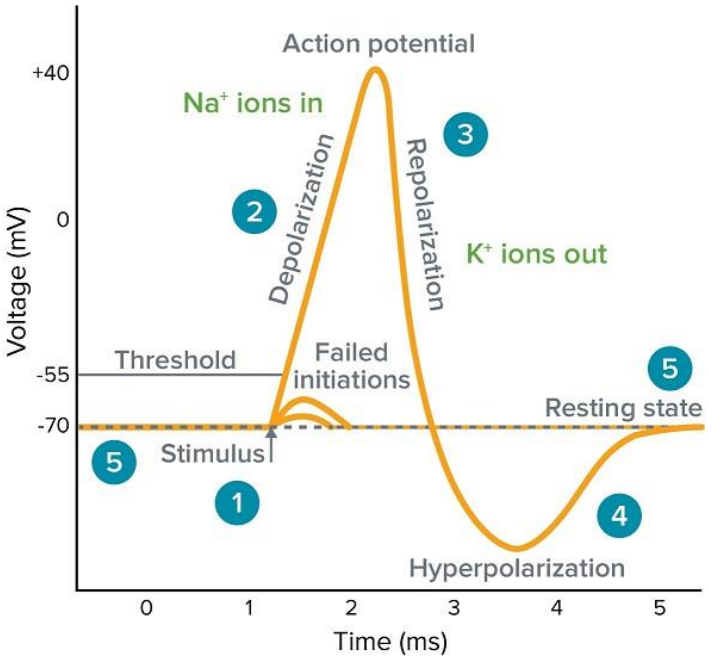


How neurons communicate

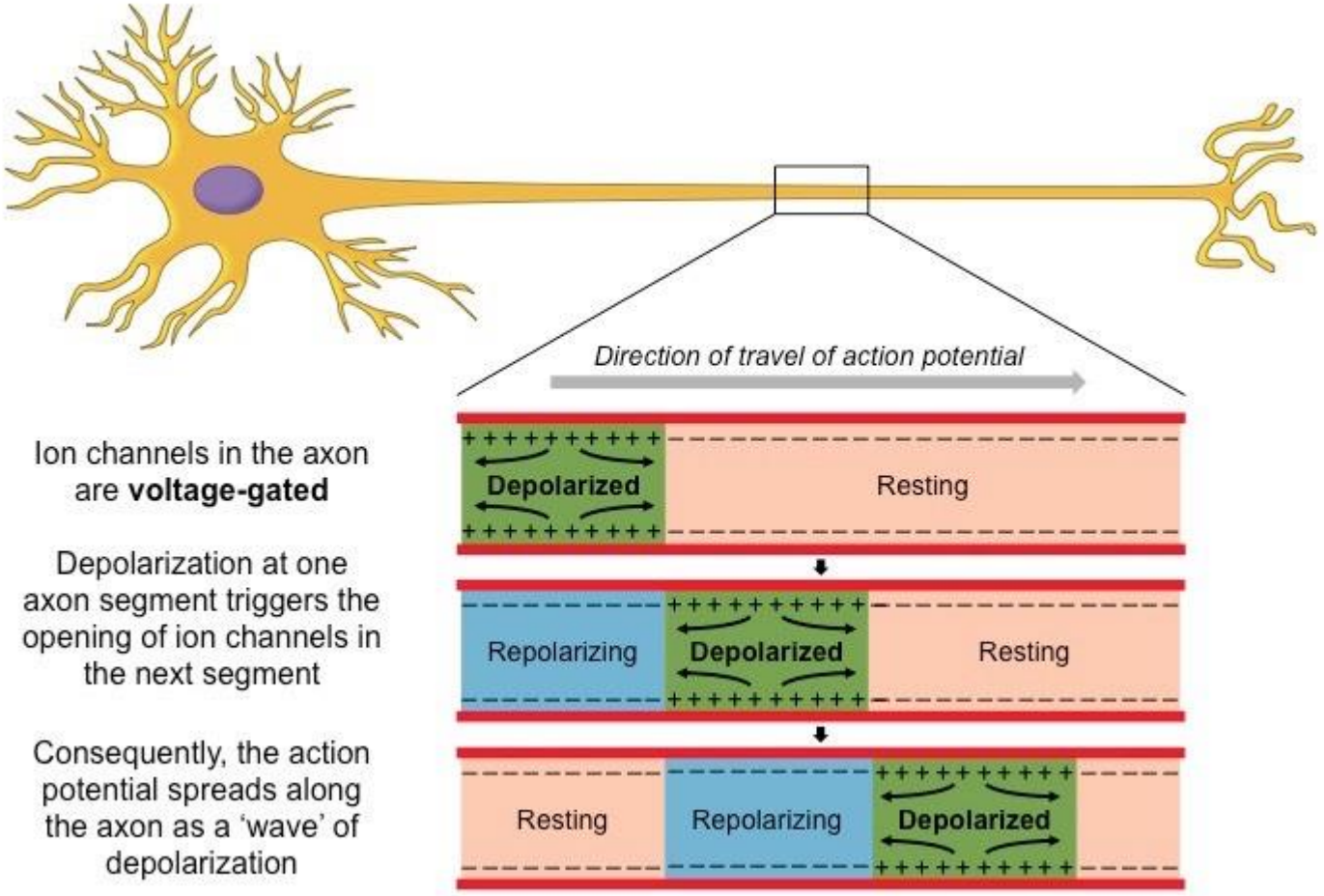
- 1. Electrical signalling (within a neuron)
  - Travels from the dendrite through the cell body to the axon
- 2. Chemical signalling (between neurons)
  - Sent from the axon of one neuron to the dendrite of another

Action potential





Propagation



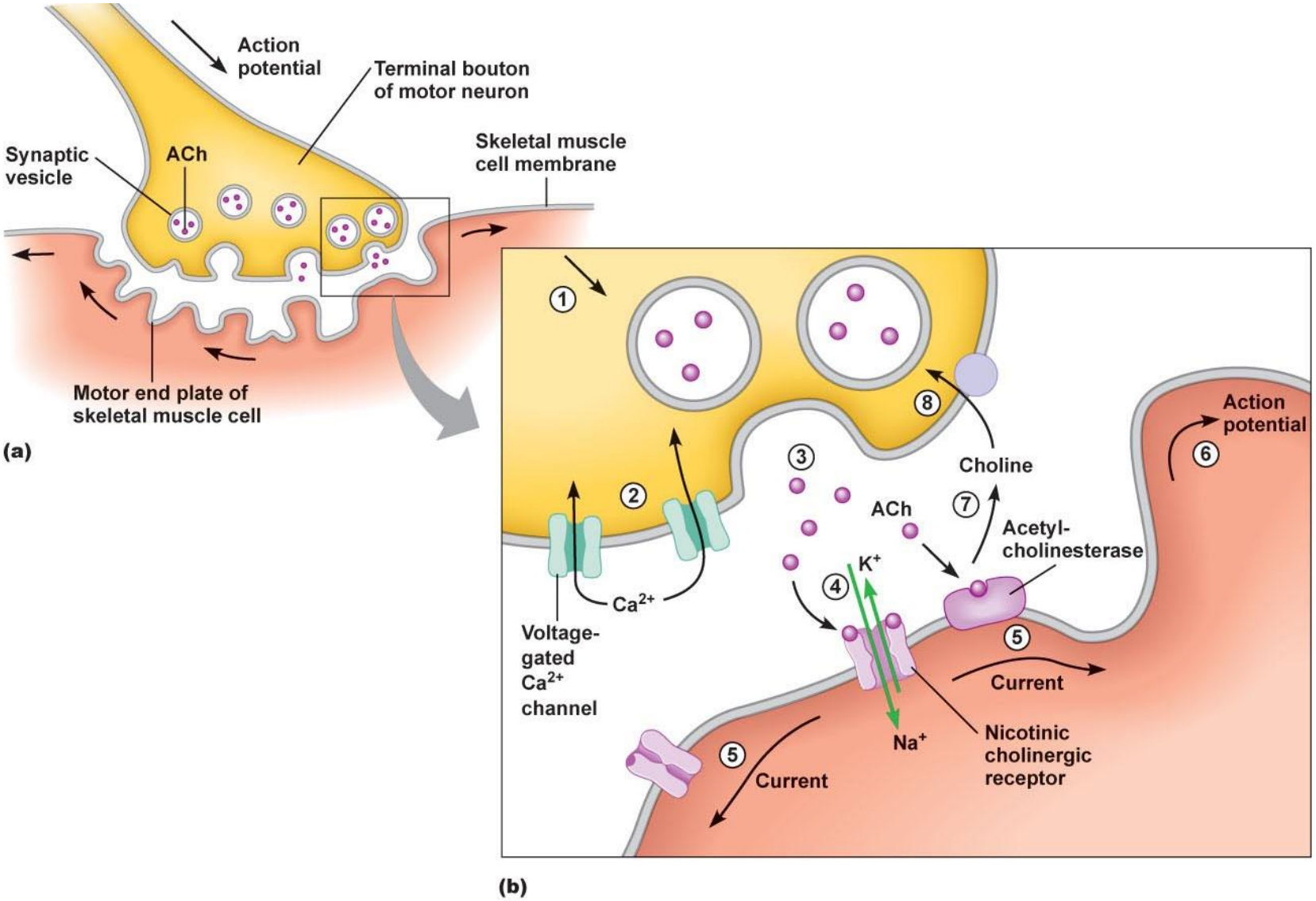
Ion channels in the axon are **voltage-gated**

Depolarization at one axon segment triggers the opening of ion channels in the next segment

Consequently, the action potential spreads along the axon as a 'wave' of depolarization

Up to 120 m/s

Between neurons: The Synapse



How do things go wrong:

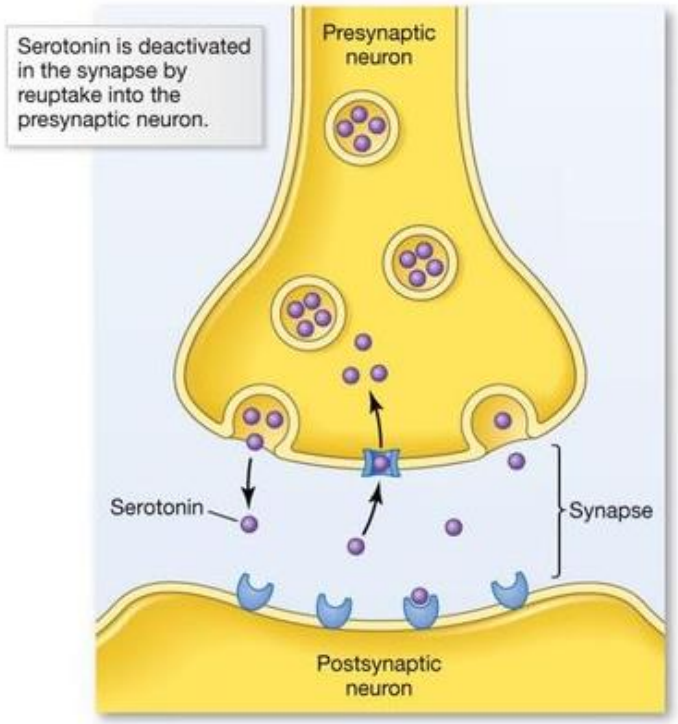
- Dementia: neuronal loss
- MS: demyelination which affects signalling along axons
- Parkinson's disease: loss of neurotransmitter, dopamine
- Schizophrenia: excess dopamine

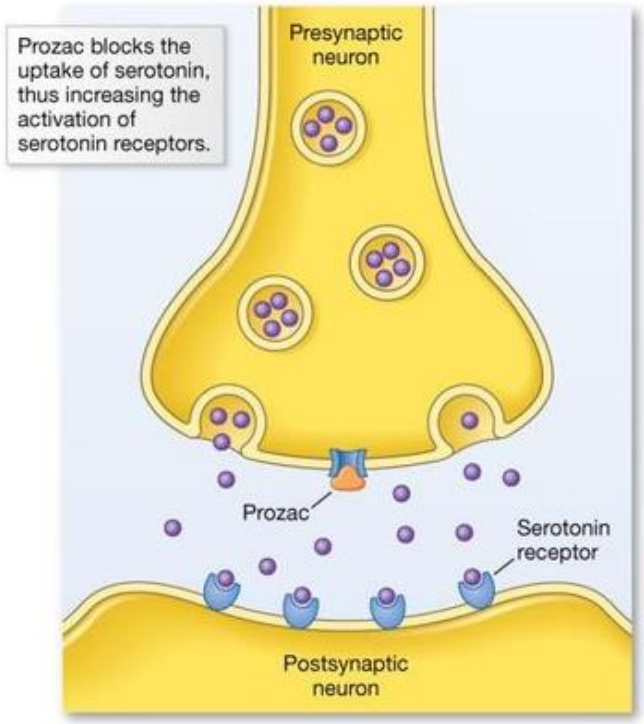
NB: these are gross oversimplifications!

Treatments

Preventing/reversing neuronal loss is the holy grail…..

Psychoactive drugs:

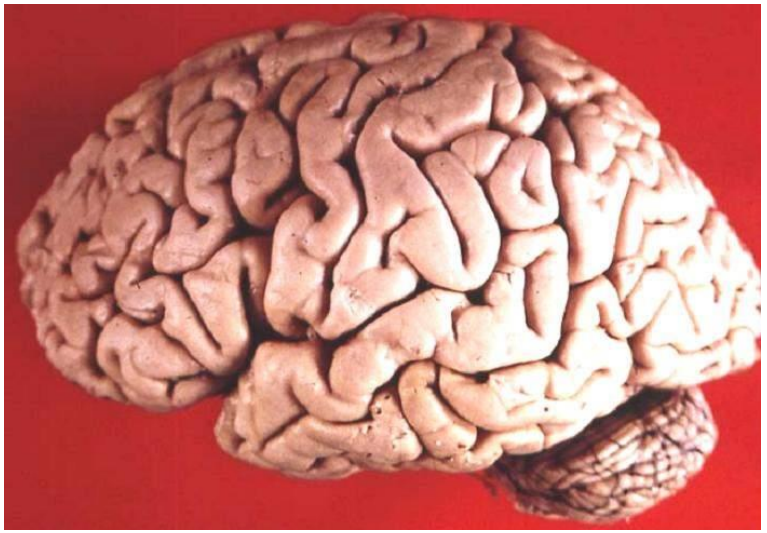




Structure and function of the brain

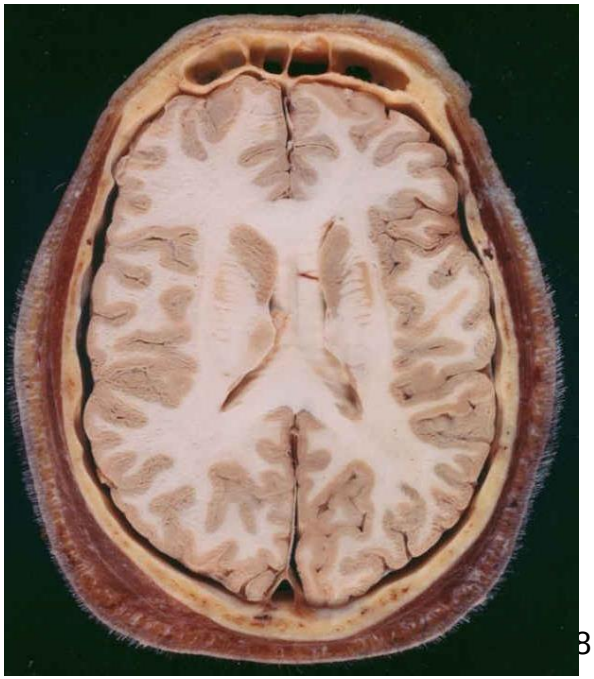
The Brain

- 1400g (~2% body weight)
- Cerebral hemispheres



- Convolutions = folding= gyri (gyrus)
- Separated from each other by sulci (sulcus)

- White matter – fiber tracts
- Grey matter – cell bodies and dendrites (lack myelin)



- ***What do different bits do??***

I. "Old Brain"

A. Brain Stem

1. Medulla
2. Pons
3. Reticular Formation

B. Thalamus

C. Cerebellum

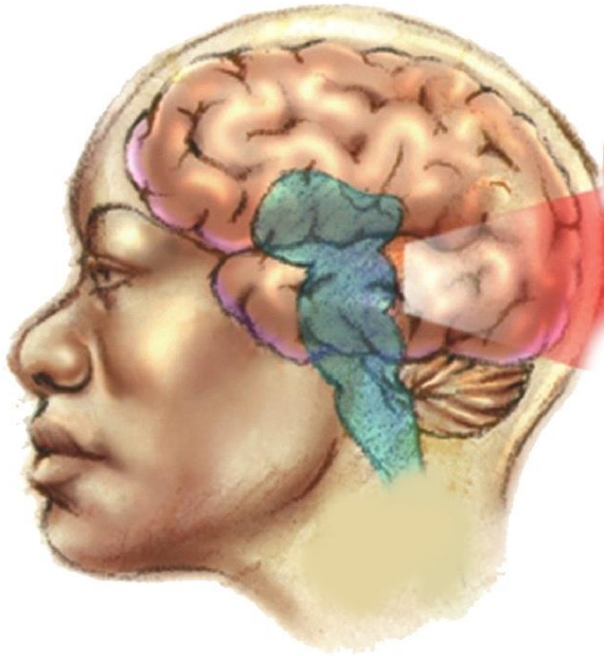
D. Limbic System

1. Amygdala
2. Hypothalamus
3. Hippocampus

I. Older Brain Structures

A. Brainstem:

Oldest part of the brain.
Base of spinal cord
Automatic survival functions.



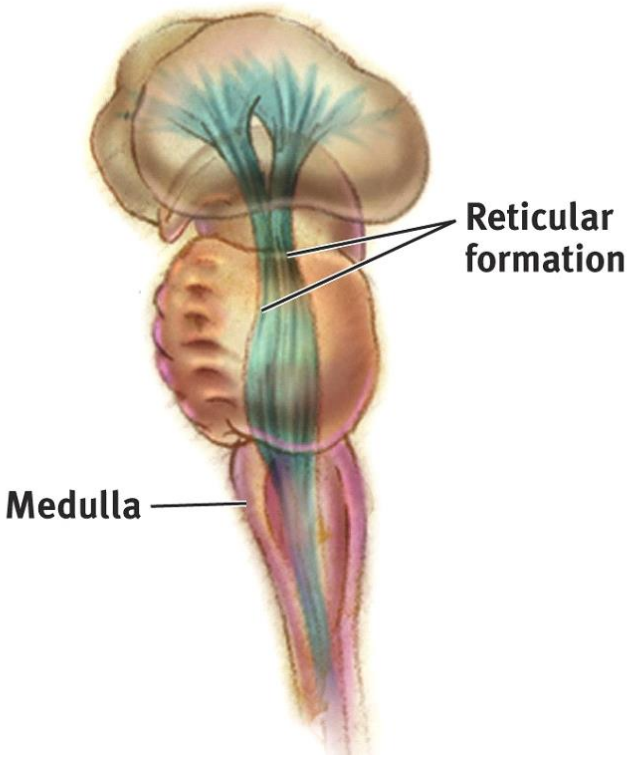
Newborn babies:

Mostly brainstem function

Brain Stem

1. Medulla controls heartbeat, breathing, blood pressure

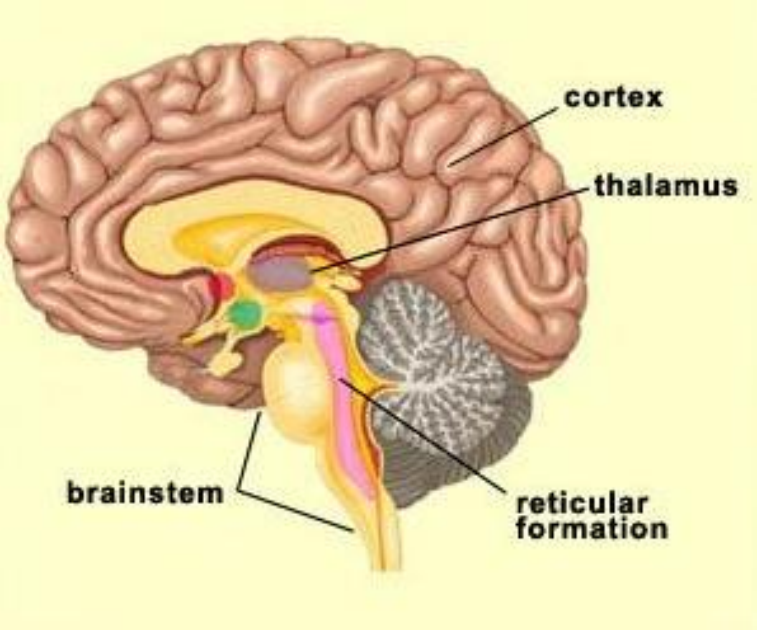
2. Pons- coordinates movement

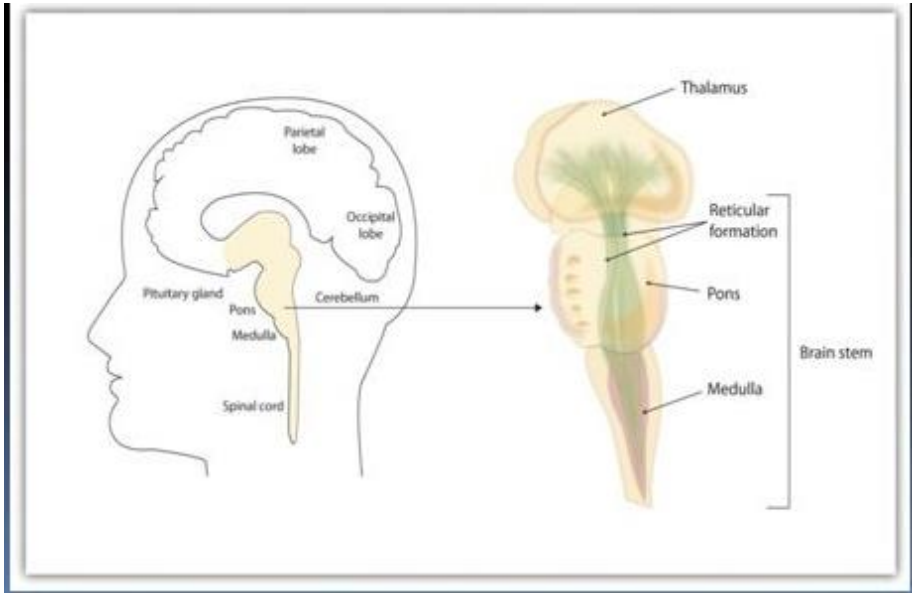


Damage often fatal or can lead to coma or persistent vegetative state

Reticular Formation

- Controls arousal:
- Severed = coma
- Dysfunction can cause narcolepsy

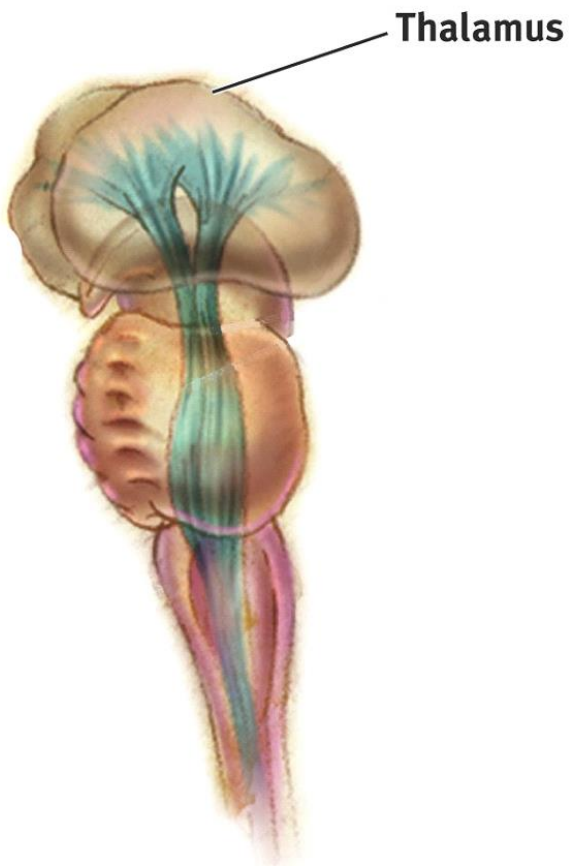




Thalamus

Thalamus: brain's sensory switchboard

It directs messages to the sensory areas in the cortex

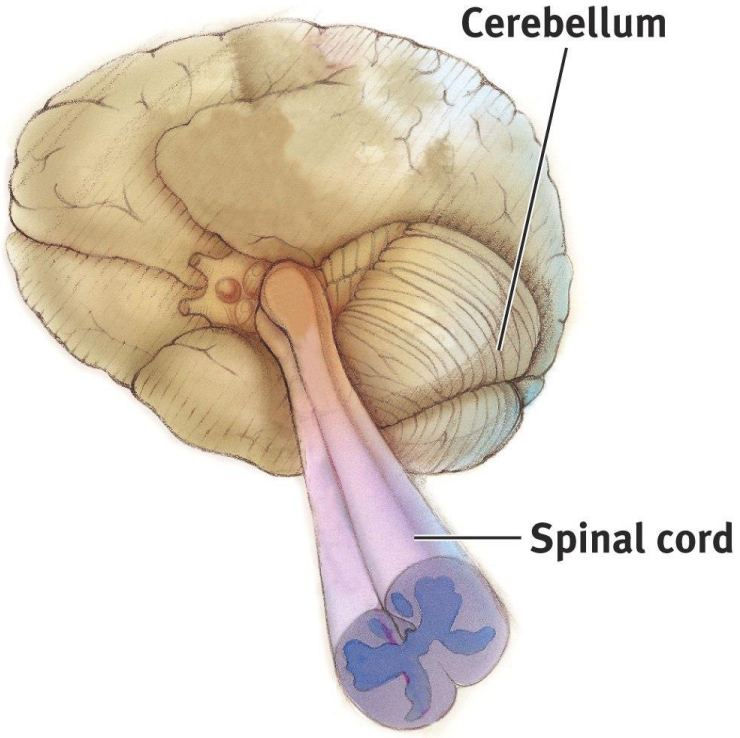


Damage to the thalamus is very rare but can cause a range of sensory problems

Cerebellum

The **“little brain”**

It helps coordinate voluntary movements and balance.



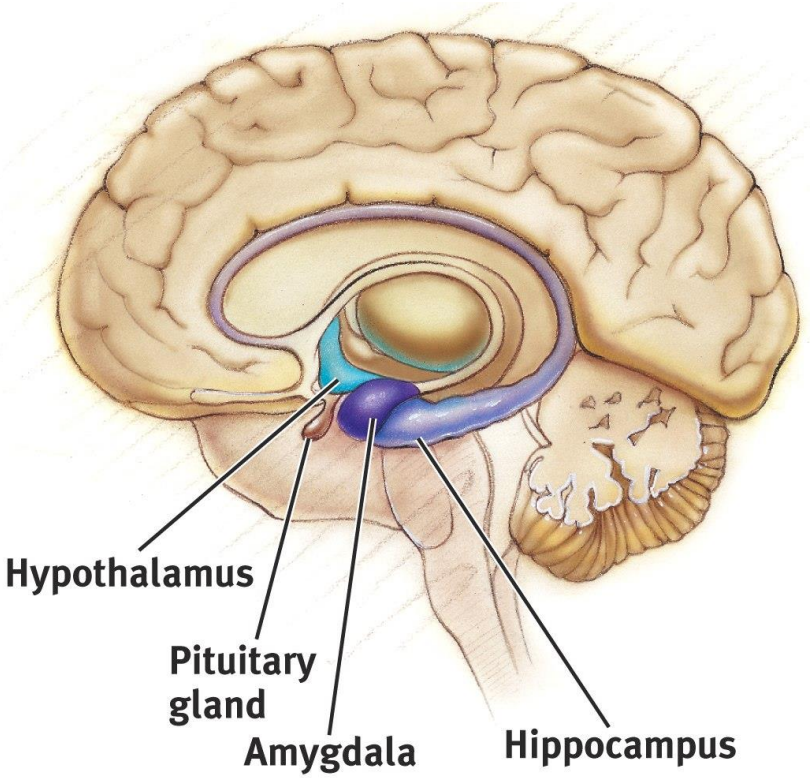
Damage causes a range of problems with movement and balance (including slurred speech and impaired eye moments)

NB: Alcohol intoxication has profound effects on the cerebellum

The Limbic System

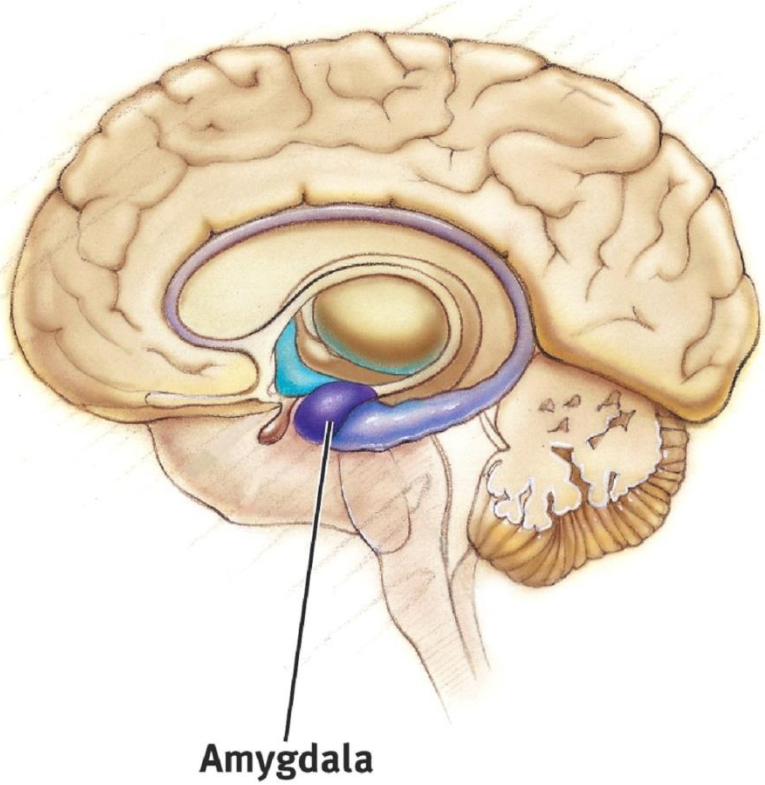
The Limbic System is associated with **EMOTIONS (such as fear, aggression and drives for food and sex**) and MEMORY

It includes the **hippocampus, amygdala, and hypothalamus**.



Amygdala

Linked to emotion (especially threat)

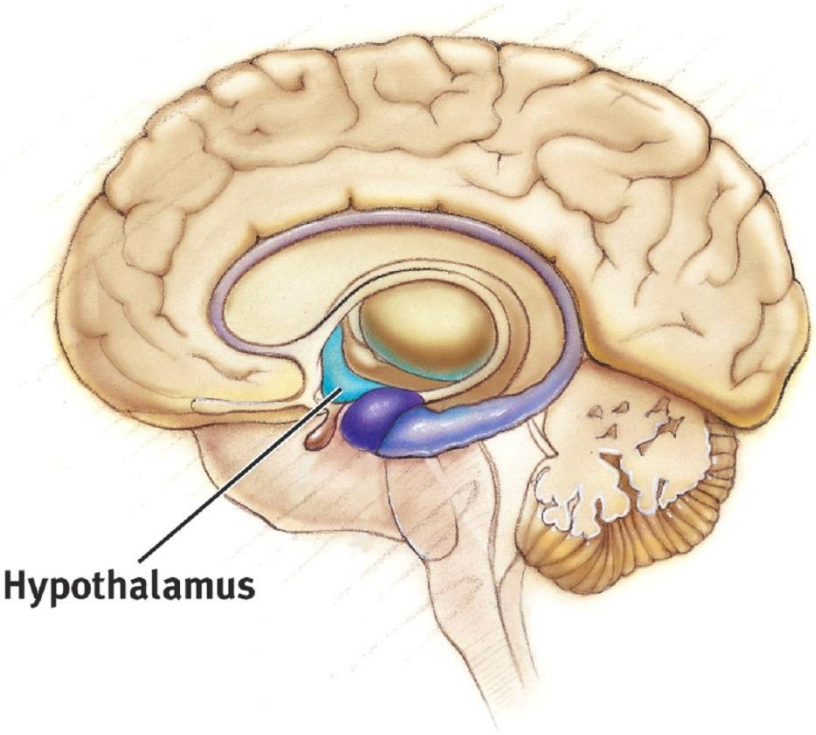


Damage causes “Kluver-Bucy” syndrome

Hypothalamus

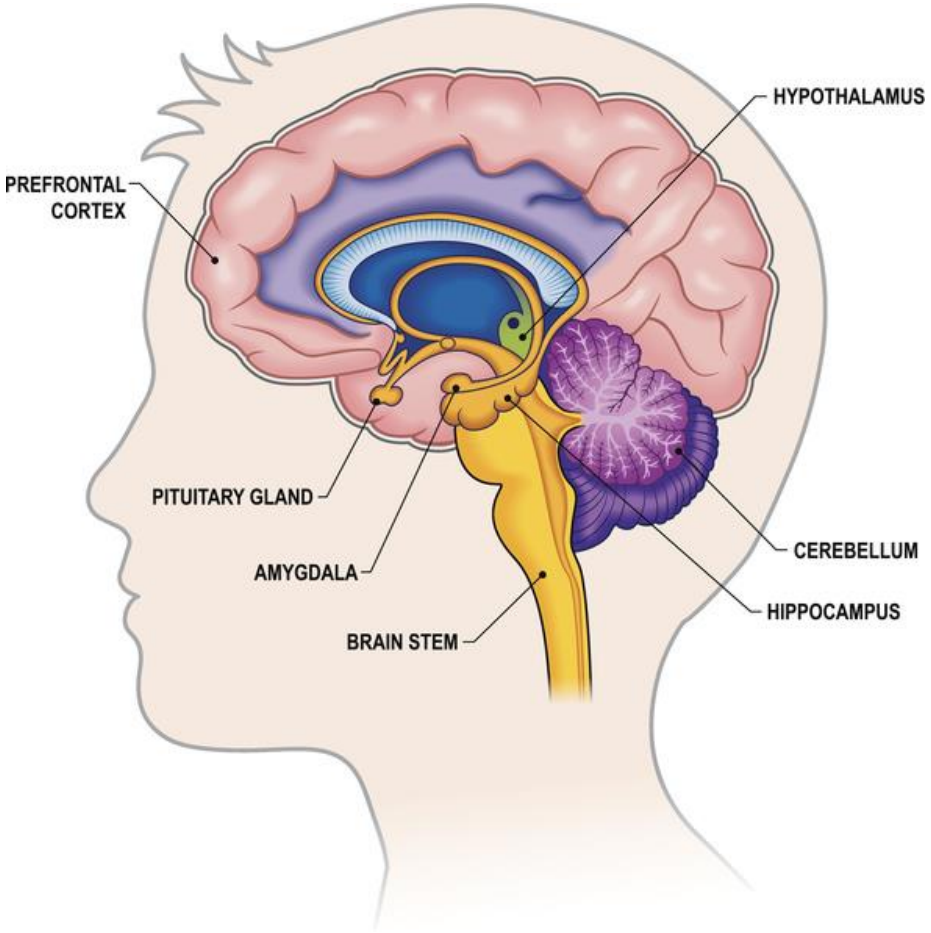
Hypothalamus: regulates eating, drinking, body temperature, and emotions, libido.

It controls the endocrine system



Hippocampus

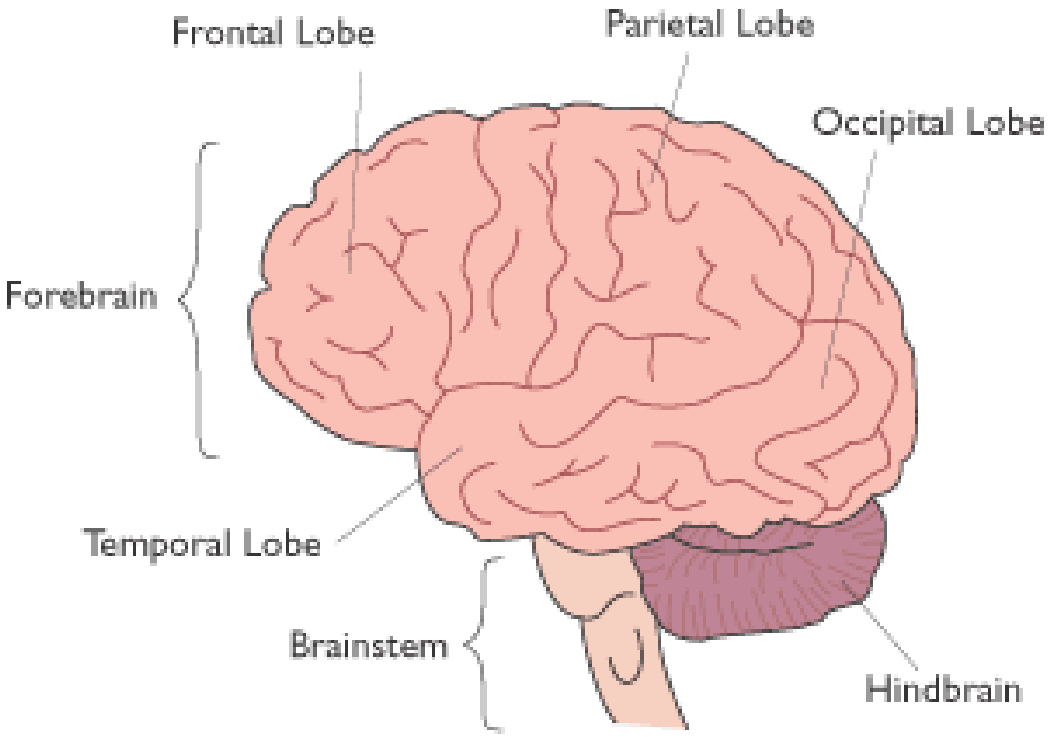
- Learning and Memory



Forebrain

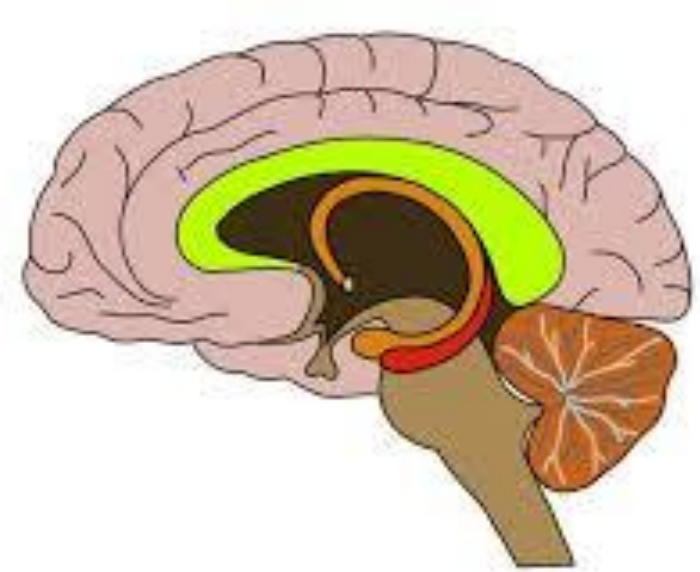
- Cerebral hemispheres, thalamus, hypothalamus

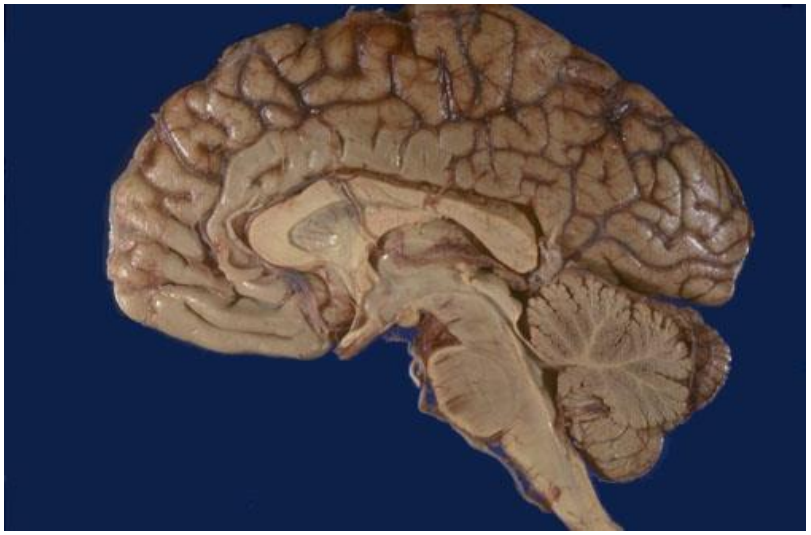
- Cerebral hemispheres
  - Frontal
  - Parietal
  - Occipital
  - Temporal



Structure	Major Function
Frontal Lobe	
Motor cortex	**Plans and executes voluntary movements**
Broca's area	Controls speech
Prefrontal cortex	Planning, impulse control
Parietal lobes	
Somatosensory cortex	**Projection area for body senses**
Association cortex	Location of body and objects in space
Temporal lobes	
Auditory cortex	**Auditory information**
Wernicke's area	Language area – meaning
Inferior temporal cortex	Visual identification of objects
Occipital lobes	
Primary visual cortex	**Projection area for visual information**
Visual association cortex	Processes components of visual information

Corpus callosum





Thick bundle of fibres connecting left and right hemispheres

Allows inter-hemispheric communication

Test of corpus callosum function

- In pairs.
- One of you close your eyes and put your hands face up.
- Partner touches one of their fingertips with a pencil
- Person with eyes closed touches the corresponding finger OF OPPOSITE HAND with thumb of the same hand.
- Repeat on the opposite hand
- Now swap roles

- Patients who have damage to the corpus callosum usually can't do this test, because it relies on communication between the two hemispheres of the brain.
- Only works with eyes closed, because information from the eyes goes to both hemispheres

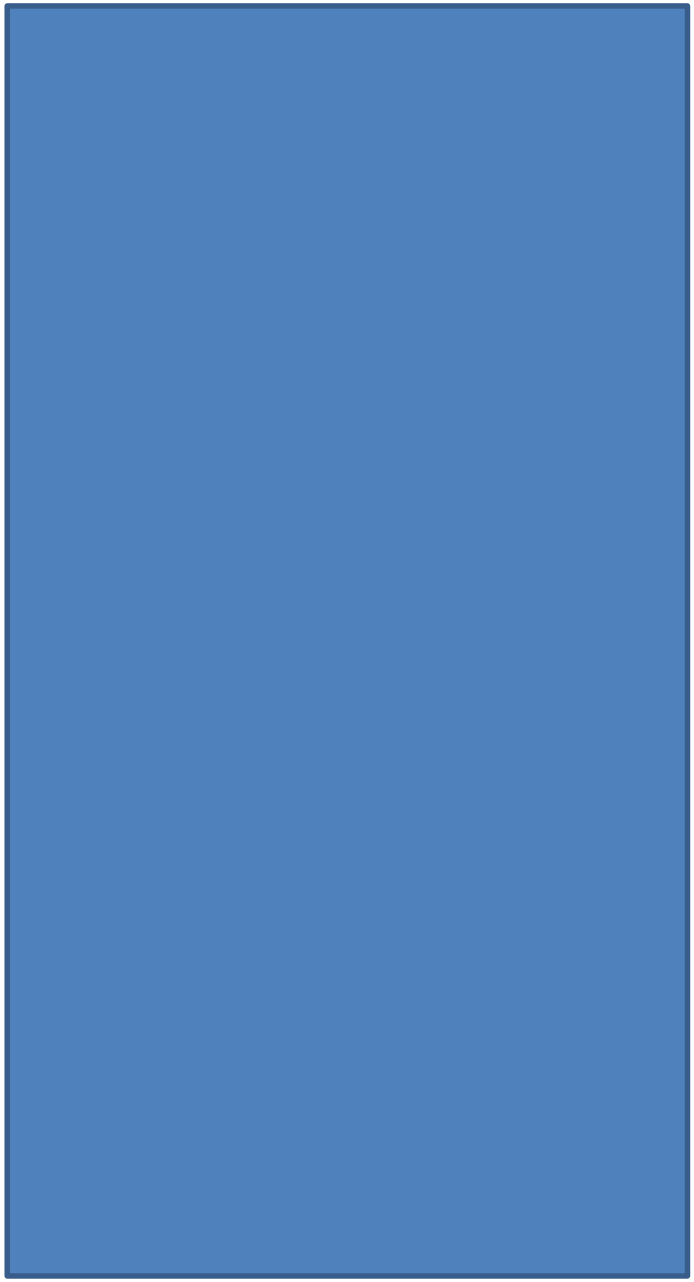
How do we know which bit of the brain does what??

- Until 1980s relied on:
  - Animal studies (limitations – eg language)
  - Cognitive psychology
  - Neuropsychology
- Some examples:

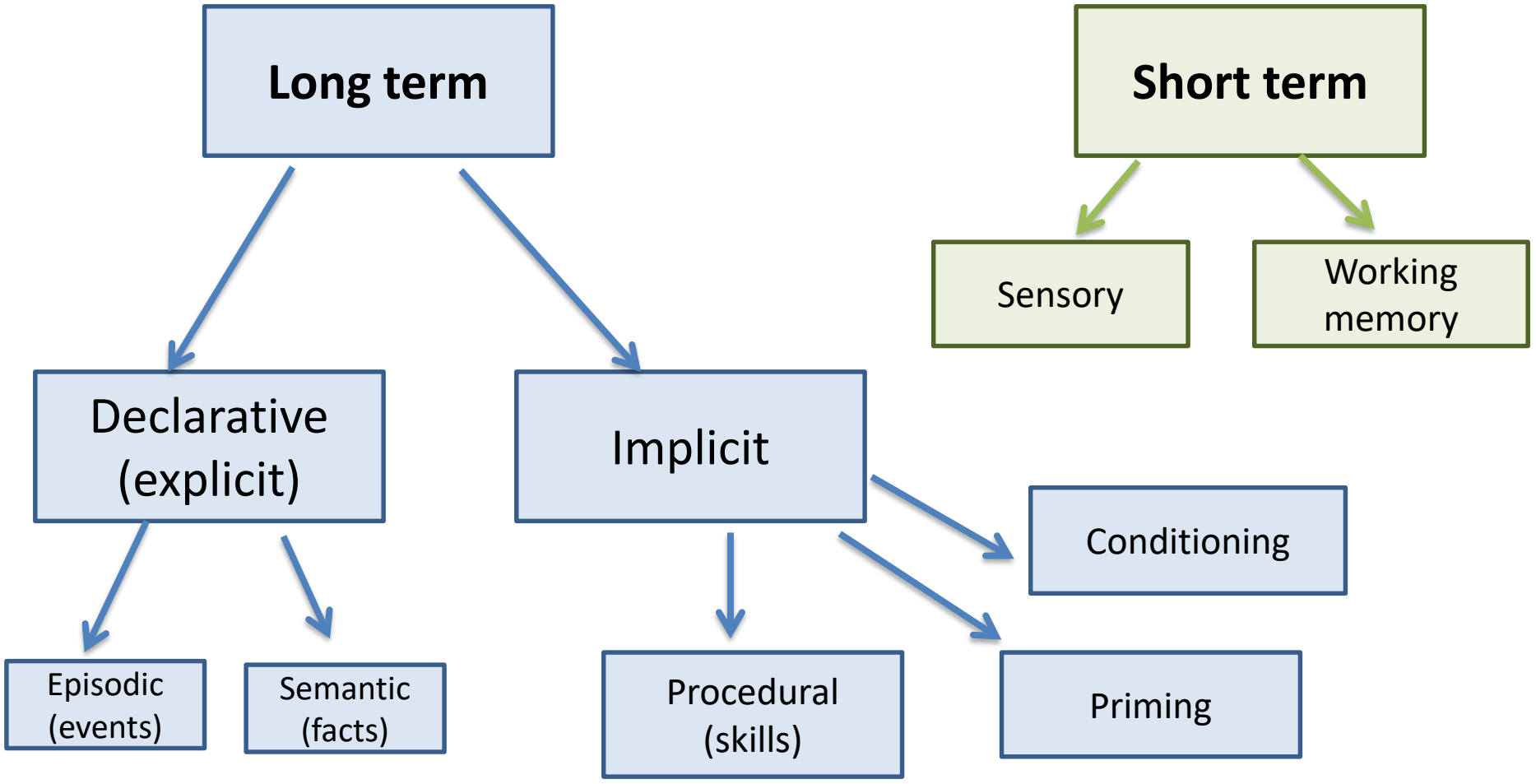
- Also see many popular science books (eg “The man who mistook his wife for a hat” by Oliver Sacks)

What is memory?

- Different types of memory: *short-term, long-term, autobiographical, semantic, sensory, spatial, procedural etc etc*
- Different component processes: *encoding, storage, retrieval*
- Different brain regions/mechanisms and different types of dysfunction



Types of memory



Short term memory

- Memory for “nonsense syllables”
- Memory for number strings
  - Digit span (remembering phone numbers)
  - 7 (plus or minus 2)

D R T H N L

C F G A Y P K

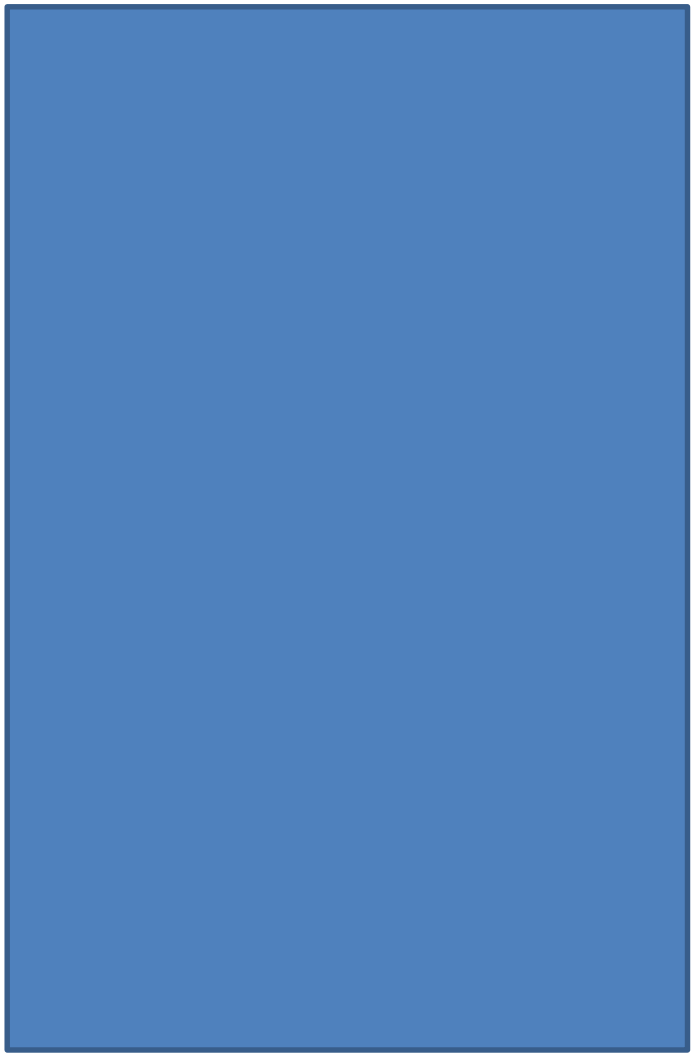
E R F P T H N Q

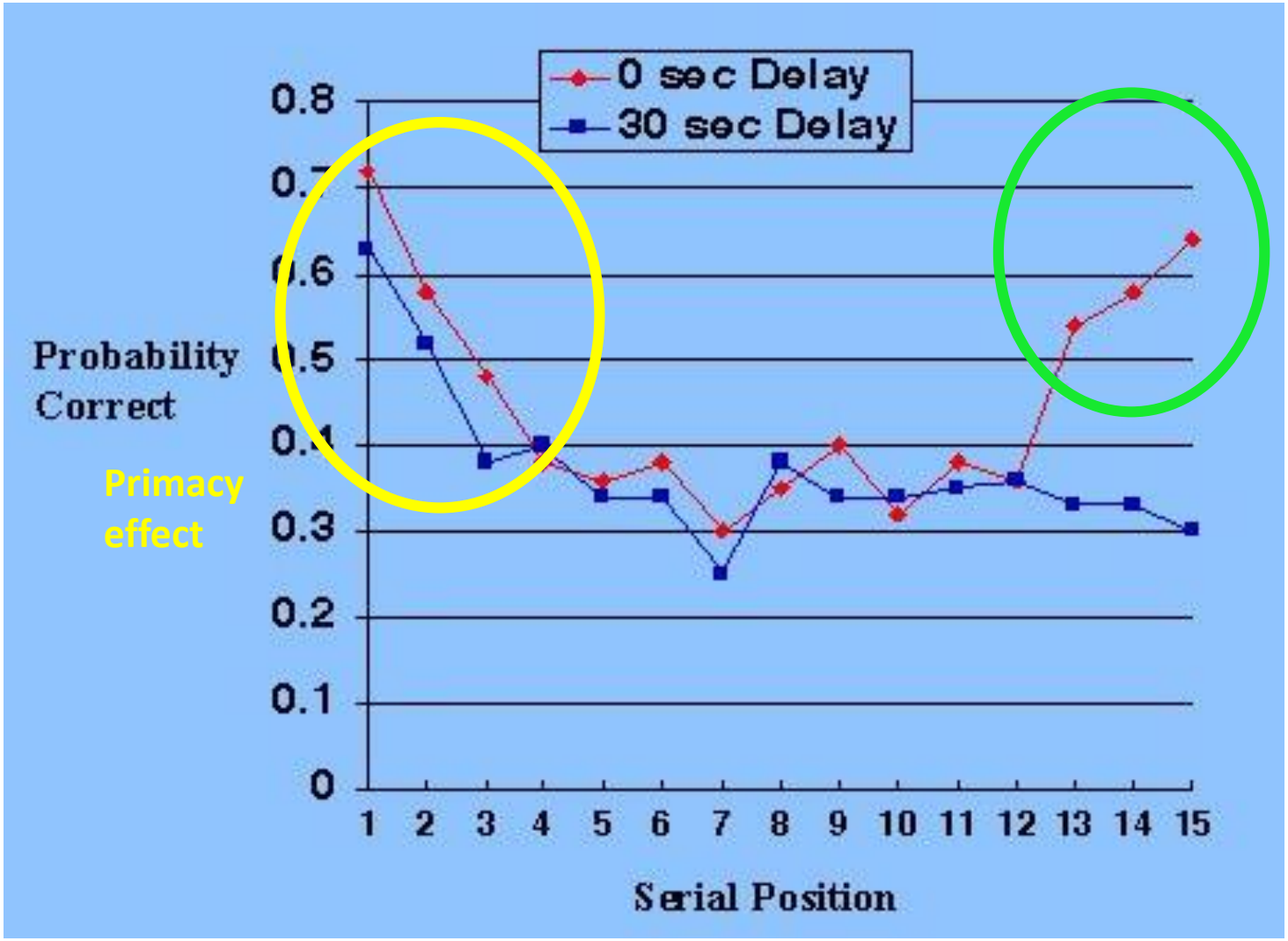
W J U S C D H V C

What was the first series of 6 letters I showed you?

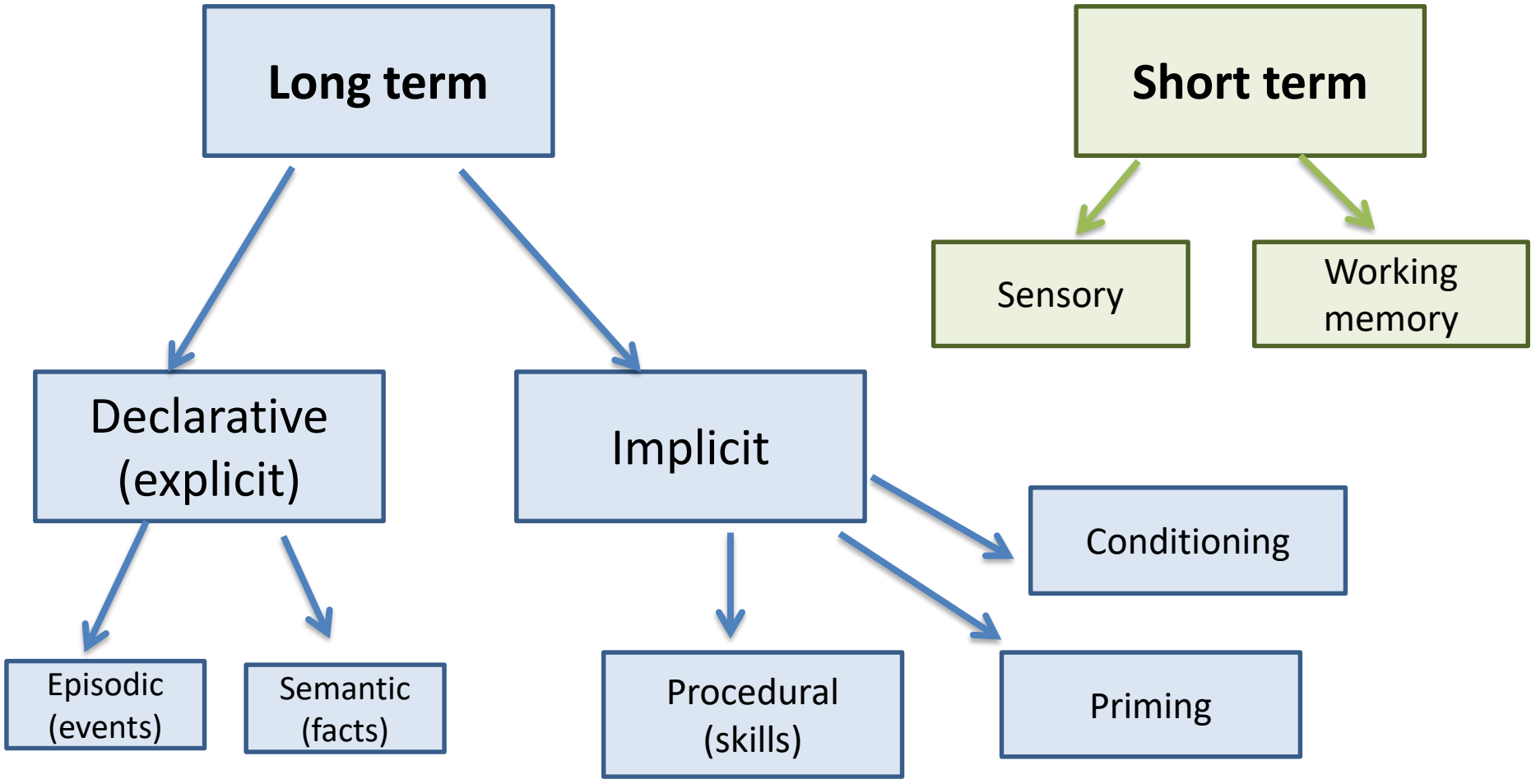
What was the name of your favourite primary school teacher?

Primacy and recency effects




0 sec Delay
30 sec Delay
Probability Correct
0.8
0.6
0.3
0.2
0.1
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Serial Position
Primacy effect
Recency effect

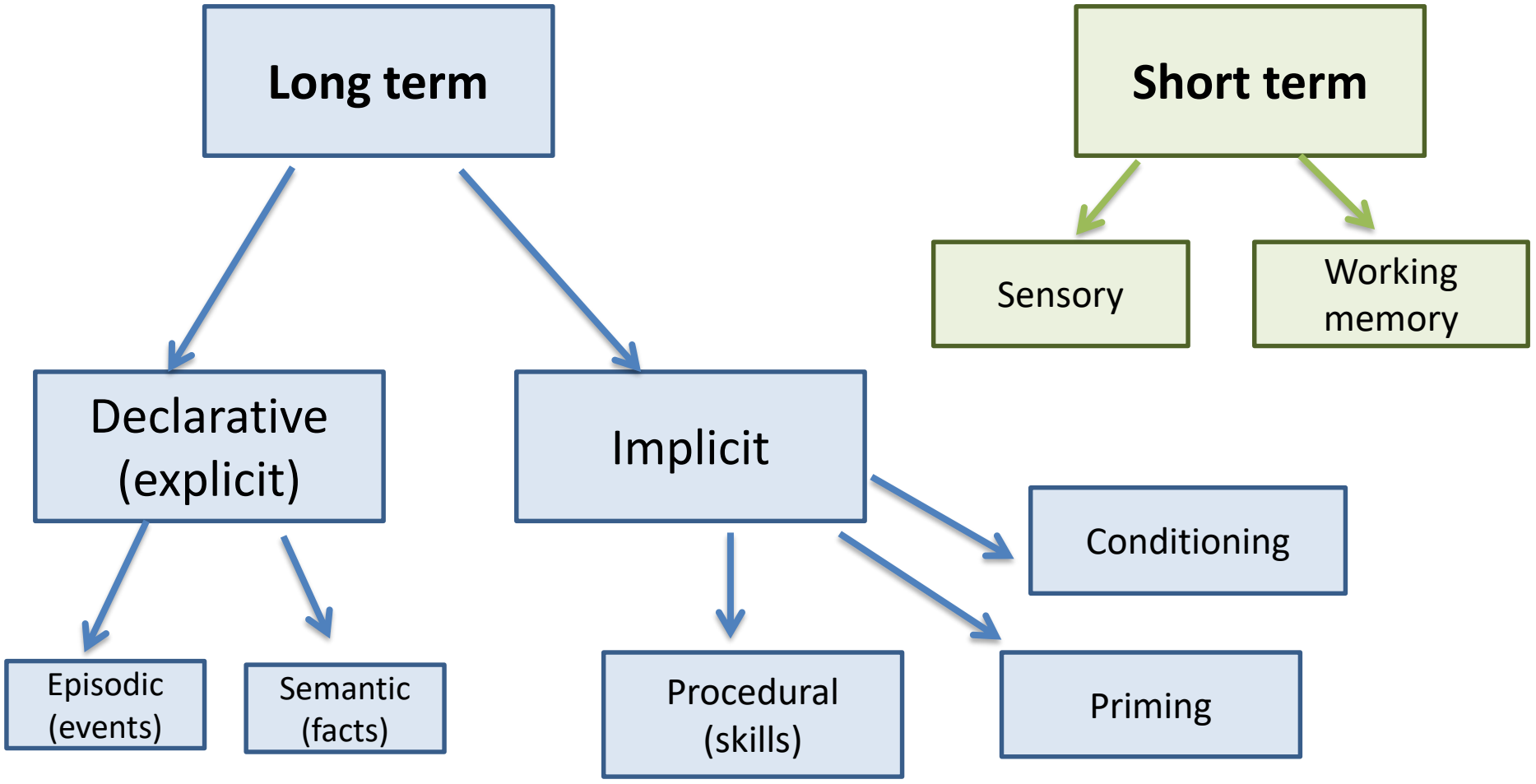
Types of memory



Short term memory impairment

- Patient KF: Left occipito-parietal lesion
- Digit span of 2
- No recency effect in free recall
- Normal learning
- No amnesia

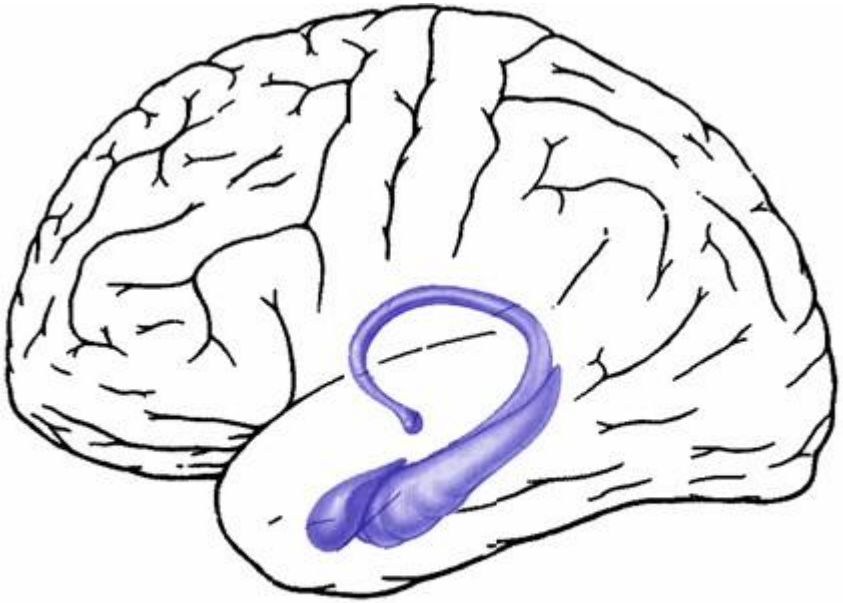
Types of memory

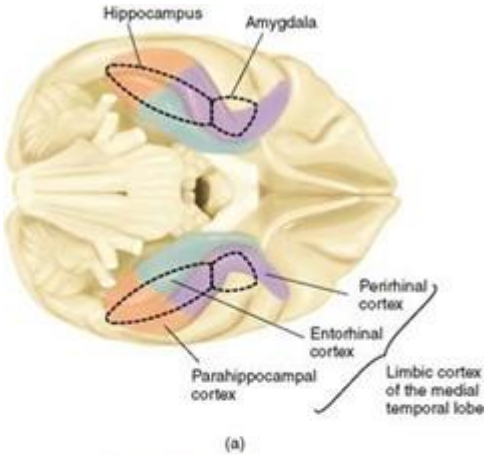


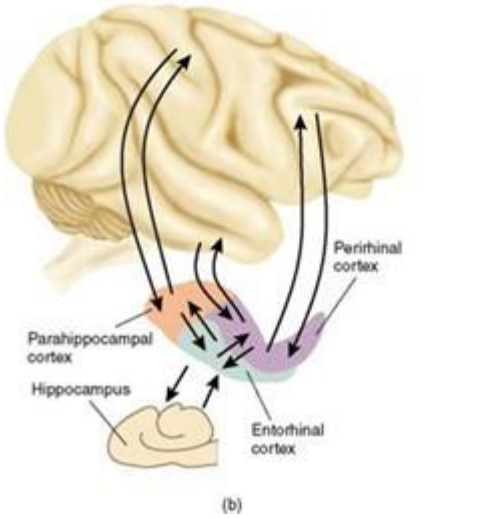
Long term memory: Patient HM

- Medial temporal lobectomy
- Damage to hippocampus

and surrounding cortex

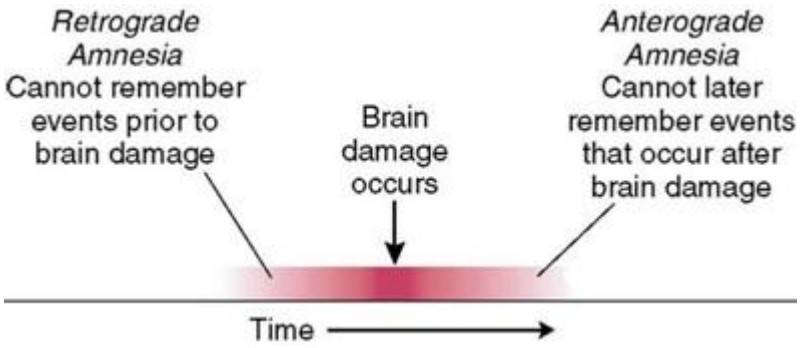






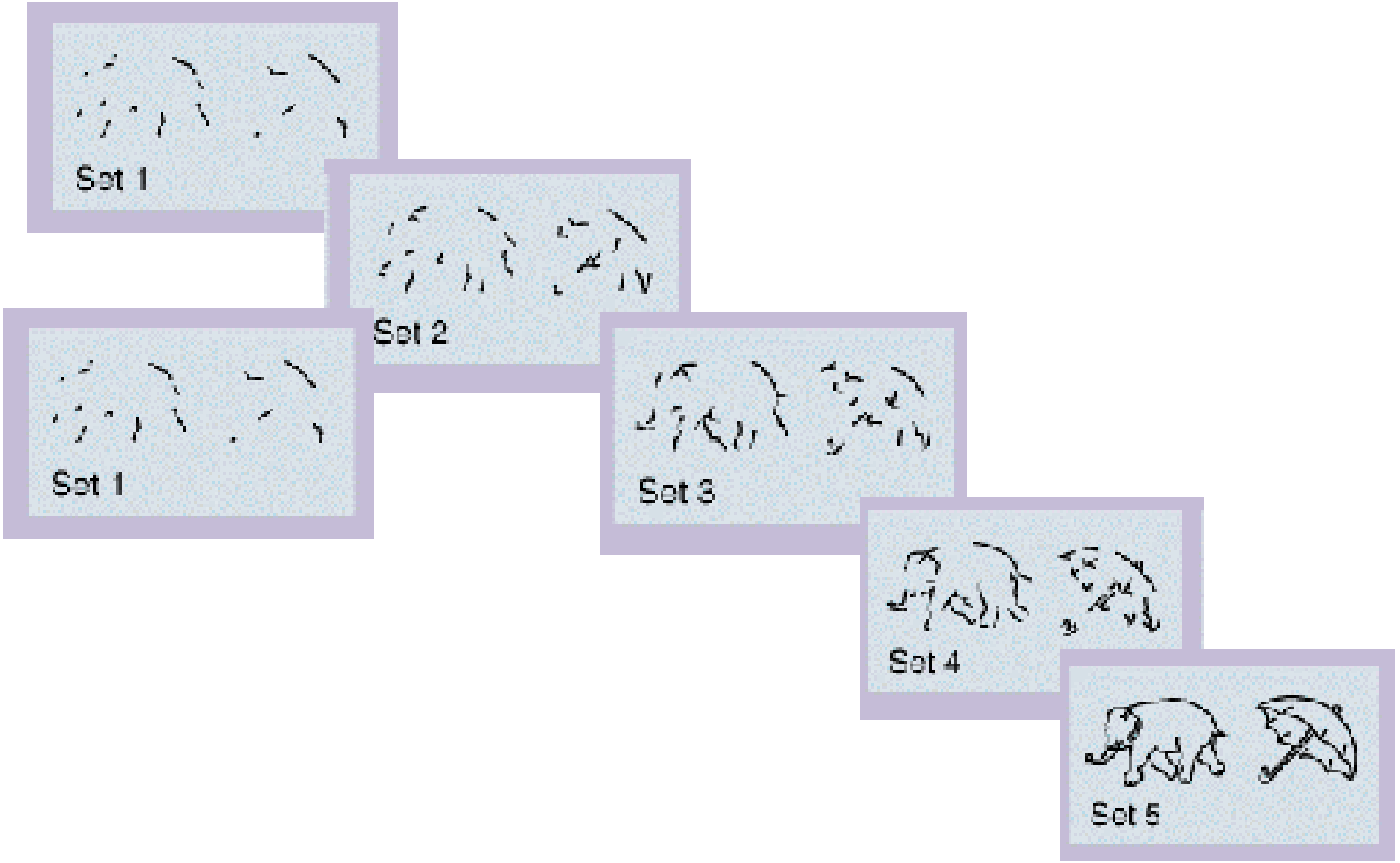
Neuropsychology

- Personality and IQ intact
- Massive anterograde amnesia (couldn't form new memories)
- Moderate retrograde amnesia (for memories 1-3 years pre-op)

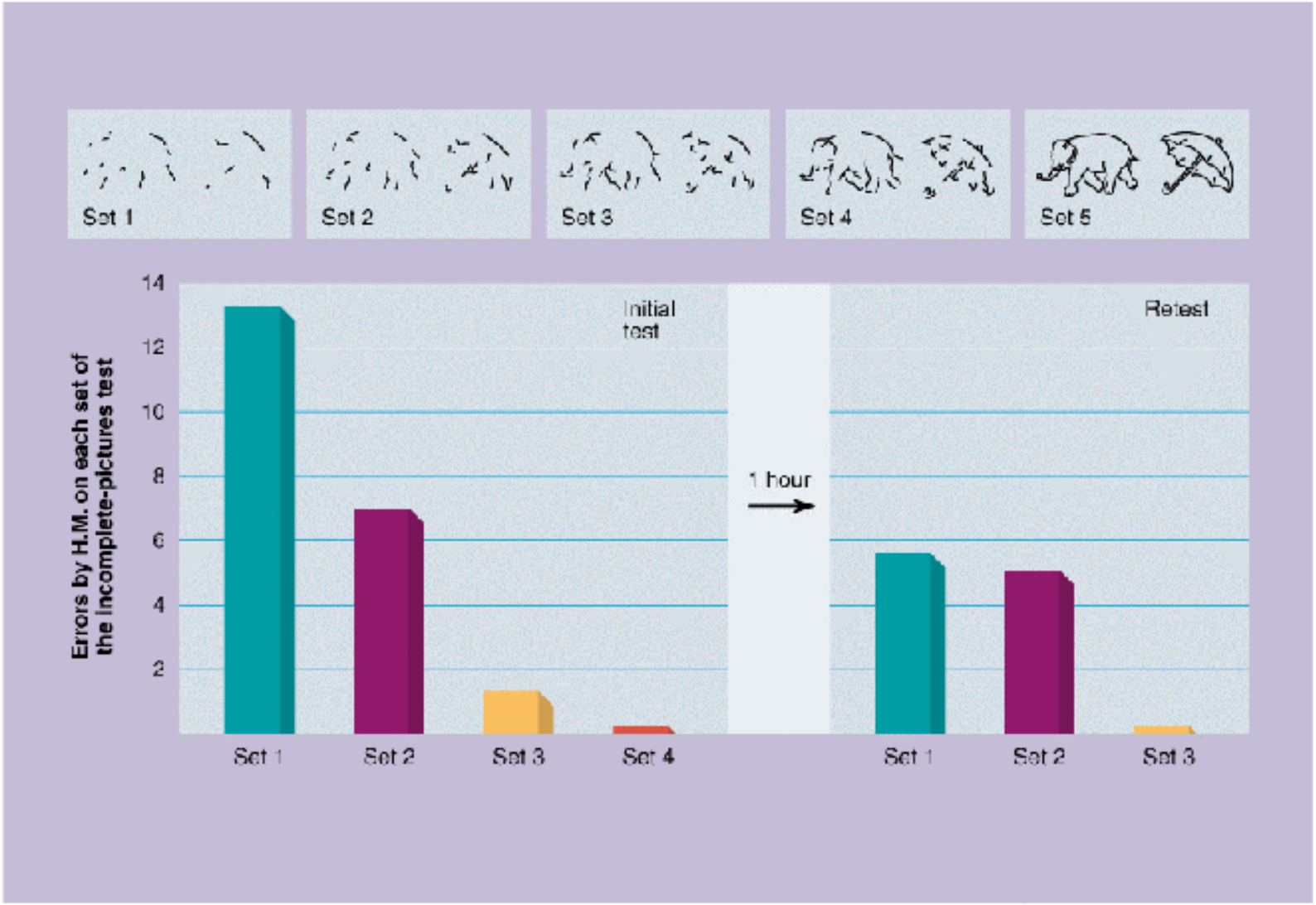


- Normal digit span
- Could not learn new facts
- Could acquire new skills (in absence of explicit memory of learning them)

Incomplete pictures



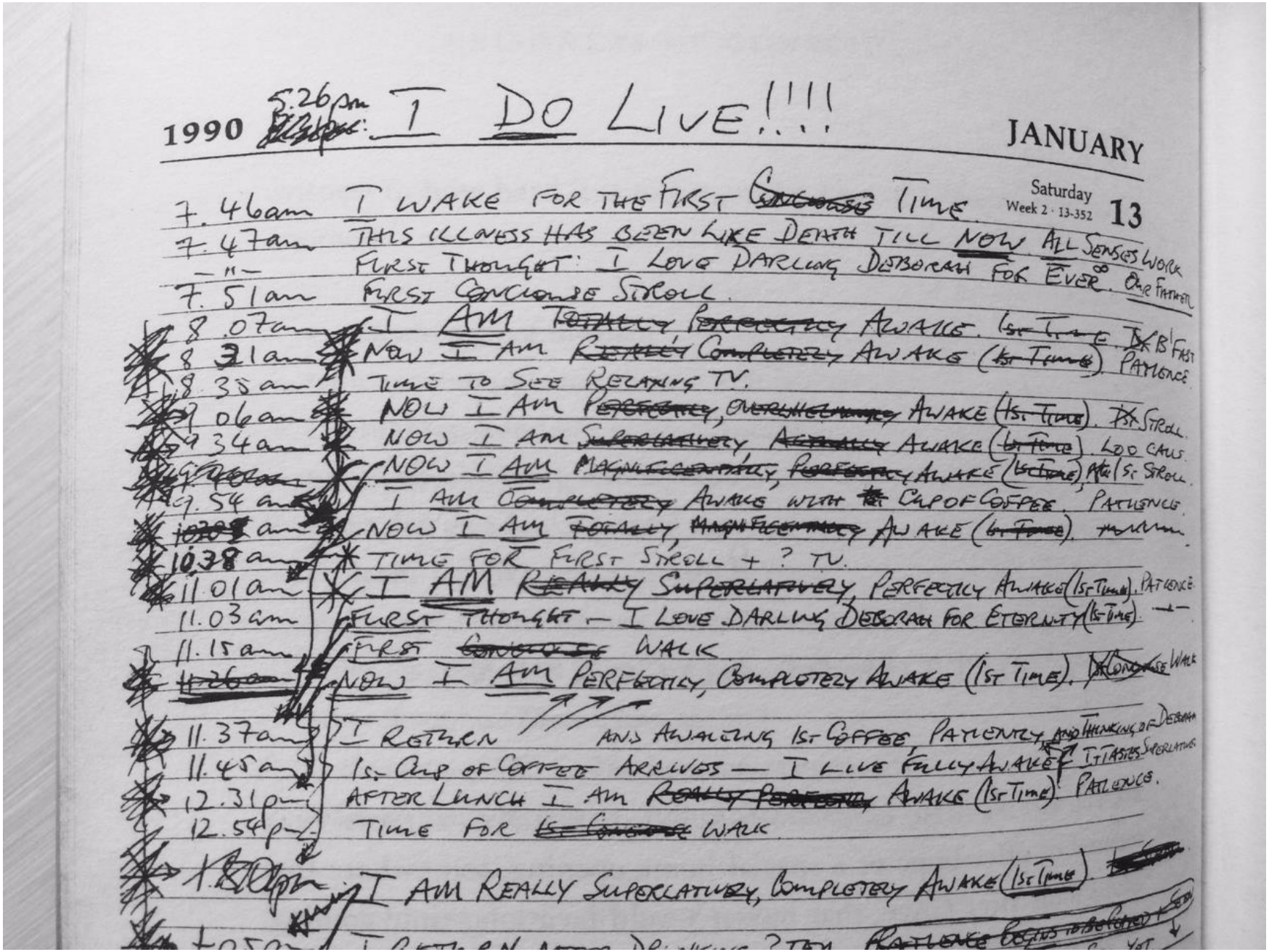
▸ Incomplete-Pictures Test



Clive Wearing

- Massive hippocampal damage after viral infection

https://www.youtube.com/watch?v=Vwigmktix2Y



1990 5.26pm I DO LIVE!!!! JANUARY

Saturday Week 2 · 13-352 13

7.46am I WAKE FOR THE FIRST ~~CONSCIOUS~~ TIME

7.47am THIS ILLNESS HAS BEEN LIKE DEATH TILL NOW ALL SENSES WORK

—"— FIRST THOUGHT: I LOVE DARLING DEBORAH FOR EVER. OUR FATHER

7.51am FIRST CONSCIOUS STROLL.

8.07am I AM ~~TOTALLY PERFECTLY~~ AWAKE. 1ST TIME. ~~IN~~ IS FIRST PATIENCE

8.31am NOW I AM ~~REALLY~~ ~~COMPLETELY~~ AWAKE (~~1ST TIME~~).

8.35am TIME TO SEE RELAXING TV.

9.06am NOW I AM ~~PERFECTLY~~, ~~OVERWHELMINGLY~~ AWAKE (1ST TIME). 1ST STROLL.

9.34am NOW I AM ~~SUPERLATIVELY~~ ~~ACTUALLY~~ AWAKE (~~1ST TIME~~). LOO CALLS.

~~9.40am~~ NOW I AM ~~MAGNIFICENTLY~~, ~~PERFECTLY~~, AWAKE (~~1ST TIME~~), AT 1/2 STROLL.

9.54am I AM ~~COMPLETELY~~ AWAKE WITH ~~THE~~ CUP OF COFFEE. PATIENCE.

~~10.08am~~ NOW I AM ~~TOTALLY~~, ~~MAGNIFICENTLY~~ AWAKE (~~1ST TIME~~).

10.38am TIME FOR FIRST STROLL + ? TV.

11.01am I AM ~~REALLY~~ SUPERLATIVELY, PERFECTLY AWAKE (1ST TIME). PATIENCE.

11.03am FIRST THOUGHT — I LOVE DARLING DEBORAH FOR ETERNITY (1ST TIME).

11.15am FIRST ~~CONSCIOUS~~ WALK

~~11.26am~~ NOW I AM PERFECTLY, COMPLETELY AWAKE (1ST TIME). ~~CONSCIOUS~~ WALK

11.37am I RETURN AND AWAITING 1ST COFFEE, PATIENTLY AND THINKING OF DEBORAH

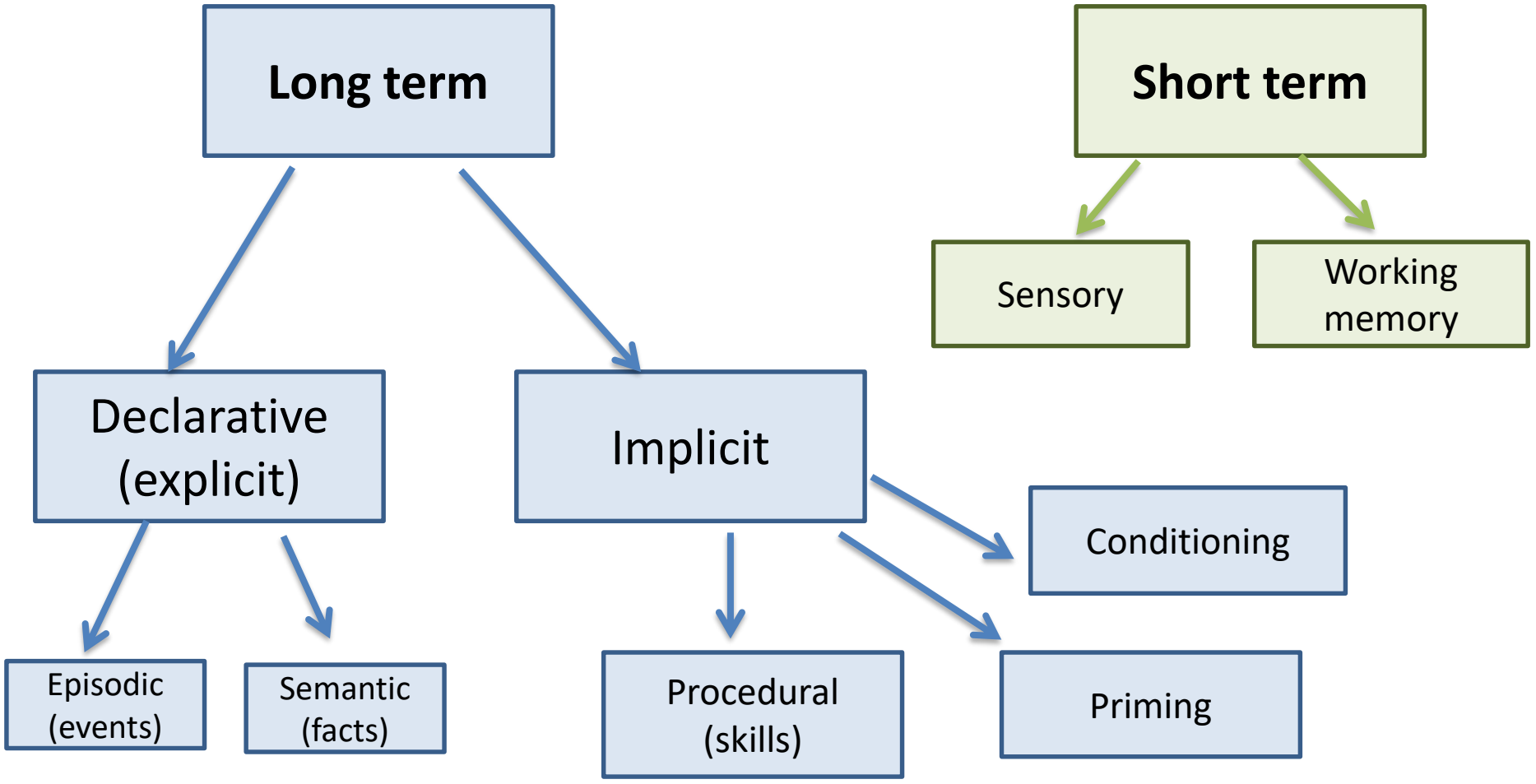
11.45am 1ST CUP OF COFFEE ARRIVES — I LIVE FULLY AWAKE IT TASTES SUPERLATIVE

12.31pm AFTER LUNCH I AM ~~REALLY PERFECTLY~~ AWAKE (1ST TIME). PATIENCE.

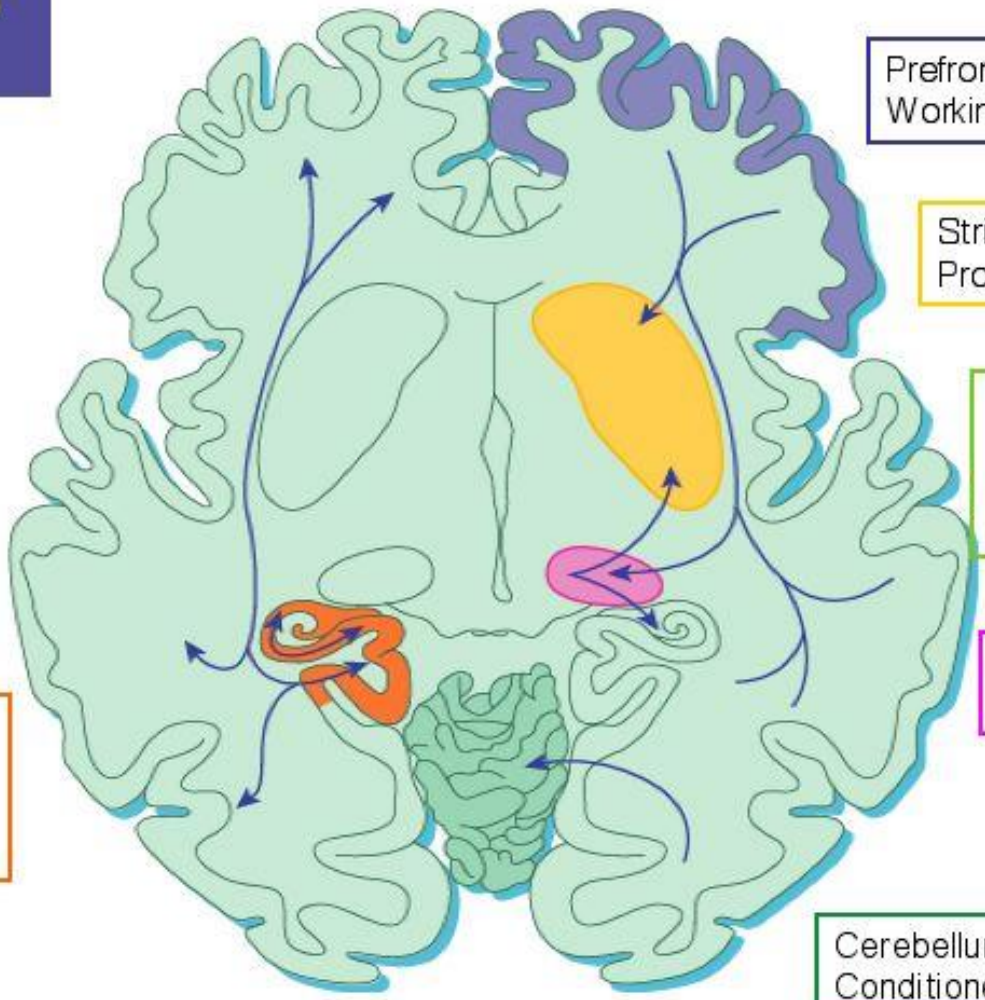
12.54pm TIME FOR ~~1ST CONSCIOUS~~ WALK

I AM REALLY SUPERLATIVELY, COMPLETELY AWAKE (1ST TIME)

Types of memory



Memory and the Brain



Prefrontal cortex:
Working memory

Striatum:
Procedural memory

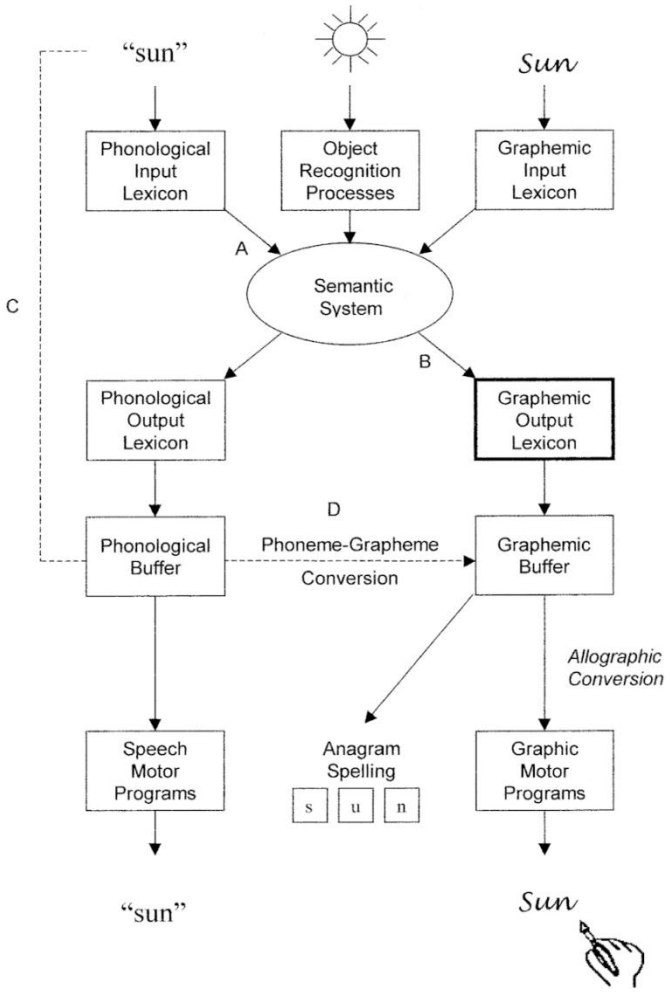
Cerebral cortex:
Perceptual memory,
semantic memory,
priming

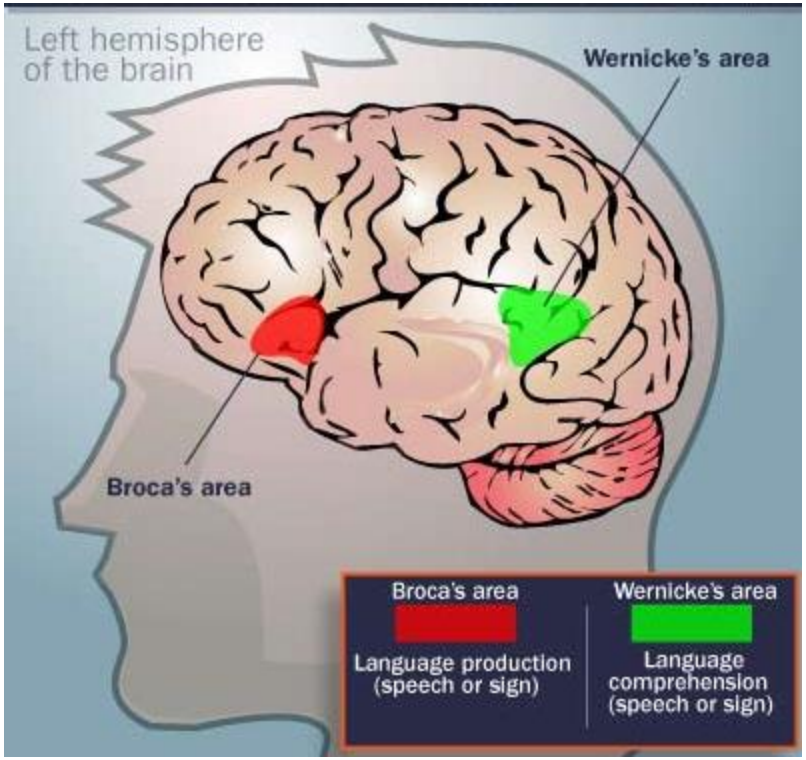
Amygdala:
Emotional memory

Hippocampus:
Dedarative memory
--Episodic memory
--Semantic memory

Cerebellum:
Conditioned timing

Language


"sun"
Sun
Phonological Input Lexicon
Object Recognition Processes
Graphemic Input Lexicon
A
Semantic System
C
B
Phonological Output Lexicon
Graphemic Output Lexicon
D
Phonological Buffer
Phoneme-Grapheme Conversion
Graphemic Buffer
Allographic Conversion
Speech Motor Programs
Anagram Spelling
s u n
Graphic Motor Programs
"sun"
Sun


Left hemisphere of the brain
Wernicke's area
Broca's area
Broca's area
Language production (speech or sign)
Wernicke's area
Language comprehension (speech or sign)

Bryan (Wernicke's aphasia)

- Speech is apparently fluent but has limited meaning

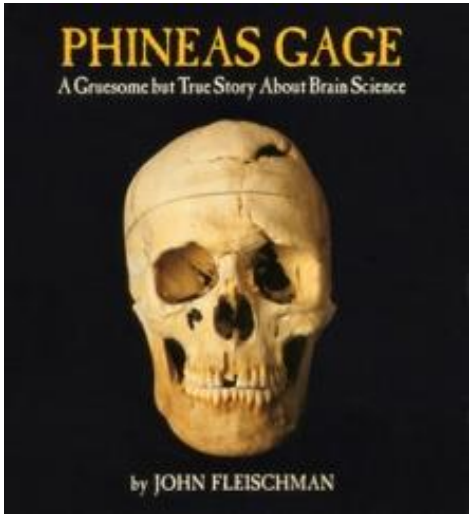
https://www.youtube.com/watch?v=3oef68YabD0

Mike (Broca's aphasia)

- Meaning is intact but non-fluent

https://www.youtube.com/watch?v=JWC-cVQmEmY

Emotion and personality: The Strange Tale of Phineas Gage



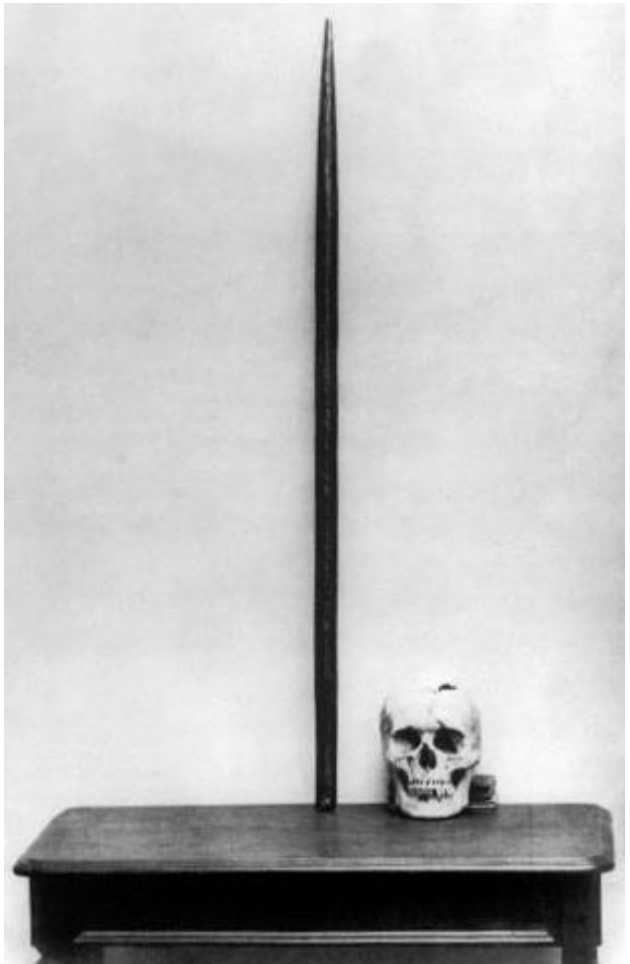
Phineas Gage's Terrible Accident

- On September 12, 1848, Phineas Gage, a railroad foreman was blasting rock in Cavendish, Vermont.
- Gage was responsible, well-liked, and hardworking. He was in charge because he was dependable.

The Blast

- Gage was an expert in blasting rock. He used a tamping rod to pack down gun powder after a layer of sand was placed over top.
- ….but on this occasion he forgot the sand
- The RESULT: The pointed end of the rod shoots through the left cheek bone and the brain

- Tamping Rod



A Miracle?

- The rod exploded with such force that it landed about half a football field away.
- Gage remained conscious and was able to walk with assistance.
- Talking on the way to the hospital
- Memory, language, motor function all normal

- Artist Drawing

Horrible Accident.—As Phineas P. Gage, a foreman on the railroad in Cavendish, was yesterday engaged in tamkia for a blast, the powder exploded, carrying an iron instrument through his head an inch and a fourth in circumference, and three feet and eight inches in length, which he was using at the time. The iron entered on the side of his face, shattering the upper jaw, and passing back of the left eye, and out at the top of the head.

The most singular circumstance connected with this melancholy affair is, that he was alive at two o'clock this afternoon, and in full possession of his reason, and free from pain.—*Ludlow, Vt., Union.*

But…..

- Gage recovered by January of 1849. He attempted to earn a living travelling around New England with his rod and his story
- “Gage was no longer Gage”
- Significant changes to personality and behaviour. Poor judgment, “feckless”, “irrsponsible”
- (Plus…. Lost an eye and had massive seizures)
- *IMPLIES: Personality and judgment separate functions (of orbitofrontal cortex)*

Neuropsychology: limitations

- Patients with focal damage are rare
- Usually major trauma involved which can have other effects
- Never studying “normal” brain function
- Considerable functional recovery is possible: what is abnormal is not just what is damaged
- Making inferences about human behaviour/cognition from N=1 (or N = not many)

In the last 30 years we've had a new technique:

Biomedical Imaging

X ray of brain?

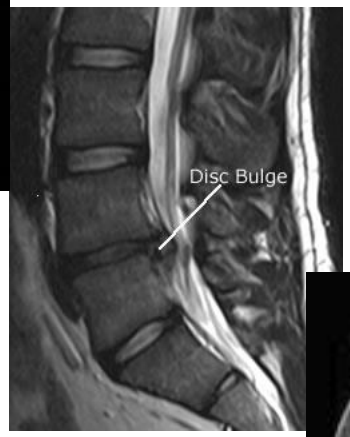

a

Ultrasound of brain?

- Doesn’t work!

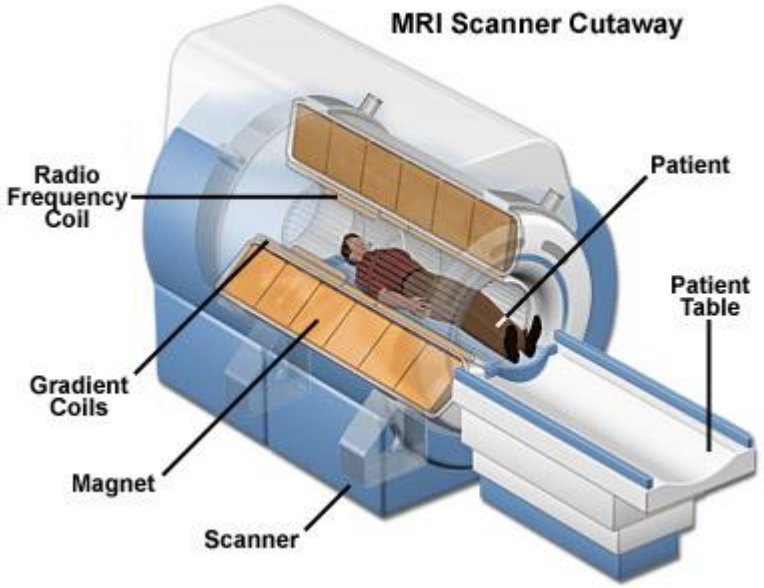
- Bone blocks sound waves.

Magnetic resonance imaging (MRI)



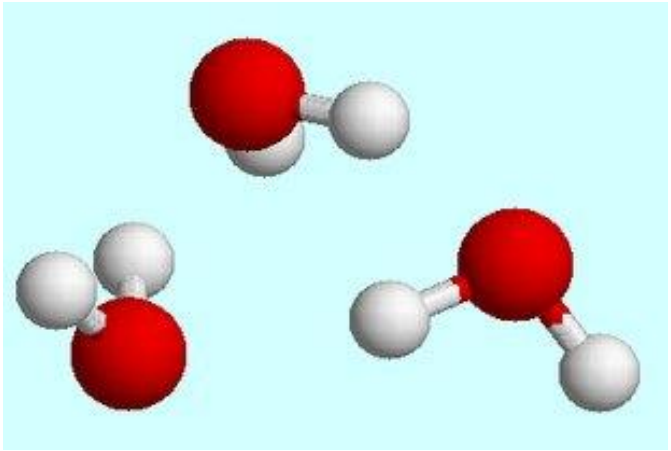
What is MRI?

- Basically a large electromagnet



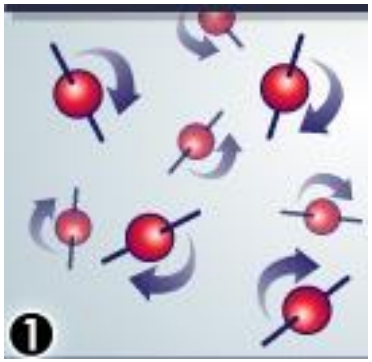
- It’s always on

How does MRI work?

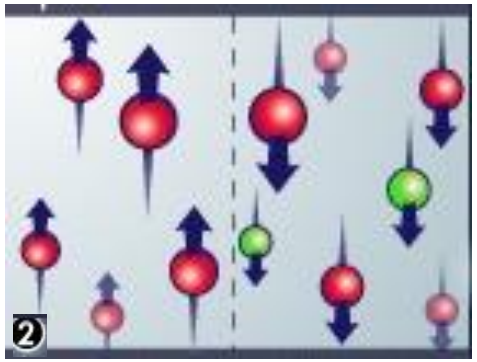


- Human body is 60% water, brain is 75% water
- Exact concentration varies between different tissue types (grey matter vs white matter)

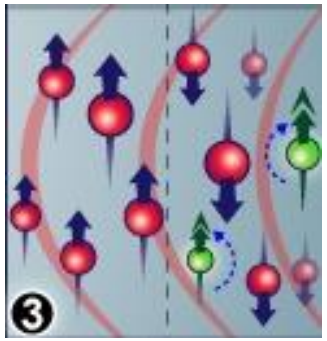
- Measuring protons in tissue water



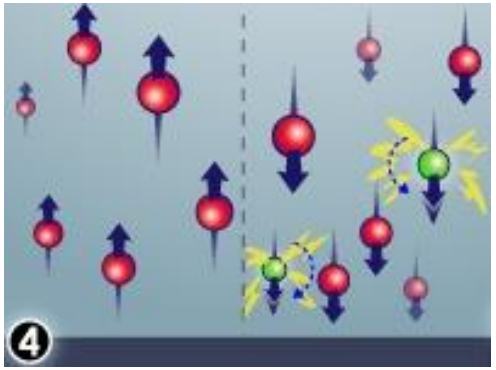
Hydrogen atoms spinning



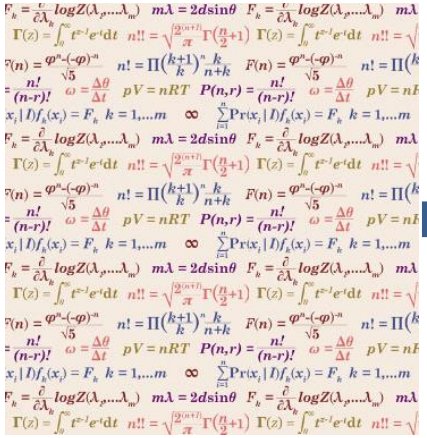
In a magnet
(note unmatched protons)



Radio pulse on

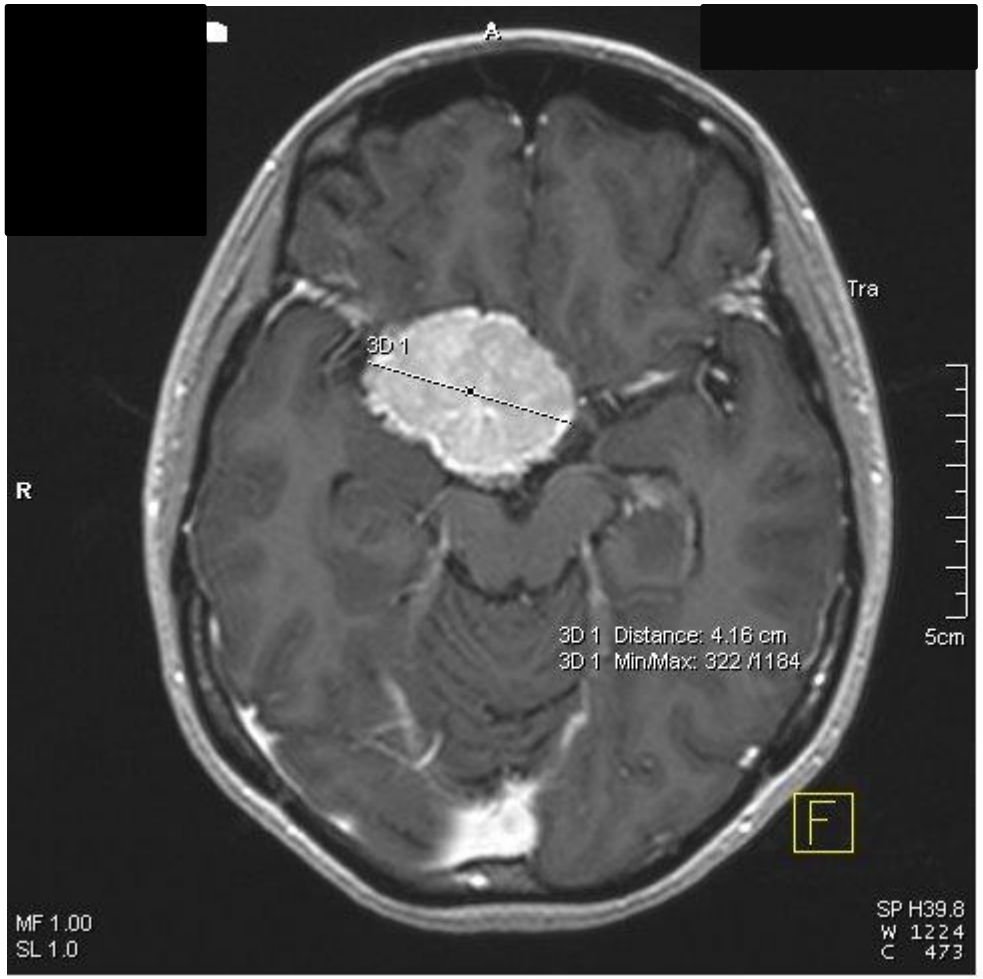


Radio pulse off



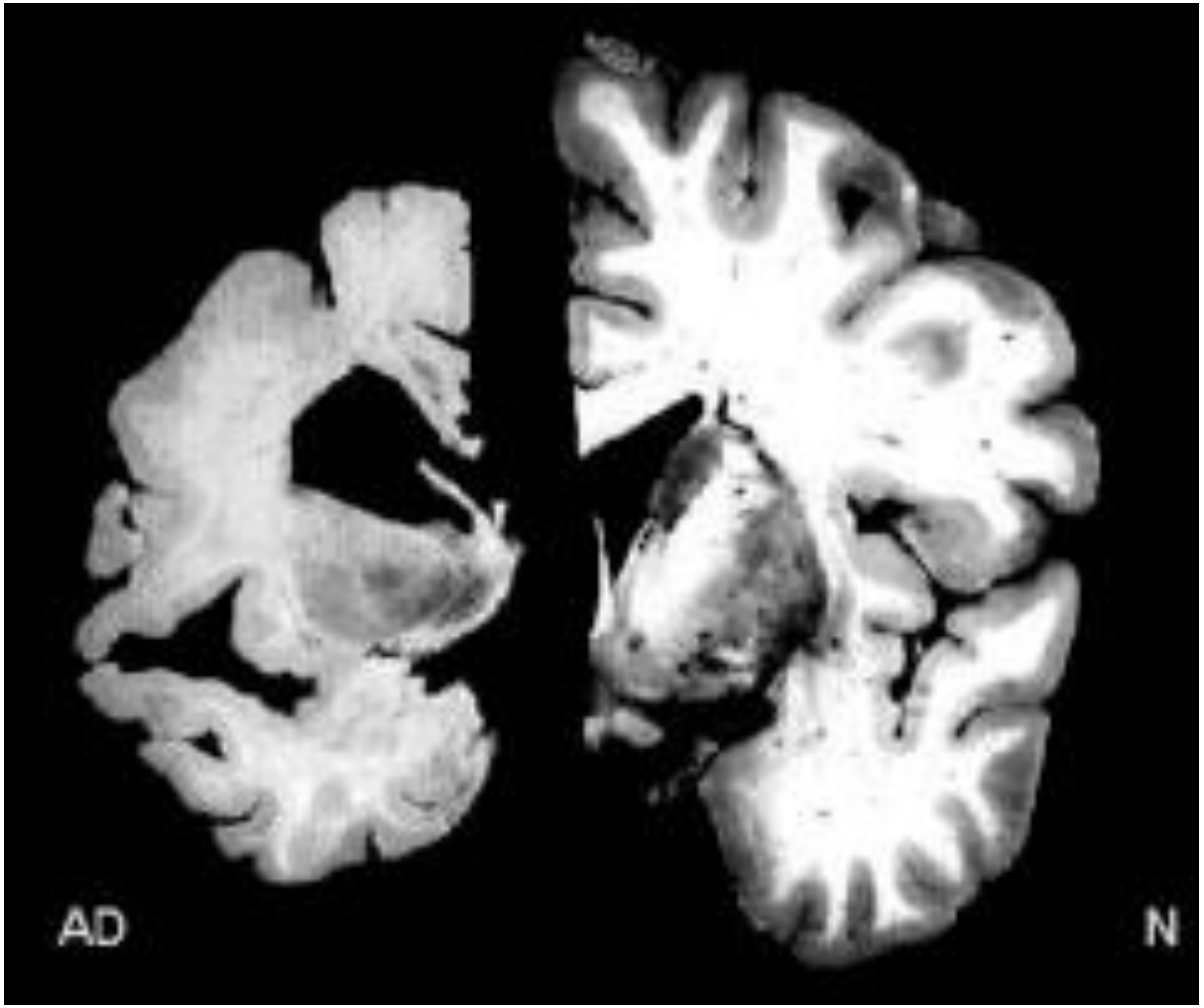
Maths

Image



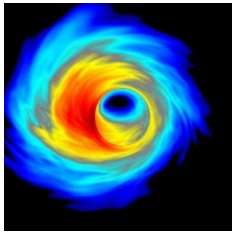
Brain tumours

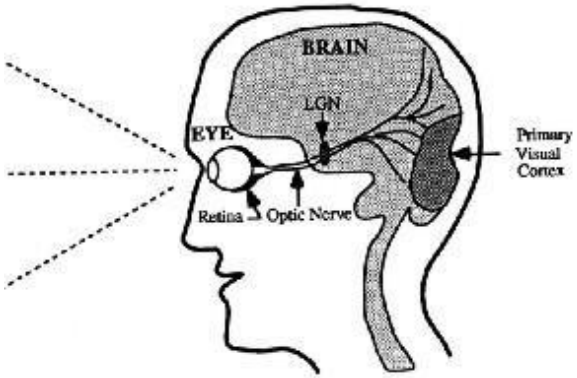
Dementia

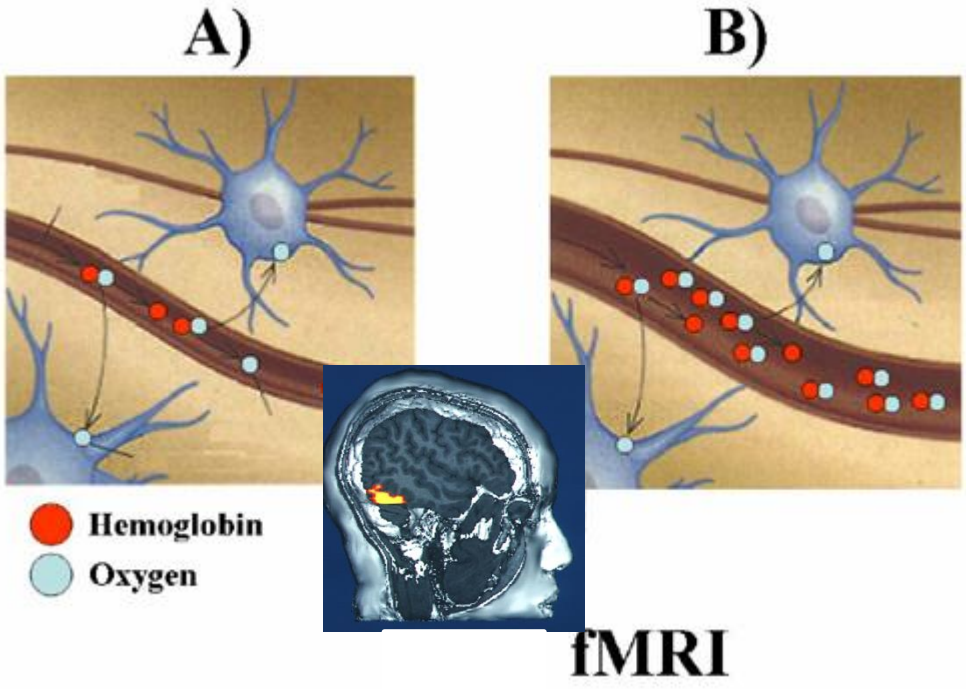


How the brain works?

- People are awake in the scanner
- A bit noisy but painless
- Can ask people to look at things or think about things and see which parts of the brain react.




BRAIN
LGN
EYE
Primary
Visual
Cortex
Retina
Optic Nerve


A)
B)
Hemoglobin
Oxygen
fMRI


wiseGEEK

We can look at:

- Perceiving
- Thinking
- Behaving
- Feeling

- And how they go wrong

Perceiving: colours and words

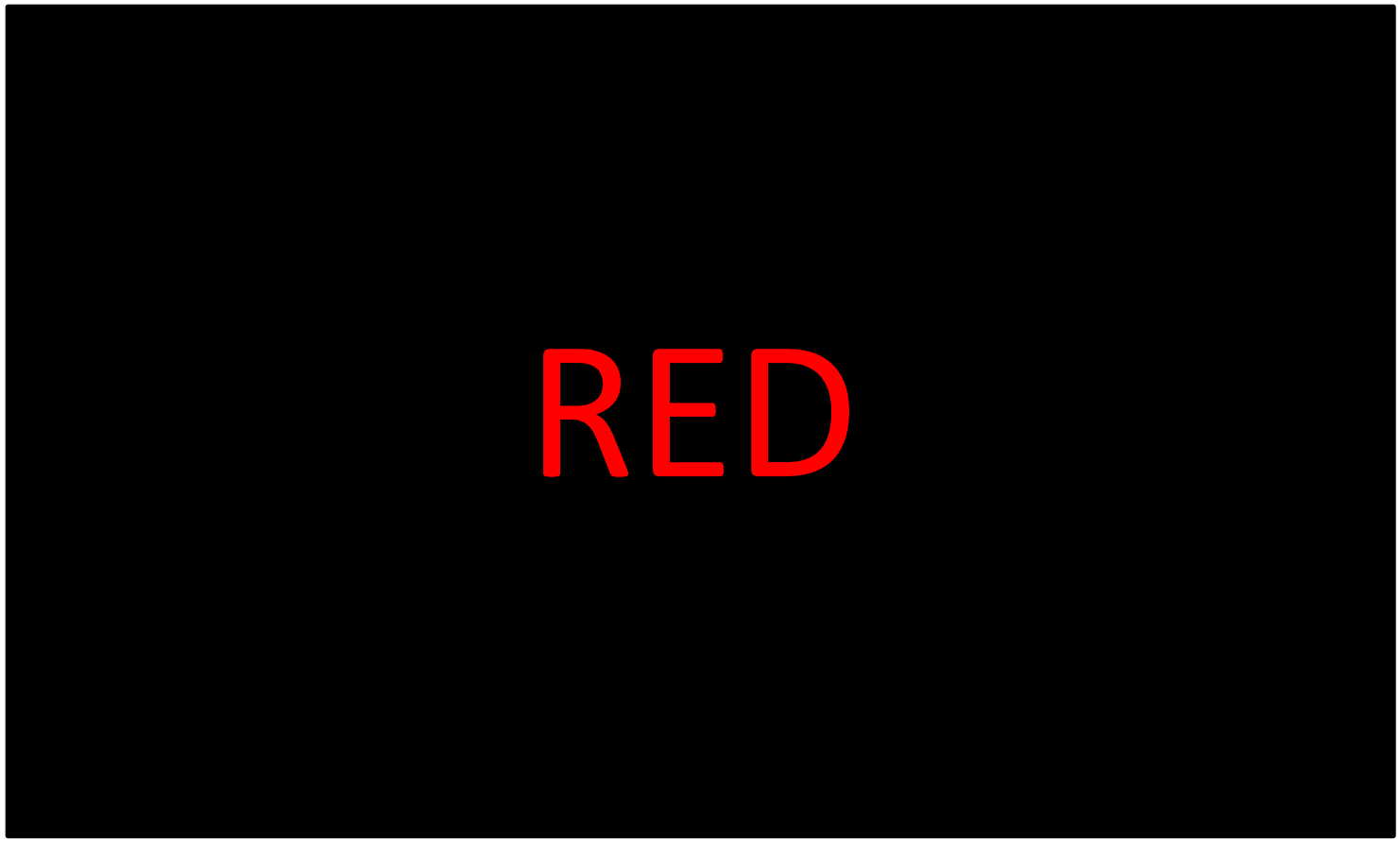
Colour Naming: What colour is it written in??

RED

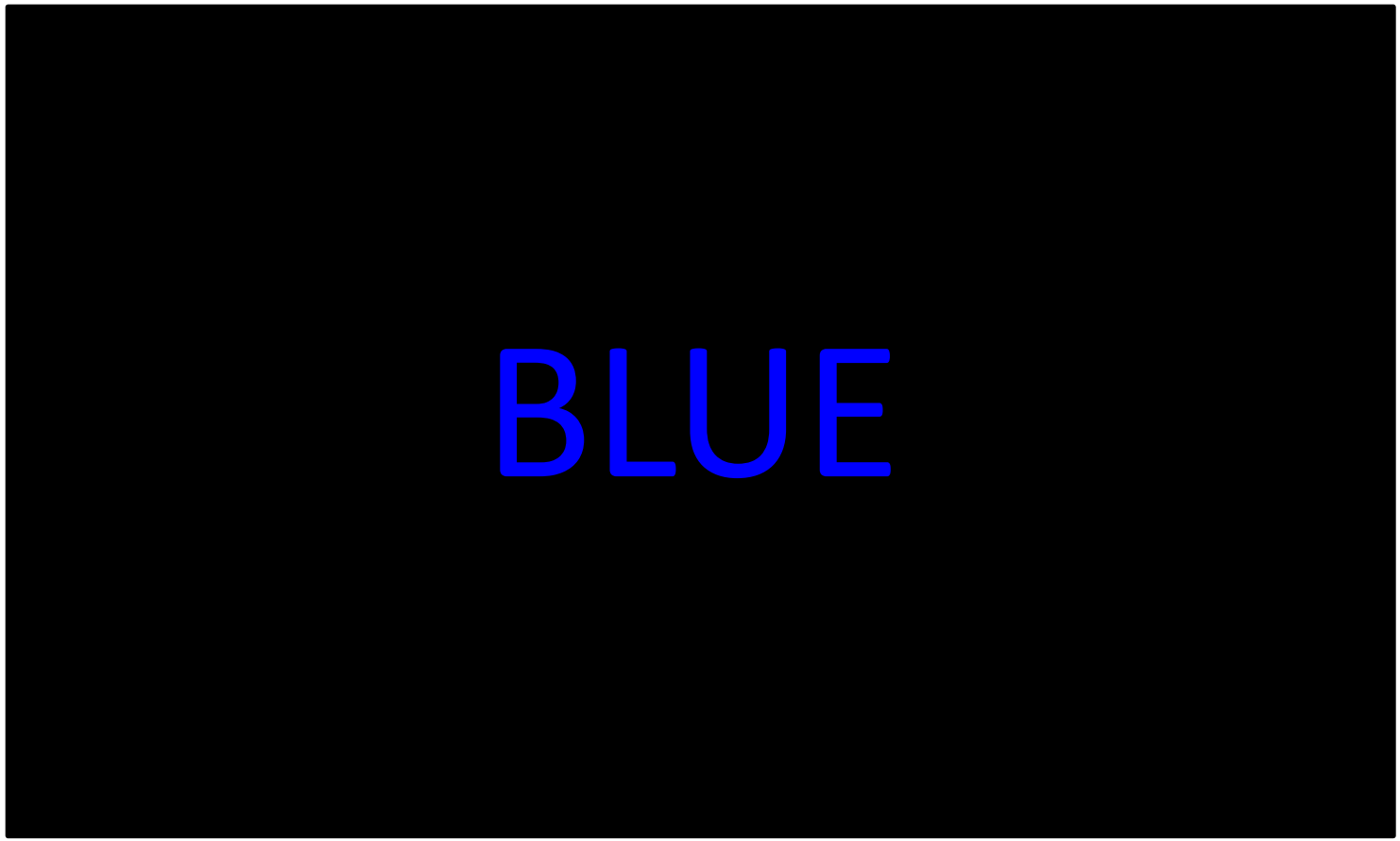
BLUE

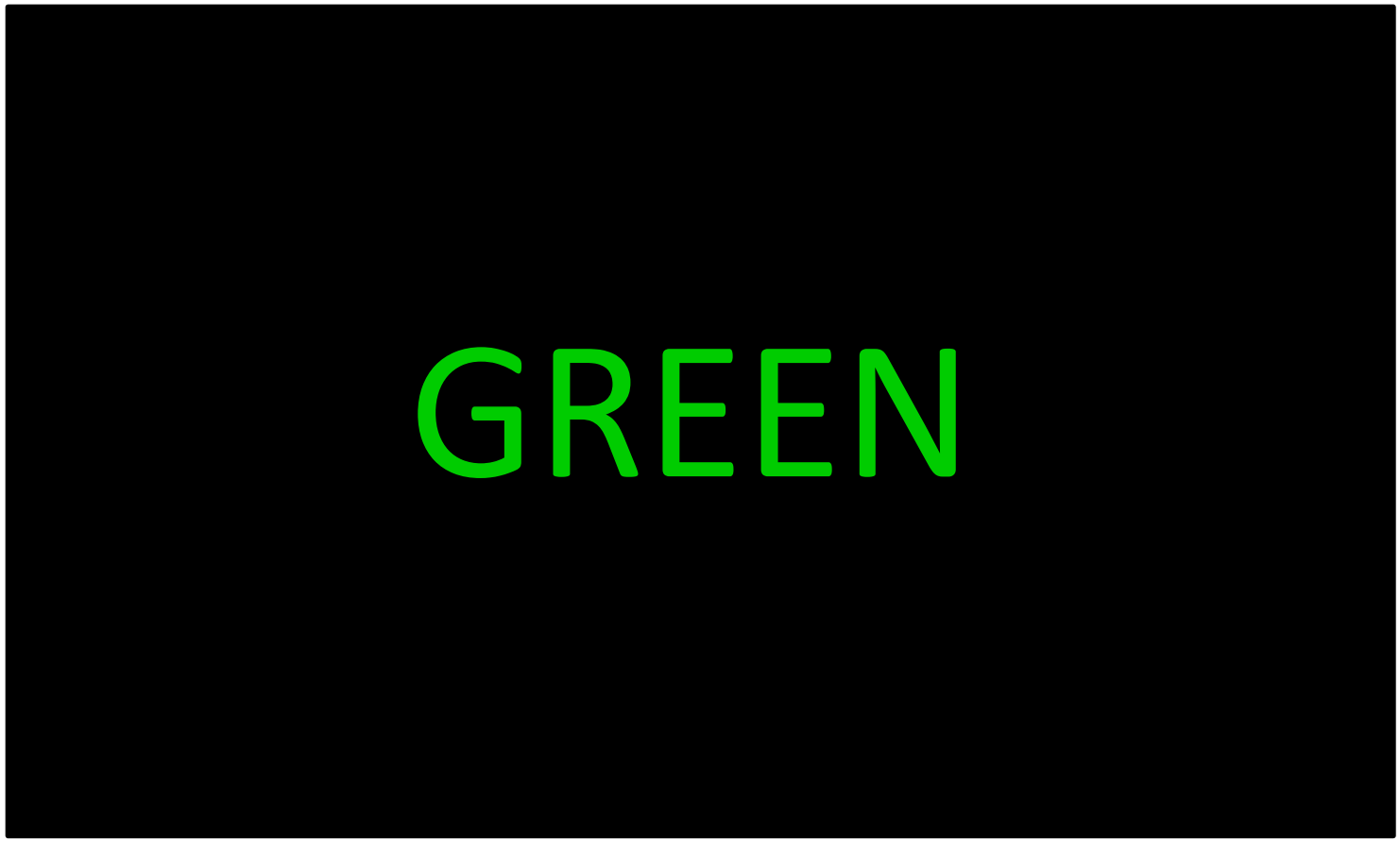
Shout out the colour of word

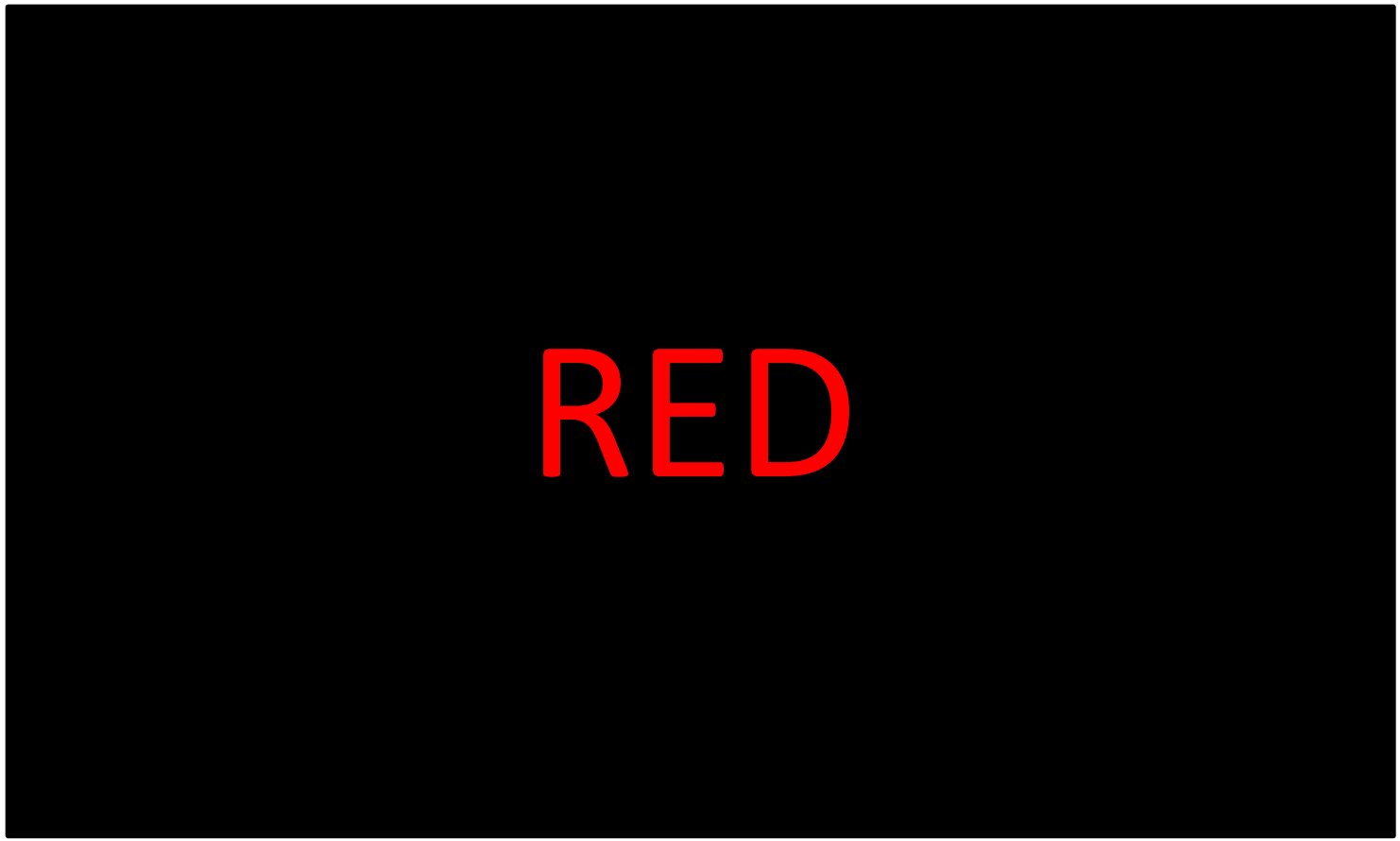
Get ready to start

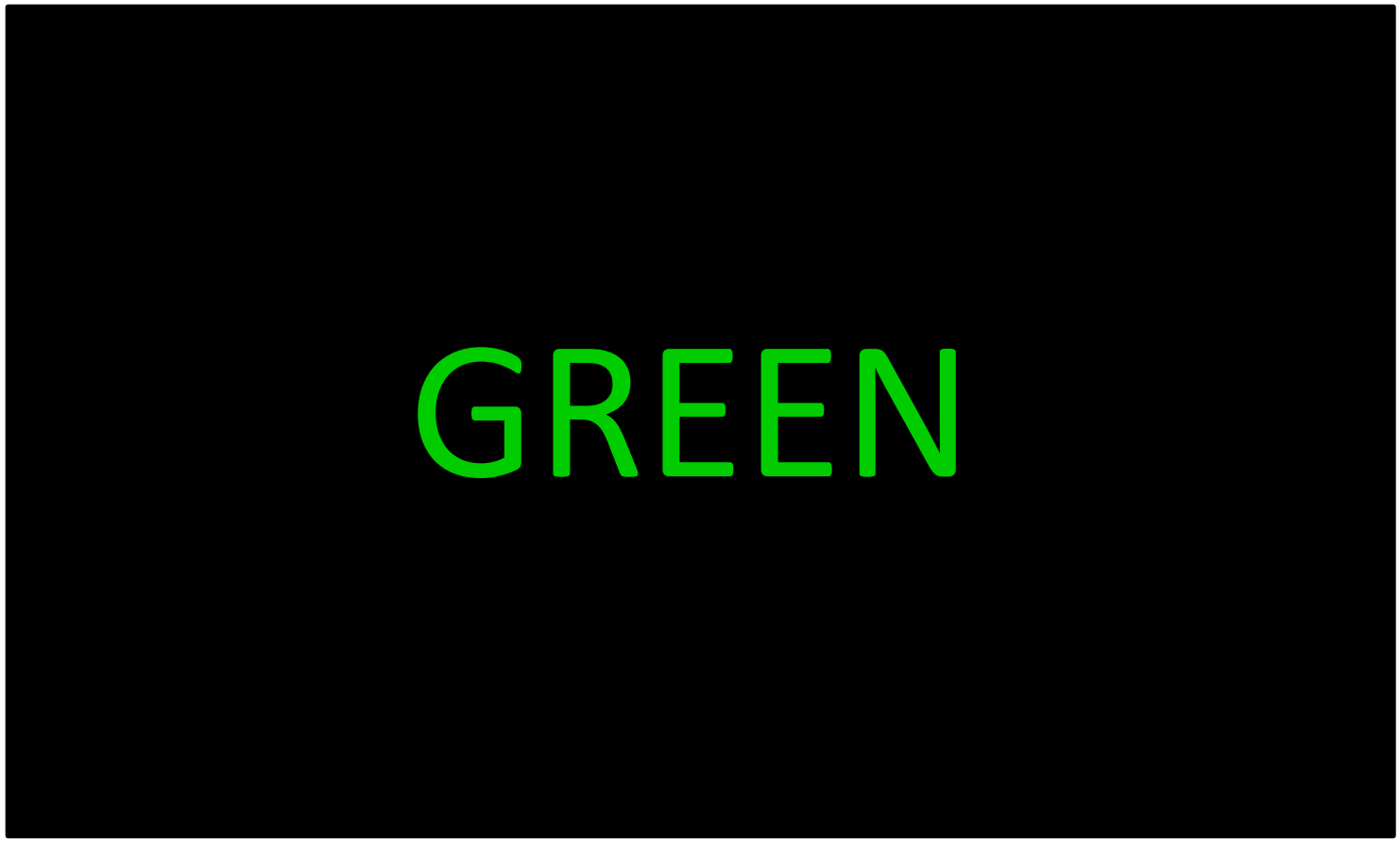

RED

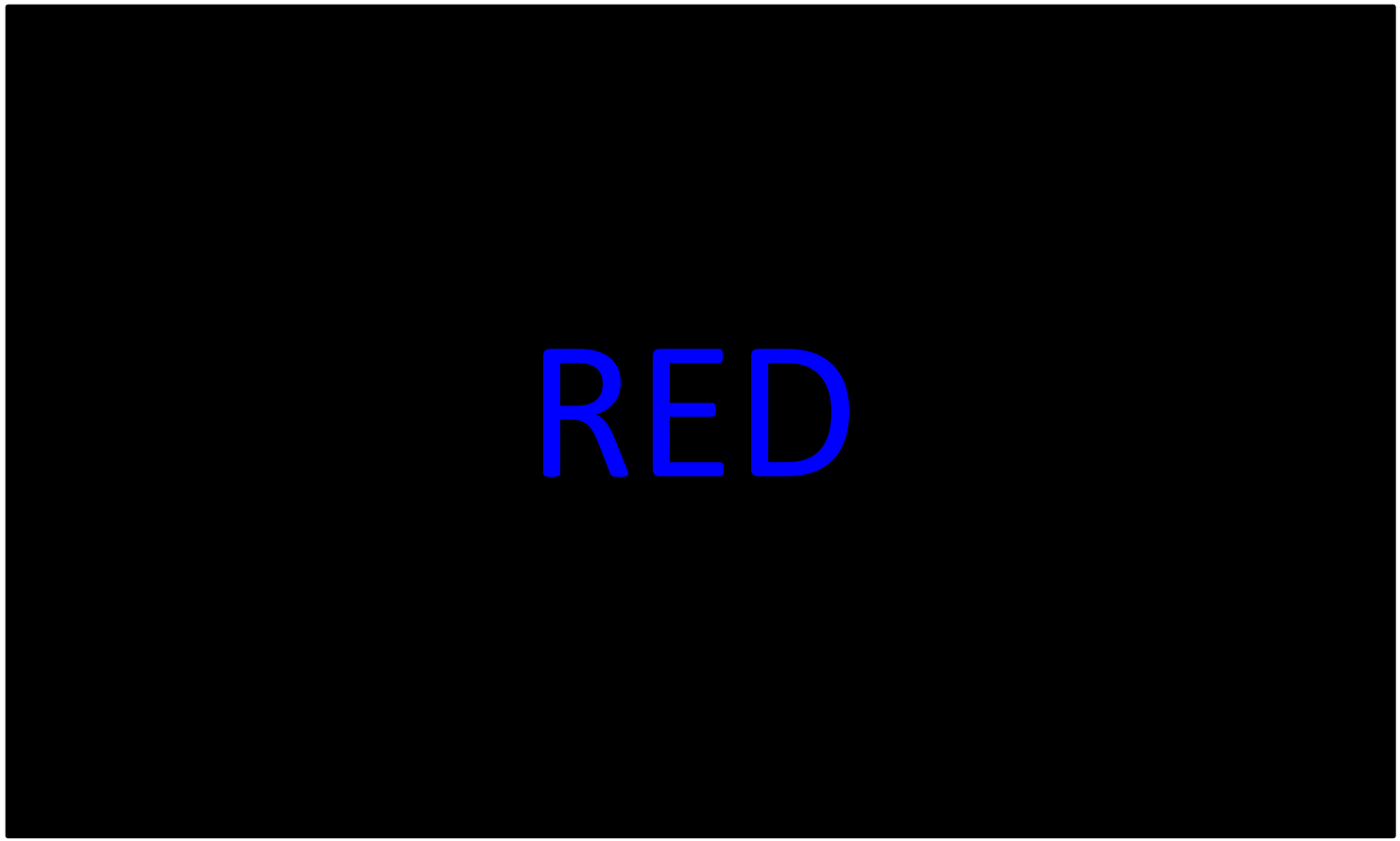
YELLOW

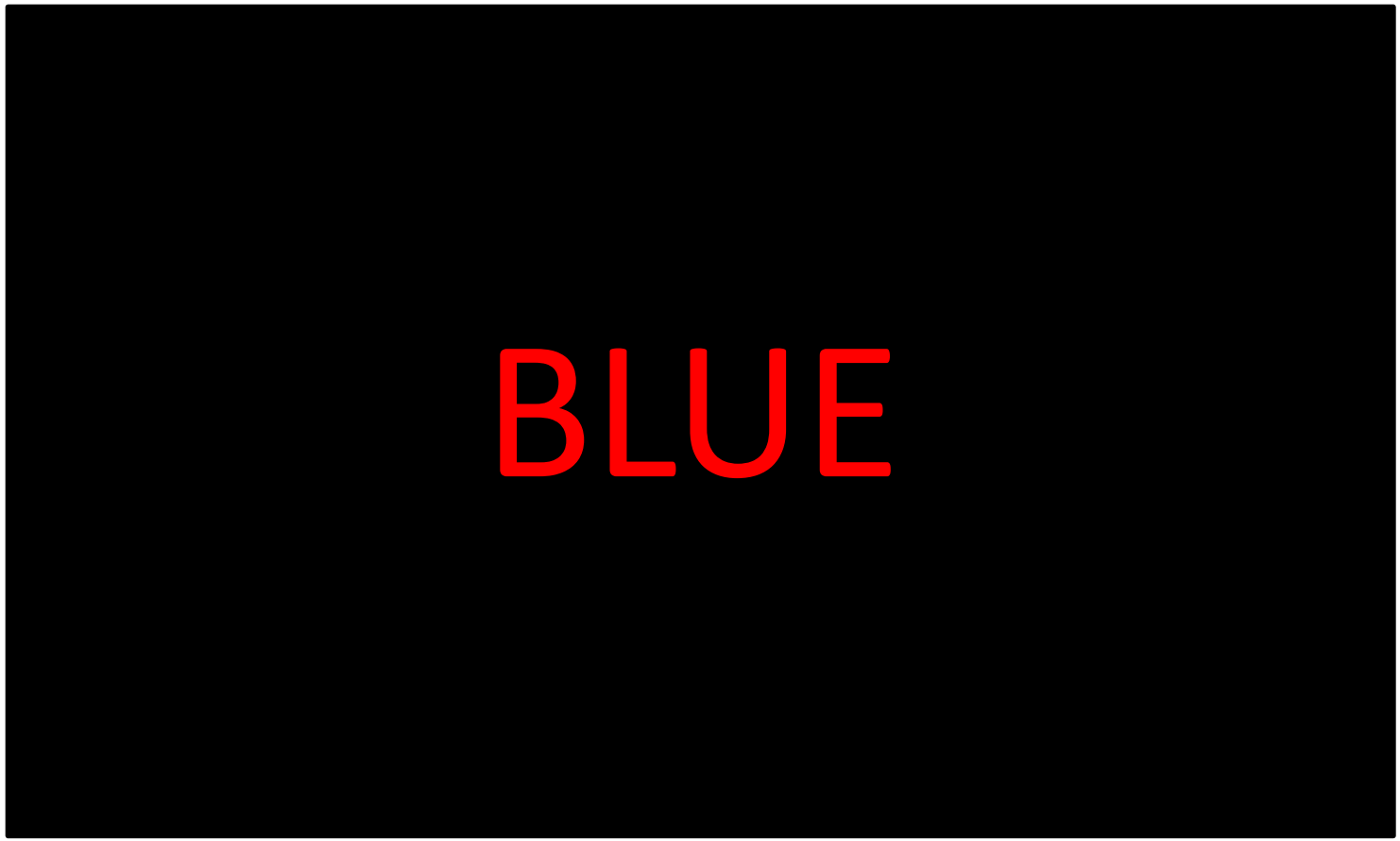

BLUE

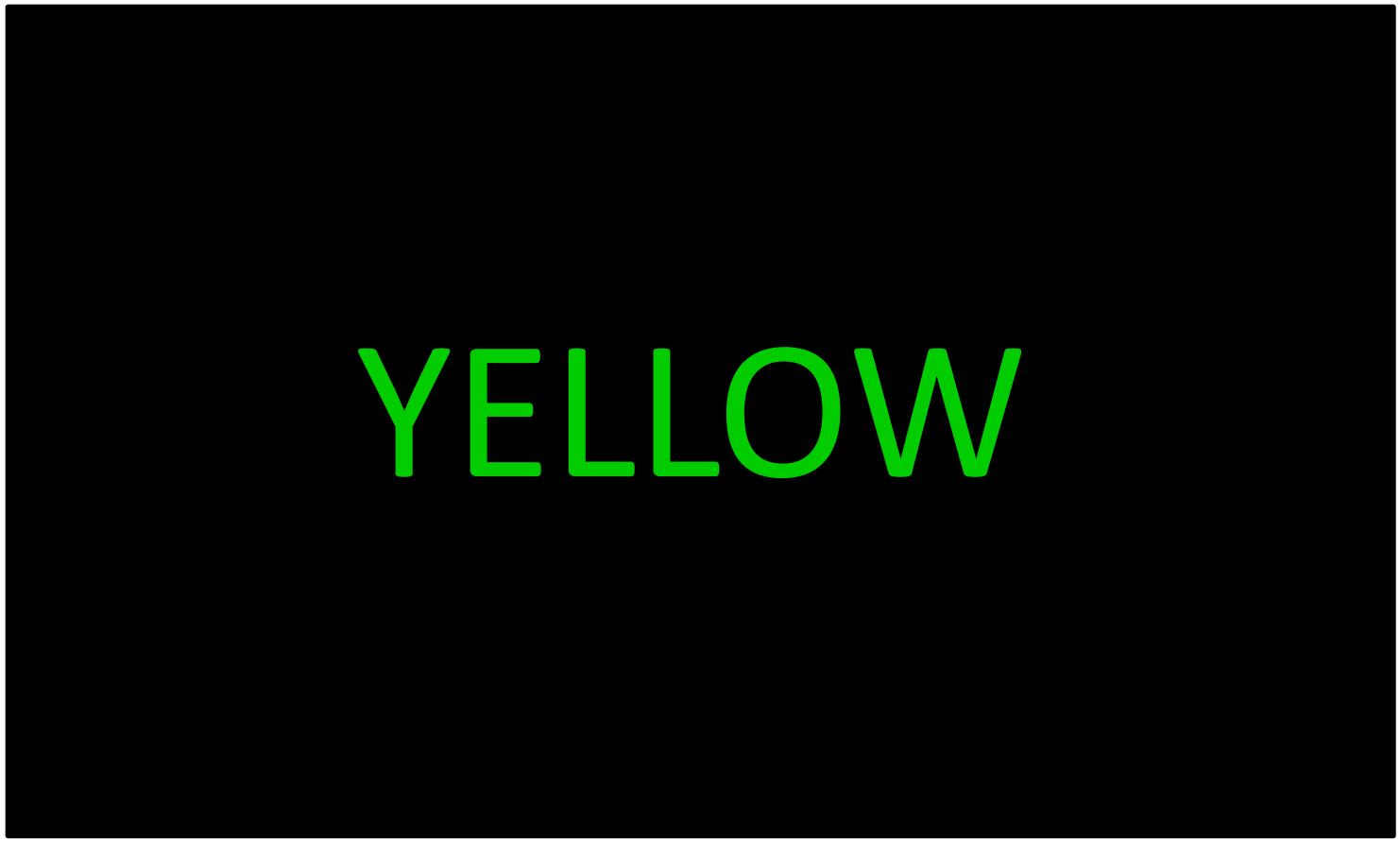

GREEN

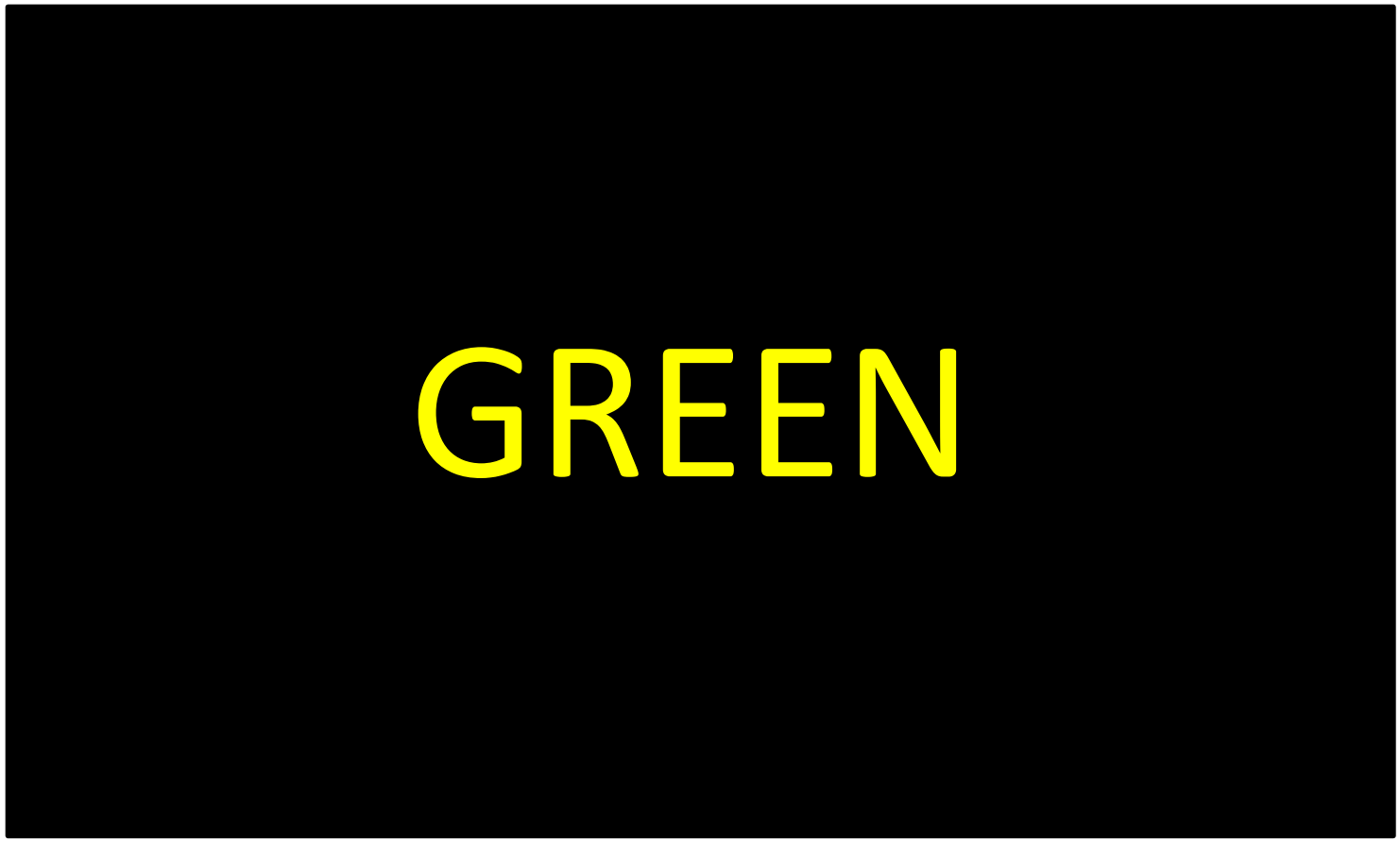

RED

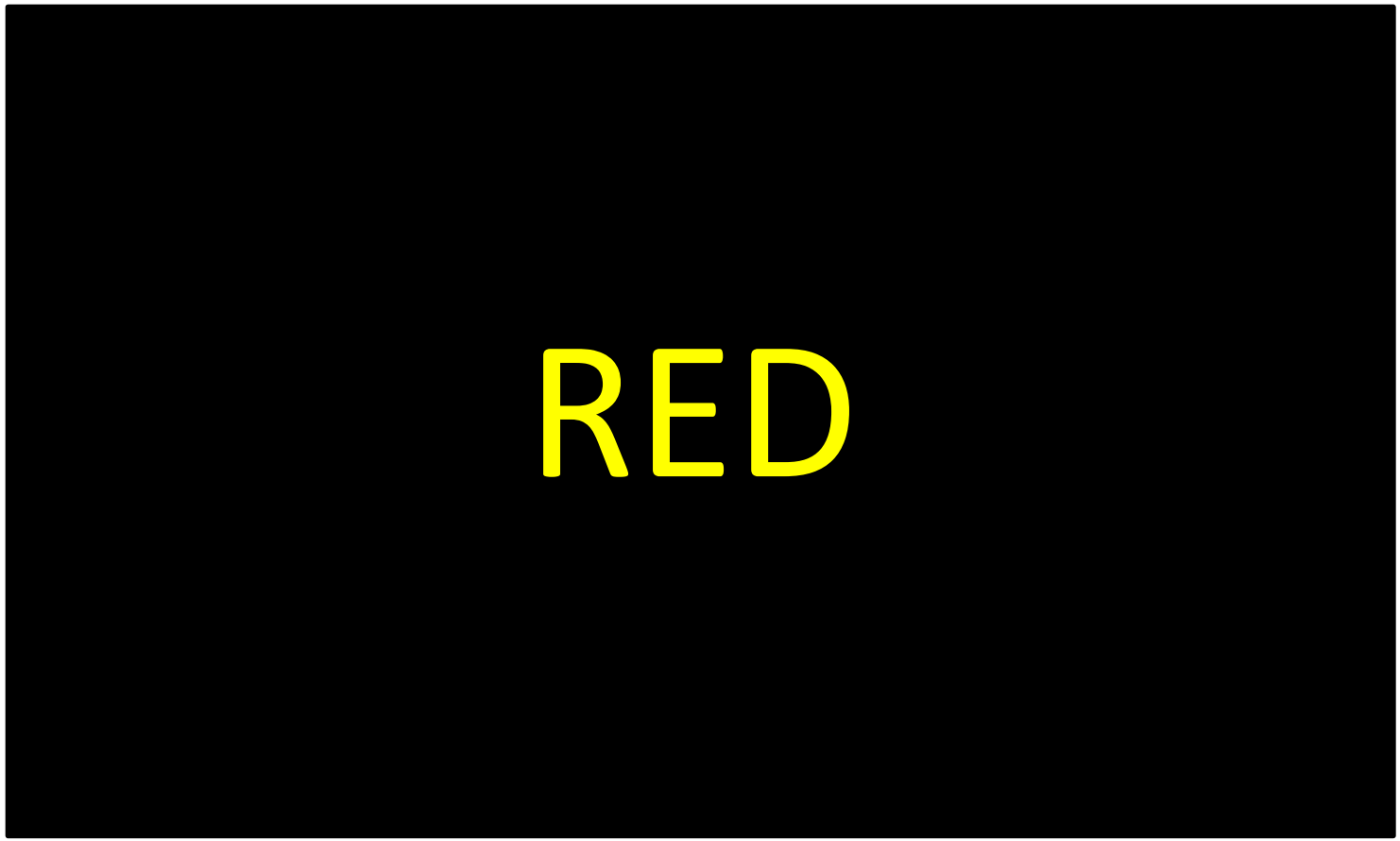

GREEN

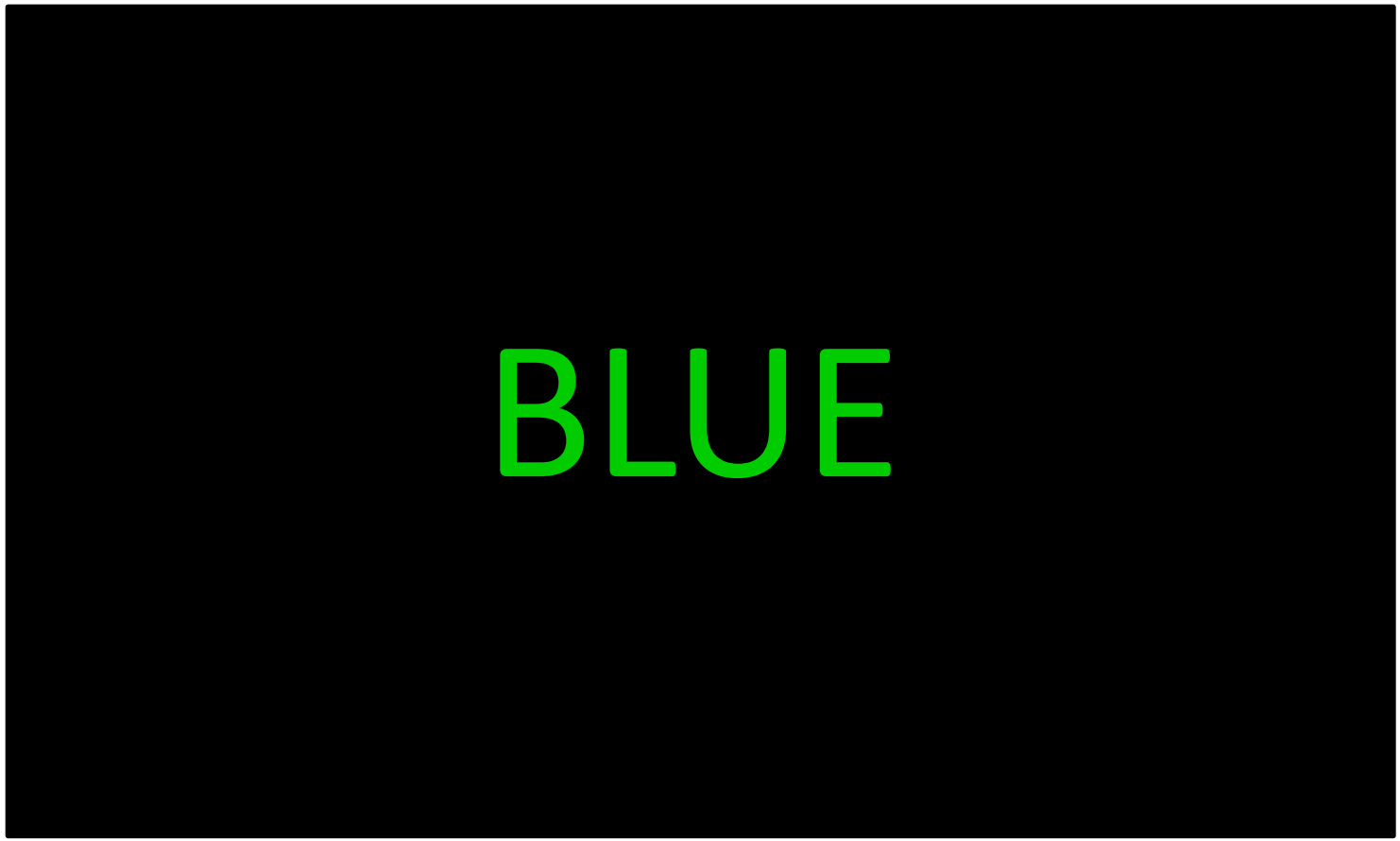

RED


BLUE


YELLOW


GREEN

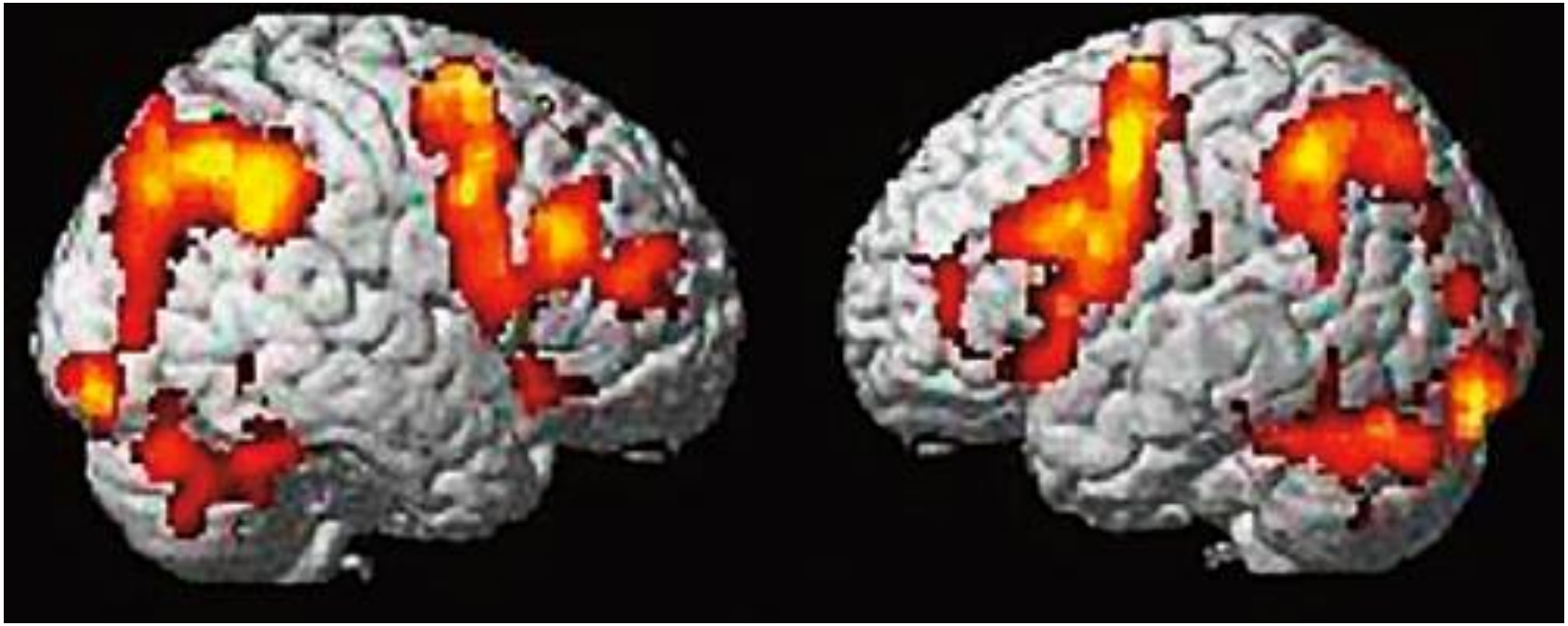

RED


BLUE

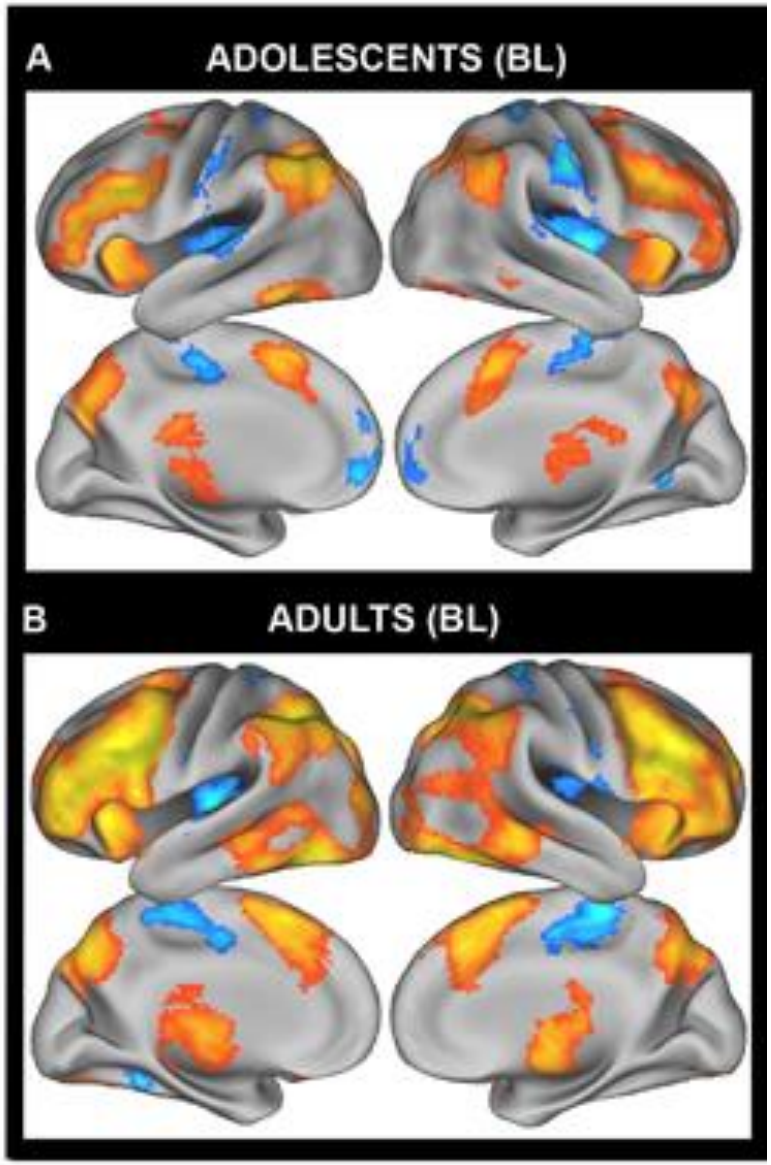
You have finished this task

Why is it so hard??

Conflict between the colour and the word.



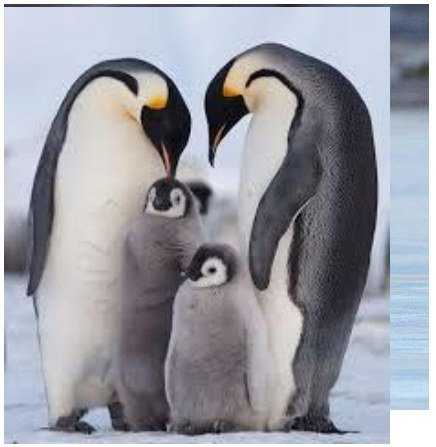
Adolescents vs. adults

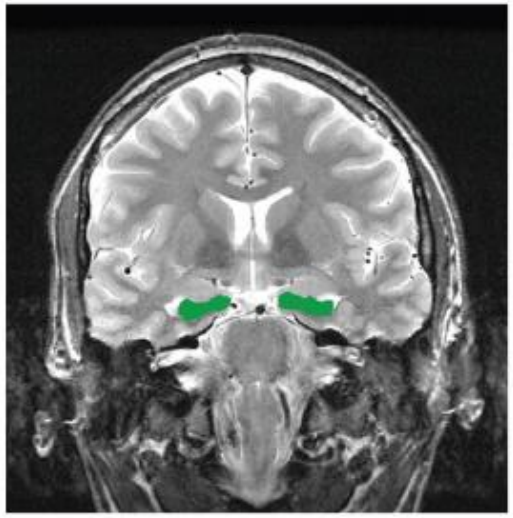


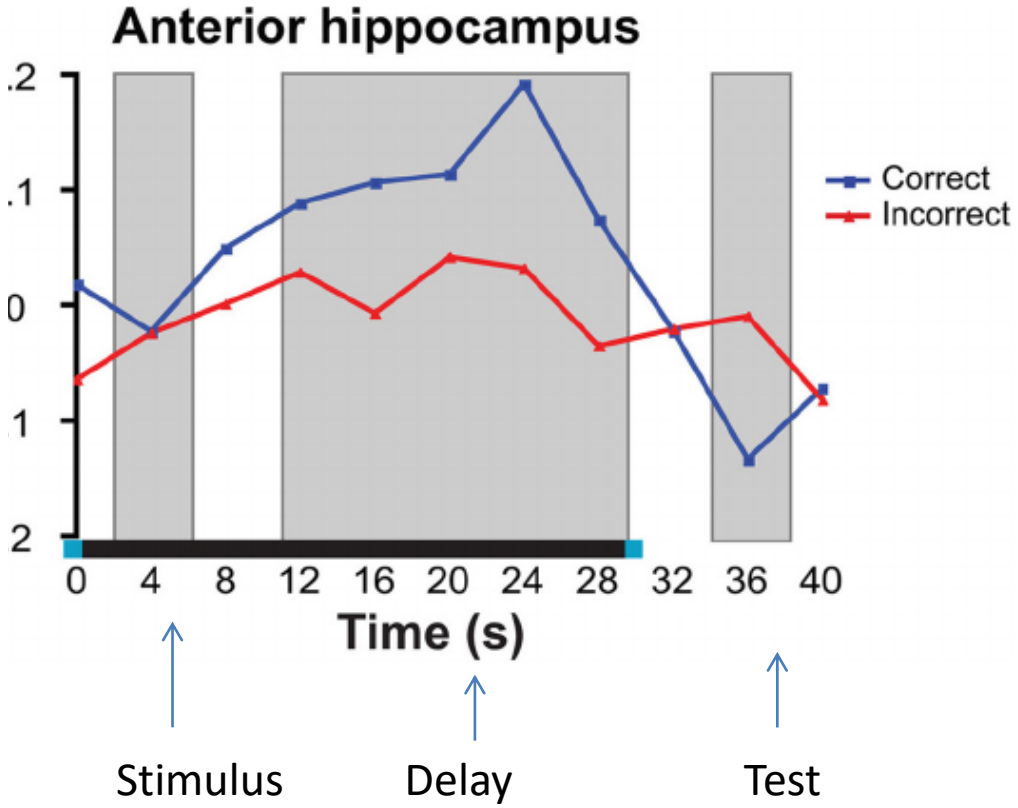
Thinking: Memory

?

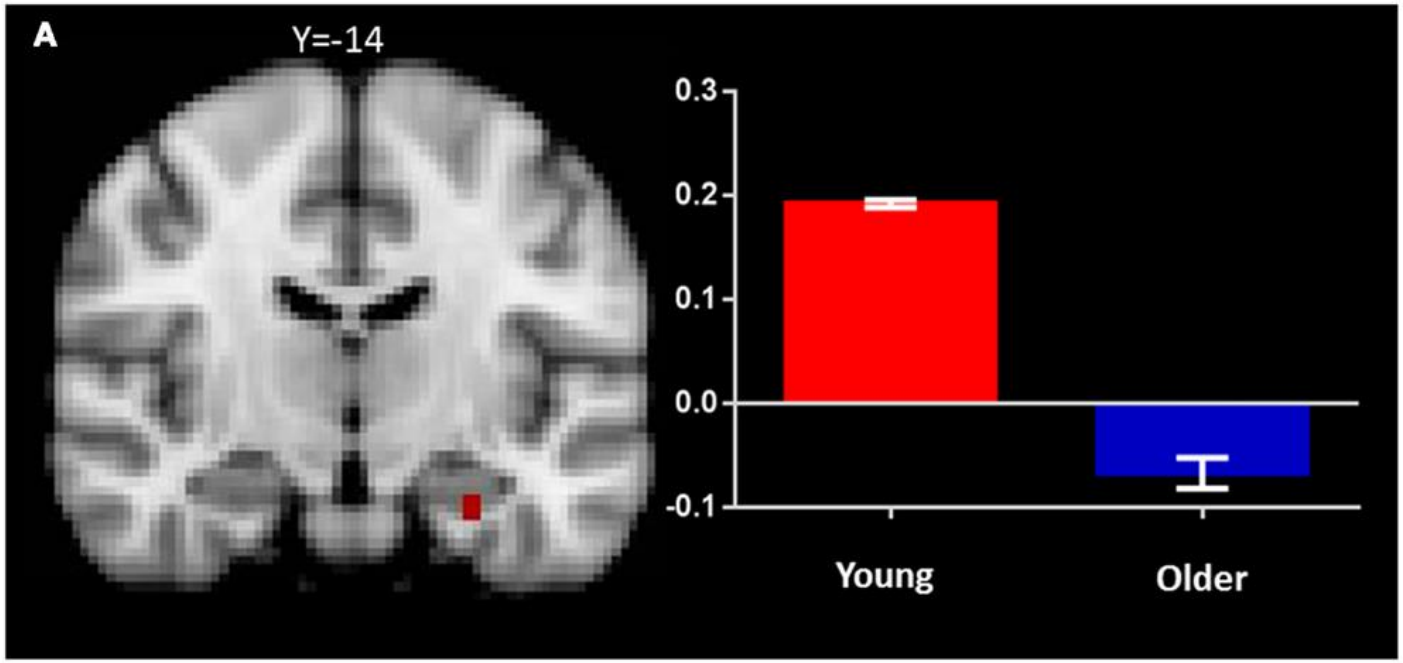
?






Anterior hippocampus
.2
.1
0
.1
.2
0
4
8
12
16
20
24
28
32
36
40
Time (s)
Correct
Incorrect
Stimulus
Delay
Test

Age-related memory decline



Behaving: stopping

Clap when you see any letter except “V”

Get ready to start

C

D

N

H

L

B

F

C

V

M

F

V

N

V

M

F

L

B

V

V

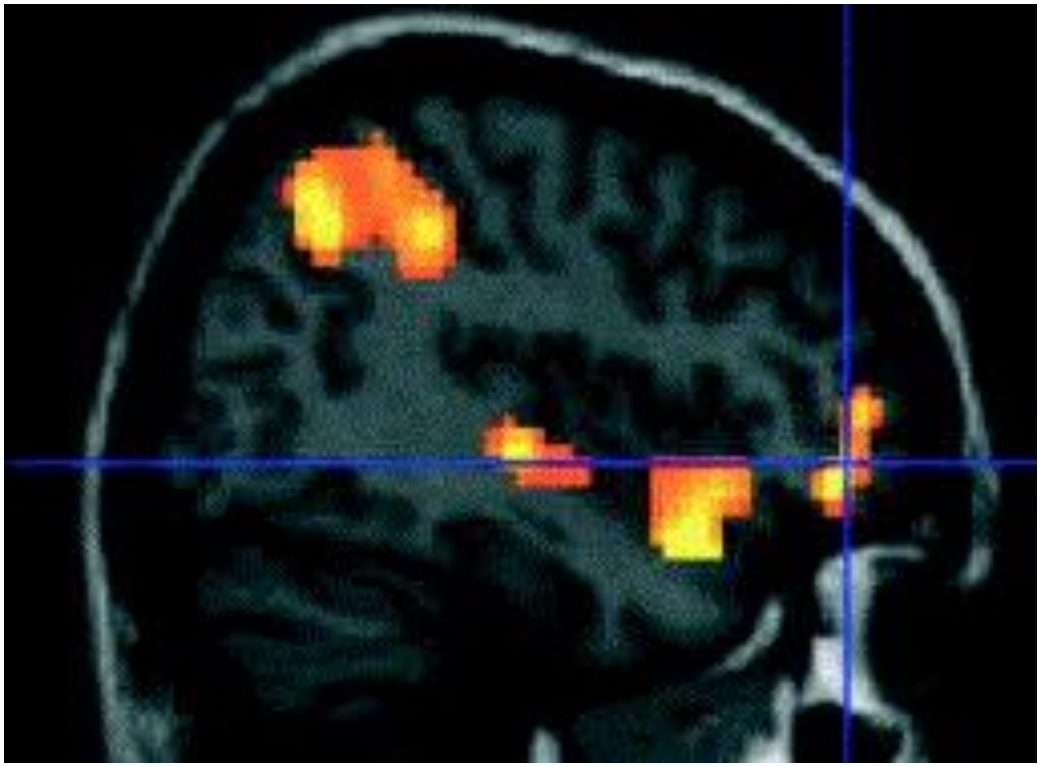
H

N

C

B

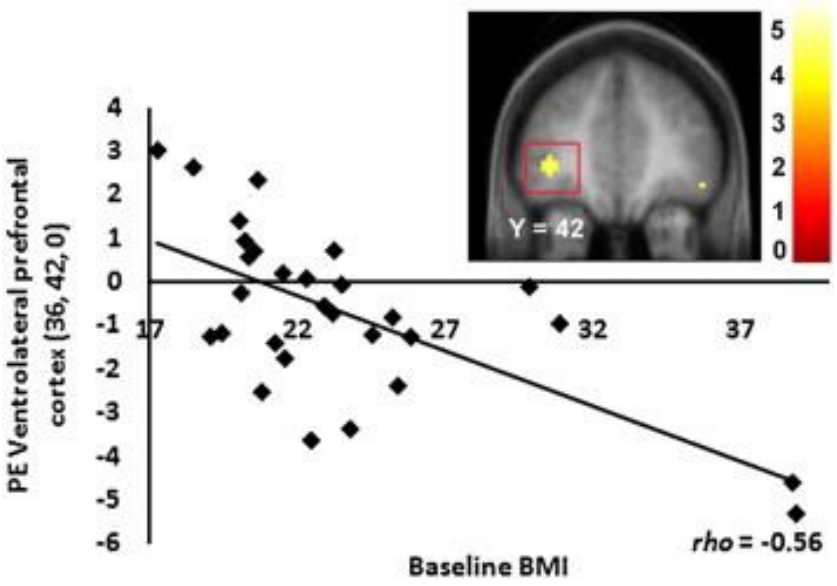
You have finished this task

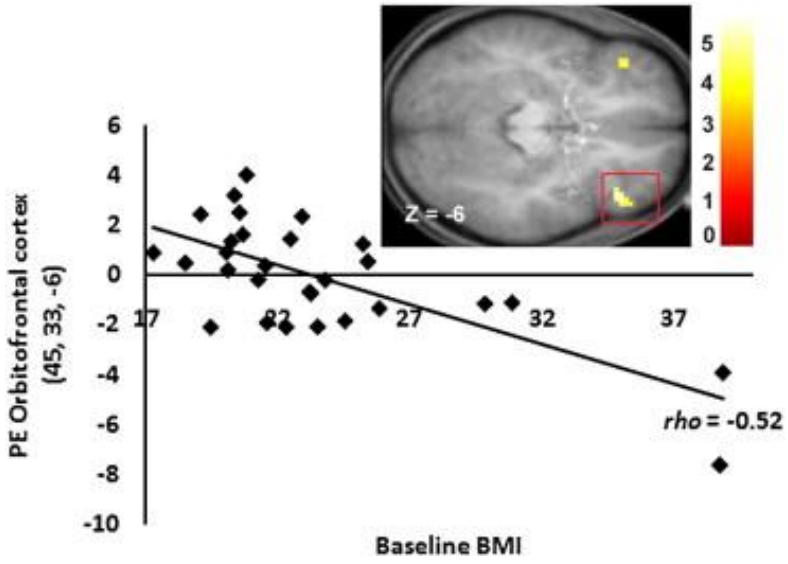


- Impulse control
-Various problems if it doesn’t work properly


Addiction
(Dependence)


© Alamy

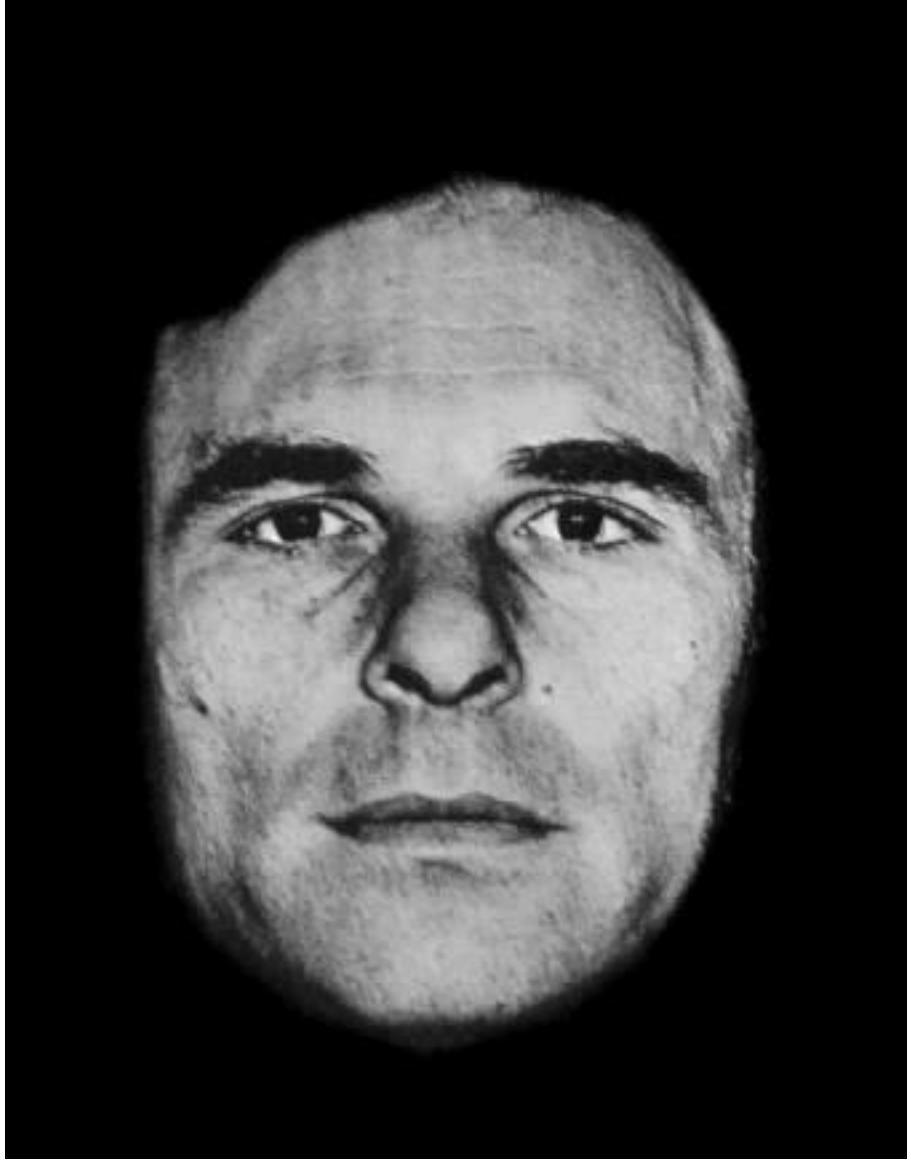

PE Ventrolateral prefrontal cortex (36, 42, 0)
Baseline BMI
rho = -0.56
Y = 42
4
3
2
1
0
-1
-2
-3
-4
-5
-6
17
22
27
32
37
5
4
3
2
1
0

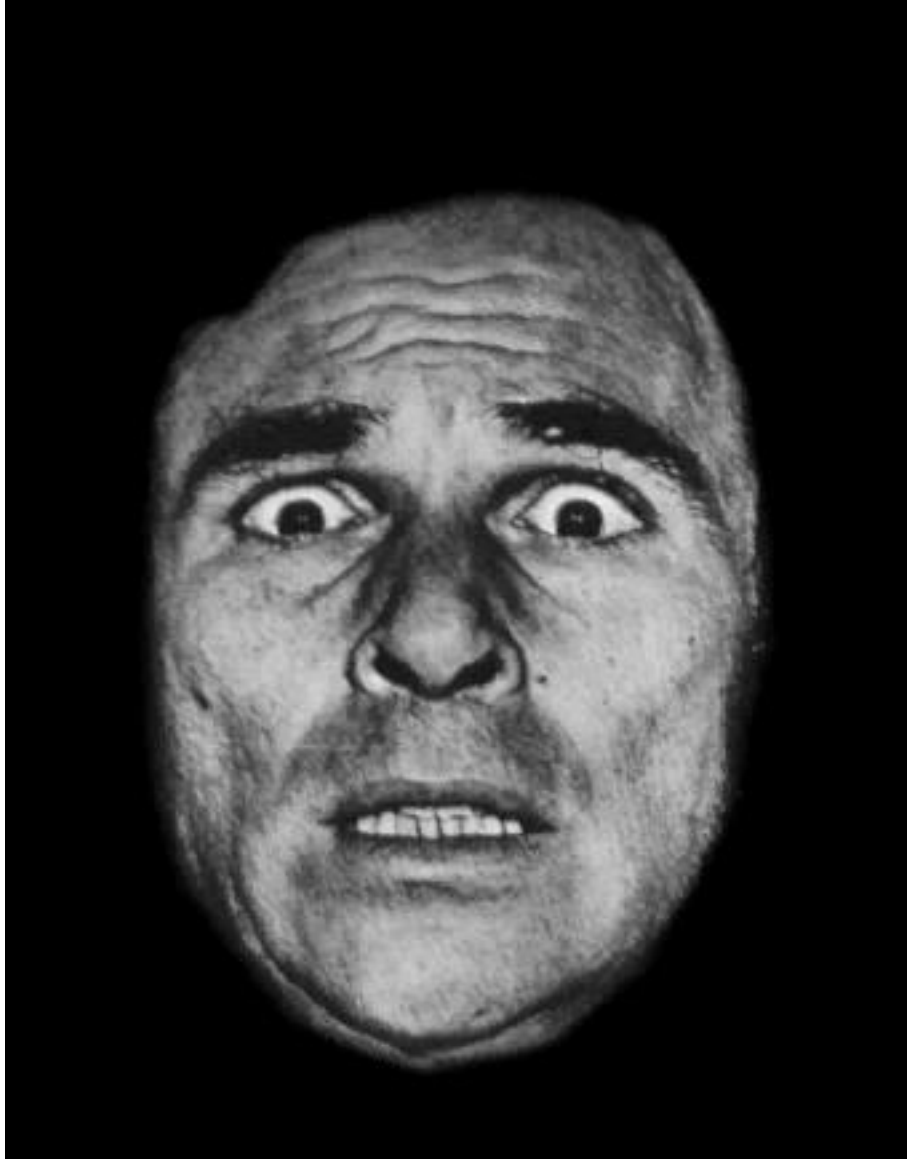

PE Orbitofrontal cortex (45, 33, -6)
Baseline BMI
rho = -0.52
Z = -6
6
4
2
0
-2
-4
-6
-8
-10
17
22
27
32
37
5
4
3
2
1
0

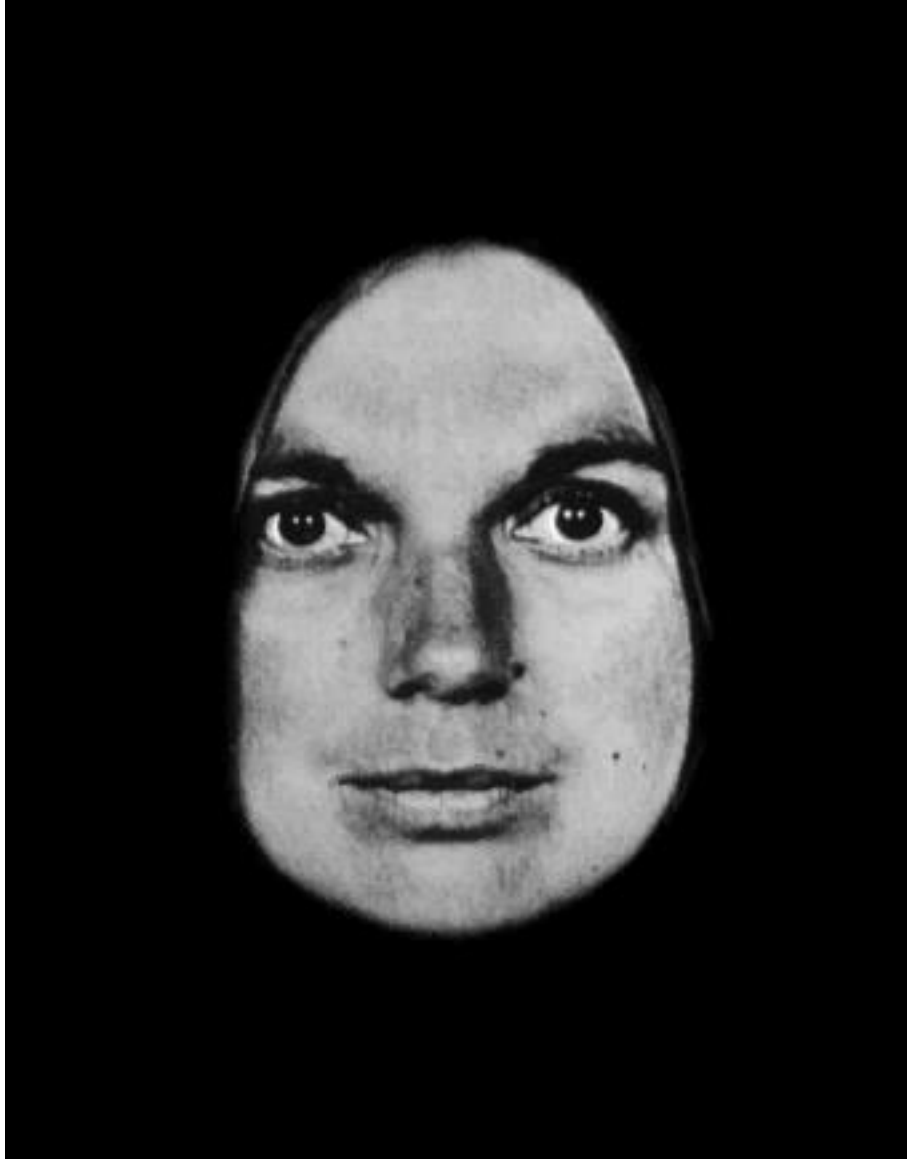
Feeling: emotional faces

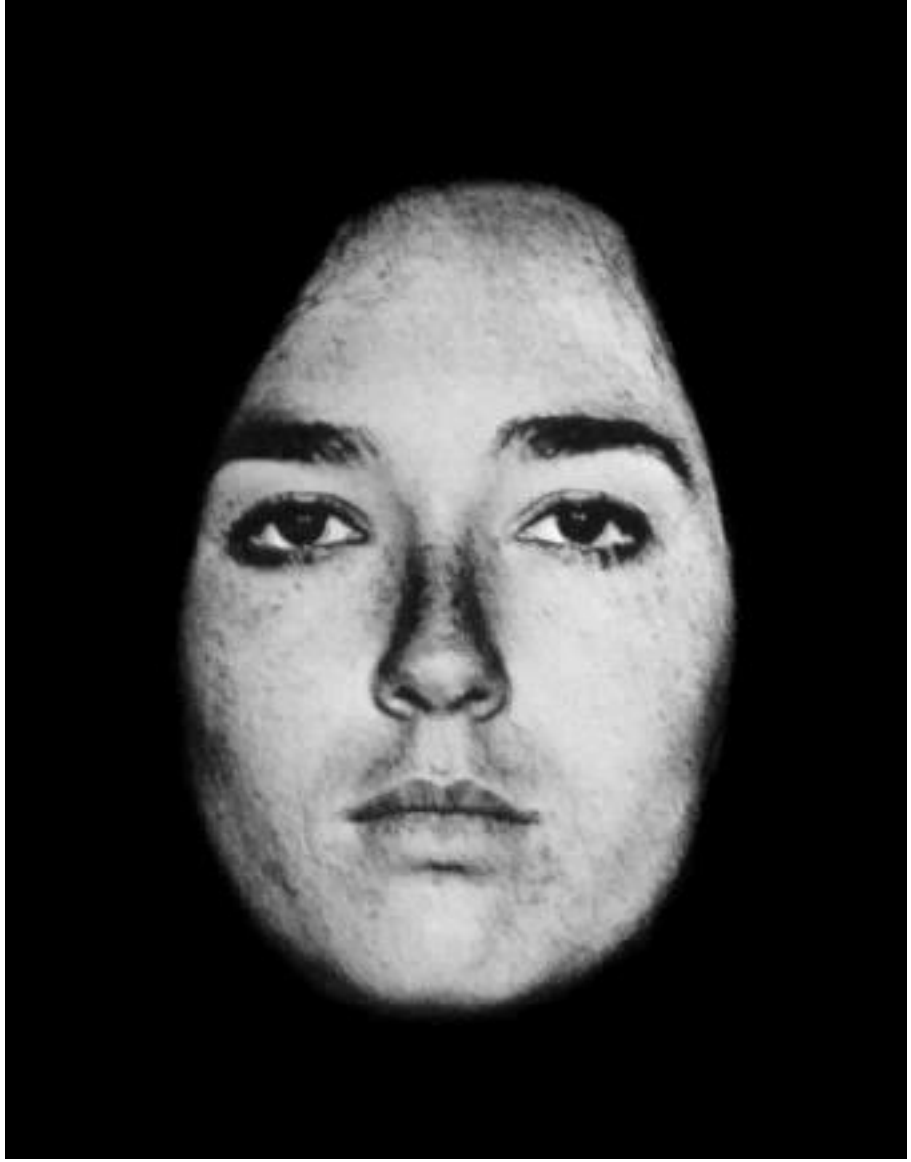
Shout out FEMALE or MALE when see face

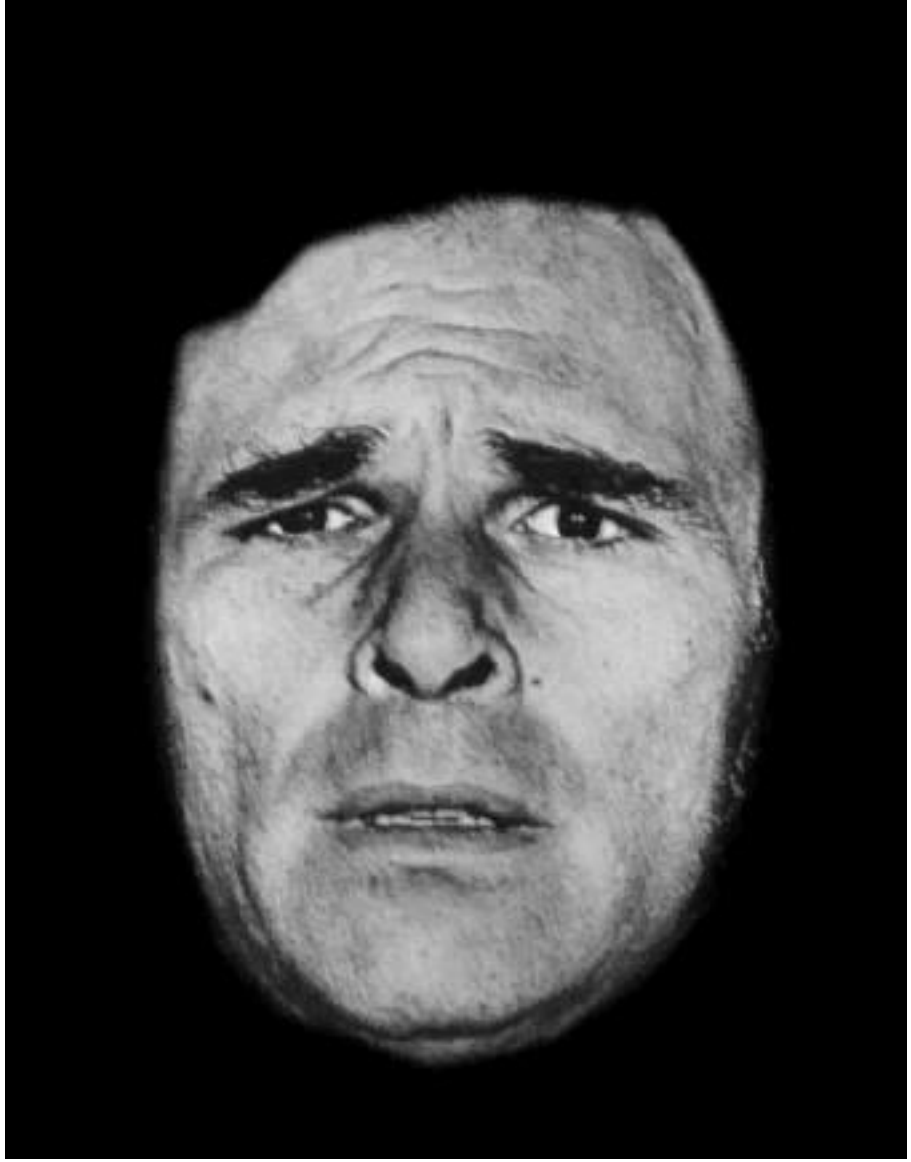
Get ready to start

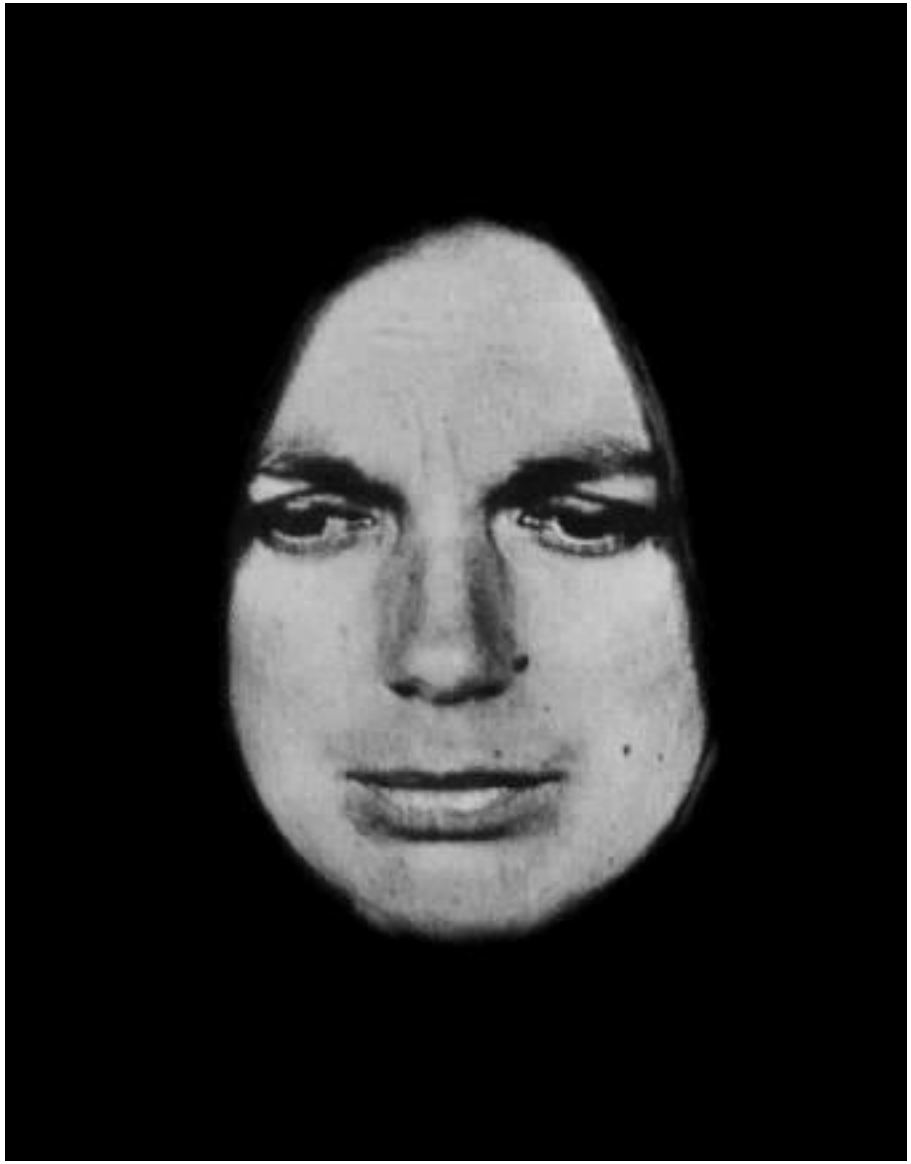




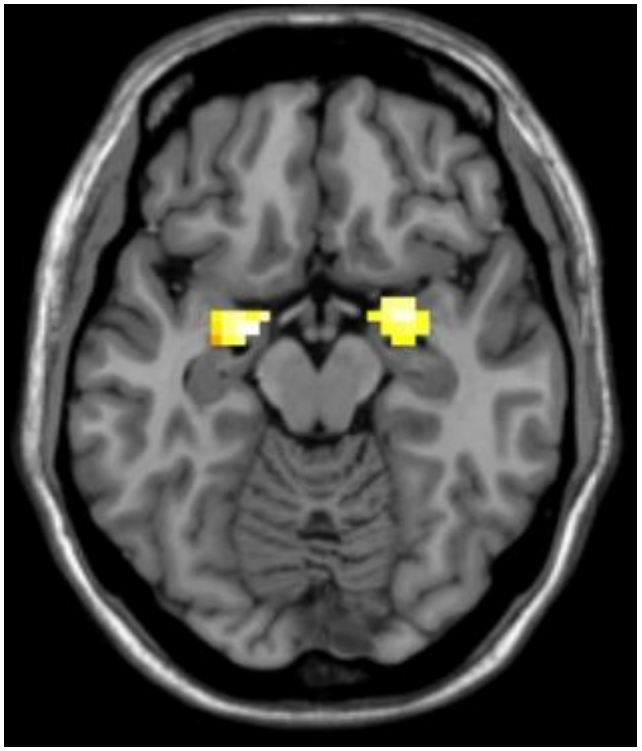








You have finished this task



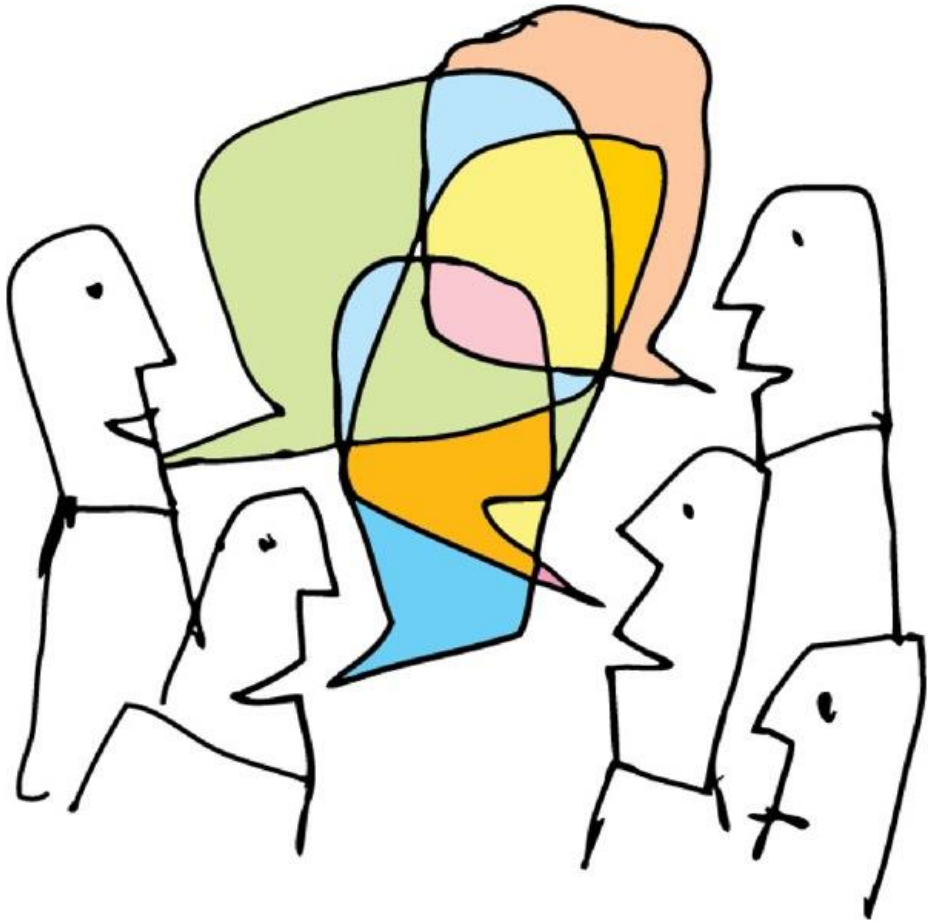
The Amygdala

Most of us

Anxiety

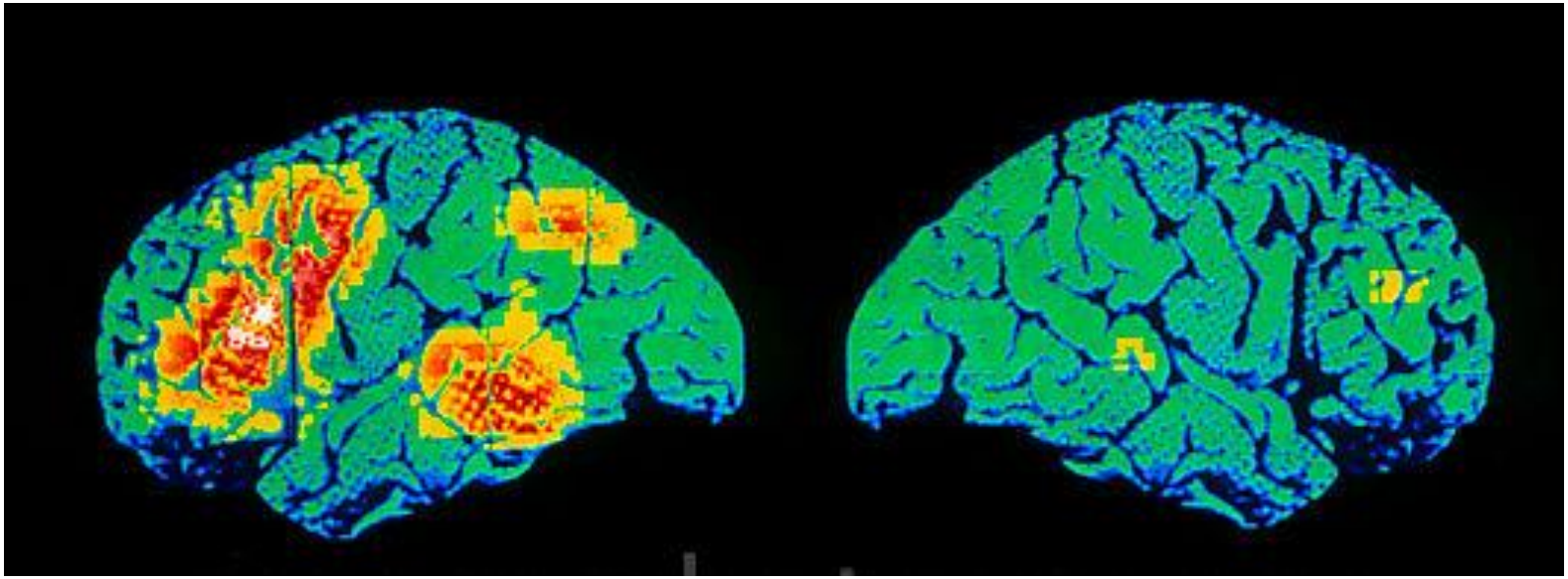
Depression

Brain damage and recovery

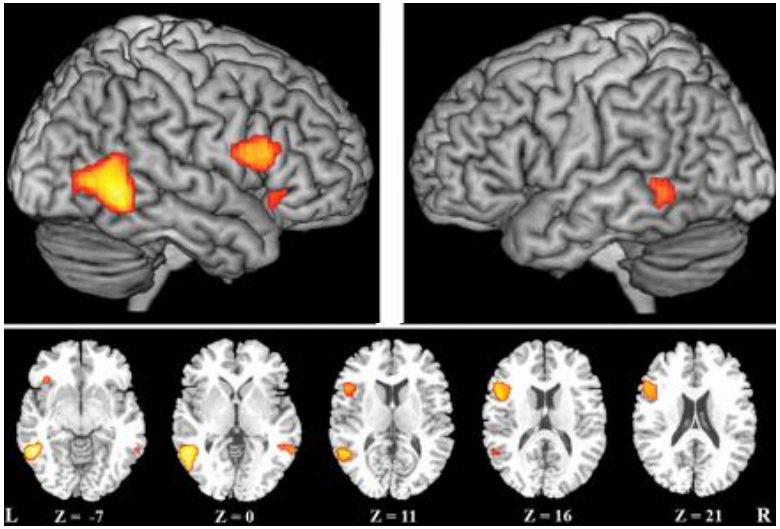


Talking……

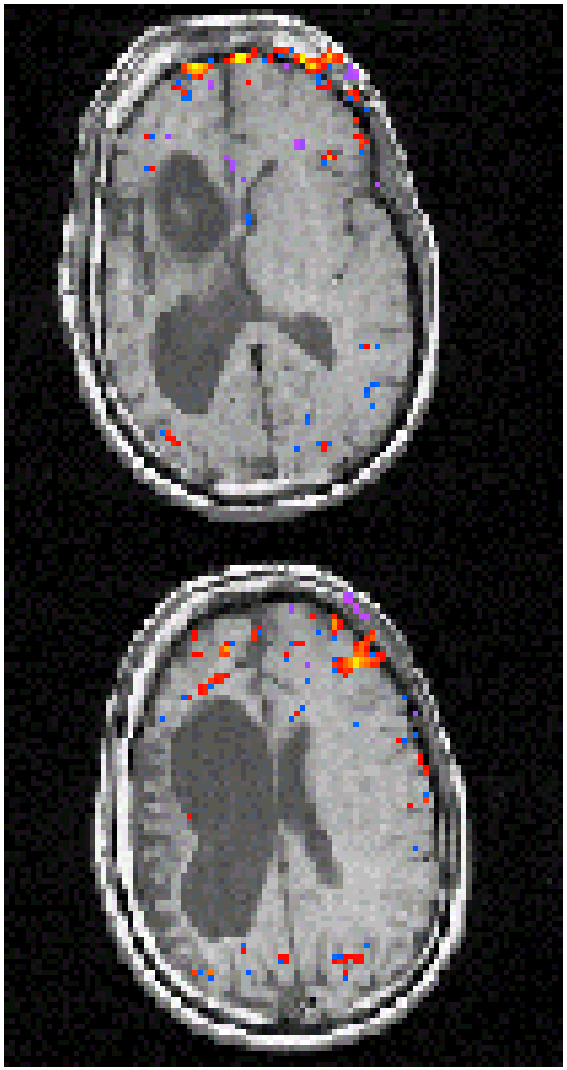
What happens in the brain when we talk?



LEFT



RIGHT



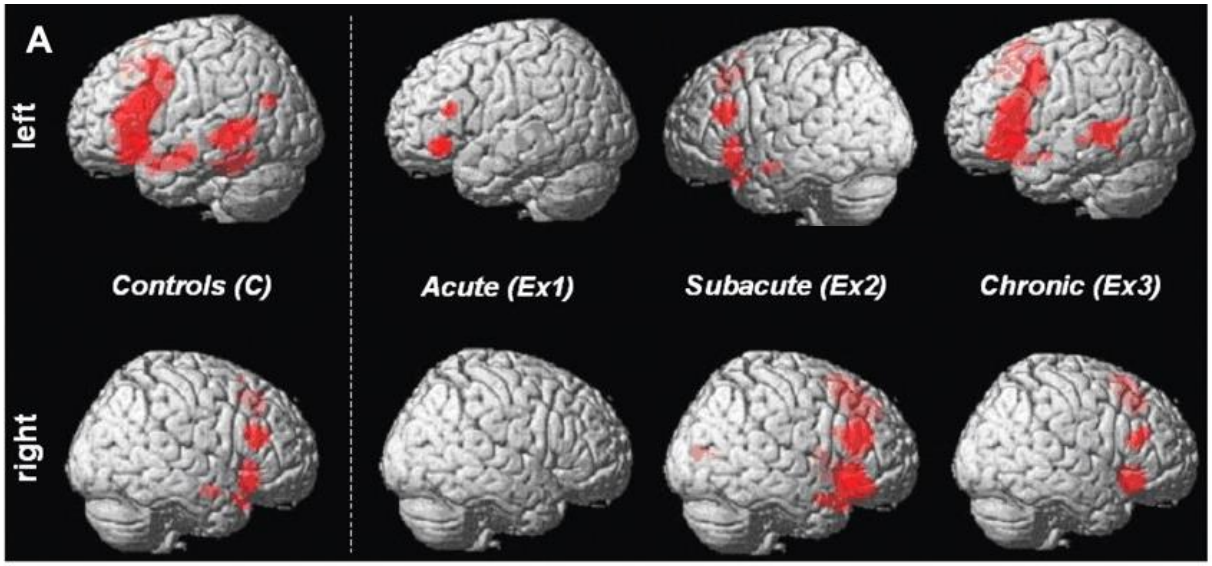
fMRI of 25 year old.

Brain damage from birth.

Speech is normal.

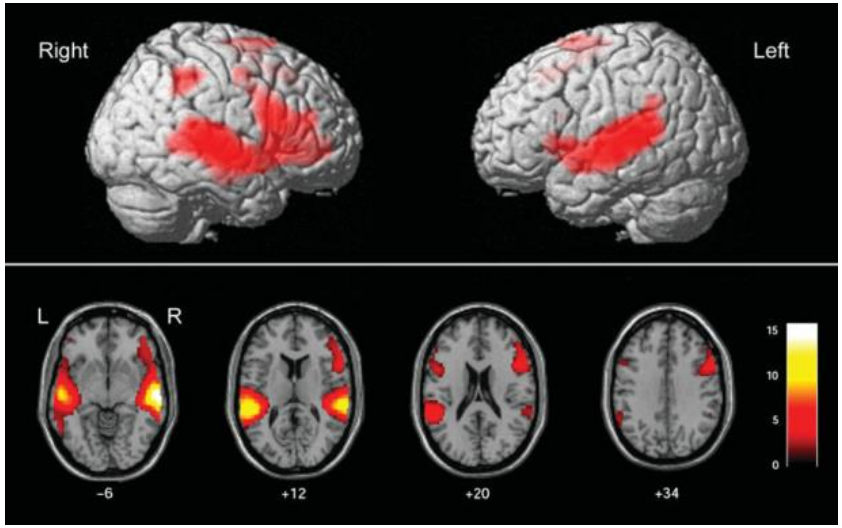
Stroke in older people:

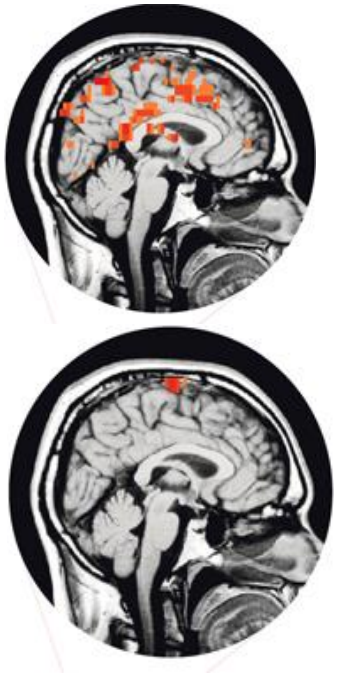
Language may be very bad at first then get better



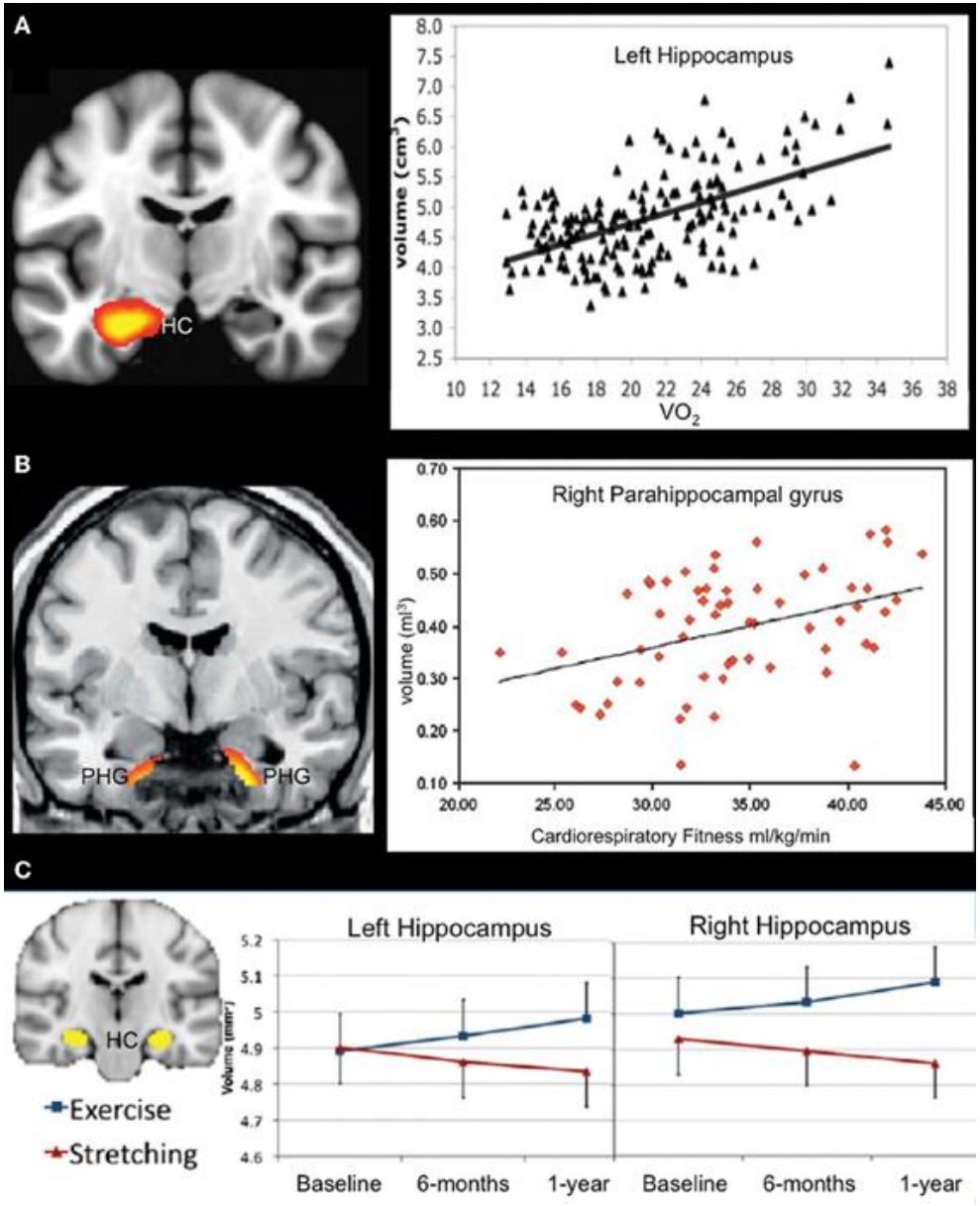
Healthy 2 Days 2 weeks 9 months

Can behaviour change your brain?



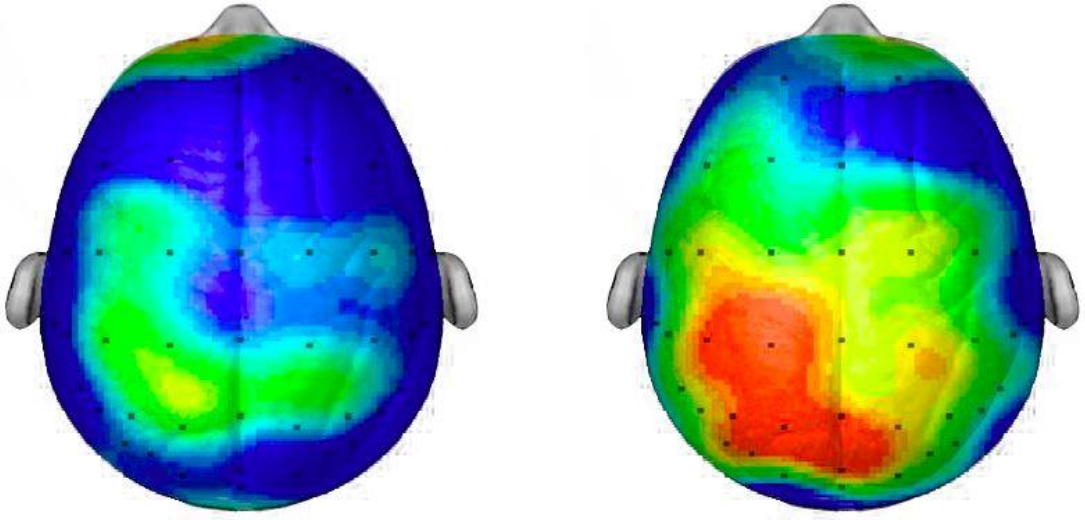


Lifestyle changes?



Shorter term?

Composite of 20 student brains taking the same test



After sitting quietly

After 20 minute walk

Brain Imaging

- How we perceive
- How we think
- How we behave
- How we feel

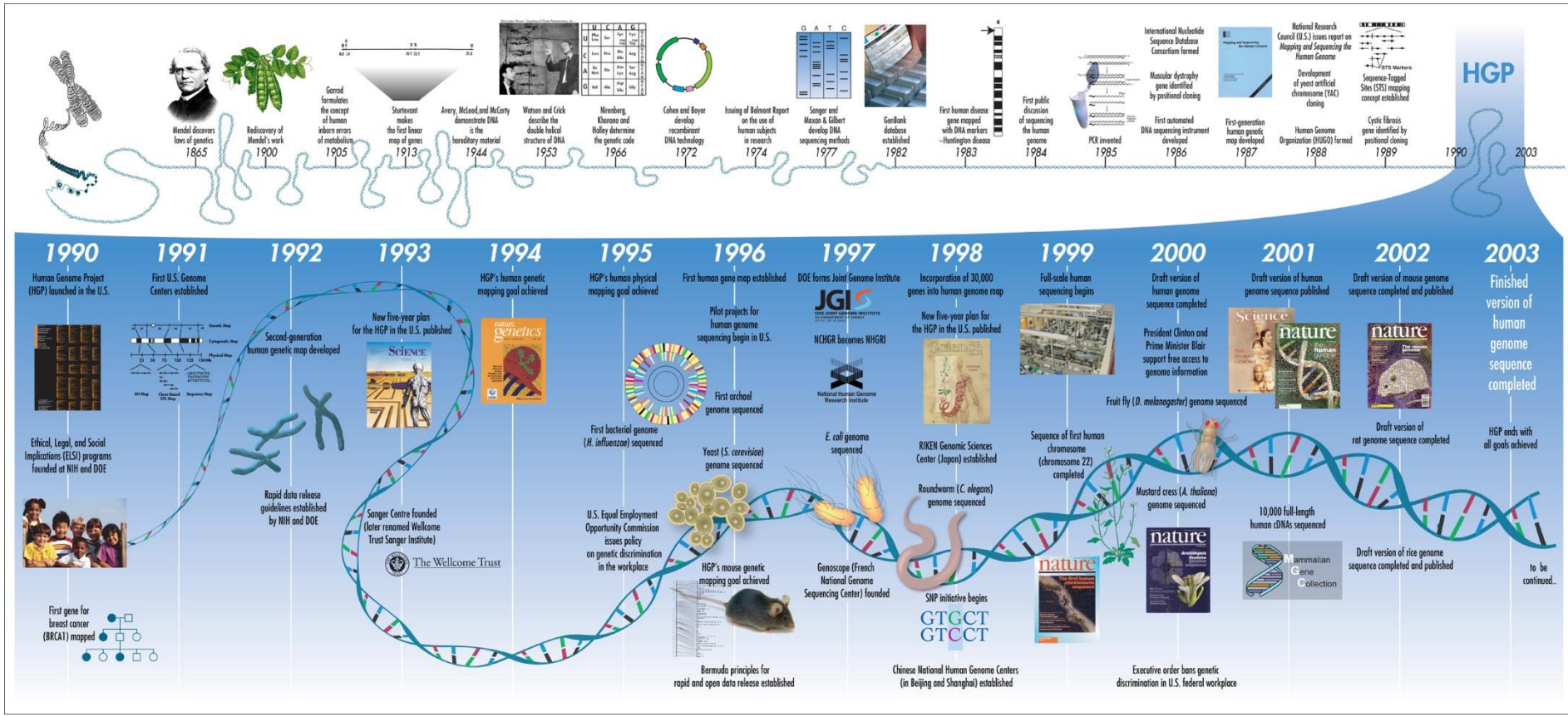
- Normal changes (age, behaviour)
- Pathology and (sometimes) recovery

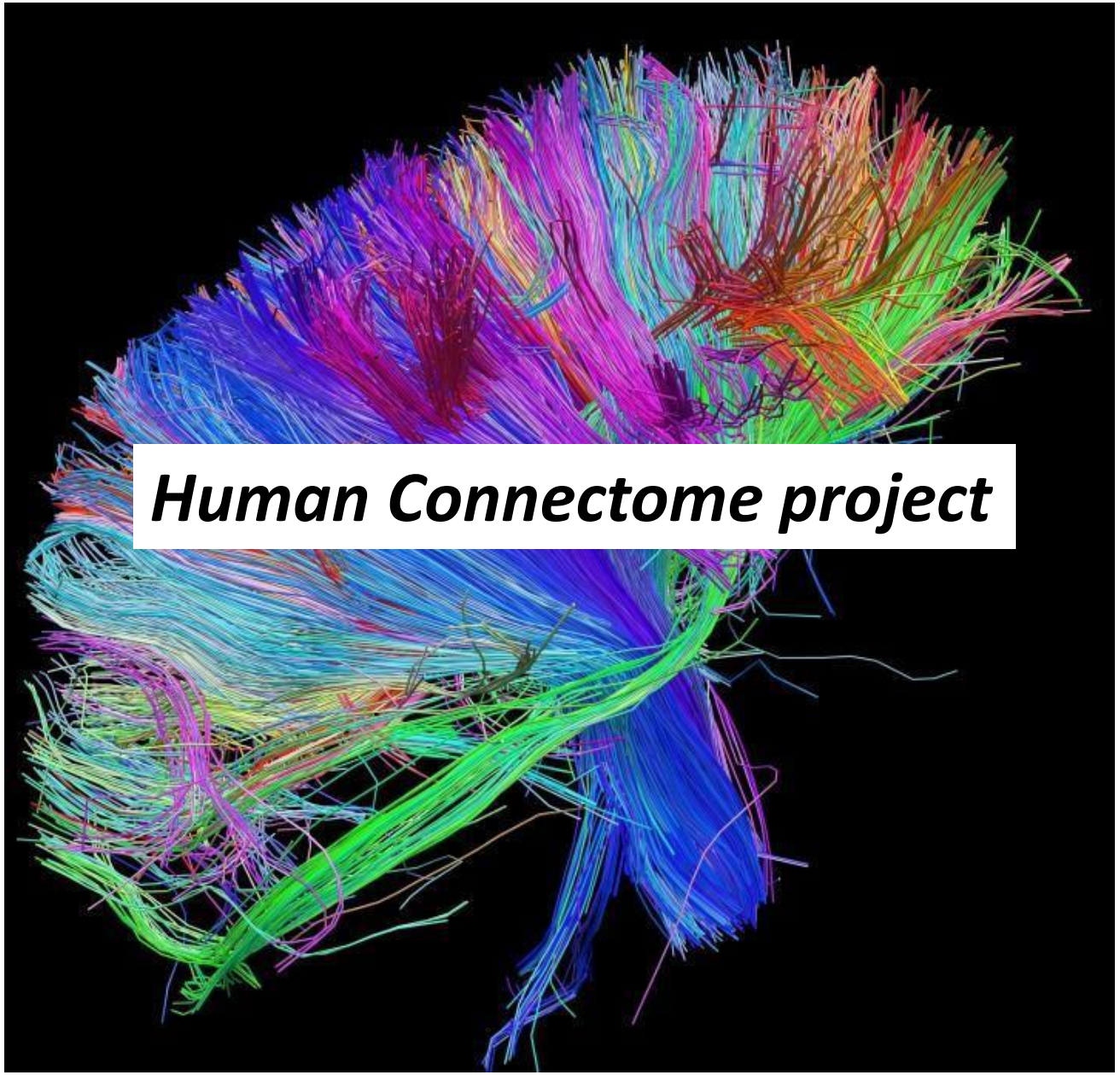
The future of neuroimaging

- Traditional neuroimaging study ~10-50 participants using single modality
- Increased use of multimodal imaging
- Increased collection of concurrent (clinical, biological) variables
- Increased awareness of sources of variability

>>>>> “Big Data” neuroimaging (big means big)

Human Genome project



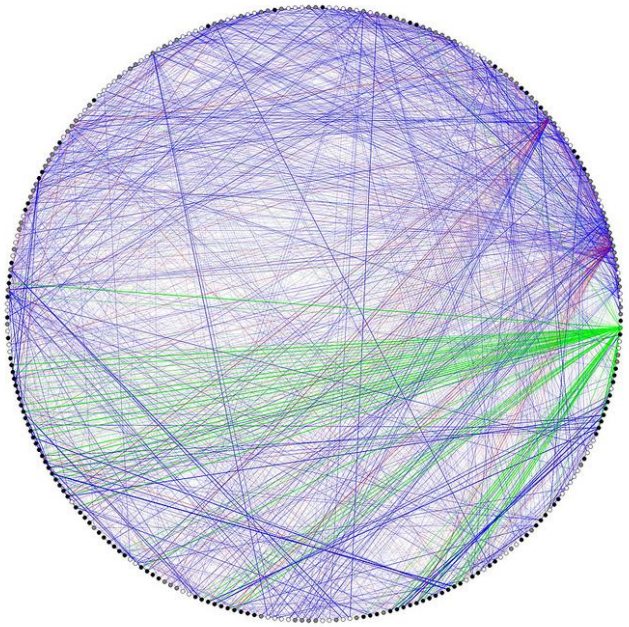

Human Connectome project

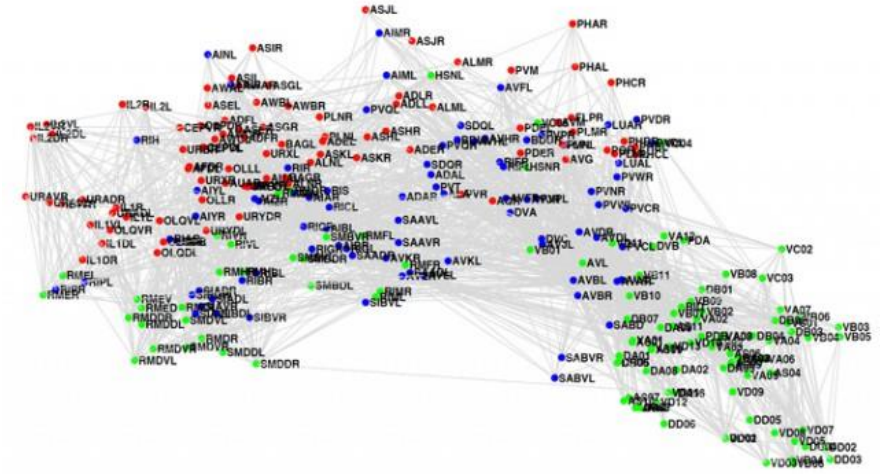
What is a connectome

- Complete description of the structural connectivity of an organism's nervous system

History

- 1986 → worm C. elegans (300 neurons = 7000 connections)
- Electron Microscope





Technical Challenges

- One Petabyte (1 million GB) of computer memory stores the image of 1mm cube of mouse brain.

- To map the human brain at the cellular level ~ 1 million petabytes of information.
  - more than the digital content of the world right now
  - Would take 10 million years to compute

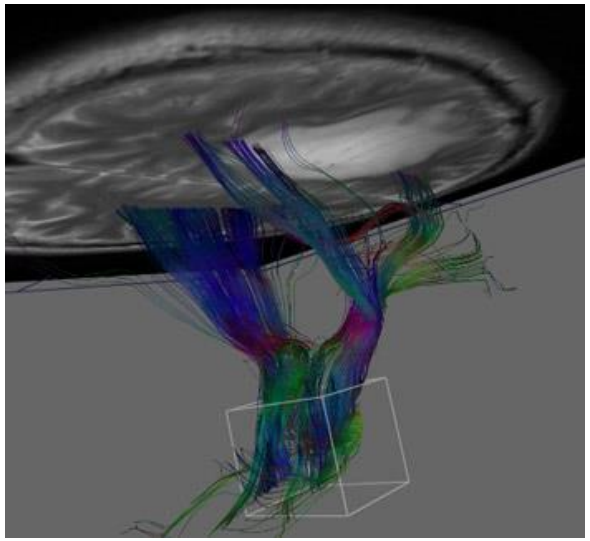
- The human genome consists of about 3.3 billion base pairs. Since there are only four types of pair, that amounts to 0.8 gigabytes of information

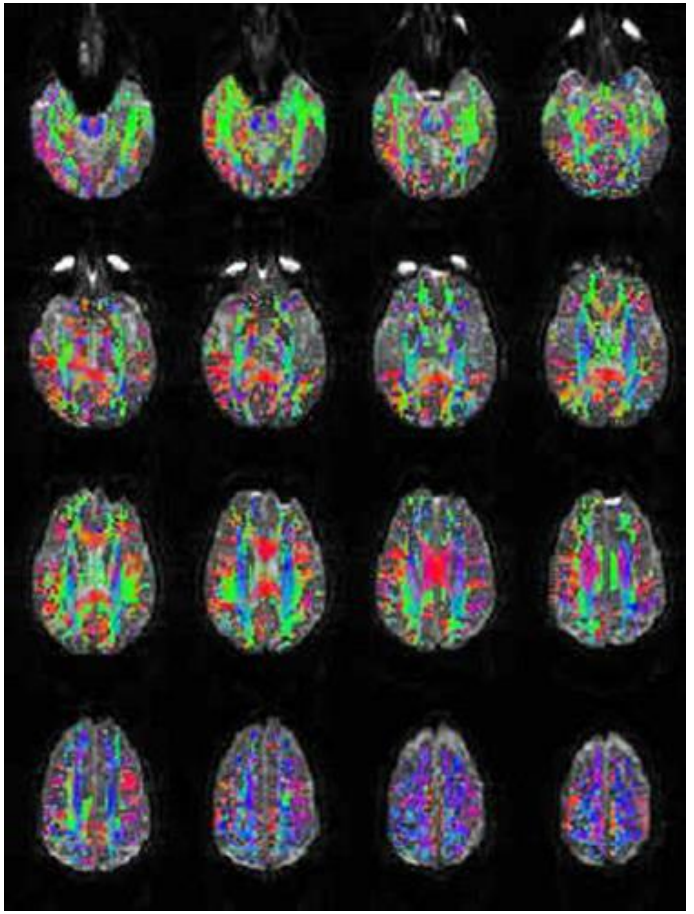
State of play

- Not operating at the cellular level!
- Human Connectome project: international effort to map the connectomes of 1,000 people on a macro scale using MRI.

New ways to scan the brain

- Diffusion MRI
- Diffusion Tensor Imaging
- Diffusion Spectrum Imaging.



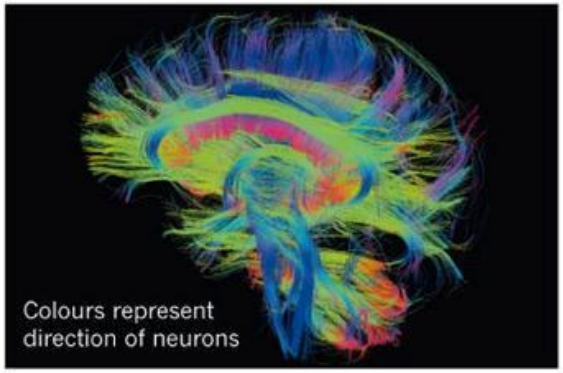


SCANNING THE CONNECTOME

The Human Connectome Project aims to trace the brain's long-range communication network using two main techniques, both of which rely on magnetic resonance imaging (MRI) to obtain data from living people.

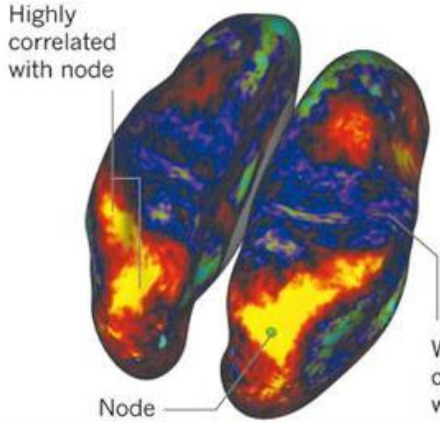
Mapping structure

Diffusion spectrum imaging detects the movement of water molecules that flow along nerve fibres in the brain. The result is a map of the brain's neuronal network.



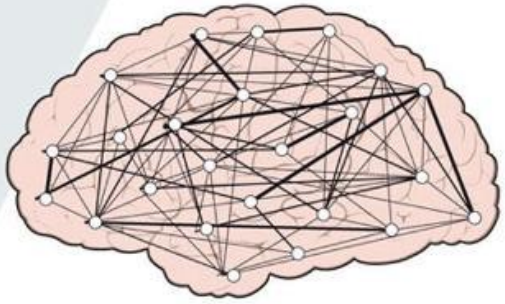
Mapping function

Resting-state functional MRI maps resting brain activity, then looks for correlations between one area and another. Highly correlated areas are thought to have some kind of functional link.



The brain has many areas specialized for specific functions, some of which are shown here.

Data on structure and function can be combined and analysed using tools such as network theory.



The connectome ties these areas together, allowing the brain to function as a coherent whole. The project's goal is to understand how the connectome works.

Open science and biobank imaging

- Move to share data from structural/functional/connection imaging
- Large multi-centre projects doing secondary analysis
- Biobank projects including imaging measures: will result in large databases with accompanying demographics/biomarkers/lifestyle factors etc

UK Biobank project

- 5000/500000 participants to date – aiming for 100000
- Largest health imaging project
- Findings (using big data modelling approaches):

1. Strong associations between people's cognitive processing speed and markers of the integrity of the brain's "wiring" and the size of brain structures
2. Strong associations between higher blood pressure, greater alcohol consumption, and several measures that could reflect injury to connections in the brain.
3. Correlations, linking intake of alcohol and tobacco and changes in red blood cells and cardiac fitness, to brain imaging signals associated with increased iron deposits in the brain.
4. More complicated patterns of correlation, eg one pattern links brain imaging to level of education, and a set of lifestyle factors that at first appear unrelated – including amount of time spent outdoors and how much cheese people eat!!

Conclusions

- Human brain is massively complex
- Effects of brain damage/dysfunction have profound personal, social and economic consequences
- Huge normal variation in brain structure and function, which may relate to a whole range of developmental and lifestyle factors
- New approaches to data sharing and “big data” analysis likely to lead to significant advantages over the next decade

- ***“The greatest challenge in science is sitting right here on our shoulders”***