Psychiatric comorbidity of frontal lobes

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Disclosures

- Prof M Madhusudhanan, Amirtha Institute of Medical Sciences, gave me many of the slides here, I am eternally grateful to him
- Regarding the case vignettes presented here, none of them are my own cases; All are borrowed from literature, used ONLY for teaching, with no commercial intention

Frontal lobes
Introduction

- Most recently developed parts of brain
- Make up 1/3 of the mass of cerebral hemisphere: the largest lobes
- Play major role in many forms of human behavior especially regulation of complex activities

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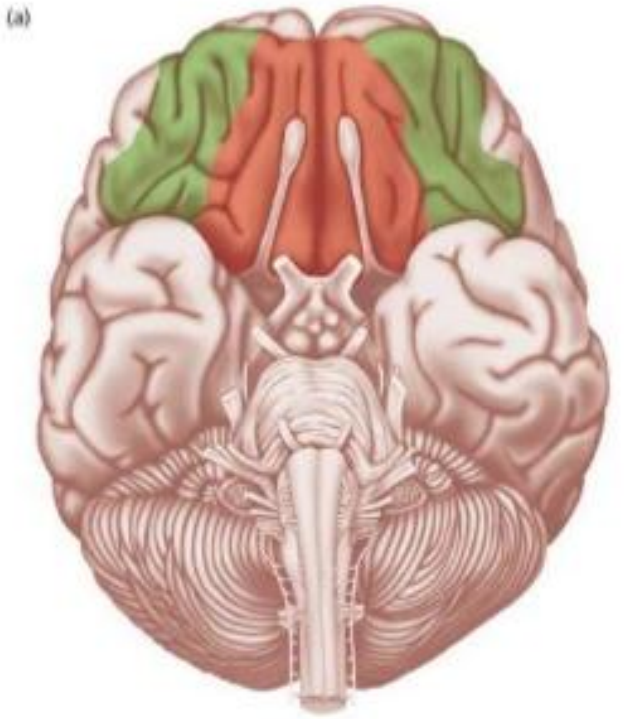
Three distinct functional anatomic regions

- Dorsolateral frontal cortex
- Mesial frontal cortex
- Lateral orbitofrontal region

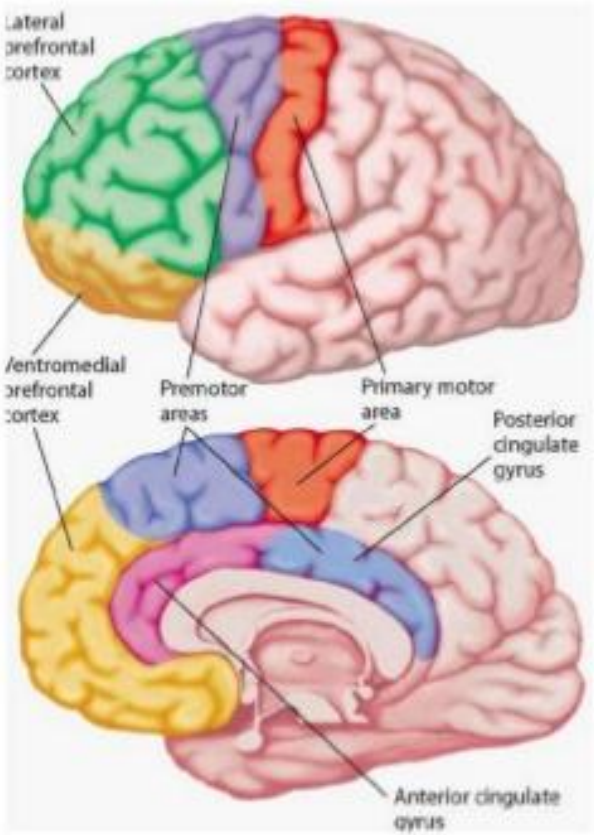
Functional anatomy

Lateral orbitofrontal



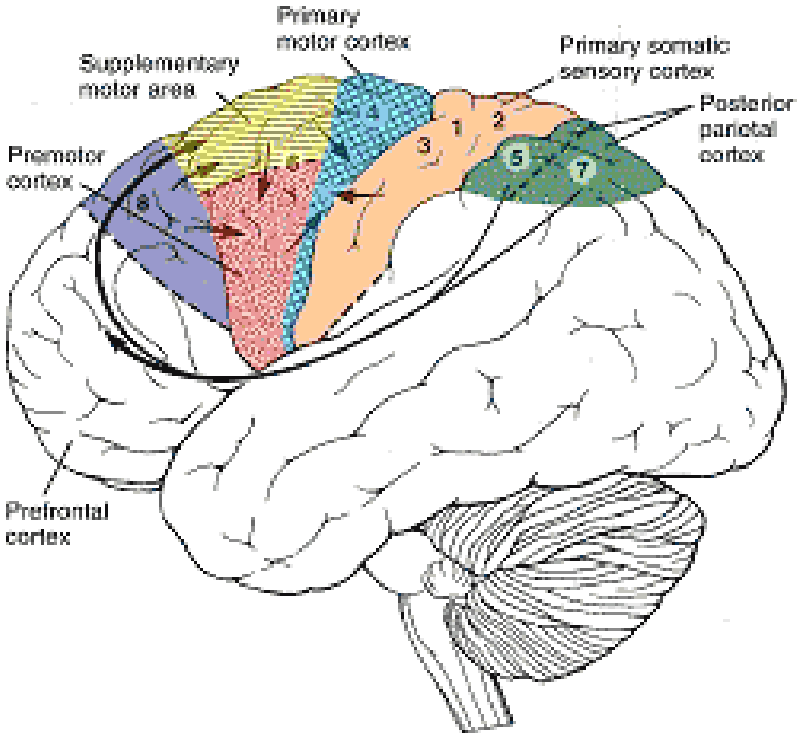
The orbitofrontal cortex is divided into **ventromedial** (reddish in the anterior view: above and yellow in the convex-lateral and median-sagittal view) and the **lateral** orbitofrontal cortex (green)

Dorsolateral prefrontal



Antero or Ventro medial orbitofrontal

Dorsolateral prefrontal connections



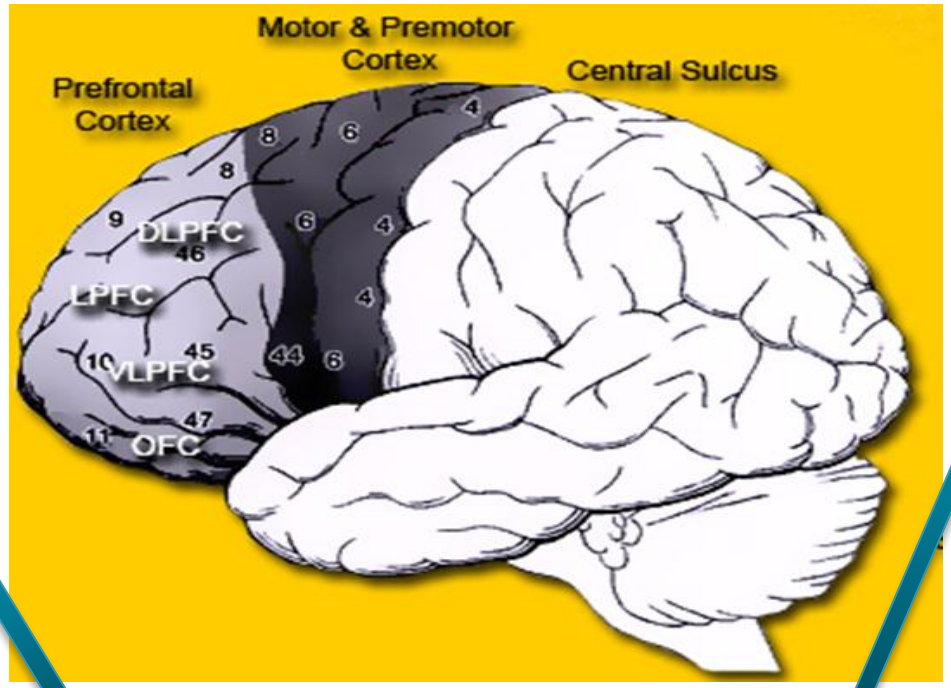
- Connects prefrontal lobes with other cortical regions: motor and sensory
- Organize and execute goal-directed or purposive activities

Sensory system analogy

- Primary sensory cortex
- Receives primary sensory input
- Sensory association cortex
- Associates various sensory input
- Tertiary sensory cortex
- Integrates and interprets sensory data

Hierarchical arrangement
Dorsolateral frontal lobe

Build a house



Architect

You and architect

Civil engineer

Mason

Plan → Higher integration → Motor organization → Motor

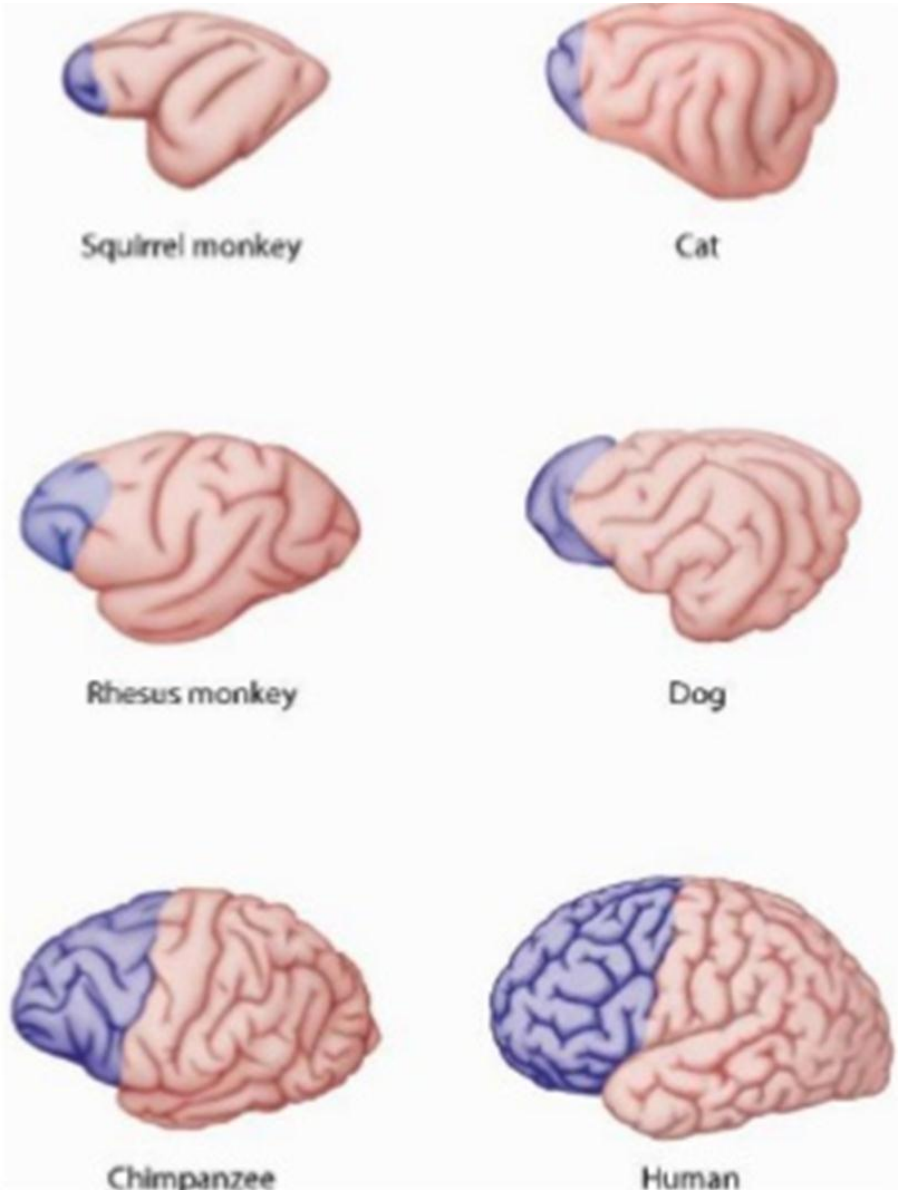
Plan-execution mismatch

Disintegration

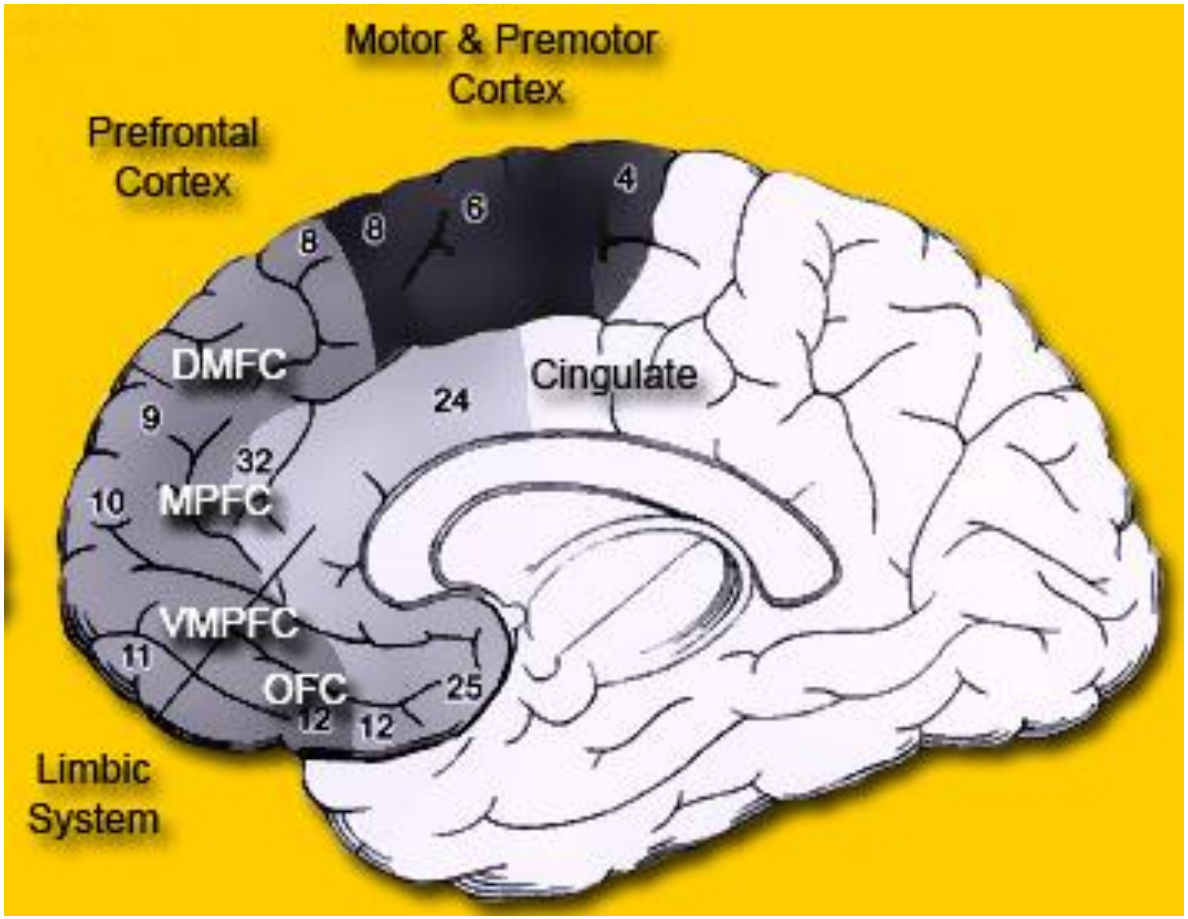
Disorganization

Paralysis

- Frontal lobe size has increased with evolution, importantly dorsolateral portion



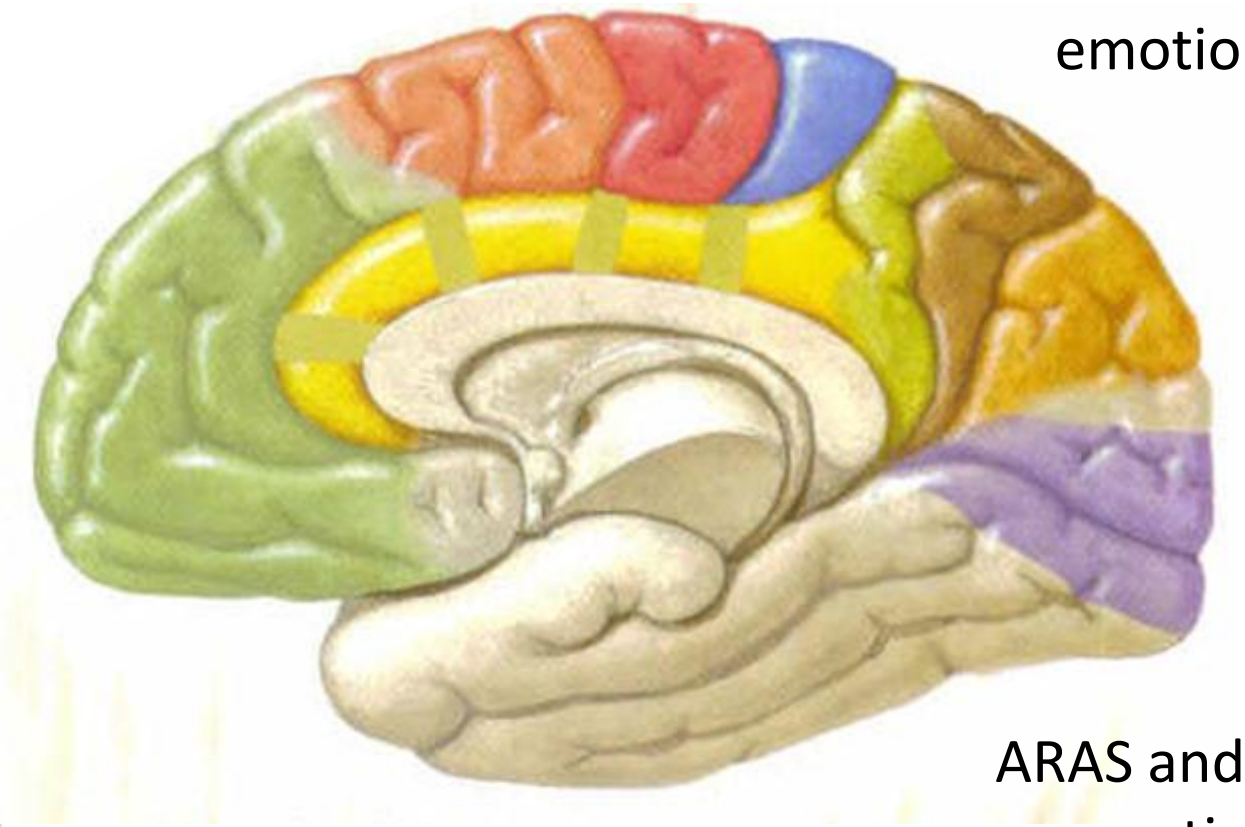
Antero/Ventro medial frontal



Limbic connections

Anterior cingulate system

Basal and Medial prefrontal connections



Limbic connections: emotional aspects

Connects prefrontal lobes with upper parts of brainstem and thalamus

ARAS and brainstem connections: alertness

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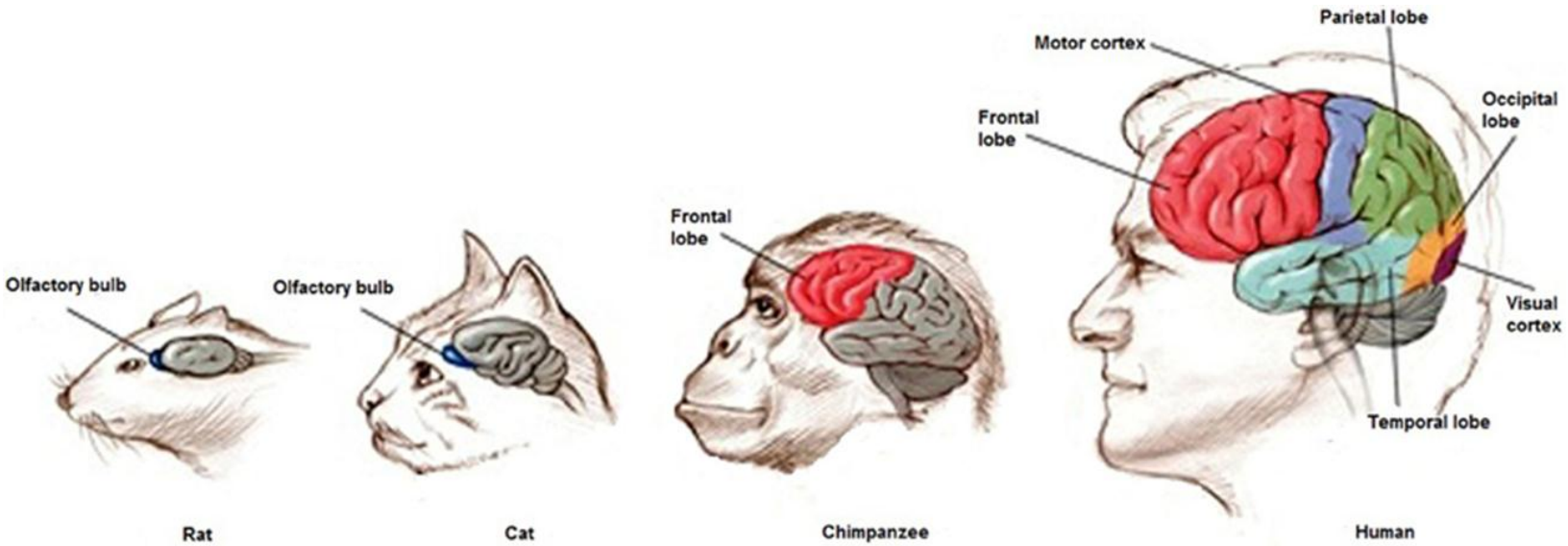
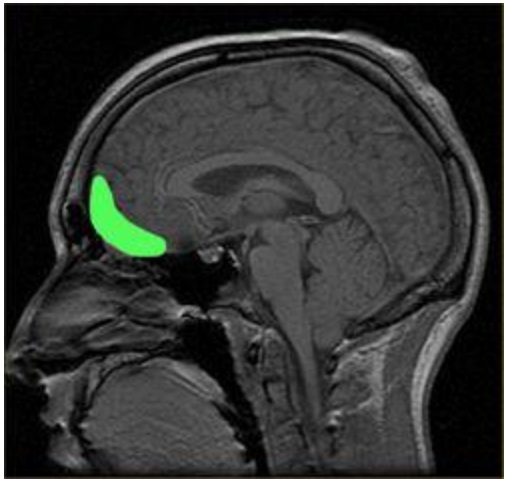
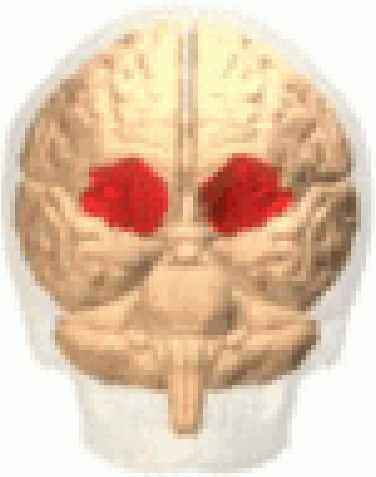
Evolution of the limbic system



Orbitofrontal cortex





Inhibitory influences

3 main changes with frontal lesions

Personality

Orbitofrontal

- ↓ anxiety and concern for future
- Impulsiveness
- Facetiousness and mild euphoria
- Lack of initiative and spontaneity

Intellectual

Dorsolateral

- Impaired integration of behavior over time: recent memory
- Abstract thinking disturbance
- Plan and follow through deficit

Adynamia

Mesial frontal

- Lack of verbal or overt behavior

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Is frontal lobe important for intellect?

- No: Feuchtwanger 1923, Jefferson 1937
- Jefferson 1937: 6 cases of frontal lobectomy: No loss of intellect, rather improvement only
- Higher functions not ‘localized’ to frontal lobes
- Psychosurgical procedures were getting popular
- Cutting the silent part of the brain!!
- Yes: Jackson 1874, Phelps 1897, Papez 1929
- Rylander 1939: 21 out of 32 frontal lesions had intellectual changes: he warned against psychosurgery

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Why frontal lesions not 'picked' up? From silent parts to silencing parts!!!

- Outwardly frontal patients may appear normal, hence may not be subjected to analysis
- The 'right' tests may not be applied
- Some parameters are difficult to assess: intellect, abstract thinking
- Confounding factors for normative data: culture, emotional background, intellect, education
- Statistical analysis difficulties: may need sophisticated analysis like multiple discriminant function analysis, cluster analysis

Clinical evaluation of frontal lobe

- Motor cortex evaluation
- Prefrontal evaluation

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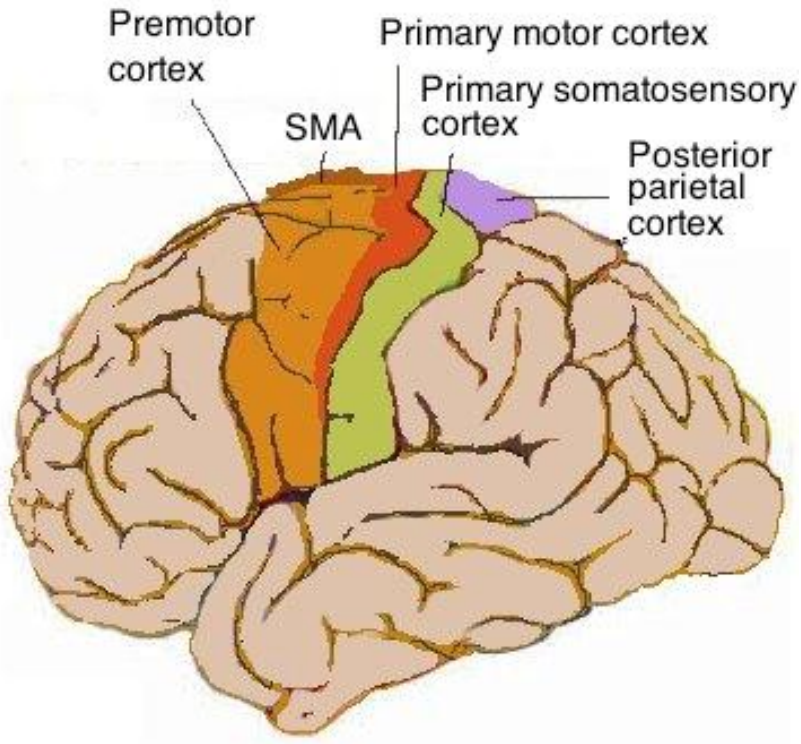
Motor cortex

- Primary motor
- Premotor
- Supplementary motor
- Frontal eye field
- Broca's



Motor evaluation
Eye movement evaluation
Language evaluation

Neurology course @ SHINE

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Clinical evaluation of pre frontal lobe
Clinical evaluation of 'frontal lobe syndrome'

- Dorsolateral prefrontal function evaluation
- Mesial frontal function evaluation
- Orbitofrontal function evaluation

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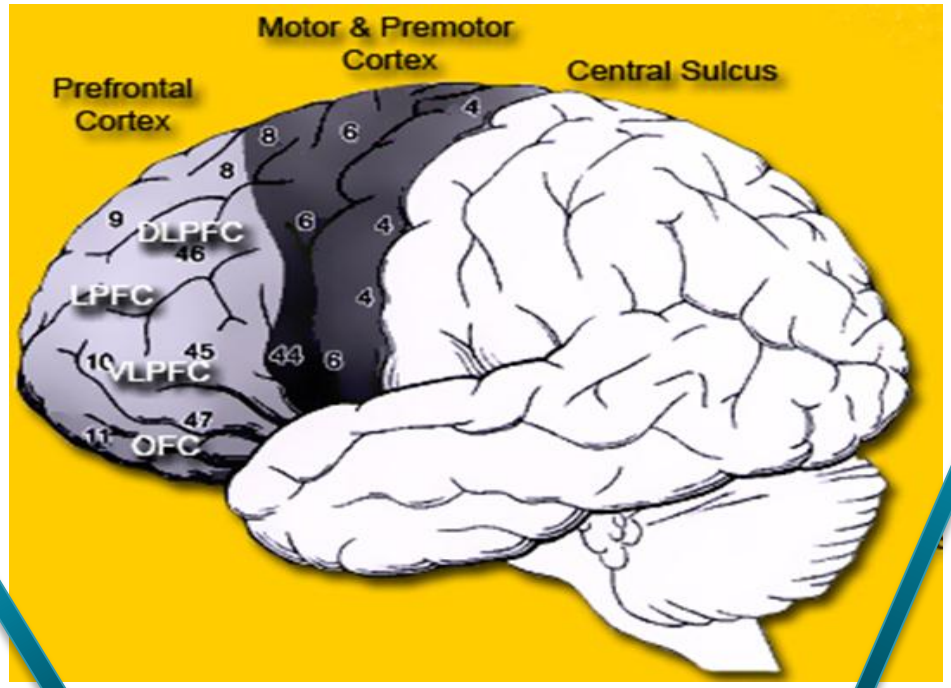
Hierarchical arrangement
Dorsolateral frontal lobe

Build a house



Architect

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Plan → Higher integration → Motor organization → Motor

Plan-execution mismatch

Disintegration

Disorganization

Paralysis

Dorsolateral prefrontal function evaluation

- Execution of an act
- Executive dysfunction or dysexecutive syndrome

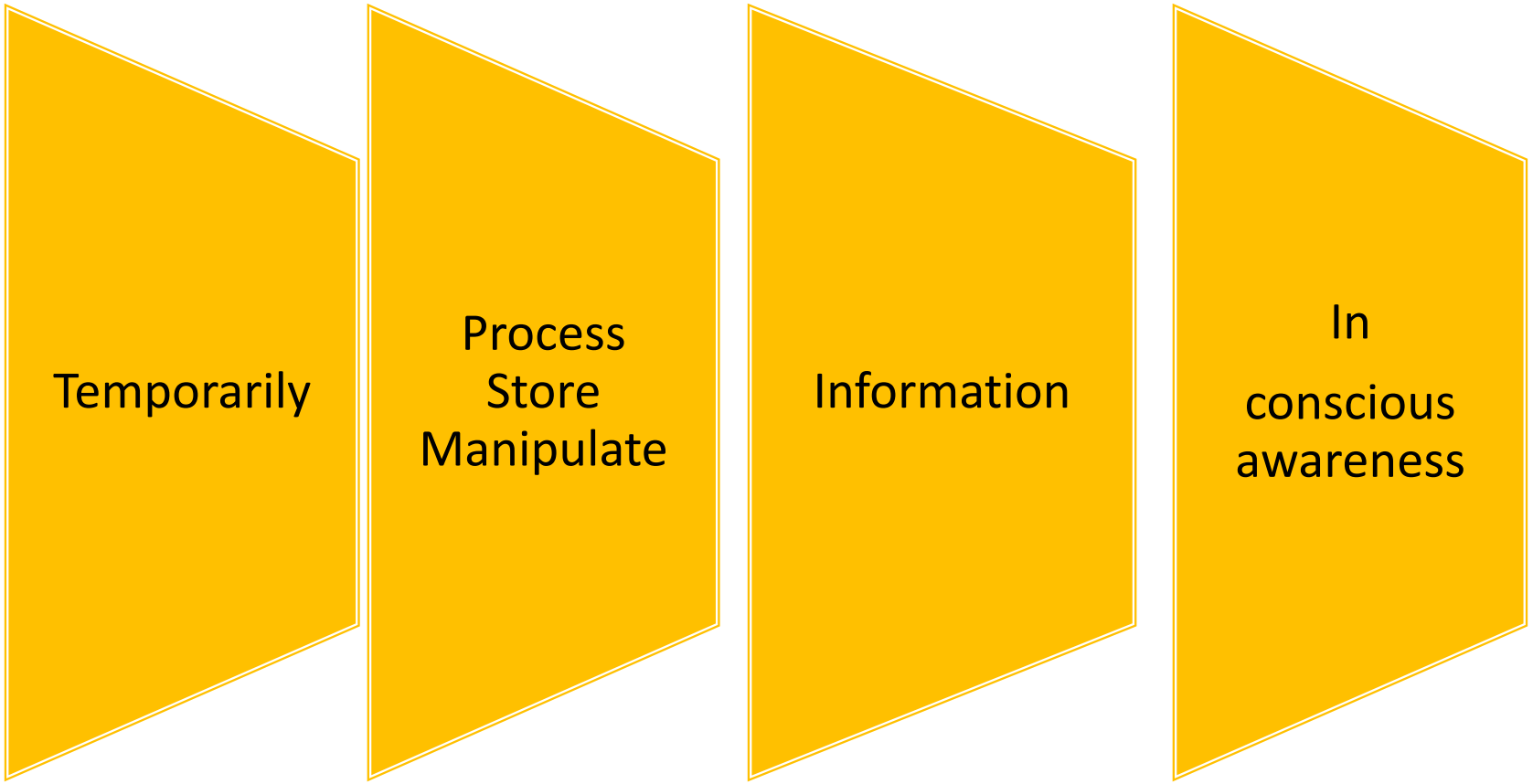
Executive functions

- Constellation of cognitive abilities that enable and drive adaptive, goal-oriented behavior
- Ability to
  - Generate thought
  - Think flexibly
  - Update and manipulate information mentally
  - Inhibit what is irrelevant to current goals
  - Self-monitor
  - Plan and adjust behavior as appropriate to the present context

Executive function: 4 components

- The first component is called ‘working memory’

Working memory



Case vignette

- 74/M, retired college professor
- Memory loss * 1 year
- Spouse died of breast cancer 9 months ago
- Can’t focus or concentrate, couldn’t read a book
- Anhedonia, crying spells, insomnia, weight loss
- MMSE, MoCA, Neurology: Normal
- Impaired working memory tests and fluency
- Geriatric depression scale positive
- Rx: SSRI, cognitive-behavioral Rx: Normalized

Learning points from the case

- Executive dysfunction can accompany mood disorders and many other psychiatric disorders
- Primary problem is attention and executive functioning but called loosely or misrepresented as ‘memory’
- Depression screen must be part of neuropsychological evaluation
- Functional deficits out of proportion to formal test scores: common in depression
- Still needs f/u as late-life depression could be a prodrome of a neurodegenerative disease

Working memory

- Digit span: Forward, Backward
  - Normal ? Abnormal ?
- Count backwards
- Spell backwards a word “world”
- Recite months in reverse
- Serial 7s

Working memory

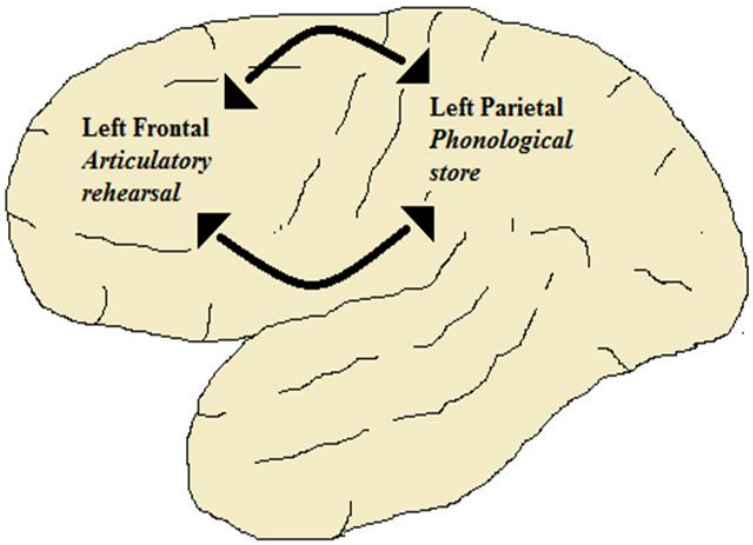
- Ability to hold information for short period of time and mentally manipulate information
- Keeps information online
  for eg: Remembering a phone number

Working memory

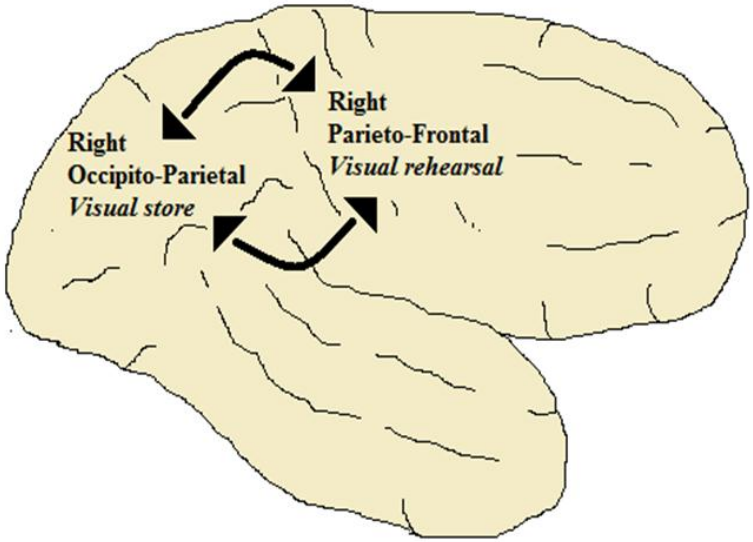
- Temporary storage and maintenance
  - For attentional on-line maintenance of information
  - Depends on slave systems
- Mental manipulation
  - Regulate how information is analyzed and accessed
  - Executive control processes

Working memory-slave systems Baddeley and Hitch, 1974

Phonological Loop – Left Hemisphere



Visuo-Spatial Sketchpad - Right Hemisphere



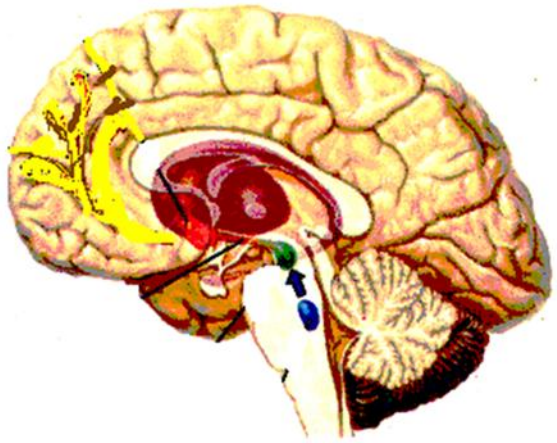
- Reverberating circuitry involving prefrontal cortex and areas concerned with short term storage

Mental manipulation
Executive control processes

- Higher order operations- such as strategic retrieval for appropriate use

DLPFL

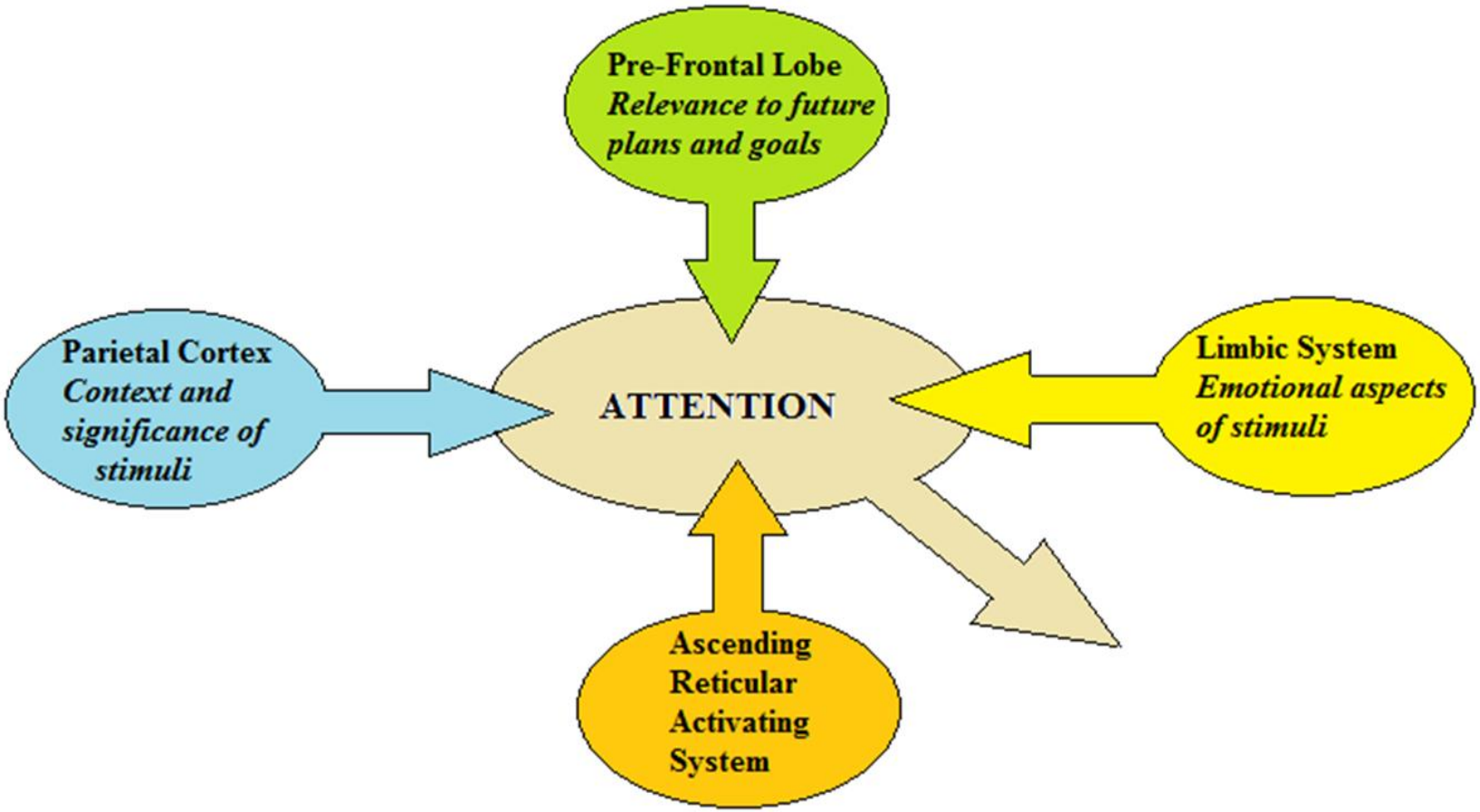
Anterior cingulate



Attention and concentration

- Attention is the ability to focus on a particular sensory stimulus to the exclusion of others
- “Attention is the ability to inattend to unimportant stimuli”
- What is concentration?
- Concentration is sustained attention

Mediators of attention



Thus to do a task

- Step 1: Must attend to the task, keep it in working memory and manipulate
- Step 2: Must not be distracted (Must be able to say no to what is unnecessary): Inhibition

Stroop test

Blue	Green	Purple
Red	Yellow	Red
Green	Red	Green
Yellow	Yellow	Black
Black	Orange	
Yellow	Blue	Yellow
Orange		Green
	Blue	Red
Purple	Red	Purple
Blue	Green	Blue

Response inhibition

- Stroop test
- “Go-no- go” test
- Antisaccade test

Inhibition

- A previously learned response
- But this is inappropriate or irrelevant in the present context
- Ability to hold back this predominant, automatic response
- Automatic response normally is due to either (a) familiarity or (b) reward
- This is cognitive inhibition as against behavioral inhibition (different correlate)

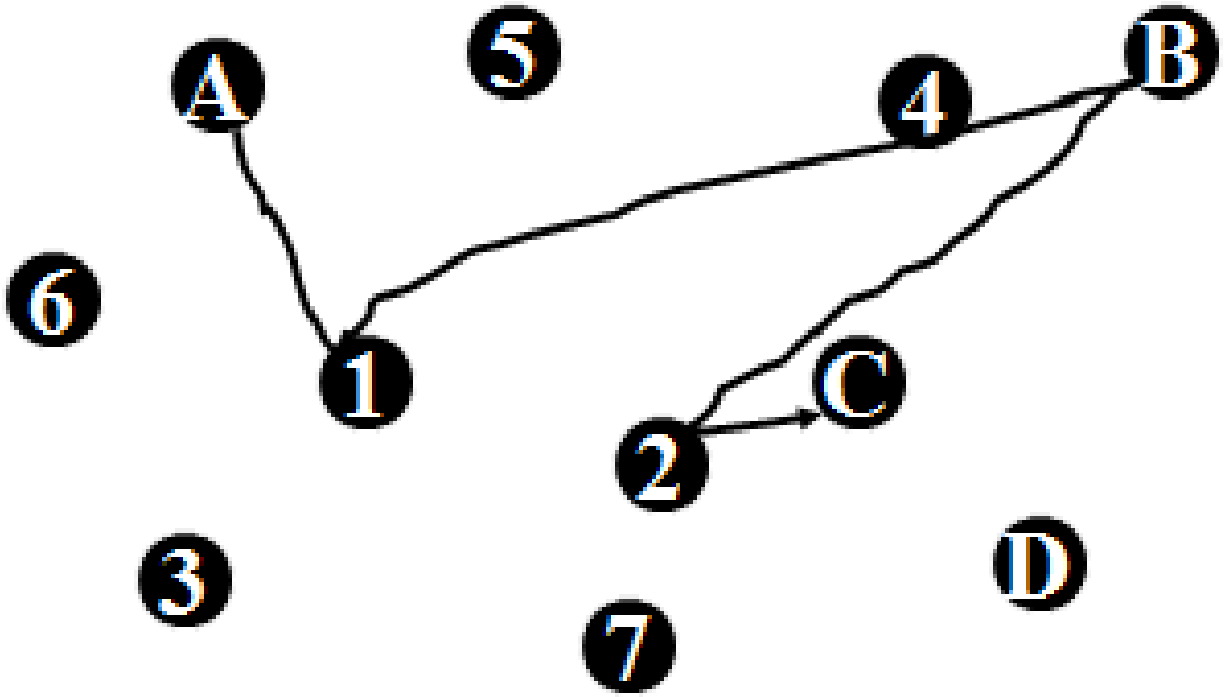
Effects of failure of inhibition

- Can’t ignore irrelevant stimuli even if penalizing
- Easily distracted, stimulus bound and impulsive
- Enslavement to environmental cues
- Utilization behavior and environmental dependency syndrome
- Automatic imitation of gestures of others
- Echopraxia
- Echolalia

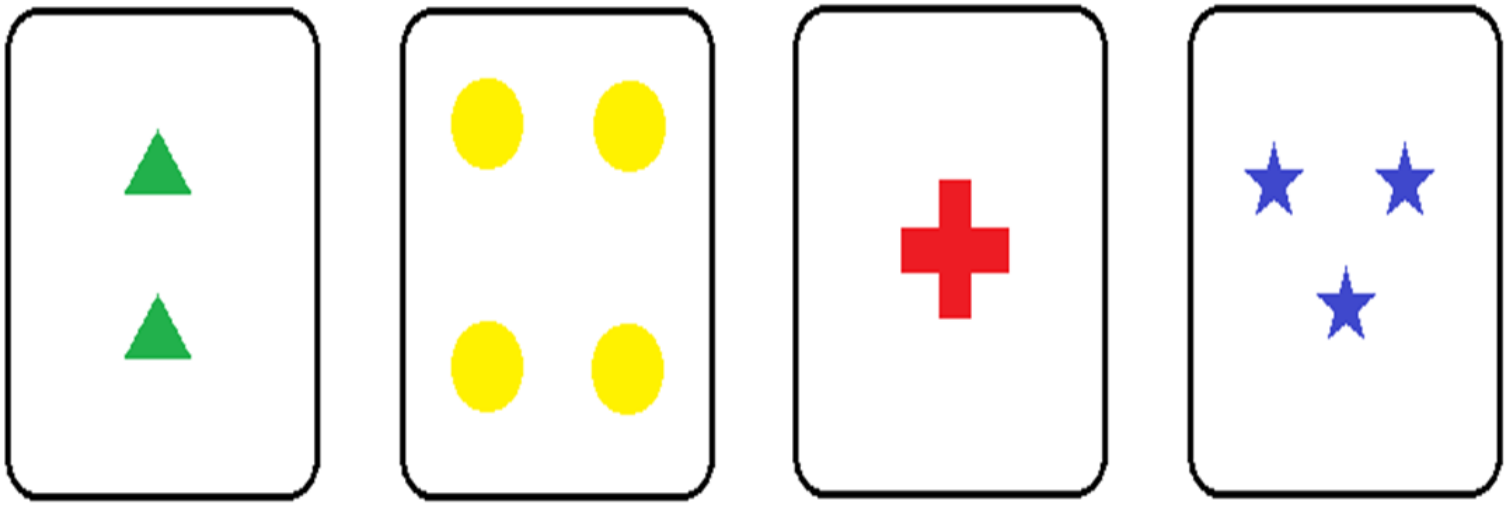
Thus to do a task

- Step 1: Attend to task: Must attend to the task, keep it in working memory and manipulate
- Step 2: Must not be distracted (Must be able to say no to what is unnecessary): Inhibition
- Step 3: Set shifting: Ability to modify attention and behavior in response to changing circumstances and demands

Trail Making Test



Establish, maintain and shift response set



Wisconsin card sorting test

Handle sequential behavior

- Motor programming tasks
- Luria 3-step alternating sequential motor test
- Ring –fist test, Side-palm –fist
- Visual pattern completion test

Problems faced

- Cannot multitask
- Rigid in thinking
- Perseveration

Perseveration

- Abnormal repetition of a specific behavior
- Aftermath of inability to shift thought process/ response inhibition
- Cognitive perseveration
- Motor perseveration
- Recurrent perseveration
- Continuous perseveration

Perseveration

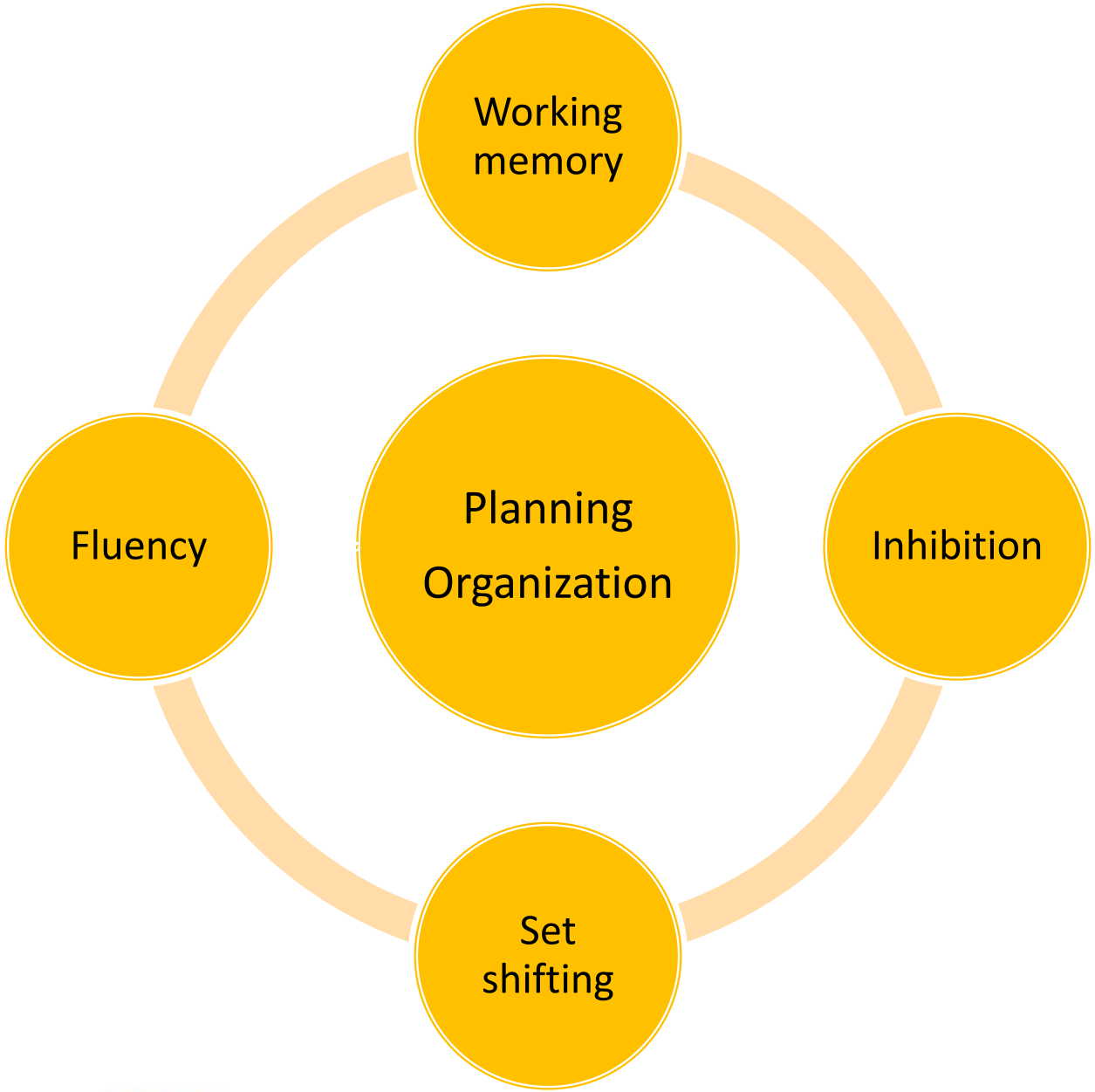
- Series of Ms and Ns
- Expected response: MN MN MN
- Frontal response: MN MMMMM

Fluency: the 4th component

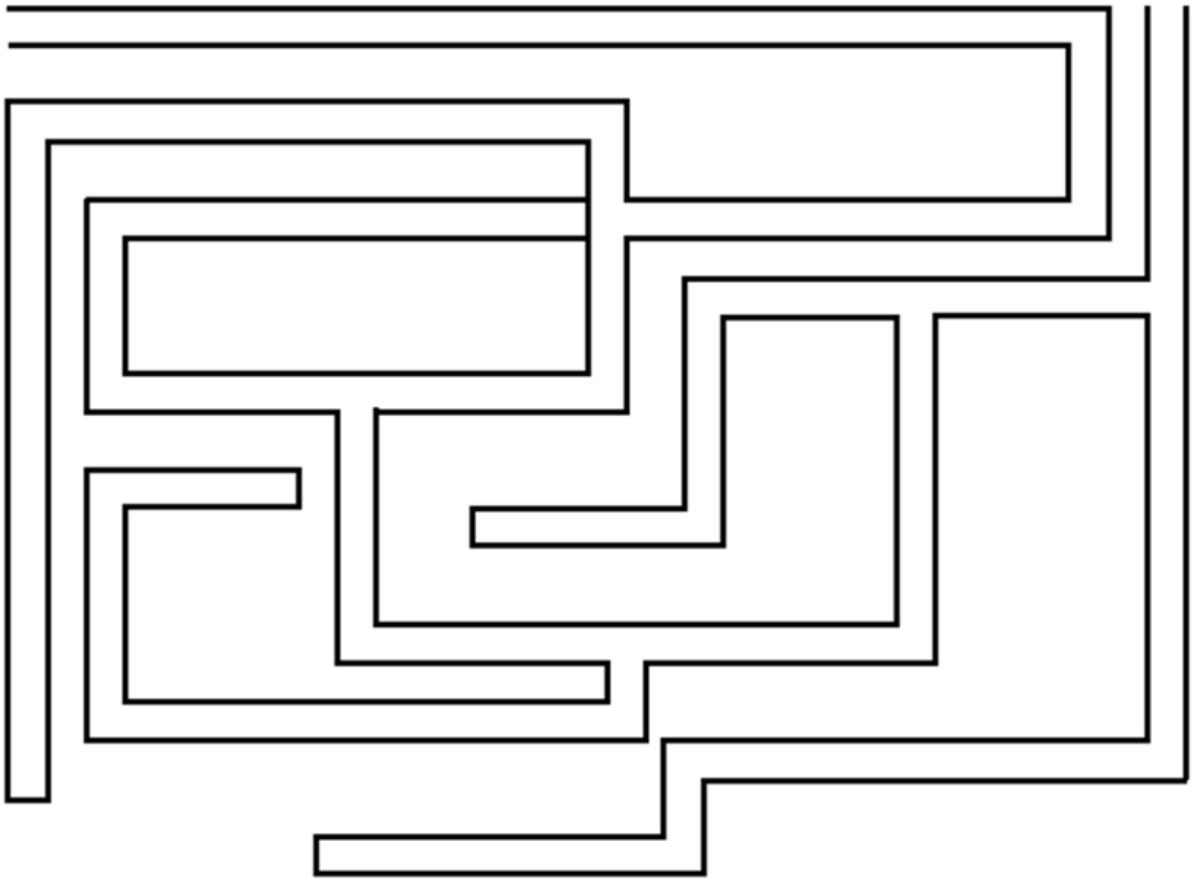
- Ability to maximize the production of verbal or visual information in a specific time period, while avoiding repeating responses
- Three types of tasks
  - Category fluency: Semantic fluency
  - Letter fluency: Phonemic fluency
  - Design fluency
- Clinical deficits: 'Tip-of-the-tongue' in the absence of true anomia, inertia, disorganization

Word Fluency test

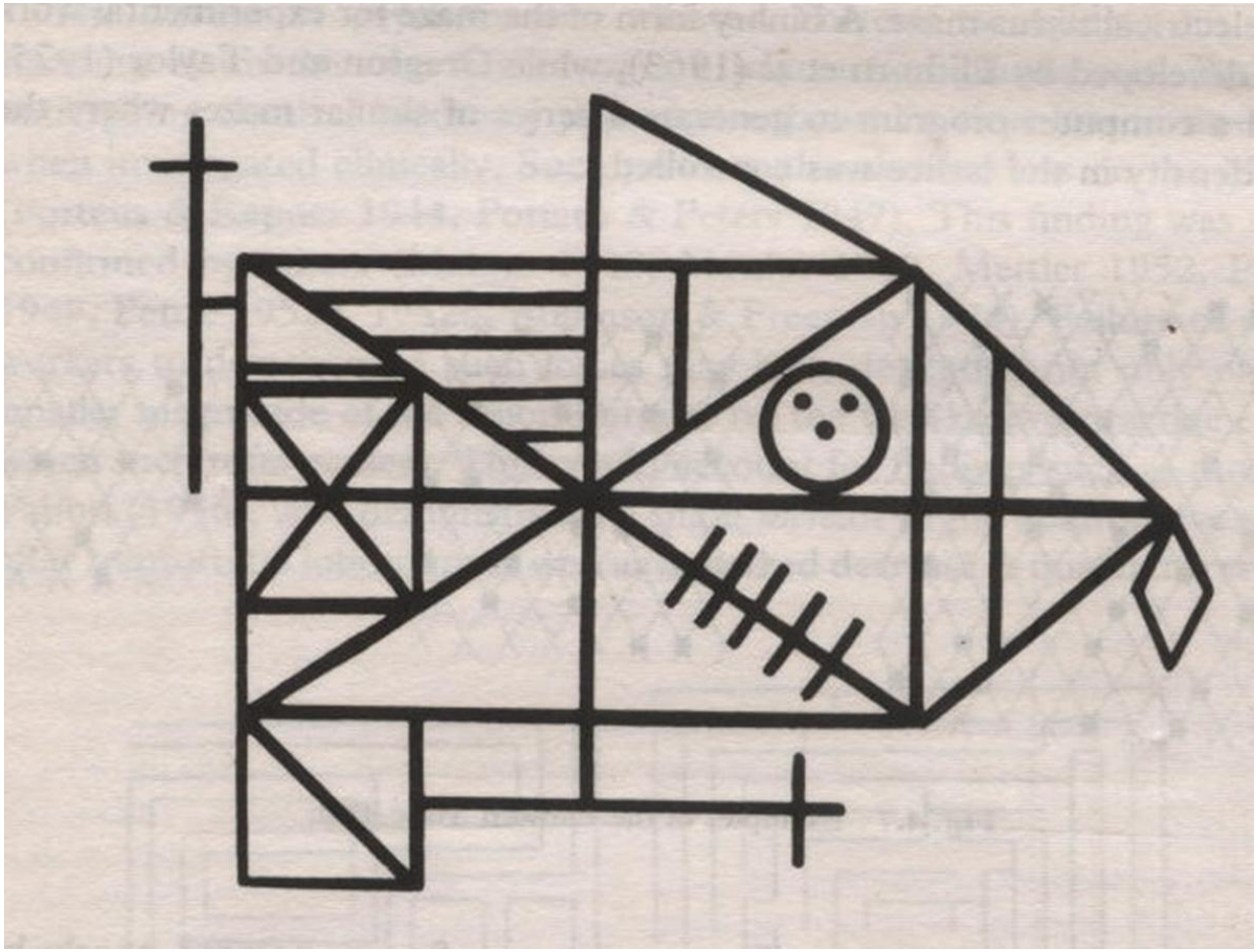
- Tests the ability to scan mental content and retrieval strategies.
- Patient to generate examples in a specific category
- Generate words beginning with specified letters or belonging to semantic categories


Working memory
Fluency
Planning
Organization
Inhibition
Set shifting

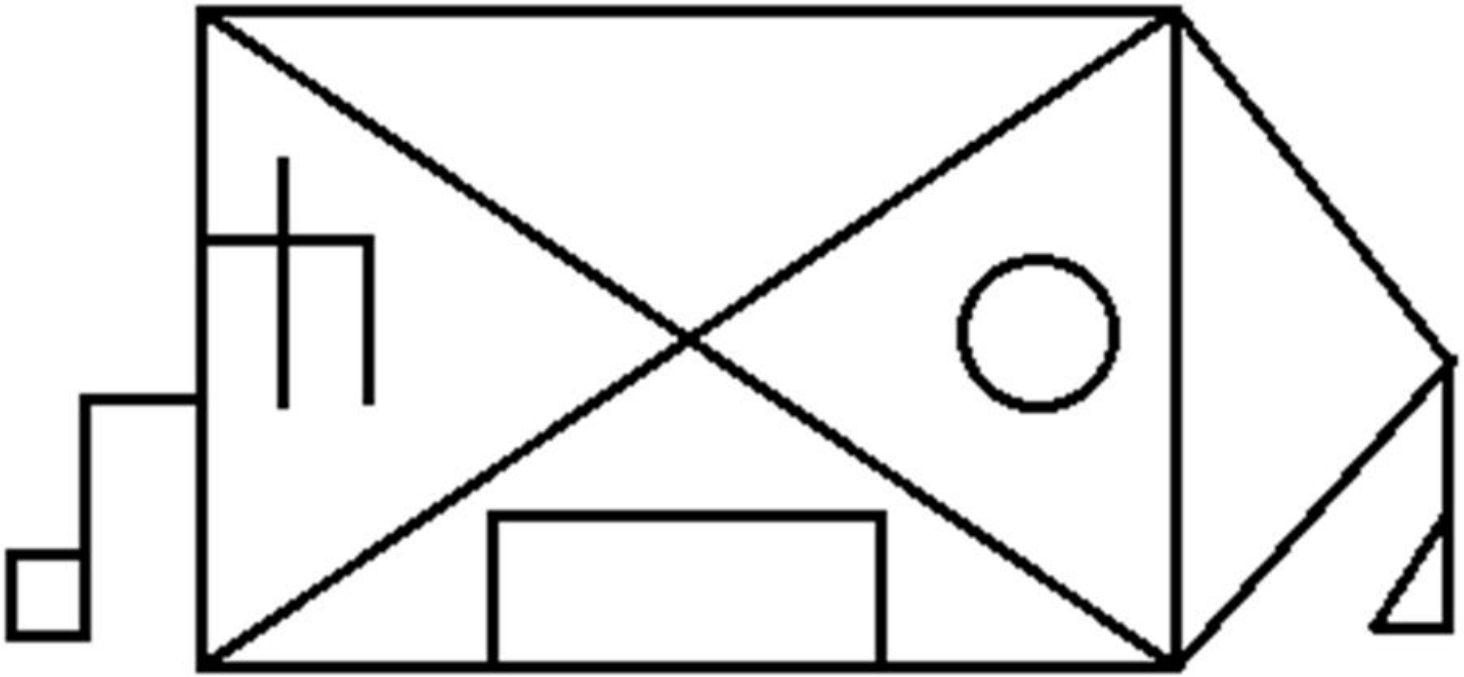
Porteus maze



Visuo-constructive task
Complex figure of Rey



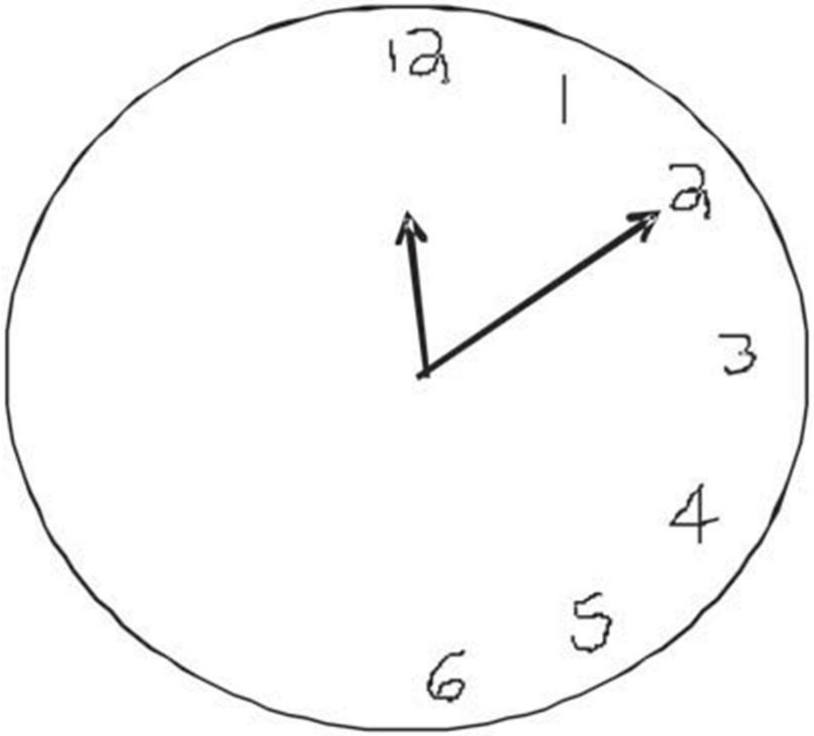
Modified Ray-Osterrieth figure



Organizing, planning

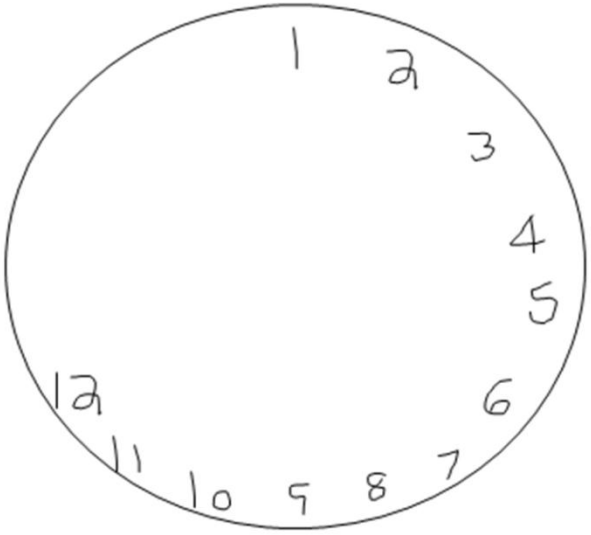
- Porteus Maze
- Visuoconstructive tasks
  - Clock drawing
  - Rey figure

Defective planning

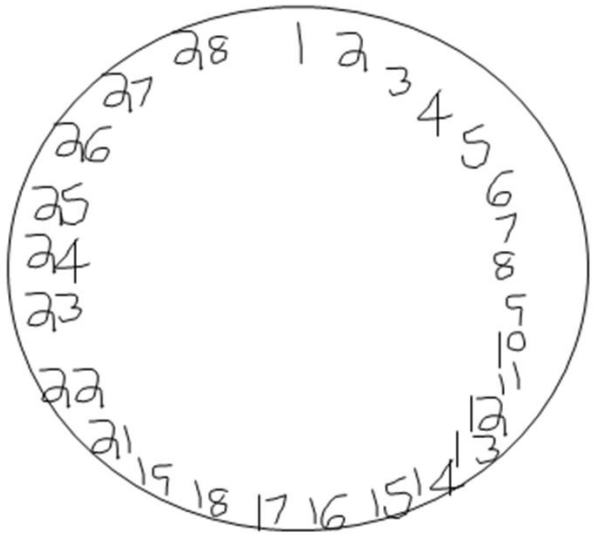


Draw quarter to 7

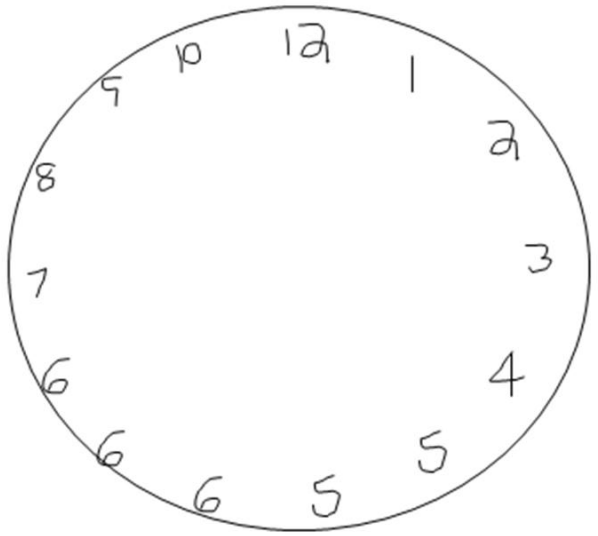
Defective planning and organization



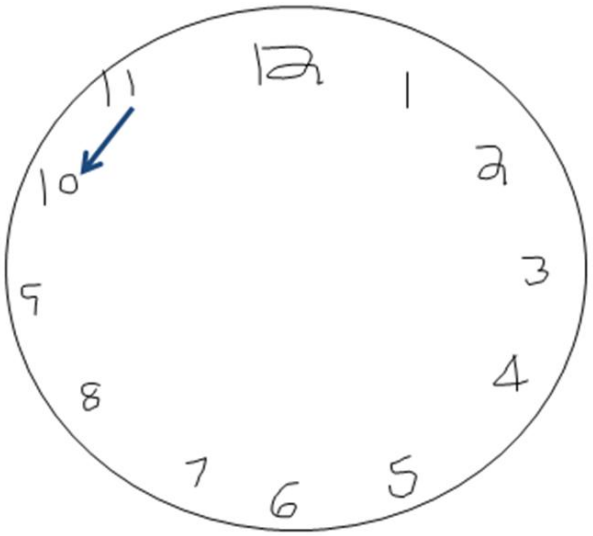
Defective response set



Perseveration

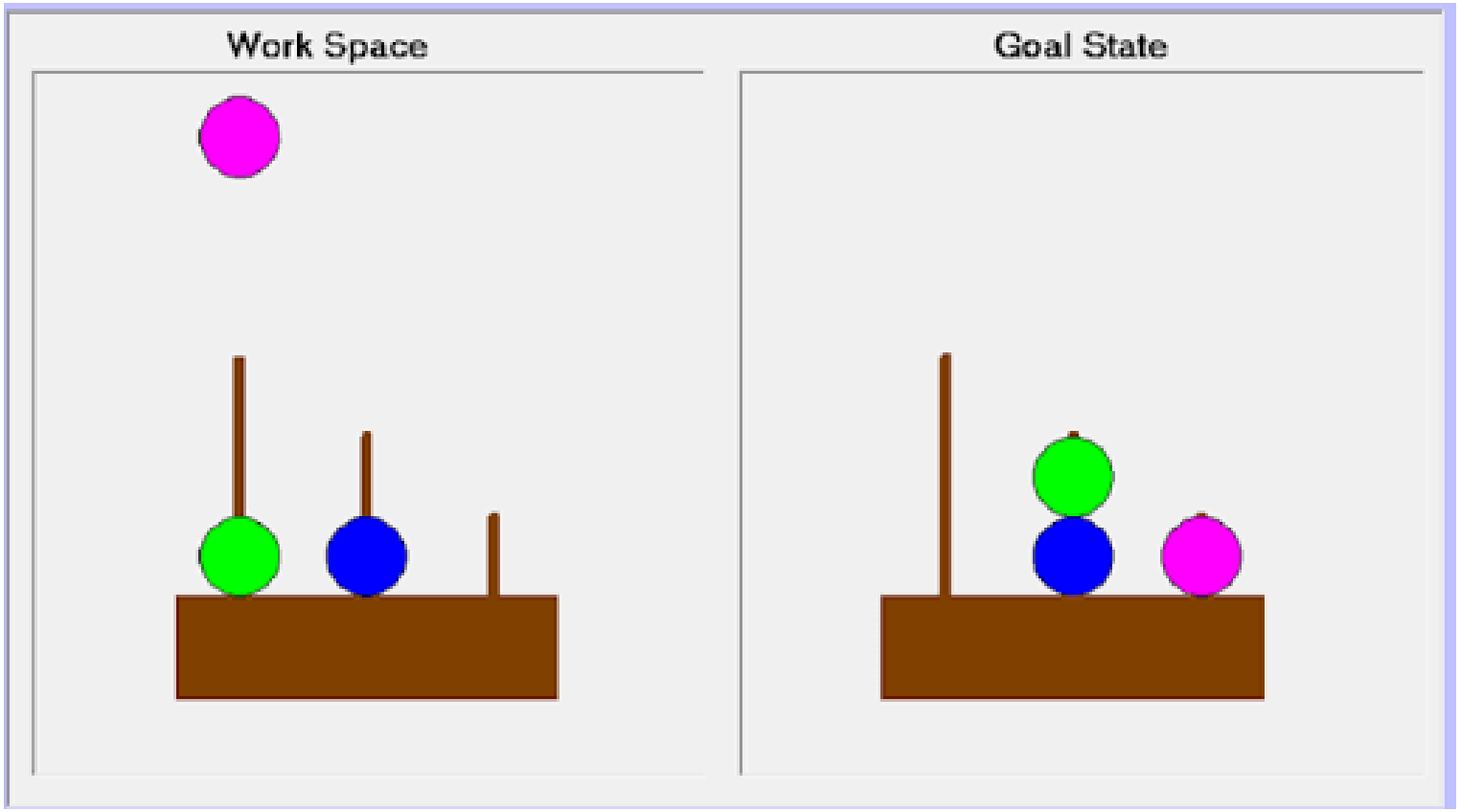


Impaired abstraction



- Impaired abstraction and stimulus boundedness
- Set the hands to read 10 after 11
- Patient draws a hand from the 11 pointing to the 10

Tower of London test



Other executive function tests

- Judgment
- Abstraction and concept formation
- Ability to understand the conceptual meaning of the situation
  - Tests:
    - Tests of similarities
    - Proverb interpretation
    - Conceptual series completion

Evaluation of executive functions
Problem solving

- Jumping to conclusions on the basis of incomplete information
- Difficult to explore alternative solutions to the same problem

Problems

- Orange price problem
- Estimation of speed problem

Localization

- Set shifting, planning, working memory: Dorsolateral prefrontal cortex
- Self-monitoring and spatial tasks: Right prefrontal
- Design fluency: Right frontal or parietal
- Verbal fluency and processing: Left side
- Response selection: Pre-supplementary motor cortex
- Error detection: Anterior cingulate cortex
- Reward punishment contingencies, inhibition of inappropriate responses: orbito frontal

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Executive dysfunction

Primary psychiatric diseases: Depression, Anxiety, Bipolar disorder, OCD, Schizophrenia

Neurodegenerative diseases: FTD, DLBD, PD, AD, CBGD, PSP, MSA, ALS, Chronic traumatic encephalopathy

Developmental conditions: ADHD, ASD, Learning disability

Neurologic diseases: TBI, Epilepsy, MS, Tumor, VCI

Medical disorders:

Electrolytes, Organ failures, B1/B12 deficiency, thyroid disease

Infections: Delirium in systemic infections, AIDS dementia, Syphilis, Lyme

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Executive dysfunction: Rx

- Treat the cause
- Occupational therapy evaluation
- Cognitive rehab
  - Environment manipulation eg. minimize distractions, simplify tasks
  - Compensatory techniques: planners, smart phones
  - Direct interventions: Repetitive training
- Experimental approaches
  - Dopaminergic therapy in TBI, stroke
  - Computer-based brain exercises
  - TMS

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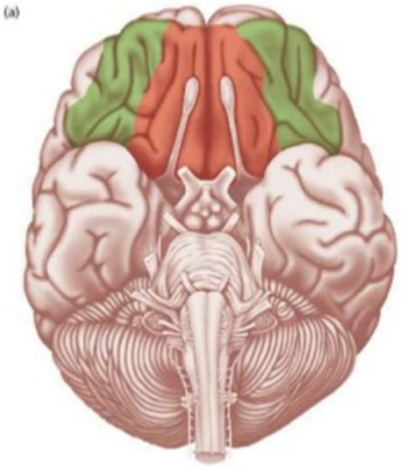
The “salience system”

- Lateral orbitofrontal cortex and amygdala receive sensory information about social and emotional stimuli from temporal visual areas
- Processing tuned by “salience system”: representation of value or ‘salience’
- Insula and orbitofrontal cortex determine this
- Involvement in bv-FTD



Disinhibition and impulsivity of thought and action

- Disinhibition
  - Socially inappropriate behaviors, totally against the social customs or the way in which one was socially groomed
  - Inappropriate remarks, undress in front of others, urinate in public
- Decreased impulse inhibition
  - Loss of social tact
  - Inappropriate jocularity
  - Irritability

- Lack of self awareness
  - Loss of insight
  - Denial of disability
- Motor hyperactivity
  - Wandering
  - Excessive pacing
  - Nocturnal ambulation
  - Leaving one’s house

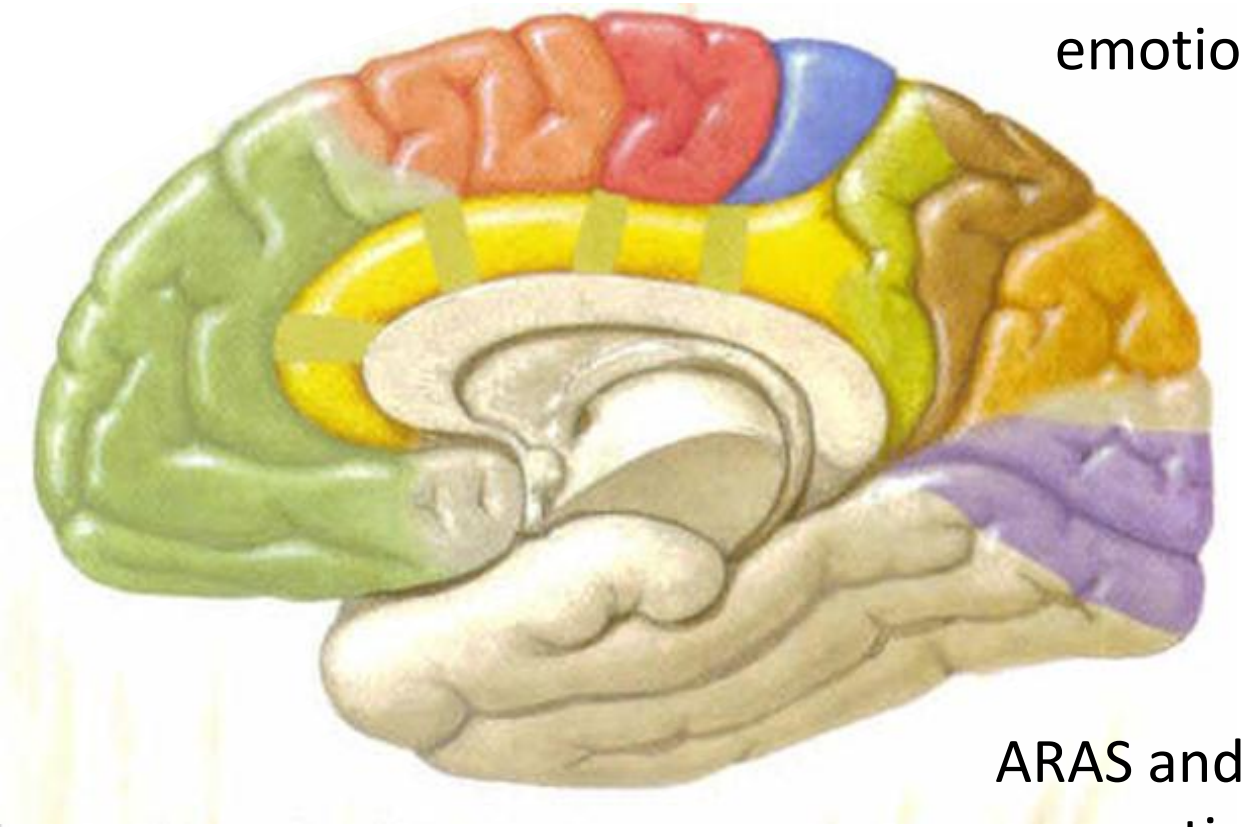
Witzelsucht

- From German
- Witzeln: To joke or wise-crack
- Sucht: Addiction or earning
- Tendency to make puns, inappropriate jokes or pointless stories in inappropriate situations
- Sexual comments can also be made
- No insight
- A disorder of humor (not laughter)
- Rx: Venlafaxine

Orbito frontal function evaluation

- Disinhibition and impulsivity of thought
- Judgment
- Insight
- Personality
- Hyperoralism
- Gluttony
- Utilization, imitation

Basal and Medial prefrontal connections



Limbic connections: emotional aspects

Connects prefrontal lobes with upper parts of brainstem and thalamus

ARAS and brainstem connections: alertness

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Adynamia

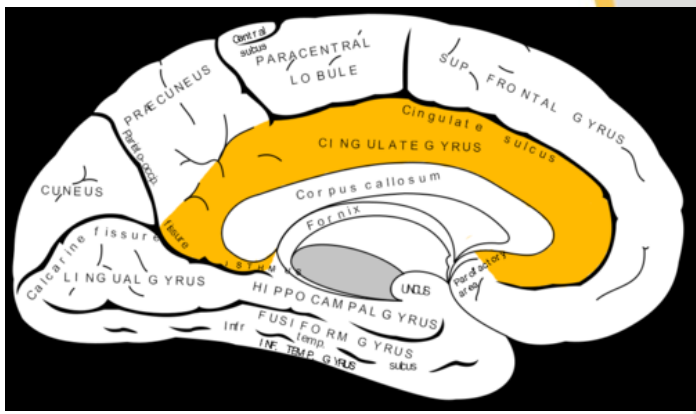
- Apathy
  - Absence of feeling, emotion, interest, concern, or motivation
- Akinetic –mute syndrome
  - Extreme state of apathy with indifference to pain, thirst and hunger
  - Absence of motor and psychic initiative
  - Manifested by lack of spontaneous movement, absent verbalization and failure to respond to questions and commands

Mesial frontal function evaluation

- Apathy
- Akinetic-mute
- Observation of spontaneous motor and verbal behavior
- Time to response to a question or command: delayed
- Count backwards from 20

Cingulate cortex

- Influences affective state and expression
- Influences motor activity
- Influences autonomic activity
- Increased activity
- Tics, OCD, aberrant social behavior
- Decreased activity
- Akinetic mutism, depression, decreased self awareness, reduced response to pain and impaired motor initiation



Psychosurgery

- First report of psychosurgery: Burckhardt 1891: topectomies
- Egaz Moniz and Pedro Almeida Lima 1935: Frontal lobectomy
- Lobotomy vs Leucotomy
- Post-lobotomy syndrome
- Dax and Radley Smith 1945: Modified procedure: Ventromedial leucotomy with MacGreogor-Crombie leucotome
- Bradley et al 1958: Orbitomedial leucotomy
- Stereotaxy 1960s

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Case vignette

- 58/M, physician, progressive difficulty in work
- Lecture of 45 minutes done in 10 minutes, unfazed
- No longer loquacious, withdrew from active social life
- Still engaged in home photography hobby, almost compulsively
- Cut the line, gluttony, lost his way
- Neuropschology, MRI and PET: Frontal dysfunction
- Frontotemporal dementia

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Why this is not a psychiatric illness?

- Why not just apathy in depression?
- Engaged in hobby, even in a compulsive manner
- No sadness, not concerned
- Anatomic substrate: Anterior cingulate, dorsolateral prefrontal and striatal involvement
- Disinhibition, loss of social behavior
- Anatomic substrate: orbitofrontal and cingulo-opercular abnormalities

Why this is not a psychiatric illness?

- Hobby pursued compulsively, why not OCD?
- No obsessive thoughts, no relief by activity
- Anatomic substrate: Striatal and anterior temporal atrophy
- Eating disturbances: Gluttony, hyperoralism, similar to Kluver-Bucy
- Anatomic substrate: Right-lateralized ventral insula, striatum, orbitofrontal cortex
- Lack of insight differentiates it from psychiatric disorders
- Anatomic substrate: Right-lateralized ventromedial prerontal cortex
- Personality changes especially lack of concern, verbal and physical interruptions

MISSING LINK

Case vignette

- 57/M, bipolar disorder, Li withdrawn due to adverse effects, doing well with valproate
- Behavioral changes, social withdrawal, apathy, loss of empathy, difficulty in starting and completing tasks
- Neuropsychology: executive dysfunction, MRI: Mild B/L dorsolateral prefrontal atrophy
- Diagnosed as Frontotemporal dementia

But.....

- Never an empathic person
- Withdrawal part of a broader apathy syndrome
- No disinhibition, impulsivity, compulsivity or altered eating behavior
- Preserved insight, distressed about the loss of cognitive function
- FDG PET: normal
- Review of MRI: Sulci widening in dorsolateral frontal and parietal cortex: seen in biopolar disorder
- F/U: No worsening, rather he improved

Learning points

- History is very very important
- Correlation with premorbid state is important
- Radiology cannot just dictate diagnosis
- FDG-PET is a useful test if available
- F/u is important

FTD versus Psychiatric illnesses

	FTD	Psychiatric disease
Duration	Shorter (few years)	Longer (years to decades)
Progression	The rule	Not seen often
Episodicity	Not seen	Seen
Emotional distress	Not seen	Seen
Insight	Absent	Present
MRI	Specific pattern	Non-specific
FDG	Hypometabolism	Normal
Treatment response	Poor	Favorable

FTD: 3 types

- Behavioral variant FTD (bvFTD) or “frontal variant” (commonest)
- Semantic variant primary progressive aphasia (PPA) or “temporal variant” FTD or semantic dementia
- Nonfluent variant primary progressive aphasia (PPA) or agrammatic PPA
- The third variant of PPA, logopenic variant: associated with Alzheimer pathology; not FTD

FTD Treatment

- Serotonin reuptake inhibitor (eg, paroxetine 10 mg od or bd) or trazodone (25 mg od) for troubling neurobehavioral symptoms
- Atypical antipsychotics: last resort; vulnerable for EPS; low dose quetiapine (12.5 to 25 mg)
- Cholinesterase inhibitors: no convincing benefit; potential for worsening ; try if uncertainty about diagnosis (Alzheimer versus FTD)
- Nonpharmacologic interventions: exercise program, home environment modification, increased supervision, physical, occupational, and speech therapy, behavioral modification techniques, and caregiver support and respite

Thank You

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