

A Neuroanatomy Primer

Neuropsychiatry: A Comprehensive Update
Harvard Medical School CME Course
October 24th 2024

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Boston, MA



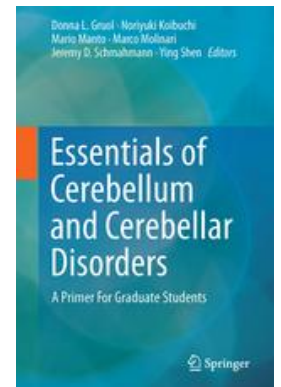
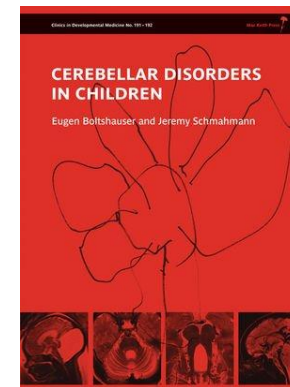
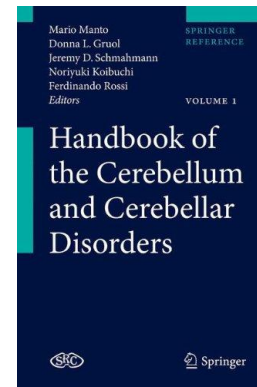
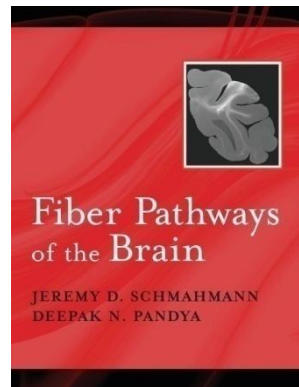
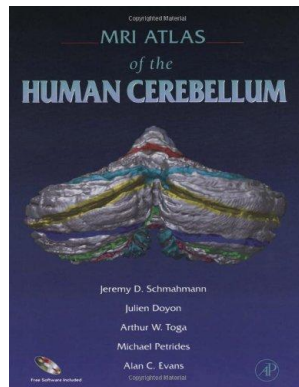
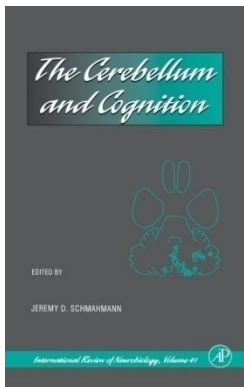
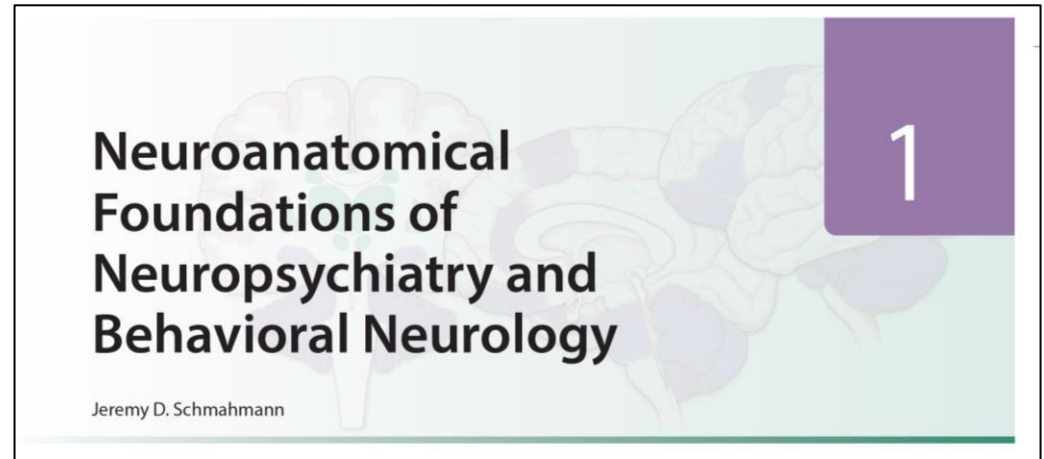
jschmahmann@mgh.harvard.edu



[@SchmahmannLab](https://twitter.com/SchmahmannLab)

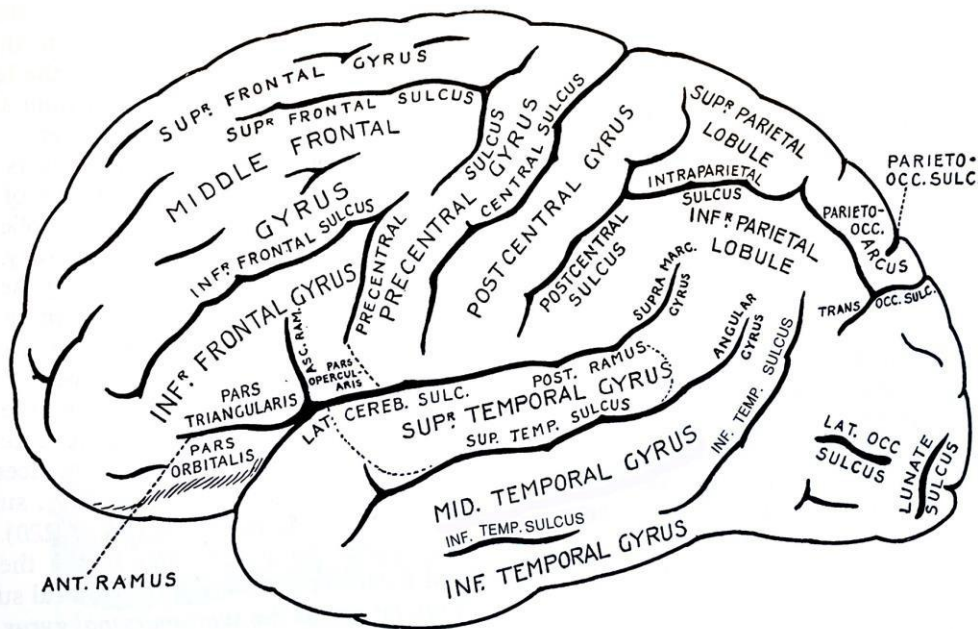
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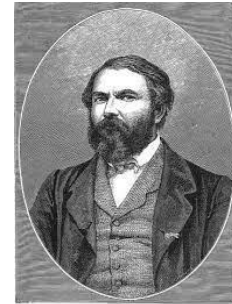


- Licensing
 - BARS, BARSc, CCAS/Schmahmann Scale, PROM-Ataxia, CNRS
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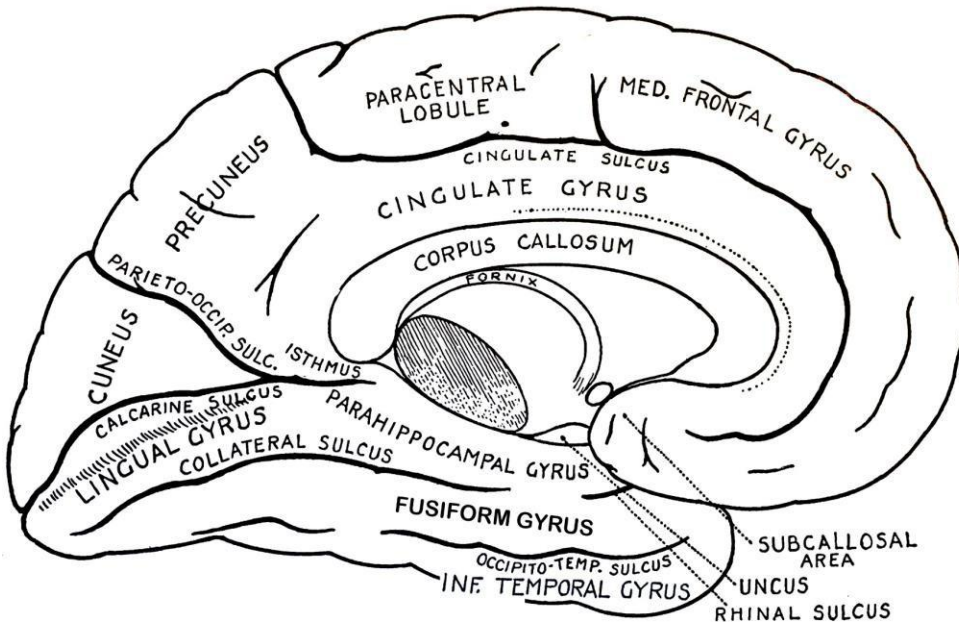
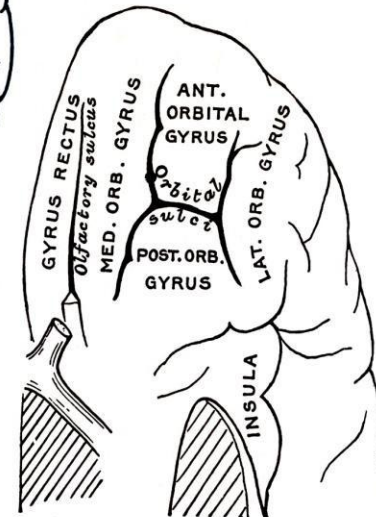




Luigi Rolando
1773-1831



Luigi Pierre Gratiolet
1815-1865



Layer I
Molecular

Layer II
External granular

Layer III
External pyramidal

Layer IV
Internal granular

Layer V
Internal pyramidal

Layer VI
Multiform

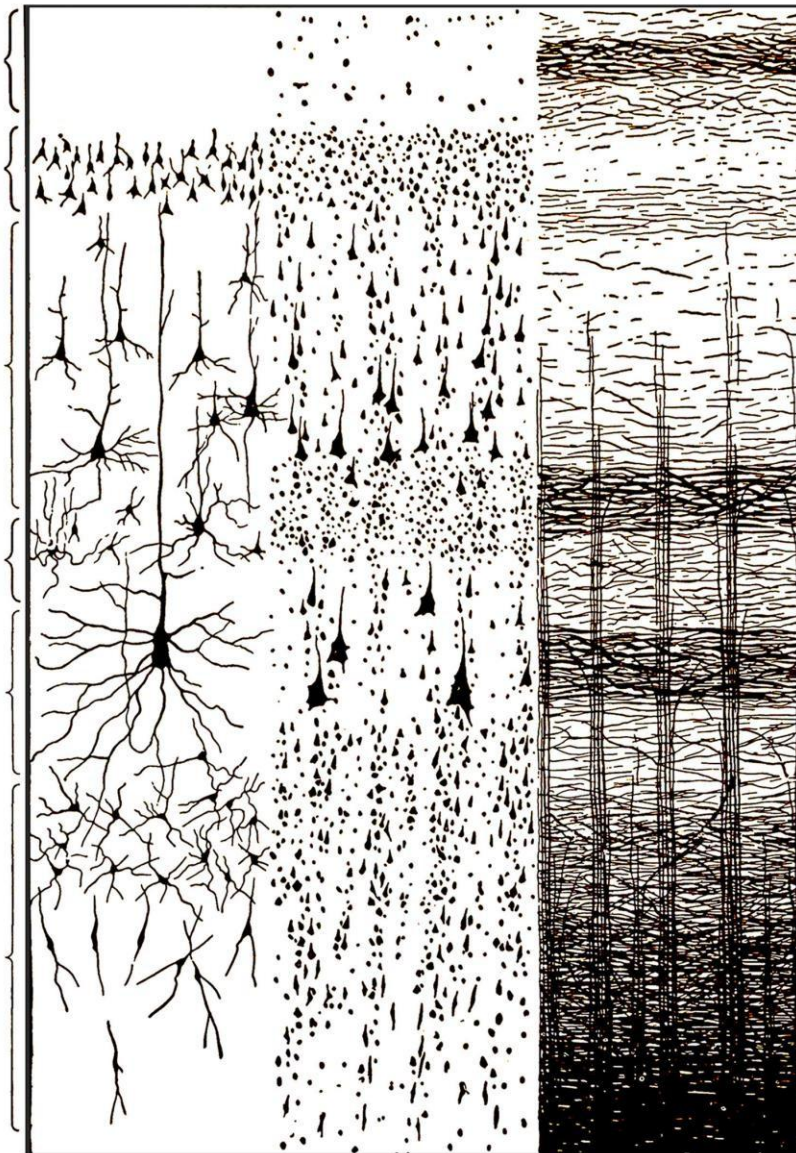
Plexus of Exner

Band of Kaes-Bechterew

**Outer (external)
band of Baillarger**

**Inner (internal)
band of Baillarger**

Deep tangential fibers



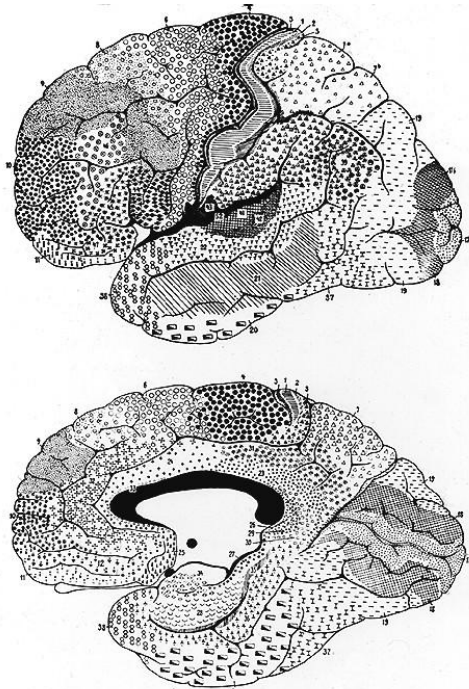
Golgi

Nissl

Weigert

Cerebral cortex is divisible into multiple discrete regions

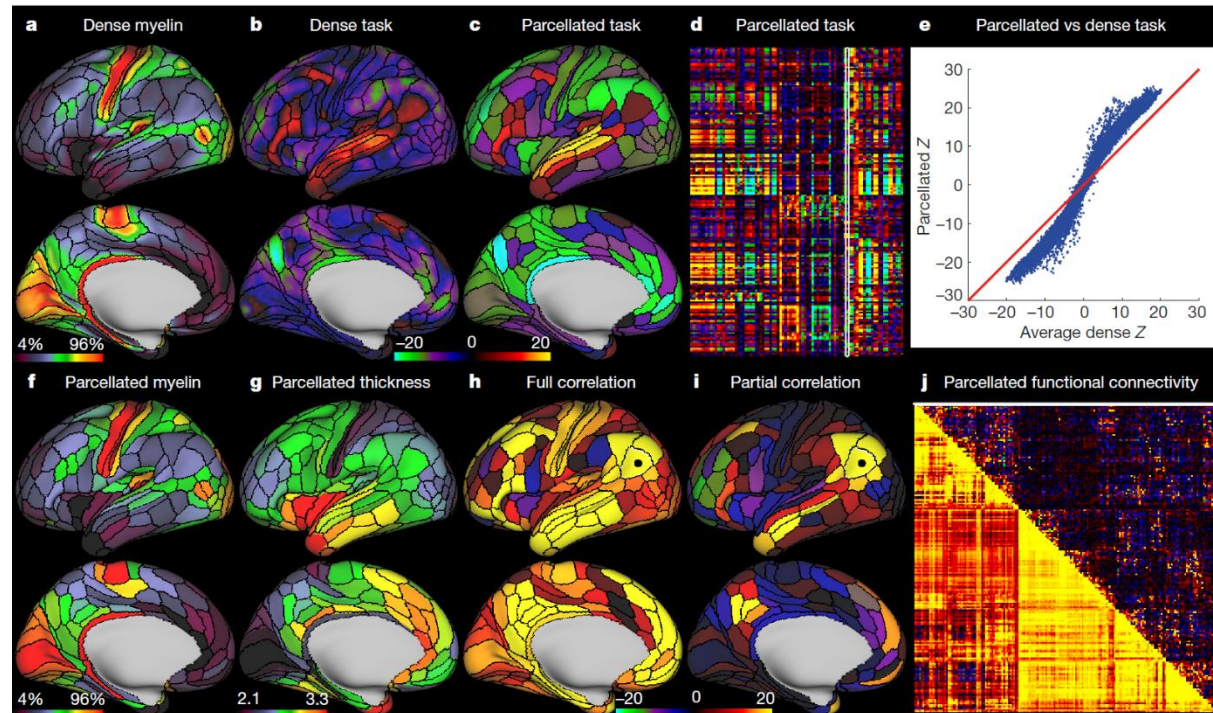
Brodmann's (1905)
cytoarchitectonic
parcellation of human
cerebral cortex



Brodmann, 1905

Multimodal parcellation of human cerebral cortex

Glasser et al., Nature. 2016;536:171-8



- Architecture (myelin content, cortical thickness)
- Function (task-based fMRI)
- Connectivity of cortical areas – rsfMRI
- Topographic organization within some areas

From corticoid to idiotypic cortex, gradual increase of cell density, laminar differentiation

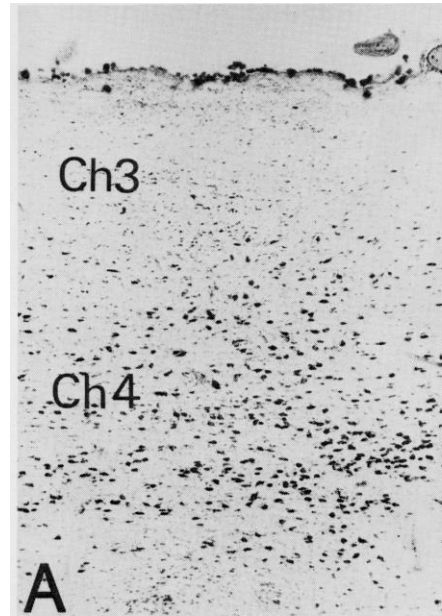
Corticoid cortex

Substantia innominata

Horizontal limb, diagonal band of Broca (Ch3)

Nucleus basalis of Meynert (Ch4)

No uniformity in neuron orientation



Allocortex

Hippocampal subiculum

2 distinct layers

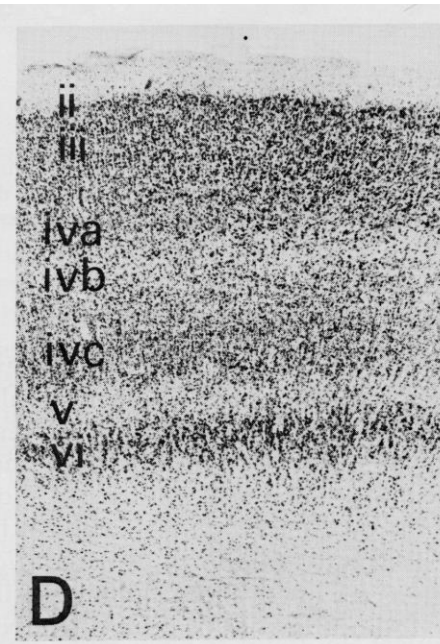
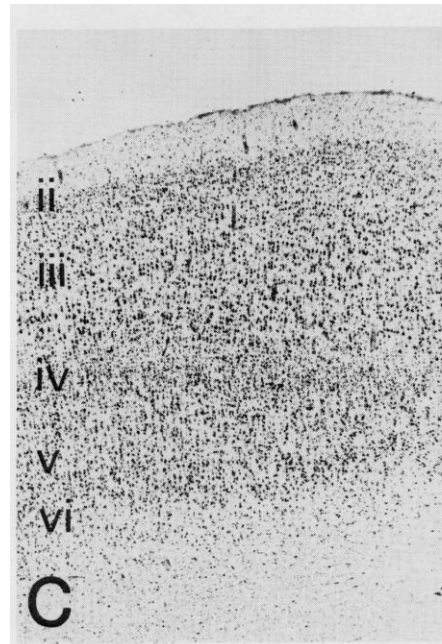
External pyramidal (pe)
internal pyramidal (pi)

Dendrites have uniform orientation

Homotypical isocortex

Prefrontal heteromodal region

6 distinct layers
Differentiated granularity in layers II and IV



Idiotypic cortex

Striate visual area

At least 7 layers,
many strongly granular

EXTRAPERSONAL SPACE

primary sensory and motor
areas

IDIOTYPIC CORTEX

modality-specific (unimodal)
association areas

HOMOTYPICAL ISOCORTEX

high-order (heteromodal)
association areas

temporal pole - caudal orbitofrontal
anterior insula-cingulate-parahippocampal

PARALIMBIC AREAS

septum - s. innominata-
amygdala-piriform c.-hippocampus

LIMBIC AREAS (CORTICOID + ALLOCORTEX)

HYPOTHALAMUS

INTERNAL MILIEU



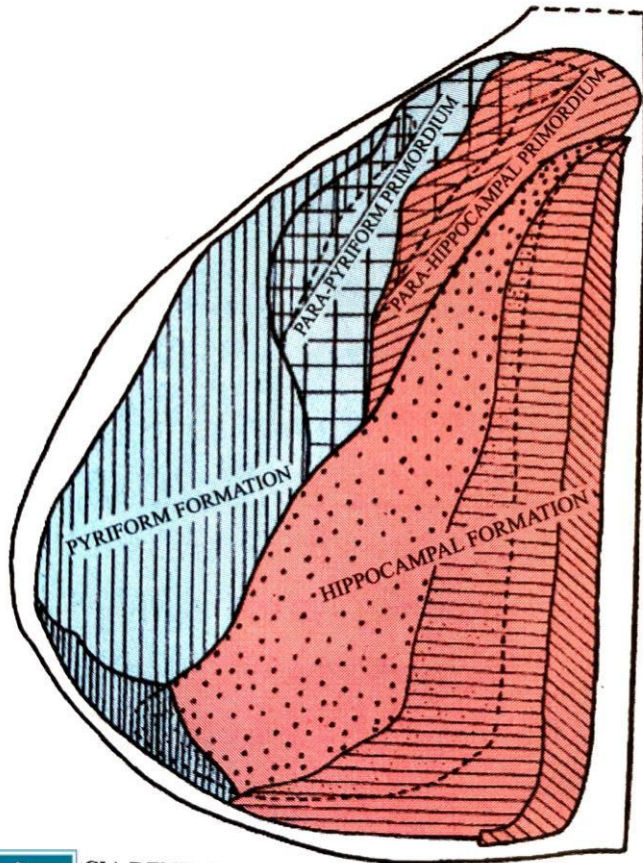
Dual origin of cerebral cortex

Dart-Abbie-Sanides-Pandya

Allocortex

Hippocampal-Archicortex (dorsal)

Pyriform/Olfactory-Paleocortex (ventral)



CIA DENTATA

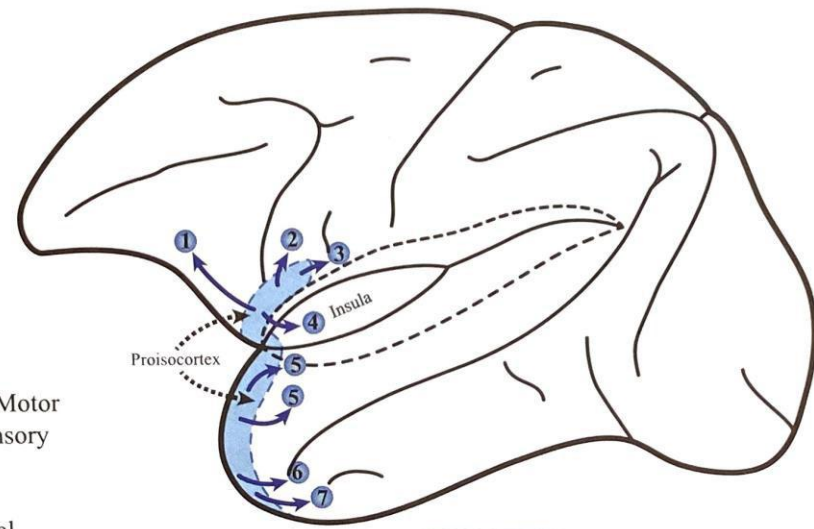
POCAMPUS

BICULUM HIPPOCAMPI

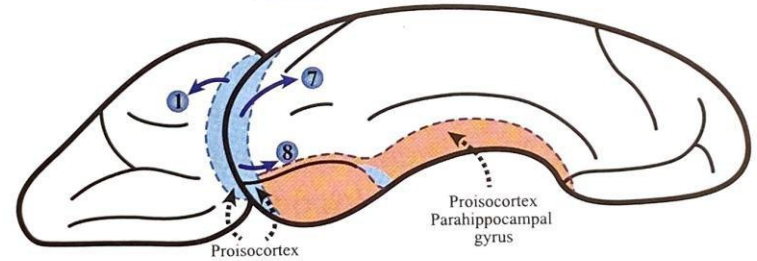
||| PALLIAL PYRIFORM CORTEX P1

|||| PALLIAL PYRIFORM CORTEX P2

A

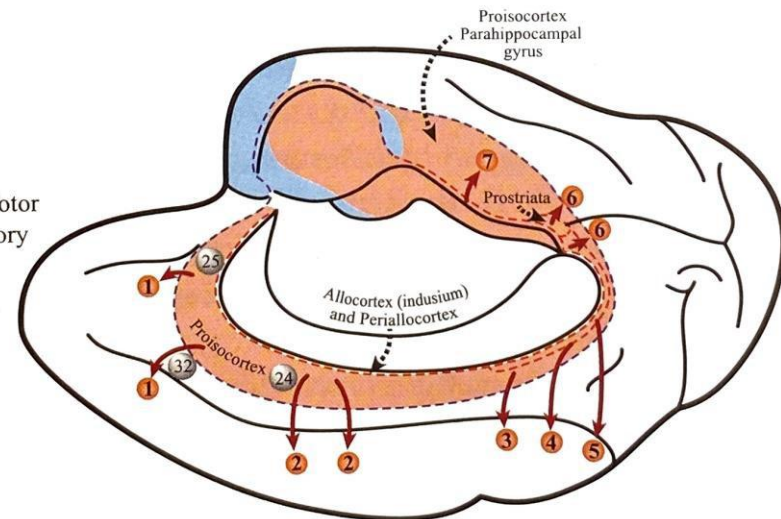


- 1- Prefrontal
- 2- Premotor-Motor
- 3- Somatosensory
- 4- Insular
- 5- Auditory
- 6- Multimodal
- 7- Visual
- 8- Limbic



B

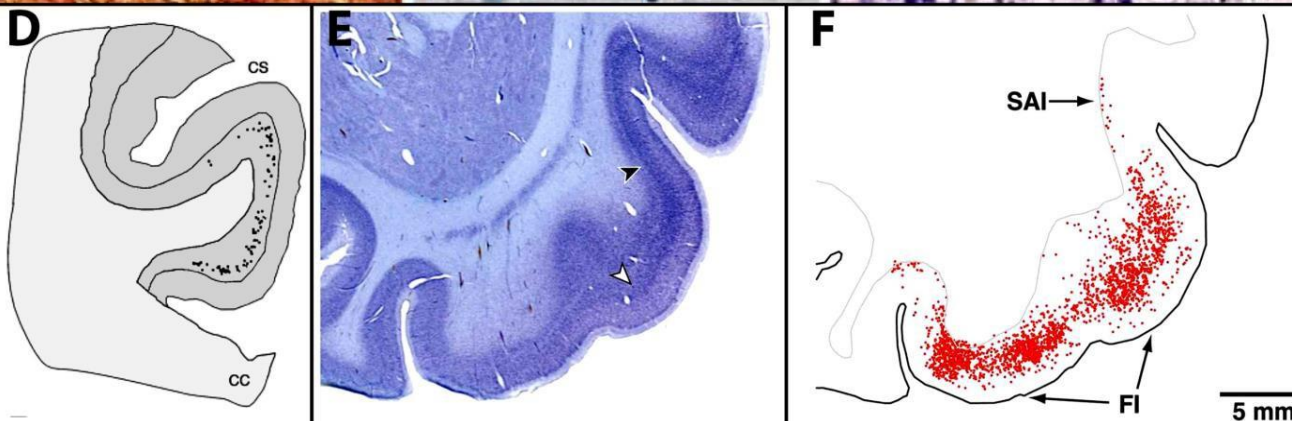
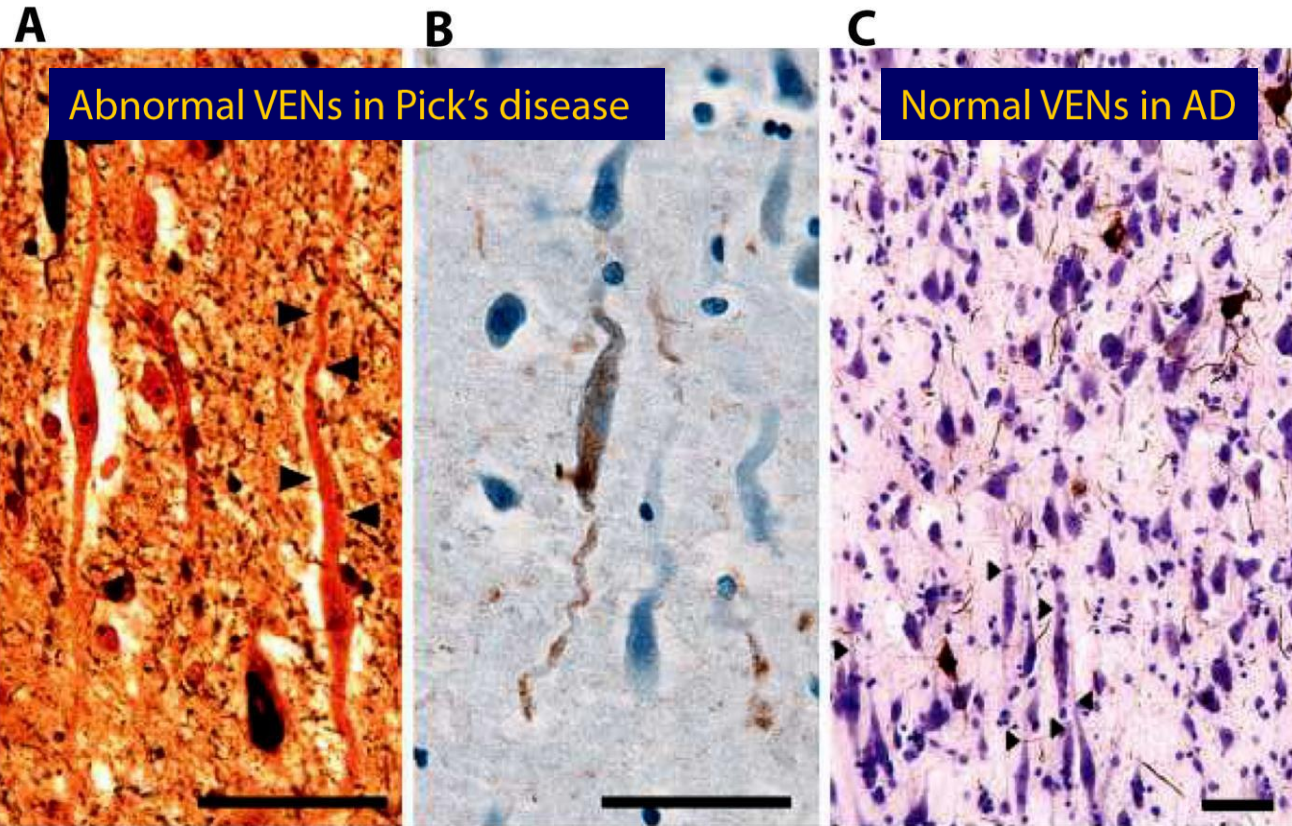
- 1- Prefrontal
- 2- Premotor-Motor
- 3- Somatosensory
- 4- Multimodal
- 5- Auditory
- 6- Visual
- 7- Limbic



Von Economo neurons



Constantin von Economo
1876-1931

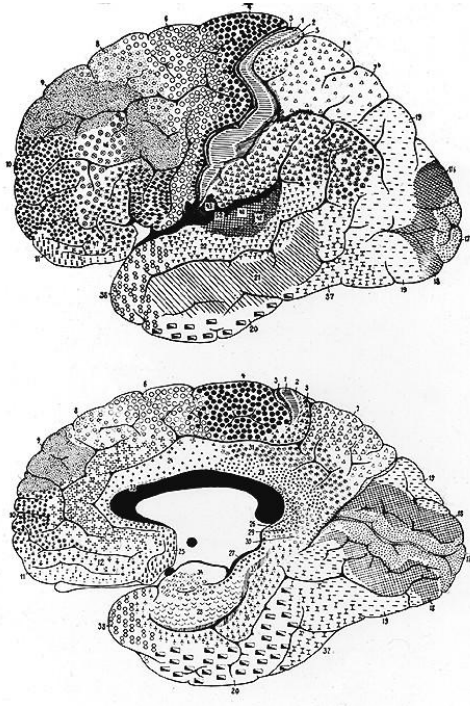


Anterior cingulate cortex

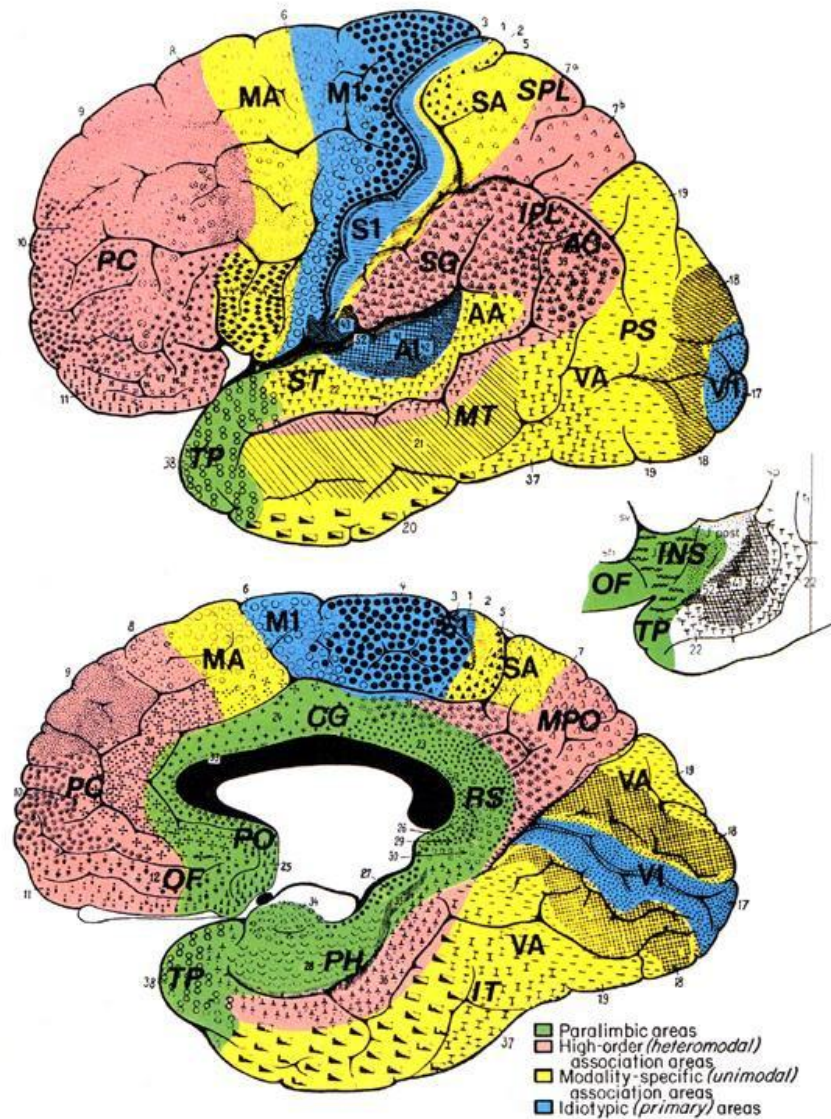
Fronto-insular cortex

Seeley et al, 2006 (A,B)
Nimchinsky et al., 1999 (C)
Allman et al., 2011 (D-F)

Cortical areas grouped by architecture and overarching functional domain



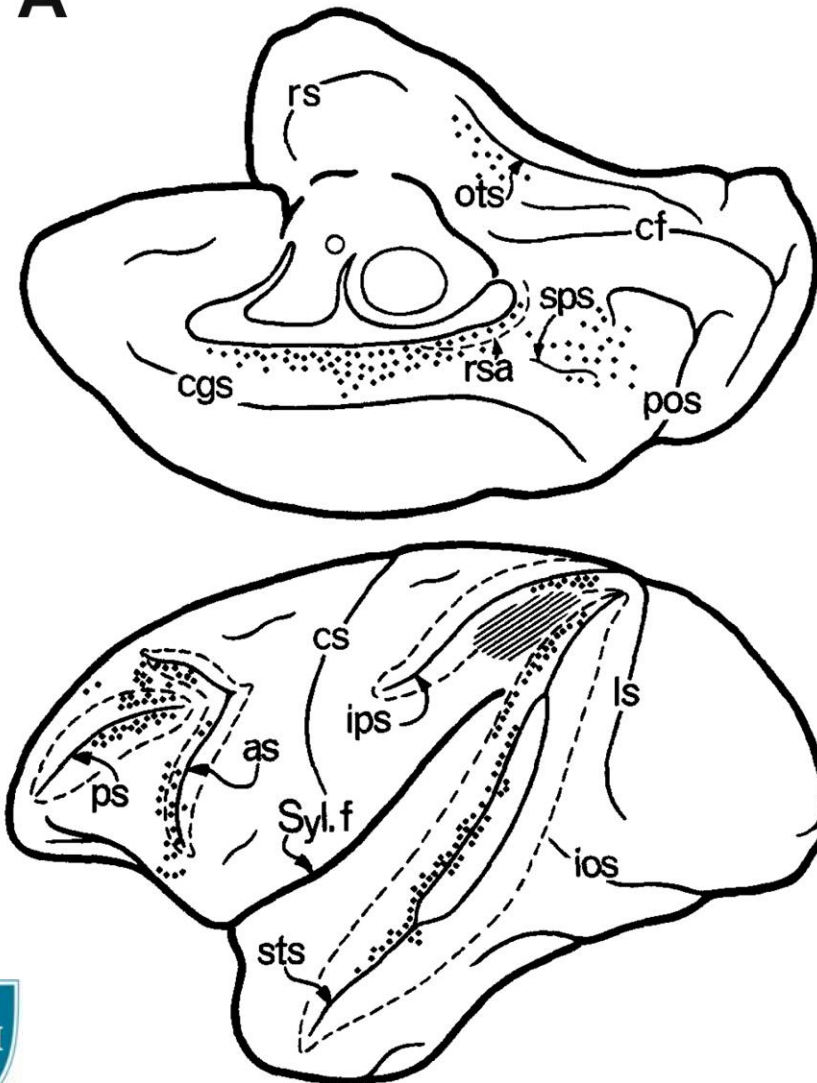
Brodman, 1905



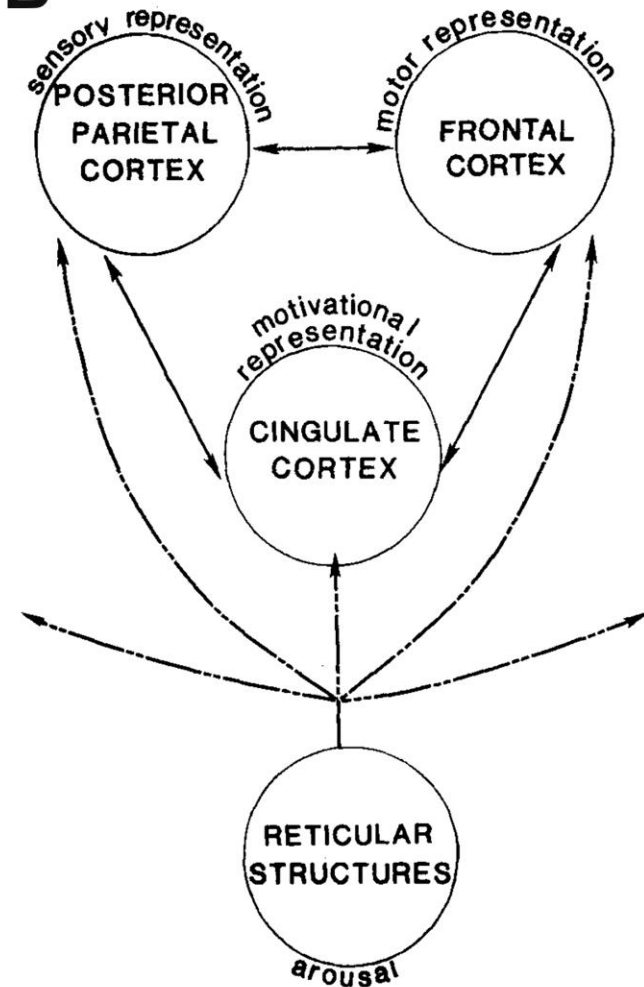
Mesulam, 2000

A Cortical Network for Directed Attention and Unilateral Neglect

A



B



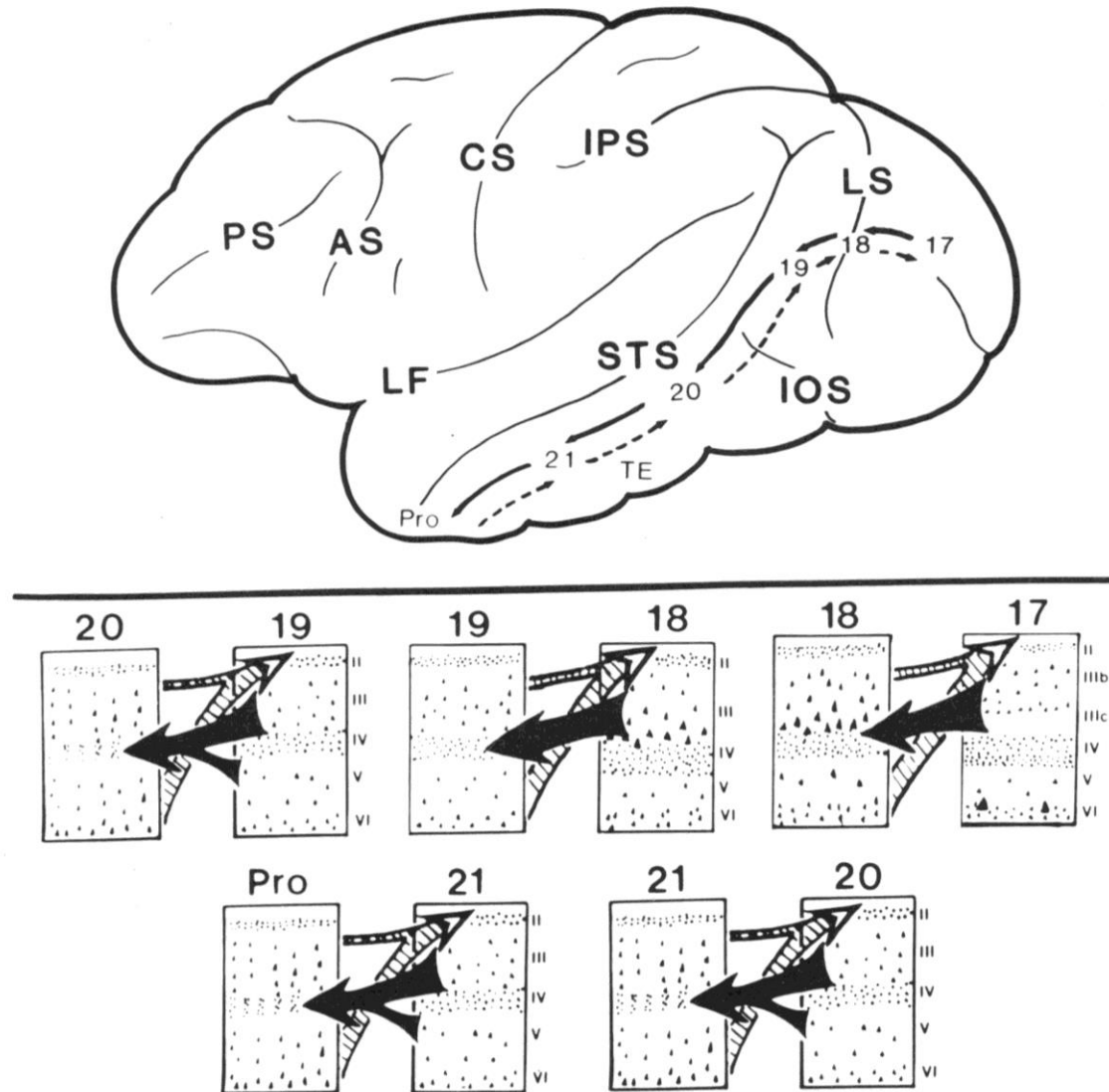
Mesulam, Van Hoesen, Pandya, Geschwind, 1977
Mesulam, 1981

Distributed neural systems

Comprise anatomic regions, or nodes
Each with unique architectural properties
Geographically arranged throughout cortical and subcortical areas
Linked anatomically in a precise and unique manner

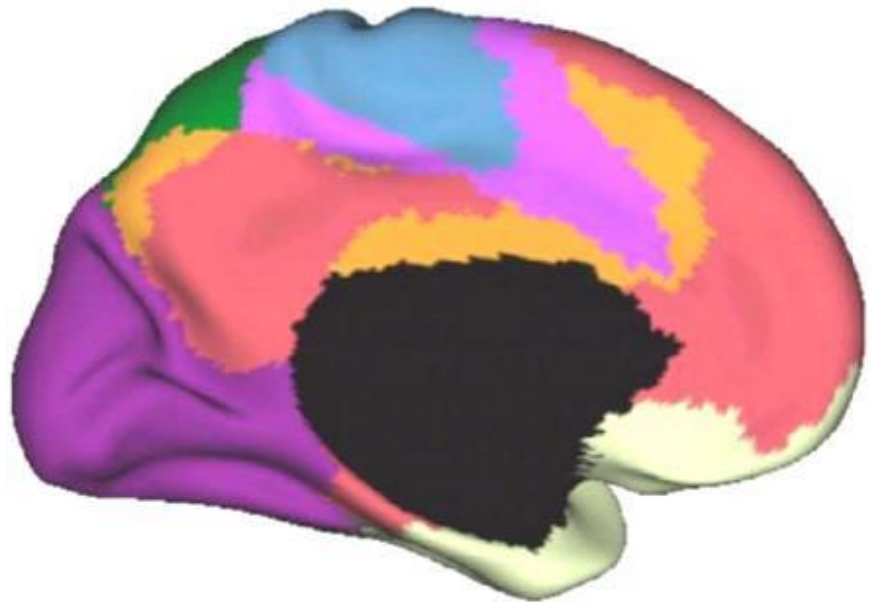
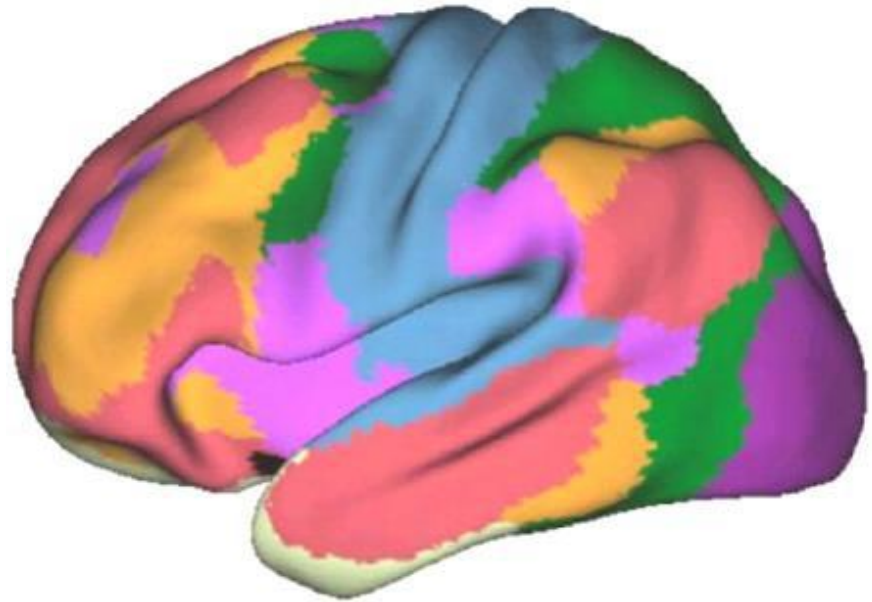


Laminar specificity of the Feedforward and Feedback Cortical Connections



Intrinsic functional connectivity networks - rsfcMRI

-  Purple (Visual)
-  Blue (Somatomotor)
-  Green (Dorsal Attention)
-  Violet (Ventral Attention)
-  Cream (Limbic)
-  Orange (Frontoparietal)
-  Red (Default)



Principles of Organization of Cerebral Connections. I

General principle: Multiple connectivity

Association fibers

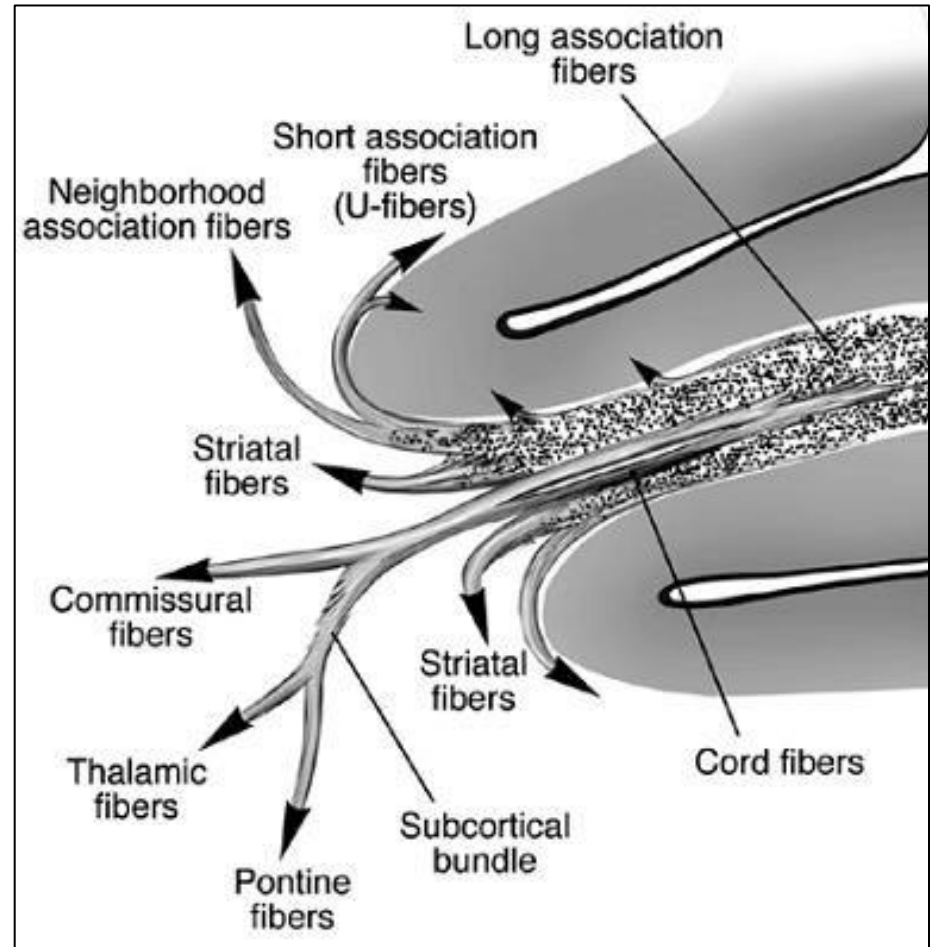
Striatal fibers

Commissural fibers

Projection fibers

- Thalamic bundle

- Pontine bundle



Principles of Organization of Cerebral Connections. II

Specific principle: Connectional topography

1. Architecture determines the transform

Each architectonically distinct cortical and subcortical node contributes a unique transform to information processing

2. Cerebral cortical architecture drives connections

And/or is determined by underlying genetic influences

3. Connections enable behavior

Connections between nodes of the distributed neural system are:

- precisely organized

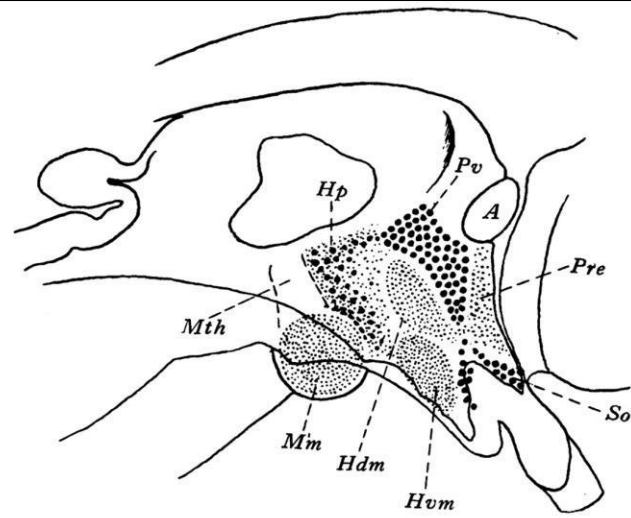
- facilitate network integration of different transforms

- provide the anatomical underpinnings of behavior

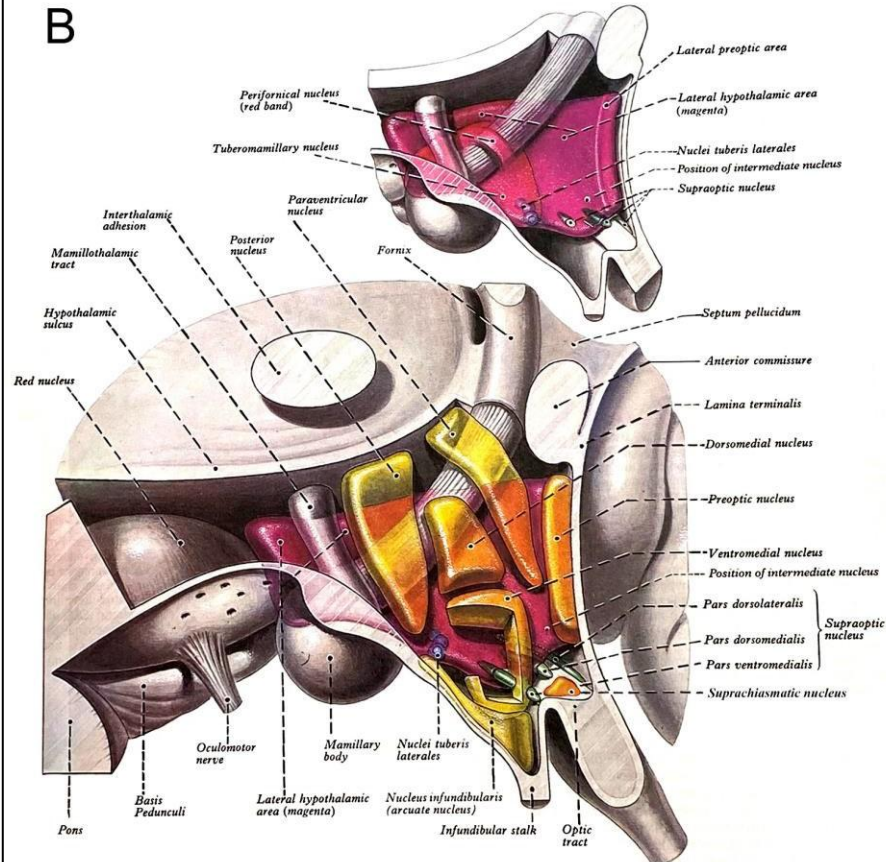
4. Cross modal integration - domain of the cerebral cortex



A



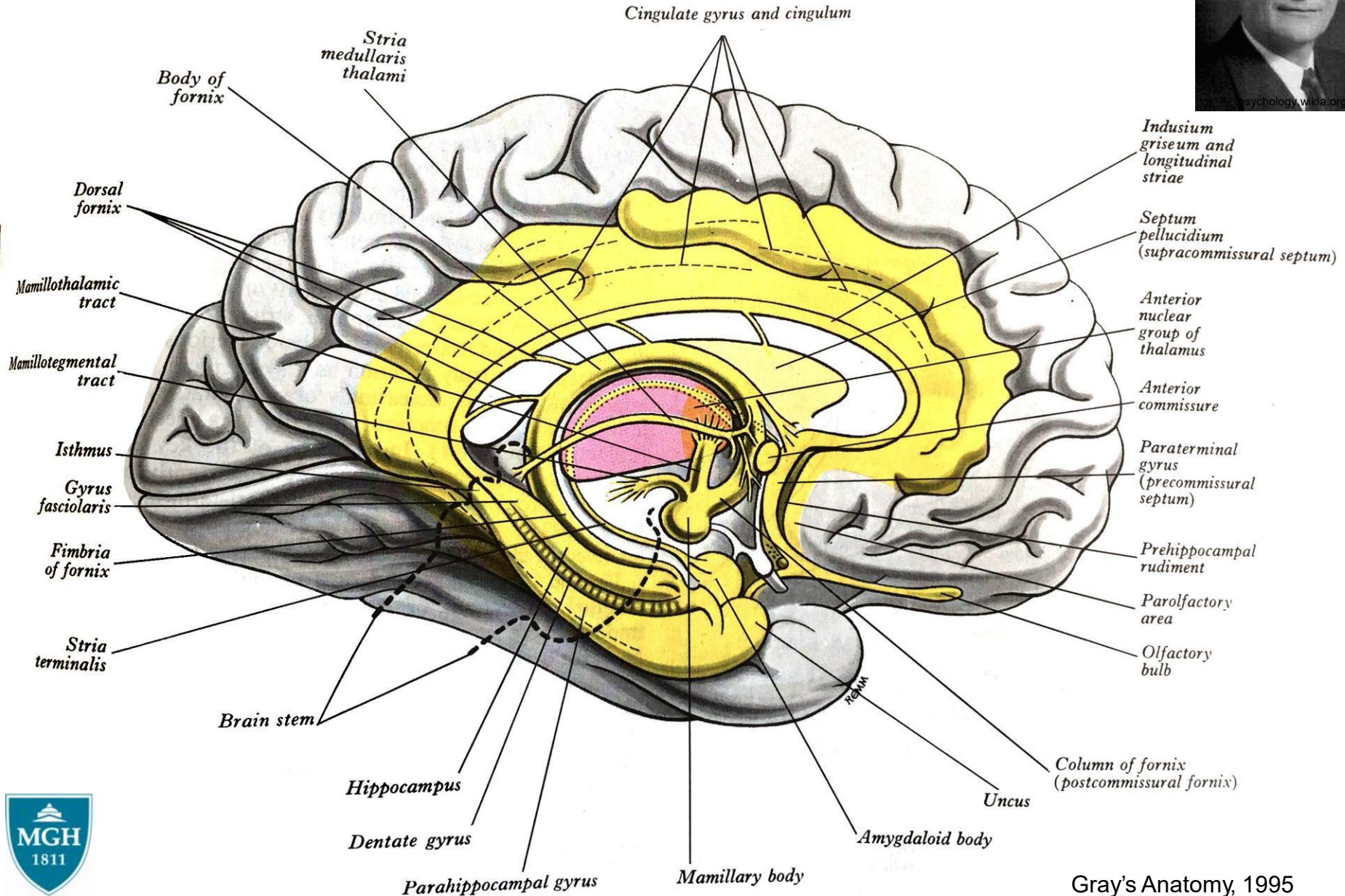
B



Papez Circuit

James W. Papez (1883 – 1958)

A PROPOSED MECHANISM OF EMOTION. *Arch Neur Psych.* 1937;38(4):725-743.



Fornix

Hippocampus
TO
mammillary bodies

**Mammillothalamic tract
(Vicq d'Azyr)**

Mammillary body
TO
anterior thalamic nucleus

Stria terminalis

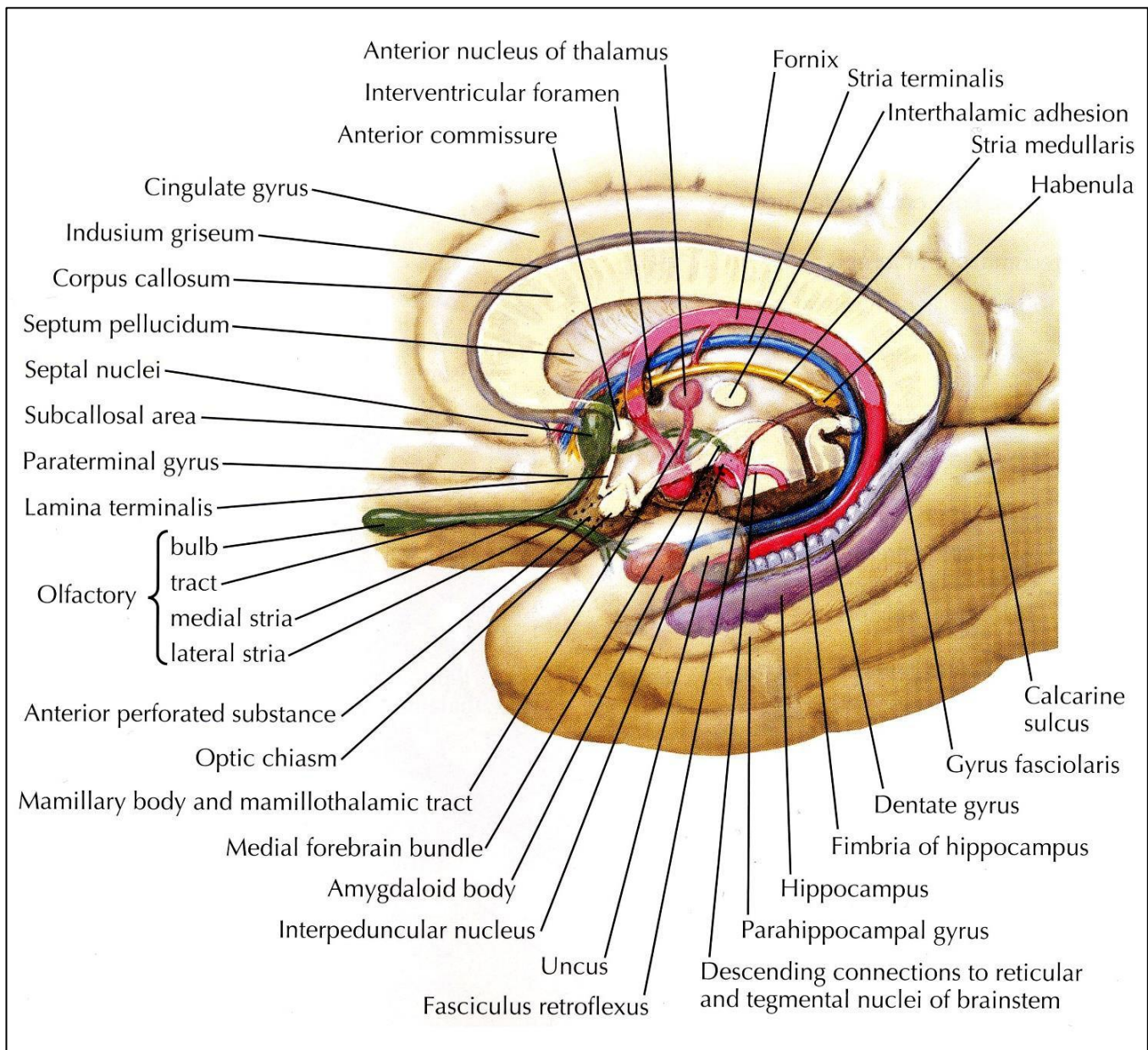
Amygdala (CM)
TO
hypothalamus (VM)

Stria medullaris

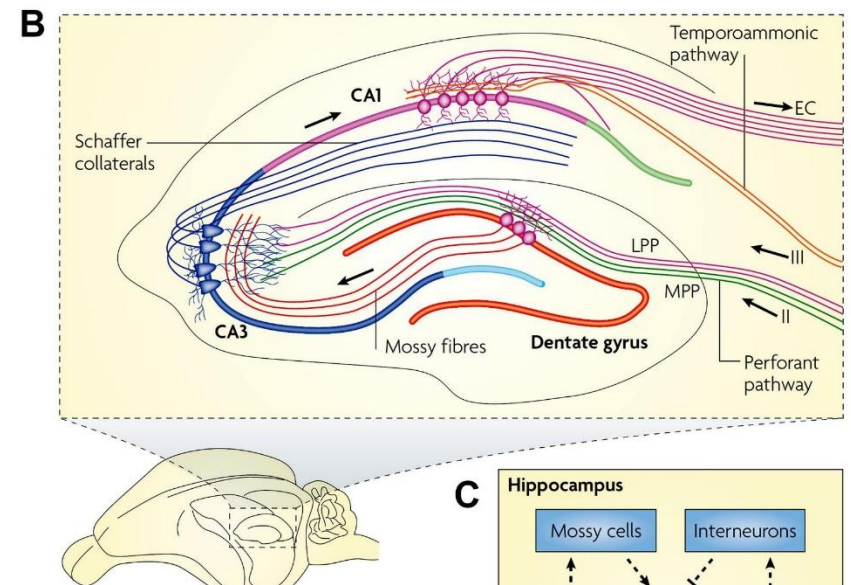
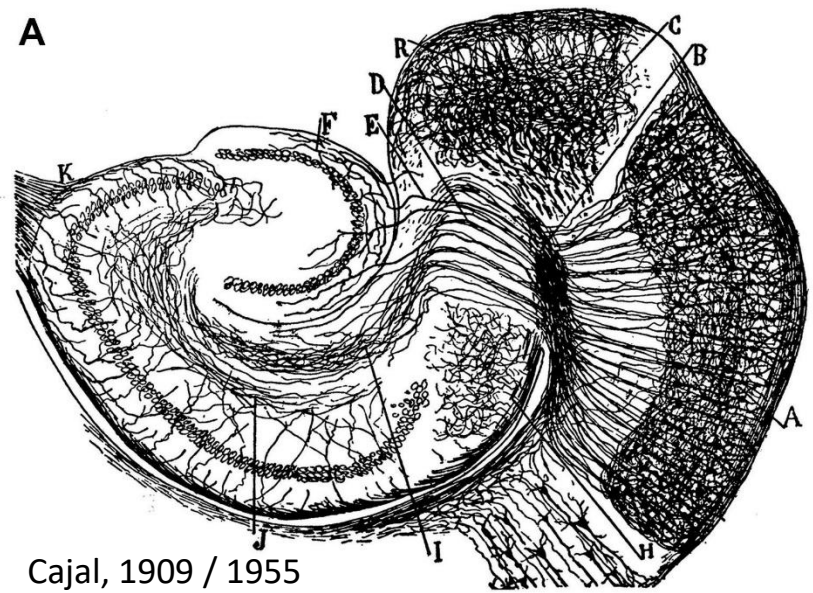
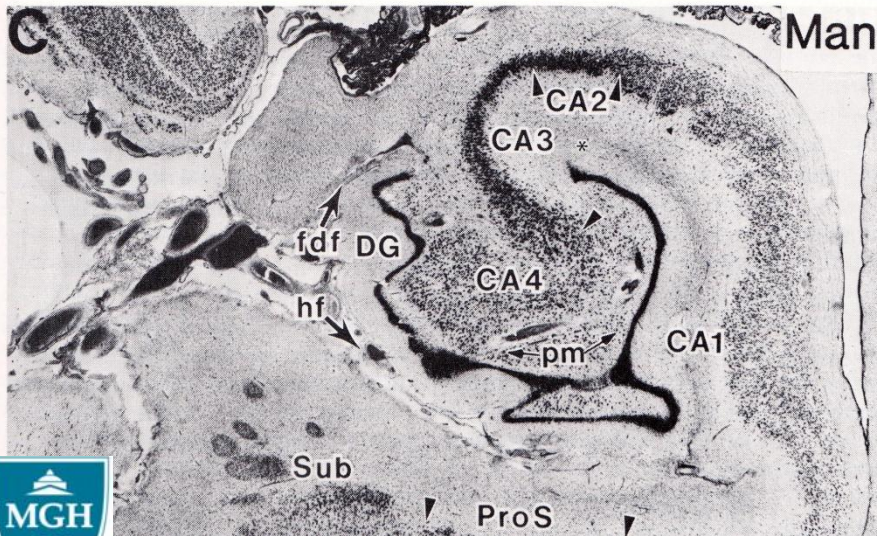
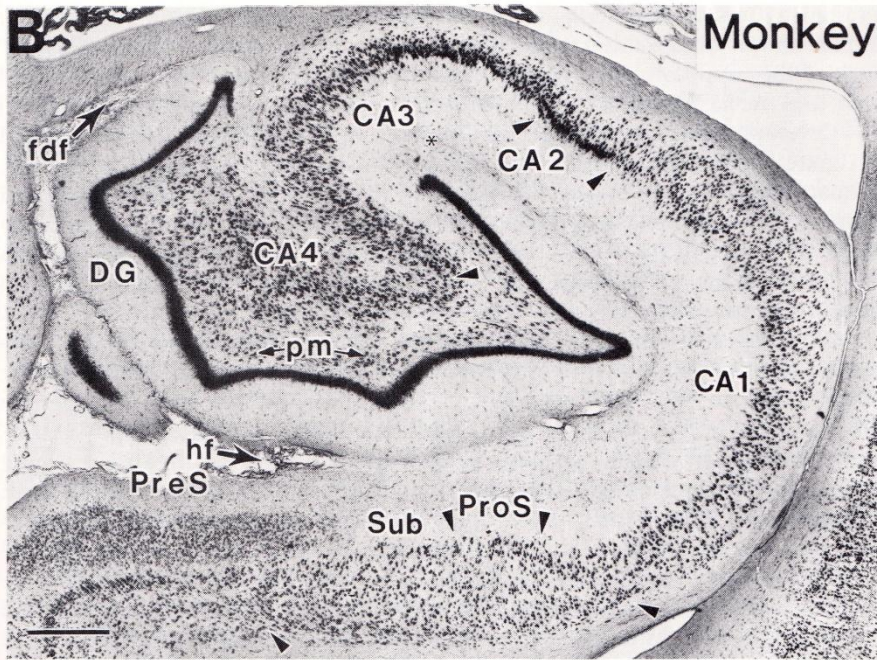
septal nuclei
lateral preoptic-hypothalamus
anterior thalamic nuclei
TO
Habenula

**Habenulo-interpeduncular tract
(Fasciculus retroflexus)**

Habenula
TO
Interpeduncular nucleus



Hippocampus





HIPPOCAMPAL PHYSIOLOGY

■ The Papez Circuit

FUNCTION

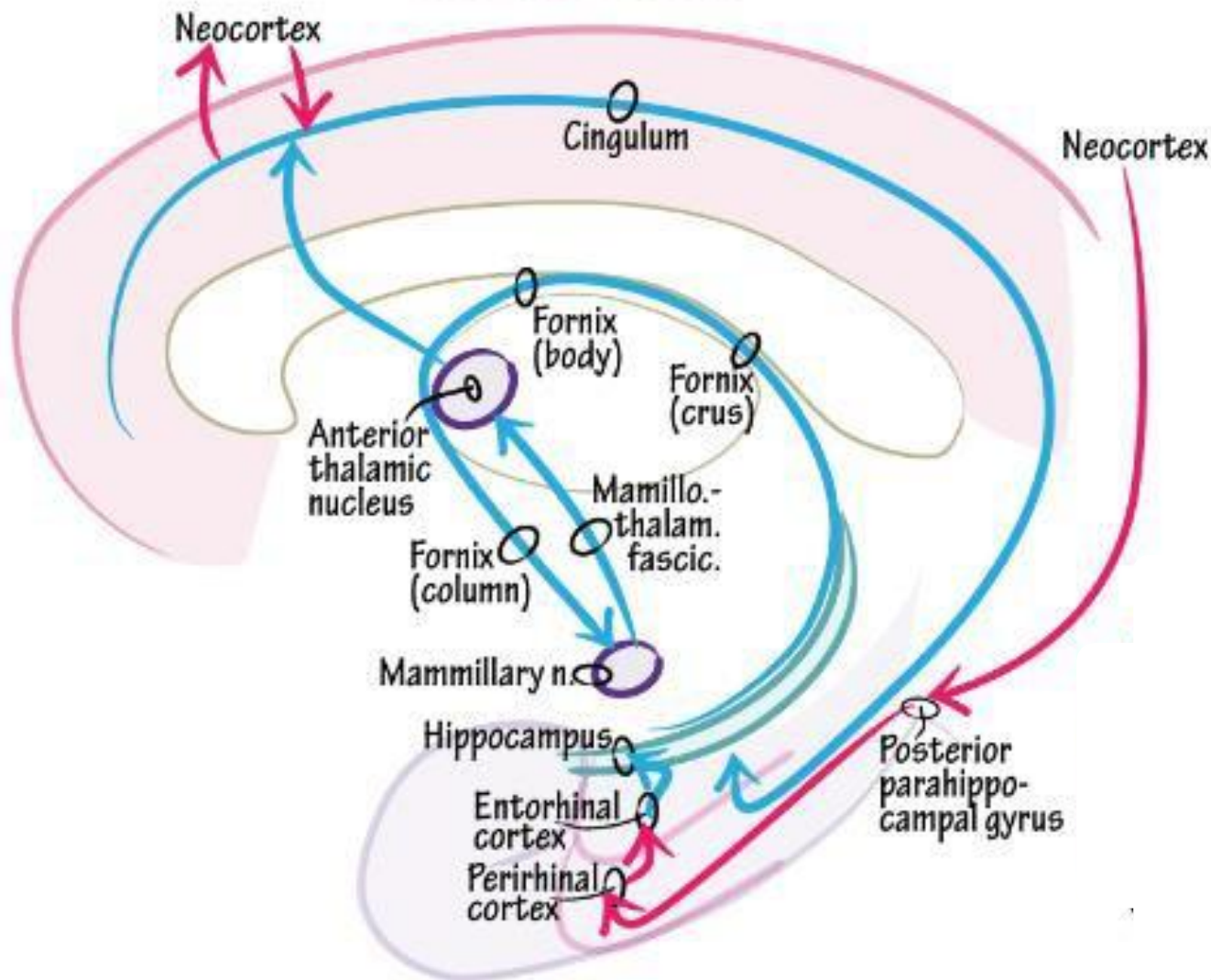
Originally, believed to function in emotional regulation.

Now, understood to function in memory processing.

STEPS



Extra-Hippocampal Circuitry The Papez Circuit



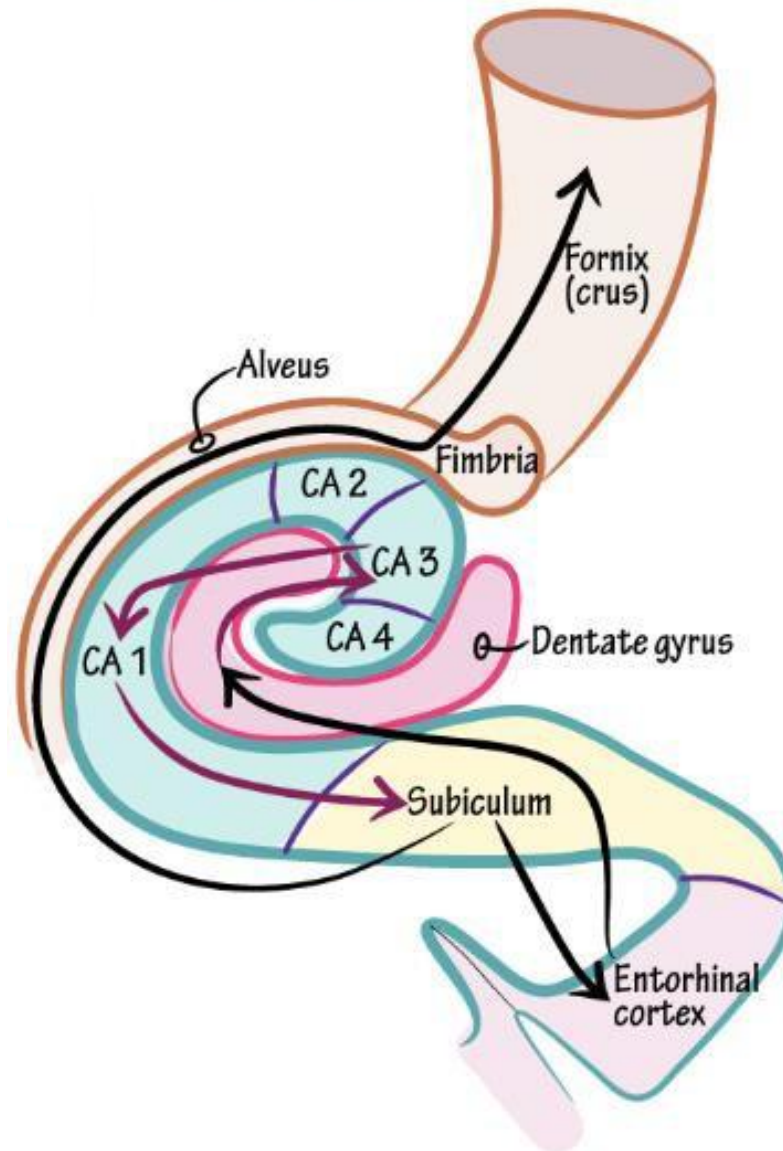
■ The Perforant Pathway

Whereas most cortical projections are bidirectional, perforant pathway follows a specific unidirectional progression.

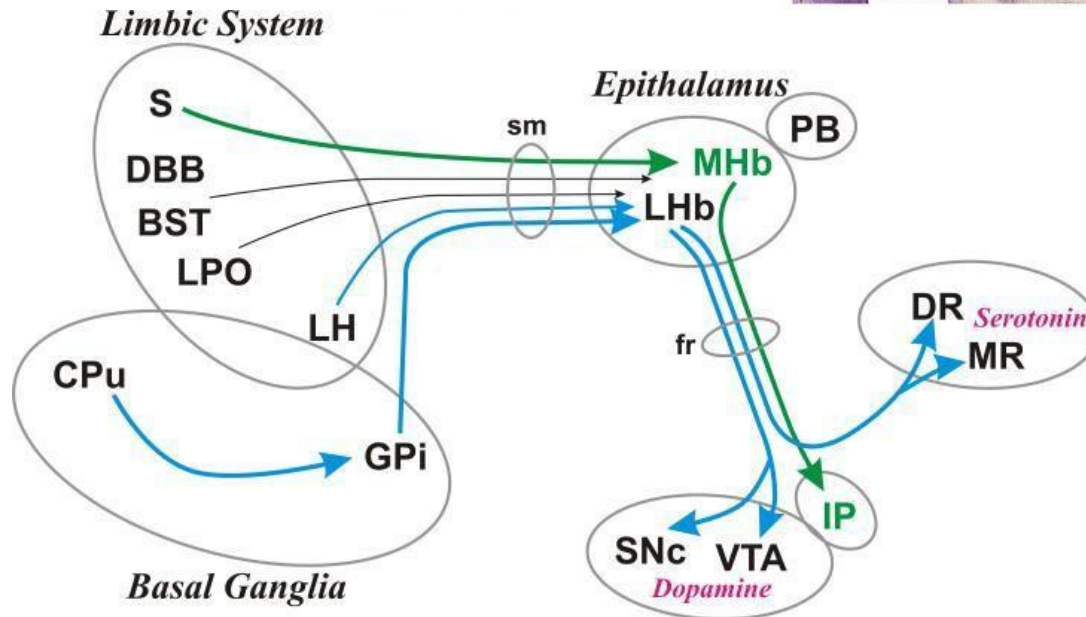
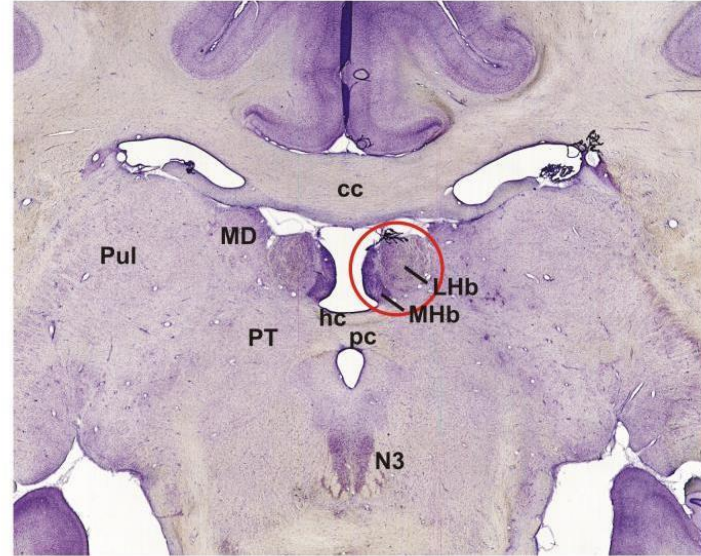
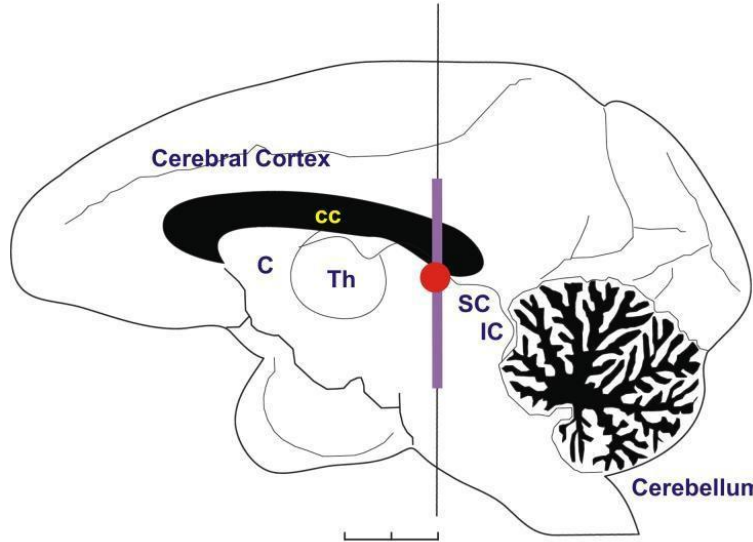
STEPS

- Dentate gyrus
- CA3 (via Schaffer collaterals)
- CA1
- Subiculum

Intra-Hippocampal Circuitry The Perforant Pathway



Habenula

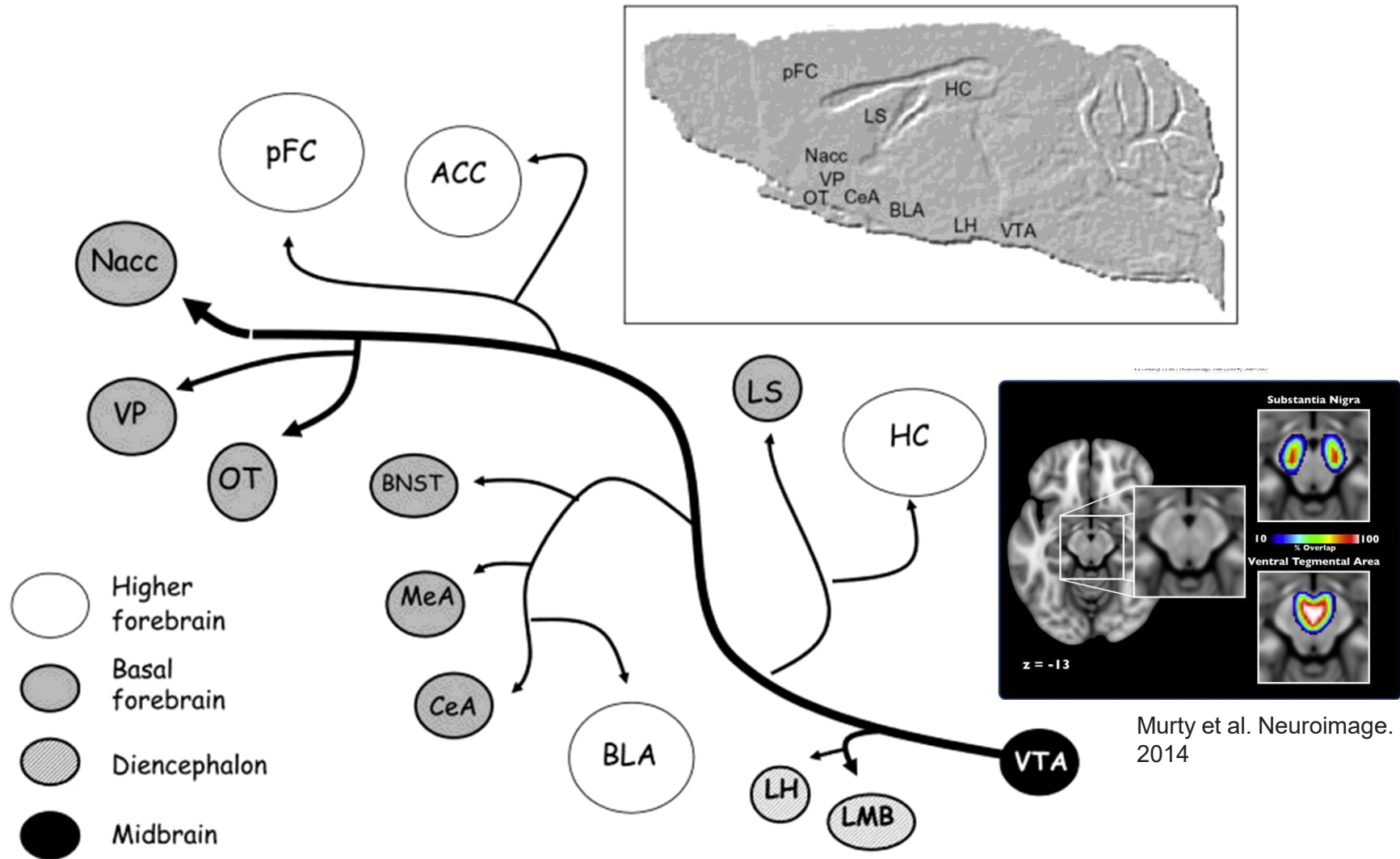


Emotional decision making

Lateral habenula influences dopamine and serotonin neurons

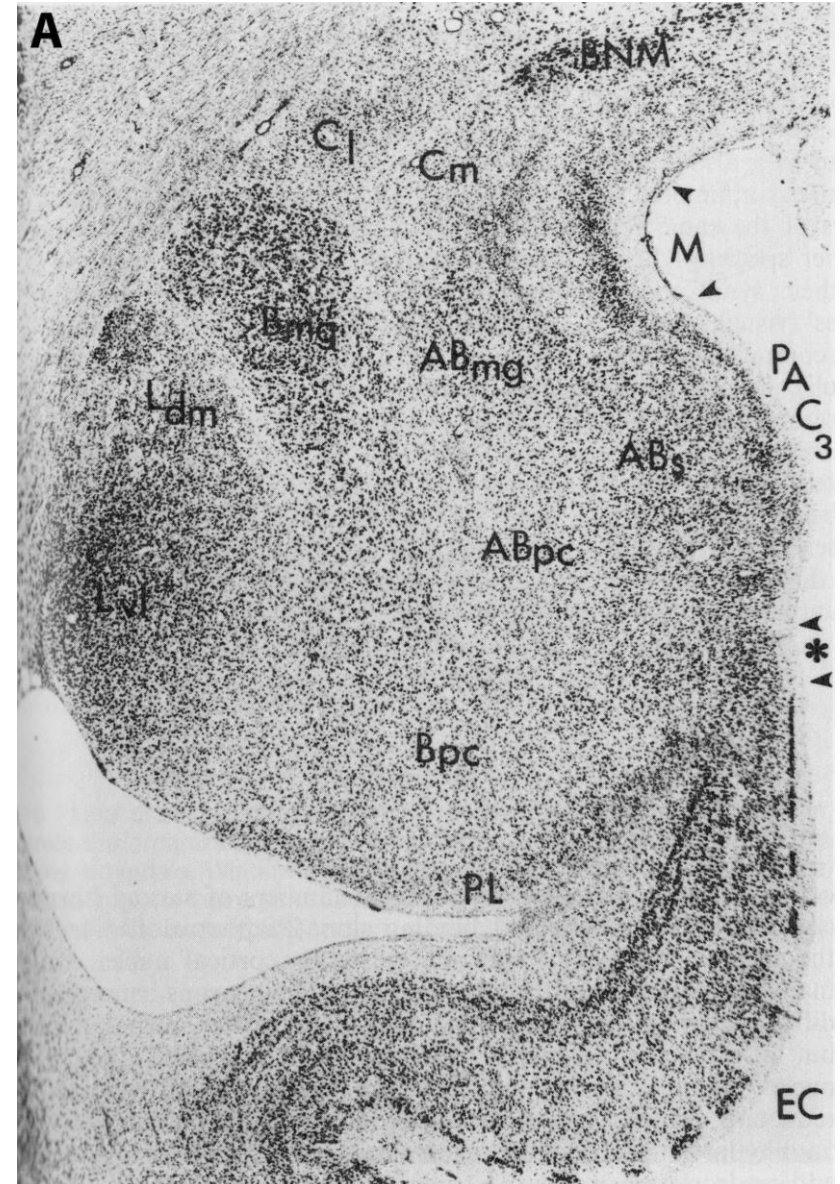
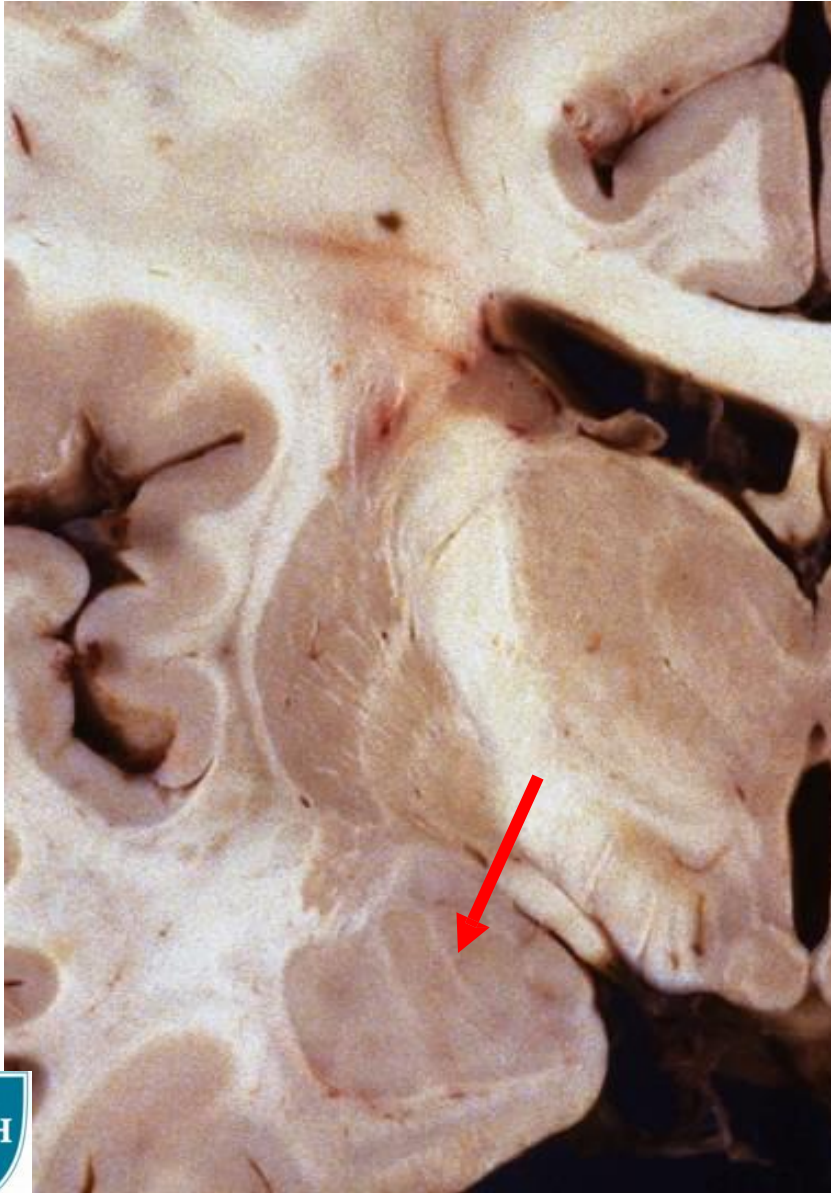
Implicated in depression, schizophrenia, drug-induced psychosis.

Ventral tegmental area (VTA)



Amygdala

Amygdaloid Complex contains multiple different nuclei



Amygdala

Cortical, medial and central nuclei

Primitive division associated with the olfactory system

Lateral, basal, and accessory basal nuclei

Newer division associated with the neocortex

3 fiber tracts convey afferent and efferent connections

Lateral olfactory stria

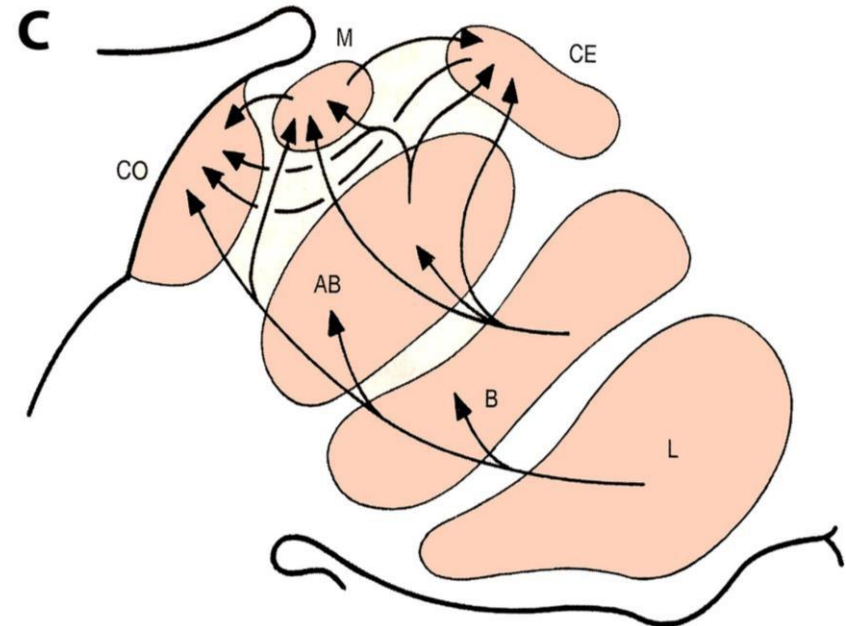
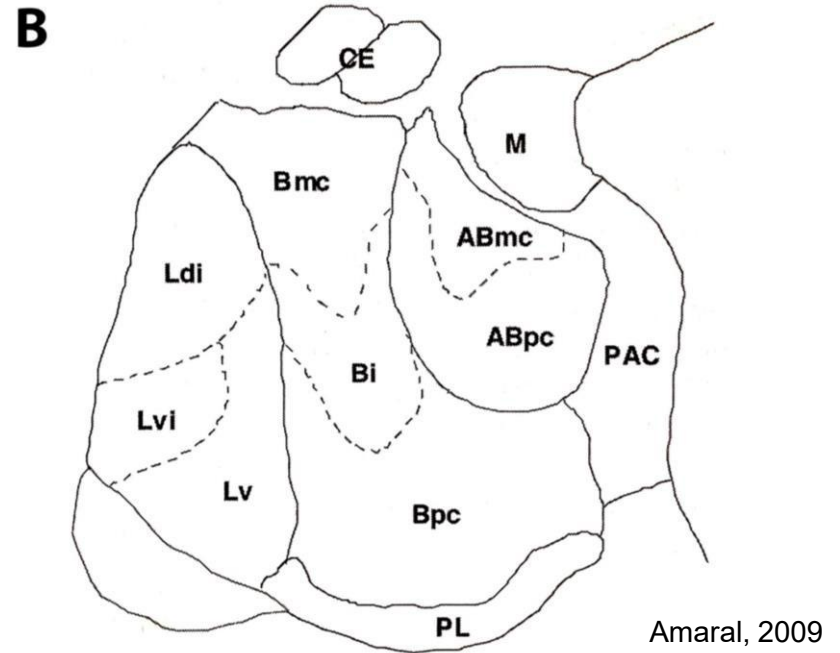
Carries secondary olfactory fibers to cortical and medial nuclei

Ventral amygdalofugal pathway

In sublentiform substantia innominata, bidirectional pathway links dorsomedial part of amygdala with lateral pre-optic hypothalamus, MD thalamic nucleus, and medial prefrontal cortex

Stria terminalis

Dorsal amygdalofugal pathway links amygdala with hypothalamus



Extended amygdala

Heimer et al., 1999

Central and medial nuclei

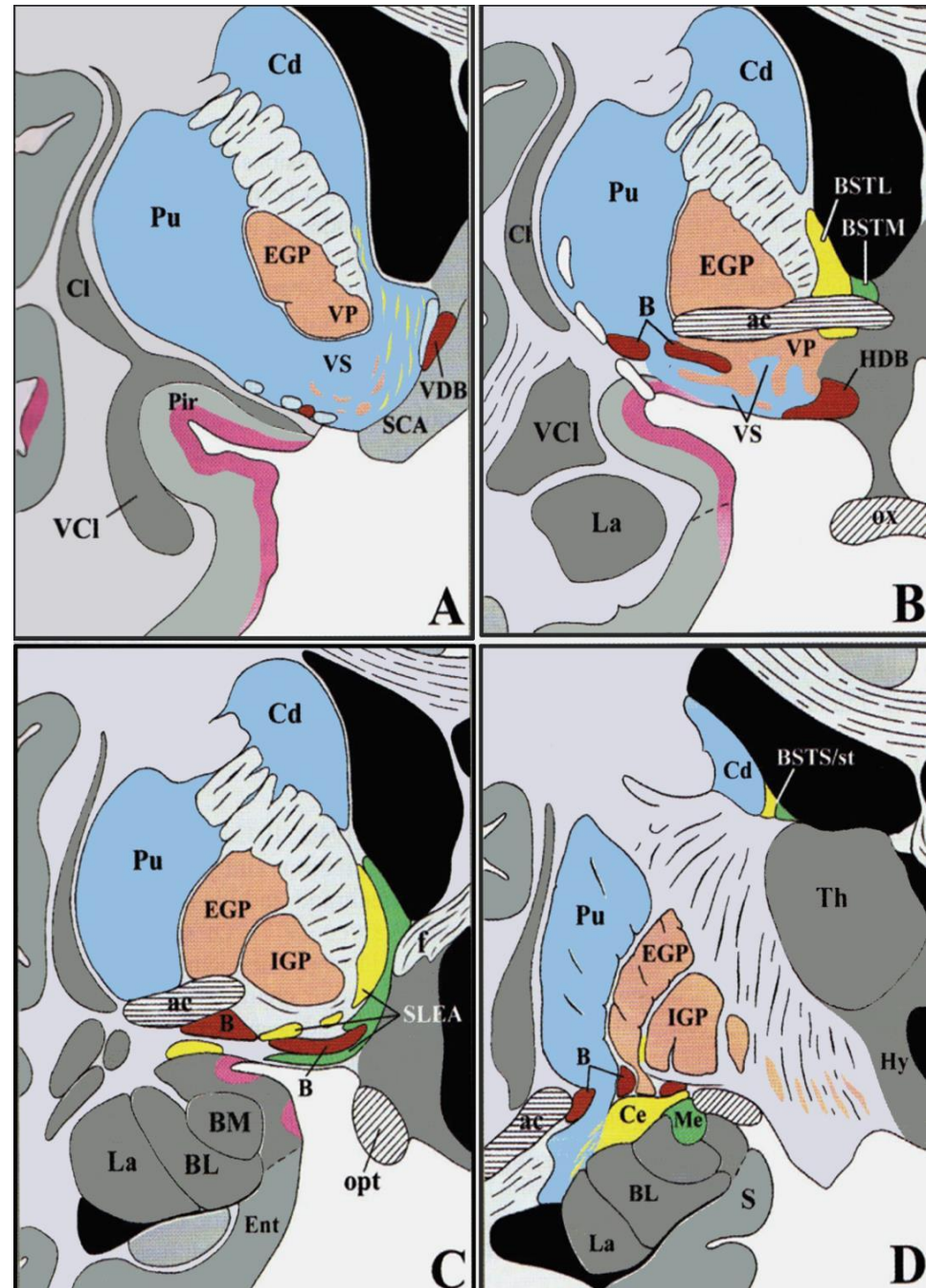
Cell columns traversing the sublenticular substantia innominata

Ventral striatopallidal system

Bed nucleus of stria terminalis
(BNST)

12 to 18 sub-nuclei surrounding
caudal part of anterior commissure

Nucleus basalis of Meynert



Gyrus precentralis (M)

This diagram illustrates the motor homunculus, a representation of the human body mapped onto the precentral gyrus of the left hemisphere of the brain. The homunculus is shown in a distorted, upside-down orientation. The head is at the bottom right, with the face and mouth open, showing teeth. The tongue is represented by a red, elongated shape. The neck and upper torso are shown in the middle. The arms and hands are at the top, with the right hand holding the left arm. The legs and feet are at the top left. The body is shaded in a stippled pattern. Labels with leader lines point to various parts: 'Trunk' points to the upper body, 'Foot' points to the right leg, 'Hand' points to the right arm, 'Face' points to the face, 'Tongue' points to the tongue, and 'Sulcus lateralis' points to the groove separating the homunculus from the rest of the brain. A dashed line runs along the length of the homunculus, representing the midline of the body.

Trunk

Foot

Hand

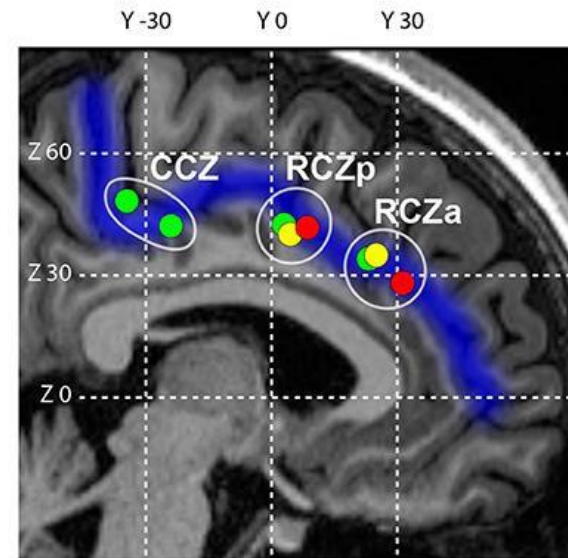
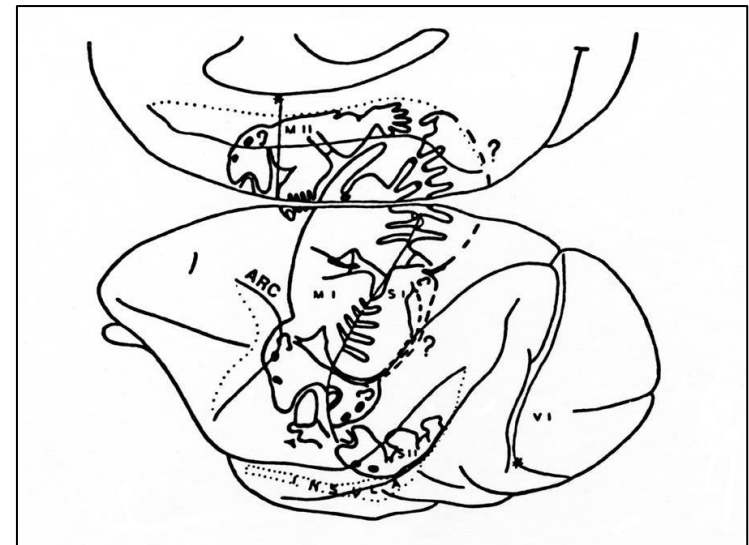
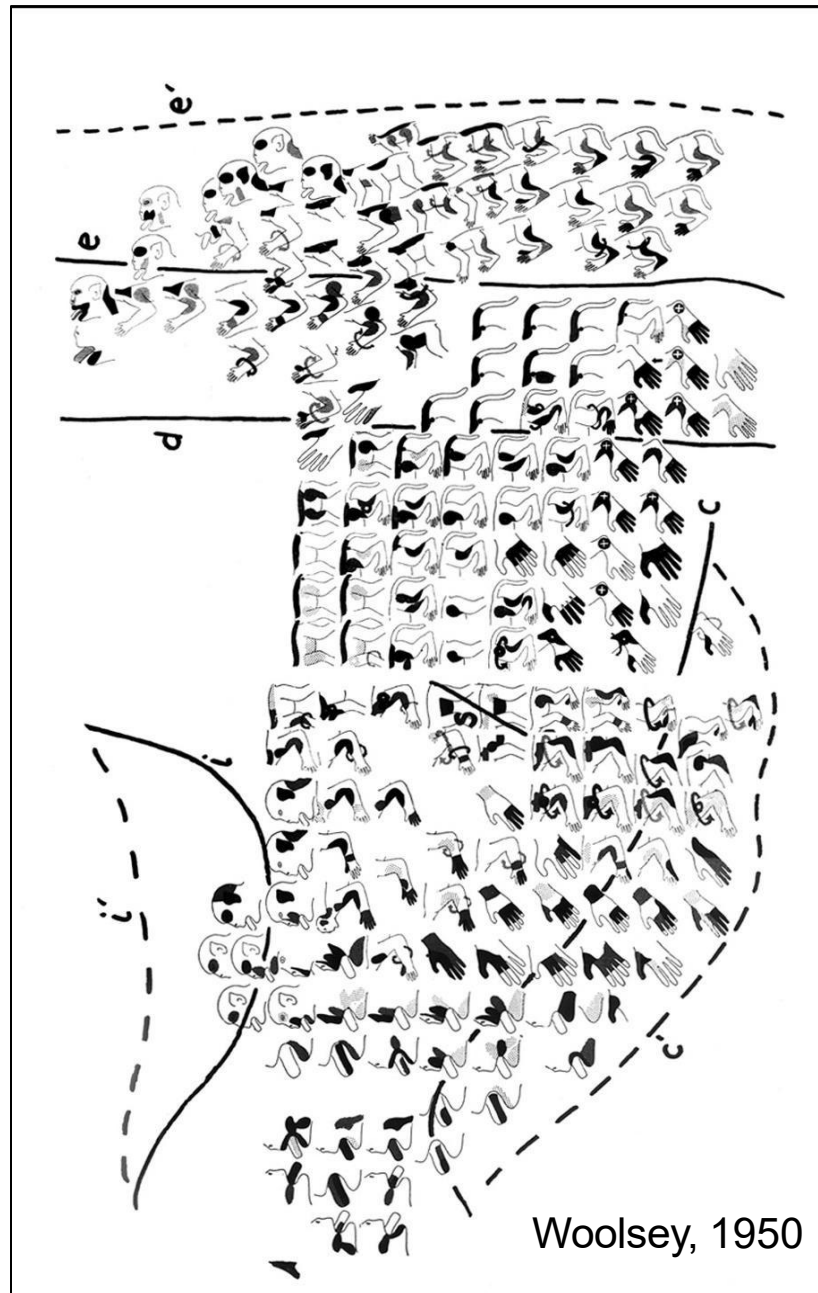
Face

Tongue

Sulcus lateralis



Multiple cortical representations in the sensorimotor system

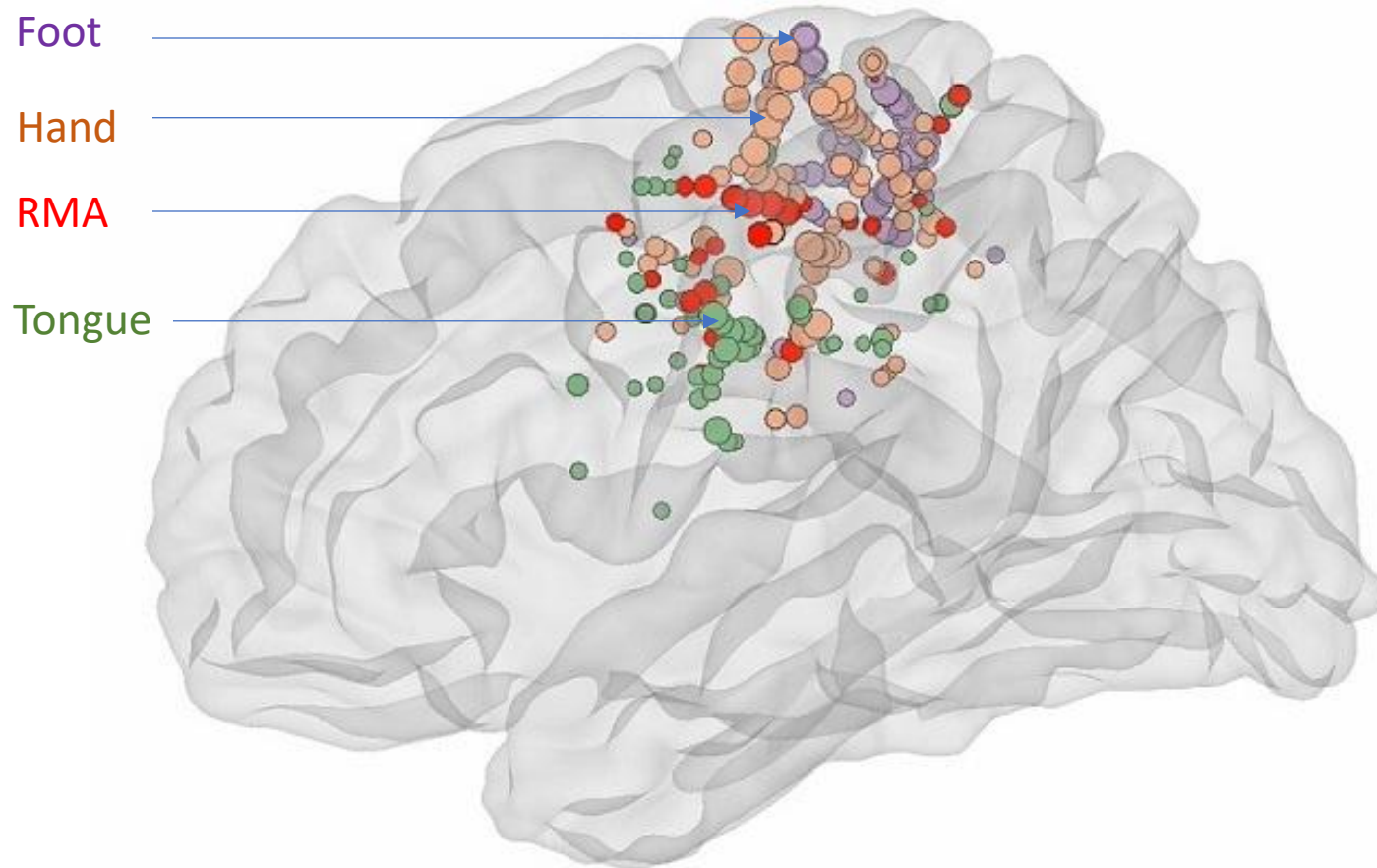


Average coordinates in RH

- Hand motor representation
- Tongue motor representation
- Eye motor representation

Loh, Petrides, 2018

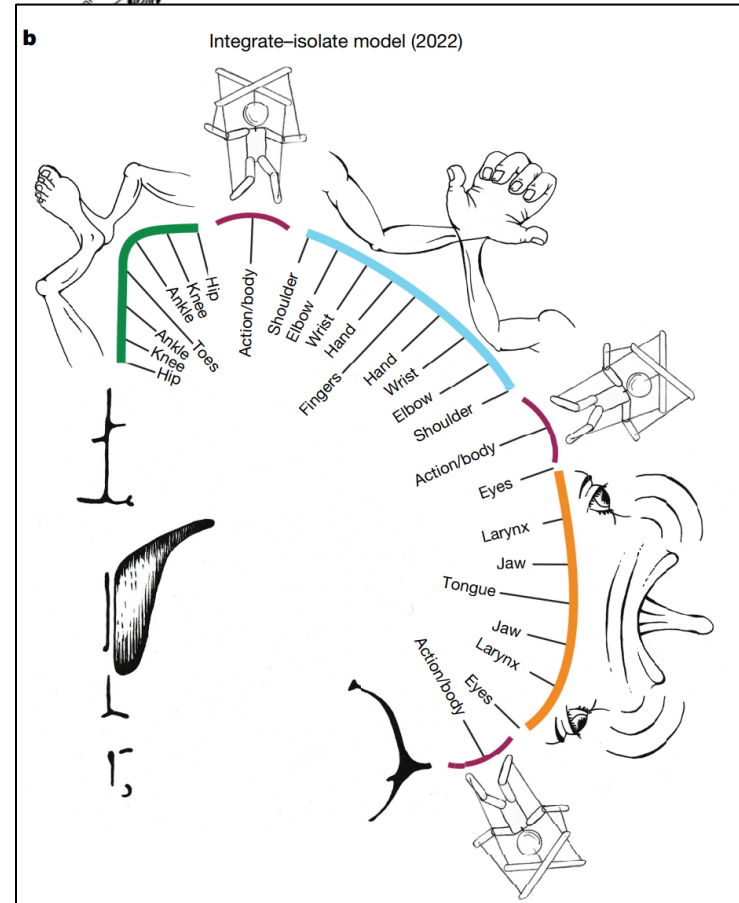
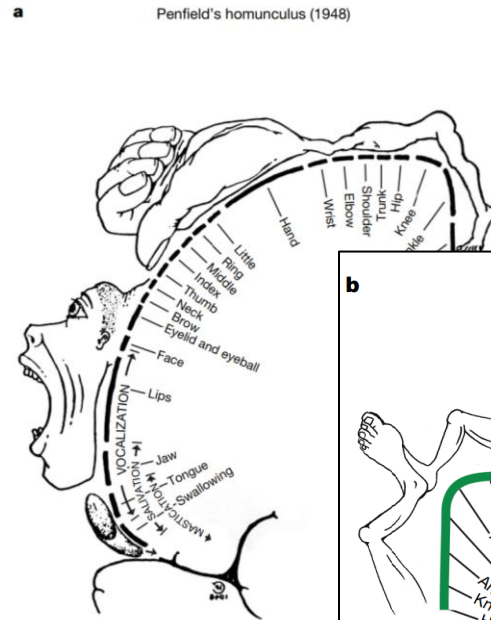
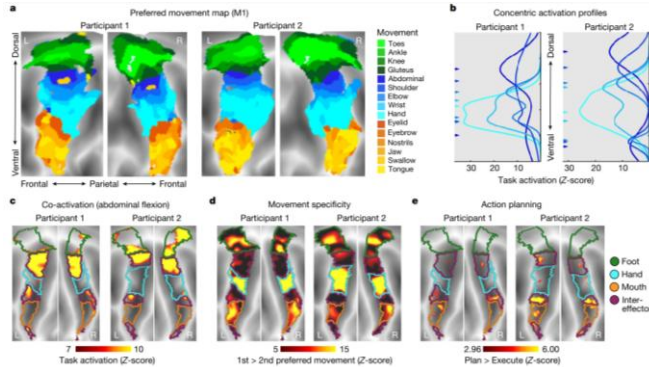
Rolandic Motor Association area (RMA) in the central sulcus



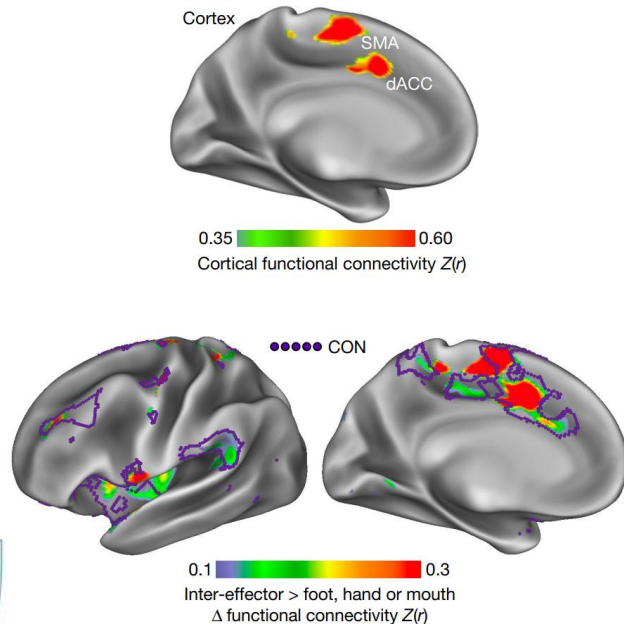
Precentral gyrus somatomotor organization is interrupted by a motor association area in the depths of the midlateral aspect of the central sulcus. This 'Rolandic motor association' (RMA) area is active during movements of different body parts from both sides of the body and may be important for coordinating complex behaviors.

Somatomotor cognitive action network. (?)

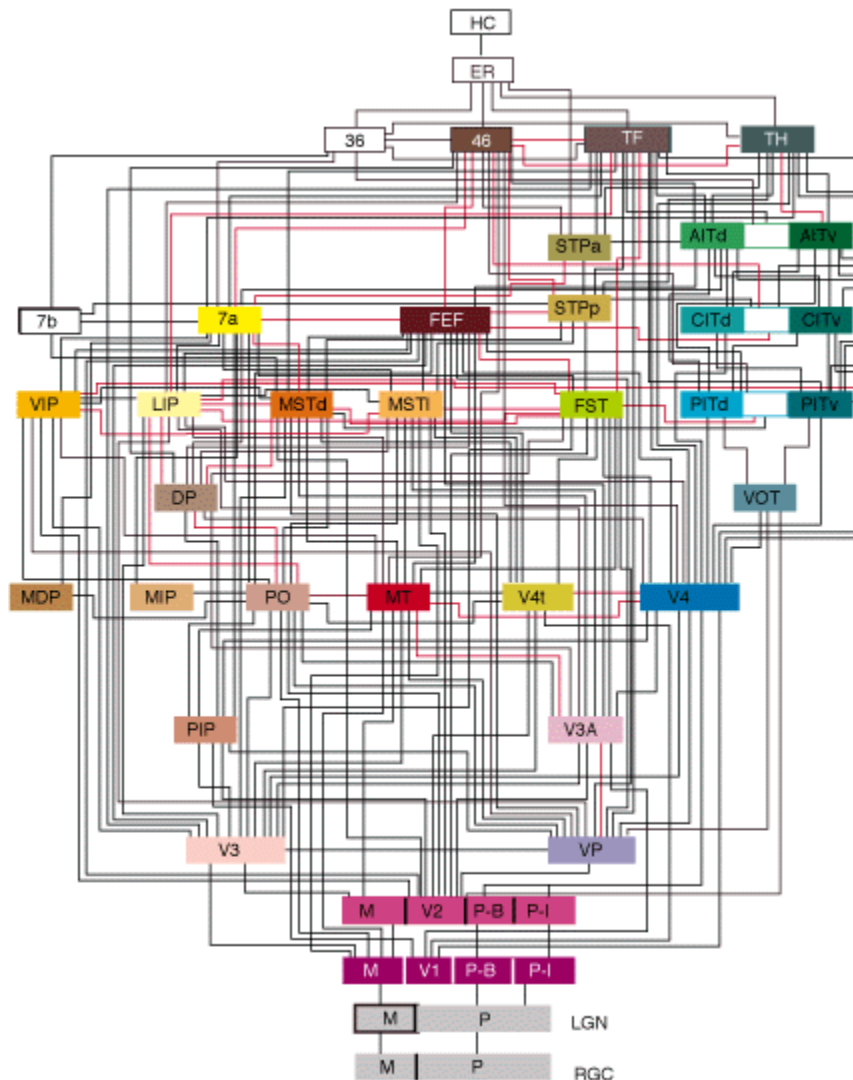
- derived from fMRI -



Inter-effector functional connectivity



Circuit Diagram of Macaque Visual Areas

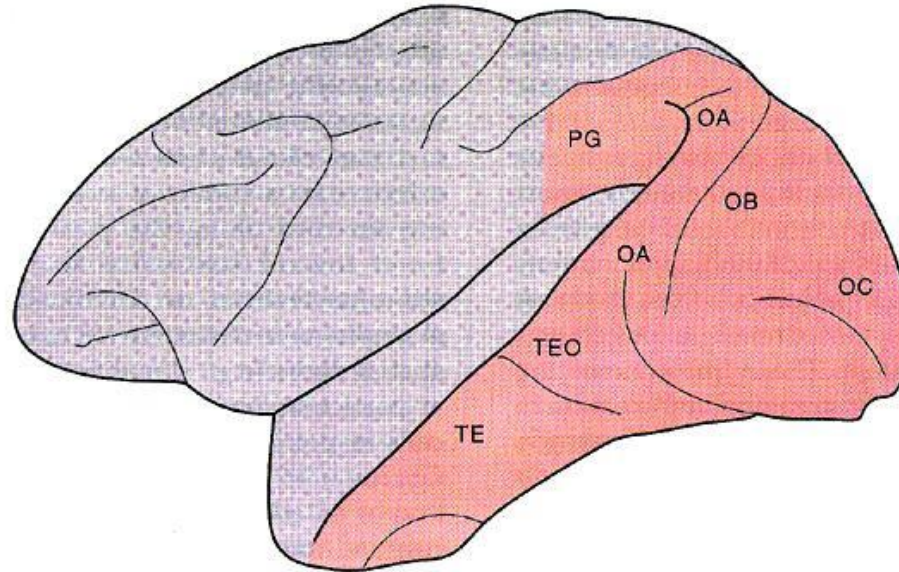


Felleman, Van Essen.
Cerebral Cortex 1991: 1; 1-47.

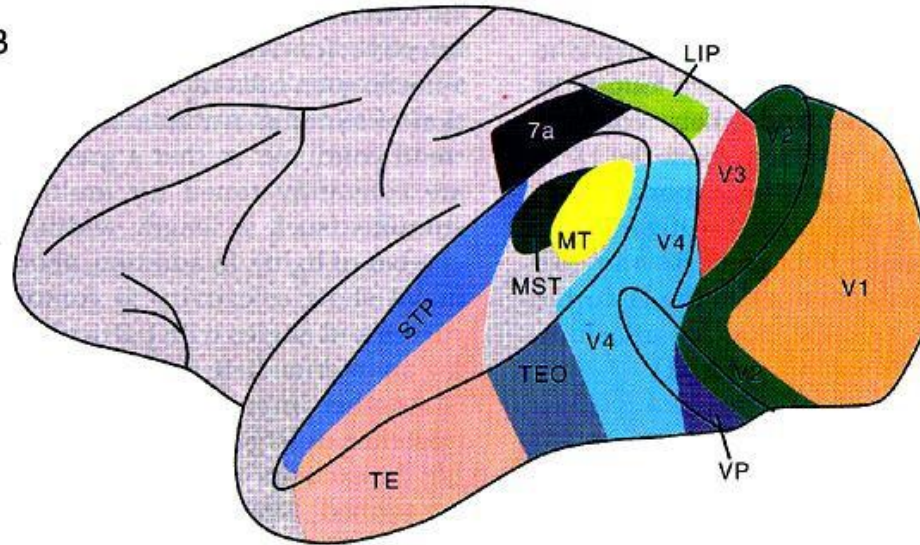
Dual visual pathways from occipital lobe

Dorsal – visual spatial; Ventral – feature identification
(after Mishkin and Ungerleider, Van Essen and others)

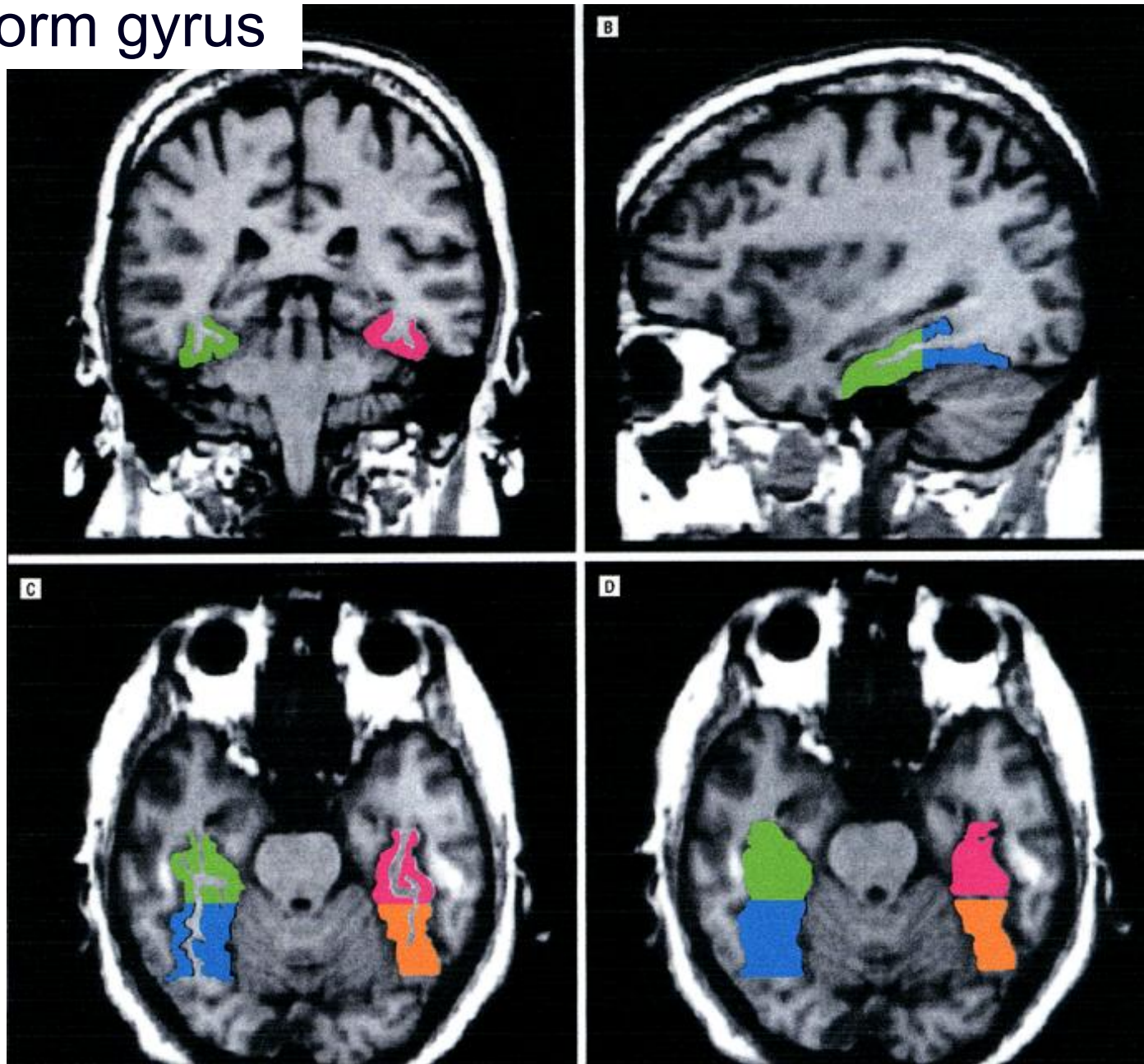
A



B



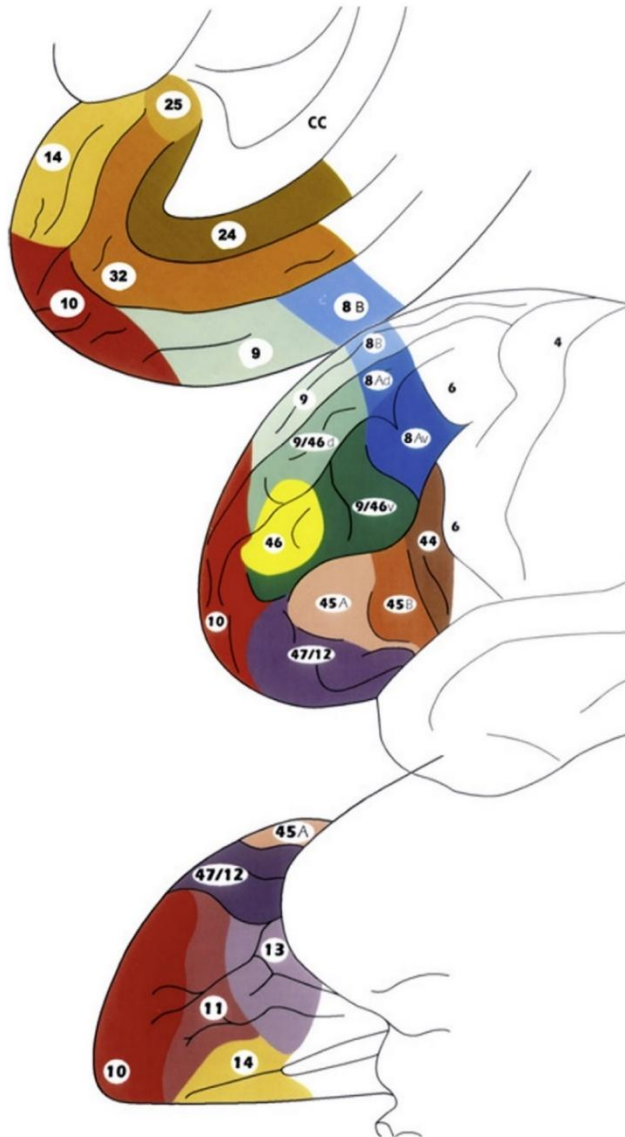
Fusiform gyrus



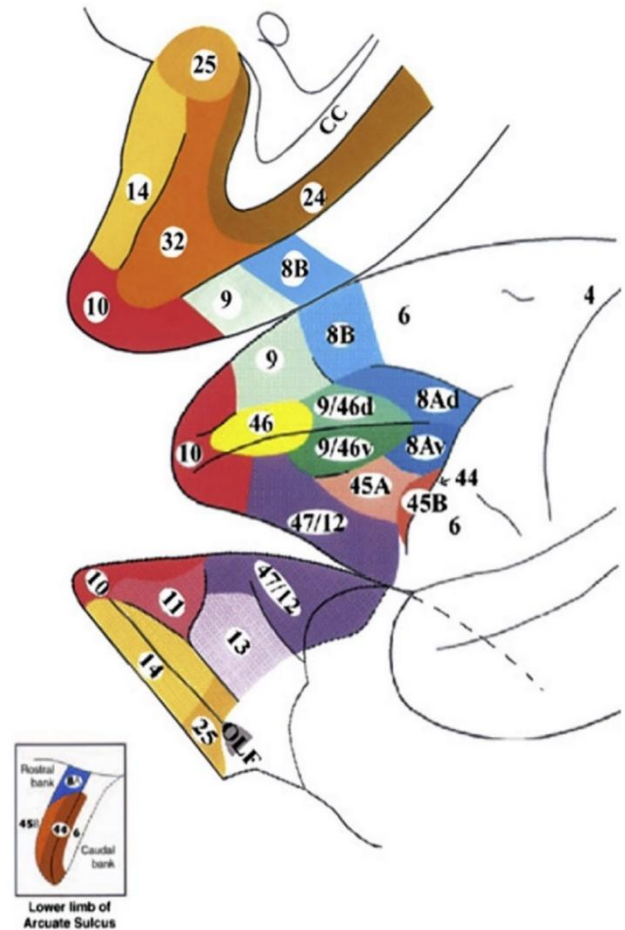
Onitsuka, Shenton, Kasai, Nestor, Toner, Kikinis, Jolesz, McCarley.
Archives of general psychiatry 2003; 60: 349-55.

Prefrontal cortex

A

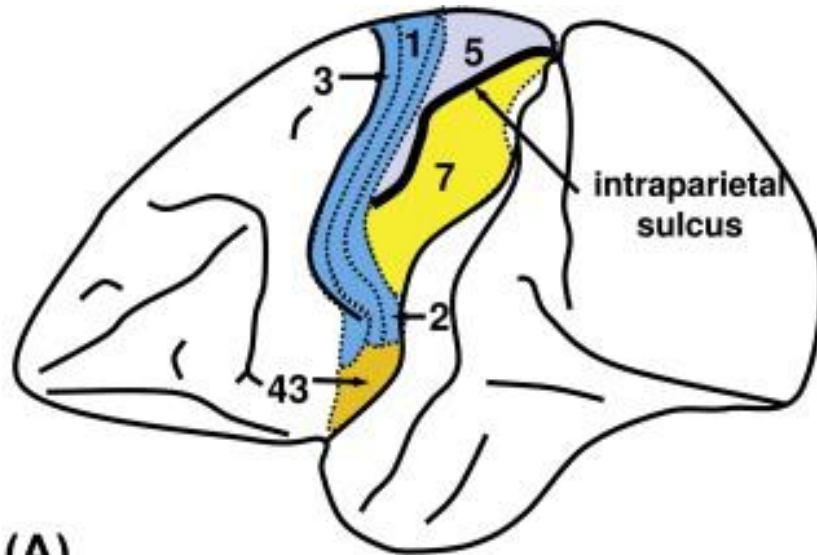


B



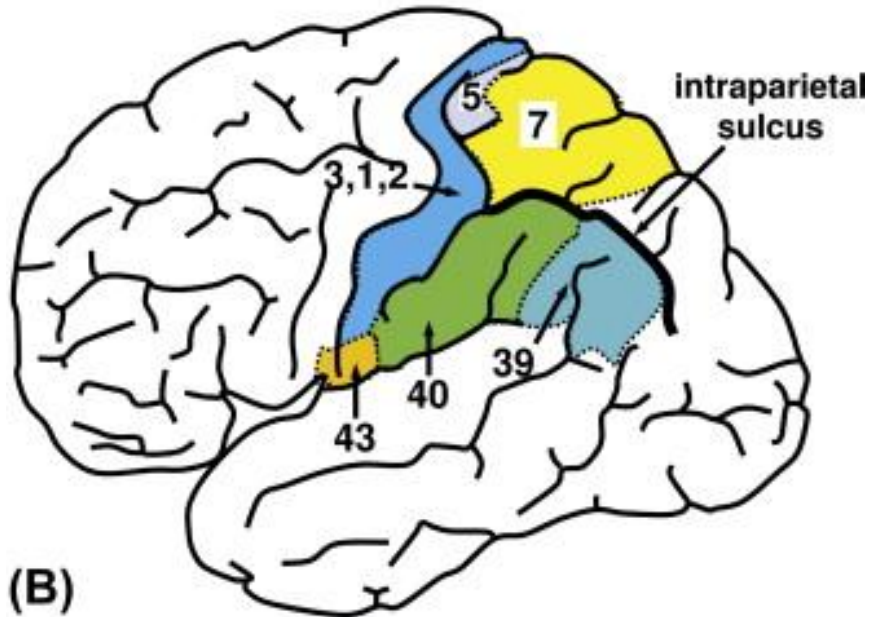
Parietal lobe

Monkey



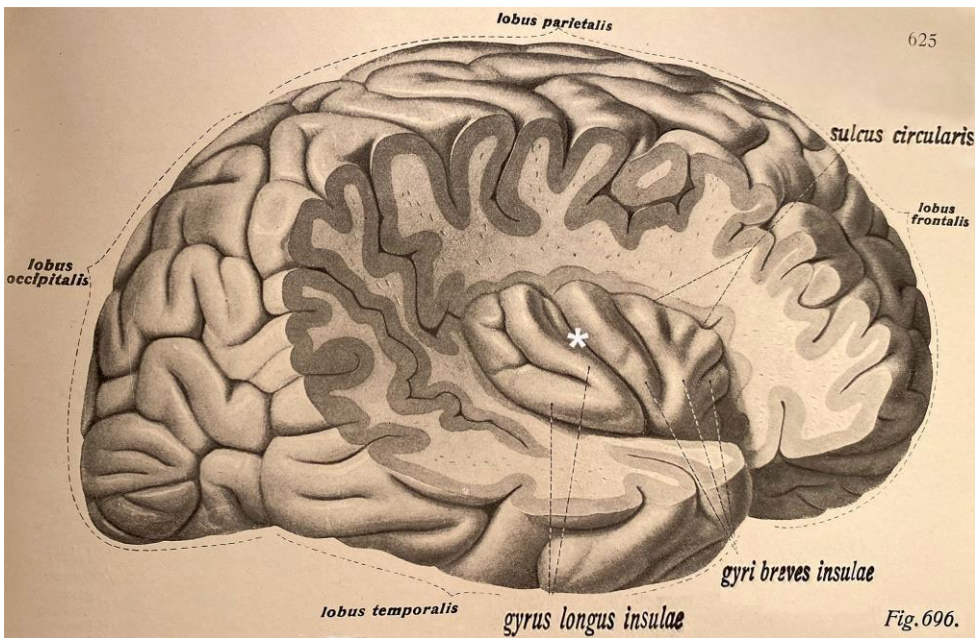
(A)

Human

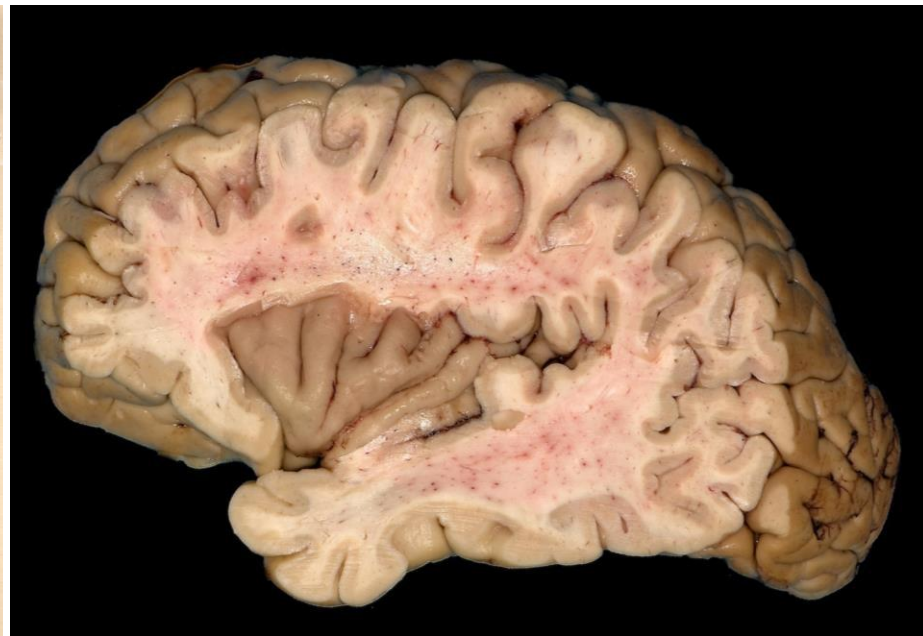


(B)

Insular cortex



Sabotta, 1928



Courtesy, Dr. Tom Naidich

Insular cortex regional specialization

Sensori-Motor:

**Somatic sensation, Pain,
Visceral sensation, Motion**

Chemical sensory:

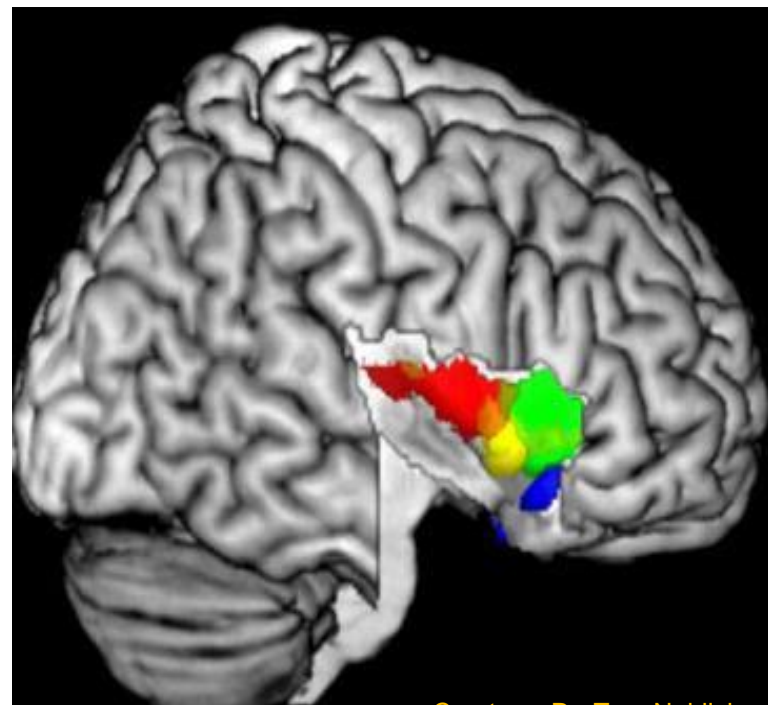
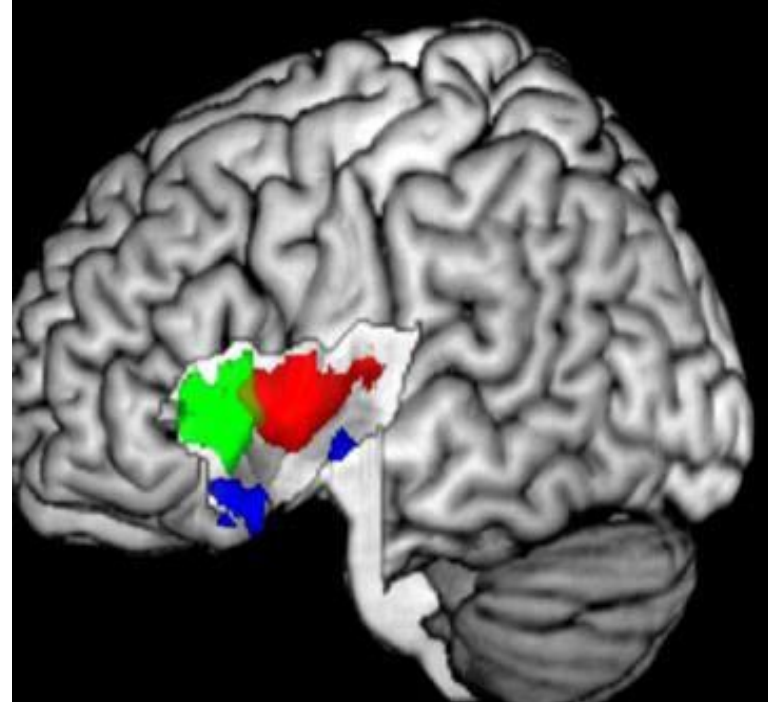
Olfactory, Gustatory

Cognition:

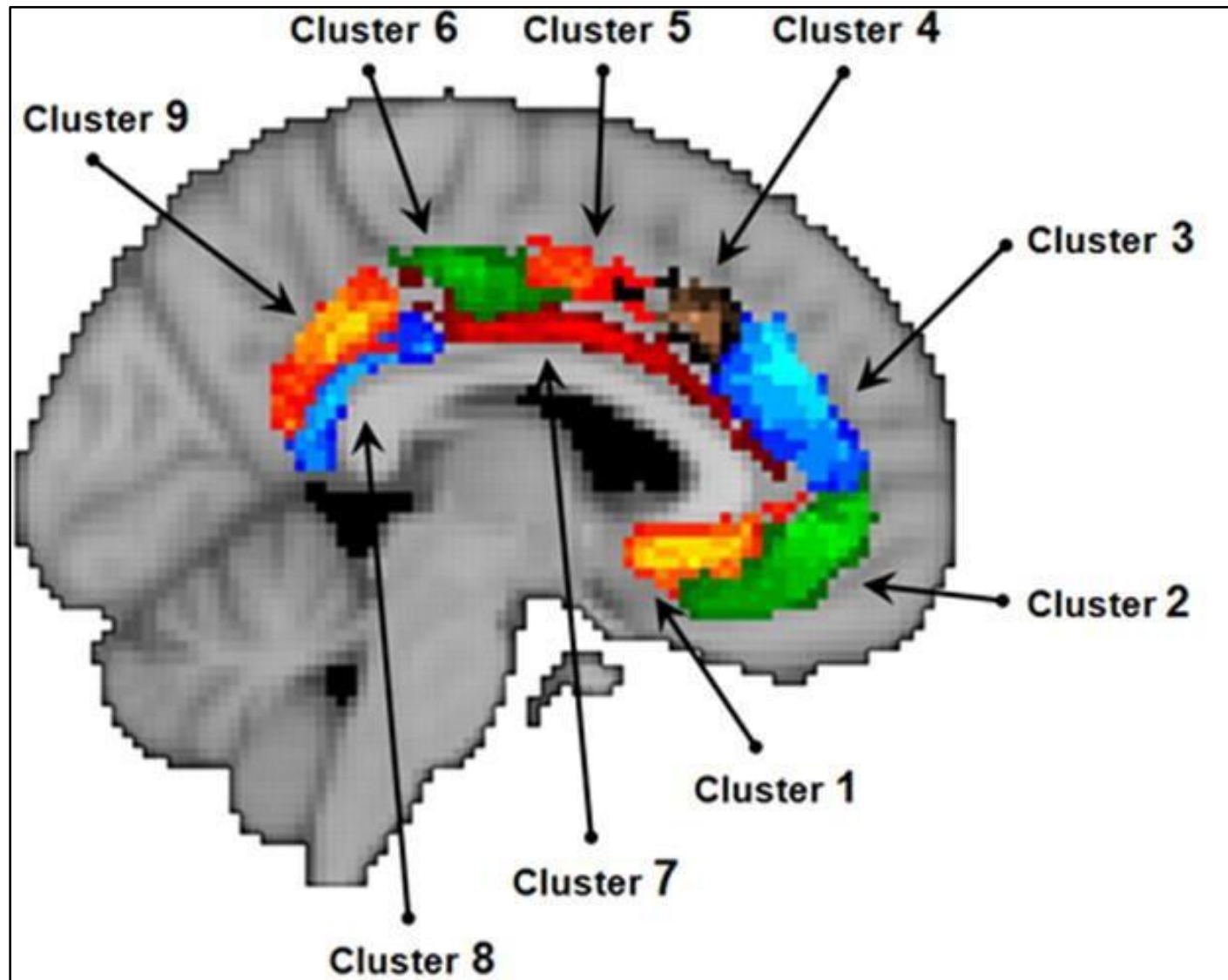
**Attention, Language,
Speech, Memory
Working memory**

Social-Emotional:

Emotion, Empathy



Connectivity-Based Parcellation of Human Cingulate Cortex and Its Relation to Functional Specialization



Beckman, Johansen-Berg, Rushworth, J Neurosci, 2009

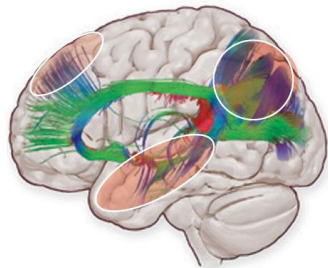
Mapping Symptoms to Brain Networks with the Human Connectome

Michael D. Fox, M.D., Ph.D.

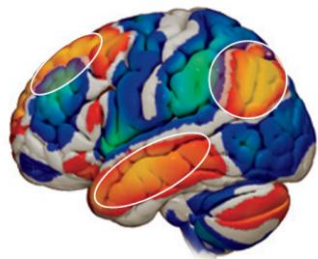
A Lesions Causing the Same Symptom



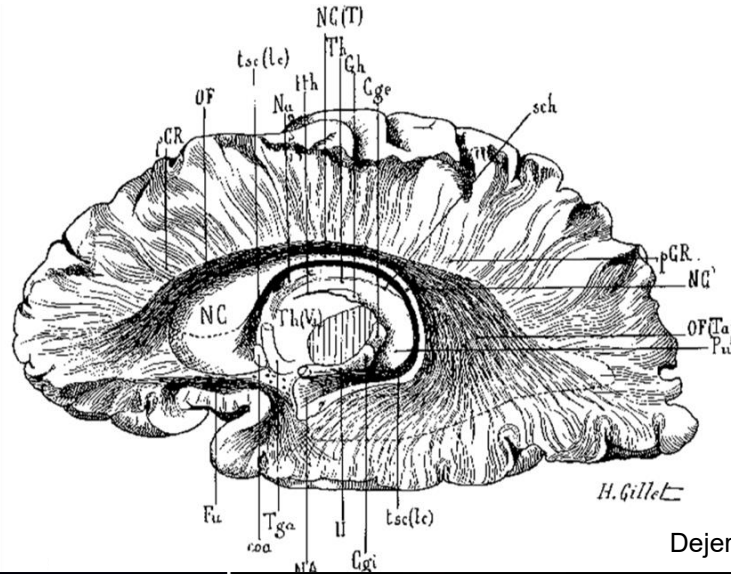
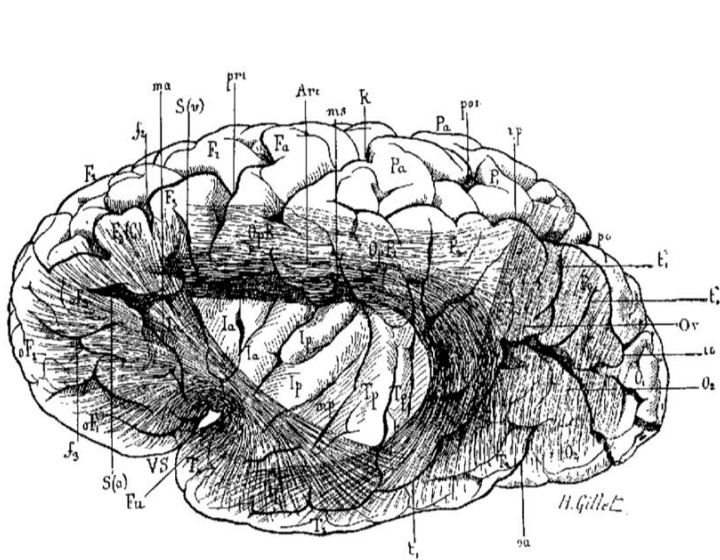
B Map of Anatomical Connectivity



C Map of Functional Connectivity

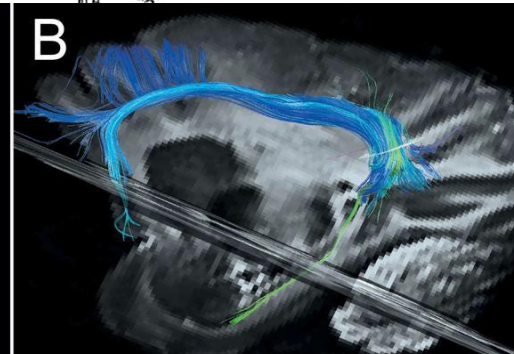
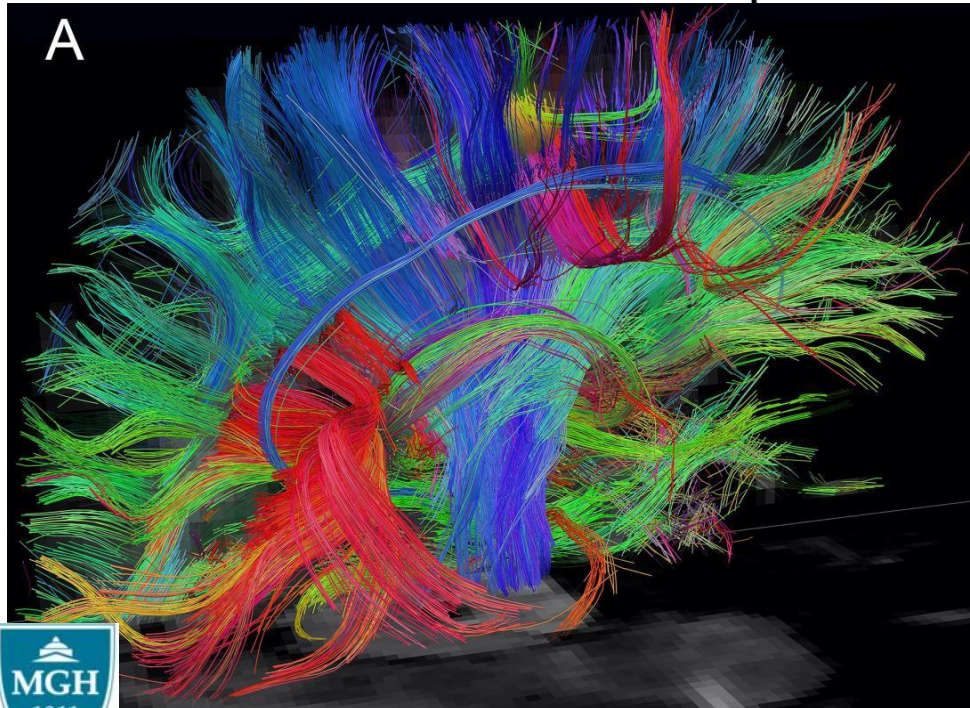


Lesion Syndrome			Network Overlap
Hemichorea			
Delusions of familiarity			
Freezing of gait			
Criminality			



Joseph Jules Dejerine
1849-1917

Dejerine, 1895



Long association fibers

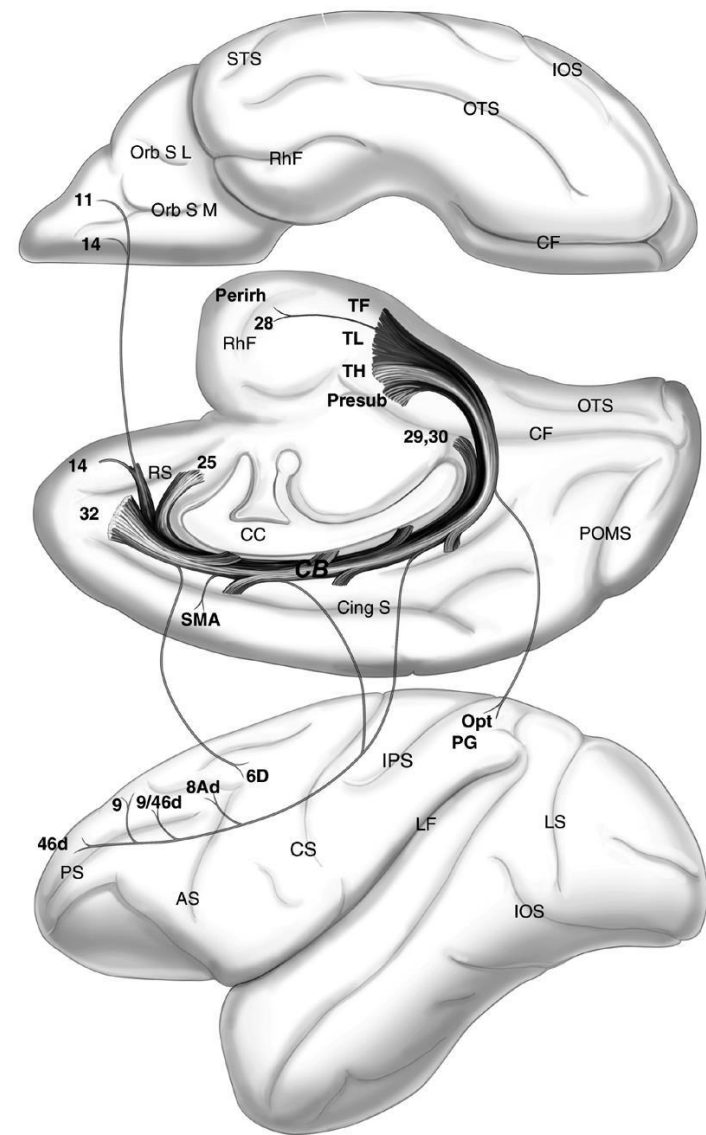
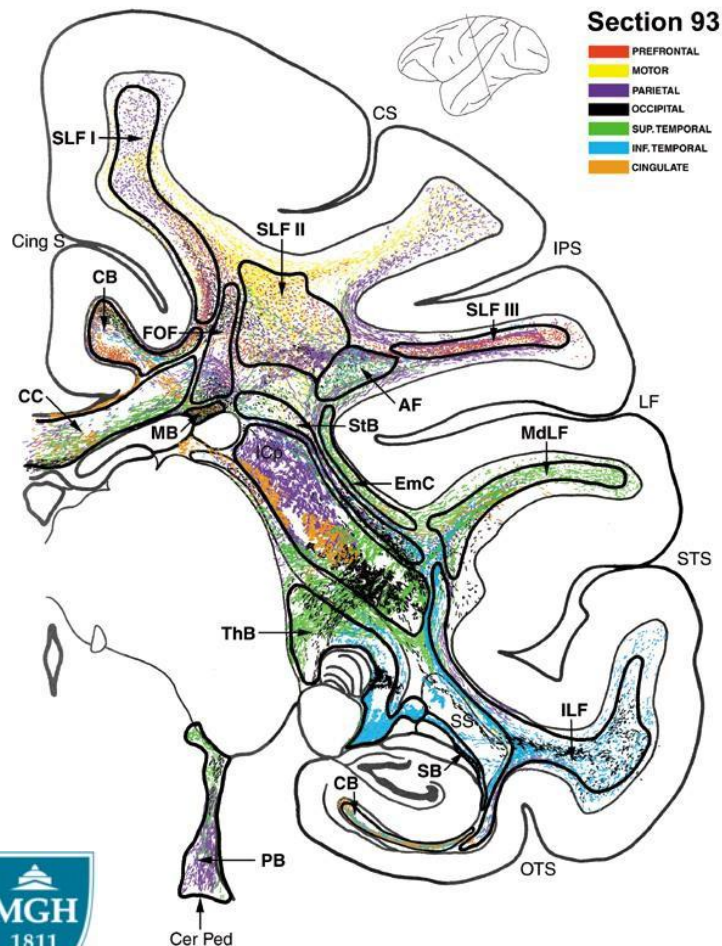
- Cingulum Bundle
- Uncinate Fasciculus
- Extreme Capsule
- Arcuate Fasciculus
- Middle Longitudinal Fasciculus
- Superior Longitudinal Fasciculus; SLF I, II, III
- Inferior Longitudinal Fasciculus
- Fronto-occipital fasciculus

Cingulum Bundle

Dorsal limbic pathway

Motivational and emotional
aspects of behavior

Spatial working memory

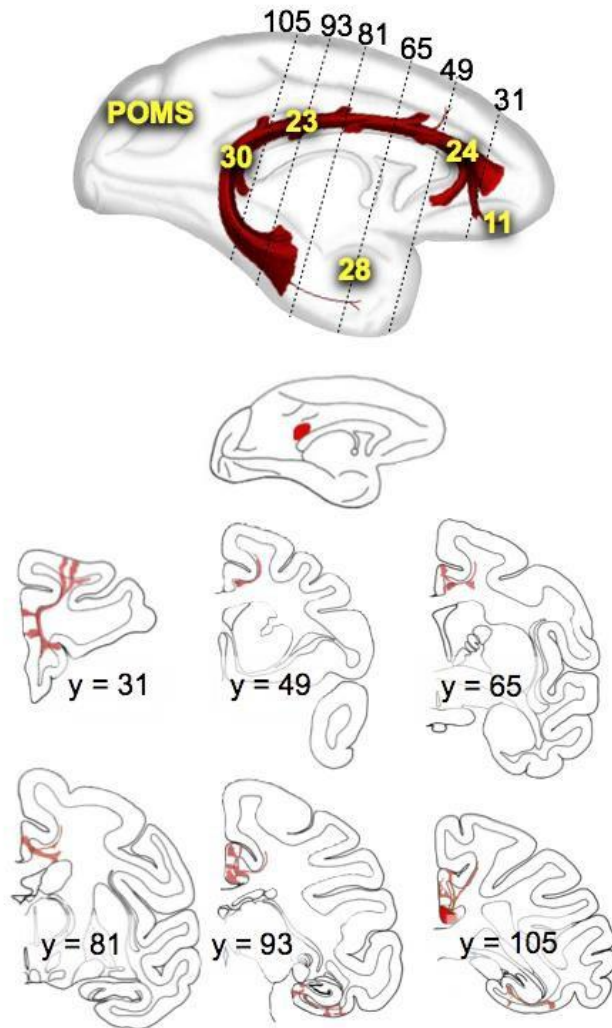


Caudal cingulate gyrus
linked with

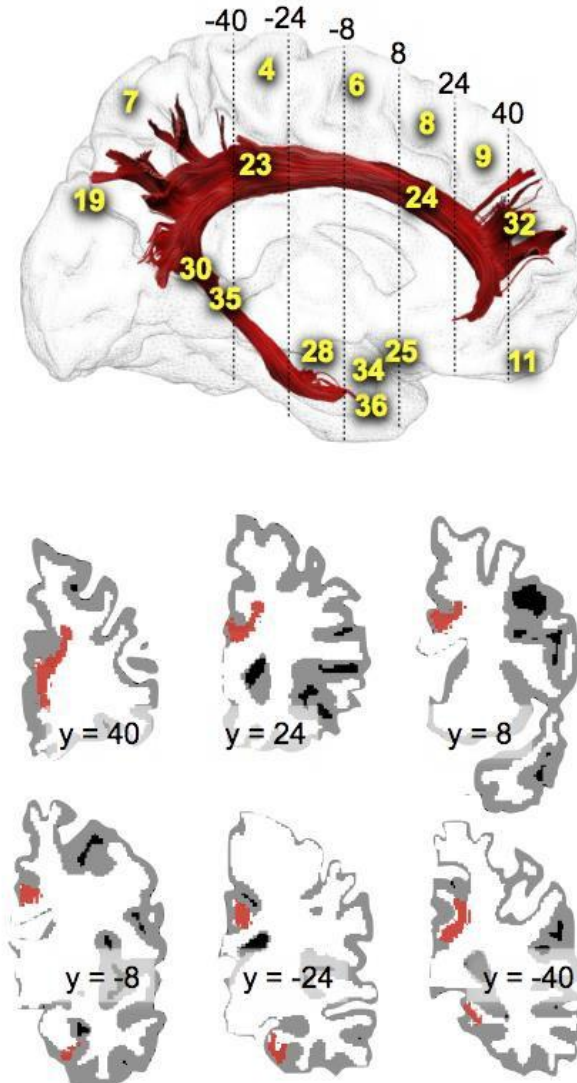
Areas 9, 46 – manipulating, monitoring, working memory
Parahippocampal gyrus, hippocampus

CINGULUM

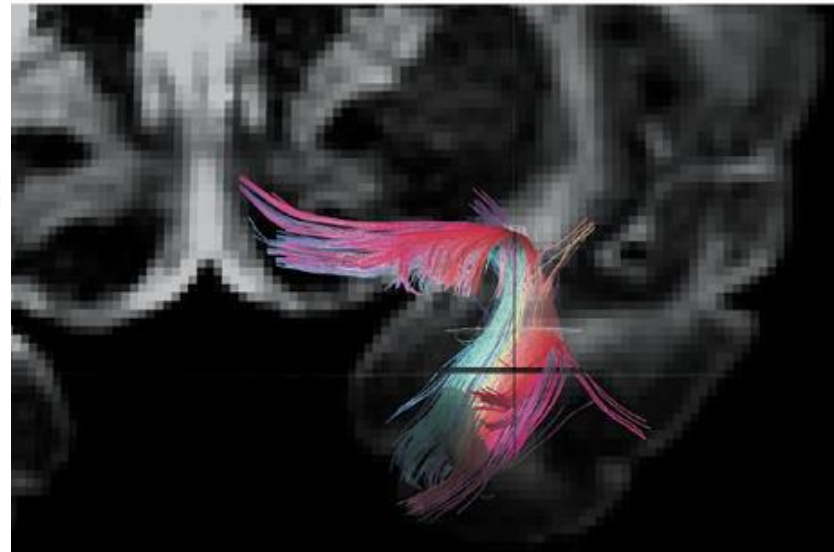
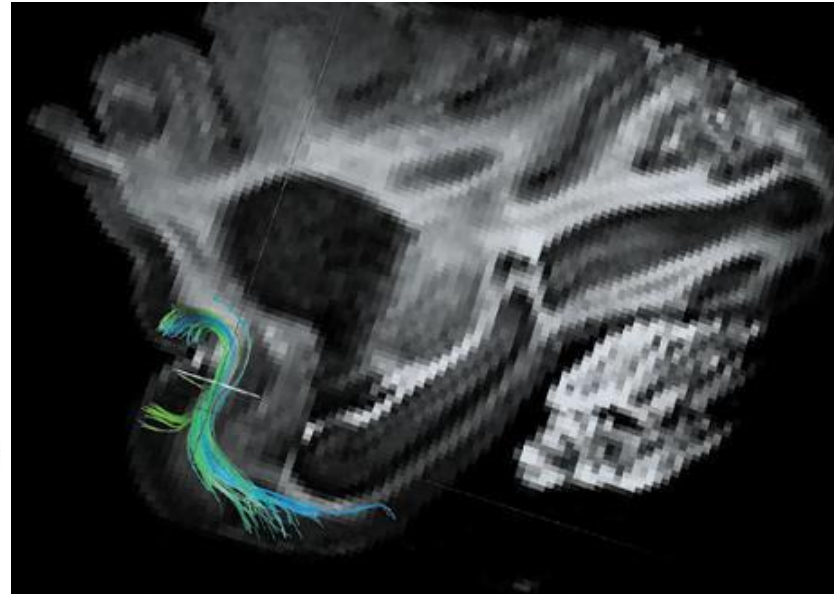
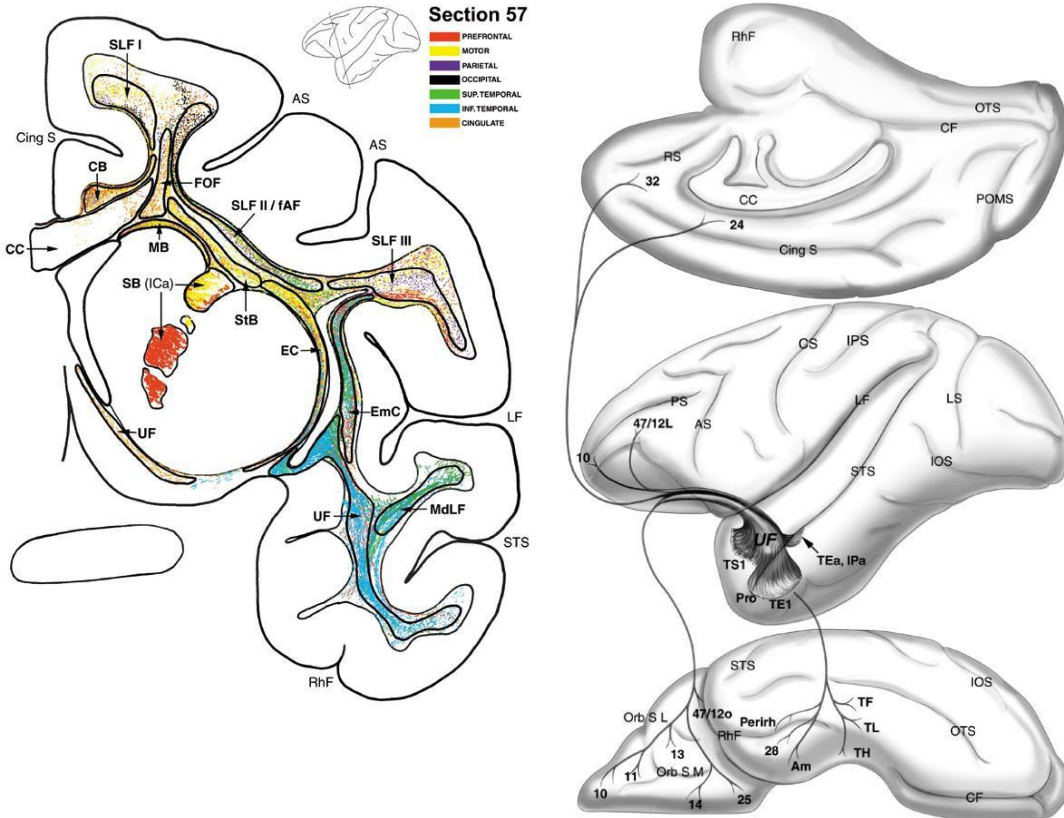
Monkey



Human



Uncinate fasciculus



Processing of novel information
Emotional response to auditory stimuli

Rostral superior temporal gyrus
- sound recognition

Medial temporal (entorhinal, perirhinal, parahippocampal)
recognition memory

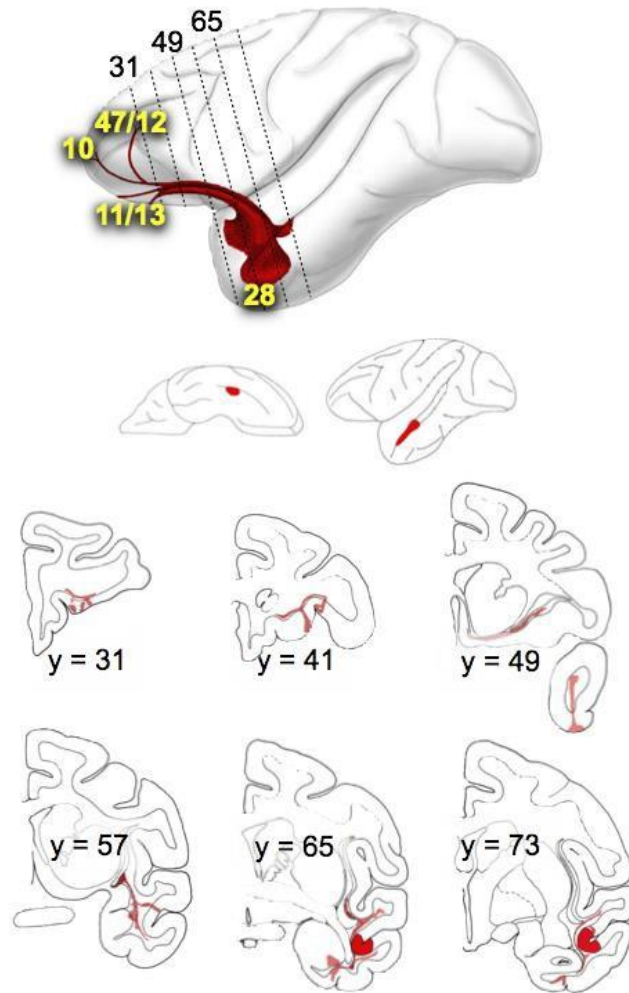


l, medial prefrontal
- emotion, inhibition, self regulation

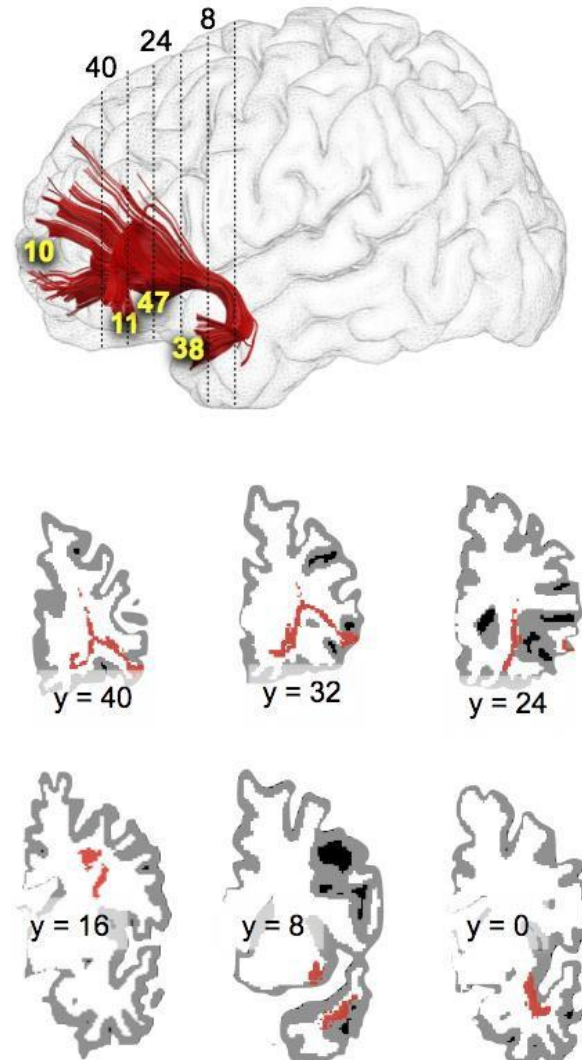
Schmahmann and Pandya, 2006;
Schmahmann, Pandya, Wedeen et al., Brain 2007

UNCINATE

Monkey



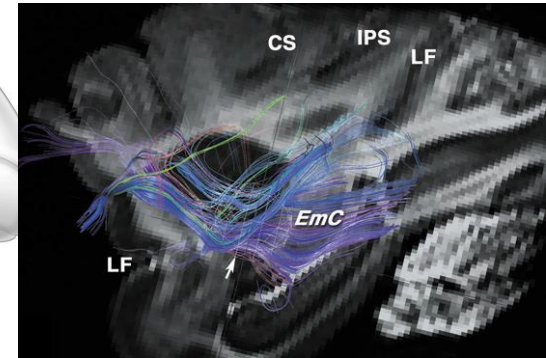
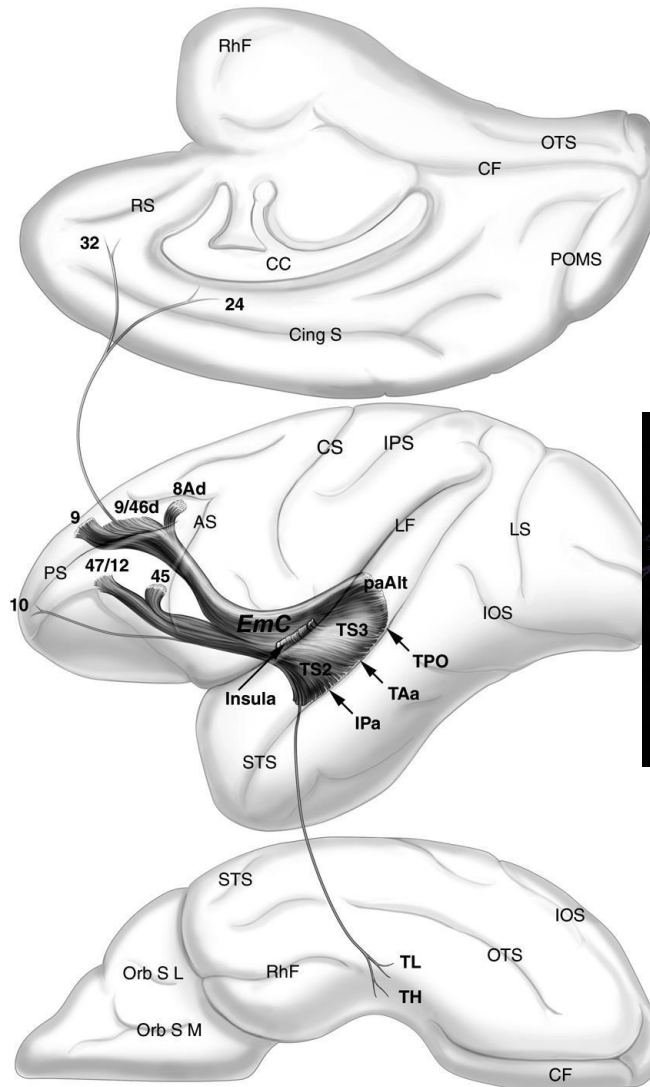
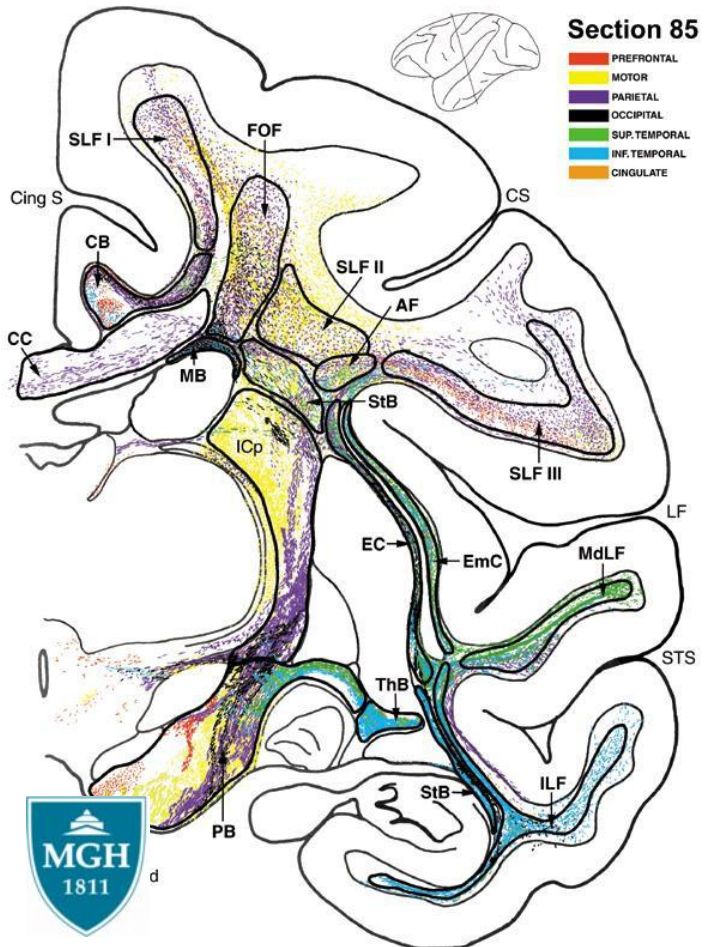
Human



Schmahmann and Pandya, 2006
Thiebaut de Schotten et al., Cortex, 2012

Extreme Capsule

Language; Strategic regulation of behavior



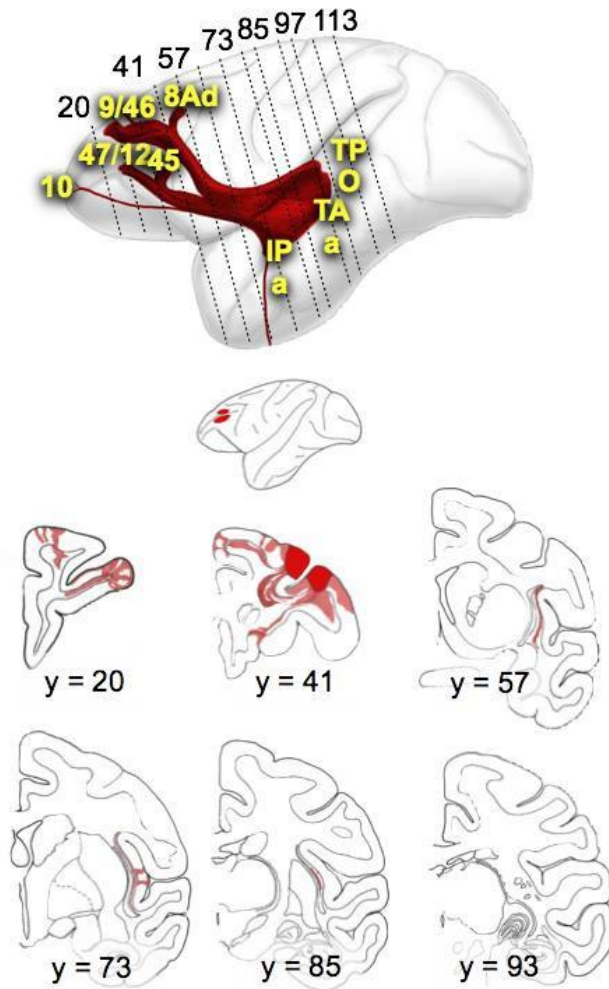
Wernicke homologue linked with area 45 ~ Broca
Facilitates judgment encoding, retrieval by areas 45 and 47 of information perceived and coded in caudal cortices

Schmahmann and Pandya, 2006;

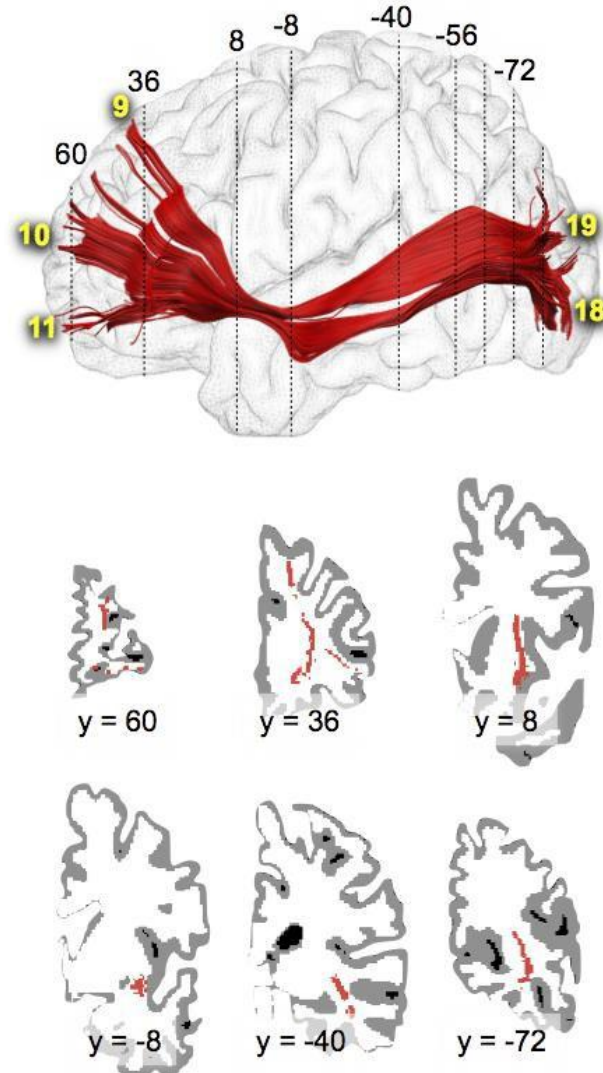
Schmahmann, Pandya, Wedeen et al., Brain 2007

INFERIOR FRONTO-OCCIPITAL

Monkey



Human



Arcuate Fasciculus

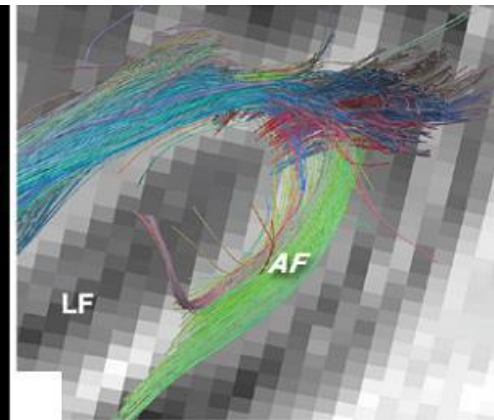
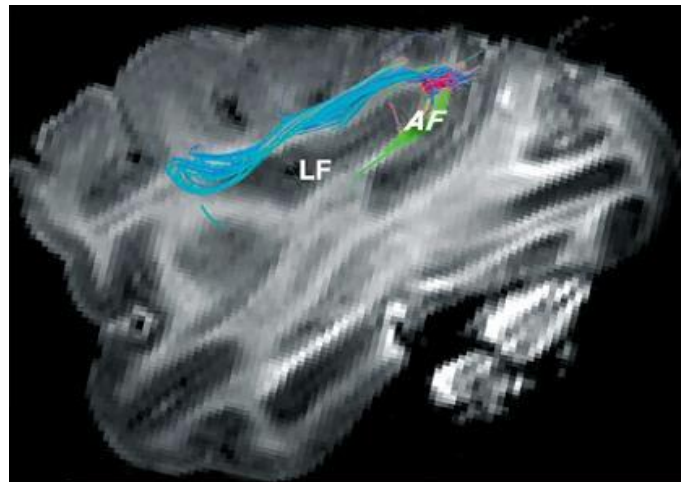
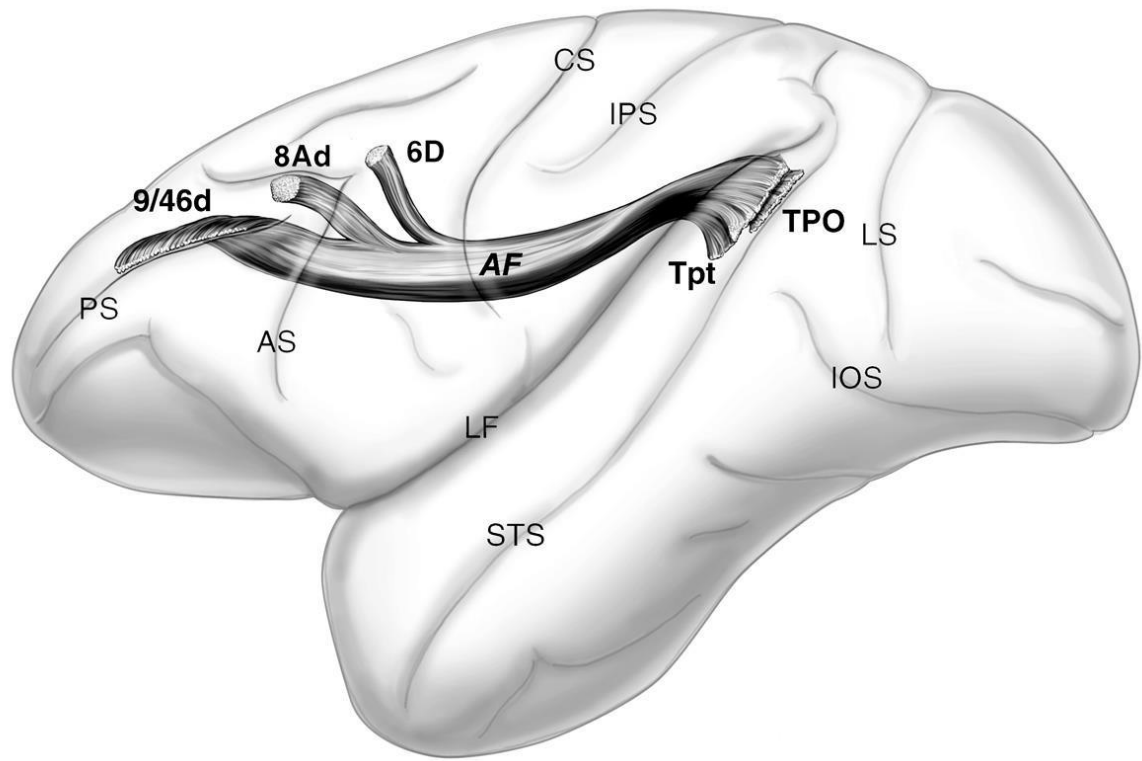
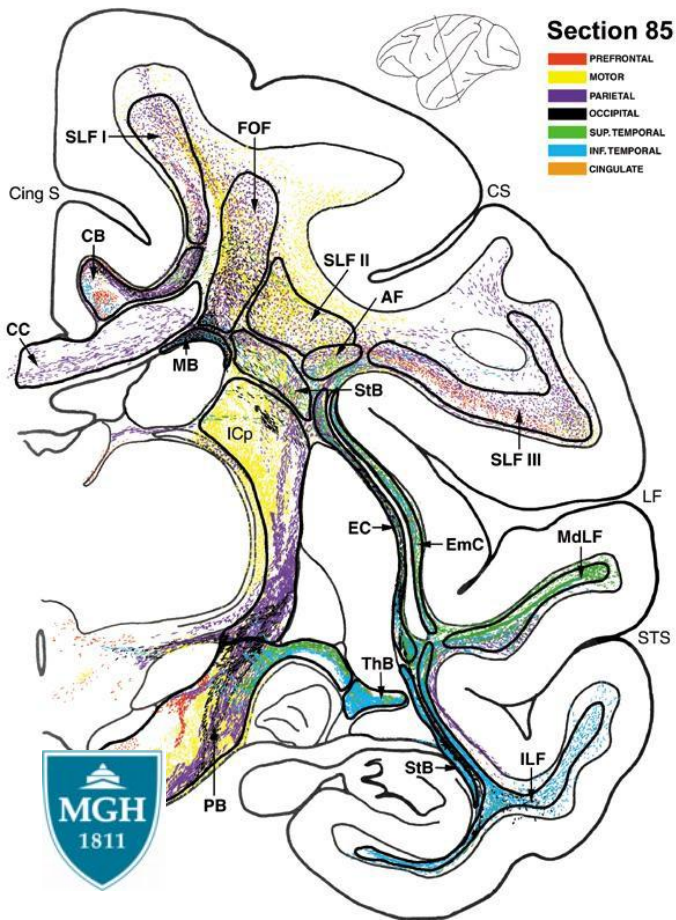
Audio-spatial processing

Caudal superior temporal gyrus
- sound localization

Linked with

Dorsal prefrontal area 8

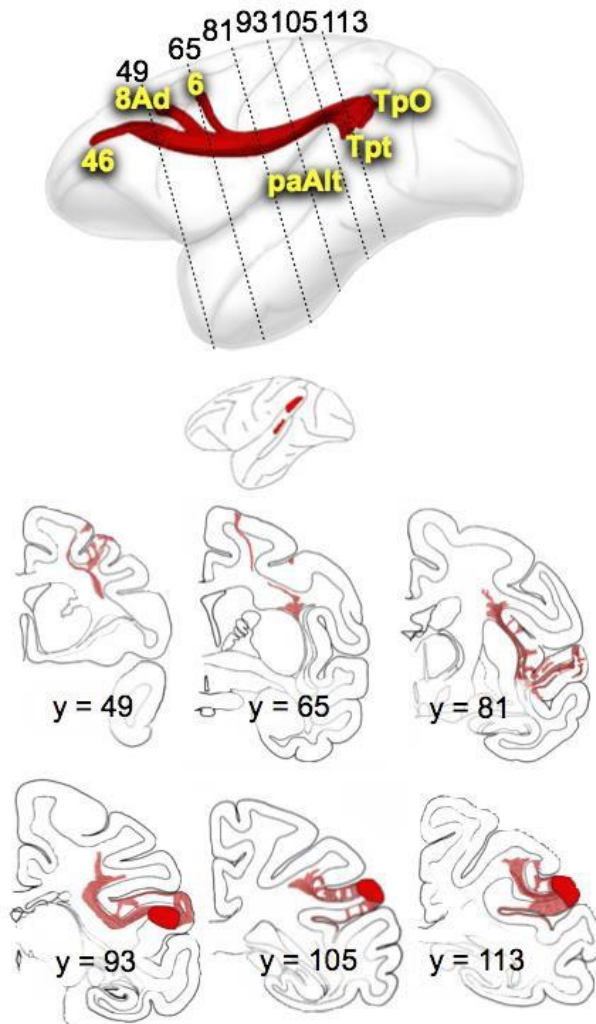
- spatial attention, working memory



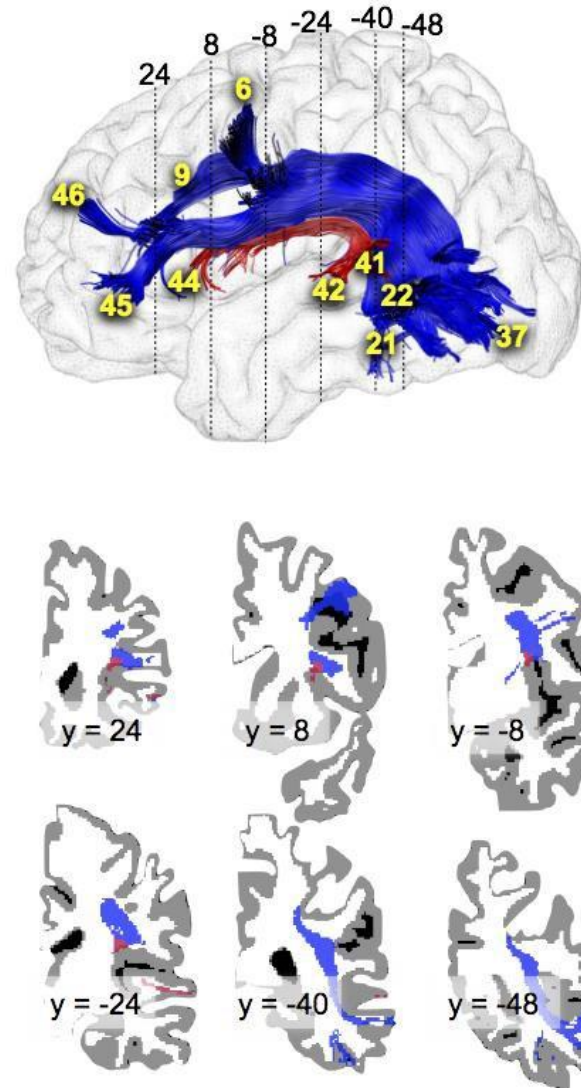
Schmahmann and Pandya, 2006;
Schmahmann, Pandya, Wedeen et al., Brain 2007

ARCUATE

Monkey

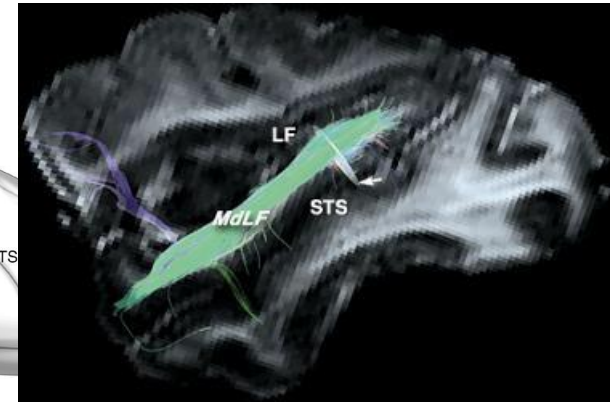
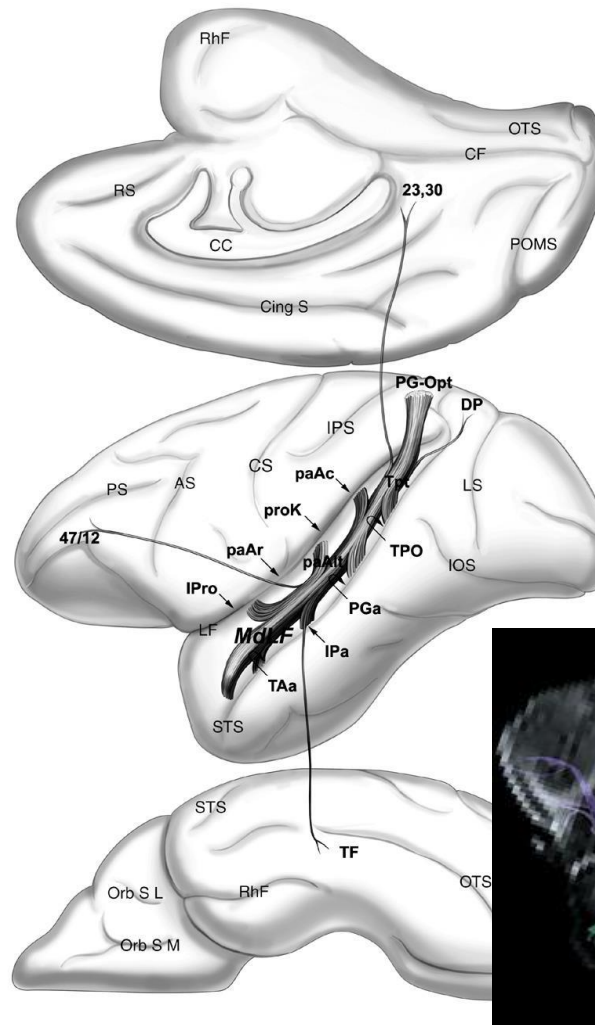
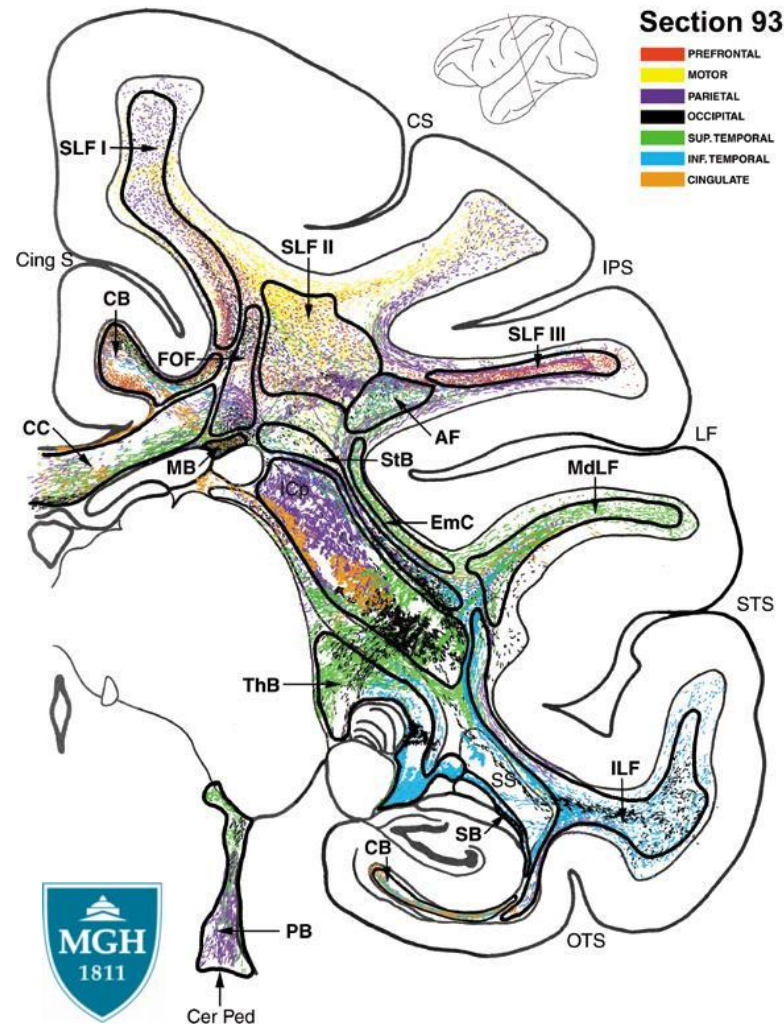


Human



Middle Longitudinal Fasciculus

Multimodal association bundle
Role in language



Associative and paralimbic cortices (parietal, cingulate, parahippocampal, prefrontal)

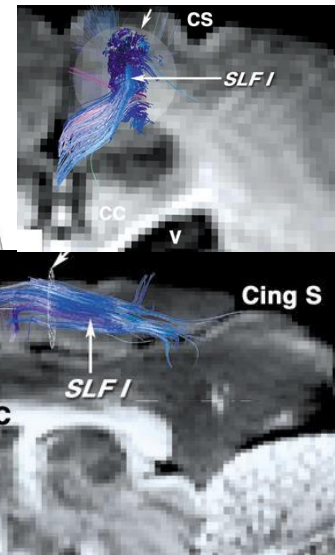
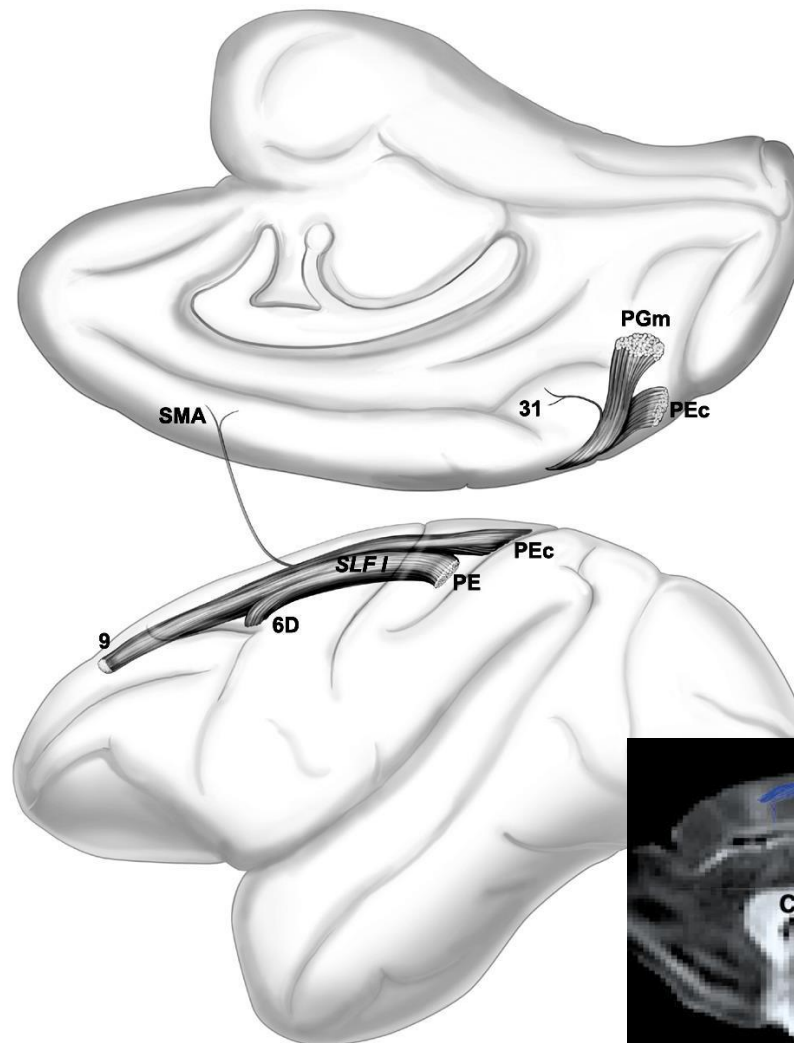
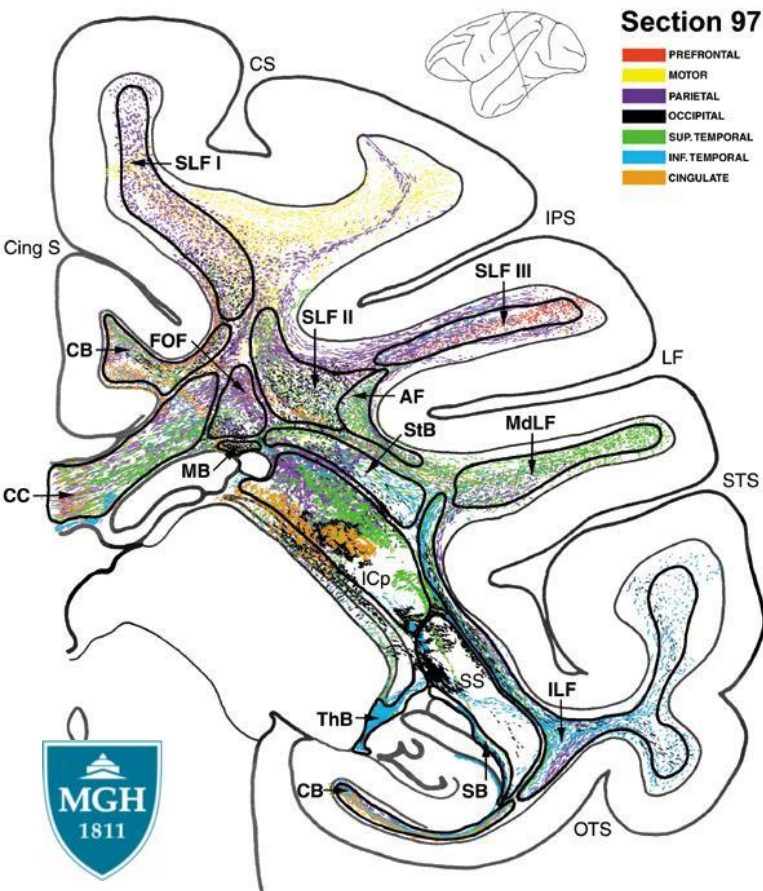
Linked with

multimodal areas in the superior temporal region

Schmahmann and Pandya, 2006;
Schmahmann, Pandya, Wedeen et al., Brain 2007

Superior Longitudinal Fasciculus I

High order control of body-centered action.
Initiation of motor activity



Superior parietal lobule - limb, trunk location in body centered coordinate system

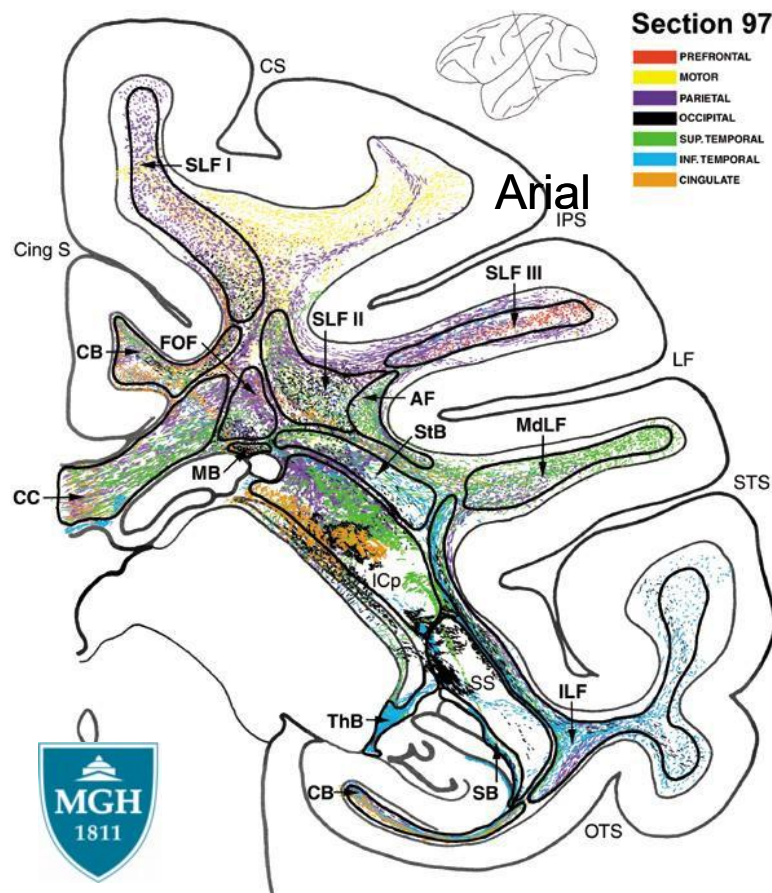
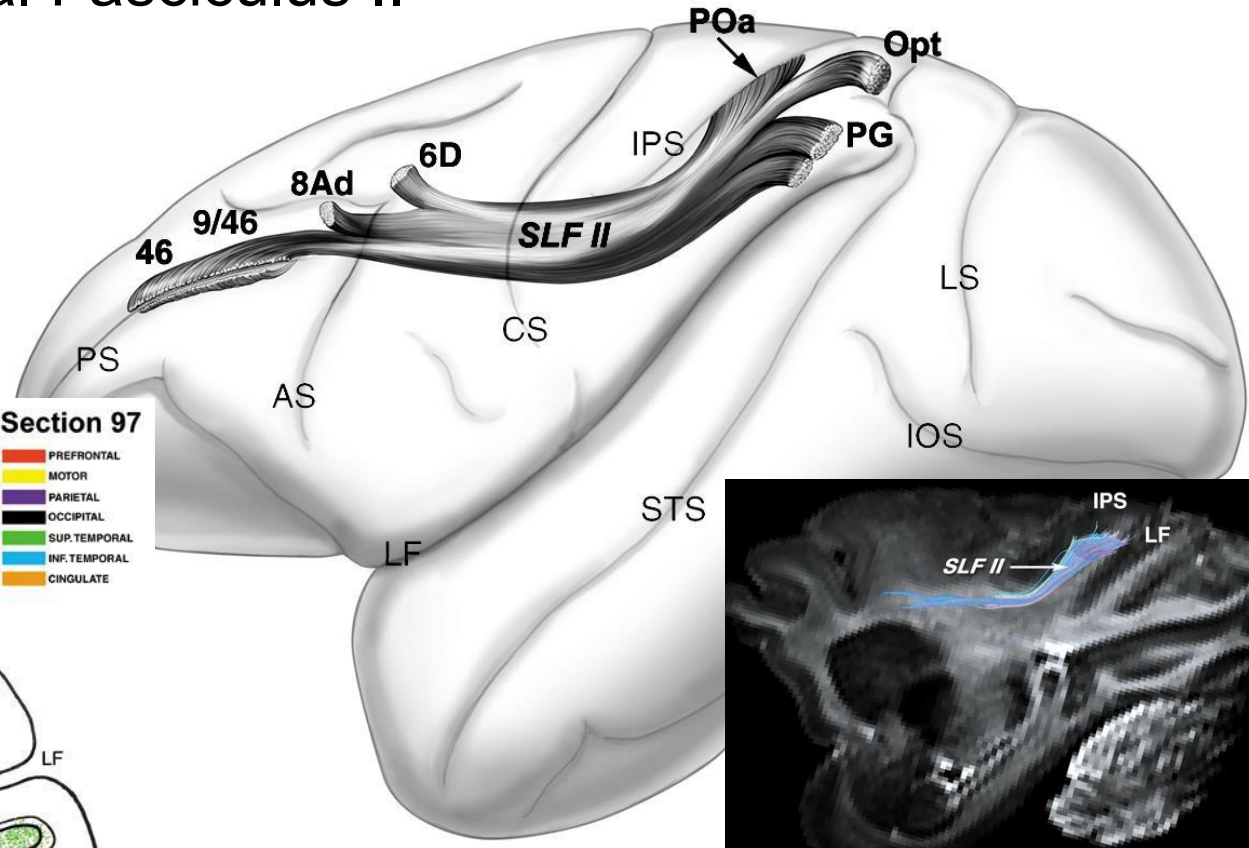
Linked with

premotor areas - higher aspects of motor behavior
M II – intention and initiation of motor activity

Schmahmann and Pandya, 2006;
Schmahmann, Pandya, Wedeen et al., Brain 2007

Superior Longitudinal Fasciculus II

Spatial attention



Inferior parietal lobule – visual-spatial attributes

Linked with

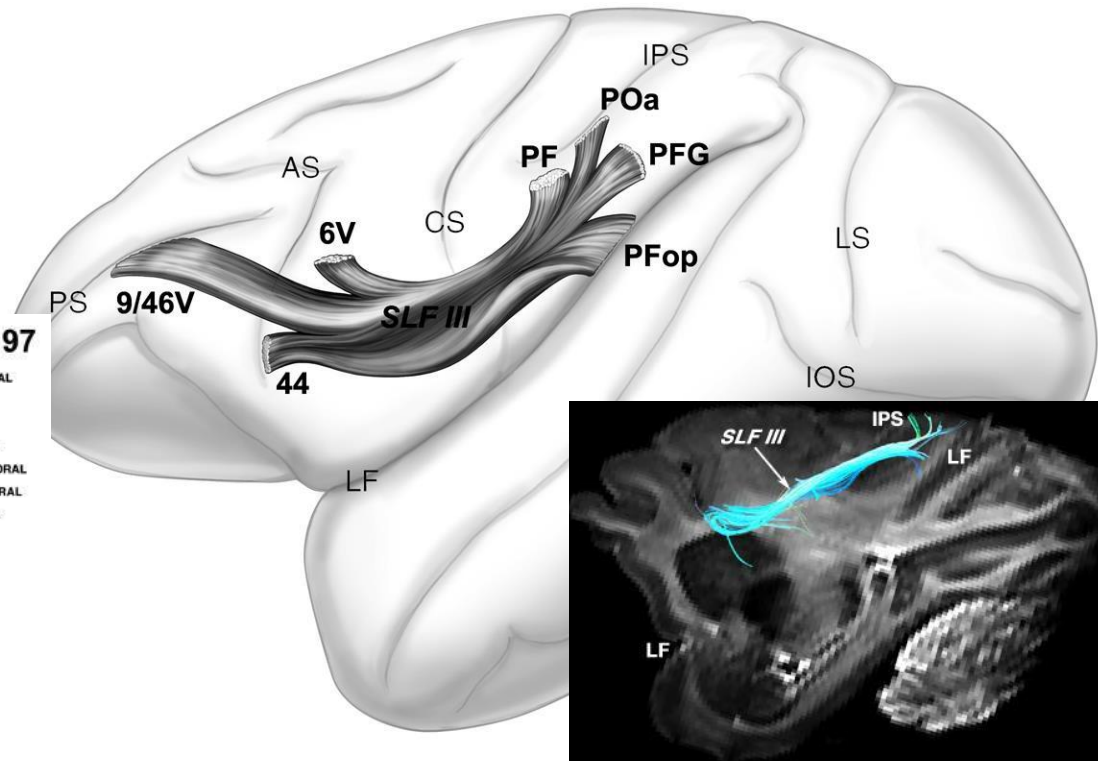
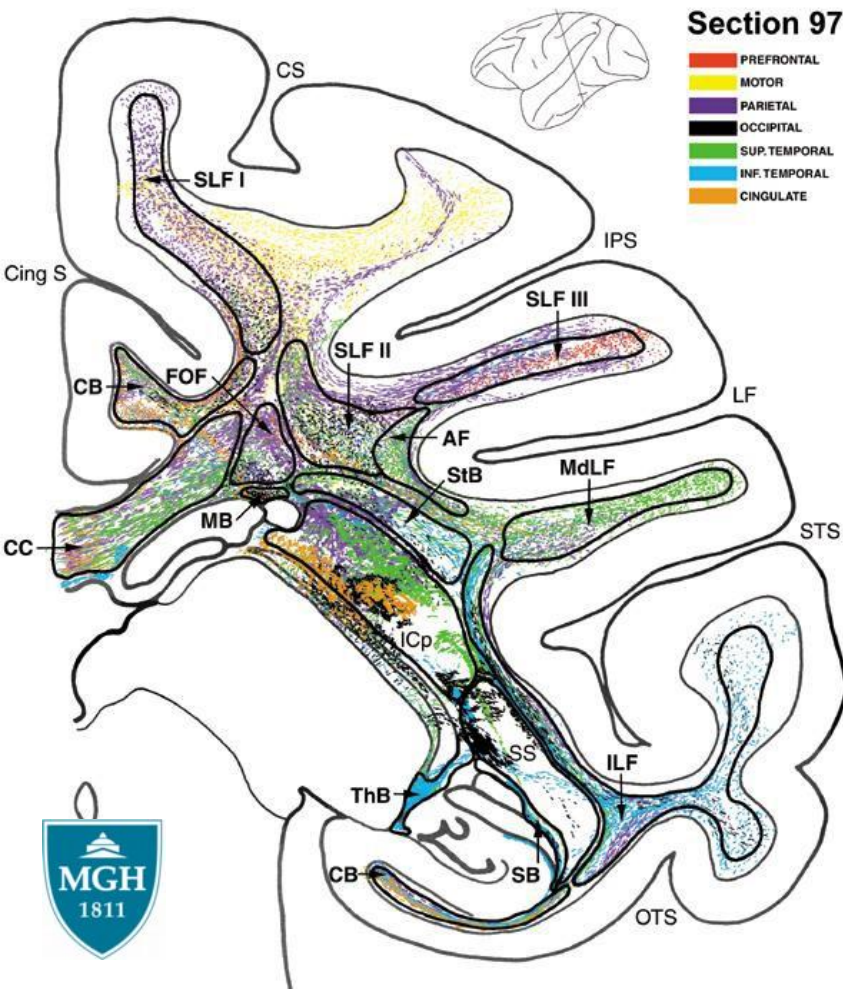
Posterior prefrontal cortices - perception, awareness

Feedback fibers - focusing of spatial attention

Schmahmann and Pandya, 2006;
Schmahmann, Pandya, Wedeen et al., Brain 2007

Superior Longitudinal Fasciculus III

Gestural component of language.
Orofacial working memory



Rostral IPL (supramarginal gyrus)

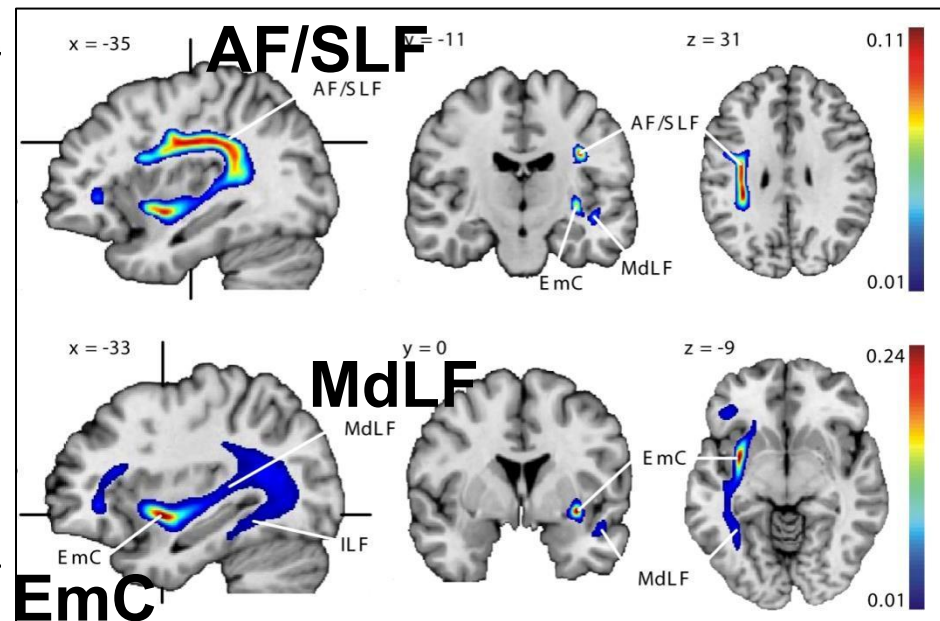
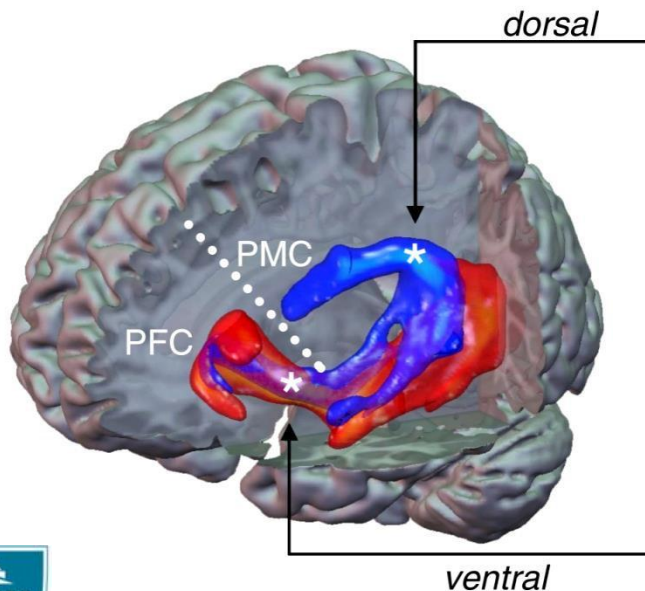
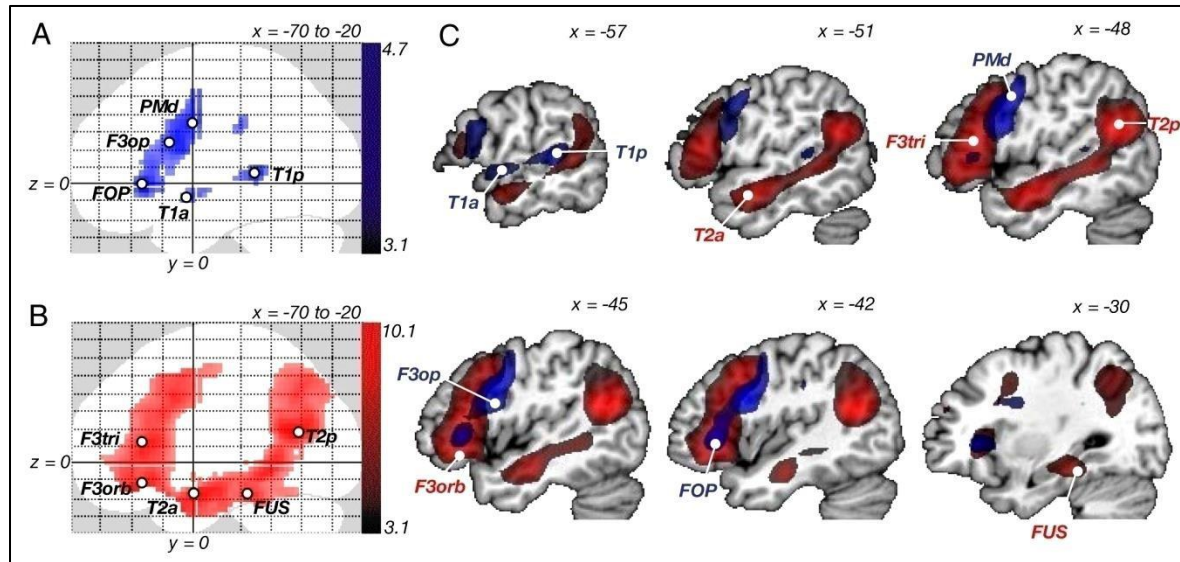
- input from S1 face, head, and neck
- high order somatosensory information

Linked with

- ventral premotor area (6, 44 – pars opercularis)
 - action, mirror neurons, imitation
- ventral prefrontal area 46
 - working memory

Schmahmann and Pandya, 2006;
Schmahmann, Pandya, Wedeen et al., Brain 2007

Ventral and dorsal pathways for language

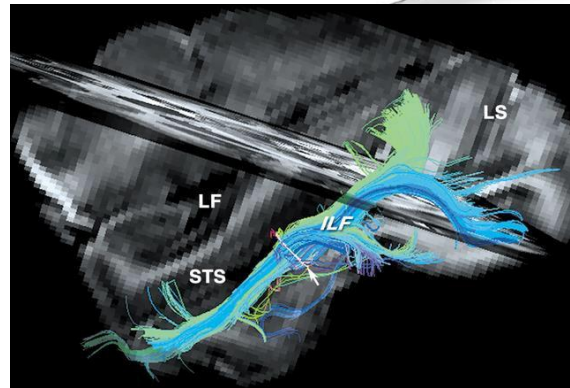
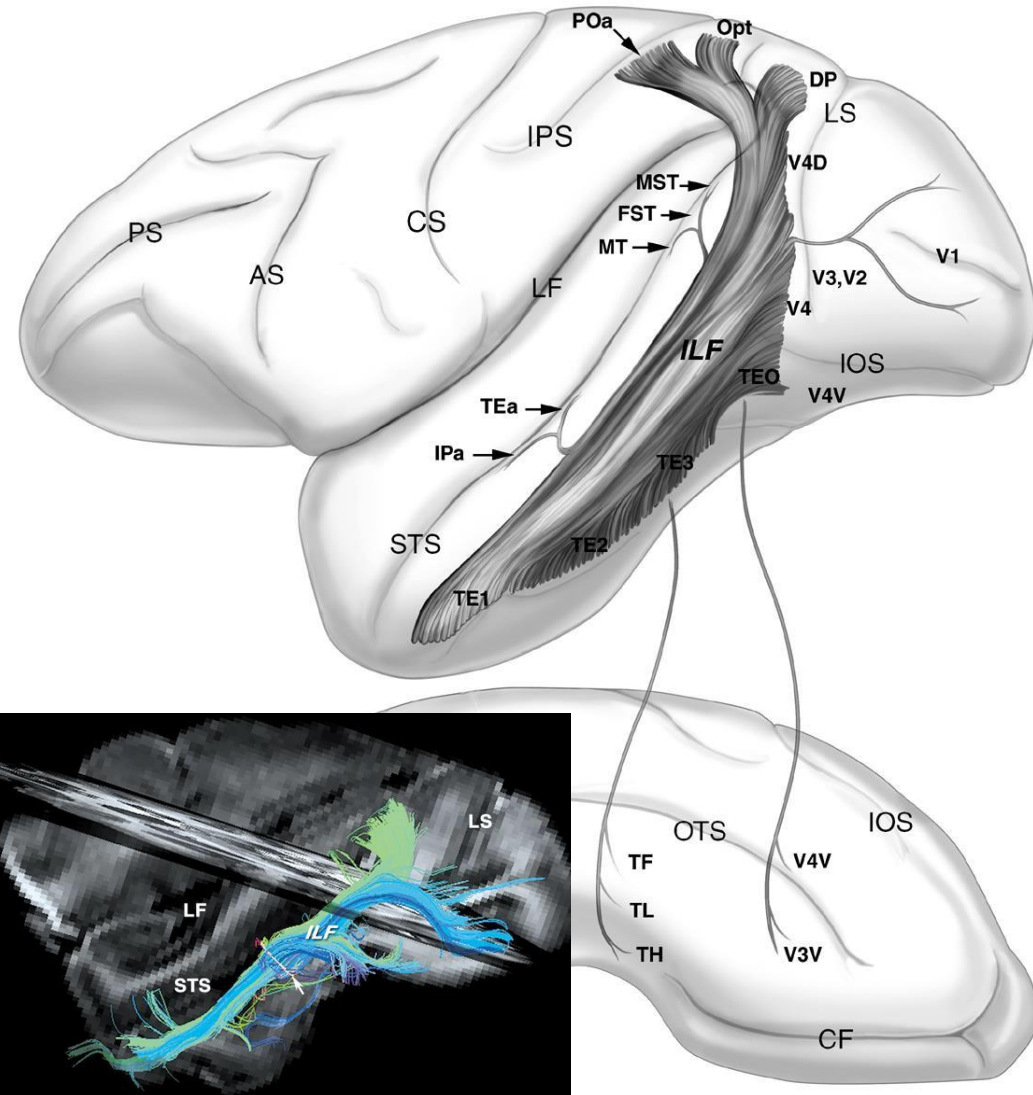
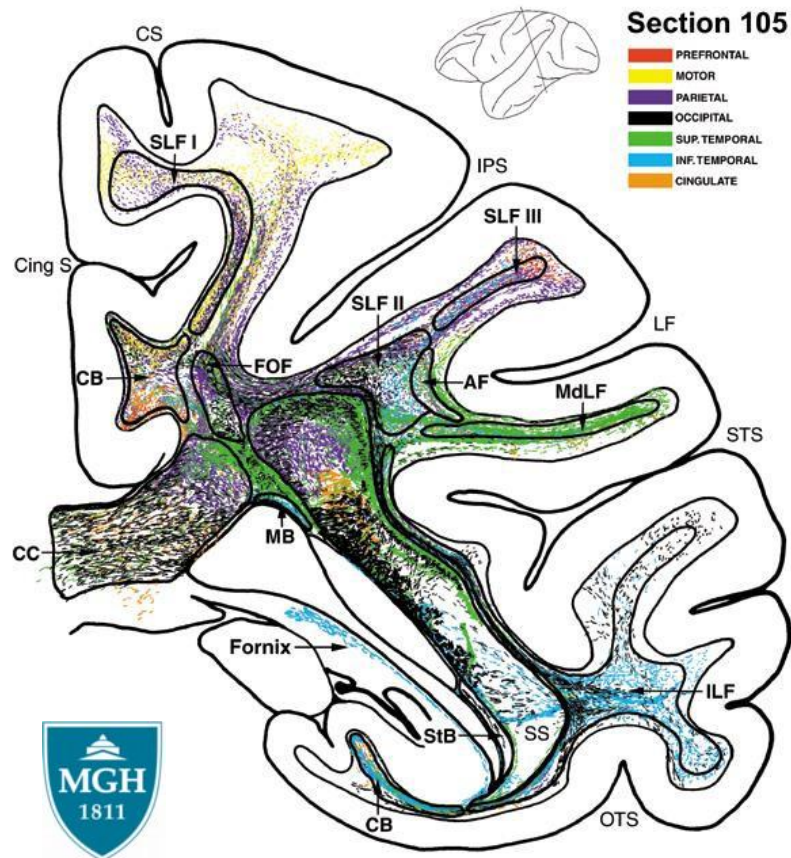


Saur et al., PNAS, 2008

Weiller et al., Brain & Language, 2011

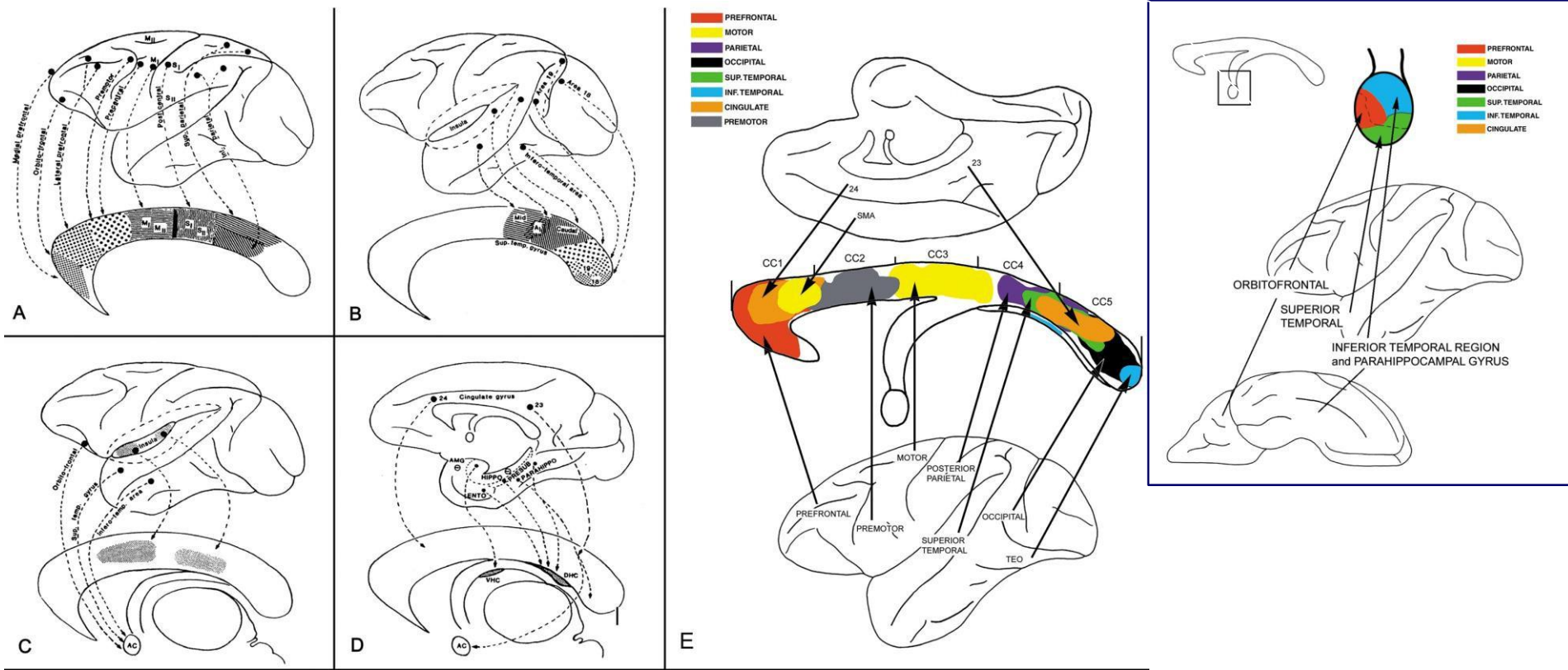
Inferior Longitudinal Fasciculus

Object discrimination
Face / object recognition
Object memory



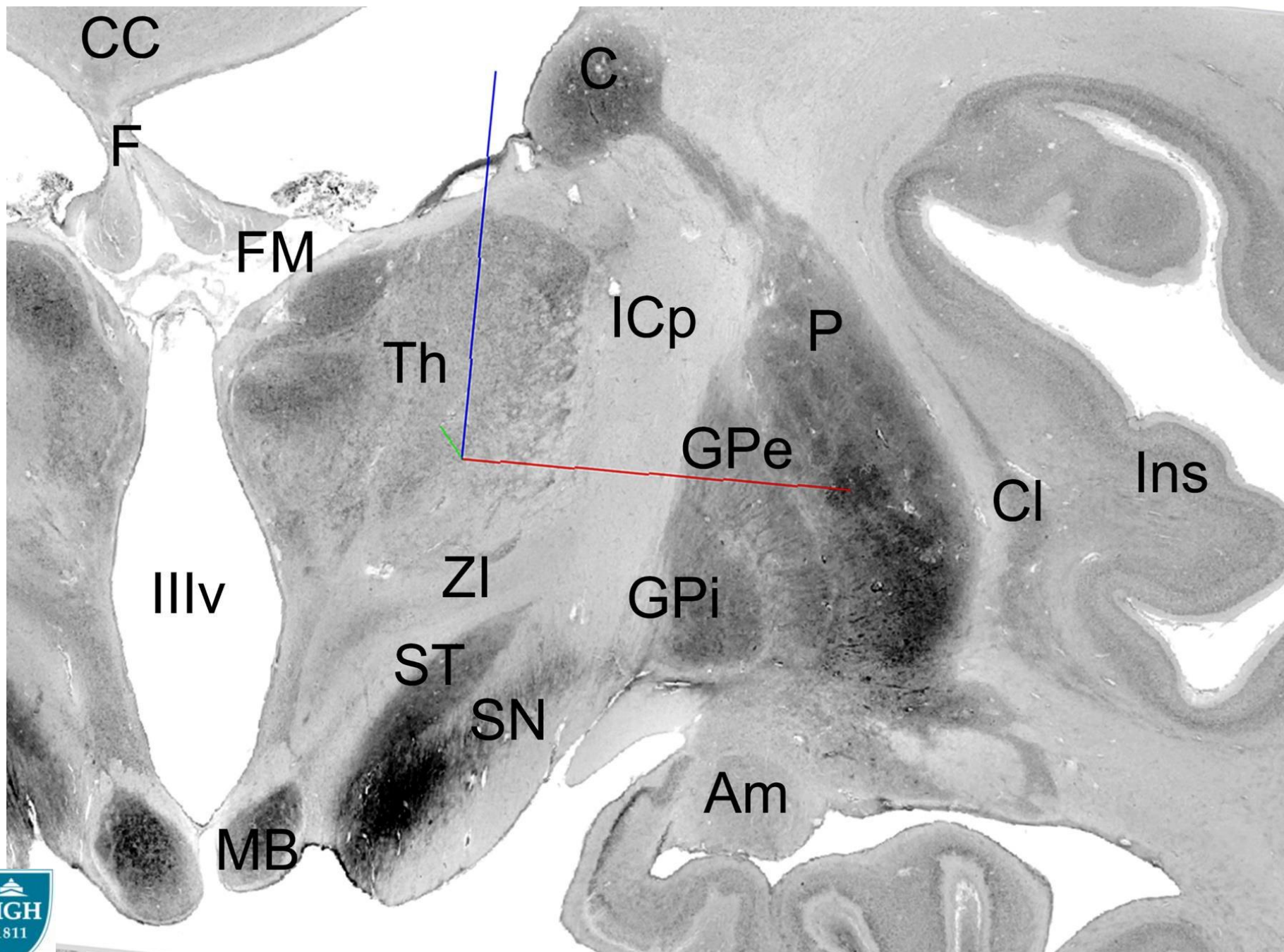
Ventral occipital - central vision
Ventral temporal - object recognition
Posterior parahippocampal gyrus - memory

Schmahmann and Pandya, 2006;
Schmahmann, Pandya, Wedeen et al., Brain 2007



Interhemispheric (callosal) connections

Pandya and Rosene, 1985
Schmahmann and Pandya, 2006
Chao et al., 2009



Basal Ganglia

striatum

dorsal striatum - caudate nucleus, putamen

ventral striatum – nucleus accumbens, septum

globus pallidus

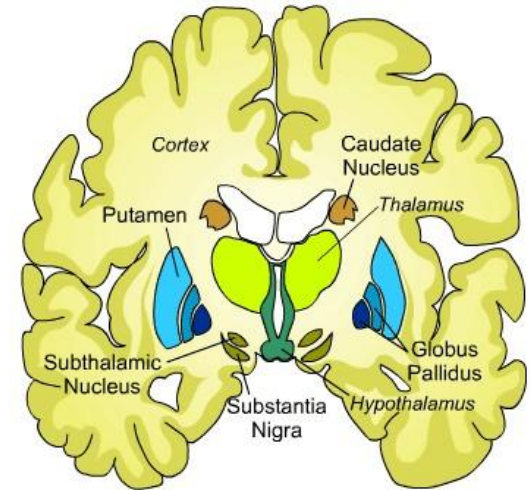
GPe, GPi, ventral pallidum

substantia nigra

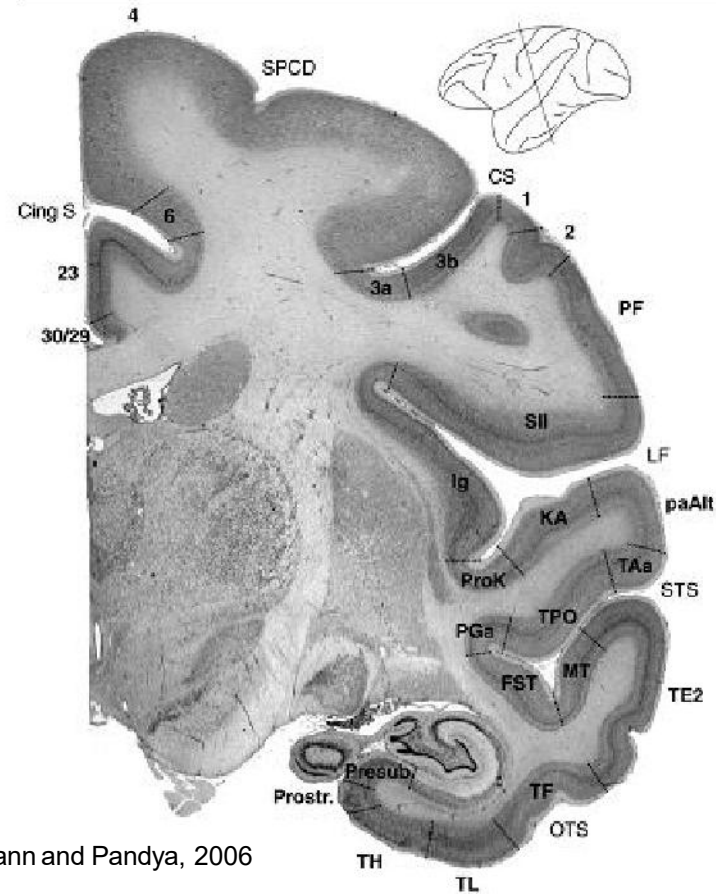
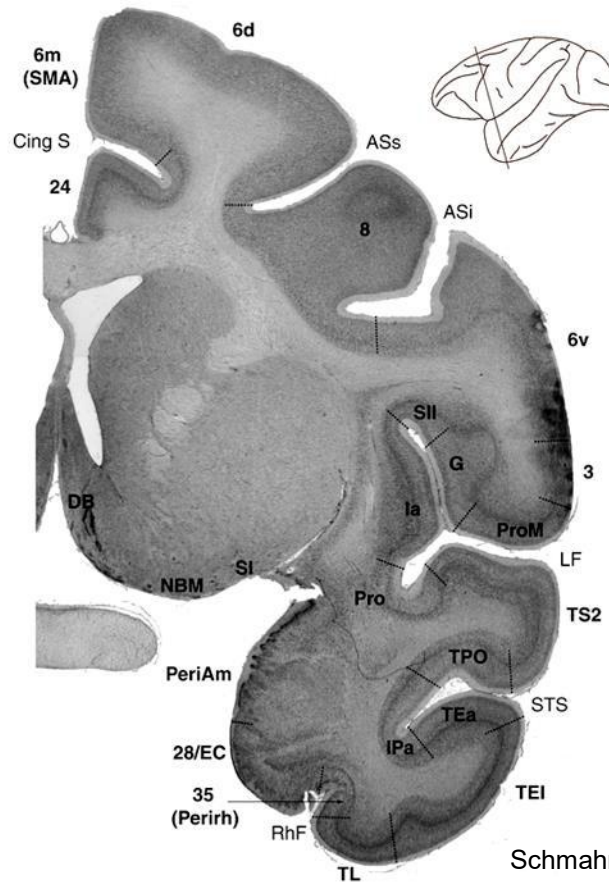
pars compacta

pars reticulata

subthalamic nucleus



www.stanford.edu/group/hopes/basics/braintut

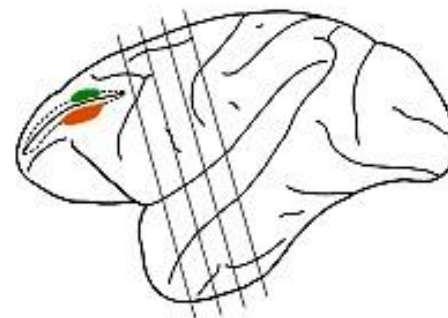
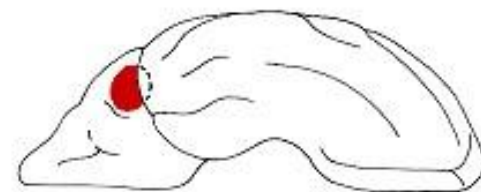
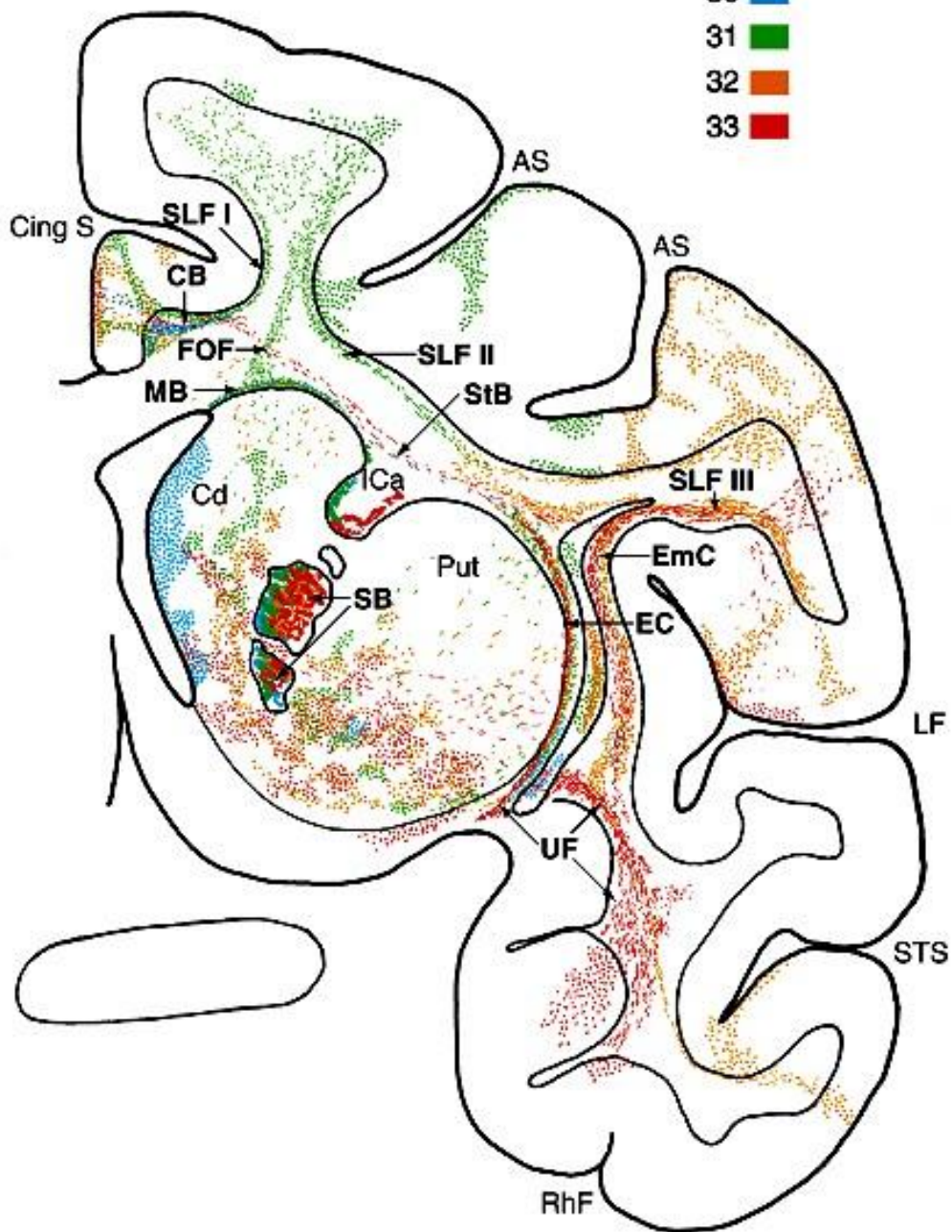


Schmahmann and Pandya, 2006

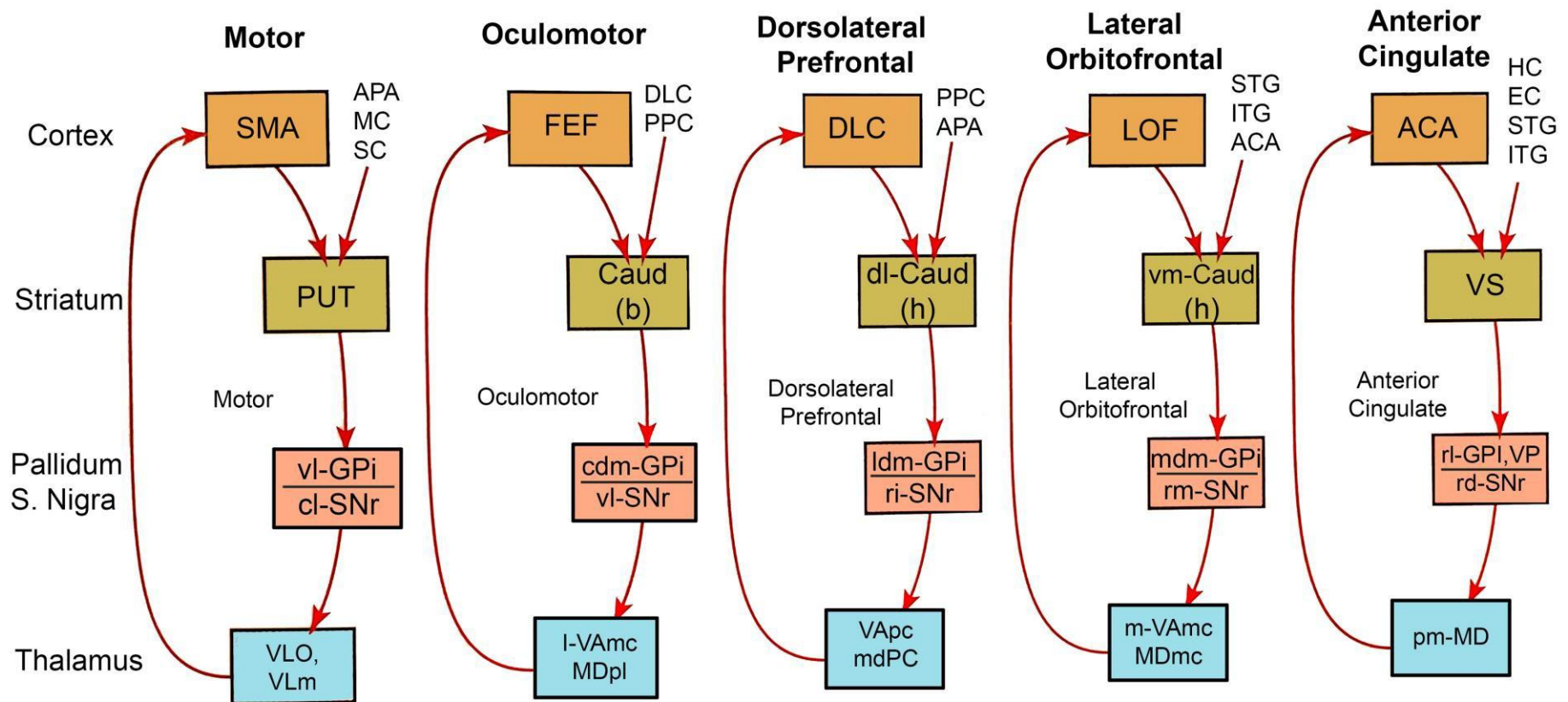
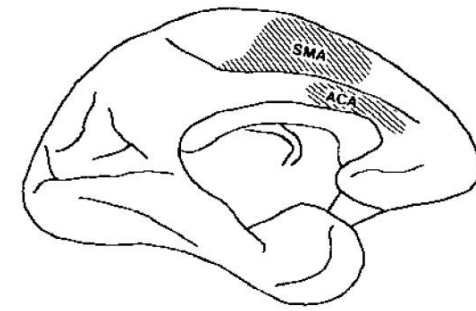
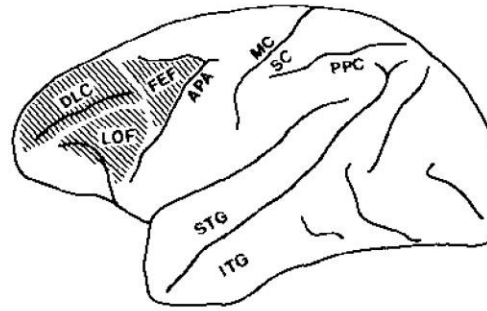


CASE

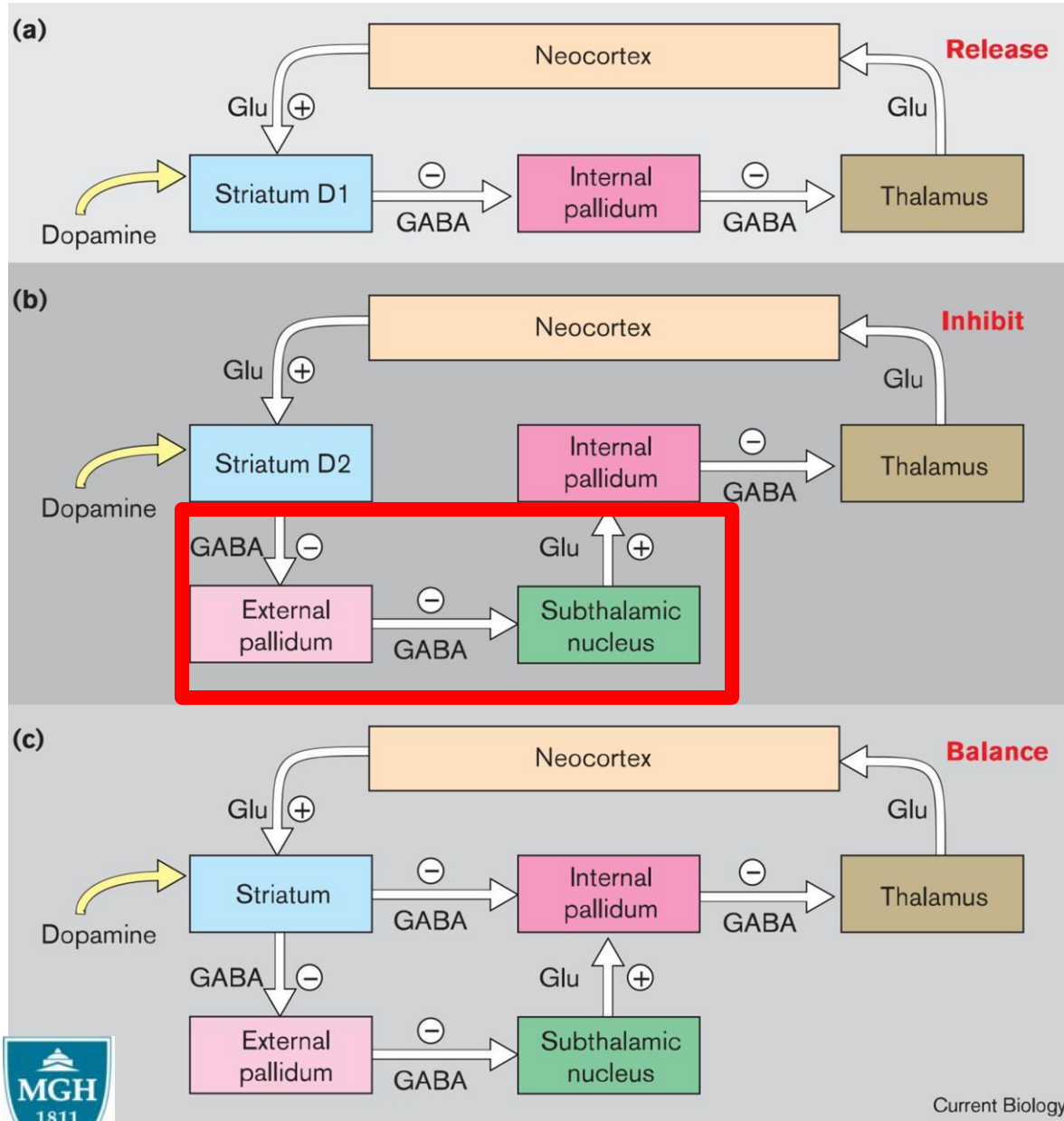
- 30
- 31
- 32
- 33



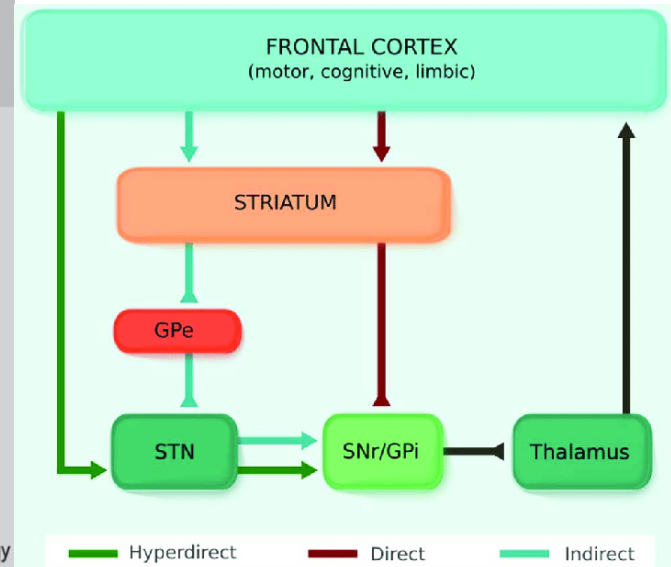
Multiple loops of information processing link functionally specified prefrontal cortices with subcortical structures



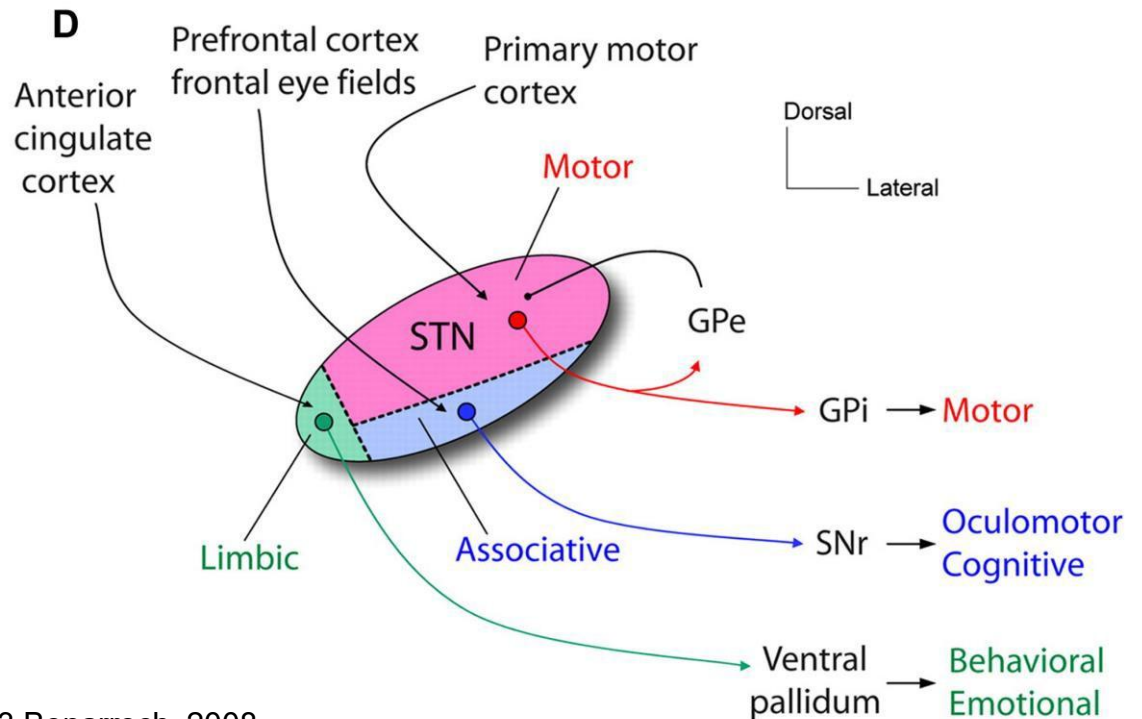
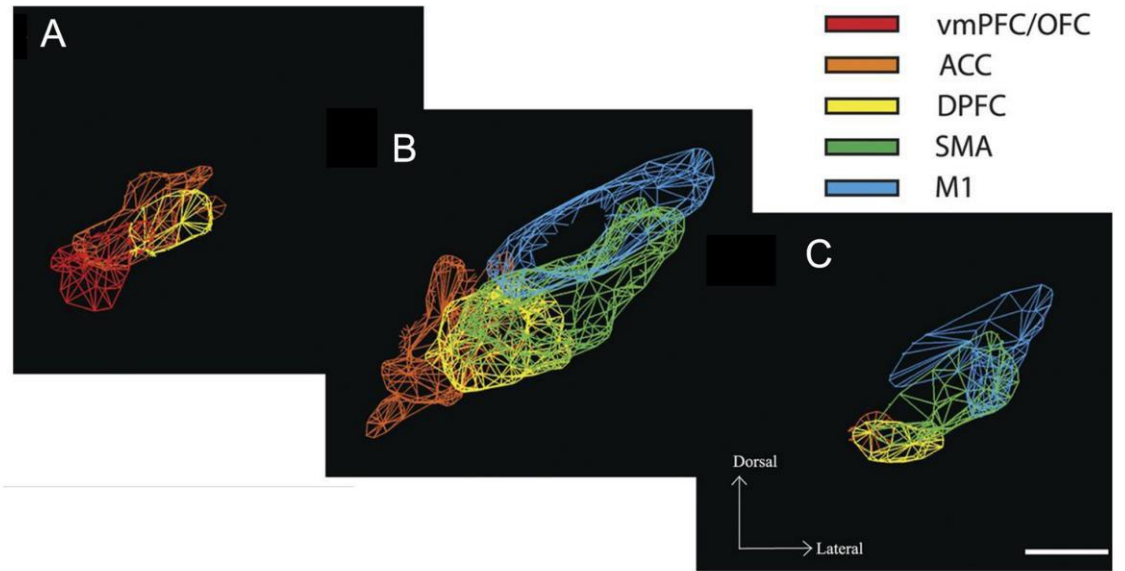
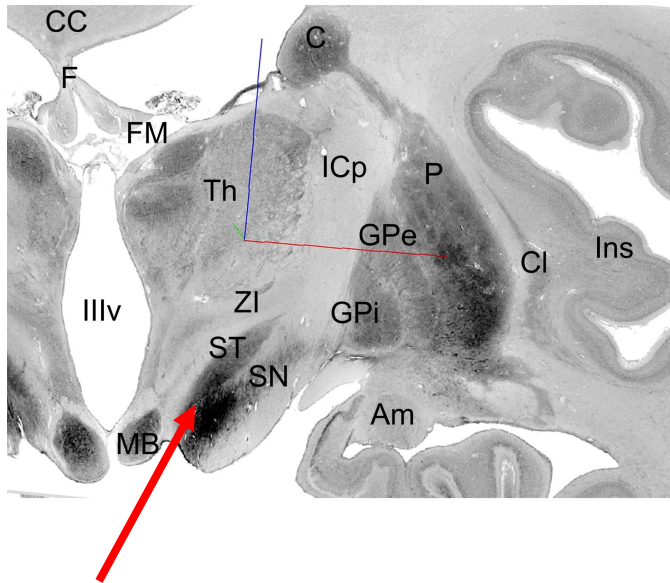
Alexander, DeLong, Strick, 1986
in Mink, Fundamental Neuroscience, 2003



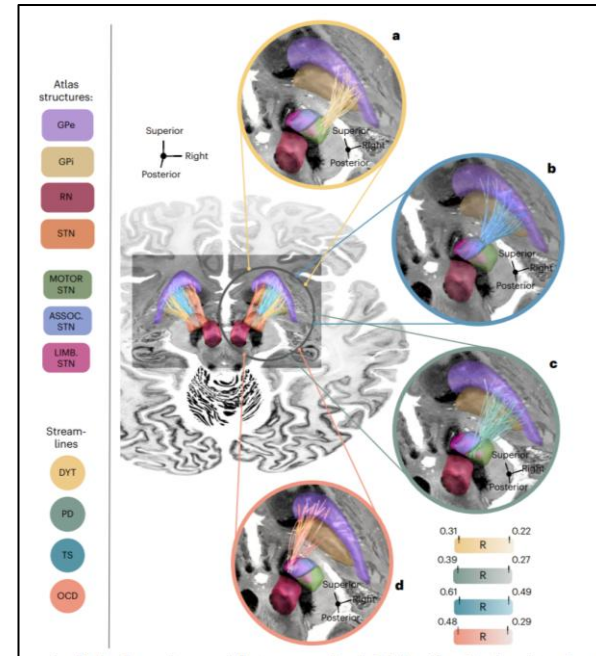
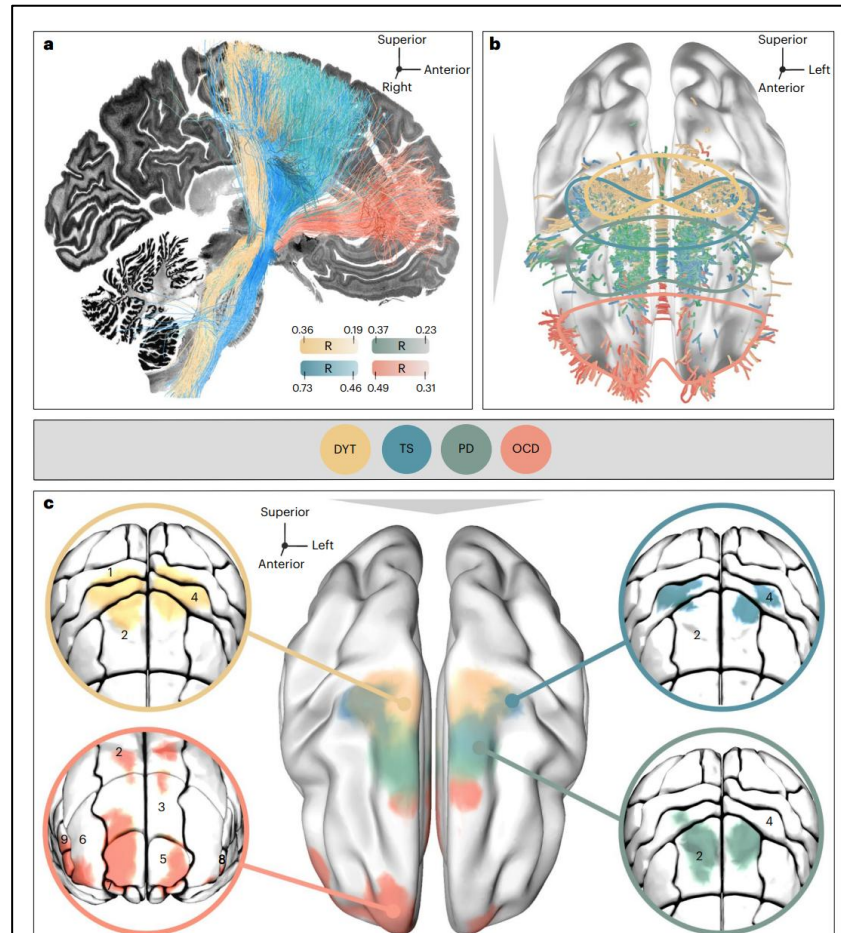
Basal ganglia: direct and indirect loops



Subthalamic Nucleus (STN)



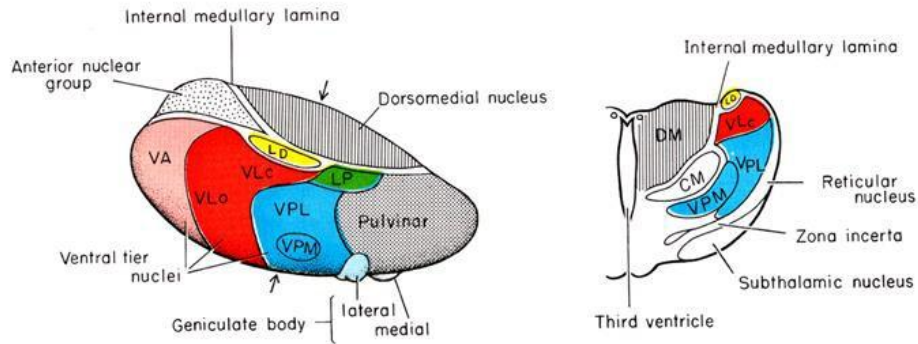
Mapping dysfunctional circuits in the frontal cortex using deep brain stimulation in STN



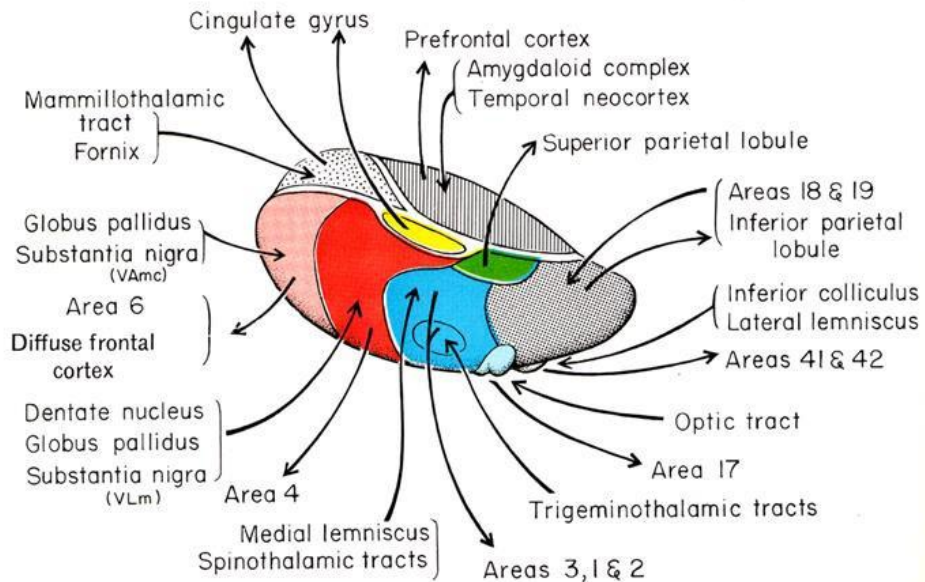
Dysfunctional circuits:

- Sensorimotor cortex – Dystonia
- Motor cortex - Tourette's
- Supplementary motor area - PD
- Ventromedial prefrontal, anterior cingulate cortices - OCD

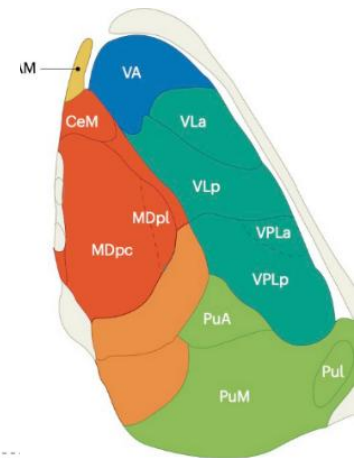
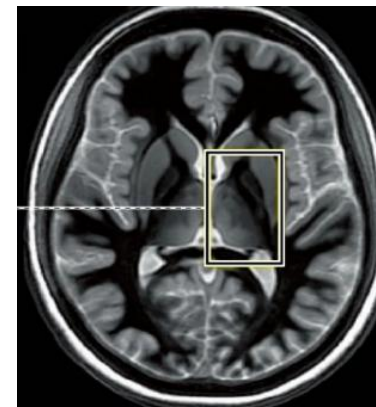
Thalamus



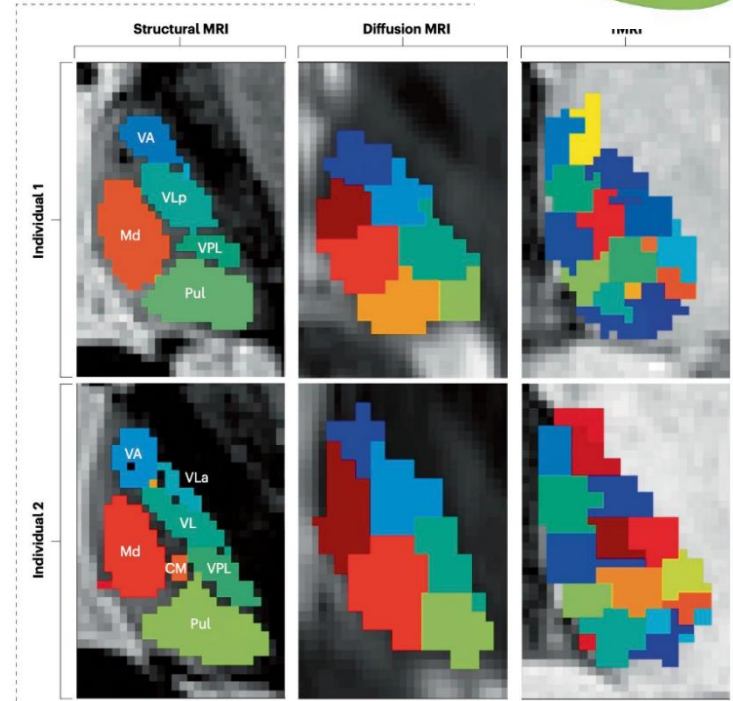
A.



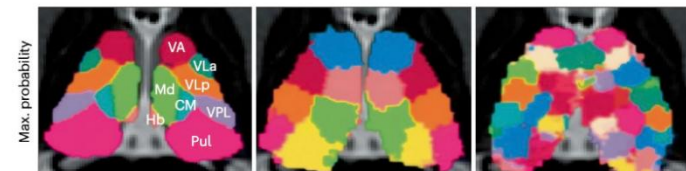
Carpenter, 1979



a Axial view



c



Segobin et al. Nat. Rev. Neurosci. (2024).

Thalamic nuclear groupings

RETICULAR

INTRALAMINAR

LIMBIC

SPECIFIC SENSORY

EFFECTOR

ASSOCIATIVE

CL, CM-Pf, Pcn

Central laminar, centromedian-parafascicular, paracentralis

AD, AV, AM, LD, parts of MD, PM

Anterodorsal/ventral/medial, lateral dorsal, medial dorsal, pulvinar medialis

VPL, VPM, VPI, LGN, MGN

Ventral posterolateral/medial/inferior, lateral and medial geniculate

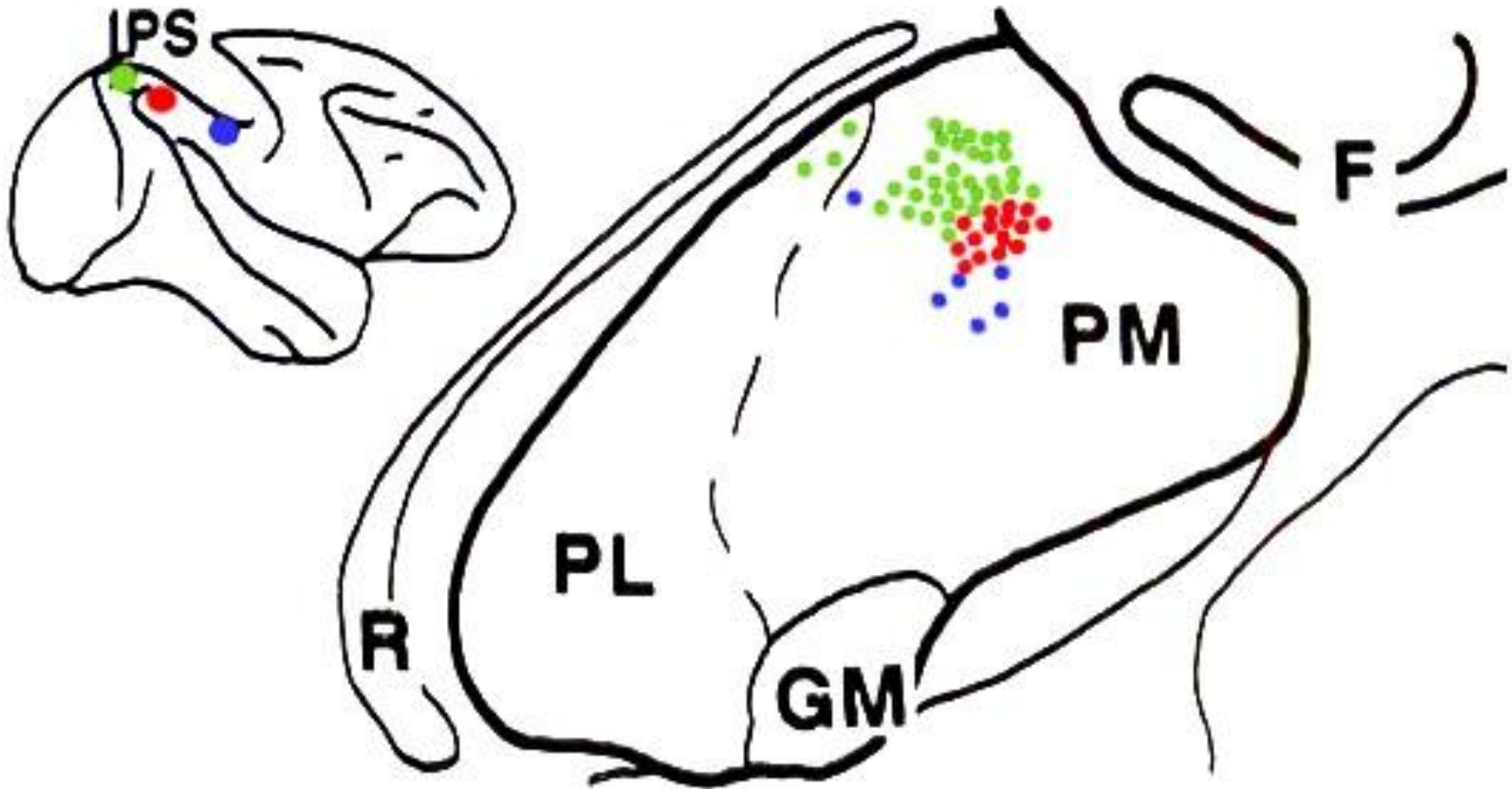
VL, VA

Ventral lateral / anterior

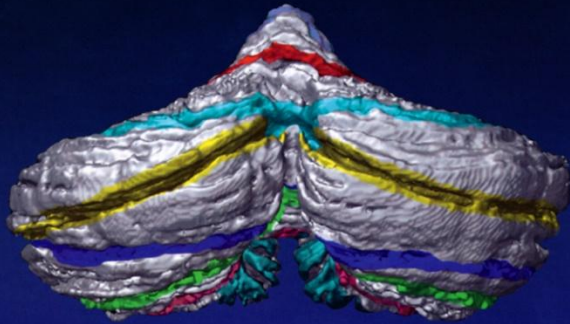
MD, Pulvinar, LP

Medial dorsal, pulvinar, lateral posterior

Topography of projections to parietal lobe from pulvinar medialis



MRI ATLAS of the HUMAN CEREBELLUM



Jeremy D. Schmahmann

Julien Doyon

Arthur W. Toga

Michael Petrides

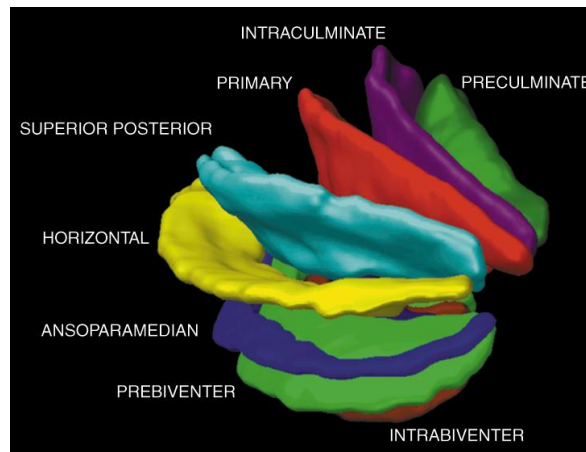
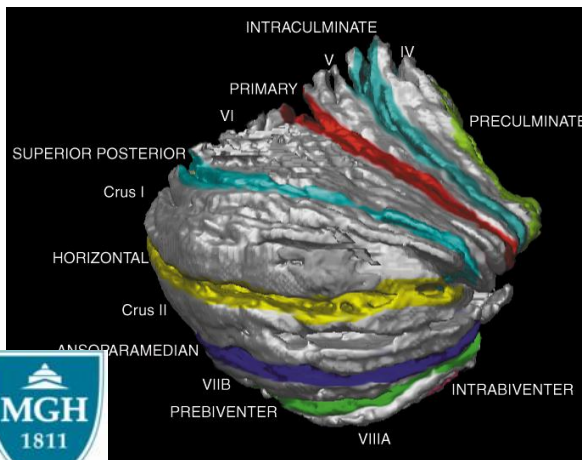
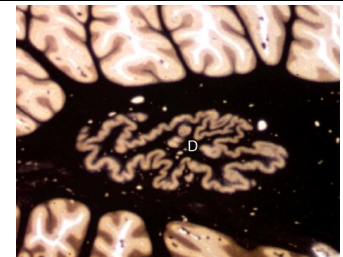
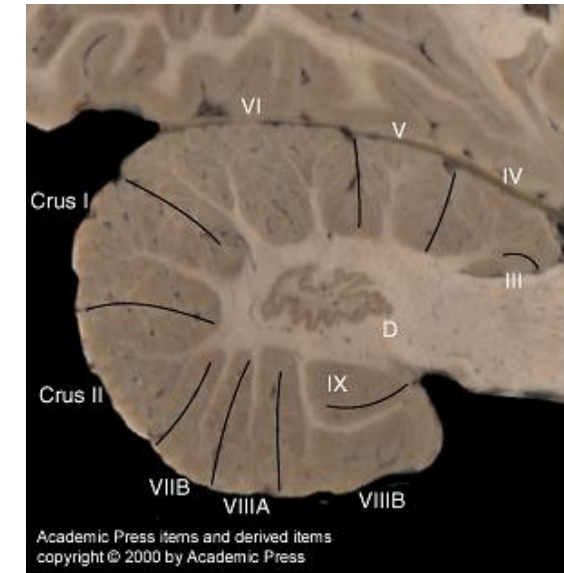
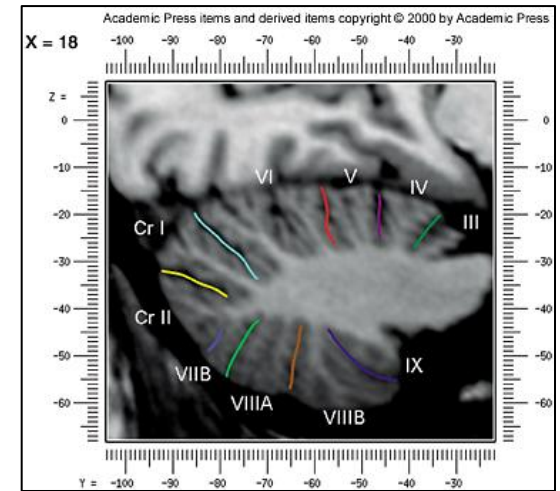
Alan C. Evans



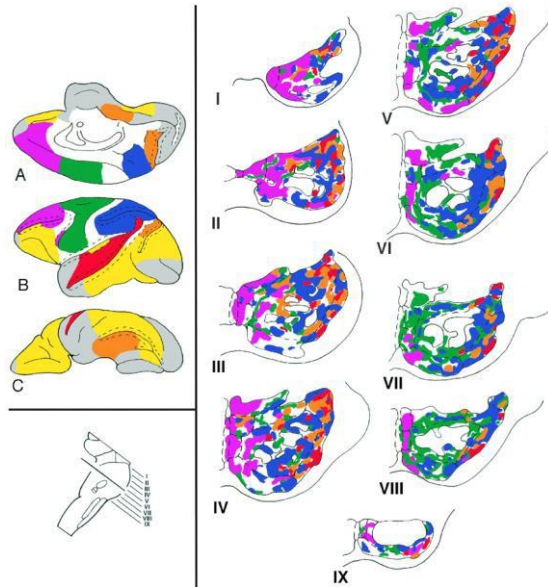
Free Software Included



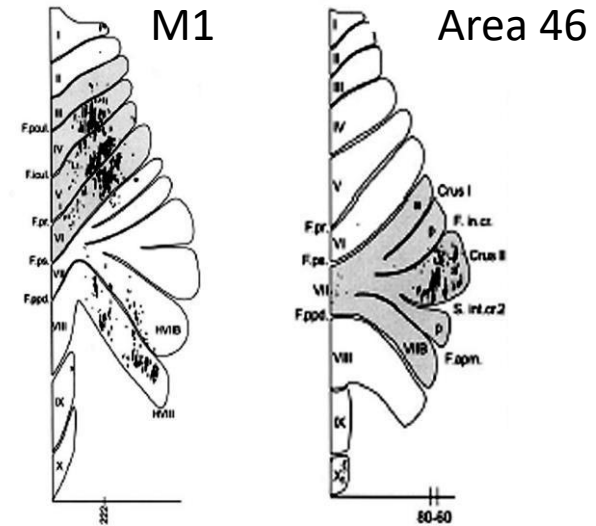
VERMIS	FISSURE	HEMISPHERE
Lobule I,II	Precentral	Lobule I,II
III	Preculminate	III
IV	Intraculminate	IV
V	Primary	V
VI	Superior Posterior	VI
VIIAf	Horizontal	Crus I
VIIAt	Ansoparamedian	Crus II
VIIIB	Prepyramidal/Prebiventer	VIIIB
VIIIA	Intrabiventer	VIIIA
VIIIB	Secondary	VIIIB
IX	Posterolateral	IX
X		X



Cerebellum: Connectional & functional topography

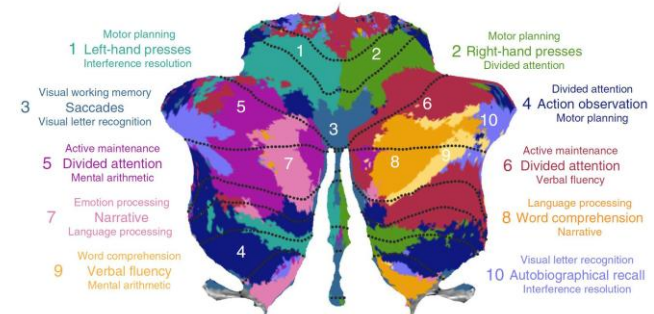
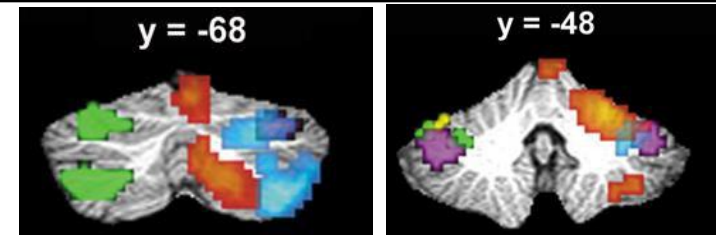
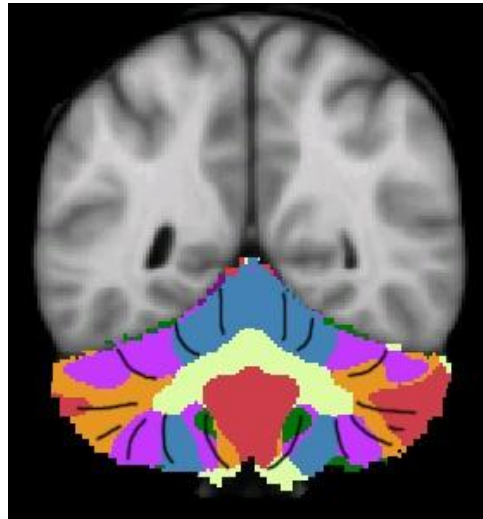
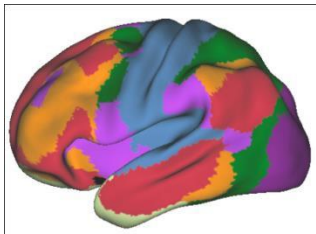


Schmahmann, 1994, 1996; Schmahmann and Pandya, 1987, 1997



Kelly and Strick, 2003

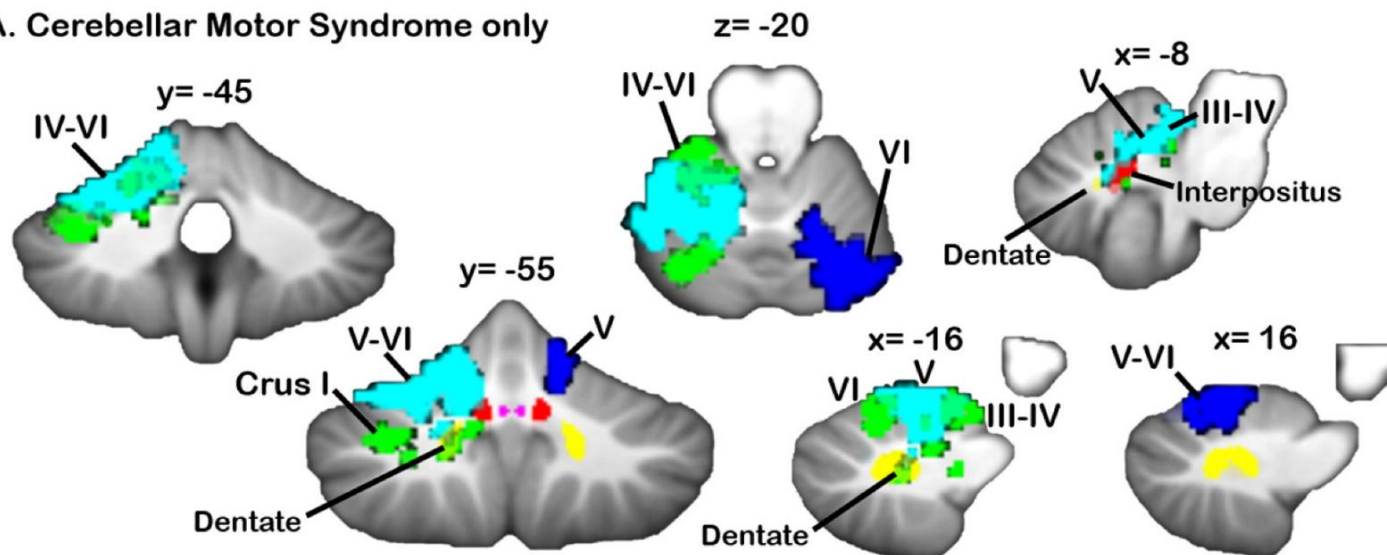
King et



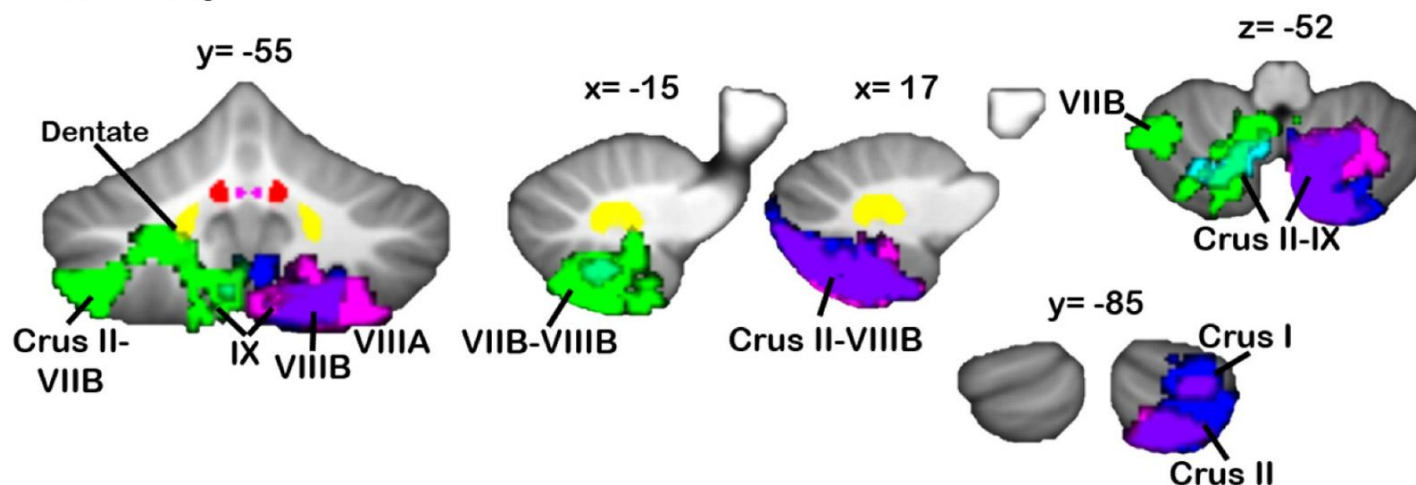
Stoodley, Schmahmann, 2009 Stoodley, Valera, Schmahmann, 2010, 2012; King et al., 2019

Location of lesion determines motor vs. cognitive consequences in patients with cerebellar stroke

A. Cerebellar Motor Syndrome only



B. CCAS only



Stoodley, MacMore, Makris, Sherman, Schmahmann. NeuroImage Clinical, 2016
 Also – Schmahmann, MacMore, Vangel. Neuroscience 2009; Schmahmann and Sherman, 1998

Cerebellar Cognitive Affective Syndrome (CCAS)

- Executive Function

Planning, set-shifting, verbal fluency, abstract reasoning, working memory

- Spatial Cognition

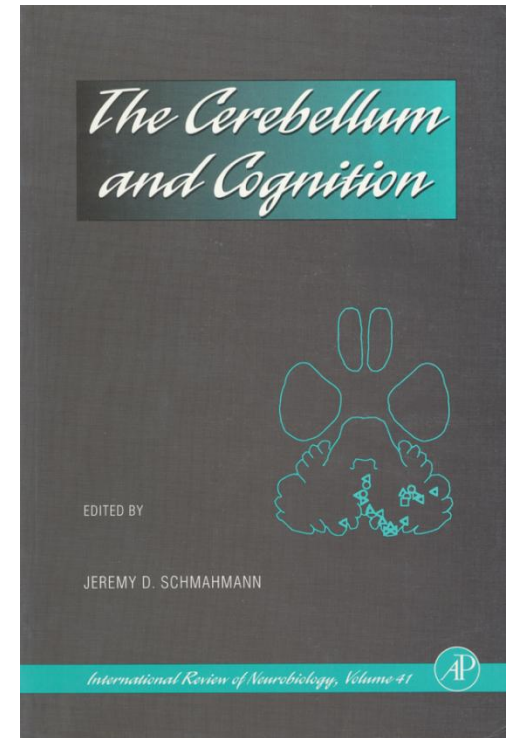
Visual spatial organization and memory

- Language Deficits

Agrammatism, aprosodia, anomia

- Personality Change

Blunting of affect, disinhibited and inappropriate behavior



Schmahmann and Sherman. Brain, 1998



Schmahmann's syndrome - identification of the third cornerstone of clinical ataxiology

Mario Manto and Peter Mariën. Cerebellum and Ataxias 2015;2:2

Dysmetria of Thought: Conceptual Model of Cerebellar Function

In the same way that cerebellum regulates rate, rhythm, force, and accuracy of movements, so does it regulate the speed, consistency, capacity, and appropriateness of mental or cognitive processes.

Universal Cerebellar Transform Theory

Cerebellum optimizes performance by modulating behavior around a homeostatic baseline automatically, implicitly, and according to context.

Universal Cerebellar Impairment = Dysmetria

Lesions of sensorimotor cerebellum produce dysmetria of movement:

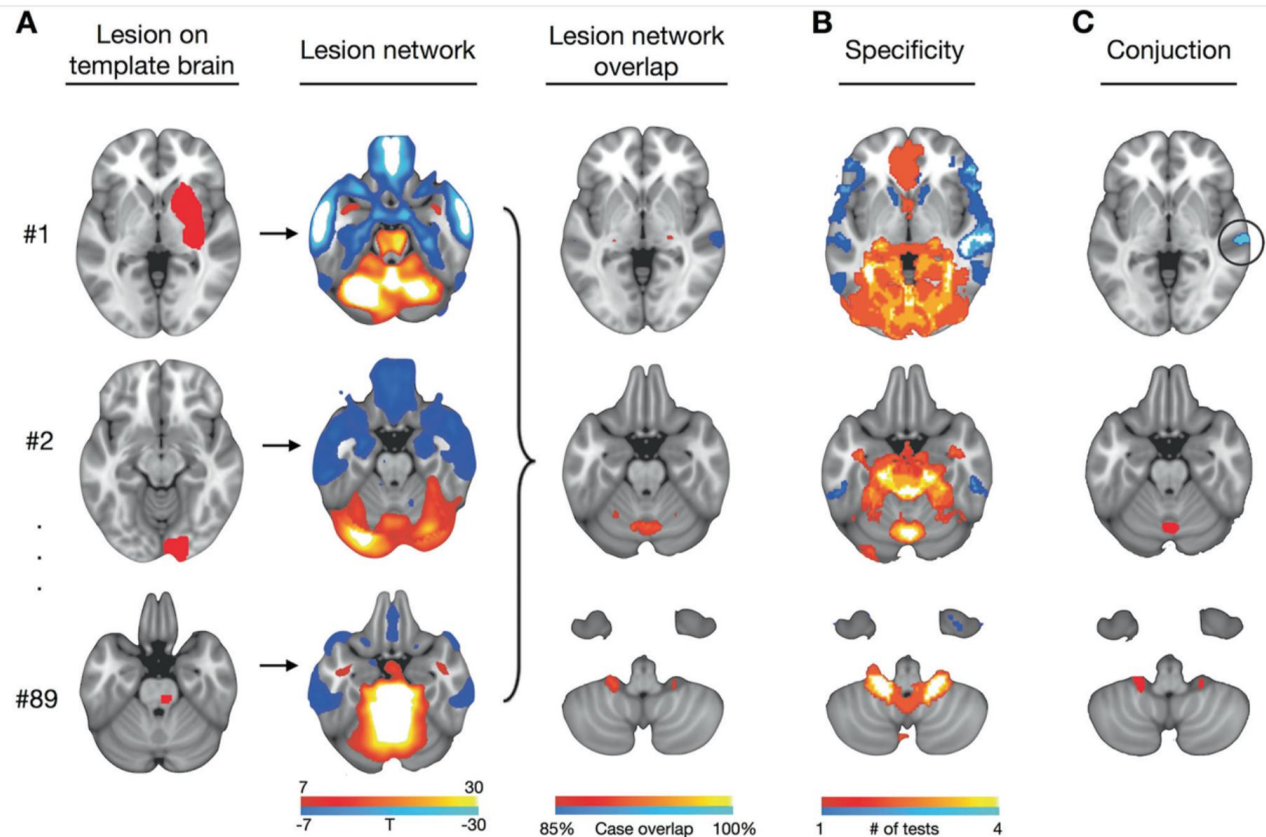
The cerebellar motor syndrome

Lesions of cognitive / limbic cerebellum produce dysmetria of thought and emotion:

The cerebellar cognitive affective syndrome



Lesion network mapping: Hallucinations map to a common brain network



Cerebellar vermis VI (positive correlations)

Cerebellar lobules X bilaterally (positive correlations)

Right superior temporal sulcus (negative correlations)

LGN connections – visual hallucinations

Cerebellar dentate connections – auditory hallucinations

Some references

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- Posterior Fossa Society
- Multiple System Atrophy Global Working Group

Primate behavior

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