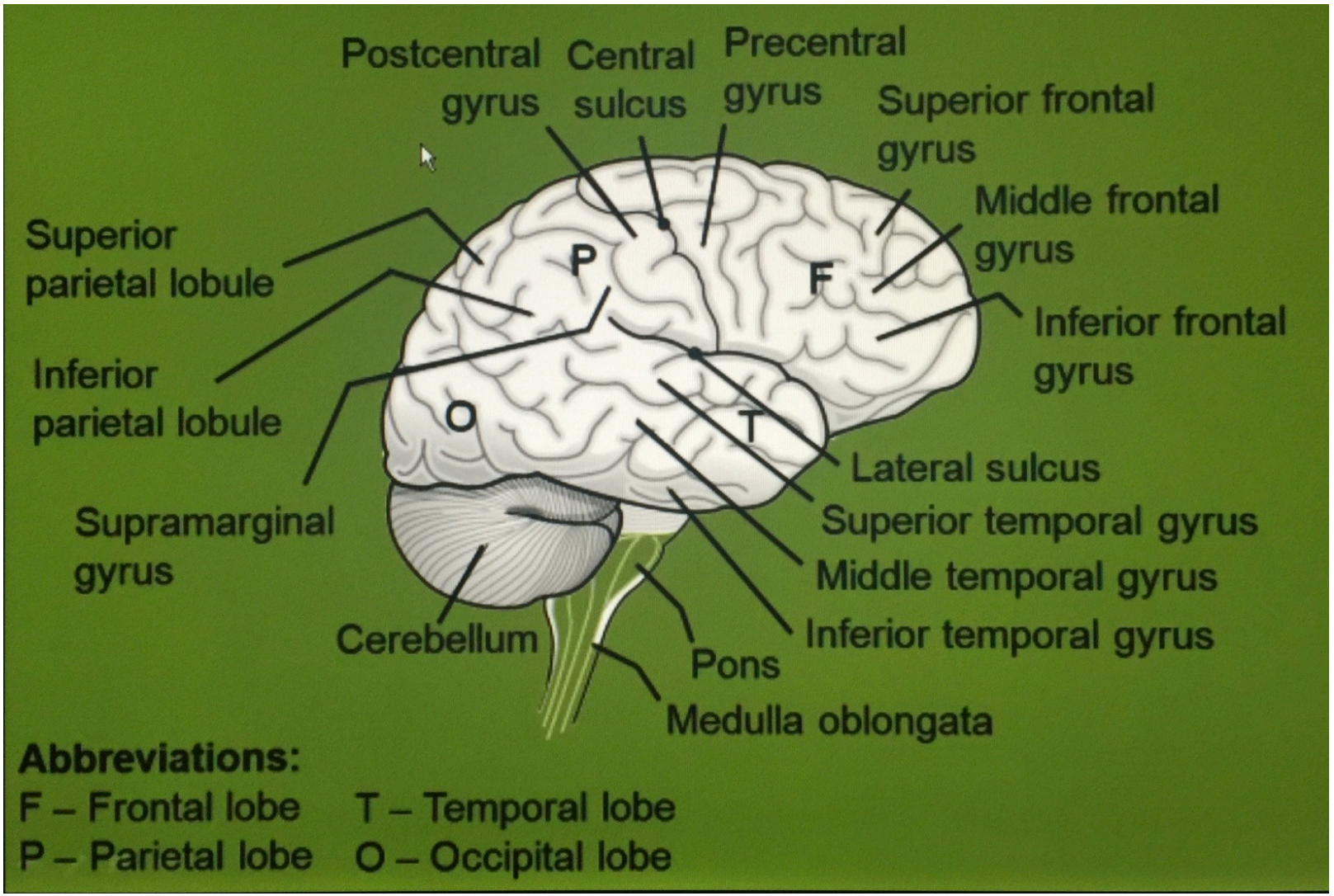
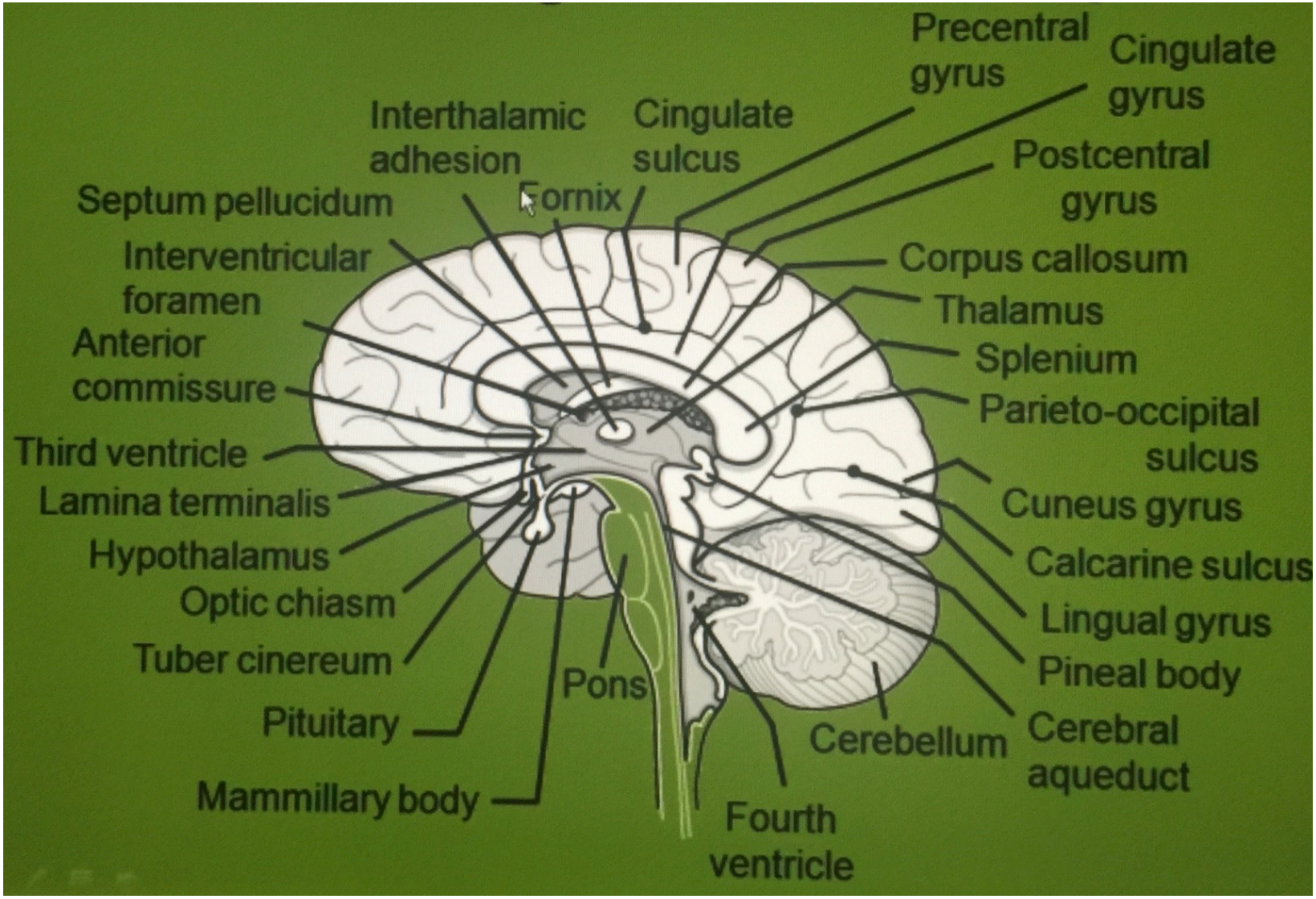
CEREBRAL CORTEX

Prof. M. GAVRILIUC

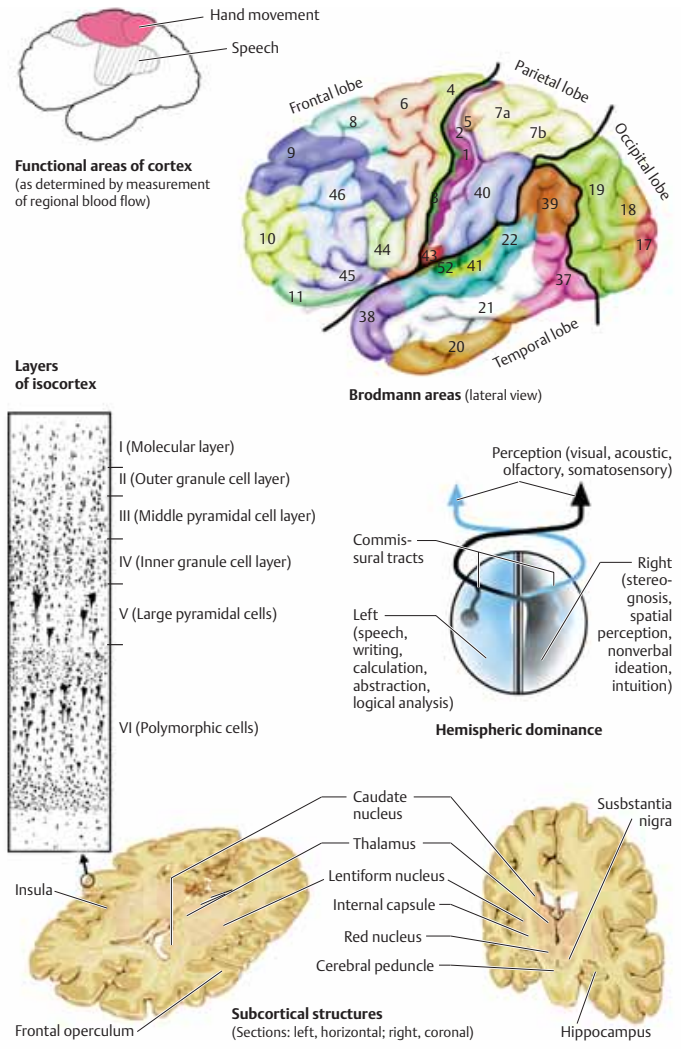
Lateral View of Right Cerebral Hemisphere



Medial View of Right Cerebral Hemisphere



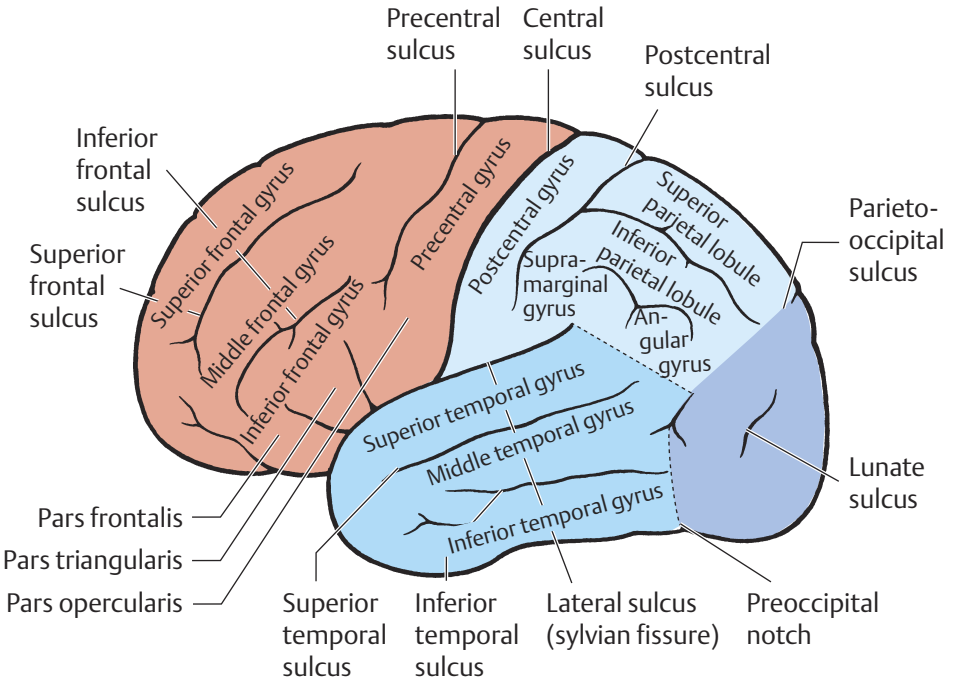
Cortical Structures



- Different areas of the *cerebral cortex* (neocortex) may be distinguished one another by their histological features and neuroanatomical connections.

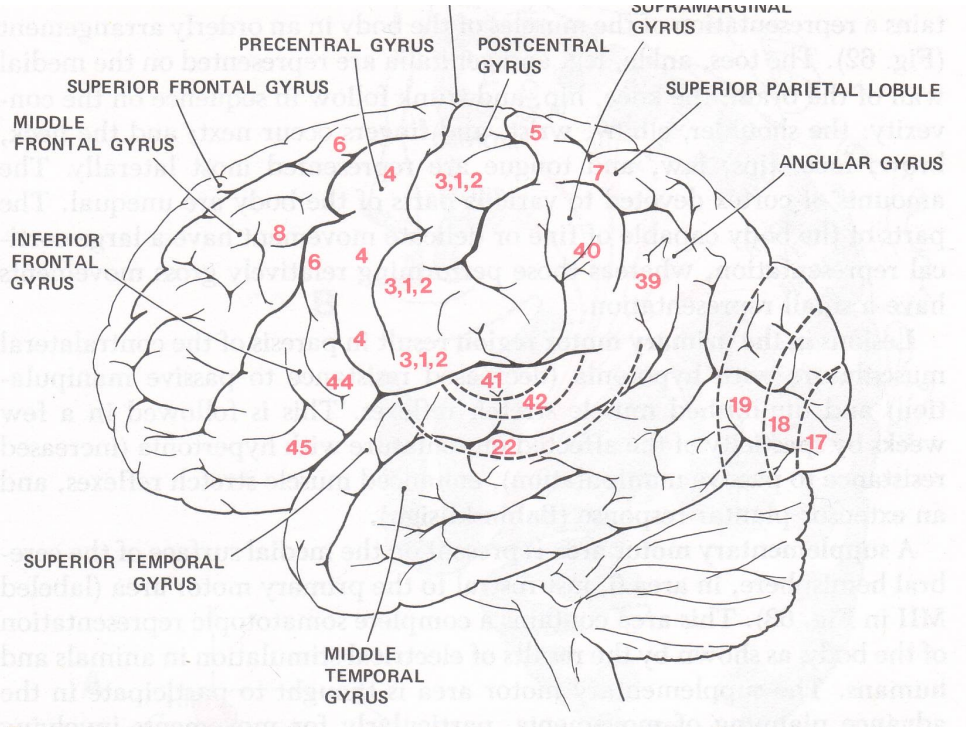
Cortical Structures

- **Projection areas.** By following the course of axons entering and leaving a given cortical area, one may determine the other structures to which it is connected by afferent and efferent pathways.



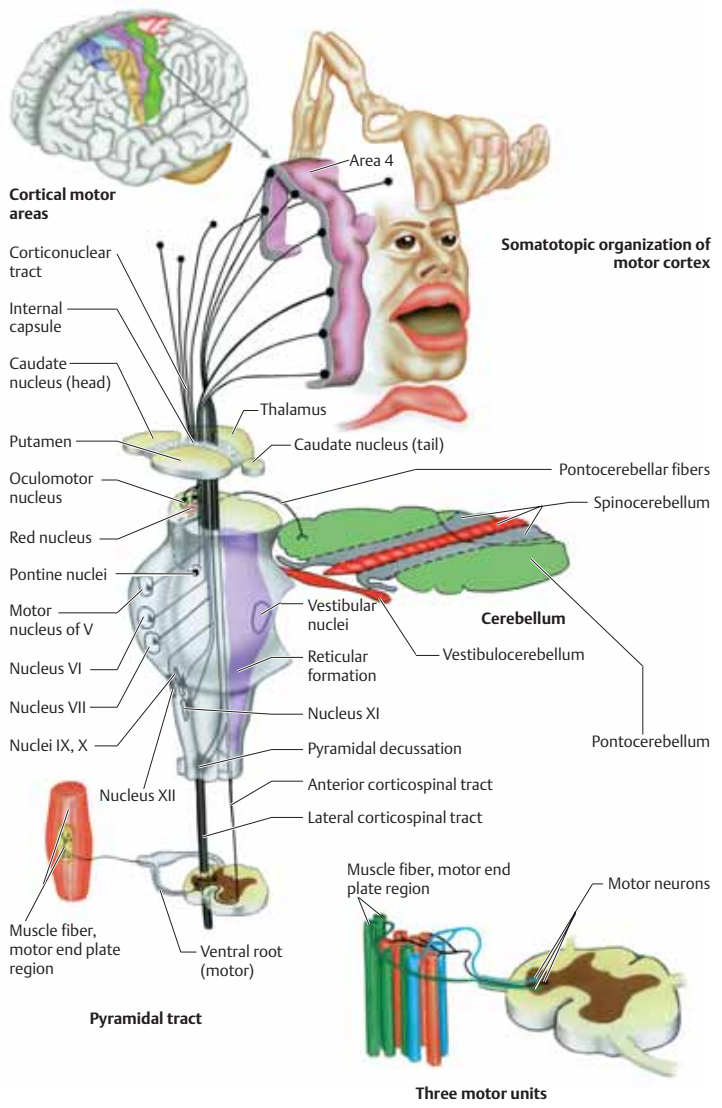
Cortical Structures

- **<u>The primary projection</u>** areas are those that receive most of their sensory impulses directly from the thalamic relay nuclei (primary **somatosensory cortex**; Brodmann areas 1, 2, 3), **the visual** (area 17), or **the auditory** (areas 41, 42) pathways.



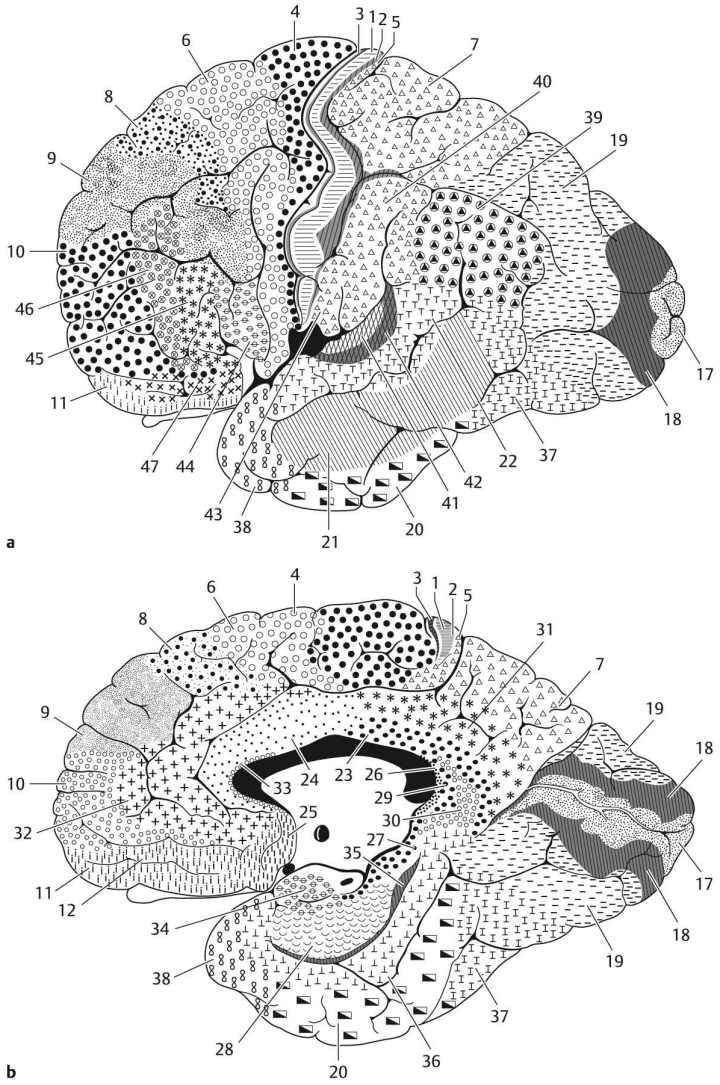
Cortical Structures

- **The primary motor cortex** (area 4) sends motor impulses directly down the pyramidal pathway to somatic motor neurons within brainstem and the spinal cord. The primary projection areas are somatotopically organized and serve the contralateral half of the body.



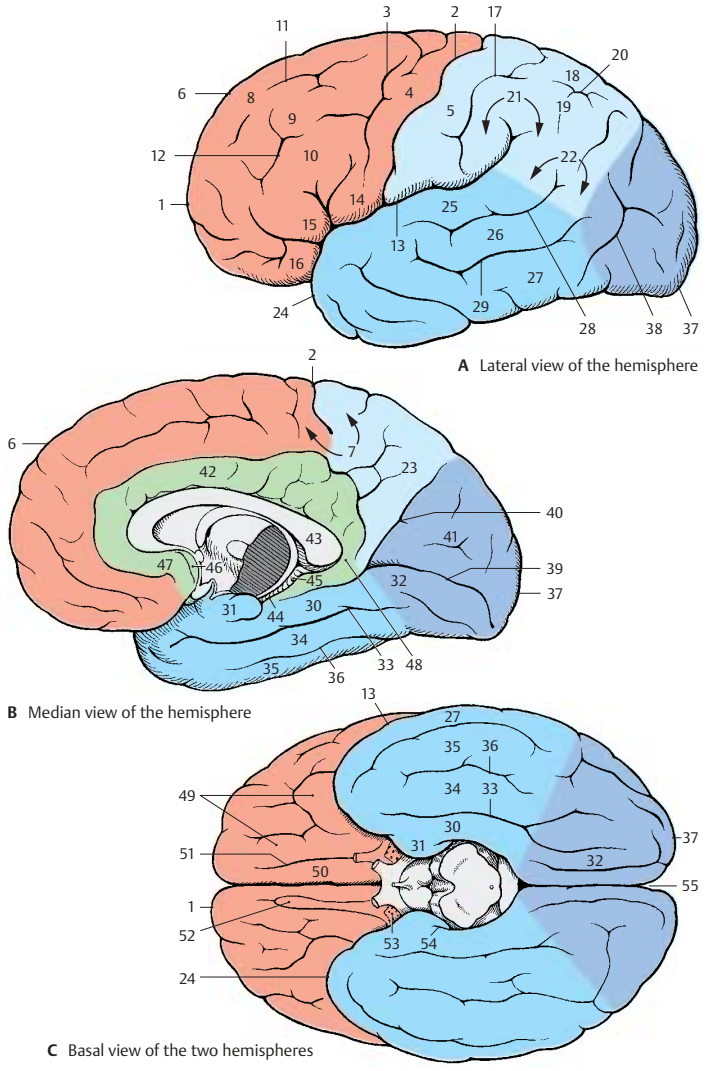
Cortical Structures

- Proceeding outward along the cortical surface from the primary projection areas, one encounters the **secondary projection areas** (motor, areas 6, 8, 44; sensory, areas 5, 7a, 40; visual, area 18; auditory, area 42), which subserve higher functions of coordination and information processing



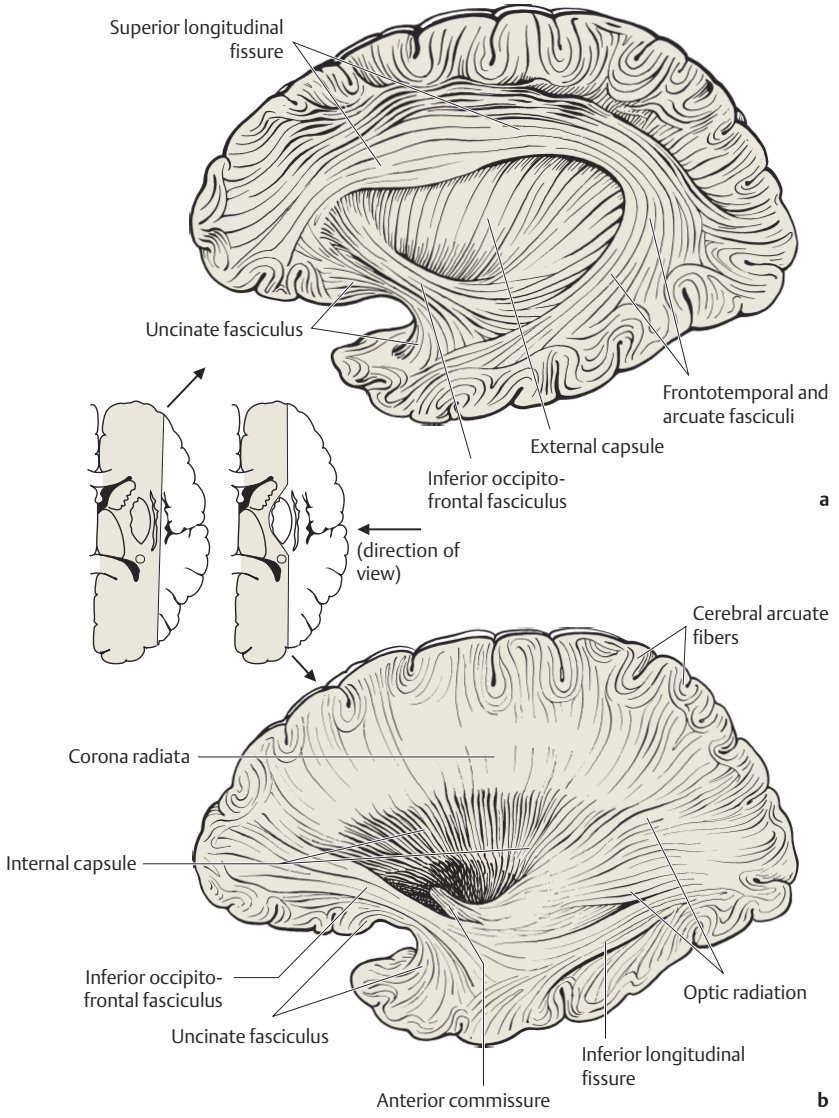
Cortical Structures

- **<u>The tertiary projection</u>** areas (motor, areas 9, 10, 11; sensory, areas 7b, 39; visual, areas 19, 20, 21; auditory, area 22), which are responsible for complex functions such as voluntary movement, spatial organization of sensory input, cognition, memory, language, and emotion.



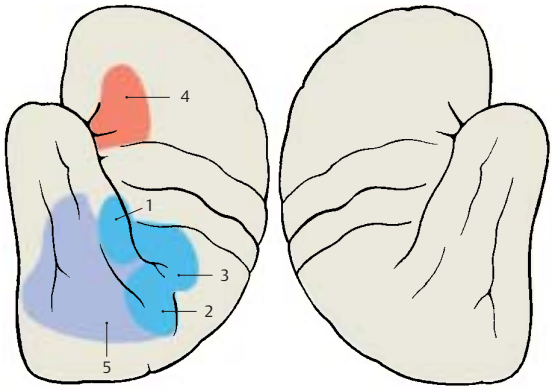
Cortical Structures

- The two hemispheres are connected by **commissural fibers**, which enable bihemispheric coordination of function. The most important commissural tract is **the corpus callosum**;

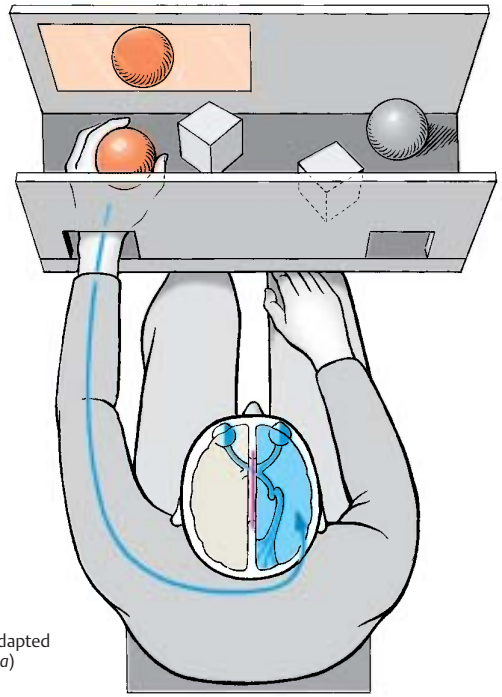


Cortical Structures

- Because many tasks are performed primarily by one of the two hemispheres (**cerebral dominance**), interruption of the corpus callosum can produce various **disconnection syndromes**.



A Areas for speech and writing in a right-handed person

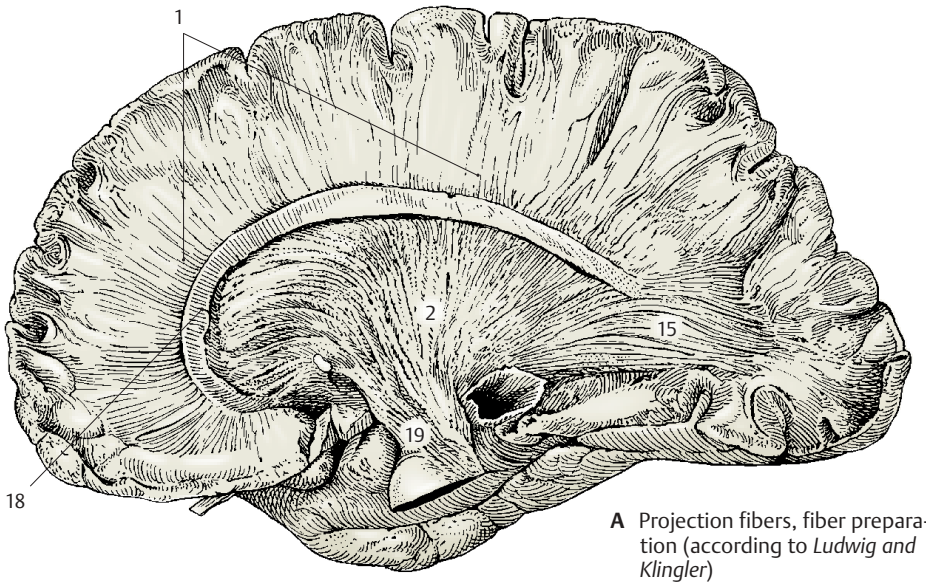


B Split brain experiment (adapted from *Sperry and Gazzaniga*)

Cortical Structures

- Total callosal transection causes **splitbrain syndrome**:

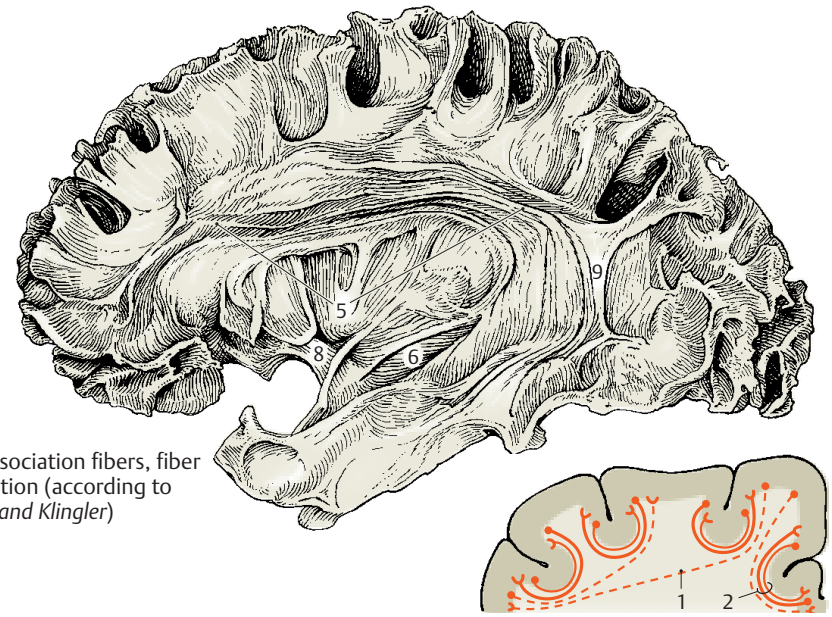
- left tactile anomia
- left optic anomia
- left hemialexia
- left hemiagraphia
- left hemiapraxia



A Projection fibers, fiber preparation (according to *Ludwig and Klingler*)

Cortical Structures

- Anterior callosal lesions cause ***alien hand syndrome*** (diagonistic apraxia), in which the patient cannot coordinate the movements of the two hands.



A Long association fibers, fiber preparation (according to *Ludwig and Klingler*)

Cortical Structures

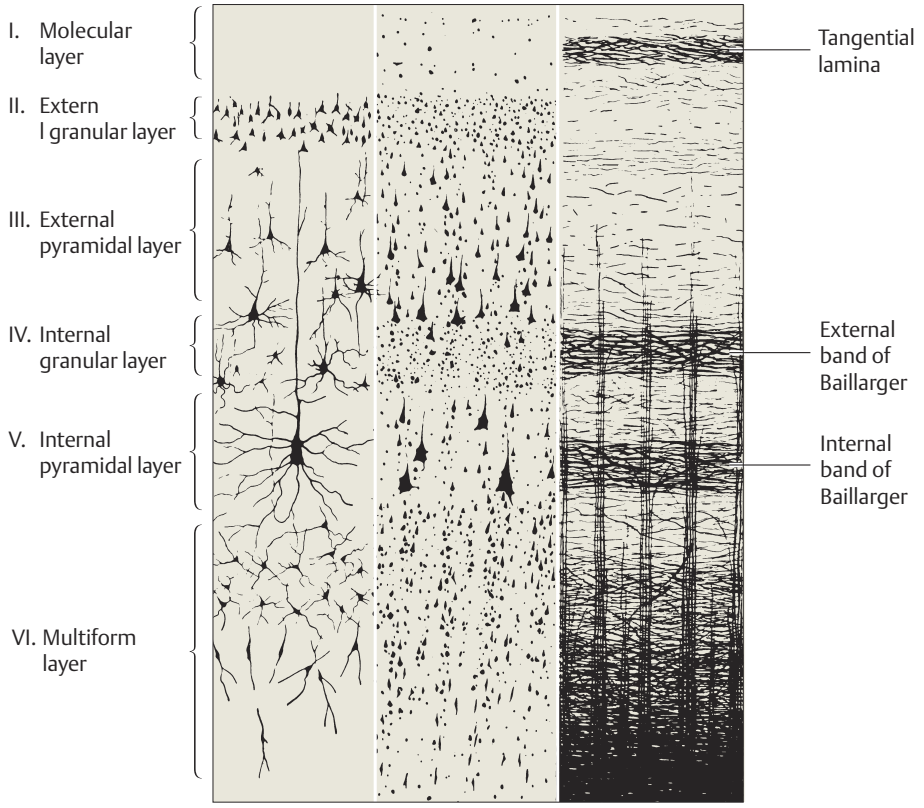


Fig. 9.**12 Cytoarchitecture of the human cerebral cortex** as revealed by three different staining techniques. (Diagram after Brodmann, from Rauber-Kopsch: Lehrbuch und Atlas der Anatomie des Menschen, 19th ed., vol. II, Thieme, Stuttgart, 1955.)

- **Cytoarchitecture.** Most of the cerebral cortex consists of isocortex, which has six distinct cytoarchitectural layers. The Brodmann classification of cortical areas is based on distinguishing histological features of adjacent areas of isocortex.

Cortical Structures

- **Functional areas.** The specific anatomic patterns of functional localization in the brain are the key to understanding much of clinical neurology.

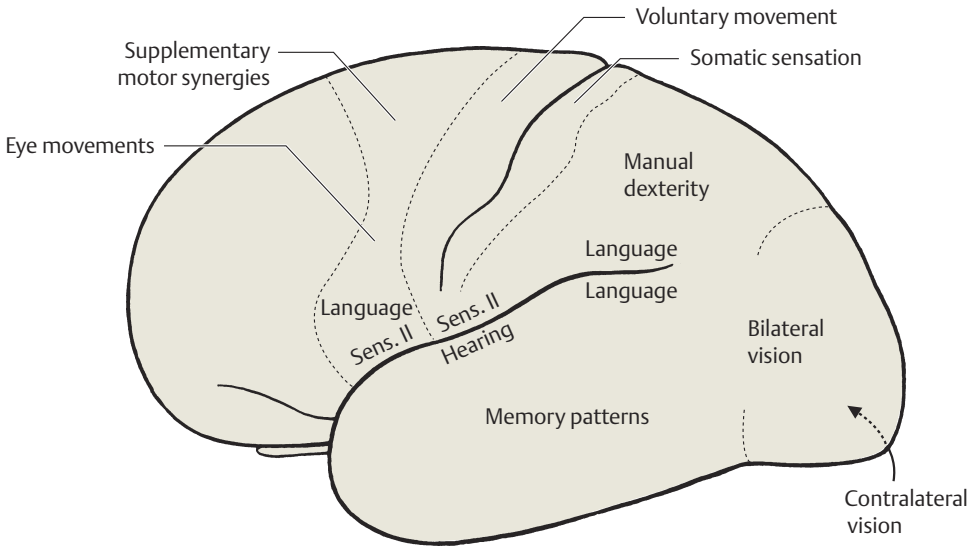
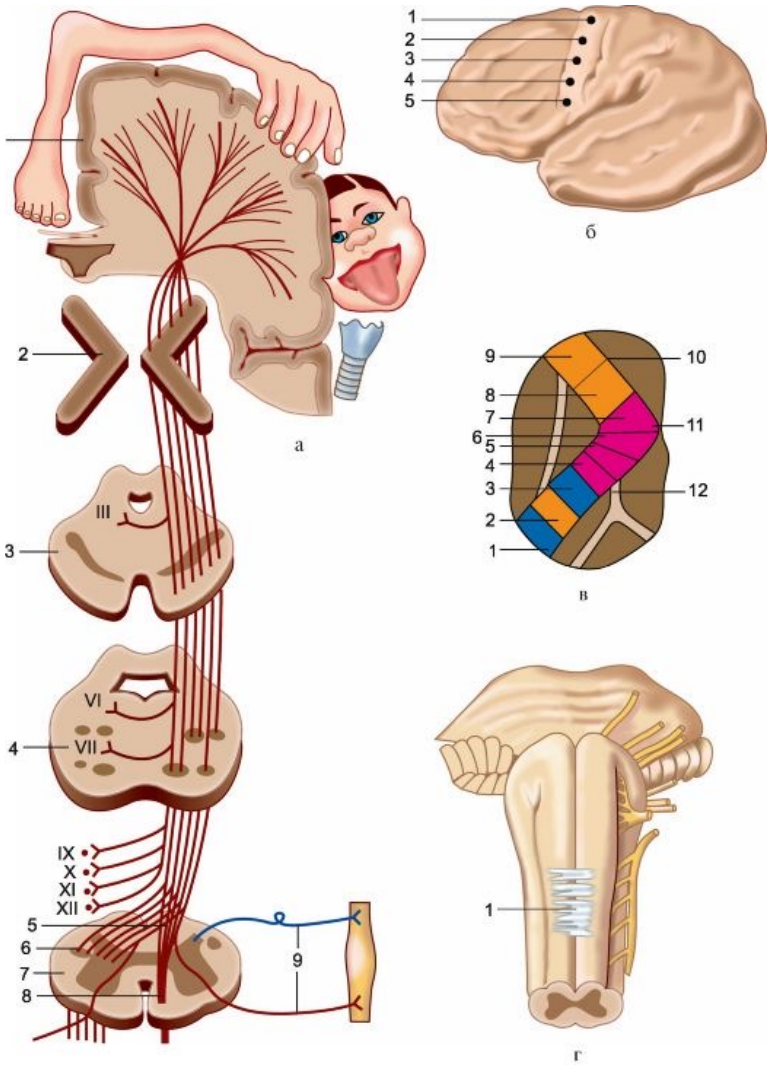


Fig. 9.**17 Functional areas of the cerebral cortex** as determined by electrical stimulation of the cortex during neurosurgical procedures. (From: Penfield W and Rasmussen T: The Cerebral Cortex of Man, Macmillan, New York, 1950.)

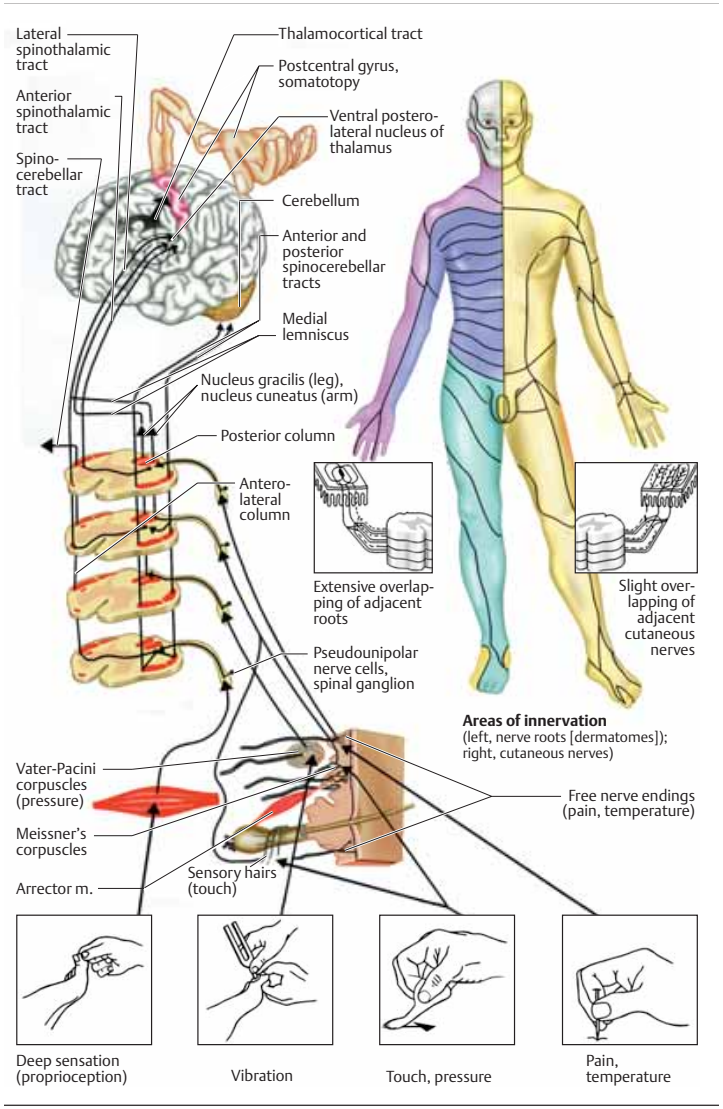
MOTOR CORTEX

- **Monoparesis.** Isolated lesions of the primary motor cortex (area 4) cause flaccid weakness of the contralateral face, hand, or leg. Lesions affecting adjacent precentral or postcentral areas, or areas deep to the cortex, cause spasticity and possibly an associated sensory deficit.



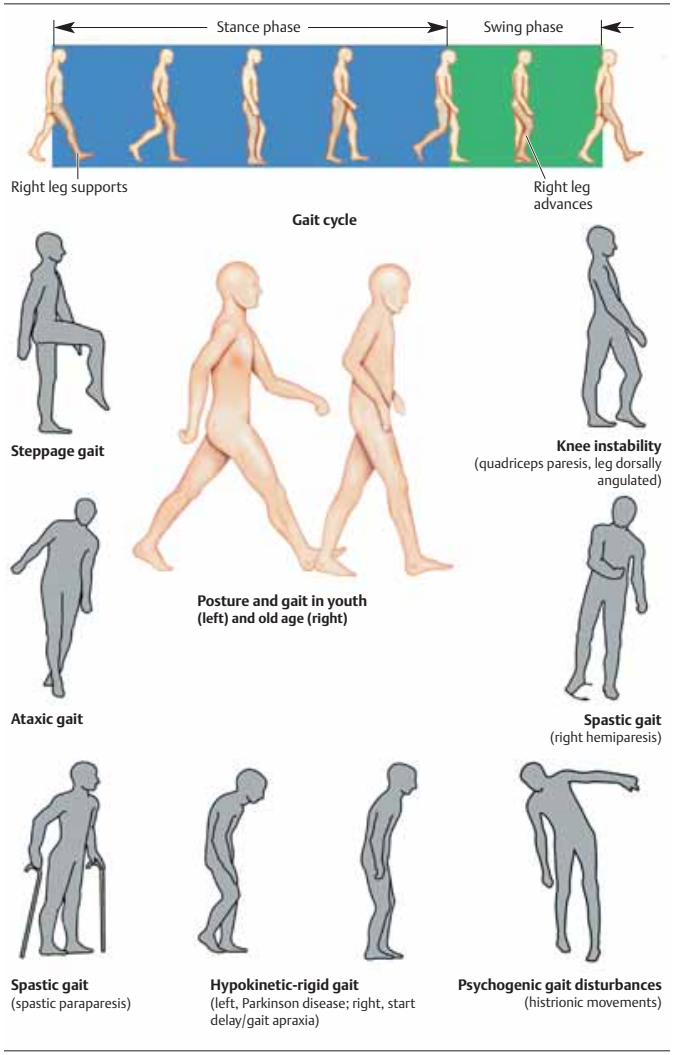
SENSORY CORTEX

- **Postcentral cortex.** Paresthesia, contralateral sensory deficits (astereognosis, loss of position sense and two-point discrimination, inability to localize a stimulus, agraphesthesia)



CORTICAL (CEREBRAL) GAIT DISTURBANCES

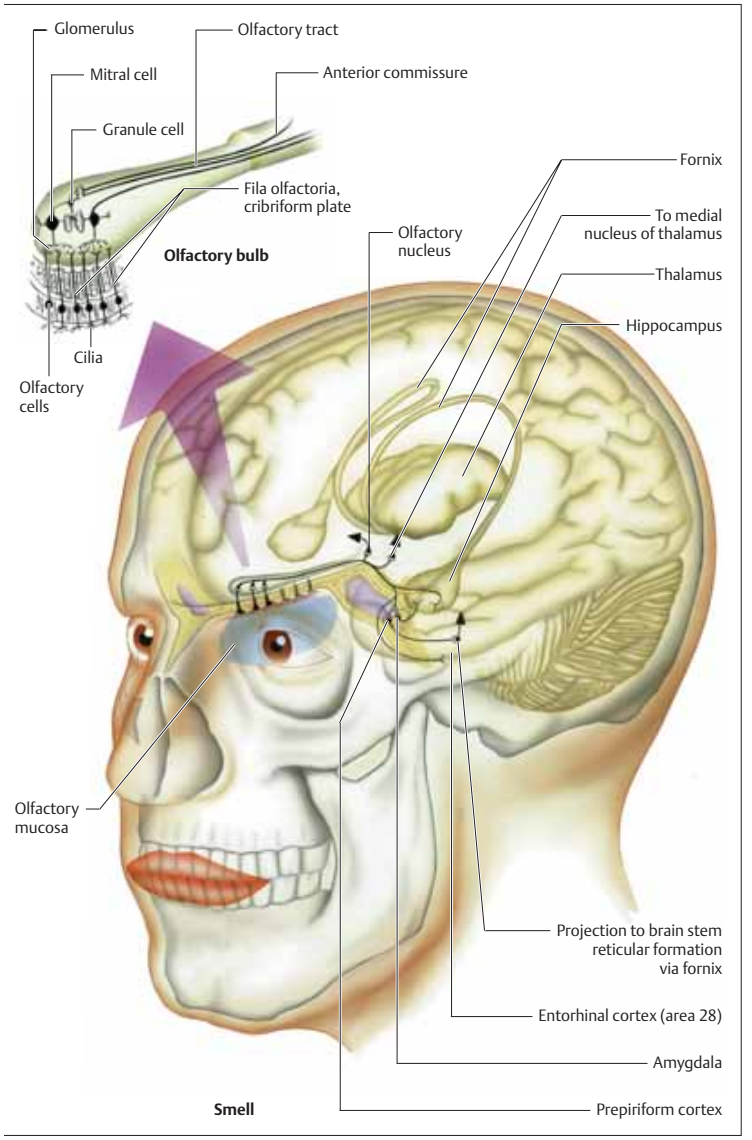
- **Spastic gait** (pyramidal tract)
- **Ataxia of gait** (postcentral cortex)
- **Dystonic gait** (basal ganglia)
- **Start delay** (frontal lobe, basal ganglia, extensive white matter lesions)



CORTICAL (CEREBRAL) OLFACTORY DISTURBANCES

odor recognition indicates that the cortical portion of the olfactory pathway is intact

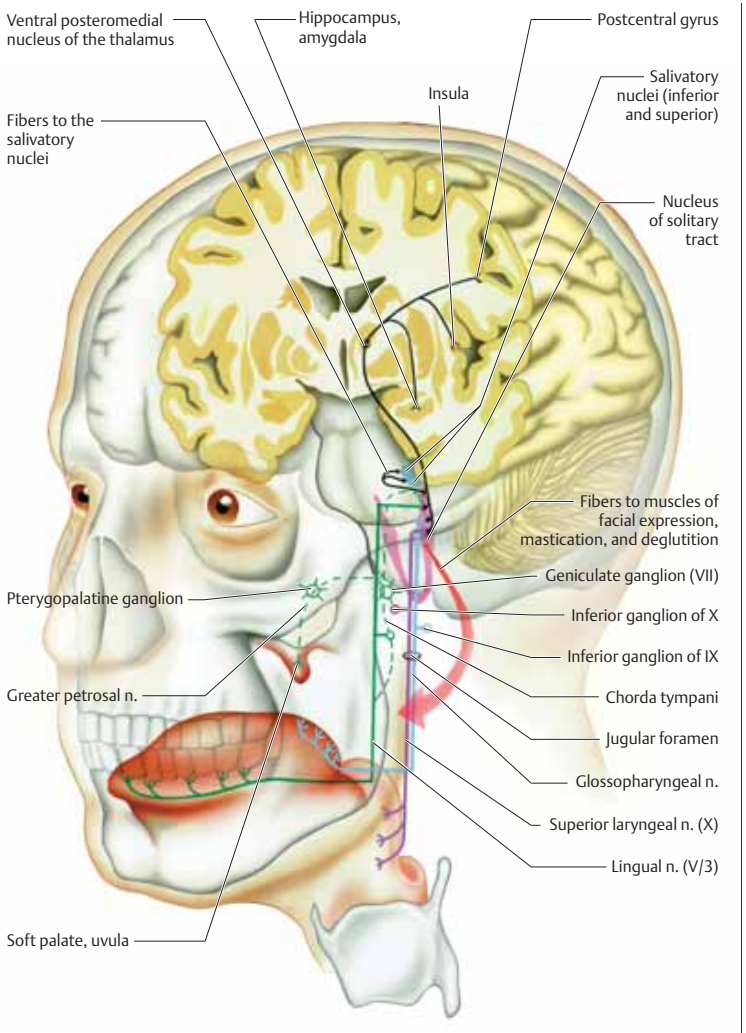
- **Quantitative** (anosmia, hyposmia, hyperosmia)
- **Qualitative** (parosmia, cacosmia)
- **“Olfactory blindness”** (congenital)
- **Olfactory hallucinations**



CORTICAL (CEREBRAL) GUSTATORY DISTURBANCES

the taste zones are not organized in a strict topographic pattern

- **Dysguesia**



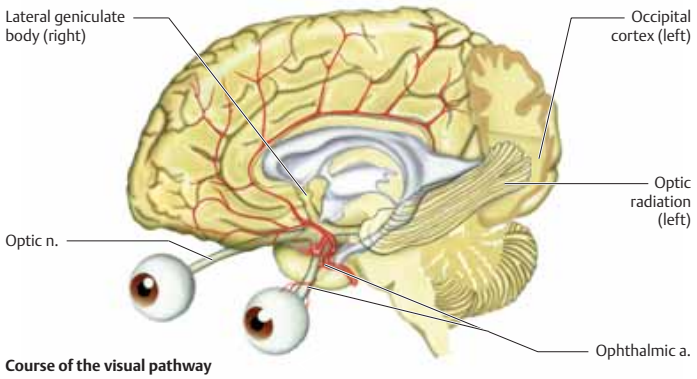
CORTICAL (CEREBRAL) VISUAL DISTURBANCES

- **Stereoscopic vision** (very important for depth perception).
- **Color vision.**

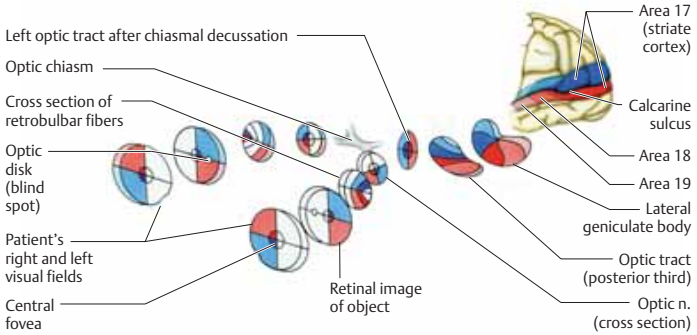
Lesions of area 18:
- color agnosia

Lesions of area 19:
- object agnosia
- prosopagnosia
- visuospatial agnosia

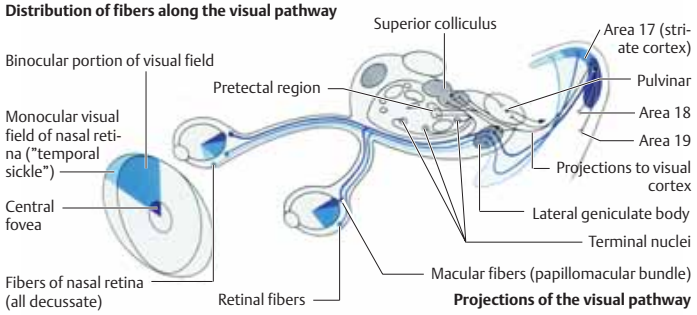
Connections with the limbic system (hippocampus, amygdala, parahippocampal gyrus) account for the ability of visual input to evoke an emotional response.



Course of the visual pathway



Distribution of fibers along the visual pathway



Projections of the visual pathway

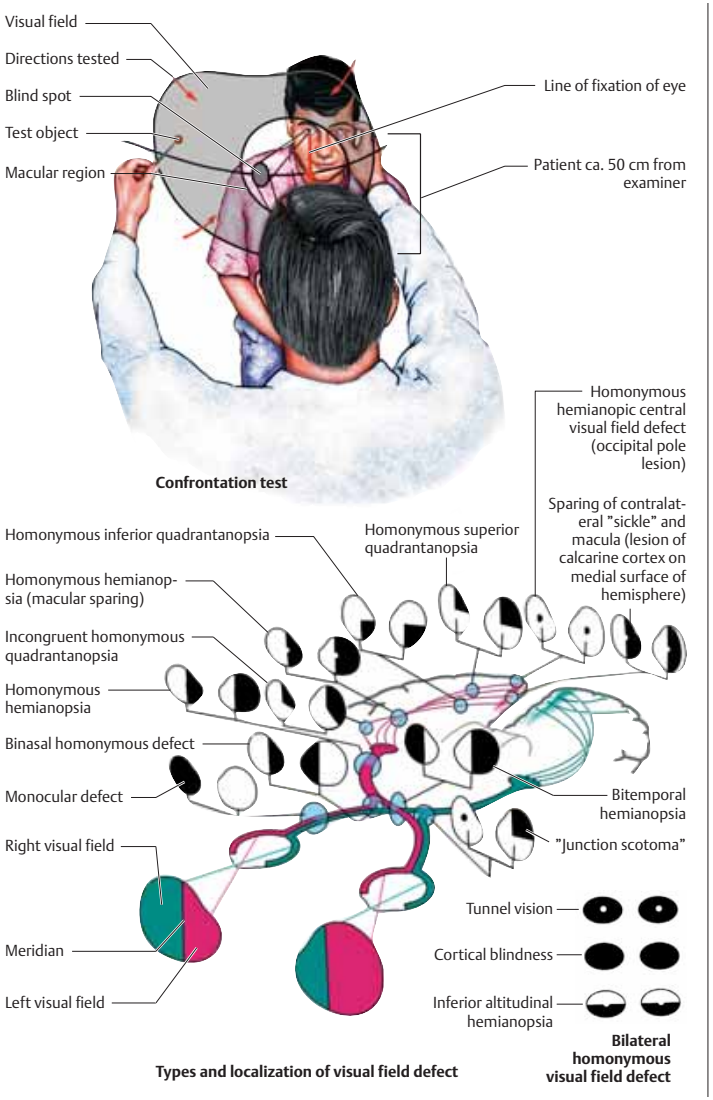
CORTICAL (CEREBRAL) VISUAL DISTURBANCES

- **Visual Field Defects:**

- **homonymous unilateral**
scotoma
***quadrantanopsia* or**
hemianopsia

Temporal lesions cause contralateral superior quadrantanopsia, while parietal lesions cause contralateral inferior quadrantanopsia.

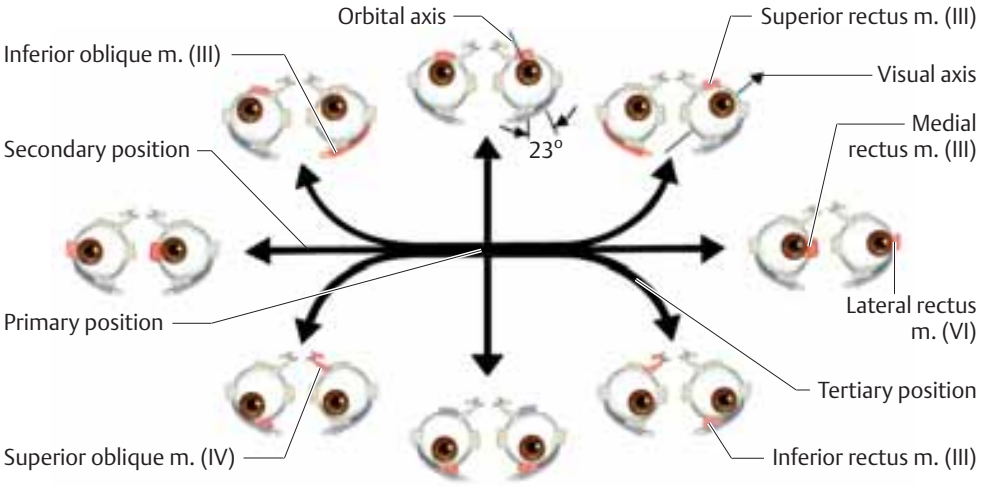
Cortical blindness refers to subnormal visual acuity due to bilateral retrogeniculate lesions.



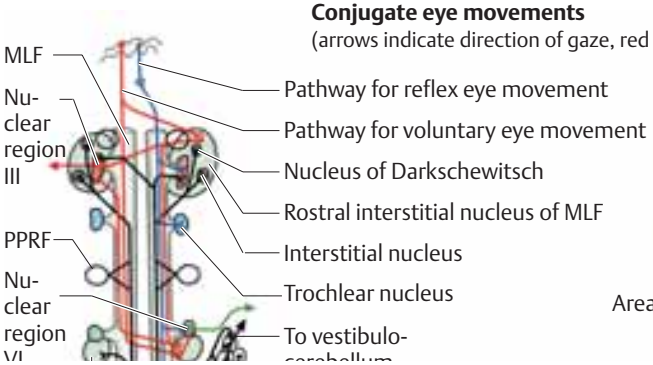
CORTICAL (CEREBRAL) OCULOMOTOR FUNCTION DISTURBANCES

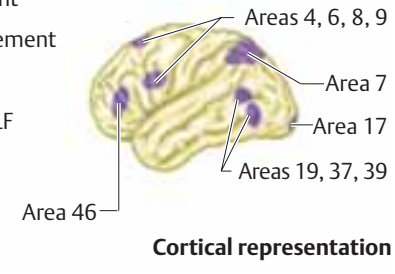
Voluntary eye movements are subserved by the frontal system, which consists of the frontal eye fields (areas 4, 6, 8, 9), the supplementary eye field (area 6), the dorsolateral prefrontal cortex (area 46), and portion of the parietal cortex (area 7).

- gaze palsy
- gaze deviation



Conjugate eye movements
(arrows indicate direction of gaze, red = active muscle)



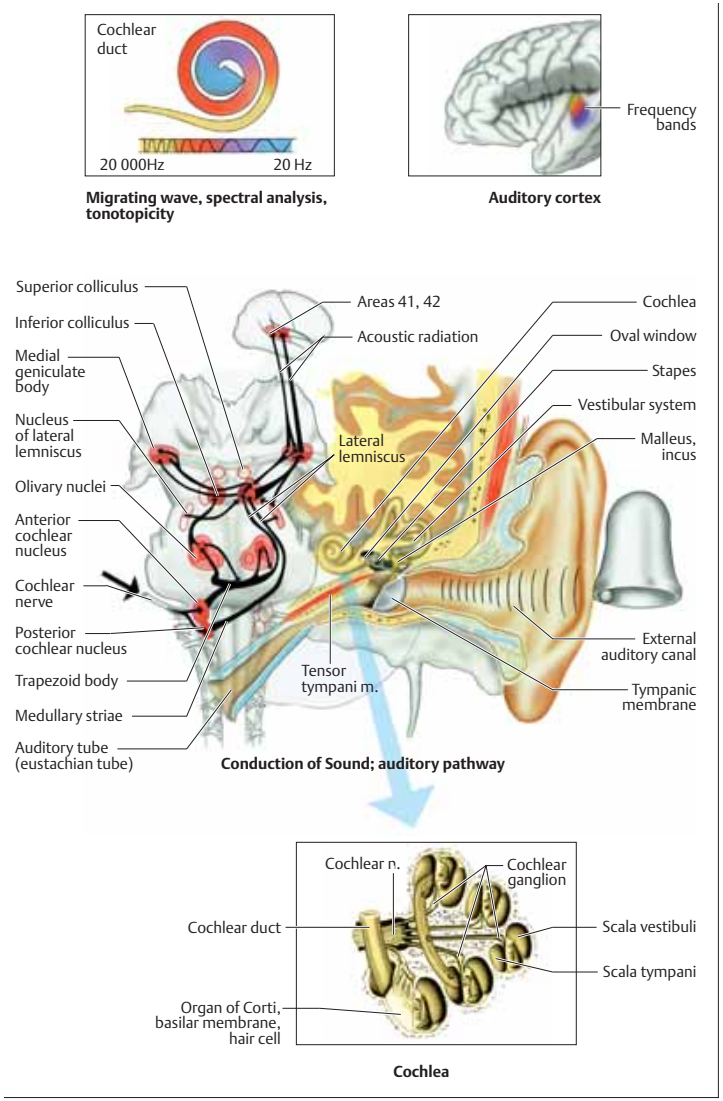


Cortical representation

CORTICAL (CEREBRAL) HEARING DISTURBANCES

The primary auditory cortex (area 41: Heschl's gyrus, transverse temporal gyri) is located in the temporal operculum (i.e., the portion of the temporal lobe overlying the insula and separated from it by the sylvian cistern). Areas 42 and 22 make up **the secondary auditory cortex**, in which auditory signals are further processed, recognized, and compared with auditory memories.

- **Hypoacuzia**
- **Auditory hallucinations**



Lateralized Frontal Lobe Lesions

Left frontal lobe lesions

- right hemiparesis or hemiplegia
- transcortical motor aphasia
- diminished verbal output
- buccofacial apraxia
- depression or anxiety

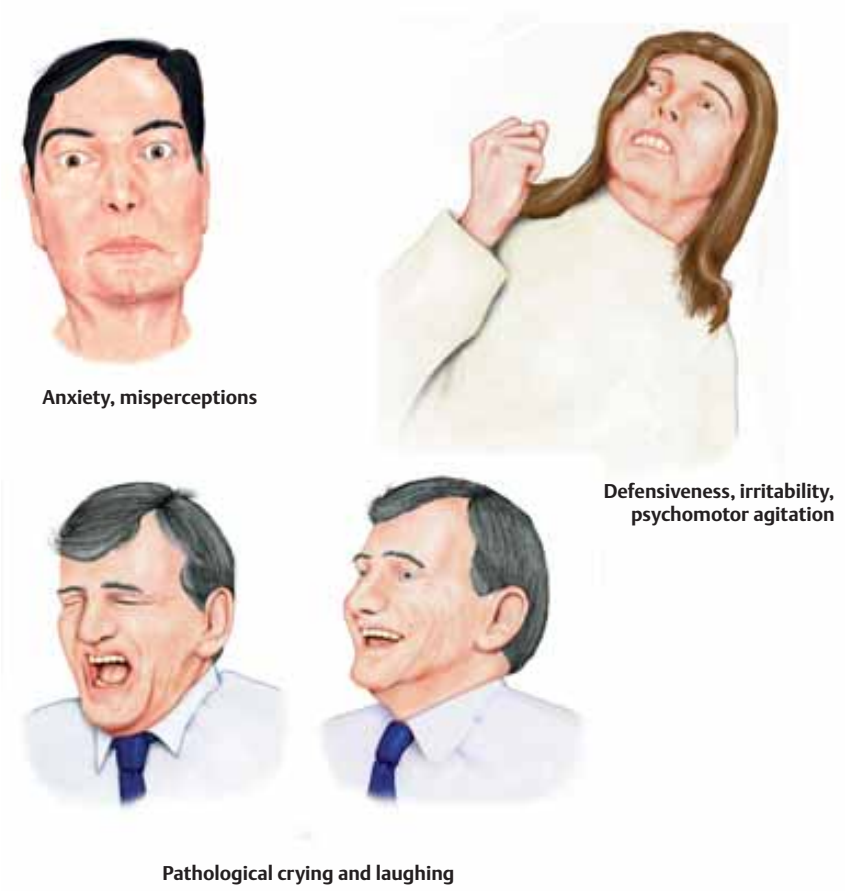
Right frontal lobe lesions

- left hemiparesis or hemiplegia
- left hemineglect
- mania
- increased psychomotor activity

Nonlateralized Frontal Lobe Syndromes

- Fronto-orbital lesions produce increased drive, memory impairment with confabulation, and disorientation.

- Disinhibition and impaired insight into one's own behavior may produce abnormal facetiousness (German Witzelsucht), abnormal social behavior (loss of distance, sexual impulsiveness), indifference, or carelessness.



Nonlateralized Frontal Lobe Syndromes

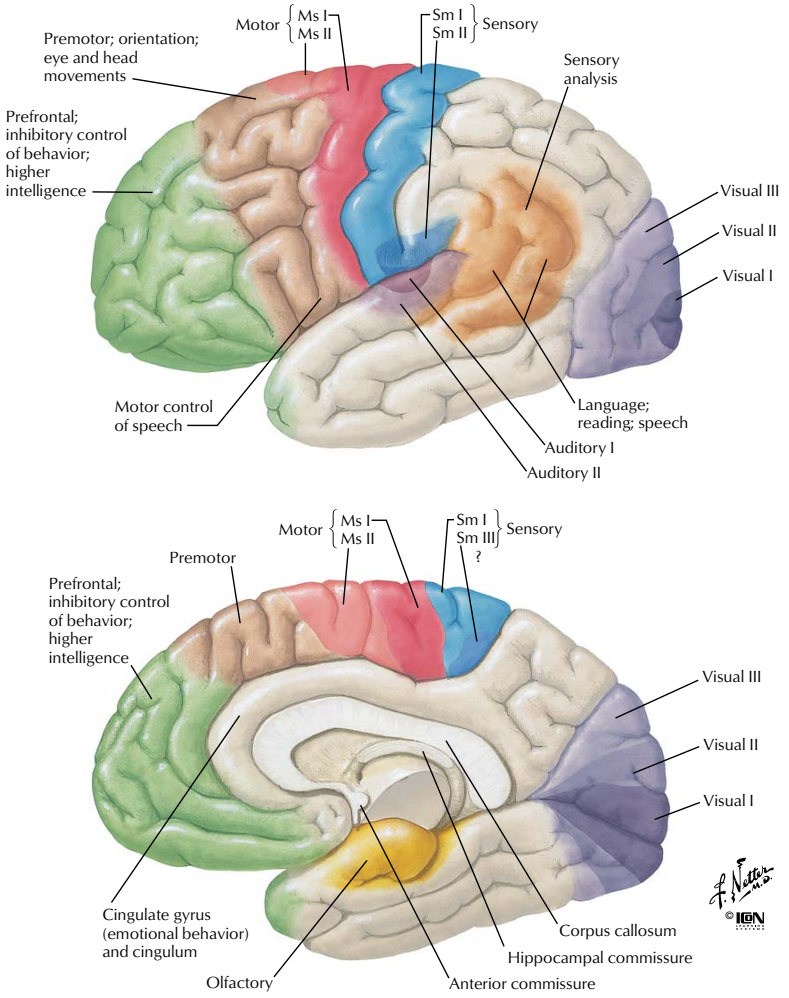
Lesions of the *cingulate gyrus* and premotor cortex produce syndromes ranging from abulia (loss of drive) to akinetic mutism and generally characterized by apathy, loss of interest, inertia, loss of initiative, decreased sexual activity, loss of emotion, and loss of planning ability.

Abulia

Concentration and attention deficits

Nonlateralized Frontal Lobe Syndromes

Urinary and fecal incontinence occur because of the loss of (cortical) perception of the urge to urinate and defecate. Altered voiding frequency or sudden voiding is the result.



Nonlateralized Frontal Lobe Syndromes

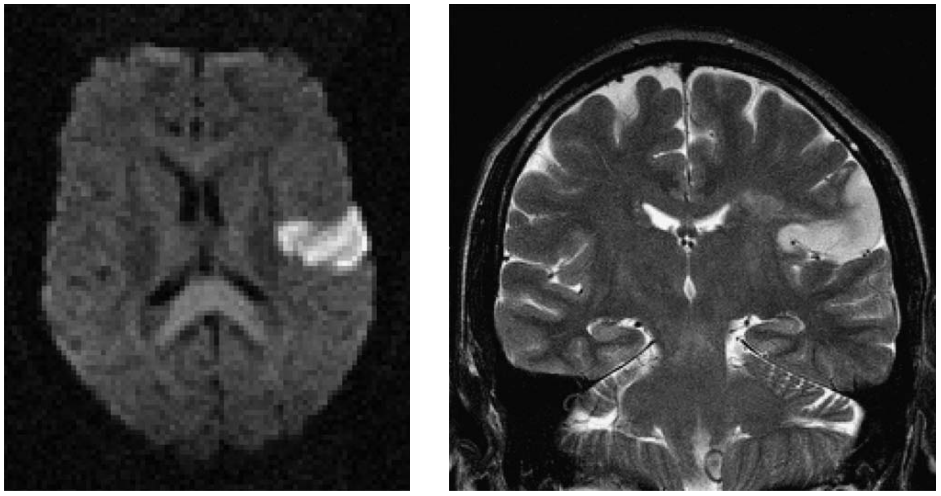
These patients are usually impaired in their capacity for divided attention (the processing of new information and adaptation to altered requirements, i.e., flexibility) and for directed attention (selective attention to a particular thing or task).

Their attention span is short, they are easily distracted, they have difficulty in the execution of motor sequences, and they tend to perseverate (to persist in a particular activity or thought).

LANGUAGE

Language is a means of transmitting and processing information, organizing sensory perceptions, and expressing thoughts, feelings, and intentions.

The content of language encompasses the past, present, and future.



a **b**

Fig. 9.**27 Cerebral infarct in Broca's area due to dissection of the left internal carotid artery** (MRI).

(a, b) a The axial diffusion-weighted image reveals the infarcted brain tissue, which appears brighter than the surrounding normal tissue. It lies in the central portion of the territory of the middle cerebral artery, mainly in the inferior frontal gyrus (Broca's area, area 44). This area is supplied by the prerolandic artery. **b** The coronal T2-weighted image reveals hyperintense signal, corresponding to infarction, in Broca's area. The infarct focally involves this portion of the inferior frontal gyrus on the upper bank of the sylvian fissure.

LANGUAGE

Linguistic messages are transmitted and received through speaking and hearing, writing and reading, or (in the case of sign language) the production and interpretation of gestures.

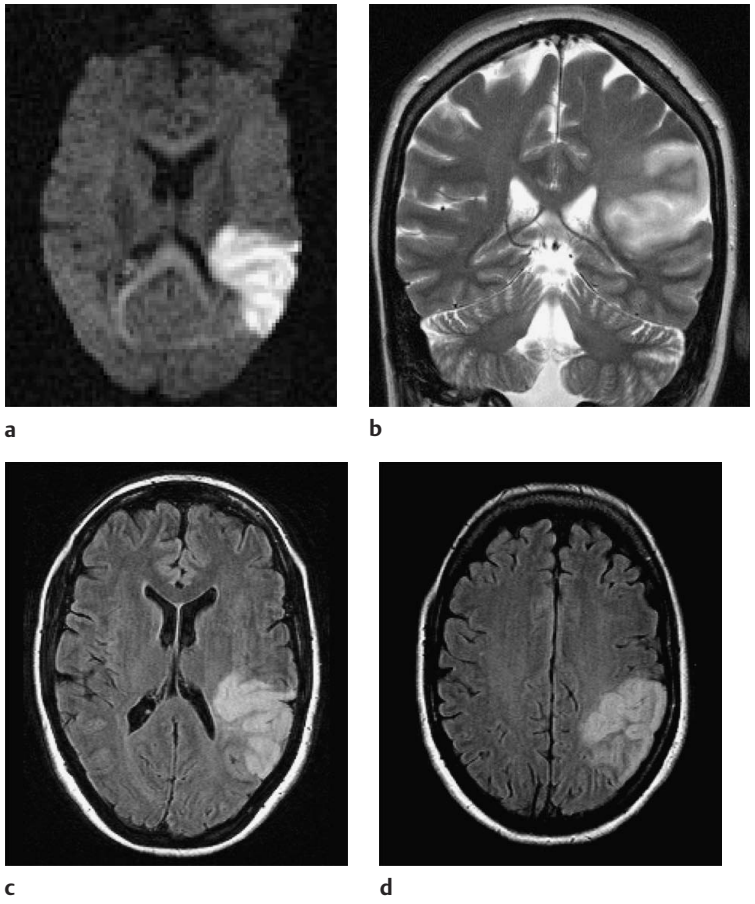
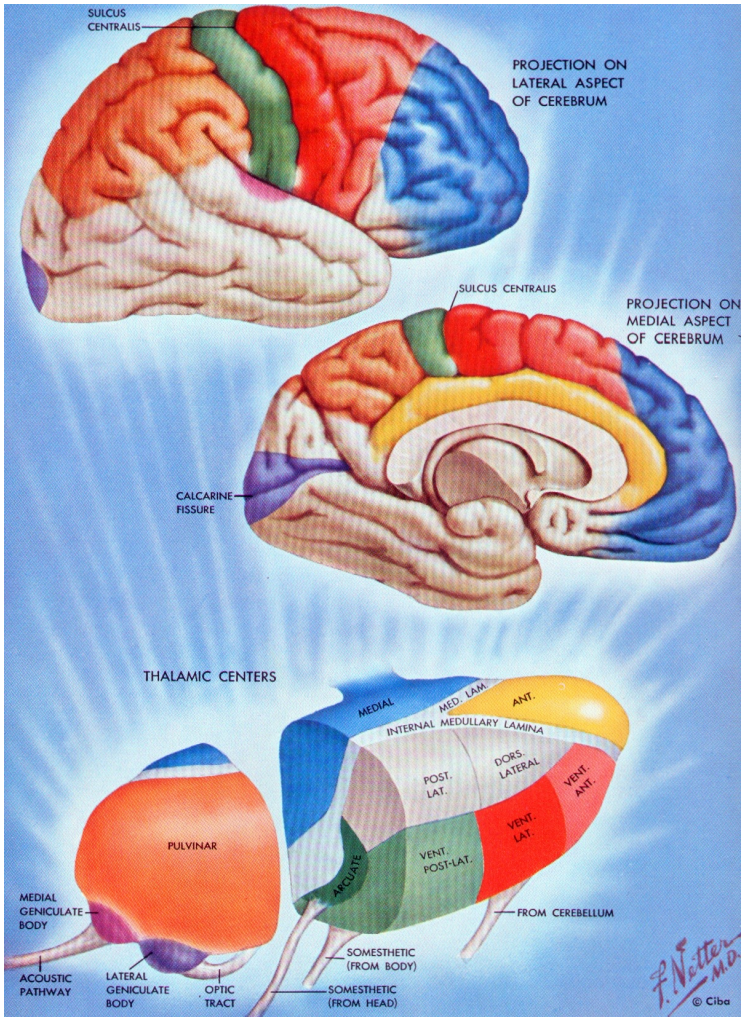


Fig. 9.**28 Infarct in Wernicke's area** (MRI).
(a, b) a The axial diffusion-weighted image reveals the infarct as a zone of hyperintensity in the posterior (i.e., parieto-occipital) portion of the territory of the middle cerebral artery, mainly involving the angular and supramarginal gyri. This area is supplied by the angular and posterior parietal arteries. **b** The coronal T2-weighted image reveals the infarct as a zone of hyperintensity above the sylvian fissure. The focal involvement of Wernicke's area is evident.
(c, d) Axial T2-weighted FLAIR sequences. The infarct, which is hyperintense in these images as well, is mainly in the cortex rather than the underlying white matter. It lies mainly in the parietal lobe, involving the parietal operculum and the angular and supramarginal gyri. The apical portion of the infarct likewise lies mainly in the parietal, postcentral region, but one can see that it also involves a small portion of the precentral gyrus, accounting for the patient's hemiparesis. **c** shows the infarct extending to the wall of the lateral ventricle; it thus presumably involves the optic radiation. This would be expected to cause a right visual field defect.

LANGUAGE

The cerebral language areas are located in the left hemisphere in over 90% of right-handers and in 60% of left-handers; the remaining individuals have bihemispheric or (in 1–2 %) exclusively right-hemispheric dominance for language.



LANGUAGE

The left (dominant) hemisphere is responsible for the cognitive processing of language, while the right (nondominant) hemisphere produces and recognizes the emotional components of language (*prosody* = emphasis, rhythm, melody).

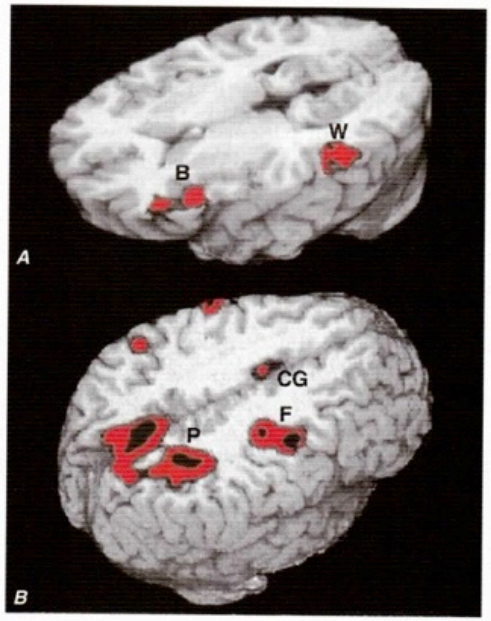
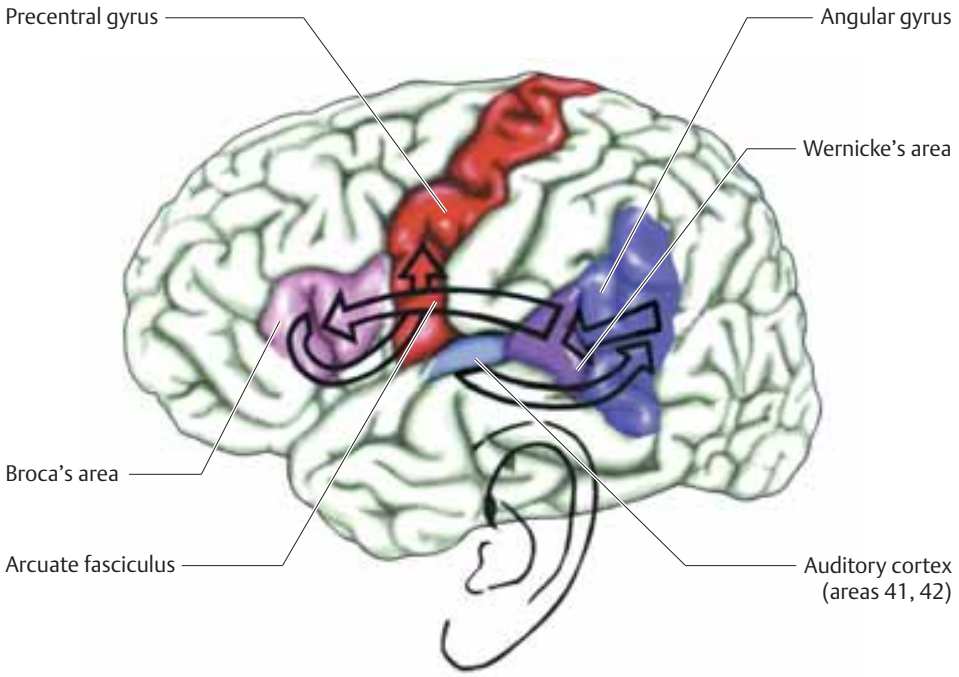


FIGURE 15-2

Functional magnetic resonance imaging of language and spatial attention in neurologically intact subjects. The dark areas show regions of task-related significant activation. (***A***) The subjects were asked to determine if two words were synonymous. This language task led to the simultaneous activation of the two epicenters of the language network, Broca's area (B) and Wernicke's area (W). The activations are exclusively in the left hemisphere. (***B***) The subjects were asked to shift spatial attention to a peripheral target. This task led to the simultaneous activation of the three epicenters of the attentional network, the posterior parietal cortex (P), the frontal eye fields (F), and the cingulate gyrus (CG). The activations are predominantly in the right hemisphere. (*Courtesy of Darren Gitelman, MD; with permission.*)

LANGUAGE

Hearing and speaking. From primary and secondary auditory, the information is sent to Wernicke's area (the "posterior language area"), consisting of Wernicke's area proper, in the superior temporal gyrus (Brodmann area 22), as well as the angular and supramarginal gyri (areas 39, 40).



Hearing spoken language

LANGUAGE

The angular gyrus processes auditory, visual, and tactile information, while Wernicke's area proper is the center for the understanding of language. It is from here that the arcuate fasciculus arises, the fiber tract that conveys linguistic information onward to Broca's area (areas 44 and 45; the "anterior language area").

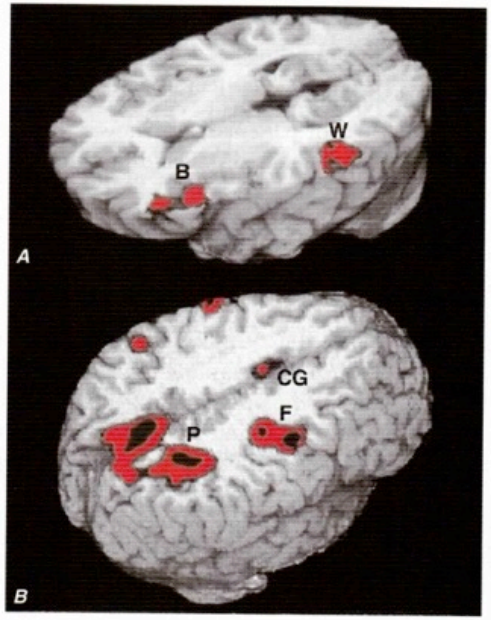
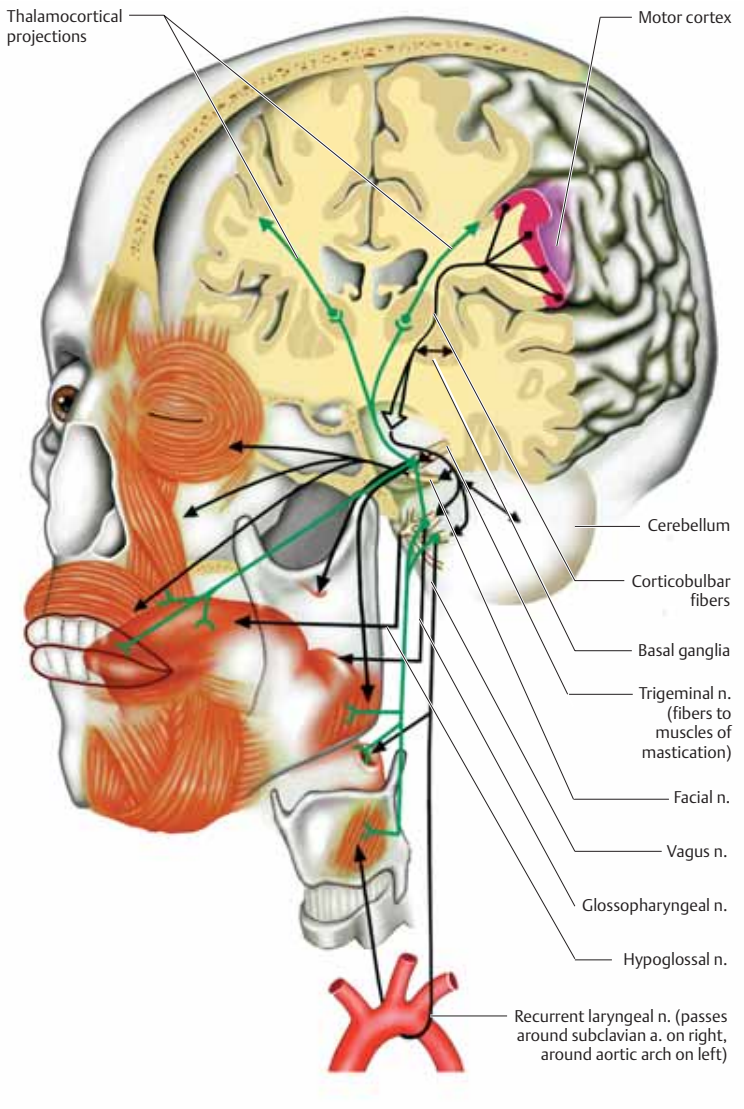


FIGURE 15-2
Functional magnetic resonance imaging of language and spatial attention in neurologically intact subjects. The dark areas show regions of task-related significant activation. (***A***) The subjects were asked to determine if two words were synonymous. This language task led to the simultaneous activation of the two epicenters of the language network, Broca's area (B) and Wernicke's area (W). The activations are exclusively in the left hemisphere. (***B***) The subjects were asked to shift spatial attention to a peripheral target. This task led to the simultaneous activation of the three epicenters of the attentional network, the posterior parietal cortex (P), the frontal eye fields (F), and the cingulate gyrus (CG). The activations are predominantly in the right hemisphere. (*Courtesy of Darren Gitelman, MD; with permission.*)

LANGUAGE

Grammatical structures and articulation programs are represented in Broca's area, which sends its output to the motor cortex.

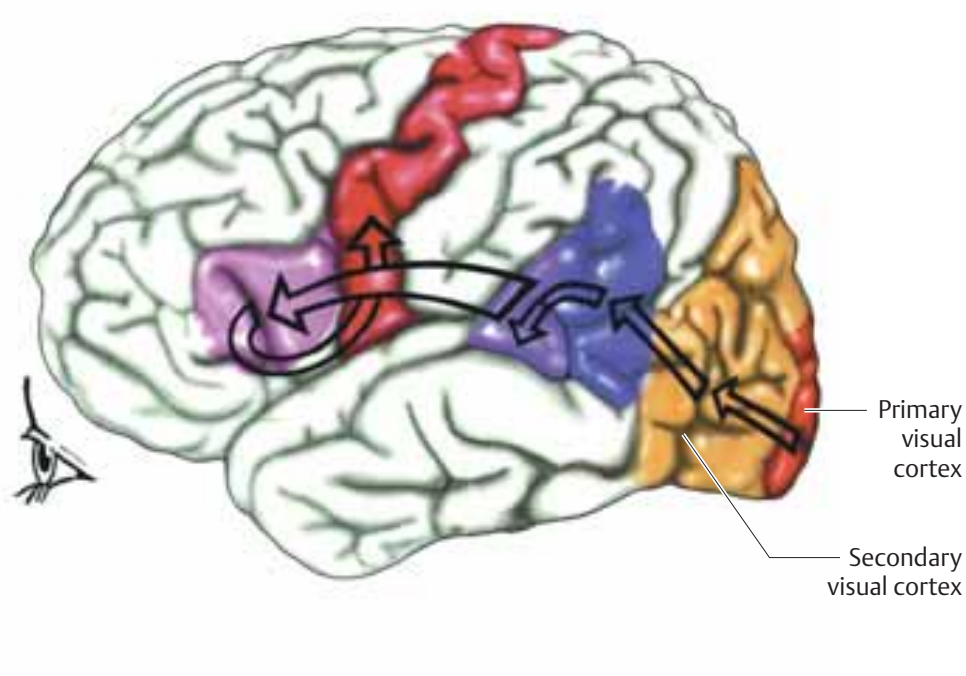
Spoken language is regulated by an auditory feedback circuit in which the utterer hears his or her own words and the cortical language areas modulate the speech output accordingly.



Neural control of speech (afferent fibers are green)

LANGUAGE

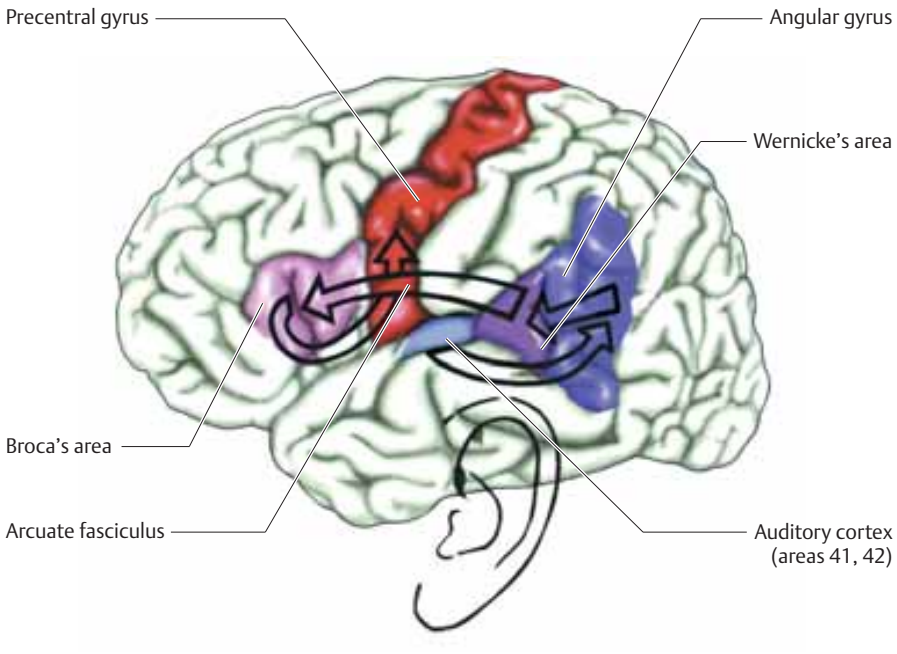
Reading and writing. The visual pathway conveys visual information to the primary and secondary visual cortex, which, in turn, project to the angular gyrus and Wernicke's area, in which visually acquired words are understood, perhaps after a prior "conversion" to phonetic form.



Reading written language

LANGUAGE

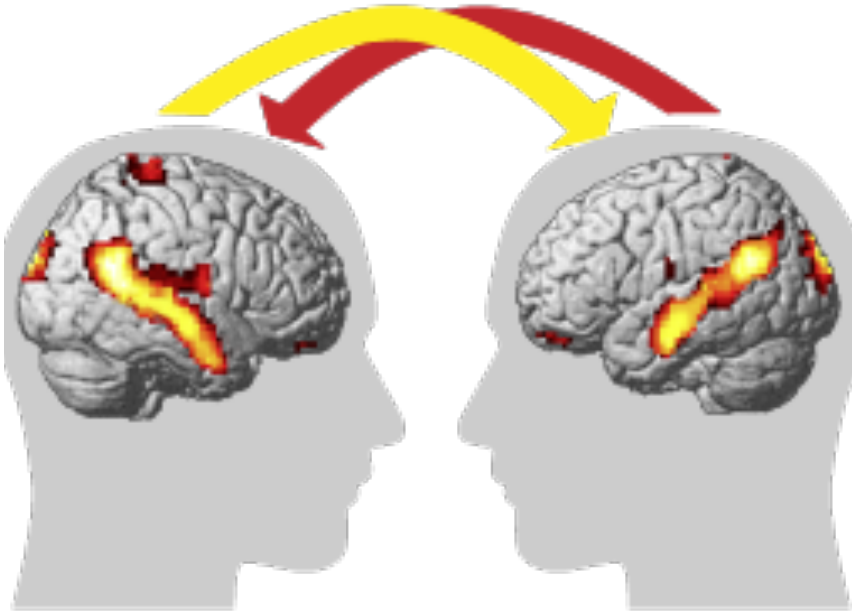
Wernicke's area then projects via the arcuate fasciculus to Broca's area, as discussed above; Broca's area sends its output to the motor cortex (for speech or, perhaps, to the motor hand area for writing). This pathway enables the recognition and comprehension of written language, as well as reading out loud.



Hearing spoken language

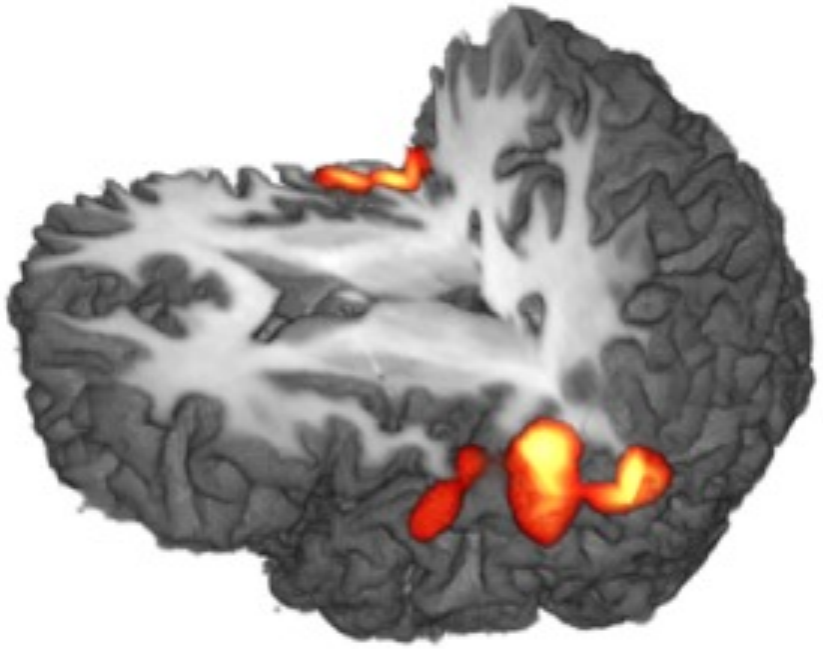
LANGUAGE

Examination. The clinical examination of language includes spontaneous speech, naming of objects, speech comprehension, speech repetition, reading, and writing. The detailed assessment of aphasia requires the use of test instruments such as the Aachen aphasia test, perhaps in collaboration with neuropsychologists and speech therapists.



LANGUAGE

Disturbances of speech may be classified as fluent or non-fluent. Examples of the former are paragrammatism (faulty sentence structure), meaningless phrases, circumlocution, semantic paraphasia (contextual substitution, e. g., “leg” for “arm”), phonemic paraphasia (substitution of one letter for another, e. g., “tan” for “can”), neologisms (nonexistent words), and fluent gibberish (jargon).



LANGUAGE

Agrammatism - word chains without grammatical structure,

Echolalia - repetition of heard words,

Automatism – repeating the same word many times.

Prosody and **dysarthria** (if present) are evaluated during spontaneous speech.

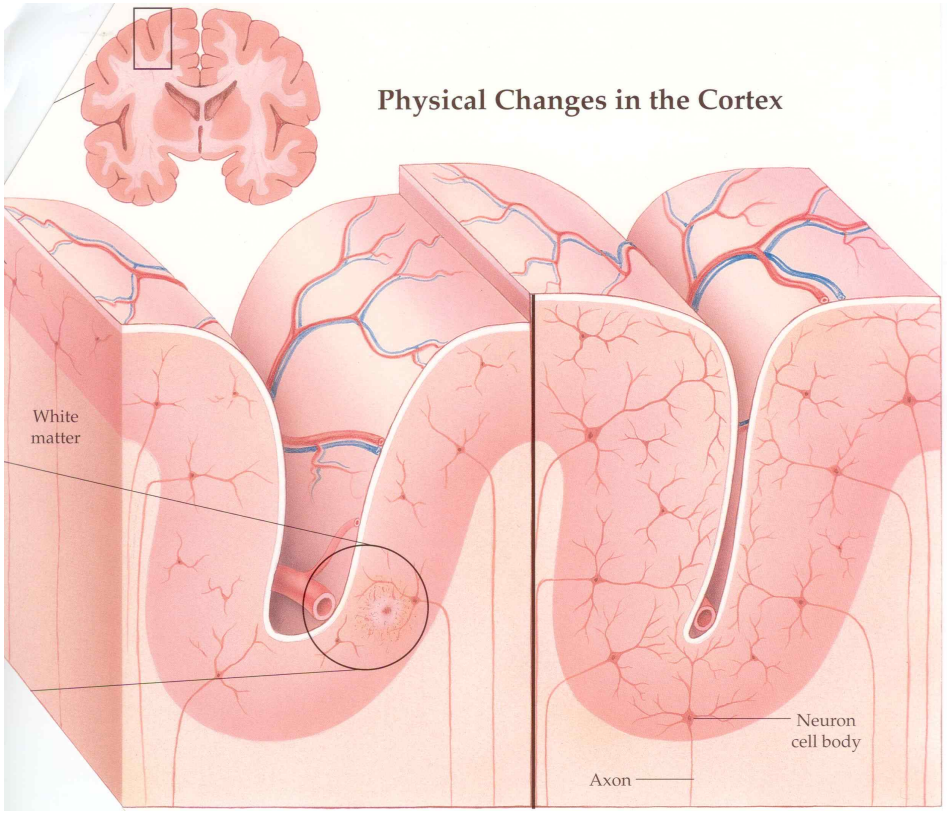
Anomia - inability to name objects.

Aphemia – patients can read, write, and understand spoken language but cannot speak.

APHASIA

Aphasia is an acquired disturbance of language. Focal lesions do not cause total loss of all language functions simultaneously.

Aphasia is most commonly due to stroke or head trauma and may be accompanied by apraxia.



GLOBAL APHASIA

Involves all aspects of language and severely impairs spoken communication.

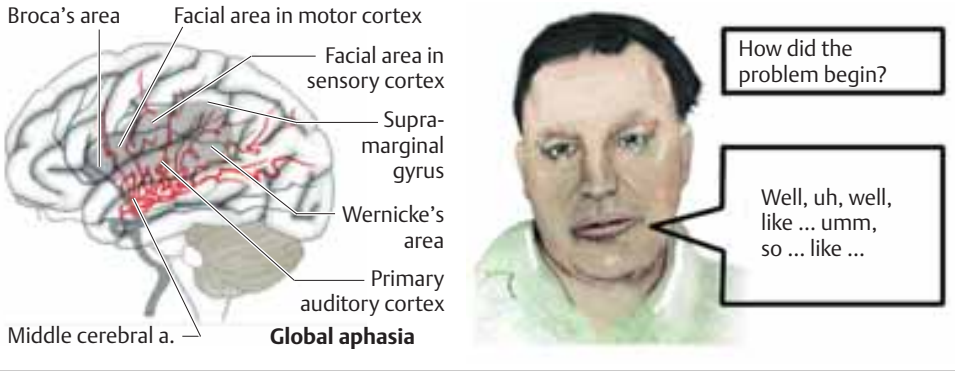
Speech comprehension is usually absent.

Perseveration (persistent repetition of a single word/subject) and neologisms are prominent.

The ability to repeat heard words is markedly impaired.

Language automatism (repetition of gibberish) is a characteristic feature.

Site of lesion: Entire distribution of the middle cerebral artery, including both Broca's and Wernicke's areas.



BROCA'S APHASIA

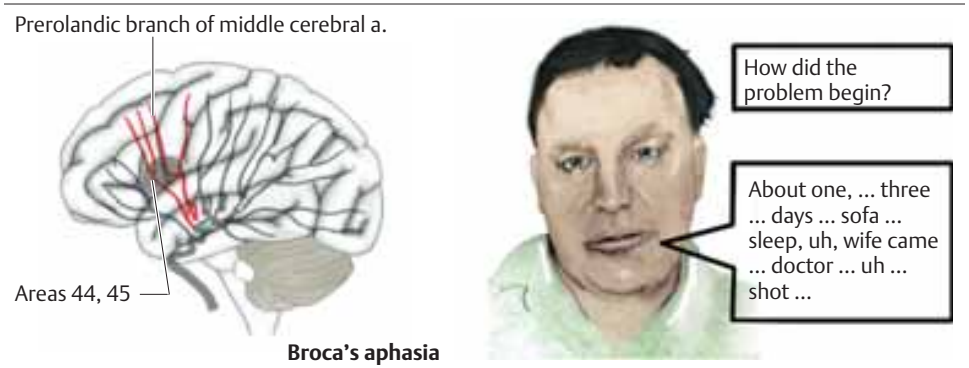
Also called anterior, motor, or expressive aphasia - the absence or severe impairment of spontaneous speech, while comprehension is only mildly impaired.

The patient can speak only with great effort, producing only faltering, nonfluent, garbled words.

Phonemic paraphasic errors, agrammatism, "telegraphic" speech).

Naming, repetition, reading out loud, and writing are also impaired.

Site of lesion: Broca area.



Broca's aphasia

WERNICKE'S APHASIA

Also called posterior, sensory, or receptive aphasia is characterized by severe impairment of comprehension.

Spontaneous speech remains fluent and normally paced, but paragrammatism, paraphasia, and neologisms make the patient's speech partially or totally incomprehensible (word salad, jargon aphasia).

Naming, repetition of heard words, reading, and writing are also markedly impaired.

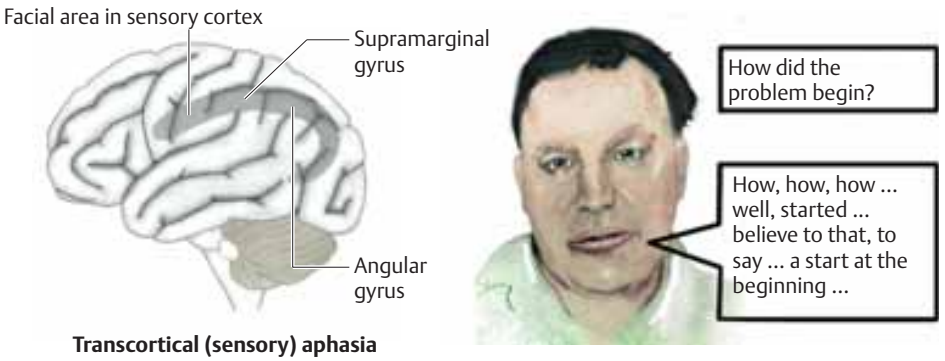
Site of lesion: Wernicke's area (area 22). May be due to infarction in the distribution of the posterior temporal artery.

Wernicke's aphasia (phonemic paraphasias)

TRANSCORTICAL APHASIA

Heard words can be repeated, but other linguistic functions are impaired: spontaneous speech in transcortical motor aphasia (syndrome similar to Broca's aphasia), language comprehension in transcortical sensory aphasia (syndrome similar to Wernicke's aphasia).

Site of lesion: Motor type, left frontal lobe bordering on Broca's area; sensory type, left temporo-occipital junction dorsal to Wernicke's area. Watershed infarction is the most common cause.



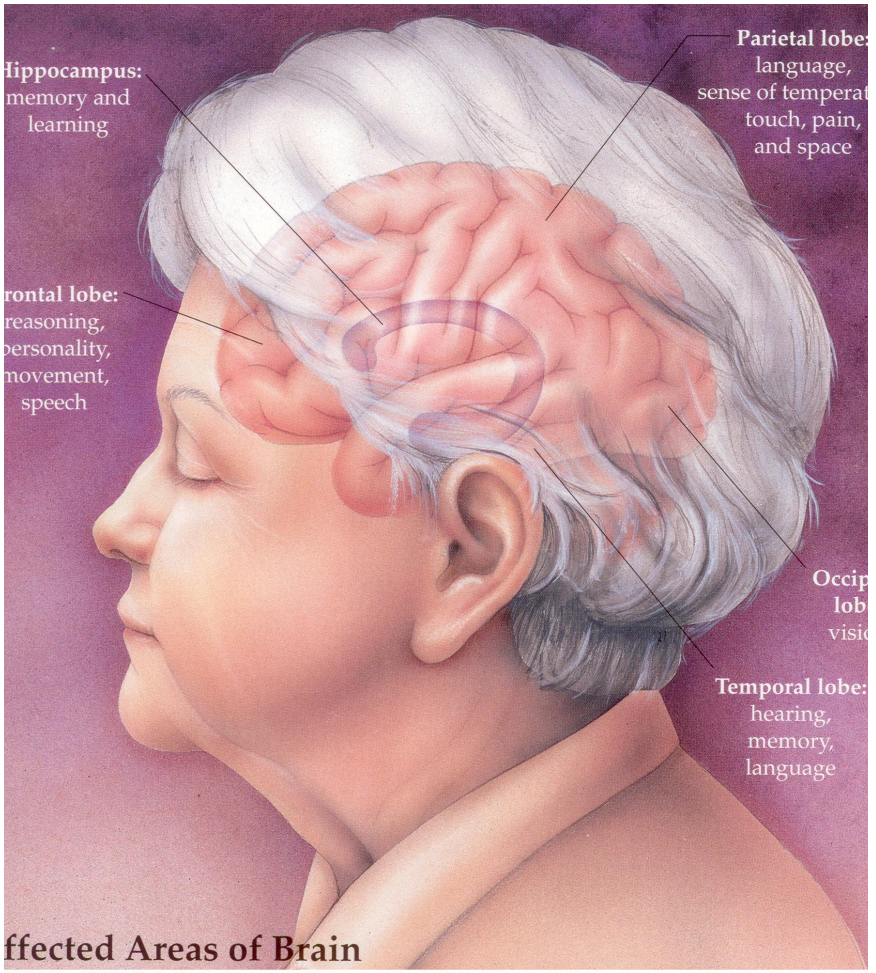
Transcortical (sensory) aphasia

AMNESTIC (ANOMIC) APHASIA

This type of aphasia is characterized by impaired naming and word-finding. Spontaneous speech is fluent but permeated with word-finding difficulty and paraphrasing.

The ability to repeat, comprehend, and write words is essentially normal.

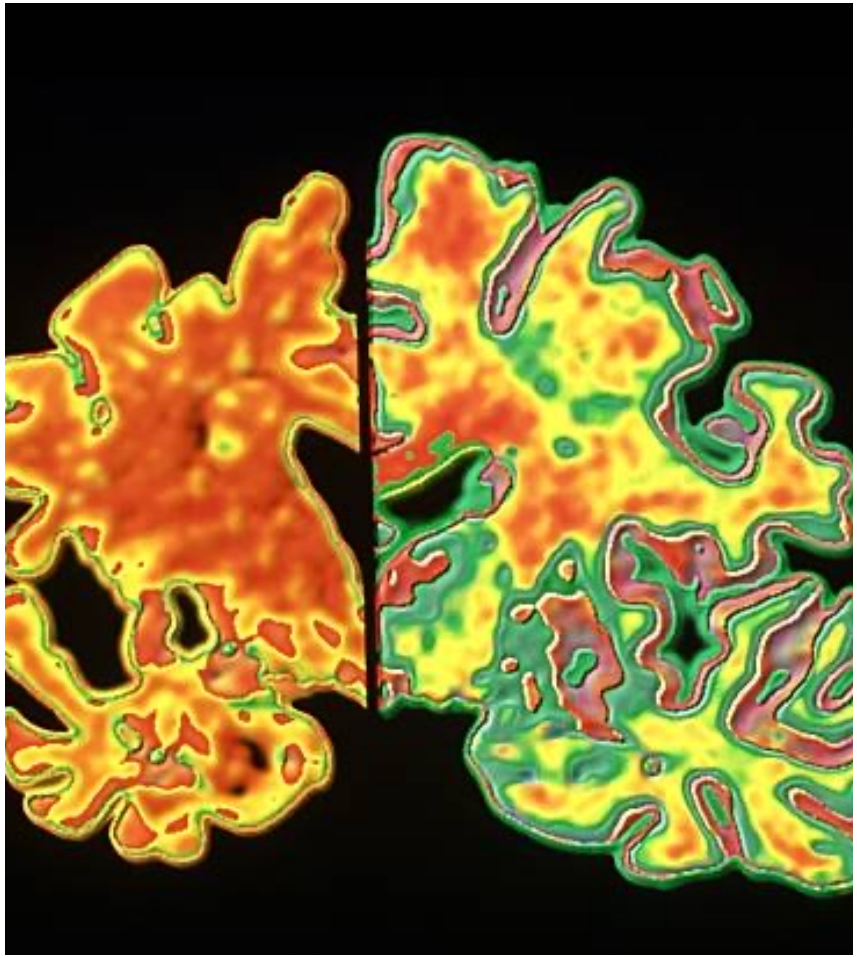
Site of lesion: Temporoparietal cortex or subcortical white matter.



CONDUCTION APHASIA

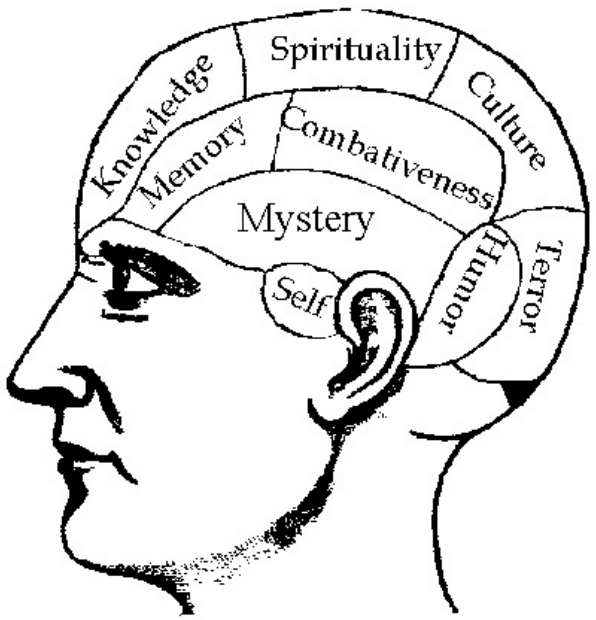
Repetition is severely impaired; fluent, spontaneous speech is interrupted by pauses to search for words and by phonemic paraphasia. Language comprehension is only mildly impaired.

Site of lesion: Arcuate fasciculus or insular region.



SUBCORTICAL APHASIA

Types of aphasia similar to those described may be produced by subcortical lesions at various sites (thalamus, internal capsule, anterior striatum).



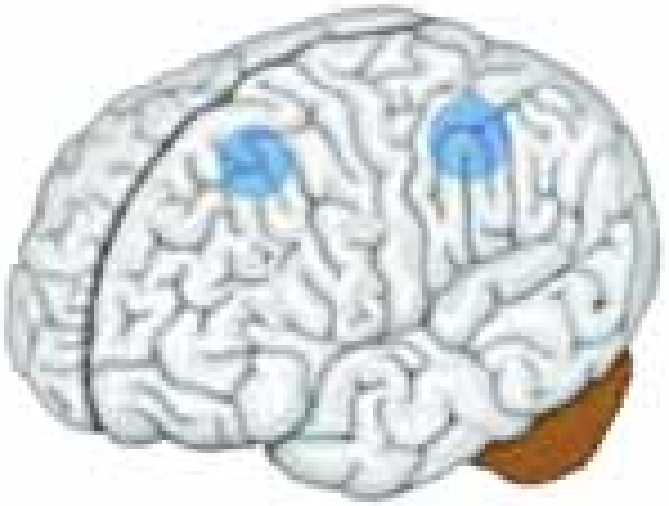
AGRAPHIA

Agraphia is the acquired inability to write.

Agraphia may be isolated (due to a lesion located in area 6, the superior parietal lobule, or elsewhere) or accompanied by other disturbances.

Various forms of agraphia are common in Alzheimer disease.

Examination: The patient is asked to write sentences, long words, or series of numbers to dictation, to spell words, and to copy written words.



Sites of lesions causing agraphia

ALEXIA

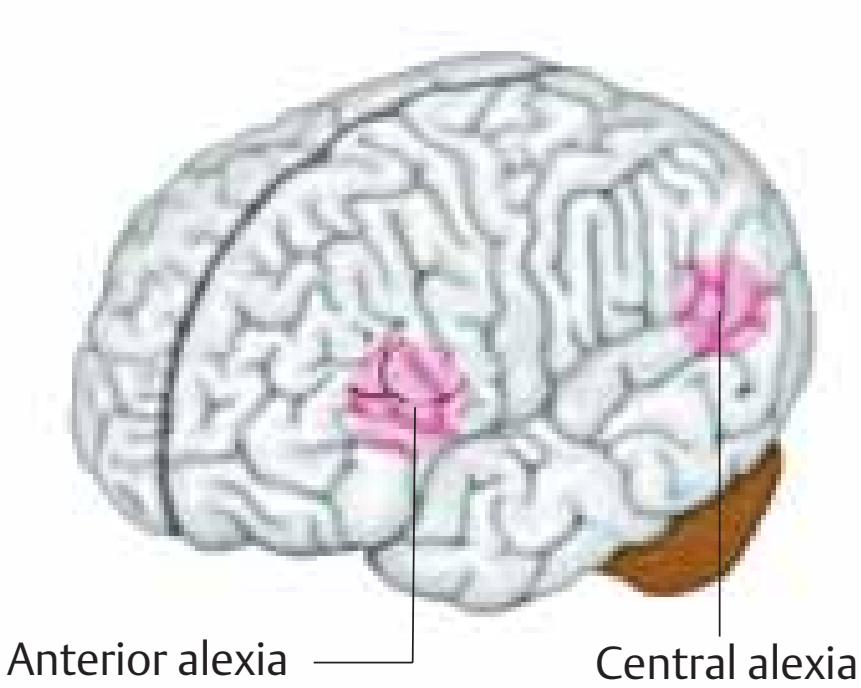
Alexia is the acquired inability to read. The responsible lesion is typically in the left temporooccipital region with involvement of the visual pathway and of callosal fibers.

Anterior alexia (difficulty and errors in reading aloud; impaired ability to write, spell, and copy words) is usually associated with Broca's aphasia.

Central alexia (combination of alexia and agraphia) is usually accompanied by rightleft disorientation, finger agnosia, agraphia, and acalculia (Gerstmann syndrome; lesions of the angular and supramarginal gyri), or by Wernicke's aphasia.

Other features include the inability to understand written language or to spell, write, or copy words.

Examination: The patient is asked to read aloud and to read individual words, letters, and numbers; the understanding of spelled words and instructions is tested.



Topography of lesions in alexia

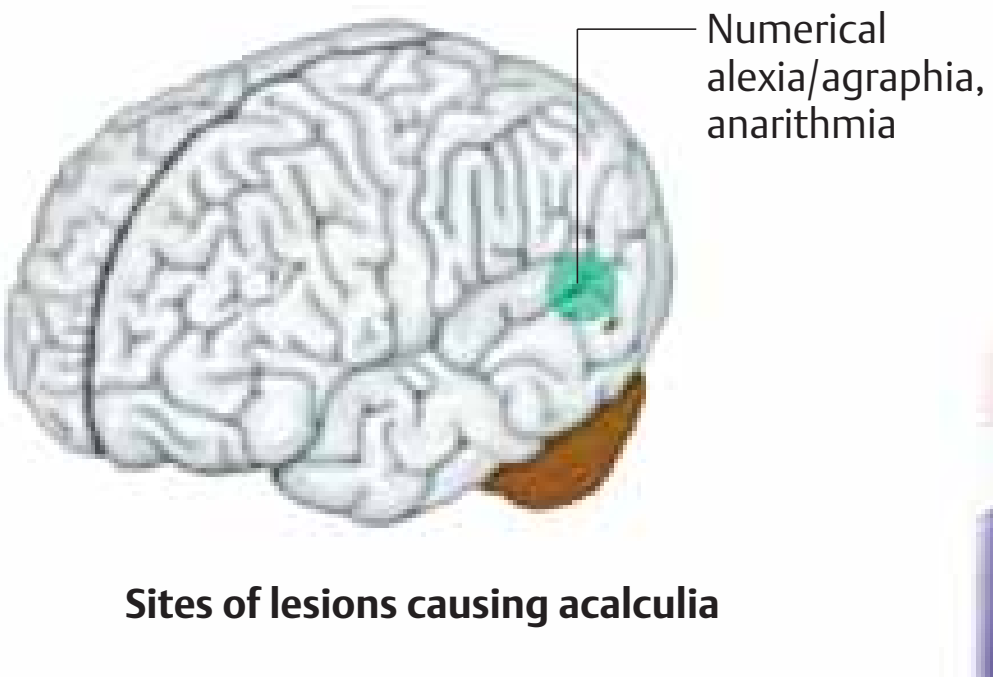
ACALCULIA

Acalculia is an acquired inability to use numbers or perform simple arithmetical calculations.

Patients have difficulty counting change, using a thermometer, or filling out a check.

Lesions of various types may cause acalculia.

Examination: The patient is asked to perform simple arithmetical calculations and to read numbers.



Sites of lesions causing acalculia

APRAXIA

Apraxia is the loss of the ability to correctly carry out certain movements in response to stimuli that normally elicit them, in the absence of weakness, other motor disorders, or sensory loss, and with an intact comprehension of language.

There are several kinds of apraxia:

Ideomotor apraxia

Ideational apraxia

Kinetic apraxia

Gait apraxia

IDEOMOTOR APRAXIA

Ideomotor apraxia involves the faulty execution (parapraxia) of acquired voluntary and complex movement sequences; It can involve the face (buccofacial apraxia) or the limbs (limb apraxia). It is due to a lesion in the association fiber pathways connecting the language, visual, and motor areas to each other and to the two hemispheres (disconnection syndrome).

Examination (pantomimic gestures on command): face (open eyes, stick out tongue, lick lips, blow out a match, pucker, suck on a straw); arms (turn a screw, cut paper, throw ball, comb hair, brush teeth, snap fingers); legs (kick ball, stamp out cigarette, climb stairs).

The patient may perform the movement in incorrect sequence, or may carry out a movement of the wrong type (e. g., puffing instead of sucking).

Ideomotor apraxia

IDEATIONAL APRAXIA

Ideational apraxia is impairment of the ability to carry out complex, learned, goal-directed activities in proper logical sequence. A temporal or parietal lesion may be responsible.

Examination: The patient is asked to carry out pantomimic gestures such as opening a letter, making a sandwich, or preparing a cup of tea.

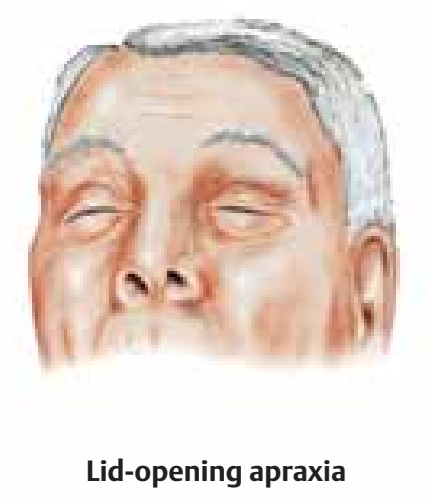
CONSTRUCTIONAL APRAXIA

Constructional apraxia is characterized by the inability to represent spatial relationships in drawings, or with building blocks.

Affected patients cannot copy a picture of a bicycle or clock. Everyday activities are impaired by the inability to draw diagrams, read (analog) clocks, assemble pieces of equipment or tools, or write words in the correct order (spatial agraphia).

APRAXIA-LIKE SYNDROMES

- **Apraxia-like syndromes.** The following disturbances are termed “apraxia” even though actual parapraxia is absent:
- Lid-opening apraxia is difficulty opening the eyes on command. Gait apraxia is characterized by difficulty initiating gait and by short steps.
- Dressing apraxia is often seen in patients with nondominant parietal lobe lesions. They cannot dress themselves and do not know how to position a shirt, shoes, trousers, or other items of clothing to put them on correctly. An underlying impairment of spatial orientation is responsible.



Lid-opening apraxia

Dressing apraxia

DISTURBANCES OF ORIENTATION

- Agnosia is defined as a disturbance of recognition in which perception, attention, and general intelligence are (largely) unimpaired.

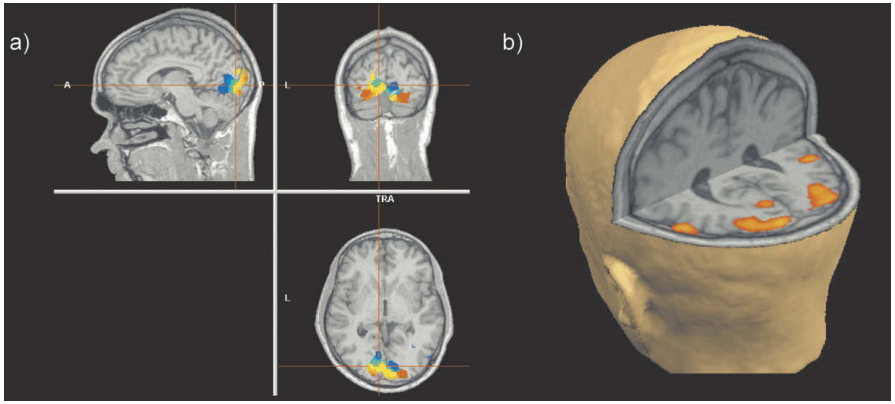


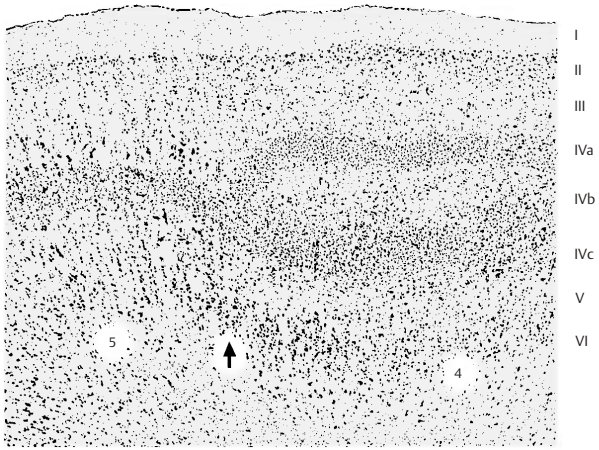
Fig. 9.**23 Functional localization in the primary visual cortex as revealed by fMRI.** Normal subjects viewed visual stimuli in the form of expanding rings, and the associated cortical activity is depicted, projected onto a model of the brain surface. There is activation of the primary visual cortex at the calcarine sulcus, as well as of the secondary visual areas. Images obtained by Professor Grodd. (From: Kammer T, Erb M, Beck S, and Grodd W: Zur Topographie von Phosphenen: Eine Studie mit fMRI und TMS. 3. Tübinger Wahrnehmungskonferenz (3rd Tübingen Conference on Perception), 2000).)

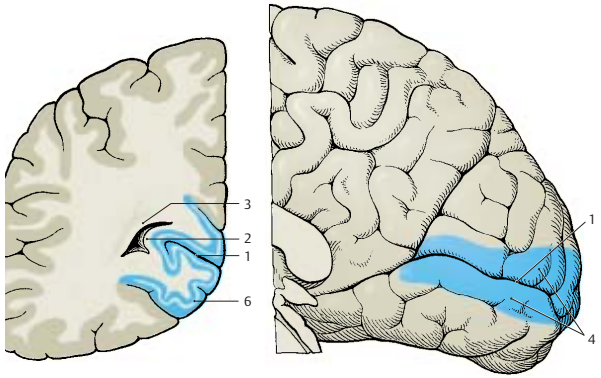
AUTOTOPAGNOSIA

Autotopagnosia (body-image agnosia) is the inability to correctly orient or perceive different body parts; patients cannot obey commands to point to parts of their own or the examiner's body (e. g., foot, hand, nose).

The responsible lesion is usually, though not always, in the temporoparietal region (angular and supramarginal gyri).

An aphasic patient may appear to have autotopagnosia because he cannot understand verbal instructions, but aphasia may also coexist with true autotopagnosia.





B Occipital lobe, frontal section

C Median view of hemisphere, showing area 17

FINGER AGNOSIA

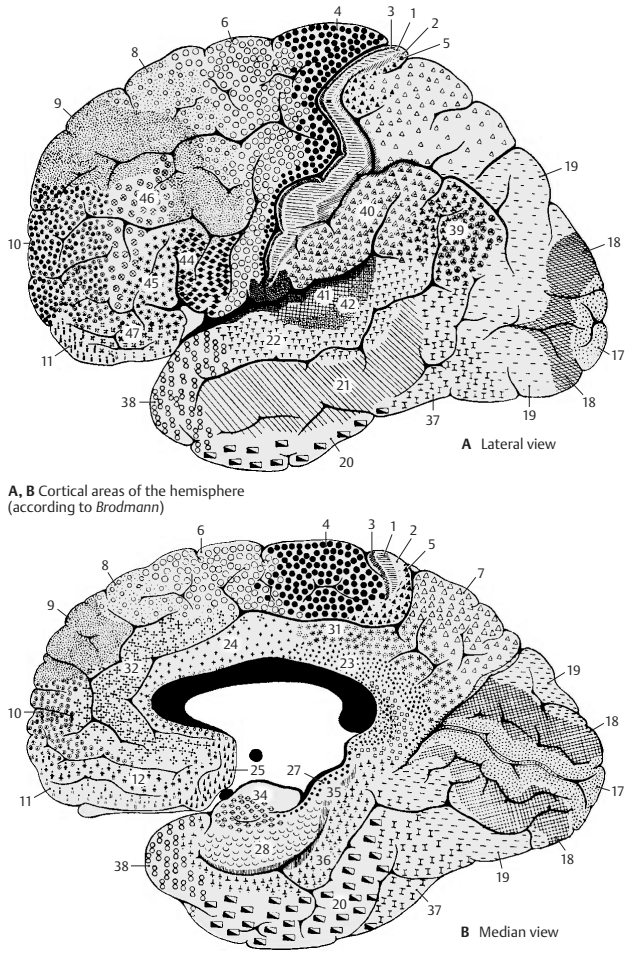
Finger agnosia is the inability to identify, name, or point to fingers.

These patients cannot mimic the examiner's finger movements or copy finger movements of their own contralateral hidden hand with the affected hand.

RIGHT–LEFT DISORIENTATION

Right–left disorientation is the inability to distinguish the right and left sides of one's own or another's body; these patients cannot obey a command to raise their left hand or touch it to their right ear.

This type of disorientation can cause dressing apraxia and similar problems.



A, B Cortical areas of the hemisphere (according to *Brodmann*)

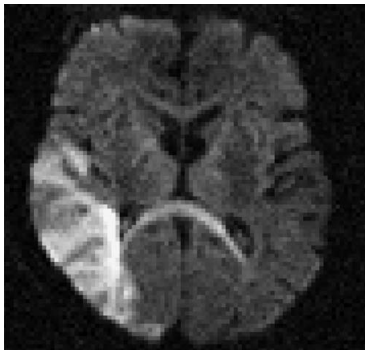
ANOSOGNOSIA

Anosognosia is the unawareness or denial of a neurological deficit, such as hemiplegia. Patients may claim that they only want to give the paralyzed side a rest, or attempt to demonstrate that their condition has improved without realizing that they are moving the limb on the unaffected side.

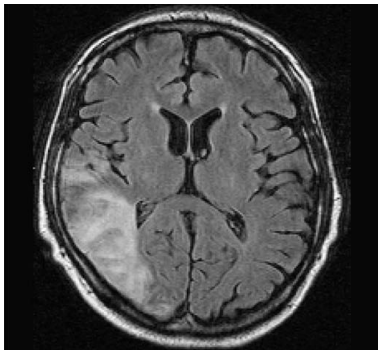
Most such patients have extensive lesions of the nondominant hemisphere.

Anosognosia may also accompany visual field defects due to unilateral or bilateral lesions of the visual cortex (homonymous hemianopsia, cortical blindness).

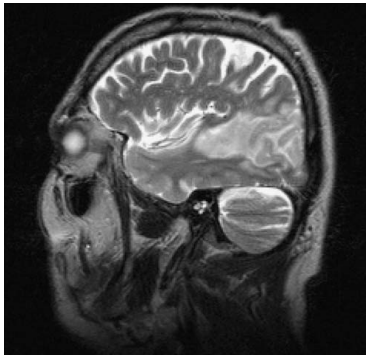
The most striking example of this is Anton syndrome, in which cortically blind patients act as if they could see, and will even “describe” details of their surroundings (incorrectly) without hesitation.



a



b



c

Fig. 9.**29 Infarct in the territory of the right middle cerebral artery, causing neglect** (MRI). **a** Axial EPI sequence. **b** Axial T2-weighted FLAIR sequence. The axial images reveal an infarct affecting the posterior portion of the middle cerebral artery territory on the right, reaching far back into the occipital lobe and to the wall of the lateral ventricle. Involved areas include the temporal lobe, the angular and supramarginal gyri of the parietal lobe, and the occipital lobe. The patient’s hemianopsia is due to involvement of the optic radiation and occipital lobe. **c** Sagittal T2-weighted image. The hyperintense zone of infarction is seen behind and under the sylvian fissure.

HEMINEGLECT

Hemineglect is the inability to consciously perceive, react to, or classify stimuli on one side in the absence of a sensorimotor deficit or exceeding what one would expect from the severity of the sensorimotor deficit present.

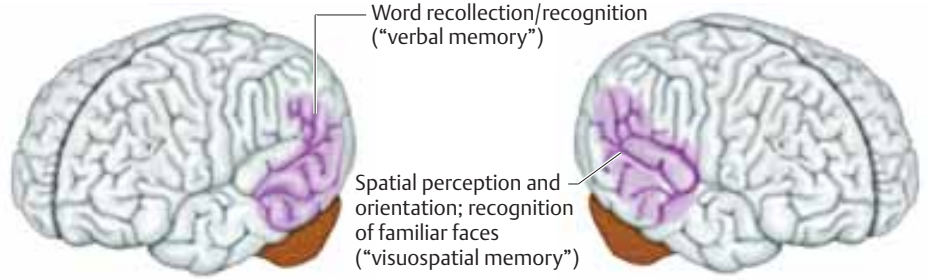
Neurological examination reveals that double simultaneous stimulation (touch, finger movement) of homologous body parts (same site, e. g., face or arm) is not felt on the affected side (extinction phenomenon).

Hemispatial neglect
(left side)
(task was to draw a clockface and set it to "quarter past 12")

Hemispatial neglect (left side)

MEMORY

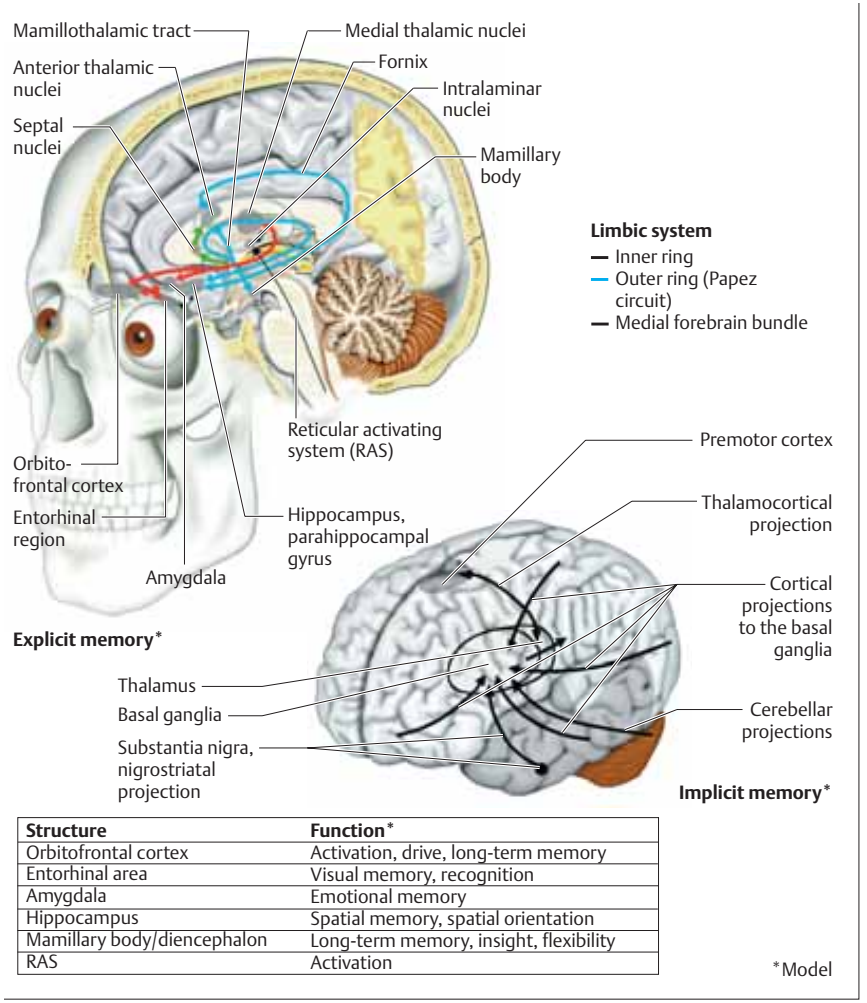
Memory involves the acquisition, storage, recall, and reproduction of information. Memory depends on intact functioning of the limbic system and areas of the brain that are connected to it.



Temporal cortical representation

MEMORY

Declarative or explicit memory (i.e., memory for facts and events) can be consciously accessed and depends on intact functioning of the mediobasal portion of the temporal lobe. The duration of information storage may be relatively short (short-term, immediate, and working memory) or long (long-term memory).

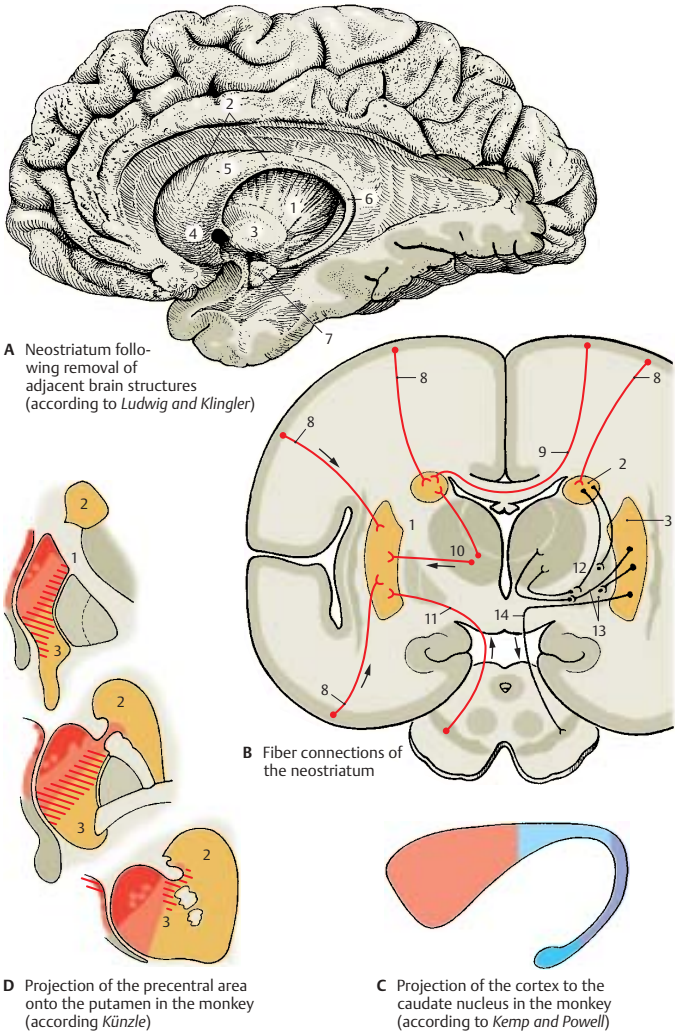


Structure	Function*
Orbitofrontal cortex	Activation, drive, long-term memory
Entorhinal area	Visual memory, recognition
Amygdala	Emotional memory
Hippocampus	Spatial memory, spatial orientation
Mamillary body/diencephalon	Long-term memory, insight, flexibility
RAS	Activation

*Model

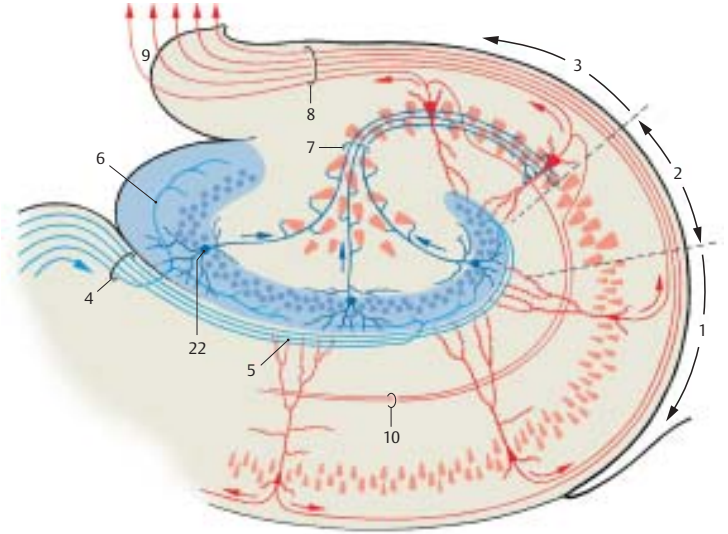
MEMORY

Verbal (telephone number) or visuospatial information (how to find a street) can be directly recalled from ***short-term memory***. The entorhinal cortex plays a key role in these memory functions: all information from cortical regions (frontal, temporal, parietal) travels first to the entorhinal cortex and then, by way of the parahippocampal and perirhinal cortex, to the hippocampus. There is also a reciprocal projection from the hippocampus back to the entorhinal cortex.

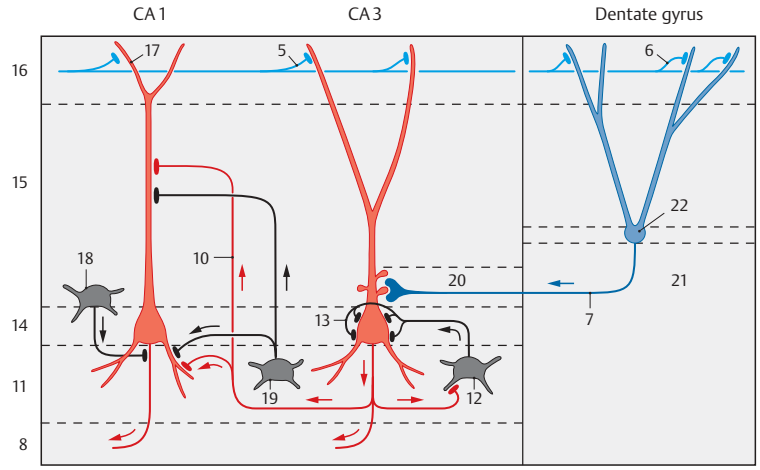


MEMORY

Long-term memory stores events of personal history that occurred at particular times (episodic memory for a conversation, one's wedding day, last year's holiday; orbitofrontal cortex) as well as conceptual, non–time-related knowledge (semantic memory for the capital of Spain, the number of centimeters in a meter, the meaning of the word "stethoscope"; subserved by different cortical regions).



A Organization of the hippocampus (according to *Cajal*)

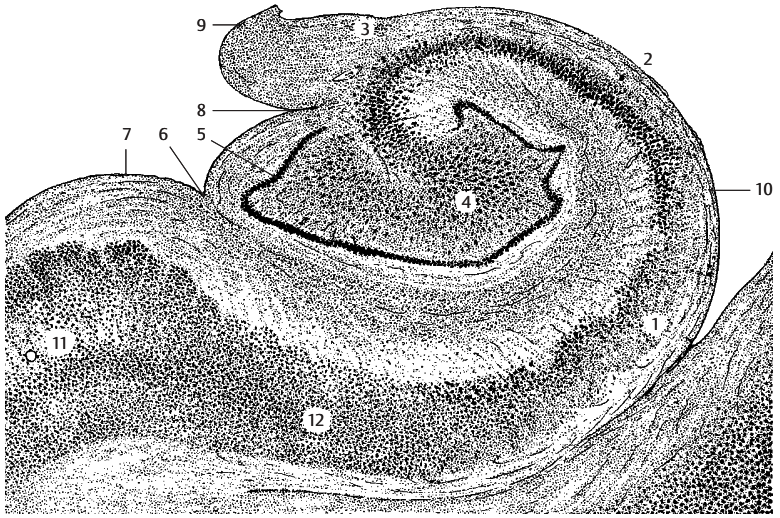


B Neuronal circuits in the hippocampus

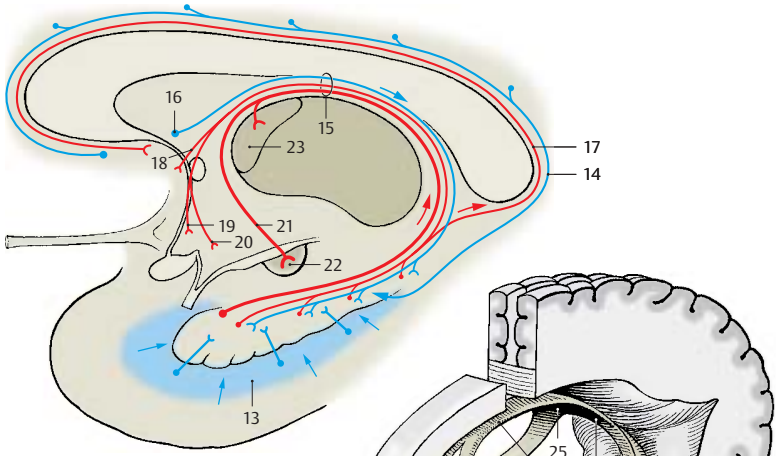
MEMORY

Nondeclarative (procedural, implicit) memory, on the other hand, cannot be consciously accessed. Learned motor programs (riding a bicycle, swimming, playing the piano), problem-solving (rules), recognition of information acquired earlier (priming), and conditioned learning (avoid- ing a hot burner on the stove, sitting still in school) belong to this category.

Nondeclarative memory is mediated by the basal ganglia (motor function), neocortex (priming), cerebellum (conditioning), striatum (agility), amygdala (emotional responses), and reflex pathways.



A Ammon's horn, frontal section through the hippocampus



B Fiber connections of the hippocampus

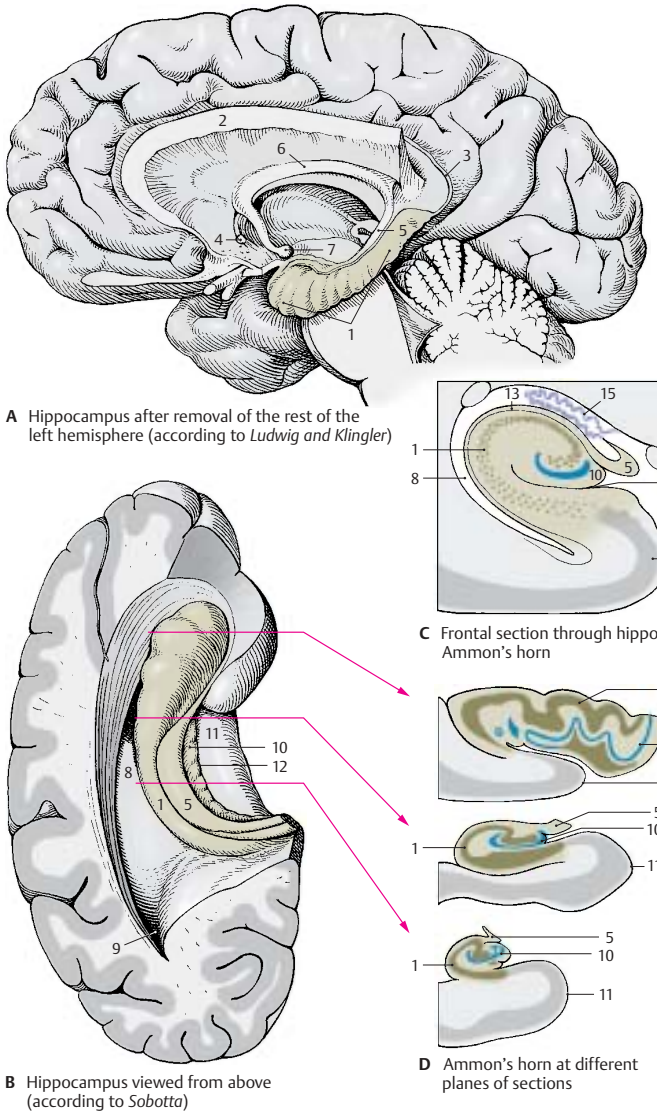
C Hippocampus and fornix (according to *Feneis*)

MEMORY

- **Examination.** Only disturbances of declarative memory (amnesia) can be studied by clinical examination.

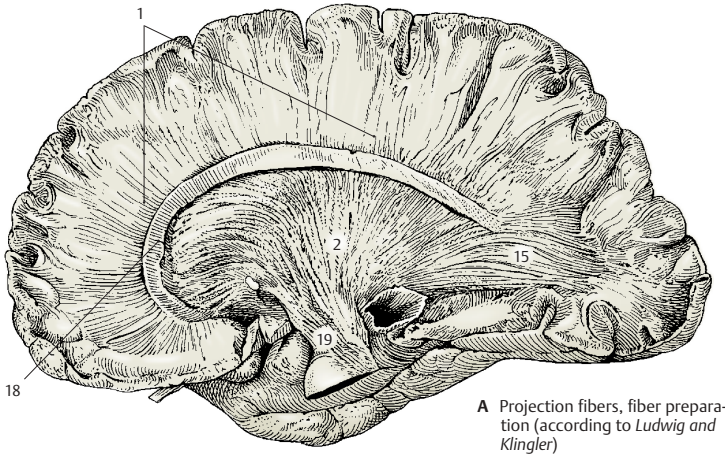
Short-term memory: the acquisition of new information is tested by having the patient repeat a series of numbers or groups of words and asking for this information again 5–10 minutes later.

The patient's orientation (name, place of residence/address, time/date) and long-term memory (place of birth, education, place of employment, family, general knowledge) are also tested by directed questioning.

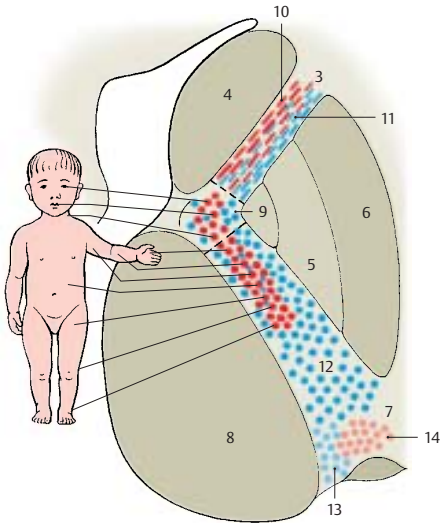


MEMORY DISORDERS (AMNESIA)

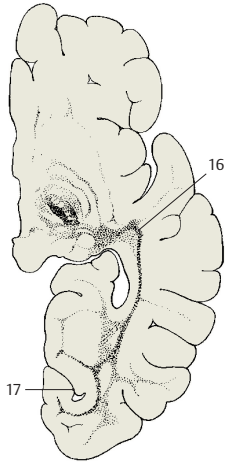
- **Forgetfulness.** Verbal memory does not decline until approximately age 60, and even then only gradually, if at all. Aging is, however, often accompanied by an evident decline in information processing ability and attention span (benign senescent forgetfulness). These changes occur normally, yet to a degree that varies highly among individuals, and they are often barely measurable. They are far less severe than full- blown dementia, but they may be difficult to distinguish from incipient dementia.



A Projection fibers, fiber preparation (according to *Ludwig and Klingler*)



B Somatotopic organization of the internal capsule



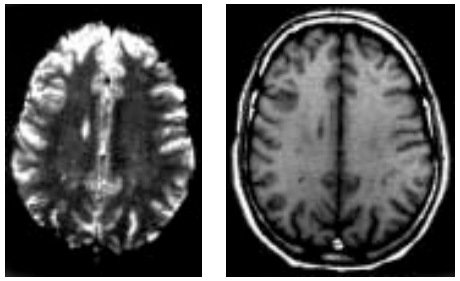
C Optic radiation during myelin maturation (according to *Flechsig*)

MEMORY DISORDERS (AMNESIA)

Amnesia.

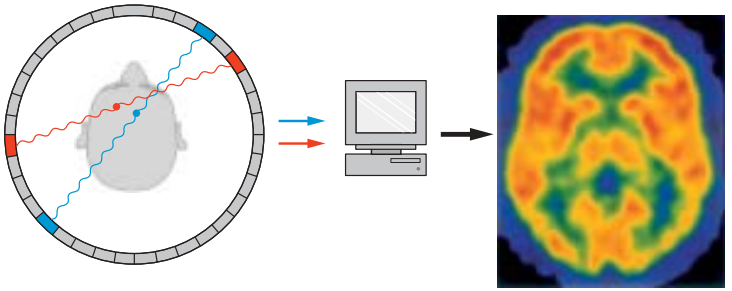
Anterograde amnesia is the inability to acquire (declarative) information, for later recall, from a particular moment onward; retrograde amnesia is the inability to remember (declarative) information acquired before a particular moment.

Amnestic patients commonly confabulate (i.e., fill in gaps in memory with fabricated, often implausible information); they may be disoriented and lack awareness of their own memory disorder.

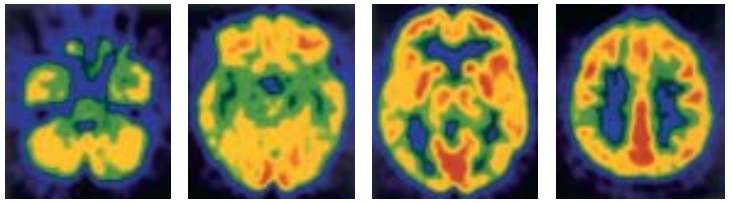


A Spin–lattice relaxation, T1 **B** Spin–spin relaxation, T2

A, B Magnetic resonance imaging (MRI): Two different scans of the head at the level above the ventricles



C Principle of positron emission tomography (PET): Detection of gamma rays emitted simultaneously in opposite directions during the decay of a radioisotope (Courtesy of *F. Jüngling*, Department of Radiodiagnostics, University of Freiburg, Germany)



D PET scans of four parallel slices (intensity of glucose utilization in the brain)

ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

Prof. M. GAVRILIUC

DEFINITION

Dementia is a syndrome with many causes. It is defined as an acquired deterioration in cognitive abilities that impairs the successful performance of activities of daily living. Memory is the most common cognitive ability lost with dementia.

An old man diagnosed as suffering from senile dementia. Colour lithograph, 1896, after J. Williamson, ca. 1890.

DEFINITION

A woman diagnosed as suffering from chronic dementia. Colour lithograph, 1896, after J. Williamson, ca. 1890.

In addition to memory, other mental faculties are also affected in dementia; these include language, visuospatial ability, calculation, judgment, and problem solving.

DEFINITION

Neuropsychiatric and social deficits also develop in many dementia syndromes, resulting in depression, withdrawal, hallucinations, delusions, agitation, insomnia, and disinhibition.

FUNCTIONAL ANATOMY OF THE DEMENTIAS

Dementia results from the disruption of cerebral neuronal circuits; the quantity of neuronal loss and the location of affected regions are factors that combine to cause the specific disorder.

FUNCTIONAL ANATOMY OF THE DEMENTIAS

- Behavior and mood are modulated by noradrenergic, serotonergic, and dopaminergic pathways,
- while acetylcholine seems to be particularly important for memory.

FUNCTIONAL ANATOMY OF THE DEMENTIAS

AD ➔ cholinergic neurons loss ➔ memory impairment.

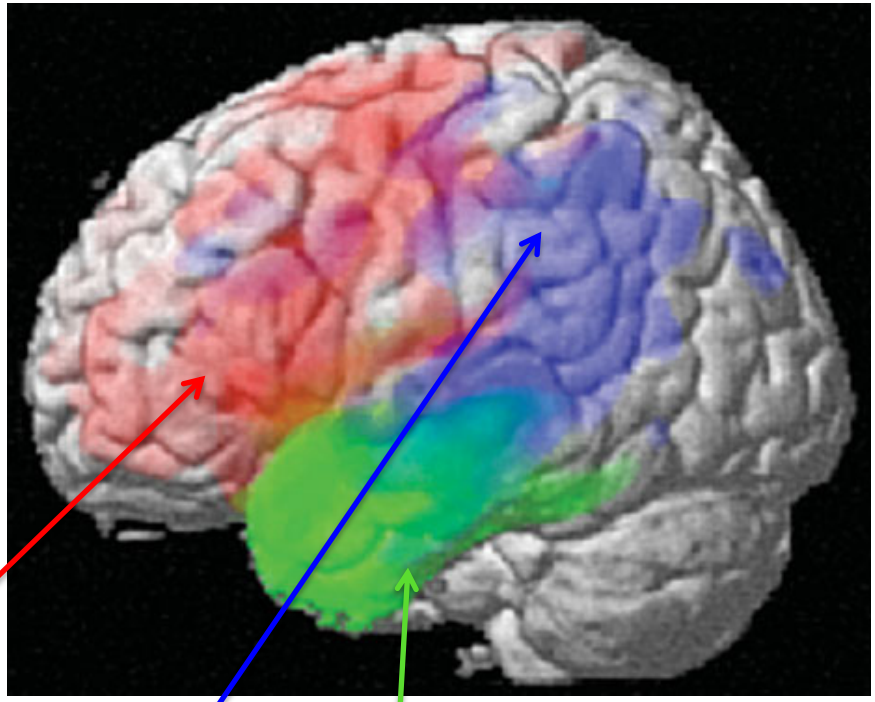
Non-AD dementias ➔ serotonergic and glutaminergic neurons loss ➔ primarily behavioral symptoms.

FUNCTIONAL ANATOMY OF THE DEMENTIAS

Neurotrophins are also postulated to play a role in memory function, in part by preserving cholinergic neurons, and therefore represent a pharmacologic pathway toward slowing or reversing the effects of AD.

FUNCTIONAL ANATOMY OF THE DEMENTIAS

Dementias have anatomically specific patterns of neuronal degeneration that dictate the clinical symptomatology.

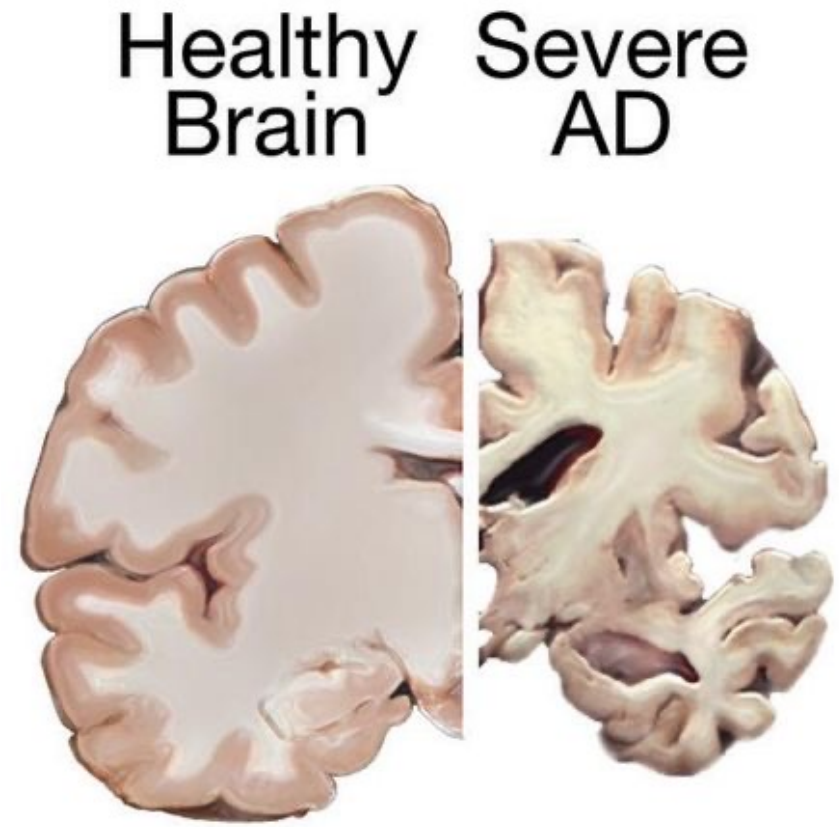


Voxel-based morphometry analysis showing differing patterns of brain atrophy in the frontal variant of **frontotemporal dementia (red)**, **temporal variant of frontotemporal dementia green)**, and **Alzheimer's disease (blue)**. (Image courtesy of M Gorno-Tempini, University of California at San Francisco; with permission).

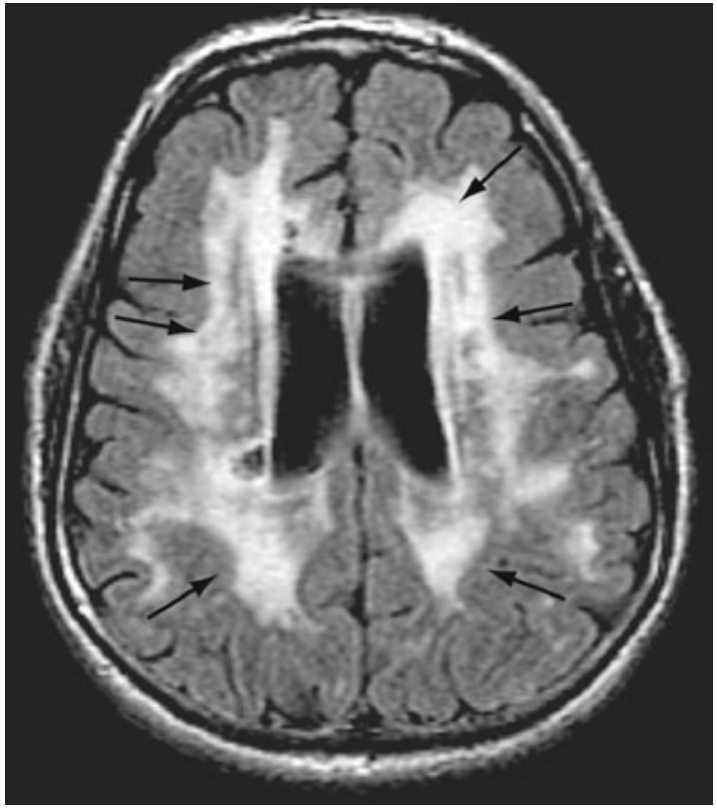
FUNCTIONAL ANATOMY OF THE DEMENTIAS

AD begins in the entorhinal cortex, spreads to

the hippocampus, and then moves to posterior temporal and parietal neocortex, eventually causing a relatively diffuse degeneration throughout the cerebral cortex.



FUNCTIONAL ANATOMY OF THE DEMENTIAS

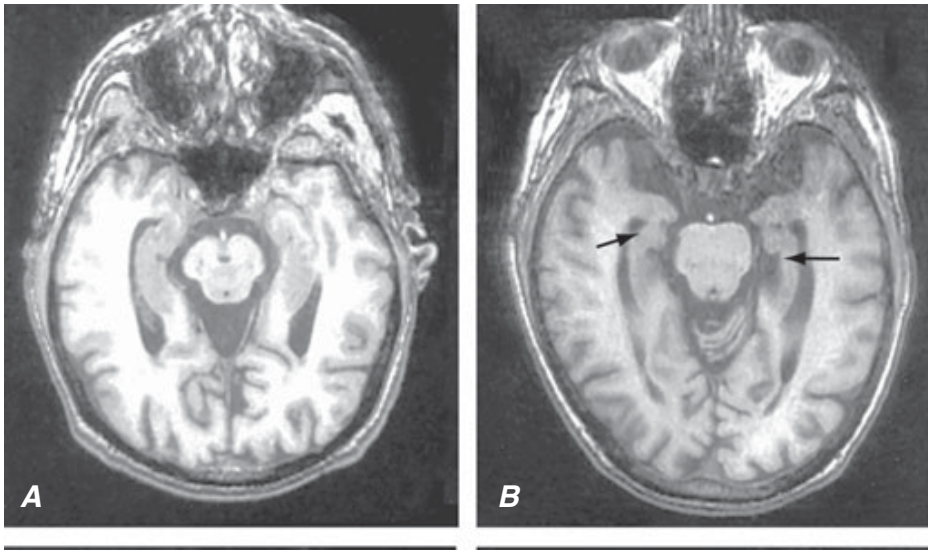


Multi-infarct dementia is associated with focal damage in a random patchwork of cortical regions.

Diffuse white matter disease (Binswanger's disease). Axial T2-weighted MR image through the lateral ventricles reveals multiple areas of abnormal high signal intensity involving the periventricular white matter as well as the corona radiata and lentiform nuclei (arrows).

FUNCTIONAL ANATOMY OF THE DEMENTIAS

Subcortical structures, including the caudate, putamen, thalamus, and *substantia nigra*, also modulate cognition and behavior in ways that are not yet well understood.



MRI in Alzheimer's disease. Reduction in the volume of the hippocampus of the patient with AD **(B)** (arrows) compared with that of the normal-for-age hippocampus **(A)**.

FUNCTIONAL ANATOMY OF THE DEMENTIAS

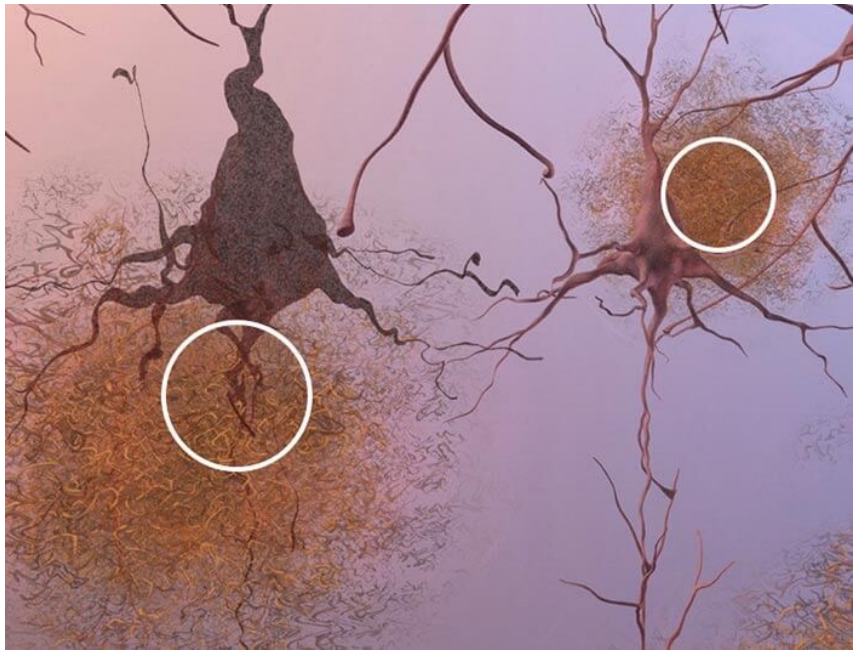
The single strongest risk factor for dementia is

increasing age. The prevalence of disabling memory loss increases with each decade after 50 years of age and is associated most often with the microscopic changes of AD at autopsy.

Most Common Causes of Dementia

- **Alzheimer's disease**
- **Vascular dementia**
  - Multi-infarct
  - Diffuse white matter disease (Binswanger's)
- **Alcoholism[a]**
- **Parkinson's disease**
- **Drug/medication intoxication[a]**

[a]Potentially reversible dementia.



Plaques, abnormal clusters of protein fragments, build up between nerve cells in AD.

Less Common Causes of Dementia

Vitamin deficiencies

- Thiamine (B1): Wernicke's encephalopathy[a]
- B12 (pernicious anemia)[a]
- Nicotinic acid (pellagra)[a]

[a]Potentially reversible dementia.

Less Common Causes of Dementia

Endocrine and other organ failure

- Hypothyroidism[a]
- Adrenal insufficiency and Cushing's syndrome[a]
- Hypo- and hyperparathyroidism[a]
- Renal failure[a]
- Liver failure[a]
- Pulmonary failure[a]

[a]Potentially reversible dementia.

Less Common Causes of Dementia

Head trauma and diffuse brain damage

- Dementia pugilistica
- Chronic subdural hematoma[a]
- Postanoxia
- Postenechephalitis
- Normal pressure hydrocephalus[a]

[a]Potentially reversible dementia.

Less Common Causes of Dementia

Neoplastic

- Primary brain tumor[a]
- Metastatic brain tumor[a]
- Paraneoplastic limbic enchephalitis

[a]Potentially reversible dementia.

Less Common Causes of Dementia

Toxic disorders -

Drug, medication, and narcotic poisoning[a] -

Heavy metal intoxication[a]

- Dialysis dementia (aluminum)
- Organic toxins

[a]Potentially reversible dementia.

Less Common Causes of Dementia

Psychiatric

- Depressions (pseudodementia)[a]
- Schizophrenia[a]
- Conversion reaction[a]

[a]Potentially reversible dementia.

Less Common Causes of Dementia

Degenerative disorders (1)

- Huntington's disease
- Pick's disease
- Dementia with Lewy bodies
- Progressive supranuclear palsy (Steel-Richardson syndrome)
- Multisystem degeneration (Shy-Drager syndrome)
- Hereditary ataxias (some forms) -Motor neuron disease [amyotrophic lateral sclerosis (ALS); some forms]

[a]Potentially reversible dementia.

Less Common Causes of Dementia

Degenerative disorders (2)

- Frontotemporal dementia
- Cortical basal degeneration
- Multiple sclerosis
- Adult Down's syndrome with Alzheimer's
- ALS–Parkinson's–Dementia complex of Guam

[a]**Potentially reversible dementia.**

Adult Down's syndrome with Alzheimer's

Less Common Causes of Dementia

Miscillaneous

- Sarcoidosis[a]
- Vasculitis[a]
- CADASIL etc
- Acute intermittent porphyria[a]
- Recurrent nonconvulsive seizures[a]

[a]Potentially reversible dementia.

Less Common Causes of Dementia

<u>Additional conditions in children or adolescents</u>

- Hallervorden-Spatz disease

- Subacute sclerosing panencephalitis

- Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations).

EVALUATION OF THE PATIENT WITH DEMENTIA

ROUTINE EVALUATION

History

Physical examination

Laboratory tests

- Thyroid function (TSH)
- Vitamin B12
- Complete blood count
- Electrolytes

Imagistic examination

- CT/MRI

EVALUATION OF THE PATIENT WITH DEMENTIA

OPTIONAL FOCUSED TESTS

Psychometric testing
Chest x-ray
Lumbar puncture
Liver/Renal function
Urine toxin screen
HIV
Apolipoprotein E
RPR or VDRL

EVALUATION OF THE PATIENT WITH DEMENTIA

OCCASIONALLY HELPFUL TESTS

EEG
Parathyroid function
Adrenal function
Urine heavy metals
RBC sedimentation rate
Angiogram
Brain biopsy
SPECT
PET

MENTAL STATE

Mental state

The mental state relates to the mood and thoughts of a patient. Abnormalities may reflect:

- *neurological disease, such as frontal lobe'disease or dementia*

- *psychiatric illness which may be causing neurological symptoms (e.g. anxiety leading to panic attacks)*

- *psychiatric illness secondary to neurological disease (e.g. depression following stroke).*

MENTAL STATE

Mental state

Mental state examination attempts to distinguish:

- **focal neurological deficit**
- **diffuse neurological deficit**
- **primary psychiatric illness** such as depression, anxiety or hysteria presenting with somatic symptoms
- **psychiatric illness** secondary to, or associated with neurological disease.

MENTAL STATE

Appearance and behavior

Are there signs of self-neglect?

- Dirty or unkempt — consider *depression, dementia, alcoholism or drug abuse.*

Does the patient appear depressed?

- Furrowed brow, immobile, downcast fades, speech (parkinsonism)

Does the patient appear anxious?

- Fidgety, restless.

Does the patient behave appropriately?

- Overfamiliar and disinhibited or aggressive – consider *frontalism*
- Unresponsive, with little emotional response – *flat affect*

Does the patient's mood change rapidly?

- Crying or laughing easily—*emotional lability.*

Does the patient show appropriate concern about his symptoms and disability?

- Lack of concern in the face of significant disability ('belle indifference') — consider *hysterical disease.*

MENTAL STATE

Mood

<u>Ask the patient about his mood</u>

- How are your spirits at the moment?
- How would you describe your mood?

<u>If you consider the patient may be depressed, ask:</u>

- Are you ever able to cheer up?
- Do you see any hope in the future?

Patients with depression say they find it difficult to cheer up and see little hope in the future.

Patients with schizophrenia often have an apparent lack of mood — *blunted affect* — or inappropriate mood, smiling when you expect him to be sad — *incongruous affect.*
In mania, patients are euphoric.

MENTAL STATE

Higher function

Higher function is a term used to encompass thought, memory understanding, perception and intellect.

The purpose of testing is to:

- document the level of function in a reproducible way
- distinguish focal and diffuse deficits
- assess functional level within the community. Higher function can be divided into the following parts:
- attention
- memory (immediate short-term and long-term)
- calculation
- abstract thought
- spatial
- visual and body perception.

All testing relies on intact speech. This should be tested first. The tests cannot be interpreted if the patient has poor attention as clearly this will interfere with all other aspects of testing. Results need to be interpreted in the light of premorbid intelligence.

MENTAL STATE

Mini mental state test

Orientation

Score one point for correct answers to each of the following questions:
What is the: time? date? day? month? year?

(5 points)

What is the name of this: ward? hospital? district? town? country?

(5 points)

Registration

Name three objects. Score up to 3 points if, at the first attempt, the patient repeats, in order, the three objects you have randomly named. Score *2* or one if this is the number he repeats correctly. Endeavour, by further attempts and prompting, to have all three repeated, so as to test recall later. (3 points)

MENTAL STATE

Mini mental state test

Attention and calculation

Ask the patient to subtract 7 from 100, and then 7 from the result— repeat this five times, scoring one for each time a correct subtraction is performed. (5 points)

Recall

Ask for the three objects repeated in the registration test, scoring one for each correctly recalled. (3 points)

MENTAL STATE

Mini mental state test

Language

Score one point for two objects (a pencil and a watch) correctly named.
(2 points)

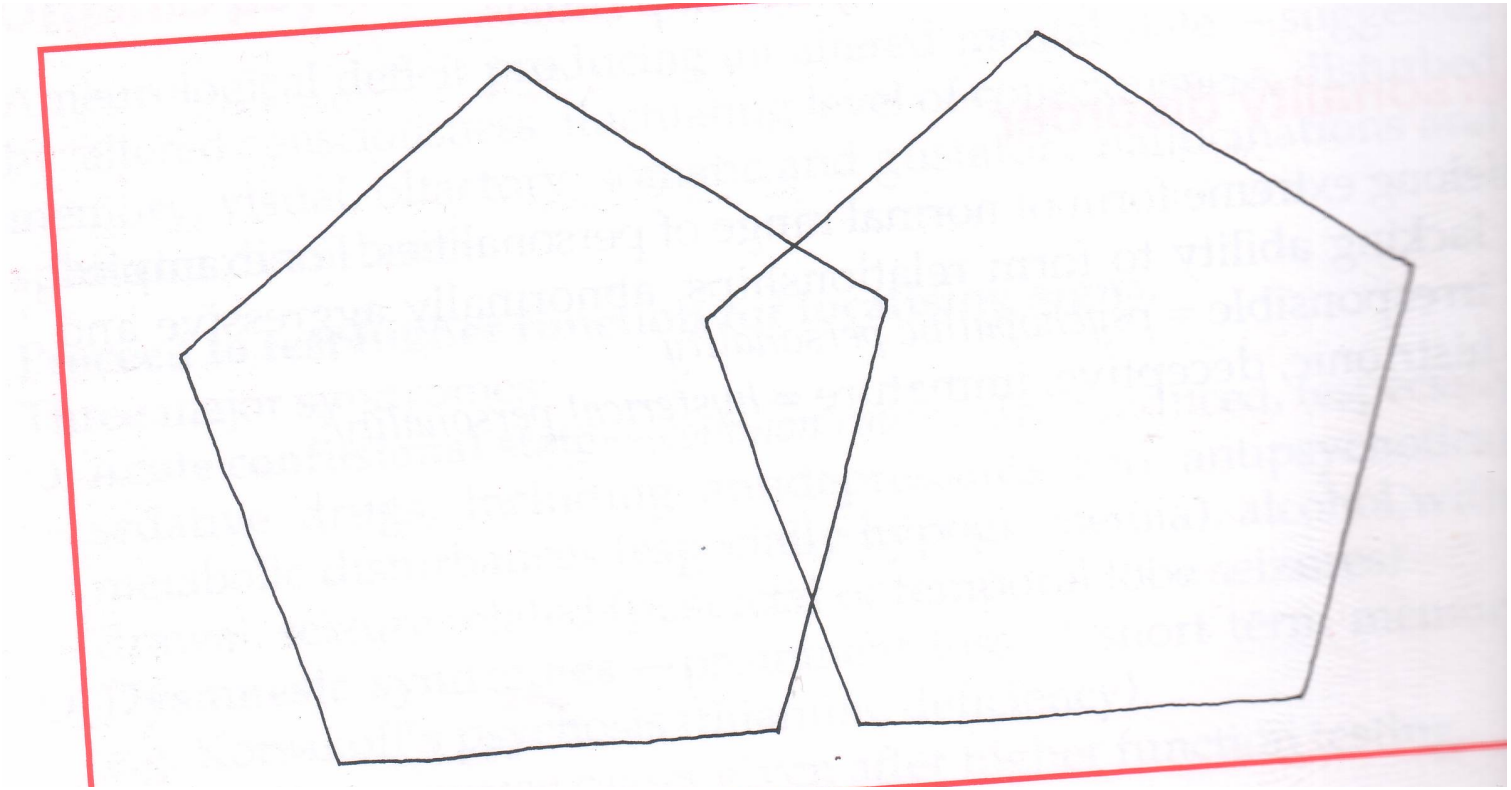
Score one point if the following phrase is correctly repeated
'No ifs, ands or buts'. (1 point)

Score 3 if a three-stage command is correctly executed; score 1 for each stage: for example, 'with the index finger of your right hand touch the tip of your nose and then your left ear,' or 'take this piece of paper in your right hand, fold it in half and place it on the floor.' (3 points)

On a blank piece of paper write, 'Close your eyes' and ask the patient to obey what is written. Score one point if he closes his eyes. (1 point)

Ask the patient to write a sentence. Score one if the sentence is sensible and has a verb and a subject. (1 point)

Construct a pair of intersecting pentagons, each side 1 inch long
Score one if this is correctly copied.



Pair of intersecting pentagons for mini mental state test

MENTAL STATE

Mini mental state test

TOTAL
30 points

What it means
Less than 23 = *cognitively impaired*
N.B. Does not distinguish focal from diffuse disease. Aphasic patients do especially badly.

It is a useful guide for documenting the level of function

CLINICAL DIFFERENTIATION OF THE MAJOR DEMENTIAS

DISEASE	FIRST SYMPTOM	MENTAL STATUS	NEUROPSYCHIATRY	NEUROLOGY	IMAGING
AD	Memory loss	Episodic memory loss	Initially normal	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy; poor judgment/insight, speech/language; hyperorality	Frontal/executive, language; spares drawing	Apathy, disinhibition, hyperorality, euphoria, depression	Due to PSP/CBD overlap; vertical gaze palsy, axial rigidity, dystonia, alien hand	Frontal and/or temporal atrophy; spares posterior parietal lobe
DLB	Visual hallucinations, REM sleep disorder, delirium, Capgras' syndrome, parkinsonism	Drawing and frontal/executive; spares memory; delirium prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy; hippocampi larger than in AD
CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/executive, focal cortical, memory	Depression, anxiety	Myoclonus, rigidity, parkinsonism	Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/flare MRI
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or subcortical infarctions, confluent white matter disease

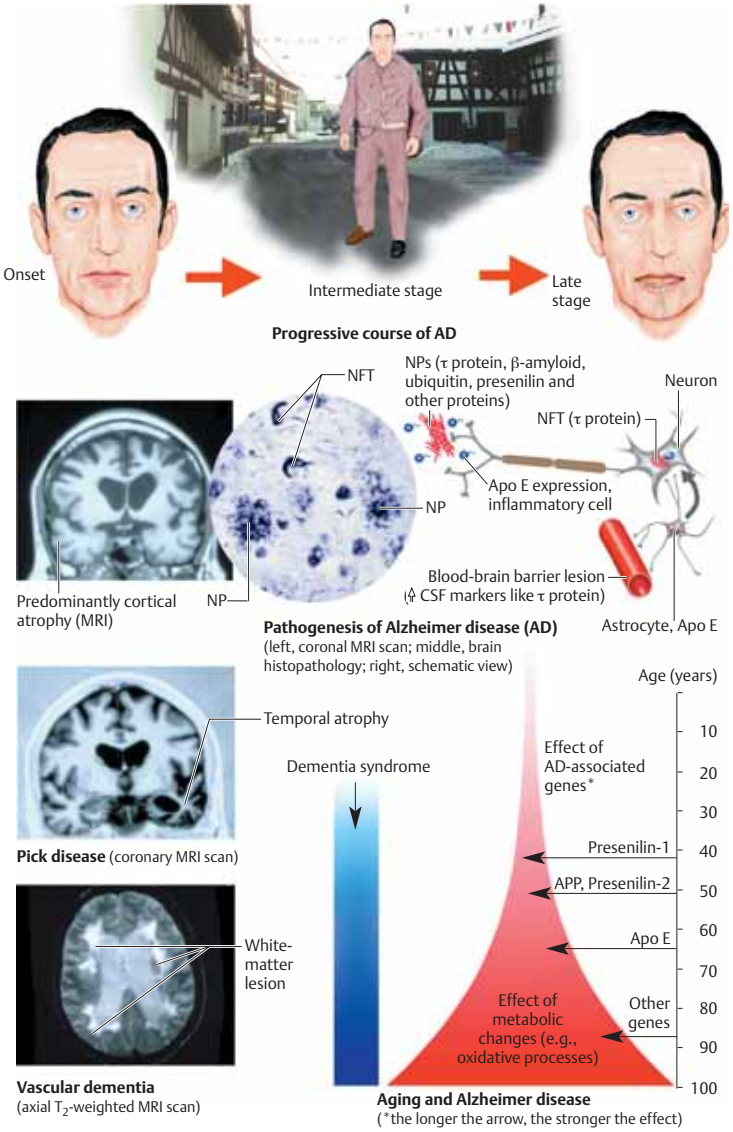
Note: **AD**, Alzheimer's disease; **FTD**, frontotemporal dementia; **PSP**, progressive supranuclear palsy; **CBD**, cortical basal degeneration; **DLB**, dementia with Lewy bodies; **CJD**, Creutzfeldt-Jakob disease.

DEMENTIA

Approximately 90% of all cases of dementia are caused by Alzheimer disease or cerebrovascular disorders; diverse etiologies account for the rest.

The physician confronted with a case of incipient dementia must distinguish primary dementia from that secondary to another disease.

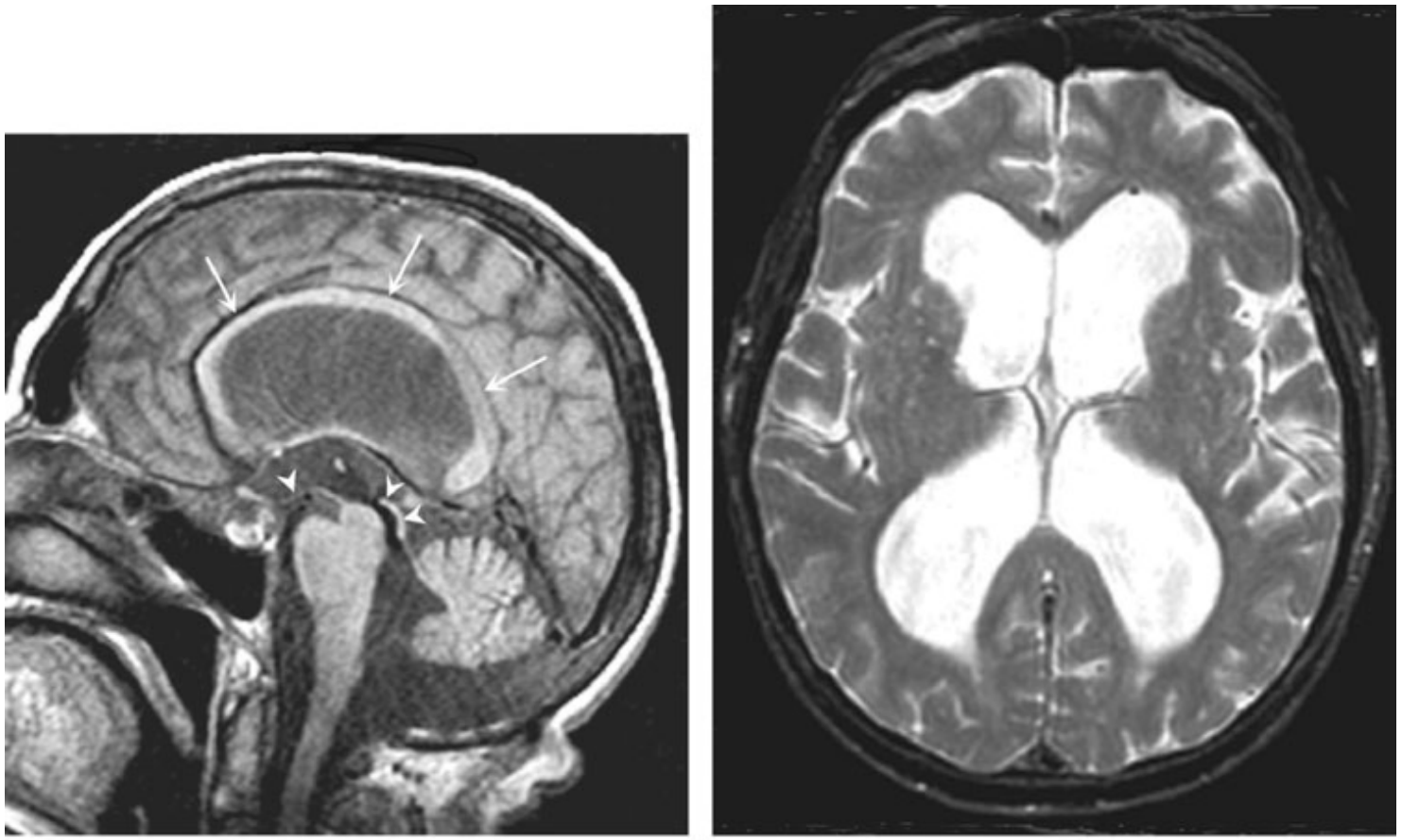
The objective is early determination of the etiology of dementia, especially when these are treatable or reversible.



DEMENTIA:

TREATMENT

Treatment of underlying causes might include thyroid replacement for hypothyroidism; vitamin therapy for thiamine or B12 deficiency or for elevated serum homocysteine; antibiotics for opportunistic infections; ventricular shunting for NPH; and appropriate surgical, radiation, and/or chemotherapeutic treatment for CNS neoplasms.



Normal-pressure hydrocephalus. A. Sagittal T1-weighted MR image demonstrates dilatation of the lateral ventricle and stretching of the corpus callosum (arrows), depression of the floor of the third ventricle (single arrowhead), and enlargement of the aqueduct (double arrowheads). Note the diffuse dilatation of the lateral, third, and fourth ventricles with a patent aqueduct, typical of communicating hydrocephalus. B. Axial T2-weighted MR images demonstrate dilatation of the lateral ventricles. This patient underwent successful ventriculoperitoneal shunting.

TREATMENT of Hydrocephalus

In general, the treatment of hydrocephalus is a CSF shunt or a 3rd ventriculostomy.

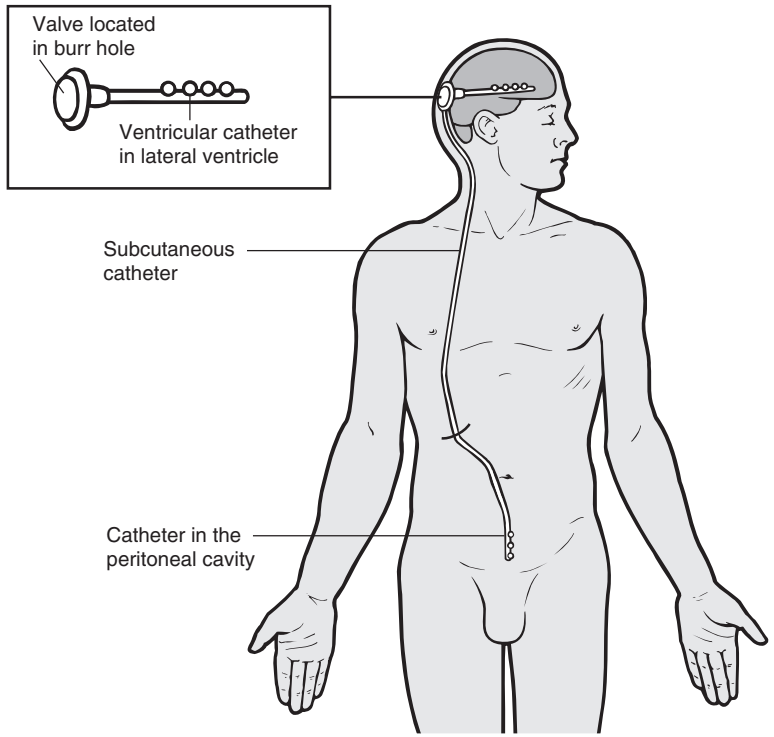
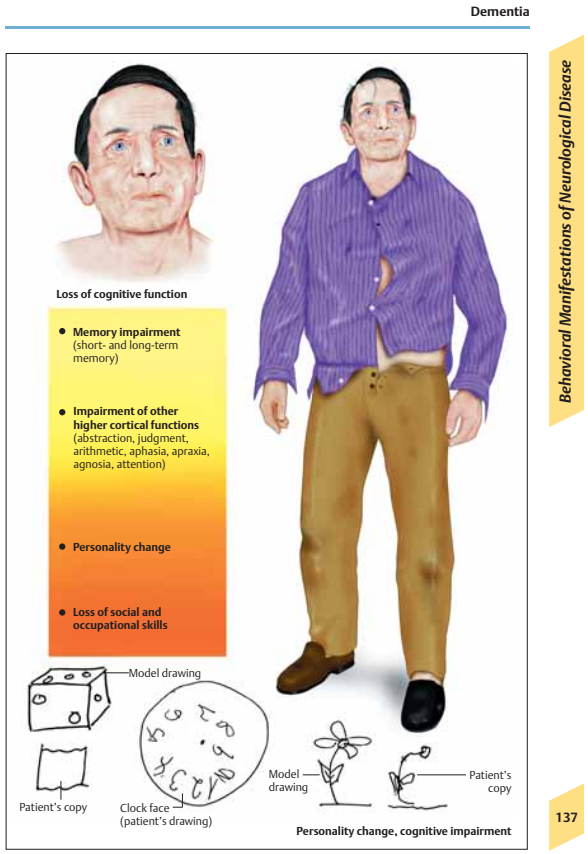


Diagram of ventriculoperitoneal shunt.

DEMENTIA:
TREATMENT

The major goals of management are to treat any correctable causes of the dementia and to provide comfort and support to the patient and caregivers.

No medications have been shown to prevent or cure dementia.



DEMENTIA:

TREATMENT

Removal of sedating or cognition-impairing drugs and medications is often beneficial.

If the patient is depressed rather than demented (pseudodementia), the depression should be vigorously treated.

Antidepressants that are low in cognitive side effects, such as SSRIs (e.g. *Escitalopram).*

DEMENTIA:

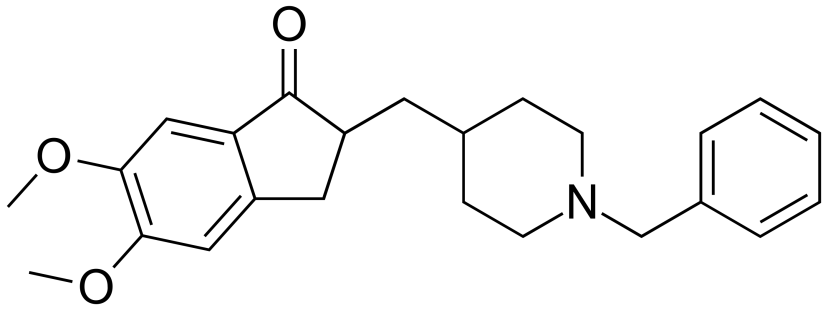
TREATMENT

Agitation, hallucinations, delusions, and confusion are difficult to treat. These behavioral problems represent major causes for nursing home placement and institutionalization.

Before treating these behaviors with medications, a thorough search for potentially modifiable environmental or metabolic factors should be sought.

DEMENTIA:
TREATMENT

Acetylcholinesterase inhibitors, such as ***donepezil***, may be useful for Alzheimer disease and dementia in Parkinson's, DLB, or vascular dementia. The quality of the evidence is poor and the benefit is small.



DONEPEZIL

DEMENTIA:
TREATMENT

N-methyl-D-aspartate (NMDA) receptor (*glutamate receptor)* blockers such as ***memantine*** may be of benefit but the evidence is less conclusive than for AChEIs.

Chemical structures of ***MEMANTINE***

DEMENTIA:

TREATMENT

Hunger, lack of exercise, toothache, constipation, urinary tract infection, or drug toxicity all represent easily correctable factors that can be treated without psychoactive drugs.

Drugs such as ***phenothiazines*** and ***benzodiazepines*** may ameliorate the behavior problems, but have untoward side effects such as sedation, rigidity, and dyskinesias.

DEMENTIA:

TREATMENT

Nondrug behavior therapy has an important place in the management of dementia. The primary goal is to make the demented patient's life comfortable, uncomplicated, and safe.

Preparing lists, schedules, calendars, and labels can be helpful. It is also useful to stress familiar routines, short-term tasks, walks, and simple physical exercise.

DEMENTIA:

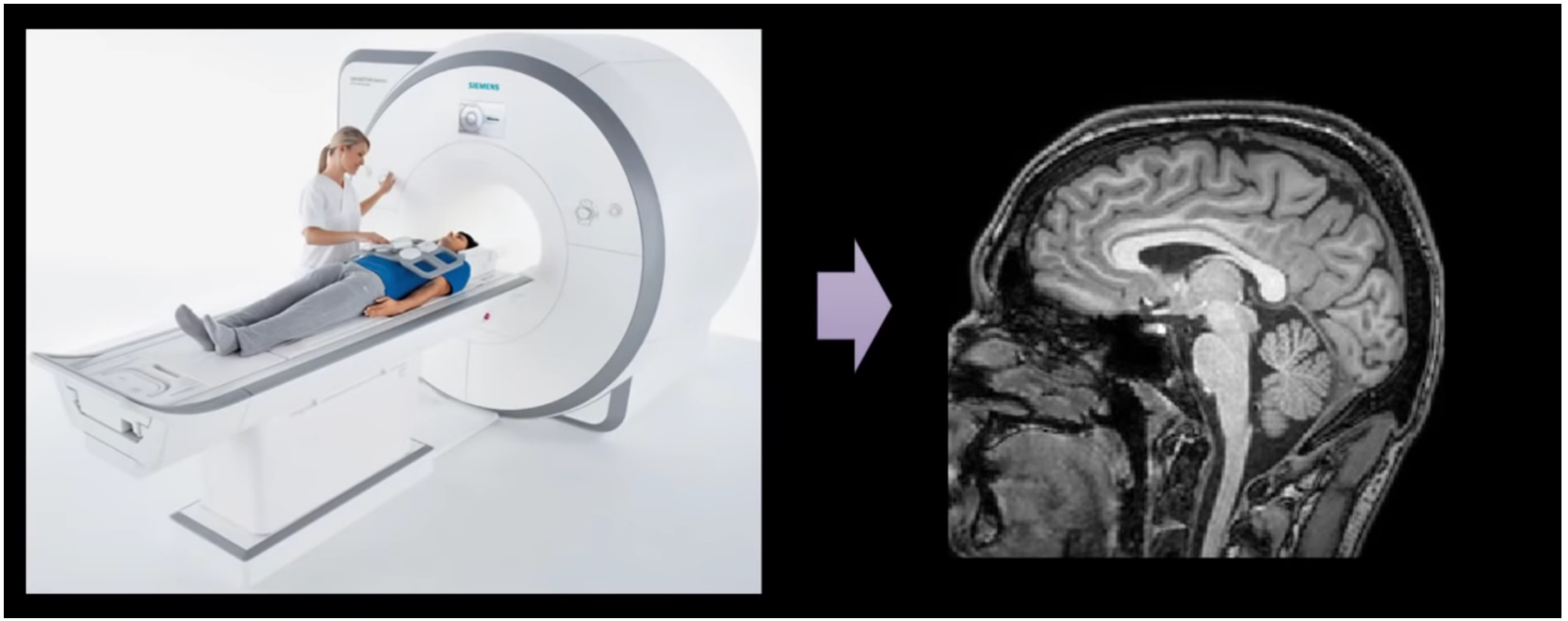
TREATMENT

Attention should also be paid to frustration and depression in family members and caregivers. Caregiver guilt and burnout are common. Family members often feel overwhelmed and helpless and may vent their frustrations on the patient, each other, and health care providers.

MAGNETIC RESONANCE INVESTIGATION: PRINCIPLES, CLINICAL UTILITY

Prof. M. GAVRILIUC

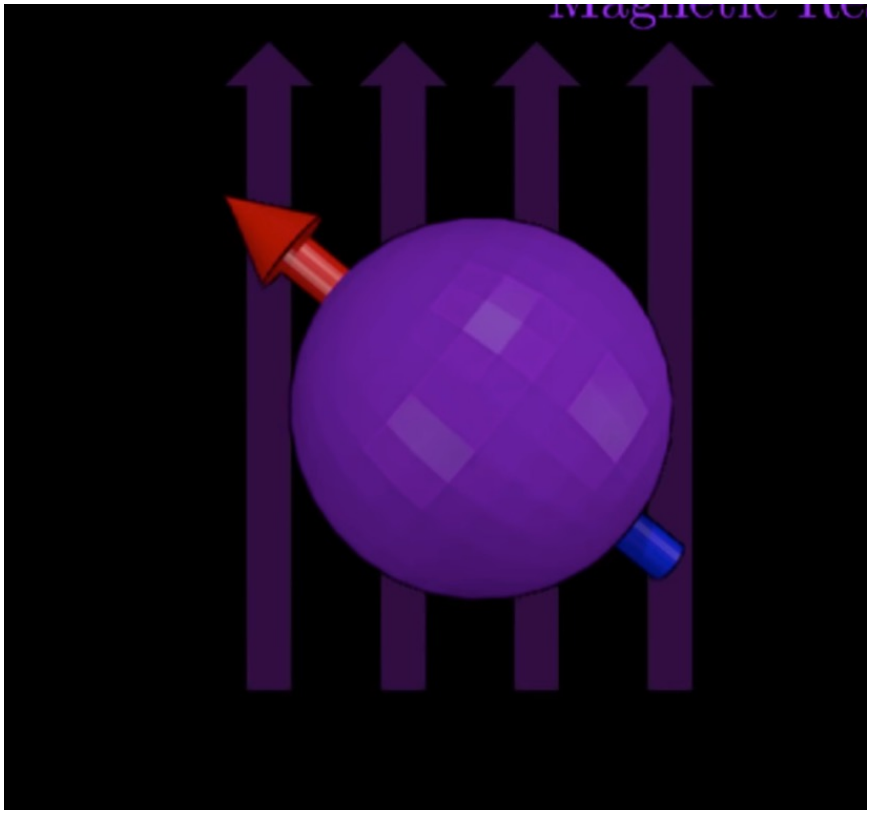
How does an MRI work?



MRI: MAGNETIC RESONANCE IMAGING

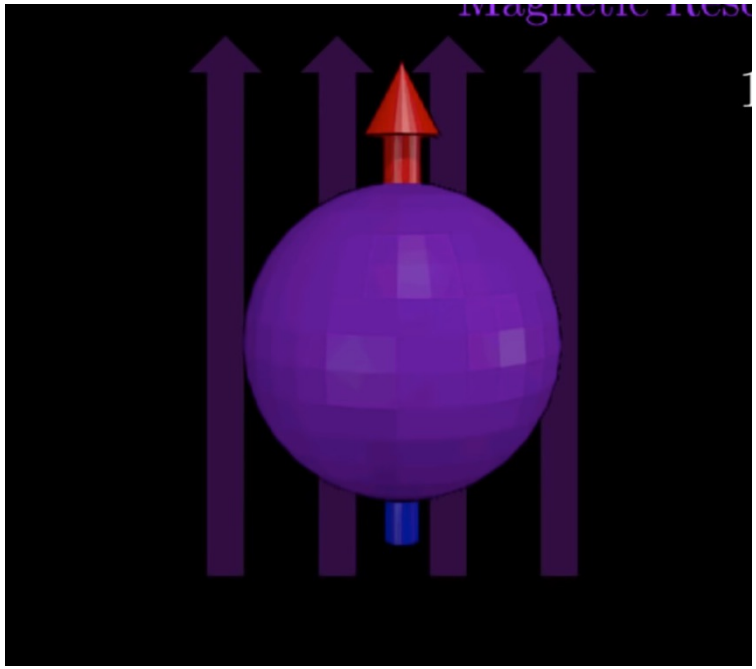
PRINCIPLE OF MRI

Protons inside hydrogen atoms are exposed to a strong magnetic field (the power of the field is measured in Tesla units - 1.5T, 3T etc.) for several milliseconds.

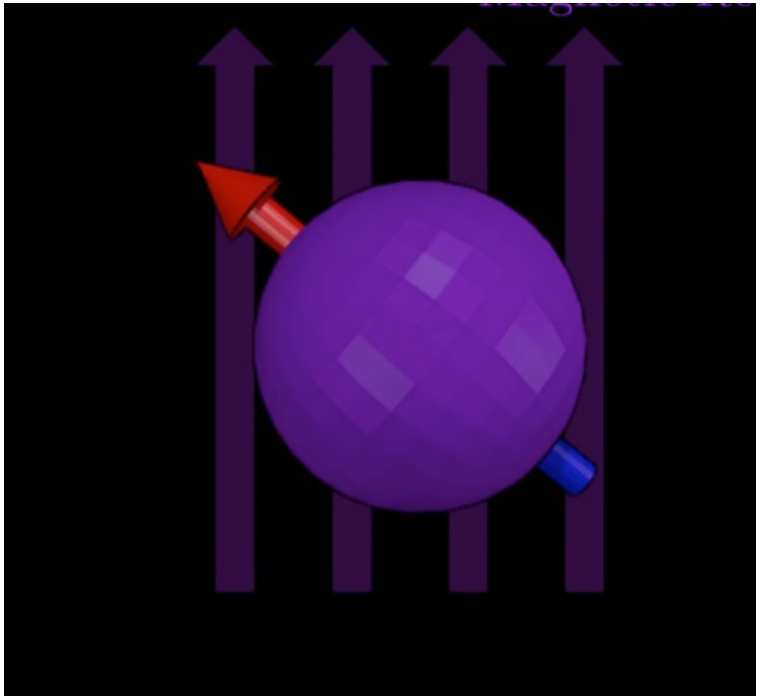


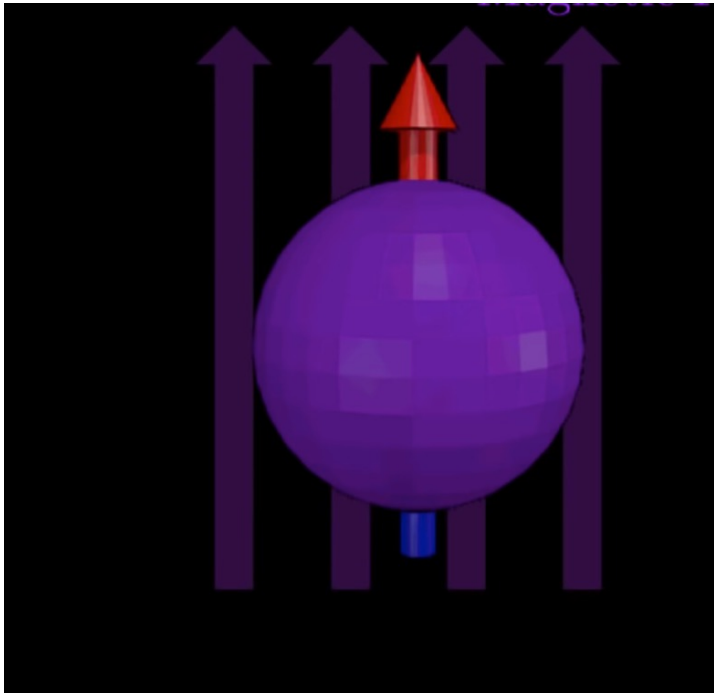
PRINCIPLE OF MRI

Because of this they come out of their equilibrium state and align (resonate with the magnetic field) in one direction or another.



Magnetic field aligns nuclei

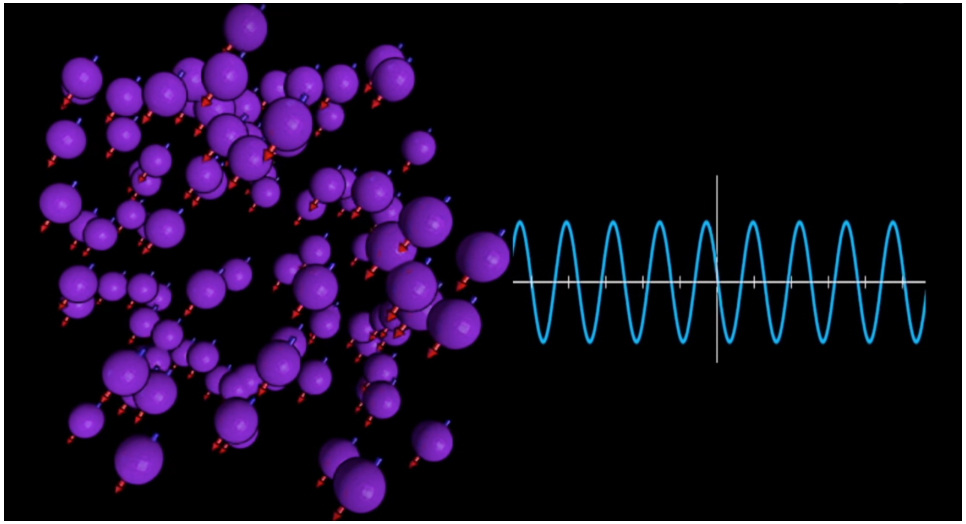




Disconnecting the magnetic field leads to their relaxation.

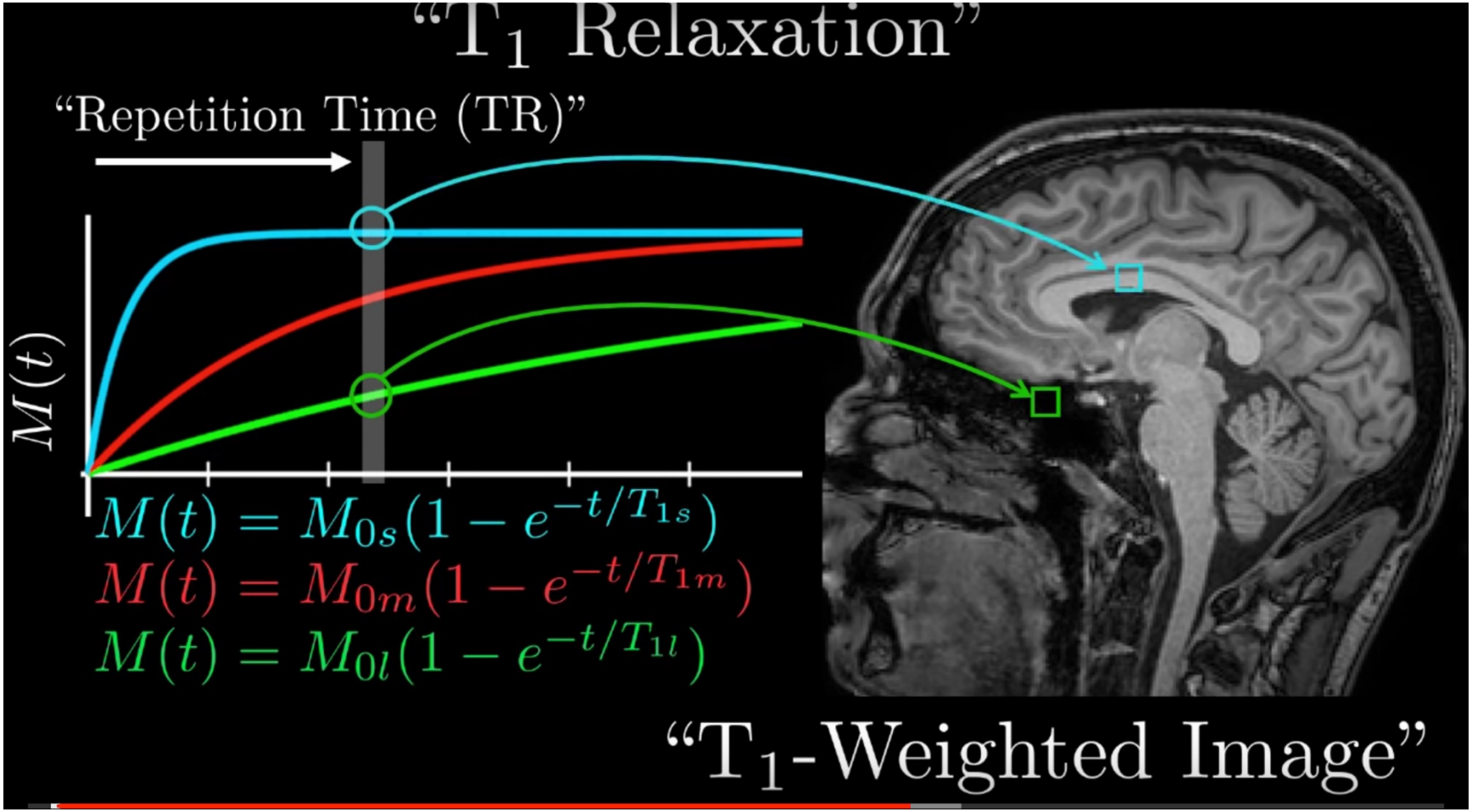
PRINCIPLE OF MRI

Both the alignment (T1 regime) and the relaxation (T2 regime) result in the emission of a very weak radio signal captured and analyzed according to a special program by the RM apparatus.

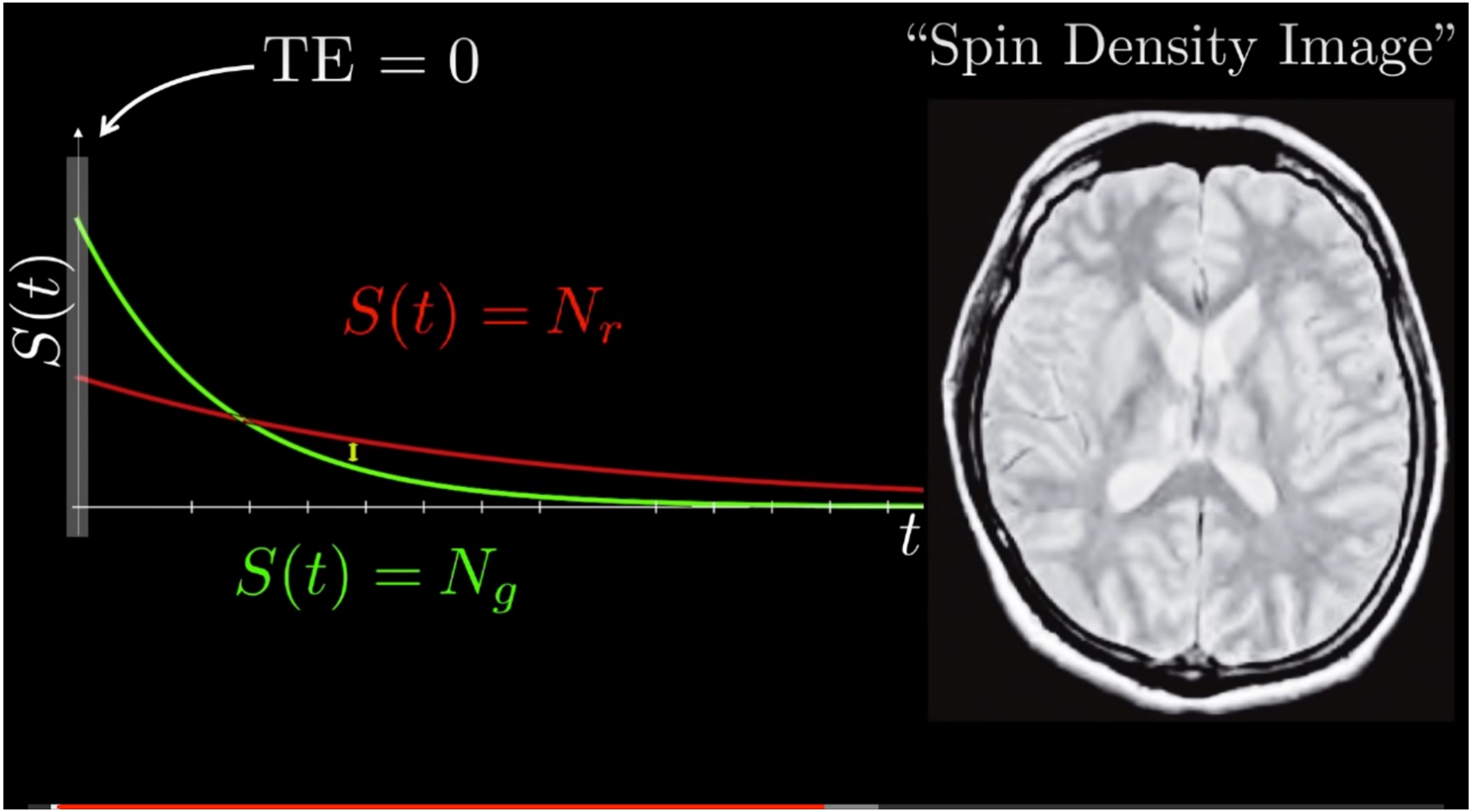


The patient inside the MR machine hears some strange sounds that correspond to the start / stop of the magnetic field generator coils.

Various tissues generate different responses, which can be attenuated or canceled by the waves emitted by the MR machine, so that only the desired tissue can be "visualized" to be explored.

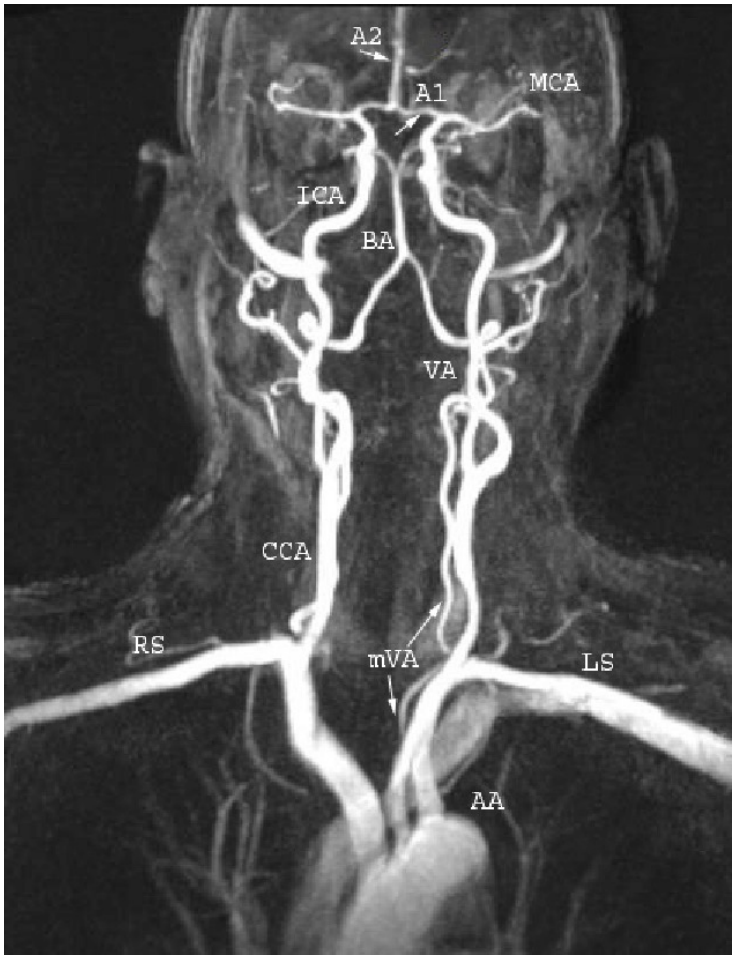


Various image contrasts can be obtained by combining repetition and echo times.

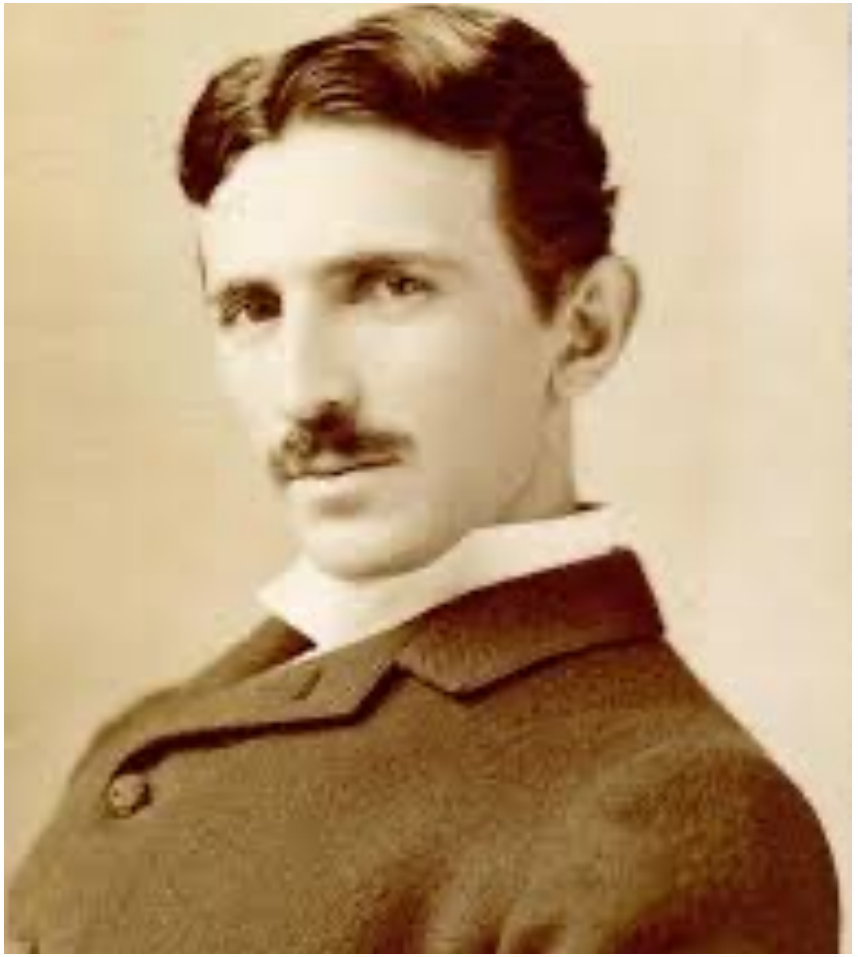


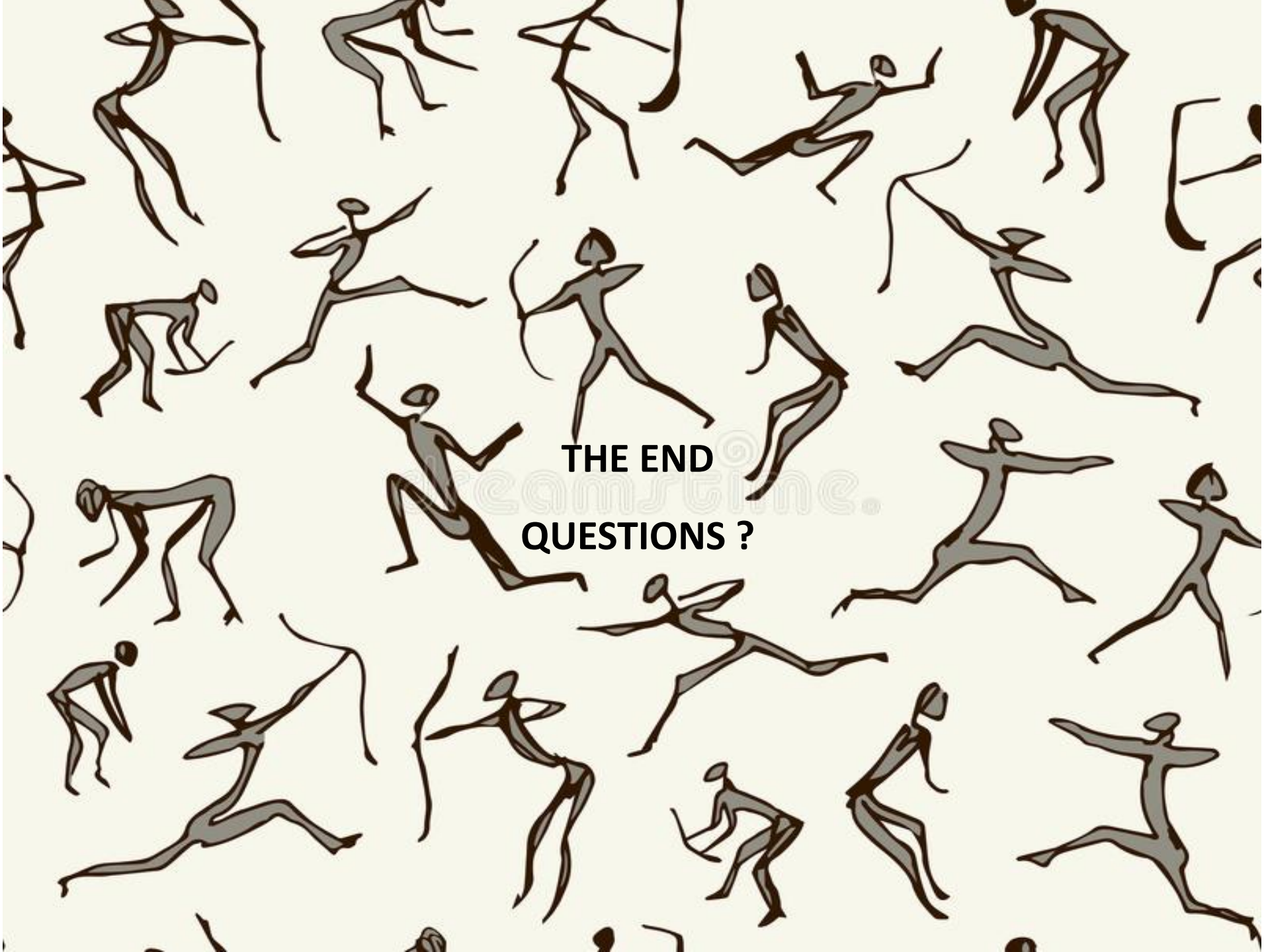
PRINCIPLE OF MRI

Protons after a certain time reach "saturation" and no longer respond to the connection / disconnection of the magnetic field, at this time it is possible to record the signal coming from the hydrogen protons of the "fresh, unsaturated" blood entering the tissue.



The inventor of the RM device is Peter Mansfield; Nikola Tesla discovered the magnetic resonance effect.




THE END
QUESTIONS ?