Annals of the Academy of Romanian Scientists
Series on Philosophy, Psychology and Theology
ISSN 2067-113X Volume **1**, Number **1**/**2009**

THE NEURAL BASIS OF CONSCIOUSNESS

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Rezumat. *Probabil că nici un alt concept nu este la fel de dificil de înţeles cum este conştiinţa umană. Natura sa a fost dezbătută de secole de filosofi (cum ar fi Haldane şi Ross, 1911), timp de decenii de psihologi (Gray 1995) şi în ultimii 10 ani de specialiştii din domeniul neuroştiinţelor (Crick şi Koch 1990), pe măsură ce au avansat cunoaşterea şi tehnicile până la punctul în care în sfârşit este posibilă o abordare experimentală mai complexă a subiectului (Grossman 1980).*

Puţini specialişti din domeniul neuroştiinţelor declară făţiş că interesul lor principal de studiu îl reprezintă conştiinţa. Aceasta nu este o sarcină facilă: să ne amintim că avem de-a face cu un fenomen presupus neobservabil.

Divizând conştiinţa în atribute variate, auto-reflexivitate, atenţie, memorie, emoţie, percepţie, excitare, şi ordonându-le într-o ierarhie funcţională putem face legătura dintre anatomie şi funcţie.

Astfel, conştiinţa trebuie să fie o funcţie a numeroase sisteme aflate în interacţiune. Nici una dintre structurile neurale nu este necesară şi suficentă pentru conştiinţă. Nu toate zonele creierului contribuie egal la conştiinţă. Structurile majore care se presupune că ar juca un rol cheie în corelatele neurale ale conştiinţei sunt: brainstemul, diencefalonul (mai ales hipotalamusul şi talamusul), sistemul limbic (mai ales hipocampusul şi amigdala) şi cortexul cerebral.

În acord cu această perspectivă, brainstemul ocupă baza polului totem, asigurând mecanismul bazal de excitare fără de care regiunile superioare ale creierului nu pot opera.

Oricum, creierul este o asemenea structură complexă încât chiar şi acum ştim numai o mică parte din ceea ce este de ştiut.

Abstract. *Perhaps no concept is as difficult to define and understand as human consciousness. Its nature has been intensively debated for centuries by philosophers (Haldane and Ross 1911), for decades by psychologists (Gray 1995), and for the past 10 years by neuroscientists (Crick and Koch 1990) as knowledge and techniques have advanced to the point at which an experimental approach to with a complex issue is finally possible (Grossman 1980).*

Few neuroscientists declare frankly that consciousness is their main research interest. This is not an easy task; let's remember that we are dealing with a supposedly unobservable phenomenon.

By dividing consciousness into various attributes self-reflexion, attention, memory, emotion, perception, arousal, and ordering these into a functional hierarchy we can link anatomy and function.

So, consciousness must be a function of numerous interacting systems. No single neural structure is necessary and sufficient for consciousness. Not all areas of the brain contribute equally to consciousness. The major structures supposed to play key role in the neural correlates of consciousness are: brainstem, diencephalon (especially

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hypothalamus, and thalamus,), limbic system (especially hippocampus, and amygdala), and cerebral cortex.
According to this view, the brainstem occupies the bottom of the totem pole, providing the basis arousal mechanism without which the higher brain regions cannot operate.
Anyhow, the brain is such a complex structure that even now we know only a tiny portion of what is to be known about it.

Keywords: consciousness, neuroscientists, self reflexion, interacting systems, brainstem

Brain stem

Brain stem is the portion of the central nervous system rostral to the spinal cord and caudal to the cerebral hemispheres.

Neuroanatomists commonly confine the term to the midbrain, the pons, and the medulla oblongata, without the cerebellum (the little brain). This is the meaning adopted by us for the term brain stem.

Certain brain stem neurons (including lower motoneurons, premotor neurons, and interneurons) are arranged diffusely in regions of the medulla, pons, and midbrain, scattered between ascending and descending fiber bundles.

The net-like appearance of the regions containing these neurons led to the designation "reticular formation", a term that was originally used in a purely descriptive anatomical sense.

Reticular formation

The reticular formation (RF), a phylogenetically old set of neurons, is called "reticular" (i.e., network-like) because the neuronal axons in this system are usually very short, suggesting a great amount of interaction between adjacent neurons that function like networks of reticulum.

Reticular formation, beginning in the medulla and extending to the midbrain plays a major role in the sleep-wakefulness cycles of animal and human (fig. 1).

It occupies a significant portion of the dorsal brainstem and forms a network of reticular fibers that synapse with and modulates many ascending and descending fiber tracts.

The neurons of the reticular nuclei are structurally distinct in that they possess exceptionally long dendrites that extent to all parts of the brainstem making connections quite distant from their cell bodies. The reticular formation has been the subject of widespread investigation in an attempt to better understand the activation of intellectual and emotional functions, circadian rhythms, movement coordination, and sensory pathway modulation (Paxinos 1990).

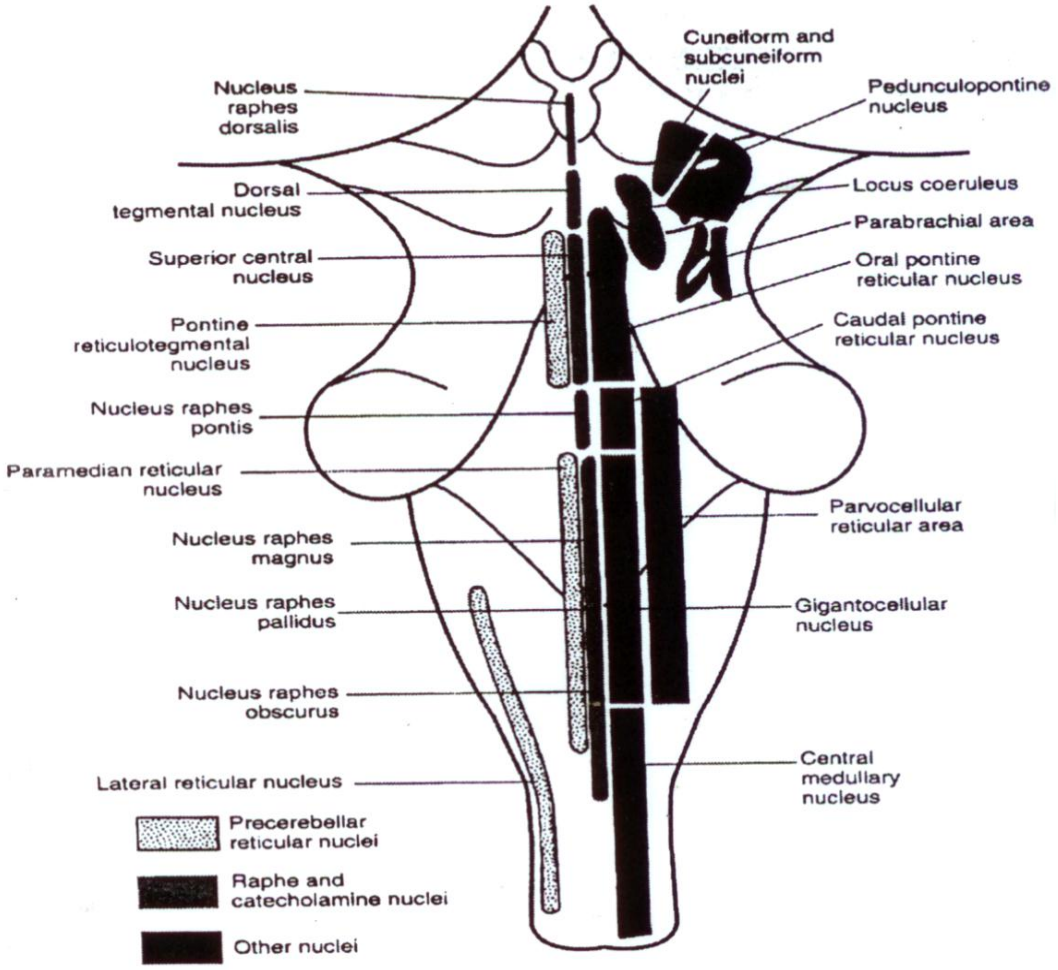


Fig. 1. Reticular formation of the brainstem. (From Barr ML, Kiernan JA –The Human Nervous System: An Anatomical Viewpoint, 6th ed. Philadelphia, JB Lippincott, 1993).

Nuclei of RF receive afferents and information from all sensory (visual, auditory etc.) and motor systems as from other major structures of the brain, and projected their axons upwards and downwards to virtually all parts of the nervous system.

Through their connections with the thalamus they can send information to, and receive it from all areas of the cortex.

The RF is also known as reticular activating system and the reticular inhibiting system (Dănăilă, 1972; Arseni and Dănăilă, 1977).

So, brain stem is the source of massive reticular formation pathways that activated or inhibit higher and lower brain centers. They are the core of the basic arousal and sleeping cycle.

Gastaut (1958) described the brain stem reticular formation as an area of: "convergence... where signals are concentrated before being redistributed in a divergent way to the cortex".

Anyhow, any cortical activity must trigger extended reticular-thalamic system support in a circulating flow of information, before it can be broadcast globally and become conscious (Scheibel and Scheibel 1965, Shevrin and Dickman 1980).

Dixon (1971) has also argued that a circulating flow of information between the reticular formation and sensory areas of the cortex is required before sensory input become conscious.

However, the reticulo-thalamic system does not work in isolation with all modes of sensory processing (sight, hearing, touch).

The role of reticular formation (this broadcast system in the brain) is to awake or to sleep the cerebral cortex.

After awake the cortex allows all modes of sensory processing (sight, hearing, touch, etc.) to combine with conscious thought and experience in order to focus on some inputs and suppress other.

His clearly that RF does not work in isolation in these types of brain function. The hypothalamus, the thalamus and the cerebral cortex are likely closely intertwined with RF who plays a key role in consciousness.

Neuroscientists now recognize that the various nuclei within the brainstem serve many functions and that only a few take parts in waking and sleeping.

So, functionally there are different subgroup within the reticular formation: cardiac and respiratory centers within the medullary reticular formation; pontine and medullary nucley of the reticular formation who contribute to motor control via the cortico-reticulo-spinal system, and the muscle tone; ascending projection system who ascend to the hypothalamus and the thalamus, and project to various nonspecific thalamic nuclei and diffusely to the cerebral cortex.

Anyhow, both the periaqueductal gray of the midbrain and the locus ceruleus are considered part of the reticular formation.

The cerebral cortex sends fibers to the RF nuclei, forming part of so-called cortico-bulbar fibers. Those nuclei that give off the pathways to the spinal cord form part of an indirect motor system – the cortico-reticulo-spinal pathways. These pathways are known to have an important role in the voluntary control of the muscles of the spine (axial musculature) and those of large joints (proximal joints of the shoulder and hip).

In addition, this system is known to play an extremely important role in the control of muscle tone.

Lesions of the cortical input to the reticular formation have a very significant impact on muscle tone and reflexes (Hendelman 2000).

Instead of being used in a descriptive analogical way, the reticular formation was promoted to a functional concept, a brain stem system which, by virtue of its nonspecific connectivity, could act as a kind of volume control for the degree of conscious arousal and sleeping.

The rostral part of the brain stem reticular formation becomes the "ascending reticular activating system" and loss of consciousness with brain stem injury was attributed to the damage to this system.

The caudal part of the brain stem reticular formation was seen as a source of descending excitatory or inhibitory inputs to various brain stem centers and to the spinal cord.

Ascending reticular activatory system (ARAS)

The reticular formation is more commonly known as the reticular activating system. It obtained this designation in 1949 when Moruzzi and Magoun stimulated it electrically in anesthetized cats and found that the stimulation produced a waking pattern of electrical activity in cat's cortex.

The reticular formation and the reticular activating system are interrelated but do not have the same structure and are not physiologically equivalent (Moruzzi and Magoun 1949).

A state of wakefulness requires that the reticular activating system be active in its projections to the cerebral hemispheres. A variety of pathways are available for this.

The most important reticular nuclei for arousal and consciousness are the raphe nuclei and the central nuclei.

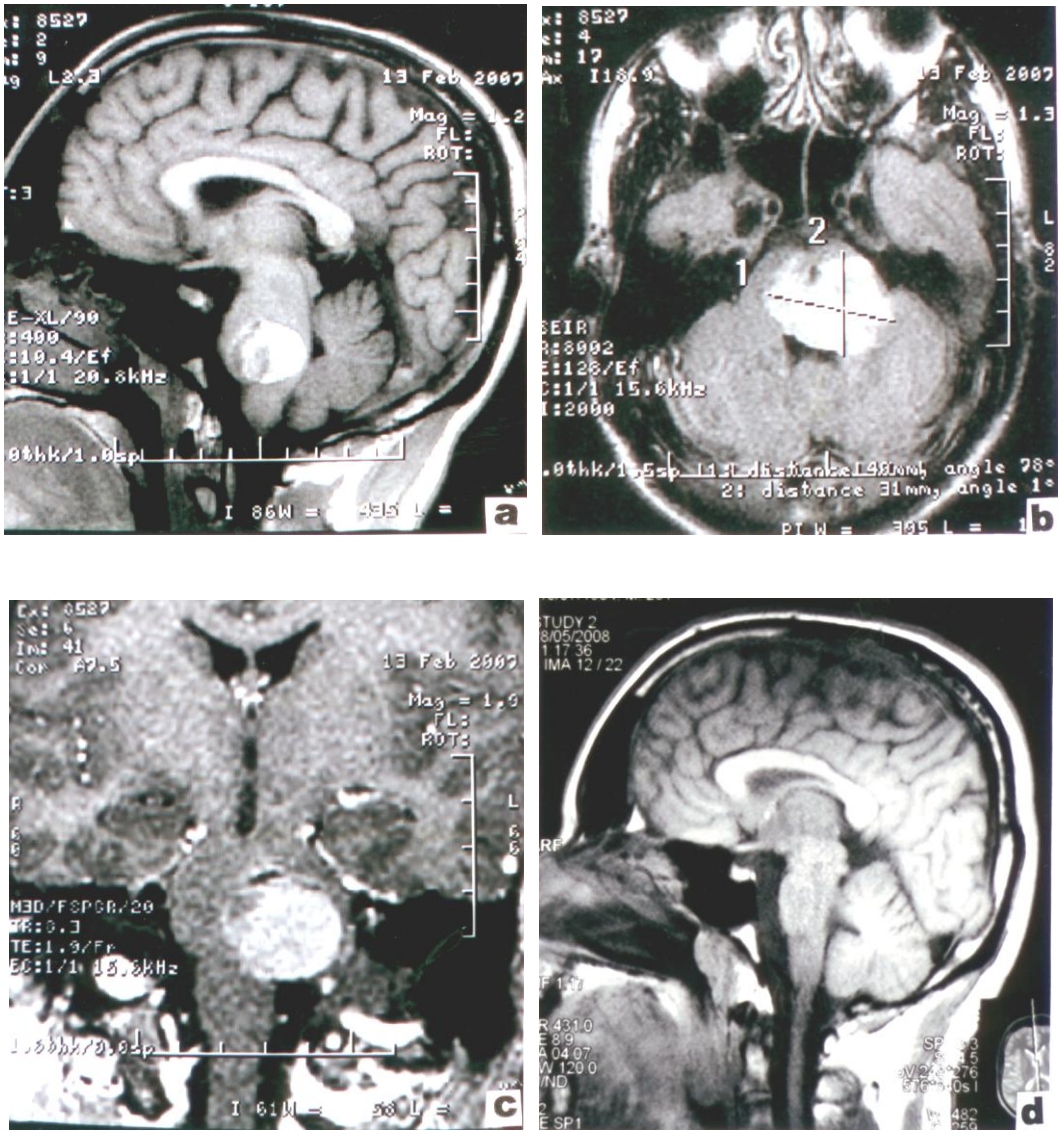
The central group of nuclei forms the major component of what is commonly referred to as the reticular activating system. This group receives significant converging sensory input from all sensory modalities and projects to the thalamus (i.e. intralaminar nuclei), cholinergic basal forebrain nuclei, and the entire cerebral cortex. An important component of the central reticular activating system is thought to be the noradrenergic nuclei, particularly the locus ceruleus, at the pontomesencephalic junction.

The neurons of the locus ceruleus project to the thalamus, hypothalamus, basal cholinergic nuclei, and neocortex (Moore and Bloom 1979).

Immediate coma results from destruction of the central reticular nuclei at or above the upper pontine level (fig. 2).

In vivo recordings reveal that the cells of the locus ceruleus are active only in animals in the awake state (Barr and Kierman 1993).

These interactions are complex and require a complete feedback loop from the cerebral hemispheres to the diencephalon, as well as through the reticular formation in the brainstem.



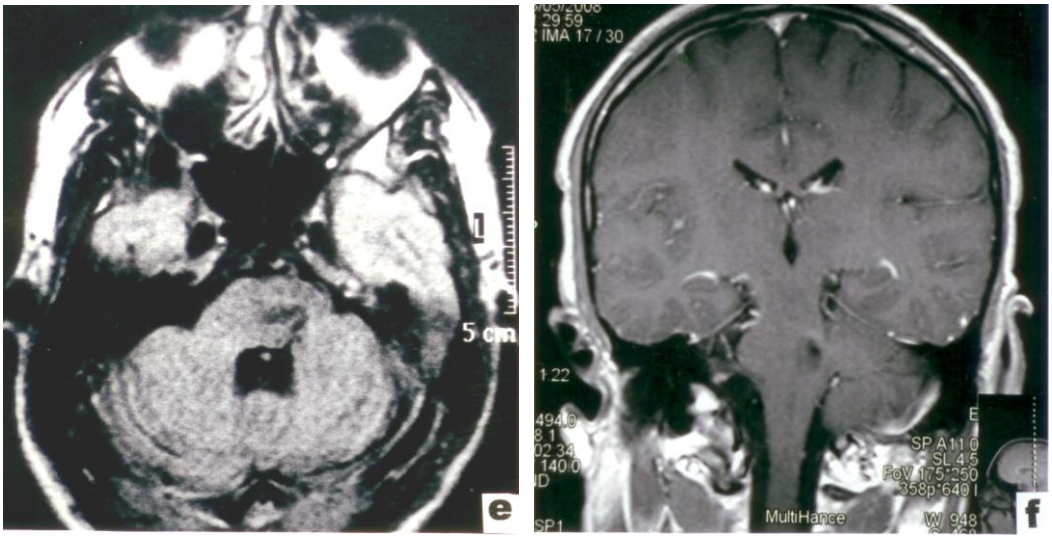


Fig. 2. A 21-year old man who presented with a history of sudden onset of coma.

Sagital (a), axial (b) and coronal (c) T1-weighted resonance imaging (MRI) scans revealed a gross pontine hemorrhage (1,9cm) from a cavernous malformation that reached the surface of the floor of the fourth ventricle and in the cerebelopontine angle. The lesion was resected through a subcortical approach. Sagital (d), axial (e), and coronal (f) MRI scans 1 year later reveal no recurrence. Two month after consultation, the patient presented with minimal right sided weakness and hemisensory deficits. Now the patient is student.

Anyhow, ascending reticular activatory system, acts on the cerebral cortex through the thalamus, directly, and through the arousal caudal hypothalamic neurons (see the hypothalamus) who are connected with suprachiasmatic nuclei (fig. 3).

Moruzzi and Magoun concluded that the function of the reticular formation was to control sleeping and waking.

As a result, the reticular formation comes to be known as the reticular activating system, that is to maintain “general arousal” or “consciousness” and as the reticular inhibitory system for sleeping.

Data from electrophysiologic recordings classically have demonstrated that the transition from the sleeping to the alert state is accompanied by transitions assessed by electroencephalography (EEG) from high-voltage low-frequency (HVLF) to low-voltage high- frequency (LVHF) cortical activity (Berger 1929). This has been called desynchronization of the EEG. Transection experiments by Bremer (1968) at the first cervical segment produced an isolated brain with cortical activity that alternated between HVLF and LVHF.

In contrast, intercollicular transection resulted in an isolated cerebrum that remained in the HVLF state and was unarousable (Bogen 1997).

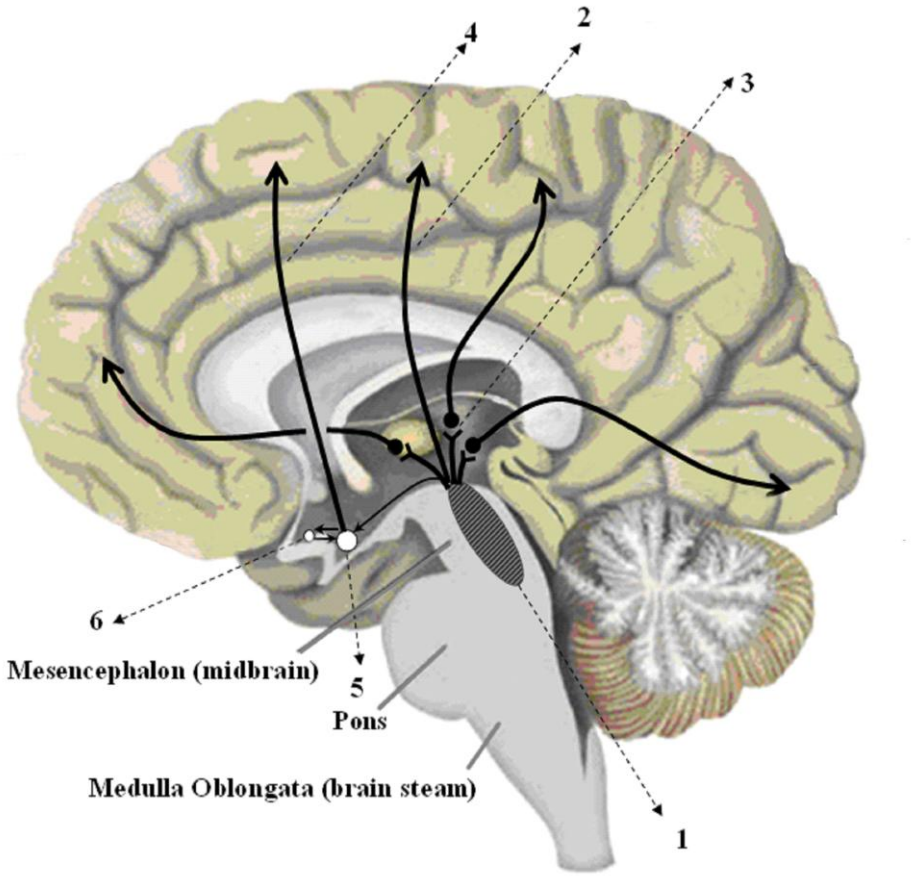


Fig. 3. The Ascending Reticular Activating System (ARAS) is found in the brain steam (1), and sends projections throughout the cortex: directly (2), through the talamus (3), or trough the hypothalamus (tuberomammilary neurons) (4), (5), who receives influence from suprachiasmatic nucleus (6).

Classic experiments on the reticular formation by Morruzi and Magoun (1949) demonstrated that stimulation of portions of the reticular formation resulted in EEG desinchronization. These initial experiments led to the concept of a reticular activating system. If, however the intercolliculary transected cats are chronically maintained, the activity return to the LVHF state (Jouvet 1967). This finding seems to indicate that the thalamocortical activity that produces a mechanism of consciousness can arise in the absence of direct reticular activating system input.

The careful analysis of human brainstem stroke causes performed by Plum and Posner (1982) demonstrated that functional transections near the level of the nucleus of cranial nerve VIII are capable of "the outward appearance of consciousness".

Experiments in the cat demonstrated also that animals with transections as high as the cranial nerve V entry zone are capable of responses to visual and olfactory stimuli, as recorded by EEG and visual tracking, that seem to represent awareness (Batini et al., 1959).

In this situation, the thalamic reticular system and the arousal hypothalamic neurons operate. Anyhow, exact physiologic role of the reticular activating system in consciousness in unclear.

Ascending reticular inhibitory system (ARIS)

It is impossible that the two important functions of the central nervous system make-up and sleep, or activation and inhibition depend only on the ascending reticular activatory system (ARAS).

Dănăilă (1972 and Arseni and Dănăilă (1977) have clinically demonstrated, that besides the ARAS there is an ascending reticular inhibitory system (ARIS) as well, whose lesion leads to the appearance of the logorrhea syndrome with hyperkinesia.

The lateral group of the reticular formation localized in the pons and rostral part of the brain stem, gives origin to the ascending reticular inhibitor system (ARIS).

When ARIS is activated, the cerebral cortex becomes inactive and the person asleep.

This system receives inhibitory signals from the cerebellum and sends output signals to the thalamus to the hypothalamic sleeping center and directly to the cerebral cortex (fig. 4).

The raphe nuclei, in the midline of the brainstem, use serotonin as their primary neurotransmitter and have diffuse connections to cerebral cortex and subcortical gray matter (More et al., 1978)

Increased activity in this region is important in the induction of sleep and therefore in the decreased arousal (Lindsley 1960). Thus, correlated activity between reticular neurons leads to strengthened connection between them, both excitatory and inhibitory.

Same studies indicated that reticular activating system stimulation, which desynchronizes the EEG below 20 Hz, can facilitate synchrony in the gamma range of 20 to 70 Hz (Munk et al., 1996).

Anyhow thalamic reticular nuclei efferent use gamma-amino-butiric acid (GABA), a major inhibitory neurotransmitter (Bogen 1997).

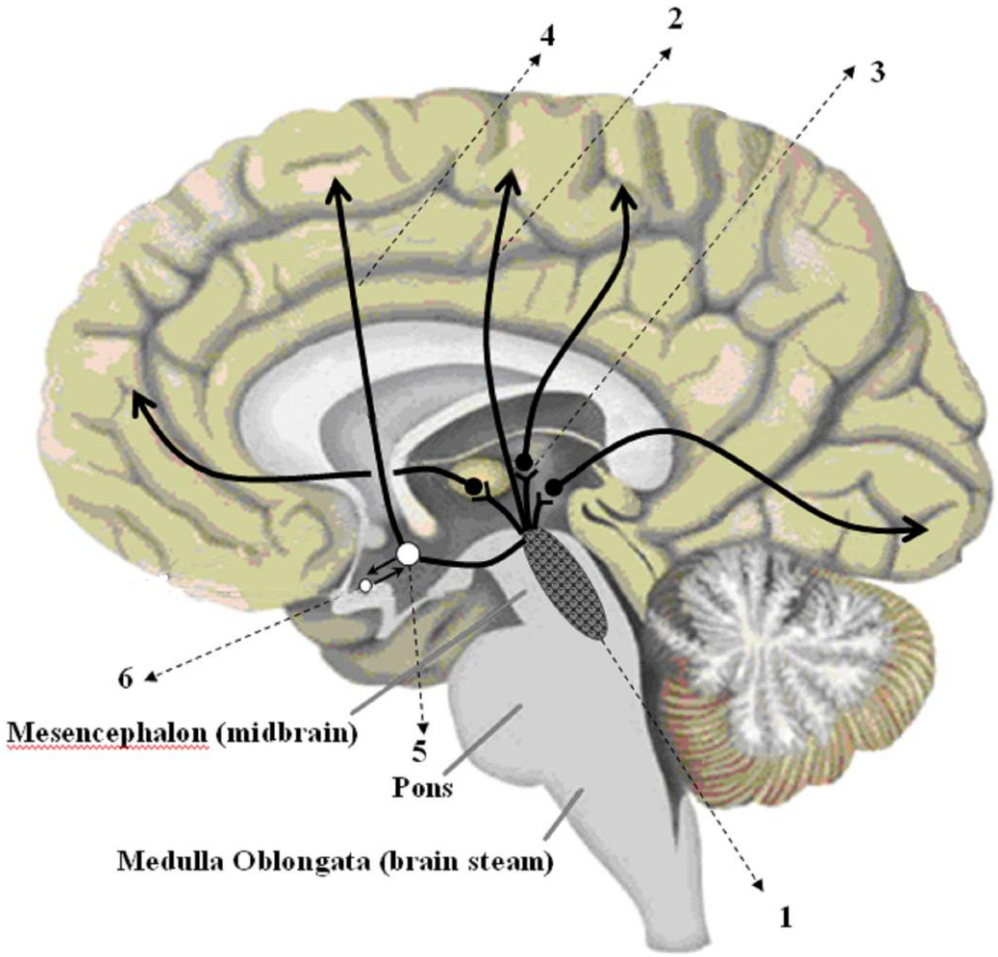


Fig. 4. The Ascending Reticular Inhibitory System (ARIS) is found in the brain steam (1), and sends projections throughout the cortex: directly (2), through the talamus (3), or trough the hypothalamus (ventrolateral nucleus preoptic nucleus-VLPO) (4), (5), who receives influence from suprachiasmatic nucleus (6).

The problem was that the very nonspecific and all-inclusive nature of the reticular formation, conceived as a kind of functioning neuronal system, made it difficult to generate research hypotheses. This extended use of the term, meant that the reticular formation becomes elevated to a magical entity, an easy shorten explanation of complex and little understood physiological process.

Clinical aspects

Alterations in consciousness have been discussed in the literature for more than 100 years. Anyhow it is important to distinguish between alertness and impairment of the wakeful state.

It is possible to be awake and not conscious, but it is impossible to be conscious and not awake.

Confusion also is introduced in the description of a patient's state of mentation; for example a patient with Alzheimer's disease is awake and usually alert in the early stages of disease, but he or she is also confused.

This term must be precisely defined (Ames and Marshall 2003). In their landmark text in 1966, Plum and Posner offered helpful suggestions for defining these terms, and in a later review, Plum provided an eloquent discussion of coma and related global disturbances (Plum 1991).

Locked-in syndrome

In severe brain stem dysfunction, the patient may be unable to move any more of the four limbs (quadraplegia) or even the head or any of the facial muscles so that the only way the patient can signal "yes" or "no" is by moving the eyes from side to side.

Such patients, with normal consciousness and normal higher intellectual function are described as being "locked in". Plum and Posner, developed the term locked-in syndrome in 1966 to reflect a state of quadriplegia and anarthria with preservation of cognition.

Typically, this unfortunate condition results from distructive lesions in the ventral pons or ventral midbrain.

Locked-in syndrome superficially resembles persistent vegetative state, minimally conscious state, and akinetic mutism in that the pacient is awake, but there is little or no purposeful movement.

In the classic complete locked-in syndrome, only consciousness, vertical eye movements and eyelid blinking are preserved.

Persistent vegetative state

The term persistent vegetative state was introduced by Jannet and Plum in 1972 to describe the state of preservation of autonomic function and primitive reflexes, without the ability to interact meaningfully with external environment.

In summary, the reticular formations (ARAS and ARIS) are connected with almost all parts of the central nervous system. Although it has a generalized influence within the CNS (controls arouse and sleep), it also contains subsystems that are directly involved in specific CNS function.

Its extensive system of ascending fibers produces the arousal necessary for attention, and consciousness, and the sleep.

Activity in the reticular formation is also the mechanism that provoke (determine) the sleep and awakens you from sleep and brings you back to full consciousness.

Thus damage here typically sends a person into coma because this is an on/off switch for all higher brain centers or determines the logorrhea syndrome with hyperkinesia (Dănăilă 1972, Arseni and Dănăilă 1977).

Many lines of evidence point to the importance of the brain stem in maintain the normal awake state of awareness.

Humans with damage to the region of the dorsal pons, midbrain, and thalamus (by trauma, brain tumor, viral or bacterial infection, ischemic or hemorrhagic stroke) may exhibit an impaired state of alertness, possibly becoming stuporose or comatose.

In animals, experimental transection at various levels of the spinal cord and brain stem established that coma issued after lesions through the level of the colliculi, but not after lesions through the level of the medullospinal junction.

Dysfunction of the upper brain stem (especially the more dorsal portion of the rostral pons), the midbrain region just ventral to the aqueduct, and the thalamus can cause the patient to be drowsy, stuporose, or unconscious. This presumally reflects damage to the ascending pathways of RF.

Extensive damage to the lower brain stem by any disease process usually ends the person's life because neural circuitry mediating vital respiratory and/or cardiovascular control no longer functions.

In a study on the behavior of patients with brainstem tumors and another neurosurgical condition, Dănăilă (1972), Arseni and Dănăilă (1977) observed that, apart from the akinetic mutism syndrome locked-in syndrome or coma the patients may also manifest various other aspects, especially logorrhea syndrome with hyperkinesia (fig. 5).

We consider that the logorrhea syndrome with hyperkinesia is an opposed syndrome to that of akinetic mutism, locked-in syndrome or coma.

At the basis of the akinetic mutism syndrome there is a clear-cut lesion in the ascending reticular activator system (ARAS). The logorrhea syndrome with hyperkinesia is produced by lesion of the ascending reticular inhibitory system (ARIS).

The lesions found in our cases (pons, rostral part of the brain stem, hypothalamus, anterior, and internal side of the temporal lobe) mark the pathways of the ARIS. The cerebral symptomathology exhibited by our patients was so varied (logorrhea with or without hyperkinesia) that it can only be accounted for

by intricate, concomitant and greater or lesser damage of the two antagonist ascending reticular system, the activator and the inhibitor systems.

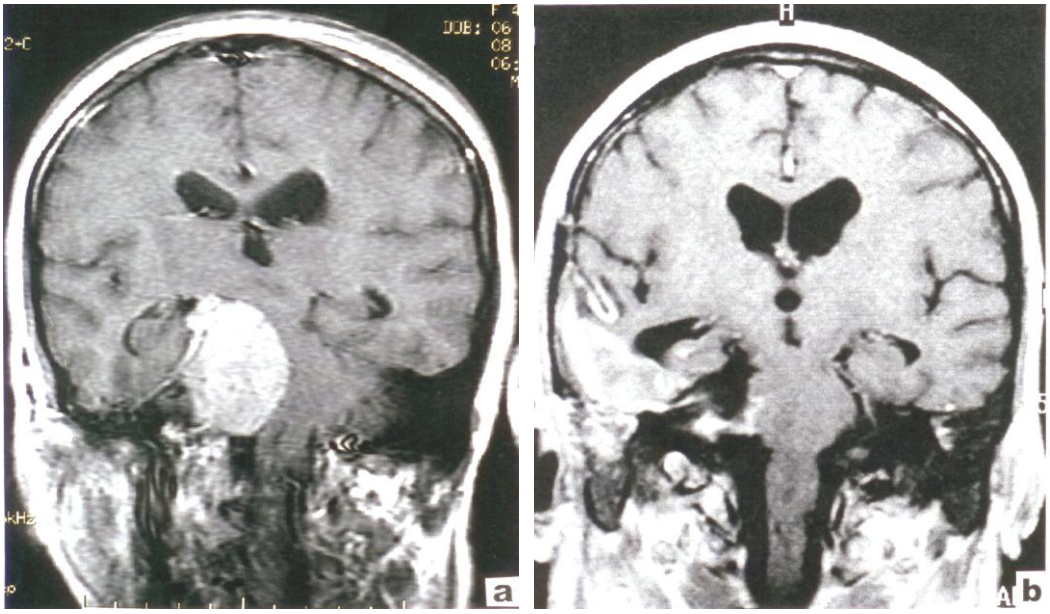


Fig. 5. MRI studies of a petroclival meningioma (a) who compress from outside the brain stem provoke logorrhea syndrome with hyperkinezia. Postoperator (b) this syndrome disappear.

Besides the other homeostatic systems, the reticular systems represents an actual regulator system of the entire neuraxis, as proven by its participation in the regulation of all the psychical processes (attention, memory, reasoning, behavior, etc), speech, muscular tonus, and the physiognomy of movement, etc. With input to the muscular tonus it must by recalled that rigidity following decerebration, decortication or ventricular seizures is likewise caused by lesion of the ARIS (Arseni şi Dănăilă, 1977).

Diencephalon

The diencephalon contains the hypothalamus, thalamus, subthalamus (substatia nigra, the zona incerta, the nucleus of the tegmental fields of Forel, ansa lenticularis, Forel's field H1-thalamic fasciculus- Forel's field H2 –lenticular fasciculus-, and subthalamic fasciculus), metathalamus (medial geniculate body and lateral geniculate body), and epithalamus (pineal gland, habenular trigones, stria medullaris, and roof of the third ventricle. Sometimes the thalamus and hypothalamus (grouped together as the diencephalon) have been included with the brain stem, especially by physiologists, who developed the concept of the reticular activating system.

In the following we are going to study only the role of hypothalamus and thalamus in sleep and arousal.

The hypothalamus in sleep and arousal

Introduction

The hypothalamus has long been recognized as an important integrative area for the regulatory control of behavioral state and the temporal organization of behavior.

Early evidence from lesion and stimulation paradigm implies regions of the hypothalamus in the control of sleep, arousal states, and other rhythmic aspects of behavior and physiology.

Sleep

According to sleep researcher Hobson and associates (1998), "sleep is characterized by a recumbent posture, a raised threshold to sensory stimulation, decreased motor output and a unique behavior, dreaming".

Sleep is, ironically, one of the least well-understood biological phenomena, yet over one third of our lives are spent in this behavioral state.

Various hypotheses of sleep function and the functional significance of sleep have been proposed. Whereas each theory most likely holds some truth, a unified sleep theory remains elusive.

Lesion studies correlating anterior hypothalamic damage with insomnia and caudal hypothalamic damage with somnolence were particularly informative.

These and subsequent studies resulted in the concept of hypothalamic "sleep centers".

It is now apparent that at least two distinct populations of neurons in the rostral and caudal hypothalamus are responsible for the hypothalamic effect of sleep.

It was demonstrated that neurons in a circumscribed region of the preoptic area (the ventrolateral preoptic nucleus - VLPO) in rats express Fos, the protein product of the protooncogene c-fos, which appears shortly following the onset of sleep. Since Fos expression reflects neuronal activation, this observation raised the possibility that VLPO neurons involved in the initiation of sleep.

Specifically, evidence now supports the conclusion that VLPO neurons are inhibit arousal through projection to histaminergic neurons in the tuberomammillary (TM) nuclei of the caudal hypothalamus (Parent 1997, Card et al., 1999).

In support to this conclusion, it was shown that GABA-ergic neurons in VLPO synapse on TM neurons and that pharmacological inhibition of TM neurons or blockade of histaminergic receptors promote sleep (Card et al 1999).

Importantly, neuromechanical lesions of VLPO and surrounding neurons have revealed greater functional parcellation of the anterior hypothalamic circuitry involved in sleep regulation.

Lesion confined to the compact portion of VLPO dramatically reduces non-REM sleep and, in circumstances in which lesions are incomplete the amount of non-REM sleep is linearly correlated with the number of Fas-expressing neurons in the portion of the VLPO that survived the lesion.

Interestingly, lesions dorsal to VLPO that eliminate galanin-containing neurons that project to TM produce sleep deficits more closely associated with REM than with non-REM sleep.

These observations provide compelling evidence in support of a prominent role for the hypothalamus in sleep regulation and further indicate that there is functional parcellation in the neurons of the VLPO which participate in this control.

It is also clear that the hypothalamus plays an important role in the temporal organization of the sleep-wake cycle.

Sleep is a circadian function, and although the suprachiasmatic nuclei (SCN) are not essential for the generation of sleep, it is responsible for consolidation of sleep within cycles that occur within a circadian framework.

Thus, if the SCN are destroyed, rats will sleep approximately the same amount of time but this sleeping time will be distributed in many short bouts throughout the light-dark cycle rather in a consolidated period.

The circuitary through which the ascending reticular inhibitory system localized in the upper pons and rostral parts of the brain stem influence the sleep include the hypothalamic ventrolateral preoptic nuclei (VLPO), suprachiasmatic nuclei (SCN), thalamus, and the cerebral cortex.

Arousal

The waking-up, as the sleep, exhibits more steps: a rapid one which has a short lifetime and which is determined by the direct action of ascending reticular activatory system (ARAS) on the cerebral cortex; another one with a longer lifetime out of the 24 hours, which is caused by indirect action of ARAS on the cerebral cortex via thalamus; and the third one which is rhythmic is caused (determined) by the ARAS action on the cerebral cortex via the hypothalamic

waking-up system which at its turn, is found under the influence of the suprachiasmatic nucleus.

Recent studies have demonstrated that the influence of the hypothalamus on arousal is not restricted to the tuberomammilary (TM) neurons in caudal hypothalamus.

In particular, a prominent group of neurons confined to the lateral hypothalamus has been implicated in the sleep disorder known as narcolepsy (Card et al 1999).

These neurons express novel neuropeptides known as hypocretins or orexins and are differentially concentrated within the perifornical nucleus that surrounds the fornix in the tuberal hypothalamus.

Mapping studies have shown that hypocretin/orexin neurons are similar to tuberomammillary neurons in that they are confined to hypothalamus and give rise to extensive projections throughout the neuraxis.

However, it is also clear that these neurons densely innervate areas (e.g., locus coeruleus) involved in the control of arousal, and there is good evidence that pathology of signaling pathways involving hypocretin neurons may be causal in narcolepsy (Parent 1997).

In this disorder individuals exhibit daytime sleepiness and lapse unexpectedly into bouts of REM sleep.

Examination of postmortem human brains of narcoleptics has revealed substantial reduction in the number of hypocretin neurons, raising the possibility that the disease may be due to an autoimmune attack on the neurons (Card et al. 1999).

Thus, there is strong evidence that caudal hypothalamic neurons play an integral role in the regulation of arousal states.

Anyhow, destructive hypothalamic lesions that may increase histamine release or decrease sympathetic outflow have a globally depressive effect.

This untoward effect is familiar to neurosurgeons who have approached craniopharingyomas of the inferior third ventricle and achieved an excellent resection, only to experience on otherwise unexplained protracted postoperative course characterized by a globally depressed level of consciousness.

Circadian rhythm (CR)

Human circadian rhythms include the daily oscillations of the sleep-wake cycle, body temperature, growth hormone, cortisol, and urinary potassium excretion.

Circadian rhythms provide temporal organization and coordination for physiological, biochemical, and behavioral variables in all eukaryotic organisms and some prokariotes.

Circadian rhythms are genetically determined not learned (Hall 1990, Rosato et al., 1997)..

Circadian rhythms are generated by an endogenous self-sustained pacemaker.

The Thalamus

The highest level at which this kind of absolute change to consciousness can occur is apparently the thalamus, a structure crucial for binding together experiences. The thalamus is a small, paired, somewhat oval structure located in approximately the center of the brain underneath the cerebral cortex.

It contains approximately 10^7 neurons, and anatomists classified them into about 50-80 nuclei.

Thalamic nuclei have extensive reciprocal connections with the cortex that are topographically organized (Sherman and Koch 1998) (fig. 6).

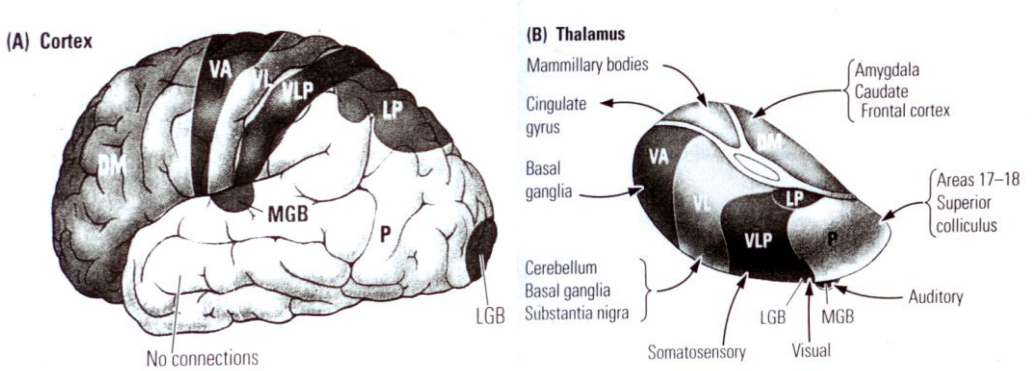


Fig. 6. Relation between thalamic nuclei and various area of the cortex to which they project. The arrows indicate the sources of input and output from the thalamus: anterior nucleus. A; dorsal medial nucleus, DM; ventral anteriornucleus, VL; lateral posterior nucleus, VP; ventral lateral posterior nucleus VLP; pulvinal P; lateral geniculate body, LGB; and medial geniculate body, MGB. (Kolb and Whishaw 2003).

Physiological understanding of the human thalamus is limited.

The fundamental function of the thalamus is the relay and it modulates peripheral information to the cerebral cortex and to the basal ganglia, keeping the somatosensory, mental, and emotional activity of a living individual in harmony.

Sensory nuclei serve as major sensory relay centers for all senses except smell and project to primary sensory cortices. Body sensation in particular may be

degraded or lost with damage to appropriate thalamic nuclei (Caplan 1980, Graff-Radford et al 1985), with an associated impairment of the ability to make tactile discriminations and identifications of what is felt (tactile object agnosia) (Caselli 1991, Bauer and Demery 2003).

Other thalamic nuclei are relay pathways for vision, hearing, and taste (Kim 2001).

Still other areas are relay nuclei for limbic structures. Motor nuclei receive input from the cerebellum and the basal ganglia and project to the motor association cortex. As the termination site for the ascending reticular system, is considered it is not surprising that the thalamus has important arousal and sleep-producing function (Green 1987, Steriade et al., 1990, La Berge 2000) and that it alerts activates or inhibit specific processing and response system. Its involvement in attention shows up in diminished awareness of stimuli impinging on the side opposite the lesion (unilateral inattention) (Dănăilă 1972, Arseni and Dănăilă 1977, Ojemann 1984, Posner 1988, Heilman et al., 2003)

Intralaminar nuclei

This nucleus, embedded in the internal medullary lamina, consists of centralis lateralis, paracentralis, central medial nuclei (anterior group), and centromedial and parafasciculus nuclei (posterior group) (Ohye 2002). The latter is often called the centromedian-parafascicular complex.

The anterior group receives different projections from the spinothalamic tract, deep cerebellar nucleus, brain stem reticular formation, etc.

The posterior group has a reciprocal connection with the basal ganglia. The efferent connection with the cerebral cortex is very wide and was once thought to be a diffuse projection. Each intralaminar nucleus has its own topographic projection area. The intralaminar nuclei were classified as representatives of the “nonspecific system” rather than the “specific system”, such as the thalamic station for the visual, auditory, or somatosensory system with definite modality-specific peripheral input.

Functionally, on the basis of recent knowledge the mechanism of sleep-wakefulness, the dual behavioral basis of animal life including humans is gradually becoming clearer.

Reticular nucleus

The reticular nucleus wraps around the thalamus. It originates from the ventral thalamus embryologically, being different from other neurons of so-called

dorsal thalamus. It has a wide network with thalamic nuclei as well as cerebral cortex and brain stem reticular formation.

This nucleus is considered to be related to arousal, attention, cognitive function etc. Also, as discussed later, it plays a role in maintaining cortical activity in a disease state of epilepsy (Ohye 1990, Ohye 1998).

A Russian group studied the human thalamus using microrecordings during stereotactic thalamotomy for dyskinesia and found verbal command neurons in this nucleus and adjacent area. They classified three types of neurons: A-type neurons exhibited irregular sporadic spikes that were usually activated by imperative verbal command, B-type neurons showed spontaneous rhythmic burst that was inhibited during the command presentation, and C-type neurons showed aperioding long-lasting burst discharge without responding to verbal command. They discussed a possible role for a basic regulatory mechanism allowing the performance of speech-mediated voluntary movements (Ohye 2002).

Some data have implied the thalamic reticular nuclei as the putative neuroanatomic substrate of selective attention (Yingling and Skinner 1977, Crick 1984). Several qualities of the thalamic reticular nuclei make this a reasonable hypothesis (Bogen 1997):

1. The thalamic reticular nuclei envelope most of the ipsilateral thalamic nuclei.

2. Thalamic reticular nuclei efferent terminate in the subjacent thalamic nuclei.

3. Thalamic reticular nuclei efferent use γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter.

4. Collaterales of ipsilateral thalamic nuclei efferent terminate in the thalamic reticular nuclei.

This model provides a plausible mechanism for consciousness gating of sensory phenomenon such that threshold levels would be required to overcome feed-back inhibition mediated by the thalamic reticular nuclei (Bogen 1997).

Surround-type inhibition mediated by thalamic reticular nuclei may selectively gate out extraneous stimuli while allowing focused relay important sensory data to the thalamocortical circuits, which endow a given neural activity pattern with the property of conscious perception (Ames and Marshall 2003). But how this neurophysiologic activity is coordinated in time to produce a somewhat unified conscious stream? Data suggest the answer may lie in the aquisition of gamma synchrony, most commonly at approximately 40 Hz (Gray and Viana di Prisco G. 1997).

This activity has been invoked to explain phenomena such as blind sight and visual binding (Bogen 1997). For example, the verbal conveyance of motion direction information seems to use gamma synchronization mediated by the ipsilateral thalamic nucley interaction with superior temporal sulcus (i.e., prymary area for motion direction detection) and the primary visual cortex. Ablation of the primary visual cortex results in an inability to communicate motion direction information but retention of the ability to adapt behavior accurately based on a correct direction identification.

The person denies seeing a moving stimulus and is not conscious of a moving stimulus but produces other behaviors that seem to indicate that he is still accurately detecting the direction of the movement (Stoering and Cowey 1995).

Gamma synchrony has also been hypothesized to "bind" disparate features of a given object, such as color, size, texture, and motion, into a temporally unified sensory stimulus (Singer and Gray 1995).

Summary

The diencephalon consists of the three important structures: the thalamus; the hypothalamus; and epithalamus.

Almost all the information that the cortex receive is first relayed through the thalamus. Although the modern techniques of neuroscience are limited to use in human meticulous clinical observation and stereotactic surgery experience with microrecording provide useful information about the structure and function of the human thalamus.

Many problems remain to be solved, but with the development of new techniques the future of thalamic study is promising.

In the cases of unilateral thalamic lesions (tumors, hemorrhage etc) the patients haven't coma.

We had a case of 26-year-old woman who for a month complained of headache, nausea, vomiting, imbalance, decrease in visual acuity in the right eye, mild language disturbances, memory loss, right neocerebellar syndrome, left hemiparesis, left hemisensory loss, left lateral homonymus hemianopsia and mild spatial desorientation.

Computed tomography demonstrated a spontaneous hypodens tumor, located in the right thalamus.

On MRI the tumor appeared hypointense in T1-weighted image and hyperintense in T2-weighted image, surrounded by a moderate edema (fig. 7 a, b, c and d). At the operation the tumor was resected.

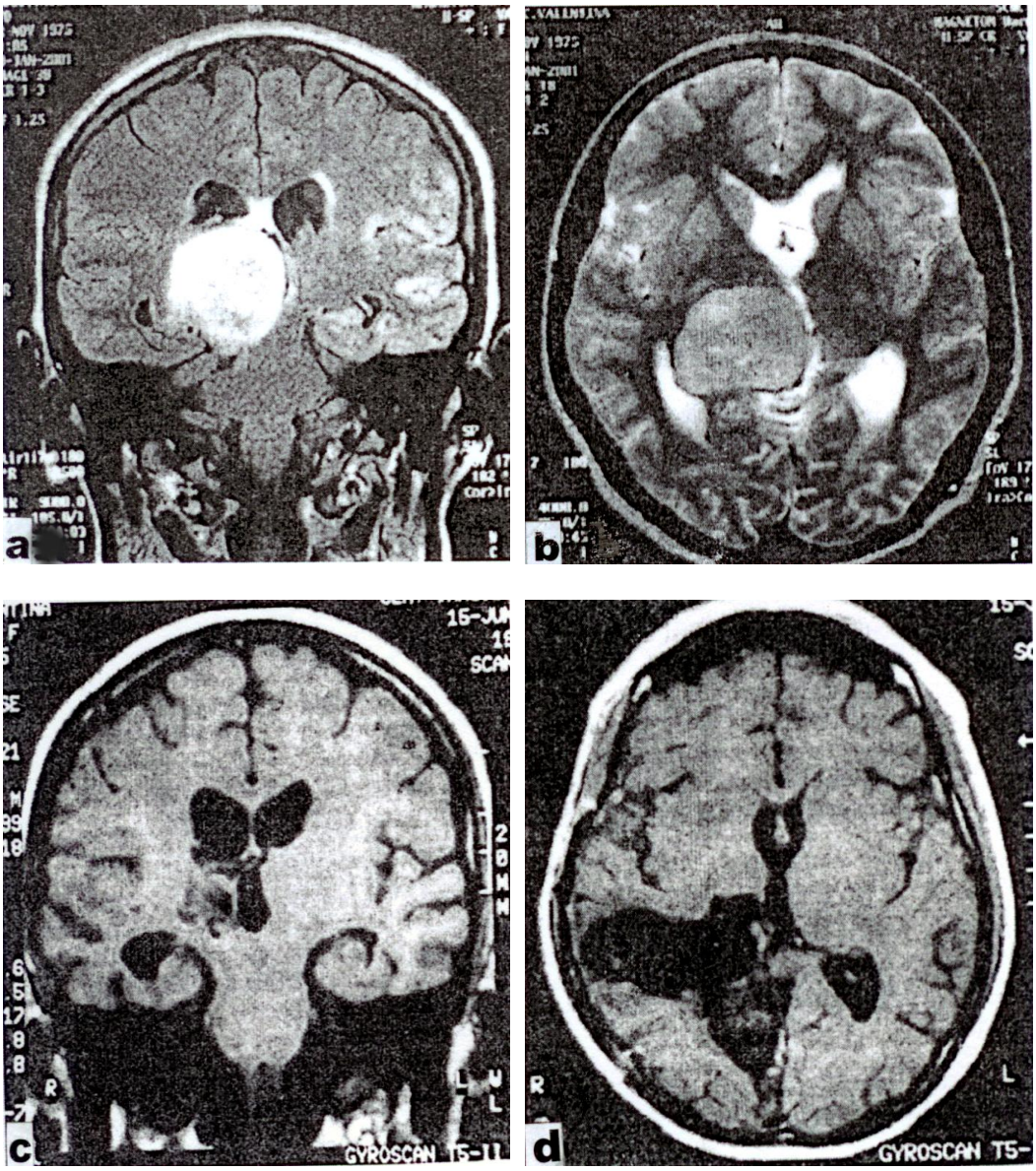


Fig. 7. Contrast medium-enhanced coronal (a) and axial (b) magnetic resonance imaging showing a big right thalamic tumor that proved to be an astrocytoma. Thirteen months fallowing resection and radiotherapy coronal (c) and axial (d) magnetic resonance imaging demonstrates the absence of tumor. The patient was consciousness and in good state.

The histological exam showed an astrocytic cell population, having numerous mitoses, and areas of neurosis and intratumoral hemorrhage, and small calcified area.

Thirty-five days after surgery, the patient started radiation therapy using a 10meV photons energy linear accelerator (LINAC).

The clinical examination, performed thirteen month after surgery, demonstrated a very good health condition of the patient.

The motor and sensory deficits as well as the balance disorders were very much improved. A mild deficit in the left visual field was still present.

Control cerebral MRI showed absence of any intracerebral tumoral mass and reduced hydrocephalus.

The hypothalamus is composed of about 22 small nuclei, fiber systems that pass through it, and the pituitary gland. Although comprising only about 0,3% of the brain's weight, the hypothalamus takes part in nearly all aspects of motivated behavior, including sexual behavior, sleeping, temperature regulation, emotional behavior, endocrine function, and movement.

The function of the epithalamus is not well understood but one of its structures, the pineal body, seems to regulate seasonal body rhythms.

Lesions in the bilateral diencephalic region result in deep coma and death, despite an intact cortex (fig. 8).

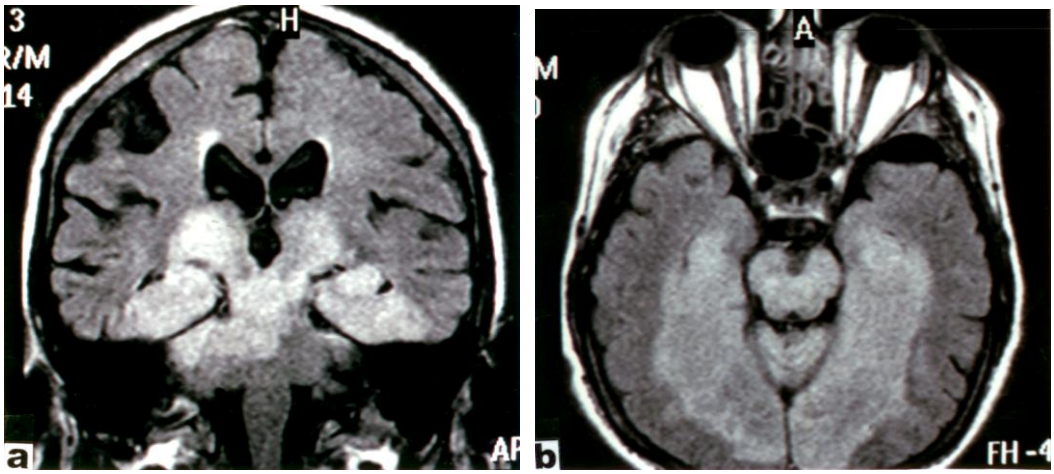


Fig. 8. A 56-year old men who presented with a sudden onset of coma and fever. Coronal (a) and axial (b) T1-weighted magnetic resonance imaging (MRI) scans revealed edematous, demyelination symmetrically changes infra-and supratentorial which involve, entire midbrain, both thalamic formations, bilateral basal ganglia, two-side temporo-occipital convolution and hippocampus, determined by encephalitis. After 9 days of coma the patient died.

Limbic system and hippocampus

As the hippocampus is part of the limbic lobe, this latter structure will be described first. The limbic lobe is situated on the inferomedial aspect of the hemisphere, separated from adjoining cortex by the limbic fissure (fig. 9). This

fissure is a discontinuous sulcus composed successively of the cingulate, subparietal, anterior calcarine, collateral, and rhinal sulci (Duvernoy 2005). Broca (1878) divided the limbic lobe into the limbic and intralimbic gyri, something which has become an established tradition.

The limbic gyrus consists of the subcallosale, cingulate and parahippocampal gyri.

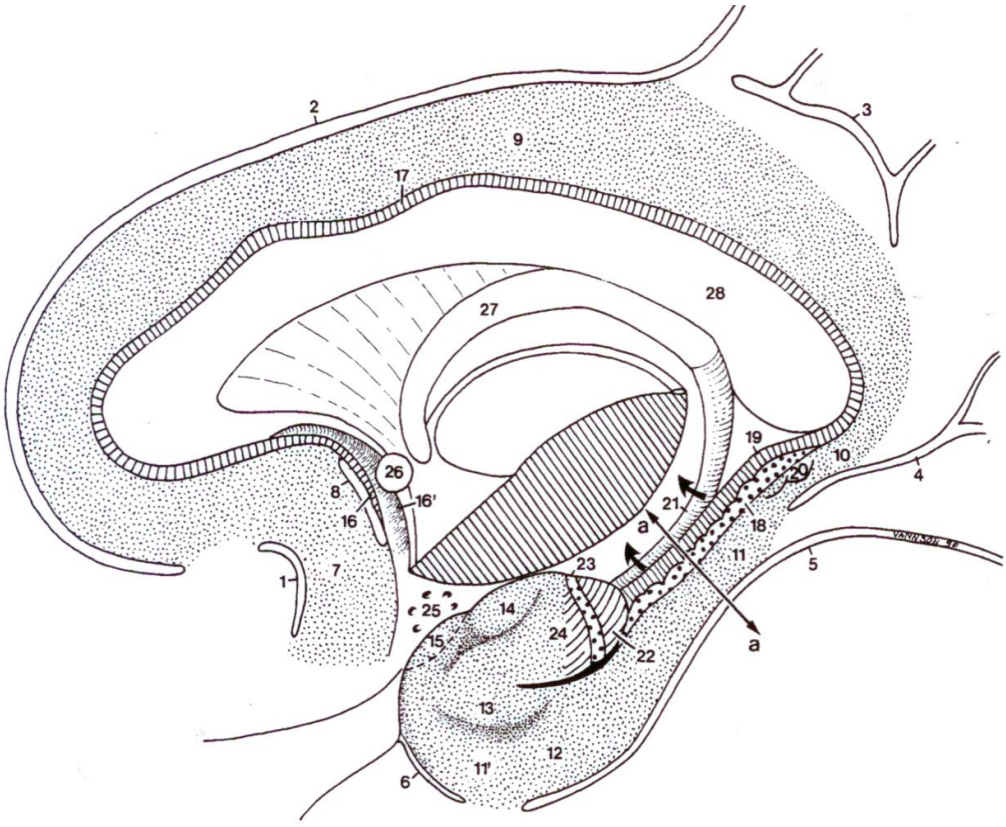


Fig. 9. Drawing shows a sagittal section in right hemisphere. The limbic lobe is separated from the isocortex by the limbic fissure and may be divided into two gyri: the limbic and intralimbic gyri. The line a-a indicates the plane of the section in fig. 10.

Limbic fissure: 1. anterior paraolfactory sulcus (subcallosal sulcus); 2. cingulate sulcus; 3. subparietal sulcus; 4. anterior calcarine sulcus; 5. collateral sulcus, 6. rhinal sulcus.

Limbic gyrus: 7. subcallosal gyrus; 8. posterior paraolfactory sulcus; 9. cingulate gyrus; 10. isthmus; 11. parahippocampal gyrus, posterior part; 11'. parahippocampal gyrus, anterior part (piriform lobe).

Piriform lobe: 12. entorhinal area; 13. ambient gyrus; 14. semilunar gyrus; 15. prepiriform cortex.

Intralimbic gyrus: 16. prehippocampal rudiment; 16'. paraterminal gyrus; 17. indusium griseum.

Hippocampus: 18. gyrus dentatus; 19. cornu Ammonis; 20. gyri of Andreas Retzius; 21. fimbria (displaced, upward, arrows); 22. uncal apex; 23. band of Giacomini; 24. unciate gyrus; 25. anterior perforated substance; 26. anterior commisure; 27. fornix; 28. corpus callosum (Duvernoy 2005).

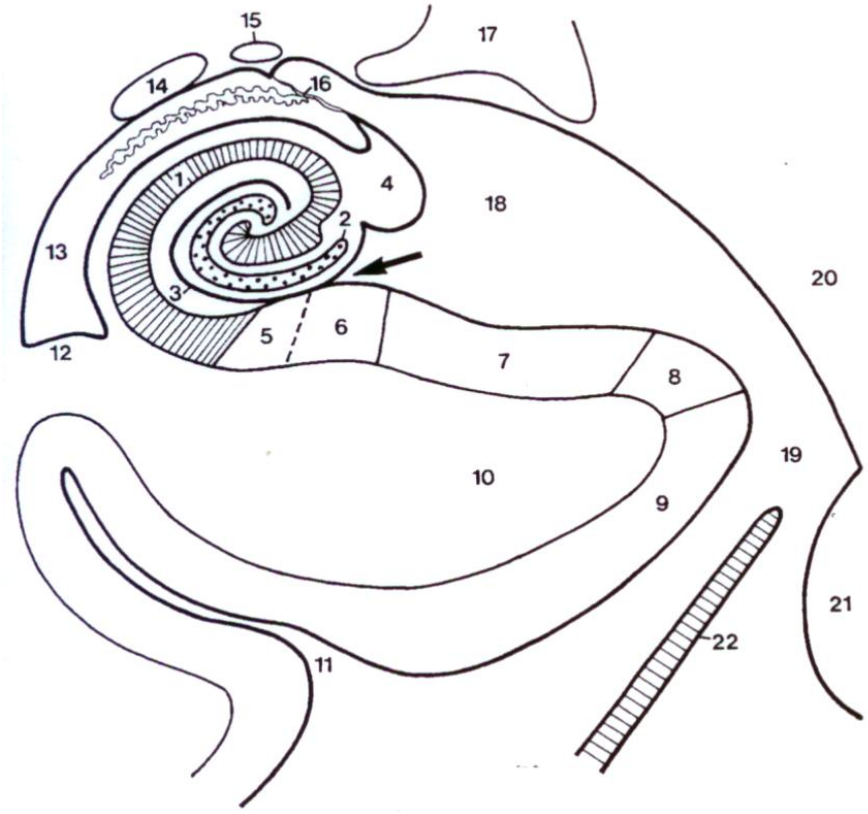


Fig. 10. Disposition of the gyrus dentatus (dotted areas) and of the cornu Ammonis (hatched area). Arrow indicate the hippocampal sulcus (superficial part). (Modified by Duvernoy 2005, after Williams 1995).
1.cornu Ammonis; 2. gyrus dentatus; 3. hippocampal sulcus (deep or vestigial part); 4. fimbria; 5. prosubiculum; 6. subiculum proper; 7. parasubiculum; 9. entorhinal area; 10. parahippocampal gyrus; 11. collateral gyrus; 12. collateral eminence; 13. temporal (inferior) horn of the lateral ventricle; 14. tail of caudate nucleus; 15. stria terminalis; 16. choroidal fissure and choroidal plexures; 17. lateral geniculate body; 18. lateral part of the transverse fissure (wing of ambient cistern); 19. ambient cistern; 20. mesencephalon; 21. pons; 22. tentorium cerebelli.

The parahippocampal girus can be divided into two segments:

1) the posterior segment is narrow, and its flat superior surface, the subiculum, is separated from the hippocamppal sulcus;

2) the anterior segment is more voluminous and is called the piriform lobe, comprising the uncus and the entorhinal area.

The sulcus is functionally divided into anterior and posterior parts. The posterior parts belong to the hipocampus (Duvernoy 2005). The anterior parts display two protrusions: the semilunar gyrus and the ambient gyrus, which are separated by semianular sulcus, both covering a deep nucleus, the amygdala.

The intralimbic gyrus arches within the limbic gyrus. Its anterior segment includes a narrow zone in the subcallosal region, the prehippocampal rudiment, partially belonging to the paraterminal gyrus and to the septal region (Brodal 1947); its superior segment, a continuation of the perihippocampal rudiment, is the indusium griseum, situated on the superior surface of the corpus callosum.

The indusium griseum, is covered on each side of the midline by two small white fasciculi, the medial and lateral longitudinal striae. Passing around the splenium, the indusium griseum reaches the inferior segment of the intralimbic gyrus, the hippocampus, which is the only part that is well developed.

The hippocampus, separated from the subiculum by the hippocampal sulcus, extends farward to the uncus to occupy its posterior segment. The hippocampus is bordered by the fimbria.

In relation to the corpus callosum, the intralimbic gyrus is sometimes derived into three parts (Elliot Smith 1897): 1) the precommissural hippocampus (prehippocampal rudiment); 2) the supracommissural hippocampus (indusium griseum); 3) the retocommissural hippocampus (the hipocampus proper).

The development of conceptions about the anatomy and function of the limbic lobe was clearly presented by Nieuwenhuys (1985).

Broca (1878) first described and named the limbic lobe. From its comparative anatomy, he attributed olfactory functions to these structures. It was therefore later named the rhinencephalon (Turner 1891). In a subsequent phase in speculation on the limbic lobe by observers such as Papez (1937) and Brodal (1947), it was suggested that, in humans, this lobe is partially olfactory and is mainly concerned with emotional behavior. In addition, the amygdala was seen as part of limbic lobe. Mac Lean (1970) subsequently included numerous subcortical structures such as the septum, midline thalamus, habenula, and hypothalamus in the limbic lobe, something which was later criticized by Le Doux (1989). Thus from the single entity of Broca, the limbic lobe became an organization, the so-called limbic system, composed of disparate anatomical units whit common functions. Nauta (1958) developed this concept further, insisting on the functional importance of certain regions of the neural axis, such as the septum, preoptic area, hypothalamus and mesencephalon, regions closely related to the hippocampus.

Hypothalamus makes a link between the limbic and endocrine system reasonable. The limbic cortex flows continuously into the hippocampus and amygdala, which are hidden inside the temporal lobe. Recent research shows very close interaction between these ancient regions of cortex and episodic memory, i.e., memory for conscious experiences. This is the ancient reptilian brain, which is flower, still a vital center of activity in humans and other mammals.

The mesencephalon, said to from a "mesolimbic system" through its paramedian structures, could enable visceral information ascending in the brain stem to influence general functioning of the limbic system (Duvernoy 2005).

Hippocampus

The hippocampus forms an arc whose anterior extremity is enlarged and whose posterior extremity narrows like a comma. It has a total length of between 4 and 4.5cm; the body is an average 1cm wide, and the head is 1.5-2cm wide (Poirier and Charpy 1921, Testut and Latarjet 1948).

The hippocampus occupies medial part of the floor of the temporal horn and is divided into three parts: head, body and tail.

Structure

The hippocampus is bilaminar, consisting of the cornu Ammonis (or hippocampus proper) and the gyrus dentatus (or fascia dentata), with one lamina rolled up inside the other (fig.10). Two formations are thus studied here: the cornu Ammonis and the gyrus dentatus.

The cornu Ammonis and the gyrus dentatus are the simplest part of the cortex, the allocortex (or archaeocortex), as compared with the more complex isocortex. As shown by Giacomini (1884) and later by Mutel (1923), the position of these two cortical laminae is the same in all three parts of the hippocampus.

Function and connections

The possible functions of the hippocamp are divided into four categories: 1) learning and memory, 2) regulation of emotional behavior, 3) certain aspects of motor control, and 4) regulation of hypothalamic functions (Duvernoy 2005).

Regulation of hypothalamic functions

The hippocampus is involved in the regulation of the hypothalamo-hypophyseal axis.

Through its projecttions to the paraventricular hypothalamic nucleus, it may inhibit the hypophysial secretion of adrenocorticotrophic hormone (ACTH) (Jacobs et al., 1979, Teyler et al., 1980, Herman et al., 1989, Diamond et al., 1996).

The amygdala

The amygdala, which belongs to the limbic lobe, is often described together with the hippocampus as far as its function is concerned.

Its structure is described by Braak and Braak (1983) and Amaral et al (1992) (fig. 11).

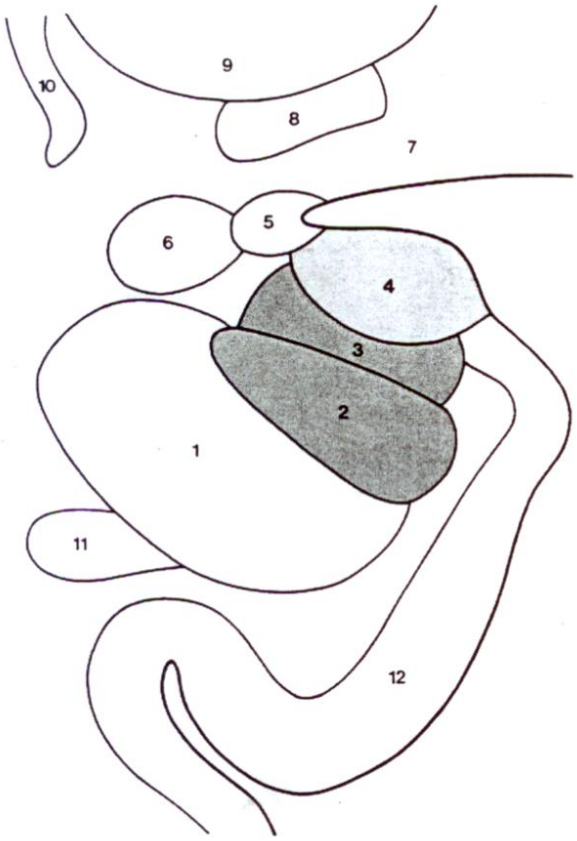


Fig. 11. Structure of the amygdala. 1, lateral nucleus; 2, basal nucleus, 3, accessory basal nucleus; 4, cortical nucleus; 5, medial nucleus; 6, central nucleus; 7, anterior perforated substance; 8, anterior commissure, lateral part; 9, putamen; 10, claustrum; 11, uncal recess of the temporal horn; 11, ambient gyrus (Duvernoy 2005).

The cortical and medial nucley are olfactory centers, whereas the basal, lateral and central nuclei have limbic functions (Aggleton 1992).

Memories, including fear memories, become permanent through a process of protein synthesis called consolidation.

When retrieved, the memory becomes labile again and it is susceptible to further manipulation and alteration prior to reconsolidation.

Evidence shows that reconsolidation of fear memories in rats involves additional protein synthesis in the amygdala (Nader et al 2000, Nader 2003). Infusion of an antibiotic that interrupts protein synthesis eliminates the conditioned response at test the next day.

The basolateral complex can be further subdivided into lateral, basal and accessory-basal nuclei. The lateral amygdala, which is afferent to the rest of basolateral complex as well as the centromedial nucleus, receives input from sensory systems. The centromedial nucleus is the main output for the basolateral complex, and is involved in emotional arousal in mammals. The cortical nucleus is involved in smell and pheromone processing; it receives input from the olfactory bulb.

Efferent pathways from the amygdala mirror afferent pathways, returning signals to subcortical locations and to the brainstem. Of significance for our study of cognition-emotion interactions is the direct efferent pathway from the amygdala to entorhinal cortex, inferior temporal lobe cortex, and finally to visual cortex including the fusiform face area. There top-down and bottom-up relationship between amygdala and cortex as they work together to tune the brain for adaptive responses to significant environmental threats (Mc Govern 2007).

Afferent signals to the amygdala arrive via four pathways. Olfactory information, arrives directly at the amygdala from the olfactory cortex without preprocessing in the thalamus; this may account for the profound ability that odors have to evoke emotional memories.

Visceral information reaches the amygdala from the hypothalamus and septal area through the stria terminalis.

Affect-relevant information about internal states also arrives from the hypothalamus, thalamus, and brainstemas well as the orbital cortex and anterior cingulate cortex via the ventral pathway.

Sensory information arrives directly from temporal lobe structure such as the primary auditory cortex and the hippocampus.

Fusiform gyrus of the ventral temporal lobe is activated greater for fear faces regardless of attentional level (Vuillemier et al., 2003).

The finding supports the idea that there are independent conscious and unconscious pathways to the fear processing system of the amygdala.

In a review of the role of the amygdala in emotional processing, Phelps and Le Doux (2005) identified fine areas in which there is converging evidence from animal and human studies of cognition-.emotion interactions involving the amygdala:

1. implicit emotional learning and memory,
2. emotional modulation of memory,
3. emotional influences on perception and attention,
4. emotion and social behaviour,
5. emotion, inhibition and regulation.

Conclusions

According to Mc Govern (2007), mammals have separate emotional systems in the brain, related to survival. Systems such as the ***fear*** system and ***seeking*** system have been shown to have both unconditioned and conditioned responses to significant "calling conditions" supported by separate neural networks, ***fear*** relying on the amygdala and its connections, ***seeking*** relying heavily on the mesolimbic and mesocortical pathways of the ventral tegmental area. Each can come under cognitive control and also reciprocally influence higher decision-making appraisal system, and consciousness (Mc Govern 2007).

Cerebral cortex

The cerebral cortex of the cerebral hemispheres, the convoluted outer layer of gray matter composed of tens billions of neurons and their synaptic connections, is the most highly organized correlation center of the brain, but the specific of cortical structures in mediating behavior is neither clear-cut nor circumscribed (Collins 1990, Franckowiak et al., 1997). The bulk of the cerebral cortex is comprised of the neocortex.

The phylogenetically older parts of the cortex include the paleocortex (olfactory cortex, entorhynal and periamygdaloid areas) and the archicortex (the hyppocampal formation). The tens of billion of neurons send a large number of axon in all directions, convered by supportive myelin. These form the white matter of the cortex that fills the large subcortical space.

The cerebral cortex receives sensory information from the internal and external environments of the organism, processes this information and than decides on and carries out the response to it. To receive information regarding the external and internal milieu and to generate commands to control the muscles and organs, the cerebral cortex has both direct and indirect connections with all other

While the cortex is vital for cognitive functions it interacts constantly with major satellite organs, notably the thalamus, basal ganglia, hypothalamus, cerebellum, brain stem and limbic regions, among others.

Different regions of the cerebral cortex have modular specific functions (somatic sensory and motor, visceral sensory and motor, integrative cognitive functions, speech functions etc.) responsible for the high-order cognitive processing or conscious mind. These correspond to the Brodmann areas, as well to each of the four cerebral lobes (frontal, parietal, temporal and occipital).

Partial or total lesion of same Brodmann specialized areas or one of the lobes leads to the modular lose of a consciousness.

When all the cerebral cortex is destroyed as well as the white matter, the patient becomes unconsciousness (fig 12).

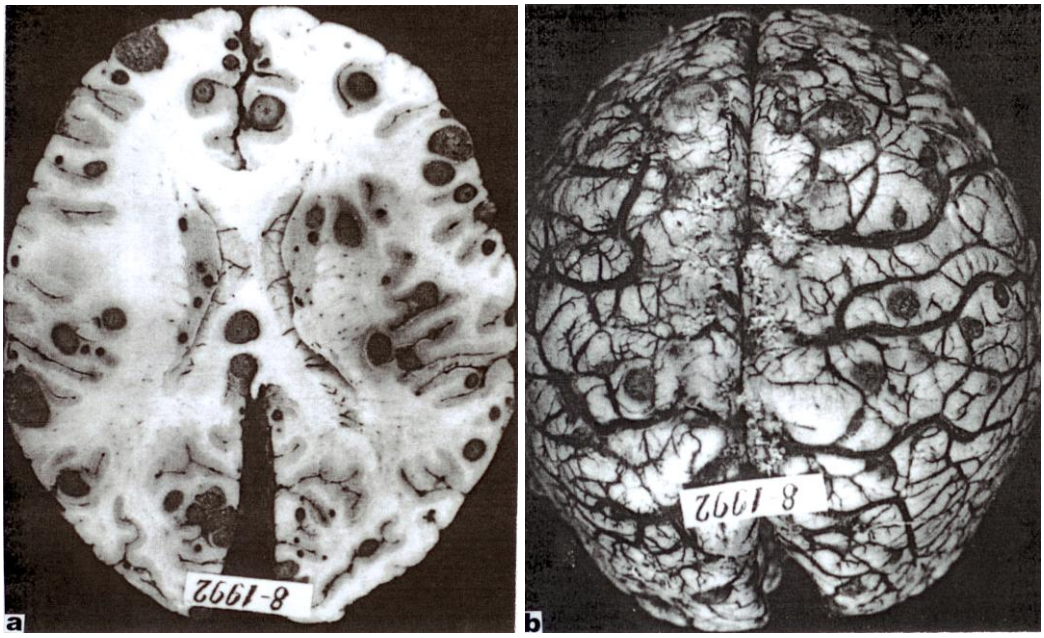


Fig. 12. Bilateral, cortical and subcortical metastases (a and b). The primitive tumor was a melanocarcinoma.

The term modular or functional localization is used to indicate that the certain functions can be localized to particular areas of the cerebral cortex.

The mapping of cortical function began with inference made from the deficits produced by cortical lesions in humans.

Subsequently, techniques such as single-cell recording and electrical stimulation of cells in the cerebral cortex have been used in animal, nonhuman primates, as well as humans undergoing surgery for diseases such or epilepsy and Parkinson's disease to map out functional areas of the brain (Jones 2000).

Functional neuroimaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) have been used to confirm previous knowledge about localization of function within the cerebral cortex as well as to conduct studies in healthy human subjects that were previously not possible.

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