

## Historical aspects of the anatomy of the reticular formation

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### ABSTRACT

The reticular formation was one of the last neuroanatomical structures to be described. Even today, there is no consensus on the nervous system elements that make up this anatomical structure.

Such famous anatomists as Reil, Deiters, Burdach, and Cajal, among others, have progressively contributed with new findings regarding the description of the reticular formation. Nevertheless, experiments performed in particular by Bremer, Moruzzi, Magoun, and Jasper have helped enormously to complement and clarify the growing body of knowledge regarding the neurophysiology of the reticular formation.

### KEYWORDS

History of anatomy, neurophysiology, *cerveau isolé*, ascending reticular activating system

### Introduction

The establishment of an anatomical description of the reticular formation (RF) began at the beginning of the 19th century, both in macro and microscopic terms. However, the lack of a definitive description has persisted until today.

Neurophysiological studies conducted during the first half of the 20th century have enabled a better understanding of RF organic structure and function. For this reason, we will analyse not only the strictly anatomical description proposed by leading authors, but also a series of studies which describe neurophysiological experiments with reference to the reticular formation.

### Development

Background of the anatomical description of the RF

In 1809 Reil provided one of the first anatomical descriptions of what we know today as the RF.<sup>1</sup> This author described a series of grey matter structures and white matter fibres in the brain stem. Some of these fibres originated from cell groups adjacent to the fourth ventricle floor. Fibres were grouped along the medial

superior sulcus and they became thinner as they ascended, passing above the commissure of the superior cerebellar peduncles to reach the thalamus.

In 1855, Lenhossék<sup>2</sup> used the word *processus* to denominate a network of fibres and nerve cells located on the upper section of the spinal cord and up along the whole brainstem. This author believed that these fibres originated from cells in the anterior and posterior horns of the spinal cord, as well as from the equivalent cell formations in the brainstem.

Deiters<sup>3</sup>, in 1865, was the first to use the designation RF for the group of grey matter formations that intermingled with longitudinally projecting nerve fibres in the brainstem. He located these structures beside the pyramidal tracts which are also found in this anatomical region.

In 1877, Forel<sup>4</sup> reviewed the evidence in humans, rodents, and carnivores, and he admitted that little was known about the origin and endings of these fibres located in the brainstem. This author stated that these ascending nerve fibres reached the red nucleus, the nucleus basalis of Meynert, and the third cranial nerve nuclei.

In 1882, Burdach<sup>5</sup> described ascending tracts in the brainstem with intercalated nuclei such as the superior olivary complex among others. These tracts were connected to the corpora quadrigemina. He considered that these fibres came from the rostral region of the anterior grey column of the spinal cord.

The rudimentary and imprecise descriptions by Reil and Burdach could be interpreted as an outline of what we know today as the RF and its ascending fibres.

Bechterew also contributed to the description of the RF.<sup>6</sup> In 1885 he described the connection between the olivary bodies and the midbrain, which Bechterew named the central tegmental tract.

This author also identified nuclei in the pontine reticular formation, including the nucleus of Roller. Fibres from the lateral and posterior grey columns terminate in these nuclei. According to Bechterew, the most important rostral connections in the ascending fibres of the RF were with the inferior colliculi, with the areas adjacent to the third ventricle, and probably also with the thalamus. The RF was regarded as a structure which carried sensory stimuli from the spinal cord. Bechterew stated that the RF was a significant reflex centre, although the author admitted that he was unsure as to the type of reflexes.

In 1885, Mislawski<sup>7</sup> experimentally stimulated the RF at the medullary level and found a respiratory control centre in the formatio reticularis and a vasomotor centre at the level of the central nucleus of the inferior colliculus.

Ramón y Cajal,<sup>8</sup> in his 1897 treatise *Histology of the nervous system of man and vertebrates*, described the RF in detail but without assigning it any specific function. In the section titled “Interior configuration of the spinal cord”, he wrote:

The appearance of the gray matter varies somewhat in the different zones of the spinal cord (...) the white matter, fragmented into independent bundles, invades the gray matter. Such a pattern, that starts already in the thoracic region reaching its maximum in the upper cervical cord and medulla, gives a reticulated aspect to the intercalated grey matter (procesus reticularis of Lenhossék Sr.). We designated these inter-fascicular partitions as the interstitial nucleus.

This description corresponds to what came to be known as the RF. Cajal continues describing the configuration of the white matter in the medulla:

Because the extent of this territory of white matter mottled with gray is very large, it is convenient to divide it into fields or areas with conventional limits. In general, it is arranged in two fields. 1st. A medial zone, called the white reticular formation, due to the predominance of longitudinal bundles of nerve fibres, and which is limited medially by the raphe, laterally by the roots of the hypoglossal nerve and the olive, dorsally by the hypoglossal nucleus, and ventrally by the pyramidal pathway. 2nd. The gray reticular formation, a very extensive field where neurons predominate, have the following borders: medially, the roots of the hypoglossal nerve; dorsally, the central gray matter and nuclei of the 12th and 9th nerves, and laterally, the nucleus cuneatus and the substantia gelatinosa that contours the spinal tract of the trigeminal nerve.

Cajal continues detailing the white matter, describing the presence of disseminated cells, some of them forming accumulations:

Thus, dorsal to the olive and lateral to hypoglossal rootlets, Kölliker finds abundant cells of large size (diffuse magnocellular nucleus of this author, nucleus reticularis tegmenti of Bechterew). Ventral to the hypoglossal nucleus there is also a special cell accumulation (nucleus of Roller).

The RF has received different designations in many acclaimed anatomy textbooks. In the 9th revised edition of 1954 of *Traité d'Anatomie Humaine* by Testut and Latarjet,<sup>9</sup> which is considered a classic text of anatomy, RF is considered a deep lateral tract. They state that:

...a forth fascicle is found inside the crossed pyramidal tract and the posterior part of the fascicle of Gowers, which adapts perfectly to the external surface of the grey column. Due to its location, it is called the deep lateral fascicle. *It has been called the lateral limiting layer by Flechsig.*

Testut and Latarjet describe fibres originating from the nerve cells of the anterior, lateral, and posterior horns. These are thin fibres between 2 and 5 µm in diameter, which follow a longitudinal direction after leaving the grey matter. After a very short trajectory, they enter the grey matter again. These fibres are classified as short association fibres, and are in fact spinospinal columns.

At the medullary level, the RF is considerably developed. Its boundaries are: in the sagittal plane, the reticular formation of the medulla oblongata extends from the posterior region of the pyramids to the grey matter

nuclei that form the fourth ventricle. Cross-sectionally, it extends from the raphe to the posterior column or restiform body in both halves of the medulla oblongata.

At the level of the pons, the authors describe association pathways or short pathways, which establish reflex arcs within the brainstem. Adjacent to these well-defined association tracts, other less uniform structures can be observed.

...there are also descending tracts from the corpora quadrigemina and terminate in the grey motor nuclei of the pons. (...)

The reticular formation of the peduncle is a continuation of the bulbar and pontine reticular substance, which is formed by small grey columns set up as a network including longitudinal fibres which are in turn crossed by arcuate and radiate fibres. This formation is observed up at the junction of the midbrain and suboptic region which form an edge, which is a continuation of the field of Forel and Reil's band.

This paragraph suggests, although not conclusively, the relationship of the RF with the thalamus.

#### Current knowledge of RF anatomy

Today, there is no consensus on the nervous system elements that make up this anatomical structure. *Gray's Anatomy* textbook, which was later continued by Williams and Warwick,<sup>10</sup> mentions that some authors consider that the deep areas of the medulla oblongata, the pons, and the mesencephalon are part of the RF. Some authors even include the grey matter of the brainstem, which they classify as the reticular centre, while others include the cerebellar nuclei, the red nucleus, and most hypothalamic nuclei.

The RF is regarded as a phylogenetically primitive part of the nervous system, on which more differentiated and organised areas of the nervous system have developed. The reticular formation is especially important with respect to the reception of and response to stimuli, whether they come from the external environment or one's own body.<sup>10</sup>

Multiple areas of grey and white matter are found in the RF; grey matter neurons form clusters of varying sizes. The fibres are more or less uniform in diameter, and can be longitudinal, cross-sectional, or curved.

The reticular formation spans the upper end of the cervical spinal cord along with the mesencephalon, cor-

pora quadrigemina, diencephalon, hypothalamus, subthalamus, and thalamus.

Some nuclei are formed by Golgi type II cells; they have short axons and dendrites which are perpendicular to the brainstem, making their anatomical disposition comparable to the spokes of a wheel, which may spread into half of the cross-sectional area of their half of the brainstem. Moliner and Nauta<sup>11</sup> have designated this disposition as an 'isodendritic' configuration.

Dendrites form synapses with ascending and descending tracts; ascending tracts span the whole brainstem, reaching the hypothalamus and the dorsal nuclei of the thalamus. Descending tracts extend to the intermediate grey matter of the spinal cord.

In other locations, neurons are sited in the nuclei of the cranial nerves and olivary body; while axons are short, dendrites have short and sinuous branches, and are situated in such a way that they form well-defined cell groups. This configuration is called 'idiodendritic'.<sup>10</sup>

There are also neurons of intermediate complexity, which are called 'allodendritic'.

In the RF we can observe three longitudinal cell columns extending from the brainstem to the hypothalamus and the dorsal nucleus of the thalamus. The first column occupies the central part of the structure. The medial column is made up primarily of medium-sized cells, and bigger sized cells form the gigantocellular nucleus of the medulla oblongata and the pons. The nucleus coeruleus and subcoeruleus are found in this same column.

The lateral column is made up of a few small cells which are grouped to form two nuclei, a central nuclei, and a ventral nuclei, which intersect with each other and contain the nucleus ambiguus.<sup>10</sup>

Afferent connections to the RF come from the spinal cord, cranial nerves, and cerebellum. It receives afferences from such superior structures as the cortex, limbic system, thalamus, subthalamus, and striate body<sup>10</sup>.

Efferent connections are to the spinal cord, brainstem pathways and centres, cerebellum, substantia nigra, red nucleus, and hypothalamic, subthalamic, and thalamic nuclei. Through these, efferences reach the cerebral cortex, including the limbic system.<sup>10</sup>

As we have previously mentioned, RF anatomy is most clearly organised based on studies regarding its neuro-

physiological activity. Knowledge of its functions enables a better definition of the morphology and topography of this structure.

Among the authors who have contributed the most to the understanding of RF functions, Frédéric Bremer stands out (Figure 1). In 1935, this researcher published his studies on sleep physiology and the bioelectrical activity of the cerebral cortex.

Bremer describes the technique he used, called *cerveau isolé*, in a cat anaesthetised with ether. It consisted of a transection of the brainstem between the pons and the midbrain, while continuously ensuring cerebral irrigation through the carotid and vertebral systems.

By using oscillographic records, he reported that the telencephalon maintained its bioelectrical activity, similar to that of normal sleep, spontaneously and automatically.

Bremer concludes his article by saying:

In short, complete deafferentation (with the exception of the olfactory and optic nerves) of the cat's brain caused by a section of the brainstem caudal to the nucleus of the third cranial nerve, immediately leads to a functional state which is similar if not identical, to that of natural or barbiturate sleep. This state persists for an indefinite period. It is characterised by extreme miosis, and olfactory and optical cortical areflexia which contrasts with an intense spontaneous electrical activity which is regularly periodical.<sup>12</sup>

With this experiment, he showed that the brain, in order to maintain a state of wakefulness, needs to receive stimuli from the brainstem or from the brain itself. Removal of these stimuli leads to a state of persistent sleepiness.

In his article *New research on the mechanism of sleep*,<sup>13</sup> Bremer reported on the results of new neurophysiological research which in subsequent studies would enable the establishment of the organic structure of an intricate system, which would later be called the reticular system or formation.

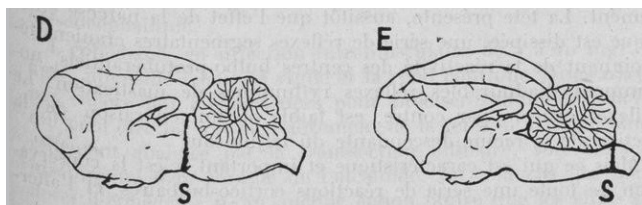
This article described the differences between clinical and electrobiological manifestations in a cat after experimental transections of the brainstem at the pontine-midbrain level and at the lower level of the medullary-spinal junction; the pons and the medulla oblongata, with the corresponding cranial nerves, remain intact above the last transection (Figure 2).



**Figure 1.** Frédéric Bremer (1892–1982). With permission from History of Medicine (NLM). U.S. National Library of Medicine, History of Medicine Division.

The outcomes observed at the low medullary level are very different from those obtained after the transection above the pons. In the first case, the experiment permits the observation of how a series of cortico-medullary functions are preserved, which in turn enable the spontaneous rotation between sleeping and waking states. In animals subjected to transection at the pontine-midbrain level or higher, the sleep state is continuous; there is no alternation of sleep-wakefulness.

According to the author these experiments have demonstrated the role of sensory influences on the cortex, which retain the necessary cerebral activity to maintain wakefulness; cortical neuron activity is maintained by a mechanism which responds to proprioceptive and exteroceptive stimuli.



**Figure 2.** Experimental sectioning of the brainstem at the pontine-mid-brain level and sectioning at the medullary-spinal junction<sup>13</sup>

In another article, Bremer presents his conclusions on experiments with cats related to the electrical activity of the cerebral cortex during sleep and wake states.<sup>14</sup> The author confirms that after the bulbar transection, the animal alternates states of sleep and wakefulness, and that traces of cortical bioelectrical activity in one state or the other showed different characteristics. The brain cortex at rest emits waves similar to the Berger's waves obtained in a human electroencephalogram.

The article finishes with the following paragraph:

...the state of wakefulness translates into a more or less complete disappearance of these rest waves and their second order periodicity. These waves are replaced by short waves, with a frequency and amplitude proportional to the degree of surveillance (attention) as could be observed by the ocular reactions of the cat. The amplitude of short waves (homologous to Berger's beta waves) can reach that of rest waves (Berger's alpha waves).

This study clearly demonstrates that pontine-midbrain transection causes a deafferentation in the cortex, leading to a continuous sleep state. Transection at the medullary level enables alternating between sleep and wakefulness; this reveals the existence of an activating system located at the medullary level, whose function is to stimulate cortical activity. This function emerges from the reticular activating system.

Regarding the origin and nature of brain waves, Bremer<sup>15</sup> concluded that these are synchronous pulsations that show a fundamental autorhythmicity of a neuronal aggregate of the cortical grey matter. To create this rhythm, the participation of thalamic nuclei, whose activity is sustained by sensitive and sensory stimuli, as well as stimuli of cortical origin is necessary.

Therefore, Bremer distinguished two categories of cortical activity, one of which was spontaneous alterations originating from cortical neurons, and another type caused by stimuli from sensory, proprioceptive, and stereoreceptive receptors.

Regarding the hypothesis by Bremer with respect to bioelectrical activity of the cerebral cortex showing EEG alpha waves, Kristiansen and Courtois<sup>16</sup> published their findings in which they analysed whether rhythmic cortical activity depends upon the interaction of the cortex and subcortical structures, or whether the cortex is able to produce spontaneous rhythms. These authors experimented on cats, comparing bioelectrical activity in the intact cortex, the deafferentiated cortex after a thalamectomy, and in portions of the cortex which had been completely isolated.

The spontaneous electrical activity recorded in the three preparations corresponded to a normal alpha rhythm. Bioelectrical activity in the brain in response to chemical or electrical stimuli applied to these preparations was the same as that registered in normal brain hemispheres.

One of the conclusions of the study was that rhythmic electrical activity, closely related to the alpha rhythm, is an inherent property of the cortex itself; it is not necessarily dependent upon thalamo-cortical circuits, though these circuits, when present, may modify its form and amplitude.

Herbert Jasper<sup>17</sup> studied diffuse projection systems to the cortex, and the integrative action of the thalamic reticular system; their functions are closely related to the reticular system of the brainstem. The reticular formation acts by provoking a diffuse and unspecific activation of the brain by eliciting waking. It also triggers discriminatory functions.

Their conclusion was that the diffuse thalamic reticular system, with its cortical connections, possesses a topographical organization and uses afferent and efferent impulses closely related to those of the regulatory systems of the hypothalamus, midbrain, striate body, and the cortex itself, thus coordinating the mechanisms of brain activity.

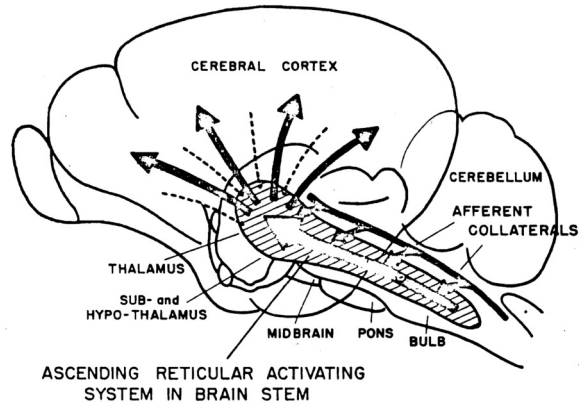
G. Moruzzi and H.W. Magoun<sup>18</sup> studied the changes in the EEG using Bremer's *encéphale isolée* method of experimental preparation (Figure 3).

These researchers observed that EEG traces from experimental animals responding to stimuli applied to the RF in an intact brainstem experienced changes analogous to those registered when the animal entered a state of wakefulness.

The first hypothesis analysed by the authors was whether the transection of the brainstem at the mesencephalic level elicited the sleep state by sensory deaf-ferentation or if it was due to the interruption of the ascending activating system, located in the pontomedullary reticular formation.

Moruzzi and Magoun sectioned the sensory pathways in an experimental animal at the level of the two lateral portions of the midbrain and interrupted the sensory stimuli from cranial nerves I and II, while not damaging the reticular formation; the authors observed that the EEG recording showed characteristics of the state of wakefulness. However, when sectioning the base of the diencephalon and the anterior part of the midbrain, therefore interrupting the reticular formation while leaving the sensory pathways to the cortex intact, the animal showed an EEG with sleep state characteristics. The experiment showed that the integrity of the RF and its stimulating activity on the cortex was more important to maintain wakefulness than the stimuli from the sensitive and sensory pathways.

The authors observed that the stimulation of the RF at different levels (medial medullary, pontine, mesen-



**Figure 4.** Diagram of the ascending activating reticular system. In: Starzl TE, Taylor CW, Magoun HW. Collateral afferent excitation of reticular formation of brain stem. *J Neurophysiol* 1951;14:479-96.

cephalic tegmentum, subthalamus, and dorsal thalamus) caused EEG desynchronisation and low voltage fast activity.

Moruzzi and Magoun concluded that the arousal reaction to natural stimuli mediated by collaterals of afferent pathways to the brain through the reticular formation, rather than by afferent impulses at the sensory receiving areas of the cortex; therefore, there is an ascending reticular activating system (Figure 4).

Decreased activity of the reticular activating system, mediated by medication or experimental structural lesions, led to somnolence or deep sleep.

After these experiments, the authors concluded that the conceptual idea that sleep is due to a sensory deaf-ferentation of the brain should also include the interruption of stimuli from an ascending reticular activating system, which seems to be more important to preserving wakefulness than stimuli from sensory pathways. This activating system is located on the RF of the central lower part of the brainstem.

In 1956, Roger, Rossi and Zirondoli<sup>19</sup> studied the importance of sensory afferences from cranial nerves in sustaining wakefulness. They used Bremer's *cerveau isolé* preparation and sectioned the brainstem at the medullary level. These authors observed that sectioning the olfactory, optical, acoustic, vestibular, and vagal pathways did not modify the state of wakefulness of the



**Figure 3.** Giuseppe Moruzzi and H.W. Magoun returning from the "Moscow Colloquium" (Colloquium on Electroencephalography and Higher Nervous System Activity, 1958). UCLA Neuroscience History Archives.

experimental animal. However, sectioning or destroying the gasserian ganglion, which inhibited trigeminal afferent inputs, caused the animal to both enter a clinical sleep state and to show the characteristic EEG trace.

These experiences are sufficient to affirm that the state of wakefulness is the result of RF activity which stimulates the cerebral cortex. Since RF activity alone cannot keep the animal awake, proprioceptive and stereoreceptive stimuli are added.

Nauta and Kuypers<sup>20</sup> expanded the anatomical knowledge of the ascending pathways of the RF. These authors identified several ascending fibres in the brainstem and midbrain tegmentum, joining Forel's tractus fascicularum. These fibres are made up of multiple axons originating from the medial and magnocellular region of the medullary and pontine reticular formation, intermingled with axons from the spine and the trigeminal system, along with numerous axons from the inferior olivary nucleus. These fibres are distributed in the periaqueductal grey matter, corpora quadrigemina, pretectal area, intralaminar thalamic nuclei, and subthalamus. Most of these fibres reach the hypothalamus, preoptic area, and the medial septal nucleus of the thalamus. At the cortical level, they connect with the limbic system, which regulates the endocrine system and autonomic functions.

The reticular formation as an organic and functional structure

From the different anatomical studies, we can confirm that the RF is made up of a collection of more or less specific, intermingled clusters of neurons. The various neuronal groups were differentiated according to the presence of certain neurotransmitters.

Noradrenergic, dopaminergic, serotonergic, cholinergic, and histaminergic cell groups were identified in the RF. Every group presented its specific neurobiological activity, using their multiple connections to perform such roles as modulating the state of sleep and wakefulness, motor function, sensitivity, autonomic and endocrine functions, affective behaviour, and cognitive functions.

One of the latest contributions to the knowledge of RF activity on the cerebral cortex was provided by Herbert H. Jasper.<sup>21</sup> This author proposes the existence of differences in the transmission of impulses to the cortex

by the reticular activating system. According to Jasper, the RF prompts non-specific diffuse activation of the whole cerebral cortex, to elicit the state of wakefulness from the state of sleep or unconsciousness, and at the same time to cause a cortical activation of the different sensory afferents for discriminatory purposes.

Machne and Magoun<sup>22</sup> applied microelectrodes to monkeys and found that during arousal, in some areas of the thalamic RF there is an overall increase in the activity of RF units, and clear inhibitory signals are shown in other areas.

This is also demonstrated by the fact that stimulation of areas which trigger a burst of movements registers an increase in bioelectrical stimulation, while an inhibition of said activity is observed in other areas.

EEG activity upon awakening is associated with complex neuronal activity, both excitatory and inhibitory, caused by the influence of the cortical cells themselves.

In short, the confluence of a great variety of messages takes place in the RF. Their meaning and the information they contained should be retained in order to make an appropriate data selection to provoke an action.

Functional significance of the RF is understood by analysing the afferent and efferent pathways, and their interconnections along their whole anatomical structure, whose delimitation is still undetermined. These interconnections act by modelling the afferent stimuli, and thanks to this, efferent pathways influence multiple functions of the nervous system.

Efferent pathways of the RF are in contact with the red nucleus, substantia nigra, striate body, thalamic nuclei, and motor cortex. They control and modulate motor activity. They also regulate sensory functions and pain through connections with the spinothalamic tract and the posterior spinal roots.<sup>23</sup>

These pathways participate in the regulation of autonomic functions, which are controlled by the orbitofrontal and entorhinal cortices and limbic structures.

RF function is involved in the regulation of biological rhythms, and in higher and cognitive brain functions through its connection with the hypothalamus and the limbic system.<sup>23</sup>

Cortical desynchronisation depends on the activity of the aminergic and cholinergic systems of the reticular

formation, located in the ascending activating system. Deep sleep stage with slow and synchronised waves depends on the activity of the serotonergic neurons of the raphe nuclei; paradoxical or REM sleep depends on the functioning of adrenergic and cholinergic cells, located in the central portion of the locus coeruleus. These pontine cells show pacemaker-like activity.

## Conclusions

We can state that the anatomical configuration of the RF lacks specific limits; anatomists have not reached a consensus on the structures of the nervous system that comprise it. The neurophysiological study of the reticular formation basis, as shown by the articles mentioned, provides a better knowledge of this complex structure of the nervous system.

## Conflicts of interes

The author has no conflicts of interes to declare

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