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Historical Issues in Sleep Medicine

Encephalitis lethargica epidemic milestones in early sleep neurobiology researches



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ABSTRACT

Around 100 years ago, the outbreak of peculiar encephalitis promoted knowledge advancement regarding sleep and psychomotricity control. This epidemic is believed to have disappeared ten years after it started, and it remained from 1916 to 1927. Since then, only a few sporadic cases have been reported, but previously, they happened in occasional and epidemics forms. Two pioneers in describing the cases were Jean-René Cruchet and his collaborators, and Constantin Von Economo. The firsts described diffuse symptomatology, “sub-acute encephalomyelitis.” However, the reports by the Austrian aristocrat had a localized aspect which was admitted by him as a new disease, “Encephalitis lethargica” (EL). In his suppositions, based on clinical and anatomopathological material analysis, von Economo found distinct centers for sleep, in the rostral hypothalamus, and wakefulness, posterior hypothalamus. He plays an essential role in new achievements about EL and sleep neurobiology comprehension.

These basic structural sleep-arousal regulatory neural systems had a lasting impact on contemporary sleep research, unfolded initially mainly by Frédéric Bremer, Giuseppe Moruzzi, and Horace Winchell Magoun, based on a passive theory of sleep induction. The last arrived at the conception of “diffuse” and “unspecific” ascending reticular activating system (ARAS) of the brain stem. This notion was unfolding until the idea of various interconnected “waking centers” and “sleep centers” levels, and also, active sleep induction.

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1. Introduction

Jean-René Cruchet (1875–1959), and Constantin von Economo (1876–1931), identified the main manifestations of patients with uncommon disease signs, and two communications marked the beginning of the recognition of a new disease, soon to be part of a worldwide pandemic [1–3].

Cruchet, Moutier, and Calmettes, presented on April 1, 1917, at the Société Médicale des Hôpitaux de Paris, observations from forty hospitalized military personnel in Bar-le-Duc, at the First World War, who showed unusual signs that encompassed: fatigue, headache, numbness, fever and polymorphic disorders such as mental and ocular trouble, chorea, cerebellar and bulbo-protuberantial or even spinal cord signs – the so-called “subacute encephalomyelitis” [1,4].

Von Economo, on April 17 of the same year, to the Vienna Psychiatric Society, presented a more localized polioencephalitis with

a predominantly mesocephalic location characterized by hypersomnia, ocular paralysis, and fever. He reported that he saw in Vienna in the first half of 1917 in the Psychiatric Clinic, he observed a number of cases of encephalitis, the majority expressed in the form of a peculiar slumber with paralysis of the eye muscles, which he termed Encephalitis lethargica (EL) [2–4]. It was different from tsetse fly-transmitted sleeping sickness, but some other names were schlafkrankheit, sleeping sickness, nona, brain influenza, and, more recently, lethargic encephalitis, epidemic encephalitis or subacute encephalomyelitis [1–5].

EL appeared around the same time as the great influenza pandemic of 1918, but without an influenza epidemic in Vienna at the time of von Economo's first reports [2,3]. Indeed, regarding the sleep, it raises human curiosity thought the ages, and about a century ago, noteworthy advancement was made in the understanding of the sleep neuronal regulation. Von Economo (1930) (Fig. 1), was the first to examine a neuronal mechanism for sleep/wake regulation in mammals, soon followed by many others. He has published several reports on EL, no less than 27, since his pioneering publications made about a month after his Viennese April

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Constantin Alexander Freiherr Economo von San Serff (* August 21, 1876, Brăila - † October 21, 1931, in Wien) was an Austrian Baron, Romanian born and from an aristocratic Greek family, brought up in Austrian Trieste.

He was a cultured man, a music lover, a talented poet, and a multilingual and experienced pilot.

Von Economo began studying engineering, but he shifted to medicine in Vienna and received his medical degree in 1901. After graduation, he spent one year in medicine with Hermann Nothnagel. Later, he went to Paris, where he worked for one year under Pierre Marie / Fulgence Raymond, in neurology, and Valentin Magnan / Alexis Joffroy, in psychiatry. Besides, in Nancy, he learned Hippolyte Bernheim's techniques of hypnosis, in Strassburg, he trained in anatomy with Albrecht von Bethe and physiology with Julius Ewaldand. In Berlin, he worked with Georg Theodor Ziehen and Hermann Oppenheim. He also went to the clinic of Emil Kraepelin in Munich, where he worked for six months in neurohistology under the supervision of Alois Alzheimer. He finished this internship trip to the Zoological Experimental Station at Trieste, where he worked on comparative neuroanatomy with Carl Isidor Cori.

He came back to Vienna to the Clinic for Psychiatry and Nervous Diseases at Vienna's General Hospital as an assistant of Julius Wagner von Jauregg, where he carried out clinical duties, besides laboratory research in neuroanatomy and neuropathology. In this Clinic, von Economo described his first cases of the strange disease, "Encephalitis lethargica" (EL).

Later, he was appointed as a lecturer in 1913 and professor of Psychiatry and Neurology in 1921, at the Vienna University.

On May 7, 1931, von Economo initiated the new Brain Research Institute in Vienna as its first principal.

His mainly medical contributions are on EL, sleep regulation (1925, 1929), Cytoarchitecture of the Cerebral Cortex in Adult Man (1925), Wilson's disease, spindle neurons, nowadays called von Economo neurons, and the theory of "progressive cerebation" (constant evolution of the mind and brain through successive generations).

He published 27 papers and a book on Economo's Disease (EL): clinical features, pathology, and histology. Von Economo was designated three times for the Nobel Prize in Physiology or Medicine for the detection of EL. He was married to Princess Karoline von Schönburg-Hartenstein (1892-1986). He died of heart failure [2], [3], [6], [7],[18],[19],[22].

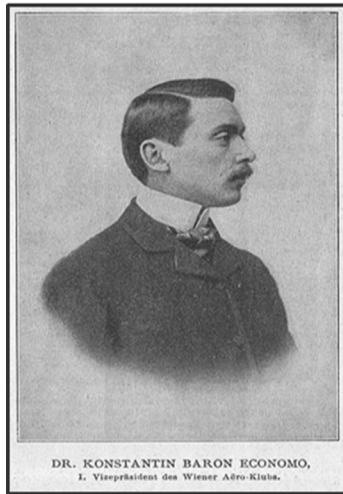


Fig. 1. Constantin von Economo (1908). Photo: Public domain – Wiener Luftschiffer-Zeitung, 1908; VII. Jahrgang, Nr. 12, S. 311.

1917 presentation followed by another one in the same year [2–4,6] (Fig. 2).

EL has attracted much medical attention since its initial outbreak. Even this mysterious illness has become the central element of the book "Awakening," written by Oliver Sacks, a famous English neurologist fond of "romantic science." This book was later reproduced in a film that was awarded three Oscars in 1990 [6].

This article aims to pay tribute to the leading pioneer researcher on EL, von Economo, who collected and studied the findings of it and presented fundamental milestones of the sleep neurobiology comprehension.

2. Clinical manifestations and diagnosis

The disease can present a broad and sometimes confusing range of symptoms and signs, often with unusual and bizarre behavior, in a clinical polymorphism. However, von Economo, since the first publications (1917) [2,3], already captures the EL essential findings: "It is a kind of sleep disorder of usually slow progression, but the first symptoms are commonly acute with headache and nausea and show slight meningeal symptoms; then a state of somnolence occurs, often coupled with vivid deliriums, from which the patient can be easily awakened and give fairly orderly information, This delirious somnolence can now lead to death in a progressive rapid manner or in the course of weeks and months, or it can last for weeks or even months with hourly, daily or even greater amplitudes of fluctuation of the depth of the clouding of consciousness, ..., or it can gradually improve, but the patients are then still mentally weakened for a long time". "The disease can begin under a

fever The general symptoms are usually accompanied by signs of paralysis, both in the area of the cranial nerves and the extremities, especially the eye muscle nerves are often affectedexamination of the cerebrospinal fluid often, but not regularly, reveals increased pressure, the cerebrospinal fluid is free of bacteria, only exceptionally does it contain pleocytosis, only rarely is its protein content increased".

On the contrary, Cruchet [1] had a broader view of EL, in the general infectious context, highlighting a series of clinical forms, namely, mental (amnesia, cerebral numbness, disorientation, pupillary disorders, tremor, dysarthria, even paraphasia), convulsive, choreic, meningitic, hemiplegic, ponto-cerebellar, ponto-medullary, acute ataxic and anterior poliomyelitis. Thus, he emphasized that EL was nothing more than one of the forms of his described diffuse encephalomyelitis [1].

Regarding von Economo, after years of careful observation, he collected and analyzed thousands of cases and classified them into three clinical syndromes: **Amyostatic-akinetic forms** (Particularly prevalent in the chronic cases, "Parkinsonism," may simulate a state of profound secondary dementia); **Hyperkinetic** (Chorea and hemichorea, as well as myoclonic twitches which were observed, may degenerate into wild jactations. Restlessness of an anxious or hypomanic type. In most, troublesome sleeplessness); **Somnolentophthalmoplegic** (Sleep may last for weeks or months, frequently deepens to a state of stupor or coma and death. First days of the illness, cranial nerve palsies as ptosis, frequent bilateral ocular palsies, incomplete usually asymmetrical, in most cases, a nuclear paralysis, rarely supranuclear paralyzes, paresis of convergence, nystagmus, optic neuritis, papilledema, pupillary disturbances, and may occur Argyll Robertson's sign) [7].

changed, and he said that his insomnia had started when he was a despatch rider in 1916. Besides, there is an account of an episode in which Hitler's eyes suddenly looked strained and turned upward, suggesting an oculogyric crisis that does not occur in PD.

3. Epidemiology

EL occurs sporadically or epidemically, but the retrospective diagnosis suggests that there have been several reports of EL throughout history. Sporadic cases were already noted in the past, as by Sydenham (1673) Albrecht de Hildesheim (1695), Pinel (1802), Gayet (1870), Gillet de Grandmont (1890), but supposed unusual cases continue to appear [9,10]. In the core of World War I, this new disease took place in 1915, in Roumania. Shortly afterward, epidemics happened in Vienna in 1917, followed by France and England in 1918. By 1919, the plague had overrun most of Europe, the USA, Canada, Central America, and India, affecting mainly children, adolescents, and young adults. Most of them were male [10,13].

There were temporal and regional nuances, because, during the first epidemic climaxes of 1917–1918 and 1918–1919, mental disorders mainly affected the aspect of drowsiness, stupor or catatonia, with considerable local variations. However, in 1919–1920 and 1919–1921, delusional forms with agitation and myoclonus dominated the clinical picture [9]. Finally, it spread across the planet to disappear from 1926 [11].

MacNalty (1936) [10] reports that EL has been notifiable in England and Wales since 1919, and the highest year of incidence was 1924 when 5039 cases were notified, with 1407 deaths. Since then, the incidence has gradually declined, and from 1930 onwards, the deaths have exceeded the notifications.

The Matheson Commission, established by a wealthy businessman, in its first survey (1929), reported 52,781 cases of EL, between 1919 and 1928. This data is about cases that had been formally diagnosed from 14 countries where EL was a reportable illness. EL affected all ages, but 50% of the cases were 10–30 years old, with no preference for sex. However, specific outbreaks had a higher incidence in one sex or the other. Regarding ethnic predilection, some reports are suggesting more significant involvement of EL among Jews and “natives” of South Africa, India, and the Philippines. Also, there higher incidence of EL in urban than in rural areas, perhaps due to better diagnosis in the former [10].

4. Etiology

The etiology of EL is still unknown, but many may be raised as environmental, infectious, autoimmune, or multifactorial to explain the full range of peculiar clinical expression.

The viral etiology of EL has always been suspected. Still, the responsible agent has never been isolated, neither the influenza virus, nor herpes, nor poliovirus [11]. Still, many believed the flu might be a predisponent factor for EL.

Also, von Economo ruled out any toxic process, and he established that EL was produced by an infectious virus grounded on findings of brain tissue from deceased patients injected on experimental animals [3,10].

Since EL partially overlapped the 1918–1920 flu epidemic – H1N1 or “Spanish flu,” some consider it to have caused EL, and von Economo suspected a link between the two conditions, due to their similar seasonality. Nonetheless, e. g., in Vienna through 1917, there was no epidemic of influenza. There were no fatal cases of it come for necropsy at the Pathological Institute, despite the recorded cases of EL [3,5].

Although all observers reported similar findings in the brains of patients with EL, the changes were nonspecific.

However, the marked involvement of the brain stem, including the substantia nigra and, to a lesser extent, the locus ceruleus, characterize a more definite pattern of disease in PEP [10,11]. In the chronic phase of EL, brain findings were of modest degrees of focused or generalized atrophy, and, microscopically, evidence of old injury and new inflammation suggests persistent infection. Neurofibrillary tangles were discovered in 1932, in the brain stem of a post-encephalitic patient who showed no signs of dementia. However, similar findings are seen in Alzheimer's disease [10].

In addition, even with modern technologies, studies using RT-PCR did not indicate the presence of the influenza virus in the tissues of patients suffering from EL.

Dale et al. [14] assisted 20 patients with an EL-like phenotype and proposed an autoimmune etiology comparable to that of Sydenham's chorea. Consequently, post-streptococcal disease was considered one of the etiologies of EL [14]. Thus, there would be a common factor for both inflammations of the throat and for EL [6]. However, today, this relationship appears mainly related to anti-N-methyl-D-aspartate (NMDA) receptor encephalitis [10,15].

Within the current knowledge, a hypothesis would be that the initial virus would provoke an inadequate immune response. Besides, the co-occurrence of encephalitis and the influenza pandemic would have affected the brain causing EL. Also, discoveries about the effects of inflammatory molecules on neuronal circuits and the molecular interactions between immunity and sleep, on health and disease, also shed light on the pathogenesis of African human trypanosomiasis and EL [16]. Although these disorders differ in etiology, synaptic interactions with molecules derived from the immune response could play a pathogenic role.

Despite the last major epidemic of EL occurred about a century ago, its cause has never been scientifically proven and remains controversial today [10].

5. Sleep neuroanatomy and physiology, initial scientific researches

5.1. Von Economo's center for the regulation of sleep

A sleep-regulating center was not accepted by many in von Economo's days. Still, his findings at EL favored this idea. Von Economo's previous idea about sleep center was suggested by Troemner (1912), who understood that the thalamus opticus would be the site of nerve fiber conduction block for sleep promotion. However, previously, Ludwig Mauthner (1890), based on Wernicke's encephalopathy, presumed that the lesion would be in the periaqueductal gray matter linked to oculomotor nuclei and abnormal eye movements, in addition to sleep disorders. Consequently, von Economo assumed that the sleep centers were close to these structures, since 1917, and that sleep is promoted by active nervous inhibition of distinct parts of the central nervous system [4,7,8,17].

In relation to Pavlov's experiments, animals began to fall asleep in monotonous tests, and the performance of conditioned reflexes ceased. Accordingly, von Economo believed that the brain was responsible for the cessation of consciousness and inhibition of sensory flow, as a kind of Pavlovian conditioned reflex. This would imply the inhibition of sensory flow that would occur through a reflex inhibition initiated in the center of sleep, promoted by substances that circulate in the blood, with extension to other brain sections [18].

However, based on his clinical observations, von Economo disfavored a simple passive sleep theory in favor of one in which sleep is an active state-initiated and controlled by the synchronized activity of specific structures in the central nervous system. In this way, the sleep theory changed from one of just a passive role to one

of an active role, indeed of a “safety circuit” whose sensitivity to hypotoxines guarantee the protection of the whole brain [18].

In a lecture to the Society of Physicians in Vienna in March 1925, von Economo underlined that sleep and wakefulness have quantitative and qualitative differences, active and reversible function of a “sleep-regulatory center” located near the oculomotor nucleus, the aqueduct of the third ventricle and the infundibular region. He also offered a synthesis of his concepts in a series of lectures in New York (1929), and at the First International Neurological Congress, in Berne (1931) [7,19]. The hallmarks of von Economo’s work on EL are recorded in his two monographs, where he documented its neuropathological basis and complete clinical spectrum, an initial (1917), and a wrap-up one (1929) [2,3,8,20]. In 1929, he proposed a “center for regulation of sleep” based on anatomical and clinical studies of EL at the Psychiatric Clinic of Wagner von Jauregg, in Vienna [8,20].

Thus, for the first time, von Economo generated a better understanding of the brain genesis of sleep when he proposed a “center for the regulation of sleep”. These conclusions were based on the analysis of anatomopathological material of patients with EL with drowsiness or insomnia. Most commonly, the first was associated with ophthalmoplegia. Consequently, in most cases, necropsy invariably revealed mild lesions in the midbrain, where the nucleus of the oculomotor nerve is located, in addition to the substantia nigra lesion. However, a smaller number of patients with EL had insomnia, and their injuries were found in the anterior hypothalamus.

Therefore, von Economo deduced that there are distinct centers in the brain to regulate sleep and wakefulness. He assumed that the sleep-regulating center, in general, is located close to the oculomotor nucleus, the aqueduct of the third ventricle, and the infundibular region, close to other critical vegetative centers. Concerning these findings, von Economo proposed a structure in the midbrain that maintains the overlying thalamus and the neocortex in an activated and awake state. In contrast, von Economo inferred the existence of another center controlling the onset and depth of sleep. Consequently, injuries to the frontal preoptic area (AOP), (Schlafteil, sleeping area) cause insomnia, but lesions located behind (Wachteil, awakening area) induce sleep.

Indeed, von Economo was among the first to suggest that waking and sleeping systems were confined in distinct regions of the forebrain. Besides, he rejected all the prevailing sleep theories because they are not ample to elucidate the sleep mechanism, which looked much more complicated [8,17].

Von Economo described the neuropathological findings that included lymphocytic infiltration of the blood vessel adventitia, mainly small and medium veins, and diffuse hemorrhagic and inflammatory lesions, prevailing in an acute infectious process. He also noted that the upper midbrain and the substantia nigra showed the most evident changes, followed by the ganglia of the base, pons, medulla, and thalamus [7].

Later, the EEG revealed much more about the mysteries of sleep. In 1928, Hans Berger picked up brain electrical signals in the human scalp and demonstrated differences in the rhythms of the awake individual. Thus, for the first time, the presence of sleep can be conclusively established and measured continuously and quantitatively without disturbing the individual in sleep. Then, in the 1930s, Nathaniel Kleitman characterized EEG patterns during sleep in an active brain, and in 1953 he published with Aserinsky their seminal paper about regularly occurring periods of Rapid eye movement sleep (REM sleep) [21].

5.2. Von Economo’s heritage for the sleep neurobiology studies

At the beginning of the 20th century, some more advanced thoughts on the origin of sleep were concerned with the configuration of the sleep brain center and its mode of action.

This enigma began to be unveiled by the related scientific theories in the 19th century, in the discoveries in animals and humans when there were then three major theoretical groups for the origin of sleep, namely, vascular, chemical and deafferentation, basically passive theories for the origin of sleep [20,22].

Regarding “sleep center” theories, presumably, the sleep was due to the release of an active “sleep center” or a passive event resulting from inhibition of a “waking center” [14,17]. However, the theory of sleep center did not have much support; on the contrary, it has been criticized by several authors, such as Veronese and Lhermitte [23,24].

Nevertheless, von Economo’s findings supported this localized conception, besides Nauta (1946) [17] reached, based on experiments in rats, similar conclusions to von Economo’s regarding the location of the brain regions related to sleep and wakefulness. Regarding the sleep center control, Von Economo proposed that it was under the influence of substances circulating in the blood [23].

The new researches have been refining the issues regarding wake and sleep induction, concerning passive or active sleep induction, besides a more precise locus for these functions. The main forerunners of these achievements were Frédéric Bremer (1892–1982) and Giuseppe Moruzzi (1910–1986) & Horace Winchell Magoun (1907–1991), besides many others such as Walter Rudolph Hess (1881–1973), and Batini et al. from Pisa School [20,23,25,26]. Some of these researches milestones are presented in the Fig. 3, based on human EL and experimental findings regarding sleep–wake centers and deafferentation, passive, and active sleep theories.

Indeed, at the beginning of the modern sleep neurobiology studies, mainly in the first half of the XX century, prevailed the passive sleep theories, that shift to an active one.

Frédéric Bremer (1892–1982), 1935, did two types of experiments reinforcing the “deafferentation” sleep theory of stimuli withdrawal in the “isolated” brain and the “isolated” cerebral cortex [27,28]. In these situations, a cut was made in the inferior part of the bulb. The EEG then indicated sleep/wake cycles, “encephale isolée,” the animal alternates states of sleep and vigilance, and even increased alertness (hypervigilant cats). Another one, “Cerveau isolé,” of the isolated anterior brain when it was cut the upper part of the brain stem, which produced waves in the EEG of continuous deep sleep (hypersomnolent cats), deafferentation in the cortex [25,29]. The first preparation allowed the study of cortical electrical rhythms under the influence of olfactory, visual, auditory, vestibular, and musculocutaneous impulses; in the second preparation, the field was reduced almost entirely to the impact of olfactory and visual actuation.

The reason for the Bremer’s cats falling into a “deep sleep” was not exposed until 1949 when Moruzzi and Magoun completed their experiments. They implanted electrodes in the brain stem and electrically stimulated the reticular formation that promoted behavioral and EEG excitation. The researchers went on to establish that the brainstem “system of ascending reticular relay, whose direct stimulation activates or desynchronizes the EEG, replacing high-voltage slow waves with low-voltage fast activity” [30]. Consequently, the ascending reticulum activating system of the brain (ARAS) and the posterior hypothalamus were necessary for the maintenance of a waking state [31]. It was then realized that the brainstem transection studies did not produce sleep because of stimuli “deafferentation”. However, the sleep was the consequence of the loss of the stimulus from the ARAS. Consequently, sleep was still seen as a passive phenomenon. Bremer (1935) [27] published his classics works with the understanding that sleep in mammals, whether natural, toxic (such as that caused by barbiturate) or pathological (such as that of narcolepsy), implies the more or less complete deafferentation of the telencephalon.

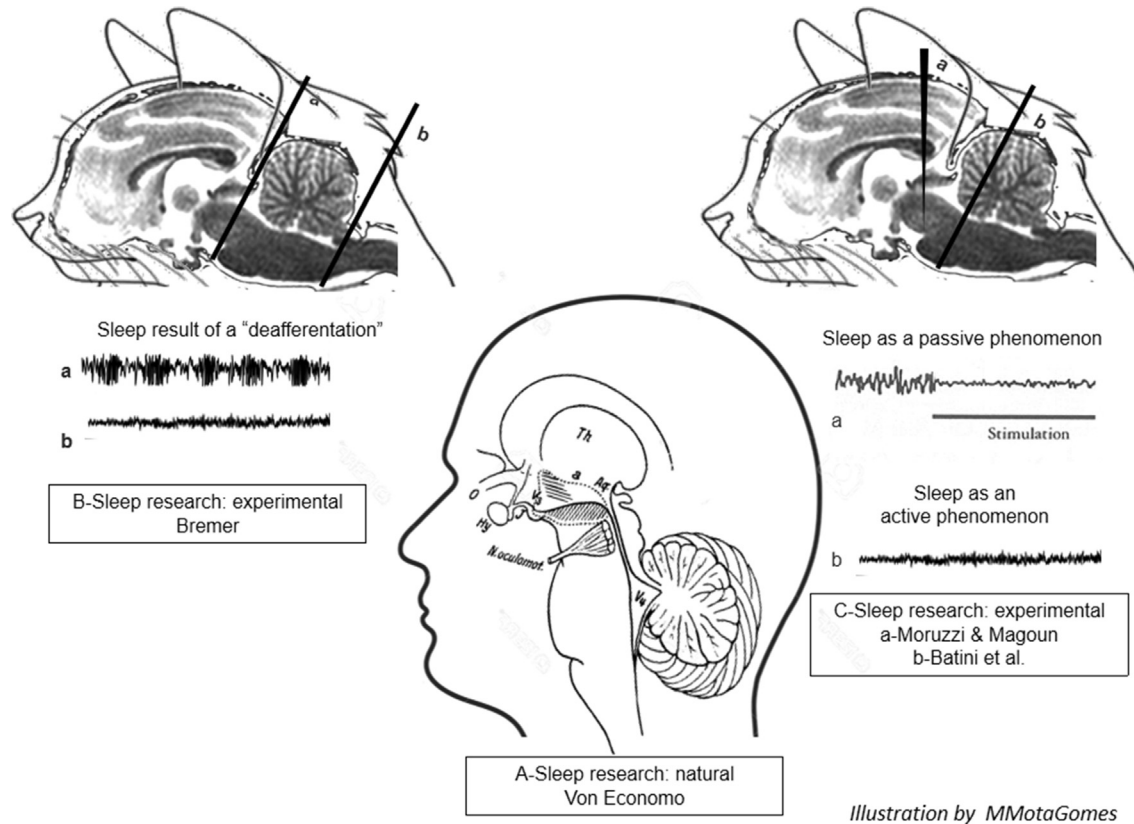


Fig. 3. Schema of the brain researches made by some founders of the modern sleep neurobiology understanding. Bottom: Von Economo (1929) [8], the necropsy of patients with EL, indicated that those with an insomnia-like phenomenon had damage in the anterior hypothalamus. In contrast, those with abnormally increased sleep periods showed an abnormal posterior hypothalamus. Top left: Bremer (1935) [27–29], performed experimental preparation of the “Encephale Isolé” (caudal lesion) (b) and “Cerveau Isolé” (rostral lesion) (a). Top right: Moruzzi & Magoun (1949) [30], demonstrated activity in the ascending reticular activating system of the brain that triggers wakefulness (ARAS) (a); Batini et al. (1958–9), sleep as an active process “center” in the medulla oblongata (b) [26,33]. Abbreviations are Aq, aqueduct; Hy, hypophysis; J, infundibulum; O, optic chiasm; Th, optical thalamus; V3, third ventricle; V4, fourth ventricle. Adapted figure: Human brain from von Economo (1929) [8], already previously presented in 1918 [17].

However, as demonstrated by Moruzzi and Magoun (1949) [30], the sleep would be due to the merely passive mechanism of the absence of activating reticular inflows on the cerebral cortex, as supposed in the deafferentation theory. Indeed, as stated by Dement [21], the ARAS theory was an anatomically based passive theory of sleep or an active theory of wakefulness. Anyway, it weakened the widely held deafferentation sleep theory, reinforced by Bremer.

Regarding the “sleep center” of von Economo, located at the anterior hypothalamus, it was later recognized and localized as ventrolateral and median preoptic areas (VLPO/MnPO), at the end of 1980s–beginning of 1990s [32]. However, far ahead, it was confirmed that there are many medullary and hypothalamic non-REM and REM “sleep centers” [32].

Active sleep theory through sleep-promotion neurons determines the sleep onset; its theories arose according to the ascending or descending hypothesis [33].

The first was proposed by members of the School of Pisa - Batini et al. [26], based on experiments on cats after a pre-trigeminal mediopontine section. These researchers admitted the existence of synchronizing and sleep-inducing structures in the medulla oblongata that was able to inhibit the activation of the pontomesencephalic reticular formation or to activate the synchronized structures of the thalamus directly. As the animal was always awake, the researchers concluded that sleep induction was active and was not limited to the most rostral part of the hypothalamus

(1958, 1959). However, most research on the non-REM sleep circuit has focused on POA and basal forebrain [23].

As for the descending hypothesis of the theory of active sleep, it has the classic experiments of Walter Rudolph Hess (1881–1973) [34]. Hess (1929–1944) observed in the cat, with electrodes implanted chronically, that the weak stimulation in the medial thalamus, close to the intermediate-mass, produced sleep. However, other researchers have failed to repeat sleep induction at this location, perhaps because of the used techniques [17,34].

Later, Michel Valentin Marcel Jouvet (1925–2017) and many others gave more details of the cerebral and neurochemical structures implicated on sleep synchronized (non-REM) and desynchronized (REM) [23,33].

More achievements have been made since then, revealing the mechanisms of waking mechanisms. In this way, Moruzzi and Magoun’s discoveries represent at the end of the 1940s, the upper level of the studies initiated by von Economo and followed by Bremer, and many others. Indeed, the ARAS discovery by Magoun and Moruzzi led to the hypothesis of a “diffuse” and “unspecific” ARAS of the brain stem [32]. These researchers contradicted the simplified deafferentation theory of sleep as Moruzzi et al. [30] stated that “In the present experiments, typical EEG arousal reactions have been reproduced by stimulating the brain stem reticular formation, without exciting classical sensory paths.”

The subsequent studies were carried out with more precise neurophysiological and histochemical methods, mainly in

chronically operated free-moving cats and rats. Consequently, the idea of undifferentiated ARAS has distressed as researchers recognized that the primary stimuli on arousal arise from neurochemically diverse systems [23]. The ARAS was already formulated as an organized hierarchy of the cerebral “waking centers” distributed along the entire cerebral axis. These “centers” are localized at all the cerebral axis levels, from the medulla to the prefrontal cortex, together with the lateral hypothalamic neurons releasing orexin/hypocretin peptide (1998). Indeed, the orexin neurons are scattered across the lateral hypothalamus, as stabilizers of wake–sleep bistable systems that avoid intermediate states [35].

However, in the last years, there is also a revision regarding the ARAS, as the glutamatergic activating system has been discovered. Supposedly, it is responsible for the appearance of EEG arousal response and maintenance of the neocortex in the tonic depolarization state through wakefulness, and, also, at the REM sleep. Besides, the activity of all other “waking centers” is probably the result of the cortical activation [32].

In conclusion, according to nowadays knowledge, the neuroanatomic substrates of wakefulness and sleep are distributed along the CNS, and they are modulated by neurotransmitters and neuromodulators.

Furthermore, regarding the circadian rhythm of sleep and wakefulness, it is proposed that it is controlled by two process models. The first is related to sleep regulation (1982, 1984), the homeostatic (process S), based on past theories, and the other of circadian factors (process C) [36]. This last one is under the genetic determination of the cellular circadian oscillators, the main one, located at the suprachiasmatic nucleus that is regulated by entrainment pathways from the retina for precise timing of its activity.

For complementation of wake–sleep cycles function control, regarding centers and neurotransmitters, there is one model of a bidirectional inhibitory “flip-flop switch” (2010). This ensures rapid transitions from sleep to wakefulness and vice versa. It has also been proposed a complementary “switch” mechanism for non-REM sleep control (2006) [31,37].

6. Conclusions

The EL epidemic provided clues for a better understanding of brain functions, as the regulation of the sleep–wake cycle and a variety of brain diseases, such as sleep and those with psychomotor symptoms, including PEP, and mental disorders. Also, this disease linked to influenza pandemics, still without a proven causal relationship between them, it has high morbidity and mortality, especially in young people. Consequently, there is a significant concern about the recurrence of EL in a future influenza plague. This would be pertinent at the time of the COVID-19 pandemic, since the repetition of mysterious EL outbreaks appears to be a fact in world health history. However, it is not yet known whether COVID-19 will demonstrate its neurological consequences, exceptional or with temporary or late secondary manifestations, as occurred with EL.

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CRedit authorship contribution statement

M. da Mota Gomes: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration.

Conflict of interest

The author declares no competing interests.

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Appendix A. Supplementary data

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