Chapter 1 Pioneering steps in studies on sleep and epilepsy

This book is essentially devoted to analyses of neuronal substrates underlying sleep with low-frequency oscillations, so-called sleep with synchronized electroencephalogram (EEG) or resting sleep [1], and a series of seizures that preferentially develop during this state of sleep. The reader will find data on intrinsic neuronal properties and network operations in corticothalamic, hippocampal-entorhinal and neuromodulatory systems that control forebrain normal and paroxysmal activities. This brief introductory chapter is not intended to discuss in detail the history of ideas on two bedfellows, sleep and epilepsy, but only to resurrect some of the most important figures and concepts that are directly related to what is discussed at length, essentially at the neuronal level, in the following chapters.

1.1. Brain, neurons and sleep across centuries

Different states of vigilance, such as waking and sleep states with or without dreams, have been recognized in ancient cultures [2]. The deafferentation theory of falling asleep dates back to Lucretius, in the first century B.C. [3], was revitalized in the early 19th century by Macnish [4] and Purkinje [5], and was finally developed during the past century by three major figures of sleep research: Bremer, Moruzzi and Kleitman. As discussed in Chapter 3, the concept of passive or active sleep is a false dilemma as both brain deafferentation from external signals and actively sleep-inducing (humoral and neuronal) factors may lead to sleep, since the presumed actively hypnogenic neurons exert their inhibitory effects on activating neurons in the brainstem and posterior hypothalamus, thus disconnecting the forebrain, as postulated in the passive theory.

Two of the above-mentioned modern scientists, Bremer and Moruzzi [6] (Fig. 1.1), initiated their research on states of vigilance within the framework of the passive sleep concept, but finally turned their attention to structures that were hypothesized to play an active role in the process of falling asleep.

[1] None of the terms is fully deserved. Although the term "EEG-synchronized" is usually taken in contrast with the conventional term of "desynchronized" activity in wakefulness and REM sleep, fast rhythms in the beta and gamma range (~20–60 Hz) occur during the depolarizing phase of the slow oscillation in natural non-REM sleep and are synchronized over restricted cortical territories and thalamocortical systems, as is also the case in waking and REM sleep (Steriade et al., 1996a-b). As to the term "resting", it was designed to underline that virtually nothing mentally important happens in the brain during this state of sleep, in line with a series of older concepts that regarded sleep similar to cerebral death (Hypnos brother of Thanatos, as in Homer's *Iliad*) or, closer to us, an "abject annihilation of consciousness" (see note [224] in Chapter 3). This obsolete view can be refuted on the basis of high firing rates of neocortical neurons, short-term plasticity, and mental processes during this state (see section *3.2.4.2* in Chapter 3 and section ***4.3.3*** in Chapter 4). Therefore, I shall use, throughout this book, the descriptive term slow-wave (or non-REM) sleep. It is justified by the fact that the slow oscillation (generally 0.5–1 Hz), which was initially discovered in intracellular recordings from neocortical neurons in animals and found with the same characteristics in natural sleep of both animals and humans, appears from the very onset of non-REM sleep and groups other sleep rhythms, spindles, and delta oscillation (see section ***3.2.3*** and Fig. 3.6 in Chapter 3).

[2] The Indian textbook of philosophy, *Upanishad* (~1,000 B.C.), described different states of consciousness, among them wakefulness, dreamless sleep (*susupta*) and dreaming sleep (see Wolpert, 1982; and Chapter 1 in Borbély, 1984).

[3] See the 1988 translation of Lucretius' book *On the Nature of the Universe* (55 B.C.).

[4] Macnish (1830).

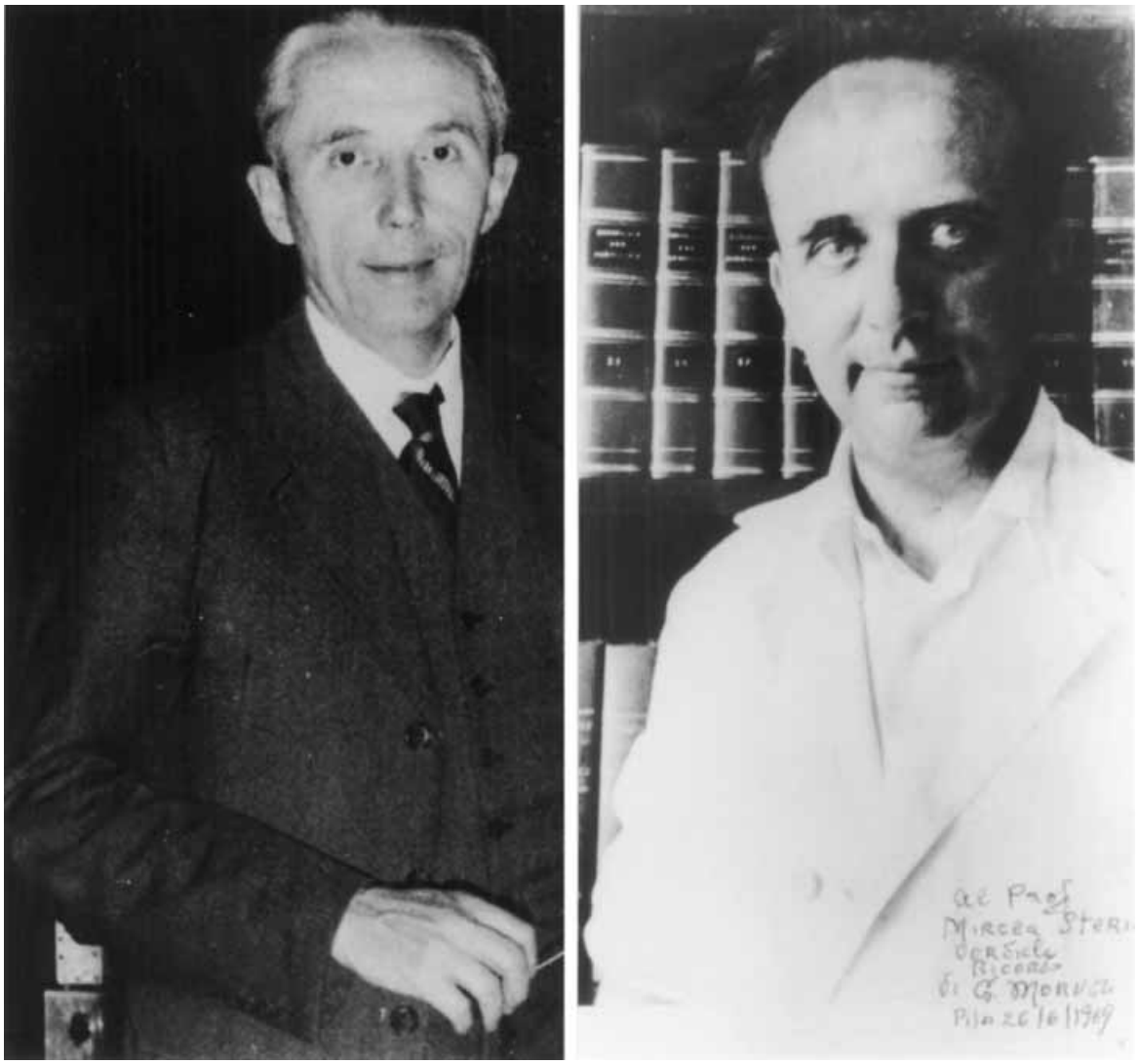

Fig. 1.1 Two pioneers in the research on slow-wave sleep and brain activation: Frédéric Bremer (1892–1982, left) and Giuseppe Moruzzi (1910–1986, right).

[5] Cited in Moruzzi's (1964) historical essay.

[6] Short biographical notes of these two great neurophysiologists can be found in a recent monograph (Steriade, 2001b; see notes [14] and [16] in Chapter 1 of that book). For Moruzzi, see also the interview by Marshall (1987).

[7] Bremer (1935). In his 1937 paper (see Fig. 1.2), Bremer clearly stated his concept that, after disconnection from brainstem influences, the effect at the EEG level is the "*expression d'une diminution de ce que l'on pourrait appeler le tonus cortical et diencéphalique*" (p. 78–79). The concept of a diminished cerebral tone after brainstem disconnection by intercollicular transection announced Moruzzi and Magoun's experiments, a decade later (see below, [11]). As to the apparent contradiction concerning the role played by *specific* (Bremer) versus *nonspecific* (Moruzzi) structures in the maintenance of brain arousal, see the main text and section ***3.1.2*** in Chapter 3. Besides his seminal contributions in the field of states of vigilance, Bremer was among the first scientists to emphasize the "fundamental autorhythmicity" of neurons ("*l'automatisme rythmique des cellules nerveuses*", 1949, p. 177 and 191), a notion that led to modern investigations on intrinsic neuronal properties (reviewed in Llinás, 1988). In that visionary 1949 paper, Bremer emphasized the "cortico-diencephalic interactions", an idea supported by recent dual intracellular recordings from cortical and thalamic neurons demonstrating the coalescence of different sleep rhythms within corticothalamocortical loops (see Steriade, 2001a-b).

[8] Bremer (1975, p. 268; and p. 271).

[9] The often made distinction that Bremer specified the role of ascending *specific* projections in maintaining the state of waking whereas Moruzzi discovered the role of *nonspecific* brainstem reticular pathways is tenuous (but possibly efficient in lectures to undergraduate students) because forebrain activation is maintained by both these systems. Sleep EEG patterns are not only produced by interruption of ascending reticular activating systems but also appear, confined to the visual cortical areas, after bilateral transection of optic nerves (Claes, 1939) and bilateral interruption of trigeminal nerves similarly produces a state of brain electrical synchronization (Roger et al., 1956).

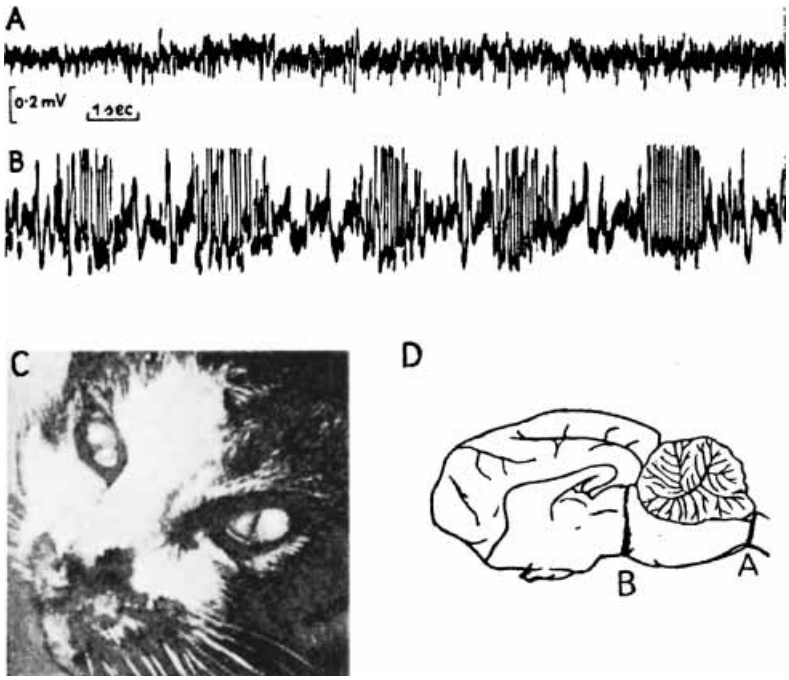

Fig. 1.2 EEG and ocular behavior in the acute *encéphale isolé* (isolated encephalon; EEG trace in *A* and bulbo-spinal section in *D*) and *cerveau isolé* cat (isolated forebrain; EEG trace in *B* and transection at the collicular level in *D*). *A*, activity typical for the waking state. *B*, spindling activity interrupted by inter-spindle lulls, as in the sleeping brain (see also fissurated myosis in *C*). From Bremer (1937).

Bremer left the isolated forebrain of the decerebrate cat *in situ*, instead of destroying it, and discovered that brain electrical activity contains spindles, associated with another sleep sign, extreme myosis (Fig. 1.2) [7]. He had "the shock one experiences in the face of a novel natural phenomenon" [8] and, indeed, we now know that sleep spindles occur by disconnecting thalamic neurons from the depolarizing influence of brainstem reticular cells. Although Bremer continuously emphasized that afferent signals maintain the *tonus cérébral* and that the EEG/ocular sleep syndrome he described in 1935 was due to interruption of sensory pathways [9], as in the passive theory of sleep, he turned in the early 1970s to the idea that the preoptic area in the anterior hypothalamus may play a hypnogenic role by inhibiting the rostral mesencephalic reticular core [10] that was known to exert activating effects on the thalamus and cortex. In one of his later contributions, Bremer, while well aware of the role played by the ascending reticular ("nonspecific") formation in arousal (and acknowledging that if he would have

"been more anatomically minded", he would have concluded that an activating structure lies between the medulla and midbrain), remained firmly within the concept of passivesleep maintained by specific sensory projections [8]. In his words, "there is little doubt that sensory lemniscal impulses impinging *without a reticular participation* on cat's somatosensory area contribute efficiently to the maintenance of its local tone" (see also experiments mentioned in note [9]). Anyway, Bremer was the first neuroscientist to place emphasis on "brain sleep", when all were turned on "body sleep".

Moruzzi, a pupil of Bremer in the late 1930s, also interpreted the results of his 1949 experiments with Magoun as indicating wakefulness maintained by the ascending brainstem reticular system,"while reduction in its activity . . . may . . . precipitate normal sleep" [11]. The reticular formation activation concept became so famous in the 1950s and 1960s that "wherever any really interesting fun was going on in brain research, that part was immediately claimed as part of the reticular system" [12]. However, that discovery fell into desuetude during the 1970s because of lack of knowledge on connectivity and neurotransmitters used by brainstem reticular cells. More recently, with the disclosure of pathways and chemical codes of these neurons, the concept of brainstem-thalamic activation has repeatedly been supported by single-cell recordings of midbrain reticular neurons during natural waking-sleep states. Also, the facilitatory action from the mesencephalic reticular core upon thalamocortical neurons was demonstrated at the intracellular level showing depolarization and increase in the apparent input resistance, and activation of thalamic intralaminar neurons, major targets of the upper brainstem reticular formation, was detected during complex tasks in humans [13].

While Bremer focused on the presumed hypnogenic properties of the preoptic area, Moruzzi and his younger colleagues (among them Berlucchi, Pompeiano, Batini, Rossi, and Zanchetti) proposed another candidate for an actively sleep-promoting area, which they located in and around the nucleus of the solitary tract in the medulla. This view was based on experiments using low-frequency stimulation of that nucleus and other experimental manipulations, including transections at the midpontine level that created a virtually permanent state of brain arousal due to the removal of a hypothesized inhibitory role of hypnogenic medullary structures [14]. However, at variance with the destiny of preoptic neurons, which became more and more fashionable in sleep research, no cellular data have as yet confirmed the presence of sleep-promoting neurons in the medulla. By contrast, Moruzzi and Magoun's 1949 findings and conclusions were, and still remain,

[10] Bremer's (1973) study, using electrical stimulation and field potential recordings, followed a series of lesions and stimulation experiments initiated by Nauta (1946) and inspired by earlier clinico-anatomical data of von Economo (1918, 1929). These studies are continued and, nowadays, neurons in the ventrolateral part of the preoptic area are considered as best candidates for playing an inhibitory, GABAergic role in promoting sleep (see section *3.1.2.3* in Chapter 3).

[11] Moruzzi and Magoun (1949). Before his stage with Magoun in U.S.A., Moruzzi worked with Adrian in Cambridge and, during 1937–1938, with Bremer in his laboratory at the Université de Bruxelles, where he published some papers as sole author. At the 1980 Pisa symposium in honor of Moruzzi, he recalled Bremer in terms of "vivid imagination and clear scientific thinking". My recollection of that 1980 symposium was the pleasure I experienced presenting experimental data with unit recordings relating the upper brainstem reticular core neurons with thalamic intralaminar neurons, which fully supported Moruzzi and Magoun's seminal data and major theoretical issues (Steriade, 1981).

[12] Jefferson (1958, p. 729).

[13] Reviewed in previous monographs by Steriade and McCarley (1990); and Steriade (2001b); for human studies, see Kinomura et al. (1996).

[14] Reviewed in Moruzzi (1972); see also section *3.1.2.1* in Chapter 3.

[15] Kleitman (1963). He was born at the end of the 19th century in Kishinev (then Russia), came to America in 1915, earned a Ph.D. at the University of Chicago where he did research until he retired as a full professor in 1960 (but remained productive; see his 1993 chapter), and died in 1999, at the age of 104. At the 1995 celebration for his 100th birthday, only 20–25 people were present at the *Sleep and Aging* session in Nashville meeting, but Kleitman was among them. William Dement was his student; he recorded Kleitman's EEG during full nights in 1954 and finished the revision of Kleitman's 1963 book on *Sleep and Wakefulness*, first published in 1939 (see Dement, 2001).

[16] Aserinsky and Kleitman (1953, 1955). Aserinsky was Kleitman's graduate student in physiology.

[17] Dement and Kleitman (1957) scored recordings over 126 nights in 33 subjects and found a cyclic variation in EEG and eye movements, with waking developing to different stages of slow-wave sleep and, after termination of stage 4, entering REM sleep. This cyclic variation repeated throughout the night at intervals of 90 to 100 min from the end of one REM period to the end of the next.

[18] Jouvet and Michel (1959); Jouvet et al. (1959). The neuronal mechanisms underlying muscular atonia have been worked out by Pompeiano and colleagues (reviewed in Pompeiano, 1967a-b). Later on, intracellular recordings of spinal cord neurons in naturally sleeping cats have further revealed the mechanisms of tonic inhibition of motoneurons during REM sleep (Morales and Chase, 1978; Glenn and Dement, 1981; Chase and Morales, 1983).

[19] Jouvet (1962, 1972). Jouvet, his colleagues in Lyon, as well as some other fellows call REM sleep "*sommeil paradoxal*", to emphasize that during this sleep state the brain is aroused, but paralyzed because of motoneuronal inhibition.

[20] Jouvet (1986). In his recent "monologue which traces the life of a handful of neurobiologists", Jouvet (1999) is aware that the scientific intelligentsia may not appreciate the idea of psychological inheritance, but states that this has nothing to do with his hypothesis (see p. 15–16 and Chapter 7 in that book). Those who are familiar with French may want to read his novel *Le Château des Songes* (1992), with fabulous dreams and commentaries on them by a character of the 18th century.

Fig. 1.3 Nathaniel Kleitman, a prominent figure for the concept of passive sleep (1895–1999).

among the most influential discoveries in sleep research and continue to be supported by modern experiments conducted at the single-cell level [13].

Kleitman (Fig. 1.3) is another leading proponent of the passive theory of sleep, as he emphasized that what needs to be explained is not sleep, but wakefulness, because there was not a single fact in those times supporting the theory of active sleep, and all data could be interpreted as a let down of the waking activity [15]. Since the 1920s, Kleitman conducted experiments on prolonged sleep deprivation and argued that his observations were incompatible with Piéron's notion of a continual buildup of hypnotoxin (see section ***3.1.1*** in Chapter 3). Probably, the major discovery of Kleitman pertains to the sleep stage with rapid eye movements (REMs) that he reported in three seminal papers, first with Aserinsky [16] and then with Dement [17].

The man who further described all major signs of REM sleep, including muscular atonia that typically characterizes this sleep stage and differentiates it from other states of vigilance [18], and performed the first animal experiments to localize the brainstem and forebrain structures responsible for the physiological correlates of this sleep state [19], is Jouvet. Some of the seminal contributions of Jouvet in the monoaminergic control of waking and sleep states are dealt with in Chapter 3 (section *3.1.2.2*). Jouvet hypothesized that REM sleep is a guardian of psychological personality, a repeated reprogramming of individuality during dreaming [20].

[21] Hobson et al. (1975); McCarley and Hobson (1975).

[22] See mathematical model of McCarley and Massequoi (1986), Steriade and McCarley (1990), and a more recent paper (Hobson et al., 2000) in which the original and revised models of reciprocal interactions between cholinergic and monoamine-containing neurons are discussed.

[23] Sakai et al. (2001).

[24] Chandler et al. (1980); Chase et al. (1980); Ito and McCarley (1984); Ito et al. (2002).

[25] Hirsch et al. (1983).

[26] Steriade et al. (2001a); Timofeev et al. (2001b).

[27] Among the numerous *in vitro* studies on brainstem, thalamic and cortical neurons devoted to analysis of phenomena observed during states of vigilance, here are some of them: Greene et al. (1986); Kita and Kitai (1990); Leonard and Llinás (1990, 1994); Von Krosigk et al. (1993); Huguenard and Prince (1992, 1994a-b); Bal et al. (1995a-b); Sanchez-Vives and McCormick (2000).

[28] Computational studies related to sleep states and their physiological correlates, performed by Sejnowski and his colleagues Destexhe and Bazhenov in collaboration with *in vivo* experimenters using intracellular recordings, may be found in Destexhe et al. (1994a-b, 1996, 1998, 1999b) and Bazhenov et al. (1998a-b, 1999, 2000).

[29] John Hughlings Jackson (1835–1911).

[30] Penfield and Jasper (1954, p. 20). However, see also note [33] with Jasper's opinion on seizures with prevalent inhibitory processes.

[31] Jackson (1864, 1931) isolated a form of epilepsy with localized paroxysms, now called Jacksonian seizures (also called Bravais-Jacksonian seizures, because of a 1827 doctorial thesis presented at the Université de Paris by a young physician, Bravais, who described focal seizures). Jackson also surmised that several symptoms, now known to define temporal lobe epilepsy, constitute "a particular variety of epilepsy". He remarked that not all epileptic seizures are associated with

Tentative models of the waking-sleep cycle and REM generation varied according to the evolution of knowledge on connections and transmitters released by brainstem cholinergic, glutamatergic and monoaminergic systems. The attention focused on the brainstem because of Jouvet's demonstration that cardinal signs of REM sleep occur in brainstem-transected animals [19]. During the mid-1970s, it was proposed that the executive elements of REM sleep are gigantocellular cholinergic neurons located in the medial pontine reticular formation, which were thought to be self-excitatory and inhibited by serotoninergic dorsal raphe and noradrenergic locus coeruleus neurons [21]. As immunohistochemical studies could not reveal cholinergic neurons in the medial pontine reticular formation, emphasis was more recently placed on neurons in the mesopontine cholinergic nuclei that project to thalamocortical systems, produce tonic activation of the forebrain, and generate ponto-geniculo-occipital waves (see section 3.3 and Fig. 3.55 in Chapter 3). The postulated inhibitory actions of monoaminergic, especially serotoninergic, neurons on mesopontine cholinergic cells have been confirmed. Cholinergic neurons become increasingly active toward the end of slow-wave sleep and, further on, during REM sleep, because of their disinhibition, as monoaminergic neurons are virtually silent in REM sleep. This sequence of events [22] was further elaborated by adding the actions of medullary adrenergic, ponto-medullary noradrenergic and, to a lesser extent, hypothalamic dopaminergic neurons to the inhibitory (or permissive) mechanisms exerted on executive, REM-on brainstem cholinergic and glutamatergic neurons [23].

The evolution of research into neuronal and molecular substrates of sleep states during the 1980s and 1990s led to significant advances in the field of connectivity among chemically coded neurons in various brain areas that proved in earlier studies to be critical for waking and sleep by using stimulation and electrolytic or excitotoxic lesions. Intracellular recordings of brainstem, thalamic and cortical neurons, whose input-organization has to be identified by standard electrophysiological criteria, revealed their behavior during contrasting EEG patterns under different types of anesthesia and, importantly, during shifts in natural states of vigilance. The intracellular recordings during long periods of natural waking and sleep states in chronically implanted animals, which seemed science fiction not long ago because of stability problems, have been performed in the spinal cord [18], brainstem reticular and trigeminal motoneurons [24], thalamocortical neurons [25], and neocortical pyramidal and local-circuit inhibitory neurons [26]. *In vitro* studies of brainstem, thalamic and cortical

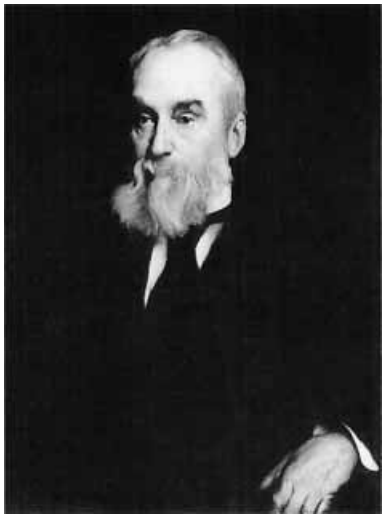

Fig. 1.4 John Hughlings Jackson (1835–1911) was a pioneer of clinical neurology in the United Kingdom.

motor components and that there are also sensory discharges that take the form of "reminders of common sensations". The publication of Jackson's observations on localized motor seizures preceded by a few years the experimental work by Fritsch and Hitzig (1870) and by Ferrier (1876), using motor cortex stimulation (it seems that Jackson discussed his data with these colleagues). Two decades later, Beevor and Horsley (1890) mapped the orang-outan's precentral cortex with extreme precision. Another contribution of Jackson is his concept on non-abrupt delineations of various neocortical areas, which was developed in experiments conducted by the Italian physiologist Luciani (1840–1919) showing that each sensory modality in dog's cerebral cortex "possesses a territory of its own, (but) in addition has a common territory, the parietal lobe, . . . *where partial fusion of the sensation occurs*" (Luciani, 1911, p. 159; italics mine). This concept of associational areas in the parietal lobe eventually led to the disclosure of neocortical areas 5 and 7 in the suprasylvian gyrus of dogs and cats, and of homologous areas in a primate's brain.

[32] Wilson et al. (1955); Jasper et al. (1969).

slices have worked out the biophysical properties and different receptor types of neurons implicated by *in vivo* experiments in the generation of different physiological correlates of waking and sleep states [27]. And studies *in computo* have predicted a series of mechanisms underlying behavioral states and their electrographic correlates, which led to new experiments [28].

This avalanche of analytical investigations brought sleep to the scene of modern science, performed with methods that are dealt with in the next section (**1.2**), together with those employed in analyses of epileptic seizures. All in all, it is my opinion that the most significant advance in sleep research is not the identification of various ionic channels or the expression of different neuronal types during shifts in natural states of vigilance, but the recent disclosure that, far from being a neuronal desert, as postulated since ancient times until quite recent days [1], the cerebral cortex is highly active during slow-wave sleep, capable of developing synaptic plasticity, and displaying during this state noble properties, such as consolidating memory traces acquired during the state of wakefulness. These properties have recently been investigated at the neuronal level (see Chapter 4) and human studies have demonstrated the overnight improvement of discrimination tasks, some steps depending on the early stages of slow-wave sleep (see section *3.2.4.2* in Chapter 3).

1.2. Evolution of concepts and methods used in studies on epileptic seizures

Classical definitions of epileptic seizures, such as that proposed by Jackson [29] (Fig. 1.4) and re-formulated by Penfield and Jasper as "state(s) produced by an abnormal excessive neuronal discharge within the central nervous system" [30] may apply to many, but not all, paroxysms. This is why, along with the term used by Jackson [31] and others [32], "*the epilepsies*" indicate that these neurological diseases are produced by a variety of factors. The "abnormal excessive neuronal discharge" characterizes grand-mal, tonico-clonic epilepsy and other paroxysms, but certainly not thalamocortical neurons during spike-wave seizures of the absence or petit-mal type, when the majority of those neurons are silent, being tonically and phasically inhibited by thalamic GABAergic reticular cells [33]. Also, some seizures resembling the pattern of the Lennox–Gastaut syndrome may display sustained hyperpolarization of neocortical cells, associated with largely decreased input resistance and no spike discharges [34].

Epileptic fits have been described since ~1700–1600 B.C. in China and Egypt [35], and both Hippocrates and Aristotle mentioned that epileptic seizures, "the sacred disease", may occur during sleep [36]. The appearance of grand-mal seizures during sleep was also reported in the 19th century by Gowers [37]. The role played by lesions in the Ammon's horn in what is now known as temporal lobe epilepsy was mentioned more than a century ago [38].

Major advances in studies on sleep and epilepsy have been due to the discovery that the brain of animals and humans displays electrical activity, which varies with the behavioral state and becomes paroxysmal during epileptic seizures. Caton [39] is credited for having first observed, in rabbits, cats and monkeys under anesthesia, that "feeble currents of varying directions" are "markedly influenced by stimulation of light", and that "a variation of the current intensity occurred when the rabbit awoke from sleep". These observations (between 1870 and 1880) have been followed by similar findings reported by Eastern European physiologists, such as Beck and Cybulski in Poland, Danilevski and Prawdicz-Neminsky in Ukraine, and Kaufman in Russia [40]. They led, four decades later, to Berger's [41] fundamental observations (between 1929 and 1938) of alpha and beta waves recorded from the human scalp, and of alpha blockade by visual stimulation [42]. In 1931, Berger also reported that interictal EEG "spikes" are common in epileptic patients and recorded spike-wave activity in some patients [43]. In North America, the Gibbs couple, Lennox, and Jasper used the EEG in clinical investigations on different forms of epilepsy, starting in the mid-1930s [44]. In the 1937 article by Gibbs, Gibbs and Lennox, the term *cerebral dysrhythmia* can first be found, used to describe the state of epilepsy, during which "the harmony of the orchestra becomes a single note" [45]. The cellular basis of EEG activity related to sleep and seizures began to be studied three decades later, from the early 1960s, with intracellular recordings from cortical and thalamic neurons performed by Purpura, Creutzfeldt and Andersen [46], continuing since the early 1980s with single, dual and triple intracellular recordings from identified excitatory and inhibitory neurons, both *in vivo* and *in vitro* [47].

Experimental and clinical studies on epileptic seizures rely on various methods and models, conceived to mimic different types of epileptic fits in humans. The main methods used are as follows: recordings of EEG, local field potentials, extracellular and intracellular activities (which will not be discussed here because they are exposed at length in all following chapters), electrical

[33] Steriade and Contreras (1995). Long ago, Jasper (1975) emphasized that, although some seizures are characterized by excessive discharges of cortical neurons, "there may be excessive inhibition" (p. 586) in other types of seizures. This is the case of thalamocortical neurons during spike-wave (sw) seizures, as shown in our 1995 study, using dual intracellular recordings from neocortical and thalamocortical neurons (see details in section *5.5.3.2* and Figs. 5.39–5.41 in Chapter 5). For a discussion of the hypothesized origin of SW seizures in the "centrencephalic system" and some arguments against that concept, see section **5.1** in Chapter 5.

[34] See Fig. 5.63 in section *5.6.2.6* of Chapter 5.

[35] Temkin (1971); Scott (1993).

[36] Cited by Passouant (1984).

[37] Gowers (1885). He is also known for having warned of the side effects of potassium bromide, an anticonvulsive drug that had been introduced in the second half of the 19th century.

[38] Sommer (1880); Bratz (1899).

[39] Caton (1842–1926) was a British physician and physiologist. The two citations in the main text are from his 1875 and 1887 papers.

[40] See books and book chapters on the history of brain electrical activity by Brazier (1961), Niedermeyer (1993), and Marshall and Magoun (1998).

[41] Berger (1873–1941) studied medicine in Berlin and, later, in Jena where he worked at the Psychiatric Clinic.

[42] Berger (1929, 1937). The alpha blockade by visual input was confirmed by Adrian and Matthews (1934) using the beetle's electrical activity and Adrian's own brain activity. All Berger's papers on human EEG have been translated into English by Gloor (1969).

[43] Reproduced in O'Leary and Goldring (1976).

[44] The studies by Gibbs and Gibbs, Lennox, and Jasper are reported in Chapter 5.

[45] Gibbs et al. (1937, 1938). The term *dysrhythmia*, introduced by Gibbs and his colleagues for epilepsy, was reproduced more than 60 years later, to characterize abnormalities in electrical activity of thalamocortical systems in a series of neurological and psychiatric disorders, such as Parkinson's disease, neurogenic pain, tinnitus, depression and obsessive-compulsive syndrome (Llinás et al., 1999, 2001; Jeanmonod et al., 2001).

[46] Purpura and Cohen (1962); Purpura and Shofer (1963); Purpura et al. (1966); Creutzfeldt et al. (1966); Andersen and Andersson (1968).

[47] The results of these modern intracellular studies on intrinsic neuronal properties and network operations related to sleep and epilepsy are fully discussed in Chapters 2 to 5.

[48] Collins (1975); Naquet and Meldrum (1975); Naquet and Valin (1990). See also sections **5.1** and **5.3** in Chapter 5.

[49] Jasper (1975) gave as example the focal cortical afterdischarge produced by cobalt powder applied on the precruciate gyrus of a chronically implanted cat, associated with clonic movements during waking, less often during slow-wave sleep, and completely lacking the convulsive movements in REM sleep (because of motoneuronal inhibition in the latter sleep state). He concluded that, under these conditions, cortical electrical activity becomes the most reliable index of a seizure (p. 588). The same is valid in modern studies using intracellular recordings in acute experiments carried out in paralyzed animals, for stability purposes.

[50] Nadler et al. (1978); Ben-Ari (1985).

[51] Ylinen et al. (1995); Kandel and Buzsáki (1997); Traub et al. (2001); Grenier et al. (2002).

[52] Marcus et al. (1968a-b); Steriade and Contreras (1998).

[53] See Figs. 1–2 in Ajmone-Marsan (1975).

[54] Gloor (1997, p. 713).

stimulation and lesions, production of seizure foci in various animal species by topical convulsants and freezing, repetitive sensory (auditory and photic) stimulation [48], local or intraventricular perfusion with high K^+, different genetic epileptic-like states (convulsive or non-convulsive), and magnetic resonance imaging and positron emission tomography for the detection and localization of different epileptic disorders. Several criteria have been proposed to judge the validity of a given experimental model for human epilepsy, the cardinal one being the similarities between the electrical (as well as, possibly, behavioral) manifestations of the model and those known to characterize that form of human epilepsy [49].

To begin with, electrolytic or excitotoxic lesions and electrical or chemical stimulation have been performed in various animal species and humans to demonstrate the locus of seizure initiation, to challenge the role that has been conventionally ascribed to some structures in the generation of seizures, and to provide diagnostic and/or therapeutic tools in human epilepsy. For example, the preferential sensitivity and vulnerability of hippocampus and related systems to intraventricular injection of kainic acid have been used in attempts to replicate in rodents the pathology found in temporal lobe epilepsy [50]; electrical stimuli applied to central structures mimic fast oscillations (ripples, ~100 Hz) that are thought to initiate electrical seizures in neocortex and hippocampus of rats, cats and humans [51]; and decortication or thalamectomy have been used to demonstrate the role of neocortex in the generation of electrical and behavioral seizures with spike-wave complexes at ~3 Hz in monkeys and cats [52]. Electrical stimulation has also been used during neurosurgery procedures in epileptic patients, with pulse-trains applied to neocortex to elicit focal afterdischarges [53] or to amygdala in a patient with temporal lobe epilepsy, who displayed dysphasia and some degree of unresponsiveness [54]. In the latter case, stimulation of the left amygdala, applied to reproduce typical aspects of pure amnestic seizures, evoked an electrical seizure that spread to also involve the right amygdala and hippocampus; however, the patient's behavior remained entirely normal during the time the seizure involved only the left temporal lobe, as she was vivacious and in full contact with the physician, "named pictures correctly and repeated a test phrase correctly . . . Yet, after the seizure she had not the slightest recollection of any of these items . . ." [54] (Fig. 1.5). During the 1990s, deep brain stimulation (DBS) in thalamic nuclei, especially the centromedian-parafascicular (CM-Pf) complex, has been used in intractable seizure patterns [55]. The mechanism(s) underlying DBS' effects are still unresolved. It has

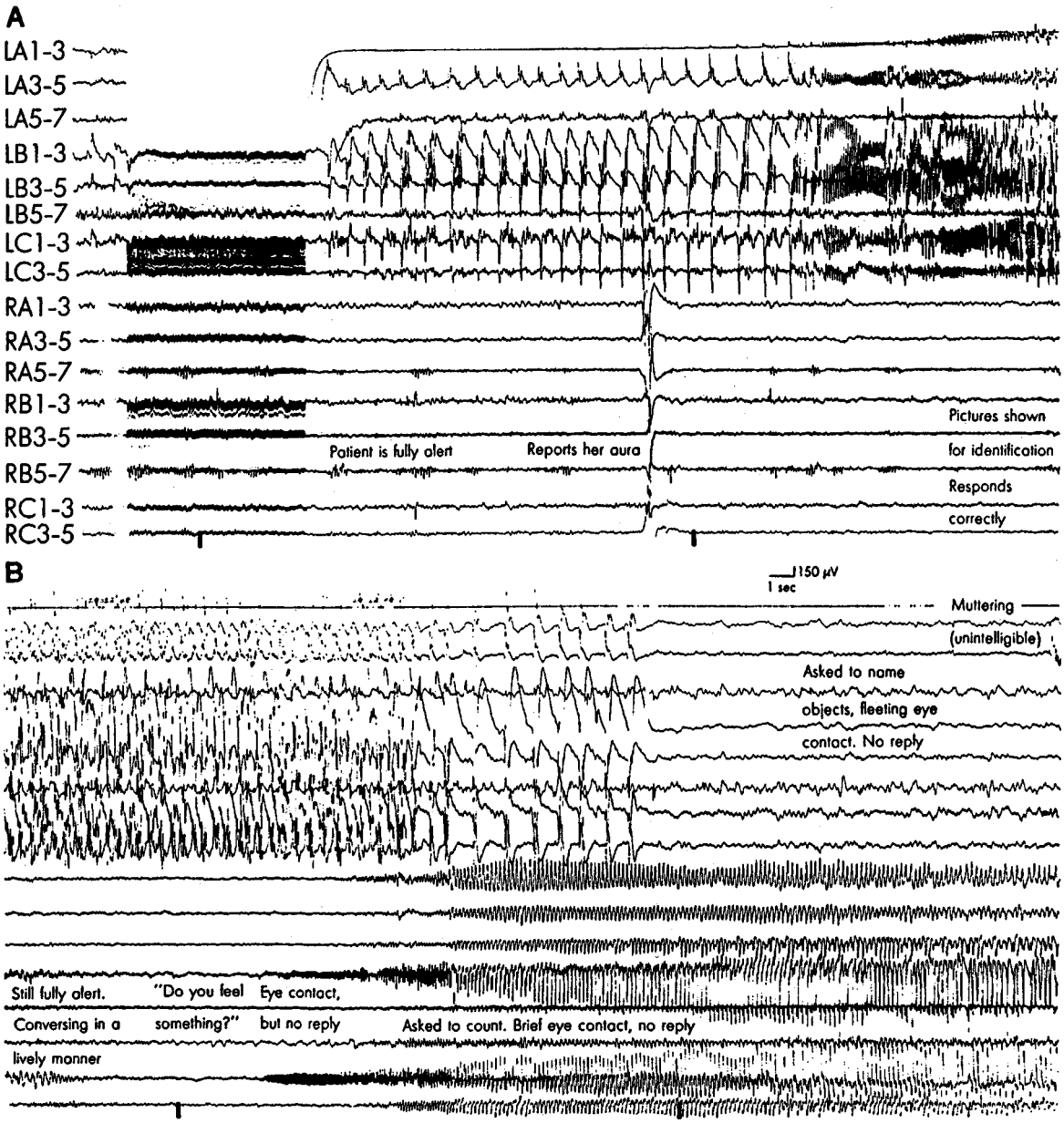

Fig. 1.5 Response to electrical stimulation of the left amygdala (0.75 mA, 60 Hz, 0.5 ms biphasic square wave for ~7 s; see stimulation artifact in panel *A*). Patient (36-year-old woman) with pure amnestic seizures in temporal lobe epilepsy. *A*, electrical afterdischarge involving the left mesial temporal (MT) structures (LA1-3, LA3-5, LB1-3, LB3-5, LC1-3, LC3-5), with no spread to the superficial isocortical contacts (LA5-7, LB5-7), during which the patient behaved and responded entirely normally. *B*, spread of afterdischarge (which starts after a gap of 58 s) to the contralateral temporal lobe, first to the hippocampus (RB1-3, RC1-3), then to the amygdala (RA1-3) and shortly thereafter to the more superficial right temporal isocortex (LA5-7, RB5-7). The patient became verbally unresponsive and was probably aphasic. Modified from Gloor (1997).