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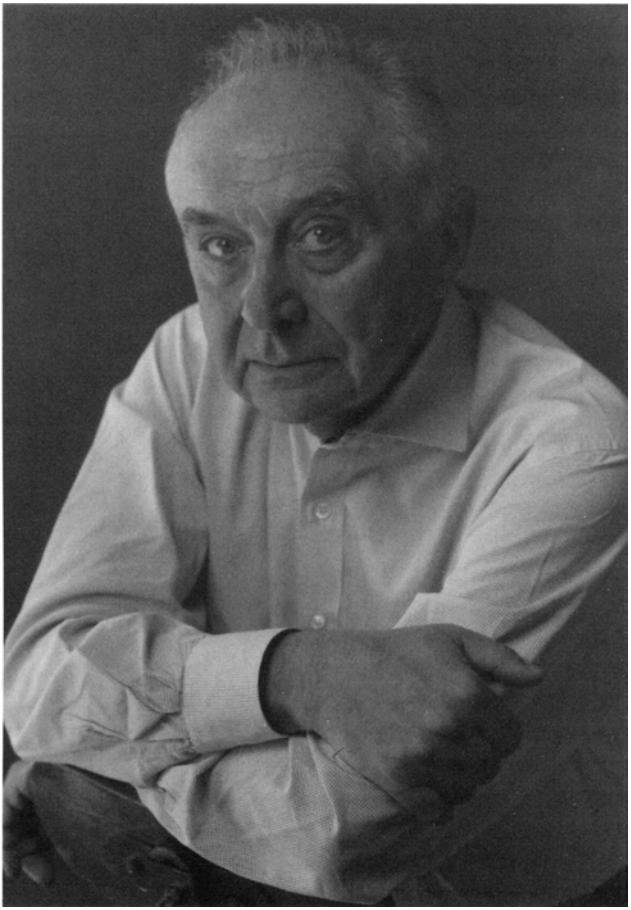

Mircea Steriade

BORN:

Bucharest (Romania)
August 20, 1924

EDUCATION:

Faculty of Medicine, Bucharest, M.D. (1945–1952)
Institute of Neurology, Romanian Academy of Sciences, D.Sc. (1952–1955)
Université de Bruxelles, with F. Bremer (1957–1958)

APPOINTMENTS:

Head of Neurophysiology Laboratory, Institute of Neurology, Bucharest (1958–1968)
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HONORS AND AWARDS (SELECTED):

Membre d'Honneur de la Société de Neurologie de Paris (1957)
Médaille Claude Bernard de l'Université de Paris (1965)
Distinguished Scientist Award, Sleep Research Society (1989)
Scientific Prize of Québec (1991).
Member of the Academy of Sciences, Royal Society of Canada (1994)
Award of the American Society for Clinical Neurophysiology for Outstanding Achievements in Research (1998)
Presidential Lecture at the Society for Neuroscience Meeting (1999)
Editor-in-Chief, *Thalamus & Related Systems* (2001, Elsevier)
Honor Member of the Romanian Academy of Medical Sciences (2003)

Mircea Steriade pioneered research that identified the network operations and neuronal properties in corticothalamic systems, which are implicated in the generation of normal brain rhythms during different states of vigilance and different types of electrical seizures. He was the first to demonstrate the role of GABAergic thalamic reticular neurons in the production of sleep spindles. Using intracellular recordings in animals and field potential recordings during human sleep, he also discovered a new type of sleep rhythm, the slow oscillation, which is generated intracortically.

Mircea Steriade

Initiation in Neurosciences

I was interested in neuroscience since my first year of medical studies in Bucharest (1945) when I was reading, aside from the usual textbooks, Lorente de Nõ's chapter and other chapters on the cerebral cortex and thalamus in Fulton's 1938 book *Physiology of the Nervous System*. I remember being fascinated during those early years at the Faculty of Medicine by the hypothesis of Dusser de Barenne and McCulloch, who postulated the presence of connections from cortex to thalamus and back to different cortical areas. I tried to convey to some classmates my excitement by drawing esoteric arrows running from the motor cortex to basal ganglia and thalamus and back. These reciprocal projections that occurred to me right at the initiation in neuroscience anticipated the core of my entire research life, which is centered on the role of corticothalamic reciprocal loops in the generation of various (normal and paroxysmal) brain rhythms and their control by generalized modulatory systems. In 1950, an article by Hsiang-Tung Chang, then at Yale, presented convincing electrophysiological evidence in favor of reverberating circuits between cortex and thalamus. My inclination toward neuronal operations in these reciprocally connected networks explains why I was rather disappointed during the 1960s when Per Andersen and John Eccles discarded the influence of the cerebral cortex on thalamic spindles, a hallmark sleep rhythm. I first challenged their idea in 1972 by eliciting spindles from the contralateral cortex, through the callosal and corticothalamic pathways (to avoid backfiring of thalamocortical cells), and, more recently (1996), we demonstrated the crucial role played by corticothalamic projections in the spatiotemporal coherence of this oscillation.

I became actively involved in neuroanatomical work during the third year at the Faculty of Medicine when, as an Assistant in the Department of Anatomy, I sectioned brains of human embryos and stained monkey cerebral cortex with a modified Golgi technique in the histology laboratory of Professor I.T. Niculescu. (He repeatedly advised me to "be more patient and ally yourself with time." I respectfully disobeyed then as well as now.) I used to look through the microscope all day long, at the expense of some medical disciplines that I regarded as marginal and for which I remained a layman. I already knew that all my life would be spent with the brain and its operations.

After earning an M.D., I was offered in 1952 a position as a young research scientist working toward a D.Sc. (Ph.D.) at the Institute of Neurology of the Romanian Academy of Sciences. It is vivid in my memory how puzzled I was when, a few days after entering that institute, I was asked to deliver a talk on iron metabolism. I had been ignorant of the fact that heavy metals are present in the brain. Because the literature on this topic was mainly from German authors, I used my knowledge of German and the seminar appeared to go well, but I retained some resentment about the idea that unorthodox chemical elements were found in such a noble tissue.

The years of my doctorial studies, until 1955, were busy with experiments on cats and dogs, which led to a thesis on cerebello-cortical relationships. I also underwent training in neurology and neurosurgery. After seven years of clinic, I realized that what mainly interested me in patients was the site(s) of their lesion(s). I subsequently abandoned clinical work to be free for experiments. Nevertheless, those years (1952–1960) of clinical neurology and animal experiments contained the embryo of my future scientific life. In 1955, I became an independent researcher in the Laboratory of Neurophysiology of the Institute of Neurology.

Thus, in the clinic, I had the privilege to follow up an elderly woman who had had a hypersomnia for more than two years. I fed and nurtured that patient until her end, and, in histology, I found bilateral, butterfly-like lesions in thalamic intralaminar nuclei. We published in 1958 a paper in *Revue de Neurologie (Paris)* with those clinical-anatomical data, which were confirmed several years later by French neurologists at the Salpêtrière hospital in Paris. That report was my first important study, and it marked my first foray into research on brain stem activating systems relayed by thalamic intralaminar nuclei with widespread cortical projections. In a similar vein, I published two cases of akinetic mutism, one of them with a dorsolateral pontine tegmental lesion. In that case, there was an interruption of ascending projections, but no loss of effector pathways because the patient, a young boy, could answer complex questions by raising a finger or two. This was a case of pure *Antriebsmangel* (lack of incitement to action) due to interruption of ascending activating systems, a topic that occupied part of my research time with immunohistochemical/tracing studies and intracellular recordings during the 1980s and early 1990s.

The defense of my D.Sc. thesis in 1955 caused a bit of a stir. This was the first thesis defense to take place at the Romanian Academy of Sciences. (To give an idea of my enthusiasm when I had entered the fray three years before, I should say that when I heard, while fulfilling my obligation in the army, that a competition had been open for those wishing to pursue the D.Sc. degree, I obtained leave, immediately took the train, and, without changing from my soldier's uniform, went directly to the Academy of Sciences to register.) My thesis defense was attended by many people. One of them, who seemed to be viewed favorably by the regime, attacked the assumption

implied by my title that cerebellar lesions influence neocortical electrical activity and conditioned reflexes. He bitterly questioned such a possibility, arguing that Ivan Pavlov had taught us that the cerebral cortex governs subcortical structures and not the other way around. If this man were aware of my present views according to which, indeed, the cortex exerts a powerful influence on the thalamus and other brain sites, he would have been satisfied. At that time, however, his point was simply political: how could the "rank-and-file" influence the "top?" My thesis became a monograph at Masson in Paris (1958), but it paled in comparison with the book on the cerebellum by Dow and Moruzzi published in the same year. Nonetheless, Wilder Penfield sent a congratulatory letter. I also remember that Alf Brodal asked me details about transneuronal degeneration in red nucleus neurons after cerebellar lesions, and, notably, Frédéric Bremer wrote me very nice words about the results of my experiments. Bremer remained highly vivid throughout my scientific life. In those early years, I also did my first experiments on epilepsy, succeeding to establish conditioned Jacksonian seizures in dogs by combining sound with electrical stimulation of the motor cortex.

The topics of brain stem-thalamic activating systems, relationships between the cerebral cortex and subcortical structures, and the neurophysiology of epileptic seizure, which I approached in the 1950s with global electrophysiological methods, morphological techniques, and clinical observation, have remained close to my heart during my entire career. These developments are discussed below.

Encountering Frédéric Bremer

When the proofs of my book on the cerebellum arrived in 1957, I finally obtained permission to go to the publishing house in Paris (after repeated failures to obtain an exit visa for the International Congress of Neurology in Brussels, 1957) and, then, to stay on as a postdoctoral fellow in Bremer's laboratory in Brussels. Bremer was well known as a world-leading neurophysiologist for his work on the spinal cord and cerebellum (this is why he accepted me in the laboratory after I sent him my D.Sc. thesis). Bremer was especially well known for the crucial discoveries made possible by the two types of brain stem transections he introduced during the 1930s: the *encéphale isolé* preparation (with a bulbo-spinal cut), whose brain fluctuates between electrical activity patterns of waking and sleep; and the *cerveau isolé* preparation (with an intercollicular cut), which is comatose and displays uninterrupted sequences of spindle waves, virtually identical to those that occur during natural sleep. These discoveries led a decade later (in 1949) to the experiments by Moruzzi and Magoun on a brain stem reticular substrate of arousal. The Moruzzi–Magoun concept of sleep as a consequence of fall in the activity of brain stem reticular ascending impulses had the flavor of Bremer's ideas about the *tonus cortical* maintained by specific afferents

acting on brain stem structures. Giuseppe Moruzzi had worked in Bremer's laboratory during the late 1930s, before he went to work with Lord Adrian in Cambridge. Most investigators used to consider the idea of a non-specific brain stem reticular activating system as opposite to Bremer's concept that specific sensory systems are responsible for the maintenance of the waking state. However, these two views are not irreconcilable because sensory pathways, which have access to discrete thalamocortical projections, also lead (through cortico-brain stem projections) to more widespread activation. Thus, Bremer and Carlo Terzuolo showed that cortical actions of specific sensory and motor systems have a descending effect on the upper brain stem reticular core, with the consequence that widespread cortical activation results from this cortico-brain stem feedback. Terzuolo worked in the Brussels laboratory a few years before me, and technicians in that lab told me that we were equally impetuous (to use a euphemism).

Bremer explained to me, from the very beginning, that he did not have the means to provide the cats I needed for my own experiments. So I asked him if he would agree that, after the end of the experiments he conducted with Nicolas Stoupel, I could continue on the same *encéphale isolé* cat until the nighttime. He accepted my proposal and afterwards he called me "*l'infatigable monsieur Steriade.*" In line with my previous work on cerebello-cortical relations, I stimulated the auditory cerebellar area (revealed in the 1940s to 1950s by Ray Snider) and recorded different types of evoked potentials in the auditory cortex. To substantiate the hypothesis that longer latency responses in the postero-inferior ectosylvian area (in contrast to the primary responses recorded from the antero-superior ectosylvian field) are transmitted to cortex through a relay in the brain stem core, I lesioned the brain stem reticular core and abolished long-latency responses. (The possibility that connections between the primary and secondary ectosylvian areas may account for differences in latency, which came to my mind later, was not tested.) Bremer was interested in my findings and spent many afternoons discussing the data with me. Yet, when I asked him to co-author my article (in collaboration with Stoupel, who showed me how to do the electrolytic lesions), he said that when you see one or two authors on a paper, you may be (almost) sure who did the experiments, but beyond two ... then, he declined. One day, Bremer asked for my opinion about his manuscript on cerebral and cerebellar potentials that would be published in 1958 in *Physiological Reviews*. I first thought that he was joking because I did not feel capable of giving any useful opinion, certainly not about Bremer's article. But he insisted, so I read and made some minor comments that, obviously, couldn't basically change his review.

When I remember now those experiments (Bremer with Stoupel, and my own work), which began in the morning and ended quite late, I cannot forget how we made the photographs of evoked potentials on large, thick, glass slides, as was done by professionals until recent times. I am often

amused to compare this technique with the faster method used during the 1970s, when my technician spent the day developing hundreds of meters of 35-mm films, or with the method of today, when we no longer use such techniques and instead whole figures with numerous panels (as in Eccles' illustrations) are made on computers.

I could not return to Brussels until 1965 because I was prevented for seven years from obtaining a passport (because of many, many errors on my part ...). One of those errors was that I had already been able to go abroad when, generally, Romanians were not allowed (exceptions were made, for example, for the Director of my Institute who went to many different congresses and symposia, but used to ask me about the polarity of evoked potentials before lecturing in Western countries). The other "error" (the Romanian word in the *langue de bois* of that time was "weakness," generally used in the plural) was that I continued to publish in international journals, such as the *Journal of Neurophysiology*, *Brain*, or *The EEG Journal*, instead of publishing in Russian, Bulgarian, or other highly recommended journals in "brotherly" countries. When Hsiang-Tung Chang arrived from Shanghai to lecture in Bucharest in 1965, he asked to see me (as he knew and had cited my 1960 *Journal of Neurophysiology* paper with Demetrescu, showing brain stem reticular effects on light-evoked responses in the lateral geniculate nucleus). However, I was "very ill" according to his officially appointed guide. Chang insisted, and eventually, I met him. He organized my visit at his brain institute in Shanghai. I did numerous experiments on cats in Shanghai, one every day, performing (rather bad) impalements of visual cortex neurons, which oscillated when the lateral geniculate nucleus was stimulated (one of those recordings is in my 1968 *Brain Research* paper on flash-evoked after-discharges). Chang taught me how to enter the thalamus without a stereotaxic apparatus (!), as he didn't have the equipment at that time. "Look," he said, while taking an oblique position with his stimulating electrode in his hand, positioned as in a martial art exercise. In exchange, I taught him the *encéphale isolé* preparation that I had learned in Bremer's laboratory because I wished to avoid the barbiturate anesthesia that Chang usually employed. But Chang was an immensely capable physiologist (his chapter on evoked potentials in the 1959 *Handbook of Physiology* is a gem), and I was a child compared to him and his knowledge. I met him for the last time in Pisa in 1980 at a symposium in honor of Moruzzi.

After so many years, things apparently changed a little (not very much) in Romania, and I was able to return to see Bremer in 1965. It was an afternoon, sometime in the spring, about 3:00 or 4:00 PM, when we had our rendezvous in his Brussels laboratory. I knocked at the door, and he opened, embraced me effusively, and, just a minute later, asked (after six or seven years of absence): "Tell me, Steriade, do you think there is an active inhibition in the cerebral cortex?" I don't know if my young colleagues know what was believed in the early 1960s, but at that time Bremer accepted

inhibition in the spinal cord, while still thinking that there was no consistent evidence for active inhibitory processes in forebrain structures. I must say that the poor quality of some intracellular recordings in the 1960s might well have inspired Bremer's earlier skepticism about active inhibition in the thalamus and cortex. Nevertheless, I was amazed. I reminded him of his question later, in the 1970s, during a meeting in Bruges, and he laughed. Not only had he become aware of the presence of IPSPs in thalamic and cortical neurons, but he also assumed that inhibitory processes from the preoptic area to the upper brain stem reticular core may be operational in the process of falling asleep. He was among the first to conceive of this circuit. It was later that excitement developed about the hypnogenic properties that preoptic neurons might exert by inhibiting activating systems.

It must be clear by now what role Bremer played in my life: he was the only mentor that I highly admired and continue to love. In fact, I succeeded to impart this feeling to some of my former students, certainly to Diego Contreras. I remember the thrill while, on a tramway in Bucharest in 1961, I opened Moruzzi's *Archives Italiennes de Biologie* and found the (for me) astonishing sentence of Bremer's 1960 paper in which he confirmed my results with the brain stem reticular facilitation of photically evoked responses in the visual thalamus. I don't know if I cried, but, if not, I was not far from it. Generally, French investigators, among them some of my friends in Paris, do not much like Bremer because, they say, he was harsh in his public comments about some speakers (possibly themselves).

The place of Bremer in neuroscience is not assured by his place in the Medline or Citation Index because, as it sadly happens, our field is for today and possibly tomorrow, and (with some exceptions) the young researchers do not bother with papers published before yesterday. But Bremer's contributions are not limited to his crucial discoveries about the role played by brain stem structures in states of vigilance, which opened the path to modern investigations. He was the first, well before the 1990s work on gamma oscillations (the magical "40-Hz" rhythm), to report an "*accélération synchronisatrice*" of cortical electrical activity in response to arousing brain stem reticular stimulation (see the legend of Fig. 5 in his 1960 *Archives Italiennes de Biologie* paper [Bremer, Stoupel, and Van Reeth, 1960]). This expression sounded unorthodox at that time and for most investigators today, in view of the fact that Moruzzi's epigones describe this response as a "desynchronizing" reaction. Bremer's paper preceded by more than three decades the description of spontaneously occurring, synchronized gamma rhythms during brain-alert states, as demonstrated with multisite, extra- and intracellular recordings from cortical and thalamic neurons in my laboratory, as well as with magnetoencephalographic recordings in humans by Llinás and Ribary. Also, Bremer should be credited for his concept of autonomous neuronal activity (1949) that evolved into what is now known as *intrinsic* neuronal activity, a concept that has been added to the purely

reflexologic (input-output) view of brain operations. Intrinsic neuronal properties have been intensely studied since the early 1980s by Rodolfo Llinás and many younger fellows working in brain slices maintained *in vitro*. Lately, I have had to fight the simplistic assumptions of some colleagues who are not shy to jump from a 0.4-mm-thick slice to global states of behavior; but this occurred during the most recent (hopefully not last) period of my scientific life and is discussed toward the end of this chapter.

Out of Romania

I left Romania in 1968. I intended to settle abroad because of the lack of resources for science in that country and difficulties in maintaining normal relations with my colleagues in Western countries. This was indeed an adventure for a man in his mid-40s. My first daughter, Donca, advised me to follow regular procedures and ask for a legal passport to emigrate. It was difficult to follow such advice. Those who did so were first forced to leave their job and then waited for long years, long enough to forget their earlier scientific training. Instead, I left Bucharest in May 1968 with a passport valid for three months. Pierre Buser had invited me to deliver a lecture at the University of Paris, but the students were busy with the May "revolution" and had better things to do than attend lectures. My French colleagues, Buser and Yves Galifret, have been very friendly and generous with me; even my first visit at the Institut Marey in 1966 could not have been possible without the kind invitation of Denise Albe-Fessard, whom I had met in Warszaw in 1961, when both of us had been asked by Jerzy Konorski to give alternating lectures during one week.

Turmoil reigned in Paris in May 1968, but that period is still favorably colored for me by several encounters with Emil Cioran, a philosopher and moralist of Romanian origin who is now appreciated as one of the most accomplished stylists in French literature, a kind of improved Chamfort. I tried first to talk with Cioran in Romanian, but he answered in French "because I'm not yet perfect in this language" (he had been in France since 1938). We walked through the *Jardin du Luxembourg* (he lived next door at the top floor of a building in an apartment like a monastery with a patio that had a *vue imprenable sur le Théâtre de l'Odéon*), and we walked in the garden of the *Palais Royal*, talking about Mao and minor dictators, such as the man governing Romania at that time. While Cioran is known for his sharp mind, he surprised me by saying "the truth is with you, with science." I laughed and explained to him the ephemeral nature of scientific "truth," but I am sure he stood by his convictions. I never could explain the style of Cioran, who wrote with joy, delight, and roguishness about the inconvenience of being born, the black despair of decomposition, and the syllogisms of bitterness. He seemingly liked suffering those states of the soul or, more probably, regarded ours with an Olympian eye.

As Paris was busy, I went to Marseille where Jean Massion, a distinguished investigator of motor control, asked me to meet Jean-Pierre Cordeau, who was a visiting professor from Montréal spending his sabbatical in Marseille. I had lunch with Cordeau. He knew me from some papers and, like that, without introduction, asked if I would accept a position of visiting professor at the Université de Montréal. I didn't think too much before saying yes. Back in Paris, I called the Director of my Institute in Bucharest to ask for permission to remain abroad for a longer period. He summoned me back immediately, but the Secretary of the Academy of Science, Professor Ştefan Milcu, wrote a very kind letter that permitted to stay. Cordeau asked when I would like to go (he paid for my flight ticket, for I was as poor as Job). I thought that August 20th (my birthday) would be a good start for a new life, and I left Paris with mixed hope and anguish.

Working in Canada: The Beginnings

I arrived in Montréal on the day Russians invaded Prague. My wife at the time sent me word from Bucharest, through a painter friend, to remain and try to bring our daughter, Donca, to Canada. My attempt to do this continued until 1973, when the Romanian ambassador invited me for lunch in Ottawa and asked me for my fondest wish. When I asked why I deserved the honor of this question, he answered candidly that I was known in circles of scientists and that I had never complained publicly about the regime. I simply said: my daughter. This took place on a Friday. The following Monday, two strapping fellows arrived at the University in Bucharest where my daughter was a student in classical philology, took her out of the amphitheater, and told her to pack her luggage immediately, as she would be leaving for Canada. Donca was not so ready to leave and certainly not on these terms. It was another year before I obtained a tourist passport for her, which was not the same as a definitive emigration. This passport has had the same destiny as mine: she arrived (greeted me with "hello" at the airport as if we had seen each other the day before), began studying linguistics, and received a Master's degree from Laval University. She then moved to Yale and MIT and is now a full Professor of Phonology at MIT (I don't know if she kept that 3-month 1974 passport). Those six years, from 1968 to 1974, until my daughter came, and the fear of what might happen to her and my wife at that time, cost me much sleep. This is not, however, the reason why I was, and continue to be, working on the topic of sleep for I do not deal with practical issues such as insomnia (and those who deal with such issues cannot influence the politics of bizarre governments or bosses who make life and sleep difficult).

I began working at the Université de Montréal, in collaboration with J.P. Cordeau, on brain stem reticular influences on auditory cortical responses, a topic we were both interested in. We had both published a series of papers on state-dependent changes in thalamic and cortical responses that are evoked

by electrical stimuli applied to central pathways (see Steriade, 1970). At the first seminar I delivered, on fluctuations of cortical and thalamic responses evoked by central volleys during states of vigilance, Herbert Jasper asked me if we receive electrical stimuli during normal life and wondered why I did not use light flashes instead. Results with flash-evoked responses were also presented in my talk, but I preferred to answer that stroboscopic flashes are as abnormal as electrical stimuli applied to central pathways, with the disadvantage that there are additional synapses in the retina that may further complicate the data. Cordeau was delighted and told me after the seminar that my reply was the only way to deal with the great man if one did not want to be crushed. In any case, Jasper was extremely favorable to me throughout my Canadian career.

I never trusted Jasper's concept of a "centrencephalic system" that has no anatomical reality. Nor do I think that 3-Hz stimulation of the medial thalamus induced spike-wave complexes similar to those in absence (petit-mal) epilepsy, as he claimed in his 1949 paper with Drooglever-Fortuyn. This paper is a favorite citation for those who have read only the title and the abstract, without looking at the figure showing *responses* but no self-sustained activity, as should be the case in a seizure. Curiously, despite his preference for the idea that spike-wave seizures are generated by some deep-lying brain structures, Jasper was probably the first to show, in his 1938 paper with Hawkes, that EEG local epileptic activities may shift from one cortical region to another. Later, topographical analyses of spike-wave complexes in humans, carried out by others, showed that the "spike" component can propagate from one hemisphere to another with time lags as short as 15 ms, too quickly to be estimated by visual inspection. All these data are incompatible with the conventional notion of "suddenly generalized, bilaterally synchronous" spike-wave seizures due to a pacemaking "centrencephalic system." Since the 1970s, I have claimed that spike-wave seizures are cortical in origin, a conclusion based on experiments in behaving monkeys. In the 1990s, we strengthened this hypothesis with multisite, extra- and intracellular recordings from various cortical fields and thalamic nuclei. I fully disagreed with Jasper on this issue, and we publicly expressed our contradictory views in Marseille in 1974, when Henri Gastaut invited both of us to lecture in the same morning on the origin and mechanisms of spike-wave seizures.

In any case, I have always believed that Jasper's contribution to neuroscience was invaluable, and I am sure that some of his lapidary statements had a great influence on thinking in neuroscience, certainly on me. For example, Jasper's idea (1958) that activation processes are not entirely ascribable to a globally energizing process and that sculpturing inhibition should be included in the activated response was fully confirmed experimentally with extra- and intracellular recordings. Some very good investigators had reported during the 1960s and 1970s that a global disinhibition occurs

in the thalamus as a consequence of brain stem reticular activating impulses (we learned later that this might have been due to the hyperpolarization of thalamic GABAergic reticular neurons). However, studies in several laboratories (mine and others, including the laboratory of Livingstone and Hubel) showed that prolonged and rhythmic inhibitory processes are blocked upon brain stem reticular stimulation or natural awakening, but that short-lasting inhibition is preserved, the specificity of the response in thalamic as well as neocortical neurons is enhanced, and irrelevant responses are eliminated. These findings made sense for a response that occurs during the waking state, at a time when sculpturing inhibition and discrimination processes would seem important. With my students Denis Paré and Roberto Curró Dossi, we showed that the earliest IPSP in thalamocortical neurons is enhanced during reticular-induced arousal (see below), in full confirmation of Jasper's idea that inhibition is included in the activation process. In the late 1950s, Jasper also asked rhetorically: "Can the melody of the mind be played on a (brain) keyboard ... with *rigidly determined functional characteristics*?" (italics mine), and he considered the role of widely distributed neuronal networks as well as the behavioral state of vigilance as determined by the effects of generalized activating systems. This simple question anticipated my view that the mechanisms underlying global states of behavior cannot be investigated in extremely simplified preparations that are fashionable nowadays and which were at the basis of research performed *in vivo* in my laboratory during the past decade. Moreover, the above question by Jasper anticipated our intracellular data obtained in the late 1990s, which showed that the firing patterns due to intrinsic properties of single neurons are not inflexible because they can be overwhelmed and drastically changed by synaptic activities in complex neuronal networks and by shifts in behavioral states of vigilance (see below).

In My Québec Laboratory during the 1970s and 1980s

After my arrival in Montréal, I was invited to lecture at many Canadian universities, including McGill where I always had friendly relations with Krnjević, and I received various proposals for a position as professor and researcher in neurosciences. Eventually, I accepted an offer for a permanent position at the Faculty of Medicine of Laval University in Québec, because there was no neuroscientist in that University and I thought it would be exciting to create a team. Québec, about 240 km northeast of Montréal (I mention this because many of my colleagues still ask me: "How is it in Montréal?"), is a small city, a provincial capital, and a university town. You can visit the old city, for which many tourists come to see "Europe," in about 1 hr. Otherwise, the city is a monastery for work in the lab, dinner with family, and sleep (with some recitals and chamber music, more and

more rare because the public has come increasingly to prefer other types of entertainment).

I arrived in December 1968 and gave a lecture. The Head of the Physiology Department took me to his home and between the car and the house asked me if I would accept the salary he proposed. I thought I was becoming scandalously rich. Later on, he asked me why I did not bargain; I did not have any bargaining technique, and, to this day, I prefer to have none. (I have always thought that the salaries of researchers like me are too high. To avoid the entrance of undesirable people into the temple, one should give them less and see if they still express a passion for science. Otherwise, they may begin immediately to think about tenure and, not so long afterwards, to dream about retirement.) I immediately accepted, and we went for dinner in the old city. The rector (Rector Magnificus, a bishop, Monseigneur Parent, as it was a Catholic university at that time) sent me a long letter, containing the memorable words: "*Monsieur, vous êtes professeur à vie.*" I wish it were as simple as that for my younger colleagues.

The initial space provided for my research was minuscule, but it progressively increased. As first pieces of equipment, I had some amplifiers, an oscilloscope, and one stimulator (not significantly more sophisticated than in Bucharest), but the laboratory continuously evolved into what it has now become. These days (especially when I arrive, about 6:00 AM), I go into the labs alone, look at them, and I do not believe my eyes. The Medical Research Council of Canada accepted my first grant application, and, since 1969, I have been continuously funded by this federal agency to the point that I received an award for maintaining uninterrupted grants during these 33 years. This is not the place to acknowledge the financial support for my research, but without it (from different Canadian federal agencies, the Human Frontier Science Program, and an RO1 from the U.S. National Institutes of Health), our research would not have been possible.

During 1969 I did experiments alone, recording along the cerebello-thalamo-cortical pathway. Thereafter, I accepted Ph.D. students. As I mentioned above, initially, I had few experimental facilities to offer my students. Improved facilities came later, during the luxurious 1980s and 1990s. This is why I decided to share a chronically implanted macaque monkey, making the left hemisphere available to one team for cortical recordings and the other hemisphere available to another group from my laboratory. One morning, they all came in my office and asked to have one animal for each team. (Don't forget that I came from Romania, where such an action would have caused trouble for the petitioners.) I had to make a quick decision: either I remain alone or I agree. I did the reasonable thing. During the 1970s my most gifted student was Martin Deschênes, who left his training in psychology to do experiments with me on neuronal activity in the motor cortex of cats and monkeys. The reason he left psychology, he explained to me, was that he had read my book on the physiology of visual pathways,

which was published again at Masson in Paris (Steriade, 1969) and dealt mainly with my experiments.

Several findings came out of the work with Deschênes, and these were published as two companion papers in the *Journal of Neurophysiology* (Steriade and Deschênes, 1974). First, we dissociated the arousal-related firing rates of fast-conducting pyramidal cells from those of slow-conducting cells that were identified antidromically, and we characterized the discharge features of presumed local interneurons during sleep and waking. Interestingly, fast-conducting pyramidal cells stopped firing for about 10 sec upon natural arousal, but their antidromic responses were enhanced and the break between the initial segment and somadendritic components of action potentials disappeared. This observation suggested that the arrest in spontaneously occurring discharges does not reflect inhibition but disfacilitation, a hypothesis later confirmed by Oshima and his colleagues in Japan. Second, testing feedback and feedforward inhibitory processes in pyramidal neurons of monkey precentral gyrus during natural states of vigilance showed that well-pronounced (but short-lasting) inhibition during wakefulness provides a mechanism for accurately analyzing excitatory signals and for following rapidly recurring messages. Currently, we are doing experiments on the same topic using intracellular recordings in chronically implanted cats. Last, but not least, after Deschênes left for a postdoctoral term with Mike Bennett at the Albert Einstein School of Medicine in the Bronx, I was left to analyze the data, and, in addition to the sleep–waking findings, I discovered on tapes what subsequently became one of my favorite topics: the occurrence of seizures with spike-wave complexes during states of drowsiness or light sleep. This was an accidental finding. While the tape showed that the monkey was sleepy, the EEG potentials suddenly became so ample that the pen of the ink-writing machine started jumbling. I thought these were artifacts, but I fortunately diminished the gain and what I saw were beautiful, typical, spike-wave complexes in a seizure lasting about 12–15 sec that recurred in the same form several times. Simultaneously, there was an increased firing of neurons in the monkey's motor cortex during the EEG "spike" component, which was rhythmically interrupted by long pauses of the "wave" component. Focal field potentials recorded from the cortical depth, together with action potentials, displayed typical spike-wave complexes at 3 Hz (though the surface EEG did not always reflect the drama that was occurring in the cortical depth). Notably, at the beginning and end of these seizures the monkey had tonic eye movements, as in the absence epilepsy of children and adolescents. I wrote a paper, and this was the beginning of my current claim that spike-wave seizures originate in local neuronal pools of the cerebral cortex, only to spread later to other pools and, eventually, to the thalamus. Those 1974 data were at the origin of all our efforts in this direction during the late 1990s.

During the 1980s, our experiments multiplied in several directions. One set of studies dissected the electrophysiological basis of neuronal steps in the brain stem activating reticular system. With Lloyd Glenn, a postdoctoral fellow who did his Ph.D. with William Dement at Stanford, we identified in 1982 "beyond hypothesis the final corticopetal link in the anatomical substratum of the phenomenon of diffuse cortical arousal," as Nauta and Kuypers wrote in 1958, describing it as a topic for future experiments. In other words, we demonstrated monosynaptic excitation from midbrain reticular neurons to thalamocortical cells in intralaminar nuclei, which could be antidromically activated from different cortical areas. This bisynaptic, brain stem-thalamic-cortical link, which explained the prolonged somnolence of my 1958 patient with bilateral thalamic intralaminar lesions (see above), proved also to be the basis of PET activation in the midbrain reticular core and intralaminar thalamus during complex tasks in humans, as shown in 1996 by Roland's group in Stockholm. The widespread cortical projections of thalamic intralaminar nuclei, first shown anatomically by E.G. (Ted) Jones, explain the importance of this nuclear complex in the maintenance of alertness. With Glenn, we also investigated the firing patterns and excitability of thalamic intralaminar neurons during the whole waking–sleep cycle of cats. Another line of research during the 1980s was the combination of retrograde tracing techniques with immunohistochemistry to demonstrate the projections of mesopontine cholinergic neurons to thalamic relay, associational, intralaminar, and reticular nuclei in cats and monkeys.

The most important achievements of my laboratory during the 1980s have been the disclosure of the pacemaker role played by thalamic reticular GABAergic neurons in the generation of sleep spindles and the analysis of the low-threshold spike (LTS) response of thalamocortical neurons *in vivo*. To start with the LTS, Deschênes and I published this phenomenon in the early 1980s (a short paper in 1982 and a full-length paper in 1984). During the very same two years, Llinás and Jahnsen revealed this current and its ionic nature in thalamic slices maintained *in vitro*. It is fair to state, however, that Llinás discovered the LTS in an earlier paper on the inferior olive, published with Yosi Yarom in 1981, in which he suggested that similar events may take place in the thalamus (possibly, this guess may have been emboldened by some experiments on thalamic cells that were already in place). Of course, the transient Ca^{2+} current (I_T) that gives rise to the LTS was revealed *in vitro*, because the *in vitro* condition allows manipulations that can disclose ionic conductances (this is the *raison d'être* of slice work). We then decided to move *in vivo* and see how the LTS looks in the intact-brain animal. Actually, the animal was not so intact, as we worked intracellularly in the thalamus with a partially removed cortex to allow for the safe penetration of micropipettes. This technique is what we still use, although it is possible that completely intact corticothalamic as well as other synaptic projections may influence the intrinsic properties of thalamic cells.

In fact, more recently, Igor Timofeev, a postdoctoral fellow, and I have shown that the LTS is greatly modified by afferent synaptic activities arising in prethalamic relays such as the cerebellum (Timofeev and Steriade, 1997).

The Ca^{2+}-mediated LTS, which is de-inactivated (uncovered) by membrane hyperpolarization, is probably the best example of similarity between the results obtained *in vitro* and *in vivo*. The LTS of thalamocortical neurons gives rise to a high-frequency burst of fast Na^{+} action potentials (the postinhibitory rebound) that reach cortex. Therefore, this intrinsic neuronal property accounts for the transfer of thalamically generated sleep spindles to the cerebral cortex and their expression at the macroscopic level of the EEG. Nevertheless, the dissimilarities between data from slices and from intact-brain structures exceed the similarities. This is what we realized beginning in the mid-1980s and especially during the 1990s and is discussed below. To anticipate, the LTSs of thalamic anterior neurons are similar to those of other thalamocortical neurons, but, at least in cat, anterior nuclei do not receive synaptic connections from the pacemaker spindle generator (the thalamic reticular nucleus), and therefore, the anterior nuclei as well as their projection areas in the anterior cingulate gyrus do not display this sleep oscillation. Thus, intrinsic properties alone cannot generally account for the generation of oscillation. The only exception is the clock-delta rhythm of thalamocortical neurons, but that oscillation is also under the influence of corticothalamic and brain stem-thalamic synaptic activity (see below).

The description of LTSs in thalamic neurons and their role in spindle oscillations during sleep have been the topics of two symposia I organized in 1984 at The Neurosciences Institute of the Neuroscience Research Program, when it was at the Rockefeller University in Manhattan. The first symposium dealt mainly with the structure of thalamocortical systems, and the second symposium dealt with their functional properties. These two symposia have initiated a fruitful collaboration with Rodolfo Llinás and Ted Jones, which led to our 1990 monograph on the thalamus (Steriade, Jones, and Llinás, 1990).

Coming to sleep spindles, the neuronal mechanisms of this major brain rhythm have been elucidated intracellularly, first in my laboratory working *in vivo* since the 1980s (but also more recently) and, subsequently, in other laboratories working on thalamic slices during the 1990s. However, with the exception of hypotheses that have been tested in my laboratory very recently, showing that rhythmic sequences of spindle oscillations (or their experimental model, augmenting responses) may strengthen synaptic responses, the functional significance of these waxing-and-waning brain waves is not yet completely elucidated.

Despite the uncertainty as to their functional role, spindles have become quite fashionable due to numerous *in vitro* and *in computo* studies that followed our *in vivo* experiments. The slice work was done by David McCormick and his team at Yale. At a University of California at Los Angeles (UCLA)

symposium on the thalamic reticular nucleus, organized by Arne Scheibel during the early 1990s, the speakers were asked to give publicly a brief explanation of what pushed them into research on the thalamus. McCormick kindly acknowledged that it was my 1984 review with Deschênes that opened his eyes and persuaded him to work on the thalamus. This statement has touched me, especially because I appreciated McCormick's experiments done with David Prince at Stanford and the collection of papers he produced with Prince on neurotransmitter actions on thalamic neurons. McCormick's work on spindle activity analyzed this rhythmic activity in lateral geniculate slices, as did Alain Destexhe's computational models, done first with Terry Sejnowski at the Salk Institute and later with me in Québec. One of the discrepancies between David's experimental results in slices and our data *in vivo* mainly concerned the absence of spindles in the isolated thalamic reticular nucleus in slices. *In vivo*, spindles are abolished in thalamocortical systems after lesions of thalamic reticular neurons, whereas this oscillation is preserved in the deafferented thalamic reticular nucleus. We agreed to explain the difference between our results in our 1993 long article in *Science* by a lack of intact collections of reticular neurons *in vitro*. The slicing procedure cuts the very long dendrites of these neurons (which are crucial in the generation of spindles) and thus mutilates the equipment required for this oscillation. Numerous modeling studies, reviewed in the recent monograph by Destexhe and Sejnowski (2001), predict the occurrence of spindles in the isolated GABAergic reticular nucleus. Other divergent results between *in vivo* and *in vitro* studies in the thalamus came later and are discussed in the next section.

The Last Decade Was the Most Exciting, in the Company of Gifted Students Who Taught and Tolerated Me

Throughout my career, I had a large number of excellent Ph.D. students and postdoctoral fellows, which reached a climax in the late 1980s and during the 1990s when I worked with (in chronological order) Denis Paré, Roberto Curró Dossi, Angel Nuñez, Florin Amzica, Diego Contreras, Igor Timofeev, Dag Neckelmann, and François Grenier, some of them Ph.D. students, some postdoctoral fellows, but all technically gifted and intellectually creative. The work was impressive: the experiments were done by a team in a room with the main electrophysiological setup, and the analysis of data was done the next day in another room with a similar setup while a second team took the experimental room. Note that before Denis left for Rutgers in December 2001, I had just one experimental room; in the past few months, I organized a second laboratory (the first for intracellular recordings in chronic animals, the second for acute experiments). People who visited me were amazed that, with a single setup, my young colleagues were able to produce the amount

of data that came out of our laboratory. The man in charge of the electronic part of the work was, and is, responsible for the technical achievements; without Pierre Giguère, I don't think we would have been so happy.

Now, what did we do? The main topics are still (1) brain oscillations during states of vigilance and neuronal plasticity related to these rhythms; (2) the influences exerted by modulatory systems on thalamic and cortical responsiveness; and (3) the neuronal mechanisms of different types of electrical seizures, a project that has marked my scientific life since its beginnings. These three facets of my activity are closely interrelated. Thus, brain rhythms in the cerebral cortex and the thalamus are under the control of brain stem and forebrain modulatory systems, and the types of seizures we investigate occur with much greater propensity during slow-wave sleep than during waking or REM sleep. Although I have not changed radically the focus of my research, in that what we do currently reflects my early years in neuroscience, the techniques have greatly improved during the past seven or eight years. This apparently minor matter (minor only for those who do not rely on the electrical activity of neurons) has been essential in changing concepts in our field. Thus, dual intracellular recordings *in vivo*, which was science fiction a decade ago, have been accomplished by Florin Amzica in the neocortex and by Diego Contreras in cortex, as well as in related cortical and thalamic neurons (even triple such recordings are now feasible in Igor Timofeev's cortical slabs *in vivo*). Florin's analyses revealed unexpected temporal relations among neurons recorded from multiple sites; Diego demonstrated that thalamic oscillations are under the control of neocortex; and Igor succeeded in obtaining intracellular recordings in naturally sleeping and awake cats, which opens new windows in our research. All these studies, related to global behavioral states, require intact-brain preparations: for me, this is probably the most important notion I acquired during these recent years. This notion does not mean that we are inattentive to the host of ionic conductances in the neurons that we are recording. In fact, I think that each laboratory also needs an *in vitro* setup if the researcher wants to put his/her finger on the ionic nature of channels, the different subtypes of receptors, and so forth. But I am allergic to the use of great words, such as "sleep," "waking," "absence epilepsy," and even "consciousness," when referring to a 0.4-mm-thick brain tissue. In sum, we continue to work *in vivo* because this is the reality of the brain. Not long ago, we were regarded as the last of the Mohicans. However, this was illusion, or wishful thinking, as we (the Mohicans) are alive and well and some of the best *in vitro* investigators recently discovered the brain in its entirety and now perform nice experiments this way.

The 1990s began with a series of papers on neuronal activity recorded from mesopontine cholinergic neurons during the natural waking–sleep cycle and done with my Ph.D. students Denis Paré and Roberto Curró Dossi and other fellows. During transition from slow-wave sleep to either waking or REM sleep, we showed increases in firing rates in those neurons, in

advance of the most precocious changes in global electrical activity of the forebrain. This finding suggests that a cardinal role is played by brain stem cholinergic neurons in these shifts from disconnected to activated states. Also, we described five types of neurons that fire or cease firing in conjunction with ponto-geniculo-occipital (PGO) potentials during REM sleep, while only one type had been known before. This led us to propose a plausible circuitry for the genesis of these potentials, "the stuff dreams are made of."

The very friendly relations between Denis and Roberto have been beneficial for the laboratory as they collaborated on a series of experiments. One of the most important of these led to the 1991 disclosure of a new type of IPSP in thalamocortical neurons, occurring before the well-known, biphasic $GABA_{A\text{-}B}$ components. The earliest, shortest, small-amplitude IPSP is Cl^- dependent (like the $GABA_A$-receptor-mediated one), and we postulated, on physiological and morphological grounds, that it is generated by presynaptic dendrites of local interneurons in glomeruli. The other series of experiments revealed that this IPSP, called $GABA_a$, which was confirmed one year later by Soltesz and Crunelli in another thalamic nucleus, is not obliterated by brain stem reticular arousing volleys and may even be enhanced. I cherished this finding in view of my earlier extracellular experiments at the cortical and thalamic level, which demonstrated that some inhibitory processes *must* be included in the process of brain activation (see above). The actions of brain stem cholinergic neurons on thalamocortical cells are not confined to simple depolarization and increased input resistance, as these actions lead to prolonged potentiation of synaptic responses in thalamic anterior (limbic) neurons. In papers and a book chapter published with Paré, we showed the muscarinic nature of this prolonged facilitation of synaptic responses that is induced by stimulating brain stem cholinergic nuclei, and we suggested that the cholinergic system could provide a way to regulate the flow of information along the mammillothalamic axis and modify the strength of the functional relationship between the hippocampal formation and cortical memory storage sites (see also Squire and Alvarez, 1995).

Other projects, with Curró Dossi and Nuñez, explored the relationships between oscillatory events generated by interplay between the ionic currents of thalamocortical cells and network (potentiating and suppressing) influences on these intrinsic properties. *In vitro* studies by McCormick and Pape, as well as by Leresche, Crunelli, and their colleagues in the early 1990s, have applied DiFrancesco's description of a pacemaker current (I_H) in cardiac cells to the level of thalamic neurons, which happen to oscillate, due to the interplay between I_H and I_T, within the frequency range of 1–4 Hz. We investigated intracellularly this oscillation *in vivo* and proposed that it represents the thalamic component of sleep delta waves. More importantly, we demonstrated that, despite the fact that this is an intrinsic oscillation of single cells, pools of thalamic neurons can be synchronized by corticothalamic inputs, which drive thalamic reticular GABAergic neurons and thus

set thalamocortical neurons at a hyperpolarized membrane potential that is required for delta generation. Then, singly oscillating thalamic neurons can be synchronized by synaptic activity in corticothalamic networks, and this coherent activity is then reflected at the macroscopic EEG level. By contrast, data in the same 1991 paper showed that depolarization of thalamocortical cells by ascending activating cholinergic impulses results in obliteration of sleep delta potentials, as is indeed the case upon awakening. Our work had such an impact that many people in the EEG field took it for granted that *all* delta waves are generated in the thalamus, despite my cautionary note that this is just one component of delta waves, with the other being cortical in nature.

Looking for generators of delta activity (1–4 Hz) in visual thalamic reticular neurons, we did not find convincing evidence in this sector of the nucleus or in more rostral sectors. However, to our surprise, Curró Dossi and Contreras recorded a *slow* oscillation of intracellularly recorded thalamic reticular cells, with a frequency of less than 1 Hz. Where could such an oscillation possibly arise, which has the typical features of a synaptically generated rhythm and which has never been described before? Then, I decided to ask Nuñez and Amzica to look at the neocortical level, knowing that the most potent drive for GABAergic thalamic reticular neurons is the corticothalamic projection. We recorded neocortical neurons, and, indeed, in the first experiment in the summer of 1991, the *slow* oscillation appeared in its entire splendor, generally between 0.3 and 1 Hz. The disclosure of a novel brain rhythm in virtually all neocortical neurons (both pyramidal and local-circuit inhibitory cells, as subsequently identified by Contreras using intracellular staining) was surprising because of previous intensive investigations of cortical neurons. Probably, this sleep oscillation was ignored (like other slow or very slow rhythms) because low frequencies of EEG activity are so often filtered out. On the other hand, small cortical regions *in vitro* may exhibit synchronous activity, but such limited circuits are not adequate to support oscillations for prolonged periods of time unless the bathing milieu contains an abnormally high K^+ or other ionic manipulations that set cortical or thalamic neurons into action. The slow sleep brain oscillation gradually became so fashionable after our 1993 papers that it came to occupy researchers at many levels, ourselves *in vivo* in the beginning, but also EEG and MEG researchers of human sleep, and believe it or not, even *in vitro* investigators.

Francis Crick once asked me: "Why so many oscillations?" There are indeed at least three major types of brain rhythms during slow-wave sleep (spindle, delta, and slow oscillations). Their variations in frequency, patterns, origins, and underlying cellular mechanisms are due to the different electrophysiological and connectivity features of thalamocortical, thalamic reticular, and neocortical neurons that generate these brain rhythms. Nonetheless, to answer now Crick's reasonable question, the cortically generated slow oscillation, which we revealed in a series of three papers

in one 1993 issue of *Journal of Neuroscience*, has the virtue of including other sleep rhythms generated in cortex and thalamus within complex wave sequences that contain both the slow oscillation and spindles as well as delta waves. This is due to the powerful impact of corticocortical and corticothalamic projections. Thus, *the variations in oscillation frequency are less important than the unified picture of sleep oscillations* that was detected by performing intracellular recordings from cortex or cortex and thalamus in collaboration with Nuñez, Amzica, Contreras, and Timofeev. In other words, the apparently "many oscillations" can be simplified into one complex oscillatory type. A recent paper on human sleep by other investigators (Mölle et al., 2002) supports this view. The cortical nature of the slow oscillation (it survives thalamectomy and brain stem transection) was recently confirmed in cortical slices by Mavi Sanchez and McCormick, and the impact of cortical inputs on metabotropic receptors of thalamic neurons was nicely demonstrated in thalamic slices by Crunelli and his group (Hughes et al., 2002). Still, the combination of slow and spindle oscillations within complex sequences can be seen only in intact corticothalamic networks. This combination gives rise to K-complexes, known for a long time in clinical EEG but only recently investigated intracellularly in our laboratory.

The slow sleep oscillation was studied in our laboratory during the past decade because it provided the best example of a unified corticothalamic network. At this point, let me confess that I am less interested in sleep per se than in the miraculous arrangement of long- and short-axoned neurons in the cortex and thalamus and in the control exerted by brain stem and basal forebrain modulatory systems upon them. We do not know why we sleep. One can speculate, but one can also approach the problem experimentally. We have tested our hypothesis that some sleep oscillations (in particular, spindles) contribute to plasticity and consolidation of memory traces acquired during wakefulness. These experiments were done in our laboratory, and computational models of experimental data were elaborated in collaboration with Maxim Bazhenov and Terry Sejnowski from The Salk Institute. First (1997) we demonstrated that short-term plasticity occurs in thalamic neurons of decorticated animals. This progressively increased synaptic responsiveness occurs in two forms: low-threshold and high-threshold augmentation. Second, in intact thalamocortical networks, we showed (1998) that cortical augmentation of responses is dependent on spike bursts fired by thalamic relay neurons, but cortical neurons oscillate in a self-sustained manner within the same frequency range as the evoked responses during the prior period of stimulation, whereas thalamic neurons simultaneously remain under the hyperpolarizing pressure from the GABAergic thalamic reticular neurons. If prolonged, the self-sustained cortical activity may reach dramatic intensity, and, ultimately, it becomes paroxysmal. Thus, the cortical neuronal equipment is itself capable

of displaying normal as well as paroxysmal forms of plasticity, even in the absence of the thalamus.

Sleep and waking are reproducible behaviors that change the internal states of, and linkages among, all these neurons, thus teaching us how the brain operates on time scales from milliseconds to hours. This is why we (1) analyzed the effects of brain stem cholinergic and monoaminergic systems on cortical slow oscillations; (2) determined the ionic nature of the rhythmic, hyperpolarizing phase of the slow oscillation in acutely prepared and chronically implanted animals and demonstrated that this phase is not (as expected) inhibitory, i.e., it is not produced by local-circuit GABAergic actions, but is due to disfacilitation and some K^+ currents; (3) tested the responsiveness of cortical and thalamic neurons during different components of the slow oscillation; and (4) above all, realized that the slow sleep oscillation progressively develops, without discontinuity, into spike-wave seizures or the pattern of the Lennox-Gastaut syndrome that is a more severe epileptic disease than absence epilepsy. Needless to say, what we have studied in the past seven years is the neuronal basis of an electrographic pattern, strikingly resembling that seen in humans, and not the disease itself. This is why I never use the term *epilepsy*, but, instead, I refer to electrical seizures of one type or another, and I am always bemused when I read about "absence epilepsy" in some studies conducted on thalamic slices.

The studies on neuronal substrates of seizures strengthened the views expressed in my 1974 paper on behaving monkeys, namely, that spike-wave seizures originate in neocortex. I remember the summer of 1993, when I realized with Diego, using dual intracellular recordings from cortex and thalamus, that, during tempestuous activity in neocortical neurons, thalamic reticular neurons faithfully follow the paroxysmal depolarizing shifts in cortex, but thalamocortical neurons (targets of thalamic reticular GABAergic neurons) are steadily hyperpolarized and display phasic IPSPs that are closely related to each spike burst of cortical and thalamic reticular cells. The finding of thalamic reticular paroxysmal excitation, which contrasts with the sustained inhibition of thalamocortical cells (without rebound bursts), may be astonishing, but only for those who think that thalamic relay cells are actively implicated in the generation of spike-wave seizures. We published these findings in a 1995 *Journal of Neuroscience* paper, and they are now fully confirmed in genetic strains of rats that develop spike-wave seizures. Indeed, Crunelli's group showed, on the one hand, paroxysmal excitation of thalamic reticular neurons (Slaght et al., 2002) and, on the other hand, sustained hyperpolarization and phasic IPSPs in thalamocortical neurons during cortical spike-wave seizures in a strain of rats with inherited absence epilepsy (Pinault et al., 1998). The contrasting effects of corticothalamic paroxysmal volleys on thalamic reticular GABAergic neurons and on thalamocortical neurons have recently been explained

by Ted Jones' team. They showed that the numbers of glutamate receptor subunit GluR4 are 3.7 times higher at corticothalamic synapses in thalamic reticular neurons, compared to thalamocortical neurons, and that the mean peak amplitude of corticothalamic excitatory postsynaptic currents (EPSCs) is about 2.5 times higher in thalamic reticular neurons than in thalamocortical neurons (Golshani, Liu, and Jones, 2001). In a series of four papers published in a 1998 issue of *Journal of Neurophysiology*, we showed that spike-wave seizures occur initially in the neocortex and spread only later to the thalamus.

If asked what have been the main achievements during the past decade, I would of course enumerate the above, but my personal focus was also to shed light on the innumerable differences between the results obtained by us and a few other colleagues working *in vivo* and those coming from extremely simplified preparations. Data from my laboratory, mentioned above, justify my assumption that topics dealing with complex behavioral states, from sensory experiences to motor control, states of vigilance, memory, and paroxysmal discharges, can only be approached in the intact brain. This may seem a trivial statement. Still, "those studying the intact brain are often asked to justify findings that diverge from those obtained *in vitro*." This sentence, from a book review (*Neuroscience*, 2003) of my 2001 MIT monograph by a distinguished *in vitro* researcher, Alex Thomson, working at the University College in London, seemed to her "humorous if it were not so dangerous." I remember, for example, that the depolarizing envelope of spike bursts fired by thalamic reticular neurons during spindles *in vivo* contrasted with a hyperpolarizing envelope found *in vitro*. Although everyone knows now that thalamic reticular neurons fire during spindles over a depolarizing envelope, the inference of the *in vitro* investigators was that the membrane *should be* deteriorated in experiments performed *in vivo*; later on, however, they realized by examining their own data that the depolarizing envelope is the reality at the level of membrane potential usually seen *in vivo*. Another example, from very recent intracellular recordings in behaving animals, involved my challenge of the idea that intrinsically bursting patterns of some pyramidal neurons are inflexible. One of the two reviewers (most probably an *in vitro* researcher who never did chronic experiments) asked that we provide morphological evidence using intracellular staining (note: in a chronically implanted animal who is studied for many long weeks!) that we were indeed recording from a pyramidal cell, as if this were the issue, rather than the change in firing pattern with shift in behavioral state. These are technical matters for most readers, but they indicate the climate of this kind of work.

Thus, in view of what we have learned since the 1980s, throughout the 1990s, and during the first years of this millennium, we continue to work *in vivo*, and my students who left the laboratory to become professors elsewhere have taken the same main path in their own research.

A Few Words on Some Subtle Issues: Circumscribed Neuronal Circuits, Neuronal Types, and Consciousness

I expressed my view on the tantalizing issue of the role played by specific neuronal types or circuits in consciousness in my book *The Intact and Sliced Brain* (Steriade, 2001b). This question excites nowadays many distinguished minds, especially theoreticians, as very few active neuroscientists devote more than a few brief sentences on this topic at the end of their papers, if they do so at all. This does *not* mean that consciousness, as a whole, is generated outside the brain, nor does it imply that some elementary components cannot be studied at the single neuron level. Indeed, different forms of memory have been investigated using neuronal recordings, attentive behavior has been studied in the cortex and thalamus, the brain stem circuitry that gives rise to thalamocortical processes that are implicated in dreaming mentation has been identified, and the sites of brain stem and thalamic lesions that produce loss of wakeful conscious states in humans have been described. These relations between neuronal activities and behavioral states merely refer to some *fragments* of activity that build up states of consciousness, but none of those studies (so numerous that is difficult to cite them here) were aimed at revealing the role of specific neuronal types or brain circuits in the generation of the global state of consciousness, which includes, of necessity, subjective experience. The crucial issue is that even the basic elements of first-order consciousness, namely, perceptual experience, imply subjective states, but the mechanisms behind the emergence of subjectivity are hidden.

Knowing that recordings of identified neuronal types cannot be made systematically in humans, and knowing that animals can perform behavioral tasks but do not possess the virtue of expressing their subjective states, how can consciousness be studied at the neuronal level? This is the major obstacle in understanding how action potentials can give rise to a subjective sensory experience—which is just a first step in consciousness.

Some authors have suggested that there are special sets of awareness neurons somewhere in cortical layer V, that these are bursting cells, and that it is only a matter of time before specific molecular markers are found in those neuronal elements of consciousness (Crick and Koch, 1998; Koch, 1998). It remains difficult to understand why layer V is important and not also layers III–IV or other layers; why only bursting and not also regular-spiking neurons are important; and what role fast-spiking inhibitory interneurons may have, which play a cardinal role in focusing attention on relevant messages by ignoring non-relevant signals during conscious states. The issue is that the firing patterns of cortical neuronal types are not inflexible, but change with the level of membrane potential and during epochs rich in synaptic activity, as is the case for wakeful consciousness. One of the most striking examples is the transformation of bursting cortical neurons into

regular-spiking neurons, which occurs during transition from slow-wave sleep to brain-activated states, such as REM sleep or wakefulness (Steriade, Timofeev, and Grenier, 2001). Moreover, we showed in the same article that intrinsically bursting cells represent fewer than 5% of the cortical neuronal population, because their firing patterns transform into regular spiking during the waking state when consciousness arises. Thus, it is difficult to speculate about the role in consciousness of specific neuronal types having distinct firing patterns, because the intrinsic properties of neurons are overwhelmed by synaptic activities when shifts occur in the state of vigilance.

Confronted with these difficulties in relating consciousness to specific neuronal types, which are located in distinct cortical layers or neuronal circuits, thereby leaving aside many other brain systems, and confronted with the impossibility of having simultaneous access to electrophysiologically identified neurons belonging to all structures that organize conscious processes in a concerted way, those interested in subtle mental states may continue to read Flaubert, Dostoyevsky, Proust, and Joyce, among others, and to devote their research time to topics that can be defined more precisely and successfully attacked.

How Did My Life Arise and Develop?

These final lines remind me of those who created a privileged environment for my development.

My mother was not easygoing, and I am sure that my drive and working ability come from her. Her memory is always present, and I often think that she played a critical role in my career. She gave me professors for French and piano lessons beginning at age 5 and for German and English beginning at age 10 or 11. I stopped studying German when I entered the Faculty of Medicine. As for English, I tried to learn it again alone, much later, when I started writing papers. All these lessons beyond the usual schoolwork, especially the piano and French, completely filled my days. My mother used to come at 10:00 AM to the high school to bring me a sandwich (which she could have given me in the morning). But the point was not the sandwich. She wanted to know what grade I got on the math quiz or in natural sciences or history. If it was 9 or 10 out of 10, did someone else have the same or a better grade? The gap between my grades and those of other students was never satisfactory for her. She never spent the afternoon going out, as her friends did; all her time was devoted to me. Having quit school before the 10th grade, she could not always monitor efficiently my work in physics or other such subjects. For this reason, I had to learn the lessons in all their details to convince her that the job had been done. In her 90s, a decade ago, she often asked me on telephone (I was in Canada and she in Bucharest) if I was productive enough that year, "because, you know, you never worked

very much." All in all, the relationship was not always peaceful, but she remained for me an example of how work could be done well and on time. My father, who completed only four years of elementary school classes but had intellectual inclinations (he wrote poems), was an admirable man whom I also loved. The only regret is that I did not spend enough time telling him about my work when I became a researcher.

I was blessed with two families, both of which I adore. I was first married to Fana, who gave me Donca in 1951. The family was close knit and we had extended, friendly debates around the dinner table, but at that time I was not very smart, as I often wanted to go out with my wife instead of being with my daughter at home. Since high school Donca grew very well, read the great novels of the Russian and French literature of the 19th century, and began publishing papers in literary periodicals. Now that she has become a well-known Professor of Phonology at UCLA and recently at MIT, those beginnings do not mean a lot for her, but they do for me. I suspect that she is more attracted to so-called hard science than to soft science, and this might explain why she lately moved closer to phonetics. Yet to me, the general rules of linguistics and the underlying brain mechanisms seem more exciting than the peripheral aspects. In any case, she was and continues to be a very close friend with whom I consult on every crucial occasion. There was a time when I used to call her my moral conscience, an expression that some of my friends strongly disapproved of. Besides my former wife, who remained a close friend, Donca is the only person with whom I use my native language. Our only opportunity to speak Romanian is during phone conversations and, more rarely, when we go together to Paris or elsewhere.

My second wife is French-Canadian. Jacqueline gave me the second daughter, Claude, in 1989, when I was 65. This was indeed a gift at my age, especially because being wiser I spend my evenings with her. We spend more time together on her piano and less at her schoolwork: she no longer needs supervision. My wife tells me that I am too demanding and that her gift for piano was acquired through tears (no longer now), but after all I am my mother's son. As with Fana and Donca, every evening is spent around the dinner table with Jacqueline and Claude discussing North American, France or Middle East politics, listening to classical music, and having fun. Claude is the best in her class and very good also at the Music Conservatory. We never leave her alone and do all our traveling in Europe with her. Donca is a very good advisor to Claude for readings of great literature and recommended *War and Peace* to her as well as other novels. I suggested that she read Flaubert, and Claude is now a great reader of French, Russian, and English literature. More recently, Donca suggested Plato's *Apology of Socrates*. To be sure that this would fit Claude, I took Plato's book on one of my travels and read and annotated it, identifying the passages I thought essential. Claude is now reading what seems to me was beyond my abilities when I was her age or even older. I do not know if her taste for classical music, literature, and good

painting accounts for the closer relations she has with us, her parents, than with her peers, but I am not dissatisfied when it comes to the development of her inclination toward art and literature. When asked what will she do, she answers (of course) neurophysiology, but she may change her mind.

I spend all day at the laboratory, from very early in the morning, 6:00 AM or so, until late afternoon. I was the Head of the Department for a few years, but when asked if I would consider renewing my candidacy for the position, I declined because I dislike the administrative work. To me, the only activity that seems worth spending time on is the research. I am fully active, have grants for many years (possibly beyond my biological limit), and my country is wise enough not to ask for mandatory retirement of those who still want to work. Am I satisfied with what I have done? Yes and no. I am sure that some of our data have created paths for research and that what we are doing right now holds some promise toward an understanding of the functional significance of brain rhythms. Some of my former students and postdoctoral fellows continue to explore the thalamic and neocortical world with passion and with exciting results. But I am not so happy with my mathematical and physical background (despite my mother's supervision!). This is partially due to the fact that, since my arrival in Canada, I have always been in a hurry to produce and to produce, to prove to myself that I did not come for reasons other than research. Besides my laboratory and my family, I am also blessed with my love for music. However, knowing what really playing piano well means, I do feel pain when I sit and play. I also take a different approach from other non-professional pianists who, as a rule, go through the piece as best they can and take pleasure in it. I cannot play this way and instead work on a few lines at a time until I am satisfied, but I often get no further than some short parts of a sonata movement. Then, I decide to put on a CD and listen to Argerich, Benedetti Michelangeli, or Solomon or Sokolov or Perahia, and I get depressed. But afterward, I am able to show Claude how to play a few bars in a piece!

Everything is fine. Let's work.

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