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# Mircea Steriade, the master of cerebral rhythms

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ABSTRACT

*Mircea Steriade (1924-2006), an outstanding Canadian neuroscientist of Romanian origin, has made an invaluable contribution in elucidating the mechanisms of sleep and epilepsy, the cellular basis of electroencephalography, the intrinsic properties of thalamic, cortical and brainstem neurons, as well as the description of dynamic network processing in the thalamocortical system. This article describes how the early scientific discoveries of Frédéric Bremer and Giuseppe Moruzzi have influenced Steriade at the beginning of his career. In addition, the article highlights Steriade's scientific contributions to the understanding of the subcortico-cortical interactions, which marked the last decades of neurophysiology of the 20th century and represent milestones in neuroscience.*

***Key words***

*Electroencephalography • Sleep • Epilepsy • Thalamus • Neocortex • Giuseppe Moruzzi • Frédéric Bremer*

## The beginning and the influence of Bremer and Moruzzi

Mircea Steriade was born in Bucharest, Romania on August 20, 1924 and sadly passed away on April 14, 2006 in Montreal, Canada, at age 81, while still writing books, supervising the research of his graduate students and caring for the medical and scientific education of his younger daughter. During his scientific career, which spanned over more than six decades, he became one of the principal founders of systems neuroscience, a giant personality in sleep and epilepsy research, and the most prominent Canadian neurophysiologist. "He was an extremely energetic man, passionate, uncompromising, forever driven by scientific discovery … still consumed by his work even after 50 years of research in neuroscience" as Denis Paré, one of his students and later on colleague at Laval University that he much valued, has described him in the preface of their last book (Steriade and Paré, 2007).

Steriade's interest in neuroscience developed since his first year of medical studies in Bucharest (1945). In his autobiography Steriade recalls reading, aside from the usual textbooks, Lorente de No's chapter and other chapters on the cerebral cortex and thalamus in Fulton's 1938 book Physiology of the Nervous System (Steriade, 2004). In his third year, he became actively involved in neuroanatomy and histology and he worked as an assistant in the histology laboratory of Ion T. Niculescu at the Department of Anatomy of the Faculty of Medicine, sometimes at the expense of other medical disciplines that were less appealing to him.

In 1952 at the end of the medical school Steriade was offered a position as a young research scientist working toward a D.Sc. at the Institute of Neurology of the Romanian Academy of Sciences. The next three years included neurology and neurosurgery training and the experimental work that led to a thesis on cerebello-cortical relationships. As also mentioned further on, this became a monograph published by Masson in Paris (Kreindler and Steriade, 1958). In 1955 Steriade was recruited as an independent researcher in the Laboratory of Neurophysiology

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of the Institute of Neurology. He considered those years (1952-1960) of clinical neurology and animal experiments as the embryonic stage of his future scientific life. Despite being a declared and passionate experimentalist in many personal discussions he emphasized to us the benefit of the medical training that he received in defining the scientific questions pertinent for specific clinical contexts.

The studies Steriade carried out during his D.Sc. were published under the title "La Physiologie et la Physiopathologie du Cervelet" together with Arthur Kreindler, successor to Gheorghe Marinescu (the founder of the Romanian School of Neurology). Kreindler was the director of the Institute of Neurology and Head of the postgraduate chair of Neurology at the Faculty of Medicine in Bucharest. It seems that Steriade was already interested at that time in the modulation of neocortex by the subcortical structures. He had previously reported a clinical case of hypersomnia secondary to bilateral lesions in the thalamic intralaminar nuclei (Facon et al., 1958) and he described the electroencephalographical changes seen in patients with brainstem tumors (Arseni et al., 1956). The electrophysiological studies of Steriade at that time dealt with the effects of the electrical stimulation of the cerebellum and brainstem on the neocortical electrical activity and seizures. Steriade and his colleagues described that electrical stimulation of the cerebellar cortex causes "electrical activation of almost all cortical areas, motor and sensory, homo- and heterolateral, in the form of a marked "arousal reaction", consisting in desynchronization of the cortical rhythms, with increase in the frequency of the waves and the marked decrease in their amplitude" (Kreindler et al., 1958).

Just three years before Steriade had started his research, Giuseppe Moruzzi and Horace Magoun had published in the inaugural volume of Electroencephalography and Clinical Neurophysiology their landmark study on "Brain stem reticular formation and activation of the EEG" (Moruzzi and Magoun, 1949). The original intent of Moruzzi and Magoun's study was to stimulate the superior cerebellar peduncle, the nervous fiber bundle that relays in the ventro-lateral thalamic nucleus and that finally projects to the motor cortex. Their study intended to demonstrate an inhibitory effect of the cerebellum on the electrical cortical activity and on the muscle activity driven by the motor cortex. However, by stimulating the fibers of the superior cerebellar peduncle in this region they were in fact stimulating the mesencephalic and pontine reticular formation and this was producing a desynchronized EEG (Siegel, 2002). Their findings became the first demonstration of the control of subcortical structures over the cortex: this was a milestone in the development of neuroscience in the 20th century.

Giuseppe Moruzzi had previously worked in Frédéric Bremer's laboratory during the late 1930s, before he went to work with Lord Adrian in Cambridge. Frédéric Bremer had developed during the 1930s two experimental preparations that facilitated the experiments by Moruzzi and Magoun, the *encéphale isolé* and the *cerveau isolé*, in the sense that they allowed electrophysiological recordings in experimental animals without the confounding effects of anesthesia. The *encéphale isolé* preparation fluctuates between the electrical activity patterns of waking and sleep after the transection of caudal medulla and artificially maintained respiration; the *cerveau isolé* preparation is instead comatose after a mesencephalic intercollicular cut but displays uninterrupted sequences of spindle waves, virtually identical to those that occur during natural sleep.

Steriade was aware of both the work of Moruzzi and Magoun at Northwestern University in Chicago and of the work of Frédéric Bremer in Brussels. He wrote in his autobiography that his monography published at Mason "paled in comparison with the book on the cerebellum by Dow and Moruzzi published in the same year". As a young researcher he felt encouraged when he received a congratulatory letter from Wilder Penfield and when Frédéric Bremer wrote to him "very nice words" about the results of his experiments (Steriade, 2004). Steriade had also sent a summary of his PhD dissertation on the cerebellum to Giuseppe Moruzzi just prior to the book being published, and Moruzzi answered by proposing to do more additional joint experiments. In a later letter to Moruzzi from 1982, Steriade evoked that period (Fig. 1a).

In 1957 Steriade was allowed by the Romanian communist authorities to join the laboratory of Frédéric Bremer as a postdoctoral student and this represented a turning point in his carrier. Bremer is the individual that Steriade recognized as "the only mentor" that he "highly admired and continue to love" (Steriade, 2004). On the other hand Bremer

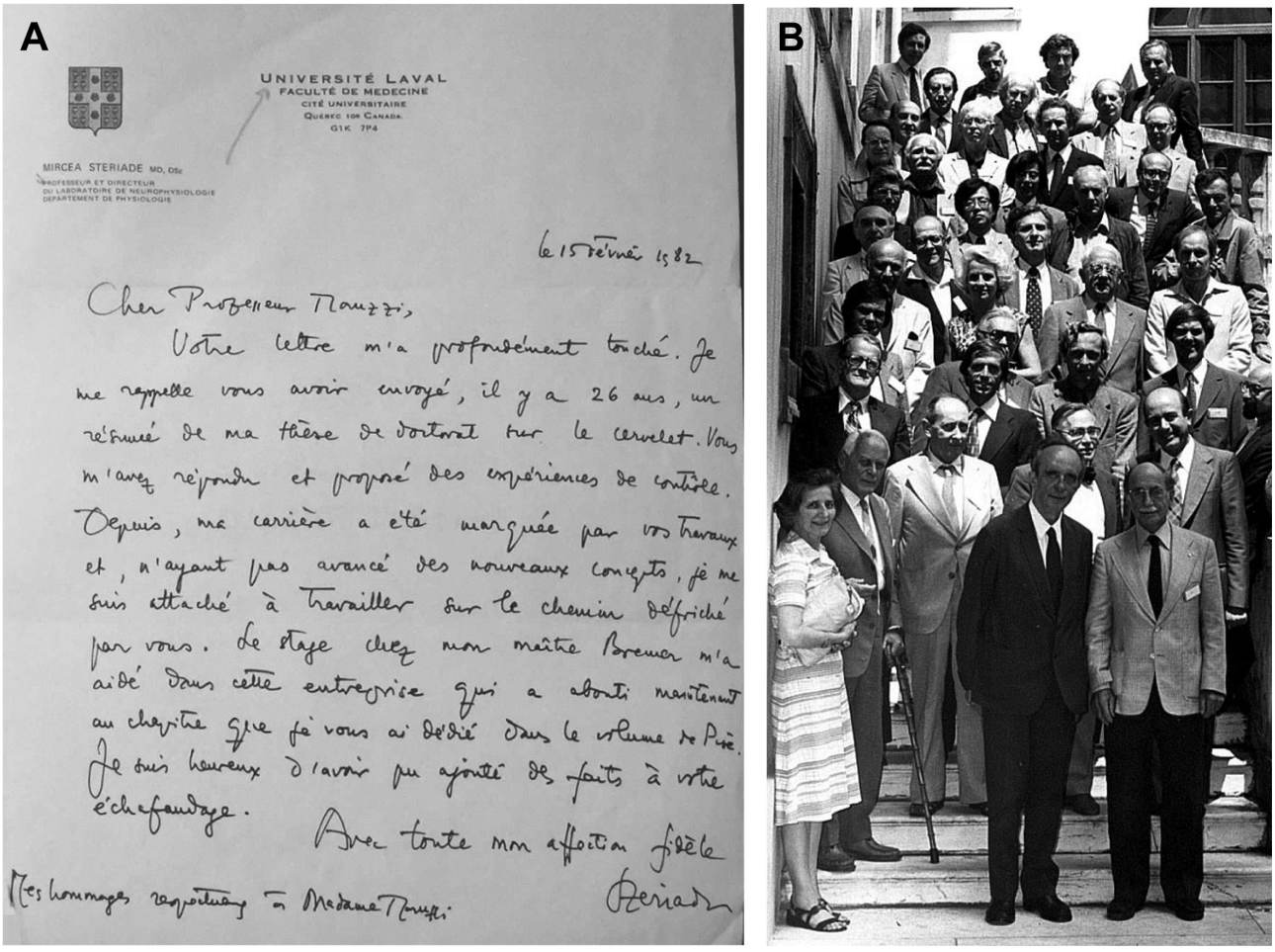


Fig. 1. - A) Response letter addressed to Giuseppe Moruzzi by Mircea Steriade, B) group photo at the meeting "Brain Mechanisms and Perceptual Awareness" organized for the 70th birthday of Giuseppe Moruzzi (standing at the center in the front); Mircea Steriade is the first on the left in the fourth line from top.

identified the most prominent feature of Steriade's personality, an intense and singular drive to achieve his scientific goals, by calling him "l'infatigable Monsieur Steriade" (Amzica, 2006). In Bremer's laboratory, Steriade continued his work on subcortico-cortical relations. He used the advantages of Bremer's experimental models which did not require anesthesia, stimulated the auditory cerebellar areas and recorded different types of evoked potentials in the auditory cortex.

On his return in Romania, Steriade became the director of the Neurophysiology Laboratory at the Institute of Neurology, but he soon became disillusioned with the communist government. He continued to be interested in the modulatory effects of the reticular formation on the auditory evoked potentials and in the brainstem reticular facilitation of photically evoked responses. In his autobiography he notes: "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" (Steriade, 2004). This is the period when "Steriade's favorite structures, the brainstem, thalamus and neocortex, took their significance" (Buzsáki and Paré, 2006) and Steriade started approaching them by relating the structural connectivity to the functional processing, in the light of the pioneering work of Bremer and Moruzzi.

Steriade decided to leave Romania because of the lack of resources for science and increasing dif-

ficulties in keeping up his scientific relations with his colleagues in the Western countries. In 1968 he got a visa valid for three months and a passport to attend a scientific meeting in France. He was invited to give a lecture at the Sorbonne but in May 1968 French students have started their "revolution". In Marseille, however, Steriade met Jean-Pierre Cordeau from the University of Montreal who was on a sabbatical in France who invited him to Canada as they were both interested on brain stem reticular influences on auditory cortical responses.

Steriade arrived in Canada in Montreal at the end of August 1968, just when the Soviet tanks crushed the Prague Spring. During his "exile" Steriade began a new life and established a very productive laboratory. He decided eventually to accept an offer for a permanent position at the Faculty of Medicine of Laval University in Québec City, despite the fact that at that time McGill's Montreal Neurological Institute was the most advanced Canadian neuroscience center gathering big personalities like Wilder Penfield, Theodore Rasmussen and Herbert Jasper, pioneers of Neurosurgery, Neurology and Neuroscience. For Steriade it was more important to be able to build his own research team, rather than to join a renamed group, in order to pursue his own research interests in the light of his predecessors, Bremer and Moruzzi. At Laval University he quickly reverted to full time research "the only activity that seems worth spending time on" and he attracted talented students and fellows (Buzsáki and Paré, 2006).

During the 1970s one of the students that he appreciated was Martin Deschênes. Steriade and Deschênes initiated a series of experiments on the electrophysiological properties of the cortical motor pyramidal neurons during different states of vigilance. They reported the different arousal firing rates of fast-conducting pyramidal cells and those of slow-conducting cells that were identified antidromically (Steriade and Deschênes, 1974; Steriade et al., 1974). At this point Steriade's research could be considered pure systems neuroscience, as he was integrating the modulatory effects of the ascending reticular activating system and the cortical activation phenomenon described by Moruzzi and Magoun into the analysis of the activity of target structures, such as the thalamus and the cerebral cortex. After Deschênes left to do his postdoctoral training, Steriade observed, while reviewing their recordings, the occurrence of seizures with spike-wave complexes during the states of drowsiness or light sleep. This accidental finding in 1974 was at the origin of his later efforts during the 1990s. During this period he followed his interest in the thalamic modulation by the brainstem by studying the reticular influences on the lateral posterior thalamic neurons (Steriade et al., 1977) but also in the opposite way, the thalamic inputs and subcortical targets of the cortical pyramidal neurons (Steriade et al., 1978).

## Early work in 1980s

In 1980, Steriade was invited to attend the meeting "Brain Mechanisms and Perceptual Awareness" that was convened for Giuseppe Moruzzi for his 70th birthday in Pisa (Fig. 1b) and he contributed to volume that was published following the meeting with a chapter on the mechanisms underlying cortical activation and the neural organization and properties of the midbrain reticular core and thalamic intralaminar nuclei (Steriade, 1981). In this chapter he emphasized that the research lead by Moruzzi conceptually changed the understanding of the states of vigilance: "Moruzzi and his colleagues … shaped the early concept into an increasingly mature one … the notion of passive sleep … was replaced by the idea of active hypnagogic structures". His appreciation for Giuseppe Moruzzi is also illustrated by the 1982 letter in which Steriade states with modesty: "My career has been influenced by your work, and, despite not advancing new concepts, I worked on the pathway that was cleared by you … I am happy that I was able to contribute to the scaffolding that you have initiated" (Fig. 1a).

In 1980s Steriade demonstrated, with Lloyd Glenn, the existence of monosynaptic excitation from midbrain reticular neurons to thalamocortical cells in the intralaminar nuclei. This bi-synaptic connection between the brainstem, thalamus and cortex represents the anatomical substrate of the pathology of the patient that Steriade had first reported in 1958 with bilateral thalamic intralaminar nuclei lesions. But far more important for the 1980s was the analysis of the low-threshold spike (LTS) response of thalamocortical neurons *in vivo* and the discovery of the pacemaker role played by GABAergic neurons

of the thalamic reticular nucleus in the generation of sleep spindles.

From this on, Steriade witnessed the rise of *in vitro* techniques in neuroscience, and he subsequently fought passionately for the place of *in vivo* experimentation as an irreplaceable method for understanding the behavior of complex systems. He repeatedly stated that complex behavioral states, such as sleep, awareness and motor control, could only be approached *in* vivo. "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" (Steriade, 2004). One of the actual prominent neuroscientists György Buzsáki commented: "In response to objections about technical limitations in intact brains, he went back to the lab and emerged with double and triple intracellular recordings, often in drug-free awake animals" (Buzsáki and Paré, 2006).

The LTS was initially revealed *in vitro* by Llinás and Jahnsen in thalamic slices. These researchers demonstrated that the transient $Ca^{2+}$ current ($I_T$) gives rise to the LTS (Llinas and Jahnsen, 1982). However, a slice is a very simplified experimental condition primarily designed to allow the manipulation of the ionic conductances in order to quantify the different ionic currents. With Martin Deschênes, Steriade published evidences for LTS *in vivo* first in 1982 and then in a more detailed paper in 1984 (Deschênes et al., 1982; Steriade and Deschênes, 1984). He continued to emphasize that the completely intact corticothalamic as well as other synaptic connections that are maintained *in vivo* may influence the intrinsic properties of thalamic cells. Even later in his career Steriade was seeking evidence to support this belief and he demonstrated this for $I_T$ in 1997 (Timofeev and Steriade, 1997) and much later for $I_H$, the other intrinsic current of the thalamic neurons involved in the delta oscillation, in 2003 (Nita et al., 2003).

The LTS of thalamocortical neurons gives rise to a high-frequency burst of action potentials that reach the cortex and transfers an otherwise intrinsic neuronal property into a network phenomenon. These initial experiments represent the basis of later concepts that have elucidated the genesis of spindles.

The later discoveries on the "pacemaker" role of the thalamic reticular nucleus in the generation of sleep spindles and the importance of low-threshold calcium spikes *in vivo* were done by linking the *in vivo*, *in vitro* and *in silico* approaches. Despite philosophical and scientific clashes Steriade created a synthesis of the different approaches that allowed cross-fertilization in thalamic research and should remain as an example for investigators in other fields (Buzsáki and Paré, 2006).

## Work in the last decades

Like few other scientists, Steriade attained the apogee of his career in the last three decades of his life. From the late 1980s until his death, Steriade was able to bring together many technically gifted and intellectually creative individuals whom he trained for brilliant academic carriers. He worked with (in chronological order) Denis Paré, Roberto Curró Dossi, Angel Nuñez, Florin Amzica, Diego Contreras, Igor Timofeev, Dag Neckelmann, François Grenier, Pablo Fuentealba, Sylvain Crochet, Youssouf Cissé and Dragos A. Nita. In the preface of the last book he co-authored with Denis Paré, Steriade acknowledged the skilful and creative collaboration of all this Ph.D. students and postdoctoral fellows, but he was especially grateful to the role that Pierre Giguère played in the technical development of his laboratories.

The 1990s began with a series of papers on neuronal activity recorded from mesopontine cholinergic neurons during the natural waking-sleep cycle, work done mainly by Denis Paré and Roberto Curró Dossi, PhD students in his lab at that time (Steriade et al., 1990a, 1990b). Other projects, with Curró Dossi and Angel Nuñez, explored the relationships between oscillatory events generated by the interplay between the ionic currents of thalamocortical cells and network influences (potentiating and suppressing) on these intrinsic properties (Steriade et al., 1991). In the light of the *in vitro* studies by McCormick and Pape (McCormick and Pape, 1990), as well as by Leresche, Crunelli, and their colleagues in the early 1990's (Leresche et al., 1990), Steriade started to investigate this oscillation *in vivo* intracellularly and proposed that it represents the thalamic component of sleep delta waves. More importantly, he 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 required for delta generation (Steriade et al., 1991).

While searching for generators of delta activity (1-4 Hz) in visual thalamic reticular neurons, Roberto Curró Dossi and Diego Contreras recorded a slow oscillation of intracellularly recorded thalamic reticular cells, with a frequency of less than 1 Hz. This was unexpected and not previously reported, Steriade decided to ask Nuñez and Florin Amzica to start looking at the neocortical level, knowing that the most potent drive for GABAergic thalamic reticular neurons is the corticothalamic projection.

In 1993, Steriade with his trainees published three milestone papers in the Journal of Neuroscience which described the main features of the cortically generated slow oscillation that occurs during slow-wave sleep and some forms of anesthesia and which is reflected in thalamocortical and reticular thalamic neurons (Steriade et al., 1993a, 1993b, 1993c). The slow oscillation was described as the recurrence of alternate periods of intense synaptic activity and periods of dysfacilitation. The new pattern became legendary because it brought together basic and clinical investigations on sleep delta patterns, cortical spindles, K-complexes, as well as neocortical seizures.

Since the early studies with Martin Deschênes, Steriade recognized the connection between synchronous sleep patterns and epileptic discharges. The mechanisms of paroxysmal epileptic activity in the neocortex and the plasticity of thalamocortical network related to epilepsy became an important research topic in the last decade of his life. With Dag Neckelmann they studied the spike-wave complexes and the fast components of the cortically generated seizures (Neckelmann et al., 1998; Steriade et al., 1998). With Florin Amzica, one of his closest collaborators who also shared his passion for music, Steriade studied the slow sleep oscillation, the cellular substrates of the K-complexes, the coalescence of the sleep rhythms and their paroxysmal developments in the neocortex (Amzica and Steriade, 1997; Steriade and Amzica, 1998; Amzica and Steriade, 1999). Igor Timofeev, at that time postdoctoral trainee, succeeded in obtaining the first *in vivo* intracellular recordings in naturally sleeping and awake cats and his technical abilities and zeal were cherished by Steriade. Together they investigated the cellular mechanisms underlying the intrathalamic augmenting responses, the gating role of the thalamus and the very fast oscillations (ripples) (Timofeev and Steriade, 1998; Grenier et al., 2001).

With François Grenier they studied the contribution of intrinsic neuronal factors as well as the effect of field potential on plasticity of neocortical neurons during epileptic seizures (Grenier et al., 2003; Timofeev et al., 2004). Youssouf Cissé focused on the plasticity of callosal pathways in the association cortex and on the plasticity of the epileptic neocortex (Cissé et al., 2003, 2004). Sylvain Crochet, another postdoctoral student, worked on synaptic plasticity and on the amplification of the output of the neocortical neurons by fast pre-potentials (Crochet et al., 2004). Pablo Fuentealba brought new experimental results *in vivo*, *in vitro* and *in silico* showing that interactions through chemical synapses, as well as electrical coupling of inhibitory thalamic reticular neurons, lead to the generation and synchronization of spindle sequences within the reticular nucleus itself (Fuentealba and Steriade, 2005).

An erudite, passionate and articulate scholar, Steriade won respect from supporters and competitors alike. He received many prizes, of which he most cherished the Claude-Bernard Medal from the University of Paris and the Marie-Victorin prize from Québec; he became member of the Royal Academy of Sciences of Canada and honorary member of the Romanian Academy of Medical Sciences.

## Personal recollections

Steriade frequently underlined the importance of early 20th century neuroscientific work to his students, as well as to his daughters. His oldest daughter became a linguist, yet is quite familiar with the names of Ramón y Cajal, Bremer and Moruzzi, from hearing her father frequently speak with enthusiasm and admiration of the early 20th century pioneers of neuroscience. His younger daughter (the second author on this manuscript) is currently engaged in neurology residency, a career choice which arose early on from the dinner table conversations during which her father would animatedly yet clearly attempt to describe to a child how electrical rhythms could control a person's consciousness. During those same dinner table conversations, Steriade

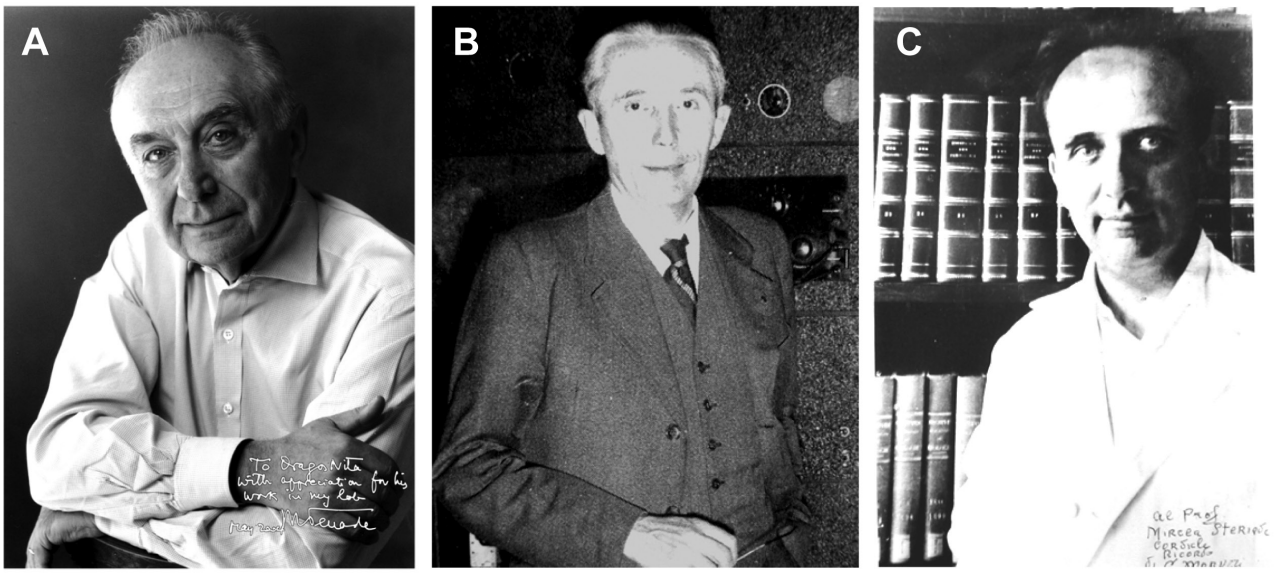


Fig. 2. - A) A photograph Mircea Steriade (1924-2006) has dedicated to the senior author of this article ("To Dragos Nita with appreciation for his work in my lab. May, 2004 Mircea Steriade"), B) Frédéric Bremer (1892-1982) and C) Giuseppe Moruzzi (1910-1986) (photograph dedicated to Mircea Steriade, translation "To Prof. Mircea Steriade best regards of G. Moruzzi").

frequently spoke to his family about Moruzzi with much professional and personal admiration, and expressed regret at the fact that too often young neuroscientists do not learn early works such as Moruzzi's, which have guided the development of modern neuroscience.

I (the first author on this manuscript) am not Steriade's last PhD student (the last one that he accepted in his lab is my wife Sînziana Avramescu), but the last one that has published with Steriade. He supervised me on my projects on the modulation of neocortical seizures by the naturally occurring states of vigilance and on the properties of seizure propagation related to the state of the cortical network following brain trauma (Nita et al., 2006; Nita et al., 2007); and I worked with Florin Amzica on the very slow (DC) cortical oscillations and the comatose brain and with Igor Timofeev on the mechanisms of post-traumatic epilepsy and homeostatic plasticity.

From a personal point of view I consider Mircea my mentor that "I highly admire and continue to love" as he himself considered Bremer. Beyond the fruitful discussions, authoritative critics and support throughout the progression of my thesis I will always remember his innate charisma and the strict coherent value system of hard working, motivation, dedication, and perseverance to which he was committed and which he imposed to his students. More than a mentor however, I consider him a friend whose support and advice had a decisive influence in my life. I am pleased to know that appreciation was mutual (Fig. 2a).

When I asked him to advise me to if I should dedicate myself fully to either a medical or a scientific career in order to be able to advance the clinical or experimental science of my time he answered that for a too long time the gap between neuroscientists and clinicians was increasing, and that science and progress will require more clinicians who get involved in basic research and more basic researchers that get trained in clinical sciences to bridge this gap as knowledge expands. I am now just pursuing this vision.

Another strong belief that Steriade shared with me is that people who make a leap in the progress of the mankind with their scientific contribution are the ones that live science with passion. The difference between a "laboratory" scientist and a "cubicle" scientist is the difference between the ardor and the obsession for advancement, and the convenience of a fixed salary and of a retirement plan. It is useless to say that Steriade never retired, as it also is to mention that he never lived to see his laboratory and legacy transformed into "cubicle" science. This

only happened because his true disciples inherited his fervor.

In writing this article, I am further realizing to what extent the work of Steriade overlaps with the development of the Neuroscience in the 20th century. His invaluable contribution to the study of mechanisms of sleep and epilepsy, the cellular basis of electroencephalography, the intrinsic properties of thalamic, cortical and brainstem neurons, as well as the description of dynamic network processing in the thalamocortical system under the influence of brainstem and cerebellum originate from the pioneering experiments of Bremer and Moruzzi (Fig. 2b,c). These researchers have remained the predecessors that he proudly acknowledged in the books he has published.

As Florin Amzica prophesied in Steriade's obituary "His strong personality and high standards will continue to influence the neuroscience and epilepsy research fields, through those who knew him … and those inspired by his creative legacy" (Amzica, 2006). Mircea Steriade would have very much appreciated being part of an issue dedicated to Giuseppe Moruzzi and he would have told us: "Everything is fine. Let's work".

## References


Amzica F. and Steriade M. The K-complex: its slow (< 1-Hz) rhythmicity and relation to delta waves. *Neurology*, **49**: 952-959, 1997.

Amzica F. and Steriade M. Spontaneous and artificial activation of neocortical seizures. *J. Neurophysiol.*, **82**: 3123-3138, 1999.

Amzica F. In memoriam. *Epilepsia*, **47**: 1585-1585, 2006.

Arseni C., Kreindler A., Steriade M. Electroencephalographic changes in tumors of the brain stem. *Rev. Neurol. (Paris)*, **94**: 728-731, 1956.

Buzsáki G. and Paré D. Mircea Steriade 1924-2006. *Nat. Neurosci.*, **9**: 713-713, 2006.

Cissé Y., Grenier F., Timofeev I., Steriade M. Electrophysiological properties and input-output organization of callosal neurons in cat association cortex. *J. Neurophysiol.*, **89**: 1402-1413, 2003.

Cissé Y., Crochet S., Timofeev I., Steriade M. Synaptic enhancement induced through callosal pathways in cat association cortex. *J. Neurophysiol.*, **92**: 3221-3232, 2004.

Crochet S., Fuentealba P., Timofeev I., Steriade M. Selective amplification of neocortical neuronal output by fast prepotentials in vivo. *Cereb. Cortex*, **14**: 1110-1121, 2004.

Deschênes M., Roy J.P., Steriade M. Thalamic bursting mechanism: an inward slow current revealed by membrane hyperpolarization. *Brain Res.*, **239**: 289-293, 1982.

Facon E., Steriade M., Wertheim N. Prolonged hypersomnia caused by bilateral lesions of the medial activator system; thrombotic syndrome of the bifurcation of the basilar trunk. *Rev. Neurol. (Paris)*, **98**: 117-133, 1958.

Fuentealba P. and Steriade M. The reticular nucleus revisited: intrinsic and network properties of a thalamic pacemaker. *Prog. Neurobiol.*, **75**: 125-141, 2005.

Grenier F., Timofeev I., Steriade M. Focal synchronization of ripples (80-200 Hz) in neocortex and their neuronal correlates. *J. Neurophysiol.*, **86**: 1884-1898, 2001.

Grenier F., Timofeev I., Crochet S., Steriade M. Spontaneous field potentials influence the activity of neocortical neurons during paroxysmal activities in vivo. *Neuroscience*, **119**: 277-291, 2003.

Kreindler A. and Steriade M. La physiologie et la Physiopathologie du Cervelet. Paris, Masson, 1958.

Kreindler A., Steriade M., Zuckerman E. The relationship between cortical and peripheral effects of cerebellar stimulation in the cat. *Brain*, **81**: 348-353, 1958.

Leresche N., Jassik-Gerschenfeld D., Haby M., Soltesz I., Crunelli V. Pacemaker-like and other types of spontaneous membrane potential oscillations of thalamocortical cells. *Neurosci. Lett.*, **113**: 72-77, 1990.

Llinas R. and Jahnsen H. Electrophysiology of mammalian thalamic neurones in vitro. *Nature*, **297**: 406-408, 1982.

McCormick D.A. and Pape H.C. Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. *J. Physiol.*, **431**: 291-318, 1990.

Moruzzi G. and Magoun H.W. Brain stem reticular formation and activation of the EEG. *Electroencephalogr. Clin. Neurophysiol.*, **1**: 455-473, 1949.

Neckelmann D., Amzica F., Steriade M. Spike-wave complexes and fast components of cortically generated seizures. III. Synchronizing mechanisms. *J. Neurophysiol.*, **80**: 1480-1494, 1998.

Nita D.A., Steriade M., Amzica F. Hyperpolarisation rectification in cat lateral geniculate neurons modulated by intact corticothalamic projections. *J. Physiol.*, **552**: 325-332, 2003.

Nita D.A., Cissé Y., Timofeev I., Steriade M. Increased propensity to seizures after chronic cortical deafferentation in vivo. *J. Neurophysiol.*, **95**: 902-913, 2006.

Nita D.A., Cissé Y., Timofeev I., Steriade M. Waking-sleep modulation of paroxysmal activities induced by partial cortical deafferentation. *Cereb. Cortex*, **17**: 272-283, 2007.

Siegel J. The Discovery of the Ascending Reticular Activating System. In: *The Neural Control of Sleep and Waking*. Springer, 2002.

Steriade M. and Deschênes M. Inhibitory processes and interneuronal apparatus in motor cortex during sleep and waking. II. Recurrent and afferent inhibition of pyramidal tract neurons. *J. Neurophysiol.*, **37**: 1093-1113, 1974.

Steriade M., Deschênes M., Oakson G. Inhibitory processes and interneuronal apparatus in motor cortex during sleep and waking. I. Background firing and responsiveness of pyramidal tract neurons and interneurons. *J. Neurophysiol.*, **37**: 1065-1092, 1974.

Steriade M., Oakson G., Diallo A. Reticular influences on lateralis posterior thalamic neurons. *Brain. Res.*, **131**: 55-71, 1977.

Steriade M., Kitsikis A., Oakson G. Thalamic inputs and subcortical targets of cortical neurons in areas 5 and 7 of cat. *Exp. Neurol.*, **60**: 420-442, 1978.

Steriade M. Mechanisms underlying cortical activation: Neuronal organization and properties of the midbrain reticular core and intralaminar thalamic nuclei. In: Pompeiano O. and Ajmone Marsan C. (Eds.) *Brain Mechanisms and Perceptual Awareness*. New York, Raven Press, 1981.

Steriade M. and Deschênes M. The thalamus as a neuronal oscillator. *Brain Res.*, **320**: 1-63, 1984.

Steriade M., Datta S., Pare D., Oakson G., Curro Dossi R.C. Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *J. Neurosci.*, **10**: 2541-2559, 1990a.

Steriade M., Paré D., Datta S., Oakson G., Curro D.R. Different cellular types in mesopontine cholinergic nuclei related to ponto-geniculo-occipital waves. *J. Neurosci.*, **10**: 2560-2579, 1990b.

Steriade M., Dossi R.C., Nuñez A. Network modulation of a slow intrinsic oscillation of cat thalamocortical neurons implicated in sleep delta waves: cortically induced synchronization and brainstem cholinergic suppression. *J. Neurosci.*, **11**: 3200-3217, 1991.

Steriade M., Contreras D., Curro D.R., Nuñez A. The slow (< 1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks. *J. Neurosci.*, **13**: 3284-3299, 1993a.

Steriade M., Nuñez A., Amzica F. A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J. Neurosci.*, **13**: 3252-3265, 1993b.

Steriade M., Nuñez A., Amzica F. Intracellular analysis of relations between the slow (< 1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. *J. Neurosci.*, **13**: 3266-3283, 1993c.

Steriade M. and Amzica F. Slow sleep oscillation, rhythmic K-complexes, and their paroxysmal developments. *J. Sleep. Res.*, **7** Suppl 1: 30-35, 1998.

Steriade M., Amzica F., Neckelmann D., Timofeev I. Spike-wave complexes and fast components of cortically generated seizures. II. Extra- and intracellular patterns. *J. Neurophysiol.*, **80**: 1456-1479, 1998.

Steriade M. In: Squire L.R. (Eds.) *The History of Neuroscience in Autobiography*. Elsevier Academic Press, 2004.

Steriade M. and Paré D. Gating in cerebral networks. Cambridge University Press, 2007.

Timofeev I. and Steriade M. Fast (mainly 30-100 Hz) oscillations in the cat cerebellothalamic pathway and their synchronization with cortical potentials. *J. Physiol.*, **504** (Pt 1): 153-168, 1997.

Timofeev I. and Steriade M. Cellular mechanisms underlying intrathalamic augmenting responses of reticular and relay neurons. *J. Neurophysiol.*, **79**: 2716-2729, 1998.

Timofeev I., Grenier F., Steriade M. Contribution of intrinsic neuronal factors in the generation of cortically driven electrographic seizures. *J. Neurophysiol.*, **92**: 1133-1143, 2004.