

Giuseppe Moruzzi, experimental epilepsy and reticular homeostasis: the French connection

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ABSTRACT

This is a brief history of the connection between Giuseppe Moruzzi and the French scientists at time when the EEG method was an important tool for both, neurologists and neurophysiologists, while cellular electrophysiology was only starting. A special interest will be given to the work of Moruzzi on the experimental epilepsy and his relative monograph, "L'epilessia Sperimentale" (1946) translated in French in 1950. This monograph started the connection between Moruzzi and French clinicians leading to the development of human and animal researches on epilepsy in France. Successively, the discovery of the "Ascending Reticular System" by Moruzzi and Magoun, (1949) raised a connection with already established scientists having intellectual relations with Moruzzi, exchanging theories and working hypotheses on the mechanism of sleep and wakefulness. During this period the Paul Dell's concept of "Reticular Homeostasis" was achieved.

Key words

History • Giuseppe Moruzzi • French Neurology and Research • Epilepsy • Reticular homeostasis

Introduction

It is definitely recognised that Giuseppe Moruzzi had a wide influence on the research of foreigner countries very early on his career of scientist. We will describe his relations with the French scientists and clinicians and will try to understand whether the scientific interest was reciprocal and whether a long term benefit occurred. We chose to study an early period, the 1940th to 1960th, which include World War II, a period of low development of science in Europe. The subjects of investigations concern the epileptic activities and the Activating Reticular System (ARS), the former attracted the interest mostly of clinicians, the latter of scientists. While ARS received much attention since the 50th (see Rossi and Zanchetti, 1957), much less has been written about epilepsy. Therefore a special

interest will be attached to this research subject. We will briefly recall those parts of the scientific training of Moruzzi and of his own researches which will be useful for a better understanding of the French connection on epilepsy. We then describe the reciprocal connection of Moruzzi with French clinicians on epilepsy research, before and after the discovery of ARS. We will terminate on the connection, again reciprocal, with French scientists on the ARS.

The documents that we have consulted for the present work are the originals. We have also consulted the collection of letters addressed to Moruzzi, classified and donated by Paolo Moruzzi. Of course we also used our own memories (we were respectively pupils of G. Moruzzi, 1910-1986, of H. Gastaut, 1915-1995 and of P. Dell, 1915-1976) and those of some colleagues.

The training of Giuseppe Moruzzi

Moruzzi secondary school and family education (see Moruzzi G., 2010 and Moruzzi P., 2010) was oriented on humanities. He learned French language and literature very early and he enjoyed tourism in France. Later on, his relations with French scientists were facilitated. We should notice however that he never had with France the scholar or collaborative type of relations that he entertained with scientists of other countries. Since 1929, with the work of Hans Berger (1873-1941) (see Gloor, 1969) who recorded the brain activities in Man normal or affected by various brain pathologies, the electroencephalography (EEG) became a new discipline. It had a rapid expansion and was considered a very promising method for diagnostic in clinic and for investigation in neurophysiology. An idea of the advancement of the EEG interest in different countries is given by the international congress held in London in 1947. In Italy however the use of the EEG was delayed compared to other countries and the Italian EEG Society was born only after that congress (Moruzzi, 1949). After his first training in biochemistry and neuroanatomy, Moruzzi became interested in cerebellar physiology very early. Frédérique Bremer (1892-1982) appreciated his cerebellar work and invited him to his laboratory to implement his research with the tools of electrophysiology. However, arriving in Bruxelles in 1937, he found that Dow was already there, working in cerebellar physiology with Bremer. Thus he started a kind of self-initiation to electrophysiology in the laboratory of Bremer. His first research project consisted in studying the electro-cortical activity during hypoglycemia and epileptic manifestations. The idea was to combine biochemistry and bioelectricity: “Nous pensons que l’activité spontanée est un index assez fidèle du métabolisme cortical” (Moruzzi, 1939). Some 40 years later, Sokoloff et al. (1977) described the method of glucose metabolism to visualise the brain activity. Moruzzi also described facilitation and propagation of the epileptic discharges recording EEG activity. Essentially, he used the method of Baglioni and Magnini (1909) consisting in evoking clonus by the strychninization of the motor cortex and that of evoking Jacksonian seizures (starting with localized motor jerks corresponding to a motor cortex focus and leading to generalized convulsions)

by cortical faradisation. That was 10 years after the first EEG report on man by Berger and 3 years after the first EEG report on animal reflex epilepsy (RE) by Gozzano (1935). RE is a type of epilepsy which need a particular stimulus to precipitate seizures.

In 1938, in his way from Bruxelles to Cambridge, he spend a few days in Paris. There he had his first contact with the French physiology, while he visited the laboratory of Pieron at the College de France where Alfred Fessard (1900-1982) was working.

During the academic year 1938-39, he was initiated to the electrophysiological technique of single unit recording in the pyramidal tract with Edgar Douglas Adrian (1889-1977) in Cambridge. The contribution of Moruzzi for the identification of the activity of pyramidal fibres was definitely essential (Moruzzi G., 2010). Applying again the method of Baglioni and Magnini, they found that the pyramidal units discharge in bursts of very high frequency up to 1000/sec during strychnine clonus, while the frequency for normal movement was no more than 60/sec. (Adrian and Moruzzi, 1939). In addition to the general physiological interest raised by recording identified unit activities from the central nervous system of mammals, this research opened the investigations of epileptic activities at the neuronal scale. At the end of his first year in Cambridge, while he was in Holland for a meeting, he rushed home because the II World War started with Poland invasion in September 1939. We identify this moment as the end of his training in research.

Moruzzi’s epilepsy research before the French connection

“Ritornando in Italia, nel settembre 1939, non prevedo che sarei stato costretto a interrompere la ricerca elettrofisiologica per un periodo di ben 9 anni. Per tutto il periodo della guerra, dal 1939 al 1945, e per il triennio successivo (1945-48) non vi fu infatti alcuna possibilità di acquistare gli strumenti necessari a questo tipo di ricerca” (Moruzzi G., 2010).

Nevertheless, during this period, Moruzzi continued to work in University of Bologna (than Siena, Parma, Ferrara) and for two years in Roma during his war service. Combining his knowledges on cerebellar physiology and epileptiform activities and using the only available myographic techniques, he obtained pioneer results, namely the first indirect

demonstration of a cerebello-cortical inhibition (see Dow and Moruzzi, 1958).

Two publications concerning the epilepsy research have been the significant sign that catalyzed the French connection. First, when Moruzzi was called in Roma to serve at the *Direzione Generale di Sanità Militare, Laboratorio di Biologia e Fisiopatologia* he wrote a review article with his captain on the problems of pathogenesis and diagnostic in human epilepsy (de Niederhausern and Moruzzi, 1942). Moruzzi was not interested in practicing medicine (Moruzzi G., 2010), then why working on humans? He explained that a consistent number of symptomatic epilepsies resulted from war trauma and that EEG investigation was a successful tool for the interictal identification of the focus epilepticus. “Nostro obiettivo è di gettare un ponte tra indagine sperimentale e osservazione clinica” he says. We are not aware of any comment on his motivation to write this review neither we know about his ideological position during these two years. We have two possible interpretations: his desire to accomplish the duty to which he was appointed and his duty to claim the importance of developing the clinical EEG method in Italy against the difficulties imposed by the regime, “avevo sempre detestato il fascismo” he says in his memories.

The second publication is a book, *L'Epilessia Sperimentale*. This is an important and exhaustive monograph which was more the result of an intense meditation and bibliographic study on epilepsy than a report of several years of his own researches. It appeared in 1946 (Moruzzi, 1946) just after the end of the war, indicating that thinking, elaborating and writing the manuscript occupied Moruzzi during the war time. With this publication started the French connection.

In synthesis, the outstanding contribution of Moruzzi on epilepsy research was two fold: he initiated the cellular research of the paroxysmal discharges with Adrian; he is the founder of the electrophysiology applied to the pathogenesis of epilepsies.

The experimental epilepsy and the connection with French clinicians

The personal work of Moruzzi was performed with the experimental method of Baglioni and Magnini which we consider to be the precursor of the REs.

While strychnine and RE activation were used by physiologists as a method for the functional exploration of the nervous system, they also incremented the interest for clinical researches.

We have identified two waves of French clinicians, mostly epileptologists, all electroencephalographers, that were influenced by the investigations and the personality of Moruzzi in the hope of developing the human experimentation with the EEG method. The first is clearly related to the publication of the *Epilessia Sperimentale*, the second to the discovery of the ARS.

The first wave

Professor Hermann Fischgold (1899-1982) was a roumenian physician emigrated in France in 1929. He created a department of Neuroradiology at Hôpital de la Pitié in Paris and was one of the founder of the EEG in France. He happened to be in the laboratory of Bremer and had the opportunity of reading the monograph of Moruzzi. He immediately understood how important it could be for the physicians. He asked Moruzzi to send a copy and to participate to the second French EEG meeting to be held in 1948, to talk about it. He asked permission to have the book translated into French and updated in order to catch up with the war unpublished investigations. Moruzzi accepted and this started a collegial exchange of letters, visits, seminars with Fischgold which lasted several years. To illustrate the interest of the EEG for the French epileptologists, we mention the title of the conference of Fischgold in Parma: “L’EEG peut elle fixer les frontières de l’épilepsie?”.

Meanwhile many other clinicians were interested in Moruzzi’s investigations and became real admirers of his work and personality. In the collection of letters we find A. Remond, J.L. Parrot, L. Binet and D. Cordier as electroencephalographers. Of particular interest are the letters of Henry Gastaut, founder of epileptology in Marseille, who was actively trying to raise Moruzzi’s attention in inviting him to Marseille. The two men had very different personalities, they build up nonetheless a tight long lasting collegiality and friendship. Very likely, Gastaut was attracted by the charisma of Moruzzi while Moruzzi was fascinated by the passionate imagination of Gastaut.

The first wave culminated in 1950 with the publication of *L'Epilepsie Experimentale*, the translation of

Moruzzi's monograph for which he performed a consistent work of updating thus becoming the reference book for epileptologists in France (Moruzzi, 1950). While the epileptic manifestations were described way before the EEG was invented and routinely used, the merit of Moruzzi has been to expand the investigations towards electrophysiological methods. We should notice however that the last part of the book concerning the human epilepsy was totally omitted in the French translation, why we do not know. The question is particularly intriguing since the translation had been asked by clinicians and the purpose of the original monograph was still standing. Moruzzi's general ideas concerning the pathogenesis of the epileptic seizures formulated after a careful evaluation of his and other's investigation, remain essentially valid up to now. We cannot comment the entire monograph, here we only mention few points.

Concerning the motor seizures, while for Mettler (Smith et al., 1940) the clonic contraction was the result of a rhythmic proprioceptive autogenic inhibition, for Moruzzi, the tonic and clonic epileptic contractions are essentially the same, an exhaustion of the neurones preventing spike emission, continuous during the tonic phase and intermittent during the clonic phase. He calls this mechanism an "intrinsic phenomenon of exhaustion" and we now know that the recurrent rhythm of the epileptic bursts is indeed the result of intrinsic cellular mechanisms. Moreover, Moruzzi explains that "le mode de réponse du neurone apparait fondamentalement semblable, quelque soit la cause et le mécanisme qui en déchaînent l'activité convulsive". Up to now there are no objections to this, at least not for the neuronal types tested.

The origin of the epileptic seizures, cortical and/or sub-cortical was an unsolved problem and is still a controversial one for the clinicians. The method of experimentally inducing epileptic manifestations was almost exclusively cortical, essentially strychninization and faradization whereas the method of detecting epileptic manifestations was both, cortical (EEG and electrocorticography) and peripheral (electrophysiology of the pyramidal tract and electromyography). In other words, the experimentalist as well as the physician could directly see and analyse only the classic cortico-motor activity and nothing in between. Therefore a cortical ori-

gin of the epileptic seizures was the predominant belief. Nevertheless, "Il ne peut exister un accès épileptique purement pyramidal sans participation extrapyramidale", wrote Moruzzi. With this sentence he admits the participation of subcortical structures interposed between cortex and spinal cord. Reading carefully, it appears that he also recognises "l'existence d'accès épileptiforme purement sous-corticaux", taking for demonstration only the experiments (all performed in decorticated animals) of Samaja (1904) on transcranial faradization, the famous dog of Pavlov who died in status epilepticus (Speranski, 1935) and the convulsive activity induced by injection of strychnine (Moruzzi, 1942). Following the centrencephalic theory (see next section), seizures start sub cortical and secondarily involve the cortex. Recently however, it has been demonstrated that RE seizures are induced in rodents and birds with no sign of convulsive cortical activities (see Naquet and Valin, 1998).

The problem of predisposition to epilepsy was clearly revealed first by Amantea (1921) since sensory stimulation precipitated seizures only in 25% of the animals tested with cortical strychninization. Some 30 years later Moruzzi dedicates a chapter of his monograph to discuss this problem. His theoretical position was that the clonus of Baglioni and Magnini does not concern predisposition, since epileptiform manifestations are obtained in every animal. The difference with the Amantea epilepsy would be quantitative, a larger number of neurons being involved in the sensory-induced seizures. Moruzzi accepts the old interpretation of Amantea following which the RE seizures needs three factors, one predisposing (constitutional), one preparing (strychninization) and one starting (sensory stimulation). Nevertheless, while for Amantea predisposition is a problem of etiology, for Moruzzi is a problem of pathogenesis: "Chez l'animal non prédisposé les neurones normaux doivent présenter une impossibilité insurmontable à devenir épileptique simplement par l'effet d'un bombardement d'influx nerveux", this idea became obsolete with the method to assess epilepsy called kindling (Goddard, 1967) with no need for predisposition. On his reasoning Moruzzi analyses almost exclusively REs, reviews the predisposed animal species and the candidate factors that could be responsible for it. However, he omits to mention the

RE discovered in 1939 (Morgan and Morgan) on a predisposed strain of rodents in which the auditory stimulation precipitates seizure with no strychnine so ever, with no preparing factor. In a preceding chapter although he recognizes the absence of strychninization in those rats, he classifies them as non predisposed. Moreover, he did not mention in his monograph, nor in the successive publications, that in 1947 Gastaut described the photogenic RE in predisposed man (see Beaumanoir et al., 1989), a fundamental discovery in the chapter of the REs. For a modern researcher it appears strange that Moruzzi never mentioned a possible inherited factor. We have to wait decades before the words genetically determined could be evoked for predisposition as, at that time, genetic was only green and yellow peas.

The second wave

Before the publication of his French monograph, Moruzzi went to Chicago and worked with Horace Winchell Magoun (1907-1991). They described the ARS (Moruzzi and Magoun, 1949), a discovery which gave to the authors a large international visibility. One year later Moruzzi became director of the *Istituto di Fisiologia* in Pisa build on Roman ruins (Pompeiano, 1999). He rapidly built up efficient research laboratories and started accepting postdoctoral fellows. In the five following years Moruzzi received three physicians from France. His research projects now concern the ARS. French epileptologists are also interested in ARS as part of the centrencephalic system. The conception of a "Centrencephalic Integrating System" responsible of certain types of epilepsy was postulated by Penfield since 1938 and located in the non specific thalamus (see Penfield and Jasper 1954). Successively, the recently discovered ARS was considered a substantial part of the system.

Catherine Lairy-Bounes from the EEG laboratory of Sainte-Anne was the first foreigner postdoctor in 1951. In collaboration with the local staffs, her project was to test the influence of the ARS-induced arousal on strychnine spikes. They were either blocked or facilitated depending on the cortical state of excitability (Lairy-Bounes et al., 1952; Lairy-Bounes and Arduini, 1952). While these results showed the involvement of the ARS in triggering epileptic activities as predicted by the centrencephalic theory, they also revealed a variable

reticulo-cortical influence thus preceding the idea of "reticular homeostasis" (see next section).

In 1952 went to Pisa Robert Naquet (1923-2005), an already outstanding epileptologist, scholar of Gastaut, partially working on research and occasionally a painter. Working with Amilcare Mollica (1924-2011) on single unit recording in cat, they described the epileptic discharges of cerebellar cortex (Mollica and Naquet, 1953) and made the first demonstration of the cerebellar inhibitory influence on bulbo-reticular neurons (Mollica et al., 1953). After Pisa he had a second training period on ARS with Magoun at UCLA. Back to France, he was more and more interested in experimental epilepsy and became director of a CNRS laboratory first in Marseille, then in Paris. Meanwhile more sophisticated and multidisciplinary techniques were developed to build experimental models of different kind of epilepsy. In 1966 Naquet discovered in Casamance colonies of Baboons affected by photic reflex epilepsy in proportion clearly indicating a genetic inheritance (Killam et al., 1967). Postulating a genetic origin of the REs predisposition, his interest was to identify the mutation in the Baboon. Unfortunately, due to political reasons in Casamance, he could not collect more subjects. We have to wait the late 80th to start approaching epilepsy with molecular tools. From 1989 to the end of his life, Naquet worked in an avian model of genetic epilepsy, the Fepi strain of chicken affected by photic and acoustic REs, raising the interest of physiologists, embryologists, geneticists and molecular physiologists for the study of this model (see Batini et al., 1996). At present, there is a profusion of genes found involved in various epileptic syndromes (see Lucarini et al., 2007; Reid et al., 2009). For the REs with genetically or familiarly transmitted predisposition, we dispose of only one model, the Fepi, in which the transmission is monogenic and the gene has been localized and identified (Douaud et al., 2011). These results were achieved by French teams under the direct influence of Naquet and very likely under the indirect influence of the far back work of Moruzzi on REs.

In 1955, one of us, A.B., also an epileptologist from Marseille, was the last French postdoctor of Moruzzi. Her project with the local staff consisted on understanding the relative participation of extrinsic and intrinsic reticular mechanisms maintaining

wakefulness (Roger et al., 1956), a work that has been somehow the precursor of the insomniac pretrigeminal midpontine preparation (Batini et al., 1958; see also Berlucchi, this volume). In a second project, she found the off-effect on strychnine spike upon optic nerve stimulation (Arduini et al., 1955) which was later interpreted as the mechanism for the scotogenic RE in man (Beaumanoir, 1983). After Pisa she continued to be a very active epileptologist particularly competent on REs. Recently, in her memories (Beaumanoir, 2010) she remembers Moruzzi as a “delicious man” and explains that when she was prosecuted for participation to the Algerian resistance, Moruzzi and his co-workers, as well as Fessard and his co-workers, sent a message on her favour to the president of the tribunal.

We must mention that the second wave of the French connection moved in both directions. Two Italian postdoctoral fellows were received by Gastaut in Marseille to learn human EEG. The first was Mario Parma (1924-1999), a brilliant neurologist who spent few months in 1954 and later (1972) became director of the *Clinica Neurologica* in the University of Parma. The second was one of us, C.B. who was accepted in 1961-62 to work at the center for epileptic children, *Centre Saint Paul*, and at the new research laboratory of *Institut National d'Hygiène* (INH) both directed by Gastaut. There she learned clinical EEG; developed the all night sleep research in normal and pathological subject (Batini et al., 1962a,b) investigated with Michel Imbert from Buser's laboratory temporally visiting the INH, the circadian organization of the midpontine preparation, the results of which were then taken on by Michel Jouvet who was interested in REM sleep (see Jouvet, 1962). Later, kindly invited by Pierre Buser, she integrated CNRS and remained permanently in Paris.

While Moruzzi abandoned the experimental epilepsy (his last article appeared in 1955 (Moruzzi 1955) on oxigene-induced convulsions) Gastaut and his teams remained interested in both, experimental and clinical epilepsies with special interest for the REs. In 1989 Beaumanoir, Gastaut and Naquet were editors together of the international symposium held in Geneva on “Reflex Seizures and Reflex Epilepsies”. Gastaut remained attached to the centrencephalic theory of Penfield identifying the ARS as a driver of the generalized epilepsies (Gastaut, 1987).

The Activating Reticular System and the connection with French scientists

There is no need to describe the discovery of the ARS and its impact on researches performed during the following years, many others have already done that. We will only mention what concerns the French connection. The discovery of the ARS raised the interest of two groups of physiologists, one directed by Alfred Fessard and one directed by Paul Dell.

Fessard (see Barbara, this volume), ten years older than Moruzzi, was director of a large laboratory, the *Institut Marey*, since 1939. He had already attracted many French and foreigner scientists and the research projects were multiple and diversified, from cellular physiology in invertebrate to psychophysiology and psychology in man. Moruzzi had a very high opinion of Fessard as a scientist and as a man. They shared something very important they both were the promoters of the modern physiology respectively in France and in Italy. Together they entertained intellectual exchanges including visits, seminars, meetings.

Some of the collaborators of Fessard were routinely using glass microelectrodes for neuronal recording taking advantage of the de Fonbrune microforge originally built for other types of researches. Moruzzi was interested to apply the technique in his laboratory and sent Mollica, the most competent in unit recording among his assistants, to Marey to learn it and order the French instrument. Not long after, Pierre Buser went to Moruzzi's laboratory to help settle the experiments. Buser was an already well known researcher who made the first intracellular record in Torpedo (Albe-Fessard and Buser, 1952). However he could not do very much since the microforge was blocked at the custom! Few years later, Moruzzi and Fessard materialized their intense intellectual communication in organizing together, with the uncountable Herbert Jasper (1906-1999), the first IBRO meeting in Pisa. It was an historical colloquium on “Brain Mechanisms” held in 1961 and published in 1963 (Moruzzi et al., 1963), attended by international researchers of which however about half were French and Italians.

Paul Dell (see Tyc Dumont, 1978) was in Chicago in 1949 collaborating with McCulloch together with the recently founded interdisciplinary cybernetics

group having a new way to approach the nervous system. He was definitely marked by the work of McCulloch and in the same time visited Magoun and followed the discovery of the ARS. Back to France in 1952, he founded with Marthe Bonvallet (1908-1978) an electrophysiology laboratory in Hôpital Henry Roussell, part of the asile Saint-Anne (Tyc-Dumont 2008). Soon after joined André Hugelin from Saint-Anne and one of us, S T-D, who was back from the Maudsley psychiatric laboratory of GW Harris in London. They all remained together for 15 solid years, mostly working on the reticular system, with collaboration of French and foreigners scientists. The two teams of Moruzzi and Dell performed independently their investigations exchanging however ideas and working projects, confronting the obtained data during meeting and seminars. Working in parallel with overlapping projects they both participated to the theory of the “Reticular Homeostasis”, homeostasis according to the definition of Cannon, build up by Dell and presented to the first IBRO meeting (Dell, 1963): it is the contribution of the two teams to the study of the relationship between the “milieu intérieur” (see Claude Bernard, 1865), the cerebral cortex and the reticular formation which finally resulted in the theory of the “Reticular Homeostasis” a concept which was, following Moruzzi, “rigorously defended” by Dell. Exemples of such parallel researches are the observations on the humoral activation of the ARS (Bonvallet et al., 1954; Bradley and Mollica, 1958), those on the synchronizing bulbotreticular structures (Bonvallet and Bloch, 1961; Magnes et al., 1961) and of particular interest the demonstration that one of the function of the ARS is the “mise en condition” of the sensory-motor systems (Tyc-Dumont, 1964). Before closing this chapter we like to mention that Marthe Bonvallet published a monograph on *Nervous System and Wakefulness* (1966) translated into Italian as *Veglia e sonno* (1967). Bonvallet was a very gifted scientific worker whose collaboration to the theory of “Reticular Homeostasis” was determinant. Her book is excellent but surprisingly was not very popular. Not ignored however neither by Fessard nor by Moruzzi, as they both forwarded respectively the French and the Italian publication. With them we believe that:

“Nous devons à cette école la découverte de tout un ensemble de faits très importants, ainsi que

leur interprétation dans le meilleur esprit d’une Physiologie soucieuse de reconnaître, à travers le détail des processus, les fonctions d’intégration et de régulation qui sont à la base de l’unité et de la stabilité des organismes vivants” (A. Fessard)

“Il libro di Marthe Bonvallet è permeato da quella visione unitaria delle funzioni nervose che ha ispirato anche le ricerche di Dell, dell’autrice e di vari ricercatori appartenenti allo stesso laboratorio. Meccanismi umorali e nervosi, funzioni somatiche e vegetative, il sistema nervoso ci appare come un tutto unico” (G. Moruzzi).

References

- Adrian E.D. and Moruzzi G. Impulses in the pyramidal tract. *J. Physiol. (London)*, **97**: 153-199, 1939.
- Albe-Fessard D, and Buser P. Réception intracellulaire de l’activité d’un neurone des lobes électriques de Torpedo marmorata. *C.R. Acad. Sci.*, **235**: 1688-1690, 1952.
- Amantea G. Sur les rapport topographiques entre l’écorce cérébrale et la sensibilité cutanée chez le chien. *Arch. Int. Physiol.*, **18**: 474-483, 1921.
- Arduini A., Magni F., Roger A. Effet de la stimulation répétitive sur les ondes strychniques du cortex cérébrale. *J. Physiol. (Paris)*, **47**: 849-856, 1955.
- Baglioni S. and Magnini M. Azione di alcune sostanze chimiche sulla zona eccitabile della corteccia cerebrale del cane. *Arch. Fisiol.*, **6**: 240-249, 1909.
- Batini C., Moruzzi G., Palestini M., Rossi G.F., Zanchetti A. Persistent patterns of wakefulness in the pretrigeminal midpontine preparation. *Science*, **128**: 30-32, 1958.
- Batini C., Fressy J., Gastaut H. A propos du sommeil nocturne chez le sujet normal. *Rev. Neurol.*, **106**: 221-224, 1962a.
- Batini C., Criticos A., Fressy J., Gastaut H. A propos du sommeil nocturne chez les sujets présentant une épilepsie à expression EEG bisynchrone. *Rev. Neurol.*, **106**: 221-224, 1962b.
- Batini C., Teillet M.-A., Naquet R., Le Douarin N. Brain chimeras in birds: an application to study a genetic form of reflex epilepsy. *Trends In Neurosci.*, **19**: 246-252, 1996.
- Beaumanoir A. Infantile epilepsy with occipital focus and good prognosis. *Eur. Neurol.*, **22**: 43-52, 1983.
- Beaumanoir A. *Le feu de la memoire*. Paris, Bouchene, pp. 253, 2010.

- Beaumanoir A., Gastaut H., Naquet R. *Reflex seizures and reflex epilepsy*. Geneva, Medecine & Hygiene, 1989.
- Bernard C. *Introduction à l'étude de la médecine expérimentale*. Paris, Bailliere J.B., pp. 400, 1865.
- Bonvallet M., Dell P., Hugelin A. Influence de l'adrénaline sur le contrôle réticulaire des activités corticale et spinale. *J. Physiol. (Paris)*, **46**: 262-265, 1954.
- Bonvallet M. and Bloch V. Bulbar control of cortical arousal. *Science*, **133**: 1133-1134, 1961.
- Bonvallet M. *Système nerveux et vigilance*. Paris, Presse Universitaire de France, pp. 131, 1966.
- Bonvallet M. *Veglia e sonno*. Torino, Universale Scientifica Boringhieri, pp. 154, 1967.
- Bradley P.B. and Mollica A. The effect of adrenaline and acetylcholine on single unit activity in the reticular formation of the decerebrate cat. *Arch. It. Biol.*, **96**: 168-186, 1958.
- Dell P. Homeostasie reticulaire et reactivite critique. In: Moruzzi G., Fessard A., Jasper H.H. (Eds.), *Brain mechanisms. Progress in Brain Research I*, Amsterdam, Elsevier, I: 82-114, 1963.
- De Niederhausern A. and Moruzzi G. Problemi patogenetici e diagnostici nello studio dell'epilessia umana. *Giorn. Med. Mil.*, **90**: 3-31, 1942.
- Douaud M., Feve K., Pituello F., Gourichon D., Boitard S., Leguern E., Coquerelle G., Vieaud A., Batini C., Naquet R., Vignal A., Tixier-Boichard M., Pitel F. Epilepsy caused by an abnormal alternative splicing with dosage effect of the SV2A gene in a chicken model. *PLoS ONE*, **6**: e26932, 2011.
- Dow R.S. and Moruzzi G. *The physiology and pathology of the cerebellum*. Minneapolis, University of Minnesota Press, pp. VII-675, 1958.
- Gastaut, H. Forward to: Fromm G.H., Faingold C.L., Browning R.A., Burnham W.M. *Epilepsy and the reticular formation: the role of the reticular core in convulsive seizures*. Pp. XI-XII, 1987.
- Gloor P. *Hans Berger on the electroencephalography of men*. *EEG Clin. Neurophysiol., Suppl.*, **28**: 350, 1969.
- Goddard G.V. Development of epileptic seizures through brain stimulation at low intensity. *Nature*, **214**: 1020-1021, 1967.
- Gozzano M. Ricerche sui fenomeni elettrici della corteccia cerebrale. *Riv. Neurol.*, **8**: 212-261, 1935.
- Jouvet M. Recherches sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. *Arch. It. Biol.*, **100**: 125-206, 1962.
- Killam K.F., Killam E.K., Naquet R. An animal model of light sensitive epilepsy. *EEG Clin. Neurophysiol.*, **22**: 497-513, 1967.
- Lairy-Bounes G.C. and Arduini A. Action de la stimulation électrique de la formation réticulaire du bulbe et des stimulations sensorielles sur les ondes strychniques corticales chez le chat "encéphale isolé". *EEG Clin. Neurophysiol.*, **4**: 503-512, 1952.
- Lairy-Bounes G.C., Parma M., Zanchetti A. Modifications pendant la réaction d'arrêt de Berger de l'activité convulsive produite par l'application locale de strychnine sur le cortex cérébral du lapin. *EEG Clin. Neurophysiol.*, **4**: 495-502, 1952.
- Lucarini N., Verrotti A., Napolioni V., Bosco G., Curatolo P. Genetic polymorphisms and idiopathic generalized epilepsies. *Pediatric Neurol.*, **37**: 157-164, 2007.
- Magnes J., Moruzzi G., Pompeiano O. Synchronization of the EEG produced by low-frequency electrical stimulation of the region of the solitary tract. *Arch. Ital. Biol.*, **99**: 33-67, 1961.
- Mollica A and Naquet R. Activité convulsive et silence électrique dans l'écorce cérébelleuse. *EEG Clin. Neurophysiol.*, **5**: 585-587, 1953.
- Mollica A., Moruzzi G., Naquet R. Décharges réticulaires induites par la polarisation du cervelet: leurs rapports avec le tonus postural et la réaction d'éveil. *EEG Clin. Neurophysiol.*, **5**: 571-584, 1953.
- Morgan C.T. and Morgan J.D. Auditory induction of an abnormal pattern of behaviour in rats. *J. Comp. Psychol.*, **27**: 505-560, 1939.
- Moruzzi G. Etude de l'activité électrique de l'écorce cérébrale dans l'hypoglycémie insulinaire et dans différentes conditions modifiant le métabolisme des centres. *Arch. Int. Physiol.*, **48**: 45-101, 1939.
- Moruzzi G. Convulsioni extrapiramidali da stricnina. *Arch. Fisiol.*, **43**: 86-108, 1942.
- Moruzzi G. *L'epilessia sperimentale*. Bologna, Zanichelli, 1946.
- Moruzzi G. and Magoun H.W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1**: 455-473, 1949.
- Moruzzi G. Commentary. *EEG Clin. Neurophysiol.*, **1**: 230, 1949.
- Moruzzi G. *L'epilepsie expérimentale*. Paris, Hermann, pp. 139, 1950.
- Moruzzi G. Les mécanismes nerveux des convulsions causées par l'oxygène. Journées Inter. Med. Sport. Milit., 21-25 juin 1954, 1955.

- Moruzzi G., Fessard A., Jasper H.H. *Brain mechanisms. Progress in brain research I*. Amsterdam, Elsevier, 1963.
- Moruzzi G. Recollections. In: Meulder M., Piccolino M., Wade N.J. (Eds.). *Giuseppe Moruzzi: Portraits of a scientist*, Pisa, ETS, pp. 41-121, 2010.
- Moruzzi, P. The unbroken thread. A family portrait of Giuseppe Moruzzi. In: Meulder M., Piccolino M., Wade N.J. (Eds.) *Giuseppe Moruzzi: Portraits of a scientist*, Pisa, ETS, pp. 147-161, 2010.
- Naquet R. and Valin A. Experimental models of reflex epilepsy. *Adv. Neurol.*, **75**: 15-28, 1998.
- Penfield W. and Jasper H.H. *Epilepsy and the functional anatomy of the human brain*. Boston, Little, Brown, 1954.
- Pompeiano O. Roman ruins in the basement of the institute of physiology of the University of Pisa. *Arch. It. Biol.*, **137**: 227-234, 1999.
- Reid C.A., Berkovic S.F., Petrou S. Mechanisms of human inherited epilepsies. *Prog. Neurobiol.*, **87**: 41-57, 2009.
- Roger A., Rossi G.F., Zirondoli A. Le rôle des afférences des nerfs crâniens dans le maintien de l'état vigile de la préparation encéphale isolé. *EEG Clin. Neurophysiol.*, **8**: 1-13, 1956.
- Rossi G.F. and Zanchetti A. The brain stem reticular formation. *Arch. It. Biol.*, **95**: 199-435, 1957.
- Samaja W. Le siège des convulsions épileptiques toniques et cloniques. *Rev. Med. Travaux du Lab. Physio. Univ. Genève*, **IV**: 49-121, 1904.
- Smith C.G., Mettler F.A., Culler E.A. The phasic response to cortical stimulation. *J. Neurophysiol.*, **3**: 182-187, 1940.
- Sokolov L. Relation between physiological function and energy metabolism in the central nervous system. *J. Neurochemistry*, **29**: 13-26, 1977.
- Speranski A.D. A basis for the theory of medicine. Moscow, Inra Cooperative Publishing Society, 417 pp., 1935.
- Tyc Dumont S. *Contribution à l'Étude du Contrôle Réticulaire des Intégrations Sensory-motrices au Cours de la Vigilance*. Paris, Thèse, pp. 151, 1964.
- Tyc-Dumont S. Paul Dell, His life and work. In: Buser P. and Rougeul-Buser A. (Eds.), *Cerebral Correlate of Conscious Experience*. Elsevier, INSERM Symp. n. 6, pp. 1-13, 1978.
- Tyc-Dumont S. Le laboratoire de neurophysiologie de l'hôpital Henri Rousselle, 1954-1964. In: Debru C., Barbara C., Cherici J.G. (Eds.), *L'essor des neurosciences, France, 1945-1975*. Paris, Hermann Editeurs, pp. 57-66, 2008.