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Summary

This article describes the history of EEG and epileptology in Geneva, characterised first by the early semiological work of Herpin in the XIXth century and, later, by the installation of one of the first 3 EEG systems in Switzerland in the beginning of the 1940'. The role of the principal actors in the field is described with a particular focus on the important increase in the epileptological and electrophysiological activity in Geneva in the past 20 years. The epilepsy surgery program, in strong collaboration with Lausanne, and the combined work of clinicians and neuroscientists have transformed EEG into a modern tridimensional neuroimaging technique. Geneva has also pioneered the combination of 3D EEG with functional MRI. The article finishes by browsing current activities and future perspectives.

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Key words: Geneva, EEG, epilepsy, history

L'histoire de l'EEG et de l'épileptologie à Genève

Cet article décrit l'histoire de l'EEG et de l'épileptologie à Genève, caractérisée tout d'abord par les travaux sémiologiques précoces de Herpin au XIX siècle puis par l'installation de l'un des 3 premiers systèmes EEG en Suisse au début des années 1940. Le rôle des acteurs principaux dans le domaine est décrit avec un intérêt particulier pour l'augmentation importante de l'activité en épileptologie et électrophysiologie à Genève dans les 20 dernières années. Le programme de chirurgie de l'épilepsie, en collaboration intense avec Lausanne et les travaux combinés de cliniciens et de neuroscientifiques ont transformé l'EEG en une technique moderne d'imagerie tridimensionnelle. Notre centre a également réalisé des travaux pionniers concernant la combinaison simultanée d'EEG et IRM fonctionnelle. L'article passe finalement en revue les activités actuelles et les perspectives d'avenir.

Mots clés : Genève, EEG, épilepsie, histoire

Die Geschichte des EEGs und der Epileptologie in Genf

Dieser Artikel beschreibt die Geschichte des EEG und der Epileptologie in Genf, zuerst charakterisiert durch das frühe semiologische Werk von Herpin im 19. Jahrhundert, später durch die Einrichtung eines der ersten drei EEG-Systeme in der Schweiz am Anfang der 1940er Jahre. Die Rolle der Hauptakteure auf diesem Gebiet wird beschrieben mit besonderem Fokus auf der wichtigen Zunahme der epileptologischen und elektrophysiologischen Aktivität in Genf in den vergangenen 20 Jahren. Das Epilepsiechirurgie-Programm in enger Zusammenarbeit mit Lausanne und die kombinierten Anstrengungen von Klinikern und Neurowissenschaftlern haben das EEG in eine moderne dreidimensionale Bildgebungstechnik verwandelt. Genf spielte auch eine Pionierrolle in der Kombination von 3D EEG mit funktionellem MRI. Am Schluss werden noch laufende Aktivitäten und Zukunftsperspektiven angesprochen.

Schlüsselwörter: Genf, EEG, Epilepsie, Geschichte

The early years

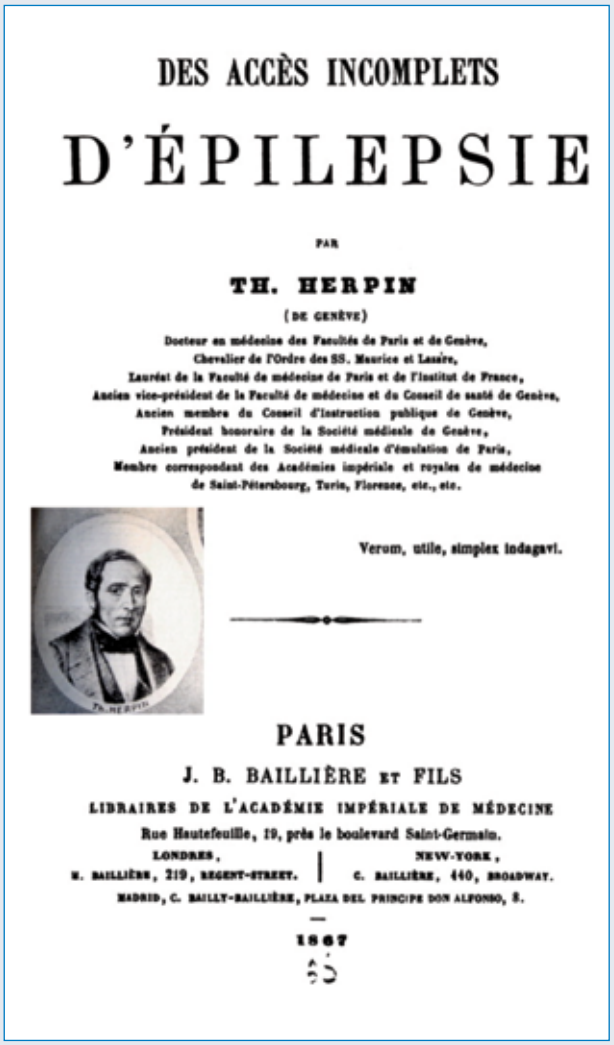
The early history of epileptology in Geneva is personalised by Théodore Joseph Dieudonné Herpin (1799-1865). Born in Lyon, France, he studied in Geneva and Paris before returning to Geneva where he practised as a medical doctor and surgeon in Geneva and the nearby city of Carouge. Besides his clinical activities, Herpin exerted several mandates for the local government as a deputy and vice-president of the "Conseil de santé" (Health Board). On top of being the founder and director of the Medical Society of Geneva (1823),

Herpin shall be remembered essentially for two of his publications that contain pioneering observations and interpretations on patients suffering from epilepsy, notably with respect to juvenile myoclonic epilepsy and to the semiology of focal onset seizures.

In the first of these works, "Du traitement et du pronostic des épilepsies", he describes 38 patients treated with monotherapies of valeriane or zinc oxyde but "never both simultaneously" (sic!). Important observations still valid today were reported, namely that seizures were controlled in half of the patients and that 26% of patients did not respond to the available treatments. Thus the concept of pharmaco-resistance was born, still valid today.

Herpin also noticed that early treatment seemed to improve seizure outcome. Herpin's greatest contribution to epileptology can be found in his work "des accès incomplets d'épilepsie" (**Figure 1**) where he provides an exquisite description of a patient with juvenile myoclonic epilepsy, using the work "commotion" to refer to myoclonic jerks:

"A l'origine du mal, la commotion ou secousse était



DES ACCÈS INCOMPLETS

D'ÉPILEPSIE

PAR

TH. HERPIN

(DE GENÈVE)

Docteur en médecine des Facultés de Paris et de Genève,
Chevalier de l'Ordre des SS. Maurice et Lazare,
Lauréat de la Faculté de médecine de Paris et de l'Institut de France,
Ancien vice-président de la Faculté de médecine et du Conseil de santé de Genève,
Ancien membre du Conseil d'instruction publique de Genève,
Président honoraire de la Société médicale de Genève,
Ancien président de la Société médicale d'émulation de Paris,
Membre correspondant des Académies impériale et royales de médecine
de Saint-Pétersbourg, Turin, Florence, etc., etc.

Verum, utile, simplex indagavi.

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1867

Figure 1: Théodore Joseph Dieudonné Herpin: "Des accès incomplets d'épilepsie", 1867

bornée à la partie supérieure du corps ; bientôt elle est devenue générale ; si l'enfant est debout ou marche, il peut tomber, mais cela est rare, s'il y a chute ; il se relève à l'instant même. Il lâche ou lance ce qu'il tient à la main, surtout à la main droite.

Le patient dit qu'il perd la vue au moment de la commotion, mais il la recouvre immédiatement après ; la mère donne à ces accidents le nom de tremblement, le père les appelle secousses.... L'attaque est précédée de deux ou plusieurs commotions (on en a observé jusqu'à neuf consécutives) dont la dernière, au moins, avec cri. Les mains se projettent en avant et la chute aurait toujours lieu si on ne retenait pas le patient ; yeux renversés en haut, rotation de la tête, rigidité générale, promptement accompagnée de convulsions cloniques, signes d'asphyxie, lèvres violettes plus tard pâleur, émission salivaire, râle guttural." (At the onset of the attack, the commotion or jerk was limited to the upper part of the body; soon it became generalised; if the child was standing or walking, fall could follow but this is rare; then the child would get up again right away, dropping or throwing whatever is in the hand, especially the right hand.The patient says that he loses eyesight during the commotion but recovers it immediately after ; the mother gives to these accidents the name of shaking, the father calls them jerks... The fit is preceded by two or more commotions (up to nine in a row were observed) and the last, at least with a scream. The hands are projected forward and the fall would always follow if the patient was not refrained; eyes turned upwards, rotation of the head, general rigidity, quickly accompanied by clonic convulsions, signs of asphyxia, purple lips, later pallor, salivary emission, guttural moan) (translated by the authors) [1].

In his work, Herpin precisely describes the semiological features "peripheral motor seizures" (Jacksonian), "visceral" (epigastric aura) "encephalic" (sensory seizures, "déjà-vu") and "concussions" (myoclonic jerks).

Herpin also introduced the concept of localisation and propagation, usually attributed to John Hughlings Jackson whose description was done later than Herpin's: « Chez la même personne, toutes les crises commencent toujours de la même manière, bien que le développement d'une crise peut par la suite varier d'une crise à une autre ». (In the same person, all seizures always start in the same way, although the development of a seizure can thereafter vary from one seizure to another) (translated by the authors) [1].

Indeed, Jackson, more often remembered in the epilepsy textbooks than Herpin, insisted on the heritage of Herpin:

« I take this opportunity of advising the younger medical neurologists to study carefully Herpin's writing on epilepsy. I have long known his valuable work "Du pronostic et du traitement curatif de l'épilepsie" (1852) but I have only recently heard of his still more valuable work "Des accès incomplets d'épilepsie" (1867) » (John Hughlings Jackson , 1899 [2]).

Figure 2: Marcel Monnier, (1907-1996), director of the „Laboratoire d'EEG clinique neurologique" and the „Laboratoire de recherche en neurophysiologie appliquée".

Figure 3: Ferdinand Morel (1888-1957), who introduced the EEG in the psychiatric hospital of Bel-Air in 1957

Electroencephalography (EEG) and modern epileptology in Geneva

In 1941, the neurophysiologist PD Dr Marcel Monnier (**Figure 2**) and the engineer Marc Marchand provided the first description of the installation of an EEG equipment in Geneva, in the Institute of Physiology. The system was based on an electrocardiogram coupled to a preamplifier and a powerful amplifier allowing the recording of electrical activity in a bipolar or monopolar montage, as proposed by Berger and Tönnies. Monnier and Marchand initially presented the localisation of head trauma using EEG. In 1952, Monnier became director of the newly created "Laboratoire d'EEG clinique neurologique" and the "Laboratoire de recherche en neurophysiologie appliquée"[3].

In 1958, Prof. François Martin took over from M. Monnier. Under his direction, Geneva partnered the University Hospital of Zurich in EEG teaching: the Swiss School of Electroencephalography and Epileptology. Between 1970-72 Martin also served as president of the Swiss Society for Clinical Neurology, founded in 1948 (as the "Schweizerische Arbeitsgemeinschaft für Elektroencephalographie") [4].

EEG also became an important instrument in Swiss psychiatric institutions, in the early 1950'. In Geneva, an EEG Laboratory was installed in 1957 by Prof. Ferdinand Morel **(Figure 3)**, a theologian, medical doctor and director of the psychiatric hospital of Bel-Air outside Geneva. Actually, close collaborations between psychiatrists Serge Mutrux, Claude Horneffer and M. Monnier already existed before 1950. The use of EEG in psychiatry was later strongly supported by Prof. Julian de Ajuriaguerra in the 1960' notably by the creation of the "Laboratoire d'EEG et de Neurophysiologie appliquée" in 1964, which included beds, equipped with EEG, for the study of sleep. This Lab was initially directed by René Tissot, a French neurologist trained in Paris notably under Alajouanine and Lhermitte [3].

In 1966 Dr Annette Beaumanoir, a French neurologist, took the lead of the EEG laboratory in the hopital cantonal of Geneva **(Figure 4)**. A. Beaumanoir had been trained in the famous epileptology school of Marseille under Henri Gastaut. She contributed to the characterisation of paroxystic occipital discharges of idiopathic focal occipital epilepsies, today referred to as "Gastaut syndrome" and "Panayiotopoulos syndrome". The arrival of A. Beaumanoir in Geneva is strongly related to her political activities. Member of the French Resistance at age 18, she was a member of the Communist Party and later supported the war for Algeria's independence ("Front National de Libération"). She became a member of the Algerian cabinet before being forced to leave the country after a coup in 1965, and found refuge in Geneva where she directed the EEG Unit until her retirement. She continued working with Gastaut, notably in descriptions of the Lennox-Gastaut syndrome with an interest in pediatric EEG, installed the first EEG-telemetry with videoscopic recordings in Switzerland (and one of the first in Europe) and also reported important observations on non-convulsive status epilepticus, "état de mal à expression confu-

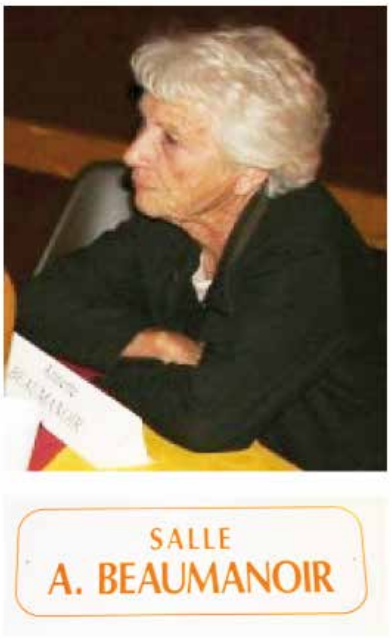

Figure 4: Annette Beaumanoir (1923*) and her „Salle Annette Beaumanoir", still perpetuating her memory in the University Hospital of Geneva.

sionnelle", together with her colleague PD Dr Josette Le Floch-Rohr.

In 1989, she was followed by Prof. Pierre Jallon, another French epileptologist, trained in Bordeaux and former director of the EEG unit of the French military hospital of Val de Grâce in Paris. Interested in epidemiology, Jallon conducted several prevalence and incidence studies in Switzerland, notably and on the incidence of status epilepticus (EPISTAR) [5], new-onset epilepsy (EPIGEN) [6] as well as similar studies in French overseas territories (EPIREUN, EPIMART). From an EEG perspective, he reported toxic-metabolic encephalopathies related to the accumulation of the antibiotic agent cefepime in patients with concomitant renal failure [7] as well as work investigating the origin of periodic lateralised discharges [8]. Jallon was also dedicated to educational aspects and destigmatisation of epileptic patients, as reflected by his activity in "l'Ecole de l'Epilepsie" and two mountaineering expeditions to 4000m summits uniting patients and epileptologists ("Sport et Epilepsie" at the Bishorn 4153 m, Valais and the Gran Paradiso 4061 m, Piedmont, **Figure 5**). Jallon witnessed the transition from ink and paper EEG to digital recordings at the very end of the XXth century. This radical evolution offered not only an easier offline clinical interpretation, but opened new avenues for EEG research.

Figure 5: Epileptic patients and epileptologists, (Pr Jallon and colleagues) after the ascension of Gran Paradiso, 2005.

Epilepsy surgery and EEG-based neuroimaging

In 1995 the Unit for Presurgical Epilepsy Evaluation was founded by Prof. Theodor Landis, head of Neurology. Its direction was given to Prof Margitta Seeck, a German epileptologist trained in Germany and Boston, USA. Under her leadership, in close collaboration with Prof. Paul-André Despland, head of the EEG laboratory in the Centre Hospitalier Universitaire Vaudois (CHUV), the presurgical evaluation unit (**Figure 6**) and the epilepsy surgery program was quickly established. A sophisticated multimodal electrophysiological and imaging platform flourished with intense collaborations with clinical experts in the Neuroradiology, Nuclear Medicine, Neuropsychology and Psychiatry as well as neuroscientists for the development and application of new imaging techniques. The surgical program is placed in the context of an intense and fruitful collaboration with the CHUV and the Institution of Lavigny (see the Lausanne contribution in this issue) defining a Geneva-Vaud epilepsy surgery program with the partnership of the surgical teams of Prof. JG Villemure, Prof. N. de Tribolet and Dr C. Pollo, followed by Prof. K. Schaller and Prof. R. Daniels, PD Dr Momjian.

The program, celebrating its 20th anniversary in 2015, currently offers all aspects of epilepsy surgery including invasive peroperatory and extra-operatory EEG recordings using subdural electrodes or stereotactically placed depth electrodes tailored to the clinical need. Resective potentially curative surgery as well as palliative surgery such as corpus callosotomy can be proposed. Functional surgical approaches using vagal nerve stimulation and deep brain stimulation, in the amygdalo-hippocampal structures or the nucleus anterior of the thalamus are also part of the therapeutic armamentarium. Cognitive studies involving some patients of our centre with intracranially implanted electrodes have led to some important scientific contributions for the understanding of brain functions. Probably the most striking is the localisation of feelings of "out-of-body experiences" to the temporo-parietal junction [9, 10], giving an unambiguous organic substrate to these symptoms often perceived as having a

Figure 6: Today's view of the presurgical evaluation unit

purely psychiatric origin.

Approximately at the same time as the Presurgical Evaluation Unit was founded, Professor Landis also founded the Functional Brain Mapping laboratory (1994), led by Prof. Christoph M. Michel, a neuroscientist and EEG expert, trained by Prof. Dietrich Lehmann in Zurich. C. Michel became a renowned international figure in the analysis of scalp voltage topography and Electric Source Imaging, consisting in the estimation of the brain electric generators of scalp EEG. This approach largely benefitted from the development of high density EEG systems with up to 256 scalp electrodes, initially used only for non-clinical human research. Dr L. Spinelli, physicist, developed a head model called SMAC (Spherical Model with Anatomical Constraints) describing the propagation of electromagnetic fields across the head and allowing the localisation of electrical sources taking into account the individual brain anatomy [11]. This model has proved very reliable in clinical studies and not inferior than more sophisticated later models [12].

More broadly, the presurgical evaluation unit and the functional brain mapping lab established a very strong collaboration that led to pioneering methodological advances and clinical applications, in the field of functional and structural brain imaging in patients with epilepsy, while pursuing stringent validation using concordance with invasive EEG or resection area in patients with post-operative seizure-freedom. Electrical Source Imaging (ESI) has also been applied to the localisation of eloquent brain regions such as the somatosensory cortex [13].

At the retirement of Prof. Jallon, in 2007, the routine EEG and epilepsy clinic was fused with the presurgical evaluation unit under the unified direction of Prof. M. Seeck who continued to expand both the clinical and scientific activity in EEG and epileptology. Margitta Seeck also served as president of the Swiss Society for Clinical Neurophysiology in 2011-15. The clinical research axis led to enhanced validation of ESI as a presurgical localising technique in larger patient groups thanks to invasive validation in patients with subsequent intracranial EEG or post-surgical follow-up [14, 15]. Clinical studies in simultaneous EEG-fMRI also followed the earlier first validation of this new technique with invasive EEG [16].

The focus on epilepsy imaging was further developed by PD Dr Serge Vulliémoz, an epileptologist and physicist trained in Geneva and in Queen Square, London, who further developed EEG-fMRI recordings and its combination with ESI, contributing to its increasing consideration as a clinically relevant imaging tool. A seminal study showed that even in the absence of visible interictal epileptic spikes, epileptogenic activity can be identified and localized [17]. The current brain imaging research focuses on the mapping of functional and structural relationships between brain regions involved in the occurrence of epileptic activity (**Figure 7**) [18]. Nowadays, ESI and EEG-fMRI are routinely performed in the presurgical work-up of patients with focal epilepsy and their results integrated in the clinical case discussion.

The pediatric aspect of epileptology and electroencephalography and epilepsy surgery has also increased in recent years, corresponding to about a third of the presurgical evaluations. Geneva has the largest Swiss pediatric presurgical evaluation program, performed on children referred from most parts of the country under the joint supervision of Prof. Seeck's team and neuropediatricians. Initially, the pediatric part of the program was developed together with Prof. Eliane Roulet-Perez in Lausanne who has special interest in the role of epilepsy in the development of the child and potential of children to catch up developmental retardation if the operation is carried out early and successfully [19]. The pediatric epilepsy surgery team was later joined by PD Dr Christian Korff, expert in pediatric epileptology trained in Geneva and later in Chicago and Dr Joël Fluss, expert in cognitive aspects trained in Paris and Toronto.

PD Dr Fabienne Picard, a French neurologist trained in Strasbourg, is particularly interested in specific genetic forms of epilepsies, notably Autosomal Dominant Nocturnal Frontal Lobe Epilepsy syndrome that she has contributed to characterise in several large families [20] and which is related to a mutation in the nicotinic receptor. These studies led her to further investigate the functional aspects of the insula and the distribution of nicotinic receptors in the brain, using nuclear imaging.

Psycho-social and education aspects have been further developed by Dr Anne-Chantal Héritier Barras, a Swiss epileptologist trained in Geneva and expert in therapeutic education of patients with chronic medical conditions. She introduced modern methodology in pa-

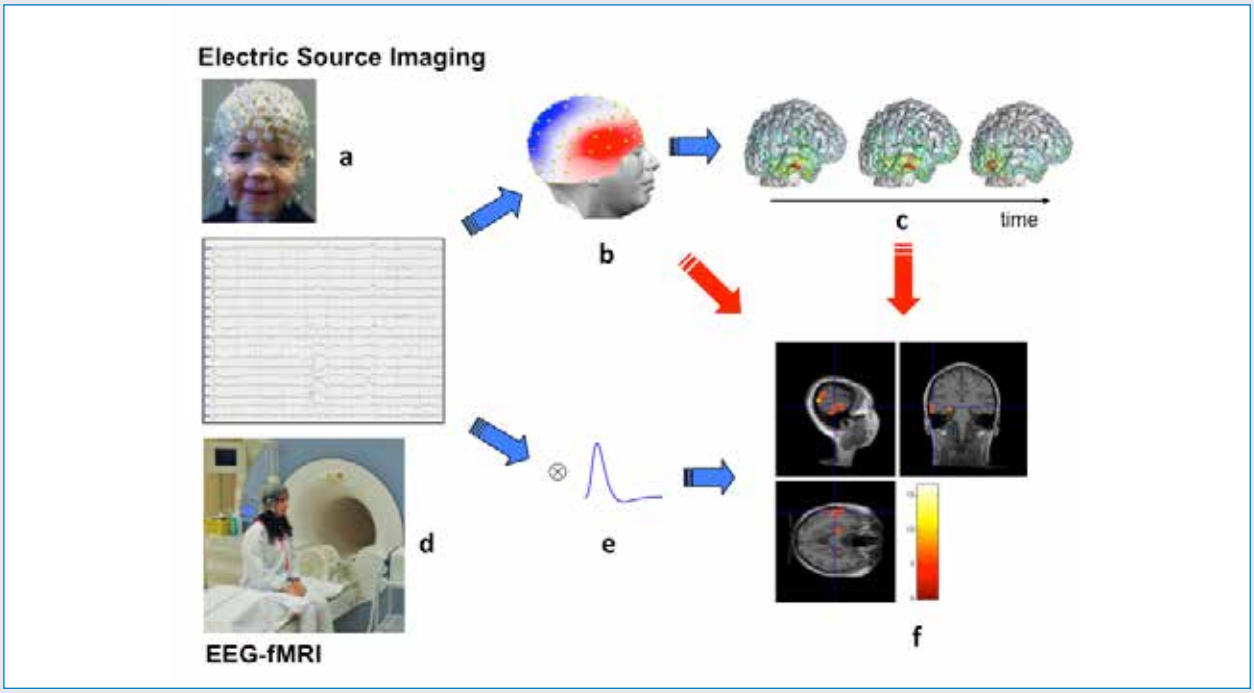

Figure 7: In the past 20 years, collaboration between the EEG and Epilepsy Unit and the Functional Brain Mapping Lab has contributed to the transformation towards a neuro-imaging technique. Electrical Source Imaging: (a) high resolution EEG recordings and (b) topographic representation of the scalp voltage together with sophisticated mathematical algorithms allow to estimate the 3D localisation of the cortical generators of interictal epileptic activity (spikes) (c) . (d) EEG combined to simultaneous fMRI and the estimation of the neurovascular coupling (e) allow to map the hemodynamic changes correlated to the occurence of interictal epileptic activity (spikes) (f).

tient's interviews [21] and management to offer them better strategies to understand and accept their condition and improve their care for themselves and their quality of life.

Other more recent developments in epileptology include a first seizure clinic aiming to rapid extensive diagnostic evaluation and follow-up of patients with first seizure of probable epileptic origin.

Beyond their joint epilepsy program, the centres of Geneva and Lausanne have also strongly collaborated since 2006 by organising the "Université d'Eté d'EEG", a yearly training program for Neurologists and EEG technicians.

Conclusion and perspectives

The complementarity of the medical, nursing and technical team as well as the strong local, regional, nationwide and international clinical and scientific collaborations allow our centre to continue evolving to offer patients the best diagnostic and therapeutic approaches, from diagnostic clarification to presurgical evaluation and to comprehensive care of the patients' condition. A great number of clinical and non-clinical collaborators worked towards this goal over the years. They could not be explicitely named in this article but their contribution should be strongly acknowledged.

The proximity of a strong methodological and clinical research team with internationally recognised EEG expertise ensures that new development in EEG-based neuroimaging are rigorously validated and then rapidly integrated into the clinical work-up for an increased quality of care.

The very recent large reorganisation of the neurosciences in Geneva in the Biotech Campus in 2014, joining engineering, neuroscientific and clinical teams from the University of Geneva and the Ecole Polytechnique Fédérale de Lausanne will enhance multidisciplinary collaborations with a special focus on new imaging techniques and neuromodulation. New implantable diagnostic and therapeutic devices using electrophysiological recordings and electrical stimulation, as well as neuroprosthetic tools developed in the Geneva-Lausanne area will hopefully be part of epileptological care in the not so far future.

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