FILADELFIA

ANNUAL RESEARCH REPORT 2018

Content

1. Introduction – Filadelfia.

The Danish Epilepsy Center Filadelfia is a non-profit foundation with an independent Board of Directors, and more than 120 years old tradition of medical treatment of patients with epilepsy.

It is the only specialized hospital in Denmark treating epilepsy and concomitant disorders as well as treatment of patients within the related medical fields of acquired brain injury. Filadelfia also includes patients with neurohabilitation treatment.

Filadelfia comprises apart from the epilepsy hospital, also specialized social institutions within rehabilitation and the only special school for children and young people with epilepsy in Denmark. The Epilepsy Hospital is legitimiced to recieve patients from the 5 Danish Regions i.e. the public hospitals and practitioners due to The Central Health Authorities and minimum block grants from the Danish State. The specialized social institutions recieve clients from the Danish Municipalities.

The hospital is internationally acclaimed for its highly specialized diagnostic services, comprehen-sive research within particularly genetics and neurophysiology as well as clinical development activities. Research at the Neurophysiology Department as well as Department of Epilepsy Genetics and Personalized Medicine, is clinically oriented and focuses on development, validation and implementation.

Filadelfia's expertise is based on many years of specialization in diagnosis and treatment of patients with severe epilepsy. Long-standing specialized focus has resulted in the attainment of a high level of medical expertise in the fields of diagnostics, treatment, special care, attendance and support of patients diagnosed with epilepsy and/or acquired brain injury.

The hospital has close collaboration with several international centers and our specialists have several positions of trust in national and inter¬national scientific societies. We have close collaboration with other Danish research teams as well as Copenhagen, Aarhus and Odense Universities whom several of Filadelfias professors and associated professors are affiliated to.

Within the broader discipline of epilepsy care there is an ongoing process of also constituting a more holistic systematic research approach towards patient care and family perspectives and in general quality of life. It is part of our strategy to investigate these issues from a nursing and neuropsychological perspective. This is in accordance with the Danish National Goals for Health Services.

Filadelfia Research, Department of Epilepsy Genetic and Personalized Medicin, Department of Neurophysiology as well as contributing clinically departments, all comprises the team that has put research on the agenda for 2018.

2. Primary Research Team 2018

Sándor Beniczky
MD and PhD from University of Szeged, Hungary (1997, 2004)
Specialist in Neurology (2002).
Specialist in Clinical Neurophysiology (2006).
European certification as epileptologist (2010).
Current position: Professor, consultant, head of department
Editor-in-chief, Epileptic Disorders

Email: sbz@filadelfia.dk

Guido Rubboli
MD and PhD from University of Bologna, Italy
Specialist in Neurology
WHO course in Epileptology and clinical electroencephalography (1985)
Training in experimental and clinical neurophysiology, Chicago USA (1989-91)
Current position: Professor

Email: guru@filadelfia.dk

Rikke Steensbjerre Møller
M.Sc. Biomedicine from University of Southern Denmark (2003) and PhD from University of Copenhagen (2008)
Geneticist
Current Position: Ass. Professor, head of department of Epilepsy Genetics and Personalized Medicine

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Elena Gardella
MD and PhD from University of Bologna, Italy (1995, 2003)
Specialist in Neurology (2001). Post doctoral, clinical neurophysiology (2005)
Member of the faculty of 1000 of the ILAE (epilepsy teaching)
Senior consultant – Department of Clinical Neuropsysiology, Danish Epilepsy Center, 2012-present.
Clinical Neurophysiologist 2012-present
Current position: Ass. Professor

Email: elga@filadelfia.dk

Marina Nikanorova
PhD and MD, Moscow Medical University, Russia (1988 and 1999)
Specialist in Neurology (1988)
Neurologist – 1988 - present
Senior consultant – Children Department, Danish Epilepsy Center, 2002 – present
Current position: Ass. Professor, SDU 2010 – present.

Email: mnk@filadelfia.dk

Over-all Presentations 2018

57 Publications in Peer-review Journals	**59 Oral Presentations**	**19 Posters**
Two Professors	**3 Ass. Professors**	**3 PhD students**

Present PhD projects:

Genotype-phenotype correlations in severe epileptic encephalopathies.
With special focus on channelopathies. **MD, PhD. Katrine Marie Harries Johannesen**. Defence; 29/5 2019

Mapping of experienced stressors and resourcefulness in caregivers of children with severe epilepsy for a better patient centered treatment and care. **Neuropsychologist. PhD Anne Vagner Jacobsen**. Defence 2020

How does health staff and patients experience the human related conversation in a health care context at Filadelfia, **Diacon PhD student Conny Hjelm**. Defence 2020.

Present PhD projects, supervised from Filadelfia:

Sàndor Beniczky, Professor

“Clinical practice of EEG revisited: Improved spike identification, localization and characterization” (in collaboration with Aarhus University Hospital). Mustafa Aykut Kural, Defence 2021.

Guido Rubboli, Professor

“Endophenotyping patients of genetic generalized epilepsy – a population-based study” (in collaboration with Syddansk Universitet/ Odense). Joanna Gesche, Defence 2020.

3. Positions of Trust

Professor Sàndor Beniczky

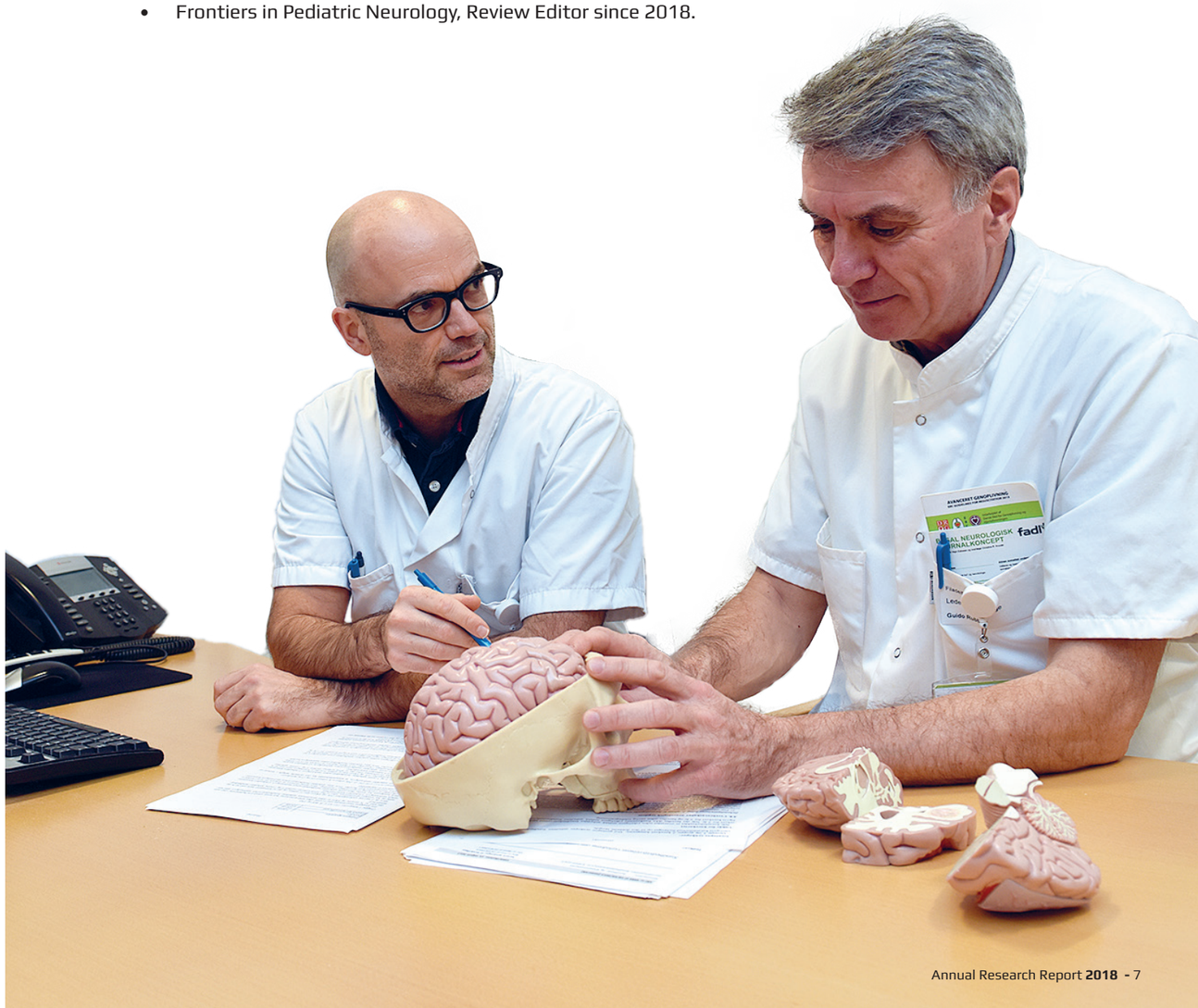
- Executive board member, and treasurer of ILAE-Europe
- Chair of the IFCN-ILAE EEG taskforce
- Member of the Epilepsy Education Taskforce of the ILAE
- Member of the Diagnostic Methods commission of the ILAE

Professor Guido Ruboli

- Member of the “Sleep and Epilepsy” Task Force of the ILAE (International League Against Epilepsy) - ESRS (European Sleep research Society) – EFNS (European Federation of Neurological Societies), 2013-present.
- Member of the ILAE Task Force “Transitions in Child to Adult Care”, 2017-2021.
- Chair of the Epilepsy Scientific Panel, European Academy of Neurology, 2018-present.

Editorial boards

- Epileptic Disorders - Official Journal of ILAE: Associate Editor since 2017
- Behavioral Neurology: Section Editor since 2015
- Clinical Cases and Reviews in Epilepsy: member of the Editorial Board, since 2014
- Frontiers in Pediatric Neurology, Review Editor since 2018.



4. Research Projects

Neurophysiological department

Automated seizure detection based on surface electromyography and accelerometry

Generalized tonic-clonic seizures (TCS) increase the risk of sudden unexpected death in epilepsy patients, especially when they are unattended. In sleep, they often remain unnoticed, which can result in suboptimal treatment decisions. Hence, there is need for wearable devices that can automatically detect TCS, both to prevent injury and death, and to provide objective data on seizure frequency. We have developed and validated wearable devices, based on movement-signals (accelerometry) and based on surface electromyography (EMG) for detection of TCS.

In a phase-III, multicenter, prospective, blinded study using real-time detection of TCS in epilepsy monitoring units, we demonstrated that the accelerometry-device had a sensitivity of 90% and a false alarm rate of 0.2/day for detecting TCS. However, that study was conducted in an artificial environment. Therefore, we extended it with a phase-IV, open study to assess the performance, applicability and usability of the device in the home-environment of patients, using a modified form of the standardized questionnaire developed by IBM to evaluate user satisfaction and applicability of technical/ computer-based devices: Post-Study System Usability Questionnaire (PSSUQ). Median time patients had been using the device was 15 months. In 10% of cases, patients stopped using the device due to reasons related to the device. Sensitivity (90%) and false alarm rate (0.1/day) were similar to what had been determined in the phase-III trial. Patients and caregivers were overall satisfied with the device (median: 5.5 on the 7-point Likert-scale). Adverse effects occurred in 11%, but were only mild. In 55%, the device influenced the number of seizures noted into the seizure-diary, and in 40% it contributed to fewer seizure-related injuries.

We found quantitative EMG changes that are specific for TCS. They are characterized by a dynamic evolution of low (LF) and high frequency (HF) signal components. Algorithms targeting increase in HF EMG signals are biomarkers of TCS. They can be used both for seizure detection and for distinguishing TCS from convulsive psychogenic non-epileptic seizures (PNES). We have conducted a large-scale, blinded, prospective multi-center, phase-III study on the accuracy of real-time seizure detection, using a wearable EMG-device, based on an algorithm with pre-defined threshold values. The device had a sensitivity of 94% and a false alarm rate of 0.7 / day.

Although recently there has been a considerable increase in the number of publications on seizure detection devices, the way studies were designed and reported was very heterogeneous and often confusing. We developed standards for seizure detection clinical trial. Using a set of key features, the studies are categorized from I to IV, similar to the therapeutic studies.

Papers:

Beniczky S, Conradsen I, Henning O, Fabricius M, Wolf P. Automated real-time detection of tonic-clonic seizures using a wearable EMG device. Neurology. 2018; 90:428-434.

Pirgit Meritam, Philippe Ryvlin, Sándor Beniczky. User-based evaluation of applicability and usability of a wearable accelerometer device in detecting bilateral tonic-clonic seizures: a field study. Epilepsia. 2018;59 Suppl 1:48-52. doi: 10.1111/epi.14051.

Sándor Beniczky, Isa Conradsen, Peter Wolf. Detection of convulsive seizures using surface electromyography. Epilepsia. 2018;59 Suppl 1:23-29. doi: 10.1111/epi.14048.

Sándor Beniczky and Philippe Ryvlin. Standards for testing and clinical validation of seizure detection devices. Epilepsia. 2018;59 Suppl 1:9-13. doi: 10.1111/epi.14049.

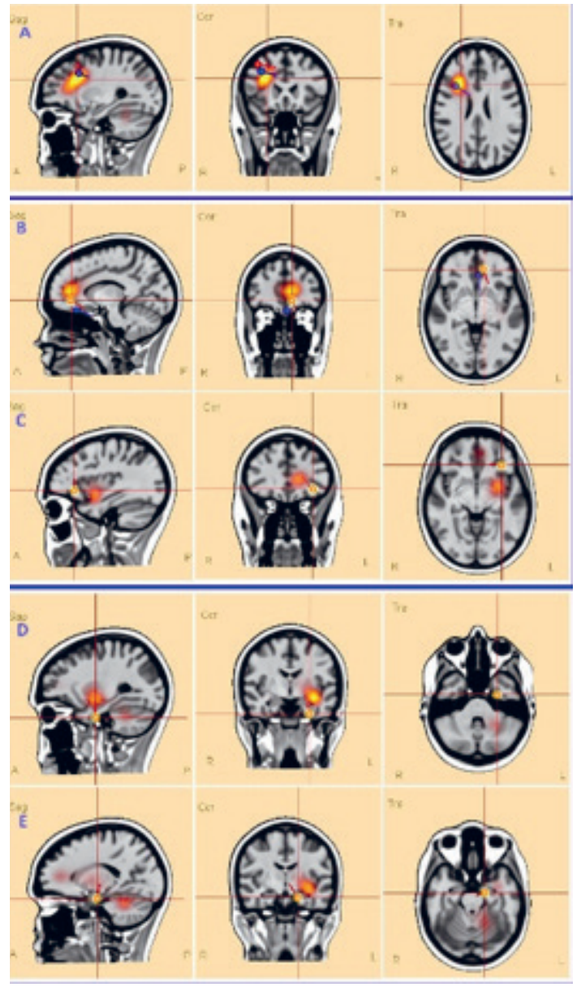
Electromagnetic source imaging in epilepsy

Electroencephalography (EEG) and magnetoencephalography (MEG) signals are generated in the cortex and recorded at the surface of the scalp. Traditionally, in clinical practice, EEG is recorded with 19 electrodes of the 10-20 array, covering the upper part of the head (scalp), and location of these signals is given as the location of the peak negativity on the scalp. However, this region on the scalp does not necessary correspond to the location of the source, thus there is need for better recordings and advanced methods of source localization.

In a large prospective study we prospectively recorded magnetoencephalography (MEG) simultaneously with EEG and performed electromagnetic source imaging (EMSI), comprising electric source imaging, magnetic source imaging, and analysis of combined MEG-EEG datasets, using 2 different software packages. As reference standard for irritative zone (IZ) and seizure onset zone (SOZ), we used intracranial recordings and for localization accuracy, outcome 1 year after operation. We concluded that EMSI had accuracy similar to established imaging methods and provided clinically useful, new information in 34% of the patients.

In a retrospective, blinded study we have validated an automated algorithm for EEG source imaging, in 41 consecutive patients with focal epilepsy who underwent resective surgery. Accuracy was 61% (95% CI: 45-76%) for the fully automated approach and 78% (95% CI: 62-89%) for the semi-automated approach. We concluded that automated ESI has an accuracy similar to previously reported neuroimaging methods.

In a large prospective study we prospectively analysed long-term video-electroencephalography recordings (LTM) of 87 consecutive patients admitted for pre-surgical evaluation. We performed interictal and ictal source imaging. We concluded that the II-ESI and IC-ESI of LTM data have high feasibility and their localization accuracy is similar to that of conventional neuroimaging methods.



Papers:

Duez L, Tankisi H, Hansen PO, Sidenius P, Sabers A, Pinborg LH, Fabricius M, Rásonyi G, Rubboli G, Pedersen B, Leffers AM, Uldall P, Jespersen B, Brennum J, Henriksen OM, Fuglsang-Frederiksen A, Beniczky S. Electromagnetic source imaging in presurgical workup of patients with epilepsy: A prospective study.
Neurology. 2019; pii: 10.1212/WNL.0000000000006877. doi: 10.1212/WNL.0000000000006877.

Baroumand AG, van Mierlo P, Strobbe G, Pinborg LH, Fabricius M, Rubboli G, Leffers AM, Uldall P, Jespersen B, Brennum J, Henriksen OM, Beniczky S. Automated EEG source imaging: A retrospective, blinded clinical validation study. Clin Neurophysiol. 2018;129:2403-2410. doi: 10.1016/j.clinph.2018.09.015.

Sharma P, Scherg M, Pinborg LH, Fabricius M, Rubboli G, Pedersen B, Leffers AM, Uldall P, Jespersen B, Brennum J, Henriksen OM, Beniczky S. Ictal and interictal electric source imaging in pre-surgical evaluation: a prospective study. Eur J Neurol. 2018;25:1154-1160. doi: 10.1111/ene.13676.

Standardization and quality assurance in clinical neurophysiology

Most of the neurophysiological methods in clinical neurophysiology are based on local traditions, expert-opinions and on old studies lacking proper reference standard and study-design. To improve patient care it is important to revisit the old techniques and to validate new methods, using robustly designed diagnostic studies. Our group contributed to this, in several areas of clinical neurophysiology.

Under the auspices of the International Federation of Clinical Neurophysiology (IFCN) we participated in development of the clinical guideline on the utility of EEG in diagnosing and monitoring epilepsy.

In a large retrospective study we demonstrated the clinical added value of sleep EEG, following standard EEG recordings. We investigated the diagnostic added value of supplementing the 10-20 with six electrodes in the inferior temporal chain (“low-row). We analyzed 500 consecutive standard and sleep EEG recordings, using the 10-20 array and the extended array. We identified the recordings with EEG abnormalities that had peak negativities at the inferior temporal electrodes, and those that only were visible at the inferior temporal electrodes. We found that adding six electrodes in the inferior temporal electrode chain to the 10-20 array improves the localization and identification of EEG abnormalities, especially those located in the temporal region.

Papers:

Tatum WO, Rubboli G, Kaplan PW, Mirsatari SM, Radhakrishnan K, Gloss D, Caboclo LO, Drislane FW, Koutroumanidis M, Schomer DL, Kasteleijn-Nolst Trenite D, Cook M, Beniczky S. Clinical utility of EEG in diagnosing and monitoring epilepsy in adults. Clin Neurophysiol. 2018;129:1056-1082. doi: 10.1016/j.clinph.2018.01.019

Meritam P, Gardella E, Alving J, Terney D, Cacic Hribljan M, Beniczky S. Diagnostic yield of standard-wake and sleep EEG recordings. Clin Neurophysiol. 2018;129:713-716. doi: 10.1016/j.clinph.2018.01.056

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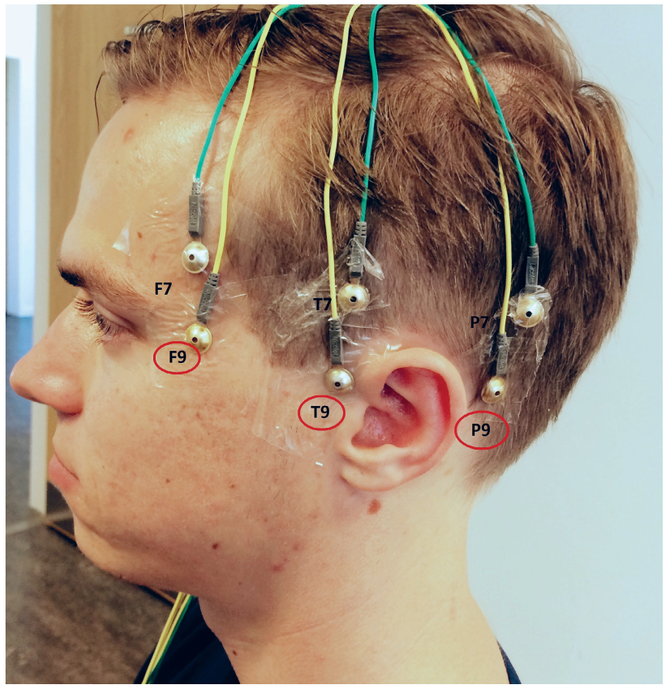


Alternative seizure provoking techniques at the Epilepsy Monitoring Unit

Investigators
Elena Gardella, Jane Palm Eriksen, Lærke Dunkan, Tanja Kristina Jensen, Conny Merete Olsen, Ida Vibeke Mæhl, Ole Lundgren Hansen, Sándor Beniczky.

Background
Provocation may be of particular value in patients who have infrequent seizures and would otherwise be unsuitable for telemetry. Routine photic and hyperventilation stimuli are the most common activating procedures.
Stress in general and in some cases simple suggestion are very important provoking factor for both epileptic seizures (ES) and psychogenic non epileptic seizures (PNES), as well.

Little is known so far about the evaluability of cognitive stimulation techniques as a seizure provoking techniqueInklusionskriterier

Methods
We reviewed the long term video-EEG-recordings at the Danish Epilepsy Centre in 2016-2017, selecting patient who underwent a tailored protocol of intensive cognitive and motor stimulation (CMs).
We evaluated whether CMs was time related with the appearance of ES or PNES

Results
235 patients have been monitored and 45 (31 females, 14 males) of them underwent CMs during the recordings. Patient’s age ranged from 10 – 68 years.

Twenty-one patients did not present clinical manifestation in relation to CMs, whilst 24/45 subjects (53%) had one or more typical clinical event (9 had PNES, 15 ES) during or short after stimulation.

PNES were typically recorded during (5/9) or short after CMs. Patients with ES in relation to CMs had often a focus involving the temporal region (9/15 patients) and the seizure in most cases came (12/15 patients) a few hours after CMs.

Conclusion
Cognitive and motor stimulation during intensive video-EEG-monitoring seems to be a valuable non-invasive instrument for the provocation of both epileptic and non-epileptic seizures. On the base of our preliminary data, we estimate we were likely able to reduce the need for prolonged recordings in about one-half of patients undergoing CMs during video-EEG telemetry.

The seizure provoking technique consists in a tailored protocol of intensive cognitive (a+b) and motor (b) tasks alternated with relaxation (c) during video-EEG telemetry.

	CMs during telemetry		
	TLE	extra-TLE	PNES
Patients (nr)	17	15	13
Gender (males / females)	4 / 13	4 / 11	4 / 9
Range of age (yrs)	15 - 68	10 - 49	16 - 67
ES / PNES related to CMs (nr of pt s)	9 (53%)	6 (40%)	9 (69%)
Latency CMs → ES / PNES (nr of pt.s)			
during CMs:	1	1	5
<1 hour after CMs:	-	1	3
1- 6 hours after CMs:	8	1	1
6- 12 hours after CMs:	-	3	-

CMs: cognitive and motor stimulation; TLE: temporal lobe epilepsy; PNES: psychogenic non-epileptic seizures; ES: epileptic seizures; nr: number, pt.s: patients

Papers

Jane Palm Eriksen, Lærke Dunkan, Tanja Kristina Jensen, Conny Merete Olsen, Ida Vibeke Mæhl, Ole Lundgren Hansen, Sándor Beniczky, Elena Gardella.Epilepsia, 2018

Department of Epilepsy Genetics and Personalized Medicine

During the last decade, next-generation sequencing (targeted gene panels or whole-exome sequencing) has led to a virtual explosion of gene discovery, raising the number of bona fide genes and possible candidate genes for monogenic epilepsies to more than 400 genes, explaining 20-25% of all cases with severe early-onset epilepsies that had otherwise no identifiable causes. Finding a genetic cause is of pronounced importance for both the patient, the family and professional caretakers. Knowing the etiology can help ensuring the right support and treatment, knowledge about prognosis and recurrence risk and removal of guilt etc. Furthermore, knowing the pathophysiological mechanisms may allow us to develop more effective treatments that can be targeted to the individual patient based on his/her genetic profile. Monogenic epilepsies offer an excellent opportunity to achieve targeted treatments, mainly because of the ongoing explosion in gene discovery, the existence of good animal and in vitro models, in which targeted medications can be developed, and the ability to assess the efficacy of experimental targeted treatments in small clinical trials.

In our team pediatricians, neurologists, neurophysiologists, geneticists and basic scientists work together on projects including:

Gene discovery in neurodevelopmental disorders and epilepsy.

Genotype-phenotype correlation, including electro-clinical characterization of genetic epilepsy syndromes.

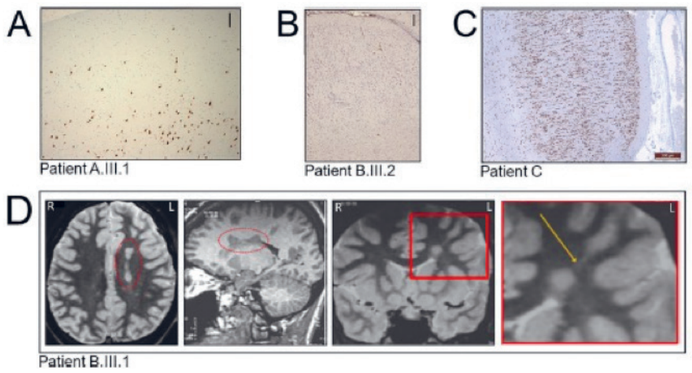
Functional characterization of genetic defects to understand their pathomechanisms which may lead to improvement of existing or development of new personalized therapies.

Research project:

"The importance of genetic mutations in epilepsies due to developmental defects of the brain and of low-grade tumors". Principal investigator: G. Rubboli (Dianalund, Denmark). In collaboration with E. Aronica (Amsterdam, The Netherlands), A. Smits (Goteborg, Sweden), K Malmgren (Goteborg, Sweden), L. Dibbens (Adelaide, Australia), S. Baulac (Paris, France), L.Pinborg, A.Sabers, K.Bonde, N.Tommerup (Copenhagen, Denmark), K. Selmer (Oslo, Norway). Started in 2015; in June 2017, the extension of the study until the end of 2019 has been accepted by the Region Sjælland ethical committee.

This project aims to investigate possible genetic substrates in patient's candidate to epilepsy surgery, with or without pathological abnormalities as demonstrated by neuroimaging and/or by histopathological analysis on brain specimens.

The significance of finding a genetic mutation in patients with focal epilepsies, with or without a brain lesion, is still unclear and currently there are scanty and conflicting data. Some data might suggest that the co-occurrence of genetic mutations and MCD in patients submitted to surgery has a poor post-surgical prognostic significance. The identification of specific genes associated with epileptogenic lesions in surgical patients might: a) contribute to clarify the continuum between non-lesional and lesional epilepsies associated with the same mutation; b) provide an additional biomarker for the presurgical evaluation with prognostic significance; c) to orient or to contribute to the development of more targeted treatments (an example is the treatment of tuberous sclerosis, with everolimus, a selective inhibitor of mTOR of the abnormally activated mTOR pathway)



Research project. Investigation of the genotype-phenotype associations of genetically-determined epilepsy syndromes and implications for precision medicine

The definition of the phenotype of various genetically-determined epileptic syndromes, including focal epilepsies and epileptic encephalopathies can provide relevant clinical information for their diagnosis, management and prognosis. In some of these syndromes, we have shown a phenotype-genotype correlation and the underlying mechanisms have been studied by investigating the functional consequences of the different mutations on protein expression, that ultimately has led to the identification of mutations with a gain-of-function (GOF) effect or a loss-of-function (LOF) effect. The results of these studies may contribute to develop novel targeted treatment approaches, in a "precision medicine" perspective, by using drugs that aim to counteract specifically the abnormal effect of the mutation.

Current international projects involving Filadelfia are:

1. (Guido Rubboli, Dragan Marjanovic) project on the evaluation of the effectiveness and safety of a potassium channel blocker (4-aminopyridine) on KCNA2 encephalopathy related to GOF mutations.
2. Project on the deep phenotyping and elecrophysiological characterization of SCN8A realted epilepsies (Elena Gardella, Rikke S. Møller, Katrine Johannesen) in collaboration with laboratories of Miriam Meisler (Michigan, USA) and Holger Lerche (Tubingen, Germany)
3. Project on the evaluation of the long term follow up of patients with STXBP1 mutations (Elena Gardella/ Rikke S. Møller , in collaboration with Sarah Weckhuysen og Hannah Stamberger, University of Antwerp)

Other ongoing projects are:

- Investigations of genotype-phenotype associations in KCNT1-related epilepsies and epileptic encephalopathies (Guido Rubboli, in collaboration with C.Bonardi, M.Fiannacca, RS Møller),
- Investigations of genotype-phenotype correlation in GABRB3 epilepsies (Elena Gardella / Rikke Møller, in collaboration with Milena Guazzi, University of Genova)
- Investigations of genotype-phenotype correlation in KCNB1 epilepsies (Elena Gardella / Rikke Møller, in collaboration with Chiara Reale, University of Messina)
- Definition of the phenotypic and genotypic spectrum of PURA syndrome (Guido Rubboli in collaboration with K.Johannesen)
- definition of the phenotype of CNKSR2 epileptic encephalopthy with ESES (Guido Rubboli E.Gardella, R. S Møller in collaboration with C.Bonardi)
- Description of a family with RORB mutation (Elena Gardella/Rikke Møller, Christina Fenger, in collaboration with Adriana Magaudda and Chiara reale, University of Messina)
- Investigations of genotype-phenotype correlation in GOSR2 (Monica Zilmer, Rikke Møller, Elena Gardella)
- Investigations of genotype-phenotype correlation in NEXMIF (Trine Hammer, Rikke Møller, Elena Gardella)
- Investigations of genotype-phenotype correlation in PIGT ang PIGA (Allan Bayat, Rikke Møller, Elena Gardella with extensive international collaborations)

References

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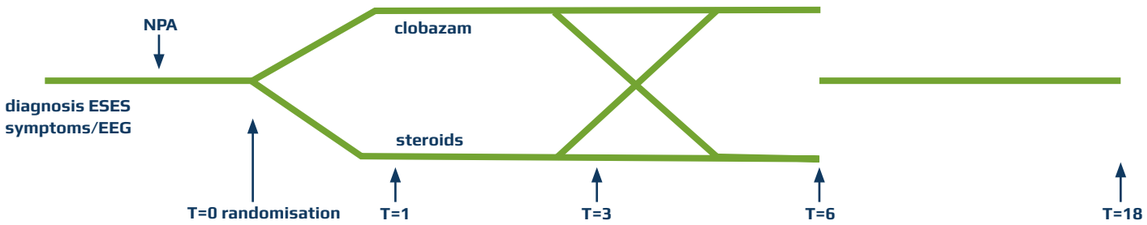
International collaborative projects

Research project "RESCUE ESES: Corticosteroids or clobazam for ESES syndrome: a European, multicenter, randomized, controlled clinical trial":

Principal investigator: F. Jansen (Utrecht, The Netherlands). Extended until 2020.

This is a European, multicentre, randomised, controlled, open clinical trial with blinded outcome assessment, comparing the effects of treatment with clobazam or methylprednisolone in patients with ESES syndrome. The primary aim is to compare the effects on cognition of treatment with clobazam and steroids in children with ESES. Secondary aims include to compare the effects of these treatments on the index of sleep induced SWs (SWI) on EEG, the incidence of seizures, safety, to assess which patients benefit most from therapy, including study of activation of the immune system as a potential biomarkers. G.Rubboli is the Principal Investigator coordinating the activity of the Research Unit at the Danish Epilepsy Center.



T=1 and 3 clinical symptoms and EEG
T=3 and T=18 clinical symptoms, EEG and neuropsychological assessment (NPA)

Research project: "Biology of Juvenile Myoclonic Epilepsy (BIOJUME)", 2017-2022.

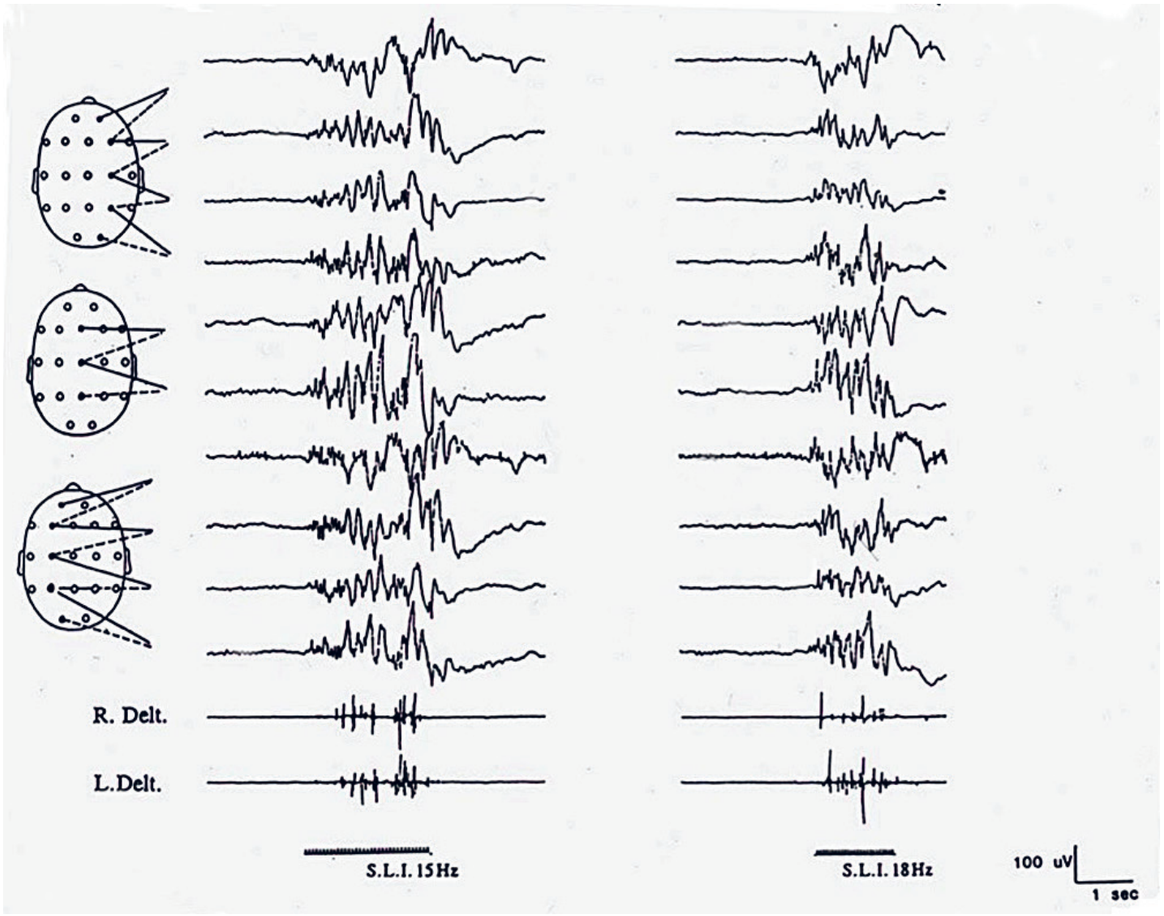
Principal Investigator: D. Pal (London, UK). Participants: Kings College Hospital, London (UK), St Thomas' Hospital, London (UK), Walton Centre, Liverpool (UK), College of Medicine, Swansea (UK), Danish Epilepsy Centre, Dianalund (Denmark), Drammen Hospital, Oslo (Norway), University Medical Center, Utrecht (The Netherlands), Italian League Against Epilepsy, Hospital for Sick Kids, Toronto (Canada), Nationwide Childrens Hospital, Columbus, Ohio (USA), Juan P Garrahan, Childrens Hospital, Buenos Aires (Argentina).

The project aims to assemble a clinical-genetic dataset of 1000 JME cases for genomewide association and future genomic resequencing analyses. Conduct hypothesis-driven GWAS (GWAS-HD), in a well-phenotyped Juvenile Myoclonic Epilepsy (JME) case-control dataset, will enable to test support for molecular networks that act on seizure susceptibility

Hypotheses to be tested:
1. JME is associated with variation in GABAA receptor genes.
2. JME is associated with molecular networks of ion-channels.
3. Endophenotypes of JME will increase power to localise disease-associated genes.

In addition the study aims to conduct GWAS-HD of a novel, quantitative EEG endophenotype (brain network ictogenicity, BNI)

The activity of the Research Unit at the Danish Epilepsy Center is coordinated by
Guido Rubboli, Rikke Møller, Elena Gardella.



Neuropaediatric department

Two drug related studies in collaboration with pharmaceutical companies:

Part 1 (ZX008-1502) ZX008-1502 – A multicenter, randomized, double-blind, parallel group, placebo-controlled trial of two fixed doses of Fenfluramine oral solution as an adjunctive therapy in children with Dravet syndrome.

12 children were screened, and 10 children were included – all fullfilled the project. Last patient was terminated December 2017.

Part 2 (ZX008-1503) – Fenfluramine in Dravet syndrome: A long-term open label flexible dose extension study. Assesment of the long term safety of the use of Fenfloramine Hydrochloride, oral solution as add-on for children and young people with Dravet syndrom.

10 children continued in the open label study. One child was excluded due to lack of efficacy and another child due to parental wish. 8 children are still ongoing; 6 children are seizure free.
The project has just been extended to last another 36 months, indicating the children according to the plan, will be terminated during 2020.

Investigator: Marina Nikanorova, & study coordinator: Klaus Ehrenreich

Pharmacokinetics variability and use of some of the newer antiepileptic drugs ("Orphan drugs") in children at 2 epilepsy centers in Scandinavia (Epilepsihospitalet & Sandvika, SSE). Ongoing Multicenter study.

Antiepileptic drugs is a complex group of drugs and has wide pharmacokinetic variation amongst patients and a high potential for interactions. "Orphan drugs" is a group of antiepileptic drugs that are used in specific epileptic syndromes and in patients with difficult to treat epilepsy and are often used in children. Treating children requires particular good follow up as changes in physiology during growing up can have an impact on the pharmacokinetic side so that a variation in efficacy and tolerability can lead to significant variations. Therapeutical Drug Monitorering (TDM) is used as a tool in treatment of patients with epilepsy in order to individualize treatment. The purpose of this project is to study the pharmaceutical variation as well as efficacy and tolerability of the newer antiepileptica in children (eslikarbazepin acetat, lacosamid, perampanel, stiripentol and rufinamid) as well as being able to further use TDM. It would potentially lead to a safer and individualized treatment, and a contribution to a better judging of efficacy as well as tolerability and patient safety.

Investigator; M. Nikanorova.

CBD oil treatment

Purpose: To evaluate the effect on seizure frequency and side effects of CBD oil treatment for epilepsy in patients started in CBD oil treatment in the Neuropediatric Department at the Danish Epilepsy Centre Filadelfia from December 2016 – December 2018 with the follow-up period until March 2019.

Inclusion criteria: Patients started in treatment with CBD oil for epilepsy at the Neuropediatric Department at the Danish Epilepsy Centre Filadelfia from December 2016 – December 2018. Approximately 53 patients.

Treatment protocol: The treatment protocol is following the any time existing protocol for CBD oil treatment at the Neuropediatric Department. Seizure frequency is registered by parents or caretaker in a seizure app for four weeks prior to CBD oil treatment initiation and throughout the treatment period. Blood tests with antiepileptic drug values, hematology, liver and kidney parameters before treatment start. Treatment start as inpatient with CBD oil 5 mg/kg/day and then treatment increase to 10mg/kg/day and then further increase to 15 mg/kg/day. Blood tests before discharge and two weeks after the latest increase. Phone consultation with medical doctor with evaluation of effect and side effects two weeks after discharge and 8 weeks after CBD oil treatment start in order to evaluate dosage, effect on seizures and further treatment plan. Dosage can be increased to a maximal dosage of CBD oil 20mg/kg/day.

Outcome measures: Reduction in seizure frequency evaluated by scoring in seizure app. Side effects evaluation. Cessation of treatment. Further outcome measures are changes in cognition, changes in blood levels of antiepileptic drugs especially clobazam and desmethyl clobazam, changes in hematology, liver and kidney parameters.

MD Monica Zilmer and MD,
Head of Neuropeadiatric dep. Kern Olofsson

5. Nursing research perspectives

The academic nursing field of Filadelfia is growing and expanding. With two established PhD positions anchored in **Filadelfia Research Unit**, there is potential for strengthing and emphazing the research field witin also more qualitative research. Systematic focus as well as educational priorities are however still in focus and has lead to additional step;

In dual collaboration between **Center of education, Filadelfia** and **Absalon College** we have created an interdisciplinary course with focus on how to approach research in clinical practice. The process has materialized in a selection of validated theoretically processed protocols/ projects description that will enable us to establish clinically relevant projects for 2019, anchored around different wards at the hospital. Along with an already existing **Journal Clubs**, and regular meetings amongst nurses occupied with development and research, this process has created a strong sense of scientific curiosity and awareness towards the importance of working systematic with an academic approach.

The **Psychotherapeutical** department has developed an electronic questionnaire in order to reveal the patients experience of their treatment and the efficacy of the different interventions.. Furthermore a questionnaire covering the long term perspective will be comleted at the 3 months control with the psychiatrist. The project is based on an UpgradeIT system, and is still ongoing.

One Nurse graduated from Århus University in 2018 with her Master thesis titled; 'Everything is as before, but nothing is as it was' (Alt er som før, men intet er som det var)' – A Phenomenological-Hermeneutic Study of Adult Epilepsy Patients' Experiences of life ½ - 2 years after participating in an eight week Interdisciplinary In-hospital Epilepsy-Rehabilitation Programme. At the moment the thesis is close to materialize itself in a scientific article.

Another nurse is working on a university degree, which underline the growing focus on academic skills in the nursing group.

Furthermore the article "PNES – a difficult and unknown disorder" by Lena G. Madsen, Head nurse, was published in the Danish Nursing Research magazine; Fag og forskning 2.11 2018

“Jump out”

2018 was also the year where Filadelfias newly established Playground; ”Jump out” opened. The Play area is financially supported in collaboration with acknowledged funding investors, and received great attention when revealed.

It is a playground that allows even severely handicapped children to be involved in playing, be active and generally take part and sense ones body in a new way.

The playground is interesting from an also **research** point of view as various research topics will be founded. In 2018 the following projects was started (still ongoing):

- *Psychical activity and its impact on sleep and life quality in children with epilepsy.*
- *In coorporation with physiotherapist monitoring via questionnaire the child’s daily activities and the opportunities of the playground.*

Head Nurse Conny Brandt
& Study Nurse Klaus Ehrenreich.

6. Conferences and Summer School

Dianalund International Conference on epilepsy 2018

Dianalund International Conference

In cooperation with national as well as international collaboraters, the **Dianalund International Conference on epilepsy** was organized and held at the end of June 2018 over two days. The topic was; Epileptic channelopaties – clinical spectrum and treatment perspectives. The conference was well visited with many international speakers as well as delegates.

Dianalund Nursing Conference

Dianalund Nursing Conference has been held for 8 years. It covers widely in topics and themes but always aiming to focus on clinical aspects within epilepsy nursing Care. 2018 focused on “Everyday life and epilepsy”. The Nursing Conferences are normally visited by up to 100 nurses, from all over the country

Dianalund Summer School

Dianalund Summer School was held for the 4 th time and concentrate on EEG patterns and methods. The Summer school is addressed to doctors from all over the world, and consist of 6 days divided between theoretical lessons and practical workshops. In 2018, 23 doctors attended.

Dianalund Summer School 2018

7. Publications in Peer-Reviewed Journals

1. Aberrant Inclusion of a Poison Exon Causes Dravet Syndrome and Related SCN1A-Associated Genetic Epilepsies. Carvill GL, Engel KL, Ramamurthy A, Cochran JN, Roovers J, Stamberger H, Lim N, Schneider AL, Hollingsworth G, Holder DH, Regan BM, Lawlor J, Lagae L, Ceulemans B, Bebin EM, Nguyen J; EuroEPINOMICS Rare Epilepsy Syndrome, **Myoclonic-Astatic Epilepsy, and Dravet Working Group**, Barsh GS, Weckhuysen S, Meisler M, Berkovic SF, De Jonghe P, Scheffer IE, Myers RM, Cooper GM, Mefford HC. Am J Hum Genet. 2018 Dec 6;103(6):1022-1029.

2. Epilepsy Surgery.Pinborg LH, Jespersen B, **Beniczky S**, Fabricius M, Rasonyi G, Uldall P, Tsiropoulos I, Leffers AM, Madsen C, Foged M, Ziebell M, Henriksen O, Jørgensen M, Vinter K, **Stauning L,** Broholm H, Brennum J, Sabers A, **Rubboli G**. Ugeskr Laeger. 2018 Mar 26;180(13).

3. Mild malformations of cortical development in Sleep-Related Hypermotor Epilepsy due to KCNT1 mutations. **Rubboli, Guido**; Plazzi, Giuseppe; Picard, Fabienne; Nobili, Lino; Hirsch, Edouard; Chelly, Jamel ; Prayson, Richard; Boutonnat, Jean; Bramerio, Manuela; Kahane, Philippe; Dibbens, Leanne; **Gardella, Elena**; Baulac, Stephanie; Møller, Rikke. Annals of Clinical and Translational Ann Clin Transl Neurol. 2018 Dec 25;6(2):386-391. eCollection 2019 Feb.

4. Encephalopathy related to electrical status epilepticus during slow sleep. An historical introduction.**G. Rubboli**, CA Tassinari. Epileptic Disorders, in press.

5. ESES: from concepts to terminology. A commentary. **G. Rubboli**, C.A.Tassinari. Epileptic Disorders, in press

6. EEG features in ESES. **E. Gardella**, G. Cantalupo, P. Larsson, E. Fontana, B. Dalla Bernardina, **G. Rubboli**, F. Darra. Epileptic Disorders, in press.

7. Encephalopathy related to status epilepticus during sleep: a link with sleep homeostasis? **Rubboli G**, Huber R, Tononi G, Tassinari CA. Epileptic Disorders, in press.

8. Encephalopathy related to Status Epilepticus during Slow Wave Sleep. Current concepts and future perspectives. Tassinari CA, **Rubboli G**, Epileptic Disorders, in press.

9. Electromagnetic source imaging in presurgical workup of epilepsy patients: a prospective study.Lene Duez, Hatice Tankisi, Peter O Hansen, Per Sidenius, Anne Sabers, Lars H Pinborg, Martin Fabricius, Gyorgy Rasonyi, **Guido Rubboli, Birthe Pedersen**, Anne-Mette Leffers, Peter Uldall, Bo Jespersen, Jannick Brennum, Otto M Henriksen, Anders Fuglsang-Frederiksen, and Sandor Beniczky. Neurology 2019 Feb 5;92(6):e576-e586

10. Update on the genetics of the epilepsy-aphasia spectrum and role of GRIN2A mutations. G. Lesca, **R.S. Møller**, G. Rudolf, E. Hirsch, **H. Hjalgrim**, P. Szepetowski. Epileptic Disorders, in press.

11. Quantitative EEG analysis in ESES. G. Cantalupo, **E. Pavlidis, S. Beniczky**, P. Avanzini, **E. Gardella**, P. Larsson. Epileptic Disorders, in press

12. Rare coding variants in genes encoding GABAA receptors in genetic generalised epilepsies: an exome-based case-control study.May P, Girard S, Harrer M, Bobbili DR, Schubert J, Wolking S, Becker F, Lachance-Touchette P, Meloche C, Gravel M, Niturad CE, Knaus J, De Kovel C, Toliat M, Polvi A, Iacomino M, Guerrero-López R, Baulac S, Marini C, Thiele H, Altmüller J, Jabbari K, Ruppert AK, Jurkowski W, Lal D, Rusconi R, Cestèle S, Terragni B, Coombs ID, Reid CA, Striano P, 14.Caglayan H, Siren A, Everett K, **Møller RS, Hjalgrim H**, Muhle H, Helbig I, Kunz WS, Weber YG, Weckhuysen S, Jonghe P, Sisodiya SM, Nabbout R, Franceschetti S, Coppola A, Vari MS, Kasteleijn-Nolst Trenité D, Baykan B, Ozbek U, Bebek N, Klein KM, Rosenow F, Nguyen DK, Dubeau F, Carmant L, Lortie A, Desbiens R, Clément JF, Cieuta-Walti C, Sills GJ, Auce P, Francis B, Johnson MR, Marson AG, Berghuis B, Sander JW, Avbersek A, McCormack M, Cavalleri GL, Delanty N, Depondt C, Krenn M, Zimprich F, Peter S, **Nikanorova M**, Kraaij R, van Rooij J, Balling R, Ikram MA, Uitterlinden AG, Avanzini G, Schorge S, Petrou S, Mantegazza M, Sander T, LeGuern E, Serratosa JM, Koeleman BPC, Palotie A, Lehesjoki AE, Nothnagel M, Nürnberg P, Maljevic S, Zara F, Cossette P, Krause R, Lerche H; Epicure Consortium; EuroEPINOMICS CoGIE Consortium; EpiPGX Consortium. Lancet Neurol. 2018 Aug;17(8):699-708.

13. Genetic variation in CFH predicts phenytoin-induced maculopapular exanthema in European-descent patients. McCormack M, Gui H, Ingason A, Speed D, Wright GEB, Zhang EJ, Secolin R, Yasuda C, Kwok M, Wolking S, Becker F, Rau S, Avbersek A, Heggeli K, Leu C, Depondt C, Sills GJ, Marson AG, Auce P, Brodie MJ, Francis B, Johnson MR, Koeleman BPC, Striano P, Coppola A, Zara F, Kunz WS, Sander JW, Lerche H, Klein KM, Weckhuysen S, Krenn M, Gudmundsson LJ, Stefánsson K, Krause R, Shear N, Ross CJD, Delanty N; EPIGEN Consortium;, Pirmohamed M, Carleton BC; Canadian Pharmacogenomics Network for Drug Safety;Cendes F, Lopes-Cendes I, Liao WP, O'Brien TJ, Sisodiya SM; EpiPGX Consortium;, Cherny S, Kwan P, Baum L; International League Against Epilepsy Consortium on Complex Epilepsies;, Cavalleri GL.Neurology. 2018 Jan 23;90(4):e332-e341. Epub 2017 Dec 29. Erratum in: Neurology. 2018 Oct 16;91(16):765.

14. The International League Against Epilepsy Consortium on Complex Epilepsies. Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies. Nature Communications .2018 Dec 10;9(1):

15. Clinical spectrum of STX1B-related epileptic disorders. Stefan Wolking, Patrick May, Davide Mei, **Rikke S. Møller,** Simona Balestrini, Katherine L. Helbig, Cecilia Desmettre Altuzarra, Nicolas Chatron, Charu Kaiwar, Katharina Stoehr, Peter Widdess-Walsh, Bryce A. Mendelsohn, Adam Numis, Maria R. Cilio, Wim Van Paesschen, Lene L. Svendsen, Stephanie Oates, Elaine Hughes, Sushma Goyal, Kathleen Brown, Margarita Sifuentes Saenz, Thomas Dorn, Hiltrud Muhle, Alistair T. Pagnamenta, Dimitris V. Vavoulis,Samantha J.L. Knight, Jenny C. Taylor, Maria P. Canevini, Francesca Darra, Ralitza Gavrilova, Zöe Powis, Shan Tang, Justus Marquetand, Martin Armstrong, Duncan McHale, Eric W. Klee, Gerhard J. Kluger, Daniel H. Lowenstein, Sarah Weckhuysen, Deb K. Pal, Ingo Helbig, Renzo Guerrini, Rhys H. Thomas, Mark I. Rees, Gaetan Lesca, Sanjay M. Sisodiya, Yvonne G. Weber, Dennis Lal, Carla Marini, Holger Lerche, and Julian Schubert. Neurology. 2019 Mar 12;92(11):e1238-e1249.

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8. Oral Presentations

Sàndor Beniczky, Professor, MD

- 4th Congress of the European Academy of Neurology, Lisbon, Portugal, June 16-19, 2018, Lectures: "How to localize EEG potentials".
- "Digital outcome assessment in epilepsy".
- 19th International Symposium on Severe Infantile epilepsies: old and new treatments. Rome, Sept. 20-22, 2018 Lecture: "SUDEP: pathogenesis and prevention"
- Sleep and Epilepsy: from clinical research to European statements for clinical practice. Bologna, Italy, April 19-20, 2018. Lecture: "Assessing seizures within the 24 hour time-span: past and future"
- Advances in Neuroscience and new strategies for preventing and treating brain diseases, Moscow, November 12-13, 2018.Lecture: "EEG in status epilepticus".
- "Electromagnetic source imaging: a prospective study of diagnostic accuracy and clinical utility in presurgical evaluation".
- "Automated EEG source imaging: a retrospective, blinded clinical validation study".
- "Epicare – prospective evaluation of ESI"
- "Non-EEG based seizure detection"
- "Clinical Utility of High Versus Low Density EEG Source Imaging in Presurgical Evaluation: Impact on decision Making" M.T. Foged*, T. Martens*, N. Hamrouni*, L.H. Pinborg*,O.B. Paulson*, M. Fabricius‡, S. Beniczky,
- Intensive Care Unit Electroencephalogram (ICU EEG) – using the standardized terminology in clinical practice.EEG Based Biomarkers in Neuropsychiatric Disorders: Pitfalls and Opportunitites.
- "ICU EEG Terminology, including ACNS Guidelines" Sandor Beniczky, MD, PhD (Denmark)
- "Automated Detection of Convulsive Seizures Using Surface EMG" Sandor Beniczky, MD, PhD (Denmark)
- "Web Based EEG Teaching Techniques" Sandor Beniczky, MD, PhD (Denmark)

Guido Rubboli. MD Professor.

- Sleep and Epilepsy, 19-20.4 18, Bologna (Italy): Speaker: "ESES as a model of slow wave sleep pathology in the developmental age"
- National Congress of the Italian League Against Epilepsy 6.6.18 Rome (Italy): Speaker: "Brivaracetam, from clinical trials to daily practice"
- New Experimental Workshop on epileptic patient management 14-15.6.18, Padova (Italy). Teacher and Discussant
- European Academy of Neurology Meeting, Lisbon (Portugal) 16-19.6.19, Chairman platform session
- 3rd Dianalund International Conference on Epilepsy, Ringsted (Denmark), 28-29.6.18, Speaker: "KCNA2: genotype-phenotype associations and treatment implications"
- Dianalund Summer School on EEG and Epilepsy, Dianalund (Denmark) 15-21.7.18, tutor and speaker: "Polygraphic recordings"
- European Congress on Epileptology, Wien (Austria), 26-30.8.18: Speaker: "KCNA2 epileptic encephalopathy"
- NESREC meeting, København (Denmark), 25.10.18, speaker: "Genetics in Epilepsy Surgery"
- Meeting on Improving the quality of life for patients living with epilepsy", København (Denmark), 4.10.18: Speaker: "Current evidences and literature review on New AEDs"
- Annual Meeting of the Regional Section of the Italian League against epilepsy, Ferrara (Italy), 17.11.18: Speaker: "Case presentation on KCNA2 epileptic encephalopathy" and "The regional hub for epilepsy surgery in Emilia-Romagna"

Elena Gardella, MD, Ass Professor

- First residential course on movement disorders in childhood, 20-23.05.2018 Tagliacozzo, Italy "Paroxysmal movement disorders in children"
- Horizon Symposium on "Dravet syndrome and other sodium channel related encephalopathies" 15-17.03.2018 Verona, Italy
- Phenotypic spectrum of SCN8A-related disorders and treatment option outcome
- Dianalund Summer School on EEG and Epilepsy.The 15th-21st.July.18 Dianalund ESES / CSWS.
- (1)EEG patterns in genetic epilepsies of childhood and adolescence: SCN8A epileptic encephalopathy
- (2) Risk factors for early mortality in SCN8A related epilepsy
- American Epilepsy Society annual meeting 30.11/04.12.18 New Orleans, USA. SCN8A Clinician, Researcher, and Family gathering meeting ; Risk factors for early mortality in SCN8A-epilepsy
- Graduate Course: Understanding the Brain through the Hippocampus and other neural systems Emergence of innate motor patterns during epileptic seizures. 2018. Århus
- Riunione policentrica. The 24.-26.01.18 Rome. Case presentation.
- "Hard Cases". 01.02. 18 RH København. Case presentation

Katrine Harries Johannesen, MD, Phd. student.

- "Presentation of the paper: Defining the phenotypic spectrum of SLC6A1 mutations" – Online/Youtube
- Precision medicine in severe epilepsies caused by mutations in voltage-gated sodium channel genes - Brain Prize Site Visit, Odense University Hospital, Denmark
- SLC6A1 – MAE with a twist – DICE, 3rd Dianalund International Conference on Epilepsy, Sørup Herregård, Denmark
- GRIN1 and Serine treatment – Holland
- From children in Africa to genetics.– Girls Day in Science, Sorø
- Genetic testing in adults – LEGOLAS, Heidelberg

Marina Nikanorova, MD

- 01.02.18 – French Neuropediatric Society meeting, Bordeaux, France " Zebinix: new data, a hands-on AEDs tailored for daily practice"
- Marts 2018 Course; "Fra svært til lært", Odense – "Choice of AEDs for children with epilepsy", "Dravet syndrome: clinical features, diagnosis and management"
- June 2018 – Baltic Sea Summer School on Epilepsy, Vilnius, Lithuania – "Non-epileptic paroxysmal conditions in childhood", "Treatment of epileptic encephalopathies", "Case-oriented learning", 5 morning sessions on seizure semiology
- August 2018 – European Epilepsy Congress, Vienna – "Perampanel add-on therapy in children with refractory focal epilepsy: are there most efficacious AED combinations?"
- Marts 2018 – neuropaediatric meeting, Århus "New treatment possibilities of Dravet & Lennox-Gastaut syndrom". "Case-oriented learning".
- September 2018 - Neuropaediatric Congress, Copenhagen – "Epileptic encephalopathies of early childhood", "Epileptic syndromes of childhood

Vibeke Stubbings, Research Nurse – Coordinator

- September 2018 Neuropediatric Congress for Paediatrics, Copenhagen; Practical Issues when a child has epilepsy"

Rikke Steensbjerre Møller, Ass. Professor

- Hope for new treatment of severe epilepsy, Saniona, Copenhagen, Denmark
- Epilepsy Genetics in the Era of Precision Medicine: Implications for Testing and Targeted Treatment. Danish Society of Clinical and Chemical Pharmacology, PharmaSchool, University of Copenhagen, Copenhagen, Denmark
- Genetics of SCN2A, Sandvika Epilepsy Centre, Oslo, Norway

- Hope for new treatment of severe epilepsy, Bio-Europe, Neuroscience event, 2018, Copenhagen, Denmark
- Somatic mutations in genes causing epilepsy, Genomic Medicine 2018, Nordic Conference, University of Southern Denmark, Denmark
- Genetics of epilepsy, 37th conference of the Nordic Neuropediatric Society, Copenhagen, Denmark.
- SLC6A1: Myoclonic Atonic Epilepsy, ECE forum on "EEG patterns in genetic epilepsies of childhood" 13th European Congress on Epileptology, Vienna, Austria
- KCNB1 encephalopathy: a neurodevelopmental disorder including epilepsy and autism, 3rd Dianalund International Conference on Epilepsy, Sørup Herregård, Denmark
- Why you need to consider genetic testing of children with epilepsy, 46th meeting of the Société Européenne de Neurologie Pédiatrique, Barcelona Spain
- Genetics of SCN8A, 4° Horizons for Dravet Syndrome, Verona, Italy
- mTOR pathway in familial focal epilepsies. Research meeting (epilepsy surgery), Rigshospitalet, Copenhagen, Denmark

Jens Borgaard Larsen, Molecular Biologist

- Therapeutically drug monitoring (TDM) – focus on antipsychotic, antidepressiva and antiepileptica, Copenhagen. Filadelfia Laboratorium.

9. Poster presentations 2018

European Congress of Epilepsy, Vienna:

Allan Bayat 1,9 , Alexej Knaus 2,3,4 , Annika Wollenberg Juul 1 , Karine Lascelles 5, Manuela Pendziwiat 6, Agnieszka Charzewska7, Ewa Obersztyn7, Dorota Hoffman-Zacharska7, Line HG Larsen8, **Helle Hjalgrim** 9,10, Deb K Pal11, Denise Horn2, Peter Krawitz 2,3,4, Yvonne Weber 12, Ingo Helbig 5,13, **Rikke S. Møller** 9,10 PIGT-CDG, a disorder of glycosylphosphatidylinositol anchors: description of six novel patients and expansion of the clinical characteristics.

Elena Gardella, Katrine Johannsen, Ingrid Scheffer, Katherine Howell Douglas M Smith, Ingo Helbig, **Rikke S. Møller, Guido Rubboli**. Risk factors for early mortality in SCN8A related epilepsy. Epilepsia 2018; 59(S3): S46.

Rubboli G , Desai S , Naidu S , Srivastava S , Helbig I , Pendziwiat M , Polster T , Koeleman B , **Møller RS , Gardella E.** ESES-like EEG pattern in KCNB1-related encephalopathy.

Fenger C.D.1,2, Larsen L.H.G.1, **Møller R.S**.2, **Hjalgrim H**.1,2, Brusgaard K.1,3, Dahl H.A.1Identification of structural and copy-number variants in previously unsolved epilepsy cases using linked-reads sequencing technique.

Adriana Magaudda, **Christina Dühring Fenger**, Chiara Reale, Helle Hjalgrim, Carlo Alberto Tassinari, **Rikke S Møller, Elena Gardella.** Familial early onset eyelid myoclonia with absences associated with RORB mutation. Epilepsia 2018; 59(S3): S316.

Daniella Terney, Marianne S Petersen Khinchi, Marina Nikanorova, Kern Olofsson, Rikke Steensbjerre Møller, Guido Rubboli, Sándor Beniczky, Elena Gardella. The diagnostic significance of long-term EEG recording for the diagnosis/follow-up of ESES/CSWS. Epilepsia 2018; 59(S3): S69.

Katrine M. Johannesen, J. Toulouse, D. Mitter, A.-L. Poulat, D. Ville, E. Brilstra, K.P. Geleijns, A.P. Born, Elena Gardella, Guido. Rubboli, G. Lesca, J. Lemke, **Rikke S. Møller.** Defining QARS: Catastrophic Epilepsy, Microcephaly and Encephalopathy. Epilepsia 2018; 59(S3): S215.

Guido Rubboli, S. Desai, S. Naidu, S. Srivastava, I. Helbig, M. Pendziwiat, T. Polster, B. Koeleman, **Rikke S. Møller, Elena Gardella**. ESES like EEG Pattern in KCNB1 Related Encephalopathy. Epilepsia 2018; 59(S3): S312 .

Marina Nikanorova, Charlotte Vittenbach, Pia Gellert, Marianne Søndergaard, Birgit Jepsen, Klaus Ehrenreich Is it worthwhile to try Eslicarbazepine acetate if Carbamazepine and Oxcarbazepine have failed?

Line Westergaard, Anne Brodersen, Klaus Ehrenreich. Epilepsy nurses makes a difference -The nurse`s new role increase(s) the quality of the cognitive examination of children with epilepsy, and binds interdisciplinary collaboration together.

Klaus Ehrenreich. "It's my worse fear" - a phenomenological study of being the parent of a 3-6 year old child with epilepsy.

AES New Orleans:

Elena Gardella, Katrine Johannsen, Ingrid Scheffer, Katherine Howell, Douglas M Smith, Ingo Helbig, **Rikke S Møller**, Guido Rubboli. Risk factors for early mortality in SCN8A related epilepsy.

Mette Thrane Foged (1), Terje Martins, Nizar Hamrouni, Minna Litman, **Guido Rubboli**, Philippe Ryvlin, Lars H Pinborg Olaf B Paulson, Martin Fabricius, **Sándor Beniczky** Clinical Utility of ESI in Presurgical Evaluation of Patients with Epilepsy.

Anders Buch Justesen, Diagnostic added value of high-density versus low-density EEG recordings.

The Danish National Conference for nurses working with developmental projects and research:

Trine Arnam-Olsen Moos. The repressed diversity'' - a critical Foucault discourse analysis of the powers of organizational patient-involvement.

Nyborg Strand at 1st Nordic Congress in Personalized Medicine

Jan B. Rasmussen, Per B. Jensen, Jens B. Larsen. Fighting adverse drug reactions (ADR), a cyp450 genetic test panel with reported allele frequencies of cyp2c9,2c19 and 2d6 in a Danish Population

Ispor, Europe 2018, Barcelona

Irwin J1, Kumar A2, Gagnon J2, Taylor J2, Nikanorova M3,4, Marjanovic D3, **Møller RS** 3,4, Busch-Sørensen M5 REAL WORLD TREATMENT PATTERNS IN PAEDIATRIC DRAVET SYNDROME PATIENTS IN DENMARK USING ELECTRONIC MEDICAL RECORD

Sixth Global Symposium on Ketogenic Therapies for Neurological Disorders, Korea

Betina Koldby Implementation of Ketogenic Diet Guidelines for infants. Attention to; fluid and protein intake and sufficient vitamin- and mineral supplements.

Birgit Jepsen, & Cathrine Tronhjem. FOXG1, two boys treated with ketogenic diet.

Helle Nielsen, Video consultation - evaluation of experience with video consultation as a form of dissemination.

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