



# ANNUAL RESEARCH REPORT 2020

Danish Epilepsy Centre Filadelfia

## Content

1	Introduction to the Danish Epilepsy Center Filadelfia	4
2	Core Research Team 2020	5
3	Ph.D. projects	7
4	Research projects	8
5	Clinical trials	23
6	Dianalund International Conference on Epilepsy	24
7	Lectures - oral presentations at congresses in 2020	25
8	Publications in peer-reviewed scientific journals	25
9	Acknowledgements	31

3  
Professors 

2 Ass.  
Professors 

7 Ph.D.  
students 

75  
Publications \*) 

28  
Oral Presentations 

\*) 75 papers published in peer-reviewed international journals, including leading journals, such as *Brain*, *Annals of Neurology*, *Genome Medicine*, *Neurology* and *Epilepsia*

## 1. Introduction – Filadelfia.

Filadelfia - The Danish Epilepsy Centre - offers highly specialized health care services to epilepsy patients of all ages. Being the only third line centre for treatment of epilepsy in Denmark, we have a unique access to rare and complex epileptic syndromes on the basis of which our centre is internationally acclaimed. In 2020 Filadelfia's three professors, two associate professors and seven Ph.D. students published 75 publications in international and national journals and contributed with 28 oral presentations. Our researchers who are affiliated to University of Copenhagen, University of Odense and University of Aarhus, occupy positions of trust in national and international scientific societies, and participate in a series of international epilepsy research networks.

The COVID-19 pandemic changed the conditions for researchers. Physical meetings has been on halt and scientific conferences have been turned into virtual events, one of which was the 4.th Dianalund International Conference on Epilepsy, which was held virtually 12th-13th November 2020.

The Danish Epilepsy Center, Filadelfia is a non-profit foundation with an independent Board of Directors and 124 years history of medical treatment of patients with epilepsy. It is publically funded and an integral part of the Danish Health-care System. Besides the Epilepsy hospital, Filadelfia comprises a centre of neurorehabilitation, specialized institutions for mentally handicapped persons and the only special school for children and young people with epilepsy in Denmark. The Epilepsy Hospital receives patients from the five Danish Regions i.e. the public hospitals and practitioners. The specialized social institutions receive clients from the Danish Municipalities.

We are proud to publish this report and wish it to encourage further collaboration for the benefit of persons with epilepsy worldwide.



## 2. Core Research Team 2020



**Sándor Beniczky MD, Ph.D.**  
**Professor, Head of Department**  
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- Editor-in-Chief, Epileptic Disorders
- Editorial board: Epilepsia; Epilepsy and Behavior
- Chair, Joint Taskforce on EEG of the International Federation of Clinical Neurophysiology (IFCN) and the International League Against Epilepsy (ILAE)
- Treasurer and executive board member, ILAE-Europe
- Member, ILAE Commission on Diagnostic Methods
- Member, ILAE Education Council; coordinator of the Virtual Epilepsy Academy (VIREPA)
- Member, ILAE Publication Council
- Member, ILAE Congress Council
- Leader of the work-package on Clinical Neurophysiology, EpiCARE: a European Reference Network for rare and complex epilepsies.



**Guido Rubboli MD, Ph.D.**  
**Professor, Senior Consultant**  
**Email: guru@filadelfia.dk**

- Associate Editor, Epileptic Disorders, Frontiers in Neurology
- Section editor, Behavioral Neurology
- Editorial board, Epilepsy and Behavior Report
- Chair, Epilepsy scientific panel, European Academy of Neurology
- Member, ILAE Task Force "Transition in care from Childhood into Adulthood"
- Member, EpiCARE: a European Reference Network for rare and complex epilepsies.
- Member of the Scientific Committee: "Fuori dall'ombra, insieme per l'epilessia"
- Scientific Advisory Board member: KCNT1 Foundation



**Rikke Steensbjerre Møller, Ph.D.**  
**Professor, Head of department**  
**Email: rimo@filadelfia.dk**

- Scientific Advisory Board member: KCNT1 Foundation
- Member, EpiCARE: a European Reference Network for rare and complex epilepsies.
- Member of the leadership team at Department of Regional Health Research, University of Southern Denmark, Odense, Denmark.
- Member of the scientific committee of Residras: a European Registry of Dravet Syndrome, Verona, Italy.



**Elena Gardella MD, Ph.D.**  
**Associate Professor, Senior Consultant**  
**Email: elga@filadelfia.dk**

- Associate editor, Functional neurology- pediatrics
- Member, Executive board, Danish Epilepsy Society
- Course director, ILAE educational program on basic-EEG (VIREPA)
- Member of the reviewer board of COSTs
- Member of the international academic network of Rome



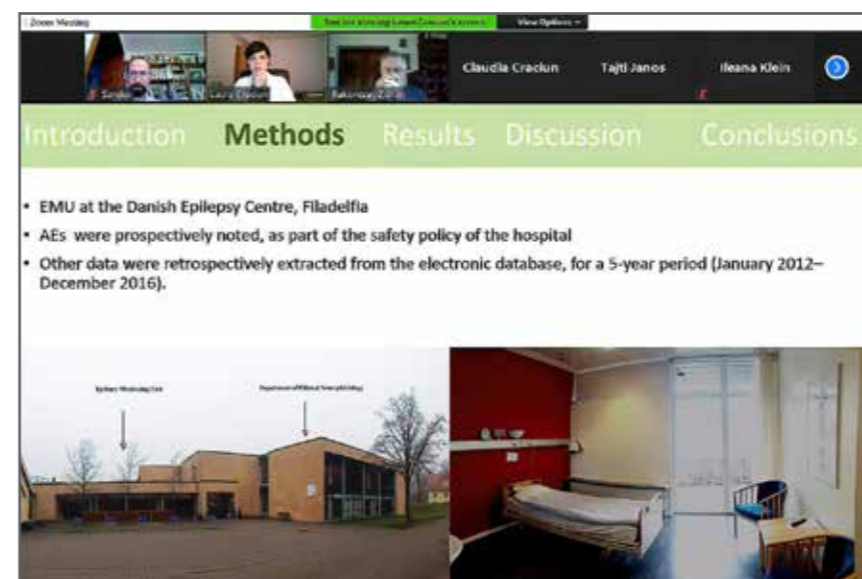
**Marina Nikanorova MD, Ph.D.**  
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## Research Team

Sidsel Armand Larsen, MSc  
Trine Arnam-Olsen Moos, RN  
Mustafa Aykut Kural, MD  
Allan Bayat, MD  
Christina Fenger, MSc, Ph.D.  
Francesca Furiá, MD  
Margherita Furlan, MSc  
Trine Hammer, MD, Ph.D.  
Mathis Hildonen, MSc  
Jesper Jeppesen, Ph.D.  
Katrine Johannesen, MD, Ph.D.  
Pirgit Meritam Larsen, MD, Ph.D.  
Nazanin Mohammadi, MSc  
Vibeke Stubbings, RN  
Daniella Terney MD, Ph.D.  
Anne Vagner Jakobsen, MSc  
Stephan Wüstenhagen, MD, Ph.D.



## 3. Ph.D. projects



*Due to the pandemic, Ph.D. defenses were online in 2020 - as shown in this screenshot from Zoom*

### Completed in 2020:

- Laura Craciun: Standardization and quality assurance in clinical electroencephalography. University of Szeged, Hungary.  
Main supervisor: Sándor Beniczky. Co-supervisor: László Vécsei
- Joanna Goetsche: Endophenotyping patients of Genetic Generalized Epilepsy – a population-based study. University of Southern Denmark  
Co-supervisor: Guido Rubboli. Main supervisor: Christoph Beier
- Cheng-Teng Ip: Towards personalized medicine: Effectiveness of pretreatment EEG biomarker in Major Depressive Disorder. University of Copenhagen.  
Co-supervisor: Sándor Beniczky. Main supervisor: Gitte Moos Knudsen.

### Ongoing:

- Mustafa Aykut Kural: Clinical practice of EEG revisited: improved spike identification, localization and characterization. Aarhus University.  
Main supervisor: Sándor Beniczky.
- Allan Bayat: Deep phenotyping, genotype-phenotype correlations and precision medicine in monogenic epilepsies. University of Southern Denmark Main supervisor: Rikke Steensbjerre Møller.  
Co-supervisor: Guido Rubboli.
- Bogdan Florea: Electroencephalography in patients with disturbed level of consciousness. University of Szeged, Hungary. Main supervisor: Sándor Beniczky.  
Co-supervisor: László Vécsei.
- Levente Hadady: Assessment of the clinical impact of electronic applications and wearable devices on the clinical management of patients with epilepsy. University of Szeged, Hungary.  
Main supervisor: Sándor Beniczky. Co-supervisor: Péter Klivényi
- Nazanin Mohammadi: Clinical and functional characterization of GABAAR-receptor related disorders: translating genetic diagnostics into personalized treatment. University of Southern Denmark Main supervisor: Rikke Steensbjerre Møller.  
Co-supervisor: Philip Ahring and Guido Rubboli
- Anne Vagner Jakobsen: Mapping of experienced stressors and resourcefulness in caregivers of children with severe epilepsy for a better patient centered treatment and care. University of Southern Denmark  
Co-supervisors: Rikke Steensbjerre Møller, Marina Nikanorova. Main supervisor: Ask Elklit.
- Karin Westin: Extending the clinical applications of magnetoencephalography. Karolinska Institute, Stockholm.  
Co-supervisor: Sándor Beniczky. Main Supervisor: Daniel Lundkvist.

## 4. Research projects

### 4.1 Source imaging:

Using mathematical algorithms, the location of the source of the EEG signals can be estimated in the brain of the patients. These techniques link neurophysiology with neuroimaging. Our research group has a decade long tradition in developing and clinical validation of source imaging. In 2020 we continued working on this research topic.

We extended these methods to investigate the source of triphasic waves - an electrographic hallmark of encephalopathy. We found that triphasic waves were generated by large bilateral networks, involving the anterior and mesial frontal cortices and the temporal pole, explain the loss of consciousness in these patients.

In a prospective study we investigated the clinical utility (i.e. diagnostic added value) of EEG source imaging in the presurgical evaluation of patients with drug-resistant focal epilepsy. We found that source imaging provided clinically useful, non-redundant information in one third of the cases. The main changes were related to decisions about the implantation of intracranial electrodes.

To increase the awareness on EEG source imaging among healthcare professionals managing patients with epilepsy, we published a seminar paper, explain the basic technical principals and we edited a special journal issue giving an up-to-date overview on source imaging in drug-resistant epilepsy.

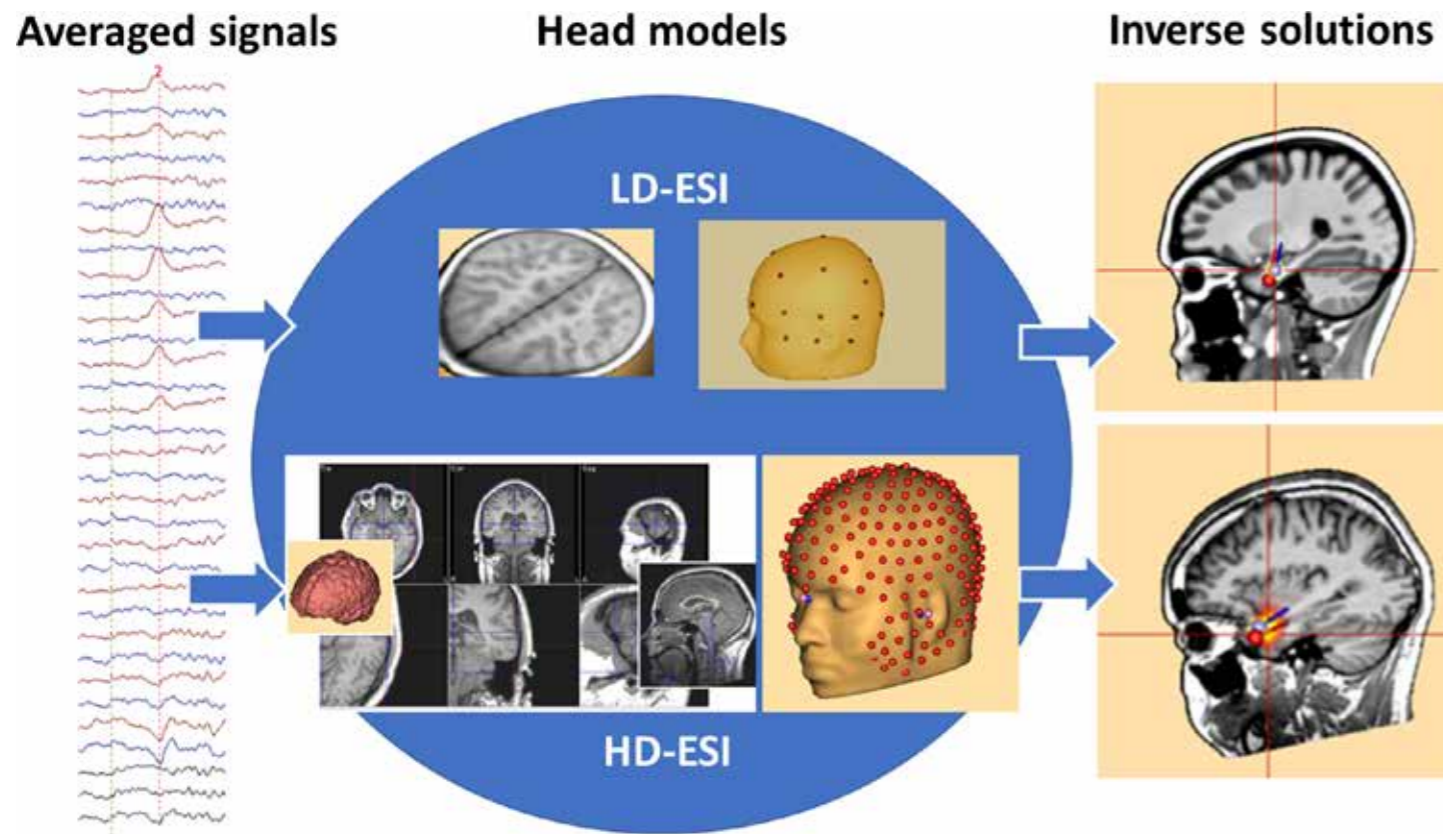


Fig.: Analysis pipeline of EEG Source Imaging

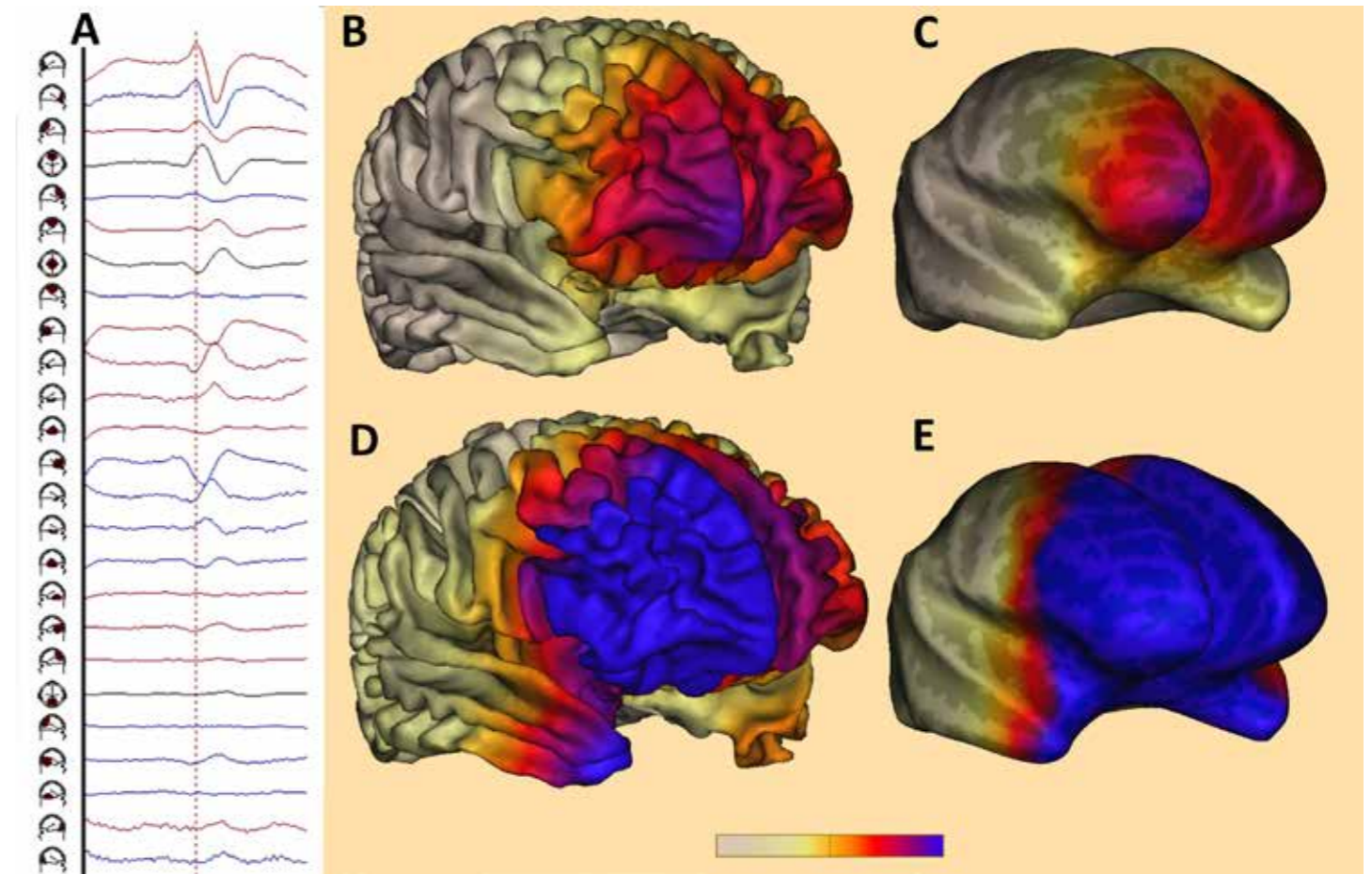


Fig.: Triphasic waves in source montage and distributed source models

### Papers:

Kural MA, Fabricius M, Christensen J, Kaplan PW, Beniczky S. Triphasic Waves Are Generated by Widespread Bilateral Cortical Networks. *J Clin Neurophysiol.* 2020; doi: 10.1097/WNP.0000000000000770.

Foged MT, Martens T, Pinborg LH, Hamrouni N, Litman M, Rubboli G, Leffers AM, Ryvlin P, Jespersen B, Paulson OB, Fabricius M, Beniczky S. Diagnostic added value of electrical source imaging in presurgical evaluation of patients with epilepsy: A prospective study. *Clin Neurophysiol.* 2020;131:324-329. doi: 10.1016/j.clinph.2019.07.031.

Beniczky S, Schomer DL. Electroencephalography: basic biophysical and technological aspects important for clinical applications. *Epileptic Disord.* 2020;22:697-715. doi: 10.1684/epd.2020.1217.

Beniczky S, Trinka E. Editorial: Source Imaging in Drug Resistant Epilepsy - Current Evidence and Practice. *Front Neurol.* 2020;11:56. doi: 10.3389/fneur.2020.00056.

### 4.2 Wearables devices and online decision support algorithms:

Technological advances will revolutionize the way we diagnose and treat epilepsy. Seizure detection using wearable devices has become a reality for generalized tonic-clonic seizures, the seizure-type that is associated with highest morbidity and mortality. In 2020, we extended our work on wearable devices and algorithms.

We demonstrated that objective measurements from wearable devices help quantifying seizure severity and identifying patients at risk.

We have validated an algorithm, based on heart-rate variability measures of ECG signals recorded with wearable devices. The algorithm achieved high sensitivity and low false alarm rate in patients with ictal autonomic changes.

We have reviewed the use of machine learning in seizure detection and we provided an overview on the advances in this field.

We have developed a freely available web-based algorithm, EPIPICK, for automated seizure-classification, linked with a decision support system for recommending optimal antiseizure therapy, tailored to the individual patient.

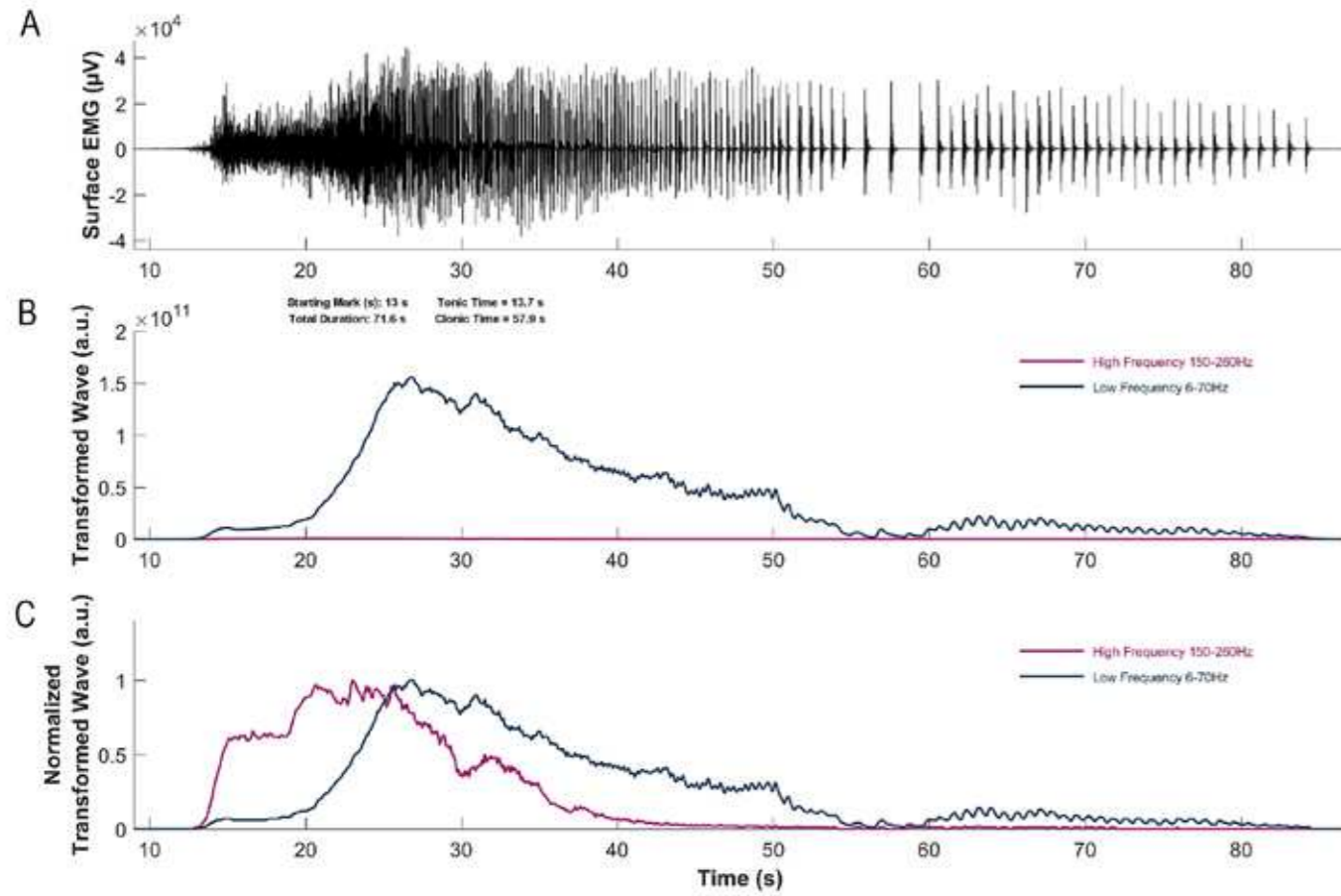


Fig.: Automated analysis of surface electromyography signals from a wearable device

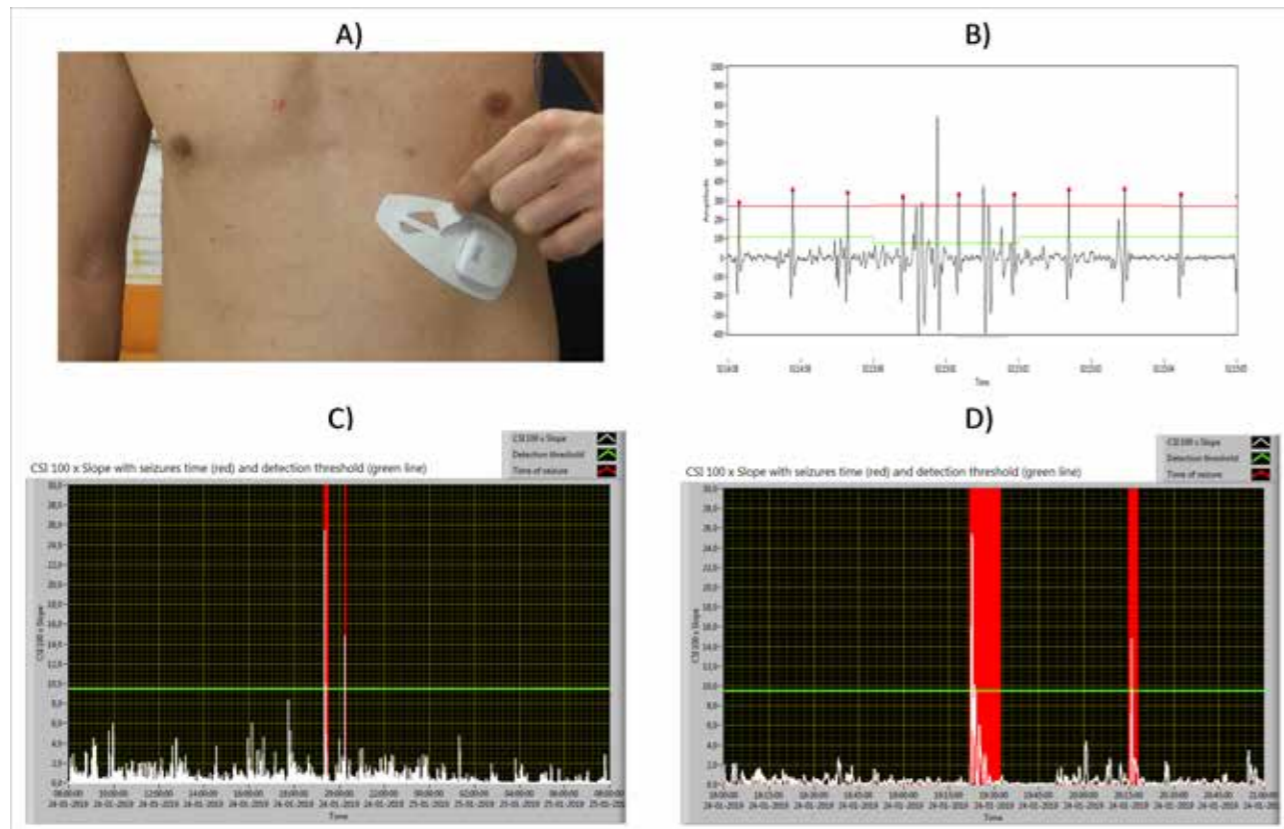


Fig.: Wearable ECG device and automated seizure detection

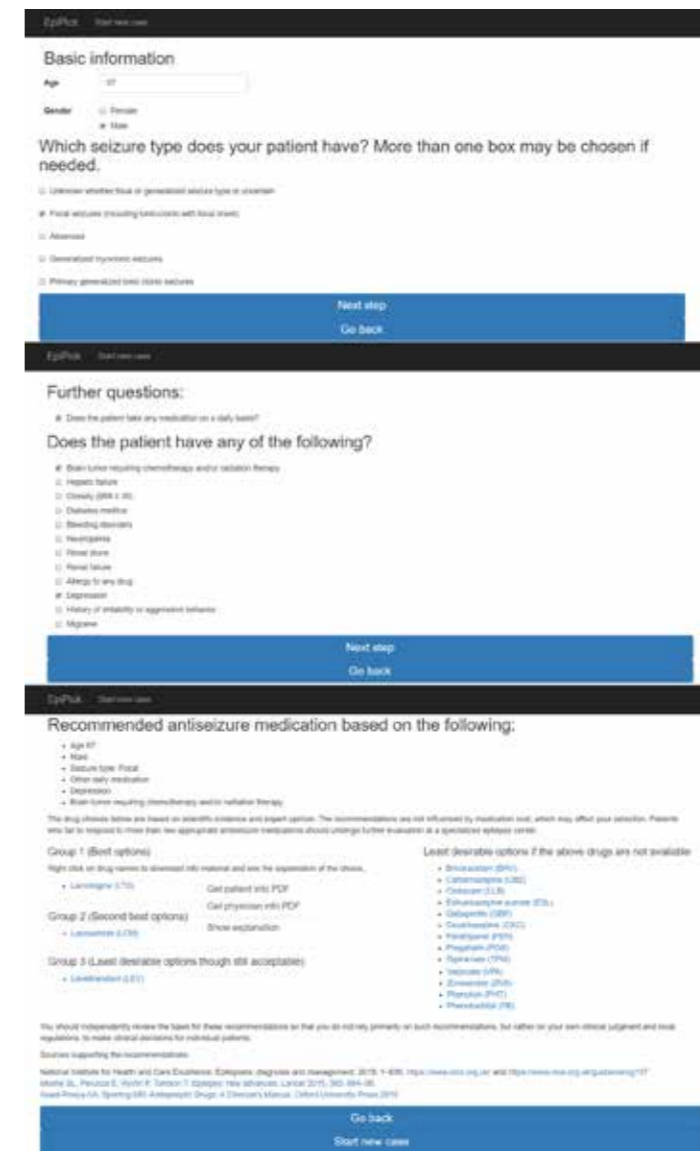


Fig.: Screenshots from the EPIPICK decision support application

## Papers:

Arbune AA, Conradsen I, Cardenas DP, Whitmire LE, Voyles SR, Wolf P, Lhatoo S, Ryvlin P, Beniczky S. Ictal quantitative surface electromyography correlates with postictal EEG suppression. **Neurology**. 2020;94:e2567-e2576. doi:10.1212/WNL.0000000000009492.

Arbune AA, Jeppesen J, Conradsen I, Ryvlin P, Beniczky S. Peri-ictal heart rate variability parameters as surrogate markers of seizure severity. **Epilepsia**. 2020;61 Suppl 1:555-560. doi: 10.1111/epi.16491.

Beniczky S, Arbune AA, Jeppesen J, Ryvlin P. Biomarkers of seizure severity derived from wearable devices. **Epilepsia**. 2020;61 Suppl 1:561-566. doi:10.1111/epi.16492.

Jeppesen J, Fuglsang-Frederiksen A, Johansen P, Christensen J, Wüstenhagen S, Tankisi H, Qerama E, Beniczky S. Seizure detection using heart rate variability: A prospective validation study. **Epilepsia**. 2020;61 Suppl 1:541-546. doi: 10.1111/epi.16511.

Ryvlin P, Cammoun L, Hubbard I, Ravey F, Beniczky S, Atienza D. Noninvasive detection of focal seizures in ambulatory patients. **Epilepsia**. 2020;61 Suppl 1:547-554. doi: 10.1111/epi.16538.

Beniczky S, Karoly P, Nurse E, Ryvlin P, Cook M. Machine learning and wearable devices of the future. **Epilepsia**. 2020; doi: 10.1111/epi.16555.

Ryvlin P, Beniczky S. Seizure detection and mobile health devices in epilepsy: Recent developments and future perspectives. **Epilepsia**. 2020;61 Suppl 1:51-52. doi: 10.1111/epi.16702.

Asadi-Pooya AA, Beniczky S, Rubboli G, Sperling MR, Rampp S, Perucca E. A pragmatic algorithm to select appropriate antiseizure medications in patients with epilepsy. **Epilepsia**. 2020;61:1668-1677. doi: 10.1111/epi.16610.

### 4.3 Clinical Electroencephalography:

EEG remains the most important functional investigation method for patients with epilepsy. Using detailed analysis of video-EEG recordings we have documented a novel generalised seizure-type that is not yet in the official seizure classification: absence-to-bilateral tonic-clonic seizures. In collaboration with a European Expert Group we have developed consensus recommendations for using EEG for diagnosing sleep-related epilepsies. We published an ILAE teaching material on the role of EEG in patients with suspected epilepsy. We demonstrated the use of the SCORE system in assessment of photoparoxysmal responses. During the COVID-19 pandemic, we mapped the consequences of restrictions and health-care restructuring, on clinical EEG practice.

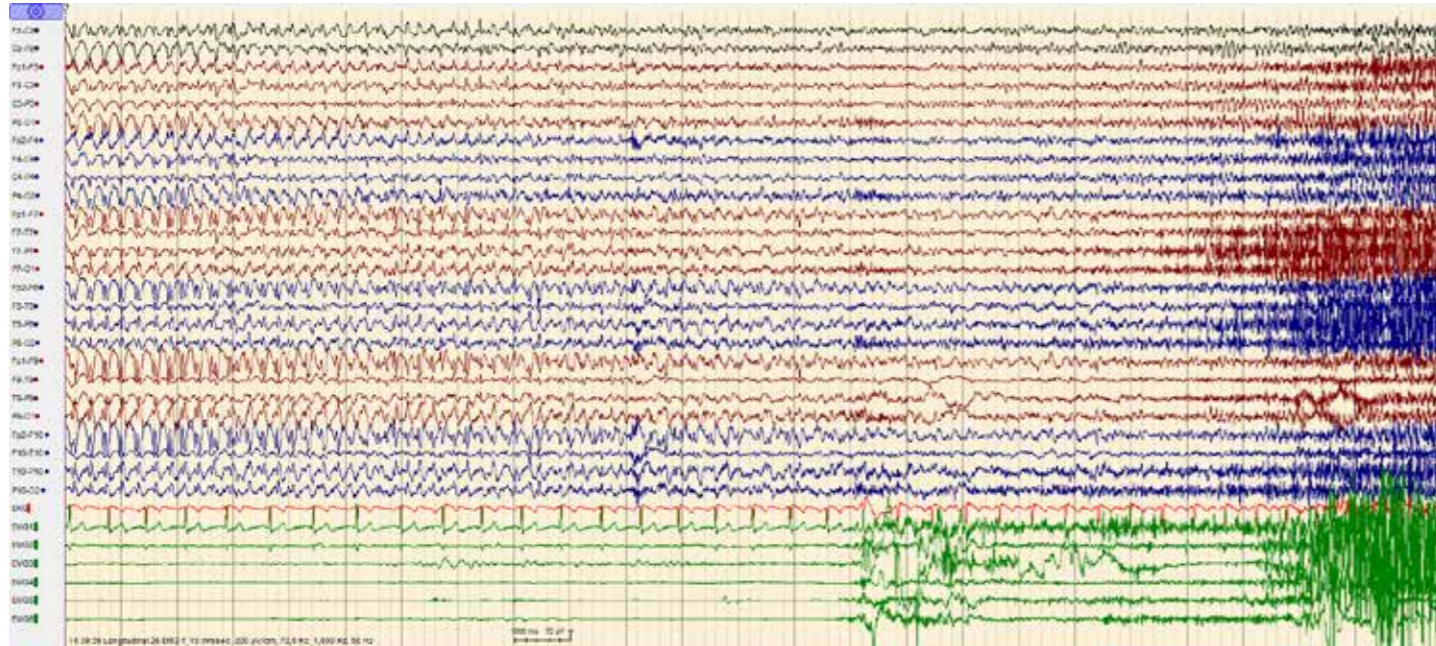


Fig.: Absence-to-bilateral-tonic-clonic seizure: polygraphic EEG and EMG recording

### Papers:

Beniczky S, Rubboli G, Covanis A, Sperling MR. Absence-to-bilateral-tonic-clonic seizure: A generalized seizure type. **Neurology**. 2020;95:e2009-e2015. doi: 10.1212/WNL.00000000000010470.

Benbadis SR, Beniczky S, Bertram E, MacIver S, Moshé SL. The role of EEG in patients with suspected epilepsy. **Epileptic Disord**. 2020;22:143-155. doi: 10.1684/epd.2020.1151.

Krysl D, Beniczky S, Franceschetti S, Arzimanoglou A. The COVID-19 outbreak and approaches to performing EEG in Europe. **Epileptic Disord**. 2020;22:548-554. doi: 10.1684/epd.2020.1208.

Nobili L, de Weerd A, Rubboli G, Beniczky S, Derry C, Eriksson S, Halasz P, Högl B, Santamaria J, Khatami R, Ryvlin P, Rémi J, Tinuper P, Bassetti C, Manni R, Koutroumanidis M, Vignatelli L. Standard procedures for the diagnostic pathway of sleep-related epilepsies and comorbid sleep disorders: A European Academy of Neurology, European Sleep Research Society and International League against Epilepsy-Europe consensus review. **J Sleep Res**. 2020;29:e13184. doi: 10.1111/jsr.13184.

Arbune AA, Nikanorova M, Terney D, Beniczky S. REM-sleep related hypermotor seizures: Video documentation and ictal source imaging. **Brain Dev**. 2020;42:503-507. doi: 10.1016/j.braindev.2020.04.003.

Beniczky S, Aurlen H, Franceschetti S, Martins da Silva A, Bisulli F, Bentes C, Canafoglia L, Ferri L, Krýsl D, Rita Peralta A, Rácz A, Cross JH, Arzimanoglou A. Interrater agreement of classification of photoparoxysmal electroencephalographic response. **Epilepsia**. 2020;61:e124-e128. doi:10.1111/epi.16655.

### 4.4 Identification of the epileptiform EEG discharges:

Epileptiform EEG discharges are the best validated and documented neurophysiological biomarker of epilepsy. In skilled hands it provides valuable information for diagnosis and classification of epilepsy. However, it is often “abused” when EEG is interpreted by physicians lacking proper training. Over-reading (over-interpretation) of the epileptiform EEG discharges is the most common cause of misdiagnosing epilepsy.

To help healthcare professionals improve their skills in identifying epileptiform EEG discharges, we have developed a set of operational criteria for identifying them. We have validated these criteria in sensor-space and in source space, and we demonstrated that high specificity and sensitivity are achieved when implementing them into the clinical practice.

Using a machine-learning approach, we have developed and validated an algorithm for identifying epileptiform EEG discharges.

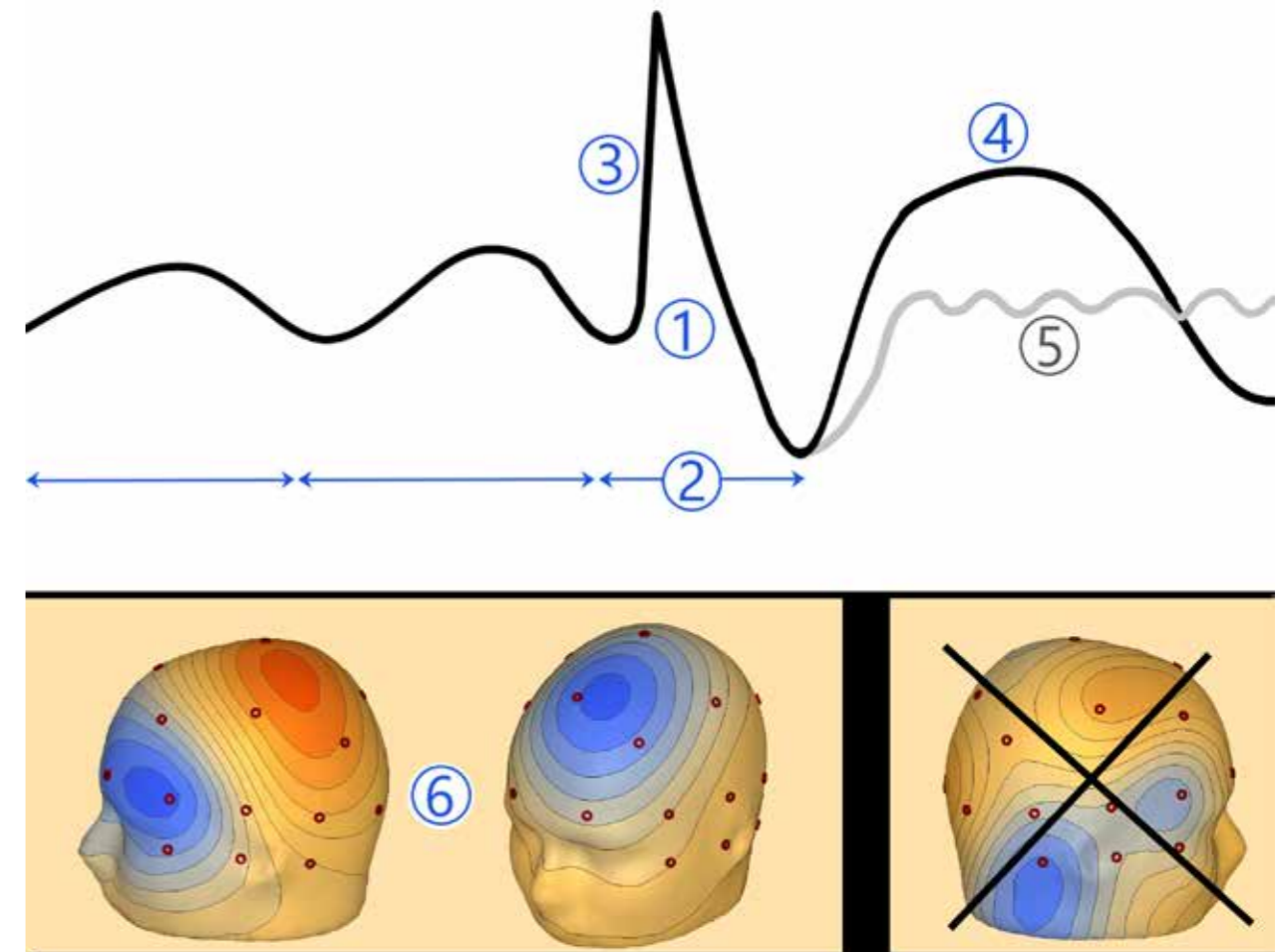


Fig.: Infographic on the operational criteria for epileptiform discharges

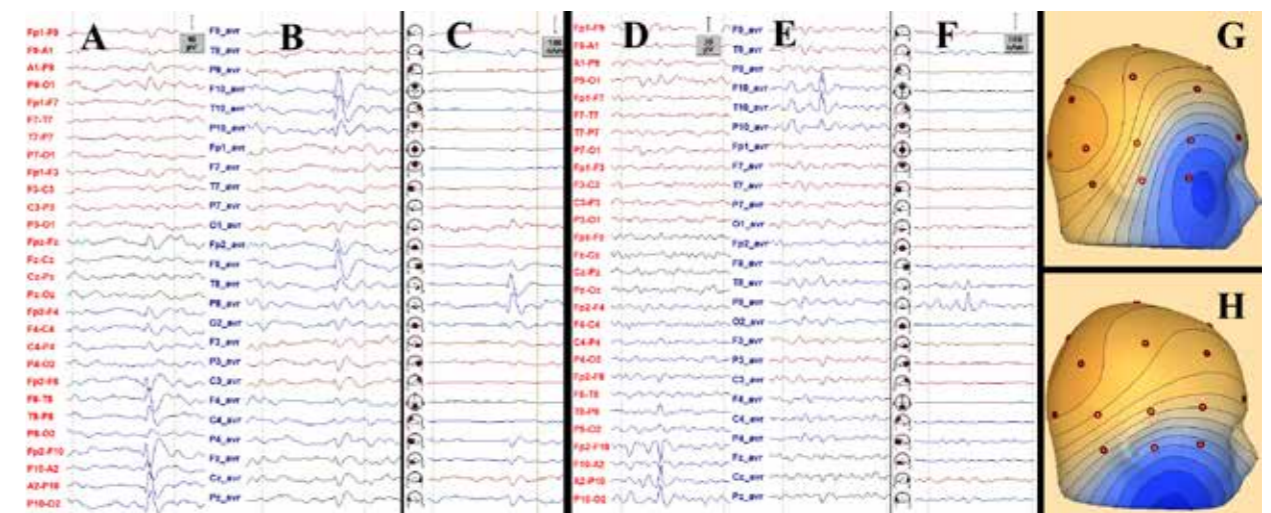


Fig.: Epileptiform discharges in sensor space, source space and their voltage map

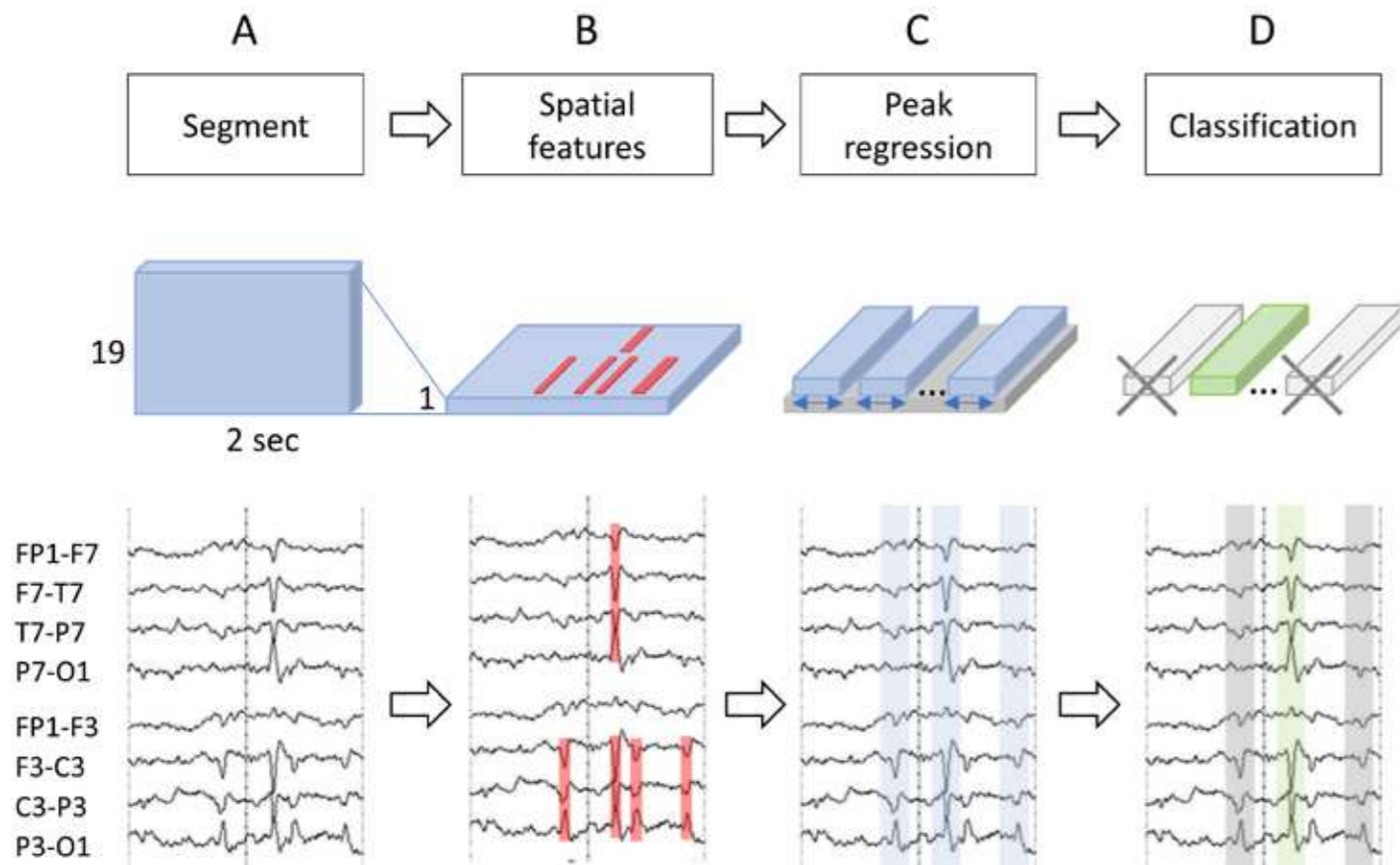


Fig.: Flow diagram of developing artificial intelligence-based spike-detection

## Papers:

Kural MA, Duez L, Sejer Hansen V, Larsson PG, Rampp S, Schulz R, Tankisi H, Wennberg R, Bibby BM, Scherg M, Beniczky S. Criteria for defining interictal epileptiform discharges in EEG: A clinical validation study. **Neurology**. 2020;94:e2139-e2147. doi: 10.1212/WNL.0000000000009439.

Kural MA, Tankisi H, Duez L, Sejer Hansen V, Udipi A, Wennberg R, Rampp S, Larsson PG, Schulz R, Beniczky S. Optimized set of criteria for defining interictal epileptiform EEG discharges. **Clin Neurophysiol**. 2020;131:2250-2254. doi: 10.1016/j.clinph.2020.06.026.

Fürbass F, Kural MA, Gritsch G, Hartmann M, Kluge T, Beniczky S. An artificial intelligence-based EEG algorithm for detection of epileptiform EEG discharges: Validation against the diagnostic gold standard. **Clin Neurophysiol**. 2020;131:1174-1179. doi: 10.1016/j.clinph.2020.02.032.

## 4.5 Connectivity studies:

It is important to investigate connectivity changes in patients with epilepsy, to understand the mechanisms of ictogenesis. Intracranial stimulation using implanted stereo-EEG electrodes, in patients evaluated for epilepsy surgery, provides a unique tool for investigating connectivity changes.

We have demonstrated that in patients with epilepsy, aberrant neural networks are established, which have an essential role in ictogenesis.

We found that sleep modulates brain excitability and reconfigures functional brain networks, depending on tissue epileptogenicity.

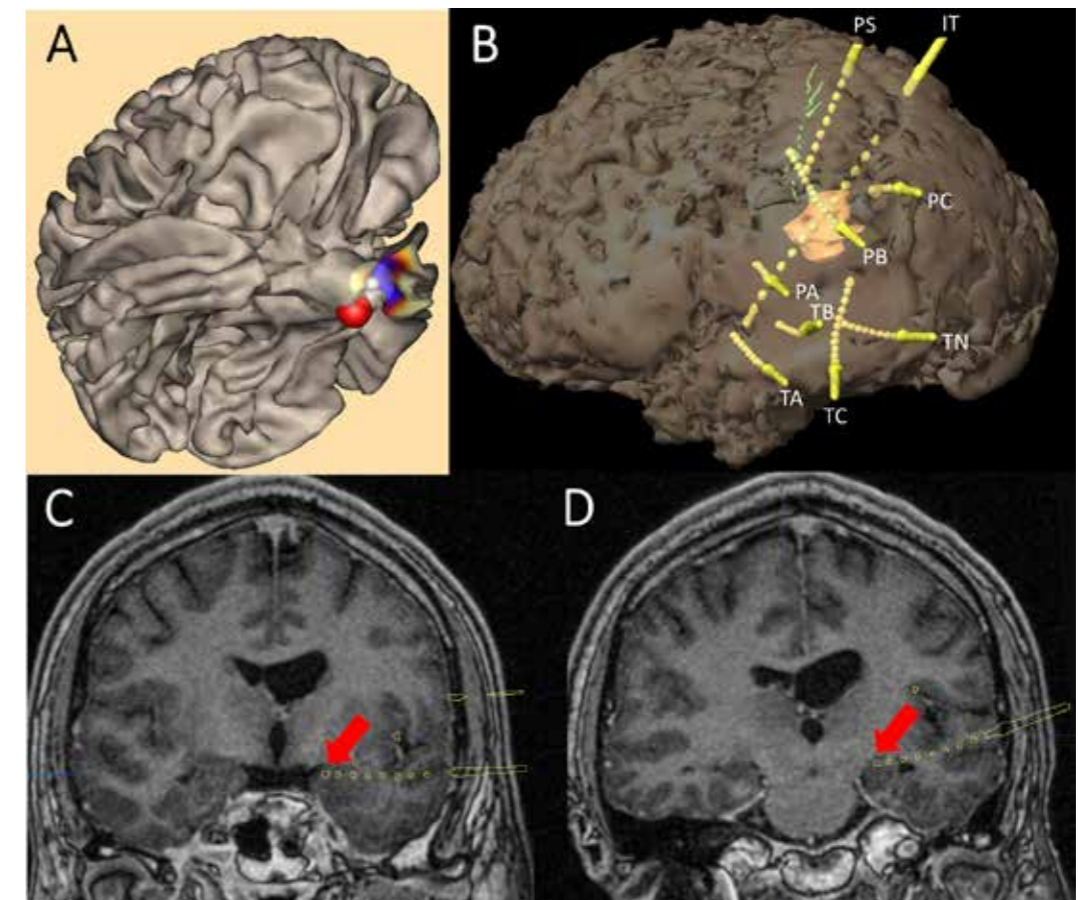


Fig.: Source imaging and stereo-EEG to map the ictal network

## Papers:

Vinding Merinder T, Rásonyi G, Tsiropoulos I, Jespersen B, Ryvlin P, Fabricius M, Beniczky S. Somatosensory phenomena elicited by electrical stimulation of hippocampus: Insight into the ictal network. **Epilepsy Behav Rep**. 2020;14:100387. doi: 10.1016/j.ebr.2020.100387.

Arbune AA, Popa I, Mindruta I, Beniczky S, Donos C, Daneasa A, Măliia MD, Băjenaru OA, Ciurea J, Barborica A. Sleep modulates effective connectivity: A study using intracranial stimulation and recording. **Clin Neurophysiol**. 2020;131:529-541. doi: 10.1016/j.clinph.2019.09.010.

## 4.6 Clinical and EEG characterization of ESES related to genetic pathogenic variants:

We have investigated the clinical and EEG features of Encephalopathy with Status Epilepticus during slow Sleep (ESES) related to CNKSR2 pathogenic variants. Neurodevelopment in infancy was normal in two patients, delayed in three. Epilepsy onset (age range: 2-6 years) was associated with appearance or aggravation of cognitive impairment, language regression and/or behavioral disorders. Worsening of epilepsy and of cognitive/behavioral disturbances paralleled by enhancement of non-rapid eye movement (NREM) sleep-related, frontally predominant, EEG epileptic discharges [spike-wave-index (SWI): range 60-96%] was consistent with ESES. In three patients, episodes of absence status epilepticus or aggravation of atypical absences occurred, in this latter case associated with striking increment of awake SWI. Speech/oro-motor dyspraxia was diagnosed in four patients. In two patients, long-term follow-up showed epilepsy remission and persistence of mild/moderate cognitive disorders and behavioral disturbances into adulthood.

Novel findings of our study are occurrence also in females, normal neurodevelopment before epilepsy onset, epilepsy aggravation associated with enhanced awake SWI, mild/moderate evolution in adulthood and language disorder due to speech/oro-motor dyspraxia.

In addition we have reported the first patient with a DEE who developed an encephalopathy related to status epilepticus during sleep (ESES) and cerebellar signs, harbouring a variant in the Kv-specific PVP motif of the KCNA1 gene. Interestingly, he showed a remarkable long-term electroclinical response to IM ACTH therapy. This report extends the range of phenotypes associated with KCNA1 variants to include that of ESES, and suggests that ACTH therapy is likely to have a positive effect in patients with these variants.



## 4.7 Clinical spectrum, ictal semiology and response to treatment in IGE/GGE:

In a large cohort of IGE/GGE patients we have investigated the pattern of treatment response and whether routinely assessed clinical and neurophysiological parameters allow predicting response to lamotrigine, levetiracetam, or valproic acid. Seizure freedom with acceptable side effects at the first attempt was achieved in 61 (18.6%) patients. One hundred four (31.7%) patients tried  $\geq 3$  antiepileptic drugs before achieving seizure control at the last follow-up. Lamotrigine, levetiracetam, and valproic acid showed differential response rates (39.8% vs 47.5% vs 71.1%) that were most pronounced in patients with juvenile myoclonic epilepsy. The risk of having side effects was higher with valproic acid (23.7%) than with lamotrigine (10.4%) or levetiracetam (20.4%) treatment, contributing to the low retention rate of valproic acid (53.7%). Treatment resistance was associated with established risk factors. Multivariate analyses aiming at identifying clinical indicators for response to specific drugs did not reveal putative biomarkers when corrected for drug resistance. Our study showed that despite a high rate of seizure control, the chance of achieving seizure control and acceptable side effects at first attempt was low due to an inverse association of effectiveness and side effects of the three most commonly used drugs. Routinely assessed clinical parameters were not indicative for response to specific drugs. This study provides Class II evidence that for patients with IGE, various clinical factors do not predict a response to specific antiepileptic drugs.

Although the genetic origin of Idiopathic/Genetic Generalized Epilepsy (IGE) is hardly disputed, only a minority of patients show Mendelian inheritance. We investigated whether clinical characteristics like long-term outcome and treatment response differ between patients with sporadic and familial IGE.

We found 121 patients (27.3%) with a positive family history of IGE, 322 (72.7%) patients had sporadic IGE. Pedigrees suggesting possible autosomal-dominant pattern of inheritance were found in 52 (11.7%) patients. Clinical characteristics, seizure frequency, surrogate markers for social outcome, psychiatric and somatic comorbidity, seizure type, EEG features, treatment response to lamotrigine, levetiracetam or valproic acid and risk of treatment resistance were similar in all groups. Our data showed that familial and sporadic IGE patients do not differ in terms of clinical phenotype and treatment response.

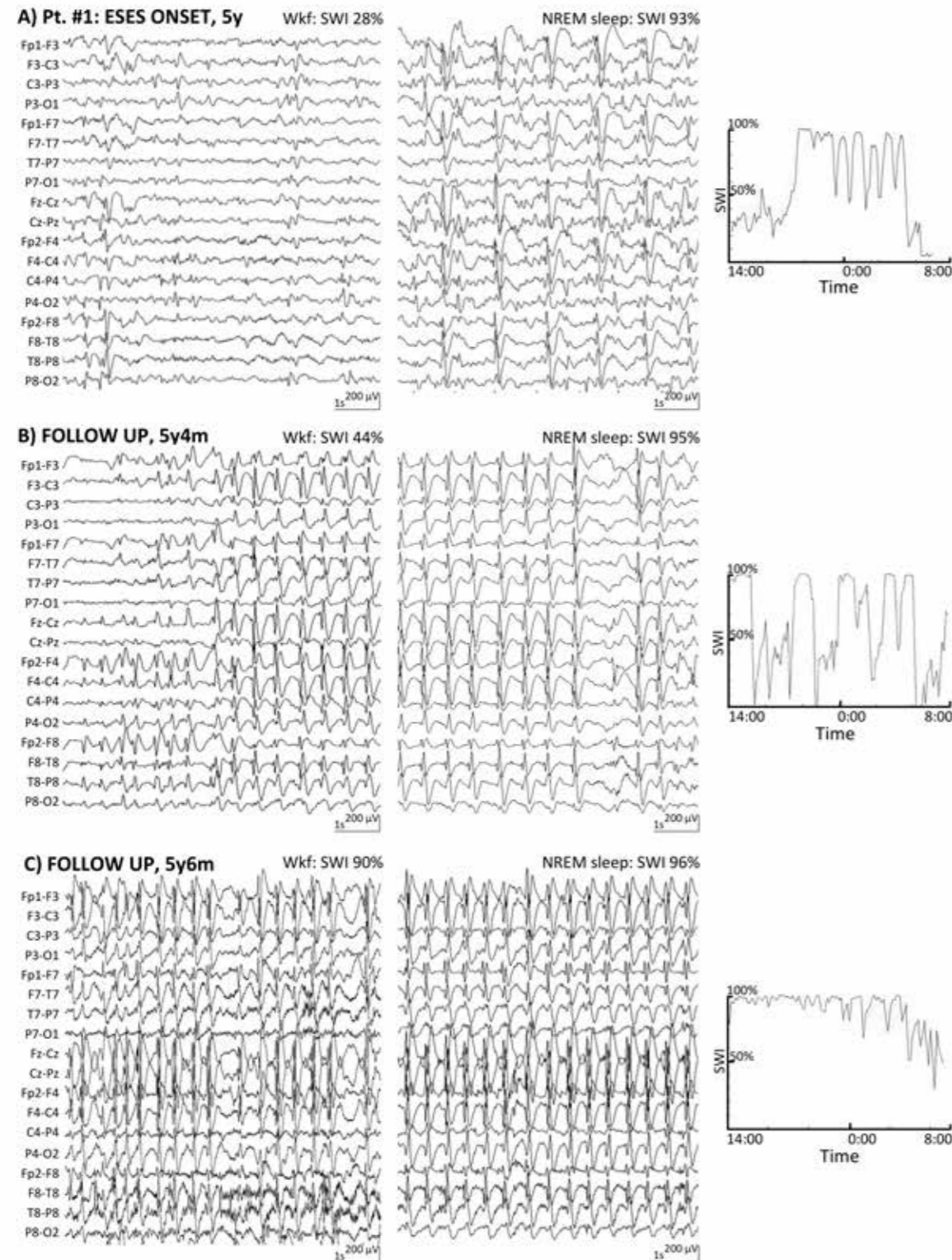


Fig.: Wakefulness and NREM sleep EEG recording in a patient with ESES and CNKSR2 mutations at three different time points in the course of the disease.

### Papers:

Russo A, Gobbi G, Pini A, Møller RS, Rubboli G. Encephalopathy related to status epilepticus during sleep due to a de novo KCNA1 variant in the Kv-specific Pro-Val-Pro motif: phenotypic description and remarkable electroclinical response to ACTH. **Epileptic Disord.** 2020;22:802-806.

Bonardi CM, Mignot C, Serratosa JM, Giraldez BG, Moretti R, Rudolf G, Reale C, Gellert PM, Johannesen KM, Lesca G, Tassinari CA, Gardella E, Møller RS, Rubboli G. Expanding the clinical and EEG spectrum of CNKSR2-related encephalopathy with status epilepticus during slow sleep (ESES). **Clin Neurophysiol.** 2020;131:1030-1039

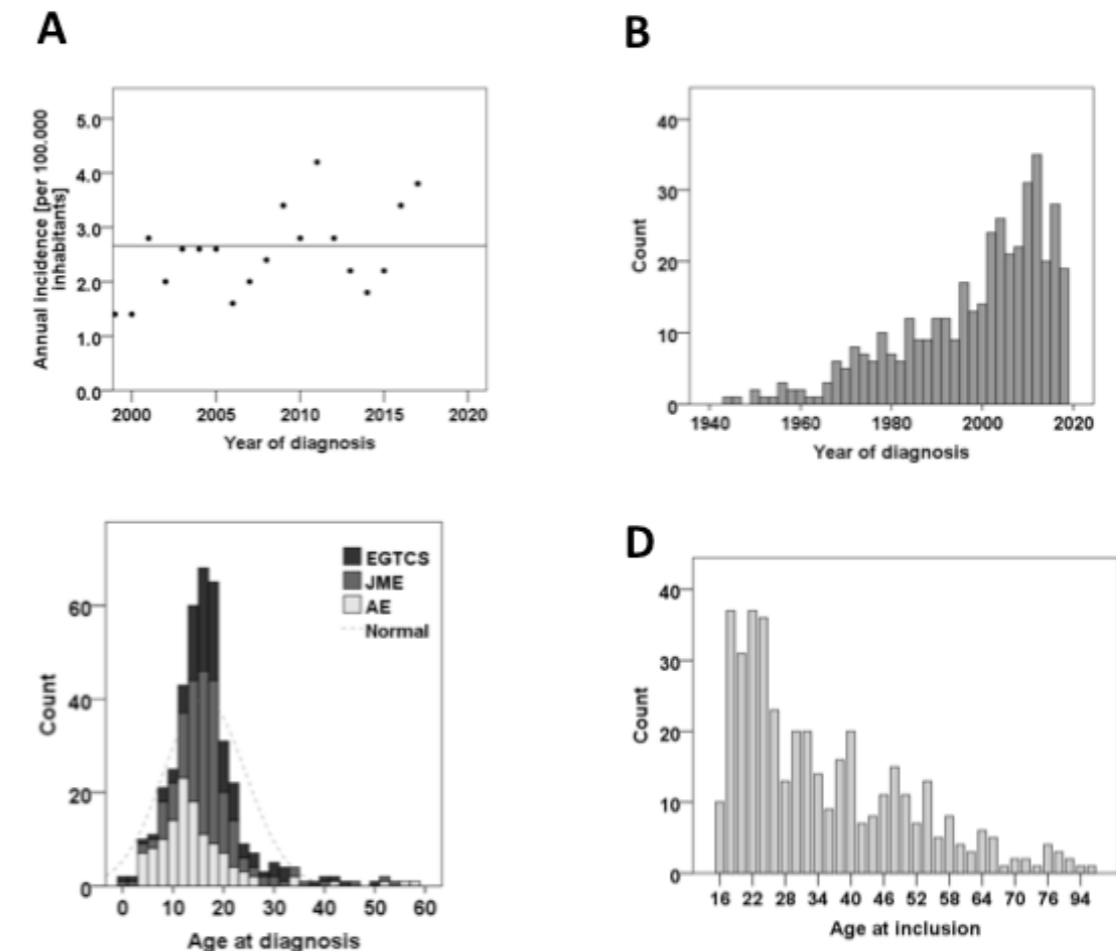


Fig.: Incidence of IGE and age distribution. (a) Incidence of IGE in the past 18 years. (b) Distribution of year at diagnosis in the cohort. (c) Distribution of the age at diagnosis of patients with EGTCs, JME and JAE (stacked bars). (d) Distribution of age at inclusion in the cohort.

## Papers:

Elmali AD, Auvin S, Bast T, Rubboli G, Koutroumanidis M. How to diagnose and classify idiopathic (genetic) generalized epilepsies. **Epileptic Disord.** 2020;22:399-420.

Gesche J, Hjalgrim H, Rubboli G, Beier CP. The clinical spectrum of familial and sporadic idiopathic generalized epilepsy. **Epilepsy Res.** 2020;165:106374

Gesche J, Hjalgrim H, Rubboli G, Beier CP. Patterns and prognostic markers for treatment response in generalized epilepsies. **Neurology.** 2020;95:e2519-e2528.

Gesche J, Christensen J, Hjalgrim H, Rubboli G, Beier CP. Epidemiology and outcome of idiopathic generalized epilepsy in adults. **Eur J Neurol.** 2020;27:676-684.

## 4.8 Genetic testing in adult epilepsy patients

In this study, we investigated the diagnostic yield and explored the gain of personalized treatment approaches in adult epilepsy patients. Two hundred patients (age span = 18-80 years) referred for diagnostic gene panel testing at the Danish Epilepsy Center were included. The vast majority (91%) suffered from comorbid intellectual disability. The medical records of genetically diagnosed patients were mined for data on epilepsy syndrome, cognition, treatment changes, and seizure outcome following the genetic diagnosis.

We found a genetic diagnosis in 46 of 200 (23%) patients. SCN1A, KCNT1, and STXBP1 accounted for the greatest number of positive findings (48%). More rare genetic findings included SLC2A1, ATP6A1V, HNRNPU, MEF2C, and IRF2BPL. Gene-specific treatment changes were initiated in 11 of 46 (17%) patients (one with SLC2A1, 10 with SCN1A) following the genetic diagnosis. Ten patients improved, with seizure reduction and/or increased alertness and general well-being. We showed that routine diagnostic testing is highly relevant in adults with epilepsy. The diagnostic yield is similar to previously reported pediatric cohorts, and the genetic findings can be useful for therapeutic decision-making, which may lead to better seizure control, ultimately improving quality of life.

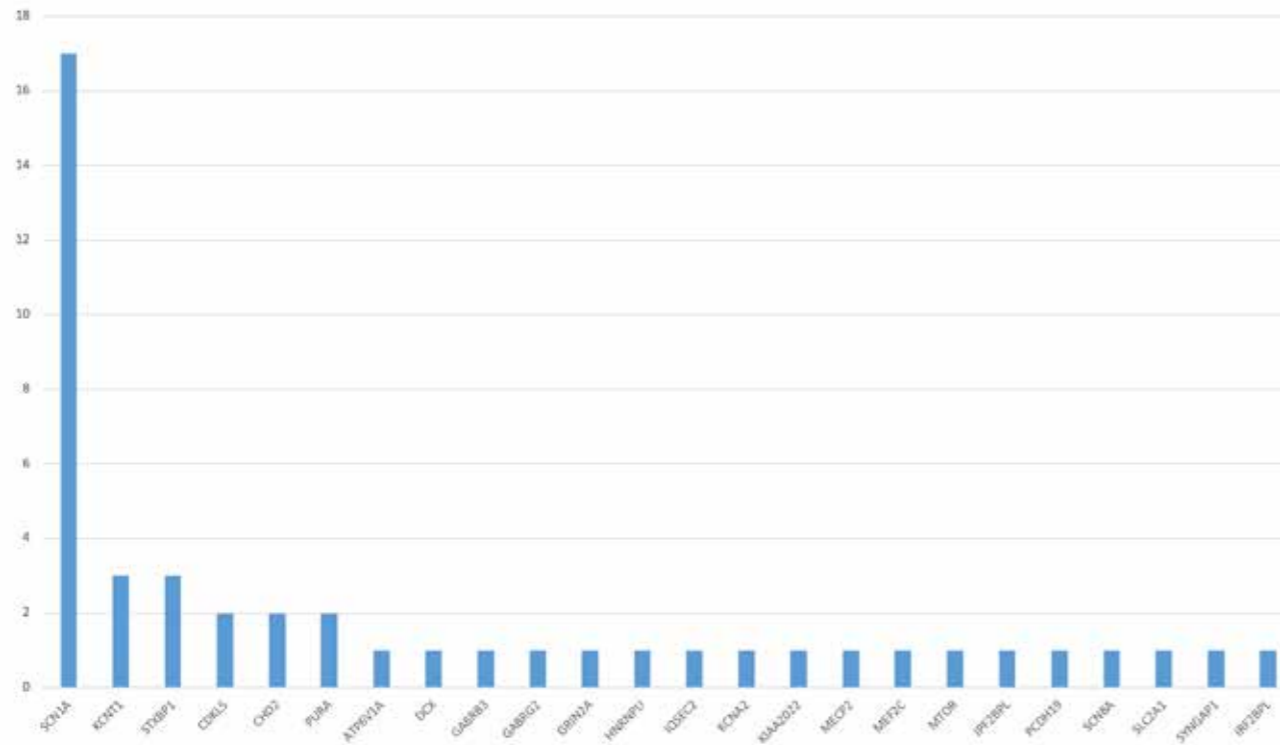


Fig.: Distribution of genetic findings across genes

## Papers:

Johannesen KM, Nikanorova N, Marjanovic D, Pavbro A, Larsen LHG, Rubboli G, Møller RS. Utility of genetic testing for therapeutic decision-making in adults with epilepsy. **Epilepsia.** 2020;61:1234-1239

Rubboli G, Møller RS, Johannesen KM. Genetic testing in adult epilepsy patients: A call to action for clinicians. **Epilepsia.** 2020;61:2055-2056.

## 4.9 Clinical and functional characterization of GABAA-receptor related disorders: translating genetic diagnostics into personalized treatment:

The overall aim of this project is to establish specific correlations between phenotype, genotype, functional effects and therapeutic response to translate genetic diagnostics into therapy. Knowing the functional effect of a genetic variant in a GABAA-receptor gene can assist clinicians to avoid ineffective or even disease-aggravating treatments.

We recruited and systematically evaluated 25 individuals with variants in GABRB2, 17 of whom are newly described and 8 previously reported with additional clinical data. Functional analysis was performed using a *Xenopus laevis* oocyte model system. Our study showed that GABRB2-related epilepsy ranges broadly in severity from genetic generalized epilepsy to developmental and epileptic encephalopathies. Developmental disability and movement disorder are key features. Experimental evidence supports loss of GABAergic inhibition as the mechanism underlying GABRB2-associated neurodevelopmental disorders.

Variants in GABRB3 are associated with various developmental and epileptic encephalopathies. Typically, these variants cause a loss-of-function molecular phenotype whereby  $\gamma$ -aminobutyric acid has reduced inhibitory effectiveness leading to seizures. Drugs that potentiate inhibitory GABAergic activity, such as nitrazepam, phenobarbital or vigabatrin, are expected to compensate for this and thereby reduce seizure frequency. However, vigabatrin, a drug that inhibits  $\gamma$ -aminobutyric acid transaminase to increase tonic  $\gamma$ -aminobutyric acid currents, has mixed success in treating seizures in patients with GABRB3 variants: some patients experience seizure cessation, but there is hypersensitivity in some patients associated with hypotonia, sedation and respiratory suppression. We sought to determine whether the molecular phenotype of the variants could explain the patients hypersensitivity to vigabatrin. Our results demonstrated that patients who responded adversely to vigabatrin had atypical gain-of-function molecular phenotypes when compared to patients that responded well to vigabatrin who had typical loss-of-function phenotype.

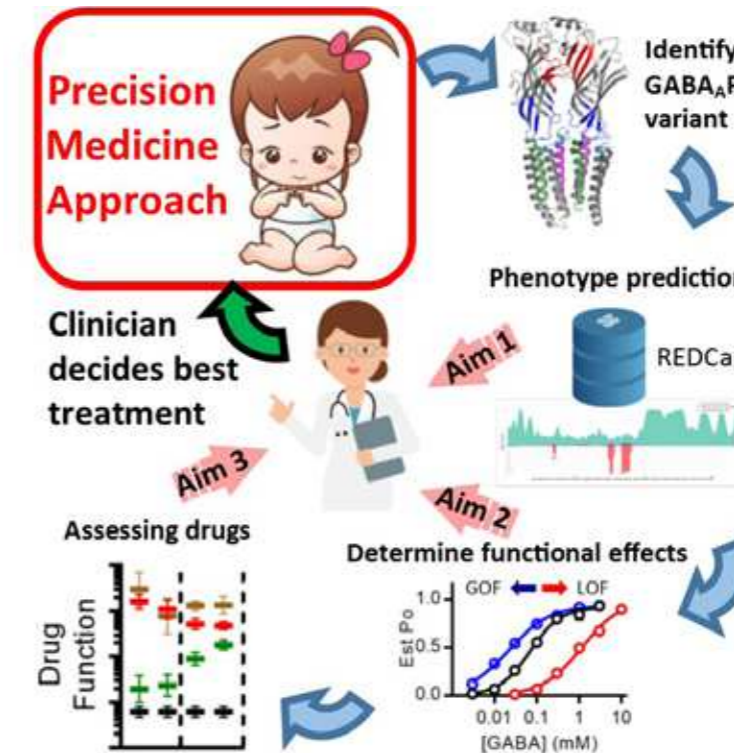


Fig.: Clinical and functional characterization of GABAA-receptor related disorders: translating genetic diagnostics into personalized treatment. Flow chart illustrating the research strategy that informs clinical intervention via all three aims independently

## Papers:

El Achkar CM, Harrer M, Smith L, Kelly M, Iqbal S, Maljevic S, Niturad CE, Vissers LELM, Poduri A, Yang E, Lal D, Lerche H, Møller RS (shared last), Olson HE; GABRB2 Working Group. Characterization of the GABRB2-Associated Neurodevelopmental Disorders. *Ann Neurol*. 2020; doi: 10.1002/ana.25985.

Absalom NL, Liao YW, Kothur K, Indurthi DC, Bennetts B, Troedson C, Mohammad SS, Gupta S, McGregor IS, Bowen MT, Lederer D, Mary S, Waele LD, Jansen K, Gill D, Kurian MA, McTague A, Møller RS, Ahring PK, Dale RC, Chebib M. Gain-of-function GABRB3 variants identified in vigabatrin-hypersensitive epileptic encephalopathies. *Brain Communications*, 2020;2:fcaa162. doi: 10.1093/braincomms/fcaa162.

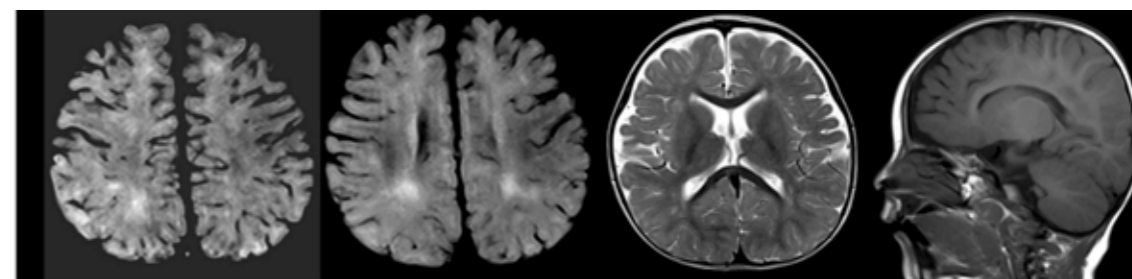
## 4.10 Clinical characterization of congenital disorders of glycosylation

Congenital disorders of glycosylation are a growing group of rare genetic disorders caused by deficient protein and lipid glycosylation. People with CDG have a wide range of health problems including global developmental delay, early onset treatment resistant seizures and multiple congenital malformations.

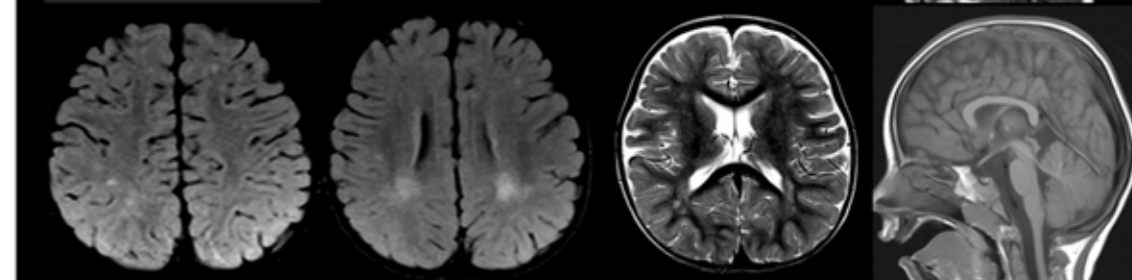
In a recent study we described a novel congenital disorder of O-linked glycosylation caused by GALNT2 loss of function. GALNT2 encodes the Golgi-localized polypeptide N-acetyl-d-galactosamine-transferase 2 isoenzyme. Patients with GALNT2-CDG generally exhibit a syndrome characterized by global developmental delay, intellectual disability with language deficit, autistic features, behavioural abnormalities, epilepsy, chronic insomnia, white matter changes on brain MRI, dysmorphic features, decreased stature, and decreased high density lipoprotein cholesterol levels. Furthermore, all patients showed loss of O-glycosylation of apolipoprotein C-III, a non-redundant substrate for GALNT2. Rodent models of GALNT2-CDG recapitulated much of the human phenotype, including poor growth and neurodevelopmental abnormalities. In behavioural studies, GALNT2-CDG mice demonstrated cerebellar motor deficits, decreased sociability, and impaired sensory integration and processing. The multisystem nature of phenotypes in patients and rodent models of GALNT2-CDG suggest that there are multiple non-redundant protein substrates of GALNT2 in various tissues, including brain, which are critical to normal growth and development.

Glycosylphosphatidylinositol anchoring disorders (GPI) belong to the group of CDGs. GPI synthesis is mediated by a large number of genes including PIGA, PIGN, PIGQ, PIGS, PIGT and PIGV. In a study of 40 novel patients with PIGA-deficiency, we defined the phenotypic spectrum of PIGA-CDG. We found that symptoms span from a pure neurological phenotype at the mild end to a Fryns syndrome like phenotype in the most severe end of the spectrum. Furthermore, we found a high frequency of cardiac anomalies including structural anomalies and cardiomyopathy, and a high frequency of spontaneous death especially in childhood. In a follow-up paper we reviewed the causes of premature death in PIGA-deficiency. We found that one third of the patients were deceased, and more than half of the them died in early childhood: most due to respiratory failure or possible SUDEP. Three patients died from severe cardiomyopathy, liver failure and gastrointestinal bleeding, respectively. Our data indicate an increased risk of premature death in patients with PIGA-CDG when compared to most monogenic developmental and epileptic encephalopathies.

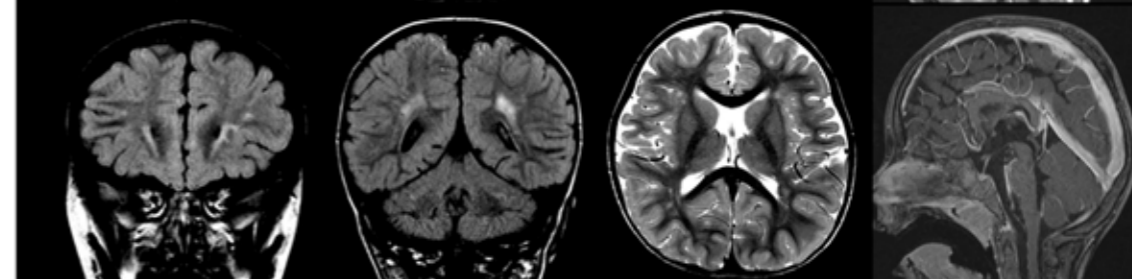
**Patient A**  
**13 months**



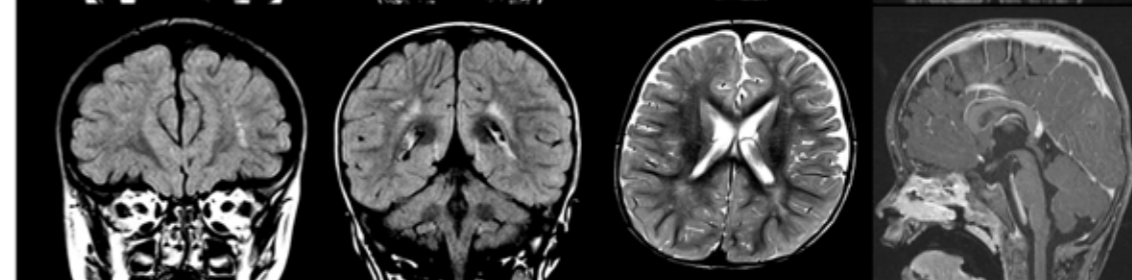
**Patient A**  
**25 months**



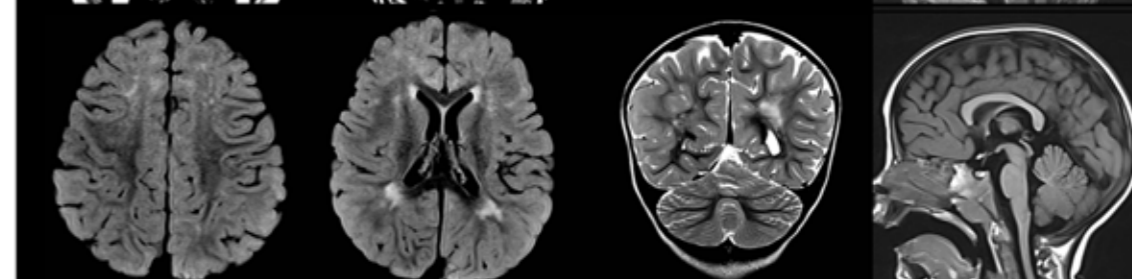
**Patient A**  
**35 months**



**Patient B**  
**21 months**



**Patient C**  
**19 months**



**Patient C**  
**4 years**

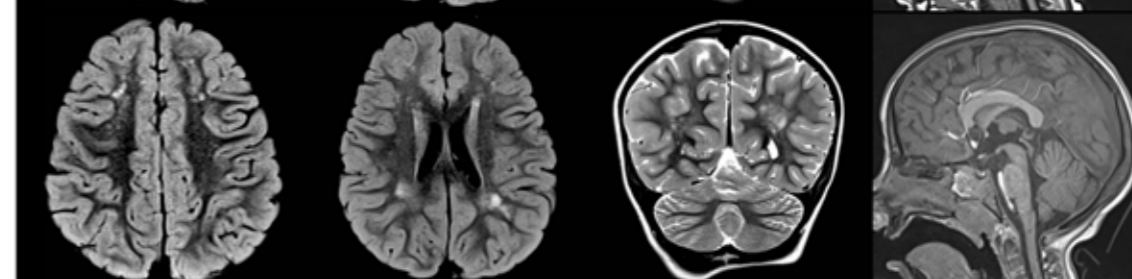


Fig.: Brain MRI results obtained from seven GALNT2-CDG patients at different ages

## Papers:

Zilmer M, Edmondson AC, Khetarpal SA, Alesi V, Zaki MS, Rostasy K, Madsen CG, Lepri FR, Sinibaldi L, Cusmai R, Novelli A, Issa MY, Fenger CD, Abou Jamra R, Reutter H, Briuglia S, Agolini E, Hansen L, Petäjä-Repo UE, Hintze J, Raymond KM, Liedtke K, Stanley V, Musaev D, Gleeson JG, Vitali C, O'Brien WT, Gardella E, Rubboli G, Rader DJ, Schjoldager KT, Møller RS. Novel congenital disorder of O-linked glycosylation caused by GALNT2 loss of function. **Brain**. 2020;143:1114-1126.

Bayat A, Knaus A, Pendziwiat M, Afenjar A, Stefan Barakat T, Bosch F, Callewaert B, Calvas P, Ceulemans B, Chassaing N, Depienne C, Endziene M, Ferreira CR, Moura de Souza CF, Freihuber C, Ganesan S, Gataullina S, Guerrini R, Guerrot AM, Hansen L, Jezela-Stanek A, Karsenty C, Kievit A, Kooy FR, Korff CM, Kragh Hansen J, Larsen M, Layet V, Lesca G, McBride KL, Meuwissen M, Mignot C, Montomoli M, Moore H, Naudion S, Nava C, Nougues MC, Parrini E, Pastore M, Schelhaas JH, Skinner S, Szczafuba K, Thomas A, Thomassen M, Tranebjærg L, van Slegtenhorst M, Wolfe LA, Lal D, Gardella E, Bomme Ousager L, Brünger T, Helbig I, Krawitz P, Møller RS. Lessons learned from 40 novel PIGA patients and a review of the literature. **Epilepsia**. 2020;61:1142-1155. doi: 10.1111/epi.16545.

Bayat A, Kløvgård M, Johannesen KM, Barakat TS, Kievit A, Montomoli M, Parrini E, Pietrafusa N, Schelhaas J, van Slegtenhorst M, Miya K, Guerrini R, Tranebjærg L, Tümer Z, Rubboli G, Møller RS. Deciphering the premature mortality in PIGA-CDG - An untold story. **Epilepsy Res**. 2020;170:106530.

Johnstone DL, Nguyen TTM, Zamboni J, Kernohan KD, St-Denis A, Baratang NV, Hartley T, Geraghty MT, Richer J, Majewski J, Bareke E, Guerin A, Pendziwiat M, Pena LDM, Braakman HMH, Gripp KW, Edmondson AC, He M, Spillmann RC, Eklund EA, Bayat A, McMillan HJ, Boycott KM, Campeau PM. Early infantile epileptic encephalopathy due to biallelic pathogenic variants in PIGQ: Report of seven new subjects and review of the literature. **J Inherit Metab Dis**. 2020;43:1321-1332.

## 4.11 Neuropsychology studies

Neuropsychological outcome studies are important to the decision on epilepsy surgery when counseling caregivers of children with refractory epilepsy. However, generalizability and comparison of cognitive outcome measures across studies are challenged partly due to methodological issues.

Our study contributes with methodological considerations when interpreting existing literature, supporting more specific counseling to caregivers. It further supports the fact that the specificity of the tests being used and the timing of assessments after pediatric epilepsy surgery are essential for outcome studies' clinical validity and should be considered in future clinical practice and outcome studies.

It is well documented that caring for a child with a chronic and life-threatening disease such as severe childhood epilepsy leaves a profound impact on caregivers. However, the impact on caregivers of children with severe epilepsy in Denmark has not previously been investigated. Acquiring specific knowledge about caregivers' mental state is a first step to understand the caregivers' needs to help them regain and preserve their resources in a Danish setting.

Our study firstly supports the fact that giving care to children with severe epilepsy has a high impact on the caregivers. Secondly, we find support for the fact that caregiver resources and behavioral difficulties in the child, rather than epilepsy-related factors, are correlated with distress and psychopathological symptoms in caregivers.

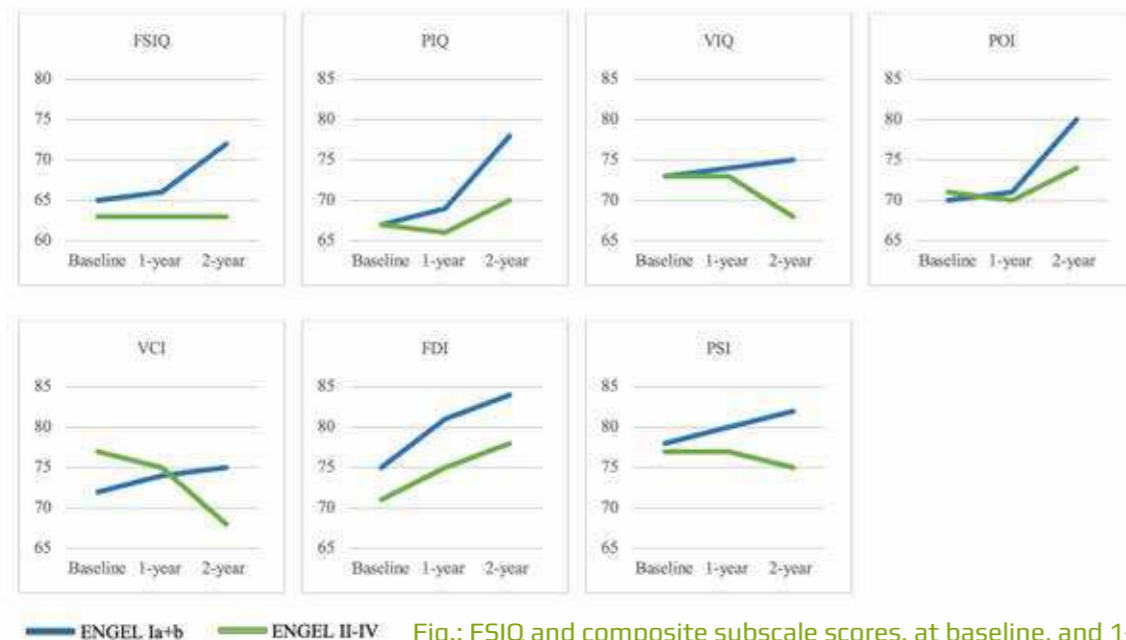


Fig.: FSIQ and composite subscale scores, at baseline, and 1- and 2 years post-surgery, in seizure-free and non-seizure-free children

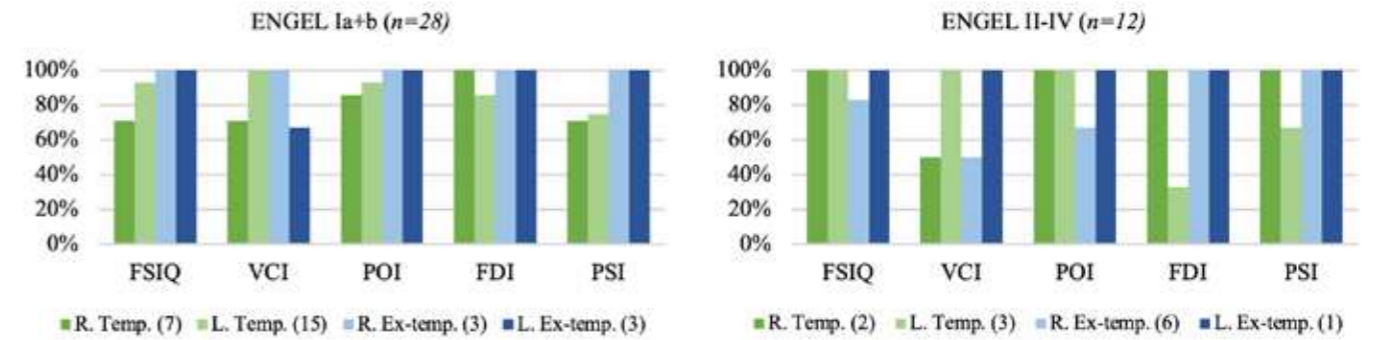


Fig.: Two-year post-surgery FSIQ and composite subscale scores ≥ -9

## Papers:

Jakobsen AV, Müller E, Uldall PV. A methodological perspective on the cognitive outcome of epilepsy surgery in children and adolescents. **Epilepsy Behav**. 2020;111:107330. doi: 10.1016/j.yebeh.2020.107330.

Jakobsen AV, Møller RS, Nikanorova M, Elklit A. The impact of severe pediatric epilepsy on experienced stress and psychopathology in parents. **Epilepsy Behav**. 2020;113:107538. doi: 10.1016/j.yebeh.2020.107538.

## 5. Clinical trials

- An open-label extension trial to assess the long-term safety of ZX008 (Fenfluramine hydrochloride) oral solution as an adjunctive therapy in children and young adults with Dravet syndrome (protocol ZX008-1503) – finished in 2020 Principal investigator: Marina Nikanorova Study coordinator: Klaus Ehrenreich

- A two-part study of ZX008 in children and adults with Lennox-Gastaut syndrome (LGS);

Part I: A randomized, double-blind, placebo controlled trial of two fixed doses of ZX008 (Fenfluramine hydrochloride) oral solution as adjunctive therapy for seizures in children and adults with LGS.

Part II: An open-label extension trial to assess long-term safety of ZX008 in children and adults with LGS (protocol ZX008-1601) – finished in 2020

Principal investigator: Dragan Marjanovic Co-investigator: Marina Nikanorova Study coordinators: Klaus Ehrenreich and Lone Olsen

- Fenfluramin efficacy and safety in children and young adults with Dravet syndrome, open-label extension study (protocol ZX008-1900) Principal investigator: Marina Nikanorova Study coordinator: Klaus Ehrenreich

## 6. 4th Dianalund International Conference on Epilepsy

Virtual conference 12-13 November, 2020

### PRECISION MEDICINE IN GENETIC EPILEPSIES

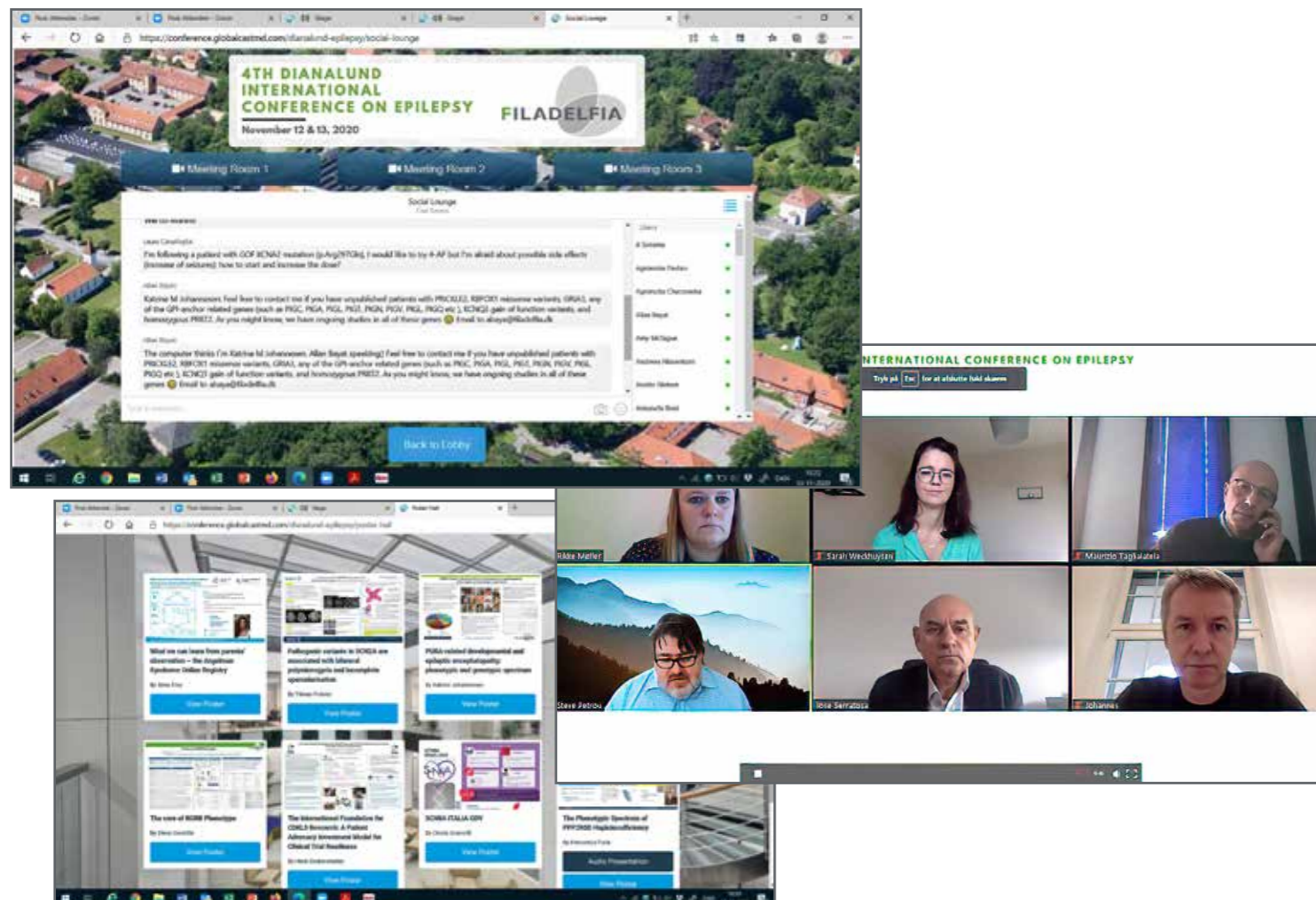
#### – WHERE ARE WE NOW, AND WHERE ARE WE HEADING?

##### Scientific Committee:

Rikke S. Møller, Elena Gardella, Johannes Lemke, Guido Rubboli Faculty: E Aronica (The Netherlands), B Ceulemans (Belgium), E Gardella (Denmark) R Guerrini (Italy), H Heyne (Finland/USA), C Høi-Hansen (Denmark), KM. Johannesen (Denmark), J Lemke (Germany), H Lerche (Germany), RS Møller (Denmark), M Nikanorova (Denmark), S Petrou (Australia), A Poduri (USA), G Rubboli (Denmark), J Serratosa (Spain), S Sisodiya (UK), N Specchio (Italy), J Symonds (UK), S Syrbe (Germany), M Taglialetta (Italy), S Weckhuysen (Belgium)

Treatment of epilepsy remains largely empirical, and individual prescribing based on the mechanism of action is generally not possible. However, recent findings in genetic epilepsies have elucidated some mechanisms of epileptogenesis, unraveling the role of a number of genes with different functions, such as ion channels, proteins associated to the vesicular synaptic cycle or involved in energy metabolism. The advent of Next Generation Sequencing is providing precision genetics enabling precision medicine in approximately one quarter of patients, illustrating the enormous utility of genetic testing for therapeutic decision-making. Although any patient with refractory epilepsy may benefit from genetic screening, such testing will be of most importance in patients with early-onset seizures (less than 3 years of age), a family history of seizures, associated neurological deficit, or learning intellectual disability. A major goal of the genetic studies is the identification of novel drug targets and tailored therapies based on the cause of disease. The discovery of specific genetic mutations has also helped us to repurpose drugs with specific actions which may have been used in entirely unrelated conditions.

In this conference, clinicians, geneticists and basic scientists aim to provide an updated overview of the state-of-the-art of precision medicine in those genetic epilepsies in which a precision medicine approach has been already implemented, or in which promising data are under evaluation. Within the next future, precision medicine will hopefully move within the reach of more patients, and as genetic technologies advance, a comprehensive approach informed also of the contribution of genetics in treatment choices will become an increasingly important part of the clinical management of the epilepsy patients.



## 7. Lectures - oral presentations at congresses in 2020

##### Sándor Beniczky:

- Automated Seizure Detection Using Wearable Devices. American Epilepsy Society Annual Meeting 2020 - Virtual congress (04/12/2020 08/12/2020)
- Non-invasive seizure detection devices: an overview. 15th Conference on New Antiepileptic Drugs & Devices - Virtual congress (03/08/2020 03/08/2020)
- EEG in status epilepticus – Webinar / webcast of the EpiCARE consortium
- Nonconvulsive status epilepticus. 6th Congress of the European Academy of Neurology – Virtual congress (23/05/2020 26/05/2020)
- Systematic approach to reading EEG in clinical practice. EEG Course, Lausanne, Switzerland (05/03/2020)
- Estimating the source localisation of the EEG signals. Optima Medical Advanced EEG Conference, London, UK (06/02/2020)
- Value and limitations of scalp EEG in children, including source imaging techniques. 10th EPODES course of the ILAE. Brno, The Czech Republic (20/01/2020 24/01/2020)

##### Guido Rubboli:

- Encephalopathy related to Status Epilepticus During Slow Sleep (ESES): State-of-the-art and future perspectives. Padua, February 8, 2020
- Precision medicine in monogenic epilepsies, EpiCare Webinar
- Clinical overview and treatment responsiveness in KCNT1-related Epilepsy, 4th Dianalund International Conference on Epilepsy
- How can genetics contribute to the clinical management is Epilepsy, European Academy of Neurology
- Update in Epilepsy, Festival della Salute, Padova, Italy
- Encephalopathy related to Status Epilepticus during Sleep (ESES): linking epilepsy, sleep disruption and cognitive impairment. Seminari in Neuropsichiatria infantile, Bologna April 14, 2020

##### Rikke Steensbjerre Møller:

- Precision medicine in monogenic epilepsies, EpiCare Webinar / webcast
- The Path Forward. 4th Dianalund International Conference on Epilepsy
- From Gene Discovery to Precision Medicine in Epilepsy, BRIC, Copenhagen University
- Genotype-phenotype correlation studies and tailored treatment for the most common monogenic epilepsies: SCN2A/SCN8A. Cleveland Clinic Epilepsy Genetics Update 2020
- From Gene Discovery to Precision Medicine in Epilepsy, BRIDGE: Brain Research - Inter Disciplinary Guided Excellence, SDU
- Epilepsy caused by ion channel mutations: pathophysiology and clinical management. Bringing junior investigators and clinicians together to talk about translational science in epilepsy. YES-ILAE Section – Italy

##### Elena Gardella:

- New insights in the clinical research of monogenic epilepsies call for fellows. Polycentric meeting of the Italian League against Epilepsy \_ Roma (Italy)
- Old and new perspectives in the treatment of SCN8A. BRIDGE meeting\_ SDU Odense
- Old and new perspectives in the treatment of SCN8A. 4th Dianalund International Congress on Epilepsy (DICE) – Virtual
- The clinical phenotype and ongoing research on SCN8A disorders. CUTE syndrome family Meeting (Virtual)
- The clinical phenotype of SCN8A disorders. Italy - family Meeting
- Sleep problems in patients with SCN8A epilepsy. Annual CUTE meeting – American Epilepsy Society 2020 (Virtual)

##### Marina Nikanorova:

- Ganaxolon treatment in females with PCDH19 - related epilepsy. 4th Dianalund International Conference on Epilepsy, November 13th 2020.

##### Trine Moos:

- Sex is healthy but hard to talk about. How do we as professionals break the taboo? The Neuro-day 2020. The Brain In a Social Perspective. The Ministry of Social services and Center for public competence development (COK), Copenhagen, Denmark.
- Everything is as before but nothing is as it was – a presentation of a Phenomenological-Hermeneutic Study of Adult refractory Epilepsy Patients' Experiences of life after participating in an interdisciplinary Rehabilitation Program. Rehabilitation in nursing perspective. Danish Nurses' Council, Copenhagen, Denmark.

## 8. Publications in peer-reviewed scientific journals

Zilmer M, Edmondson AC, Khetarpal SA, Alesi V, Zaki MS, Rostasy K, Madsen CG, Lepri FR, Sinibaldi L, Cusmai R, Novelli A, Issa MY, Fenger CD, Abou Jamra R, Reutter H, Briuglia S, Agolini E, Hansen L, Petäjä-Repo UE, Hintze J, Raymond KM, Liedtke K, Stanley V, Musaev D, Gleeson JG, Vitali C, O'Brien WT, Gardella E, Rubboli G, Rader DJ, Schjoldager KT, Møller RS. Novel congenital disorder of O-linked glycosylation caused by GALNT2 loss of function. **Brain**. 2020;143:1114-1126.

López-Rivera JA, Pérez-Palma E, Symonds J, Lindy AS, McKnight DA, Leu C, Zuberi S, Brunklaus A, Møller RS, Lal D. A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by de novo variants. **Brain**. 2020;143:1099-1105.

El Achkar CM, Harrer M, Smith L, Kelly M, Iqbal S, Maljevic S, Niturad CE, Vissers LELM, Poduri A, Yang E, Lal D, Lerche H, Møller RS (shared last), Olson HE; GABRB2 Working Group. Characterization of the GABRB2-Associated Neurodevelopmental Disorders. **Ann Neurol**. 2020.

Lal D, May P, Perez-Palma E, Samocha KE, Kosmicki JA, Robinson EB, Møller RS, Krause R, Nürnberg P, Weckhuysen S, De Jonghe P, Guerrini R, Niestroj LM, Du J, Marini C; EuroEPINOMICS-RES Consortium, Ware JS, Kurki M, Gormley P, Tang S, Wu S, Biskup S, Poduri A, Neubauer BA, Koeleman BPC, Helbig KL, Weber YG, Helbig I, Majithia AR, Palotie A, Daly MJ. Gene family information facilitates variant interpretation and identification of disease-associated genes in neurodevelopmental disorders. **Genome Med**. 2020;12:28.

Beniczky S, Rubboli G, Covanis A, Sperling MR. Absence-to-bilateral-tonic-clonic seizure: A generalized seizure type. **Neurology**. 2020;6:95. doi: 10.1212/WNL.0000000000010470.

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Masnada S, Pichiecchio A, Formica M, Arrigoni F, Borrelli P, Accorsi P, Bonanni P, Borgatti R, Bernardina BD, Danieli A, Darra F, Deconinck N, De Giorgis V, Dulac O, Gataullina S, Giordano L, Guerrini R, La Briola F, Mastrangelo M, Montomoli M, Mortilla M, Osanni E, Parisi P, Perucca E, Pinelli L, Romaniello R, Severino M, Vigeveno F, Vignoli A, Bahi-Buisson N, Cavallin M, Accogli A, Burgeois M, Capra V, Chaves-Vischer V, Chiapparini L, Colafati G, D'Arrigo S, Desguerre I, Doco-Fenzy M, d'Orsi G, Epitashvili N, Fazzi E, Ferretti A, Fiorini E, Fradin M, Fusco C, Granata T, Johannesen KM, Lebon S, Loget P, Møller RS, Montanaro D, Orcesi S, Quelin C, Rebessi E, Romeo A, Solazzi R, Spagnoli C, Uebler C, Zara F, Arzimanoglou A, Veggioni P; Aicardi Syndrome International Study Group. Basal ganglia dysmorphism in patients with Aicardi syndrome. **Neurology**. 2020;10.1212/WNL.0000000000011237

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