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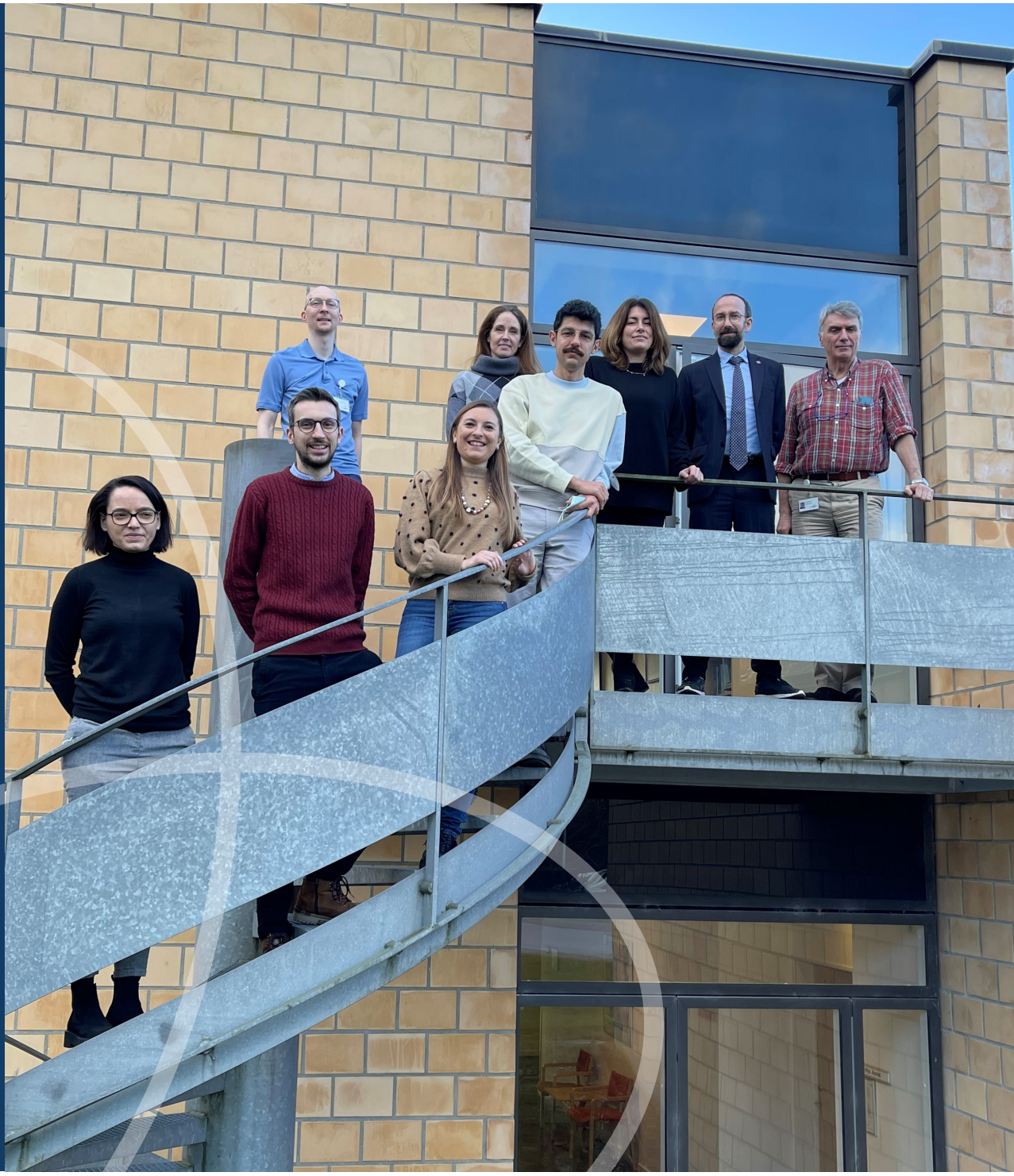

ANNUAL RESEARCH REPORT 2021

Danish Epilepsy Centre Filadelfia

Content

3 Professors

2 Ass. Professors

7 Ph.D. students

63 Publications *)

47 Oral Presentations

*) 63 papers published in peer-reviewed international journals, including leading journals, such as Nature Communications, Brain, Journal of Neurology Neurosurgery and Psychiatry, European Journal of 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 specialized hospital and tertiary referral 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 2021, Filadelfia's three professors, two associate professors and seven Ph.D. students published 63 papers in peer-reviewed scientific journals and contributed with 47 oral presentations. Our researchers who are affiliated to University of Copenhagen, University of Odense and University of Aarhus, hold positions of trust in national and international scientific societies, and participate in a numerous of international epilepsy research networks.

The Danish Epilepsy Center, Filadelfia is a non-profit foundation with an independent Board of Directors. In 2022, we will celebrate Filadelfias 125 years anniversary. 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. Filadelfia is publically funded and an integral part of the Danish Healthcare System.

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 will encourage further collaboration for the benefit of people with epilepsy worldwide.

2. Core Research Team 2020

Sándor Beniczky MD, Ph.D.
Professor, Head of Department
Email: sbz@filadelfia.dk

- Editor-in-Chief, Epileptic Disorders
- Chair, EEG Task Force, ILAE Commission on Big Data
- Past-chair, Joint Taskforce on EEG of the International Federation og Clinical Neuro-physiology (IFCN) and the International League Against Epilepsy (ILAE)
- Member, ILAE Commission on Diagnostic Methods
- Memer, ILAE Education Council; coordinator of the Virtual Epilepsy Academy (VIREPA)
- Member, ILAE Publication Counsil
- Member, ILAE Congress Counsil

Rikke Steensbjerre Møller, Ph.D.
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- Scientific advisory board member: KCNA2 Foundation
- Scientific advisory board member: KCNT1 Foundation
- Member of 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 Syn-drome

Guido Rubboli MD, Ph.D.
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- Chair of the Epilepsy Scientific Panel of the European Academy of Neurology
- Director, Advanced Course “EEG in the diagnosis & management of epilepsy”, Virtual Epilepsy Academy of the International League Against Epilepsy
- Member of the Transition Task Force of the International League Against Epilepsy
- Member of the Scientific advisory board: KCNA2 Foundation
- Member of the Scientific advisory board: KCNT1 Foundation
- Member of the Scientific Board: “Fuori dall’ombra” association
- Member of EpiCARE: a European Reference Network for rare and complex epilepsies
- Associate Editor, Epileptic Disorders
- Associate Editor, Frontiers in Neurology, Epilepsy Section
- Section Editor, Behavioral Neurology
- Member of the Editorial Board of Epilepsy and Behavior Reports

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

- Member of the board of the Danish Epilepsy Society
- Director, Basic-EEG course, Virtual Epilepsy Academy of the International League Against Epilepsy (VIREPA
- Scientific advisory board member: SCN8A Foundation
- Scientific advisory board member: SLC6A1 Foundation
- Member of EpiCARE: a European Reference Network for rare and complex epilepsies.
- Member of the BRIDGE team at Department of Regional Health Research, University of Southern Denmark.
- Associate Editor, Frontiers in Neurology, Pediatrics Section
- Associate Editor, Frontiers in Neurology, Epilepsy Section

Marina Nikanorova MD, Ph.D.
Associate Professor, Senior Consultant
Email: mnk@filadelfia.dk

Research Team

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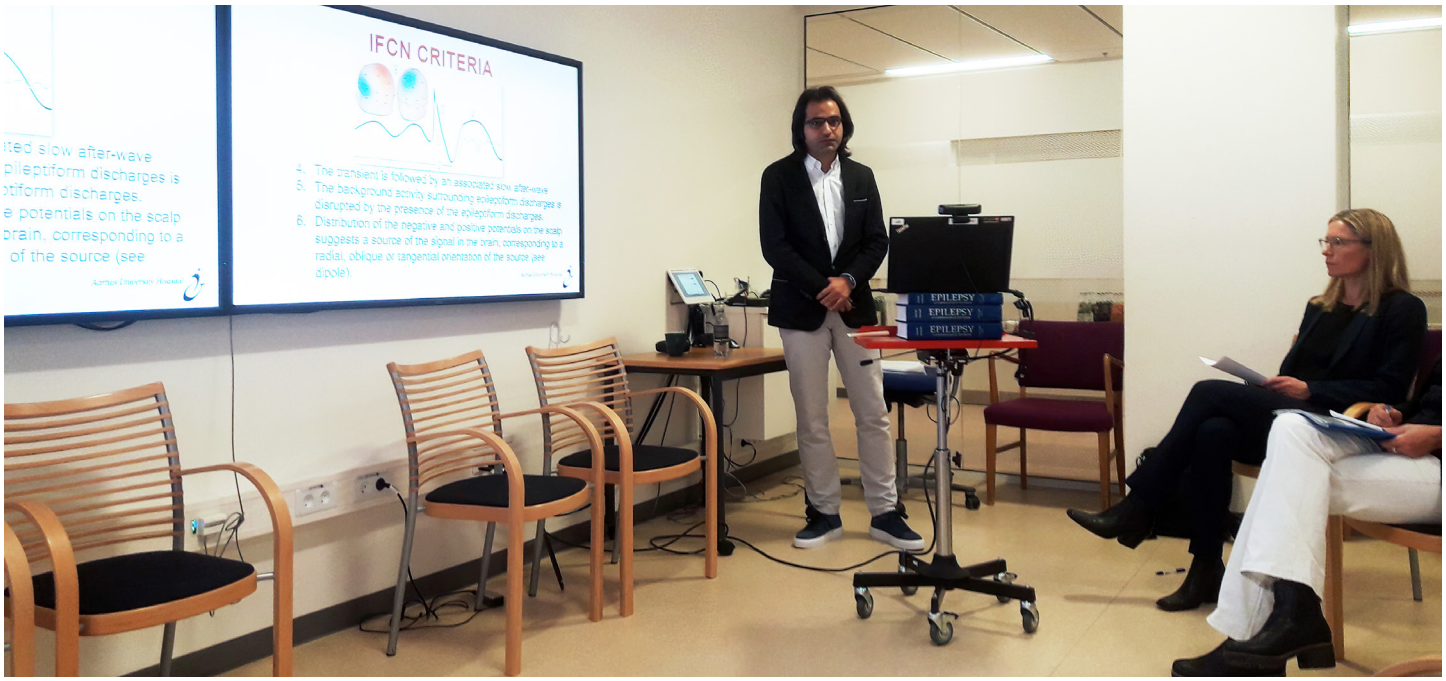
Maria Vlachou, MD
Mustafa Aykut Kural, MD
Trine Hammer
Christina Fenger
Katrine Johannesen

Allan Bayat
Anne Højte Hansen
Nazanin Mohammad
Sabrina Neri
Cristina Cioclu
Margherita Aluffi Valletti (Erasmus+ mobility)
Angelica Pisati (Erasmus+ mobility)
Alessandra Rossi
Levente Hadady, MD

3. Ph.D. projects

Completed in 2021:

Clinical practice of EEG
Mustafa Aykut Kural: Clinical practice of EEG revisited: improved spike identification, localization and characterization. Aarhus University. Main supervisor: Sándor Beniczky.



Family Impact of Complex Childhood Epilepsy
Anne Vagner Jakobsen: Family Impact of Complex Childhood Epilepsy. University of Southern Denmark/SDU. Main supervisor: Ask Elklit Co-supervisors: Rikke Stensbjerre Møller, Marina Nikanorova.

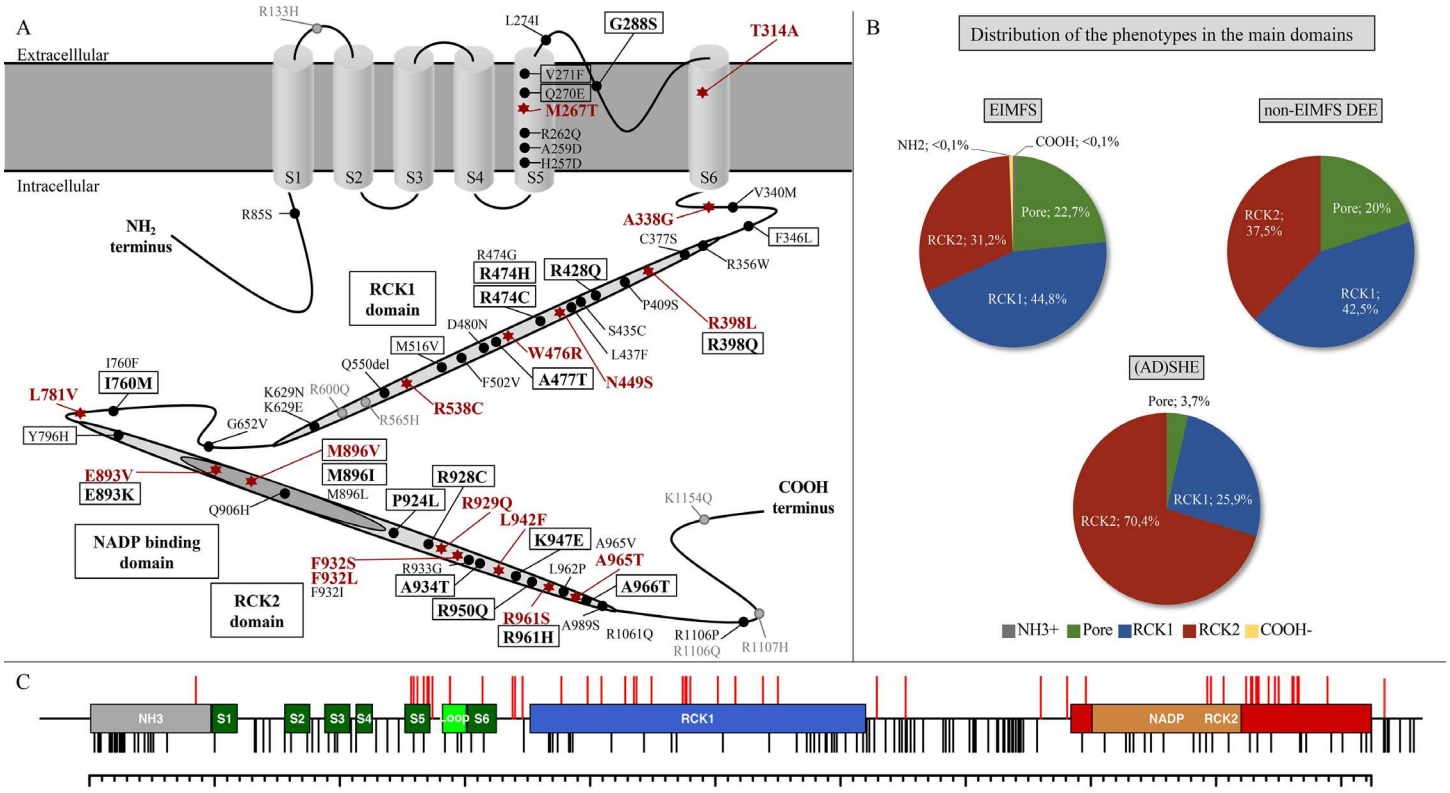
Ongoing

- Allan Bayat, MD. Title: Deep phenotyping, genotype-phenotype correlations and precision medicine in monogenic epilepsies. Faculty of Health Sciences, University of Southern Denmark. Main supervisor: Rikke Steensbjerre Møller, co-supervisors: Guido Rubboli; Elena Gardella. .
- Nazanin Azarinejad Mohammadi, M.Sc., Clinical and functional characterization of GABAA-receptor related disorders: translating genetic diagnostics into personalized treatment. Faculty of Health Sciences, University of Southern Denmark. Main supervisor: Rikke Steensbjerre Møller, co-supervisor: Philip Ahring.
- Marie Amanda Bust Levy, MSc. Genetic and Functional Mechanisms in Neurodevelopmental Disorders and Epilepsy. Faculty of Health Sciences, University of Copenhagen.Main supervisor: Zeynep Tümer, co-supervisor: Rikke Steensbjerre Møller.
- Tanya Ramdal Techlo, MSc. Leverage polygenic approaches to genetically diagnose idiopathic severe epilepsy and hemiplegic migraine. Faculty of Health Sciences, University of Copenhagen. Main supervisor: Thomas Folkmann Hansen, co-supervisor: Rikke Steensbjerre Møller.
- Francesca Furia, MD. Deep phenotyping of monogenic epilepsies towards the identification of targeted treatments. Faculty of Health Sciences, University of Southern Denmark. Main supervisor: Elena Gardella, co-supervisors: Rikke Steensbjerre Møller, Guido Rubboli.
- Frederik Nørby Friis Sørensen, MSc. Dissecting neuronal heterogeneity and epileptogenesis in focal cortical dysplasia. Faculty of Health Sciences, University of Copenhagen. Main supervisor: Konstantin Khodosevich, co-supervisor: Rikke Steensbjerre Møller.
- Maria Vlachou: Evaluation of electro-clinical findings using standardised feature extraction and machine learning. Aarhus University. Main supervisor: Sándor Beniczky.
- Bogdan Florea: Electroencephalography in patients with disturbed level of consciousness. University of Szeged, Hungary. Main supervisor: Sándor Beniczky.
- 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.
- Karin Westin: Extending the clinical applications of magnetoencephalography. Karolinska Institute, Stockholm. Co-supervisor: Sándor Beniczky.

4. Research projects

4.1 KCNT1-RELATED EPILEPSIES

KCNT1-RELATED EPILEPSIES AND EPILEPTIC ENCEPHALOPATHIES: PHENOTYPIC AND MUTATIONAL SPECTRUM. This study on 248 individuals, the largest cohort reported so far, including 66 previously unpublished cases has provided a comprehensive description of KCNT1 mutation-related epileptic disorders. Four phenotypic groups emerged: i) EIMFS; ii) DEE other than EIMFS (non-EIMFS DEE); iii) (AD)SHE; iv) other phenotypes. Genotypic analysis of the whole cohort showed only missense mutations and one inframe deletion in KCNT1. Genotype-phenotype considerations showed many of the (AD)SHE-associated mutations to be clustered around the RCK2 domain in the C-terminus, distal to the NADP domain. Mutations associated with EIMFS/non-EIMFS DEE did not show a particular pattern of distribution in the KCNT1 protein. Recurrent KCNT1 mutations were seen to be associated with both severe and less severe phenotypes. Our study further defines and broadens the phenotypic and genotypic spectrums of KCNT1-related epileptic conditions and emphasizes the increasingly important role of this gene in the pathogenesis of early onset DEEs as well as in focal epilepsies, namely (AD)SHE.

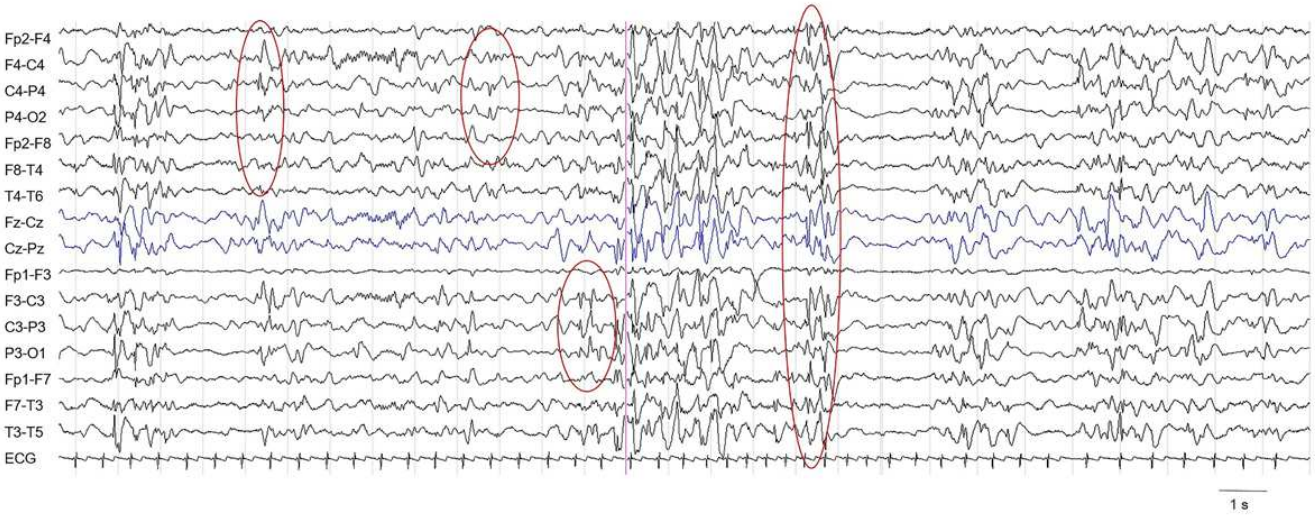


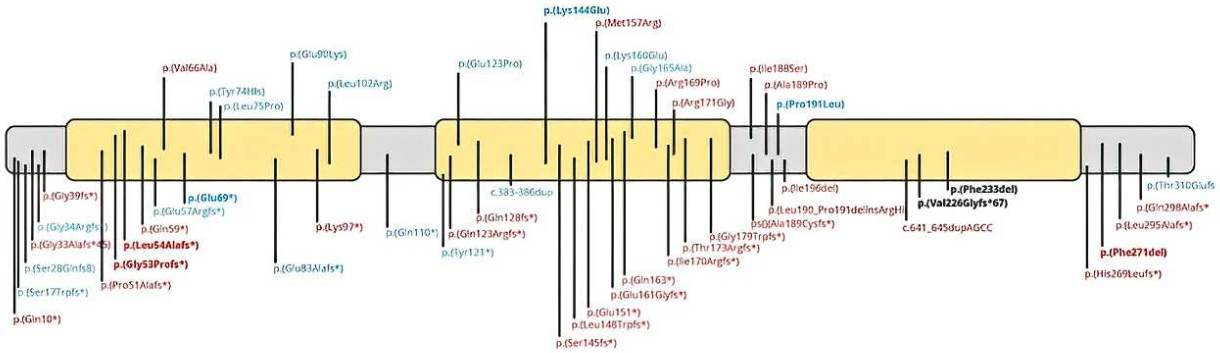
Publication

Bonardi CM, Heyne HO, Fiannacca M, Fitzgerald MP, Gardella E, Gunning B, Olofsson K, Lesca G, Verbeek N, Stamberger H, Striano P, Zara F, Mancardi MM, Nava C, Syrbe S, Buono S, Baulac S, Coppola A, Weckhuysen S, Schoonjans AS, Ceulemans B, Sarret C, Baumgartner T, Muhle H, des Portes V, Toulouse J, Nougues MC, Rossi M, Demarquay G, Ville D, Hirsch E, Maurey H, Willems M, de Bellescize J, Altuzarra CD, Villeneuve N, Bartolomei F, Picard F, Hornemann F, Koolen DA, Kroes HY, Reale C, Fenger CD, Tan WH, Dibbens L, Bearden DR, Møller RS, Rubboli G. KCNT1-related epilepsies and epileptic encephalopathies: phenotypic and mutational spectrum. Brain. 2021 Jun 11:awab219

4.2 THE PHENOTYPIC AND GENOTYPIC SPECTRUM

In this project, we recruited a cohort of 142 patients to analyze their phenotypic and genotypic spectrum. Characteristics of the PURA syndrome included neonatal hypotonia, feeding difficulties, and respiratory distress. Sixty percent of the patients developed epilepsy with myoclonic, generalized tonic-clonic, focal seizures, and/or epileptic spasms. EEG showed generalized, multifocal, or focal epileptic abnormalities. Lennox-Gastaut was the most common epilepsy syndrome. Drug refractoriness was common: 33.3% achieved seizure freedom. We found 97 pathogenic variants in PURA without any clear genotype-phenotype associations.





Publication

Johannesen KM, Gardella E, Gjerulfsen CE, Bayat A, Rouhl RPW, Reijnders M, Whalen S, Keren B, Buratti J, Courtin T, Wierenga KJ, Isidor B, Piton A, Faivre L, Garde A, Moutton S, Tran-Mau-Them F, Denommé-Pichon AS, Coubes C, Larson A, Esser MJ, Appendino JP, Al-Hertani W, Gamboni B, Mampel A, Mayorga L, Orsini A, Bonuccelli A, Suppiej A, Van-Gils J, Vogt J, Damioli S, Giordano L, Moortgat S, Wirrell E, Hicks S, Kini U, Noble N, Stewart H, Asakar S, Cohen JS, Naidu SR, Collier A, Brilstra EH, Li MH, Brew C, Bigoni S, Ognibene D, Ballardini E, Ruivenkamp C, Faggioli R, Afenjar A, Rodriguez D, Bick D, Segal D, Coman D, Gunning B, Devinsky O, Demmer LA, Grebe T, Pruna D, Cursio I, Greenhalgh L, Graziano C, Singh RR, Cantalupo G, Willems M, Yoganathan S, Góes F, Leventer RJ, Colavito D, Olivotto S, Scelsa B, Andrade AV, Ratke K, Tokarz F, Khan AS, Ormieres C, Benko W, Keough K, Keros S, Hussain S, Franques A, Varsalone F, Grønborg S, Mignot C, Heron D, Nava C, Isapof A, Borlot F, Whitney R, Ronan A, Foulds N, Somorai M, Brandsema J, Helbig KL, Helbig I, Ortiz-González XR, Dubbs H, Vitobello A, Anderson M, Spadafore D, Hunt D, Møller RS, Rubboli G; PURA study group. PURA-Related Developmental and Epileptic Encephalopathy: Phenotypic and Genotypic Spectrum. Neurol Genet. 2021 Nov 15;7(6):e613.

4.3 GABAA-RECEPTOR RELATED DISORDERS

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.

Pathogenic variants in GABRB3 have been associated with a spectrum of phenotypes from severe developmental disorders and epileptic encephalopathies (DEEs) to milder epilepsy syndromes and mild intellectual disability (ID). In a recent study, we analyzed a cohort of 71 individuals with pathogenic GABRB3 variants to deepen the phenotypic understanding and to investigate genotype-phenotype correlations. We showed that the phenotypes correlated with the structural locations of the variants. Generalized epilepsy, with a median age at onset of 12 months, and mild-to-moderate ID were associated with variants located in the extracellular domain. Focal epilepsy with earlier onset (median: age 4 months) and severe ID were associated with variants in both the pore-lining helical transmembrane domain and the extracellular domain. These genotype-phenotype correlations will aid the genetic counseling and treatment of individuals affected by GABRB3-related disorders, and future studies may reveal whether functional differences underlie the phenotypic differences.

Conventional thinking dictates that GABAAR-associated epilepsy relates to loss-of-function (LOF) perturbations in synaptic GABAA-receptor subunits. However, in a recent study we showed that increases in tonic current levels via extrasynaptic receptors, represents a novel pathway for DDEs. We identified six patients with gain-of-function (GOF) variants in GABRD, encoding the delta subunit of extrasynaptic GABAA-receptors. All six patients shared common phenotypes including neurodevelopmental disorders (NDDs) with behavioral issues, various degrees of intellectual disability, generalized epilepsy with atypical absences and generalized myoclonic and/or bilateral tonic-clonic seizures. The EEG showed qualitative analogies among the different GOF variant carriers consisting of focal slowing in the occipital regions often preceding irregular generalized epileptiform discharges, with frontal predominance. GOF GABRD variants have not previously been associated with epilepsy and the observation that increased tonic currents represent a novel pathway for NDDs significantly challenges our understanding of the role of the GABAergic system in epilepsy. Since many anti-seizure medications act by enhancing GABAergic tone, this can exacerbate symptoms in patients with GOF variants, hence determining whether GABR variants result in either gain- or loss-of-function is an essential process to ensure the correct medication is prescribed.

Papers

Johannesen KM, Iqbal S, Guazzi M, Mohammadi NA, Pérez-Palma E, Schaefer E, De Saint Martin A, Abiwarde MT, McTague A, Pons R, Piton A, Kurian MA, Ambegaonkar G, Firth H, Sanchis-Juan A, Deprez M, Jansen K, De Waele L, Briltra EH, Verbeek NE, van Kempen M, Fazeli W, Striano P, Zara F, Visser G, Braakman HMH, Haeusler M, Elbracht M, Vaher U, Smol T, Lemke JR, Platzer K, Kennedy J, Klein KM, Au PYB, Smyth K, Kaplan J, Thomas M, Dewenter MK, Dinopoulos A, Campbell AJ, Lal D, Lederer D, Liao VWY, Ahring PK, Møller RS, Gardella E. Structural mapping of GABRB3 variants reveals genotype-phenotype correlations. Genet Med. 2021 Dec 7:S1098-3600(21)05382-X.

Ahring PK, Liao VWY, Gardella E, Johannesen KM, Krey I, Selmer KK, Stadheim BF, Davis H, Peinhardt C, Koko M, Coorg RK, Syrbe S, Bertsche A, Santiago-Sim T, Diemer T, Fenger CD, Platzer K, Eichler EE, Lerche H, Lemke JR, Chebib M, Møller RS. Gain-of-function variants in GABRD reveal a novel pathway for neurodevelopmental disorders and epilepsy. Brain. 2021 Oct 11:awab391

4.4 CONGENITAL DDISORDES OF GLYCOSYLATION

Congenital disorders of glycosylation (CDG) are a growing group of rare genetic disorders caused by deficient protein and lipid glycosylation. Glycosylphosphatidylinositol anchoring disorders (GPIADs) belong to the group of CDGs. People with GPIAD have a wide range of health problems including early onset treatment resistant seizures, global developmental delay, and multiple congenital malformations. A pathway of 30 genes mediates GPI synthesis and more than 20 of these genes are linked to a neurodevelopmental disorder; commonly occurring genes include PIGA, PIGN, PIGQ, PIGS, PIGT and PIGV and these neurodevelopmental disorders are collectively called PIG-opathies. We are involved in better characterizing the core phenotype and associated comorbidities including the epileptology, identify genotype-phenotype correlations, clinical biomarkers and to explore the role of vitamin B substitution as anti-seizure medication in GPI-ADs.

In a recent study 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 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.

Papers

Bayat A, Kløvgaard 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. 2021 Feb;170:106530.

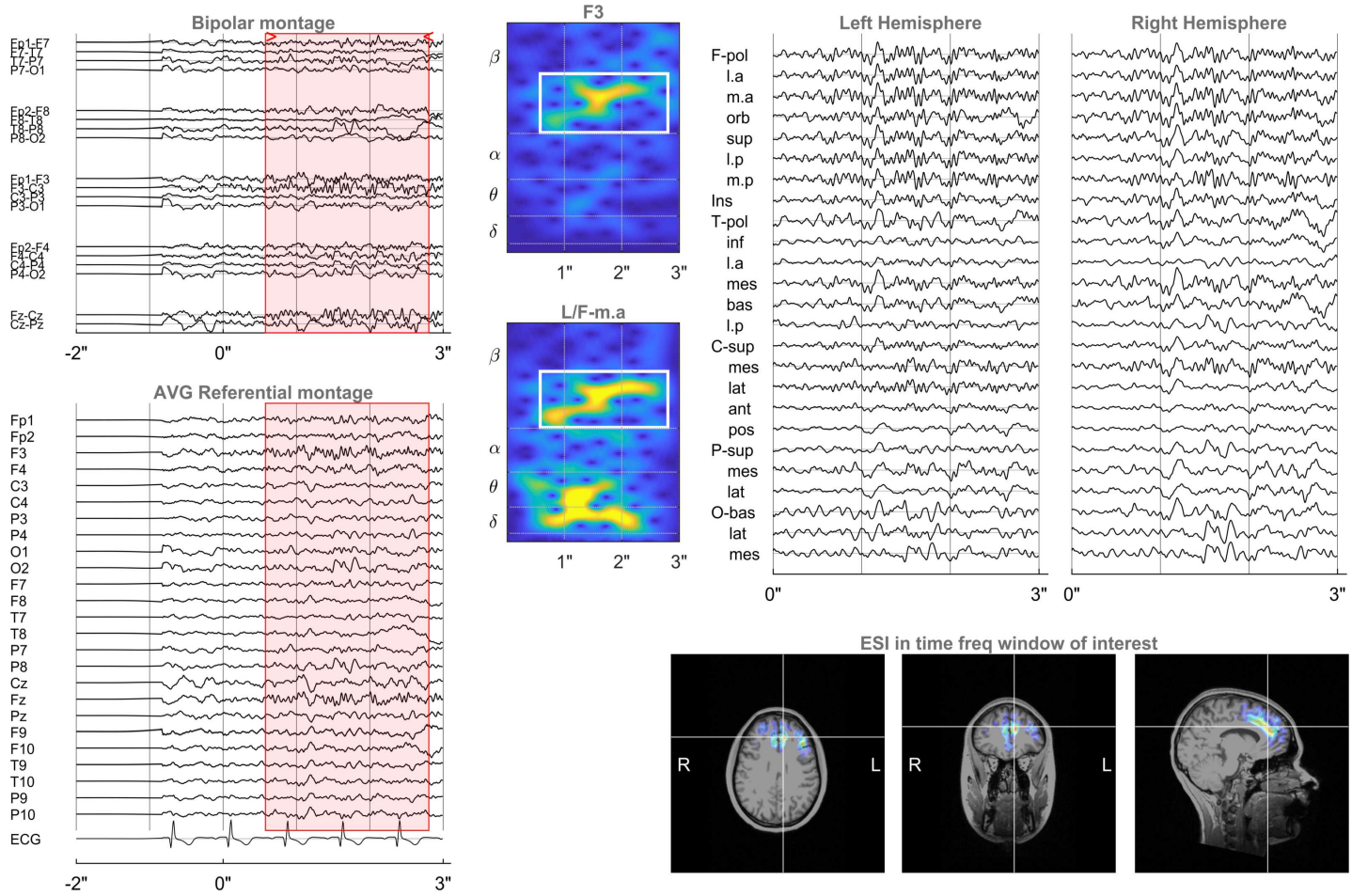
Bayat A, Pendziwiat M, Obersztyn E, Goldenberg P, Zacher P, Döring JH, Syrbe S, Begtrup A, Borovikov A, Sharkov A, Karasińska A, Giżewska M, Mitchell W, Morava E, Møller RS, Rubboli G. Deep-Phenotyping the Less Severe Spectrum of PIGT Deficiency and Linking the Gene to Myoclonic Atonic Seizures. Front Genet. 2021 May 11;12:663643

4.5 EEG SOURCE IMAGING

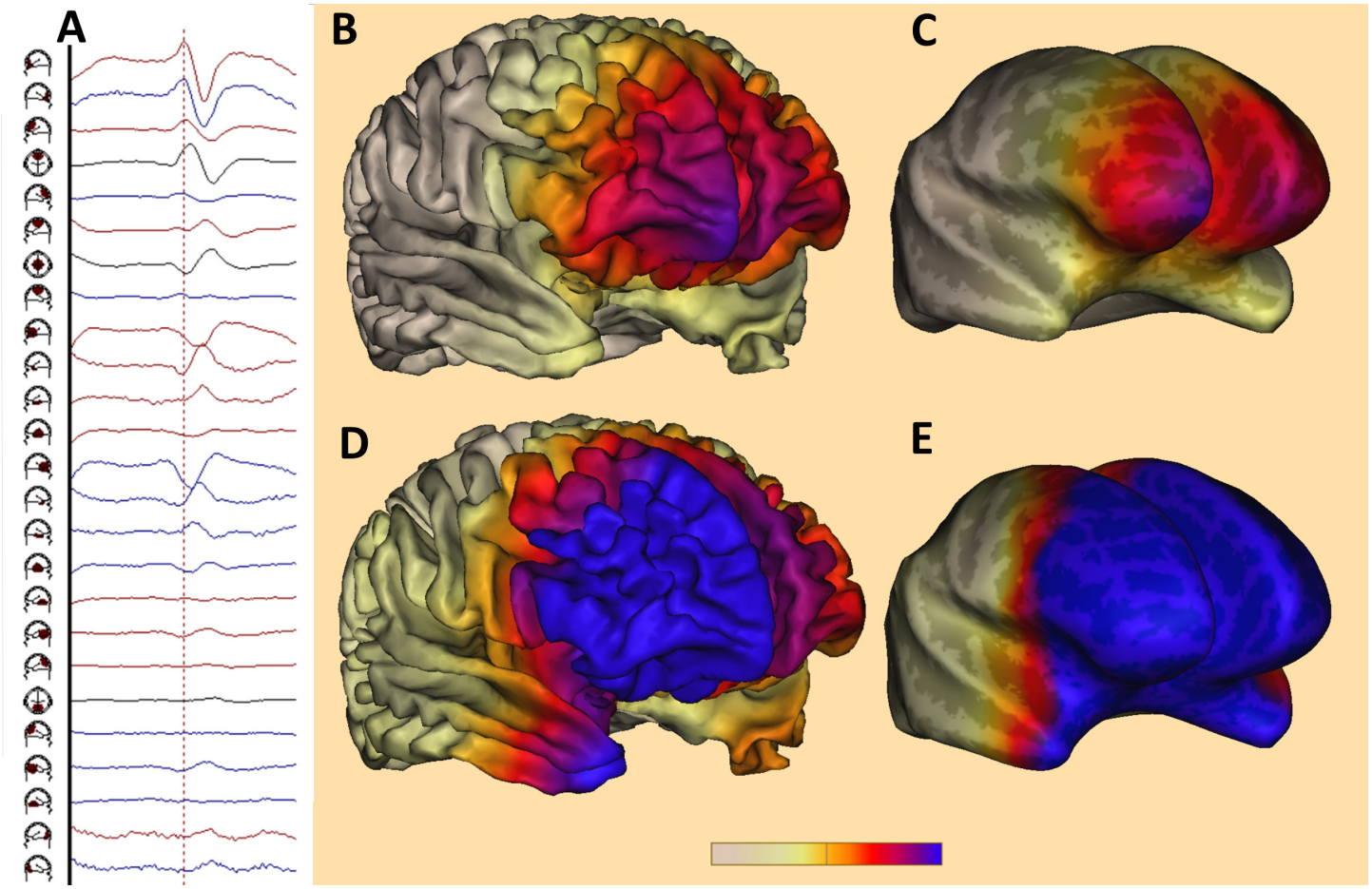
Using mathematical algorithms, the source of the EEG signal can be estimated in the brain. EEG Source Imaging (ESI) has been one of the research topics our group has been focusing on for more than a decade. In 2021 we continued this work, using ESI for presurgical evaluation and for analyzing EEGs of patients with encephalopathy.

ESI requires special expertise, not available in all epilepsy centers in the world. To circumvent this, automated analysis pipelines have been developed and validated for the interictal discharges. In the study we completed and published in 2021, we presented the clinical validation of an automated ESI for ictal EEG signals. We developed an automated analysis pipeline of ictal EEG activity, based on spectral analysis in source space, using an individual head model of six tissues. The analysis was done blinded to all other data. As reference standard, we used the concordance with the resected area and one-year postoperative outcome. We analyzed 50 consecutive patients undergoing epilepsy surgery (34 temporal and 16 extra-temporal). Thirty patients (60%) became seizure-free. The accuracy of the automated ESI was 74% (95% confidence interval: 59.66-85.37%). Our results showed that automated ictal ESI had a high accuracy for localizing the seizure onset zone. Automating the ESI of the ictal EEG signals will facilitate implementation of this tool in the presurgical evaluation.

Triphasic waves (TWs) have been observed in the EEG recorded in patients with various types of encephalopathy, yet their genesis and significance is still debated. The aim of this study was to elucidate the localization of the cortical generators of TWs using EEG source imaging. In 20 consecutive patients who had encephalopathy with TWs, EEG source imaging of the first negative and the positive phases of the TW was performed. Three different approaches were used: equivalent current dipoles, a distributed source model, and a recently described spatial filtration method for visualizing EEG in source space.Equivalent current dipole models failed to provide valid solutions. The distributed source model and the spatial filtration method suggested that TWs were generated by large, bilateral cortical networks, invariably involving the anterior frontal and the temporo-polar areas. In conclusion, source imaging localized TWs to anterior frontal and temporo-frontal structures. Involvement of these regions is consistent with the typical pathophysiological changes of altered consciousness and cognitive changes observed in patients with TW encephalopathy.



Automated ictal EEG source imaging, in a patient with a frontal focus.



Source montages and distributed source models showing that Triphasic Waves are generated by bilateral fronto-temporal networks.

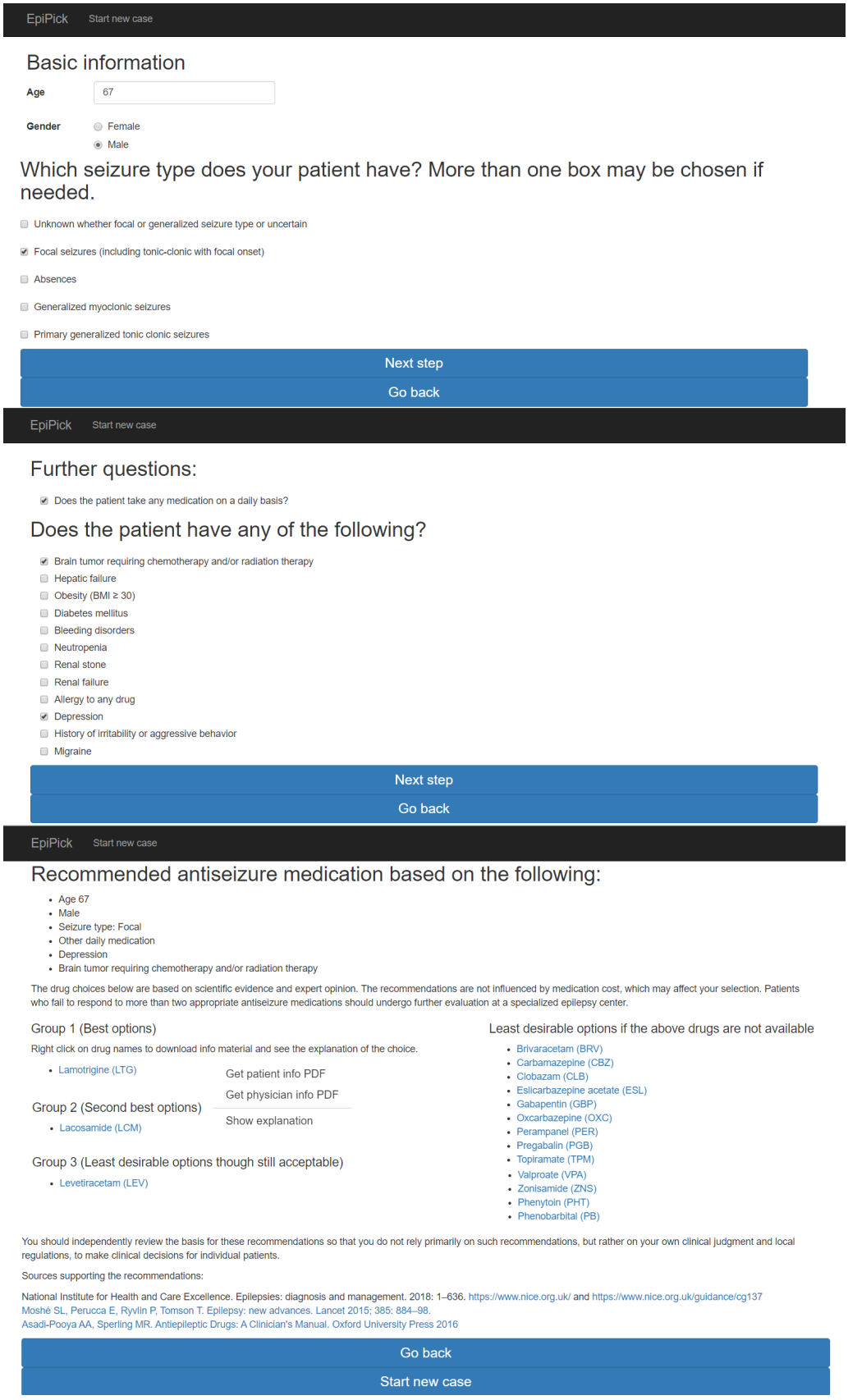
Papers

Baroumand AG, Arbune AA, Strobbe G, Keereman V, Pinborg LH, Fabricius M, Rubboli G, Gøbel Madsen C, Jespersen B, Brennum J, Mølby Henriksen O, Mierlo PV, Beniczky S. Automated ictal EEG source imaging: A retrospective, blinded clinical validation study. Clin Neurophysiol. 2021 Apr 27:S1388-2457(21)00530-7. doi: 10.1016/j.clinph.2021.03.040.
Kural MA, Fabricius M, Christensen J, Kaplan PW, Beniczky S. Triphasic Waves Are Generated by Widespread Bilateral Cortical Networks. J Clin Neurophysiol. 2021 Sep 1;38(5):415-419. doi: 10.1097/WNP.0000000000000770.

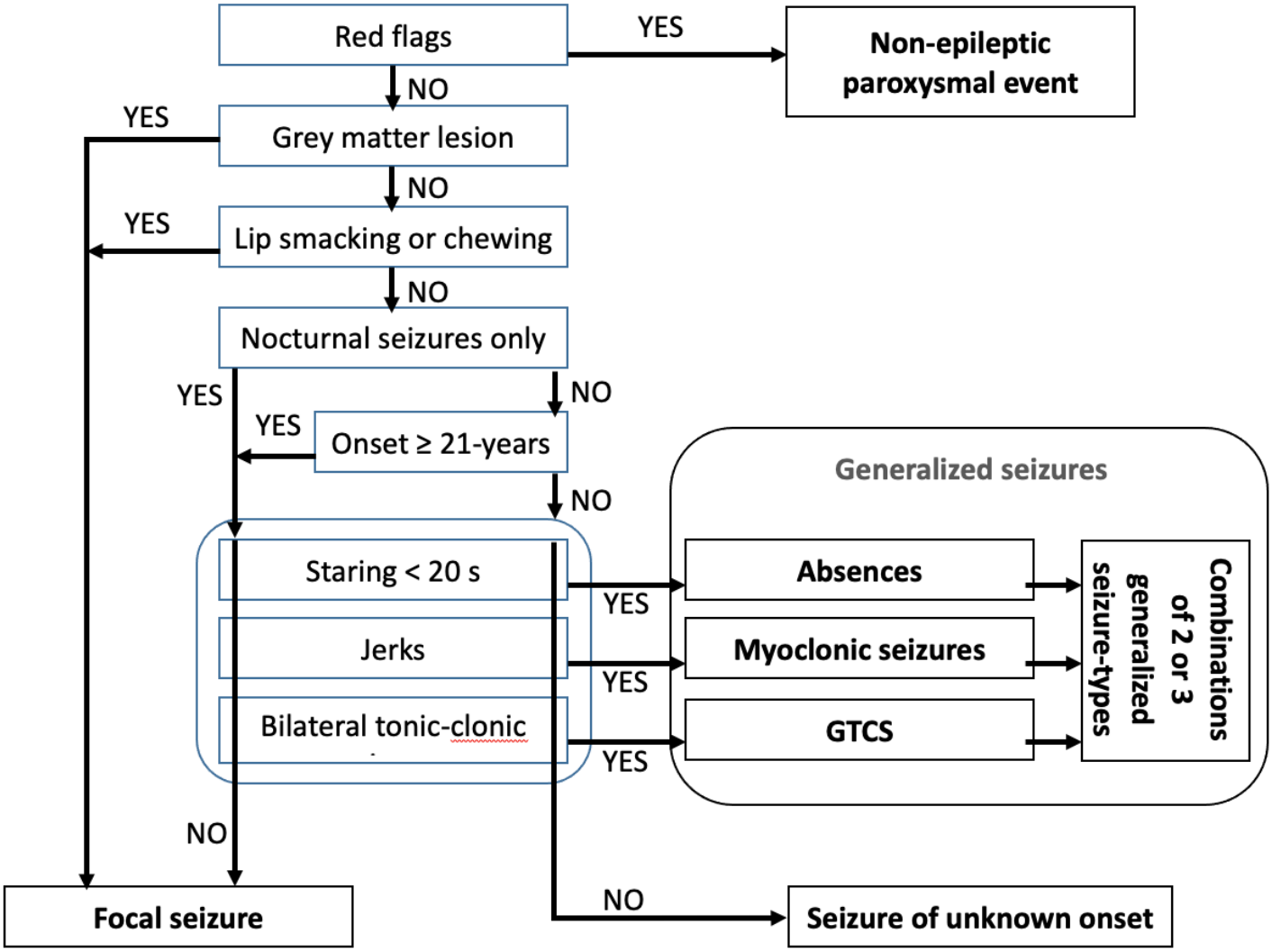
4.6 EPIPICK: A WEB-BASED DECISION SUPPORT SYSTEM FOR OPTIMAL, PATIENT-TAILORED CHOICE OF ANTISEIZURE MEDICATION

We developed the Epipick - a freely accessible web-based application (https://epipick.org) to help health care professionals select the most appropriate, patient-tailored antiseizure medication (ASM) in patients with epilepsy (seizure onset at 10 years of age or older). EpiPick considers seizure types and patient-specific variables to provide treatment recommendations, ranking ASMs in order of appropriateness based on the available scientific evidence and expert judgement. The app also provides a summary of prescribing information for each of the ASMs being suggested.

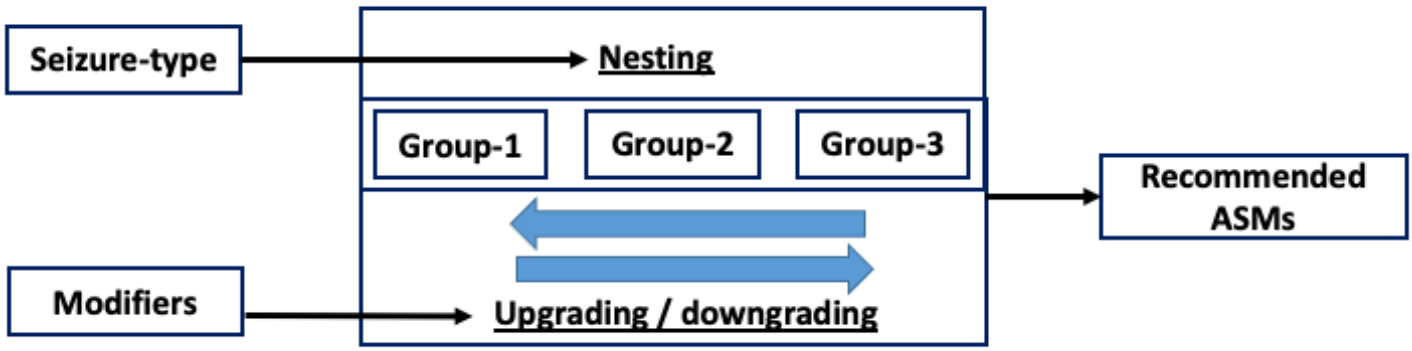
We validated the app in three studies. In a large, multicenter, prospective study, we validated the first part of the algorithm, which classifies seizure types to facilitate therapeutic decision-making. Agreement between the algorithm and the expert classification was 83.2% [95% confidence interval (CI) 78.6%–87.8%], with an agreement coefficient (AC1) of 0.82 (95% CI 0.77–0.87), indicating almost perfect agreement. In another study, we investigated the agreement among experts in selecting an ASM as initial monotherapy and used their choices to validate the app. The percent agreement between the highest ranked selections of the app and the expert selections was 73% (95% CI 64%–82%). Agreement between the app and the majority decision of the experts was higher than the agreement among the experts. Ninety-five percent of the experts considered that no incorrect or potentially harmful ASMs were ranked the highest by the application, and most experts strongly agreed with the app's selections. Finally, we conducted an external validation of the app using an independent real-life retrospective data set to assess whether ASMs recommended by the algorithm were associated with better outcomes than ASMs considered less desirable by the algorithm. Compared with ASMs considered less desirable by the algorithm, ASMs classified by the app as the best options were associated with a higher retention rate (79.4% vs 67.2%, $p = 0.005$), a higher seizure-freedom rate (76.0% vs 61.6%, $p = 0.002$), and a lower rate of discontinuation due to adverse effects (12.0% vs 29.2%, $p < 0.001$).



Graphical user interphase of the Epipick app. The input to the app are simple questions answered by the user.



The classification algorithm in Epipick.



The algorithm for optimizing individual ASM choice, in Epipick.

Papers

Beniczky S, Asadi-Pooya AA, Perucca E, Rubboli G, Tartara E, Meritam Larsen P, Ebrahimi S, Farzinmehr S, Rampp S, Sperling MR. A web-based algorithm to rapidly classify seizures for the purpose of drug selection. Epilepsia. 2021 Oct;62(10):2474-2484. doi: 10.1111/epi.17039. Epub 2021 Aug 22. PMID: 34420206.

Beniczky S, Rampp S, Asadi-Pooya AA, Rubboli G, Perucca E, Sperling MR. Optimal choice of antiseizure medication: Agreement among experts and validation of a web-based decision support application. Epilepsia. 2021 Jan;62(1):220-227. doi: 10.1111/epi.16763. Epub 2020 Dec 6. PMID: 33280100.

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 Aug;61(8):1668-1677. doi: 10.1111/epi.16610.

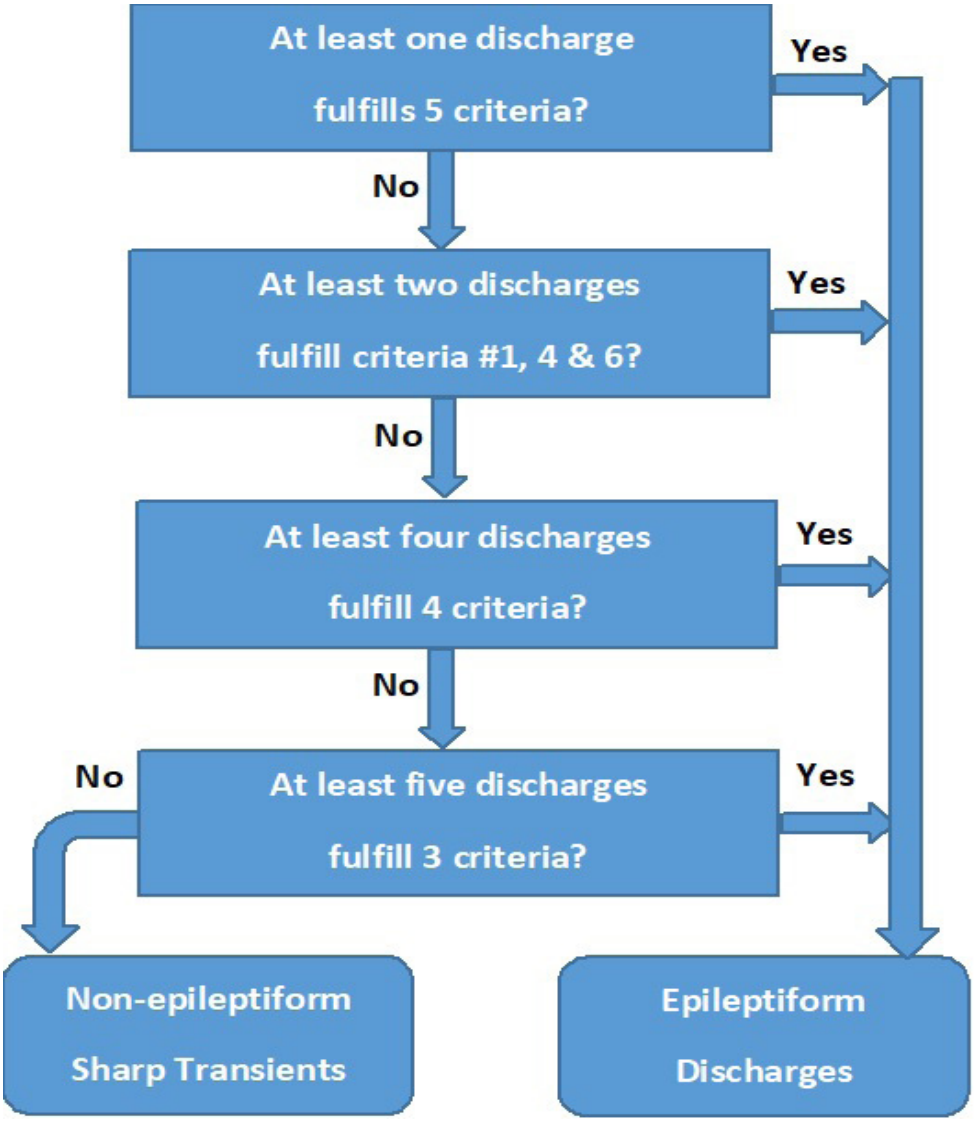
4.7 INTERICTAL EPILEPTIFORM DISCHARGES (IEDs)

IEDs (spikes, polyspikes, sharp-waves) are the best documented, electrographic biomarkers of epilepsy. Our group completed and published in 2021 several projects addressing clinical application of IEDs.

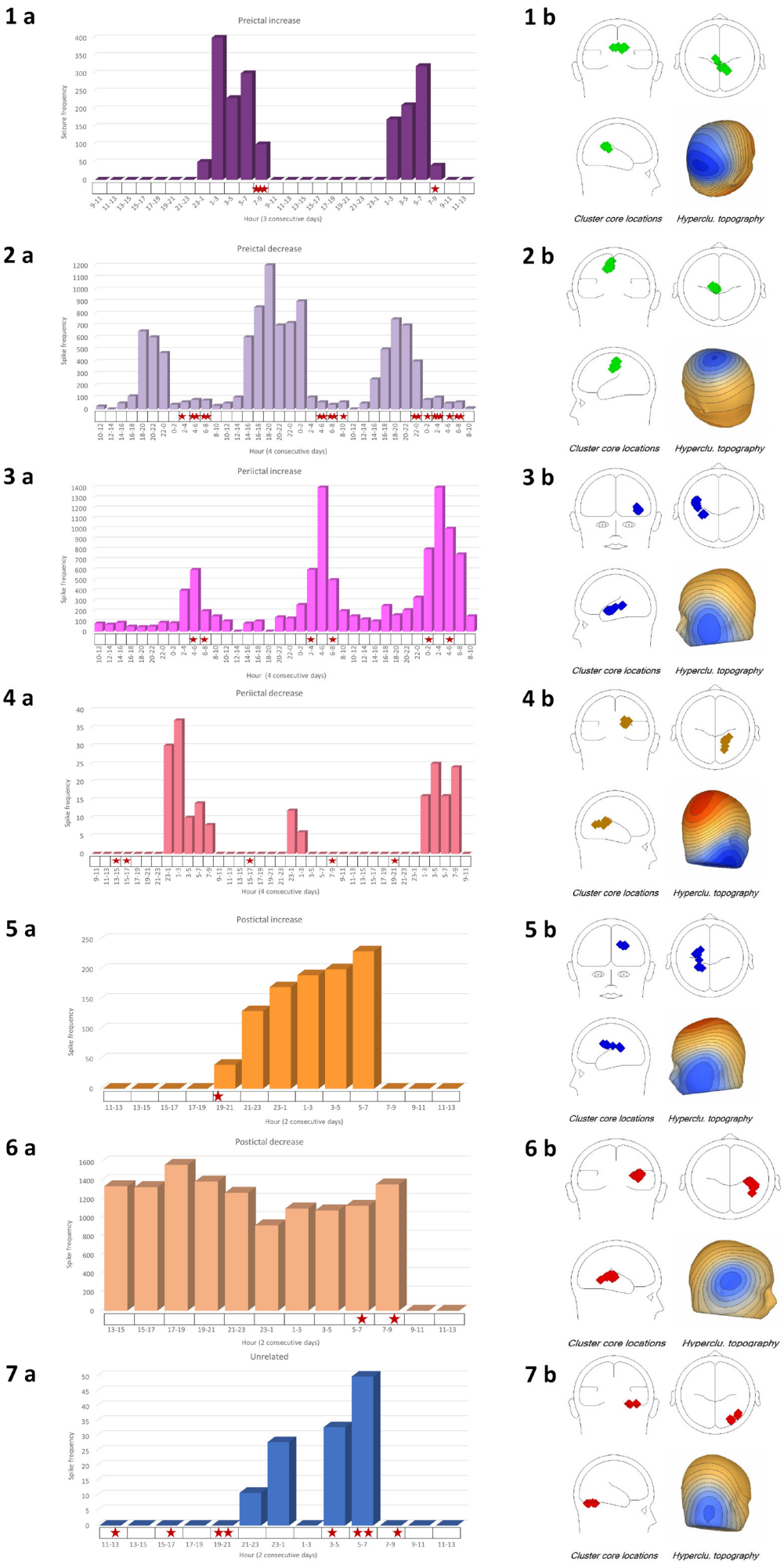
The operational definition of IEDs, by the International Federation of Clinical Neurophysiology (IFCN) described six morphological criteria. We assessed the impact of pattern-repetition in the EEG-recording, on the diagnostic accuracy of using the IFCN criteria. For clinical implementation, specificity over 95% was set as target. Interictal EEG-recordings of 20-minutes, containing sharp-transients, from 60 patients (30 with epilepsy and 30 with non-epileptic paroxysmal events) were evaluated by three experts, who first marked IEDs solely based on expert opinion, and then, independently from the first session evaluated the presence of the IFCN criteria for each sharp-transient. The gold standard was derived from long-term video-EEG recordings of the patients´ habitual paroxysmal episodes. Presence of at least one discharge fulfilling five criteria provided a specificity of 100% (sensitivity: 70%). For discharges fulfilling fewer criteria, a higher number of discharges was needed to keep the specificity over 95% (5 discharges, when only 3 criteria were fulfilled). A sequential combination of these sets of criteria and thresholds provided a specificity of 97% and sensitivity of 80%. We concluded that pattern-repetition and IED morphology influenced diagnostic accuracy. Systematic application of these criteria will improve quality of clinical EEG interpretation

We tested the hypothesis that significant changes in the occurrence of IEDs were associated with seizures: while some IEDs are pro-convulsive, increasing at seizure-occurrence, others are protective, showing decrease related to seizures. We analyzed 102 consecutive, long-term video-EEG monitoring sessions, from 98 patients. Using a semi-automated spike-detection method, we quantified the occurrence of IEDs, grouped according to their location and morphology (clusters) and we constructed graphical representation of data, showing changes in time of the spiking patterns (spike-histograms). We compared the spike-histograms with the time-points of the seizures (pre-, peri- and postictal changes). Totally 179 IED-clusters were identified. Modulation of the spiking pattern, associated with seizures, was observed in 66 clusters (37%), from 47 patients (48%). Most of these changes (40 clusters; 61%) were related to increase in the spiking-pattern. Changes in spiking-pattern were associated with more than one third of the IEDs. Both increasing and decreasing patterns were observed. IEDs are more often pro-convulsive, with increasing spiking patterns associated with seizures. However, in more than one third of the IED clusters modulated by seizures, the spiking pattern decreased, raising the possibility of an anticonvulsive function of these discharges.

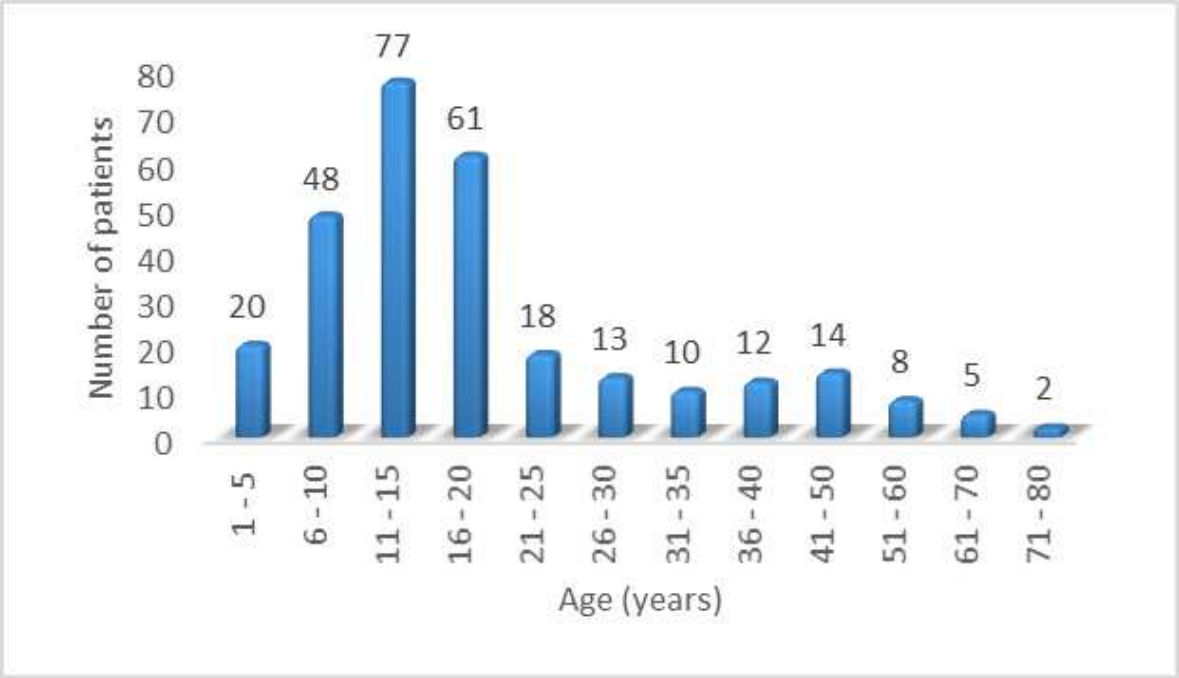
To characterize photoparoxysmal EEG response (PPR) we used a standardized protocol of intermittent photic stimulation (IPS) and standardized definitions for PPR, classified into six types. We prospectively built a large database of standardized EEG annotations esing the SCORE system (Standardized Computer-Based Organized Reporting of EEG). We extracted the features related to PPR from the structured dataset consisting of 10,671 EEG recordings with IPS, from 7,188 patients. The standardized IPS protocol elicited PPR in 375 recordings (3.5%), in 288 patients (4%), with a preponderance among young (11-20 years) and female patients (67%). PPR was persistent in patients with multiple recordings. The most frequent type of PPR was activation of preexisting epileptogenic area (58%), followed by generalized-PPR limited to the stimulus train (22%). We could not find any recording with self-sustained posterior response. Seizures were elicited in 27% of patients with PPR, most often myoclonic seizures and absences, in patients with self-sustained generalized PPR. We concluded that the most common type of PPR was accentuation of preexisting epileptogenic area. Self-sustained posterior response could not be documented. Self-sustained generalized-PPR had the highest association with seizures. Using standardized stimulation protocol and definitions for PPR types, IPS provides high diagnostic yield.



Flow-diagram with the clinical relevance of the pattern repetition.



Spike-hystograms vs. seizure occurrence.



Distribution of Photoparoxysmal response, according to the age of the patients.

Papers

Kural MA, Qerama E, Johnsen B, Fuchs S, Beniczky S. The influence of the abundance and morphology of epileptiform discharges on diagnostic accuracy: How many spikes you need to spot in an EEG. Clin Neurophysiol. 2021 Jul;132(7):1543-1549. doi: 10.1016/j.clinph.2021.03.045.

Arbune AA, Meritam Larsen P, Wüstenhagen S, Terney D, Gardella E, Beniczky S. Modulation in time of the interictal spiking pattern related to epileptic seizures. Clin Neurophysiol. 2021 May;132(5):1083-1088. doi:10.1016/j.clinph.2021.01.026.

Meritam Larsen P, Wüstenhagen S, Terney D, Gardella E, Alving J, Aurlien H, Beniczky S. Photoparoxysmal response and its characteristics in a large EEG database using the SCORE system. Clin Neurophysiol. 2021 Feb;132(2):365-371. doi: 10.1016/j.clinph.2020.10.029.

4.8 GUIDELINES

Guidelines are essential to improve the quality of care. Guidelines must be developed using a robust methodology, based on systematic review of published evidence. Developing guidelines is resource demanding, yet much deeded for clinical practice. We were happy to contribute to several, international guidelines, published in 2021.

The guideline on automated seizure detection using wearable devices was developed in collaboration between the International League Against Epilepsy and the International Federation of Clinical Neurophysiology. It recommends using validated devices for safety indications, in patients sleeping alone.

Some epilepsy syndromes (sleep-related epilepsies, SREs) have a strong link with sleep.

Comorbid sleep disorders are common in patients with SRE and can exert a negative impact on seizure control and quality of life. Standard procedures for the diagnostic pathway of sleep-related epilepsies and comorbid sleep disorders were developed by a working group representing the European Academy of Neurology, European Sleep Research Society and the International League Against Epilepsy – Europe. We contributed to the expert consensus on managing sleep disturbances in people with epilepsy.

We participated in the work of the expert panel that developed the Standardized Critical Care EEG Terminology of the American Clinical Neurophysiology Society's (2021 Version).

Papers

Beniczky S, Wiebe S, Jeppesen J, Tatum WO, Brazdil M, Wang Y, Herman ST, Ryvlin P. Automated seizure detection using wearable devices: A clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology. Clin Neurophysiol. 2021 May;132(5):1173-1184. doi: 10.1016/j.clinph.2020.12.009.
Beniczky S, Wiebe S, Jeppesen J, Tatum WO, Brazdil M, Wang Y, Herman ST, Ryvlin P. Automated seizure detection using wearable devices: A clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology. Epilepsia. 2021 Mar;62(3):632-646. doi: 10.1111/epi.16818.

Nobili L, Beniczky S, Eriksson SH, Romigi A, Ryvlin P, Toledo M, Rosenzweig I. Expert Opinion: Managing sleep disturbances in people with epilepsy. Epilepsy Behav. 2021 Oct 4;124:108341. doi: 10.1016/j.yebeh.2021.108341.

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: an EAN, ESRS and ILAE-Europe consensus review. Eur J Neurol. 2021 Jan;28(1):15-32. doi: 10.1111/ene.14468. Epub 2020 Sep 21.

Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, Lee JW, Wusthoff CJ, Hahn CD, Westover MB, Gerard EE, Herman ST, Haider HA, Osman G, Rodriguez-Ruiz A, Maciel CB, Gilmore EJ, Fernandez A, Rosenthal ES, Claassen J, Husain AM, Yoo JY, So EL, Kaplan PW, Nuwer MR, van Putten M, Sutter R, Drislane FW, Trinka E, Gaspard N. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. J Clin Neurophysiol. 2021 Jan 1;38(1):1-29. doi: 10.1097/WNP.0000000000000806.

4.9 FAMILY IMPACT OF COMPLEX CHILDHOOD EPILEPSY

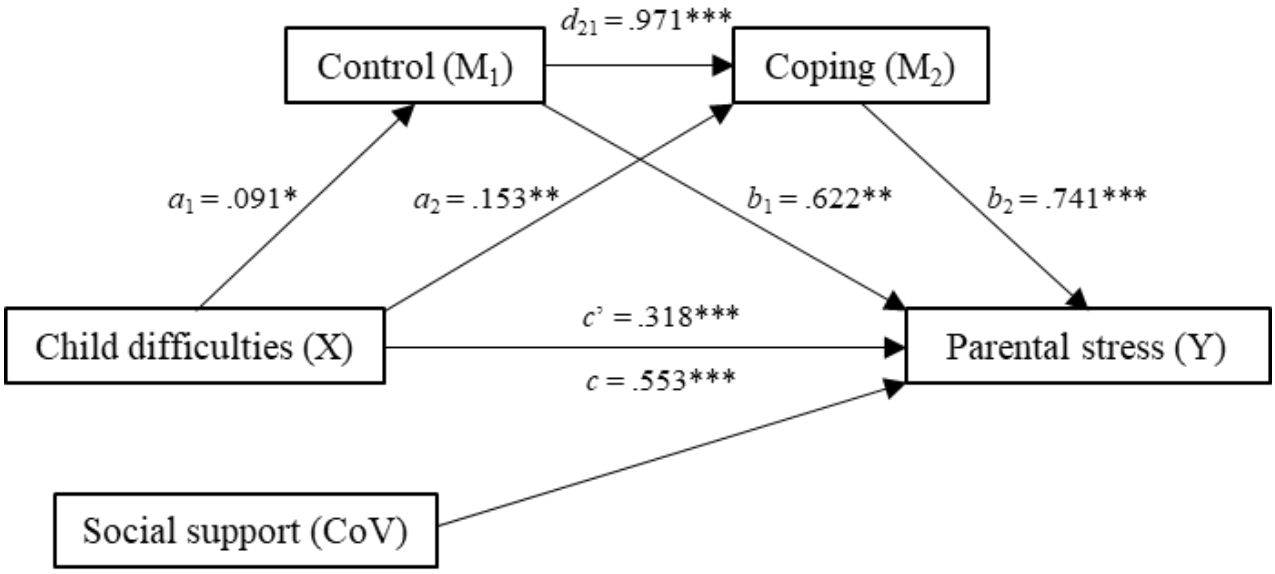
Articles published 2021 related to the Ph.D.;
Jakobsen, A. V., & Elklit, A. Self-control and coping responses are mediating factors between child behavior difficulties and parental stress and family impact in caregivers of children with severe epilepsy. Epilepsy Behav. 2021 Sep;122:108224. doi: 10.1016/j.yebeh.2021.108224

Jakobsen, A. V., & Elklit, A. Post-traumatic stress disorder (PTSD) symptoms in children with severe epilepsy. Epilepsy Behav. 2021 Sep;122:108217. doi: 10.1016/j.yebeh.2021.108217

The two papers are a result of the work included in the Ph.d. project; Family impact of complex childhood epilepsy. The first paper illustrates that parental individual psychological factors influence the extent to which parents experience stress and the family impact of living with complex childhood epilepsy.

The second paper document a concerning level of PTSD symptoms and sub-threshold symptoms in children with complex epilepsy. The paper is the first to assess PTSD symptoms in children with epilepsy with developmental-sensitive assessment tools.

Both papers accentuate the need for timely support of the family as an entity and an increased awareness of trauma exposure in clinical settings and other relevant contextual settings.



Paper not related to the Ph.D. (optional to mention, it's a collaborative work not related to epilepsy research)

Vang, M. L., Dokkedahl, S. B., Løkkegaard, S. S., Jakobsen, A. V., Møller, L., Auning-Hansen, M. A., & Elklit, A. Validation of ICD-11 PTSD and DSO using the International Trauma Questionnaire in five clinical samples recruited in Denmark. Eur J Psychotraumatol. 2021 Mar 30;12(1):1894806. doi: 10.1080/20008198.2021.1894806

5. Lectures - oral presentations at congresses in 2021

Sándor Beniczky:

- Electrographic Patterns in Focal status epilepticus. American Epilepsy Society, Annual meeting 2021 (hybrid), Chicago, USA.
- E-learning resources provided by the ILAE. American Epilepsy Society, Annual meeting 2021 (hybrid), Chicago, USA.
- Future research and development: in the aftermath of the clinical practice guideline on seizure detection. 3rd International Congress on Seizure Detection and Wearable Devices in Epilepsy, 28/10/2021 30/10/2021, Copenhagen, Denmark.
- Wearable EEG for absence seizure detection: prospective validation study. 3rd International Congress on Seizure Detection and Wearable Devices in Epilepsy, 28/10/2021 30/10/2021, Copenhagen, Denmark.
- Operational criteria for Interictal Epileptiform Discharges. 34th International Epilepsy Congress. 28/08/2021 01/09/2021. Online.
- Systematic approach to EEG interpretation: Interictal & Ictal Patterns. 34th International Epilepsy Congress. 28/08/2021 01/09/2021. Online.
- Wearables in epilepsy: what is their role in telemedicine? Presidential Symposium at the 34th International Epilepsy Congress. 28/08/2021 01/09/2021. Online.
- Added value of including the inferior temporal chain into your EEG electrode array. Annual Meeting of the American Clinical Neurophysiology Society. 10/02/2021 14/02/2021. Online.

Guido Rubboli:

- "Genetic testing in adult epilepsy patient: is it worth?" at the Nordic Experience Sharing Meeting on Personalized medicine, EISAI sponsored
- "How can genetics contribute to the clinical management in epilepsy ?" at the Update in Epilettologia, Padova (Italy)
- "How can genetics contribute to the clinical management in epilepsy ?" on-line Seminar in Child Neurology, University of Bologna, Bologna (Italy)
- "Encephalopathy related to Status Epilepticus during Sleep (ESES): linking epilepsy, sleep disruption
- and cognitive impairment" at the 17th International Epilepsy Congress, Teheran (Iran)
- "Precision medicine in genetic epilepsies", on-line Seminar in Child Neurology, University of Bologna, Bologna (Italy)
- "Management on rare epileptic syndrome : focus on adults" at the "Rare epileptic disorders: management perspectives through the patient's life" Symposium at the International Epilepsy Colloquium, BioCodex sponsored, London (UK)
- "Un PDTA che guarda lontano con l'attenzione al particolare. L'esperienza di un grande centro europeo:

- cosa importare in future" at the Fuori dall'ombra meeting on "Percorso Diagnostico Terapeutico Assistenziale delle persone affette da Epilessia", Padova (Italy)
- "Generalized Seizures: Videosession" at the virtual 34th International Epilepsy Congress
- Chairman and organizer of the 3. Annual Meeting Danish Epilepsy Center and Norwegian Epilepsy Center on
- "Adherence to Antiepileptic Drug Treatment. The Size of the Problem, Possible Consequences, and
- How to Deal with It. Copenhagen
- "Managing Epilepsy Throughout the Lifespan. Joined Experiences from the Pediatric and Adult epilepsy", on-line meeting, UCB sponsored,
- Chairman at the virtual Ology Expert Talks Debate "Predicting and detecting seizures: can digital health technologies help clinicians up their game?", withy Mark Cook and Benjamin Brinkmann,
- "Final Remarks" at the on-line meeting "Treatment outcomes and strategies in patients with focal refractory epilepsy", Arvelle sponsored meeting, Copenhagen (Denmark)

Rikke Steensbjerre Møller:

- Resistance to Na-blockers in patients with SCN2A or SCN8A gain-of-function variants; Genetic epilepsies and other neuronal ion channel disorders: Mechanisms and therapeutic perspectives, Tübingen, Germany
- Genotype-phenotype correlations in SCN8A-related disorders; Genetic epilepsies and other neuronal ion channel disorders: Mechanisms and therapeutic perspectives, Tübingen, Germany
- SCN8A: Genotype-phenotype correlations; 1st European SCN8A/SCN2A Conference and Family Gathering, Bonn, Germany
- The state of the art of the research on STXBP1, 1st Scandinavian STXBP1 Family Meeting, Dianalund.

Elena Gardella:

- The Natural History of SCN8A related diseases; 34th International epilepsy congress (Virtual)
- SCN8A: Current therapies and prognostic factors; 1st European SCN8A/SCN2A Conference and Family Gathering, Bonn, Germany
- SCN8A: Phenotypic spectrum and natural history study; 1st European SCN8A/SCN2A Conference and Family Gathering, Bonn, Germany
- SCN8A: Meet the expert and Concluding remarks; 1st European SCN8A/SCN2A Conference and Family Gathering, Bonn, Germany
- The STXBP1 phenotype in adults, 1st Scandinavian STXBP1 Family Meeting, Dianalund.
- The Natural History of STXBP1 in adulthood, annual meeting of the International STXBP1 family association (virtual).
- SCN8A precision treatment readiness from a large database to the natural history study- The Cute Syndrome Foundation Annual Gathering meeting, Chicago (USA)
- Challenges in SCN8A-complex clinical trials; Building the Epicare 2027 Horizon, EpiCARE Workshop, Rome (Italy)
- BPTF and epilepsy; BPTF Family and researchers' symposium – Virtual meeting

Allan Bayat:

- Impact of genetic testing on therapeutic decision making in childhood-onset epilepsies. European Society of Human Genetics Conference 2021. Press release (eshg.org/index.php?id=13).
- Genetic testing and precision therapy in childhood-onset epilepsies. Brain Prize Meeting.
- Impact of genetic testing on therapeutic decision-making in childhood-onset epilepsies - a study in a tertiary epilepsy centre. Danish Society for Pediatric Neurology conference.
- Genetic testing and precision therapy in childhood-onset epilepsies. 8th International Course on Drug Resistant Epilepsies.
- X-linked neonatal-onset epileptic encephalopathy associated with a gain-of-function variant p.R660T in GRIA3. Genetic epilepsies and other neuronal ion channel disorders: Mechanisms and therapeutic perspectives, Tübingen, Germany

Katrine Johannesen:

- PURA-related developmental and epileptic encephalopathy: phenotypic and genotypic spectrum. PURA syndrome 2021 Virtual Conference
- SLC6A1-related disorders. Epicare webinar
- Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications. 34th International Epilepsy Congress

Francesca Furia:

- The Scandinavian STXBP1 database, 1st Scandinavian STXBP1 Family Meeting, Dianalund
- The Scandinavian STXBP1 database, Annual meeting of the Danish Epilepsy Society _ First prize at the oral presentation competition.

6. International online courses in 2021

Rikke Møller:

- Genetics of Idiopathic/Genetic Generalized Epilepsy; Nordic IGE meetings (webinar)
- Utility of genetic testing for therapeutic decision-making in individuals with epilepsy; Cleveland Clinics, Epilepsy Grand Rounds (webinar)
- Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications; EpiCare (webinar)
- Precision Medicine and Epilepsy Genetics, ICNA, Child Neurology Teaching Network (webinar).

Guido Rubboli:

- "Cognitive and emotional reflex seizures" 3rd Bologna EPI-PED EEG Course on EEG Interpretation in Pediatric Epilepsies
- "SLC6A1-related disorders". Epicare (webinar)
- Tutor on "Epilepsy syndromes in adolescents & adults" at the 7th Advance EEG On-line Course of the VIREPA, International League Against Epilepsy

Elena Gardella:

- VIREPA courses: Basic EEG, teaching session, 34th International epilepsy congress (Virtual)
- Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications; EpiCare webinar series
- SCN8A-realted diseases: clinical spectrum, genotype-phenotype correlations and therapeutic implications. Webinar series IRCCS Mondino, University of Pavia (Italy)
- Tutor on "Interictal and Ictal EEG patterns" at the 21th Basic EEG On-line Course of the VIREPA, International League Against Epilepsy

Francesca Furia:

- The Scandinavian STXBP1 database, Webinar of the International STXBP1 family association.

7. Publication list in 2021

1. Houtman SJ, Lammertse HCA, van Berkel AA, Balagura G, **Gardella E**, Ramautar JR, Reale C, **Møller RS**, Zara F, Striano P, Misra-Isrie M, van Haelst MM, Engelen M, van Zuijen TL, Mansvelder HD, Verhage M, Bruining H, Linnenkaer-Hansen K. STXBP1 Syndrome Is Characterized by Inhibition-Dominated Dynamics of Resting-State EEG. Front Physiol. 2021 Dec 23;12:775172.
2. **Johannesen KM**, Iqbal S, Guazzi M, **Mohammadi NA**, Pérez-Palma E, Schaefer E, De Saint Martin A, Abiwarde MT, McTague A, Pons R, Piton A, Kurian MA, Ambegaonkar G, Firth H, Sanchis-Juan A, Deprez M, Jansen K, De Waele L, Briltra EH, Verbeek NE, van Kempen M, Fazeli W, Striano P, Zara F, Visser G, Braakman HMH, Haeusler M, Elbracht M, Vaher U, Smol T, Lemke JR, Platzer K, Kennedy J, Klein KM, Au PYB, Smyth K, Kaplan J, Thomas M, Dewenter MK, Dinopoulos A, Campbell AJ, Lal D, Lederer D, Liao VWY, Ahring PK, **Møller RS**, **Gardella E.** Structural mapping of GABRB3 variants reveals genotype-phenotype correlations. Genet Med. 2021 Dec 7:S1098-3600(21)05382-X.
3. Sourbron J, Jansen K, Mei D, **Hammer TB**, **Møller RS**, Gold NB, O'Grady L, Guerrini R, Lagae L. SLC7A3: In Silico Prediction of a Potential New Cause of Childhood Epilepsy. Neuropediatrics. 2021 Dec 6.
4. Kumble S, Levy AM, Punetha J, Gao H, Ah Mew N, Anyane-Yeboa K, Benke PJ, Berger SM, Bjerglund L, Campos-Xavier B, Ciliberto M, Cohen JS, Comi AM, Curry C, Damaj L, Denommé-Pichon AS, Emrick L, Faivre L, Fasano MB, Fiévet A, Finkel RS, García-Miñaúr S, Gerard A, Gomez-Puertas P, Guillen Sacoto MJ, Hoffman TL, Howard L, Iglesias AD, Izumi K, Larson A, Leiber A, Lozano R, Marcos-Alcalde I, Mintz CS, Mullegama SV, **Møller RS**, Odent S, Oppermann H, Ostergaard E, Pacio-Míguez M, Palomares-Bralo M, Parikh S, Paulson AM, Platzer K, Posey JE, Potocki L, Revah-Politi A, Rio M, Ritter AL, Robinson S, Rosenfeld JA, Santos-Simarro F, Sousa SB; Undiagnosed Diseases Network, Wéber M, Xie Y, Chung WK, Brown NJ, Tümer Z. The clinical and molecular spectrum of QRICH1 associated neurodevelopmental disorder. Hum Mutat. 2021 Dec 2.
5. **Johannesen KM, Gardella E**, Gjerulfsen CE, **Bayat A**, Rouhl RPW, Reijnders M, Whalen S, Keren B, Buratti J, Courtin T, Wierenga KJ, Isidor B, Piton A, Faivre L, Garde A, Moutton S, Tran-Mau-Them F, Denommé-Pichon AS, Coubes C, Larson A, Esser MJ, Appendino JP, Al-Hertani W, Gamboni B, Mampel A, Mayorga L, Orsini A, Bonuccelli A, Suppiej A, Van-Gils J, Vogt J, Damioli S, Giordano L, Moortgat S, Wirrell E, Hicks S, Kini U, Noble N, Stewart H, Asakar S, Cohen JS, Naidu SR, Collier A, Brilstra EH, Li MH, Brew C, Bigoni S, Ognibene D, Ballardini E, Ruivenkamp C, Faggioli R, Afenjar A, Rodriguez D, Bick D, Segal D, Coman D, Gunning B, Devinsky O, Demmer LA, Grebe T, Pruna D, Cursio I, Greenhalgh L, Graziano C, Singh RR, Cantalupo G, Willems M, Yoganathan S, Góes F, Leventer RJ, Colavito D, Olivotto S, Scelsa B, Andrade AV, Ratke K, Tokarz F, Khan AS, Ormieres C, Benko W, Keough K, Keros S, Hussain S, Franques

A, Varsalone F, Grønborg S, Mignot C, Heron D, Nava C, Isapof A, Borlot F, Whitney R, Ronan A, Foulds N, Somorai M, Brandsema J, Helbig KL, Helbig I, Ortiz-González XR, Dubbs H, Vitobello A, Anderson M, Spadafore D, Hunt D, **Møller RS**, **Rubboli G**; PURA study group. PURA-Related Developmental and Epileptic Encephalopathy: Phenotypic and Genotypic Spectrum. Neurol Genet. 2021 Nov 15;7(6):e613.

6. Manivannan SN, Roovers J, Smal N, Myers CT, Turkdogan D, Roelens F, Kanca O, Chung HL, Scholz T, Hermann K, Bierhals T, Caglayan HS, Stamberger H; MAE working group of EuroEPINOMICS RES Consortium, Mefford H, de Jonghe P, Yamamoto S, Weckhuysen S, Bellen HJ. De novo FZR1 loss-of-function variants cause developmental and epileptic encephalopathies. Brain. 2021 Nov 11:awab409.
7. Ahring PK, Liao VWY, **Gardella E, Johannesen KM**, Krey I, Selmer KK, Stadheim BF, Davis H, Peinhardt C, Koko M, Coorg RK, Syrbe S, Bertsche A, Santiago-Sim T, Diemer T, **Fenger CD**, Platzer K, Eichler EE, Lerche H, Lemke JR, Chebib M, **Møller RS**. Gain-of-function variants in GABRD reveal a novel pathway for neurodevelopmental disorders and epilepsy. Brain. 2021 Oct 11:awab391.
8. Krey I, Heine C, Frömming M, Herrmann J, **Møller RS**, Weckhuysen S, Courage C, Beblo S, Syrbe S, Lemke JR. The Angelman Syndrome Online Registry - A multilingual approach to support global research. Eur J Med Genet. 2021 Dec;64(12):104349.
9. Tenorio-Castaño JA, Arias P, Fernández-Jaén A, Lay-Son G, Bueno-Lozano G, **Bayat A**, Faivre L, Gallego N, Ramos S, Butler KM, Morel C, Hadjiyannakis S, Lespinasse J, Tran-Mau-Them F, Santos-Simarro F, Pinson L, Martínez-Monseny AF, O'Callaghan Cord MDM, Álvarez S, Stolerman ES, Washington C, Ramos FJ, The S O G R I Consortium, Lapunzina P.Tenorio-Castaño JA, et al. Tenorio syndrome: Description of 14 novel cases and review of the clinical and molecular features. Clin Genet. 2021 Oct;100(4):405-411.
10. Rinaldi B, Ge YH, Freri E, Tucci A, Granata T, Estienne M, Sun JH, Gérard B, **Bayat A**, Efthymiou S, Gervasini C, Shi YS, Houlden H, Marchisio P, Milani D.Rinaldi B, et al. Myoclonic status epilepticus and cerebellar hypoplasia associated with a novel variant in the GRIA3 gene. Neurogenetics. 2021 Nov 3.
11. **Johannesen KM**, Liu Y, Koko M, Gjerulfsen CE, Sonnenberg L, Schubert J, **Fenger CD**, Eltokhi A, Rannap M, Koch NA, Lauxmann S, Krüger J, Kegele J, Canafoglia L, Franceschetti S, Mayer T, Rebstock J, Zacher P, Ruf S, Alber M, Sterbova K, Lassuthová P, Vlckova M, Lemke JR, Platzer K, Krey I, Heine C, Wieczorek D, Kroell-Seger J, Lund C, Klein KM, Billie Au PY, Rho JM, Ho AW, Masnada S, Veggiotti P, Giordano L, Accorsi P, Hoei-Hansen CE, Striano P, Zara F, Verhelst H, Verhoeven JS, van der Zwaag B, Harder AVE, Brilstra E, Pendziwiat M, Lebon S, Vaccarezza M, Minh Le N, Christensen J, Grønborg S, Scherer SW, Howe J, Fazeli W, Howell KB, Leventer R, Stutterd C, Walsh S, Gerard M, Gerard B, Matricardi S, Bonardi CM, Sartori S, Berger A, Hoffman-Zacharska D, Mastrangelo M, Darra F, Vøllo A, Motazacker MM, Lakeman P, Nizon M, Betzler C, Altuzarra C, Caume R, Roubertie A, Gélisse P, Marini C, Guerrini R, Bilan F, Tibussek D, Koch-Hogrebe M, Perry MS, Ichikawa S, Dadali E, Sharkov A, Mishina I, Abramov M, Kanivets I, Korostelev S, Kutsev S, Wain KE, Eisenhauer N, Wagner M, Savatt JM, Müller-Schlüter K, Bassan H, Borovikov A, Nassogne MC, Destrée A, Schoonjans AS, Meuwissen M, Buzatu M, Jansen A, Scalais E, Srivastava S, Tan WH, Olson HE, Loddenkemper T, Poduri A, Helbig KL, Helbig I, Fitzgerald MP, Goldberg EM, Roser T, Borggraefe I, Brünger T, May P, Lal D, Lederer D, **Rubboli G**, Heyne HO, Lesca G, Hedrich UBS, Benda J, **Gardella E**, Lerche H, **Møller RS**. Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications. Brain. 2021 Aug 25.
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