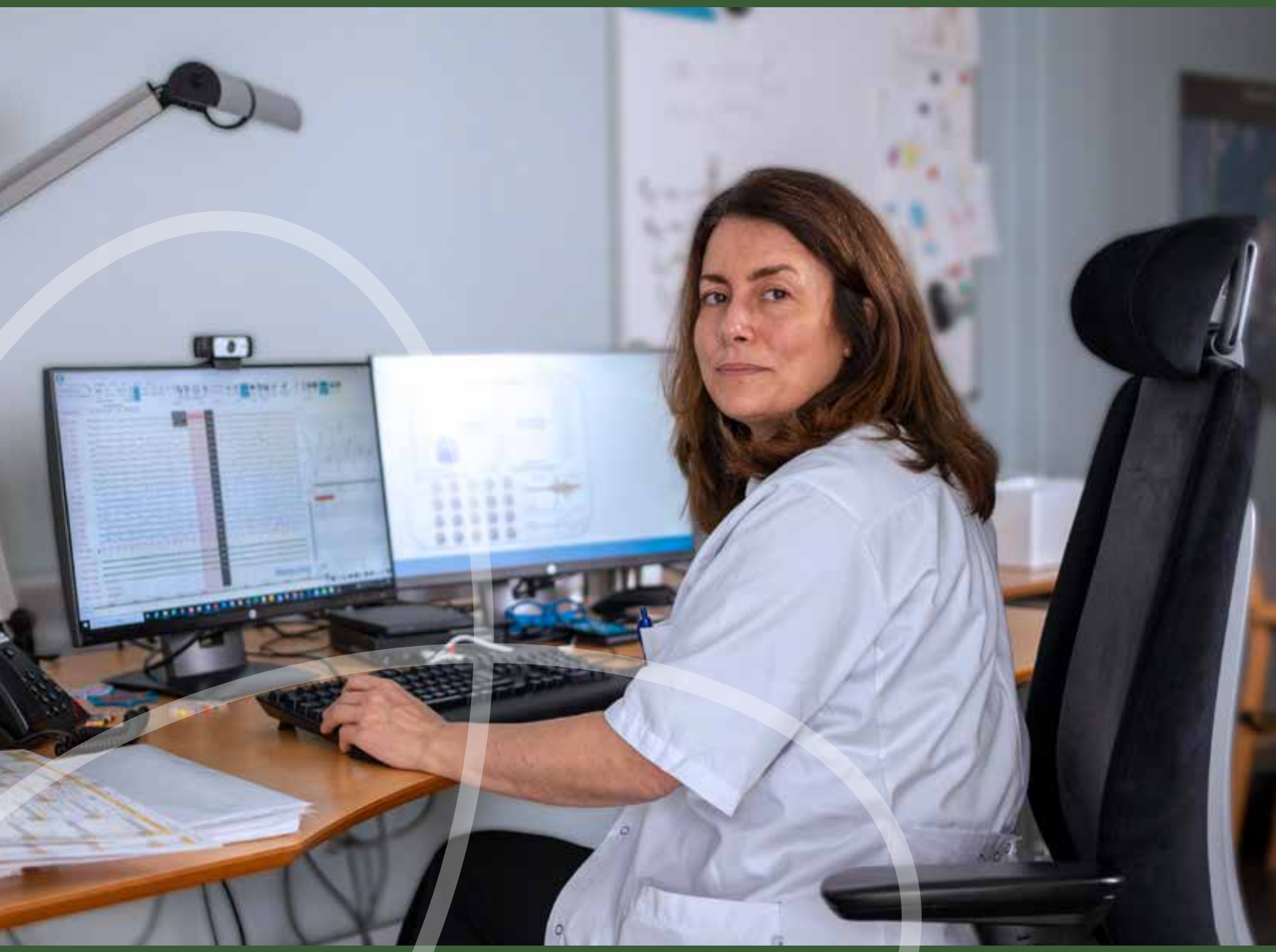
FILADELFIA



ANNUAL RESEARCH REPORT 2024

Danish Epilepsy Centre Filadelfia

Content

4 Professors

2 Ass. Professors

2 post docs

14 Ph.D. students

73 Publications *)

136 Oral Presentations

**) 4 book chapters and 69 papers published in peer reviewed journals including leading journals, such as Lancet Neurology, Nature Communications, PNAS, Annals of Neurology, EBioMedicine, Neurology and Epilepsia.*

1. Introduction – Filadelfia

Filadelfia - The Danish Epilepsy Centre - offers highly specialized healthcare services to epilepsy patients of all ages. As the sole specialized epilepsy hospital in Denmark, we receive referrals for rare and complex epilepsies. Our focus is on delivering high-quality comprehensive clinical care, research and development are internationally recognized. In 2024, our team, consisting of four professors, two associate professor, two postdocs, and 14 PhD students, published 4 book chapters and 68 research papers, including in leading journals in the field of clinical neuroscience, and delivered 136 oral presentations at international medical conferences.

Our researchers are affiliated with the University of Copenhagen, the University of Odense, and Aarhus University. They hold important positions of trust in national and international scientific societies and serve as key hubs in numerous international epilepsy research networks.

Filadelfia, The Danish Epilepsy Center, is a non-profit foundation with an independent Board of Directors. In addition to the Epilepsy Hospital, Filadelfia comprises a center for neurorehabilitation, specialized institutions for mentally handicapped persons, and the only special school for children and young people with epilepsy in Denmark. Filadelfia is publicly 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 hope it will encourage further collaboration for the benefit of persons with epilepsy worldwide.

As the Medical Director, I want to express my gratitude to all the collaborators in the research teams for their efforts and great achievements in 2024, and to Professor Sándor Beniczky for his leading role in producing this research report.

Lisbeth Nielsen
Managing Hospital Director
Danish Epilepsy Centre, Filadelfia

Mads Ravnborg
Medical Director, DMSc
Danish Epilepsy Centre, Filadelfia

2. Core Research Team 2022

Sándor Beniczky MD, Ph.D.

Professor, Head of Department

- Editor-in-Chief, Epileptic Disorders
- Chair, EEG Task Force, ILAE Commission on Big Data
- Vice-chair, ILAE Publication Council
- Founding Co-Chair, ILAE Neurotechnology Section (2022-2023)
- Past-chair, Joint Taskforce on EEG of the International Federation of Clinical Neurophysiology (IFCN) and the International League Against Epilepsy (ILAE)
- Steering committee member, European Reference Network EpiCare
- 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
- Member, IFCN Guidelines Committee
- Member, AI Taskforc

Rikke Steensbjerre Møller, Ph.D.

Professor, Head of Department

- Mentor in the ILAE Mentoring program
- Mentor in the EpiCARE Mentor-mentee program
- Associate Editor: Epilepsia
- Mentor in the REFRESH mentorship scheme at DRCMR
- SAB member: CURE GABAA Variants
- Designated as speaker of one of the 7 thematic research columns (Neurodevelopment) in Neuroscience Academy Denmark
- SAB member: KCNA2 Foundation
- SAB member: KCNT1 Epilepsy Foundation
- Member of EpiCARE: a European Reference Network for rare and complex epilepsies.
- Co-chair of WG2 on clinical genetics
- Member of the scientific committee of Residras; a European Registry of Dravet Syndrome, Verona, Italy.

Guido Rubboli MD, Ph.D.

Professor, Senior Consultant

- European Academy of Neurology, member of the Epilepsy Scientific Panel
- European Academy of Neurology, member of the Management Group of the Rare Diseases Scientific Panel on Epilepsy.
- International League Against Epilepsy (ILAE), member of the Task Force “Transition in care from Childhood into Adulthood”
- VIREPA (Virtual Epilepsy Academy) ILAE, Advanced EEG Course, Director and tutor.
- European Reference Network for Rare Disease – EpiCARE, Member of the Executive Committee.
- International league against Epilepsy (ILAE), member of the Task Force “SNOMED-CT”,
- Joint EAN/ EPNS Task Force on transition from childhood to adulthood, member
- KCNA2 Foundation, member of the Scientific Committee
- KCNT1 Foundation, member of the Scientific Committee
- Visiting Professor, Child Neurology Department, University of Verona, November 2024
- Associate Editor, Epileptic Disorders
- Section Editor, Behavioural Neurology
- Associate Editor, Frontiers in Neurology
- Editorial Board Member, Epilepsy and Behavior Reports

Elena Gardella MD, Ph.D.

Professor, Senior Consultant

- Member of the commission on Classification and Terminology of the International League against Epilepsy (ILAE)
- Co-director of VIREPA basic-EEG course of the International League against Epilepsy (ILAE)
- Member of the board of the Danish Epilepsy Society (DES)
- Member of EpiCARE: a European Reference Network for rare and complex epilepsies.
- Member of Molecular Therapeutic Board in Neurological Channelopathies of EpiCARE.
- Author/revisor of Orphacodes of Orphanet (EpiCare- working group WG2)
- Coordinator the registry database and cofounder of the European STXBP1 consortium (ESCO)
- Member of a thematic research column within Neuroscience Academy Denmark (NAD)
- Member of the BRIDGE team at Department of Regional Health Research, University of Southern Denmark
- Member of the steering committee of the Danish Epilepsy Database of RKKP (Regionernes Kliniske Kvalitetsudviklingsprogram)
- Editor of Frontiers in Neurology, sections Epilepsy and Pediatrics
- External Grant reviewer for COST (European Cooperation in Science and Technology)
- Scientific advisory board member: SCN8A Italy Foundation
- Scientific advisory board member: SCN8A Europe Foundation
- Scientific advisory board member: SCL6A1 Foundation

Allan Bayat MD, Ph.D.

Associate Professor, Head of Pediatric Research, Senior Consultant

- Senior Honorary Research Fellow University of Bristol
- Chairman for the advisory board of rare metabolic disorders at the Danish Medical Council (https://medicinraadet.dk/om-os/fagudvalg/medfodte-stofskifte-sygdomme)
- Member and cashier of the board of the Danish Pediatric Neurology Society (DNPS)
- Member of the ERN-Ithaca KBG Guideline Steering committee
- Member of Epicare WG5 on neuropsychology
- Member of a thematic research column within Neuroscience Academy Denmark (NAD)
- External grant reviewer for the Czech Science Foundation (GACR)
- External grant reviewer for Italian grant: Fondazione Telethon ETS (https://www.telethon.it/en/)
- Member of NorEpiNET
- Member of EpiCARE

Core Research Team 2024

Marina Nikanorova
MD, Ph.D.
Associate Professor,
Senior Consultant

Sigge Weisdorf
Post doc., Physician

Anne Vagner Jakobsen
Post doc., Neuropsycogist

Mads Ravnborg
Medical Director, DMSc

- Chairman Research Committe

Research Team

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Chiara Ferrazzoli, MD, Child Neurologist in training, University of Rome Tor Vergata, Italy
Matthias De Wachter, MD, Child Neurologist in training, Antwerp University Hospital, Belgium
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Emilia Ricci MD, PhD, Child Neurologist, Assistant professor, University of Milano, Italy
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Maria Vlachou, MD, PhD-student
Sidsel Armand Larsen, MSc, PhD-student
Levente Hadady, MD, PhD-student
Francesca Furia, MD, PhD-student
Frederik Nørby Friis Sørensen, MSc, PhD-student
Marie Amanda Bust Levy, MSc, PhD-student
Tanya Ramdal Techlo, MSc, PhD-student
Cathrine Gjerulfsen, MD, PhD-student
Cristina Cioclu, MD, PhD-student
Rebekka Dahl, MSc, PhD-student
Sopio Gverdtsiteli, MD, PhD-student
Amir Baroumand, MSc, PhD-student
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Anne Brodersen, Study Coordinator
Daniella Terney, MD, PhD
Pirgit Meritam Larsen, MD
Stephan Wüstenhagen, MD
Conny Hjelm, PhD
Trine Arnam-Olsen Moos, PhD
Sebastian Silva, MD
Emilie Sjøstrøm, MD, research assistant.
Ismail A. Ibrahim, Bachelor in Physiotherapy, research assistant
Anne Højte Hansen, research nurse
Anne Juul, research nurse

3. Ph.D. projects

Ongoing

- Maria Vlachou: Evaluation of electro-clinical findings using standardised feature extraction and machine learning. Aarhus University. Main supervisor: Sándor Beniczky.
- Sidsel Armand Larsen: Digital Technology in Epilepsy. Aarhus University. 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.
- Francesca Furia: Deep phenotyping of monogenic epilepsies towards the identification of targeted treatments. University of Southern Denmark. Main supervisor: Elena Gardella and co-supervisors: Rikke Steensbjerre Møller and Guido Rubboli.
- Sebastian Ortiz: Deep phenotyping and functional characterization of GABAA-receptor related disorders: Translating genetic diagnostics into personalized treatment. Main supervisor: Rikke Steensbjerre Møller and co-supervisors: Elena Gardella and Guido Rubboli.
- Frederik Nørby Friis Sørensen: Dissecting neuronal heterogeneity and epileptogenesis in focal cortical dysplasia. University of Copenhagen. Main supervisor: Konstantin Khodosevich and co-supervisor: Rikke Steensbjerre Møller.
- Marie Amanda Bust Levy: Genetic and Functional Mechanisms in Neurodevelopmental Disorders and Epilepsy. University of Copenhagen. Main supervisor: Zeynep Tümer and co-supervisor: Rikke Steensbjerre Møller.
- Tanya Ramdal Techlo: Leverage polygenic approaches to genetically diagnose idiopathic severe epilepsy and hemiplegic migraine. University of Copenhagen. Main supervisor: Thomas Folkmann Hansen and co-supervisor: Rikke Steensbjerre Møller.
- Cathrine Gjerulfsen: New therapy options and experimental drugs for the treatment of severe intractable epilepsy and developmental and epileptic encephalopathies. University of Southern Denmark. Main supervisor: Rikke Steensbjerre Møller and co-supervisor: Guido Rubboli.
- Cristina Cioclu: Focal cortical dysplasia - pathogenetic mechanisms. University of Modena (Italy). Main supervisor: Stefano Meletti and co-supervisor: Guido Rubboli.
- Rebekka Dahl: Decoding GABAA Receptor Variants: Disentangling Clinical Phenotypes Through Computational Approaches. University of Southern Denmark. Main supervisor: Rikke Steensbjerre Møller and co-supervisor: Dennis Lal.
- Sopio Gverdtsiteli: Genotype-Phenotype Associations in Brain-Expressed Sodium Channelopathies: Commonalities, Differences, and Implications for Prognosis and Therapy. University of Southern Denmark. Main supervisor: Rikke Steensbjerre Møller and co-supervisors: Elena Gardella and Thomas Folkmann

Nazanin Azarinejad Mohammadi

Completed

- Amir Baroumand: Automated EEG Source imaging. Ghent University, Belgium. Main supervisor: Pieter van Mierlo and co-supervisor: Sándor Beniczky.
- Nazanin Azarinejad Mohammadi: Clinical and functional characterization of GABAA-receptor related disorders: translating genetic diagnostics into personalized treatment, University of Southern Denmark. Main supervisor: Rikke Møller and co-supervisors: Guido Rubboli and Philip Ahring.

Amir Baroumand

4. Conferences and congresses

4.1 ILAE Summer School on EEG and Epilepsy

The 6th International League Against Epilepsy (ILAE) School on Advanced EEG and Epilepsy (DSSEE6) took place between 20 - 28 July 2024. It is a biennial course held in Dianalund since 2012. This year's event was hosted in a hybrid format and was organized under the auspices of the ILAE Academy and the Danish Epilepsy Society. The 8-day summer school brought together over 200 online participants and 36 selected on-site participants. The curriculum of this advanced course comprised 25 hours of interactive theoretical sessions and 28 hours of hands-on practical sessions. The faculty consisted of world-renowned speakers, who showcased captivating presentations on key topics in EEG and epileptology to ultimately enhance education, training, and up-to-date concepts and procedures, and refine pathways for clinical neurophysiological practice.

Figure 2. The 6th ILAE School on Advanced EEG and Epilepsy

4.2 2nd International Conference on Artificial Intelligence in Epilepsy and Neurological Disorders. April 1-4, 2024. Park City, Utah, USA.

We have co-organized the second international conference on AI in epilepsy, co-chaired by Sándor Beniczky, Samden Lhatoo, Philippe Ryvlin and Michael Sperling.
The program included 55 lectures and 49 posters on cutting-edge research. The conference attracted over 250 participants, including leading authorities in this field

Figure 3. 2nd International Conference on Artificial Intelligence in Epilepsy and Neurological Disorders

4.3 6th Dianalund International Conference on Epilepsy (DICE)

"Overlapping clinical phenotypes in monogenic epilepsies – common molecular pathways?" Køge, Denmark, May 2-3 2024

The conference was preceded on May 1st, at the same venue, by a Premeeting conference where on-going projects conducted by research fellows and PhD candidates at the Danish Epilepsy Center and on-going studies conducted by various drug companies were presented and discussed.

The topic of the 6th DICE was to explore and debate on the phenotypic expressions, overlapping features, and genotype-phenotype correlations of different epileptic disorders and epileptic encephalopathies, to identifying possible common underlying and shared pathophysiological mechanisms and molecular substrates, with the aim to ultimately guide the discovery and development of effective targeted treatments. More than 170 participants from all over the world, including United States, Australia, Chile gathered in a lively and stimulating atmosphere.

Figure 4. DICE

4.4 6th Annual Meeting Danish & Norwegian Epilepsy Management excellence

on "Epilepsy throughout the patient's lifespan – with focus on youth and the elderly, organized by Guido Rubboli in collaboration with Morten Lossius. Copenhagen, September 26, 2024

5. Research projects

5.1 Artificial intelligence and big data in electroclinical diagnosis of epilepsy

Artificial intelligence (AI) is likely to revolutionize medicine, including epilepsy. The prerequisite of training deep neural network models is the availability of large, representative datasets, with standardized, high-quality labeling. In collaboration with the commission of the International League Against Epilepsy (ILAE) and the European Reference Network EpiCARE, we contributed to promoting international collaboration and established an online platform for training and validating seizure detection algorithms. We have developed and conducted an external validation of an AI model for automated interpretation of routine, clinical EEG (SCORE-AI). The model achieved performance equal to human experts. In developed and validated an AI model for automated and semi-automated analysis of video-recordings, for seizure detection, with promising results. We used a large, structured EEG database (SCORE) to map the clinical added value of provocation methods in routine EEG.

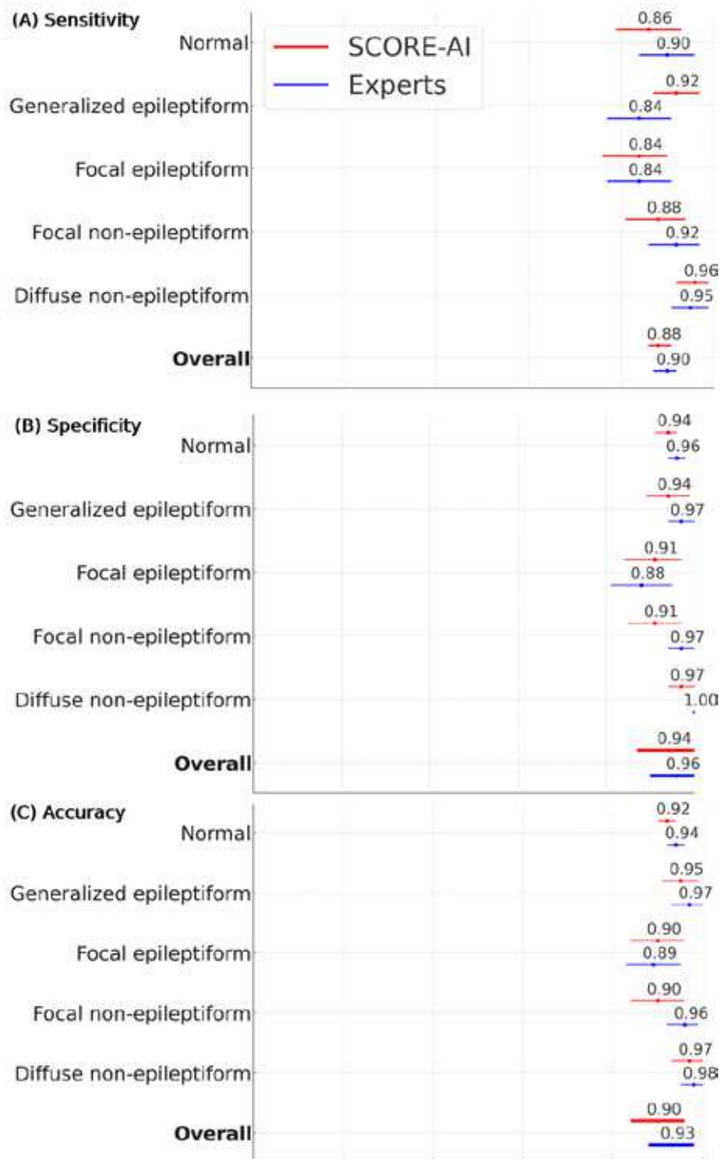


Figure 5. SCORE-AI has achieved performance equivalent to human experts, in an external validation study.

Papers

Josephson CB, Aronica E, Beniczky S, Boyce D, Cavalleri G, Denaxas S, French J, Jehi L, Koh H, Kwan P, McDonald C, Mitchell JW, Rampp S, Sadleir L, Sisodiya SM, Wang I, Wiebe S, Yasuda C, Youngerman B; ILAE Big Data Commission. Big data research is everyone's research-Making epilepsy data science accessible to the global community: Report of the ILAE big data commission. Epileptic Disord. 2024 Dec;26(6):733-752. doi: 10.1002/epd2.20288.

Dan J, Pale U, Amirshahi A, Cappelletti W, Ingolfsson TM, Wang X, Cossettini A, Bernini A, Benini L, Beniczky S, Atienza D, Ryvlin P. SzCORE: Seizure Community Open-Source Research Evaluation framework for the validation of electroencephalography-based automated seizure detection algorithms. Epilepsia. 2024 Sep 18. doi: 10.1111/epi.18113.

Mansilla D, Tveit J, Aurlien H, Avigdor T, Ros-Castello V, Ho A, Abdallah C, Gotman J, Beniczky S, Frauscher B. Generalizability of electroencephalographic interpretation using artificial intelligence: An external validation study. Epilepsia. 2024 Oct;65(10):3028-3037. doi: 10.1111/epi.18082.

Rai P, Knight A, Hiillos M, Kertész C, Morales E, Terney D, Larsen SA, Østerkjerhuus T, Peltola J, Beniczky S. Automated analysis and detection of epileptic seizures in video recordings using artificial intelligence. Front Neuroinform. 2024 Mar 15;18:1324981. doi: 10.3389/fninf.2024.1324981.

Larsen PM, Wüstenhagen S, Terney D, Gardella E, Aurlien H, Beniczky S. Seizure provocation in EEG recordings: A data-driven approach. Epileptic Disord. 2024 Jun;26(3):322-331. doi: 10.1002/epd2.20217. Epub 2024 Mar 16.

5.2 Education research

Education research in the field of epileptology and clinical neurophysiology is essential to optimize the postgraduate teaching. We have developed educational materials, such as multimedia online teaching material and seminars, and we have evaluated their output. We have surveyed the EEG education for child neurologists.

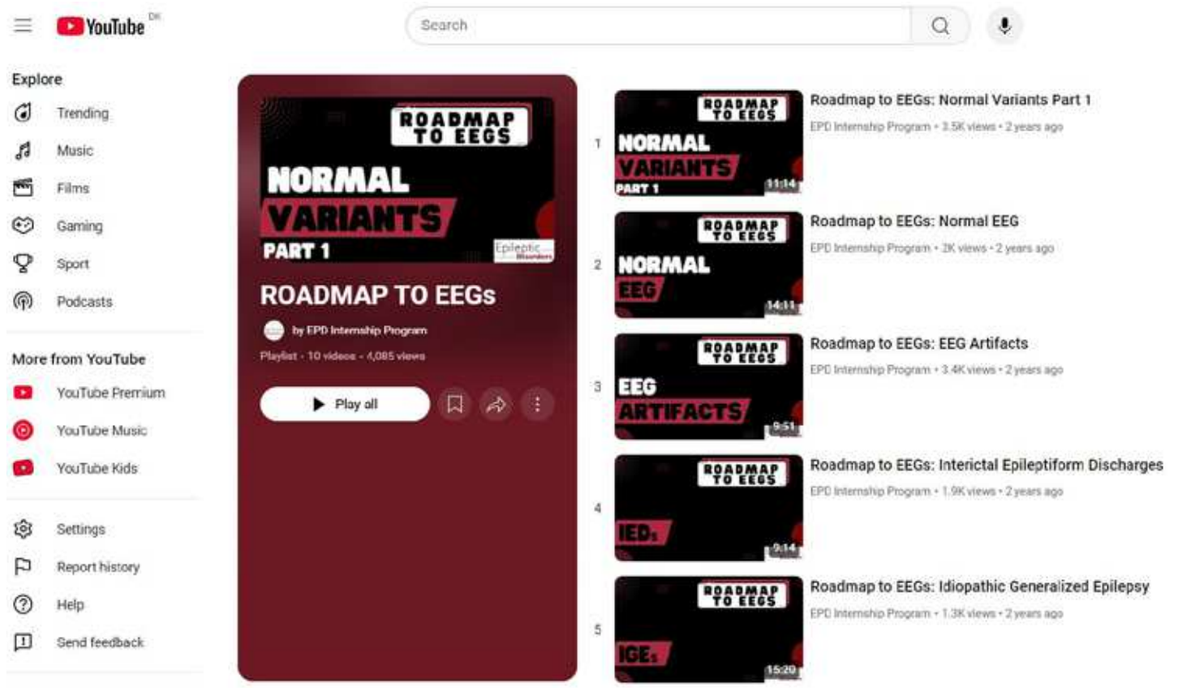


Figure 6. Our "Roadmap to EEG" - YouTube Chanel.

Papers

Marcinski Nascimento KJ, Nascimento FA, Beniczky S. Surface electromyography patterns of epileptic seizures. Epileptic Disord. 2025 Feb;27(1):130-134. doi: 10.1002/epd2.20314.
Marcinski Nascimento KJ, Beniczky S, Nascimento FA. Slow alpha variant: A normal EEG pattern. Epileptic Disord. 2025 Feb;27(1):127-129. doi: 10.1002/epd2.20313.

Katyal R, Sheikh IS, Hadjinicolaou A, Abath CB, Wirrell EC, Reddy SB, Beniczky S, Nascimento FA. Education Research: EEG Education in Child Neurology and Neurodevelopmental Disabilities Residencies: A Survey of US and Canadian Program Directors. Neurol Educ. 2024 Jan 5;3(1):e200112. doi: 10.1212/NE9.0000000000200112.
Hochstrasser K, Zhao W, Yuan D, Beniczky S, Nascimento FA. Electroretinographic artifacts on EEG in a critically ill patient. Epileptic Disord. 2024 Aug;26(4):552-555. doi: 10.1002/epd2.20230.

Sheikh IS, Katyal R, Hadjinicolaou A, Bibby BM, Olandoski M, Nascimento FA, Beniczky S. The online educational tool "Roadmap to EEGs" significantly improved trainee performance in recognizing EEG patterns. Epileptic Disord. 2024 Aug;26(4):435-443. doi: 10.1002/epd2.20227.

Frauscher B, Mansilla D, Abdallah C, Astner-Rohracher A, Beniczky S, Brazdil M, Gnatkovsky V, Jacobs J, Kalamangalam G, Perucca P, Ryvlin P, Schuele S, Tao J, Wang Y, Zijlmans M, McGonigal A. Learn how to interpret and use intracranial EEG findings. Epileptic Disord. 2024 Feb;26(1):1-59. doi: 10.1002/epd2.20190.
Nascimento FA, Katyal R, Olandoski M, Gao H, Yap S, Matthews R, Rampp S, Tatum W, Strowd R, Beniczky S. Expert accuracy and inter-rater agreement of "must-know" EEG findings for adult and child neurology residents. Epileptic Disord. 2024 Feb;26(1):109-120. doi: 10.1002/epd2.20186.

5.3 Epilepsy surgery

Rendering patients seizure free after epilepsy surgery has been one of our major goals at the Epilepsy Centre – both for clinical practice and research. Under the auspices of the European Reference Network EpiCARE, we have developed a grading system for assessing the confidence in the localization of the epileptogenic zone. We have conducted an external validation study of the predictive tools in epilepsy surgery and showed their utility for stratifying patients

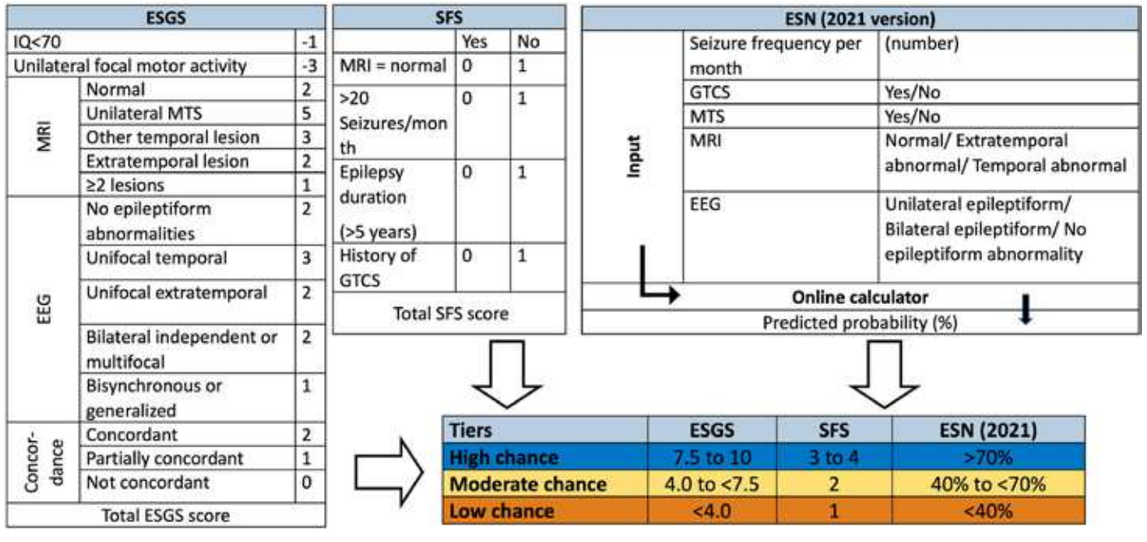


Figure 7. Nomograms for predicting outcome after epilepsy surgery

Papers

Ryvlin P, Barba C, Bartolomei F, Baumgartner C, Brazdil M, Fabo D, Fahoum F, Frauscher B, Ikeda A, Lhatoo S, Mani J, McGonigal A, Metsahonkala EL, Mindruta I, Nguyen DK, Rheims S, Rocamora R, Rydenhag B, Schuele S, Schulze-Bonhage A, Surges R, Vulliemoz S, Beniczky S. Grading system for assessing the confidence in the epileptogenic zone reported in published studies: A Delphi consensus study. Epilepsia. 2024 May;65(5):1346-1359. doi: 10.1111/epi.17928.

Hadady L, Sperling MR, Alcala-Zermeno JL, French JA, Dugan P, Jehi L, Fabó D, Klivényi P, Rubboli G, Beniczky S. Prediction tools and risk stratification in epilepsy surgery. Epilepsia. 2024 Feb;65(2):414-421. doi: 10.1111/epi.17851.

5.4 Wearable devices in epilepsy

Wearable devices are needed for automated seizure detection. In 2024 we continued our decade-long quest for achieving this goal. We reached out to patients and caregivers to understand better the needs and the perspective of real-world applications. We developed and validated a novel algorithm for detection of tonic seizures. We have developed and assessed the feasibility of a low-cost portable EEG device. We completed an external validation of a seizure detection algorithm, based on heart-rate variability. We showed that sonification of EEG recorded with a wearable device can accurately detect absence seizures.

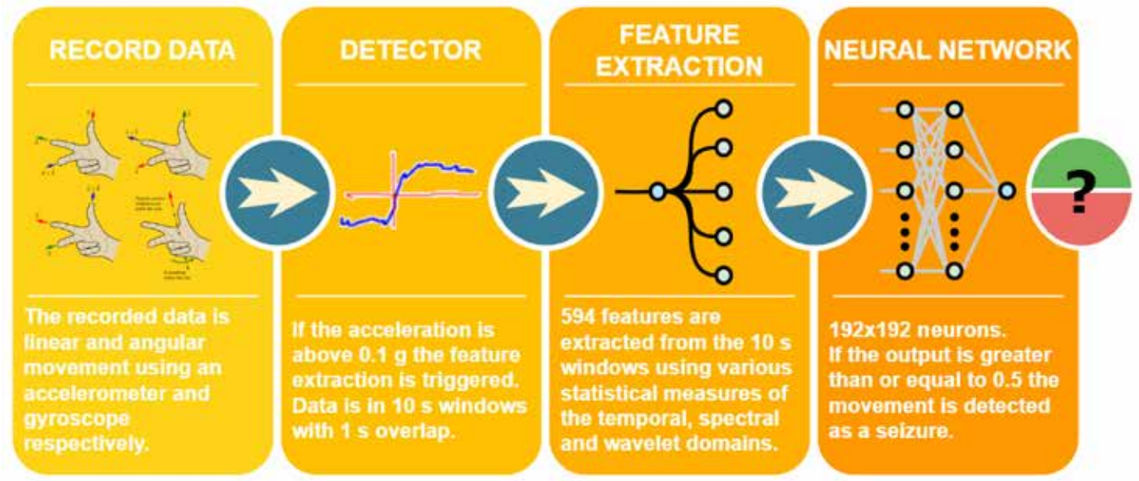


Figure 8. Flowchart of development of a tonic seizure detector, using accelerometry signals

Papers

Ferreira J, Peixoto R, Lopes L, Beniczky S, Ryvlin P, Conde C, Claro J. User involvement in the design and development of medical devices in epilepsy: A systematic review. Epilepsia Open. 2024 Dec;9(6):2087-2100. doi: 10.1002/epi4.13038.
Larsen SA, Johansen DH, Beniczky S. Automated detection of tonic seizures using wearable movement sensor and artificial neural network. Epilepsia. 2024 Sep;65(9):e170-e174. doi: 10.1111/epi.18077.

Armand Larsen S, Klok L, Lehn-Schiøler W, Gatej R, Beniczky S. Low-cost portable EEG device for bridging the diagnostic gap in resource-limited areas. Epileptic Disord. 2024 Oct;26(5):694-700. doi: 10.1002/epd2.20266.

Jeppesen J, Lin K, Melo HM, Pavei J, Marques JLB, Beniczky S, Walz R. Detection of seizures with ictal tachycardia, using heart rate variability and patient adaptive logistic regression machine learning methods: A hospital-based validation study. Epileptic Disord. 2024 Apr;26(2):199-208. doi: 10.1002/epd2.20196.

Ingolfsson TM, Benatti S, Wang X, Bernini A, Ducouret P, Ryvlin P, Beniczky S, Benini L, Cossettini A. Minimizing artifact-induced false-alarms for seizuredetection in wearable EEG devices with gradient-boosted tree classifiers. Sci Rep. 2024 Feb 5;14(1):2980. doi: 10.1038/s41598-024-52551-0.

Borges DF, Fernandes J, Soares JI, Casalta-Lopes J, Carvalho D, Beniczky S, Leal A. The sound of silence: Quantification of typical absence seizures by sonifying EEG signals from a custom-built wearable device. Epileptic Disord. 2024 Apr;26(2):188-198. doi: 10.1002/epd2.20194.

5.5 Research Project “Ultra-long sub-cutaneous EEG monitoring: reliability, safety and impact on clinical management in uncontrolled epilepsies (PI. Guido Rubboli, Dianalund, Denmark).”

This research was undertaken to assess the clinical utility, safety, and tolerability in epilepsy patients of ultra long-term monitoring with a novel subcutaneous electroencephalographic (EEG) device (sqEEG). This study showed that a) subcutaneous EEG can provide reliable information on seizure frequency in a selected patient cohort during a 3–6-month monitoring period; b) the sensitivity of a semiautomatic seizure detection algorithm depend on ictal EEG features; c) subcutaneous EEG proved to be a safe and well-tolerated procedure for ultra long-term EEG monitoring in epilepsy patients.

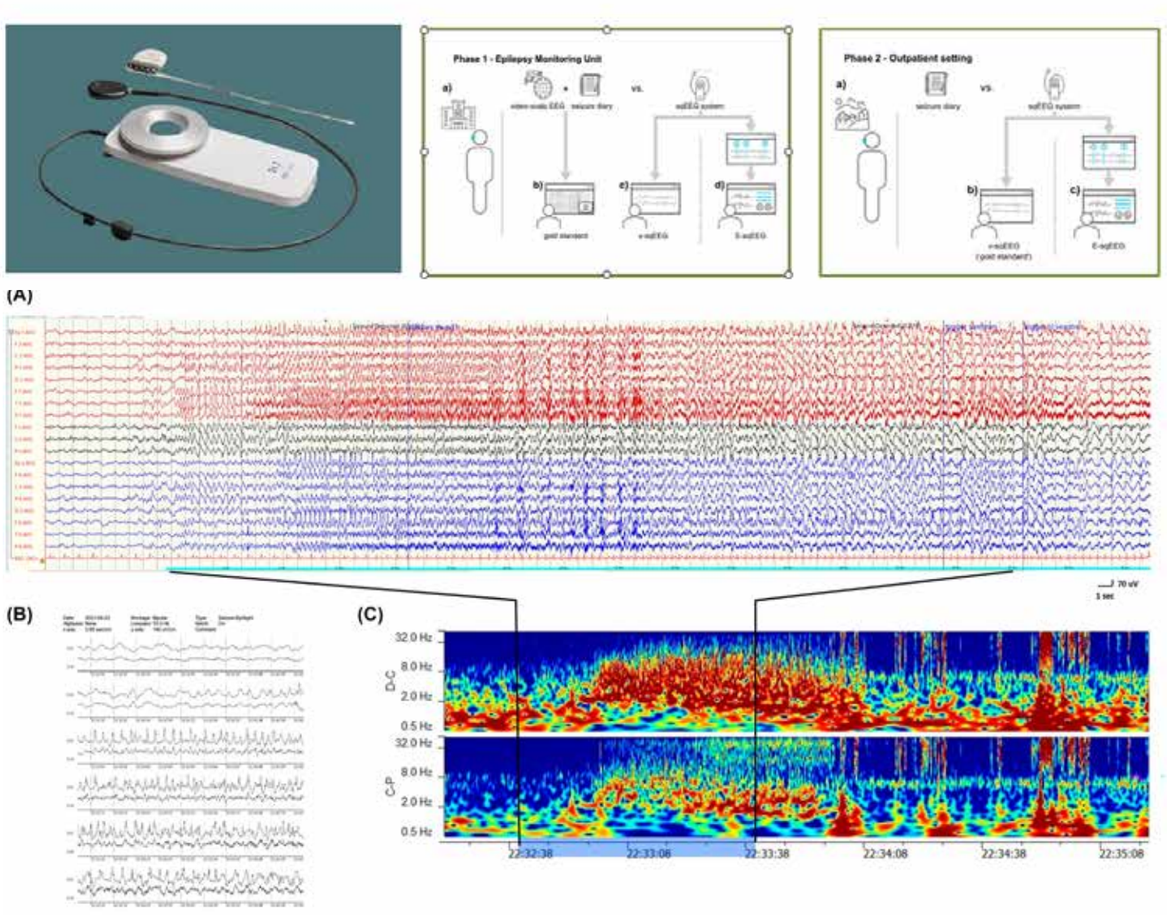


Figure 9. Upper panel: on the left, external recording device and subcutaneous electrode; on the right, study protocol for seizure recording in EMU and in an outpatient setting. Lower panel: in the upper section, ictal EEG recorded with scalp EEG in the EMU. Lower section, 2-channels sqEEG traces showing the ictal discharge recorded in EMU (left) and ictal spectrogram (right)

Papers

Rubboli G et al.: “Clinical utility of ultra long-term subcutaneouselectroencephalographic monitoring in drug-resistant epilepsies: a “real world” pilot study”. Epilepsia. 2024;65:3265-3278.

5.6 Research Project: “Randomized European Trial of Steroids versus Clobazam Usage for Encephalopathy with ESES (RESCUE ESES)” (PI: Floor Jansen, Utrecht, The Netherlands).

This research aimed to compare cognitive outcomes of children with EE-SWAS 6 months after starting treatment with either corticosteroids or clobazam. The results showed an improvement in IQ outcomes with corticosteroids compared with clobazam treatment, but no difference was seen in cognitive sum score. Our findings strengthen those from previous uncontrolled studies that support the early use of corticosteroids for children with ESES.

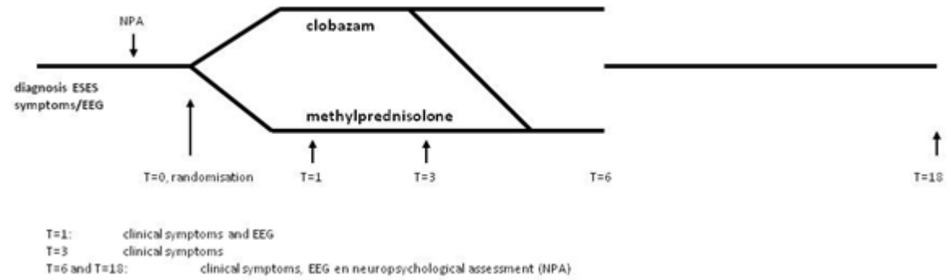


Figure 10. Time line of the RESCUE-ESES project

Papers

van Arnhem MML et al.: “Corticosteroids versus clobazam for treatment of children with epileptic encephalopathy with spike-wave activation in sleep (RESCUE ESES): a multicentre randomised controlled trial”. Lancet Neurol. 2024;23:147-156.

5.7 Research project on idiopathic generalized epilepsies

Principal Investigator: Christoph Beier, Odense University, Denmark

Idiopathic generalized epilepsies are associated with distinct behavioral traits, symptoms of frontal lobe dysfunction, and psychiatric comorbidity. Whether psychiatric symptoms are part of the IGE endophenotype or secondary to the burden of chronic disease is unknown. This study aimed at describing the sequence of appearance of psychiatric and epilepsy symptoms in patients with IGE. The results suggested a prodromal phase of IGE detectable approximately 5 years before the first seizure characterized by increased health care utilization and greater use of prescription medicine for psychiatric symptoms.

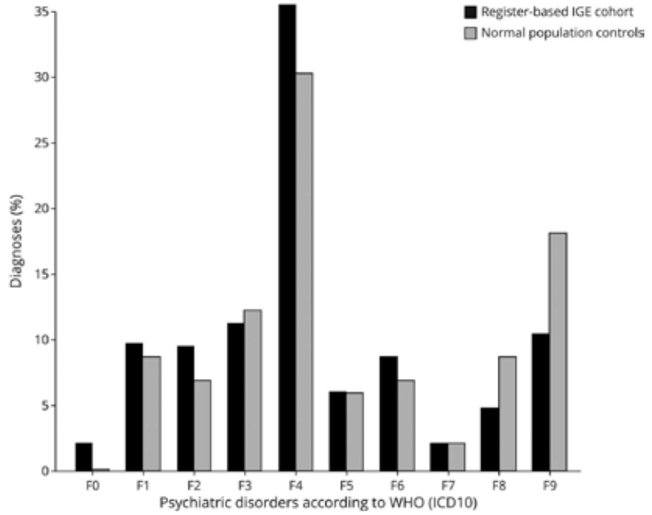


Figure 11. Distribution of psychiatric diagnoses in the register-based cohort and normal population controls at the end of study. F0 organic, F1 substance abuse, F2 delusional, F3 mood, F4 neurotic, F5 behavioral, F6 personality, F7 mental retardation, F8 developmental, F9 unspecified. IGE = idiopathic generalized epilepsy.

Papers

J Goesche, G Rubboli, C. Beier, Prodromal Phase of Idiopathic Generalized Epilepsy: A Register-Based Case Control Study. Neurology 2024;103:e209921. doi: 10.1212/WNL.0000000000209921.

Controversy exists on whether adult IGE is a group of distinct diseases or a clinical spectrum of one disease. In this study, a deeply phenotyped cohort was explored to test the hypothesis that IGE comprises three distinct clinical entities. The results of the study suggest that IGE in adults are best described as a continuum of symptoms, where age at diagnosis and executive dysfunction are two main factors explaining most of its clinical variability. The seizure-defined syndromes cover different patient groups within the clinical spectrum.

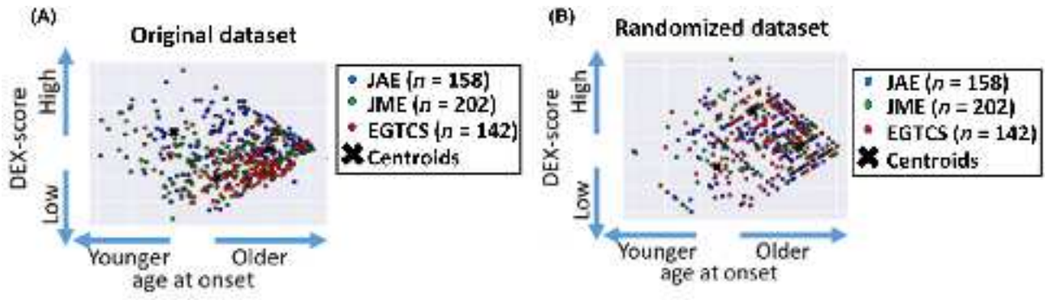


Figure 12. Association of seizure-defined syndromes with natural clusters within the dataset. (A, B) Principal component analysis of the original imputed dataset (A; n = 502) and the randomized dataset with identical characteristics (B; n = 502). The two principal components were age at diagnosis and dysexecutive symptoms measured using the Dysexecutive Questionnaire (DEX-score). The colors denote the different seizure type-defined syndromes (juvenile myoclonic epilepsy [JME], juvenile absence epilepsy [JAE], epilepsy with generalized tonic–clonic seizures alone [EGTCS]). In the randomized dataset, the assignment to the different syndromes was random.

Papers

Gavnholt L, et al. Unsupervised clustering of a deeply phenotyped cohort of adults with idiopathic generalized epilepsy. Epilepsia. 2024. doi: 10.1111/epi.18225.

5.8 Research project "CENOP. A 12-month, prospective, observational study in adult patients with focal onset seizures who are treated with adjunctive ASM in real world setting.

This is an observational, prospective, single group, multicentre, European study that aims to describe the effectiveness of the adjunctive ASM treatment on the clinical response, safety profile and quality of life of patients affected by focal onset seizures in a real-world setting. The patients recruitment is completed; the study is still on-going.

Investigator at Filadelfia: Guido Rubboli, Cathrine Gjerulfsen.

Sponsor: Angelini Pharma

5.9 From disease-causing variants to targeted therapy in GABA-A receptor related epilepsies

Developmental and Epileptic Encephalopathies (DEEs) are devastating early-onset conditions associated with intractable epilepsy, intellectual disability (ID), developmental delay/regression, movement, and autism spectrum disorders. Genetic factors play a major role in the underlying cause of DEEs, and pathogenic variants in subunits of the γ-aminobutyric acid type A receptor (GABAAR), the major inhibitory protein of the brain, are found to be a common cause of DEE.

Variants in the GABRB2 gene, which encodes the GABAA receptor β2 subunit, have been implicated in a broad range of neurodevelopmental disorders (NDDs), epilepsies, and movement disorders. Despite their significance, the underlying pathophysiology remains poorly understood. In a recently published study (Mohammadi et al, Ebiomedicine, 2024), we performed molecular and clinical analyses on 26 missense variants in the GABRB2 gene, identified from 42 affected individuals. Our findings shed light on the impact of gain-of-function (GOF) GABRB2 variants, which can lead to catastrophic early onset DEEs, severe ID, movement disorders and high risk of early death. Interestingly, we observed that the severity of clinical outcomes correlates with the degree of functional changes induced by these GOF variants. By contrast, milder forms of NDDs and epilepsies, particularly those with fever sensitivity, were associated with loss-of-function (LOF) variants. These findings highlight the importance of considering both LOF and GOF GABRB2 variants in the context of NDDs and epilepsy. In cases where functional analysis is not available, clinical biomarkers may be used to predict whether a newly identified variant causes GOF or LOF (Figure 13).

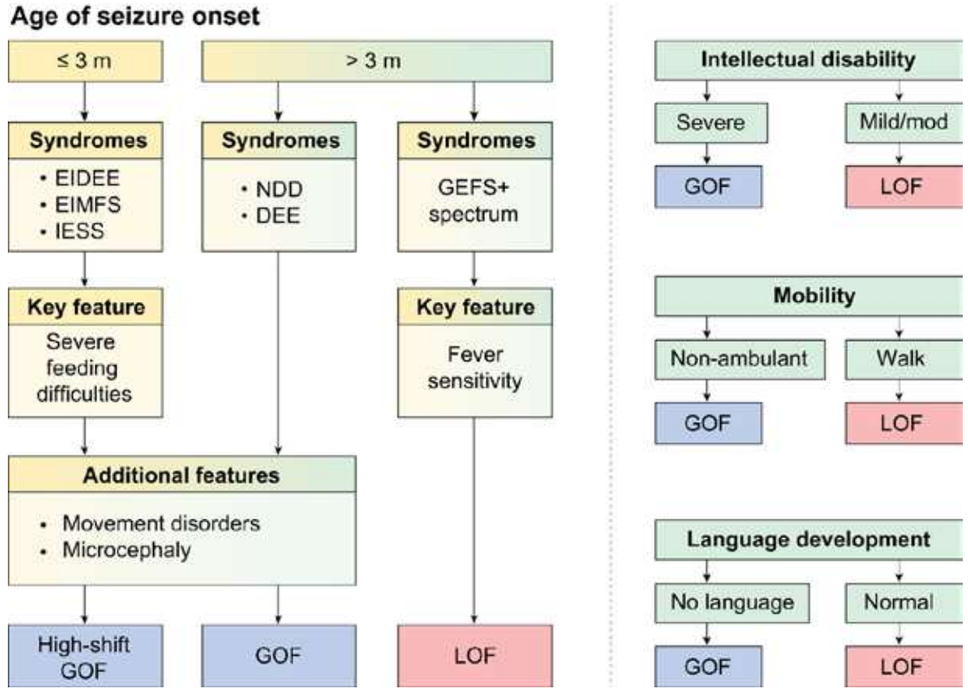


Figure 13. Clinical indicators for GOF and LOF phenotypes.

Very early seizure onset, severe movement disorders and microcephaly are strongly associated with GOF disease while epilepsy syndromes in the GEFS+ spectrum with fever sensitivity are strongly associated with LOF disease. As the child ages, intellectual disability, independent mobility, and language development support the early indicators. For cases that are not clearly defined by these indicators, functional analysis is needed to determine the effects of the variant.

Papers

Mohammadi NA, Ahring PK, Yu Liao VW, Chua HC, Ortiz de la Rosa S, Johannesen KM, Michaeli-Yossef Y, Vincent-Devulder A, Meridda C, Bruel AL, Rossi A, Patel C, Klepper J, Bonanni P, Minghetti S, Trivisano M, Specchio N, Amor D, Auvin S, Baer S, Meyer P, Milh M, Salpietro V, Maroofian R, Lemke JR, Weckhuysen S, Christophersen P, Rubboli G, Chebib M, Jensen AA, Absalom NL, Møller RS. Distinct neurodevelopmental and epileptic phenotypes associated with gain- and loss-of-function GABRB2 variants. EBioMedicine. 2024 Aug;106:105236. doi: 10.1016/j.ebiom.2024.105236. Epub 2024 Jul 11.

As the epilepsy field is progressing toward personalized medicine approaches that include both better symptomatic and disease-modifying treatments, it is crucial to know the functional outcomes of genetic variants. To investigate whether insights from paralogous genes can serve as predictors, we studied a cohort of eleven individuals harboring paralogous missense variants in a conserved proline residue within the first transmembrane helix of GABAA receptor subunits (Figure 14) (Kan et al., PNAS, 2024). Despite diverse functional outcomes, all variants led to overall GOF with increased GABA sensitivity being key to the clinical phenotype. Our findings support the use of information from paralogous variants in certain cases.

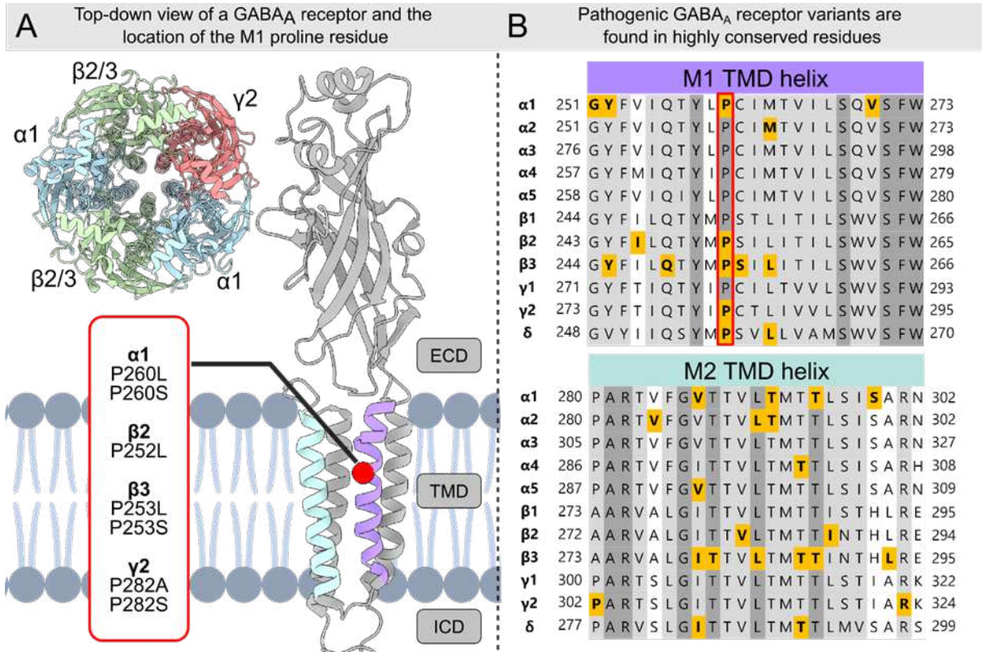


Figure 14. The M1 proline residue is fully conserved in GABAAR subunits.

Papers

Kan ASH, Kusay AS, Mohammadi NA, Lin SXN, Liao VWY, Lesca G, Souci S, Milh M, Christophersen P, Chebib M, Møller RS, Absalom NL, Jensen AA, Ahring PK. Understanding paralogous epilepsy-associated GABA(A) receptor variants: Clinical implications, mechanisms, and potential pitfalls. Proc Natl Acad Sci U S A. 2024 Dec 10;121(50):e2413011121. doi: 10.1073/pnas.2413011121. Epub 2024 Dec 6.

5.10. Understanding GRIA related disorder and translating knowledge into precision therapy for AMPA-receptor related epilepsies.

The Department of Pediatrics at the Danish Epilepsy Center is at the forefront of research and clinical understanding in GRIA-related neurodevelopmental disorders, establishing itself as one of the world's leading centers in this field. With an unparalleled natural history database of nearly 200 GRIA patients worldwide, we are pioneering efforts to understand the complex genetic and functional landscape of these devastating conditions.

Recent discoveries highlight those missense mutations in the GRIA1-4 genes, which encode subunits of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)—the brain's major excitatory receptor—are a significant cause of these conditions. Despite over 200 GRIA mutations identified in affected individuals, only a limited number have been functionally characterized to determine whether they result in gain-of-function (GOF) or loss-of-function (LOF) effects on AMPAR. This distinction is critical for treatment, as drug selection depends heavily on understanding the underlying pathomechanism.

Our research has revealed that GRIA mutations can be divided based on LOF and GOF effects, with patient phenotypes closely linked to their functional consequences. Surprisingly, both LOF and GOF mutations are associated with epilepsy and cognitive/developmental impairments, underscoring the complexity of these disorders.

Through a comprehensive translational study, we are:

- Compiling clinical and genetic data into a dedicated GRIA disorders database.
- Functionally characterizing GRIA variants to determine their impact on AMPAR signaling and establish pathogenicity.
- Identifying precision treatment strategies, including FDA/EMA-approved drugs, to correct abnormal AMPAR function and improve patient outcomes.

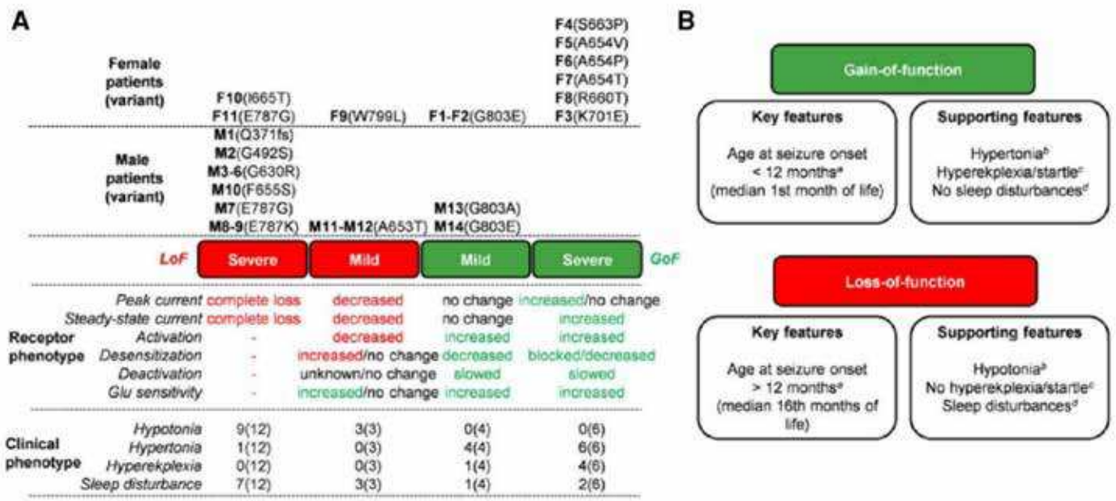


Figure 15. Clinical indicators for GOF and LOF phenotypes.

By deep-phenotyping GRIA disorders and identifying genotype-phenotype correlations, we aim to develop novel clinical biomarkers that predict mutation effects, improve diagnostic precision, and optimize targeted therapies. Our ultimate goal is to transform patient care—ensuring effective treatment while avoiding interventions that could be ineffective or even harmful.

At the Danish Epilepsy Center, we are leading the way in unraveling the complexities of GRIA-related disorders and paving the path toward personalized medicine for affected individuals worldwide. One of our next steps is to use neuronal tissue derived from iPSCs to study the underlying pathomechanism and explore rescue pharmacology that can ultimately be translated to precision therapy for these patients

Papers

Unraveling GRIA1 neurodevelopmental disorders: Lessons learned from the p.(Ala636Thr) variant. Tvergaard NK, Tkemaladze T, Stödberg T, Kvarnung M, Tatton-Brown K, Baralle D,Tümer Z, Bayat A. Clin Genet. 2024 Oct;106(4):427-436.

Gain-of-function and loss-of-function variants in GRIA3 lead to distinct neurodevelopmental phenotypes. Rinaldi B, Bayat A, (...), Kristensen AS.Brain. 2024 May 3;147(5):1837-1855.

5.11 Natural History Studies and drug trial readiness for rare genetic epilepsies

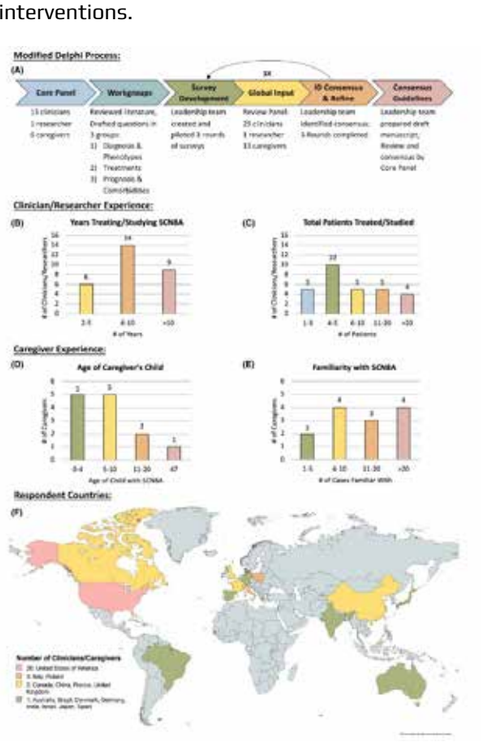
Natural history studies are crucial for understanding the progression, symptoms, and underlying mechanisms of rare diseases, such as monogenic epilepsies.

These studies track the course of the disease over time in individuals, focusing not only on epilepsy but also comorbidities and cognitive, behavioral, developmental and social aspects. By providing detailed insights into how monogenic epilepsies manifest and evolve, natural history studies help establish crucial benchmarks for assessing the effectiveness of new treatments.

In the context of drug trials for monogenic epilepsies, such studies play a key role in determining the readiness of patients for clinical trials.

A well-documented understanding of disease progression allows researchers to identify appropriate patient cohorts, define outcome measures, and design trials that address the unique aspects of these conditions. Natural history data also help in determining optimal treatment windows and the endpoints most relevant to patients' quality of life.

Our research roadmap includes the strict collaboration with clinicians around the worlds, family representatives, and pharma companies to organize consortia for disease specific drug trial readiness (Figure 15) For monogenic epilepsies, these studies are particularly important as they offer a precise framework for evaluating the impact of gene-targeted therapies or other interventions.



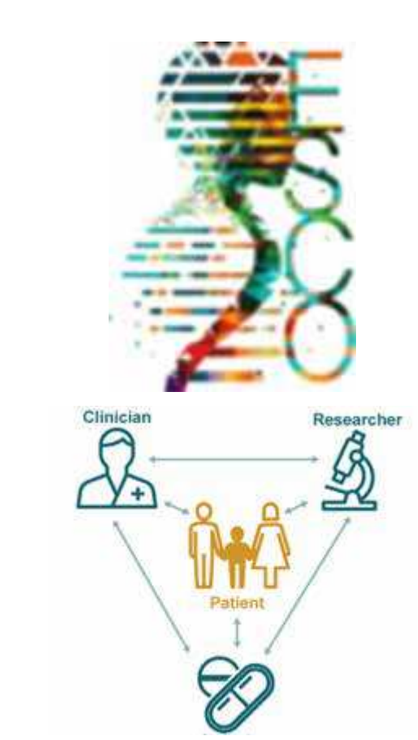


Figure 16. (A) Modified Delphi process and clinician/caregiver experience levels. (A) Modified Delphi process involved developing a Core Panel, which split into three workgroups to review the literature and draft questions. The Leadership Team created three rounds of surveys and sent them out to the Review Panel to complete. The Leadership Team also identified consensus and prepared a draft manuscript for the Core Panel to review. (B, C) Clinician/researcher experience shown via years treating/studying SCN8A and total patients treated/seen. (D,E) Caregiver experience shown via age of caregiver's child in years and familiarity with SCN8A-related disorders. (F) Respondents on the Review Panel spanned 16 countries and five continents. (B) ESCO is an investigator-driven consortium of currently 7 European countries and Israel focused on promoting trial readiness for the treatment of STXBP1-related disorders. ESCO brings together all the relevant stakeholders in the space, including industrial partners and family associations. The mission of ESCO is to promote clinical and pre-clinical research on STXBP1-related disorders, to prepare for successful and efficient evaluation of new therapies, once available and to promote equal and evidence-based access to new therapies.

5.11 EEG biomarkers

EEG biomarkers are increasingly recognized as valuable tools in the natural history studies of monogenic epilepsies, that typically present with distinct seizure types and varying degrees of impairment.

EEG can capture these patterns, revealing information on the evolution of the disease over time and response to treatment.

Therefore, EEG biomarkers play an essential role in tracking disease progression in natural history studies. In addition, EEG abnormalities often correlate with specific genetic variants, helping to refine diagnostic criteria and identify potential therapeutic targets.

Furthermore, EEG biomarkers are instrumental in evaluating the efficacy of treatments in clinical trials, providing an objective, quantifiable measure of seizure control and neurophysiological changes in response to therapeutic interventions. We recently propose quantitative-EEG as a biomarker for STXBP1- related disorders (Figure 16), potentially useful for the definition of sub-phenotypes and outcome measures in interventional and non-interventional studies of STXBP1 (Figure 17) (Cossu et al, 2024).

This approach can be extended to clinical and translational studies of other monogenic epilepsies, ultimately paving the way for more personalized, targeted approaches in both research and clinical care.

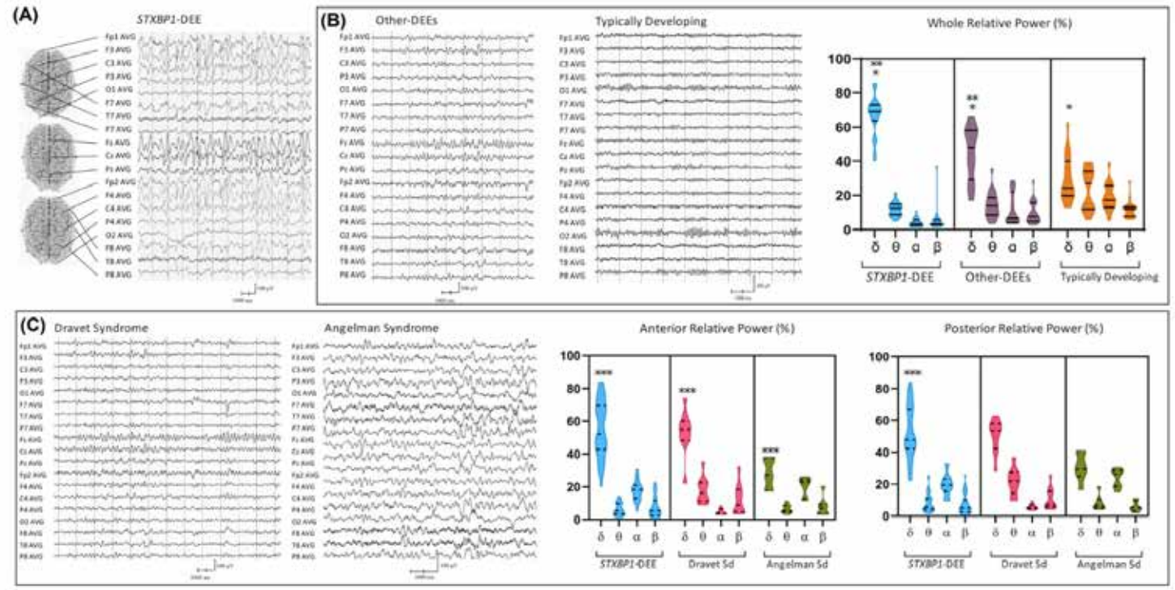
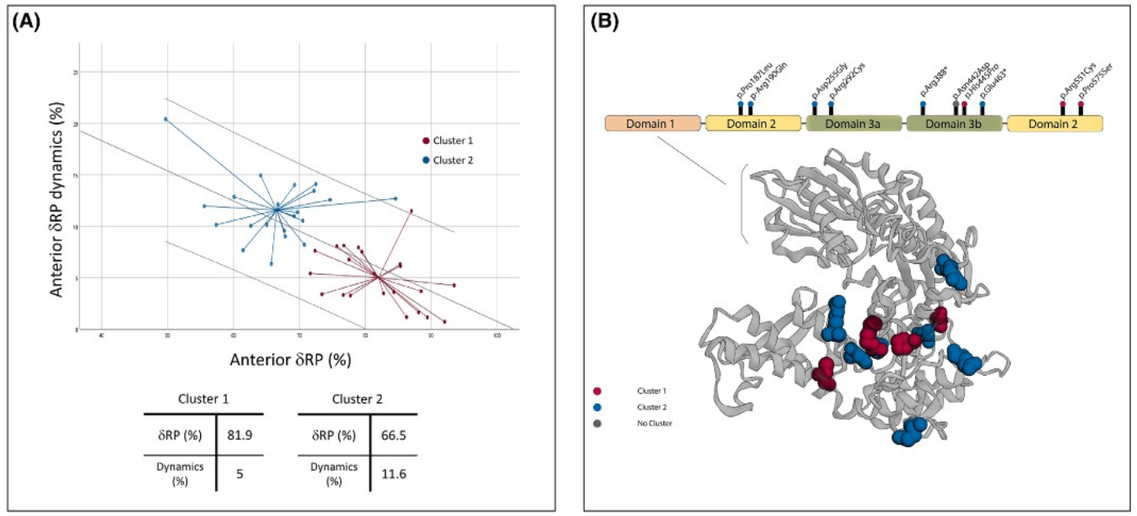


Figure 17. Comparisons of EEG features and frequency composition. (A) This is an example of the interictal EEG activity of a patient with STXBP1-DEE. (B) Examples of interictal EEG activity of the two control groups (other-DEEs and typically developing control). Theviolin plot shows the average relative power (RP) of the four bands in both regions for each patient's subgroup. The δRP is significantly higher in DEE patients compared to typically developing controls (*p < .0001), confirming the pathogenicity of this activity, and significantly higher in STXBP1-DEE compared to other- DEEs (**p < .0001), suggesting the specificity of this activity for the STXBP1- DEE group.(C) Examples of interictal EEG of the two major subgroups of other-DEEs, one patient with Dravet syndrome and one with Angelman syndrome. Two violin plots show the composition of the power spectrum analysis in the anterior and posterior scalp regions, in the three etiology groups. The control groups comprised 10 patients with Dravet syndrome (5 female, mean age 11.7 years) and 8 patients with Angelman syndrome (5 female, mean age 8.1 years). The means were significantly different between etiology groups (***p > .0001, Kruskal–Wallis analysis of variance [ANOVA]) and within the STXBP1-DEE group, showing a slower overall activity in the STXBP1-DEE group and a significant focal slowing in the anterior region (***p = .003, paired t tests).



Cluster 1	
δRP (%)	81.9
Dynamics (%)	5

Cluster 2	
δRP (%)	66.5
Dynamics (%)	11.6

Clinical Features		Cluster 1 (6 pt)
Age (range)		13.9 y (0.9-29 y)
Mobility		Non amb 83% (5)
Language		Non-verbal 100% (6)
ID		Severe 67% (4) Profound 33% (2)
Age Epilepsy Onset		7.1 mo
Sz Frequency		Sz free none Rare 50% (3) Frequent 50% (3)
Seizure Types	Tonic	71% (5)
	Tonic-clonic	100% (6)
	Focal Motor	50% (3)
	FIAS	17%(1)

Clinical Features		Cluster 2 (9 pt)
Age (range)		12.5 y (1.6-30 y)
Mobility		Non amb 11% (1)
Language		Non-verbal 44% (4)
ID		Moderate 56% (5) Severe 22% (2)
Age Epilepsy Onset		6.6 mo
Sz Frequency		Sz free 22% (2) Rare 22% (2) Frequent 56% (5)
Seizure Types	Tonic	33% (3)
	Tonic-clonic	33% (3)
	Focal motor	55% (5)
	FIAS	66% (6)

Figure 18. Electro- clinical differences in the two clusters. (A) Reports the distribution of all recordings by anterior δRP and the corresponding dynamics. Recordings are grouped by clusters and connected to the cluster centroids. Their coordinates are reported in the two tables below. (B) Position of the Syntaxin-binding protein (product of STXBP1) domain (above) and on the three-dimensional protein structure (below). Red dots indicate the position of variants carried by patients in cluster.1, and blue dots indicate variants of patients incluster.2 (C, D) Shows a significant example of interictal EEG of cluster.1 (29-year-old). (D) Shows a significant example of interictal EEG ofcluster.2 (15-year- old). In the two tables, the different clinical features and different seizure types in the two clusters are summarized.

Papers

Cossu A, Furia F, Proietti J, Ancora C, Reale C, Darra F, Previtali R, Bernardina BD, Rubboli G, Beniczky S, Møller RS, Cantalupo G, Gardella E. Quantitative EEG biomarkers for STXBP1-related disorders. Epilepsia. 2024 Dec;65(12):3595-3606. doi: 10.1111/epi.18154. Epub 2024 Oct 28. PMID: 39463124; PMCID: PMC11647438

5.12 Long-Term, Open-Label Extension Study to Evaluate the Safety and Tolerability of NBI-827104 in Pediatric Subjects with Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep

Principal investigator: Marina Nikanorova, study coordinator: Anne Brodersen

6. Lectures - oral presentations in 2024

Sándor Beniczky:

- Value and limitations of scalp EEG in children. ILAE Epilepsy Surgery Course, January 23rd, Brno, Czech Republic.
- Automated and semi-automated interpretation of clinical EEG using artificial intelligence. Swedish Clinical Neurophysiology Meeting, February 2nd, Lund, Sweden.
- EEG Voltage maps in clinical practice. Grand Rounds, University Hospitals Cleveland Medical Center. February 5th (online)
- Systematic interpretation of EEG: interictal and ictal abnormalities. ILAE Latin American Epilepsy Summer School. February 27, San Paulo, Brazil.
- EEG source imaging. ILAE Latin American Epilepsy Summer School. February 27, San Paulo, Brazil.
- The Future of AI in EEG Interpretation. February 28, Annual Meeting of the American Clinical Neurophysiology Society, Orlando, USA
- Epileptiform Activity and Benign Variants. March 1st. Annual Meeting of the American Clinical Neurophysiology Society, Orlando, USA
- Ictal ESI: Advantages and Pitfalls. March 2nd. Annual Meeting of the American Clinical Neurophysiology Society, Orlando, USA
- Interactive Workshop on Basics of Electroencephalography and Seizure Semiology for the Neurologists. NEUROCATARINA: Meeting of the Brazilian Epilepsy League, Florianopolis, Brazil.
- External validation of the SCORE-AI model for automated interpretation of routine EEG. April 3rd, Park City, USA
- Lateralization value of ictal head turning. Paros symposium: state of the art anatomo-clinical correlations of focal seizures. April 26th, Paros, Grece.
- Semiology and EEG in the elderly patients with epilepsy. May 17th, Cologne, Germany
- Algorithms and Artificial Intelligence in Epilepsy. May 22nd, The Gloor Lecture at the Canadian Neurological Sciences Federation congress, Toronto, Canada.
- Hunting for seizures. May 23rd, Canadian Neurological Sciences Federation congress, Toronto, Canada.
- AI for routine EEG and beyond.May 30th, Neuroscience colloquium, Lausanne, Switzerland.
- What´s new in seizure classification? June 16th, Latin American Epilepsy Congress, Santo Domingo, Dominican Republic (online)
- AI in epilepsy. June 16th, Latin American Epilepsy Congress, Santo Domingo, Dominican Republic (online)
- AI in clinical EEG. Annual meeting of the Hungarian Neurology Society, June 22nd, Szeged, Hungary.
- From current dipoles to scalp maps: basic technical aspects. ILAE Summer School on EEG and Epilepsy, July 20-27, Dianalund, Denmark.
- Electromagnetic source imaging. ILAE Summer School on EEG and Epilepsy, July 20-27, Dianalund, Denmark.
- Reporting the findings: SCORE. ILAE Summer School on EEG and Epilepsy, July 20-27, Dianalund, Denmark.
- Systematic approach to EEG reading. ILAE Summer School on EEG and Epilepsy, July 20-27, Dianalund, Denmark.
- Seizure semiology. ILAE Summer School on EEG and Epilepsy, July 20-27, Dianalund, Denmark.
- Clinical EEG interpretation. August 26. ILAE Baltic Sea Summer School on Epilepsy (online).
- EEG background activity and interictal abnormalities. September 7th, European Epilepsy Congress, Rome, Italy.
- EEG Source Imaging. September 8th, European Epilepsy Congress, Rome, Italy.
- The role of AI in EEG interpretation. September 10th, European Epilepsy Congress, Rome, Italy.
- Automated interpretation of routine EEG using AI. September 14th, International Congress of Clinical Neurophysiology, Jakarta, Indonesia.
- Seizure semiology and classification. September 20th, Nordic Epilepsy Masterclass, Stockholm, Sweden.
- EEG and epilepsy: technologic advancements. September 26th, Grand Rounds at Montefiore Medical Center, Albert Einstein College of Medicine, New York, USA.
- The updated seizure classification of the ILAE. October 12th, Meeting of the Hungarian Epilepsy Society. Gyor, Hungary.
- AI in clinical EEG. October 12th, Meeting of the Hungarian Epilepsy Society. Gyor, Hungary.
- How can we ascertain progress in the diagnostic assessment of Epilepsy? Freiburg Epilepsy Symposium. October 18th, Freiburg, Germany.
- What is a spike and who (or what) finds it? October 24, Annual Meeting of the Swiss Society of Clinical Neurophysiology. Aarau, Switzerland.
- Seizure detection in focal epilepsy using warble devices. November 1st, Annual meeting of the Danish Epilepsy Society, Copenhagen, Denmark.
- AI in EEG. November 8th, Annual meeting of the Danish Society for Clinical Neurophysiology, Vejle, Denmark.
- AI in epilepsy. Research Symposium, Duke University, November 11, Durham, USA
- Seizure detection using wearables. Research Symposium, Duke University, November 11, Durham, USA
- EEG Source Imaging. November 22nd, Epilepsy Symposium, Zurich, Switzerland

Rikke Steensbjerre Møller:

- Genetics of early onset epilepsies, Rome workshop (EpiCare, In search of lost time, Rome, Italy, December, When surgery fails or is not possible: targeted medication? In search of lost time 5; Rome, December, 2024
- Clinical presentation of GABAA-Receptor related disorder; Los Angeles, December, 2024
- Clinical Trial Readiness; Annual Cure GABAA variants meeting; Los Angeles, December, 2024
- Cenobamate as an add-on treatment for SCN8A DEE; SCN8A Annual Clinician, Researcher, and Family Gathering; Los Angeles, December, 2024
- Precision medicine approaches for genetic epilepsies; Romanian Society Against Epilepsy meeting; Bucharest, November, 2024
- Behandling af udviklingshæmmede med diverse syndromer. Hvorfor genetik er vigtigt. Hvornår skal vi tænke genetik? Nationalt Netværksmøde, "patienter med udviklingshæmning & Epilepsi", Glostrup, November, 2024
- SCN2A and SCN8A related disorders; EPIGENS, November, 2024
- From gene discovery to targeted therapies in individuals with genetic epilepsies; NDD networking meeting; SDU, Odense, November, 2024
- Precision medicine in epilepsy: Tailoring Treatment Based on Individual Genetics; Rigshospitalet, Copenhagen, October, 2024
- The genetic landscape of developmental and epileptic encephalopathies; Annual Meeting, NAD, Copenhagen, October 2024
- Precision medicine approaches for genetic epilepsies; University Hospitals Cleveland Epilepsy Grand Rounds, October, 2024
- Association between specific mutations and pathogenicity – which test to choose? UCB's Educational Epilepsy Webinar, September, 2024
- Importance of genetics in the identification of rare (mono)genic epilepsy; 6th Annual Meeting Danish and Norwegian Epilepsy management Excellence, Copenhagen, September, 2024
- Precision medicine approaches for genetic epilepsies; Nordic Scientific Meeting, Rome, September, 2024
- Deciphering the code: the role of genetic testing; Industry Sponsored Session, EEC2024, Rome, September, 2024
- Selecting the right genetic test for my patient and how to interpret the results; Implementing epilepsy genetics in clinical practice, EEC2024, Rome, September, 2024
- How are functional studies guiding our choice of antiseizure medication for GABAA-related disorders? Neurobiology Symposium, EEC2024, Rome, September, 2024
- Importance of genetic and functional analysis; BSPN spring meeting, Antwerp, August, 2024
- Hvordan kan genetikken hjælpe patienter og pårørende til et bedre liv; Epilepsiforeningens Årsmøde, Odense, May 2024
- Precision medicine in genetic epilepsies; 6th Dianalund international conference on epilepsy, Køge, May 2024
- What we learned from the genetic epilepsies; Aachen Epilepsy Symposium, Aachen, April 2024
- Loss or gain of function? How do you evaluate the functional effect of pathogenic variants? Annual meeting DSMG, April, 2024
- How are functional studies guiding our choice of antiseizure medication; EPIPED, Girona, April, 2024
- Why is precision medicine beneficial in epilepsies? Kuopio Epilepsy Symposium, Kuopio, March, 2024
- Epilepsy genetics in practice today, Kuopio Epilepsy Symposium, Kuopio, March, 2024
- Utility of Genetic Testing for Therapeutic Decision-making in Individuals with Epilepsy, Brain Resonance Seminar, DRCMR, Hvidovre, February, 2024
- Utility of Genetic Testing on Therapeutic Decision-making in Individuals with Epilepsy, Individualized Management of Patients with rare and complex epilepsies, Karolinska University Hospital, January 2024

Guido Rubboli:

- "Webinar "Epilepsy in neurodegenerative disease" Neuroklub, Kuopio University, 25.1.24
- Lecture on "EEG sottocutaneo prolungato: quali vantaggi clinici?" meeting Update in epileptology, Padova, 9.2.24.
- Lecture on "Epilepsy and Neurodegenerative Diseases: a bidirectional relation?" 36th Encontro Nacional de Epileptologia, Coimbra, 8-9.3.24
- Lecture on "Negative motor signs: akinetic, astatic, atonic, negative myoclonus, ictal paresis", at the meeting "State-of-the-art anatomo-clinical correlations of focal seizures, Paros, 22-26.4.24.
- Lecture on "EEG phenotyping: still a valuable tool for genotype-phenotype correlations?". 6th Dianalund International Conference on Epilepsy, Køge, 2-3.5.24.
- Lecture on "Phenotypic spectrum in individuals with pathogenic GABRG2 loss- and gain-of-function variants", Lundbeck GABAA receptor meeting, Copenhagen, 5.5.24.
- Lecture on "Polygraphic recordings", 6th ILAE Summer School on EEG and Epilepsy, Dianalund, 20-27.7.24
- Chairman and organizer of the Teaching Course ""Implementing epilepsy genetics in clinical practice", 15th European Epilepsy Congress (EEC 2024), Rome, 7.9.24.
- Lecture on "Myoclonus and myoclonic seizures" at the Teaching Session on "Challenges in diagnosis", 15th European Epilepsy Congress (EEC 2024), Rome, 8.9.24.
- Lecture on "Cenobamate as add-on in ultra-refractory epilepsies: The Dianalund experience" Angelini meeting at the 15th European Epilepsy Congress, Rome, 9.9.24
- Lecture on "Interictal EEG: is that enough?" at the Symposium "EEG: present and future", 15th European Epilepsy Congress (EEC 2024), Rome, 11.9.24.
- Mentor, neurophysiology, ILAE YES Networking table, 15th European Epilepsy Congress, Rome, 11.9.24
- Lecture on "Epilepsy and Neurodegenerative Disease", 6th Annual Meeting Danish and Norwegian Epilepsy management Excellence, Copenhagen, 26.9.24.
- Lecture on "What is from seizure, what is not", International Symposium on Transition "Empoweing patients/families, pediatric neurologists and neurologists for an optimal transition, Paris, 27.9.24.
- Lecture on "Localization of seizures foci: EEG pitfalls and caveats", Epiped Course on EEG interpretation in pediatric epilepsies, Bologna, 30.9.24.
- Lecture on "Ultra long-term EEG monitoring", at the Congress "Sleep, consciousness and epilepsy: EEG from Hans Berger to the third millennium", Parma 4-5.10.24
- Lecture on "Treatment of drug resistant IGEs", 2nd Advanced Course on the Pharmacological treatment of drug-resistant epilepsies, Palma di Maiorca (Spain) 8-10,2024
- Webinar on "Ultra long-term monitoring in epilepsy with subcutaneous EEG", Karolinska Seminar at Karolinska Institut, 11.10.24.
- Lecture on "Genetic investigations in surgical epilepsy patients" DES meeting, Copenhagen, 1.11.24.
- Lecture on "K+ channelopathies and developmental epileptic encephalopathies", Neuroscience Meeting, University of Odense, Odense 5.11.24.
- Lecture on "K+ channelopathies and developmental epileptic encephalopathies" Seminars of the School of Specialization in Child Neurology, University of Verona, Verona, 18.11.24
- Lecture on "Drug-resistant epilepsies: not only focal epilepsies. Challenges in the treatment and prognosis of IGE, meeting on "Le epilessie farmacoresistenti: nuovi orientamenti terapeutici", Bologna, 20.11.24.
- Lecture on "Polygraphic recording of myoclonic phenomena" Seminars of the School of Specialization in Child Neurology, University of Verona, Verona, 26.11.24
- Chairman, session on " Challenging the Focal Cortical Dysplasias", at the EpiCARE meeting "Challenging focal cortical dysplasisa and autoimmune diseases with epilepsy, Rome 17.12.24.

Elena Gardella:

- "The contribute of the neurophysiologist to diagnosis and management of CSWS / ESWAS: pitfalls and challenges" - Neurofysdagarna 2024_ National Training Days in Clinical Neurophysiology. Lund, February 1-2 2024
- "STXBP1: EEG data analysis" - ESCO kick-off meeting. Antwerp, Belgium, February 8 2024
- "The complexity of monogenic epilepsies" - Webinar, University of Padua. Padua, Italy,
- "The Natural history studies in practice" - Webinar GABA families
- "Dysregulation of GABAergic system" - 3rd Rome debate on DEEs: the epilepsy-autism phenotype. Rome, March 16 2024
- "Time-locked clinical correlate" 9th London-Innsbruck colloquium on Status Epilepticus and Acute Seizures _ Pre-conference teaching course Continuous EEG in the intensive care unit. London, UK, April 7 2024
- "The occurrence and clinical features of status epilepticus in the channelopathies" – 9th London-Innsbruck Symposium on Status Epilepticus and Acute Seizures. London, UK, April 8-10 2024
- "Garden variety genetic epileptic encephalopathies: treatment snapshots" - 3rd Girona EpiPed course. Girona, Spain, April 26-29 2024
- "Sodium channelopathies: clinical commonalities and differences" - 6th Dianalund International Conference on Epilepsy (DICE) – Overlapping clinical phenotypes in monogenic epilepsies: common molecular pathways? Køge, Denmark, May 2-3 2024
- "EEG in GABRD related disorders" - Lundbeck GABAA receptor meeting. Copenhagen, Denmark, May 06 2024
- "From genetic testing to the phenotype" - 10th International Residential Course on Drug Resistant Epilepsies, course (speaker/trainer). Tagliacozzo, Italy, Maj 19-25 2024
- "Precision medicine in genetic epilepsies" - Master epilepttologia UNIGE_7.4 Genetica medica ed Epilettologia. Genoa University, Italy, June 15 2024
- Difficult / ambiguous cases discussion - ILAE Summer School on EEG and Epilepsy Sixths edition. Dianalund, Denmark, July 20-27 2024
- "The international prospective SCN8A Natural History Study" - Global SCN8A Research Roadmap Meeting. Cambridge MA, USA, August 16-18 2024
- "VIREPA BEEG course" - European Epilepsy Congress. Rome, Italy, September 2024
- "Natural history registry studies" - 6th Annual Meeting Danish & Norwegian Epilepsy Management excellence_ Epilepsy throughout the patient's lifespan – with focus on youth and the elderly. Copenhagen, Denmark, September 26 2024
- "Clinical characteristics of the main types of DEEs" - 2nd Advanced Course on the Pharmacological Treatment of Drug Resistant Epilepsies (DRE): from Rare to Common Epilepsies. Palma de Mallorca, Spain, November 8-10 2024

- "Treatment of Dravet disease, Lennox-Gastaut syndrome, and other DEEs" - 2nd Advanced Course on the Pharmacological Treatment of Drug Resistant Epilepsies (DRE): from Rare to Common Epilepsies. Palma de Mallorca, Spain, November 8-10 2024
- "Sleep disturbances in SCN8A related disorders" - The CUTE syndrome foundation Annual Meeting. Los Angeles, USA, December 5 2024
- "SCN8A prospective multicenter Natural History Study" - The CUTE syndrome foundation Annual Meeting. Los Angeles, USA, December 5 2024
- "When surgery fails or is not possible: targeted medication?" - EpiCARE workshop: In Search of Lost Time 5 _ Challenging Focal Cortical Dysplasias & Autoimmune Diseases with Epilepsy. Roma, Italy, December 16-18 2024

Marina Nikanorova:

- Danish experience with Fenfluramine in treatment of Dravet syndrome – webinar with Norwegian and Swedish pediatricians and neurologists, 23rd and 25th January 2024
- 17th Baltic Sea summer school on epilepsy – 3 sessions, August 2024
- Lennox-Gastaut syndrome: diagnostic aspects and electro-clinical presentation – Nordic webinar, 3rd and 30th September 2024
- Treatment of Lennox-Gastaut syndrome – Nordic webinar, 28th October 2024
- DEE-SWAS and EE-SWAS: diagnostic criteria, clinical presentation and treatment – Conference of the Lithuanian. Chapter of ILAE, Vilnius, 15th November 2024**.**

Allan Bayat:

- "The natural history of adults with KBG syndrome: a physician's reported experience". 2024, EuroNDD-24, ERN-Ithaca, Lisbon.
- "The natural history of adults with KBG syndrome: a physician's reported experience". 2024, Dianalund International Conference on Epilepsy, Denmark.
- "Impact of genetic testing on therapeutic decision making in childhood-onset epilepsies – a study in a tertiary referral center". 2024, European Epilepsy Conference, Rome.
- "The natural history of adults with KBG syndrome: a physician's reported experience". 2024, European Epilepsy Conference, Rome.
- "The evolving phenotype of KBG syndrome". 2024, European dysmorphology meeting, Ljublana.
- GRIA related disorders: neurology and movement disorders. 2024. Cure GRIN Barcelona
- "GRIA1 and GRIA3 related disorders". 2024, online, GRI Conference.
- "Research communication". 2024. Bridge translational research, postdoc program, University of Copenhagen.

Francesca Furia:

- Søvnforstyrrelser hos patienter med udviklingshæmning og epilepsi at the Sjette Nationale Netværks møde indenfor Epilepsi og Udviklingshæmning in København in November 2024
- ESCO registry and natural history study: the European approach to clinical overview and trial readiness on STXBP1-related disorders" at the EPNS Research Meeting in Ljubljana in October 2024
- Early mortality in STXBP1-related disorders" at the STXBP1 Summit and Research Roundtable in Philadelphia in July 2024
- Cenobamate as add-on treatment in SCN8A related developmental and epileptic encephalopathy" at the 6th Dianalund international conference on epilepsy in Køge in May 2024
- Registry enrollment, timelines, analysis plan of the European STXBP1 registry" at the ESCO kick off meeting in Antwerp in February 2024

Sopio Gverdtsiteli:

- Neonatal developmental and epileptic encephalopathy with movement disorder and arthrogryposis (NDEE-MA) – common phenotype across brain-expressed sodium channelopathies; 6th Dianalund International Conference on Epilepsy; Køge, May, 2024
- A global perspective of genetic testing in the epilepsies - does one size fits all? – "Clinical state-of-the art view – Who to test and how?" 15th European Epilepsy Congress, presentation at the Genetics Forum, EEC2024, Rome, September, 2024
- Neonatal developmental and epileptic encephalopathy with movement disorder and arthrogryposis (NDEE-MA) phenotype across sodium channelopathies; 6th Annual Danish and Norwegian Epilepsy Meeting, Copenhagen, October, 2024

Sebastian Ortiz:

- Lecture on "Distinct clinical phenotypes associated with LOF vs GOF GABAA-receptor variants". 6th Dianalund International Conference on Epilepsy, Køge, 2-3.5.24
- Lecture on "Inovações e desafios da pesquisa clínica na Dinamarca". International Symposia Teaching and Research in The Health Sector. School of Medicine, Sao Jose de Rio Preto Brazil. 07.10.2024.
- Lecture on "Can Clinical Symptoms Predict the Functional Effect Of Genetic Variants In GABRA1?", 15th European Epilepsy Congress (EEC 2024), Rome, 11.9.24.
- Chairman, session on "Platform Session - Clinical Neurophysiology 1". 15th European Epilepsy Congress (EEC 2024), Rome, 11.9.24.
- Lecture on "Deep Phenotyping of GABAA Receptor Variants Reveals Functional Segregation and Predicts Risk of Gross Motor Dysfunction"6th Annual Danish and Norwegian Epilepsy Meeting. 26.09.2024

7. Publication list in 2024

1. Marcinski Nascimento KJ, Nascimento FA, **Beniczky S.** Surface electromyography patterns of epileptic seizures. Epileptic Disord. 2025 Feb;27(1):130-134. doi: 10.1002/epd2.20314. Epub 2024 Nov 22. PMID: 39576192.
2. Marcinski Nascimento KJ, **Beniczky S**., Nascimento FA. Slow alpha variant: A normal EEG pattern. Epileptic Disord. 2025 Feb;27(1):127-129. doi: 10.1002/epd2.20313. Epub 2024 Nov 19. PMID: 39560654.
3. Cossu A, **Furia F**, Proietti J, Ancora C, Reale C, Darra F, Previtali R, Bernardina BD, **Rubboli G**, **Beniczky S**, **Møller RS**, Cantalupo G, **Gardella E**. Quantitative EEG biomarkers for STXBP1-related disorders. Epilepsia. 2024 Dec;65(12):3595-3606. doi: 10.1111/epi.18154. Epub 2024 Oct 28. PMID: 39463124; PMCID: PMC11647438.
4. Josephson CB, Aronica E, **Beniczky S**, Boyce D, Cavalleri G, Denaxas S, French J, Jehi L, Koh H, Kwan P, McDonald C, Mitchell JW, Rampp S, Sadleir L, Sisodiya SM, Wang I, Wiebe S, Yasuda C, Youngerman B; ILAE Big Data Commission. Big data research is everyone's research-Making epilepsy data science accessible to the global community: Report of the ILAE big data commission. Epileptic Disord. 2024 Dec;26(6):733-752. doi: 10.1002/epd2.20288. Epub 2024 Oct 24. PMID: 39446076; PMCID: PMC11651381.
5. Katyal R, Sheikh IS, Hadjinicolaou A, Abath CB, Wirrell EC, Reddy SB, **Beniczky S**, Nascimento FA. Education Research: EEG Education in Child Neurology and Neurodevelopmental Disabilities Residencies: A Survey of US and Canadian Program Directors. Neurol Educ. 2024 Jan 5;3(1):e200112. doi: 10.1212/NE9.0000000000200112. PMID: 39360148; PMCID: PMC11441753.
6. Aanestad E, **Beniczky S**, Olberg H, Brogger J. Unveiling variability: A systematic review of reproducibility in visual EEG analysis, with focus on seizures. Epileptic Disord. 2024 Dec;26(6):827-839. doi: 10.1002/epd2.20291. Epub 2024 Sep 28. PMID: 39340408; PMCID: PMC11651379.
7. **Rubboli G**, Bø MH, Alfstad K, **Armand Larsen S**, Jacobsen MDH, **Vlachou M**, **Weisdorf S**, Rasmussen R, Egge A, Henning O, Lossius M, **Beniczky S**. Clinical utility of ultra long-term subcutaneous electroencephalographic monitoring in drug-resistant epilepsies: a "real world" pilot study. Epilepsia. 2024 Nov;65(11):3265-3278. doi: 10.1111/epi.18121. Epub 2024 Sep 28. PMID: 39340394.
8. Ferreira J, Peixoto R, Lopes L, **Beniczky S**, Ryvlin P, Conde C, Claro J. User involvement in the design and development of medical devices in epilepsy: A systematic review. Epilepsia Open. 2024 Dec;9(6):2087-2100. doi: 10.1002/epi4.13038. Epub 2024 Sep 26. PMID: 39324505; PMCID: PMC11633715.
9. Pirgit ML, **Beniczky S**. EEG and semiology in the elderly: A systematic review. Seizure. 2024 Sep 7:S1059-1311(24)00251-6. doi: 10.1016/j.seizure.2024.09.003. Epub ahead of print. PMID: 39294074.
10. Dan J, Pale U, Amirshahi A, Cappelletti W, Ingolfsson TM, Wang X, Cossettini A, Bernini A, Benini L, **Beniczky S**, Atienza D, Ryvlin P. SzCORE: Seizure Community Open-Source Research Evaluation framework for the validation of electroencephalography-based automated seizure detection algorithms. Epilepsia. 2024 Sep 18. doi: 10.1111/epi.18113. Epub ahead of print. PMID: 39292446.
11. Astner-Rohracher A, Ho A, Archer J, Bartolomei F, Brazdil M, Cacic Hribljan M, Castellano J, Dolezalova I, Fabricius ME, Garcés-Sanchez M, Hammam K, Ikeda A, Ikeda K, Kahane P, Kalamangalam G, Kalss G, Khweileh M, Kobayashi K, Kwan P, Laing JA, Leitinger M, Lhatoo S, Makhalova J, McGonigal A, Mindruta I, Mizera MM, Neal A, Oane I, Parikh P, Perucca P, Pizzo F, Rocamora R, Ryvlin P, San Antonio Arce V, Schuele S, Schulze-Bonhage A, Suller Marti A, Urban A, Villanueva V, Vilella Bertran L, Whatley B, **Beniczky S**, Trinka E, Zimmermann G, Frauscher B. Prognostic value of the 5-SENSE Score to predict focality of the seizure-onset zone as assessed by stereoelectroencephalography: a prospective international multicentre validation study. BMJ Neurol Open. 2024 Aug 21;6(2):e000765. doi: 10.1136/bmjno-2024-000765. PMID: 39175939; PMCID: PMC11340713.
12. Mansilla D, Tveit J, Aurlien H, Avigdor T, Ros-Castello V, Ho A, Abdallah C, Gotman J, **Beniczky S**, Frauscher B. Generalizability of electroencephalographic interpretation using artificial intelligence: An external validation study. Epilepsia. 2024 Oct;65(10):3028-3037. doi: 10.1111/epi.18082. Epub 2024 Aug 14. PMID: 39141002.
13. **Beniczky S**. An interview with Elissa Yozawitz, the 2024 Epileptic Disorders Prize winner. Epileptic Disord. 2024 Oct;26(5):730-731. doi: 10.1002/epd2.20262. Epub 2024 Aug 7. PMID: 39110132.
14. Thomas J, Abdallah C, Cai Z, Jaber K, Gotman J, **Beniczky S**, Frauscher B. Investigating current clinical opinions in stereoelectroencephalography-informed epilepsy surgery. Epilepsia. 2024 Sep;65(9):2662-2672. doi: 10.1111/epi.18076. Epub 2024 Aug 3. PMID: 39096434.
15. **Larsen SA**, Johansen DH, **Beniczky S**. Automated detection of tonic seizures using wearable movement sensor and artificial neural network. Epilepsia. 2024 Sep;65(9):e170-e174. doi: 10.1111/epi.18077. Epub 2024 Jul 30. PMID: 39076045.
16. **Armand Larsen S**, Klok L, Lehn-Schiøler W, Gatej R, **Beniczky S**. Low-cost portable EEG device for bridging the diagnostic gap in resource-limited areas. Epileptic Disord. 2024 Oct;26(5):694-700. doi: 10.1002/epd2.20266. Epub 2024 Jul 26. PMID: 39056249.
17. **di Micco V**, **Affronte L**, Khinchi MS, Rønde G, Miranda MJ, Hammer TB, Specchio N, **Beniczky S**, Olofsson K, **Møller RS**, **Gardella E**. Seizure and movement disorder in CACNA1E developmental and epileptic encephalopathy: Two sides of the same coin or same side of two different coins? Epileptic Disord. 2024 Aug;26(4):520-526. doi: 10.1002/epd2.20242. Epub 2024 May 23. PMID: 38780451.

18. Abdallah C, Mansilla D, Minato E, Grova C, **Beniczky S**, Frauscher B. Systematic review of seizure-onset patterns in stereo-electroencephalography: Current state and future directions. Clin Neurophysiol. 2024 Jul;163:112-123. doi: 10.1016/j.clinph.2024.04.016. Epub 2024 Apr 30. PMID: 38733701.
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21. Rai P, Knight A, Hiillos M, Kertész C, Morales E, Terney D, Larsen SA, Østerkjerhuus T, Peltola J, **Beniczky S**. Automated analysis and detection of epileptic seizures in video recordings using artificial intelligence. Front Neuroinform. 2024 Mar 15;18:1324981. doi: 10.3389/fninf.2024.1324981. PMID: 38558825; PMCID: PMC10978750.
22. Larsen PM, Wüstenhagen S, Terney D, **Gardella E**, Aurlien H, **Beniczky S**. Seizure provocation in EEG recordings: A data-driven approach. Epileptic Disord. 2024 Jun;26(3):322-331. doi: 10.1002/epd2.20217. Epub 2024 Mar 16. PMID: 38491975.
23. Ryvlin P, Barba C, Bartolomei F, Baumgartner C, Brazdil M, Fabo D, Fahoum F, Frauscher B, Ikeda A, Lhatoo S, Mani J, McGonigal A, Metsahonkala EL, Mindruta I, Nguyen DK, Rheims S, Rocamora R, Rydenhag B, Schuele S, Schulze-Bonhage A, Surges R, Vulliemoz S, **Beniczky S**. Grading system for assessing the confidence in the epileptogenic zone reported in published studies: A Delphi consensus study. Epilepsia. 2024 May;65(5):1346-1359. doi: 10.1111/epi.17928. Epub 2024 Feb 29. PMID: 38420750.
24. Jeppesen J, Lin K, Melo HM, Pavei J, Marques JLB, **Beniczky S**, Walz R. Detection of seizures with ictal tachycardia, using heart rate variability and patient adaptive logistic regression machine learning methods: A hospital-based validation study. Epileptic Disord. 2024 Apr;26(2):199-208. doi: 10.1002/epd2.20196. Epub 2024 Feb 9. PMID: 38334223.
25. Ingolfsson TM, Benatti S, Wang X, Bernini A, Ducouret P, Ryvlin P, **Beniczky S**, Benini L, Cossettini A. Minimizing artifact-induced false-alarms for seizure detection in wearable EEG devices with gradient-boosted tree classifiers. Sci Rep. 2024 Feb 5;14(1):2980. doi: 10.1038/s41598-024-52551-0. PMID: 38316856; PMCID: PMC10844293.
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27. **Vlachou M**, Ryvlin P, **Armand Larsen S**, **Beniczky S**. Focal electroclinical features in generalized tonic-clonic seizures: Decision flowchart for a diagnostic challenge. Epilepsia. 2024 Mar;65(3):725-738. doi: 10.1111/epi.17895. Epub 2024 Jan 27. PMID: 38279904.
28. Frauscher B, Rossetti AO, **Beniczky S**. Recent advances in clinical electroencephalography. Curr Opin Neurol. 2024 Apr 1;37(2):134-140. doi: 10.1097/WCO.0000000000001246. Epub 2024 Jan 17. PMID: 38230652.
29. Bayat M, **Beniczky S**, Thomsen JLS. Very late onset methylmalonic acidemia (cblB type) as a cause of status epilepticus, leukoencephalopathy and myelopathy. Neurol Sci. 2024 May;45(5):2387-2391. doi: 10.1007/s10072-023-07270-1. Epub 2023 Dec 22. PMID: 38135865.
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33. Gavnholt L, Gesche J, Cerulli Irelli E, Krøigård T, Mangaard SB, Di Bonaventura C, **Rubboli G**, Röttger R, Beier CP. Unsupervised clustering of a deeply phenotyped cohort of adults with idiopathic generalized epilepsy. Epilepsia. 2024 Dec 26. doi: 10.1111/epi.18225. Online ahead of print.
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