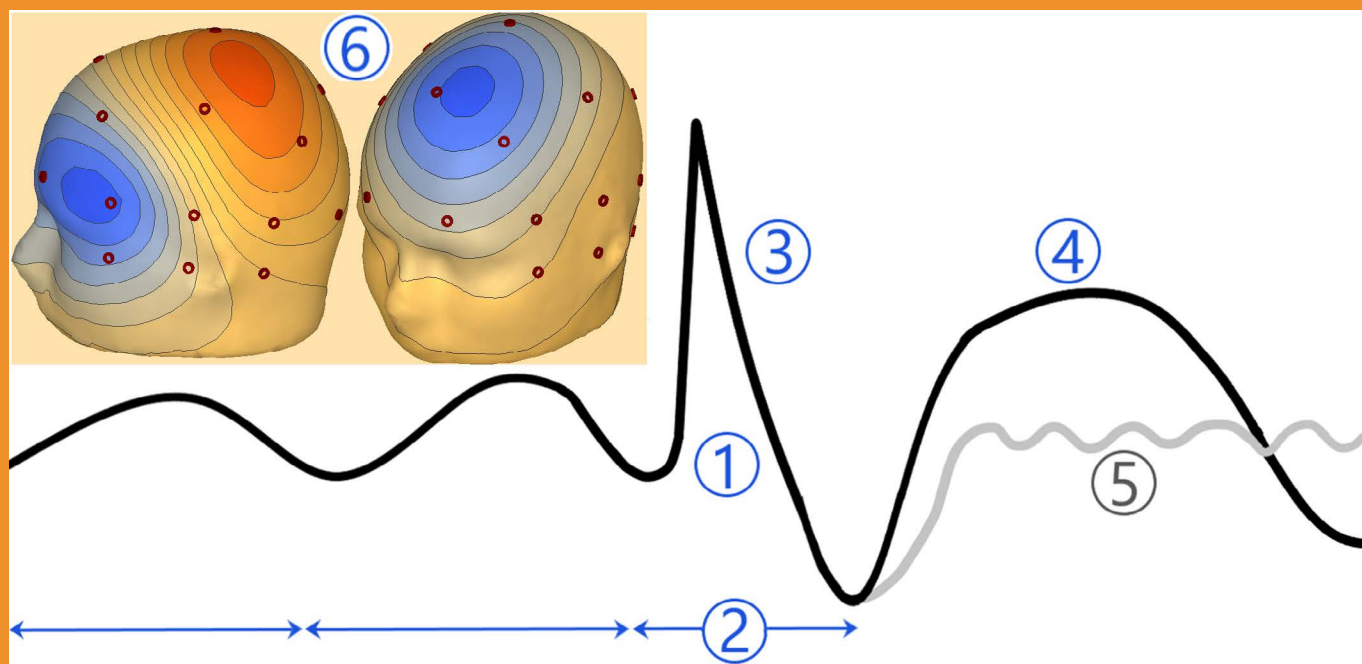




ANNUAL RESEARCH REPORT 2020-2021

DEPARTMENT OF CLINICAL NEUROPHYSIOLOGY
AARHUS UNIVERSITY HOSPITAL

CONTENT

Department of Clinical Neurophysiology

The research Group

Positions of Trust

Research Projects

Publications



DEPARTMENT OF CLINICAL NEUROPHYSIOLOGY

**The research group:**

Three professors
Two associate professors
One assistant professor
Two post-docs

Four postgraduate (PhD) students
Eight research-year (graduate) students
One research assistant



Published papers
in peer-reviewed
international journals
listed on PubMed



Contributions
of International
Congresses

Being the largest Danish neurophysiological department outside the capital area, the department of Clinical Neurophysiology at Aarhus University Hospital is internationally acclaimed for its highly specialized diagnostic services and comprehensive research and clinical development activities.

Research at the Neurophysiology Department is clinically oriented and focuses on developing, validating and implementing in clinical practice new methods for functional investigations of the central and peripheral nervous system and of the muscles.

The goal is to achieve methods that are highly accurate and feasible, in order to increase the quality of care of the patients. The research group comprises three professors, two associate professors, one assistant professor, two post-docs and four postgraduate (PhD) students. The research group uses facilities at Aarhus University Hospital.

In 2020 and 2021, we published 118 papers in peer-reviewed international journals listed on PubMed. Our department contributed as well at international congresses and meetings with 18 presentations/posters/teaching courses.

The department has close collaboration with centres in several international consortia: ESTEEM (lead), SCORE (lead) and EpiCare (lead of the Neurophysiology work-package). Our colleagues have several positions of trust in national and international scientific societies. We have close collaboration with other Danish research groups at the Danish Epilepsy Centre and Copenhagen University.

THE RESEARCH GROUP

**Sándor Beniczky**

MD and PhD from University of Szeged, Hungary (1997, 2004).
Specialist in Neurology (2002).
Specialist in Clinical Neurophysiology (2006).
European certification as epileptologist (2010).
Fellow of the European Academy of Neurology (2020)

Current position

Professor, consultant, Aarhus University Hospital.
Head of Clinical Neurophysiology, Danish Epilepsy Centre, Filadelfia.
Editor-in-chief, Epileptic Disorders.

Research interests

- Electromagnetic source imaging
- Epilepsy surgery
- Automated seizure detection
- Wearable devices in epilepsy
- Standardization and quality assurance in clinical neurophysiology.
- Artificial intelligence

224 publications in peer-reviewed journals; 6041 citations; H-index: 44.

**Hatice Tankisi**

MD from Uludag University, School of Medicine, Bursa, Turkey.
Specialist in Neurology from Ankara University, Turkey (1995) .
PhD from Aarhus University, Denmark (2004) .
Specialist in Neurology, Denmark (2010).
Specialist in Clinical Neurophysiology, Denmark (2011).

Current position

Consultant at Aarhus University Hospital, and clinical professor at Aarhus University

Research interests

- Peripheral nerve-muscle and cortical excitability tests with threshold tracking
- Quantitative EMG and Motor Unit Estimation (MUNE) methods in normal and diseased muscles/nerves
- Electrodiagnostics and pathophysiology in polyneuropathy and ALS
- Neuromuscular manifestations of long-term Covid-19.

Main supervisor for 2 and co-supervisor for 2 PhD students.
129 PubMed indexed articles, 1973 citations; H-index: 26

Editorial Board:

Associate Editor for Clinical Neurophysiology Practice, Editorial Board member for Journal of Clinical Neurophysiology, Clinical Neurophysiology and Neurophysiology Clinique

**Anders Fuglsang-Frederiksen**

MD from University of Copenhagen (1972).
DMSc from University of Copenhagen (1981).
Director of Department of Clinical Neurophysiology (2000-2011).
Professor in Clinical Neurophysiology.
Department Chair, Aarhus University (2000-2016).

Current position

Professor Emeritus, Clinical Neurophysiology, Aarhus University Hospital
Associate Editor of Clinical Neurophysiology (2003-2009)

Research interests

- Electrodiagnostics
 - Guidelines and pathophysiology in neuromuscular disorders
 - MEG and EEG in evaluation for epilepsy surgery.
- 219 publications, 189 in peer reviewed journals, H-index 49, citations 7524

**Peter Orm Hansen**

MD from Odense University (1992)
PhD from Aarhus University (2001)
Specialist in Clinical Neurophysiology (2008)

Current position

Head of Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus

Research interests

- Central and peripheral nervous system
- Magnetoencephalography
- Intraoperative monitoring

**Birger Johnsen**

MD from University of Copenhagen (1987)
PhD from University of Copenhagen (1997)
Specialist in Clinical Neurophysiology (2000)

Current position

Associate Professor, Consultant

Research interests

- Coma prognostication by neurophysiological methods
- Electrophysiological methods in neuromuscular diseases
- Diagnostic criteria for amyotrophic lateral sclerosis.

Research interests

- Coma prognostication by neurophysiological methods
- Electrophysiological methods in neuromuscular diseases
- Diagnostic criteria for amyotrophic lateral sclerosis.

PhD supervisor for 7 completed PhD studies and three research year students.
Also doing pre- and postgraduate teaching in clinical neurophysiology.

Published 64 scientific publications in peer-reviewed journals, 12 book chapters, 79 abstracts and 42 oral presentations.

**Erisela Qerama**

MD from University of Tirana (1997)
Aarhus University (1999), PhD from Aarhus University (2005)

Current position

Associate Professor, Specialist in Clinical Neurophysiology.

Research interests

- Nerve and muscle ultrasound in entrapment neuropathies and in neuromuscular disorders
- Epilepsy and status epilepticus
- Muscle pain and muscle fatigue mechanisms and treatment.

I am co-supervisor for one PhD student, and one student in special honors research program. I am clinical supervisor for residents in research and clinical training, 1-2 residents per year. Previously, I had 5 research year students as main supervisor, and co supervisor for one PhD student.

**Marit Otto**

MD from Kiel University (1995)
PhD from Odense University (2008)
Specialist in Neurology (2007)
Subspecialty in Clinical Neurophysiology (2010)
European certification as somnologist – Expert in Sleep Medicine (2014)
European board certification in neurology (2016)

Current position

Staff specialist and consultant

Research interests

- Sleep medicine
- Idiopathic REM sleep behaviour disorder
- Ear EEG in the evaluation of sleep, studies in patients with insomnia.

**Jesper Jeppesen**

Master in Biomedical Engineering
Cand.scient.med. Aarhus University (2010). PhD
Faculty of Health, Aarhus University (2015)

Current position

Assistant Professor, Aarhus University

Research interests

- Seizure detection
- Biosignal analysis
- Seizure alarm systems.

PhD entitled: Detecting epileptic seizures with heart rate variability (HRV) and near infrared spectroscopy.
Winner: Young Investigator Award, Danish Epilepsy Society Annual Meeting 2013 & 2015.
Best European Student Paper and Finalist, 36th IEEE EMBS Chicago, USA, 2014

THE RESEARCH GROUP

**Kirsten Pugdahl**

MSc in Molecular Biology from Aarhus University (2001)
PhD in Medicine from Aarhus University (2007)

Current position

Researcher and coordinator of a national quality improvement database and an international multi-center research database at Department of Clinical Neurophysiology, Institute of Clinical Medicine, Aarhus University

Research interests

- Cover electrodiagnostic examination strategies and patho physiology of neuromuscular disorders, in particularly amyotrophic lateral sclerosis
- Evidence-based quality improvement initiatives within clinical neurophysiology.

**Lene Duez**

MD from Aarhus University, (2010)
PhD from Aarhus University (2018)

Current position

Resident at Department of Neurology

Research interests

- Electromagnetic source imaging
- Epilepsy surgery
- Epilepsy.

Published 7 scientific publications in peer-reviewed journals, 2 book chapters, 9 abstracts and winner of Best poster presentation, PhD day Aarhus university 2014 and 2015 and the Mogens Fog price, Danish Neurology Society 2017 Co-supervisor for one completed PhD study.

**Mustafa Aykut Kural**

MD from Cukurova University (2008)
Specialist in Neurology from Ankara University (2014)
PhD from Aarhus University (2021)

Current position

PhD student at Department of Clinical Neurophysiology

Research interests

- Epilepsy surgery
- Voltage mapping
- Connectivity analyses
- Nerve conduction studies
- Diabetic neuropathy.

**Maria Vlachou**

MD from Aristotle University, Thessaloniki, Greece (2012)
Specialist in Neurology, Denmark (2021)

Current Position

Ph.D. student at Department of Clinical Neurophysiology, Aarhus University Hospital

Research Interests:

- Epilepsy
- Epilepsy Surgery
- Standardization in EEG reporting
- Seizure Severity-Postictal generalized EEG suppression
- Clinical Relevance of ictal electro-clinical features
- Supervised machine learning in epilepsy research

**Agnes Hauschultz Witt**

MD from Aarhus University (2008),
PhD from Aarhus University (2020)

Current position

Medical Doctor at Department of Neurology

Research interests

- The peripheral nervous system
- Spinal cord injury
- Nerve excitability
- Motor unit number estimation
- Muscle membrane properties (muscle velocity recovery cycle)

Published 4 scientific publications in peer-reviewed journals.

**Alexander Gramm Kristensen**

MD from Aarhus University (2016)
PhD from Aarhus University Clinical Institute (2020)

Current position

MD at Department of Neurology and Clinical Neurophysiology,
Aarhus University Hospital

Research interests

- Microneurography
- Nerve excitability
- Nerve conduction studies
- Motor unit number estimation
- Diabetic neuropathy
- Deep learning
- Neurology

**Zahra Nochi**

M.Sc in Microbiology - Azad University, Iran (2007)
PhD in Medicine - Aarhus University, Denmark (2016)

Current position

Assistant Professor of Mechanistic Pain Research
Danish Pain Research Center, Department of Clinical Medicine, Aarhus University

Research interests

- Pain model / biomarker
- Mitochondria in Pain

**Hossein Pia**

MD from Tabriz University of Medical Sciences, Iran (2006)
Specialist in Neurology from Ege University, Faculty of Medicine, Turkey (2016)

Current position

Research assistant at Danish Pain Research Center,
Department of Clinical Medicine, Aarhus University
and Department of Clinical Neurophysiology,
Aarhus University Hospital

Research interests

- Neurology
- Nerve conduction studies
- Effects of painkiller medicines on biomarkers of pain using Peripheral Nerve Excitability Testing (NET)
- Potential effects of High Frequency electrical Stimulation (HFS) on small sensory fibers using Perception Threshold Tracking (PTT)

THE RESEARCH GROUP



Anna Bystrup Jacobsen
MD from Aarhus University (2018)

Current position
Resident at Department of Neurology – starting in a PhD position (November 2022) at Department of Clinical Neurophysiology
Former research-year student at Department of Clinical Neurophysiology

- Research interests**
- TMS
 - MScanFit MUNE,
 - Motor unit number estimation
 - ALS, Nerve excitability
 - Nerve conduction studies



Sara Silkjær Bak
MD from Aarhus University (2020)

Current position
Resident at Department of Neurology, Aarhus University Hospital
Former research year student at Department of Clinical Neurophysiology

- Research interests**
- Nerve and muscle ultrasound
 - The diagnostic work-up of scapulae alatae patients in regard to the clinical examination, electrodiagnostic examination and ultrasound.



Christina Shen Nielsen
MD from Aarhus University (2021)

Current Position:
PhD student at Department of Biomedicine, Aarhus University
Former research year student at Department of Clinical Neurophysiology, Aarhus University Hospital (2017-2018)

- Research Interests**
- Cerebrovascular Mechanisms following acute ischemic stroke
 - Pathophysiology in ALS
 - Cortical hyperexcitability tests with threshold tracking TMS



Mette Dahl Diechmann
MSc. in Sports Science - Aarhus University, Denmark (2021)

Current position
Research Assistant
Dalgas' Group, Department of Public Health, Aarhus University, Denmark

- Research interests**
- Neurophysiology in Multiple Sclerosis
 - Connection between neurophysiological outcomes and physical function



Lotte Hardbo Larsen
MD from Aarhus University (2021)

Current position
Resident at Dronning Ingrid's Sundhedscenter, Nuuk, Greenland.

Former research year student at the Department of Clinical Neurophysiology (2019-2020). The project was entitled: The role of potassium in muscle membrane dysfunction in end-stage renal disease.

- Research interests**
- Muscle membrane properties in uremic myopathy and critical illness myopathy.
 - Muscle velocity recovery cycle measuring.

Winner of Best Poster Presentation, PhD Day Aarhus University 2018



Sigbjørn Hokland
MSc in Biomedical Engineering from Technical University of Denmark (2018)

Current position
Clinical engineer, Department of Clinical Neurophysiology, Aarhus University Hospital

- Research interests**
- Magnetoencephalography
 - Gamma-frequency neurostimulation
 - Visual processing
 - Sleep medicine



Zennia Bruus Zeppelin
MD from Aarhus University (2021)

Current position:
Medical doctor at department of General Surgery, Horsens Regional Hospital
Former research student at the Department of Clinical Neurophysiology, Aarhus University Hospital.

- Research interests**
- Disuse induced muscle weakness
 - Muscle Velocity Recovery Cycles
 - MScan Motor Unit Number Estimation



Kristine Nielsen Strunge
MD from Aarhus University (2022)

Current position:
Research student at department of Clinical Neurophysiology, Aarhus University Hospital

- Research Interests:**
- Cortical excitability
 - Transcranial magnetic Stimulation



THE RESEARCH GROUP



Søren Ørskov
Last year medical student at Aarhus University

Current position:
Medical student - Bachelor project on TT-TMS at the Department of Clinical Neurophysiology Research volunteer at the department from 2018-2021

- Research interests**
- Threshold tracking TMS



Torsten Vinding Merinder
MD from Aarhus University (2021) at Aarhus University

Current position
Research year student at the Department of Clinical Neurophysiology, Aarhus University Hospital

- Research interests**
- Epilepsy surgery and presurgical assessment
 - Long-term monitoring of epilepsy seizure manifestation
 - Automated seizure detection algorithms and seizure alarm systems
 - Connectivity analyses
 - Electromagnetic source imaging
 - Functional cortical mapping.



Daniel Mosgaard Sørensen
6th year medical student (Bsc.Med. 2019) at Aarhus University.

Current position
Research Year Student at Department of Clinical Neurophysiology, Aarhus University Hospital, using the novel method, MScanFit MUNE in an international collaboration.

- Research Interests**
- Pathophysiology and diagnosis of Amyotrophic Lateral Sclerosis (ALS).
 - Motor Unit Number Estimation (MUNE) in normal and diseased muscles/ nerves.



Marie Meldgaard
6th year medical student at Aarhus University (BSc in Medicine in 2018).

Current Position
Medical student at Aarhus University, finishing a half-year research project at the department of neurophysiology, Aarhus University.

- Research Interests**
- Muscle membrane properties in myopathy
 - Muscle velocity recovery cycles and frequency rampMyopathy

POSITIONS OF TRUST

Sandor Beniczky

- International League Against Epilepsy (ILAE): Education Council, Publication Council, Congress Council.
- Past chair of the Joint Taskforce on EEG of the ILAE and International Federation of Clinical Neurophysiology (IFCN)

Erisela Qerama

- Danish Society of Clinical Neurophysiology: board member and secretary (since 2015).

Peter Orm Hansen

- Danish Society of Clinical Neurophysiology: board member and treasurer (since 2004).

Hatice Tankisi

- President of Europe, Middle-East and Africa Chapter (EMEAC)- IFCN
- Co-Chair of Clinical Neurophysiology Panel, European Academy of Neurology

Birger Johnsen

- Danish Society of Clinical Neurophysiology: member of the education committee (since 2007).
- Danish Neurological Society: board member (since 2012)

RESEARCH PROJECTS

Absence seizures revisited

By: Sandor Beniczky

Typical absence seizures are the archetypes of generalized epileptic seizures. Using detailed electro-clinical analyses, we gained new, clinically important knowledge about absence seizures.

We showed that absence seizures may lead / immediately evolve to generalized tonic-clonic seizures. We provide detailed video-EEG documentation for these seizures, and we argue for the term: absence-to-bilateral-tonic-clonic seizure, to describe them. Clinicians should be aware of this seizure for correctly diagnosing patients. This novel seizure type may further elucidate generalized ictogenesis.

Using a machine-learning approach, we analyzed the detailed electro-clinical features of typical absence seizures, to find predictors of long-term therapeutic response. The presence of polyspikes was an independent predictor of poor therapeutic response. None of the semiological features (alone or in combination) predicted the therapeutic response.

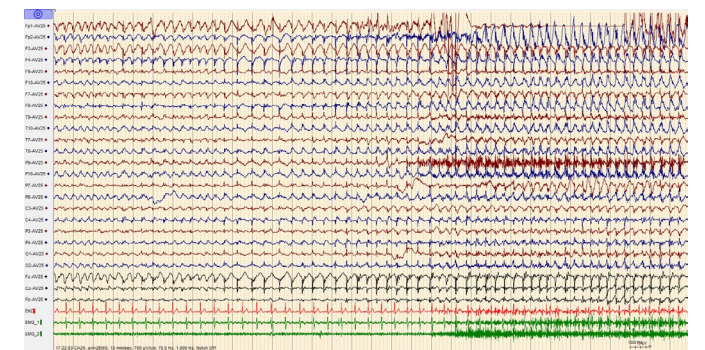


Figure-SB-A1: EEG-EMG recording at the start of an absence-to-bilateral-tonic-clonic seizure

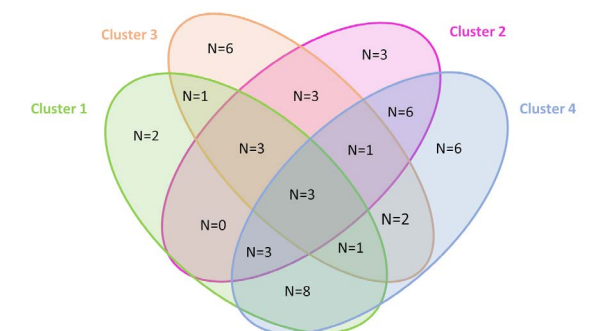


Figure-SB-A2: Cluster analysis of typical absence seizures.

PAPERS

Beniczky S, Rubboli G, Covanis A, Sperling MR. Absence-to-bilateral-tonic-clonic seizure: A generalized seizure type. **Neurology**. 6;95(14):e2009-e2015. doi: 10.1212/WNL.0000000000010470.

Vlachou M, Skrimpas GA, Kural MA, Rackauskaite G, Nikanorova N, Christensen J, Nikanorova M, Beniczky S. Electroclinical features and long-term therapeutic response in patients with typical absence seizures. **Epileptic Disord**. 2021; doi: 10.1684/epd.2021.1392.

A web-based decision-support system for diagnosis, classification and patient-tailored treatment of patients with epilepsy: the Epipick application

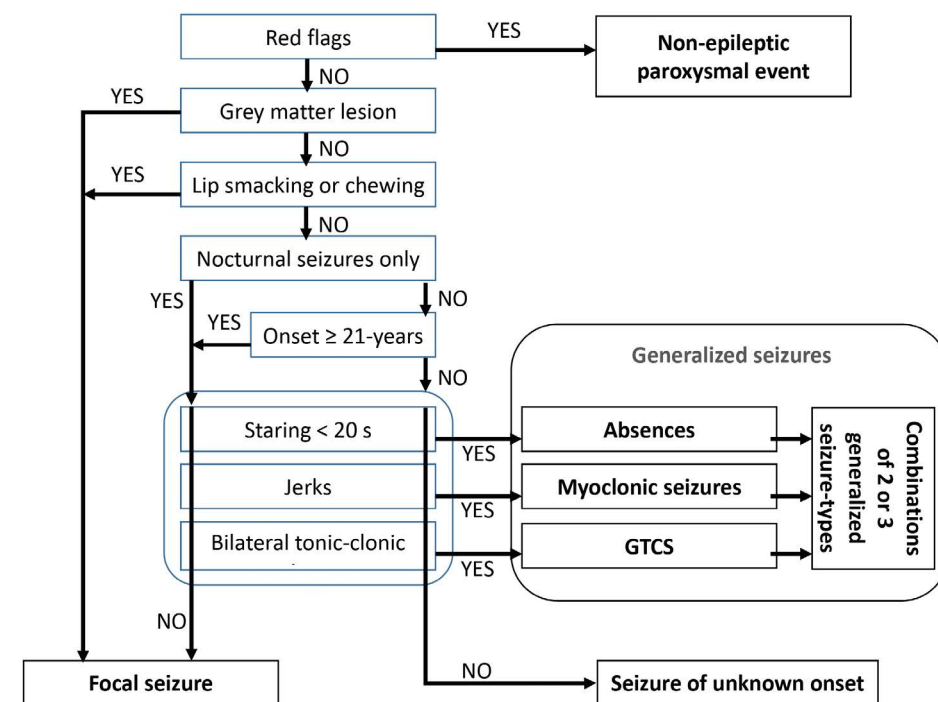


Fig-SB-E1: The classification algorithm in Epipick.

A web-based decision-support system for diagnosis, classification and patient-tailored treatment of patients with epilepsy: the Epipick application

We developed 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%, $p < 0.001$).

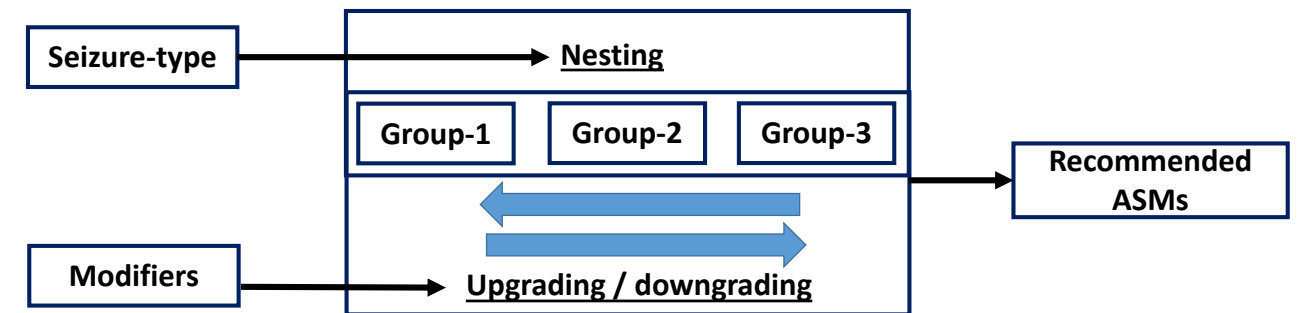


Fig-SB-E2: The algorithm for optimizing individual ASM choice, in Epipick.

Basic information

Age: 67

Gender: ☐ Female ☒ Male

Which seizure type does your patient have? More than one box may be chosen if needed.

☐ Unknown whether focal or generalized seizure type or uncertain

☒ Focal seizures (including tonic-clonic with focal onset)

☐ Absences

☐ Generalized myoclonic seizures

☐ Primary generalized tonic-clonic seizures

Further questions:

☒ Does the patient take any medication on a daily basis?

Does the patient have any of the following?

☒ Brain tumor requiring chemotherapy and/or radiation therapy

☐ Hepatic failure

☐ Obesity (BMI > 30)

☐ Diabetes mellitus

☐ Bleeding disorders

☐ Neuropenia

☐ Renal stone

☐ Renal failure

☐ Allergy to any drug

☒ Depression

☐ History of instability or aggressive behavior

☐ Migraine

Recommended antiseizure medication based on the following:

Group 1 (Best options)

- Lamotrigine (LTG)

Group 2 (Second best options)

- Lacosamide (LCM)

Group 3 (Least desirable options though still acceptable)

- Levetiracetam (LEV)

Least desirable options if the above drugs are not available:

- Brivaracetam (BRV)
- Ceftriaxone (CTZ)
- Clobazam (CLB)
- Eslicarbazepine acetate (ESL)
- Gabapentin (GBP)
- Oxcarbazepine (OXC)
- Perampanel (PER)
- Pregabalin (PGB)
- Topiramate (TPM)
- Valproate (VPA)
- Zonisamide (ZNS)
- Phenytoin (PHT)
- Phenytoin (PB)

Go back

Start new case

Fig-SB-E3: Graphical user interface of the Epipick app. The input to the app are simple questions answered by the user.

PAPERS

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

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;62:220-227. doi: 10.1111/epi.16763.

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;62:2474-2484. doi: 10.1111/epi.17039.

Hadady L, Klivényi P, Perucca E, Rampp S, Fabó D, Bereczki C, Rubboli G, Asadi-Pooya AA, Sperling MR, Beniczky S. Web-based decision support system for patient-tailored selection of antiseizure medication in adolescents and adults: An external validation study. *Eur J Neurol*. 2022;29:382-389. doi:10.1111/ene.15168.

Asadi-Pooya AA, Beniczky S, Rubboli G, Sperling MR, Rampp S, Perucca E. The EpiPick algorithm to select appropriate antiseizure medications in patients with epilepsy: Validation studies and updates. *Epilepsia*. 2022;63:254-255. doi: 10.1111/epi.17129.

SCORE and photoparoxysmal responses

Clinically important features are extracted by experts when reading EEG. When reported in free-text format, these are lost for systematic evaluation, due to the myriad of synonyms and the large number of combinations of words to describe the same phenomenon. We developed a standardized, computer-based, organized reporting system for EEGs: SCORE. The aim was to increase the inter-rater agreement, and to provide structured database for further research. In collaboration with other centers in EpiCARE (the European Reference Network for Epilepsy), we used the SCORE

system to evaluate and improve inter-rater agreement on the photoparoxysmal EEG responses and to assess the incidence of these phenomena, in a large database. With this approach we achieved moderate agreement on the photoparoxysmal responses and substantial (almost perfect) agreement on the clinical significance of the recordings. We found photoparoxysmal responses in 375 out of 10,671 EEG recordings (3.5%), with a preponderance among young (11-20 years) and female patients (67%).

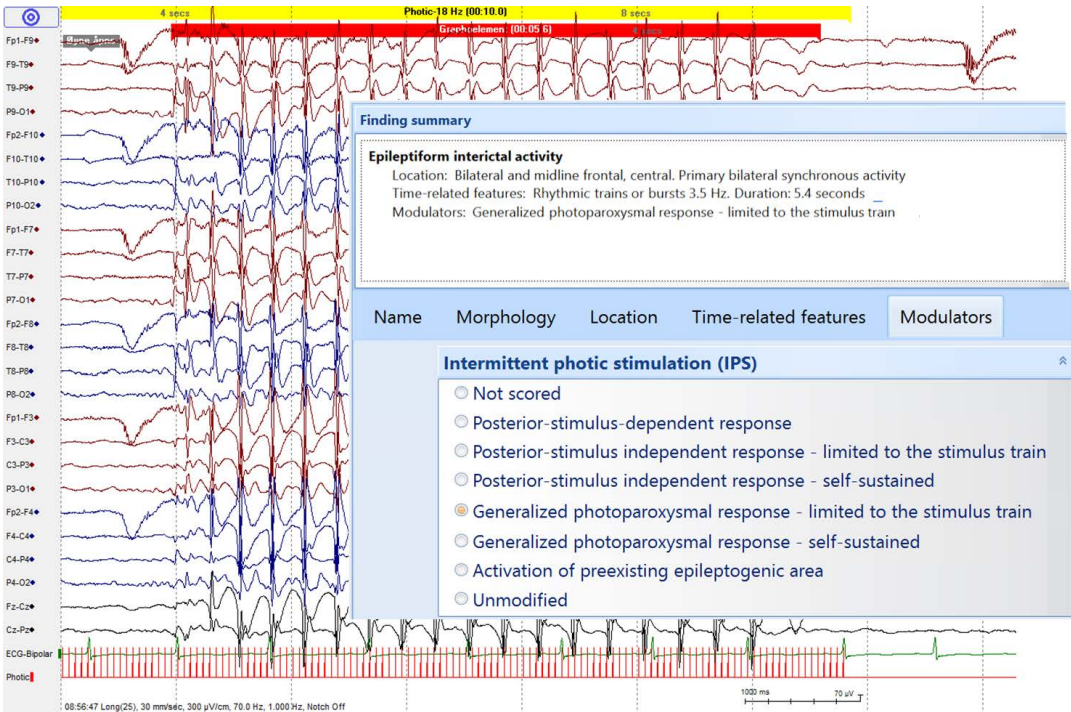


Fig-SB-S1: Feature-extraction and documentation using the SCORE system. The EEG shows photoparoxysmal response.

PAPERS

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

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

Automated seizure detection using wearable devices

The rapid technological development, advances in signal analysis, automated algorithms and artificial intelligence led to significant progress in the field of seizure detection using wearable devices. We continued our work on this topic, and achieved important milestones.

Using EMG and ECG signals, we were able to measure the severity of the seizures and predicting factors associated with high risk of SUDEP (Sudden Unexpected Death in Epilepsy) with an accuracy of 85%. In a phase-2 study, we have validated an algorithm for detection of focal seizures, using heart-rate variability calculated from a surface wearable ECG device. The sensitivity of the device was 87% in patients with ictal autonomic changes. We showed that seizures could be documented using multimodal recordings from commercially available fitness trackers.

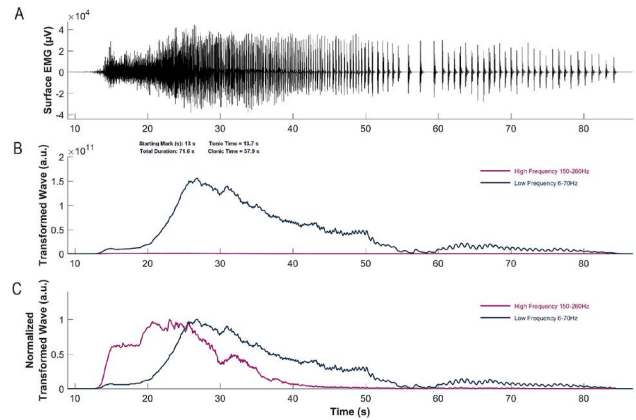


Fig-SB-SD1: Quantitative EMG parameters automatically extracted from surface EMG signals recorded with wearable devices, for objective measurement of seizure severity.

PAPERS

Arbune AA, Conradsen I, Cardenas DP, Whitmire LE, Voyles SR, Wolf P, Lhatoo S, Ryvlin P, Beniczky S. Ictal quantitative surface electromyography correlates with postictal EEG suppression. *Neurology*. 2020 Jun 16;94:e2567-e2576. doi: 10.1212/WNL.0000000000009492.

Jeppesen J, Fuglsang-Frederiksen A, Johansen P, Christensen J, Wüstenhagen S, Tankisi H, Qerama E, Beniczky S. Seizure detection using heart rate variability: A prospective validation study. *Epilepsia*. 2020 Nov;61 (Suppl 1):S41-S46. doi: 10.1111/epi.16511.

Arbune AA, Jeppesen J, Conradsen I, Ryvlin P, Beniczky S. Peri-ictal heart rate variability parameters as surrogate markers of seizure severity. *Epilepsia*. 2020;61 (Suppl 1):S55-S60. doi: 10.1111/epi.16491.

Hubbard I, Beniczky S, Ryvlin P. The Challenging Path to Developing a Mobile Health Device for Epilepsy: The Current Landscape and Where We Go From Here. *Front Neurol*. 2021 Oct 1;12:740743. doi: 10.3389/fneur.2021.740743.

Beniczky S, Rubboli G. Use of fitness trackers to identify and document epileptic seizures. *Epileptic Disord*. 2021;23:432-434. doi:10.1684/epd.2021.1271. PMID: 33926858.

Ryvlin P, Beniczky S. Seizure detection and mobile health devices in epilepsy: Recent developments and future perspectives. *Epilepsia*. 2020;61 (Suppl 1):S1-S2. doi: 10.1111/epi.16702.

Beniczky S, Karoly P, Nurse E, Ryvlin P, Cook M. Machine learning and wearable devices of the future. *Epilepsia*. 2021;62 (Suppl 2):S116-S124. doi:10.1111/epi.16555.

Beniczky S, Arbune AA, Jeppesen J, Ryvlin P. Biomarkers of seizure severity derived from wearable devices. *Epilepsia*. 2020;61 (Suppl 1):S61-S66. doi:10.1111/epi.16492.

Ryvlin P, Cammoun L, Hubbard I, Ravey F, Beniczky S, Atienza D. Noninvasive detection of focal seizures in ambulatory patients. *Epilepsia*. 2020;61 (Suppl 1):S47-S54. doi: 10.1111/epi.16538.

EEG Source imaging

Estimating the source of EEG signals in the brain is important tool in presurgical evaluation. We have developed and validated a novel source imaging method, the Relative Source Power, which proved to be accurate in our series of patients with extratemporal epilepsy, localizing the sources within 20 mms from the epileptogenic lesion. We have validated a semi-automated pipeline for ictal source imaging. In 50 consecutive patients, the accuracy of the ictal analysis was 74%.

Using source montages and distributed source models, we showed that the cortical generators of the triphasic potentials in encephalopathic patients, were localized in bilateral, widely distributed fronto-temporal networks. In a prospective study, we showed that EEG source imaging provided non-redundant information in one third of the patients undergoing presurgical evaluation. These were useful for planning the implantation strategy for intracranial recordings.

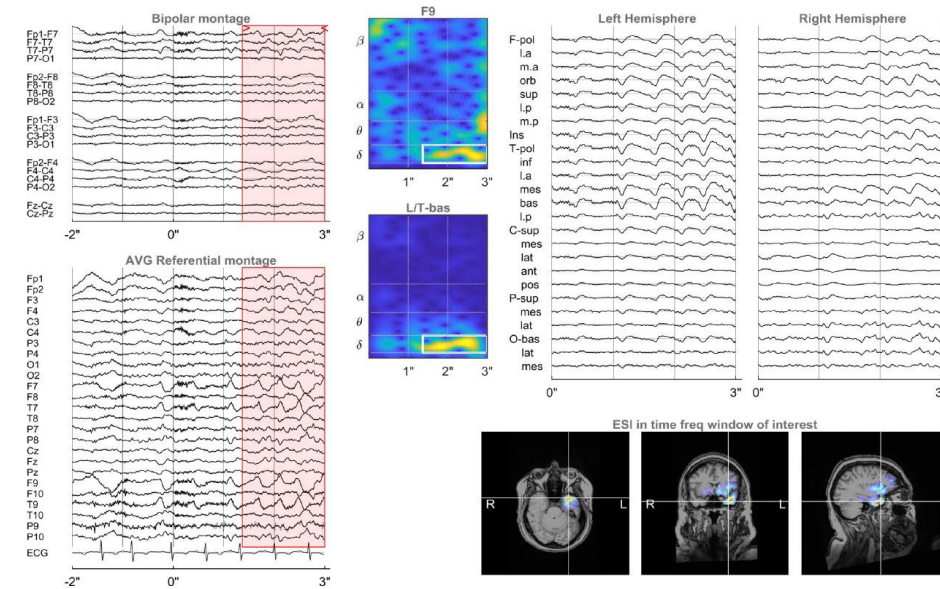


Fig-SB-SI2: Semi-automated ictal source imaging.

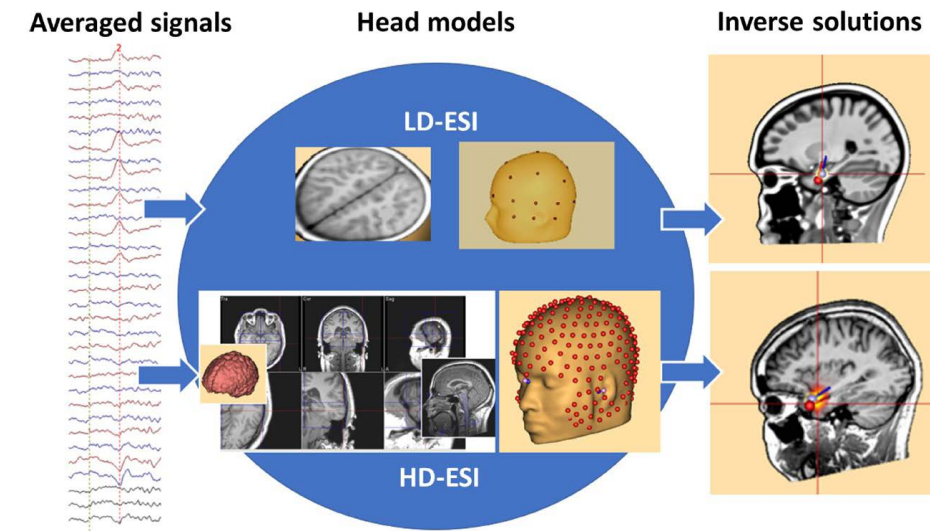


Fig-SB-SI3: Flow diagram of EEG source imaging in presurgical evaluation.

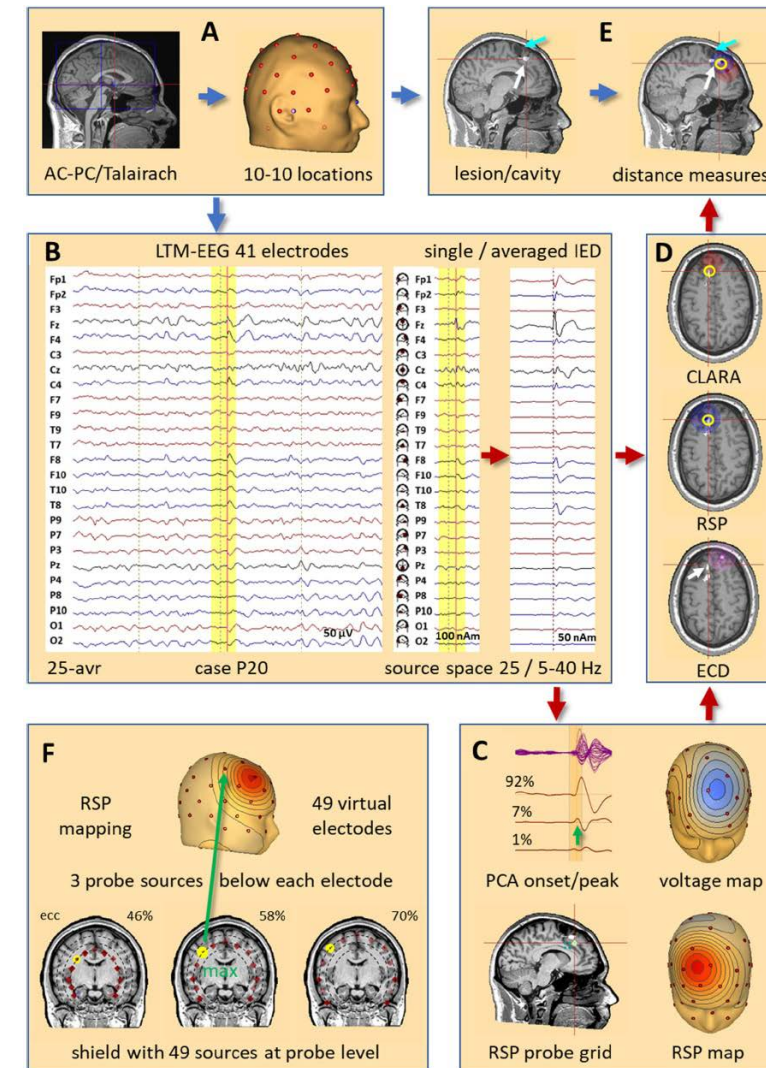


Fig-SB-S11: Workflow of the Relative Source Power method for EEG source imaging.

PAPERS

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Interictal Epileptiform Discharges

Interictal Epileptiform Discharges (IEDs) are electrographic biomarkers for epilepsy. In skilled hands, they provide valuable information for diagnosing and classifying epilepsy. However, EEG is often misread, which leads to misdiagnosing epilepsy.

We have participated in a working group of the International Federation of Clinical Neurophysiology (IFCN), which has proposed a set of 6 criteria for the operational definition of IEDs. Using a robust diagnostic gold standard, derived from the video-EEG evaluation of the patients' habitual clinical episode, we assessed the accuracy of the IFCN criteria to identify IEDs in the interictal recordings. To achieve a high specificity (>95%) and good sensitivity (>80%), one needs to identify at least 5 IFCN criteria (any combination). We showed that 3 of the criteria weigh more: the presence of pointed peak,

slow after-wave and characteristic voltage distribution. High accuracy was obtained when transforming signals from the sensor-space to the source space, and assessing the current flow in the regions of interest in the brain. We demonstrated that repetition-rate was an important factor to confirm the IEDs fulfilling less than 5 criteria. We have validated an algorithm for automated detection of IEDs, developed using Artificial Intelligence (deep learning). It achieved high sensitivity, but low specificity - hence human supervision of the automated detection is needed. Using IED-histograms, displaying the change in time of the IED-occurrence, we showed how IEDs modulate the occurrence of epileptic seizures. In a consensus statement, we called for establishing a large international database for further, collaborative studies about IEDs.

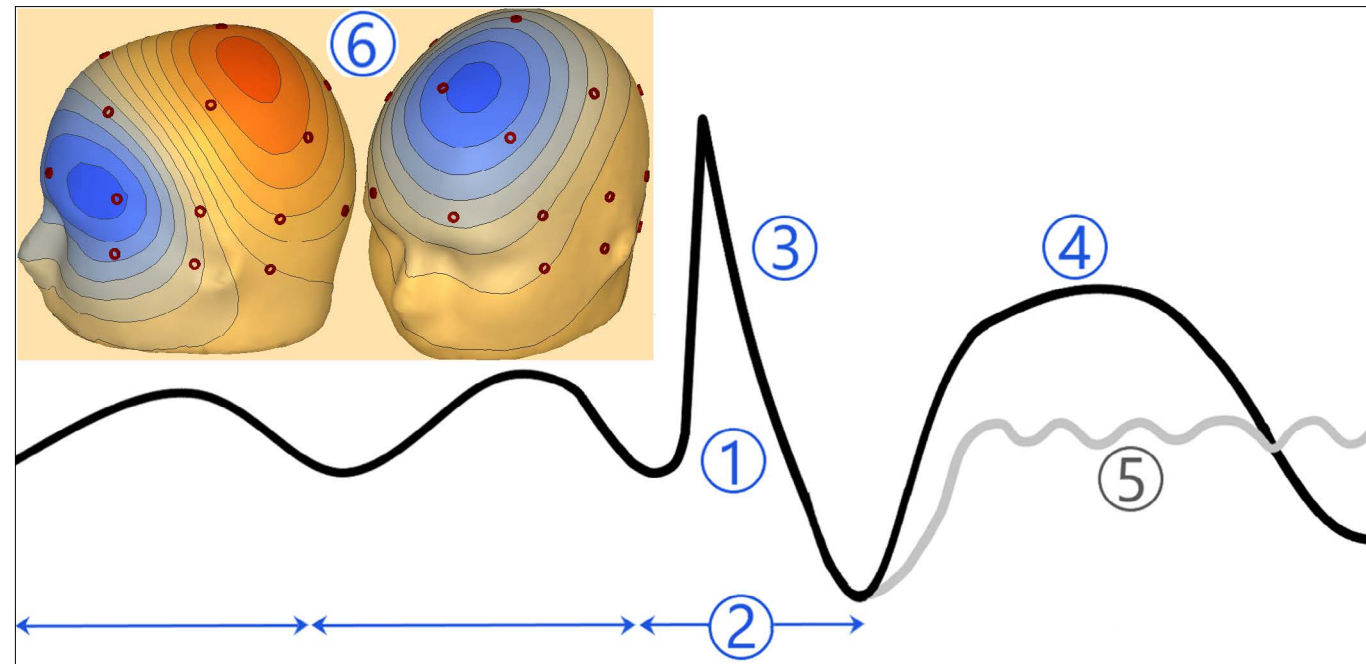


Fig-SB-IED1: Infographic with the 6 criteria in the operational definition of Interictal Epileptiform Discharges.

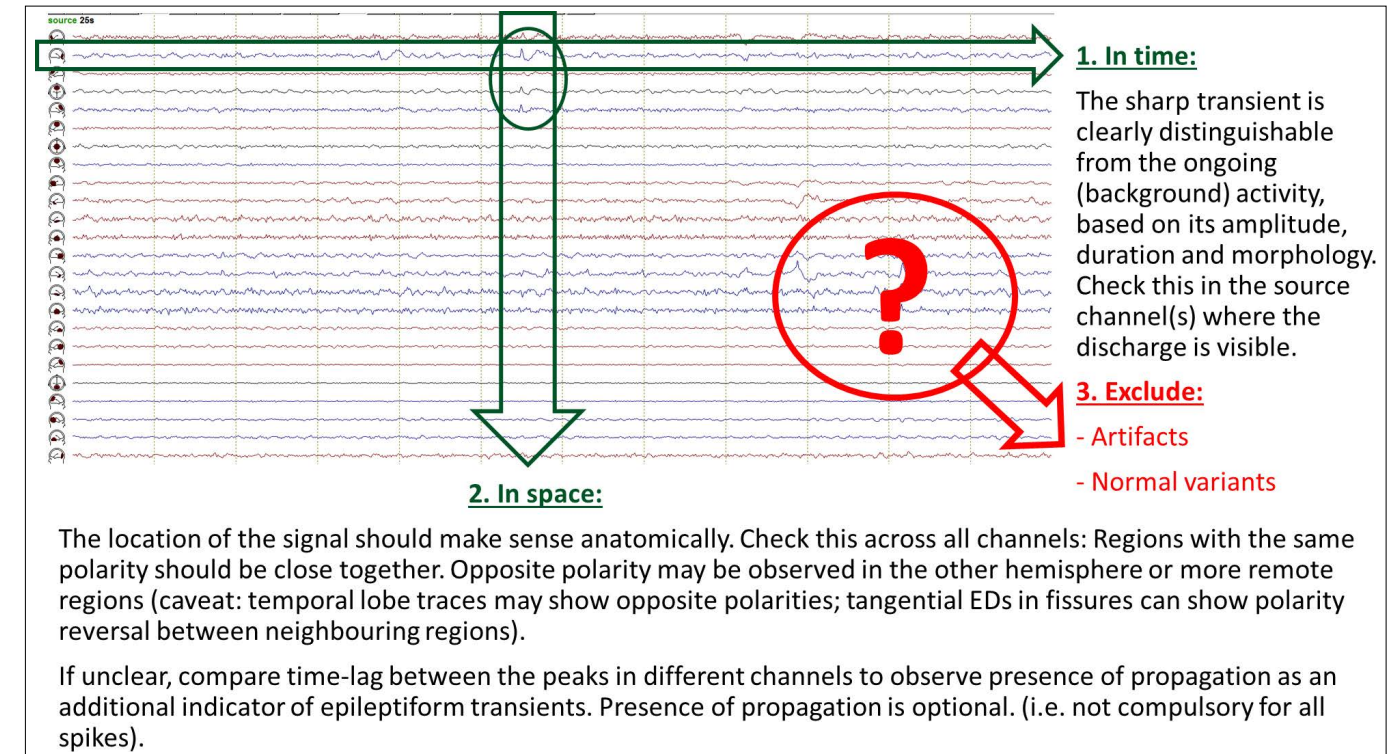


Fig-SB-IED2: Interictal Epileptiform Discharges in source-space.

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Guidelines and consensus recommendations

Evidence-based Clinical Practice Guidelines and consensus-based recommendations are essential for achieving best clinical practice. Development of guidelines is a robust and resource-demanding process. It has been an honor to participate in the guideline working groups, in collaboration with the International League Against Epilepsy, International Federation of Clinical Neurophysiology, European Academy of Neurology, American Clinical Neurophysiology Society and the European Sleep Research Society.

We developed guidelines and recommendations about automated seizure detection using wearable devices, standards for long-term video-EEG monitoring, video-EEG monitoring during the pandemic, EEG in critically ill patients, diagnosis and management of sleep-related epilepsy. Many of these guidelines have been published in form of dual-publications, in the journals of two societies. Undoubtedly, these guidelines will help improving the quality of patient care.

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Myopathy in acute and long-term COVID-19

By: Hatice Tankisi

Severe Acute Respiratory Syndrome 2 (SARS-CoV-2), causing the new coronavirus disease 2019 (COVID-19), has become a life-threatening pandemic. Among neurological complications, our research group has focused on acute and long-term neuromuscular manifestations of COVID-19.

We published the first case report of critical illness myopathy (CIM) as a consequence of COVID-19 infection. While the electrophysiological findings in this case report looked like CIM of other etiologies, later studies suggested that there is also inflammation and vascular changes in muscle biopsies and that CIM related to COVID-19 maybe a distinct entity (Tankisi, 2021).

Later, we showed that in patients with long-term muscular complains or fatigue after mild or moderate SARS-CoV-2 infection, myopathy was a common finding (Agergaard et al., 2021) (Fig 1). Our ongoing studies in relation to MULTICOV Consortium support our findings in the first study including larger cohorts and muscle biopsies. Electron microscopy of muscle biopsies showed a wide variety of histological changes with signs of mitochondrial changes, inflammation and capillary injury suggesting that skeletal muscles may be a major target of SARS-CoV-2 causing muscular post-COVID-19 symptoms (unpublished data).

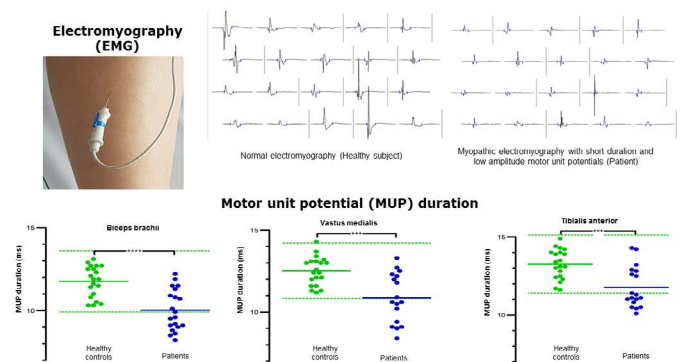


Fig. 1

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Conventional and Novel Electrophysiological Approaches in Diabetic Polyneuropathy as a part of International Diabetic Neuropathy Consortium (IDNC)

Diabetes is the most common etiology for polyneuropathies. International Diabetic Neuropathy Consortium (IDNC) has been working on this important topic to explore the mechanisms giving rise to diabetic neuropathy and pain.

Studies both in the DD2 and ADDITION cohorts have shedded light on the clinical and pathophysiological characteristics of type-2 diabetes. Additionally, large numbers of diabetics from these cohorts have been examined using conventional and novel electrophysiological methods. Among the novel methods, MScanFit motor unit estimation showed higher sensitivity of MScanFit than conventional NCS in showing motor involvement

(Kristensen et al., 2020a) (Fig 1). However, nerve excitability testing showed in a large cohort subtle changes in nerve excitability testing (Kristensen et al., 2020b). We have also published the normal material for dorsal sural NCS collected during the IDCN studies (Krøigaard et al., 2021).

Additionally, we reviewed our experience from IDNC studies on "Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management" in Brain (Jensen et al., 2021).

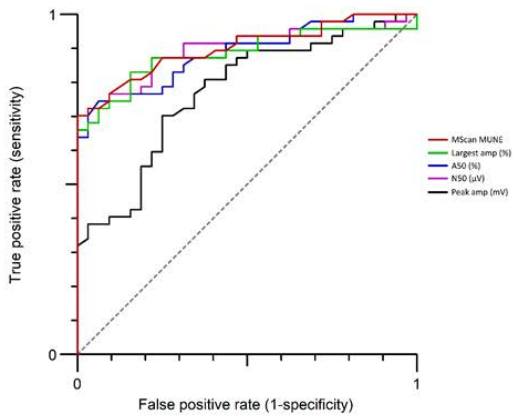
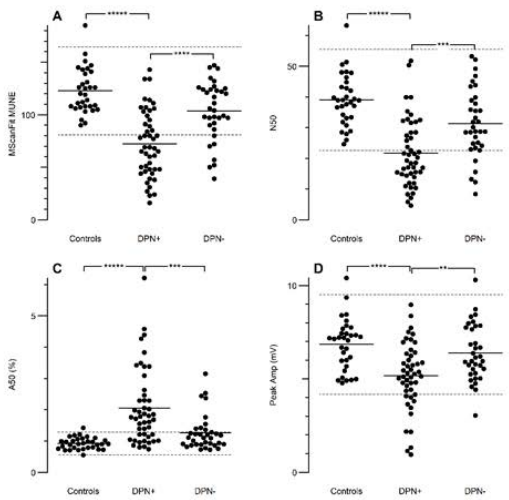


Figure 3. Receiver operating characteristic (ROC) curves describing the ability of MScanFit measures and compound muscle action potential (CMAP) amplitude to discriminate A: healthy controls from diabetic polyneuropathy positive (DPN+) patients, and B: healthy controls from all the diabetic patients.

Fig. 1



Dotplots of the MScanFit measurements with the most significant differences between patient groups and controls. A: Number of estimated motor units. B: Number of large units that make up 50% of maximal compound muscle action potential (CMAP) amplitude. C: The smallest motor unit of the units included in NSO, relative to maximal CMAP amplitude. (Note logarithmic scale to normalize distributions). D: Peak CMAP amplitude. Solid lines are the mean of the group, dashed lines are 95% confidence limits for the control group. Asterisks indicate level of significance (** = p < 0.01, *** = p < 0.001, **** = p < 0.0001, ***** = p < 0.00001).

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Muscle velocity recovery cycles and MScanFit motor unit number estimation (MUNE) in neuromuscular disorders.

Nerve conduction studies (NCS) and electromyography (EMG) are the conventional electrophysiological methods that are used for the diagnosis of neuromuscular disorders. However, NCS or EMG have limitations that can be overcome by the use of novel electrophysiological methods. The method, Muscle Velocity Recovery Cycles (MVRC) enables in vivo assessment of changes in muscle membrane potential and alterations of muscle ion channel function in pathology (Fig. 1) while MUNE methods provide information about number of functioning motor units in a nerve. Among MUNE methods, MScanFit (Fig. 1) is the most recent one, developed by Professor H. Bostock from London in close collaboration with our research group.

Our recent studies applied MVRCs in diabetic neuropathy, (Kristensen et al. 2020), spinal cord injury (Witt et al., 2020), critical illness myopathy (CIM) (Tankisi et al., 2020), and end-stage renal disease renal failure (Larsen et al., 2021), and MScanFit in chemotherapy-induced neuropathy (Bennedgaard et al., 2020), diabetic neuropathy (Kristensen et al. 2020) and spinal cord injury (Witt et al., 2020).

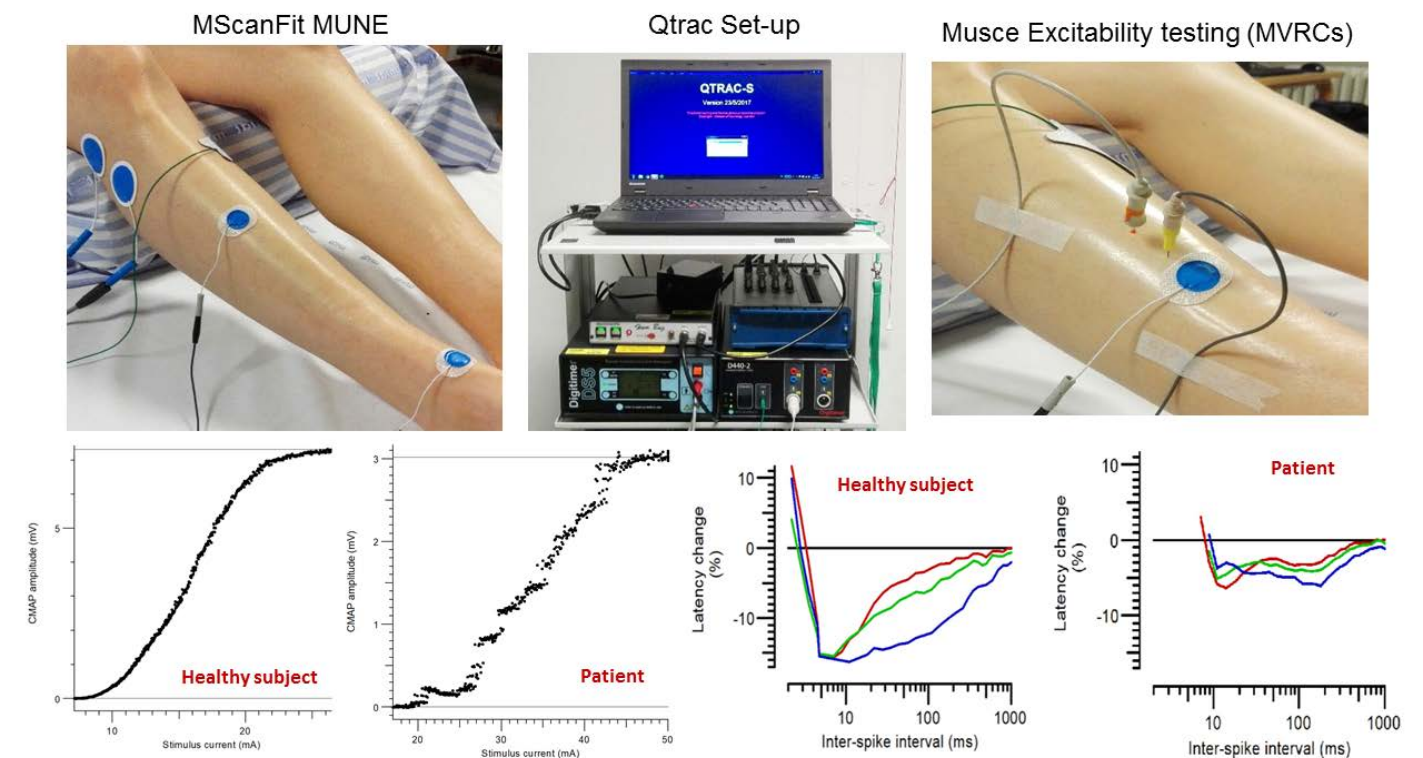


Fig. 1

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Conventional and Threshold-Tracking Transcranial Magnetic Stimulation (TMS)

Most single-pulse transcranial magnetic stimulation (TMS) parameters (e.g., motor threshold, stimulus-response function, cortical silent period) are used to examine corticospinal excitability. Paired-pulse TMS paradigms (e.g., short- and long-interval intracortical inhibition (SICI/LICI), short-interval intracortical facilitation (SICF), and short- and long-latency afferent inhibition (SAI/LAI)) provide information about intracortical inhibitory and facilitatory networks. This has long been done by the conventional TMS method of measuring changes in the size of the motor-evoked potentials (MEPs) in response to stimuli of constant intensity, so-called for example amplitude SICI (A-SICI). An alternative threshold-tracking approach has recently been introduced whereby the stimulus intensity for a target amplitude is tracked, so-called for example threshold tracking SICI (T-SICI).

The limitation of the conventional methodologies are the manual operation, poor reproducibility and time-consumption. To overcome these limitations, our research group developed a menu-driven suite of semi-automatic programs to facilitate the broader use of threshold-tracking TMS techniques and to enable direct comparisons with conventional amplitude measurements (Fig 1). The method is easy to use and fast. Each protocol takes approximately 10 minutes. We have shown the good reliability and repeatability of SICI in healthy subjects and the sensitivity and specificity of A-SICI and T-SICI in ALS (Fig 2).

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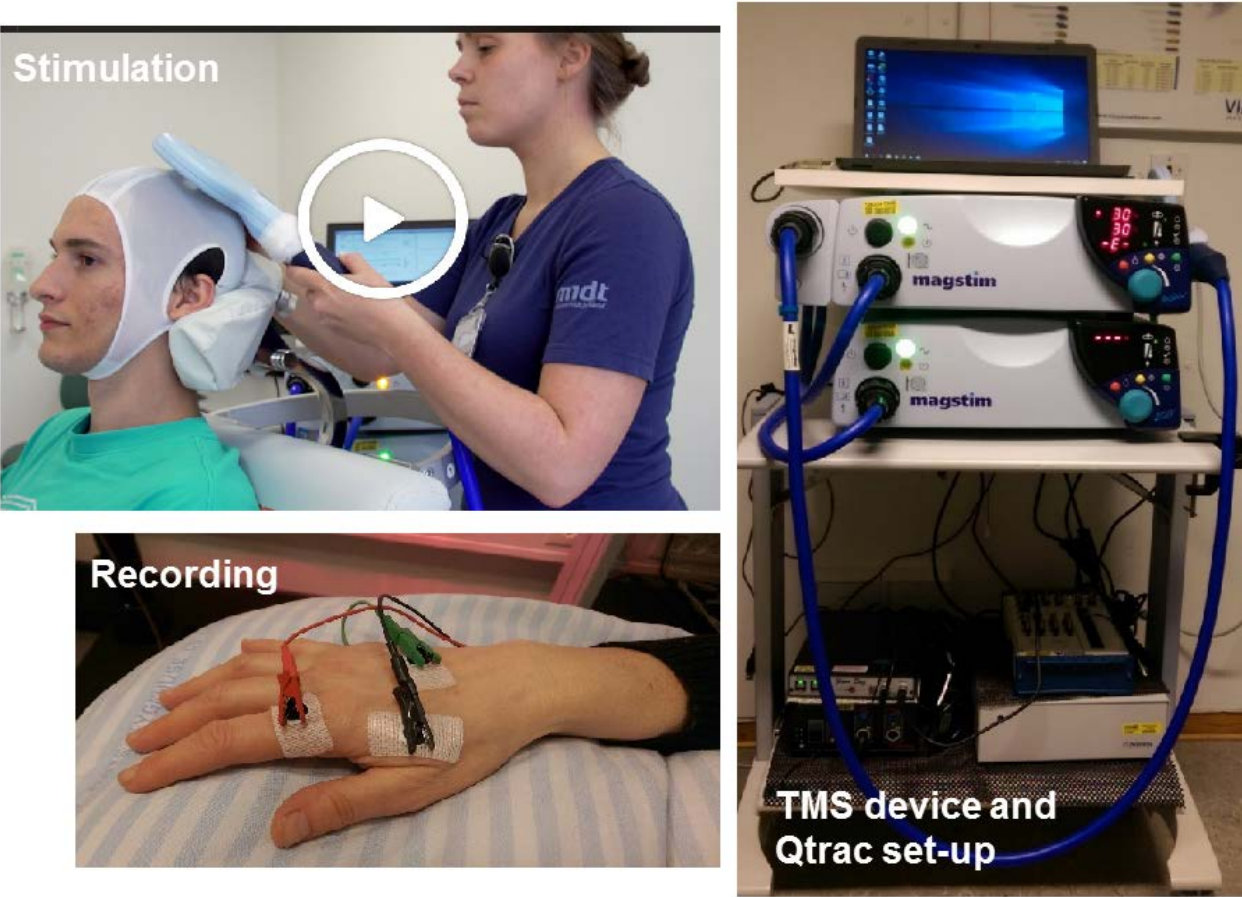


Fig. 1

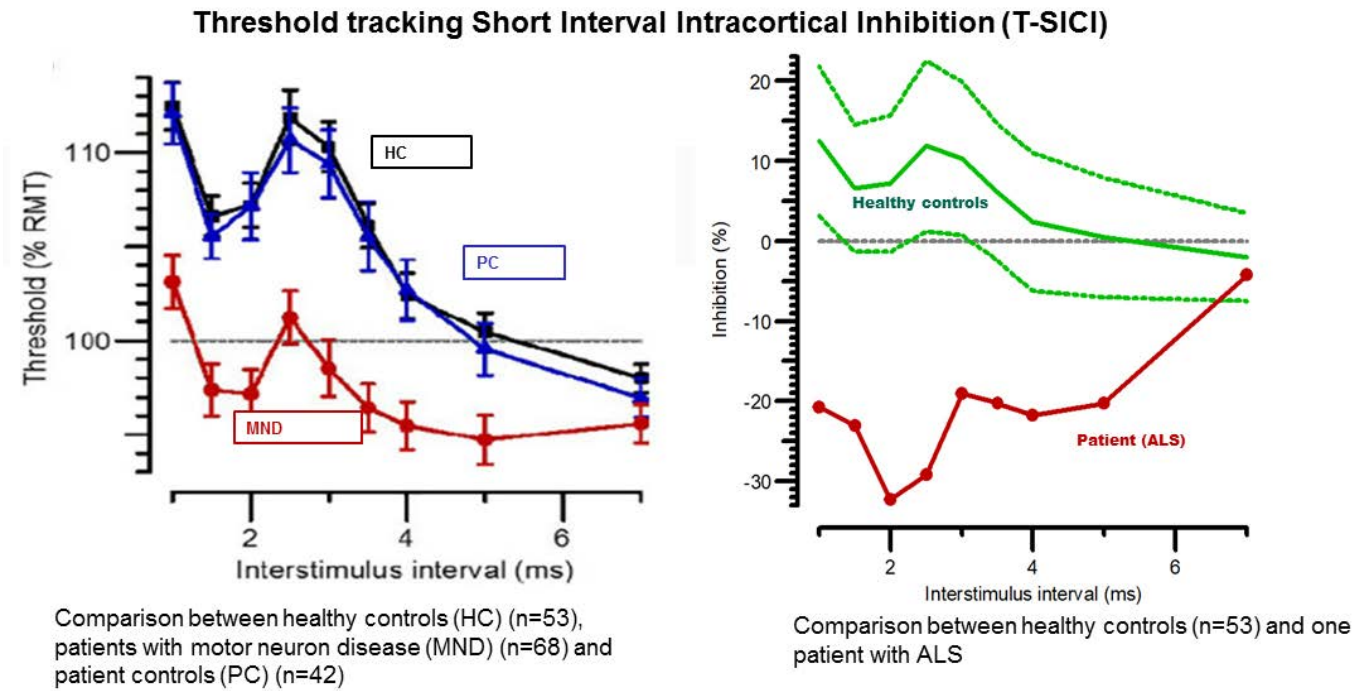


Fig. 2

Nerve and muscle ultrasound

By: Erisela Qerama

High resolution ultrasound har become an important part of our diagnostic work-up. We are examining its feasibility in visualisation of muscles and nerves in different diseases. The muscles stabilizing the scapulae are difficult to examine with an EMG needle and we turned to Ultrasound guided EMG examination to increase the yield of our diagnostic ability.

We looked at those muscles in 27 patients with scapula alata and 41 healthy subjects and found that ultrasound could differentiate patients with long thoracis nerve palsy and healthy patients and we propose that Ultraosund should be implemented as a supplement to the electrodiagnosis in the work up og patients with scapular winging. Two articles are published from this work .

Intraoperative neurophysiological monitoring

Intraoperative neurophysiological monitoring is a well established field of neurophysiological methods applied in the operation theatre. IOM during spinal and cranial surgeries has been shown to be a useful tool in the hands of neurosurgeons during tumor resection or spinal reconstructions. In this status article it was presented evidence for the combination of direct

cortex stimulation with strip and mapping in increasing the likelihood of safe resection, thereby reducing the risk of mechanically induced tissue damage. The cooperation between the three main actors, ie. the anesthesiologist, surgeon and neurophysiologist is shown to be crucial for the successful implementation of the method.

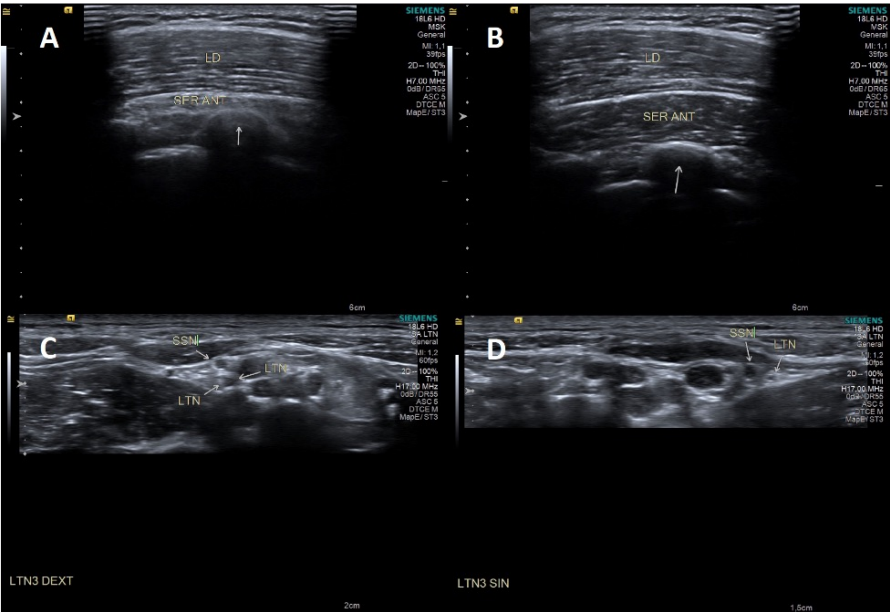


Figure Ultrasound images from a patient with medial winging. Symptomatic side is on the right side. LD: Latissimus dorsi muscle. SER ANT: Serratus anterior muscle. SSN: Suprascapular nerve. LTN: Long thoracic nerve.

A: The serratus anterior muscle on the symptomatic, right side. This muscle is seen right below the latissimus dorsi muscle. The white arrow is pointing at the underlying rib. The serratus anterior muscle is atrophied compared to image B.

C: The long thoracic nerve on the symptomatic, right side. Here, in relation to the suprascapular nerve. The long thoracic nerve is enlarged on this side compared to image D: Here, the long thoracic nerve is seen on the asymptomatic, left side. Again, in relation to the suprascapular nerve.

Animal studies

In this porcine model of donation after circulatory death , neurophysiological methods such as EEG and SSEP were used along side with measuring cerebral blood perfusion, temperature, and oxygen tension of the brain during resuscitation with normothermic regional perfusion (NRP) and following clamping or non clamping of the arch vessels.

In the non clamp group, a return of brain activity with the presence of EEG, SSEP response was seen following NRP, whereas clamping of the arch vessels stopped cerebral circulation and function indicated by the absence of cerebral perfusion parameters, isoelectric EEG and no-SSEPs, suggesting that clamping is necessary to avoid restoring cerebral circulation during NRP.

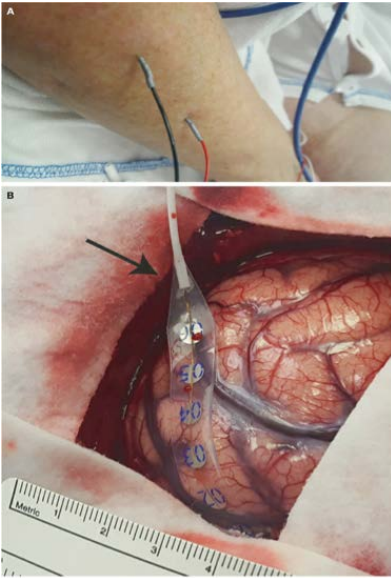


Figure shows EMG needle electrodes in Extensor dig. communis muscle and Cortical Strip Electrode on an eloquent region of the cortex.

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