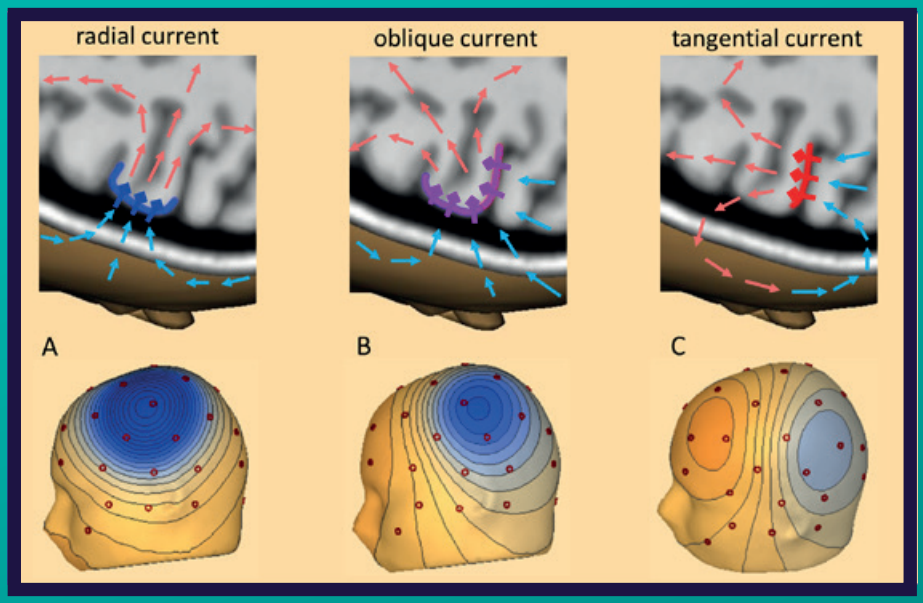


RESEARCH REPORT 2018-2019

DEPARTMENT OF CLINICAL NEUROPHYSIOLOGY
AARHUS UNIVERSITY HOSPITAL

AARHUS UNIVERSITY

Aarhus University Hospital

CONTENT

DEPARTMENT OF **CLINICAL NEUROPHYSIOLOGY**

The research group:
Two professors
One guest professor
Three associate professors
Three postdocs
Four postgraduate (PhD) students
Seven research year (graduate) students
One research intern
One research assistant

70
Published papers in peer-reviewed international journals listed on PubMed

39
Contributions at 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 specialised 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 two professors, three associate professors, three postdocs and four postgraduate (PhD) students. The research group uses facilities at Aarhus University Hospital.

In 2018 and 2019, we published 70 papers in peer-reviewed international journals listed on PubMed. At the International Congress of Clinical Neurophysiology (May 2018) our department contributed with a total of 20 presentations/posters/teaching courses. The department also had high presentation at The European Congress of Clinical Neurophysiology (June 2019) with 8 oral presentations and 11 poster presentations.

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.

149 publications, 130 in peer-reviewed journals; H-index: 33.

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

Research interests
- Electrodiagnostics
- Guidelines and pathophysiology in neuromuscular disorders
- MEG and EEG in evaluation for epilepsy surgery.

207 publications, 178 in peer reviewed journals, H-index 43, citations 5933.

Hugh Bostock
MSc in Physiology from University College London (1970)
PhD in Physiology from University College London (1974)
Professor of Neurophysiology from University College London (1996-2009)

Current position
Emeritus professor of Neurophysiology, Institute of Neurology, University College, London. Employed as Guest Professor at the Department of Clinical Neurophysiology, Aarhus University Hospital, Denmark for six months in 2018-2019. The employment was granted by Lundbeck Foundation, grant number R290-2018-751.

Research interests
Professor Bostock is the pioneer of threshold tracking methods applied to human nerve, muscle and cortical excitability, in health and disease. In addition to his extensive work in ion channels in myelinated axons, their alteration in disease, and improved understanding by computer modelling he has also done microneurographic studies on C fibres in normal subjects and in patients suffering from pain.
Number of Pubmed indexed publications: 172
H-index: 58, Number of citations: 10.374

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.

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
Associate professor, consultant

Research interests
- Peripheral nervemuscle 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.

Main supervisor for 2 and co-supervisor for 6 PhD students.
74 peer-reviewed and PubMed indexed articles. H-index: 12.

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.

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

Published 53 scientific publications in peer-reviewed journals, 12 book chapters, 79 abstracts and 42 oral presentations.

Alexander Hess Lindberg-Larsen

MD from University of Kiel (1995)
Dr. med. from University of Kiel (1996)
Specialist in Clinical Neurophysiology (2004)

Current position
Consultant in clinical neurophysiology, Odense University Hospital

Research interest
EEG in non-convulsive status epilepticus
Seizure detection
Sleep medicine

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.

At the moment co-supervisor for one PhD student, and one student in special honors research program. Clinical supervisor for residents in neurology in research and clinical training, 1-2 residents per year. Main superviser for 5 completed research year students and co-supervisor for one completed PhD student.

Published 28 articles in peer-reviewed international journals. H-index 15.

THE **RESEARCH** GROUP

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.

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 multicenter 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.

Jesper Jeppesen

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

Current position
Postdoc

Research interests
- Seizure detection
- Biosignal analysis
- Seizure alarm systems.

PhD entitled: Detecting epileptic seizures with hart 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.

Alexander Gramm Kristensen

MD from Aarhus University (2016)

Current position
PhD student at Danish Pain Research Center, Department of Clinical Medicine, Aarhus University and Department of Clinical Neurophysiology, Aarhus University Hospital.

Research interests
- Nerve excitability
- Nerve conduction studies
- Motor unit number estimation
- Diabetic neuropathy
- Deep learning
- Neurology
- Neural implants.

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.

Agnes Hauschultz Witt

MD from Aarhus University (2008)
Resident at Department of Internal Medicine and Neurology (2008-2016)

Current position
PhD student at Department of Clinical Neurophysiology.

Research interests
- The peripheral nervous system in patients with spinal cord injury using novel techniques as threshold tracking to examine nerve excitability and motor unit number estimation (axonal loss) to see if complications as spasticity and neuropathic pain are related to changes in the peripheral nervous system
- I also examine muscle membrane properties using muscle velocity recovery cycle after nerve lesion.

Mustafa Aykut Kural

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

Current position
Scientific Assistant
From February 2018 PhD student at Department of Clinical Neurophysiology

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

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

Zahra Nochi

M.Sc Microbiology - Azad University, Sceince and Research Branch, Tehran, Iran (2007)
PhD Medicine - Aarhus University, Research Unit for Molecular Medicine, Department of Clinical Medicine, Aarhus, Denmark (2016)

Current position
Postdoc at Danish Pain Research Center, Department of Clinical Medicine, Aarhus University and Department of Clinical Neurophysiology, Aarhus University Hospital

Research interests
- Peripheral nervemuscle excitability tests with threshold tracking
- Pain model / biomarker

Rikke Søgaard Kristensen

5th year medical student at Aarhus University. Has experience in teaching fellow medical students and from volunteer board work, but is novel in research.

Finished a research year project at the Department of Clinical Neurophysiology in 2018. The project was entitled: Two novel electrophysiological methods in the evaluation of ALS and myopathy patients, MScan MUNE and MVRC.

Was awarded 2nd place in oral presentation competition at "33rd National Congress of Neurophysiology, EEG-EMG" (Antalya, Turkey) in April 2017.

Sara Silkjær Bak

3rd year medical student (BSc in medicine 2016) at Aarhus University

Current position
Research year student at the 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.

Selim Kilic

6th year medical student (BSc. Med 2015 at Aarhus University)

Current position
Medical student at Aarhus University, former Research Year Student at the Department of Clinical Neurophysiology, Aarhus University Hospital

Research interests
- The diagnostic value of high-resolution ultrasound in peripheral nerve disease
- Correlation between clinical ultrasound and neurophysiology measurements.

Cecilie Qvortrup

Bachelor's degree Psychology and Neuroscience, Maastricht University, The Netherlands (2018)

Current position
Research intern at Department of Clinical Neurophysiology, Aarhus University Hospital.

Research interest
- TMS protocols in terms of ALS pathophysiology
- Intracortical inhibition

Lotte Hardbo Larsen

5th year medical student (BSc in Medicine 2016) at Aarhus University.

Current position
Research Year Student at the Department of Clinical Neurophysiology.

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

Zennia Bruus Zeppelin

5th year medical student at Aarhus University.

Current position
Finished a research half-year project in October 2019 at the Department of Clinical Neurophysiology, at Aarhus University Hospital.

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

Torsten Vinding Merinder

5th year medical student (Bsc. Med 2017) at Aarhus University focusing on presurgical assessment of patients suffering from epilepsy; functional cortical mapping and stimulation manifestations, as well as long-term monitoring and automated seizure detection constructs (ongoing protocol).

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.

THE **RESEARCH** GROUP

Christina Shen-Zhuang Nielsen
5th year medical student (Bsc. Med 2017)
at Aarhus University.

Current position
Medical student at Aarhus University.
Former Research Year Student at Department of Clinical Neurophysiology, Aarhus University Hospital (2017-2018).
Vice Chairman at Selskab for Medicinsk Studenterforskning (student organisation) at Health, Aarhus University.

Research interests
• Pathophysiology in ALS
• Cortical hyperexcitability tests with threshold tracking TMS

Daniel Mosgaard Sørensen

4th 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.

Anna Bystrup Jacobsen

MD from Aarhus University (2018)

Current position
Resident at Department of Neurology

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

POSITIONS **OF TRUST**

Sandor Beniczky
- International League Against Epilepsy (ILAE): Executive Board of ILAE Europe (elected in 2013, re-elected in 2017, treasurer since 2017),
- ILAE Education Council (since 2012).
- ILAE Commission on Diagnostic Methods (since 2017).
- Chair of the Congress Education Taskforce -ILAE.
- Chair of the Joint Taskforce on EEG of the ILAE and International Federation of Clinical Neurophysiology (IFCN).

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

Hatice Tankisi
- Secretary and treasurer of the Executive Committee, International Federation of Clinical Neurophysiology – European Chapter (since 2017).
- Co-chair Clinical Neurophysiology, Scientific Panel, European Academy of Neurology (EAN).

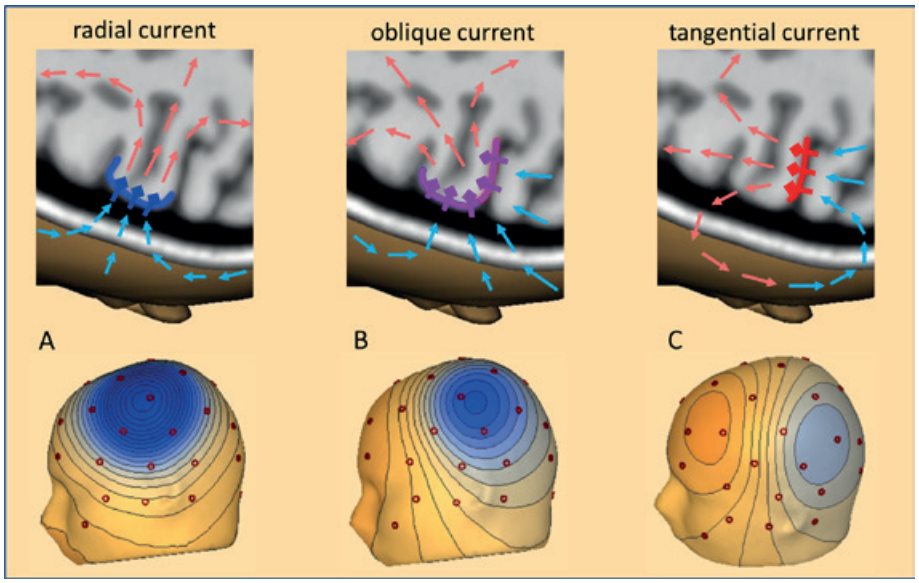
Birger Johnsen
- Danish Society of Clinical Neurophysiology: member of the education committee (since 2007).

Erisela Qerama
- Danish Society of Clinical Neurophysiology: board member (since 2015).

Marit Otto
- Danish Neurological Society: board member (since 2017).

RESEARCH PROJECTS

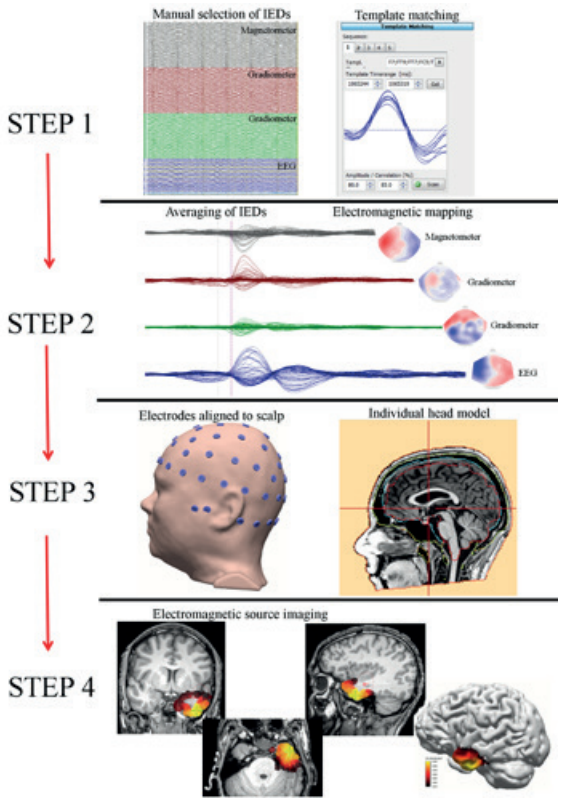
Electromagnetic Source Imaging



Electric and magnetic source imaging methods (ESI, MSI) estimate the location in the brain of the sources generating the interictal epileptiform discharges (II-ESI, II-MSI) and the ictal activity (IC-ESI, IC-MSI). These methods provide potentially valuable clinical information in the presurgical evaluation of patients with drug-resistant focal epilepsy, evaluated for surgical therapy. However, they are still underutilized in most epilepsy centers performing a presurgical evaluation, due to lack of robust clinical validation studies. We have conducted several prospective validation studies on ESI and MSI.

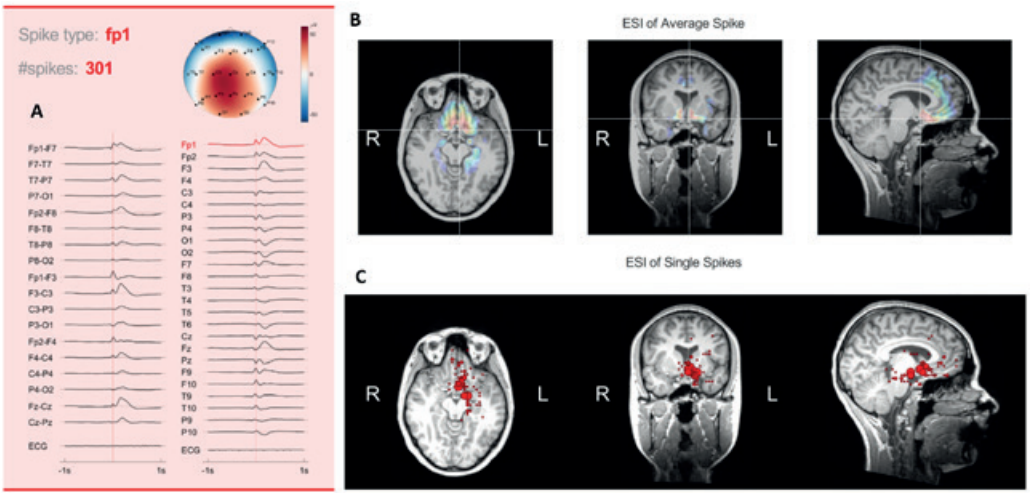
We described a novel method for transforming EEG signals from sensor space into source space. Multiple discrete sources have the power to transform the EEG back into the brain by defining new EEG traces in source space. Using standard source space 25, these can provide for improved clinical interpretation of EEG.

We investigated the clinical utility of ESI in presurgical evaluation. We found that ESI had diagnostic added value in 34% of the patients. In most cases (85.7%), these changes were related to planning of the invasive recordings. In nine out of 13 patients, invasive recordings confirmed the localization. Out of eight patients in whom the ESI source was resected, six became seizure-free.



In a large prospective study we recorded magnetoencephalography (MEG) simultaneously with EEG and performed EMSI, comprising electric source imaging, magnetic source imaging, and analysis of combined MEG-EEG datasets, using 2 different software packages. As reference standard for irritative zone (IZ) and seizure onset zone (SOZ), we used intracranial recordings and for localization accuracy, outcome 1 year after operation. We included 141 consecutive patients. EMSI showed localized epileptiform discharges in 94 patients (67%). Most of the epileptiform discharge clusters (72%) were identified by both modalities, 15% only by EEG, and 14% only by MEG. Agreement was substantial between inverse solutions and moderate between software packages. EMSI provided new information that changed the management plan in 34% of the patients, and these changes were useful in 80%. Depending on the method, EMSI had a concordance of 53% to 89% with IZ and 35% to 73% with SOZ. Localization accuracy of EMSI was between 44% and 57%, which was not significantly different from MRI (49%-76%) and PET (54%-85%). Combined EMSI achieved significantly higher odds ratio compared to electric source imaging and magnetic source imaging.

In a large prospective study we analyzed long-term video-electroencephalography recordings (LTM) of patients admitted for pre-surgical evaluation, and we performed ESI of II and IC signals using two methods, i.e. equivalent current dipole (ECD) and a distributed source model (DSM). LTM recordings employed the standard 25-electrode array (including inferior temporal electrodes). An age-matched template head model was used for source analysis. Results were compared with intracranial recordings, conventional neuroimaging methods [magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT)] and outcome at 1 year after surgery. A total of



87 consecutive patients were analysed. ECD gave a significantly higher proportion of patients with localized focal abnormalities (94%) compared with MRI (70%), PET (66%) and SPECT (64%). Agreement between the ESI methods and intracranial recording was moderate to substantial (k = 0.56-0.79). A total of 54 patients were operated (47 patients more than 1 year ago) and 62% of them became seizure-free. The localization accuracy of II-ESI was 51% for DSM and 57% for ECD, and that for IC-ESI was 51% for DSM and 62% for ECD. The differences between the ESI methods were not significant. Differences in localization accuracy between ESI and MRI (55%), PET (33%) and SPECT (40%) were not significant.

The implementation of ESI is limited by the lack of expertise in this field. Automatization of ESI could solve this problem. In a retrospective study we investigated the accuracy of an automated method. Accuracy was 61% (95% CI: 45-76%) for the fully automated approach and 78% (95% CI: 62-89%) for the semi-automated approach. Automated ESI will contribute to increased utilization of source imaging in the presurgical evaluation of patients with epilepsy.

We performed a systematic review and meta-analysis of ESI and MSI in presurgical evaluation. We found evidence for the accuracy of source imaging in presurgical evaluation of patients with drug-resistant focal epilepsy. These methods have high sensitivity (up to 90%) and diagnostic odds ratio (up to 7.9), but the specificity is lower (up to 54%). ESI and MSI should be included in the multimodal presurgical evaluation.

PAPERS

Sharma P, Seeck M, Beniczky S. Accuracy of Interictal and Ictal Electric and Magnetic Source Imaging: A Systematic Review and Meta-Analysis. Front Neurol. 2019 Dec 3;10:1250. doi: 10.3389/fneur.2019.01250. eCollection 2019.

Scherg M, Berg P, Nakasato N, Beniczky S. Taking the EEG Back Into the Brain: The Power of Multiple Discrete Sources. Front Neurol. 2019 Aug 20;10:855. doi: 10.3389/fneur.2019.00855.

Foged MT, Martens T, Pinborg LH, Hamrouni N, Litman M, Rubboli G, Leffers AM, Ryvlin P, Jespersen B, Paulson OB, Fabricius M, Beniczky S. Diagnostic added value of electrical source imaging in presurgical evaluation of patients with epilepsy: A prospective study. Clin Neurophysiol. 2020 Jan;131(1):324-329. doi: 10.1016/j.clinph.2019.07.031.

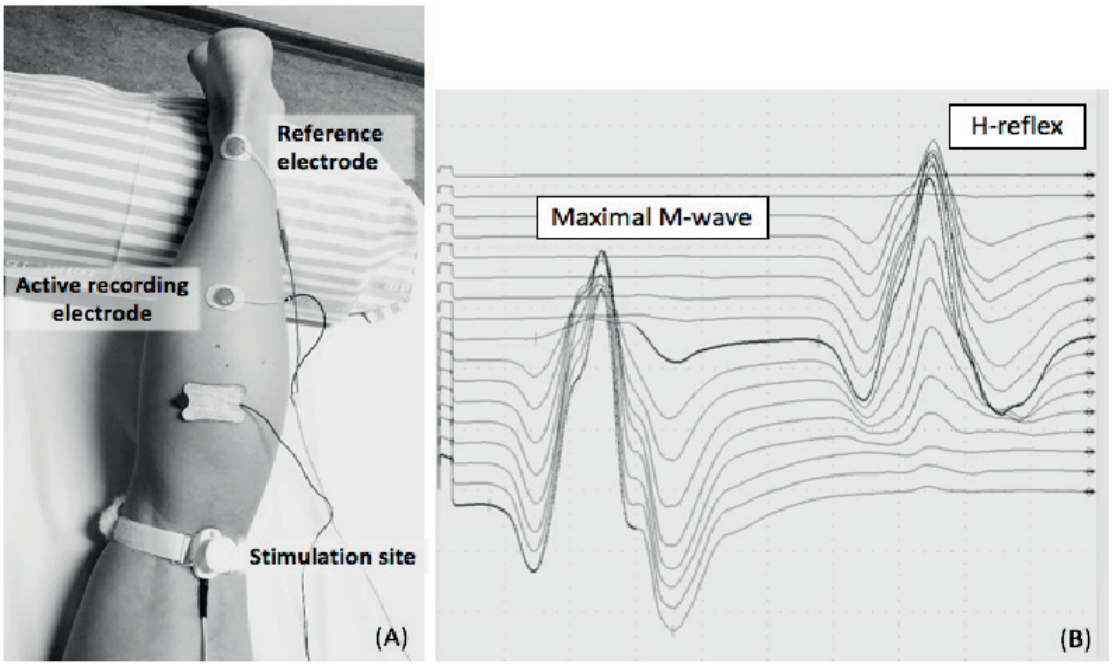
Duez L, Tankisi H, Hansen PO, Sidenius P, Sabers A, Pinborg LH, Fabricius M, Rásonyi G, Rubboli G, Pedersen B, Leffers AM, Uldall P, Jespersen B, Brennum J, Henriksen OM, Fuglsang-Frederiksen A, Beniczky S. Electromagnetic source imaging in presurgical workup of patients with epilepsy: A prospective study. Neurology. 2019 Feb 5;92(6):e576-e586. doi: 10.1212/WNL.0000000000006877.

Baroumand AG, van Mierlo P, Strobbe G, Pinborg LH, Fabricius M, Rubboli G, Leffers AM, Uldall P, Jespersen B, Brennum J, Henriksen OM, Beniczky S. Automated EEG source imaging: A retrospective, blinded clinical validation study. Clin Neurophysiol. 2018 Nov;129(11):2403-2410. doi: 10.1016/j.clinph.2018.09.015.

Sharma P, Scherg M, Pinborg LH, Fabricius M, Rubboli G, Pedersen B, Leffers AM, Uldall P, Jespersen B, Brennum J, Henriksen OM, Beniczky S. Ictal and interictal electric source imaging in pre-surgical evaluation: a prospective study. Eur J Neurol. 2018 Sep;25(9):1154-1160. doi: 10.1111/ene.13676.

Utility of the H-reflex in diagnosing polyneuropathy

An absent Hoffman (H)-reflex, the electrophysiological equivalent of the Achilles reflex, is assumed to be one of the first detectable signs of polyneuropathy (PNP). In this study we compare the H- and Achilles reflexes in patients with suspected PNP to evaluate the diagnostic utility of the H-reflex. Data from clinical examination and nerve conduction studies (NCS) were analyzed in patients with suspected PNP. The PNP diagnosis was confirmed by follow-up in 209 patients. The sensitivities of the H- and Achilles reflexes were similar (70.3% vs 71.8%), whereas the H-reflex had higher specificity (85.2% vs 70.5%) (P <.001). Adding H-reflex to the NCS protocol increased the diagnostic sensitivity from 80.9% to 87.6%. The H-reflex is a sensitive method that could provide added value to standard NCS in PNP diagnosis. The simplicity and high specificity make it superior to its clinical equivalent, the Achilles reflex.



The H-reflex setup (A) and the electrophysiological response with the H-reflex and M-wave (B). Note that a maximal stimulation gives no H-reflex response.

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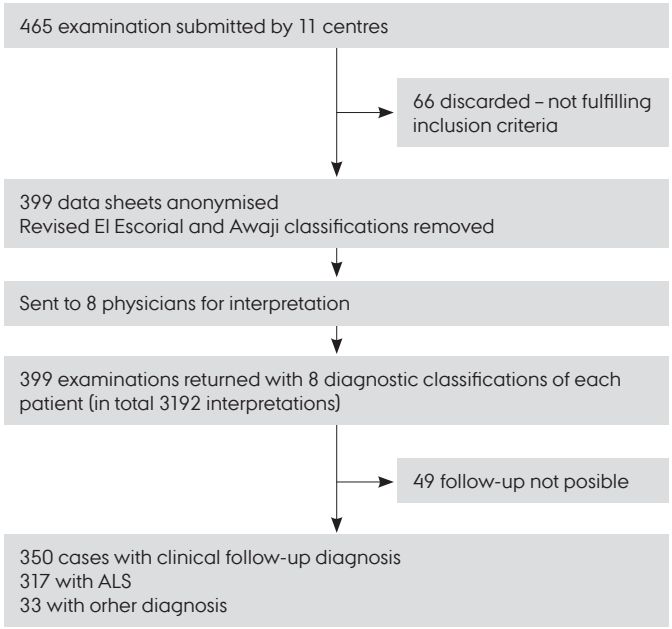
Teigland OH, Pugdahl K, Fuglsang-Frederiksen A, Tankisi H. Utility of the H-reflex in diagnosing polyneuropathy. Muscle Nerve. 2019 Oct;60(4):424-428.

Multicentre work on diagnostic guidelines

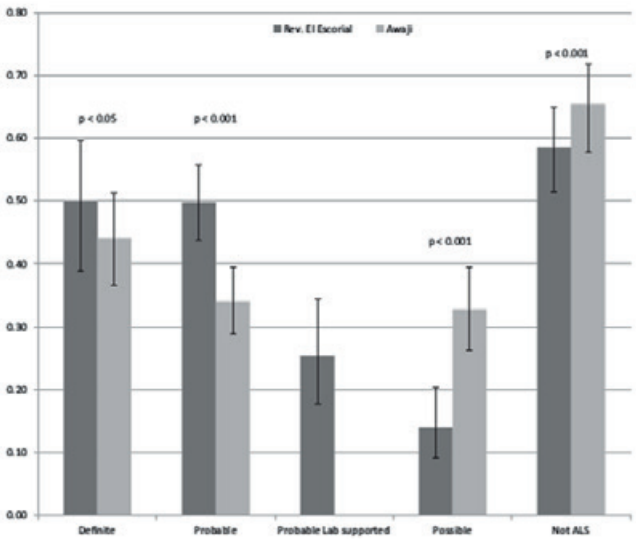
Amyotrophic lateral sclerosis (ALS) is a severe disease characterized by progressive paresis due to the dying of motor neurons in the brain and spinal cord. Despite some improvement in diagnostic sensitivity claimed with the introduction of the more electrodiagnostically oriented Awaji-Shima amendment to the revised El Escorial criteria in 2007, the criteria still have a modest sensitivity (~70%) and are often considered rather complex to use. This was documented in the large multicentre study 'Diagnostic criteria for amyotrophic lateral sclerosis: A multicentre study of inter-rater variation and sensitivity' involving 11 centres from different European countries, which revealed only low to modest inter-rater agreement in the application of both sets of criteria among experienced clinicians. A sensitivity of 64% for the revised El Escorial criteria was shown, which is consistent with previous reports. In contrast, the study showed no benefit of using the Awaji algorithm (sensitivity 63%).

The above study incited the European multicentre collaboration ESTEEM led by the Department of Neurophysiology in Aarhus to develop more simple criteria with neurophysiological results being the central part. The work is currently ongoing with the developed criteria being validated in a large multicentre trial. The group is additionally working on diagnostic criteria for neuromuscular transmission disorders and myopathy.

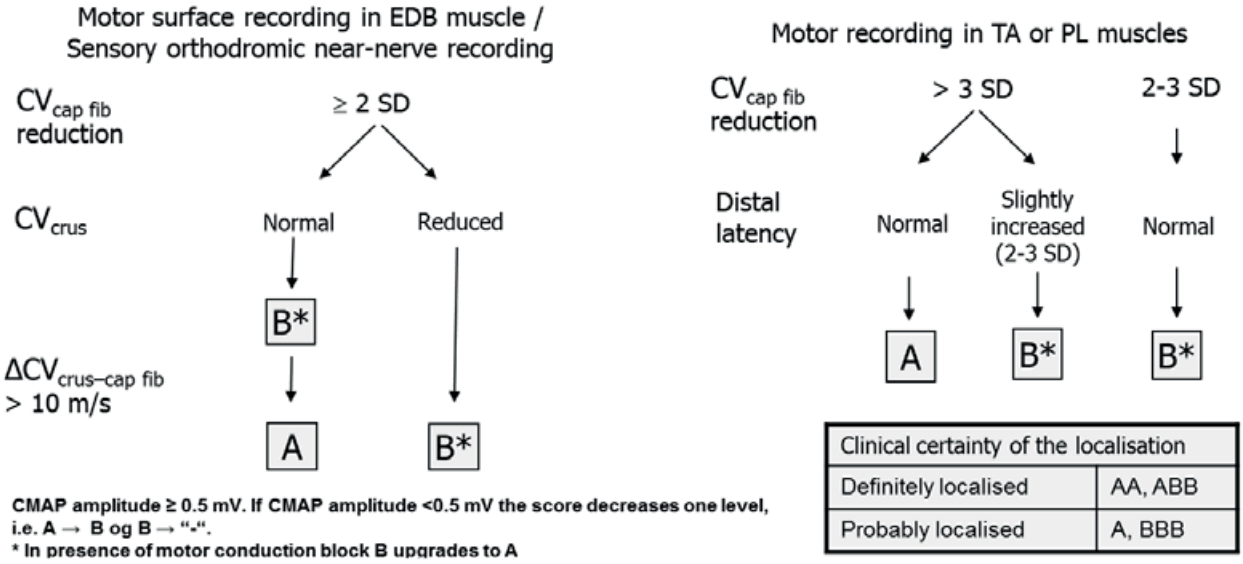
Multicentre development and implementation of electrodiagnostic guidelines is another central issue in a national quality improvement initiative led by our department. The task group has published criteria for the localization of ulnar nerve affection at the elbow and is right now validating suggested criteria for peroneal nerve affection at the fibular head.



INTER-RATER AGREEMENT
ON ALS DIAGNOSTICS CATEGORIES



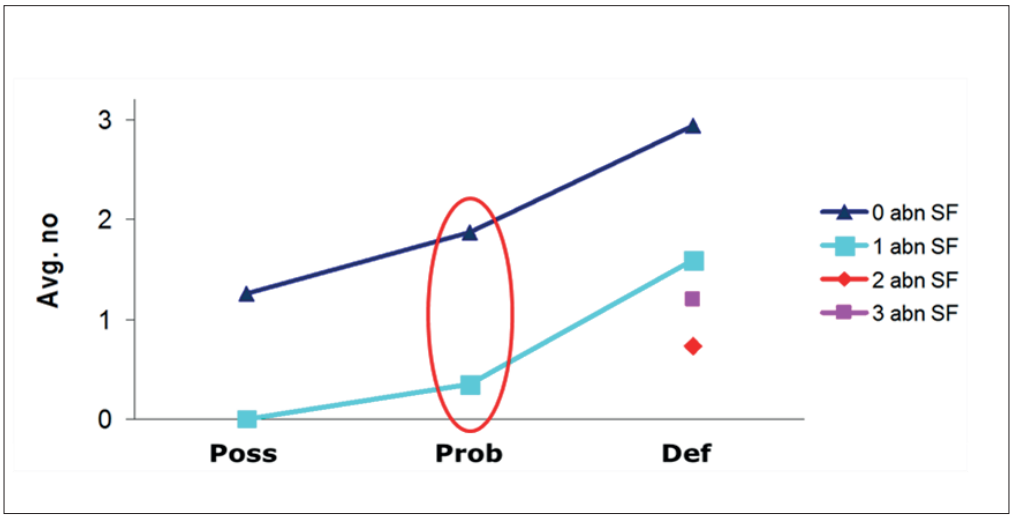
LOCALISATION OF N. PERONEUS AFFECTION



CMAP amplitude ≥ 0.5 mV. If CMAP amplitude <0.5 mV the score decreases one level, i.e. A → B og B → "-".
* In presence of motor conduction block B upgrades to A

Clinical certainty of the localisation	
Definitely localised	AA, ABB
Probably localised	A, BBB

NEUROMUSCULAR TRANSMISSION DISORDERS



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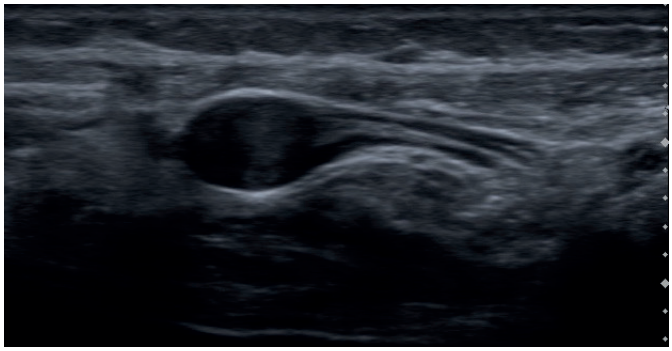
Johnsen B, Pugdahl K, Fuglsang-Frederiksen A, Kollewe K, Paracka L, Dengler R, Camdessanché JP, Nix W, Liguori R, Schofield I, Maderna L, Czell D, Neuwirth C, Weber M, Drory VE, Abraham A, Swash M, de Carvalho M. Diagnostic criteria for amyotrophic lateral sclerosis: A multicentre study of inter-rater variation and sensitivity. Clin Neurophysiol. 2019;130(2):307-314.

Pugdahl K, Johnsen B, Tankisi H, Camdessanché JP, de Carvalho M, Fawcett P, Labarre-Vila A, Liguori R, Nix W, Schofield I, Fuglsang-Frederiksen A. Electrodiagnostic criteria for neuromuscular transmission disorders suggested by a European consensus group. Clin Neurophysiol. 2018;129(Suppl 1):e15.

Nerve and muscle ultrasound



Terminal neuroma in an amputee.

Ultrasound (US) in the field of neuromuscular diseases has become an important tool to understand nerve and muscle pathology. Recent developments in the ultrasound technology with high-resolution tranducers(18-22MHz) have given ultrasound an increasing role in diagnosis of nerve and muscle disorders alongside neurophysiological tests (Qerama E 2019- editorial).

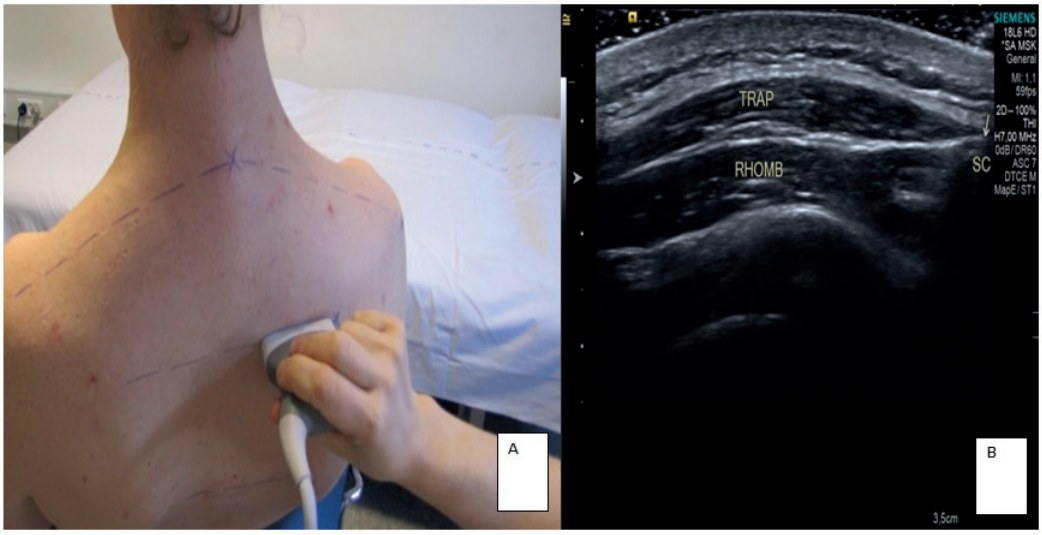
In our lab, we have conducted research with ultrasound techniques since 2008.

We examined the diagnostic role of ultrasound in brachial plexopathies (Jakobsen et al 2019) .We examined 59 healthy subjects (HS) and 42 patients consecutively referred with clinical suspicion of brachial plexopathy with routine electrodiagnostic testing (EDx) as reference standard and a blinded standardised ultrasound examination of the brachial plexus. We found that 64% of patients with EDx diagnosed plexopathy had at least one abnormal level on ultrasound. 60% of normal EDx patients had a normal ultrasound examination at all levels. Ultrasound identified the same abnormal level(s) as EDx in 73% of the patients who had both abnormal EDx and ultrasound results. We concluded that ultrasound examination showed abnormalities in patients with brachial plexopathies in good agreement with EDx and US may be an important supplement to electrodiagnostics in evaluating brachial plexopathies.

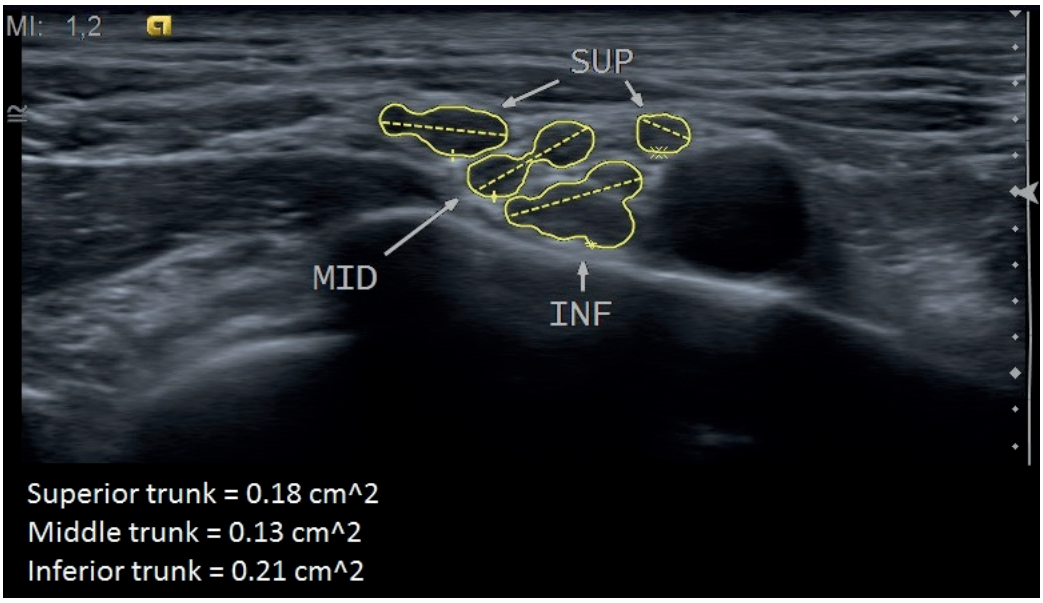
In 2018 in collaboration with the Danish Pain Research center at Aarhus University Hospital and as a part of a PhD study, we looked at the role of ultrasound in identifying neuromas following nerve injury . The neuromas are believed to be involved in both stump and phantom pain in pa¬tients with peripheral nerve injury. In the study by Buch et al 2020 we found that neuromas were present in a similar number of amputees with or without pain. We did not find any differences in stump pain intensity between amputees with and without neuromas. Our findings suggest that the neuromas may not be the source of the postamputation pain.

In 2019 we have looked at the feasibility of ultrasound examination of the muscles stabilizing the scapulae and the corresponding nerves in healthy subjects and patients with scapula alata. We included 41 healthy subjects and 27 patients that underwent a standardized ultrasound examination measuring the thickness of the muscles and nerve diameter of the nerves. We found that US is a feasible method to visualise muscles stabilizing the scapulae and the corresponding nerves. An article is submitted and an article is under preparation.

We also looked at the feasibility of ultrasound of lower extremities nerves in healthy subjects and in patients with common fibular compression neuropathy. In this prospective controlled study, we included 40 healthy controls and 24 patients with an EDX diagnosis of CFCN. We found that patients had a significantly larger common fibular nerve than healthy controls and larger nerve on the symptomatic side. Fascicle comparisons did not yield any significant differences. Further studies with a larger amount of patients and controls should be conducted to elucidate the potential role of HRUS as a supplementary tool in diagnosis of footdrop. An article is under preparation.



Ultrasound of the middle trapezius and the rhomboideus major muscle



Ultrasound of the supraclavicular plexus

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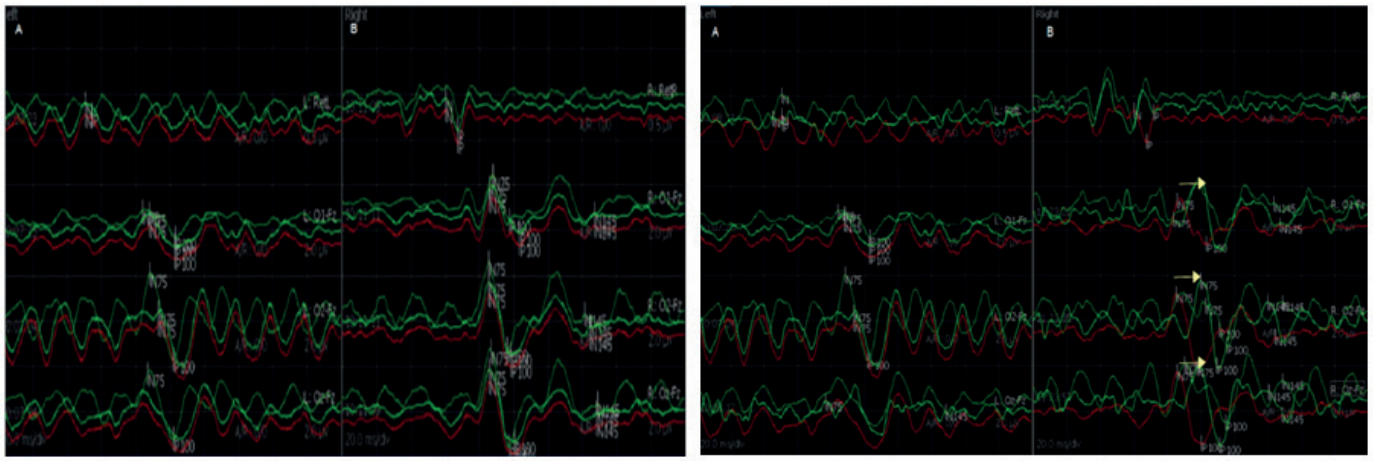
Intraoperative neurophysiological monitoring

Intraoperative neurophysiological monitoring is a relatively fast expanding 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 case we used Intraoperative visual evoked potentials (VEPs) to monitor the function of optic radiation during neurosurgery for a benign meningioma located in the atrium of the right lateral ventricle. We performed flash VEPs and simultaneous recordings of electroretinography alongside with multimodal intraoperative monitoring.

We observed a significant and sustained unilateral latency shift of the P100 component of VEPs, while amplitudes temporarily dropped to 80% of baseline but recovered entirely at the end of surgery. We speculate that the VEP (P100) latency may be a new and valuable indicator (in addition to VEP amplitude) of the visual pathways.

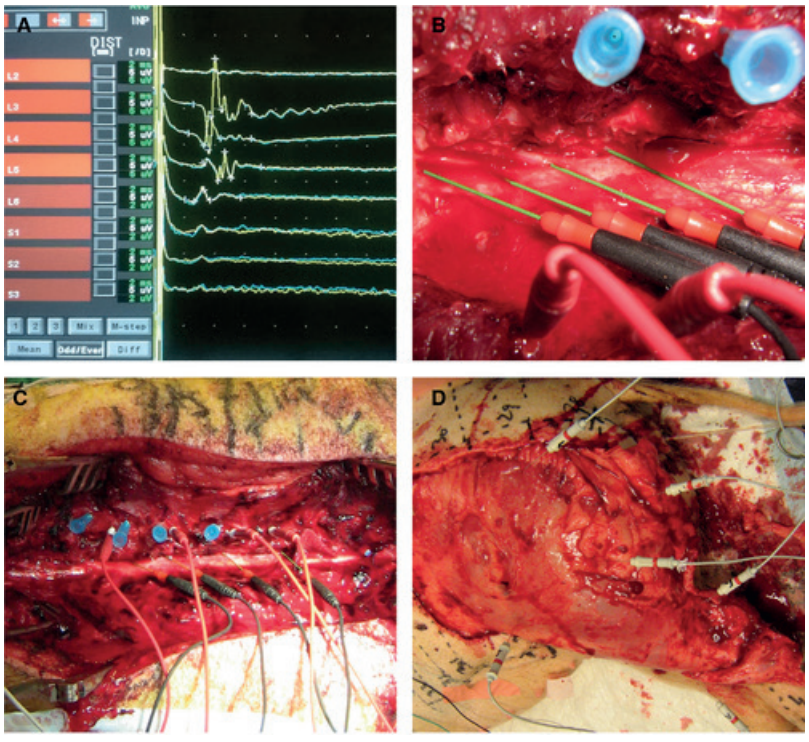


Ultrasound of the supraclavicular plexus

Qerama E, Korshoej AR, Petersen MV, Brandmeier R, von Oettingen G. Latency-shift of intra-operative visual evoked potential predicts reversible homonymous hemianopia after intra-ventricular meningioma surgery. Clin Neurophysiol Pract. 2019 Nov 14;4:224-229. doi: 10.1016/j.cnp.2019.10.004. eCollection 2019.

Animal studies

A extensive understanding of the spinal and peripheral nervous system is a prerequisite for designing human studies , and the classic dermatome map of man serves both as a clinical and experimental tool. The Göttingen minipig is increasingly being used in biomedical research as an attractive alternative to other animal models. In this study we obtained neurophysiological data from skin stimulation and muscle recordings from six adult minipigs that underwent unilateral laminectomy from L2 to S3, exposing the nerve roots . This study enabled us to map the sensory innervation of the Göttingen minipig hind body and provide information about muscular innervation.



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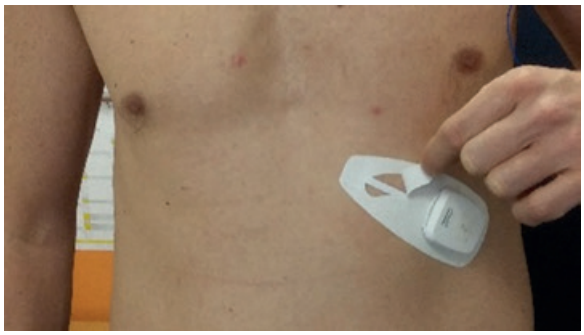
Automated seizure detection



There is need for automated seizure detection using mobile or wearable devices, for objective seizure documentation and decreasing morbidity and mortality associated with seizures. Due to technological development, a high number of articles have addressed non-electroencephalography (EEG)-based seizure detection. However, the quality of study-design and reporting is extremely heterogeneous. Fifteen studies of phase-2 or above, demonstrated that non-EEG-based devices detected generalized tonic–clonic seizures (GTCS) with high sensitivity (≥90%) and low false alarm rate (FAR) (down to 0.2/day). There has been limited published evidence for detection of motor seizures other than GTCS, mostly from subgroups in larger studies, targeting GTCS. There has been little evidence of non-EEG-based detection of non-motor seizures: sensitivity was low (19–74%) with extremely high FAR (50–216/day).

To assess the feasibility and accuracy of seizure detection based on heart rate variability (HRV) using a wearable electrocardiography (ECG) device. In this phase 2 study, we prospectively recruited patients admitted to long-term video–EEG monitoring (LTM). ECG was recorded using a dedicated wearable device. Seizures were automatically detected using HRV parameters computed off-line, blinded to all other data. We compared the performance of 26 automated algorithms with the seizure time-points marked by experts who reviewed the LTM recording. Patients were classified as responders if >66% of their seizures were detected. We recruited 100 consecutive patients and analyzed 126 seizures (108 non-convulsive and 18 convulsive) from 43 patients who had seizures during monitoring. The best performing HRV algorithm combined a measure of sympathetic activity with a measure of how quickly HR changes occurred. The algorithm identified 53.5% of the patients with seizures as responders. Among responders, detection sensitivity was 93.1% (95% CI: 86.6%-99.6%) for all seizures and 90.5% (95% CI: 77.4%-97.3%) for non-convulsive seizures. The FAR was 1.0/24 h (0.11/night). Median seizure detection latency was 30 s. Typically, patients with prominent autonomic nervous system changes were responders: An ictal change of >50 heartbeats per minute predicted who would be responder with a positive predictive value of 87% and a negative predictive value of 90%.

The automated HRV algorithm, using ECG recorded with a wearable device, has high sensitivity for detecting seizures, including the non-convulsive ones. FAR was low during the night. This approach is feasible in patients with prominent ictal autonomic changes.

PAPERS

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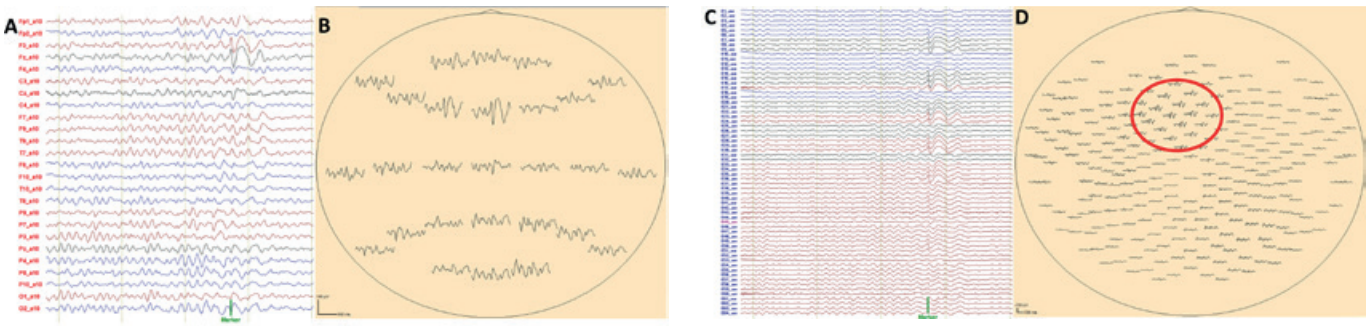
Standardization and quality assurance in clinical electroencephalography



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

Our group contributed to this in several areas of clinical neurophysiology. We demonstrated that recording duration is more important for the diagnostic yield of EEGs than increasing spatial sampling beyond the standard IFCN electrode array and we proved the diagnostic added value of sleep EEG recordings. We contributed to the IFCN guideline on EEG in epilepsy. The guideline was prepared in response to gaps present in epilepsy related neurophysiological assessment. It summarizes the scientific evidence for the utility of EEG when diagnosing and monitoring PWE.

PAPERS

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Muscle velocity recovery cycles in neuromuscular disorders

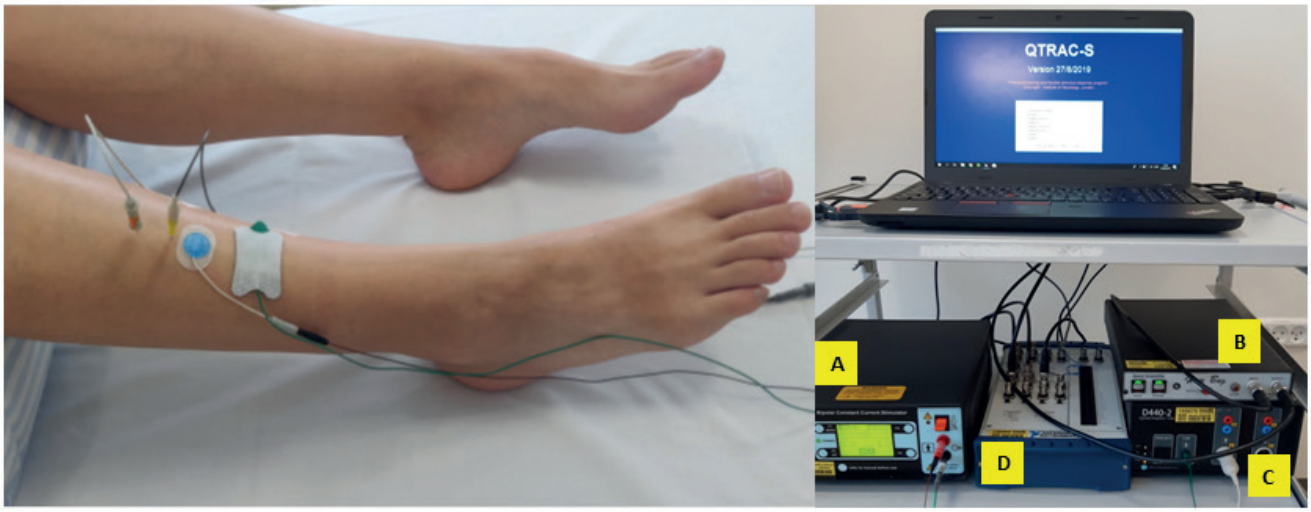

Fig. 1

Nerve conduction studies (NCS) and electromyography (EMG) are the conventional electrophysiological methods used for the diagnosis of neuromuscular disorders. However, NCS or EMG provide limited information about muscle fibre membrane properties and underlying disease mechanisms. Muscle Velocity Recovery Cycles (MVRC) is a novel electrophysiological method enabling in vivo assessment of changes in muscle membrane potential and alterations of muscle ion channel function in pathology (Fig. 1)

In a recent study (Witt et al., 2019), we showed for the first time the applicability of MVRC in neurogenic muscles. We examined muscle membrane properties in neurogenic muscles on 47 patients referred to NCS and EMG for peroneal nerve entrapment neuropathy. In addition to conventional NCS/EMG, all subjects were examined with MVRC in anterior tibial muscle. This provided parameters of muscle relative refractory period (MRRP) and early supernormality (ESN) and late supernormality (LSN). The results were compared with 29 age-matched healthy control subjects. MRRP was prolonged and ESN and LSN were reduced in neu-

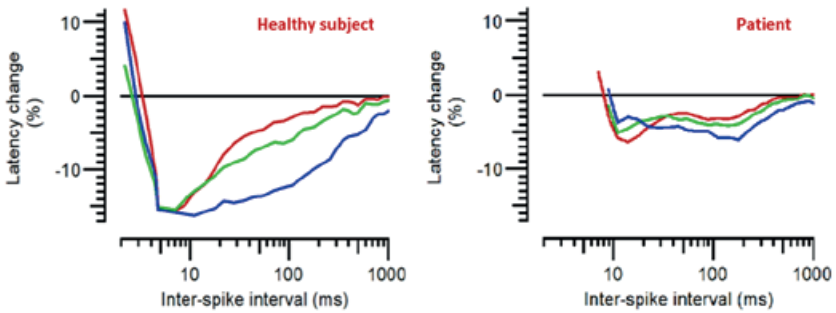

Fig. 2

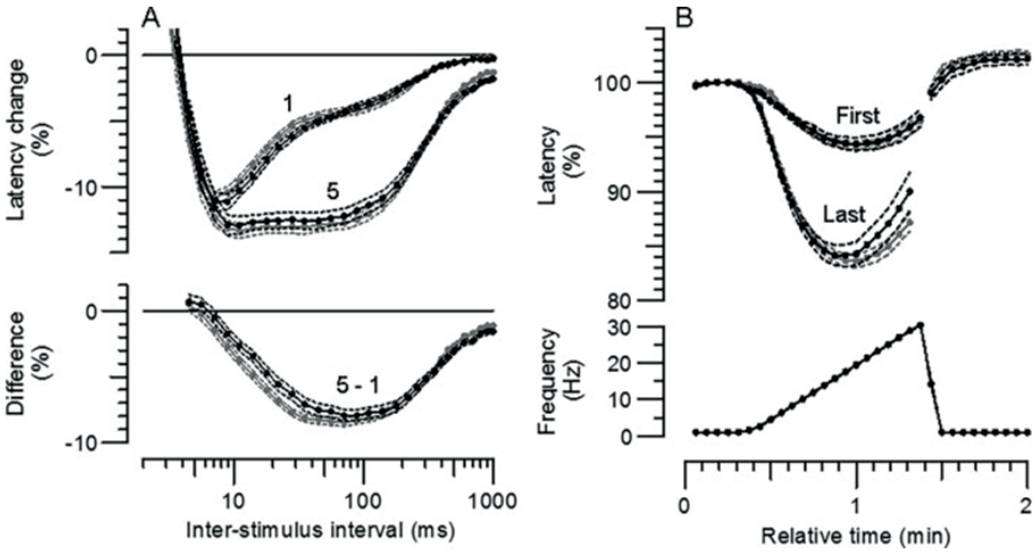

Fig. 3 8A) Upper plot: Muscule velocity recovery cycles (MVRCs) in ALS patients (n=26, black) compared to normal controls (n=25, grey) following 1 and 5 conditioning stimuli, and Lower plot: The differences between 1 and 5 conditioning stimuli. (B) Muscle frequency ramp, showing changes in latency to the first and last stimulus in train af 1 and 30 stimuli delivered in 1 s every 2 s. Means plotted as in A, with controls in grey and ALS patients in black.

rogenic muscles (Fig. 2). MRRP, ESN and LSN correlated to muscle force and incidence of spontaneous activity. MVRC changes provided in vivo evidence of depolarization in intact human muscle fibres that could underlie reduced muscle excitability and hence weakness in neurogenic muscles. MVRCs appeared to be a useful technique for revealing disease mechanism in a broad range of neuromuscular diseases.

In spite of pronounced MVRC changes in neurogenic muscles, application of the method in anterior tibial muscle in patients with amyotrophic lateral sclerosis (ALS) did not show any difference from healthy controls (Kristensen et al., 2019) (Fig. 3). This has been attributed to the unaffected muscle membrane properties, despite substantial denervation, presumably due to collateral reinnervation.

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MScanFit- A novel motor unit number estimation (MUNE) method

Since direct measurement of the number of functioning motor units is not possible in humans, motor unit number estimation (MUNE) techniques have been of interest for several years. All MUNE methods have been shown to be more sensitive than clinical and conventional electrophysiological measures, but for a long time MUNE methods have not gained a place in diagnostics or monitoring disease progression probably due to their limitations.

A limitation of the exsisting MUNE methods, particularly Motor Unit Number Index (MUNIX), which is a method gained popularity in recent years is the dependence of compound muscle action potential (CMAP) amplitude. We have recently shown MUNIX to depend primarily on CMAP amplitude, both in theory and in practice (Bostock et al., 2019) (Fig. 1).

During the last years, consultant Hatice Tankisi and co-workers have worked closely on the development of a nov¬el MUNE method (MScanFit) together with its inventor Professor H. Bostock from London. MScanFit, unlike most other MUNE meth¬ods in use, assesses all the motor units in a muscle by fitting a model to a detailed stimulus-response curve. Furthermore, it is fast and simple to perform.

Our recent study on 26 patients with amyotrophic lateral sclerosis (ALS) showed that MScanFit is a sensitive method in detecting motor unit loss in anterior tibial muscle similar to our previous studies in abductor pollicis brevis both in patients with ALS (Fig. 2) and diabetic neuropathy. In our previous study, we showed similar sensitivity of MScanFit and a tradional MUNE method multipoint stimulation (MPS). However, MPS MUNE took 3 times longer time than MScanFit and MUNIX. We investigated whether a faster modification of MPS MUNE using five surface motor unit action potentials (sMUAP) was comparable to 10. The faster modification of MPS MUNE by sampling five sMUAP had similar reproducibility, sensitivity, and specificity as 10 and we concluded that this faster modification may be suggested in future research and clinical practice (Fig. 3).

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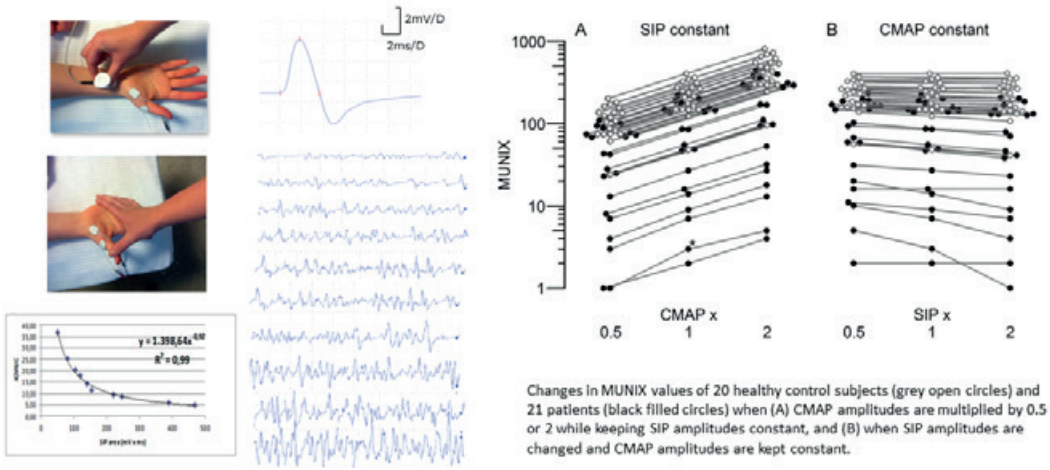
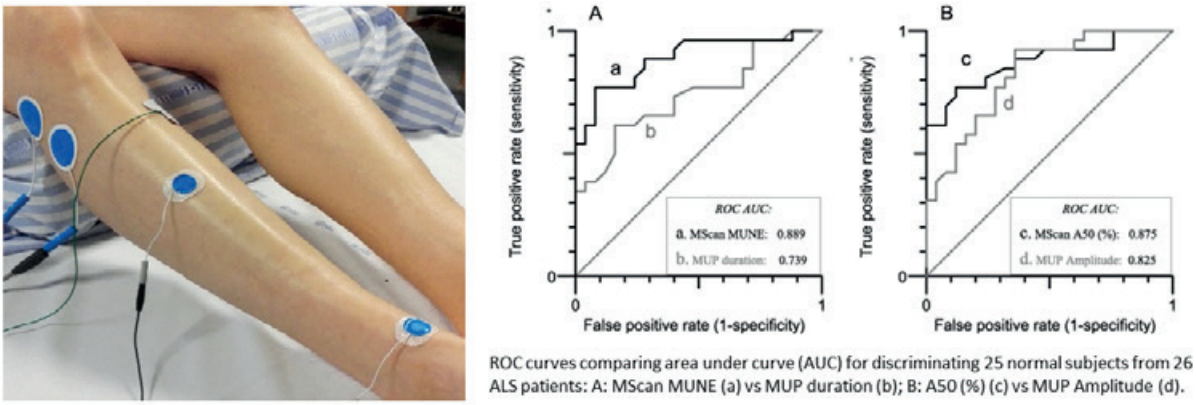


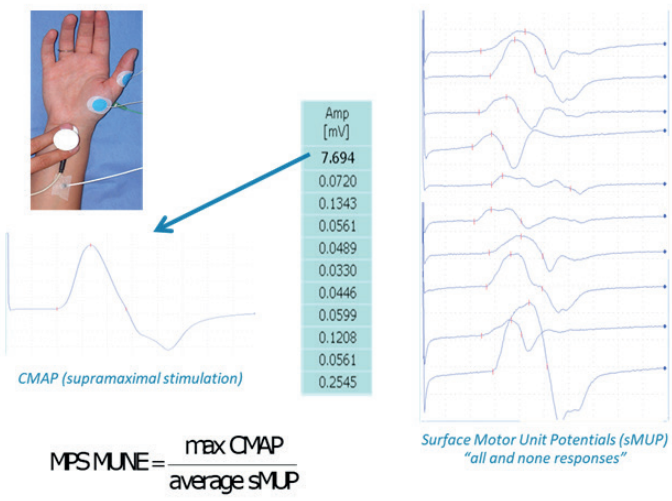
Changes in MUNIX values of 20 healthy control subjects (grey open circles) and 21 patients (black filled circles) when (A) CMAP amplitudes are multiplied by 0.5 or 2 while keeping SIP amplitudes constant, and (B) when SIP amplitudes are changed and CMAP amplitudes are kept constant.

Fig. 1



ROC curves comparing area under curve (AUC) for discriminating 25 normal subjects from 26 ALS patients: A: MScan MUNE (a) vs MUP duration (b); B: A50 (%) (c) vs MUP Amplitude (d).

Fig. 2



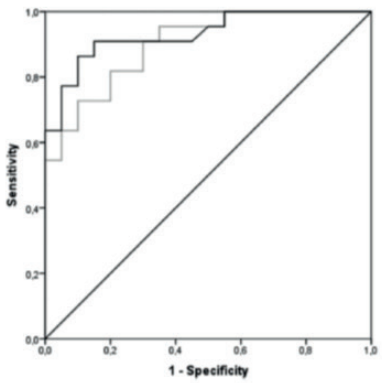


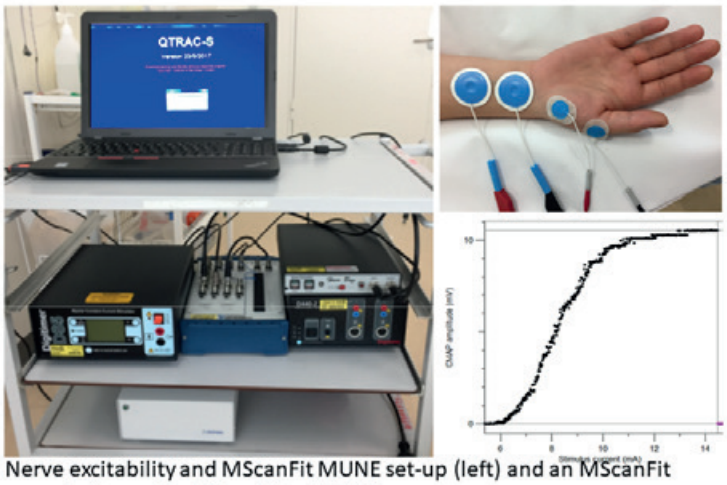
FIG. 1. ROC curves showed an excellent accuracy for ROC MUNE using either 5 (AUC = 0.900—grey line) or 10 sMUAP (AUC = 0.931—black line) in distinguishing between MND patients and controls. ROC, receiver operating characteristics; MUNE, motor unit number estimate; AUC, area under the curve; sMUAP, surface motor unit action potential.

Fig. 3

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

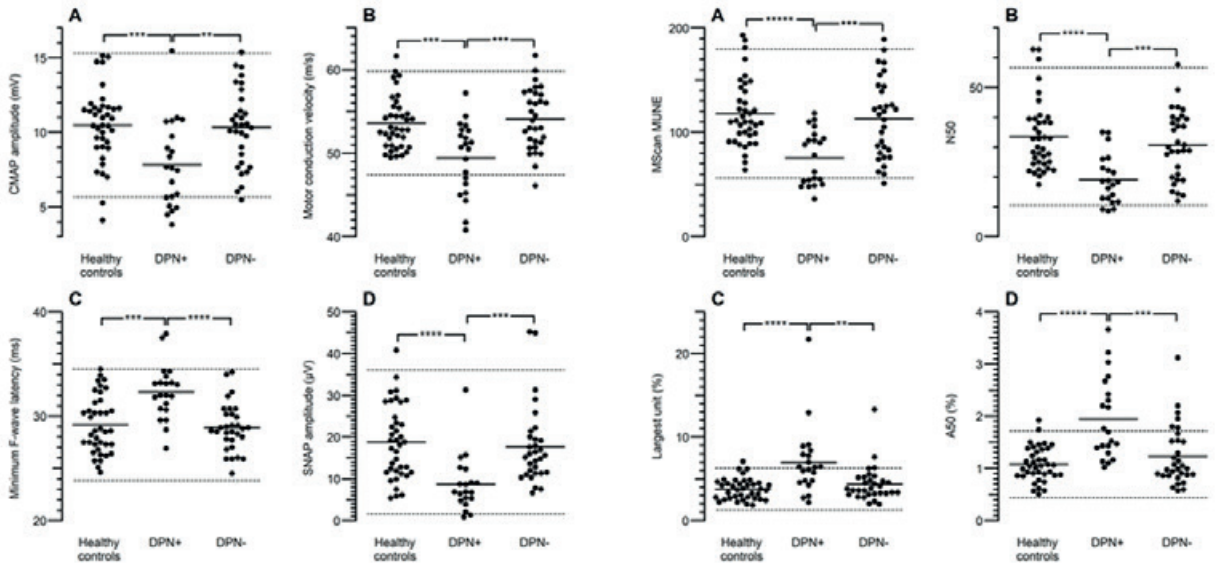
Diabetes is the most common etiology for polyneuropathies. International Diabetic Neuropathy Consortium (IDNC) has been working on this important topic to explore the mechanisms giving rise to diabetic neuropathy and pain.

Epidemiological (Gylfadottir et al., 2019; Andersen et al., 2018) and clinical studies (Andersen et al., 2019) both in the DD2 and ADDITION cohorts have sheded light on the prevalances and risk factors for type-2 diabetes. Additionally, a large numbers of diabetics from these cohorts have been examined using conventional and novel electrophysiological methods.

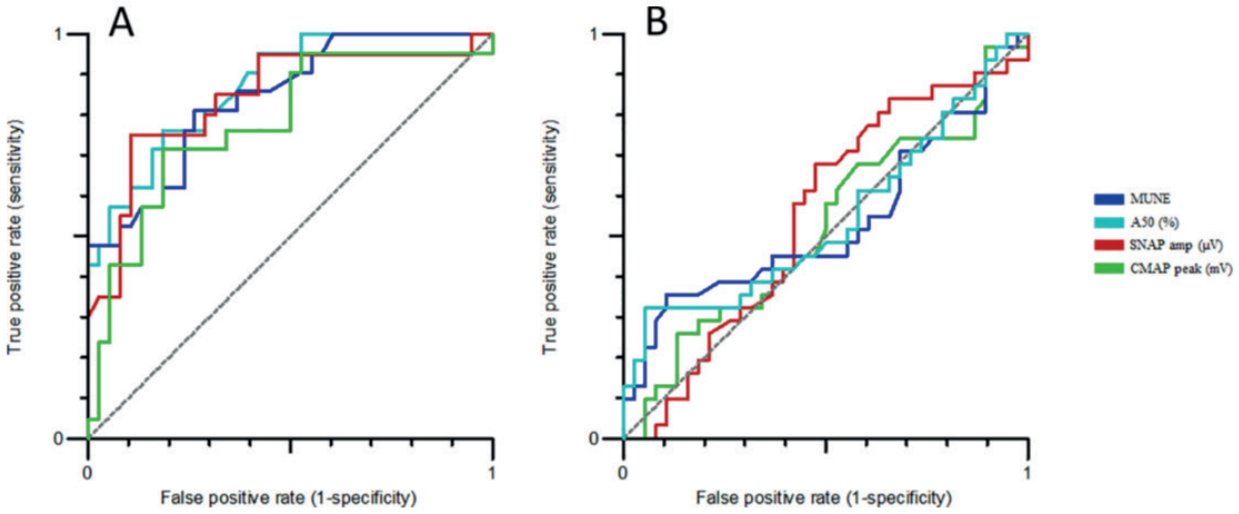


Nerve excitability and MScanFit MUNE set-up (left) and an MScanFit example from a healthy subject (right)

Sensory involvement is proposed to be earlier and more pronounced than motor involvement in DPN. However, detection of motor involvement in diabetic polyneuropathy by nerve conduction studies (NCS) does not occur until there is substantial loss of motor units, because collateral reinnervation maintains compound muscle action potential (CMAP) amplitude. Motor unit number estimation (MUNE) methods may therefore be more sensitive. Using the novel MUNE method, MScanFit, we showed in a a group of 52 type-2 diabetic patients and 38 healthy controls that motor involvement is as early as sensory (Kristensen et al., 2019) (Fig. 1 and Fig. 2)

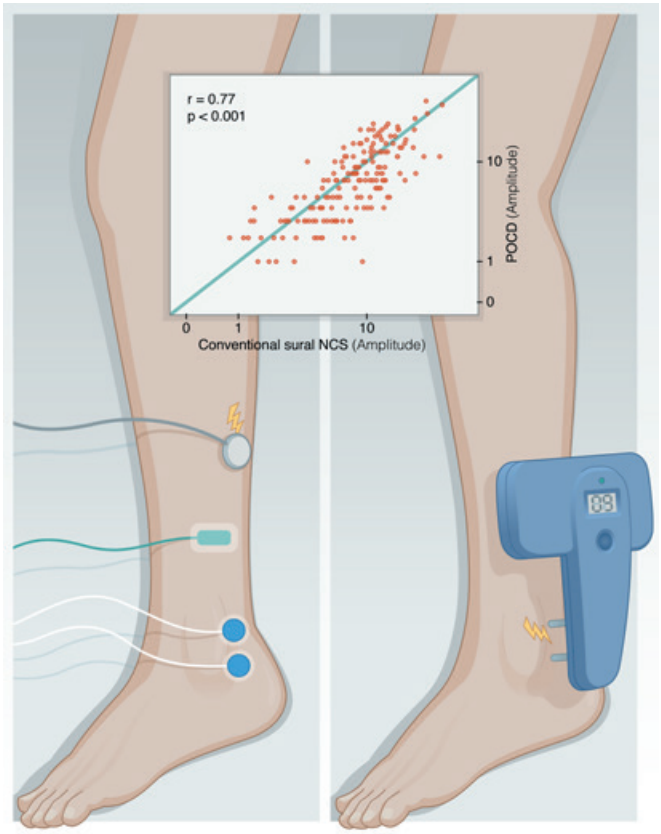


Distributions of MScanFit (left) and nerve conduction studies parameters (right) between the 38 healthy controls, 21 patients with diabetic polyneuropathy (DPN+) and 31 patients without neuropathy (DPN-). The asterisks indicate the *P* values for comparison by the t-test, as listed in Table 1 (** = P<0.01, *** = P<0.001,**** = P<0.0001, ***** = P<0.00001). Horizontal solid lines indicate means, and dashed lines indicate 95% confidence limits for the healthy subjects. CMAP = Compound muscle action potential, SNAP = Sensory nerve action potential.



ROC curves of MScan and NCS parameters' ability to discriminate between (A) healthy controls and DPN+ patients, (B) healthy controls and DPN patients.

NCS is an important tool for DPN diagnosis. However, NCS are expensive and might not be accessable for all diabetics. Rapid and accessible methods for diagnosing diabetic polyneuropathy have been developed, but not validated, in large cohorts of people with diabetes. We studied the performance of a point-of-care device (POCD) in 168 patients with type 2 diabetes. Comparisons with NCS showed that the POCD may be used as a suitable screening tool for detection of DPN. Patients with abnormal and borderline results should undergo conventional NCS (Kural et al., 2019)(Fig. 3).



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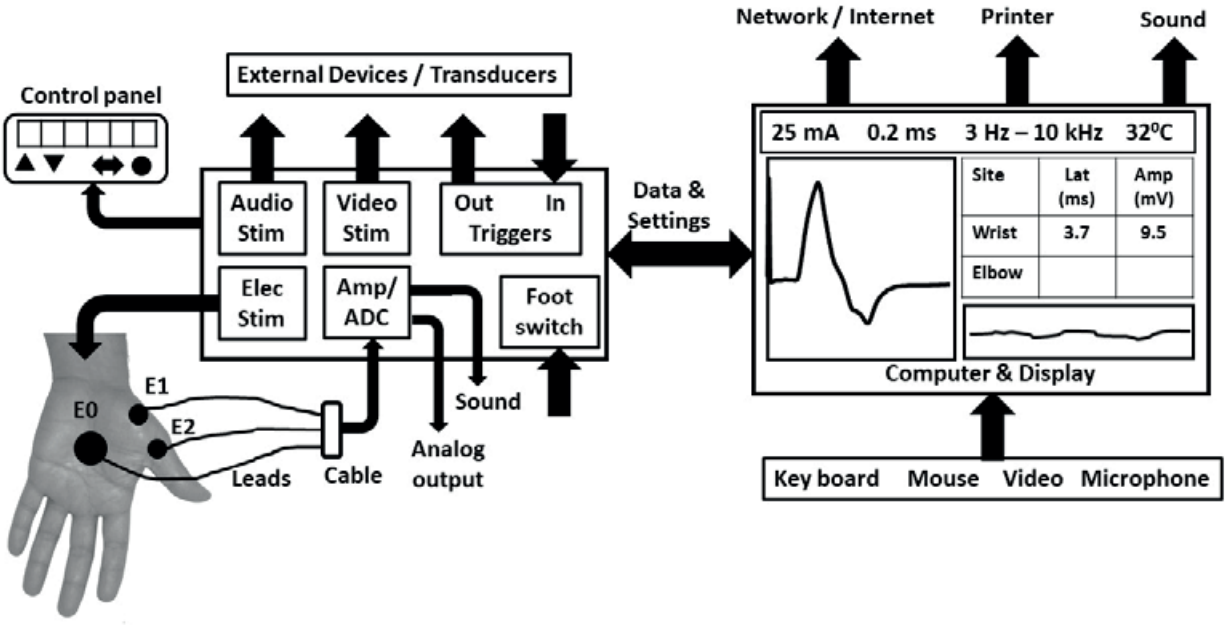
Standards and Guidelines in Electrodiagnosis of Neuromuscular Disorders

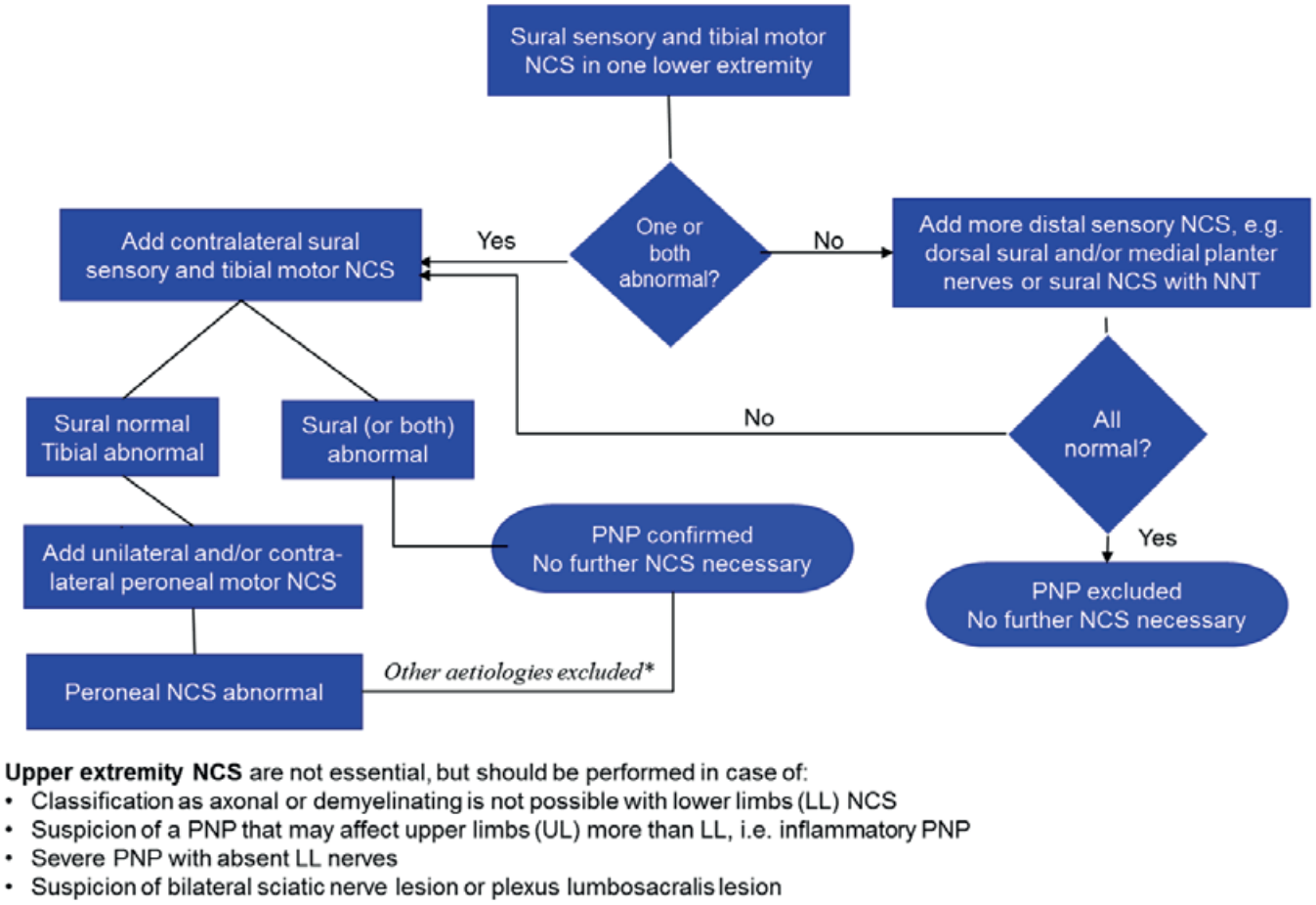
Since the first electromyography (EMG) machine was designed 70 years ago, EMG and nerve conduction studies (NCS) have been well-established electrophysiological techniques used in the diagnosis of neuromuscular disorders. Two updated guideline papers endorsed by the International Federation of Clinical Neurophysiology (IFCN) were recently published. The technological advancements in electrodiagnostic examination equipment were reviewed in *"Standards of instrumentation of EMG"*, while quantification of both conventional as well as new methods were covered in *"Standards for quantification of EMG and neurography"*.

Guidelines are required not only for instrumentation and methodology, but also for examination procedures and diagnostic strategies. In a topical issue for Journal of Clinical Neurophysiology, we reviewed the existing guidelines for large-fiber polyneuropathy and entrapment neuropathies, which are some of the disorders most frequently referred for electrodiagnostic testing.

Finally, in the paper *"Evidence-based recommendations for examination and diagnostic strategies of polyneuropathy electrodiagnosis"* from 2019, we proposed recommendations for electrodiagnosis of distal symmetrical polyneuropathy (PNP) deduced from NCS data of 313 prospectively examined patients with clinically suspected PNP. Our analysis included data of the two distal nerves, dorsal sural and medial plantar, examined in a subset of 68 patients. Distal nerves are not routinely examined in most centres, but interestingly, showed high sensitivity (68-70%) equaling near-nerve needle examination of the sural nerve. Thus, the electrodiagnosis of PNP may benefit from inclusion of distal nerves. Another important point revealed from our large data set was that examination of only one side can be sufficient for ruling out distal symmetrical PNP.



The organization of various components and accessories to an electrodiagnostic system are shown schematically



Flowchart for the electrodiagnosis of PNP

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ACKNOWLEDGEMENTS

We would like to express our gratitude for the generous support to:

Lundbeck Foundation
Independent Research Fund Denmark
Novo Nordisk
Graduate School of Health Aarhus University
Health Research Foundation of Central Denmark Region
Danish Epilepsy Centre, Filadelfia Research Foundation
Benzon Foundation
Inge Berthelsen Legat Fonden - Epilepsiforeningen
Grosserer L.F. Foghts Fond
Dagmar Marshalls Fond
Fonden til Lægevidenskabens Fremme (Mærsk)
Aage og Johanne Louis-Hansens fond
Savværksejer Jeppe Juhl og hustrus Ovita Juhls Mindelegat
Henry Hansen og hustru Karla Hansens Legat
Søster og Verner Lipperts Fond
Aase og Ejnar Danielsens Fond
Knud og Edith Eriksens Mindefond

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