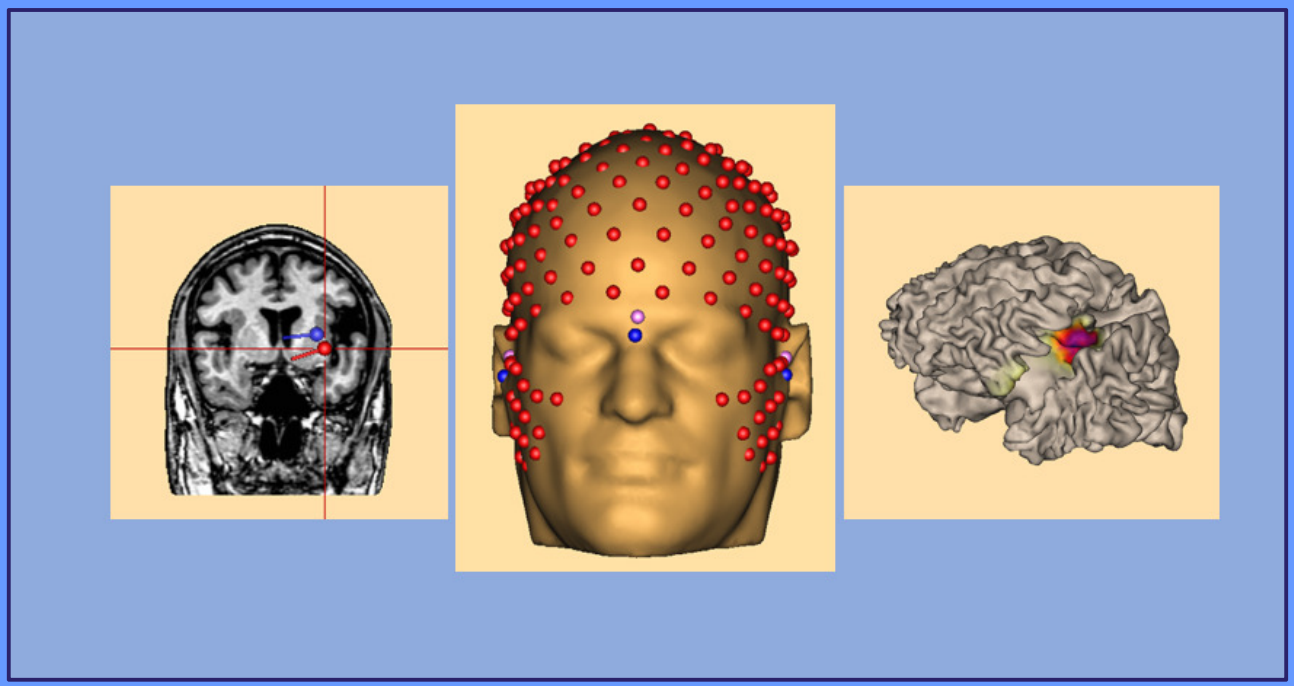
FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

## PhD Thesis

Mette Thrane Foged

# Epilepsy surgery: Outcomes of the Danish evaluation program and development of new EEG based methods



Principal Supervisor: Lars H Pinborg

Co-supervisors: Sándor Beniczky, Olaf B Paulson, Stefan Posse, Henrik BW Larsson, Troels W Kjær

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Neurobiology Research Unit
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**Cover page figure:**

To the left a dipole electrical source image with the individual MRI. To the right, in the same patient, a cortical CLARA electrical source image with the individual MRI. In the middle from another subject, illustration of the individual position file of a 256 electrode-array.

| | |
|---|---|
| **Name of department:** | Neurobiology Research Unit, Department of Neurology, Rigshospitalet, Denmark |
| **Author:** | Mette Thrane Foged, MD |
| **Title:** | Epilepsy surgery: Outcomes of the Danish evaluation program and development of new EEG based methods. |
| **Topic description:** | This thesis contains two retrospective studies assessing the outcomes of the Danish Epilepsy Surgery program. Furthermore, two prospective studies concerning development and application of new EEG based methods; concurrent EEG-fMRI and electrical source imaging. |
| **Principal Supervisor:** | Associate Professor Lars H Pinborg MD DMSci, Neurobiology Research Unit, Department of Neurology, Copenhagen University Hospital, Rigshospitalet. |
| **Co-supervisors:** | Professor Sándor Beniczky MD PhD, Department of Clinical Neurophysiology, Aarhus University Hospital and the Danish Epilepsy Hospital.<br><br>Professor Olaf B Paulson MD DMSci, Neurobiology Research Unit, Department of Neurology, Copenhagen University Hospital, Rigshospitalet.<br><br>Professor Stefan Posse PhD, Department of Neurology, University of New Mexico, and adjunct professor at University of Copenhagen.<br><br>Professor Henrik BW Larsson MD DMSci, Functional Imaging Unit, Department of Diagnostics, Copenhagen University Hospital, Rigshospitalet.<br><br>Professor Troels W Kjær MD PhD, Centre of Neurophysiology, Zealand University Hospital. |
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| **Assessment committee:** | Chair: Professor Kirsten Møller MD PhD DMSci, Department of Neuroanaesthesiology, Rigshospitalet, and department of Clinical Medicine, University of Copenhagen, Denmark.<br><br>Professor Andreas Schulze-Bonhage MD PhD, Neurozentrum der Albert-Ludwigs-Universität, Sektion Epileptologie, Freiburg, Germany.<br><br>Clinical Lecturer Antonio Valentin MD PhD, Neuroscience Academy Centre, Kings College London, United Kingdom. |

# Table of contents

# List of publications

This thesis is based on the following original papers:

1. **Efficacy of the Danish epilepsy surgery programme**. *Holm E, *Foged MT, Beniczky S, Jespersen B, Brennum J, Pinborg LH. *Acta Neurol Scand*. 2018 Feb;137(2):245-251. doi: 0.1111/ane.12857. Epub 2017 Oct 10. PMID: 28994451. *Shared 1st author

2. **Verbal learning and memory outcome in selective amygdalohippocampectomy versus temporal lobe resection in patients with hippocampal sclerosis**. Foged MT, Vinter K, Stauning L, Kjær TW, Ozenne B, Beniczky S, Paulson OB, Madsen FF, Pinborg LH; Danish Epilepsy Surgery Group. *Epilepsy Behav*. 2018 Jan 4; 79:180-187. doi: 10.1016/j.yebeh.2017.12.007. PMID: 29306849.

3. **Safety and EEG data quality of concurrent high-density EEG and high-speed fMRI at 3 Tesla.** Foged MT, Lindberg U, Vakamudi K, Larsson HBW, Pinborg LH, Kjær TW, Fabricius M, Svarer C, Ozenne B, Thomsen C, Beniczky S, Paulson OB, Posse S. *PLoS One*. 2017 May 26;12(5): e0178409. doi: 10.1371/journal.pone.0178409. eCollection 2017. PMID: 28552957.

4. **Clinical Utility of ESI in Presurgical Evaluation of Patients with Epilepsy (CUESIPE).** Foged MT, Martins T, Hamrouni N, Litman M, Pinborg LH, Paulson OB, Fabricius M, Benickzky S. *In preparation.*

Related papers:

1. **Epilepsy surgery**. Pinborg L, Jespersen B, Beniczky S, Fabricius M, Rasonyi G, Uldall P, Tsiropoulos I, Leffers AM, Madsen C, Foged M, Ziebell M, Henriksen O, Jørgensen M, Vinter K, Stauning L, Broholm H, Brennum J, Sabers A, Rubboli G. [Article in Danish]. *Ugeskr Laeger*. 2018 Mar 26;180(13). pii: V09170653.

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# Summary in English

In patients with drug-resistant epilepsy and an expected focal origin of the seizures, surgery is an option that may cure the disease and improve quality of life. However, identification of the tissue necessary to be removed to render the patients seizure-free, the epileptogenic zone (EZ), may be one of the most complicated multimodal and interdisciplinary evaluation processes in medicine. Epilepsy surgery has been performed on a regular basis in Denmark since 1993, but outcomes in the adult population have not been systematically evaluated until now.

The goals of the present thesis were to: 1) Evaluate the outcomes of the Danish epilepsy surgery program, e.g. are the patients referred according to the recommendations from the International League Against Epilepsy? does the Danish results correspond to international standards? and is the change in cognitive function affected by the surgical approach? 2) Investigate the use of new EEG based methods with potential added value in the evaluation process aiming to identify the EZ by 2.a) further development of concurrent EEG and functional MRI (EEG-fMRI) and 2.b) evaluation of the clinical utility of low-density (LD) vs. high-density (HD) electrical source imaging (ESI).

The results of the Danish epilepsy surgery program were found to be comparable to international standards but international recommendations for referral of drug-resistant patients to surgical evaluation were not all fulfilled. In patients with hippocampal sclerosis, selective amygdalohippocampectomy resulted in sustained “freedom from disabling seizures” and better memory function compared with patients operated with a temporal lobe resection.

Our EEG-fMRI results was not of use in the epilepsy surgery evaluation but showed that it is safe to perform concurrent HD EEG and high-speed fMRI which is usable in other fields. In total LD and HD ESI lead to a change in clinical decision in 34% of patients evaluated for epilepsy surgery. Changes were seen in more patients based on HD ESI than based on LD ESI ($p<0.001$). We are currently awaiting data from intracranial registrations and 1-year follow-up in patients where the decision was changed.

The failure to fulfil international recommendations for referral of drug-resistant patients to epilepsy surgery evaluation led to the establishment of an information campaign targeting medical personnel, patients and their relatives. The promising results of ESI has led to implementation of the low-cost high-efficient LD ESI modality as a routine investigation in epilepsy surgery evaluation. HD ESI will be offered to a subset of challenging cases.

# Dansk resumé

Hos patienter med medicinsk refraktær epilepsi, hvor anfaldene har et formodet fokalt udgangspunkt, kan kirurgi være en mulighed, der kan kurere sygdommen og forbedre livskvaliteten. Imidlertid er den proces, der anvendes til at identificerer det væv, det er nødvendigt at fjerne for at gøre en patient anfaldsfri, den epileptogene zone (EZ), måske en af de mest komplicerede multimodale og interdisciplinære processer, der findes indenfor lægevidenskaben. Epilepsikirurgi er blevet udført regelmæssigt i Danmark siden 1993, men resultaterne hos voksne er ikke blevet undersøgt systematisk før nu.

Målene for denne afhandling var at: 1) Evaluere resultaterne af det danske epilepsikirurgi-program, er patienterne f.eks. blevet henvist efter gældende retningslinjer fra "the International League Against Epilepsy"? Svarer de danske resultater overens med internationale standarder? Og påvirkes ændringer i kognitiv funktion af den operative teknik? 2) Undersøge anvendelsen af nye EEG baserede metoder med potentiel adderet værdi i udredningsprocessen, som er målrettet identifikation af EZ, ved at 2.a) videreudvikle simultan EEG og funktionel MRI (EEG-fMRI) og 2.b) evaluere den kliniske værdi af lav-densitets (LD) vs. høj-densitets (HD) elektrisk kildelokalisering (ESI).

Resultaterne fra det danske epilepsikirurgi-program blev fundet sammenlignelige med internationale standarder, men de internationale retningslinjer for henvisning af medicinsk refraktære patienter blev ikke opfyldt til fulde. Hos patienter med hippocampal sklerose førte selektiv amygdalohippocampektomi til vedvarende "frihed for invaliderende anfald" og bedre hukommelsesfunktion sammenlignet med patienter der fik foretaget temporallabsresektion.

Vores EEG-fMRI resultater var ikke brugbare i epilepsikirurgi-udredningen, men viste at det er sikkert at udføre simultant HD EEG og højhastigheds fMRI, hvilket er brugbart indenfor andre områder. Samlet førte LD og HD ESI til en ændring af den kliniske beslutningen hos 34% af de patienter, der blev udredt mhp epilepsikirurgi. Ændringer sås hyppigere efter HD end efter LD ESI ($p<0,001$). Vi afventer i øjeblikket data fra intrakranielle registreringer og 1-års opfølgninger hos de patienter hvor beslutningen blev ændret.

Den manglende opfyldelse af de internationale standarder for henvisning af medicinsk refraktære patienter til epilepsikirurgi-udredning førte til foranstaltning af en informationskampagne målrettet sundhedspersonale, patienter og pårørende. De lovende ESI resulater har ført til implementering af den effektive LD ESI modalitet, der har lave udgifter, som en rutine undersøgelse i epilepsikirurgi-udredningen. HD ESI vil blive tilbudt i tilfælde hvor udredningen er særligt svær.

# Abbreviations

| | |
|---|---|
| **AAN** | American Academy of Neurology |
| **AED** | AntiEpileptic Drug |
| **ATL** | Anterior Temporal Lobectomy |
| **BCG** | BallistoCardioGraphic |
| **BEM** | Boundary Element Method |
| **BESA** | Brain Electric Source Analysis |
| **BOLD** | Blood-Oxygen-Level Dependent |
| **CE** | Conformité Européenne |
| **CLARA** | Classical LORETA Analysis Recursively Applied |
| **CSF** | CerebroSpinal Fluid |
| **CT** | Computed Tomography |
| **CUESIPE** | Clinical Utility of ESI in Presurgical Evaluation of Patients with Epilepsy |
| **DNET** | Dysembryoplastic NeuroEpithelial Tumor |
| **ECoG** | ElectroCOrticoGraphy |
| **EEG-fMRI** | concurrent ElectroEncephaloGraphy and Functional Magnetic Resonance Imaging |
| **EPI** | Echo planar imaging |
| **ESI** | Electrical Source Imaging |
| **ETLE** | ExtraTemporal Lobe Epilepsy |
| **EZ** | Epileptogenic Zone |
| **EPSP** | Excitatory Post-Synaptic Potential |
| **FCD** | Focal Cortical Dysplasia |
| **FDG** | $^{18}$F-fluorodeoxyglucose |
| **FDM** | Finite Difference Method |
| **FEM** | Finite Element Method |
| **FMRI** | Functional Magnetic Resonance Imaging |
| **GLM** | General Linear Model |
| **HD EEG** | High Density ElectroEncephaloGraphy |
| **HD ESI** | High Density Electrical Source Imaging |

| | |
|---|---|
| **HRF** | Hemodynamic Response Function |
| **HS** | Hippocampal Sclerosis |
| **IC** | Ictal wave |
| **ICR** | IntraCranial EEG Registration |
| **IEC** | International Electrotechnical Commission |
| **IED** | Interictal Epileptiform Discharge |
| **ILAE** | International League Against Epilepsy |
| **IPSP** | Inhibitory Post-Synaptic Potential |
| **IZ** | Irritative Zone |
| **LAURA** | Local AUtoRegressive Average |
| **LD EEG** | Low Density ElectroEncephaloGraphy |
| **LD ESI** | Low Density Electrical Source Imaging |
| **LEAT** | Long-term Epilepsy-Associated Tumours |
| **LORETA** | LOw Resolution Electrical TomogrAphy |
| **LSMAC** | Locally Spherical Head Model with Anatomical Constrains |
| **LTLE** | Lateral Temporal Lobe Epilepsy |
| **LTM** | Long-Term video electroencephalography Monitoring |
| **MB-EPI** | Multi-Band Echo Planar Imaging |
| **MCD** | Malformations of Cortical Development |
| **MDT** | MultiDisciplinary epilepsy surgery Team |
| **MEG** | MagnetoEncephaloGraphy |
| **MEPI** | Multi-Echo Planar Imaging |
| **MRI** | Magnetic Resonance Imaging |
| **MS-EVI** | Multi-Slab Echo Volumar Imaging |
| **MSI** | Magnetic Source Imaging |
| **MTLE** | Medial Temporal Lobe Epilepsy |
| **MUSIC** | MUltiple-SIgnal Classification algorithm |
| **PET** | Positron Emission Tomography |
| **PSP** | Post-Synaptic Potential |
| **QOL** | Quality Of Life |
| **RCT** | Randomized Controlled Trial |

| | |
|---|---|
| **RF** | Radio Frequency |
| **SAH** | Selective AmygdaloHippocampectomy |
| **SAR** | Specific Absorption Rate |
| **SEEG** | Stereo ElectroEncephaloGraphy |
| **sLORETA** | Standardized LORETA |
| **SOZ** | Seizure Onset Zone |
| **SPECT** | Single-Photon Emission Computed Tomography |
| **SMAC** | Spherical Head Model with Anatomical Constrains |
| **SNR** | Signal-to-Noise Ratio |
| **STL** | Standard Temporal Lobectomy |
| **SUDEP** | Sudden Unexpected Death in EPilepsy |
| **T** | Tesla |
| **TR** | Time of Repetition |
| **TLR** | Temporal lobe resection |

# 1. Introduction

Epilepsy is one of the most common serious neurological diseases affecting individuals of all ages with a prevalence internationally in the range of 0.3-1.8% (Banerjee et al., 2009) and in Denmark 0.6% (Christensen et al., 2007). Despite the development of several new drugs with new modes of action 1/3 of the patients continues to have seizures on anti-epileptic drug (AED) therapy (Kwan and Brodie, 2000) (Chen et al., 2018). The longer the period of drug resistance the higher is the concern of social, psychologic and cognitive consequences (Mihara et al., 1996) (Wiebe et al., 2001) (Perry and Duchowny, 2013). In drug-resistant patients with an expected focal origin of the seizures, surgery is a treatment option, that may cure the disease (Engel et al., 2012) (de Tisi et al., 2011) (Wiebe et al., 2001). The reported chances of seizure freedom, at least one year after surgery, is in the range of 53-84% in patients with mesial temporal lobe epilepsy (MTLE), and 36-76% in patients with localized neocortical epilepsies (Spencer and Huh, 2008). Similar results has been shown in two recent systematic reviews (Jobst and Cascino, 2015) (West et al., 2015).

The first guideline for epilepsy surgery in adults published by the American Academy of Neurology (AAN) in 2003 recommends that: *"Patients with disabling complex partial seizures, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs should be considered for referral to an epilepsy surgery center"* (Engel et al., 2003). Subsequently they recommend surgery in patients with anteromesial temporal lobe epilepsy but emphasize that evidence is insufficient to make an absolute recommendation in patients with localized neocortical epilepsy. The International League Against Epilepsy (ILAE), has defined drug-resistant epilepsy as:*"failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom"* (Kwan et al., 2010). Additionally, The Danish Health Authority, has stressed that epilepsy surgery only is to be considered in patients with seriously invalidating seizures (The Danish Health Authority, 2004).

Locating the epileptogenic zone (EZ) remains one of the most complicated, interdisciplinary and multimodal evaluation programs in health care (Baud et al., 2018). Figure 1 illustrates the different pathways of the Danish epilepsy surgery evaluation program from inclusion to operation or rejection. Patients can be offered resective surgery if seizure semiology, long-term video electroencephalography (EEG) monitoring (LTM) and magnetic resonance imaging (MRI)

are concordant with a single focal origin of seizures in the brain. In case of discordance or a non-lesional MRI, additional investigations may be added to the evaluation program such as photon emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG) which in turn may lead to new hypothesis of the EZ to be tested with intracranial EEG electrodes (Duncan et al., 2016) (Ryvlin et al., 2014) (Pinborg et al., 2018).

Despite the extensive presurgical epilepsy surgery evaluation program 31% of patients have been found to be rejected after evaluation because a hypothesis of the EZ could not be made (Picot et al., 2016). Furthermore, sustained long-term seizure freedom is only achieved in 41 % of operated adults and 44 % of operated children (Edelvik et al., 2013). In addition, only a minority of patients fulfilling the criteria for epilepsy surgery evaluation is actually evaluated. This may reflect incomplete knowledge of outcome, morbidity and mortality of presurgical assessment and epilepsy surgery among patients, families and health care personnel. To be able to offer surgery to more patients and achieve better results it is necessary to 1) evaluate the outcome of the Danish epilepsy surgery program, and 2) develop and implement methods that allow us to identify the epileptic network and thereby the EZ at greater detail.

# 2. Objectives

The objectives of this thesis were to:

1. Evaluate results of the Danish epilepsy surgery program:
    - Are the Danish patients referred according to ILAE's recommendations with respect to the number of AED's tested and the duration of drug-resistant epilepsy before being referred?
    - Does the seizure outcome in patients operated in Denmark correspond to international standards?
    - What is the status of postoperative complications such as depression and loss of cognitive function. Is the change in cognitive function affected by the surgical approach?

2. Investigate new presurgical evaluation techniques to improve the identification of the epileptic network and the EZ. Focusing on:
    - Further development and exploration of the use of concurrent functional MRI and EEG (EEG-fMRI).
    - The clinical utility of Electric Source Imaging based on High Density (HD) and Low Density (LD) EEG.

# 3. Background

## 3.1. Epilepsy surgery

### Surgical techniques, outcomes and complications

Two randomised controlled trials (RCT) has proven that epilepsy surgery in patients with drug-resistant temporal lobe epilepsy results in a significant higher proportion of patients becoming seizure-free compared to treatment with medicine alone (Wiebe et al., 2001) (Engel et al., 2012). In the study by Wiebe et al. (2001) 23/40 operated patients (58%) were free from seizures impairing awareness at 1-year follow-up compared to 3/40 patients (8%) in the group not operated, $p < 0.001$. In the study by Engel et al. (2012) 11/15 operated patients (73%) became free of disabling seizures (Engel class I) compared to none of the 23 patients (0%) in the control group, $p < 0.001$. All patients had MTLE and the resections included more mesial tissue and spared more lateral neocortex compared to the study of Wiebe et al. (2001). A recent RCT study (Dwivedi et al., 2017) investigated both TLE and ETLE resections including hemispherectomies compared to treatment with AEDs alone in 116 drug-resistant children. Seizure freedom was seen in a significant higher proportion of children treated with surgery (77%) compared to children treated with medicine alone (7%). However, major complications to surgery were seen in 33% (19/57).

In the adult population in western countries, most resections are performed in the temporal lobe. Almost all resections are restricted to one lobe (Ryvlin et al., 2014). The three most frequent pathologies found in the resected tissue are hippocampal sclerosis (HS) (34 %), long-term epilepsy-associated tumours (LEAT) (25 %) and malformations of cortical development (MCD) (16%). The most frequent subgroup in MCD is focal cortical dysplasia (FCD). In LEAT it is ganglioglioma and dysembryoplastic neuroepithelial tumors (DNET) (Blümcke and Spreafico, 2012). In children resections in the frontal or temporal lobe are the most common followed by cerebral hemispherectomy, and multilobar resections. The three pathologies most often identified are cortical dysplasia (42 %), tumours (ganglioglioma, DNET and others, 19 %), and finally ischemic/atrophic abnormalities (10 %) (Harvey et al., 2008).

Outcomes of epilepsy surgery has traditionally been evaluated according to the “Engel classification” (Table 1) (Engel et al., 1993) which contains several subjective parameters, and a

more objective and simple classification, the "ILAE classification" has been proposed (Table 2) (Wieser et al., 2001). Study 1 and 2 of this thesis contain retrospective data and the Engel classification has been applied to be able to compare them with as many other studies as possible.

*Table 1. Engel's classification of Postoperative Outcome,*
*adapted from Engel et al., 1993.*

| |
|---|
| Class I: Free of disabling seizures[a] |
| A: Completely seizure free since surgery |
| B. Nondisabling simple partial seizures only since surgery |
| C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years |
| D. Generalized convulsions with AED discontinuation only |
| Class II: Rare disabling seizures ("almost seizure free") |
| A. Initially free of disabling seizures but has rare seizures now |
| B. Rare disabling seizures since surgery |
| C. More than rare disabling seizures since surgery, but rare seizures for the last 2 years |
| D. Nocturnal seizures only |
| Class III: Worthwhile improvement[b] |
| A. Worthwhile seizure reduction |
| B. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 years |
| Class IV: No worthwhile improvement |
| A. Significant seizure reduction |
| B. No appreciable change |
| C. Seizures worse |

[a] Excludes early postoperative seizures (first few weeks).
[b] Determination of "worthwhile improvement" will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function, and quality of life.

Nevertheless, to objectify the Engel classification we decided to interpret "Rare disabling seizures" as "One to three seizure days per year ±auras" (ILAE 3), "Worthwhile improvement" as "Four seizure days/year to 50% reduction of baseline ±auras" (ILAE 4) and "No worthwhile improvement" as "Less than 50% reduction" or worse (ILAE 5).

*Table 2. The ILAE classification of postoperative outcome,*
*adapted from Wieser et al., 2001 with permission from Wiley Online Library.*

| | |
|---|---|
| 1 | Completely seizure free; no auras |
| 2 | Only auras; no other seizures |
| 3 | One to three seizure days per year; ± auras |
| 4 | Four seizure days per year to 50% reduction of baseline seizure days; ± auras |
| 5 | Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras |
| 6 | More than 100% increase of baseline seizure days; ± auras |

The reported chances of seizure freedom, with at least one year follow-up, have been estimated to 53-84% in anteromesial temporal lobe resections, 36-76% in localised neocortical epilepsies, 66-100 % in patients with dual pathology, and 43-79 % following hemispherectomies (Spencer and Huh, 2008). In two recent systematic reviews, very similar result were published (Jobst and Cascino, 2015) (West et al., 2015). One recent review confirmed that certain pathologies are associated with better outcomes e.g. HS and benign tumours (West et al., 2015) although another review found pathology to be inconsistently associated with seizure outcome (Jobst and Cascino, 2015). Postoperatively the number of seizure-free patients decreases with time (Edelvik et al., 2013) and knowledge of both long and short-term outcomes are important when the multidisciplinary epilepsy surgery team (MDT) evaluates and inform potential epilepsy surgery candidates.

In the Danish epilepsy surgery program, a total of 67 % of all children operated from 1996-2010 was found to be in Engel class I after a median follow-up period of four years (von Celsing Underbjerg et al., 2015). Outcomes in adults had not been evaluated systematically prior to the work of this thesis.

In a comprehensive study by Mihara et al. (1996) quality of life (QOL) was tested pre- and postoperatively and patients operated at a late age were less pleased with their memory function, emotional well-being, leisure- and role activities than patients operated at a younger age (Mihara et al., 1996). In the RCT by Wiebe et al. (2001) it was found that besides seizure freedom, QOL ($p=0.003$) increased after surgery and more patients although not reaching significance ($p=0.11$) attended employment/school. In the review by Perry and Duchowny (2013) regarding cognition it is emphasized that becoming drug-resistant as an adult seems to affect attention/processing and visual/verbal memory more often than becoming drug-resistant as a child. In children verbal comprehension and perceptual organization is affected more (Perry and Duchowny, 2013). Although much insecurity exists in this field it is assumed that seizure freedom improve cognition and prevent deterioration. However, when either surgical or medical treatment is needed to obtain this, adverse effects with a potential impact on cognition comes in to play (Perry and Duchowny, 2013).

Epilepsy surgery differs from all other neurosurgical procedures because the indication to remove potential functional brain tissue is not survival and the saying “less is more” has been widely used discussing and planning these resections. Nevertheless, it is important that the entire

EZ defined as *"the minimal area of cortex that must be resected to produce seizure freedom"* (Lüders et al., 2006) is removed. In temporal lobe resections several surgical approaches have been developed, and it remains a controversy which one is the best choice, to achieve sustained seizure freedom with as little neuropsychological impairment as possible. In several centres standardized temporal lobectomy (STL) has been the approach of choice. In STL the anterior parts of the temporal lobe, amygdala, hippocampus and lateral temporal cortex are resected (Engel JJ and Pedley TA, 2008). When performed in the language dominant hemisphere STL gives rise to a well-known risk of verbal memory decline (Sherman et al., 2011) (Milner, 1972). Because of this potential risk more selective approaches have been developed. The most restricted one being the selective amygdalohippocampectomy (SAH), which has been used with different technical strategies (transsylvian, transcortical, transinsular or subtemporal) (Engel JJ and Pedley TA, 2008) (Hori et al., 2007) (Wheatley, 2008). Furthermore, a wide variety of tailor made resections in between the STL and the SAH, have been used (Engel JJ and Pedley TA, 2008). Some studies have found the selective approaches to give as good seizure outcome as STL with a better postoperative cognitive- and memory outcome (Wendling et al., 2013) (Clusmann et al., 2002) (Paglioli et al., 2006), while others have not (West et al., 2015) (Jones-Gotman et al., 1997). Still, no consensus exists, but with recent development and implementation of new very selective minimal invasive surgery approaches such as thermal ablation techniques the subject is of immediate importance (Barbaro et al., 2018) (Tao et al., 2018).

Complications in relation to resective surgery and invasive monitoring have been reviewed by Hader et al. (2013) (Hader et al., 2013). They reported medical (corresponding to surgical in other papers) and neurological/psychiatric complications and divided these two categories into major and a minor, Table 3. The major medical/surgical complications included hydrocephalus and deep infections (such as abscesses requiring surgical intervention). The major neurologic/psychiatric included one of the following lasting more than 3-month: Cranial nerve affection, dysphasia, memory disturbances (subjective), hemiparesis (all or part of a limb), hemianopia, psychiatric complications, status epilepticus and death. The minor medical/surgical consisted of: cerebrospinal fluid (CSF) leak, intra/extracranial infection not requiring surgical intervention, aseptic meningitis, deep vein thrombosis/pulmonary embolus, pneumonia, intracranial hematomas and metabolic disturbances. The number of complications in each category is displayed in table 3. Overall, complications were more frequent in children. Here, the use of subdural grid implantation via craniotomy was more frequent compared to implantation

through bore holes (Hader et al., 2013). Furthermore, the number of multilobar resections is known to be higher in this population (Hader et al., 2013) (Harvey et al., 2008).

*Table 3: Complications of epilepsy surgery in children and adults combined.* *Based on results from Hader et al.,2013.*

**Complications of resective surgery**

| | Major | minor |
|---|---|---|
| Medical/surgical | 1.5 % | 5.1 % |
| Neurologic/psychiatric | 4.7 % | 10.9 %† |
| *† Mortality was reported in 0.6% (1.2% extratemporal vs. 0.4% temporal)* | | |
| **Complications of invasive monitoring** | | |
| Neurologic and medical | 0.6% | 7.7% |

In a recent systematic review, it has been estimated that depression may arise in 4-18% after surgery, anxiety in 3-26% and psychosis in 1-12% (Jobst and Cascino, 2015). To date few studies has provided information on postsurgical psychiatric outcomes without the use of self-reporting and with data on preoperative occurrence of psychiatric disease.

### The Danish epilepsy surgery evaluation program

Epilepsy surgery has been performed on a regular basis in Denmark since 1993 when the Danish Health Authority together with an expert group of neurologists, neurophysiologist and neurosurgeons, published the first guidelines for surgical treatment of drug-resistant epilepsy (Epilepsikirurgiprotokol, 1993). It was decided that epilepsy surgery should be handled *"in one location in Denmark in the national functional center: the epilepsy surgery group"*. Only, temporal lobe resections were then allowed. Patients with extratemporal lobe epilepsy where evaluated at the national functional center but operated at epilepsy centres outside the country. In 2004 the guidelines were revised. It was recommended that intracranial EEG registration (ICR) became a part of the Danish epilepsy surgery evaluation, and it became possible to offer extratemporal lobe resections (The Danish Health Authority, 2004).

With the ICR facilities and a continues effort to implement highly advanced surgical techniques and diagnostic methods such as PET and SPECT, Rigshospitalet now fulfils the criteria of a fourth-level epilepsy surgery centre (Pinborg et al., 2018) (Labiner et al., 2010). As a natural extend to this development, The Danish epilepsy surgery group has grown and is currently comprised of neurologists, neurosurgeons, neuropediatricians, neurophysiologists, neuroradiologists, experts in nuclear medicine, neuropsychologists, psychiatrists, neuropathologists, nurses and neurophysiology assistants from Rigshospitalet and the Epilepsy hospital in Dianalund. In addition, there is a strong collaboration with other university hospitals particularly in Aarhus, Odense and Roskilde.

In the epoch from 1993 until today the Danish epilepsy surgery program can be divided in two. From 1993 till 2009 one neurosurgeon, Flemming Finn Madsen (FFM), performed all epilepsy surgery resections in Denmark. Since 2009 epilepsy surgery has been performed by Jannick Brennum (JB) and Bo Jespersen (BJ), with the main part performed by BJ. In 2006 neuropsychological testing and MRI was moved from the 1-year to the 2-year follow-up.

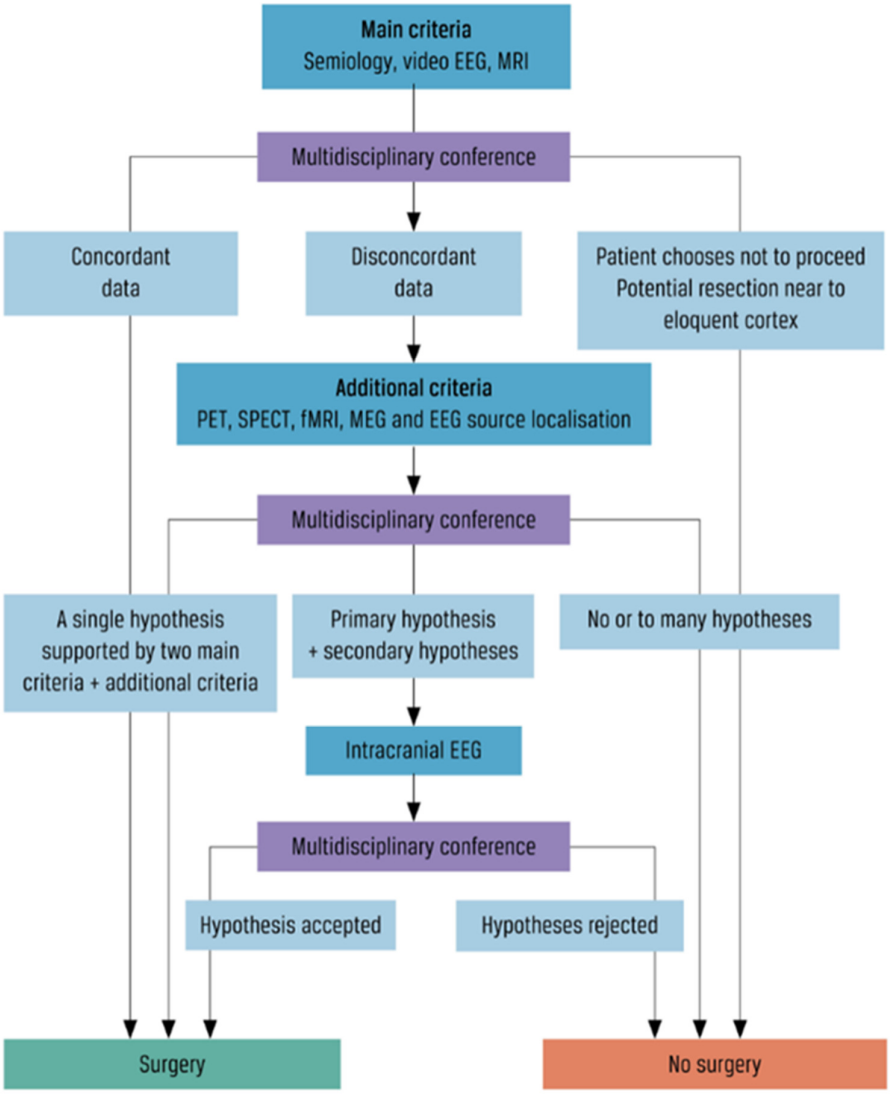
Based on international consensus the Danish epilepsy surgery evaluation program is designed as displayed in Fig 1 (Pinborg et al., 2018). If seizure semiology, LTM and MRI points at the same EZ the patient can be offered resection. In case of discordance or a non-lesional MRI, other investigations such as $^{18}$F-fluorodeoxyglucose (FDG) PET, 99mTc-hexamethyl-propyleneamine oxime SPECT [subtraction ictal SPECT co-registered with MRI (SISCOM)], MSI (magnetic

source imaging) or ESI (electrical source imaging) can be performed. When, based on these investigations, one main hypothesis can be formulated, the patient can be offered operation. In case of one primary plus additional secondary hypothesis further invasive investigation with intracranial electrodes is offered. When there is no hypothesis or to many hypotheses the patient cannot be operated neither offered further investigation with intracranial electrodes. Functional MRI (fMRI) can be used to investigate which hemisphere is the language dominant. A neuropsychological and psychiatric evaluation prior to surgery assesses risks of postoperative reduction/complications and when cognitive deficits are present the neuropsychological evaluation can potentially contribute to localization of the EZ (Pinborg et al., 2018).

*Figure 1. Flowchart of the Danish epilepsy surgery evaluation program.*

*EEG= Electro-encephalography. MRI= Magnetic resonance imaging. PET= Photon emission tomography. SPECT= Single-photon emission computed tomography. MEG = Magneto-encephalography. fMRI= functional MRI.*

*Adapted and translated from Pinborg et al, 2018.*




A quote regarding the development of the international accepted epilepsy surgery flowchart must be presented as it is general and thus also apply for the Danish program: *"It is important to*

*recognize that current epilepsy surgery practice has largely evolved as good practice points and that there is a very limited robust evidence base"* (Duncan, 2011). The most important gap of knowledge is if a patient reaches the step of "additional criteria" (Fig 1). The sensitivity, specificity, positive and negative predictive value of the methods at this step has been evaluated (Brodbeck et al., 2011) (Knowlton et al., 2008). However, exact knowledge of which patient subgroups that benefit the most from each modality is not completely established. In the latest review of the flowchart PET is suggested as a beneficial step following MRI and EEG (Duncan et al., 2016). However, a hierarchy between SPECT, MEG and ESI are not mentioned. Thus, epilepsy surgery can still be considered as a field in evolution where new approaches may gain significant impact on the flowchart.

## 3.2. Development and application of EEG based methods in the presurgical evaluation

### Electroencephalography (EEG)

EEG has since the 1930s been considered an important tool in classifying, monitoring and supporting a diagnosis in patients with epilepsy. Even after the development of computed tomography (CT) and MRI, EEG continues to have an essential role. In the beginning of its era, primarily epileptiform discharges arising interictally (IEDs) was used for a clinical purpose. The development of longer recordings simultaneous with video surveillance (LTMs) allowed the analysis of ictal EEG patterns (IC), to become of utmost importance as well, not least in epilepsy surgery evaluation (Rowan and Tolunsky, 2003a).

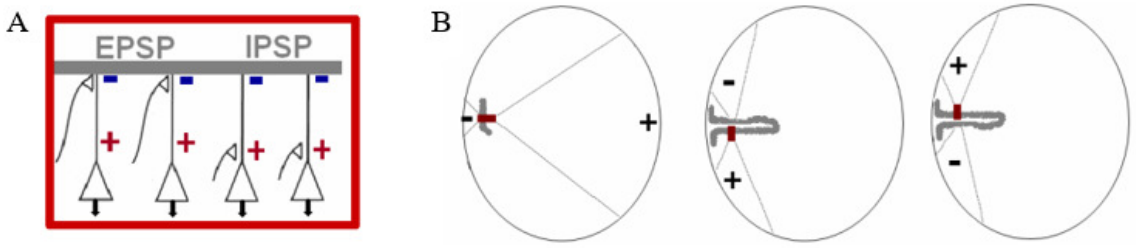
Recording scalp EEG provides an opportunity to measure brain activity noninvasively with a time resolution of milliseconds. However, the signal is weak, in range of microvolts, and its measurement is only possible because of certain physiological circumstances: 1) The pyramidal neurons in the IV and V layers of the cortex have numerous dendrites. 2) These dendrites are aligned in parallel. 3) Activation with excitatory post synaptic potentials (EPSPs), involves the dendrites from many pyramidal neurons at the same time. 4) EPSPs and inhibitory post synaptic potentials (IPSPs), have the same net effect in the extracellular space nearest the cortical surface. This is caused by their different location along the apical dendrite (excitatory synapses: far / inhibitory synapses close to the cell body) which results in negativity close to the surface and positivity deeper, towards the white matter, (Fig 2.A). 5) Finally, the nerve cell membrane functions as an electric insulator, and the current in the parallel aligned extracellular spaces sum up and becomes large enough to pass cerebrospinal fluid, bone and skin lastly reaching the scalp electrodes (Beniczky, 2012a) (Bear et al., 2007).

At a first glance, this surface signal, the EEG signal, seems irregular and ever-changing. Albeit within the randomness certain patterns can be identified and explained by physiological mechanisms. As an example, the mean duration of a postsynaptic potential (PSP) is 100 ms which corresponds to the length of a typical alpha wave, representing the component of the basic rhythm measured in a normal adult brain. The occurrence of sleep spindles can be explained by interaction of pacing cells from thalamus with cortical neurons, and interaction of large cortical network gives rise to different electric patterns in different areas of the brain (Rowan and Tolunsky, 2003b). Most important in this setting however, is that the higher the synchronous activation of the neurons, the

higher the amplitude of the EEG signal become. This causes epileptiform discharges (IEDs and ICs), to stand out from the background activity, as they are caused by exaggerated or synchronous neuron activation (Cosandier-Rimélé et al., 2008). Epileptiform discharges in a strict definition only counts spikes (20-80 ms, sharp contour, steeper rise than decline) and spike-waves (a spike followed by a slow wave). Although sharp waves (80-200 ms, not as sharp as spikes, but still steeper rise than decline) have the same significance when recorded in epilepsy patients and is therefore considered to belong to this class as well (Rowan and Tolunsky, 2003c).

The location of the cortical areas relative to the recording electrodes has a strong influence on the electrical signal as well, and source geometry is a critical parameter analysing the EEG (Tao et al., 2007). To understand the geometric basis of the EEG signal it is important to be aware that the dendrites in the V and IVs layer of the cortex, besides being arranged in parallel also is perpendicularly orientated towards the cortical surface. This together with the EPSPs and IPSPs joint effect on the extracellular space in each end of the pyramidal neuron, Fig 2.A, makes it possible to model the electric activity as a dipole. The orientation and polarity being determined by the geometry of the part of cortex that gives rise to the signal, Fig 2.B (Beniczky, 2012a).

*Figure 2. A) EPSPs and IPSPs effect on the extracellular space in the dendrites in the IVs and Vs layers of the cortex. B) The cortical geometry's effect on the dipole: The leftmost cortical (grey) source (red) lays straight beneath the scalp. The middle cortical source is placed in the posterior part of the central sulcus. The rightmost cortical source is placed in the anterior part of the central sulcus. Adapted from Beniczky, 2012.*




Having the surface signal displayed as a dipole on a voltage map, Fig 3.B., therefore provides the opportunity to track the signal back and estimate the approximate location of the cortical source. The voltage map can be considered an extra tool analyzing the EEG signal. The easiest montage to use, considering dipoles is the common average montage, because the interpretation is straight forward: a negative discharge measured on the scalp surface gives a negative (upward)

deflection, and a positive potential gives a positive (downward) deflection. The peak of the polarity is, where the amplitude of the EEG signal is the largest, Fig 3.C.

Using scalp EEG in the presurgical evaluation of epilepsy it is important to keep in mind that

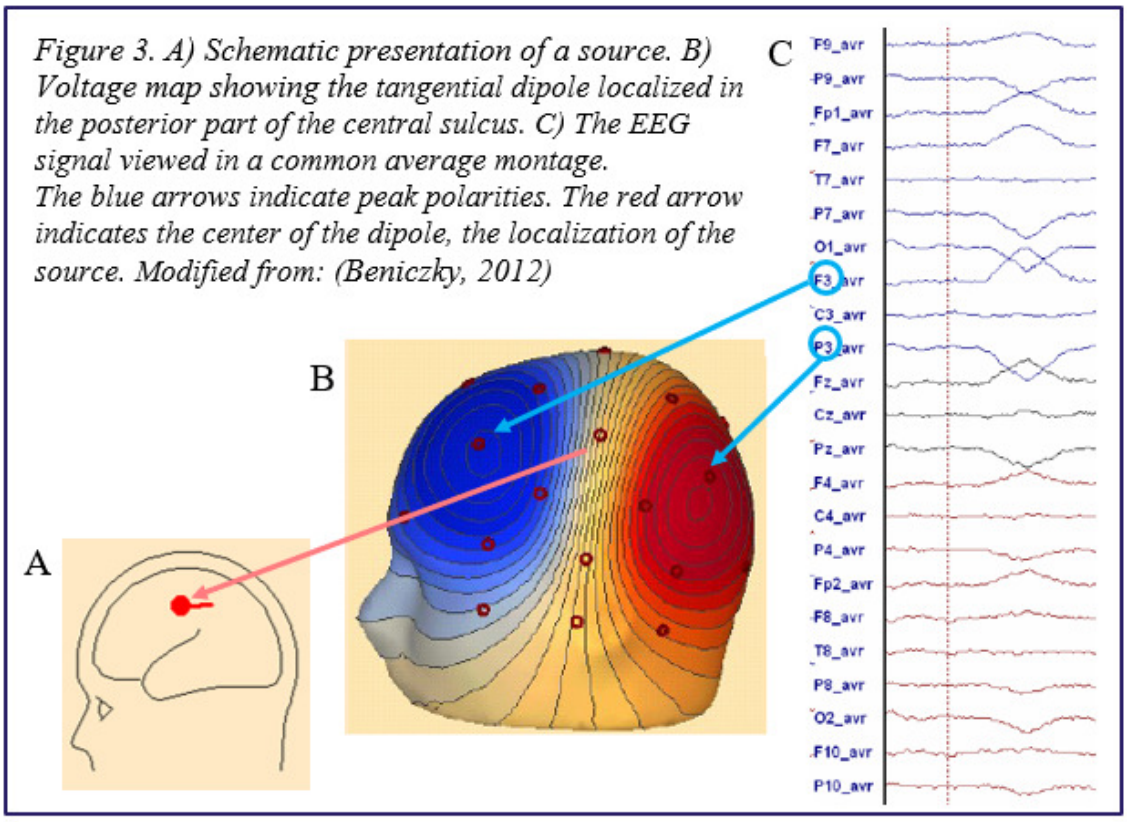



*Figure 3. A) Schematic presentation of a source. B) Voltage map showing the tangential dipole localized in the posterior part of the central sulcus. C) The EEG signal viewed in a common average montage. The blue arrows indicate peak polarities. The red arrow indicates the center of the dipole, the localization of the source. Modified from: (Beniczky, 2012)*

visualising a spike on a scalp EEG requires a rather large area of cortex to be involved in the signal generation. The study of (Tao et al., 2005) found that IEDs visualised at surface EEGs required a source area of at least 6 $cm^2$, and a reasonable detection rate required a source area of >10 $cm^2$. Another group (Cosandier-Rimélé et al., 2008) demonstrated that a spike-to-background amplitude ratio of 1.5 amounted to a cortical area of 3 $cm^2$ on ICR electrodes and 7 $cm^2$ on scalp electrodes. The amounted area responsible for a more realistic identifiable signal with a spike-to-background amplitude ratio of >2, was found to be 9 $cm^2$ for ICR electrodes and 18 $cm^2$ for scalp electrodes. During ictal periods the group of (Tao et al., 2007) found that neocortical temporal seizures had a mean of 19 $cm^2$ source area at seizure onset and produced almost simultaneous scalp ictal potentials. Mesial temporal seizures had a mean of 3 $cm^2$ source area and produced no visible scalp potentials until propagation resulted in a source area of at least 10 $cm^2$ (Tao et al., 2007).

### EEG related modalities in the evaluation program

*MEG*

It has been debated which modality is superior with respect to epilepsy surgery evaluation: EEG or MEG source imaging. Therefore, I briefly describe here the differences and similarities between MEG and EEG signals. Both methods record neuronal activity at a time resolution of milliseconds but they do so with different mechanisms and this affects some aspects of the respective recordings. In MEG, radially oriented dipoles cannot be seen (Hallez et al., 2007). These signals originate from gyral tops which comprises a third of the human cortical surface (Plummer et al., 2008). Therefore, a substantial number of epileptic discharges is not visualized by this method. MEG is also biased towards superficial sources of epileptic discharges because its field has a fast decay from the scalp. Nevertheless, its signals are less blurred by skull conductivity than those of EEG (Hallez et al., 2007). Source imaging with MEG signals is prone to the same fundamental mathematical problems as electrical source imaging and it has been said that the method is seductive but expensive (Plummer et al., 2008). However, MSI has advantages in a subset of patients (Duez et al., 2016).

*ICR*

To avoid attenuation of the EEG signal caused by the skull, to improve spatial resolution and to minimize artefacts, electrodes can be placed on the cortical surface as subdural grids (16-64 electrodes), strips or inside the cortex with stereotactic placed depth electrodes (4-8 contacts) (StereoEEG: SEEG). ICR is offered as LTM recordings in epilepsy surgery candidates when more than one hypothesis exists after MRI, EEG, semiology and possibly PET, SPECT and MEG. ICR electrodes records from a small area of the brain, hence a solid hypothesis is needed prior to implantation (Beniczky, 2012b). Complications in relation to ICR is e.g. infections, transient neurologic deficits and intracranial haemorrhages. In the review of Hader et al. (2013) minor complications were seen in 7.7% and major in 0.6% of patients, please see section 3.1 “Surgical techniques, outcomes and complications” (Hader et al., 2013). The extra cost performing ICR is in the United States tens of thousands of dollars. Therefore, it has been estimated that the majority of health care expenses in epilepsy surgery is spend on patients requiring ICR (Platt and Sperling, 2002).

### Electroencephalography - functional magnetic resonance imaging (EEG-fMRI)

EEG-fMRI has been proposed as a method with a high spatial resolution combined with a high temporal resolution (Herrmann and Debener, 2008) potentially overcoming the weaknesses of each of the methods involved in the epilepsy surgery evaluation program, Fig 4.

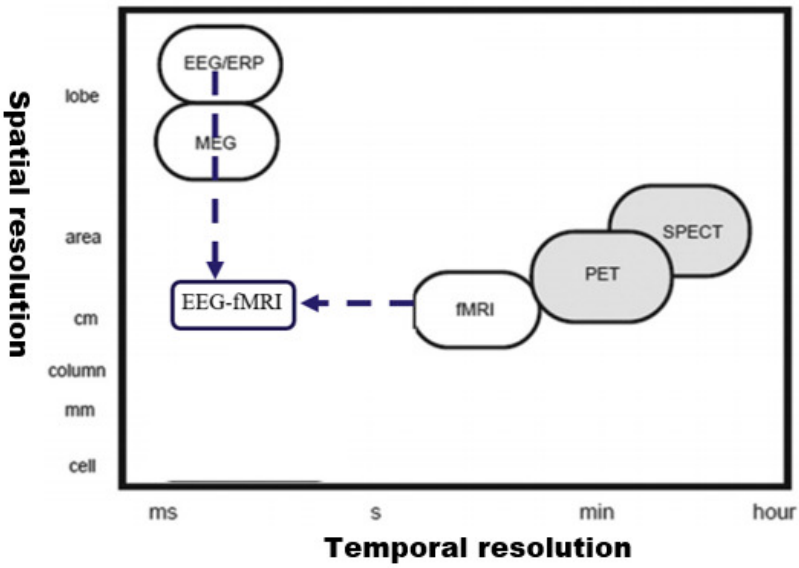



*Figure 4. Spatial and temporal resolution of most modalities used in the epilepsy surgery evaluation program. Theoretically EEG-fMRI can combine the high temporal resolution from EEG with the high spatial resolution from fMRI. Modified from:*

*Kameyama, M., Murakami, K., and Jinzaki, M. (2016). Comparison of [(15)O] H2O Positron Emission Tomography and Functional Magnetic Resonance Imaging in Activation Studies. World J. Nucl. Med. 15, 3–6*

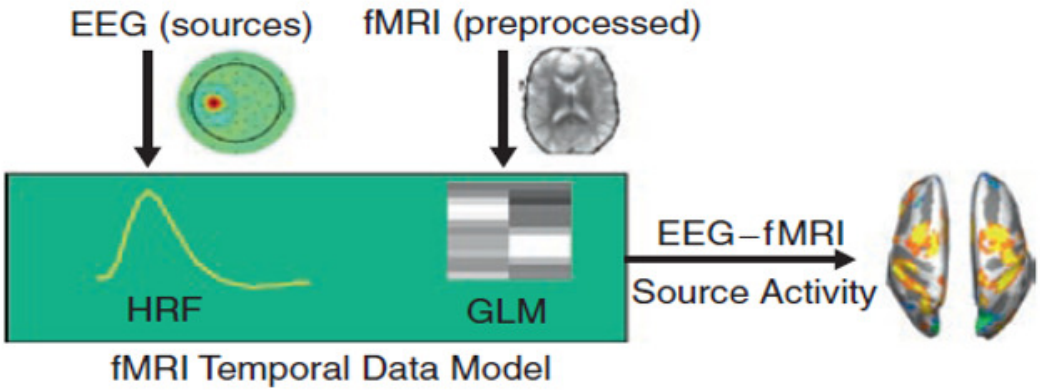
Assuming that epileptic seizures are the product of abnormal activity in a network instead of in one focal area of the brain (Laufs, 2012) this method could ideally differentiate between the EZ and seizure propagation in anatomically distinct but functionally coupled neuronal networks. This might theoretically lead to improved presurgical planning and thereby a higher chance of seizure freedom in operated patients.

To record epileptic seizures inside an MRI scanner is problematic due to the potential danger this can cause to the patient, the unpredictable nature of seizures and the high change to get substantial head movement artefacts in the data. For these reasons, the events analyzed in epilepsy surgery evaluation studies is most often interictal epileptic discharges (IEDs) (Walker et al., 2010).

To be able to assess the cortical origin of IEDs EEG-fMRI data can be analyzed in a temporal domain, Fig 5 (Goebel and Esposito, 2010). In this approach the timepoints of IED occurrence in the EEG is identified. Afterwards integration of EEG data into the fMRI temporal model is performed using a correction for the delay of fMRI hemodynamics with respect to the neuronal activity (Goebel and Esposito, 2010). This correction can be made with a hemodynamic response

function (HRF). In the classical canonical HRF the blood-oxygen-level dependent (BOLD) response is modelled to start around 2 s after a stimulus, peak at 6–9 s and return to baseline after a post-stimulus undershoot, at around 25 s (Logothetis and Wandell, 2004). After the application of the HRF model a temporal model for the actual response signals seen in the fMRI, can be made. The model of choice is often a general linear model (GLM) and it is used to extract information regarding IED-by-IED variation in the fMRI. Finally the fMRI GLM results can be used to present the cortical regions related to an IED temporal reference (Goebel and Esposito, 2010).

*Figure 5, Concurrent EEG-fMRI. A) Combining EEG and fMRI in the temporal domain.* *Adapted from Goebel and Eposito, 2010 with permission from Springer Nature.*




The spatial sampling of EEG has been shown to be increased with an increasing number of electrodes, up to 64, in electrical source imaging (ESI) (Lantz et al., 2003a). Because the aim of EEG-fMRI is to achieve the highest possible spatial resolution together with the highest possible temporal resolution high-density EEG is often used in EEG-fMRI studies. Whether the high-density EEG cap lowers the cortical signal-to-noise ratio (SNR) and the sensitivity to detect fMRI signal changes has been a question of concern. The study of Luo and Glover (2012) did not find significant differences in SNR comparing scans with and without the EEG cap but the study of Klein et al. (2015) did (Luo and Glover, 2012) (Klein et al., 2015). Nevertheless, none of the studies found a significant effect on the sensitivity to detect the BOLD signal between the two conditions.

In order to trace epileptic networks, it is necessary to be able to detect very subtle EEG changes/patterns. This is challenging in the hostile environment of the MRI scanner where especially gradient and ballistocardiographic (BCG) artefacts can lower the EEG quality. Several

approaches to remove these artefacts has been suggested but the BCG artefact remains difficult to avoid completely because its timing vary in an unpredictable manner (Debener et al., 2010).

BCG artefacts also pose a problem in the fMRI scans because cardiac and respiratory cycles lead to signal fluctuations that can interfere with signal changes caused by neuronal activation. Because traditional fMRI sequences record with a time resolution that is lower than that of the cardiac cycle, aliasing is a problem (Carmichael, 2010). By recording fMRI data with high-speed fMRI methods this aliasing is sought to be avoided. Two promising high-speed fMRI methods is multi-band (multi-slice) echo planar imaging (MB-EPI) and multi-slab echo volumar imaging (MS-EVI) (Posse et al., 2012) (Feinberg et al., 2010). However, there is a safety concern especially using MB-EPI because this method has an increased radio frequency (RF) power requirement.

The scanners RF field can induce heating due to interaction with electrode leads both by its magnetic component and its electric component (Allen, 2010). The latter component has been found to dominate and a current-limiting resistor of 12 kΩ in the EEG electrode leads has been demonstrated to limit contact currents sufficiently in settings with: an electrode lead loop of 400 cm2 (based on a head diameter of 20 cm), conditions with specific absorption rate (SAR) near the maximum allowed values, and an MRI magnet strength of 1.5 T (Lemieux et al., 1997). These resistors have been implemented in many MRI commercial EEG caps (Allen, 2010). However, to investigate safety in other settings a seemingly simple measurement of temperature is an alternative approach. Nevertheless, this requires a thorough study protocol to be able to consider other factors that can affect the measurements (Allen, 2010). A measurement of SAR unfortunately cannot replace this approach because the relation between SAR and associated temperature increases in implanted electrodes have been found to be variable even between scanners with the same tesla strength and from the same manufacturer (Baker et al., 2004). When we planned our study no safety standard for the use of EEG-fMRI had been made (Allen, 2010). Consequently, scientists had to use safety limits set for EEG and MRI individually and they were enacted as follows by the International Electrotechnical Commission (IEC) in 2002 and 2005 respectively:

> *"(1) maximum permissible cerebral temperature of 38°C, implying a maximum temperature increase due to scanner induced heating of 1°C (IEC 2002a); (2) maximum permissible temperature of an applied part in skin contact (such as an electrode) of 43°C (IEC 2005)."* (Allen, 2010).

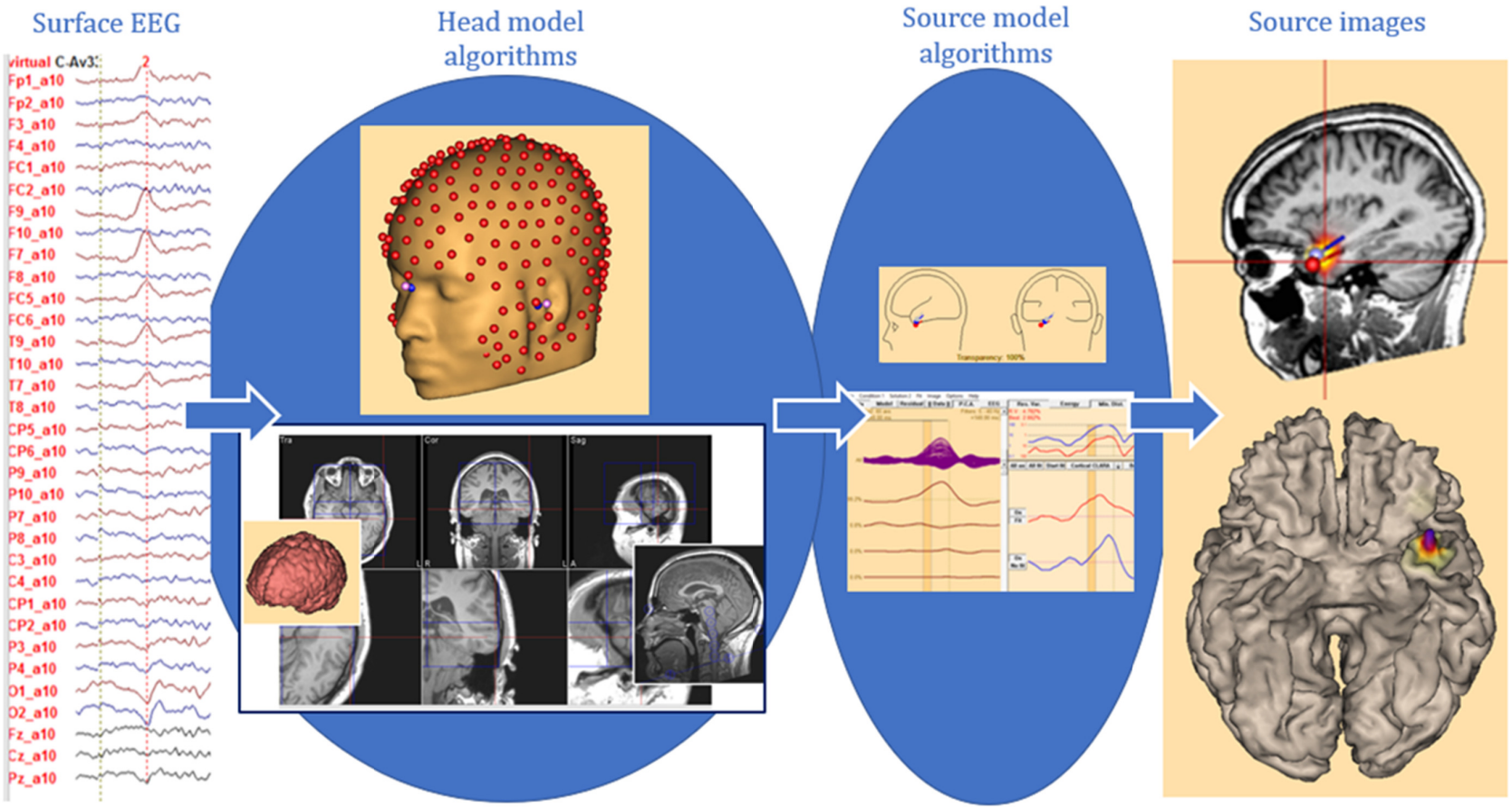
### Electrical Source Imaging (ESI)

The purpose of ESI used in the presurgical evaluation of epilepsy patients is to estimate where electric signals recorded with a conventional scalp EEG comes from, within the cortex. Thus, this analysis can be considered a tool that goes one step further than the display of voltage maps. Estimating the location of the origin of IEDs and ICs has been the aim of EEG analysis in epilepsy patients ever since its discovery. It has traditionally been performed by neurophysiologists, trained in constructing 3D images in their heads. This is a very valuable ability, but it is difficult, and it does not provide a picture to share with other specialists. It is subjective and it requires considerable training. Because of the increased computational power in recent times it has become possible to create an objective image of the source of electric surface signals an electric source image, ESI. This can be considered an extra tool analysing EEG. The first step creating an ESI is to identify epileptiform activity in the scalp EEG. The epileptiform activity is then used in combination with a head model, and other advanced algorithms to calculate an estimation of the epileptic focus, the source, within the brain (Plummer et al., 2008) (Kaiboriboon et al., 2012), Fig 6, please see next page. This method is potentially very valuable, but two fundamental problems that each demand a complex mathematical algorithm to be solved, has to be considered: the forward- and the inverse problem.

*The forward problem* lies in predicting the surface distribution of a signal from a known epileptic source in the cortex. How does the signal spread, volume conduct, when it passes CSF, bone and skin to reach the surface electrodes? Volume conduction describes the physical conduction through tissue, and not the biological conduction through neurons. Combining knowledge of the dipole location and orientation of the source, with the electrode positions, one can solve this problem with a forward model, a *head model.* (Hallez et al., 2007) (Beniczky, 2012a).

*The inverse problem,* is the opposite problem, and it is the one being asked in the clinical situation: “How can one predict the location of the source inside the cortex, when the surface distribution of the signal is known”. To solve the inverse problem, one needs the solution of the forward problem, the head model, and the actual EEG surface signal. These data can then be used together with complex algorithms to work back and estimate a solution of the inverse problem, the inverse model or *source model* (Grech et al., 2008).

*Figure 6. Steps in the ESI analysis. The last column, source images, displays an equivalent current dipole model (*Brain Electric Source Analysis*, BESA) at the top and a distributed source model (Cortical Classical LORETA Analysis Recursively Applied, Cortical CLARA) at the bottom.*



*The head model*

The head model (Hallez et al., 2007) includes a model of the: 1) shape, 2) solution space, 3) electrical conductivities and anisotropies of the brain, skull and scalp. It is based on the Poisson equation. The balance is to find the computational applicable model that results in the least error when it predicts the surface spread of the electrical signal.

1. Regarding the shape spherical and realistic models has been used, Fig 7 and Fig 8, with variations in-between. The spherical models are the simplest and consider the head to be shaped as a ball. The realistic models are more complex and often based on the individual MRI.

*Figure 7. Spherical head model.*

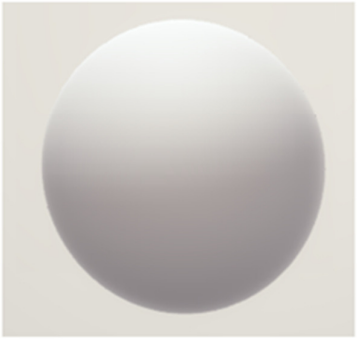
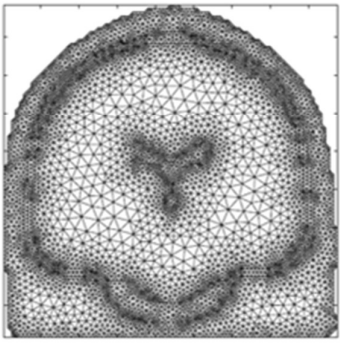


*Figure 8. Realistic head model, of the Finite Element Method (FEM) type. Adapted from Hallez et al., 2007.*



2. The solution space is defined as the locations in the brain wherefrom the EEG signal can arise. In spherical models the space between the scalp and the brain structure is the only space to be excluded. In the realistic model the solution space is often segmented from MRI and restricted to the grey matter.

3.

   a. The conductivity of grey matter, scalp and CSF is high, and equal in all directions, isotropic. In the CSF it is known to be 1.79 Siemens/meter (S/m) (Hallez et al., 2007). In the grey matter it has been estimated to 0.12 S/m in tissue samples (Gabriel et al., 1996). Measures on the entire brain in vivo have varied from 0.12 to 0.48 S/m. In the scalp the findings vary from 0.22 to 0.75 S/m (Hallez et al., 2007).
   b. The conductivities of the skull and the white matter is low, it has different properties in different directions, it is anisotropic. The skull because of its middle spongiform layer, the white matter because of its multidirectional fiber tracts. The estimated conductivity of the skull has varied from 0.006 to 0.015 S/m (Hallez et al., 2007). In the white matter it has been estimated to 0.078 S/m in tissue samples (Gabriel et al., 1996).

The difficulties estimating brain conductivity cannot be ignored because they are known to have a large influence on the forward problem, especially the scalp/skull conductivity. A scalp/skull conductivity of 80 is used in many models including BESA 2.0 MRI software (BESAGmbH, Gräfelfing, Germany). Nevertheless, the study of (Vanrumste et al., 2000) believed in a smaller ratio of 16, and showed that a ratio of 80 provided localization errors of up to 4 cm. In general deep sources are surrounded by more anisotropic tissue, and as consequence its potentials is smeared out over the scalp surface in a higher extend than superficial sources (Hallez et al., 2007).

As appointed above the shape, the solution space and the conductivities influence the identification of the source. Theoretically realistic head models are preferred, and they have become much more common (Mouthaan et al., 2016) (Hallez et al., 2007). Several realistic head models exist e.g. the boundary element method (BEM), the finite element method (FEM), Fig 8, and the finite difference method (FDM). The FEM is together with the FDM considered the most refined, and as quoted from (Hallez et al., 2007):

> *"Typically at least 500,000 computational points are considered which leads to system matrices of 500,000 equations with 500,000 unknowns which cannot be solved in a direct manner with the computers now available".*

The problem, can however be solved using iterative solvers, but it means that for each probable source the solver most be applied again. To bypass this demand a method called the "reciprocity theorem" is used. It basically makes it possible to perform calculations for each electrode position instead of for each dipole position. This is favorable since the number of electrodes is much smaller than the number of dipoles. In FEM the brain and head compartments can be segmented from a template or an individual MRI. The FEM mesh consists of multiple, three-dimensional tetrahedral elements as displayed in Fig 8. This allows implementation of conductivity values into each element, and the modeled compartments become locally anisotropic. For this reason, the FEM model can take potential focal lesions in the individual patient into account (Hallez et al., 2007). A model laying between this and a spherical model is the spherical head model with anatomical constrains (SMAC). This model does not consider local anisotropies, but creates an accurate solution space, and requires less computation. This can also be segmented from a template or an individual MRI (Birot et al., 2014).

In the clinical study of (Brodbeck et al., 2011) the use of the SMAC model based on the individual MRI in HD ESI was found to increase the sensitivity with 9 % and the specificity with 25 %

compared to the use of a template MRI. Plenty of parameters has to be considered choosing a head model, and a lot of insecurity still exists.

*The source model*

Source models, are even more difficult to create than head models, because tracking the EEG surface signal back to the location in the brain the solution can be any of a number, there are more dipole locations than electrodes, and the problem is "underdetermined" (Grech et al., 2008). Furthermore, the source models are very sensitive to noise in the EEG signal. Fortunately, there have been developed methods that makes it possible to amend these problems (Grech et al., 2008).

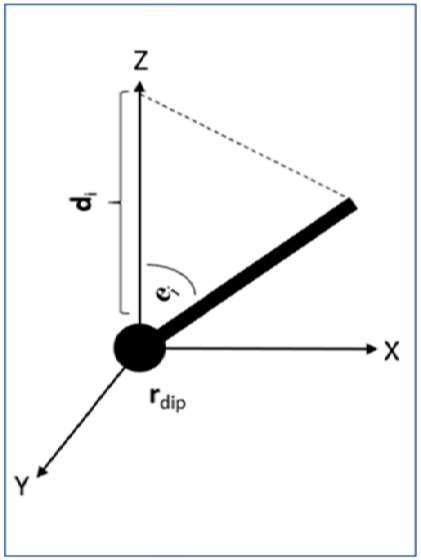
In general, two different approaches are used to solve the inverse problem (Grech et al., 2008):

1. Non-parametric Distributed Source Models e.g.
    a. Local autoregressive average (LAURA)
    b. Low resolution electrical tomography (LORETA)
    c. Classical LORETA Analysis Recursively Applied (CLARA) (Jordanov, T. et al., 2014)
    d. Cortical CLARA (Jordanov, T. et al., 2016), (Fig 6, last column, bottom)
2. Parametric Equivalent Current Dipole Methods e.g.
    a. Beam-forming approaches
    b. Multiple-signal Classification algorithm (MUSIC)
    c. Brain Electrical Source Analysis (BESA) (Fig 6, last column, top).

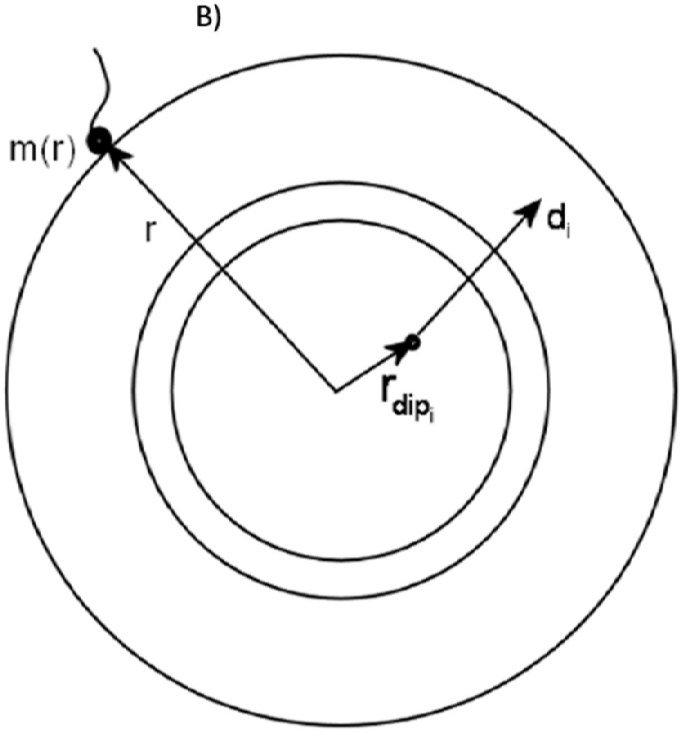
Both of the approaches are based on the concept of presenting the electric source as a dipole. This is possible because of the anatomic geometry explained in the above section regarding EEG. A dipole can be defined by: three coordinates in space, three orientation angles and the magnitude/strength, Fig 9.A (Hallez et al., 2007). To develop an algorithm some of these parameters, together with other factors most be assumed. The algorithm in a very simplified form can be displaced as shown in Fig 9.C, with the parameters explained in Fig 9.A and 9.B (Grech et al., 2008) (Hallez et al., 2007).

*Figure 9. A) Dipole parameters. B) Spherical head model with dipole and electrode parameters. C) The equation on which the solution of the inverse problem is build. These figures are partly modified with my own interpretation from a combination of (Hallez et al., 2007) and (Grech et al., 2008).*

A)




B)




C)

**M = GD + n**

**M** (**mr,** T) is the matrix of electrode potentials ($\mathbf{m}_r$) at different times (T)

**G** ($\mathbf{r}_j$, $\mathbf{r}_{dip,}$ $\mathbf{e}_i$) is the gain matrix, it describes the current flow for a given electrode through each dipole location

**r***dip* = dipole location

$\mathbf{e}_i$= dipole orientation

$\mathbf{r}_j$ = position vector from dipole to electrode

**D** (**di,** T) is a matrix of dipole magnitudes ($d_i$) at different time instants (T).

$\mathbf{d}_i$=dipole magnitude

**n** is a noise or perturbation matrix

*i* = 1, ..., *dipoles*

*j* = 1, ..., *electrodes*

T= discrete time samples

In distributed source models (Grech et al., 2008):

The assumptions are

i. Several dipoles can be active at a given timepoint
ii. Their location ($\mathbf{r}_{dip}$) and possibly orientation ($\mathbf{e}_i$) is fixed. An entire 3D matrix of dipoles with fixed location and possibly orientation covering the cortex is constructed.

The unknowns are

iii. Magnitude/strength (**D**), and possibly orientation ($\mathbf{e}_i$)

To find the magnitude/strength is a linear problem (Grech et al., 2008) and it is possible to fix the orientation of the dipole because of the orientation of the dendrites in the IV and Vs layer being stabile throughout the cortex, Fig 2.A. In general, these models allow the area in the final solution to become large, and to arise in different areas of the brain at the same timepoint (Grech et al., 2008). This is accordant with the nature of electric brain signals but because these models in particular suffer from the problem of "underdetermination" they have certain regularizations implemented, and this can lead to oversmoothed source estimations (Hallez et al., 2007). These estimations are potentially difficult to interpret in epilepsy surgery candidates with an assumed focal origin of the epileptic activity. Furthermore, these models contain the possibility of creating ghost sources.

In equivalent current dipole models (Grech et al., 2008):

The assumption is

iv. The source arises from few dipoles/ a small area of cortex can be active at a given timepoint

The unknowns are

v. Location ($\mathbf{r}_{dip}$)
vi. Orientation ($\mathbf{e}_i$)

Estimation of the location and orientation is a non-linear problem. As opposed to the distributed source models the EEG data is considered before the dipole localization. The result is restricted to a few sources, typically two, one for the onset and one for the peak of the signal. This restriction can course errors because of oversimplification, but it's often exact when focal activity is considered (Hallez et al., 2007). It is also believed to be more stable than the distributed models in handling signal-to-noise (Grech et al., 2008). Interpreting equivalent current dipole models, one must remember that the location of the dipole represents the center of gravity of the source. The actual source is often more superficial (Kaiboriboon et al., 2012). A rule of thumb is that the dipole can be

thought of as a flashlight with the head casting its light on the relevant area of cortex. For this reason, the orientation of the dipole is very important. Currently it is the most common used source model for clinical purposes (Kaiboriboon et al., 2012).

*Source models applied in study 4*

Because of the different pros and cons in non-parametric and parametric models, it is recommended to apply both in every source image procedure (Kaiboriboon et al., 2012). In the following the parametric equivalent dipole model, developed by BESA, will be described together with the most validated non-parametric distributed source model, LORETA, and a model developed therefrom, CLARA. In study 4 in this thesis we applied the BESA dipole and the Cortical CLARA model. Both models are available in the BESA software, which we chose, because it currently is the only software with a CE approval for clinical use in Europe.

In the BESA dipole model it is possible to use a single dipole, even moving from time to time. A discrete multiple source model mimics multiple active regions, e.g. of the epileptic network, to recover their temporal dynamics. In that sense it is similar to a distributed model, however not smeared out and moving, like the foci in CLARA do over time. The "onset" time interval of the spike analyzed has to be chosen subjectively, and the "peak" time interval is automatically generated at the maximum global field power (Scherg, 2014). Furthermore, a weighted combination of four conditions is incorporated in the model (Grech et al., 2008):

- A "Source Activation criterion" that considers if the source is active at another time interval than specified
- An "Energy criterion" that serves to differentiate, in cases with two sources
- A "Separation Criterion" that prioritize solutions where fewest sources are active at the same time
- The "residual variance" that calculates the share of the electric signal not being explained by the resulting source.

The LORETA model is built on a minimum weighted algorithm, which equally allows deep and superficial sources to be displayed. The algorithm uses a regularization method that "underdetermines" the inverse problem causing the accuracy of the result to increase with an increasing number of electrodes (Grech et al., 2008). Albeit being the most validated method LORETA has been claimed to provide an oversmoothed and widespread solution, that cannot distinguish sources if neighboring areas are active simultaneously (Jordanov, T. et al., 2014).

Trying to amend this the CLARA model (Jordanov, T. et al., 2014) takes into account smaller areas of source space at a time and begins by constructing a LORETA image and then adds the extra steps of:

- Another type of smoothening (with a 3D Gaussian kernel)
- Excluding grid points with amplitude below 1 % of the signal/spike amplitude
- Adding a spatial weighting term corresponding to the amplitude of the signal in each voxel

In the Cortical CLARA model, the calculation of CLARA is constraint to the cortical surface instead of being projected there (Jordanov, T. et al., 2016). In the BESA software, if no subjective timing is set the "peak" is automatically analyzed but it is also possible, to analyze the "onset" of the spike estimated subjectively with this model.

*Other parameters to consider in ESI*

Applying ESI, several other parameters than head- and source models, have to be assessed:

- Number of electrodes in the EEG array:
    - It has been found that HD EEG is to be preferred (Lantz et al., 2003a) (Brodbeck et al., 2011). At least the inferior-temporal electrodes should be included (Scherg et al., 2002). Increasing from 30 channels the highest gain was found at 63, whit a smaller gain increasing further to 123 (Lantz et al., 2003a).
- Time points of the IEDs/ICs being evaluated:
    - It is of outmost importance not only to analyze the peak of the event, but also the onset in order to address the propagation of the signal (Mălîia et al., 2016). In case of intra-discharge propagation, the earliest point with stable voltage distribution should be analyzed. If there are no clear propagation, the middle third of the rising phase is the appropriate time to analyze (Lantz et al., 2003b).
- Number and averaging of IEDs/ICs included in the analysis:
    - Averaging of events is generally performed to improve the signal-to-noise ratio (Mălîia et al., 2016). This averaging can be used to perform an automatic template search, allowing fast searches in large files and potentially incorporation of a large number of events in the final signal to be analyzed. The specifics of template generation and the least possible events identified when performing ESI lacks clarification (Plummer et al., 2008).

    - Seizures can be analyzed when a clear onset pattern is recognised, and the negative peaks can be averaged over 1–3 s (Beniczky et al., 2013).
- Clusters of IEDs/ seizure onset:
    - In a large ESI study of (Brodbeck et al., 2011) only the dominant spike cluster is analyzed. Nevertheless, the dominance of spikes clusters is known to vary with time. Therefore, in epilepsy surgery candidates all IED and seizure onset clusters should be considered providing information of the number of IEDs/ seizures from each cluster at the time of the analysis.
- Filtering of the EEG signals:
    - Using BESA software the EEG signal is applied a heavy filter of 4-50 Hz, improving the signal-to-noise ratio of the IEDs/ICs.
    - It has also been stretched that a zero-phase shift filter should not be applied because this potentially blurs the signal (Plummer et al., 2008).

*Accuracy of ESI*

The sensitivity and specificity of ESI has in a prospective study (Brodbeck et al., 2011) been found to be 84 and 88 % respectively. The sensitivity was calculated as the number of seizure-free patients in whom the source identified by ESI fell within the resection cavity. Specificity was calculated as the number of patients in Engel class III-IV having the source identified outside the resection cavity. These measures were based on 52 patients, HD EEG (128-256 channels), individual MR head model and the inverse model of LAURA. It was not described whether the electrode position file was individual or standard. Investigating LD ESI performed on a template brain the same study in a total of 152 patients found the sensitivity and specificity to be respectively 56 and 59 %.

Besides the study of (Brodbeck et al., 2011) several other studies from the group in Geneva (Lascano et al., 2016) (Mégevand et al., 2014) and (Birot et al., 2014) has confirmed that ESI is an accurate method.

From other groups the study of (Rikir et al., 2014) can be mentioned. It compared the localization of IED ESI with the location of the epileptogenic zone (EZ) identified by analyzing seizures recorded with intracerebral EEG in 28 patients included in their presurgical evaluation program expecting cortical malformation developments as the cause of their epilepsy. The comparison was made on a sublobar level (18 predefined locations). They applied a 64 channel EEG, individual MRI,

individual electrode position and two different source models (MUSIC and standardized LORETA). HD ESI and SEEG was fully concordant in 10, partial concordant in 15 and discordant in 3.

The above studies investigated ESI of IEDs, but the study of (Beniczky et al., 2013) investigated IC ESI accuracy in 22 patients and found it to be 73% comparing it to the final decision of the MDT, and 86 % in the 20 patients were comparison with resection zone and 1-year follow-up regarding seizure freedom was possible.

*The roll of ESI*

As stated by (Duncan et al., 2016) the role of ESI in the presurgical evaluation program is still not completely clear. This uncertainty also holds true concerning the choice of head and source model. At present it has been reported that eight epilepsy surgery centres in Europe perform ESI in adults and six in children, resulting in a total of nine centres counting the age groups as one. They use no less than 13 different combinations of head and- source models for the analysis, Table 4. The dipole model being the most popular source model and the individual MR-based method the most popular head model. The centres did not inform at which specific indications they applied ESI (Mouthaan et al., 2016).

*Table 4. Source (inverse method) and head model (volume conduction model) combinations currently used for EEG and MEG in European epilepsy surgery centers. LORETA: low-resolution brain electro-magnetic tomography. eLORETA: exact LORETA. sLORETA: standardized LORETA. LAURA: Local AUtoRegressive Average. MUSIC: MUltiple SIgnal Classification. (L)SMAC: (Locally) Spherical Model with Anatomical Constraints.* *Adapted from Mouthaan et al., 2016 with permission from John Wiley and Sons.*

| **Inverse method & volume conduction model combination** | # Centers for EEG (total n=9) | # Centers for MEG (total n=7) |
|---|---|---|
| Dipole | **5 (56%)** | **5 (71%)** |
| - Individual MR based | **3 (33%)** | **5 (71%)** |
| - Realistic | **1 (11%)** | **0** |
| - Spherical/Ellipsoid | **2 (22%)** | **1 (14%)** |
| sLORETA | **3 (33%)** | **1 (14%)** |
| - Individual MR based | **3 (33%)** | **1 (14%)** |
| - Realistic | **1 (11%)** | **0** |
| LORETA | **3 (33%)** | **1 (14%)** |
| - Individual MR based | **1 (11%)** | **1 (14%)** |
| - Realistic | **2 (22%)** | **0** |
| LAURA | **2 (22%)** | **0** |
| - Individual MR based | **1 (11%)** | **0** |
| - (L)SMAC | **1 (11%)** | **0** |
| MUSIC<br>- Individual MR based | **2 (22%)** | **1 (14%)** |
| Dynamic imaging of coherent sources<br>- Individual MR based | **1 (11%)** | **1 (14%)** |
| eLORETA<br>- Individual MR based | **1 (11%)** | **0** |
| Beamformers<br>- Multi spherical | **0** | **1 (14%)** |
| Current source density<br>- Spherical/Ellipsoid | **1 (11%)** | **0** |

Considering the promising results regarding sensitivity and specificity of ESI, and the fact that it is an applicable, low-cost, non-invasive method, the only missing information concerns the actual clinical utility of the method. Does it provide non-redundant information that justifies its implementation in the epilepsy surgery evaluation program. As opposed to several thorough studies of the clinical utility of MSI (Sutherling et al., 2008)(Knowlton et al., 2009)(De Tiège et al., 2012), this has only limitedly been addressed in ESI. IC ESI was performed by (Boon et al., 2002) in 31 patients of whom the surgical decision was affected in 14. Another study performed ESI in 10 children with extra-temporal lesional epileptic foci, but considered the ESI result in conjunction with their lesional MRI scan, claiming that it was useful in the surgical planning of six patients (Mirkovic et al., 2003). The added value of ESI was also investigated as a secondary purpose in the study of (Rikir et al., 2014), although not as an influence on the clinical decision, but as an added value compared to electroclinical correlation and MRI, using SEEG as a reference. In this context ESI had an added value in 12 of 28 patients.

Currently there is a request of: Blinded, prospective validation studies conducted on larger clinical groups, addressing the clinical utility of ESI (Plummer et al., 2008) (Tatum et al., 2018). The ESI in such studies should be based on realistic head models (Plummer et al., 2008).

# 4. Methods

## Study 1, Outcomes in Denmark

### Purpose and participants

The purpose was to investigate if the results of the Danish epilepsy surgery program from 2009-2014 corresponded to international standards and recommendations with respect to seizure outcome, adverse effects and referral patterns such as geographic distribution within the country, years of drug-resistance prior to referral and other patient characteristics. All 169 epilepsy patients operated in the period were included. In 2009 a new neurosurgeon took over and the start of the inclusion period was set here to assure uniform and comparable data.

### Study design

The flowchart of the Danish Epilepsy surgery evaluation program is depicted in figure 1. MEG was implemented in 2012. Presurgical clinical and demographic data together with data from postsurgical follow-up was collected from medical records. Postsurgical follow-up was performed at 6 weeks, 6 months, 1 year and 2 years. Seizure outcome was classified according to the Engel Classification, table 1. At each follow-up, complications and adverse effects were assessed. The severity was regarded as minor if the complication or adverse effect lasted less than 3 months, and major if it lasted longer and affected activities of daily living (Bjellvi et al., 2015) (Rydenhag and Silander, 2001). Patients were considered MRI positive if they had signs of HS, tumor, MCD, vascular malformation, post-traumatic lesions, infarction, bleeding residua, or encephalitis (Bien et al., 2009).

## Study 2, Surgical techniques and outcome

### Purpose and participants

We aimed to investigate the outcomes of SAH versus temporal lobe resection (TLR) in drug-resistant epilepsy patients with HS. The parameters of interest were seizure outcome and verbal cognition (learning and memory). A total of 56 drug-resistant epilepsy patients with histopathological verified HS operated at Rigshospitalet between 1995 and 2009 with left hemisphere dominance were included. Patients with intelligence level below normal range, native language other than Danish (in which the tests were performed) or dual pathology were excluded.

### Study design

Data was collected retrospectively. All resections were performed by the same neurosurgeon. Amygdalohippocampectomy and resection of adjacent temporal neocortex, TLR, was done in 34 patients. Selective amygdalohippocampectomy, SAH, was done in 22 patients. In SAH the surgical entrance was through the superior temporal sulcus. The decision about resection type and the extension of the TLR was guided by intraoperative electrocorticography (ECoG) in the majority of patients (47/56) (Kjaer et al., 2017). In the rest the choice was based on technical reasons (4/56 patients) or no detailed description for the decision-making could be found (5/56 patients). Seizure outcomes at 1-year and at 7-years after surgery were classified according to Engel (table 1). Patients in Engel class I were regarded seizure-free and weighted against patients in Engel class II-IV. Verbal learning and memory were evaluated before and one- or two-years after surgery. A Danish version of 15 Verbal Paired Associated words was applied. It consisted of 7 semantically related (e.g. mouse – cheese) and 8 unrelated (e.g. chimney – coat) pairs (Andersen, 1976). The word pairs were presented once and afterwards the patient was cued by the first word in the pair, and asked to mention the associated word. All 15-word pairs should be learned in 1 - 10 trails. Errors were counted and used as a measure of verbal learning. Retention with the cuing again by the first word was performed one hour later and the number of errors was used as a measure of verbal memory.

## Study 3, Safety and quality in EEG-fMRI

### A general comment, participants

Totally EEG-fMRI were performed in 40 subjects. After pilot scans using various fMRI sequences including fast sequences with short time of repetition (TR), our focus was directed towards heating safety aspects and the quality of the fMRI and EEG signals. In this study data from 24 of the investigated subjects was used (11 healthy controls and 13 patients with epilepsy).

### Purpose

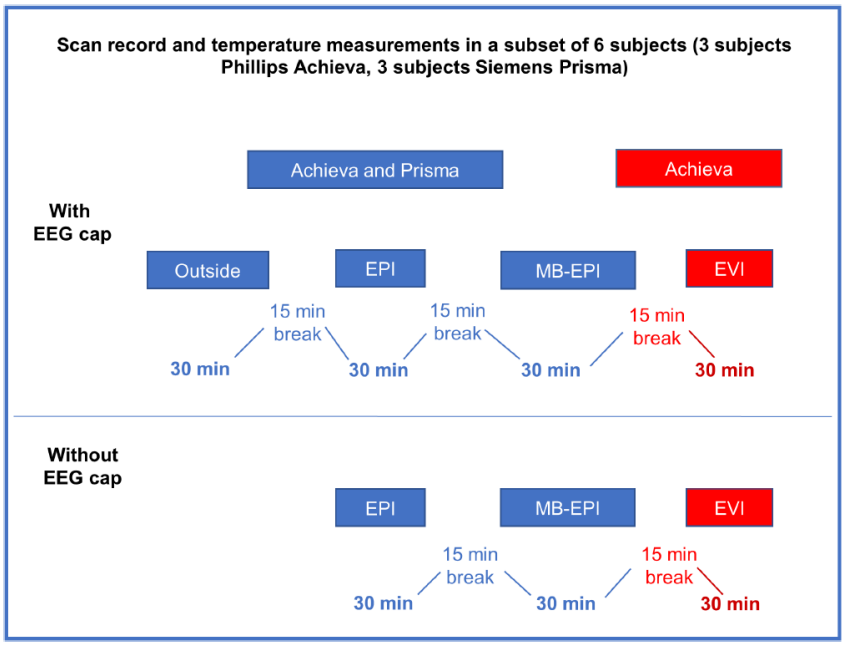
Our purpose was to investigate safety of RF related heating as well as cortical SNR in fMRI and EEG data quality in concurrent high-density EEG and high-speed fMRI.

### Study design

We compared echo planar imaging (EPI), multi-echo EPI (MEPI), MB-EPI and MS-EVI pulse sequences, using a Siemens Prisma and a Philips Achieva 3 Tesla MR scanner. Both scanners had receive-only array head coils. Three healthy controls were scanned with a 256-channel EEG system

the other subjects with a 64-channel EEG system. Initially surface temperature measurements were performed in phantoms. Thereafter scalp measurements were conducted in 5 controls and 13 patients, but not systematically for all sequences. At the end 6 controls (3 in the Achieva scanner and 3 in the Prisma scanner) had temperature measured systematically using all pulse sequences with and without the EEG cap, Fig 10. As for the temperature measurements, the scanning time for the different pulse sequences varied in the first 5 healthy controls and in the 13 patients, but in the last 6 controls, all pulse sequences were applied for 30 minutes, Fig 10.

*Figure 10 (paper 3). Flowchart of scans and temperature measurements.*
*EPI= echo planar imaging, MB-EPI= Multiband-EPI, EVI= Echo Volumar Imaging.*




To evaluate whether the EEG cap increased SNR in the fMRI, data from the same sequences investigating the same subject with and without the EEG cap was compared.
EEG quality was assessed by visual analysis in the 64 channel EEG data in seven healthy controls and in all the patients. The quality of EEG recorded during conventional (EPI, MEPI) fMRI scans was compared with the quality of EEG recorded during high-speed (MS-EVI, MB-EPI) fMRI scans.

## Study 4, Clinical utility of ESI

### Purpose and participants

Our purpose was to investigate the added clinical value of LD ESI and HD ESI on the surgical decision made by the multidisciplinary team (MDT) in epilepsy surgery candidates. We included 82 patients that went through the Danish epilepsy surgery evaluation program in the period from December 2015- June 2018.

### Study design

The study followed the protocol published in ClinicialTrials.gov May 23, 2018 (identifier: NCT03533530). For the epilepsy surgery candidates, a decision regarding surgery was first made according to the Danish epilepsy surgery evaluation program, Fig 1, blinded to the ESI results. The decision was noted, as 1) Stop, i.e. no operation or further evaluation offered, 2) Surgery can be performed, no further evaluation needed or 3) Further evaluation with ICR. Then the LD ESI result was presented and it was noted whether this changed the surgical decision as described in study 4. Finally, the HD ESI was presented and it was noted whether this changed the surgical decision according to the decision blinded to ESI (same categories as for LD ESI). Follow-up was performed when possible within the study period. In patients who underwent ICR, the irritative zone (IZ) was compared to interictal ESI, and the seizure onset zone (SOZ) to ictal ESI. If ictal ESI was not available interictal ESI was compared to both IZ and SOZ. The results were noted as concordant if they pointed to the same sublobar region (Beniczky et al., 2017). In patients being seizure-free at least 1-year after surgery, the source localization identified by ESI were compared to the resection area.

### Recordings

LD ESI was based on EEG recordings lasting several days, an EEG array with 25 channels (using NicoletOne) and a template head model with a template electrode position. The HD ESI was based on EEG recordings that lasted 1.5 to 2 hours, a 256 channel EEG array (using Philips EGI) and a head model based on an individual MRI with an individual electrode position file.

### ESI analysis

To ensure that the source images was of the best quality and based on uniform criteria, we used a very strict analysis protocol, as displayed in table 5. The software from BESA Research and MRI with the newest versions available was applied. These have the CE (Conformité Européenne) mark for medical use.

*Table 5. Electrical Source Imaging (ESI) analysis protocol.*

*IC= Ictal wave, LD= Low density, HD= High density, FEM= Finite Element Method.*

## 1. EEG inspection

- Use common average montage 33
- Choose 5-10 spikes for each focus

## 2. Averaging and template search

- "Average visually detected spikes". Document 'average spike' in power point according to step 3.
- If you analyze IC's or for other reasons wish to continue with the "averaged visually detected spikes", skip the following steps and go to step 3. If you want to search the EEG file for template matched spikes, continue with the next steps:
  - Set the filters to: 2-35 Hz in the 'average visual' file and the file to be search.
  - Apply a threshold of 85 % for the search.
  - After the search, check whether you have enough spikes detected (preferably 50), if to many (including erroneously ones) redo the search with a higher threshold, if to few spikes redo with a lower threshold, but not less than 75%.
  - "Average pattern searched spikes". Document 'average pattern spike' according to step 3.

## 3. Documentation

- Document the top view and voltage map of the peak in power point.
- Document the voltage distribution in power point.

## 4. Identification of onset

- Inspect the evolution in time of the sequence of the sequential voltage map, 0.0 ms should be in the right lowest corner.
- If you see an onset distribution different from the peak, note the time period of the onset, otherwise chose the onset to be at the middle third of the rising peak in the source analysis.

## 5. Source analysis

- Perform spike-fit for spike 1 according to the steps below. When done with spike 1, if more spikes: continue with spike 2, spike 3 etc. A filter of 5-40 Hz is applied.
  - In **LD ESI** choose the head model: "age appropriate template model" (the oldest 20-24 years, unless the patient is younger)
  - In **HD ESI** choose the head model: "individual FEM" (use the co-registered .sfh file)
  - Specify the time window for onset (using the period chosen under the sequential voltage maps). Check the principle component analysis (PCA), it should be higher than 95%. Check the residual variance (RV), it should be below 5 %.
  - Start the dipole fit. You will get one fit for onset (red) and one fit for peak (blue). Document with screen shots.
  - Start a Cortical CLARA fit, one for the onset chosen above and one for the peak. Document with screen shots.

# 5. Results and discussion

## Study 1, Outcomes in Denmark

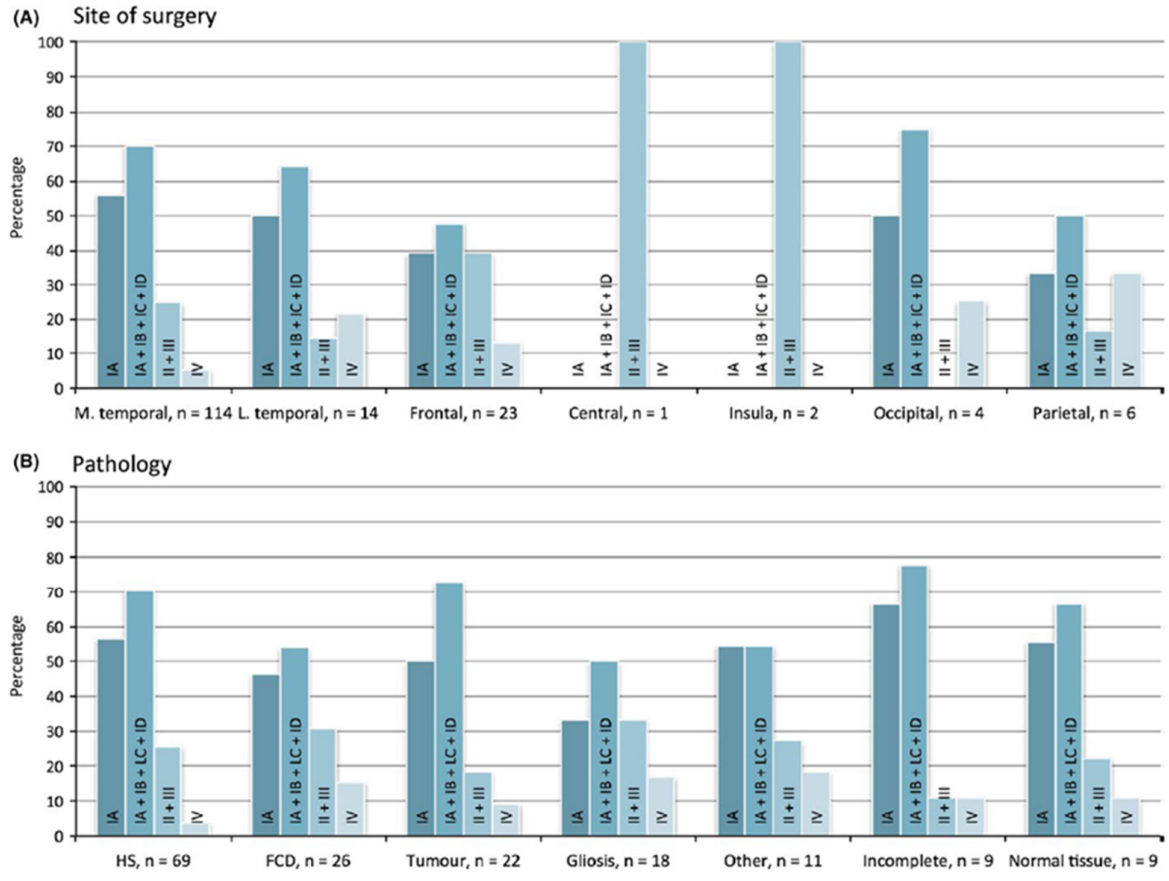
*Referral pattern*

In Denmark the total number of patients operated was 6.2 patients/year/1 000 000 inhabitants. This number corresponds to other western countries: 5.7 in Norway, 5.2 in Sweden, 8.1 in Finland (personal communication with the respective epilepsy centers; Tale Mæhre Torjussen, Anna Edelvik, Reetta Kalviainen) and 4.7 in US (Jobst and Cascino, 2015). The median number of AED's failed prior to referral for epilepsy surgery were 5 (interquartile range= 4-7). Three more than required to be diagnosed as drug-resistant (Kwan et al., 2010) and thereby to be a possible candidate for epilepsy surgery (Engel et al., 2003). Moreover, the median timespan from onset of epilepsy to operation was 19 years (interquartile range= 9-31) and the median duration of drug-resistance was 11 years (interquartile range= 4-23). We also found a significantly worse 1-year outcome in the group of patients with a duration of epilepsy of >10-years compared to patients with a duration of epilepsy <10 years (p=0.03). This association has though been rated as "inconsistent" in the recent systematic review of Jobst et al. (2015) (Jobst and Cascino, 2015). A major concern is a reduction in QOL, cognition and socioeconomic parameters if seizures remain (Mihara et al., 1996) (Wiebe et al., 2001) (Perry and Duchowny, 2013). Improvement in occupational status in patients after surgery has though not been found in the Danish study by Jennum et al. (2016) maybe due to a long period of drug-resistance prior to surgery (Jennum et al., 2016).

*Seizure outcome, "site-of-resection" and pathology*

Follow-up at 1-year were possible in 164 of the 169 patients included and follow-up at 2-years were available in 143/169. No significant difference was found, between outcomes at these two follow-ups in either MTLE (p=0.13) nor in ETLE (extratemporal lobe epilepsy) patients (p=1.00). The seizure outcome at 1-year follow-up with respect to "site of surgery" and "pathology" is displayed in Fig 11.

*Figure 11 (Paper 1). Engel outcome at 1-year follow-up with respect to A: "site of surgery" and B: "pathology". The 22 tumors consisted of 11 LEATs and 11 others. Dual pathology was seen in 10 of the 69 patients with HS. M.=mesial. L.=lateral. HS= hippocampal sclerosis. FCD = focal cortical dysplasia. Incomplete = probably HS, but did not fulfil the diagnostic criteria since part of the tissue was used for scientific purposes. Adapted from: Holm et al., 2018 with permission from John Wiley and Sons.*




In Denmark, as in accordance with other countries (Ryvlin et al., 2014), we found that most resections were performed in the temporal lobe (128/164). The distribution of identified pathologies, Fig 11.B, corresponded to the findings from the European Epilepsy Brain Bank inventory (Blümcke and Spreafico, 2012). Two notable differences were that LEATs were less frequent in our material (7% compared to 25%) and gliosis more frequent (11% compared to 5%). In our study oligodendrogliomas was not included in the group of LEAT.

Engel I was seen in 64 % off all patients at 1-year follow-up (105/164). Engel IA was observed in 51% off all patients (84/164). In 9 % (15/164) surgery did not lead to worthwhile

improvement (Engel IV). The Danish outcomes corresponds to results in systematic international reviews (West et al., 2015) (Jobst and Cascino, 2015).

A significant higher proportion of patients with MTLE was in Engel class I compared to all other patients (p=0.033). A high percentage of patients in Engel class I was also seen in the lateral temporal lobe epilepsy (LTLE) group and in the four patients resected in the occipital lobe.

Several factors can possibly affect the chance of seizure freedom. Two recent systematic reviews have defined a "history with febrile seizures" and "complete or extensive surgical resection" as positive predictors of seizure outcome (West et al., 2015) (Jobst and Cascino, 2015). "Concordant pre-operative MRI and EEG", "unilateral IEDs" and "pathologically verified HS or tumour" was also identified as positive predictors by one of the two reviews (West et al., 2015) whereas "seizures without loss of consciousness" and "long duration of being seizure-free postoperatively" was identified by the other review (Jobst and Cascino, 2015). "Normal preoperative MRI" and "need of ICR in the evaluation" was identified as negative predictors in both reviews (West et al., 2015) (Jobst and Cascino, 2015). "Pathologically verified FCD or MCD" and "left-sided resection" was identified as negative predictors by one of the reviews (West et al., 2015) and "preoperative generalized tonic-clonic seizures" and "infantile spasms or tonic seizures" by the other (Jobst and Cascino, 2015). "Duration of epilepsy" was among other factors found to have inconsistent association with seizure outcome (Jobst and Cascino, 2015). "The extent of surgical resection" and "duration of epilepsy" are the only parameters that can be affected by intervention. The other factors except pathology are prognostic and should be considered when evaluating and informing epilepsy surgery candidates. Of cause severe seizures such as the "generalized tonic clonic" will not advocate against surgery despite its identification as a negative predictor.

*AEDs and seizure outcome*

We also found that the number of AED's tested prior to epilepsy surgery evaluation was significantly higher in patients with a poor outcome (Engel class IV) than in patients with the best possible outcome (Engel IA) (p= 0.037; CI= 5.53:6.19). There was no significant difference in gender and age at operation nor in duration of drug-resistant epilepsy in Engel IA compared to Engel IV. This could imply that the patients in the Engel class IV group had a more severe and widespread disease prior to surgery and thereby an epilepsy of both medical and surgical refractoriness.

*ICR*

Patients in whom ICR was a part of the presurgical evaluation (52/164 patients) did not differ significantly in Engel I outcome compared to the patients without ICR in the evaluation (p= 0.49). It is a reassuring result because prior to 2006 when ICR became possible in Denmark these patients were not operated except for a minority sent to international epilepsy surgery centers for evaluation. Within the ICR group the MTLE patients had a significantly better outcome than the ETLE patients (p= 0.006). In the ETLE ICR group 60% of patients with frontal resections were in Engel class II+III and 10% in class IV. In the ETLE ICR group with other resections than frontal 38% were in Engel class II+III and 24% in class IV. It is a note of caution since ICR in the last couple of years has been performed in an increasing number of difficult non-MTLE patients.

From 2009-2014 one patient died in relation to ICR because of an intracranial hemorrhage. In section 3.1 "Surgical techniques, outcomes and complications" the risks of ICR from various methods combined including subdural strip and depth electrodes, often inserted with burr hole or twist drill, and subdural grid implantation with craniotomy is described (Hader et al., 2013). At present SEEG is the preferred method of ICR at our center. The pooled prevalence of mortality related to the use of SEEG has been found to be 0.3% (95% CI;0.1–0.6%) and overall morbidity 1.3% (95% CI;0.9–1.7%) excluding medical complications such as deep vein thrombosis, non-CNS infections, allergic reactions, and psychiatric changes (Mullin et al., 2016). The overall morbidity corresponds to one complication in every 29 patients implanted (presuming an average use of 10 electrodes per patient, from their entire sample of 22 085 electrodes) (Mullin et al., 2016). A recent study by Helmstaedter et al. (2018) showed that implantation of electrodes bilateral in the hippocampus along its longitudinal axis can lead to impairment in verbal learning, verbal memory and recognition performance. Consequently, the center in Bonn changed their implantation strategy to include only one hippocampus whenever possible and later started to use SEEG with lateral implanted electrodes placed orthogonally to the long axis of the hippocampus which is the same procedure used in our center (Helmstaedter et al., 2018). Risk of neuropsychological impairment caused by implantation in other brain regions and with different strategies should be systematically evaluated with the newest available neuropsychological tests.

Considering the application of ICR its limitations as a golden standard must be mentioned. In a study by Knowlton et al (2008) 84% with localized ICR was considered true positives, Engel class I or II (Knowlton et al., 2008). Of these 74% were focal and 10% multifocal. Because of the narrow sight of ICR a substantial number of patients will be false negative. Another aspect using ICR is economy and in a study from US it has been estimated that the majority of health care expenses in epilepsy surgery is spend on patients requiring ICR (Platt and Sperling, 2002). However, in case of

very severe epilepsy with a substantial seizure burden and risk of "sudden unexpected death in epilepsy" (SUDEP) it may be very difficult not to offer patients ICR if plausible hypotheses of the EZ can be formulated even though the chance of seizure freedom are small, e.g., patients with a non-lesional MRI to be implanted outside the mesial temporal lobe.

*Non-lesional MRI*

No patients with a non-lesional MRI operated outside the mesial temporal lobe (8/164) were free of disabling seizures at 1-year follow-up. In contrast 78% (14/18) of MTLE patients with no lesion on MRI were in Engel class I. In nine patients operation was performed without ICR even though MRI were non-lesional. Here the resection was based on results from other modalities (often FDG-PET). The six patients with MTLE all had an Engel I outcome or better at 1-year follow-up. None of the three ETLE patients did. It will be exciting to see results from the use of 7 T MRI that might decrease the number of non-lesional MRI patients. Currently a PhD student at our department is investigating this.

*Complications*

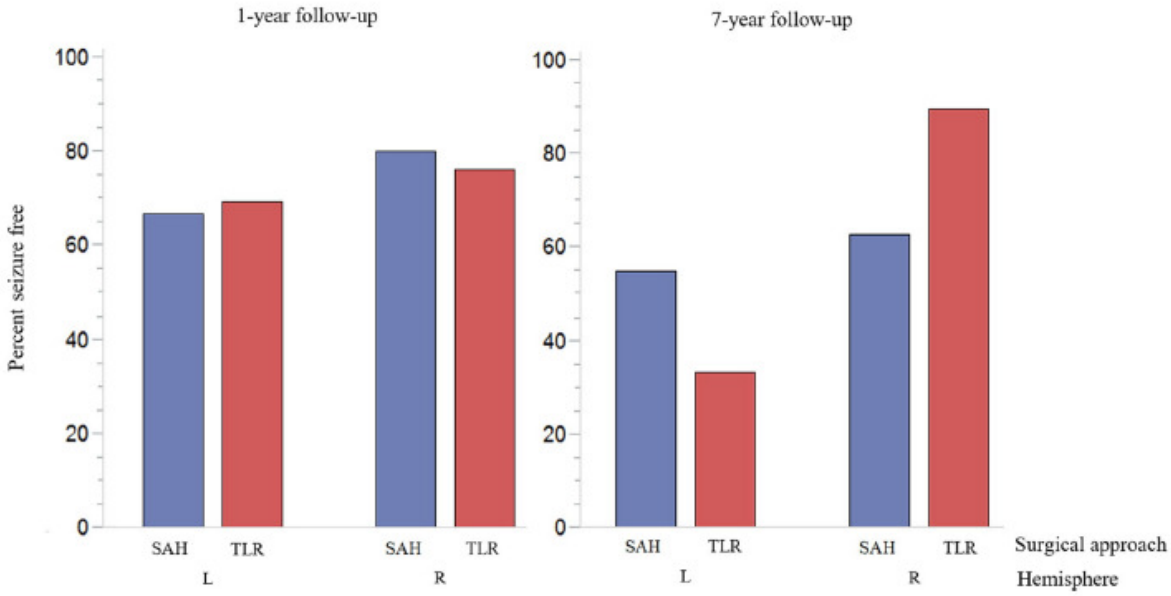
De novo depression (requiring antidepressants and/or psychotherapy) was seen in 13/164 patients, 8%, within the first year following epilepsy surgery. This is in accordance with the range of 4-18% reported in a recent systematic review (Jobst and Cascino, 2015). The majority of these patients had MTLE, 11/13 patients. Major surgical complications were rare 1.8% (3/164). This is close to the 1.5% found by (Hader et al., 2013). All incidents were caused by a postsurgical hematoma leading to severe motor impairment and in one patient also dysphasia. These complications had improved but not disappeared at 1-year follow-up.

### Study 2, Surgical techniques and outcome

At 1-year follow-up, 73% of all 56 included patients were "free from disabling seizures" (Engel class I). No significant difference was found between the SAH (72.7% Engel class I) and the TLR group (73.5% Engel class I) (p=0.951) nor between patients resected in the right hemisphere compared to patients resected in the left hemisphere (p=0.431).

At 7-years, 64% of the 50 patients with follow-up, were in Engel class I. An unadjusted model showed no difference in seizure outcome between the TLR and SAH approach in patients operated in the same hemisphere (p=0.177).

*Fig 12. Number of patients in Engel class I at 1- and 7-years follow-up with respect to hemisphere (L= left/ R=right) and surgical approach (SAH= selective amygdalohippocampectomy/ TLR= temporal lobe resection).*



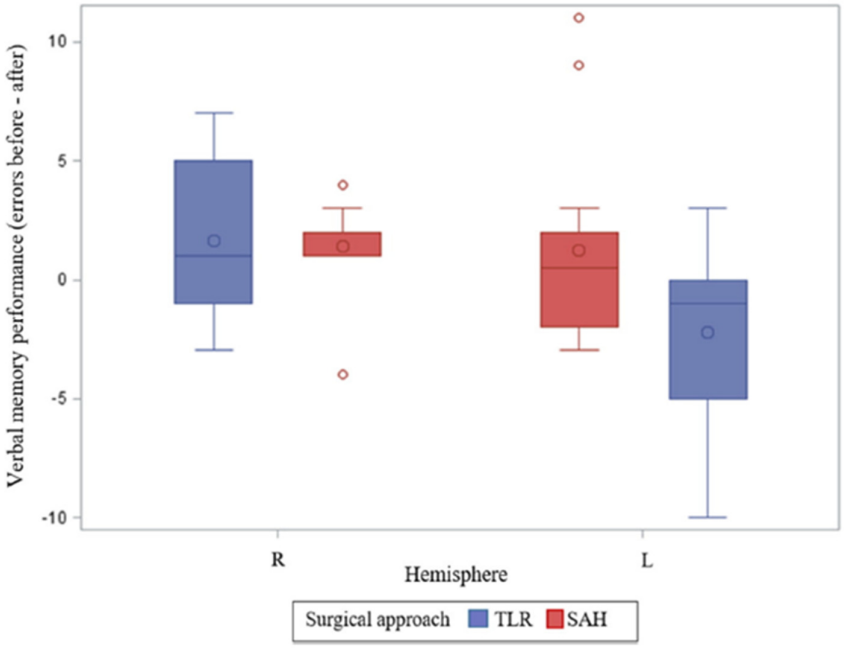

A decrease in the number of patients "free from disabling seizures" at long-term follow-up, 7-years, compared to the results at 1-year was expected (Edelvik et al., 2013) and emphasizes that patients must be informed about both short-term and long-term outcome before surgery.

With regard to the 7-year outcome, although not significant, the effect of the surgical approach in the left hemisphere on the percentage of patients in Engel class I, is unexpected, Fig 12. A low percentage of patients in Engel class I in the left TLR group could be related to a more cautious

approach when removing neocortical tissue in the language dominant left hemisphere (TLR). However, this does not explain that for patients operated on the left side the percentage of patients in Engel class I was higher in the SAH group compared to the TLR group (though not reaching significance).

In the verbal memory test, patients operated on the left side with a TLR performed significantly worse compared to all other patients (p=0.011) and compared to patients operated on the same side but with a more selective approach (left SAH) (punctual estimate: −3.49, p=0.036), Fig 13.

*Fig 13. Boxplot of the verbal memory performance in each hemisphere (L= left/ R=right) and with each surgical approach (SAH= selective amygdalohippocampectomy/ TLR= temporal lobe resection).*




With respect to the verbal learning test, patients resected on the left side performed significantly worse than patients resected on the right side (punctual estimate: −13.9, p=0.002). There was no significant difference in verbal learning between the patients who had the TLR compared to the SAH approach (p=0.978).

Impaired verbal memory has been found in the majority of previous studies and most often following dominant temporal lobe resections (Spencer and Huh, 2008). In this context it is important to note that the phrase "verbal memory" in many studies both covers the term "verbal learning" and "verbal memory" as used in our study. A general concern in this area is that the

tests applied varies considerably (Spencer and Huh, 2008). A more pronounced reduction in verbal memory after operation has been found if tissue that appears normal on MRI has been preserved prior to operation (e.g. patients without HS). Furthermore, enhancements in verbal memory and full-scale IQ following non-dominant temporal lobe resections have been described but data are biased by factors such as missing long-term follow-up and unclear retest effects (Spencer and Huh, 2008).

Important limitations in this study were:

- That not all patients had a Wada-test performed
- The neuropsychological test battery was limited
- The number of patients in each group was small
- The patients were not randomized with respect to SAH or TLR but the surgical approach was decided by ECoG results
- The surgical extend varied within the TLR group (tailormade approaches based on ECoG)

Despite the limitations it is important to note that it does not change the finding that patients resected in the dominant left hemisphere with a TLR had a worse outcome in verbal memory performance compared to all other patients and that patients resected in the left hemisphere had a worse outcome in verbal learning. The study analyzed the difference between the preoperative score and the postoperative score and therefore provided a measure of the change from baseline in the verbal learning and verbal memory test, in each patient.

As mentioned in the background section 3.1 “Surgical techniques, outcomes and complications” the extent of resection to obtain seizure freedom with limited neuropsychological deficits continues to be heavily debated. A meta-analysis of 11 studies and 1203 patients in total found that a significant higher chance of Engel Class I outcome after anterior temporal lobectomy (ATL) compared with SAH (risk ratio 1.32, 95% CI 1.12–1.57; $p < 0.01$) with the number needed to treat (NNT) of 13 patients (95% CI 7–33) (Josephson et al., 2013). The study included all patients with temporal lobe epilepsy but a subgroup analysis of 10 studies only including patients with HS confirmed the findings in the entire sample, though with a large CI for the NNT (risk ratio 1.26, 95% CI 1.05–1.51, $p < 0.01$; NNT = 14. 95% CI 8–100). The operative risks were comparable in the two groups, SAH and ATL (risk ratio 1.15, 95% CI 0.19–6.87, $p= 0.88$).

This meta-analysis is robust but has certain limitations. The investigators had to accept the authors' statement that both an ATL and SAH was performed in some studies and none of the included studies compared the extent of resection between approaches using postoperative MRI. Furthermore, the surgical technique of the SAH was not always described and when listed both contained the transsylvian and the transcortical approach. Most studies used a "standard ATL" but one study applied an anteromesial approach to the ATL. The follow-up duration ranged from 1-year to a median of 11-years and was not reported in 2 studies. Finally, the risk of publication bias must be mentioned. Although requested by the investigators a meta-analysis of neuropsychological outcome was not possible because of heterogenous testing and reporting in the included studies. For further literature on the topic please see section 3.1 "Surgical techniques, outcomes and complications". As concluded by Josephson et al. (2013) a randomized controlled trial is justified.

Currently new surgical techniques with the ability to perform minimal invasive surgery i.e. stereotactic radiosurgery and thermal laser ablation have been introduced. They already provide important knowledge of seizure and cognitive outcome in selective resections, knowledge that most likely will increase in the future. In the RCT study by Barbaro et al (2018) stereotactic radiosurgery (31/58) was compared to ATL (27/58) in 58 MTLE patients. In the radiosurgery group "freedom from disabling seizures" (Engel I) was seen in 16/31 (52%) and in the ATL group in 21/27 (78%) at follow-up between 2- and 3-years. Based on these results the authors suggest that stereotactic radio surgery should not be the first choice in MTLE patients. At 3-years no difference in improvement of QOL between patients who had radiosurgery and patients who had ATL was found ($p>0.05$). Patients "free from disabling seizures" improved more in QOL compared to patients not "free from disabling seizures" ($p=0.033$). Verbal memory was tested in 21 patients with surgery in the dominant hemisphere (14 stereotactic, 7 ATL) and was found to worsen consistently in 5 (36%) radiosurgery patients and 4 (57%) ATL patients. Serious complications were seen in 5/31 radiosurgery patients and 3/27 ATL patients. Remission occurred in all patients except one. The use of steroids was more than twice as high in the radiosurgery group. Radiosurgery can be difficult to control and more promising results are hoped for with the use of thermal laser ablation (Tao et al., 2018). In the study of Tao et al. (2018) 8/11 patients (73%) with HS were in Engel class I, but only 3/10 patients (30 %) without HS at a mean postoperative follow-up of 24±11 months. Interestingly: *"there was no significant difference in total ablation volume and the percentage of the ablated amygdalohippocampal complex between seizure-free and non-seizure-free patients"* (Tao et al., 2018).

### Study 3, Safety and quality in EEG-fMRI

This study showed that a 30-min EEG-fMRI scan with traditional (EPI, MEPI) and high-speed (MS-EVI, MB-EPI) sequences on two different scanners with different high-density EEG equipment could be conducted safely with respect to heating. Temperature increases underneath the EEG surface electrodes, expected to be induced by the RF field, did not exceed 1.0 º giving a stable temperature prior to the scan. This temperature increase is far below the maximum temperature limit of 43 º *"of an applied part in skin contact e.g. an electrode"* set by the IEC in 2005 (Allen, 2010).
It was also found that the presence of the EEG cap did not lead to any significant decrease in cortical SNR in the fMRI scans ($p > 0.05$). Nevertheless, applying the 256 channel EEG array in the Siemens Prisma scanner, let to a trend level decrease in SNR ($p < 0.063$). This was not found applying the 64 channel EEG system on the Phillips Achieva scanner. To explore the trend decrease in SNR, in the first setting, more patients could be investigated and recordings with the two different EEG systems (64-, and 256 channels) could be performed in the Siemens Prisma scanner on the same subject. We concluded that such extra investigations would not add substantially to the use of EEG-fMRI and therefore did not explore this further.

In the EEG data we did not find any significant difference in quality comparing EEG recorded while high-speed sequences were applied to EEG recorded while conventional EPI fMRI sequences were applied ($p = 0.78$). Furthermore, motion was not found to affect the quality statistically significant. Regarding the EEG quality, in total 58% of the data was rated as "poor" mainly due to residual ballistocardiographic artifacts. This is discouraging especially when the purpose was to study epileptic networks and, in this context, I must agree with the statement that:

> *"The EEG-fMRI marriage has not been so cosy".* (Plummer et al., 2008)

To sum up; temperature, SNR in fMRI and differences in EEG quality, showed that the recently developed high-speed sequences (MS-EVI and MB-EPI) together with high-density EEG recordings has a promising future in EEG-fMRI studies but the general "poor" EEG quality is a problem.

*Considerations on the use of EEG-fMRI*

At the beginning of this PhD project we explored the potentials of the EEG-fMRI method in epilepsy surgery candidates and during this process we met additional practical and theoretical problems to that of "poor" EEG quality;

1. It was difficult to obtain sleep and long-term recordings inside the scanner. Two factors important for the chance to catch IEDs.
2. In the few cases where IEDs were believed to be identified our preliminary results of "IED triggered fMRI" were not convincing.
3. We had theoretical concerns modelling the fMRI because:
    a. fMRI has a time resolution that is 1.000 times lower than that of EEG which makes it questionable what neuronal activity the fMRI measures. A lot of neuronal synchronous activation and deactivation, measured in ms, can happen within the 25 seconds of an HRF.
    b. IEDs can lead to an increase as well as a decrease in the BOLD signal which further complicates the analysis and interpretation of the fMRI results (Gotman et al., 2006)
    c. The HRF can vary between individuals (Aguirre et al., 1998) and possibly between spike populations (Bagshaw et al., 2004). This potentially requires the use of multiple HRFs, still leaving a high percentage of patients in whom no significant correlation between spikes and BOLD activation is seen (Bagshaw et al., 2004).
    d. The fMRI analysis requires a subjective application of thresholds, that has a high influence on the spatial resolution of the results (Plummer et al., 2008).
    a. Some IEDs arising from deep structures or an area smaller than 10 $cm^2$ is not visible in the surface EEG (Tao et al., 2005) but can potentially affect the BOLD signal. This complicates the interpretation of EEG-fMRI further.

To gain more knowledge of the coupling between IEDs and HRF one should study each individual epilepsy patient when they are in a condition with frequent spike activity and when they are in a condition with no spike activity. In this way, one could maybe get a sense of more prolonged activity changes between these two states. However, it is not possible to foresee such shifts in the IED frequency and challenges of how to follow the development of an IED in a temporal manner with the BOLD signal would limit the clinical usefulness of such an approach.

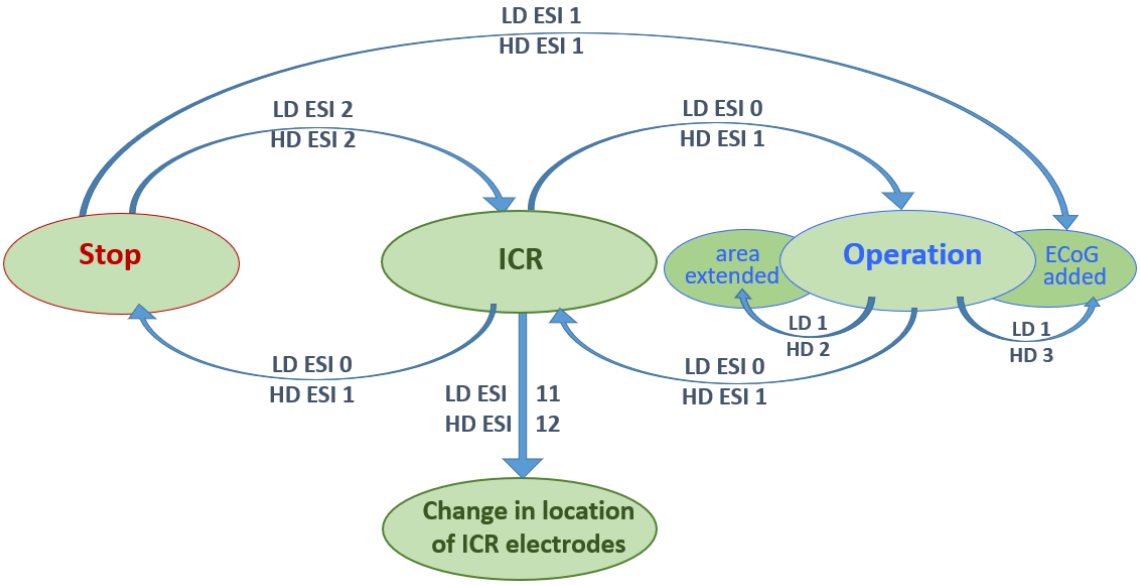
We decided not to proceed with investigations in epilepsy surgery candidates with the aim of implementing the method in the epilepsy surgery evaluation program. Instead we used our experience to perform a study of the methodological aspects and safety in concurrent high-speed fMRI and high-density EEG, which is believed to be usable in other subfields. Of relevance we can mention one ongoing study at our department were the EEG is used to assess when a patient is a sleep during an fMRI scan. Here the EEG changes have much larger amplitude than that of IEDS and the coupling in milliseconds to the fMRI isn't needed but the advantages of high-speed sequences are. In stimulation studies (e.g. pain, auditory, visual) the ERP response also have a larger amplitude than the IED and the advantage of a controlled and known onset.

### Study 4, Clinical utility of ESI

*Results*

LD ESI led to a change in the MDT decision in 20% of the patients (16/82) whereas HD ESI led to a change in 28% of the patients (23/82) evaluated for epilepsy surgery. ESI using a 256-array and individual MRI had higher impact on the clinical decision than ESI using LD EEG data from the LTM routine work-up and an age-matched template brain model ($p<0.001$). The distribution of the different types of changes in decision is shown in Fig 1. Changes were most often seen in the step of ICR planning but were also observed in all other possible steps (8/8) based on HD ESI and in 5/8 steps based on LD ESI.

**Fig. 1**. *Distribution of changes in decisions in the 82 included patients following presentation of low-density electrical source imaging (LD ESI) and high-density electrical source imaging (HD ESI) respectively. ICR= intracranial registration. ECoG= perioperative electrocorticography. Stop= No operation nor any further evaluation.*




In the LD LTM recordings the number of patients without epileptiform discharges was lower than in the 1½ to 2-hour HD EEG recordings and consequently the number of results concordant with the MDT conclusion was higher in LD ESI compared to HD ESI.

Follow-up was possible in 5/16 patients with LD ESI changes and in 10/23 patients with HD ESI changes within the timeframe of the PhD program but we will continue to collect these data. In the sample of available follow-ups, comparing ICR IZ/SOZ and seizure outcome with the ESI localization, results has varied. In 3/4 patients where LD ESI lead to a change in the

implementation plan, the change lead to identification of the IZ or SOZ. In HD ESI this was observed in 4/6 patients.

*Limitations*

Selecting the signals and especially analysing the onset of the epileptic discharges is a crucial and challenging task, only meant to be performed by neurophysiologist that besides knowledge of the fundamental principles behind the EEG signal has special training and expertise in source imaging. For example, performing the step of pattern search (table 5) the result should be cautiously evaluated minimizing the risk that erroneous spikes are included, especially in spike clusters with similarity to eye movements or other artefacts. In future studies it should be addressed how many spikes that minimally is required when ESI is applied.

Furthermore, the co-registration of the MRI and the electrode position file needs careful attention. A standardized protocol should be developed and followed also in this step of the ESI analysis. In the present project a standardized protocol was developed but applying the "electrode position file" on the "MRI computed head surface" different settings are available and here the consequence of the choice made needs to be analyzed further. Also, pictures of the patient are taken with the photogrammetry system (applied in 62 patients) and these pictures should be viewed to verify that the electrode placement in the virtual platform corresponds to the real distribution at the time of the EEG recording. This is not possible using the Geoscan system (applied in 20 patients) and whether this has any consequences should be evaluated. Furthermore, it should be recognized that the subcutis in the patients' head does not always have the same position when the EEG electrode file is registered (sitting position) as when the MRI is performed (supine position). Therefore, some electrodes might not be visible when the electrode position file is placed on the MRI computed head surface. However, the placement of the hidden electrodes will also be computed.

As touch upon in the background section 3.2 regarding EEG, the cortical area responsible for an IED, with a reasonable detection rate on a scalp EEG, has been estimated to 10 $cm^2$ (Tao et al., 2005) and with regard to IC's 10-19 $cm^2$ depending on the brain region (Tao et al., 2007). For this reason ESI cannot be regarded more accurate than sublobar level and applying the method, as summed up by Grech et al (2008), it is important to recognize that: *"The accuracy with which a source can be located is affected by a number of factors including head-modelling errors, source-*

*modelling errors and EEG noise (instrumental or biological)"* (Grech et al., 2008). A suggestion by Plummer et al (2008) that error measures, e.g. confidence ellipsoid volumes, could be incorporated into the ESI results, seems a suitable way to take these problems into account (Plummer et al., 2008). In contrast to the limitations of ESI, the opportunity of prolonged recordings provides an outstanding chance to catch and analyse IEDs and especially ICs comparing the method to other modalities e.g. MSI and EEG-fMRI and the time resolution of the method is exceptional.

*Implementation*

ESI has been implemented in the Danish epilepsy surgery evaluation program as shown in figure 1 (Pinborg et al., 2018) and LD ESI will from now on, based on results of this study together with results of the study of Sharma et al (2018) and with regard to an economic perspective, be performed in all epilepsy surgery candidates (Sharma et al., 2018). HD ESI will be performed in a selected subset of patients where the EZ is especially difficult to identify. More exact criteria for which patients to offer HD ESI are needed. Intuitively, HD EEG should not be offered to patients without epileptiform discharges recorded in the routine LD LTM work-up but in our study two such patients had interictal spikes in the HD EEG recording. Hopefully we will be able to make suggestions to criteria for application of HD ESI when more follow-up data is available. Furthermore, in the near future we hope to be able to replace our standard 25 electrode LD caps for long-term monitoring with 40 electrode LD caps achieving a higher precision in the routine work-up.

# 6. Conclusion on the thesis objectives

1. Conclusions regarding results of the Danish epilepsy surgery program

    - *Are the Danish patients referred according to ILAE's recommendations with respect to number of AED's tested and duration of drug-resistant epilepsy?*
      No, they are not. A median of 5 different AED's are tried and a median "duration of drug-resistant epilepsy" of 11 years are seen before patients are referred to surgery.

    - *Does the seizure outcome in patients operated in Denmark correspond to international standards?*
      Yes, the seizure outcomes in Denmark (65% of all resected patients in Engel class I) is in line with international results, and the number of operated patients in Denmark (6.2 patients/year/1 000 000 inhabitants) corresponds to the number of operated patients in other western countries.

    - *What is the status of postoperative complications e.g. depression and loss of cognitive function. Is the change in cognitive function affected by the surgical approach?*
      The number of postoperative major surgical complications (1.8%) are in line with what has been found internationally. This also holds true with regard to de novo depression after surgery which was seen in 8%. Concerning cognitive function, a non-selective surgical approach (TLR) in the left hemisphere was associated with a worse outcome in verbal memory. Whereas, verbal learning was found to be worse in all patients operated in the left hemisphere. We found no difference in seizure outcome between the non-selective (TLR) and the selective (SAH) approaches after one year, but results after seven years were more ambiguous.

2. Conclusions regarding new technologies, with a possible position in the presurgical evaluation program
    - *Further development and exploration of the use of concurrent fMRI and EEG (EEG-fMRI).*

Concurrent high-density EEG and high-speed fMRI data at 3 Tesla can be recorded safely with respect to potential heating caused by the RF. The fMRI signal can be interpreted despite of the presence of a high-density EEG cap. However, the EEG quality is affected to an extent that does not allow interpretation of subtle sporadic epileptic activity but may be sufficient in studies of evoked potentials and sleep. At least for now EEG-fMRI will not be implemented in the Danish epilepsy surgery evaluation program.

- *The clinical utility of Electric Source Imaging based on High Density (HD) and Low Density (LD) EEG.*

  Both LD and HD ESI have been proven useful in the clinical decision making. HD ESI has a higher impact on the clinical decision making than LD ESI ($p < 0.001$) but the time cost to perform LD ESI is lower and the chance to catch IEDs and ICs is higher. Consequently, at our center, it has been decided that LD ESI will be performed in all epilepsy surgery candidates and HD ESI in a selected subset of difficult cases. In the near future, when more follow-up data is available, we hope to be able to suggest exact criteria of which patients will benefit the most from HD ESI.

# 7. Perspectives

*How to comply with international standards: information campaign and political initiative*

At present the international recommendations regarding referral of drug-resistant patients to epilepsy surgery evaluation in Denmark are not all fulfilled (study 1). Danish patients have tried more than 3 AEDs (median number of 5, interquartile range= 4-7) before referral and have had drug-resistant epilepsy in a median of 11 years (interquartile range= 4-23) prior to surgery (study 1). Based on these facts, I have been part of an information campaign directed towards patients, relatives and health care personnel in Denmark. So far, we have published a review paper directed towards physicians in Denmark in the Danish Medical Journal (Pinborg et al., 2018) and a podcast in the same journal (Pinborg and Jespersen, 2018). I have also participated in one of two television programs about epilepsy surgery (Danish Broadcasting Corporation, 2017a) (Danish Broadcasting Corporation, 2017b) and made an information video of HD ESI directed to epilepsy surgery candidates and their relatives (Foged et al., 2017).

Besides the information campaign, a political initiative resulted in a meeting in the Danish parliament, in December 2017, with participation of The Danish Health Authority and experts in epilepsy. At this meeting it was discussed how patients with severe epilepsy could gain a higher priority in the Danish Health care system (The Danish Health Authority, 2017) and a report by the Danish Health Authority is to be published in 2018. An important step forward would be national guidelines regarding drug-resistant epilepsy patients and construction of a national quality control database that would allow monitoring of the extent to which guidelines are followed throughout the country.

*How can we learn from the past: databases – big data*

The collection of retrospective data for study 1 and 2 has been difficult and is eligible to bias. Thus, during my PhD a comprehensive prospective Danish epilepsy surgery database has been constructed that also allows for exchanging data with the database of E-PILEPSY network supported by the European Agency for Health and Consumers. Ideally data between this prospective epilepsy surgery data base and a national quality control database could be shared. With regard to the E-PILEPSY network combining data from several centers holds difficulties e.g. caused by the heterogeneous use of modalities at different hospitals (Mouthaan et al., 2016) and different organization and members of the MDTs. Nevertheless, unifying data collection is an important step forward.

Identification of the EZ may be one of the most complicated evaluation processes in medicine and involves many different modalities and techniques. Even when data appear to be concordant a substantial number of patients are not seizure-free and some patients suffer from adverse effects of surgery. Hopefully, the future integration of international datasets and the use of new tools for analyzing big data including artificial intelligence / machine learning techniques will pave the way for a more precise evaluation program with improved surgical planning and better predictions of outcome and adverse effects. Likewise, better criteria for when to stop the epilepsy surgery evaluation could be anticipated.

*Tailormade- and minimal invasive surgery*

In spite of the limitations of study 2 I believe that it has been important in the national setting. For the first time in Denmark, we analyzed outcomes of the epilepsy surgery evaluation program in adults and demonstrated promising results with the use of a unique surgical entrance through the superior temporal sulcus in the SAH approach and with perioperative ECoG to guide the approach and the extent of tissue to be removed.

However, one important question has still not been answered:

- Does surgery with ECoG provide better results with respect to seizure and cognitive outcomes than surgery without ECoG?

It is uncertain what the future will bring but maybe the collection of big data prospectively can shed light on this topic as well.

Forthcoming use of minimal invasive surgery such as stereotactic radiosurgery and laser thermal ablation (Tao et al., 2018) (Barbaro et al., 2018) could change the number of patients that are referred to and accepts epilepsy surgery. Here, open surgery can be avoided and the selectiveness of the methods may decrease the risks of neurocognitive deficits. Expectations are especially high with regard to laser thermal ablation because injury of tissue surrounding the lesion can be prevented, a sharp delineation of the lesion can be obtained and the efficacy is immediate. Currently an interventional, multicentre clinical trial: "Stereotactic Laser Ablation for Temporal Lobe Epilepsy" (SLATE) in the US is recruiting patients and aims to include 150 patients (ClinicalTrials.gov Identifier: NCT02844465).

*Implementation of new modalities – ESI*

The ratio of patients with HS undergoing epilepsy surgery has decreased from 39% of all resections in the 1990s to 20% in the 2010s but the total number of TLE resections has remained stable (Baud

et al., 2018). ETLE resections have increased from 15 to 26% of all resections in the same period and the number of multilobar and hemispheric resections have increased markedly as well (Baud et al., 2018). This development must be seen in the light of an increased focus on epilepsy surgery and improved diagnostic possibilities e.g. with the introduction of 3 T MRI (in Denmark in 2002). The area of epilepsy surgery is under constant evolution. The development and implementation of more sensitive and specific evaluation techniques together with new and possibly less invasive surgical approaches are needed to be able to offer surgery to a larger group of drug-resistant patients and with a better outcome.

The use of EEG-fMRI in epilepsy surgery evaluation has not been promising. However, ESI has during this PhD period been implemented in the presurgical evaluation program, and because of the good results, it will continue to be part of it. HD EEG will form basis of ESI in patients were the localization of the IZ is especially challenging and we hope, in the future, when more follow-up data is available, to be able to suggest more exact criteria for the selection of patients with the highest advantage of the method. Future developments of ESI might lead to an automatization of the method (Baroumand et al., 2018) which would markedly lower the costs and increase the availability of the method. However, I believe that ESI is a method that should be applied and interpreted by neurophysiologists who have received a thorough training in the method.

Forthcoming one could hope that the conductivities of tissues that the electric discharges pass to reach the scalp electrodes can be estimated with a higher precision. This is the most important limitation of the method as for scalp EEG. Another limitation is the insecurities in the co-registration process of an individual electrode position file with an individual MRI scan. Potentially these problems can be solved, but they require fine-tuning of the approach and collaboration with the soft- and hardware developers. Finally, it should be mentioned that a very elegant approach to use ESI in combination with connectivity to localize the SOZ has been published and might show yet another promise of the method (Staljanssens et al., 2017). The HD EEG dataset obtained during this PhD represent a unique database and several projects based on these data are currently being planned.

At the moment we are systematically testing the clinical utility of 7T MRI using a similar approach as for HD EEG. It will be exiting to follow the use of this modality in epilepsy surgery evaluation. Much effort is spend investigating and implementing new modalities in the epilepsy surgery flowchart. This is both justified and needed. Still, in this process one must not forget that it is the choice of application of the modalities, the question of when to stop further evaluation and the ability to organize the evaluation and the MDT meetings, which primarily makes a difference.

*A concluding remark*

On one side there is a request for more patients with focal onset epilepsy to be referred for epilepsy surgery evaluation as soon as drug-resistant epilepsy has been diagnosed but on the other side the epilepsy surgery evaluation program have limits. This dilemma was discussed at the 13th European Congress of Epileptology by Christian Elger: *"Epilepsy surgery is underused"* and John S. Duncan: *"Epilepsy surgery is overused"*. These headlines contain a very important message. Patients with drug-resistant epilepsy should be referred according to the existing guidelines and patients deemed eligible for surgery should be offered resection within a reasonable timeframe. However, it is important not to get so caught in the chase of the EZ that the epilepsy surgery evaluation is perceived as a one-way path.

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# Appendix

### Paper 1, 2, 3, 4

1. Efficacy of the Danish epilepsy surgery program.

2. Verbal learning and memory outcome in selective amygdalohippocampectomy versus temporal lobe resection in patients with hippocampal sclerosis.

3. Safety and EEG data quality of concurrent high-density EEG and high-speed fMRI at 3 Tesla.

4. Clinical Utility of ESI in Presurgical Evaluation of Patients with Epilepsy (CUESIPE).

Paper 1

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ORIGINAL ARTICLE

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# Efficacy of the Danish epilepsy surgery programme

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**Objective**: Despite optimal medical treatment, approximately one-third of patients with epilepsy continue to have seizures. Epilepsy surgery is widely accepted as a therapeutic option in the selected subset of patients with drug-resistant focal epilepsy. Here, we report the results of the Danish epilepsy surgery programme from 2009 to 2014.

**Material and methods**: A total of 169 consecutive patients, operated at Rigshospitalet, were included. Information was gathered from digital patient records. Before 1-year follow-up, two patients were lost to follow-up and three were referred to new surgery.

**Results**: The median years of drug resistance before operation were 11 years. At 1-year follow-up (n = 164), seizure outcomes were as follows: 65% Engel I (free from disabling seizures), 51% Engel IA (completely seizure free) and 9% Engel IV (no worthwhile improvement), and for patients operated in the medial temporal lobe (n = 114): 70% Engel I, 56% Engel IA, 5% Engel IV. The outcomes of the 53 patients needing intracranial EEG recording (ICR) were not significantly different from the patients only evaluated with surface EEG. None of the eight MRI-negative patients operated outside the medial temporal lobe after ICR were free of disabling seizures. 12% of MTLE patients developed de novo depression after epilepsy surgery despite good surgical outcome. Three patients required rehabilitation due to post-operative hemiplegia.

**Conclusion**: The outcomes of the Danish epilepsy surgery programme align with international results found in recent meta-analyses. Serious complications to epilepsy surgery are seldom. In accordance with international recommendations, Danish drug-resistant patients should be referred to epilepsy surgery evaluation at an earlier stage of the disease.

KEYWORDS
depression, drug-resistant, epilepsy, epilepsy surgery, outcome, seizures

## 1 | INTRODUCTION

Epilepsy occurs in 0.6% of the Danish population.[1] Despite optimal medical treatment, approximately one-third of patients with epilepsy continue to have seizures.[2] Active epilepsy disrupts important aspects of life, and imposes physical, psychological and social burden on patients and families.[2] Drug-resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used anti-epileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[3] Drug-resistant epilepsy accounts for over 75% of the cost of AEDs and over 60% of the total indirect cost.[4] The total cost of epilepsy in Europe, 2010, was €13.8 billion.[5]

Seizure freedom in highly selected drug-resistant patients after surgical removal of the epileptogenic tissue is well-documented,

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including two randomised controlled trials.[6–10] However, only a minority of patients with drug-resistant focal epilepsy are evaluated and finally operated. Patients and professionals are often reluctant to consider epilepsy surgery as it is not without risk, although the risk of fatal or permanent morbidity is small.[11,12] Here, we present the results of the Danish epilepsy surgery programme from 2009 to 2014.

## 2 | MATERIAL AND METHODS

This study includes all 169 epilepsy patients who underwent resective surgical treatment (excluding vagus nerve stimulation, deep brain stimulation and thermo-coagulations) in Denmark, from 1st of January 2009 to 31st of December 2014. The team and the epilepsy surgery evaluation process changed in 2009, and the inclusion period was chosen to assure transferability and generalisation of data. Before 2017, a Danish epilepsy register did not exist. Thus, all information was collected retrospectively from digital patient records except for patients where post-surgical follow-up was performed during data collection from September 2015 to April 2016. One-year follow-up data were available in 164 patients: Two patients with medial temporal lobe epilepsy (MTLE) and lateral temporal lobe epilepsy (LTLE), respectively, were lost to follow-up. Three patients with frontal lobe epilepsy, parietal lobe epilepsy and MTLE were re-operated (expansion of the resection) before 1-year follow-up after the first surgery. Two-year follow-up data were available in 143 patients (Figure 1). Approval for using records from routine patient records was given by the Danish Health and Medicines Authority (sagsnr. 3-3013-1030/1) and the Danish Data Protection Agency approved the study.

The epilepsy surgery evaluation process of all Danish patients takes place at the Copenhagen University Hospital, Rigshospitalet, and the Epilepsy Hospital in Dianalund. Intracranial EEG recording and resective surgery are centralised at Rigshospitalet. When patients are enrolled in the centralized epilepsy surgery programme, we take full responsibility of the patients including post-surgical follow-up at 6 weeks, 6 months, 1 year and 2 years. Patients with the MRI signs of hippocampal sclerosis, tumour, malformation of cortical development, vascular malformation, post-traumatic lesions, infarction, bleeding residua, or encephalitis were regarded as MRI positive.[13] Dual pathology refers to the presence of hippocampal sclerosis together with an additional epileptogenic lesion identified by MRI.[14] Histopathological diagnosis of hippocampal sclerosis was based on a semi-quantitative assessment of segmental cell loss patterns within hippocampal subfields, in addition to microscopic analysis.[15]

Post-operative outcome was classified according to the Engel Classification[16]: Engel I (free of disabling seizures), Engel IA (completely seizure free), Engel II (rare disabling seizures ("almost seizure-free")), Engel III (worthwhile improvement) and Engel IV (no worthwhile improvement). Disabling seizures were defined as focal seizures with impairment of consciousness, typically complex focal seizures, or secondarily generalized seizures.

Complications and adverse effects were evaluated at each post-surgical follow-up visit. A complication is defined as an unwanted, unexpected and uncommon event after a diagnostic or therapeutic procedure.[11,12] Adverse events are unwanted effects that may be expected in a substantial number of patients related to surgery. The severity of a complication and adverse effects is graded as minor if it resolves within 3 months, and major if it lasts longer than 3 months and affects the activities of daily living.[11,12]

For comparison between two groups, Fisher's exact test was used for dichotomous variables, all tests were 2-tailed and conducted at the 5% significance level. Statistical analysis was performed using R Project for Statistical Computing.

## 3 | RESULTS

### 3.1 | Baseline characteristics

Table 1 shows the baseline characteristics of the 169 patients. 69% of the patients were operated in the medial temporal lobe (n = 116). In the majority of the patients, an anterior temporal lobectomy (n = 99) was performed. In two of these patients, an additional lesionectomy was performed in the lateral neocortex. Selective amygdalohippocampectomy was performed in 16 patients, and one patient had hippocampal transection. Apart from known risk factors (Table 1) (OR = 2,16; CI = 1.11:4.19; $P$ = .03), MTLE patients were not significantly different from the patients in any category from Table 1.

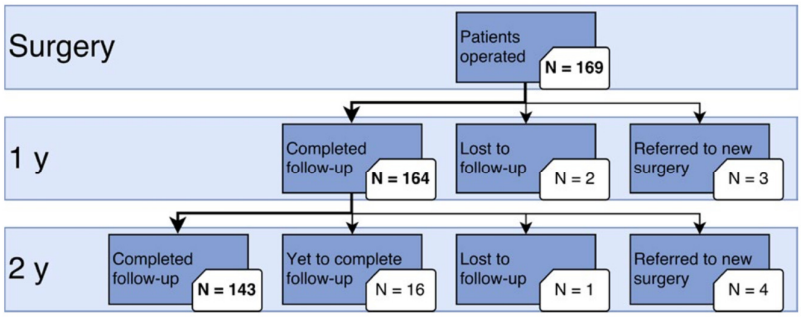


**FIGURE 1** Flowchart of patients included in study. Figure shows the number of patients being operated for epilepsy from 2009-2014 in Denmark and details on the post-surgical follow-up

**TABLE 1** Pre-surgical demographic and clinical data in relation to site of operation

| | Feature | Total | Medial Temporal | Lateral Temporal | Frontal | Other |
|---|---|---|---|---|---|---|
| n;(n%) | Total | 169 (100%) | 116 (100, 0%) | 15 (100%) | 24 (100%) | 14 (100) |
| | Female sex | 79 (46, 7%) | 54 (46, 7%) | 11 (73, 3%) | 7 (29, 1%) | 7 (50, 0%) |
| | Children (<16 y) | 36 (21, 3%) | 22 (19, 0%) | 3 (20, 0%) | 7 (29, 1%) | 3 (21, 4%) |
| | Risk factors | 89 (52, 6%) | 68 (58, 6%) | 3 (33, 3%) | 10 (41, 7%) | 6 (42, 9%) |
| | Depressive dissorder | 33 (19, 5%) | 25 (21, 6%) | 2 (13, 3%) | 2 (8, 3%) | 6 (42, 9%) |
| | Right hemisphere | 76 (45, 0%) | 47 (40, 5%) | 7 (46, 7%) | 14 (58, 3%) | 8 (57, 1%) |
| Median; 1. & 3. quartile | Epilepsy duration (year) | 19; 9 & 31 | 20; 9,8 & 33,3 | 12; 7 & 31 | 17; 7,8 & 26,8 | 20; 4,8 & 25 |
| | Drug-resistance duration (years) | 11; 4 & 23,3 | 13; 5 & 25,5 | 11; 2 & 19,8 | 10; 4 & 17 | 6,5; 2,5 & 20,5 |
| | Age at surgery | 35; 19 & 43 | 38; 22,8 & 46 | 25; 15,5 & 37,5 | 23; 13,8 & 36 | 31,5; 23,8 & 37,8 |
| | AED at referral | 2; 2 & 3 | 2; 2 & 3 | 2; 2 & 2,5 | 2; 2 & 3 | 2,5; 2 & 3 |
| | AED in total | 5; 4 & 7 | 5; 4 & 7 | 5; 4 & 6 | 5,5; 3,8 & 7,2 | 6; 4,3 & 7 |

Other: Patients operated in the central, parietal, occipital and insula regions. Risk factors: family history of epilepsy (first-degree relatives), febrile seizures, head trauma and meningoencephalitis. Depressive disorder: patients diagnosed with moderate and major depressive disorder and treated with antidepressants and/or psychotherapy.
AED: anti-epileptic drugs.

### 3.2 | Number of patients operated and referral area

The number of patients operated increased from 2009 to 2012 and stabilized thereafter at approximately 35 operations per year from 2012 to 2014 (35 in 2014). From 2012 to 2014, the average yearly numbers of patients operated per million inhabitants in each region were 8.5 in Region Zealand, 6.9 in North Denmark Region, 6.4 in Capital Region of Denmark, 5.5 in Central Denmark Region and 4.4 in Region of Southern Denmark.

### 3.3 | Epilepsy surgery outcome

Overall, 105 (65%) patients reported non-disabling seizures or auras (Engel I), 84 patients (51%) were completely seizure free (Engel IA) at 1-year follow-up, and 15 (9%) reported no worthwhile improvement (Engel IV). Figure 2A shows the 1-year outcome of patients in relation to site of surgery. The number of patients with Engel I outcome was significantly higher in MTLE patients compared to patients operated outside the medial temporal lobe ($P$ = .033; CI = 1.03:4.55) and significantly higher in patients operated in the temporal lobe (medial and lateral combined) compared to patients operated for extratemporal lobe epilepsy (ETLE) ($P$ = .018; CI = 1.11:5.82). There was no significant difference between 1- and 2-year outcome in either MTLE patients ($P$ = .13; CI = 0.87:3.14) or ETLE patients ($P$ = 1.00; CI = 0.36:3.60). Patients with short duration (under 10 years) of drug-resistant epilepsy vs over 10-year duration showed a significantly better 1-year outcome ($P$ = .03; CI = 1.03:5.09) than long-duration drug-resistant epilepsy patients (more than 10 years).

In total, 15 patients (9%) reported no worthwhile improvement in seizure control after surgery (Engel IV) one year after surgery. The number of AEDs tested before inclusion in the epilepsy surgery programme was significantly higher in Engel IV patients compared to Engel 1A patients ($P$ = .037; CI = 5.53:6.19). There was no significant difference in gender or age at operation of patients in Engel IA compared to Engel IV.

### 3.4 | Pathology

Figure 2B shows the 1-year Engel outcome in relationship to the different pathologies. Hippocampal sclerosis was identified in 69 patients equal to 41% of all patients and 59% of MTLE patients. There was no significant difference between the outcome of patients with hippocampal sclerosis and patients with other pathologies ($P$ = .15; CI = 0.08:3.32). Focal cortical dysplasia (FCD) was the most frequent single pathology in extratemporal resection and identified in 26 of all patients (16%). The 1-year outcome of patients with FCD was not significantly different from patients with other pathologies ($P$ = .26; CI = 0.23:1.51). Four patients had developmental pathology other than FCD. A tumour was identified in 22 of the patients (12%). The long-term epilepsy-associated (LEAT) group (n = 11) was dominated by dysembryoplastic neuroepithelial tumours (n = 3) and gangliogliomas (n = 6). At 1-year follow-up, 45% were in Engel IA, 63% in Engel I and 18% in Engel IV. Other tumours were identified in 11 patients (6%) and included two angiomas, one hamartoma, and eight astrocytomas or oligodendrogliomas with 1-year outcome: 55% Engel IA, 81% Engel I and 0% Engel IV. The LEAT group did not do significantly better than the other tumours ($P$ = .64; CI = 0.03:3.84). Three patients had vascular pathology (AV malformation, n = 1 and stroke, n = 2) all with 1-year outcome Engel IA. Two patients had calcification, one had cystic changes and one encephalitis. In 10 MTLE patients, part of the resected tissue was used for scientific purposes precluding a definite pathological diagnosis.

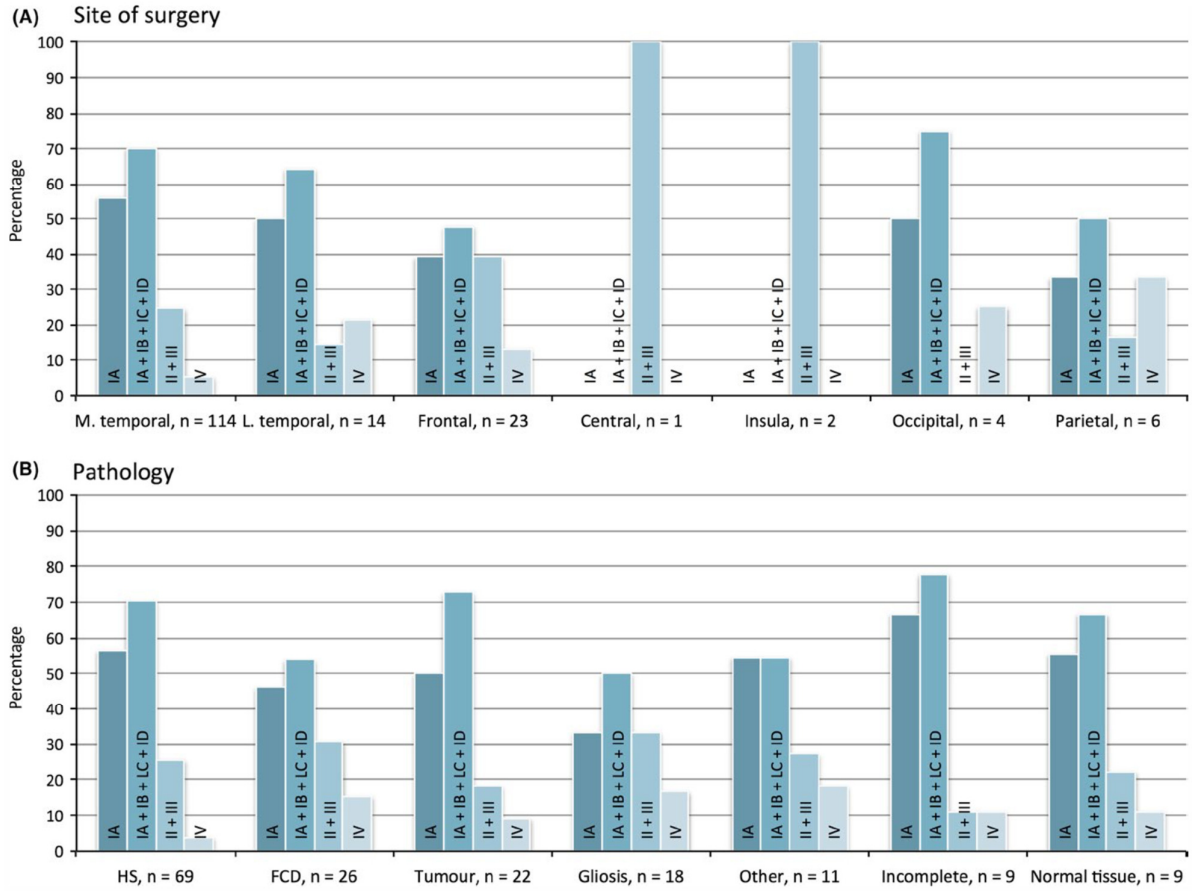


**FIGURE 2** 1-year outcome after epilepsy surgery (site of surgery and pathology). Figure shows the 1-year epilepsy surgery outcome in relation to site of surgery (A) and pathology (B). A: M. temporal: Medial temporal lobe. L. temporal: Lateral temporal lobe. B: HS: Hippocampal sclerosis. FCD: Focal cortical dysplasia. Tumour: contains both LEAT tumours as well as other tumours. Other: Vascular malformation, strokes, calcification, cystic, encephalitis and developmental malformations (pachgyria, ulegyria and polymicrogyria). Incomplete: Patients probably with HS but did not fulfill the diagnostic criteria since part of the tissue was used for scientific purposes. Engel IA: Completely seizure free since surgery. Engel I: IA, IB, IC, ID: Free of disabling seizures. Engel II + III: Rare disabling seizures - worthwhile improvement. Engel IV: No worthwhile improvement

Six of the 69 patients with pathology equal to hippocampal sclerosis were MRI negative. Dual pathology was present in 10 of the 69 with hippocampal sclerosis: Nine had a combination of HS and FCD, and one had HS plus angioma.

Of the MTLE patients operated (n = 116), the MRI diagnoses were as follows: 68 with MTS, 3 with atrophy of hippocampus, 3 with increased signal in hippocampus, 2 with malrotation of hippocampus, one with contrast enhancement in hippocampus, 4 with vascular pathology, 11 with FCD, 6 with a tumour and 18 MRI negative.

### 3.5 | Intracranial EEG recordings and MRI negative

In 53 patients (one patient lost to 1-year follow-up), ICR were part of the presurgical evaluation process (Figure 3A). There was no significant difference in Engel I outcome between ICR patients and the rest of the group ($P$ = .49; CI = 0.36:1.57). Engel I outcome in neither the MTLE ($P$ = .65; CI = 0.51:4.00) nor ETLE ($P$ = .30; CI = 0.08:2.11) patients with ICR was significantly different from MTLE or ETLE patients without ICR. However, MTLE patients with ICR had a significantly better outcome than ETLE patients with ICR ($P$ = .006; CI = 1.51:26.90). Figure 3B shows that none of the LTLE and ETLE patients with a non-lesional MRI were free of disabling seizures after operation. Temporal lobe (MTLE and LTLE) patients with non-lesional MRI had significantly better outcome than ETLE patients with non-lesional MRI ($P$ = .0003; CI = 3.62:∞). In nine patients with a non-lesional MRI, surgery was performed without ICR and supported by other modalities—especially FDG-PET; six of these were MTLE patients, and they all had a 1-year outcome of Engel I or better. Of the three ETLE patients, who had non-lesional MRI and did not have ICR, two had Engel IV outcome and one had Engel II outcome. One patient died of intracranial haemorrhage in relation to ICR.

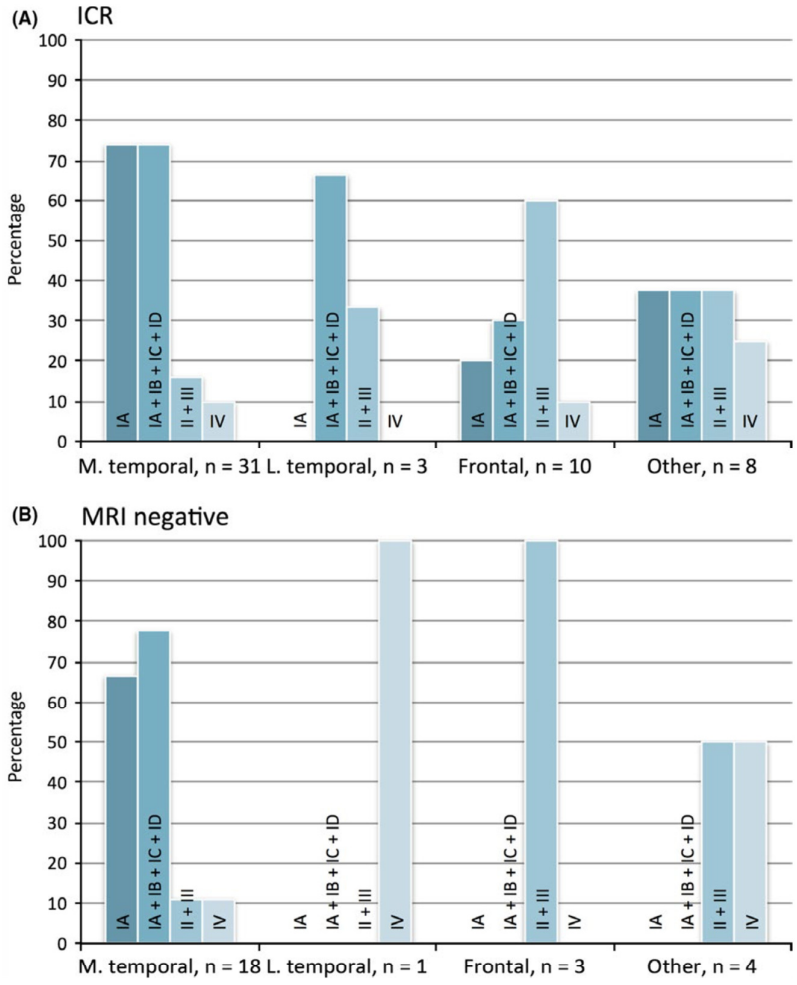


**FIGURE 3** 1-year outcome after epilepsy surgery (ICR and MRI negative). Figure 3 shows the 1-year epilepsy surgery outcome in patients after intracranial registration (A) and in MRI negative patients (B). ICR: Intracranial registration. Other: central, parietal, occipital and insula region

### 3.6 | Patients re-operated

During the inclusion period, 7 patients were re-operated. After the first surgery, five patients were classified as Engel IV, one as Engel III and one as Engel II. After the second operation, four patients were classified as Engel IA at 1-year follow-up, one of which was operated for ETLE, the other three for MTLE. One patient was classified as Engel II at 1-year follow-up, and in one patient, the outcome was unchanged after the second-operation. One patient was re-operated in 2016, and 1-year follow-up is pending.

### 3.7 | Post-surgical complication and adverse effects

The most frequent post-surgical adverse effect was depressive disorder; 21 patients were diagnosed with depressive disorder requiring antidepressants and/or psychotherapy during the first year after epilepsy surgery. Eighteen of the 21 patients (86%) had MTLE. In total, 13 patients were diagnosed with de novo depressive disorder after surgery. Eleven of the 13 patients (85%) were operated in the medial temporal lobe (10 patients were Engel I [eight were Engel IA] and one patient Engel II). The last two patients were operated in insula and the frontal lobe (both Engel III at one-year follow-up). Thus, 12% of MTLE patients developed de novo depressive disorder after epilepsy surgery. In total, 33 patients of 169 patients (20%) were diagnosed with depressive disorder before surgery (25 with MTLE).

Ten patients experienced post-operative seizures within the first week after operation. All of these patients had additional seizures during the first year after surgery. One patient was in Engel II, four in Engel III and four in Engel IV. The last patient was re-operated due to status epilepticus within the first week after the first operation. Thus, occurrence of seizures in the first week after surgery is a significant negative predictor seizure outcome ($P = .001$). Testing of the visual fields was not consistently reported in patient files. In nine patients, quadrant anopsia was demonstrated using confrontation visual field examination (Donder's test).

Three patients had major surgical complications related to severe post-surgical haematoma leading to permanent motor impairment and in one patient dysphasia. At follow-up, two patients recovered with a slight disability (modified Rankin Scale [mRS] 2) and one patient had no significant disability

(mRS 1). The most severely affected subject regained driver's licence and was able to run and ski, but daily activities were affected by a mild aphasia.

## 4 | DISCUSSION

Here, we present the most recent results from the Danish epilepsy surgery programme. In total, 169 patients were operated from 2009 to 2014 and follow-up data were available in 164 patients until 1st of July 2016. The results of the Danish epilepsy surgery programme align with international results reported in two recent systematic reviews.[7,8] Overall, 65% of patients operated in Denmark were free of disabling seizures (Engel I) 1 year after surgery, which is comparable to the results (62.5%) reported by Jobst BC et al. Only 9% of the patients reported not to benefit from surgery (Engel IV). There was no statistical difference between the 1-year (n = 164) and 2-year (n = 143) outcomes in our cohort, but long-term longitudinal Swedish data suggest that 13% of patients that are seizure free 2 years after surgery report seizures at 5- to 10-year follow-up.[9]

The majority of our patients (116/169) were operated for MTLE. In this group, 70% were free of disabling seizures (Engel I) 1 year after the operation compared to 65% in the Cochrane review by West et al. In line with international findings, the outcome of ETLE patients is poorer than the outcome in MTLE patients.[9,17,18] This is especially evident in ETLE patients with a non-lesional MRI. However, only 17% of the ETLE patients reported no benefit (Engel IV) from the operation.

The majority of patients with discordance between seizure semiology, EEG and MRI were not offered epilepsy surgery before the introduction of ICR in the epilepsy surgery evaluation process. The significance of ICR is demonstrated by the fact that the outcomes of the 53 most complex patients needing ICR were comparable to the outcomes of the patients only evaluated with surface EEG.

In Denmark, the number of epilepsy surgery patients has settled at about 35 per year from 2012 to 2014 (35 in 2015) equal to 6.2 operations per million people per year in Denmark. This number compare to 4.7 in United States,[7] 5.7 in Norway from 2013 to 2015 (personal communication, Tale Mæhre Torjussen), 5.2 in Sweden from 2013 to 2015 (personal communication Anna Edelvik) and 8.1 in Finland from 2013 to 2015 (personal communication, Reetta Kalviainen). Thus, the number of patients operated in Denmark aligns with the Scandinavian countries, but from our data, it is quite evident that the Danish patients wait too long before being referred to epilepsy surgery evaluation: the median duration of drug resistance was 11 years (1. percentile = 4. 3. percentile = 23.3) and the number of AEDs tested more than 5 (1. percentile = 4. 3. percentile = 7) before being referred for epilepsy surgery evaluation. Several studies show that long epilepsy duration and age are negative predictors of post-surgical outcome.[9,19,20] The Early Randomized Surgical Epilepsy Trial recommends that patients are referred after only 2 years of drug resistance.[21] Thus, Danish patients could benefit from being referred to epilepsy surgery evaluation at an earlier time point in the disease process.

The fact that Danish epilepsy patients are referred later than international recommendations probably reflects concerns about complications and side effects to surgery among referring neurologists, patients and relatives. Here, we only report data from the patients that were eventually operated. However, from 2009 to 2014 one patient died in relation to ICR due to an intracranial haemorrhage. After this MRI with gadolinium to visualize blood vessel has been part of the evaluation process before ICR. No patients died in relation to epilepsy surgery. However, three patients developed a significant hemiparesis in relation to surgery: two patients recovered with a slight disability (mRS 2) and one patient had no significant disability (mRS 1). The most severely affected patient was able to ski and run but unable to carry out all previous activities due to aphasia. In total, depressive disorder had a presurgical prevalence of 20% and the post-surgical prevalence of de novo depressive disorder was 10% at 1-year follow-up. 85% of patients with de novo depressive disorder were operated in the medial temporal lobe. This is in line with other studies.[7,17] In only 5% of our patients, anopsia were diagnosed. However, this probably represents an underestimation as patients were not consistently tested and only ad modum Donder's test.

The Danish epilepsy surgery programme has existed for more than 20 years. This is the first study to systematically report the results of the epilepsy surgery programme in both adults and children in Denmark. The seizure outcome and post-surgical complications align with international results. The manuscript is limited by the fact that data are mainly collected retrospectively and the presurgical evaluation programme does not follow exactly the same predefined standards defined before patients entered the study: methodology and members of the epilepsy surgery group obviously changed from 2009 to 2014. Danish drug-resistant epilepsy patients are referred to epilepsy surgery evaluation later than international recommendations advice. The current study will form the basis of an information campaign targeting Danish neurologists and epilepsy patients.

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## CONFLICT OF INTERESTS

None.

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Paper 2

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# Verbal learning and memory outcome in selective amygdalohippocampectomy versus temporal lobe resection in patients with hippocampal sclerosis

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ABSTRACT

*Purpose:* With the advent of new very selective techniques like thermal laser ablation to treat drug-resistant focal epilepsy, the controversy of resection size in relation to seizure outcome versus cognitive deficits has gained new relevance. The purpose of this study was to test the influence of the selective amygdalohippocampectomy (SAH) versus nonselective temporal lobe resection (TLR) on seizure outcome and cognition in patients with mesial temporal lobe epilepsy (MTLE) and histopathological verified hippocampal sclerosis (HS).
*Methods:* We identified 108 adults (>16 years) with HS, operated between 1995 and 2009 in Denmark. Exclusion criteria are the following: Intelligence below normal range, right hemisphere dominance, other native languages than Danish, dual pathology, and missing follow-up data. Thus, 56 patients were analyzed. The patients were allocated to SAH (n = 22) or TLR (n = 34) based on intraoperative electrocorticography. Verbal learning and verbal memory were tested pre- and postsurgery.
*Results:* Seizure outcome did not differ between patients operated using the SAH versus the TLR at 1 year ($p = 0.951$) nor at 7 years ($p = 0.177$). Verbal learning was more affected in patients resected in the left hemisphere than in the right ($p = 0.002$). In patients with left-sided TLR, a worsening in verbal memory performance was found ($p = 0.011$). Altogether, 73% were seizure-free for 1 year and 64% for 7 years after surgery.
*Conclusion:* In patients with drug-resistant focal MTLE, HS and no magnetic resonance imaging (MRI) signs of dual pathology, selective amygdalohippocampectomy results in sustained seizure freedom and better memory function compared with patients operated with nonselective temporal lobe resection.


## 1. Introduction

Epilepsy surgery is widely accepted as an effective therapeutic option in patients with drug-resistant mesial temporal lobe epilepsy (MTLE) [1–3]. However, it remains a matter of controversy whether to use a small resection with the risk of failing to obtain sustained seizure freedom or to use a large resection with the risk of causing additional neuropsychological impairment. With the advent of new techniques like thermal laser ablation [4] and MRI-guided focused ultrasound ablation [5], the controversy will gain new attention. These new techniques make promises for future much less invasive and very selective tissue destruction for the treatment of MTLE, and if proven, safe and efficient will be of utmost importance for more patients to be included in the epilepsy surgery evaluation program.

Temporal lobe resection (TLR) has been the surgical approach of choice for temporal lobe epilepsy [6,7]. There is a well-known risk of verbal memory decline after TLR in the language dominant hemisphere [8,9]. Because of this potential risk of memory impairment, more selective approaches have been developed, the most restricted one being the selective amygdalohippocampectomy (SAH) [7,10–12]. Some studies have found SAH to give as good a seizure outcome as TLR with a better postoperative cognitive and memory outcome [13–16], while others have not [3,17]. Because of the heterogenous surgical approaches, patient referrals, and preoperative evaluations, meta-analysis is difficult

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to perform. Of the two most recent papers, one indicates that SAH has a similar seizure outcome as TLR, and a better cognitive outcome [18], while the other paper indicates that seizure outcome is worse after SAH [19]. No randomized controlled trials with regard to the extent of lateral temporal resection have been performed and most studies include patients with different pathology, which have different influence on the cognitive outcomes [13,14,16,17,20].

Here, we present data on cognitive function and seizure outcome in a homogeneous group of patients operated by the same neurosurgeon and with histopathological verified HS. Our aim was to compare the effect on verbal learning, verbal memory, and seizure outcome in patients after SAH compared with TLR.

## 2. Material and methods

### 2.1. Patients

We identified all 108 adults (>16 years) with histopathologically verified HS, operated between 1995 and 2009 in Denmark. Only left hemisphere dominant patients were included (12 left handed or ambidextrous patients with right hemisphere dominance or no WADA test was excluded). Additional patients were excluded because of intelligence level below normal range (n = 9), native language other than Danish, in which the neuropsychological tests were done (n = 8), or dual pathology (n = 6). Patients were excluded because of dual pathology if the written conclusion from the presurgical MRI scan described a potential epileptogenic lesion additional to HS. The exclusion diagnoses were the following: dysembryoplastic neuroepithelial tumor (n = 1), bilateral hippocampal sclerosis (HS) (n = 2), focal cortical dysplasia (n = 1), changes caused by cortical contusion (n = 1), and hypoplasia in the temporooccipital area, which could be caused by meningoencephalitis (n = 1). Follow-up data were not available in 17 patients. Thus, 56 patients remained, and these were analyzed in the present study. Approval for using data from patient records without consent from the individual patient was given by the Danish Health and Medicines Authority (sagsnr. 3-3013-1030/1) and the Danish Data Protection Agency.

### 2.2. Surgery

All patients were operated by the same neurosurgeon. Resection of amygdala and hippocampus is done in all patients. Selective amygdalohippocampectomy was performed in 22 cases and additional resection of temporal neocortex, TLR, was done in 34 patients. There was no difference in the extent of mesial resection between the groups with SAH and TLR (details are given in Section 3.3). In 47 patients, the decision about resection type SAH or TLR and the extension of the TLR was guided by intraoperative electrocorticography (ECoG). In three patients, the TLR approach was chosen because of technical problems with the surgical entrance. In one additional case, TLR was used because a vascular malformation in the temporal lobe was suspected during the operation, but not found on the preoperative MRI, and histopathology described a small vascular area only suspicious of vascular malformation. In four patients undergoing TLR and one patient undergoing SAH, there were no detailed descriptions of the basis for decision-making.

The ECoG was performed prior to the cortical resection, and a 4-electrode strip was placed in the lateral ventricle through a 1.5 cm linear opening anterior in the superior-temporal sulcus. The strip covered the anterior 3 cm of the hippocampus. Furthermore, a 4 × 5 electrode grid was placed on the lateral and inferior aspects of the temporal lobe [21]. Electrocorticography was recorded for several minutes. When spikes were unequivocally identified on the strip but not on the grid, a SAH was performed. In all other cases, a TLR was performed. In SAH, the surgical entrance was always made through the superior temporal sulcus. The TLR operation was a tailored procedure based on the ECoG findings. Identification of spikes decided the degree of the lateral resection.

### 2.3. Seizure outcome

Seizure outcome was assessed using the Engel classification at 1 and at 7 years after surgery. Patients in Engel class I were considered seizure-free and compared with patients in Engel classes II–IV. At one-year follow-up, seizure outcome was described in the medical records, no data were missing. At seven-year follow-up, seizure outcome was rated from the medical records or when missing by a telephone interview. In three patients, seven-year follow-up was not possible: two had been reoperated and one had emigrated. Data did not exist for three patients who had died.

### 2.4. Neuropsychological assessment

In 2006, the neuropsychological follow-up together with other follow-up measures was decided to be changed from a one-year to a two-year follow-up at our hospital. Thus, in 41 patients, the follow-up test was performed 1 year after surgery; in 14 patients, 2 years after surgery; and in one subject, 3 years after surgery. Verbal learning and memory were assessed by a Danish version of 15 Verbal Paired Associated words, containing 7 semantically related/easy pairs (e.g., mouse – cheese) and 8 unrelated/hard pairs (e.g., chimney – coat) [22]. Parallel test versions have been used. The paradigm requires a deeper conceptual processing and is believed to represent two distinct memory systems, the semantic and the episodic [23,24]. First, the word pairs are presented once. Hereafter, the patient is cued by the first word in the pair, and asked to mention the associated word. Once the word pair is learned, it is put aside. All 15 word pairs are to be learned in 1–10 trails, errors are counted. This is interpreted as verbal learning. Retention with the cuing again by the first word is performed 1 h later, errors are counted. This is interpreted as verbal memory [22].

All patients were tested by Wechsler Adult Intelligence Scale (WAIS) Information [25] and Ravens Progressive Matrices, set 1 [26]. Normal range was defined as a scale score above 6 in WAIS Information and a score above 1.5 SD below mean [27] (Gade A, Mortensen EL. The influence of age, education, and intelligence on neuropsychological test performance, 1984, unpublished). Educational and occupational levels supported the test results. Only patients functioning in the normal range was included.

### 2.5. Statistical analyses

Three outcomes were considered: seizure outcome (at 1 year and at 7 years), verbal learning performance, and verbal memory performance.

A logistic regression was used to assess the effect of the surgical approach (SAH vs. TLR), the side of surgery (left vs. right hemisphere), and their interaction (SAH and left) on the seizure outcome.

A linear regression model was used to investigate the effect of the surgical approach, the side of resection (hemisphere), and their interaction on the verbal memory performance. To account for the difference in variance observed between approaches and hemisphere subgroups, a variance parameter specific to each subgroup was fitted. The model was adjusted for the occurrence of seizure after resection, which can influence the cognitive ability of the patients [28]. The same methodology was used to investigate the effect of the surgery approach and the side of surgery on the verbal learning.

Gender, chronological age, duration of epilepsy, age of onset of epilepsy, number of respectively SFS (simple focal seizures), CFS (complex focal seizures), and sGTC's (secondarily generalized tonic–clonic seizures) are possible confounders for the relation between the outcome and the surgical approach. Therefore, in addition to the previously mentioned models, a backward elimination procedure [29] with a threshold of $p < 0.1$ was used to identify variables associated with the

outcome and to check the consistency of the results regarding the set of variables that was included in the model.

Statistics were calculated by use of SAS Enterprise Guide 6.1 for Windows and R 3.3.2 [30].

## 3. Results

Patient characteristics are listed in Table 1. The two groups showed similar characteristics in age at surgery, age at epilepsy onset, duration of epilepsy, and number of seizures preoperative.

### 3.1. MRI

All patients but one had a hyperintense hippocampus at the preoperative MRI corresponding to the side of the later resection, and all but six had hippocampal atrophy also corresponding to the side of the later resection. In one, the size of the hippocampus was not described. Patients with a potential epileptogenic lesion other than HS on the side of resection on the preoperative MRI were excluded, but the patients included could have one or more of the below mentioned changes, not considered epileptogenic: abnormal positioning of the hippocampi (n = 2), gliosis (n = 3), atrophy of the temporal lobe in the same hemisphere as the later resection (n = 4), atrophy of the hemisphere contralateral to the later resection (n = 1), slight atrophy of cerebellum (n = 1), ventricular ectasia (n = 2), nonspecific white matter changes (n = 3), arachnoid cyst (n = 3), asymmetric frontal lobes (n = 1), small hyperintense change next to hippocampus in the same hemisphere as the later resection (n = 1), and slight abnormal gray matter next to the temporal horn of the lateral ventricle (n = 1).

### 3.2. Pathology

All included patients had histologically verified HS. Patients were diagnosed before publication of the most recent international consensus classification of HS in temporal lobe epilepsy [31]. However, descriptions of neuronal cell loss and gliosis in subregions of hippocampus were available in 27/34 patients with TLR and in 17/22 patients with SAH. In 21/27 patients with TLR and in 12/17 patients with SAH, neuronal loss and gliosis dominated in CA1, and in 6/27 patients with TLR and in 5/17 patients with SAH, neuronal loss and gliosis were described in CA4, too. There was no significant difference in the description of neuronal loss and gliosis in CA1 and CA4 between the patients with SAH and the patients with TLR (Fisher's exact test, p = 0.7). In patients operated with the TLR approach, the only pathology found in tissue not from the hippocampus was gliosis (n = 14), and in one patient a small vascular area.

**Table 2**
Logistic regression model for the seizure outcome at one- and at seven-year follow-up, odds ratio estimates.

| Seizure outcome at 1-year follow-up | | | |
|---|---|---|---|
| Variable | Odds ratio | Confidence interval of odds ratios | p-Value |
| | | Test main effects | |
| Approach (SAH) | 1.04 | [0.30; 3.56] | 0.951 |
| Hemisphere (R) | 1.62 | [0.49; 5.42] | 0.431 |
| Seizure outcome at 7-year follow-up | | | |
| Variable | Odds ratio | Confidence interval of odds ratios | p-Value |
| | | Test interaction | |
| Reference (R) SAH | | | |
| Hemisphere (L): approach (TLR) | 0.08 | [0.01; 1.16] | 0.064 |
| | | Difference between subgroups | |
| Hemisphere (R): TLR vs SAH | 5.10 | [0.66; 33.55] | 0.119 |
| Hemisphere (L): TLR vs SAH | 0.42 | [0.08; 2.25] | 0.309 |

### 3.3. Extent of mesial resection

The length of the hippocampus removed was measured and noted right after the resection. This gave us the opportunity to investigate differences in the extent of mesial resection between the group with SAH and TLR. In some cases, ultrasonic surgical aspiration was performed after this initial removal, and the neurosurgeon estimated the extra amount of tissue resected. In 19 patients, data on the length of the hippocampus removed were missing.

In the group with SAH, a mean of 30.2 mm (22 patients, 5 missing) (SD: 6.5, range: 18–40 mm) was resected compared with 29.7 mm (34 patients, 14 missing) (SD: 7.2, range: 22–48 mm) in the group with TLR (pooled *t*-test, p = 0.834). In the right hemisphere (31 patients, 10 missing), a mean of 31.0 mm (SD: 5.9, range: 20–40 mm) of the hippocampus was resected compared with 28.6 mm on the

**Table 1**
Patient characteristics of the two surgical groups (SAH vs. TLR).

| Patient characteristics | SAH | TLR | Total |
|---|---|---|---|
| Number of patients | 22 | 34 | 56 |
| Gender (females) | 9 | 17 | 26 |
| Age at surgery (mean ± SD) | 34.7 ± 10.3 | 36.0 ± 10.4 | |
| Duration of epilepsy in years (mean ± SD) | 27.5 ± 11.8 | 26.6 ± 11.4 | |
| Age of onset of epilepsy (mean ± SD) | 7.2 ± 6.3 | 9.4 ± 9.3 | |
| Side of surgery (left/right hemisphere) | 12/10 | 13/21 | 25/31 |
| Educational level[a] | | | |
| High (left/right hemisphere) | 4/5 | 5/11 | 9/16 |
| Low (left/right hemisphere) | 8/5 | 8/10 | 16/15 |
| Number of simple focal seizures per month preoperative (mean ± SD) | 12.2 ± 16.7[b] | 19.4 ± 36.7[c] | |
| Number of complex focal seizures per month preoperative (mean ± SD) | 6.1 ± 4.6[b] | 8.7 ± 15.9 | |
| Number of secondarily generalized tonic–clonic seizures per year preoperative (mean ± SD) | 2.3 ± 7.8[d] | 4.7 ± 10.0[d] | |
| Number of antiepileptic drugs taken preoperative (mean ± SD) | 2.1 ± 0.7 | 2.2 ± 0.8 | |
| Engel class postoperative (I/(II, III, IV)) | 16/6 | 25/9 | 41/15 |
| Decisions on the surgical approach were based on | | | |
| Intraoperative electrocorticography | 21 | 26 | 47 |
| Technical reasons | 0 | 4 | 4 |
| Not described | 1 | 4 | 5 |

[a] High educational level is defined by >3.5 years of education.
[b] Data from 2 patients missing.
[c] Data from 6 patients missing.
[d] Data from 1 patient missing.

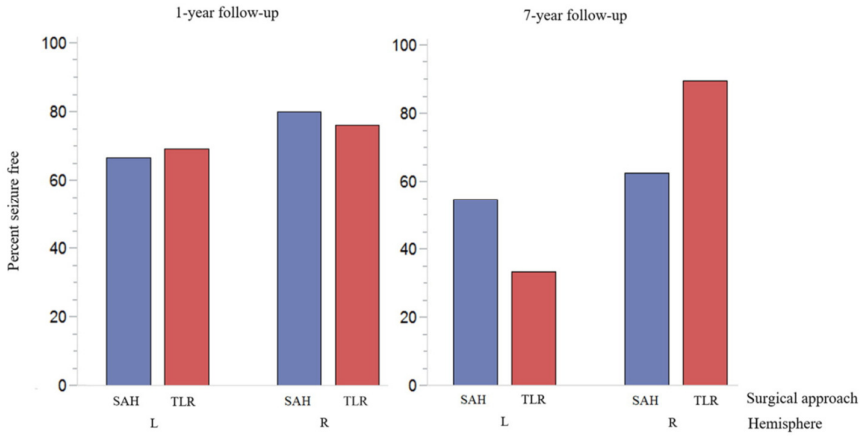


**Fig. 1.** Bar chart of percent seizure-free (Engel class I) at one-year and at seven-year follow-up in selective amygdalohippocampectomy (SAH) versus temporal lobe resection (TLR) in the right (R) and the left (L) hemispheres.

left (25 patients, 9 missing) (SD: 7.7, range: 18–48 mm) (pooled *t*-test, p = 0.293).

### 3.4. Seizure outcome

Altogether, 73.2% of the patients were seizure-free (Engel class I) at one-year follow-up, 73.5% in the group with TLR (25/34), and 72.7% in the group with SAH (16/22). No interaction between side of surgery (hemisphere) and approach was identified by the logistic model: The effect of the surgical approach and the effect of the side of resection on the seizure outcome can be interpreted separately. There was no significant difference in seizure outcome between patients in the group with TLR compared with patients in the group with SAH (p = 0.951) and no significant difference in seizure outcome between patients operated in the left and in the right hemisphere (p = 0.431). Odds ratio estimates and confidence intervals are listed in Table 2, data are presented in Fig. 1. No variables were identified by the backward elimination procedure.

At seven-year follow-up, data were accessible in 50 patients (lost to follow-up (n = 3), data not existing (n = 3)). Altogether, 64.0% of the patients were seizure-free (Engel class I). The amount of seizure-free patients in each surgical group (SAH and TLR) and for each hemisphere is displayed in Fig. 1. A borderline interaction between hemisphere and surgical approach was found by the logistic model (p = 0.064) (odds ratio = 0.08), Table 2. Therefore, we need to take the hemisphere into account when we interpret the effect of having performed SAH versus TLR.

In patients operated in the right hemisphere, there was no significant difference in seizure outcome between patients operated with TLR compared with those operated with SAH (p = 0.119) (odds ratio 5.10). In patients operated in the left hemisphere, there was no significant difference in seizure outcome between patients operated with TLR compared with those operated with SAH (p = 0.309) (odds ratio 0.42). Therefore, given an operation side (hemisphere), we did not find any significant difference in seizure outcome between the SAH and the TLR approach (p = 0.177).

The backward elimination procedure identified the following variables: age at surgery and duration of epilepsy. Adjusting for these variables, patients resected in the right hemisphere with TLR was found to have a borderline significant higher chance of being seizure-free than patients resected in the right hemisphere with SAH (p = 0.048, odds ratio: 19.29, CI: (1.03; 362.83)). No significant effect of surgical approach was observed for patients operated in the left hemisphere.

### 3.5. Neuropsychological outcome

#### 3.5.1. Verbal memory

A borderline significant interaction between hemisphere and surgical approach was found by the linear regression model (p = 0.057) with

**Table 3**
Linear regression model for the verbal memory and the verbal learning outcome, respectively. Each model is adjusted for the seizure outcome.

| Verbal memory | | | |
|---|---|---|---|
| Variable | Estimated coefficients (unstandardized) | Confidence interval | p-Value |
| | Test interaction | | |
| Reference (R) SAH | | | |
| Hemisphere (L) (SAH) | −0.11 | [−3.02; 2.80] | 0.941 |
| Hemisphere (L): approach (TLR) | −3.72 | [−7.46; 0.03] | 0.057 |
| | Difference between subgroups | | |
| Hemisphere (L): TLR vs SAH | −3.49 | [−6.75; −0.23] | 0.036 |
| Hemisphere (R): TLR vs SAH | 0.23 | [−1.61; 2.07] | 0.807 |
| Verbal learning | | | |
| Variable | Estimated coefficients (unstandardized) | Confidence interval | p-Value |
| | Test main effects | | |
| Approach (TLR) | −0.10 | [−7.13; 6.93] | 0.978 |
| Hemisphere (L) | −13.9 | [−22.21; −5.59] | 0.002 |

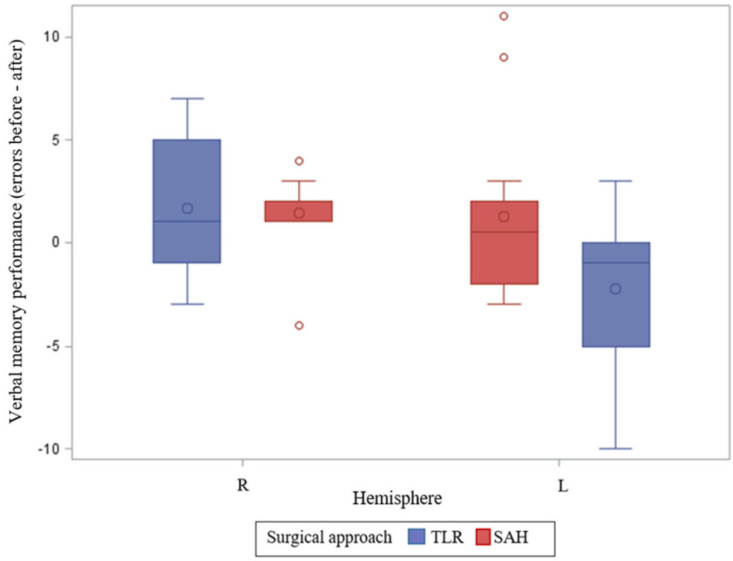


**Fig. 2.** Boxplot of verbal memory performance (errors before – after) in patients resected with selective amygdalohippocampectomy (SAH) versus temporal lobe resection (TLR) in the right (R) versus the left (L) hemisphere.

a punctual estimate of −3.72 (Table 3). Thus, we need to take the hemisphere into account when we interpret the effect of having performed SAH versus TLR. A worse performance was found in patients resected in the left hemisphere with the TLR approach compared with other patients ($p = 0.011$). This was also found when comparing the left hemisphere patients with TLR, specifically to the left hemisphere patients with SAH (punctual estimate: −3.49, $p = 0.036$). There was no significant difference between patients resected in the right hemisphere with either the SAH or the TLR ($p = 0.807$), and neither with patients operated on the left with SAH ($p = 0.941$). This is shown in Fig. 2, where the variables for the first three groups are comparable, but the fourth, representing patients operated in the left hemisphere with a nonselective approach (TLR), is shifted below the others. No variable was identified by the backward elimination procedure.

*3.5.2. Verbal learning*

No interaction between hemisphere and surgical approach was found by the linear regression model ($p = 0.574$). Patients operated in the left hemisphere performed significantly worse than patients operated in the right hemisphere ($p = 0.002$) with a punctual estimate of −13.9 (Table 3), as shown in Fig. 3. No effect of the surgical approach (SAH versus TLR) was found ($p = 0.978$).

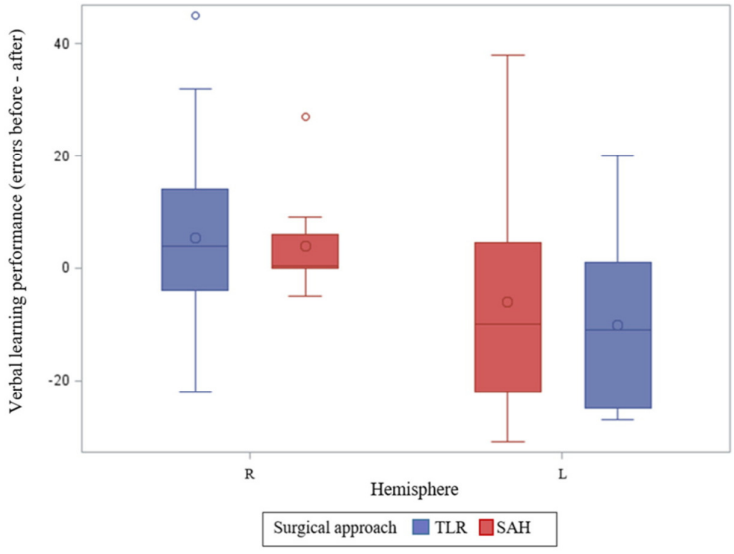


**Fig. 3.** Boxplot of verbal learning performance (errors before – after) in patients resected with selective amygdalohippocampectomy (SAH) versus temporal lobe resection (TLR) in the right (R) versus the left (L) hemisphere.

The backward selection procedure retained the following variables: age at surgery, number of CFS', duration of epilepsy, age of onset, and seizure outcome. A model accounting for these variables gave values consistent with the original model: no interaction between hemisphere and surgical approach was found with this approach either ($p = 0.811$). Patients operated in the left hemisphere performed significantly worse than patients operated in the right hemisphere ($p < 0.001$) with a slightly different punctual estimate of −15.5, no effect of the surgical approach ($p = 0.827$).

In our statistical analyses, we merge follow-up data from neuropsychological tests performed 1 year (41 patients), 2 years (14 patients), and 3 years (one patient) after surgery. Merging of neuropsychological test data is based upon the assumption that neuropsychological function stabilizes during the first year after surgery to the temporal lobe. Our material is not dimensioned to formally test this assumption; however, we performed a sensitivity analysis on the 41 patients tested 1 year after surgery. The secondary analysis showed effect sizes comparable to the primary analysis including all subjects.

## 4. Discussion

Epilepsy surgery is a safe and efficient treatment option in patients with medically resistant MTLE, but it is still controversial to which extent resection of the lateral temporal lobe in addition to the SAH affects seizure outcome and cognitive function. With the new option of thermal laser ablation and MRI-guided focused ultrasound ablation, it is becoming possible to make even more selective resections than SAH, and potentially with lesser risks for complications during the resection [4,5,32]. This possibility calls for a clarification of the old controversy.

The present study evaluated whether a selective (SAH) or a nonselective (TLR) approach to surgical treatment of MTLE has different impact on objective measures of cognitive function and seizure outcome or not. Postoperative neuropsychological follow-up was obtained more than 1 year after surgery, at a time when cognitive outcome is not directly affected by the operation and expected to be stable. Seizure outcome was evaluated 1 and 7 years after surgery.

### 4.1. Seizure outcome

The number of seizure-free patients (Engel class I) remained favorable at seven-year follow-up, 64.0% compared with 73.2% at one-year follow-up. No difference in seizure outcome between patients in the group with TLR compared with patients in the group with SAH was found at one-year follow-up ($p = 0.951$). This is in line with several other studies [13,14]. At 7 years, an unadjusted model showed no difference in seizure outcome between the surgical approaches in patients operated in the same hemisphere ($p = 0.177$). In Wendling's study from 2013 [13], no significant difference in seizure outcome between SAH and TLR, was found either, at a mean follow-up period of 7 years. These results are in favor of choosing a selective resection when operating patients with MTLE and HS. However, one must bear in mind that patients with a more widespread disease for example cortical dysplasia or dual pathology possibly still would get a better seizure outcome with a more extensive resection [3,19].

### 4.2. Verbal memory after left-sided TLR

The second main result in our study was a worsening in verbal memory performance in patients with left-sided TLR compared with all the other patient groups ($p = 0.011$), and compared specifically to patients with left-sided SAH ($p = 0.036$). In line with this finding, it was shown in Martin et al.'s study [33] that 48% of patients who underwent left-sided anterior temporal lobectomy and had moderate or severe HS performed worse in retrieval aspects of verbal memory, when comparing the preoperative score to a postoperative score measured 3 to 18 months after surgery.

The favorable neuropsychological outcome in SAH in the dominant hemisphere is widely theoretically explained by the sparring of temporal neocortex and the temporal stem. The temporal neocortical regions are by most considered critical to semantic processing, and the left hemisphere is considered especially important regarding language semantics [34,35]. The better verbal memory in the left SAH group compared with the left TLR group might as well be related to the sparring of neocortical tissue and thereby a theoretically relatively preservation of semantic processing. The verbal associate pair tests are thought to be sensitive to these processes because of the demands of a semantic function when associating words, and because of the highly semantic relation in half of the word pairs. In the temporal stem among others a fiber bundle, the uncinate fasciculus (UF), which connects the anterior temporal lobe with the orbitofrontal cortex and the anterior prefrontal cortex in a bidirectional way [36], is considered important in verbal learning and memory [37–39]. In our material, the UF was divided alongside its fiber length in the SAH approach, but across its fiber length in most of the TLR approaches, and we speculate that damage to this structure could explain the worse performance in verbal memory in the left TLR group. Disruption of the UF may cause problems in the expression of memory to guide decisions and in the acquisition of certain types of learning and memory [36]. In a recent study, abnormalities in the UF were found with diffusion tension magnetic resonance imaging showing positive correlations with disturbed verbal fluency and digit span test scores [40]. Others have argued that the UF might be compensated by alternative connections and regions in postoperative reorganization processes [41]. Functioning of the remaining posterior part of the hippocampus has been connected to verbal memory outcome in the first postoperative months [42,43] while reorganization to the contralateral hemisphere seems to be of importance for the verbal memory outcome at 12 months postsurgical [44]. The lack of consistent findings in verbal memory outcome studies comparing left SAH and left TLR might not only be due to heterogeneous patient characteristics and surgical methods but also to a substantial heterogeneity in task demands in the various verbal memory tests [45,46]. Our study supports the importance of applying various types of verbal memory tests that are sensitive to different aspect of memory processing and task demands. As a consequence, a much broader test battery is now used at our hospital.

### 4.3. Verbal learning and side of surgery

The third major result is that our data support the differing impact of the side of surgery (hemisphere) on verbal learning performances that has been reported for decades [47]. Patients operated in the left hemisphere had significantly worse performances in the verbal learning score than those operated in the right hemisphere ($p = 0.002$). This result is in line with the well-established material specific hypothesis [48].

In contrast to verbal memory, no significant difference was observed in verbal learning outcome between the left sided SAH and the left sided groups with TLR. Several other studies describe verbal learning decline both after left SAH and after different left TLR approaches, but to a lesser extent in left SAH [49–51]. Because both groups are declining following surgery, smaller differences might have been blurred by other factors, e.g., the potential trouble learning all the 15 word pairs (up to 10 trails). This might be exhausting to left patients with TLE who nearly all have some degree of language and learning problems in addition to the common executive problems [48].

### 4.4. Limitations

A potential limitation of this study is the procedure for allocating patients to the groups with SAH or TLR. Patients were not randomized. The decision about resection type SAH or TLR, and the extension of the TLR, was guided by intraoperative ECoG. A technique based on a limited time

sampling of interictal epileptiform activity that can be changed when the neuronal tissue is affected by surgery and anesthetics [52]. Good results have been shown with this technique [53], but the seizure outcome has been found to be comparable between TLR guided by ECoG and standard TLR [54]. In one prospective study [55], patients with unilateral mesial temporal lobe sclerosis diagnosed on preoperative MRI, were investigated with pre- and postresective ECoG. They received the same standard resection independent of the ECoG results. No significant difference between patients with a good (Engel class I) and a poor (Engel classs II, III, IV) seizure outcome, was found, with respect to the share of patients having spikes in unresected neighboring areas before resection, residual spikes in neighboring areas after resection, and new spikes in areas distant from the resection. This study and a newer review therefore conclude that ECoG generally is not considered to be needed in patients with mesial temporal lobe sclerosis [55,56]. In this material, the seizure outcome corresponds to what has been presented in other studies not using intraoperative ECoG [1,57]. We would like to emphasize that the goal of the present study not was to elucidate whether ECoG is needed for the operative decision-making. We would also like to enhance that whether ECoG has been used or not, this study analyzed the pre- minus the postoperative score that is the change from baseline in the verbal learning and the verbal memory test, in each patient. Therefore, this study gives information about the influence of a selective versus a nonselective procedure and of resection in the right versus the left hemisphere on these neuropsychological functions despite the allocation procedure. Since data to this article goes back to the beginning of the Danish epilepsy surgery program, the exact data on related vs. unrelated word pairs were unavailable.

The methodological strengths of the present study are the very strict inclusion criteria (intelligence within the normal range, left hemisphere dominance, Danish as native language, histopathological verified HS, age above 16 years), operation by the same neurosurgeon (1995–2009), and accounting for potential confounders, which are important when assessing neuropsychological performance.

## 5. Conclusion

In patients with drug-resistant focal MTLE, HS and no MRI signs of dual pathology SAH results in sustained seizure freedom and better memory function compared with patients operated with nonselective TLR.

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## Conflicts of interest

No conflicts of interest exist for any of the authors.

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Paper 3

PLOS ONE

RESEARCH ARTICLE

# Safety and EEG data quality of concurrent high-density EEG and high-speed fMRI at 3 Tesla

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## Abstract

### Purpose

Concurrent EEG and fMRI is increasingly used to characterize the spatial-temporal dynamics of brain activity. However, most studies to date have been limited to conventional echo-planar imaging (EPI). There is considerable interest in integrating recently developed high-speed fMRI methods with high-density EEG to increase temporal resolution and sensitivity for task-based and resting state fMRI, and for detecting interictal spikes in epilepsy. In the present study using concurrent high-density EEG and recently developed high-speed fMRI methods, we investigate safety of radiofrequency (RF) related heating, the effect of EEG on cortical signal-to-noise ratio (SNR) in fMRI, and assess EEG data quality.

### Materials and methods

The study compared EPI, multi-echo EPI, multi-band EPI and multi-slab echo-volumar imaging pulse sequences, using clinical 3 Tesla MR scanners from two different vendors that were equipped with 64- and 256-channel MR-compatible EEG systems, respectively, and receive only array head coils. Data were collected in 11 healthy controls (3 males, age range 18–70 years) and 13 patients with epilepsy (8 males, age range 21–67 years). Three of the healthy controls were scanned with the 256-channel EEG system, the other subjects were scanned with the 64-channel EEG system. Scalp surface temperature, SNR in occipital cortex and head movement were measured with and without the EEG cap. The degree of artifacts and the ability to identify background activity was assessed by visual analysis by a trained expert in the 64 channel EEG data (7 healthy controls, 13 patients).

Protection Agency Regional Committee of the Capital Region of Denmark, please contact Pernille Daksha Villadsen (Pernille.Daksha.Villadsen@regionh.dk). Once access has been granted, researchers must contact the Health Research Ethics Committee of the Capital Region of Denmark to seek approval of the use of these data in a new publication (vek@regionh.dk; https://www.regionh.dk/vek).

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**Competing interests:** The authors have declared that no competing interests exist.

**Abbreviations:** BCG, Ballistocardiographic; BOLD, Blood oxygenation level dependent MR response; EEG, Electroencephalography; EEG-fMRI, Concomitant EEG and fMRI; EGI, Electrical Geodesics, Inc; EPI, Echo planar imaging; fMRI, functional magnetic resonance imaging; ICA, Independent component analysis; MB-EPI, Multi-band EPI; MEPI, Multi-echo EPI; MS-EVI, Multi-slab echo volumar imaging; MR, Magnetic resonance; MREG, MR-encephalography; RF, Radiofrequency; rsfMRI, resting state fMRI; SAR, Specific absorption rate; TE, Time to echo; TR, Time to repetition.

## Results

RF induced heating at the surface of the EEG electrodes during a 30-minute scan period with stable temperature prior to scanning did not exceed 1.0˚ C with either EEG system and any of the pulse sequences used in this study. There was no significant decrease in cortical SNR due to the presence of the EEG cap ($p > 0.05$). No significant differences in the visually analyzed EEG data quality were found between EEG recorded during high-speed fMRI and during conventional EPI ($p = 0.78$). Residual ballistocardiographic artifacts resulted in 58% of EEG data being rated as poor quality.

## Conclusion

This study demonstrates that high-density EEG can be safely implemented in conjunction with high-speed fMRI and that high-speed fMRI does not adversely affect EEG data quality. However, the deterioration of the EEG quality due to residual ballistocardiographic artifacts remains a significant constraint for routine clinical applications of concurrent EEG-fMRI.

## Introduction

Simultaneous electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) have in recent years emerged as a new tool in brain research. EEG-fMRI combines the high temporal resolution of EEG in milliseconds range with the high spatial resolution of fMRI in the $mm^3$ range. This might enable improved localization of the sources of the electrical events based on the associated blood oxygenation level dependent (BOLD) response. Concurrent acquisition of fMRI and EEG has also emerged as a new tool for localizing the epileptogenic zone. In medically intractable epilepsy patients, removal of the epileptogenic tissue is a well-documented treatment in cases where the epileptogenic focus can be localized [1] [2] [3], and here, EEG-fMRI offers the potential for improved spatial localization of the epileptogenic zone. However, whether fMRI is capable of mapping the onset of the epileptic discharge and its spread, and how BOLD signal changes are related to the epileptic activity is an area of active research [4] [5]. The use of concurrent EEG-fMRI may have even wider application in neurobiological research, e.g., during fMRI recording of functional activation and evoked potentials as well as for MR sleep recording.

The acquisition of high quality EEG data inside the MRI scanner environment is challenging and much effort has been spent on deconvolving gradient, motion and ballistocardiographic (BCG) pulse artifacts [6] [7]. EEG recordings inside the MR scanner are prone to strong artifacts including gradient artifacts due to the currents induced by gradient switching, to head movements, and to ballistocardiographic (BCG) pulse artifacts. The BCG pulse artifacts are thought to be primarily caused by small movements of the body and the electrodes due to cardiac pulsation in arteries and to a smaller extent due to the Hall effect. Furthermore, the supine position inside the MR scanner may be associated with artifacts in the signals of the posterior electrodes during head movement. The sensitivity of measuring background activity, such as the alpha rhythm (8–13 Hz), in the EEG data has been used in studies for assessing the performance of artifact reduction algorithms [6].

The impact on fMRI data quality with concurrent use of EEG equipment has been investigated in a number of studies, which reported increased inhomogeneity of the static magnetic field in the vicinity of the electrodes causing decreases in cortical signal-to-noise ratio (SNR), but no significant effect on the sensitivity of detecting task-based fMRI signal changes and resting state networks [8] [9] [10] [11].

Recent advances in increasing the temporal resolution of fMRI using high-speed acquisition methods that enable un-aliased sampling of physiological signal fluctuation (conventional fMRI methods suffer from cardiac-related aliased signal fluctuations that interfere with activation-related signal changes) have considerably increased sensitivity for mapping task-based activation and functional connectivity, as well as for detecting dynamic changes in connectivity over time [12] [13] [14]. A concurrent EEG-fMRI study in patients with epilepsy demonstrated that ultra-fast fMRI using magnetic resonance encephalography (MREG) increased sensitivity for localizing interictal spikes when compared with conventional EPI [15]. However, MREG has limited spatial resolution and requires long image reconstruction times. RF power requirements are comparable to EPI. Simultaneous multi-slice (multi-band) EPI (MB-EPI) is now widely used for resting state fMRI and represents a promising methodology for concurrent EEG-fMRI, but increased RF power requirements of multi-band RF pulses are a safety concern. Multi-slab echo volumar imaging (MS-EVI), a 3D encoded high-speed fMRI technique that has also been shown to increase fMRI sensitivity for mapping task-based and resting state connectivity in healthy controls and patients with brain lesions [13] [16], has less stringent radiofrequency (RF) power requirements than MB-EPI.

A key concern is RF related heating of the EEG leads and electrodes, which depends on many MR acquisition related factors. RF heating has been shown to be mainly related to the specific absorption rate (SAR) of RF energy [8] [17]. Low SAR is considered a core safety requirement for EEG-fMRI. A confounding issue is that the RF pulse shapes for slice selection and lipid suppression that are used in different pulse sequences are vendor specific. Further, the EEG wire layout inside the head RF coil depends on the coil geometry and the head size relative to the coil inner diameter, leading to increases in average RF power levels and SAR. The safety of concurrent EEG-fMRI has been characterized at field strengths up to 7 Tesla [8] [17]. However, most of these studies have focused on conventional echo-planar imaging (EPI) with temporal resolution of 2–3 seconds. As stated above, MB-EPI increases SAR, whereas MREG and MEVI have low SAR. A second concern is fast gradient switching rates with high-speed fMRI increase the potential for gradient artifacts. There is thus an urgent need to assess the safety and data quality of concurrent EEG-fMRI using recently developed high-speed fMRI acquisition methods.

Our present study investigated RF heating in concurrent EEG and high-speed fMRI by comparing three different fMRI pulse sequences (EPI, MB-EPI and MS-EVI) in healthy controls and patients with epilepsy using two different 3 Tesla MRI scanners from 2 different vendors equipped with a 64- and 256-channel MR-compatible EEG system, respectively. RF heating was examined by direct multi-point temperature measurements. The effect of the EEG cap on the signal-to-noise ratio was evaluated in occipital cortex. EEG data quality was assessed using the 64-channel EEG system. Here we investigated to which extent residual gradient artifacts due to the choice of the fMRI pulse sequence (EPI and MEPI compared to MB-EPI and MS-EVI), BCG artifacts and patient movement impact the data quality of EEG and ongoing activity recorded inside an MR scanner.

## Materials and methods

### Subjects

The project was approved by the Ethics Committee of the Capital Region of Copenhagen Denmark (H-KA-20060151 and H-2-2013-038). All subjects (controls and patients) gave written informed consent before participation. The controls were recruited from an online database and by word of mouth. Recordings consisted of MR scans, EEG recordings and temperature measurements between the skin and the EEG electrodes.

## Controls

A total of 11 healthy controls were studied: 8 subjects were scanned using the Philips Achieva (3 males, age between 18 and 70 years), and 3 subjects using the Siemens Prisma scanner (3 females, age between 20 and 26 years). In the subjects studied on the Phillips scanner the EEG quality was assessed in all except 1 and systematic temperature measurements in 3. In all subjects studied on the Siemens scanner the temperature was systematically investigated.

## Patients

A total of 13 patients were scanned (8 males, age between 21 and 67) using the Philips Achieva scanner and EEG quality was assessed. Judged by EEG, MR and semiology 7 had temporal lobe epilepsy, 1 had probable temporal lobe epilepsy, 2 had frontal lobe epilepsy, 1 had epilepsy arising from the occipital lobes, 1 had idiopathic generalized epilepsy, and 1 had epilepsy arising from the central region. All patients were on anti-epileptic medication based on best clinical practice. The patient inclusion criteria were: adults ($>$ 18 years), with epilepsy and a history of frequent interictal spikes or sharp waves (aiming for $>$ 5 per 1/2 hour) with high amplitude (aiming for $>$ 70μV), who could cooperate with the examination.

## Equipment

**MR scanners.** Data were collected using two different clinical 3 Tesla MRI scanners from two different vendors: A Philips Achieva scanner (Philips, Best, The Netherlands) equipped with a 32 channel RF head array coil and a Siemens Prisma Fit (Siemens, Erlangen, Germany) scanner equipped with a 64 channel RF head array coil. The scanners were located respectively at Glostrup and Blegdamsvej campus of Rigshospitalet, Copenhagen, Denmark; The Philips Achieva scanner was equipped with a 32- and a 64-channel MR Cap (BrainCapMR, Brain Products GmbH, Munich, Germany), which consisted of 63 EEG electrodes, 1 external ECG electrode, 1 ground (AFz), and, 1 reference electrode (FCz). The Siemens Prisma scanner was equipped with a Geodesic EEG System (Electrical Geodesics, Inc., Eugene, OR) with 256 EEG channels, 2 external ECG electrodes and 1 reference electrode (Cz).

Phantom measurements were performed using a spherical daily quality assurance phantom provided by the manufacturers.

**EEG equipment.** BrainCapMR: This device was used on the Phillips Achieva scanner. The system had 64 ring-type sintered nonmagnetic Ag/AgCl electrodes. The EEG cap was selected according to the head size (56, 58 or 60 cm).

Geodesic EEG System MR: This device was used on the Siemens Prisma Fit scanner. The system had 256 channels consisting of sponge based electrodes. The EEG cap was selected according to the head circumference (54–56, 56–58 or, 58–61 cm).

**Temperature measurement equipment.** Temperature measurements in the Philips Achieva and the Siemens Prisma scanner were performed using a four channel Luxtron 3100 fiber optic thermometer (LumaSense Technologies Inc.). In the Phillips scanner, an extra 2-channel Veris MR-compatible monitoring system (MedRad Inc.) was used to monitor additionally the scanner bore and room temperature (and in the last subject also the ear temperature due to failure of one of the Luxtron channels).

## Data acquisition

**MR scanning protocols.** The acquisition parameters for the different acquisition methods are listed in Table 1.

**Table 1. fMRI acquisition parameters.**

| Scanner (array coil) | Philips Achieva (32 cha) | | | | | | Siemens Prisma (64 cha) | |
|---|---|---|---|---|---|---|---|---|
| **fMRI Method** | **EPI** | **EPI** | **MEPI** | **MEPI** | **MB4-EPI** | **MS-EVI** | **EPI** | **MB8-EPI** |
| TR [ms] | 3034 (*) | 402 | 3034 | 376 | 450 (**) | 487(***) | 1980 | 280 |
| TE [ms] | 35 | 35 | 9.6 | 9.6 | 35 | 35 | 35 | 35 |
| Number of Tes | 1 | 1 | 4 | 3 | 1 | 1 | 1 | 1 |
| Slices | 37 | 6 | 37 | 6 | 24 | 24 | 30 | 32 |
| Number of volumes | 200 | 3000 | 200 | 3200 | 1400 | 895 | 150 | 1100 |
| Scan time [min:sec] | 10:16 | 20:00 | 10:16 | 20:03 | 10:36 | 04:34 | 10:14 | 19:11 |
| Voxel size [mm] | 3.1 | 3.1 | 3.1 | 3.1 | 2.88 | 4 | 4 | 4 |
| Slice thickness [mm] | 3.1 | 3.1 | 3.1 | 3.1 | 3.3 | 4 | 4 | 4 |
| Slice gap [mm] | 0.31 | 0.31 | 0.31 | 0.31 | 0.7 | 0 | 1 | 1 |
| Matrix size | 76x73 | 76x73 | 76x73 | 76x73 | 80x79 | 64x61 | 64x64 | 64x64 |
| Flip angle [degrees] | 90 | 30 | 90 | 30 | 15 | 30 | 90 | 30 |

* In some cases a TR of 2000 ms was used

** In one case a TR of 381 ms was use

*** In some cases a TR of 300 ms was used.

Cha = Channel, TR = Repetition time, TE = Echo time (minimum TE in case of MEPI), EPI = Echo planar imaging, MEPI = Multi echo planar imaging, MB4-EPI = Multiband-4 echo planar imaging, MS-EVI = Multi-slab echo volumar imaging, MB8EPI = Multiband-8 echo planar imaging.

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Conventional whole brain EPI data with a repetition time (TR) of 2 or 3 s were acquired on both scanners. On the *Philips Achieva scanner*, additional data were acquired using partial brain EPI at shorter TR (402 ms), and using whole brain and partial brain multi-echo EPI (MEPI) with 3.2-fold SENSE acceleration, a minimum TE of 9.6 ms, an echo time spacing of 17 ms and TRs of 3034 and 376 ms, respectively. Multi-band (simultaneous multi-slice) EPI data were acquired with 4-fold acceleration (MB4-EPI) using a pulse sequence developed by GyroTools LLC (Zürich, Switzerland). Data reconstruction was performed offline. The initial version of the MB-EPI pulse sequence suffered significant temporal instability and artefactual inter-slice correlations as a result of RF pulse instability that was resolved with an update of the pulse sequence software in the middle of the study. This instability prevented removal of gradient artifacts in the initial data. Sequential multi-slab echo-volumar imaging (MS-EVI) data were acquired using a custom designed implementation by GyroTools LLC (Zürich, Switzerland) based on the method described in Posse et al., 2012 [13]. Sinc-modulated RF pulses with high time-bandwidth product were used for slab selection. The MS-EVI pulse sequence employed 3.2x2 fold 2D-SENSE acceleration along $k_y$ and $k_z$. Image reconstruction was performed online. On the *Siemens Prisma scanner*, additional data were acquired using a multi-band EPI sequence with 8-fold acceleration (MB8-EPI) and online reconstruction developed by the Center for Magnetic Resonance Research, University of Minnesota [18]. Small timing errors in the initial versions of the EPI and MB-EPI pulse sequences that changed the TR were resolved with an update of the pulse sequence software during the second half of the study. This instability prevented removal of gradient artifacts in the initial data.

In the epilepsy patients and the first 5 healthy controls the scanning time for the different pulse sequences varied. In the last 6 subjects (3 in the Philips Achieva scanner and 3 in the Siemens Prisma scanner), all available pulse sequences were applied for 30 minutes (Fig 1). The maximum scan durations and minimum TRs of MB-EPI and MS-EVI were software limited by the operating systems of the scanners to account for gradient coil heating limits and data rate constraints, which were scanner specific.

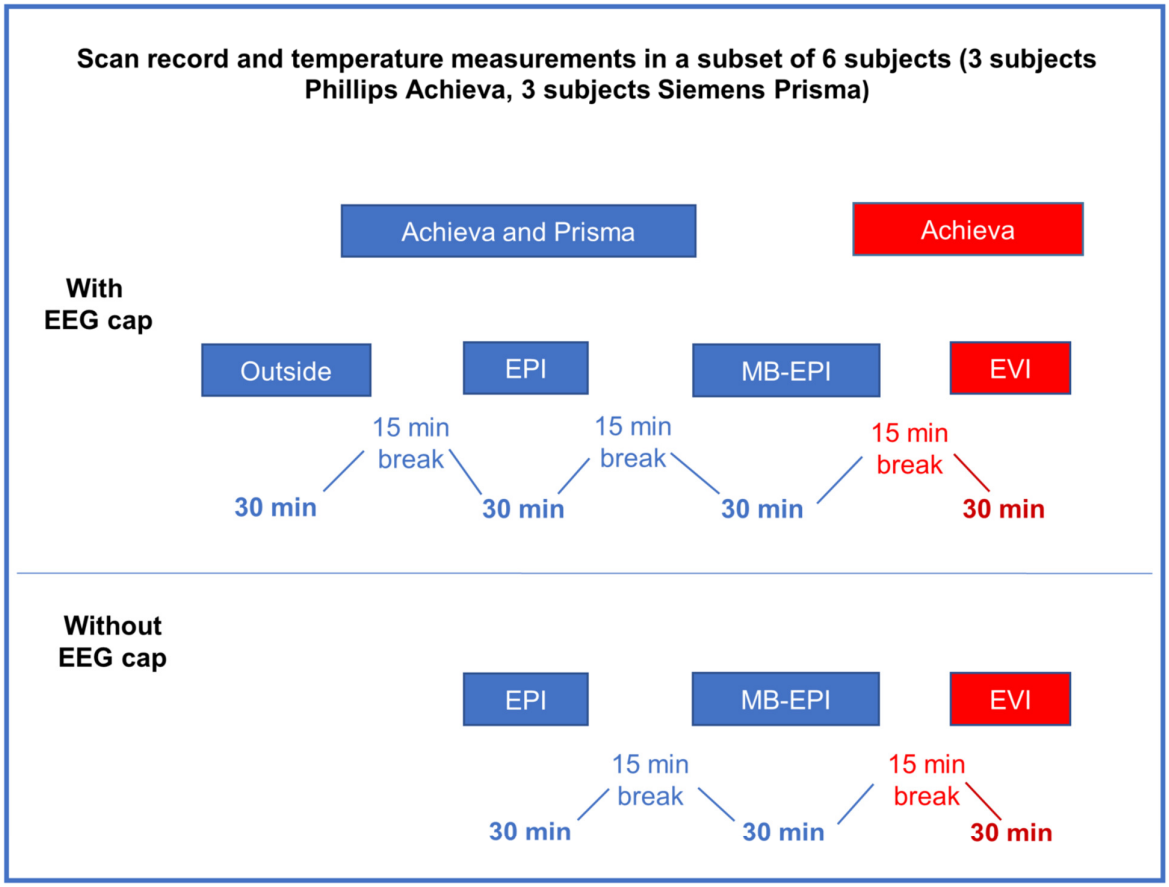


**Fig 1. Flowchart of the scan protocol during the systematically temperature measurements.**

https://doi.org/10.1371/journal.pone.0178409.g001

In the epilepsy patients and the first 5 healthy controls resting-state scans were acquired using a scan duration of 5, 10 or 20 minutes, depending on the fMRI data acquisition method and scanner type. In the last 6 subjects, all sequences were applied for 30 minutes (Fig 1). Subjects were instructed to keep their eyes open, clear their mind and relax without moving the gaze.

**EEG.** In phantom scans the EEG cap was placed on top of the phantom with electrodes touching the surface of the phantom.

BrainCapMR (Phillips Achieva): The skin was prepared using disinfectant and Nuprep gel. The cap was placed according to the international 10–20 system. Two additional channels recorded eye movements (EOG, placed on the forehead) and electrocardiogram (ECG, placed at the subject's back at the level of the heart just left of the spine). The reference channel was placed at the vertex. Conductive gel was filled in each of the electrodes after positioning the cap, and added when necessary to keep impedance below 20 kΩ. The EEG cap was kept in place by a net. The cables from the cap were run through a small hole in the back of the head coil and stretched and fixed using sandbags to avoid loops. Additional ECG was recorded with

4 leads, 3 electrodes placed along the left side of the sternum and 1 electrode placed in the axillary line. Data were acquired with 5 kHz sampling rate synchronized to the scanner clock frequency.

Geodesic EEG System MR (Siemens Prisma Fit scanner): The skin was disinfected using a non-alcoholic disinfectant. The reference electrode was placed at the vertex. The 256-channel cap was prepared with an electrolyte/shampoo solution. The cap was then applied and adjusted to ensure that selected electrodes were placed at predetermined reference points. The EEG cap was kept in place by a net, and on top of this a swim cap was placed to prevent evaporation of the preparation solution. The impedance was measured, and kept below 50 kΩ. Two ECG electrodes were placed on the left side of the sternum, one at the 3th-4th intercostal space and one at the 6th-7th intercostal space. The cables from the cap were run along the side of the head downwards towards the feet inside the head coil. Data were acquired with 1 kHz sampling rate and synchronized to the scanner clock frequency.

**Temperature measurements.** In phantom scans temperature sensors were distributed across the surface of the phantom and placed underneath EEG-electrodes. In vivo temperature measurements were performed in all subjects, but not all sequences were systematically used in the first 5 controls and in the patients. In the last 6 controls, 3 in the Achieva scanner and 3 in the Prisma scanner, temperature was measured systematically using all available pulse sequences with and without the EEG cap (Fig 1). Sensors were placed underneath EEG-electrodes (see electrode display in supporting information, S1 Fig) on the forehead (with free heat exchange with the surroundings), the left or the right ear, the neck (with limited heat exchange with the surroundings), and on the scanner bore. In two subjects room temperature, but not bore temperature were measured. In measurements performed without the EEG cap the temperature probes were fixed to the subject's scalp at the same points as with the EEG cap, using sensitive skin tape.

## Data analysis

**Analysis of signal-to-noise.** The signal-to-noise ratio in fMRI scans was computed by measuring the average signal intensity in a circular ROI in occipital cortex, subtracting the average of the signal intensity in 4 circular reference regions outside of the brain in the 4 corners of the image, and scaling the result with the average of the standard deviation of the noise in these 4 reference regions. Differences in SNR between scans with and without the EEG cap on were assessed using a two-tailed heteroscedastic t-test.

**Analysis of head movement.** Head movement in the fMRI data was analyzed using the MCFLIRT toolbox in the FSL software package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/)) and reported as relative (dynamic-to-dynamic) and absolute (relative to the middle dynamical image) motion parameters.

**EEG preprocessing.** Due to the timing errors in the EPI and MB-EPI pulse sequences on the Prisma scanner and in the EGI acquisition software, which resulted in failure of gradient artefact removal, it was not possible to assess the data quality of the high-density 256 channel EEG array implemented in the Siemens Prisma scanner.

The EEG data acquired with the 64-channel BrainCapMR equipment on the Philips Achieva scanner were preprocessed using BrainAnalyzer 2.0 (Brain Products GmbH, Gilching, Germany). These steps included gradient artifact removal using the sliding window approach with 21 averages [19], down-sampling from 5kHz to 500 Hz and correction of BCG using the sliding window approach. Data with evident noise after visual inspection were additionally run through an ICA where noise components were removed before a back-projection was applied (BrainAnalyzer 2.0).

**Evaluation of EEG recordings and scoring of data quality.** A board certified clinical neurophysiologist with more than 10 years of experience (SB) visually evaluated the EEG recordings after artifact removal. The neurophysiologist was blinded to which MR sequence was used when the individual EEG's were recorded. Signals were inspected both in sensor-space and in source-space using BESA Research software [20]. The source montages reproduces the signals in 19 brain regions in each hemisphere [21].

Data quality was scored, using the following criteria:

- good = no or minimal amount of artifact, that does not interfere at all with the visual evaluation / interpretation of > 80% of the recording (score 1).
- acceptable = significant amount of artifacts, yet good enough to distinguish artifacts from background activity and epileptiform discharges (if any) in 40–80% of the recording (score 2).
- poor = the recording is unreadable / less than 40% of the recording is relatively free of artifacts (score 3).

**Statistical analysis.** Data were described with mean and standard deviation for continuous data and sample size and percentage for categorical data.

A logistic mixed model was used to assess the influence of the fMRI type (high-speed vs. conventional), relative and absolute motion on the ratings (poor vs. acceptable and good). The model was adjusted for the disease status of the subject (healthy vs. epilepsy disease). A random intercept was used to account for a potential correlation in the ratings between scans corresponding to the same individual.

Results are reported using odds ratios and their 95% confidence interval. An odds ratio is a measure of association between an exposure (e.g. motion) and the rating. It is the ratio between the odds of occurrence of the outcome given one unit increase for the exposure (e.g. motion increased by one mm) compared to the odds of a reference level [22]. The typical scale for absolute motion is mm whereas for relative motion it is 0.1 mm. Therefore, the odds ratios for these variables are reported in units one mm increase and 0.1 mm increase, respectively. Analyses were performed with R software, version 3.2.3 [23].

## Results

### Temperature measurements

**Phantom scans.** Temperature increases during standard EPI scans of up to 20 min duration did not exceed 0.1˚C/min in the Philips Achieva. Temperature increases during MB-EPI and MS-EVI scans measured in the Philips Achieva and Siemens Prisma scanners were in the same range with a maximum of 0.1˚C/min. The dependence of temperature increases on SAR of the MB-EPI scanning protocol was further investigated on the Philips Achieva scanner by increasing the flip angle to 256˚ (8.5 times larger than the flip angle used in vivo) with a SAR value of 51% (Table 2). A 33-minute scan time resulted in a temperature increase of 0.06˚C/min.

**In-vivo scans.** The increases in temperature while the subjects were scanned with and without the EEG cap (Table 3) were comparable. The maximal temperature increase, across channels, observed in scans where the temperature was stable prior to the beginning of the scanning, was 0.50˚C in a 30-minute scan period for the Siemens Prisma scanner, and 1.0˚C in a 30-minute scan period for the Phillips Achieva scanner, for all protocols. These highest increases were measured during MB-EPI on both the Philips Achieva and Siemens Prisma

**Table 2. Temperature measurements and SAR values during MB-EPI sequences in concurrent EEG and MRI in the Phillips Achieva scanner demonstrating the impact of increased flip angle.**

| Subject | Sequence | Flip angle (degree) | Scan Duration [min] | SAR [%] (Mean/ SD) | | SAR [%] (Max) | ΔT [˚C] (Mean/SD) | | ΔT [˚C] (Max) |
|---|---|---|---|---|---|---|---|---|---|
| Phantom (n = 1) | MB-EPI | 256 | 33.00 | 51 | 0 | 51 | 0.8 | 0.3 | 1.1 |
| Phantoms (n = 2) | MB-EPI | 120 | 20.0/30.0 | 35 | 6 | 39 | 0.5 | 0 | 0.5 |
| Control (n = 1) | MB-EPI | 120 | 4.27 | 31 | 0 | 31 | 0.8 | 0.5 | 1.1 |
| Control + patients (n = 4) | MB-EPI | 15 | 10.0/20.0 | 18 | 2 | 21 | 0.2 | 0.3 | 0.8 |

Measurements with increased flip angle are in *italics*. Temperature measurements from all probes were combined.

ΔT: Absolute temperature change.

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scanners. Representative temperature curves where artifacts are minor are shown in Figs 2–6. Data from which the curves were constructed can be found in supporting information S1-S5 data.

The average head SAR values for a standard 70 kg person in the Phillips Achieva scanner without cap for EPI, MB-EPI and MS-EVI were 25%, 17% and 14%, respectively (Table 4). The mean values for these sequences in vivo with the 64 channel EEG cap on were similar: EPI 24% (± 1), MB-EPI 18% (± 2) and MS-EVI 13% (± 3). These SAR values corresponds to TR's of 3034 ms in the EPI, 450 ms in the MB-EPI and 487 ms in the MS-EVI (Table 1). In the Siemens Prisma scanner the mean SAR values showed a considerable increase with the 256 channel EEG cap on: EPI with cap 19% (± 3), MB-EPI with cap 16% (± 3), EPI without cap 8% (± 0), MB-EPI without cap 7% (± 1) (Table 4). The corresponding TR in the EPI were 1980 ms and in the MB-EPI 280 ms (Table 1).

The dependence of temperature increase on SAR during MB-EPI scans was further investigated on the Philips Achieva scanner in a healthy control using a 120˚ flip angle (4 times larger

**Table 3. Summary of temperature measurements.**

| Scanner (head RF array coil) | Siemens Prisma (64 ch) (N = 3) | | | Phillips Achieva (32 ch) (N = 3) | | |
|---|---|---|---|---|---|---|
| **Temperature Change [˚C]** | Frontal | Occipital | Temporal | Frontal | Occipital | Temporal |
| Mean outside | 1.3 | 1.5 | 1.3 | 1.2 | 0.0 | 2.2 |
| Mean inside w/o scanning | 0.1 | 0.6 | 0.9 | 0.1 | 1.5 | 0.4 |
| Mean EPI with cap | 0.2 | 0.4 | 0.6 | 0.2 | 0.1 | 0.8 |
| Mean MB-EPI with cap | 0.1 | 0.6 | 0.5 | 0.5 | 0.4 | 0.9 |
| Mean MS-EVI with cap | | | | 0.1 | 0.2 | 1.2 |
| Mean EPI w/o cap | 0.2 | 1.9 | 1.4 | -0.1 | 0.3 | |
| Mean MB-EPI w/o cap | 0.5 | 1.7 | 0.7 | -0.1 | 1.2 | 0.2 |
| Mean MS-EVI w/o cap | | | | 0.2 | 0.2 | |
| **Temperature Gradient [˚C/min]** | | | | | | |
| Mean outside | 0.041 | 0.048 | 0.041 | 0.038 | 0.000 | 0.073 |
| Mean inside w/o scanning | 0.010 | 0.057 | 0.087 | 0.005 | 0.150 | 0.035 |
| Mean EPI with cap | 0.007 | 0.013 | 0.019 | 0.005 | 0.002 | 0.025 |
| Mean MB-EPI with cap | 0.003 | 0.018 | 0.016 | 0.016 | 0.013 | 0.028 |
| Mean MS-EVI with cap | | | | 0.002 | 0.006 | 0.036 |
| Mean EPI w/o cap | 0.008 | 0.058 | 0.042 | -0.002 | 0.009 | |
| Mean MB-EPI w/o cap | 0.017 | 0.058 | 0.022 | -0.003 | 0.036 | 0.006 |
| Mean MS-EVI w/o cap | | | | 0.007 | 0.006 | |

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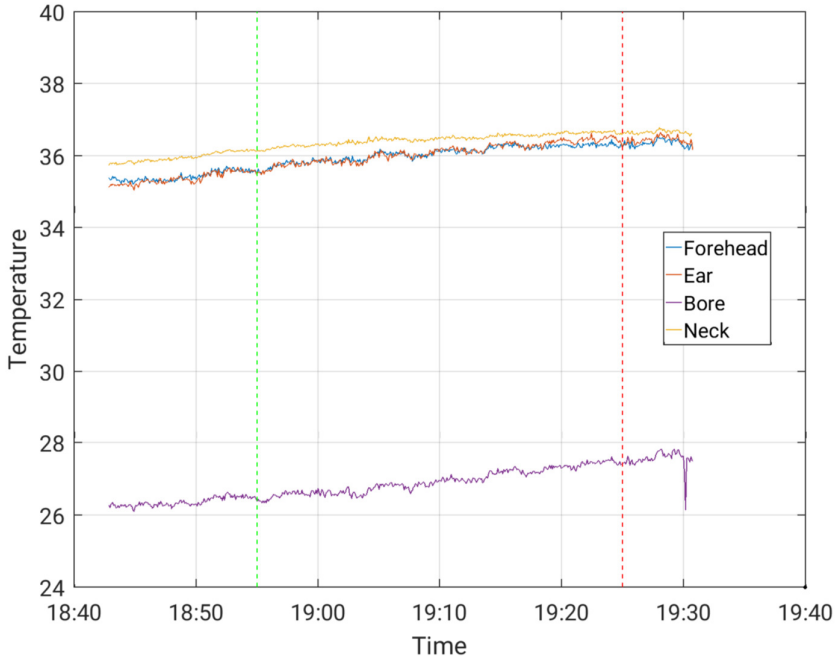


**Fig 2. Temperature measurement during a 30-minute EPI sequence with EEG cap on, in the Siemens Prisma scanner.**

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than in the standard protocol) and a 4:27 min scan duration, which resulted in a maximum temperature increase of 0.26˚C/min at an SAR of 31% (Table 2). This SAR is still considerably smaller than that of the TSE sequence reported in [24].

Additionally, temperature measurements outside of the scanner and while positioning the subjects inside the scanner prior to scanning (Table 3) show that temperature could increase irrespectively of scanning taking place. With a few exceptions, this increase inside the scanner prior to scanning was more pronounced than the temperature increases during scanning, indicating that physiological and environmental factors dominated the measured temperature increases. Temperature increases with the cap on were more pronounced outside of the MR scanner than inside the scanner during scanning (Table 3). As temperature changes, may be influenced by several factors, including MR-scanning, physiological and environmental changes (e.g. bore temperature) these factors were taken into account when analyzing the temperature changes. This was primarily done by analyzing temperature changes in the minutes before scanning was started.

Subjective temperature sensations and comfort of wearing the EEG cap were additionally assessed by asking subjects repeatedly to report on any heating sensations during the scanning. None of the subjects reported an electrode related heating sensation. The application of the EEG caps was well tolerated and the comfort of wearing the cap inside the MR scanner was comparable for both scanners. The subjects reported a similar degree of discomfort when the RF coil was closed, which was primarily a slightly claustrophobic sensation. All subjects reported some pressure from the electrodes after a scanning session lasting more than 30 minutes.

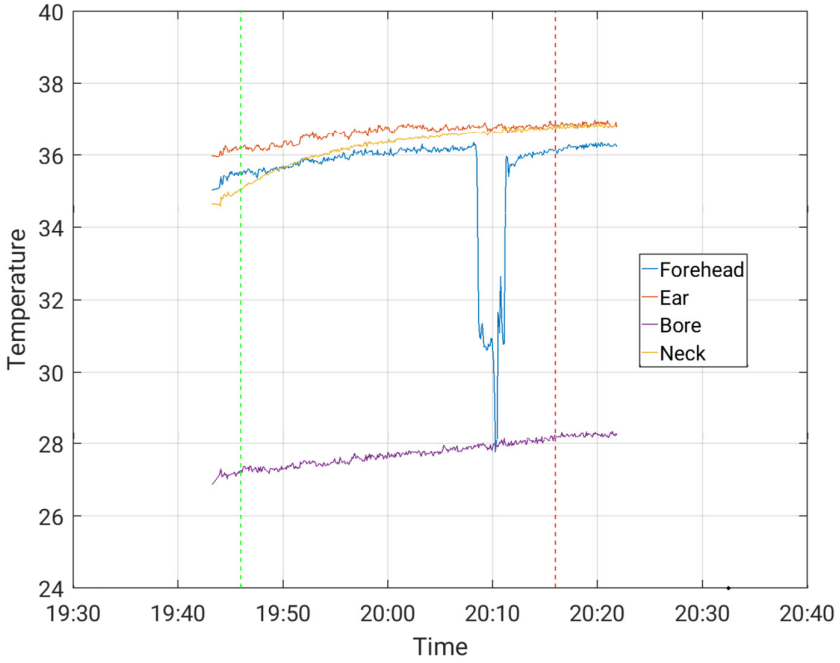


**Fig 3. Temperature measurement during a 30-minute MBEPI sequence with EEG cap on, in the Siemens Prisma scanner (forehead temperature channel disconnected at the dip).**

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## Signal-to-noise measurement

In the resting state fMRI scans using the 256 channel EEG system on the Siemens Prisma scanner, the SNR values averaged across all scans showed a trend level decrease ($p < 0.063$) when subjects were wearing the EEG cap (159+/-16) compared to when not wearing the EEG cap (171+/-19). Using the 64 channel EEG system on the Phillips Achieva scanner no such difference was found ($p > 0.90$). The cortical SNR when the subjects were not wearing the EEG cap (140+/-37) was very similar to when they were wearing the cap (138+/-38).

## EEG data quality

In the Philips Achieva scanner using the 64 channel EEG array, data quality was strongly related to electrode impedance. An impedance level below 20 kΩ was required for optimum data quality. The posterior alpha rhythm in the resting state data was clearly detectable, and located in the occipital area (Fig 7). The presence of bilateral, symmetric rhythmic activity in the range of 8–12 Hz (Shaun et al., 2013), in the posterior (occipito-parietal) region in all patients demonstrated that the normal ongoing EEG (background) activity was not distorted by the data processing [25].The 64 channel EEG data quality inside the scanner during scanning was significantly affected by the presence of residual BCG artifacts and a loss of nuances/information in the EEG compared with data acquired outside the scanner.

Descriptive data for the EEG quality and motion regarding high-speed and conventional MR sequences is shown in Table 5. Visual analysis of EEG quality by a trained expert could not demonstrate a significant difference in data quality between conventional EPI and high-

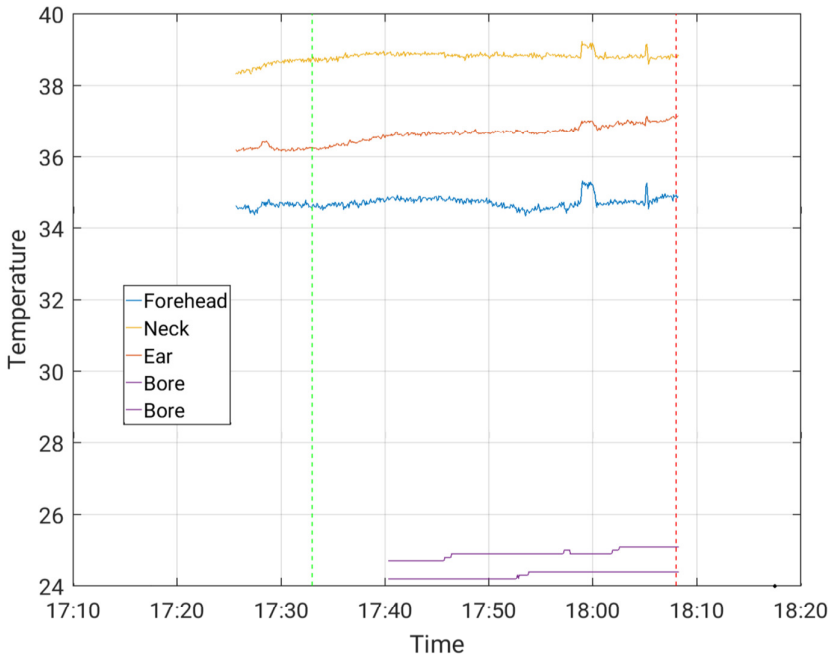


**Fig 4. Temperature measurement during a 30-minute EPI sequence with EEG cap on, in the Phillips Achieva scanner.**

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speed fMRI sequences (MS-EVI and MB-EPI) ($p = 0.78$). There was no evidence that EEG signal quality was affected by absolute ($p = 0.49$) or relative motion ($p = 0.36$).

## Discussion

The present study demonstrates that concurrent EEG and fMRI can be performed safely across the wide range of fMRI acquisition methods and the body coils used in this study. Although temperature rises of up to 1˚ C underneath some of the electrodes were measured in a 30-minute scan period, they were on average of such small magnitude that RF induced heating was not a limiting factor for the experimental settings in this study. Temperature drifts of a similar and even larger magnitude were frequently noted even without scanning. In the Prisma scanner a significant increase in SAR was observed when the subjects wear the EEG cap. The tight fit of the EEG cap inside the 64-channel head coil of the Prisma scanner in some of the subjects was a concern, since it could introduce the possibility of an incomplete mechanical closure of the coil, leading to possible coil malfunction and mistuning with the potential for increases in local SAR independent of the presence of the EEG electrodes. It may also restrict circulation, which could cause the sensation of heating. These may have contributed to the localized heating reported by one subject in the Prisma scanner during preliminary setup of the protocol. The maximum SAR values in the present studies, even for scans exploring the safety margins, were well below those reported in previous studies using Fast Spin Echo and Turbo Spin Echo pulse sequences that can reach up to 100% of the FDA approved SAR limits [26] [24]. Although gradient coil heating due to gradient switching limited data acquisition rates and maximum scan times, the present study allows to estimate safe limits for longer scan times as

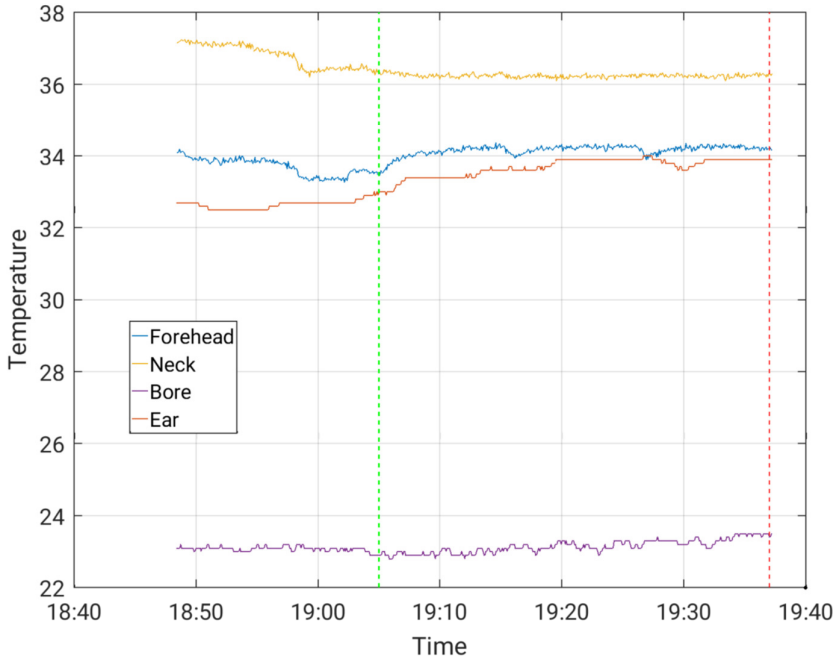


**Fig 5. Temperature measurement during a 30-minute MBEPI sequence with EEG cap on, in the Phillips Achieva scanner.**

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temperature increases are usually strongest at the beginning of the scan. Despite these still encouraging results one should not forget that placing electrodes and wires into high field scanners during high-speed fMRI requires constant attention for the safety and comfort of the subjects. There is potential for local temperatures to increase rapidly, if basic safety requirements such as adequate air circulation, proper closure of the coil, and avoidance of wire loops are not met.

The EEG data quality using the 64 channel EEG system during MR scanning was considerably degraded compared to EEG data measured outside of the scanner. However, EEG data quality was not significantly different between the conventional and the fast sequences. The quality of the EEG data was visually evaluated by a trained expert. This could be relevant, since epileptiform discharges are also identified this way (visual evaluation by trained experts). However, this visual approach is subjective, and thus represents a potential bias, although the EEG expert was blinded to the type of MR sequence when evaluating EEG quality. We consider this a limitation of the study.

Due to initial timing errors in the EPI and MB-EPI pulse sequences and in the EGI software, which resulted in failure of gradient artefact removal, we have not been able to assess the data quality of the high-density 256 channel EEG array implemented in the Siemens Prisma scanner. This comparison will be performed in a future study. There is now compelling evidence that detection and identification of spikes is significantly improved using electric source imaging with high-density electrode arrays (HD-EEG), with extended coverage including the face and neck areas [27] [28]. More than 90% of the spikes identified by HD-EEG were missed by the classical 10–20 electrode array [29]. Voltage maps derived from HD-EEG recording

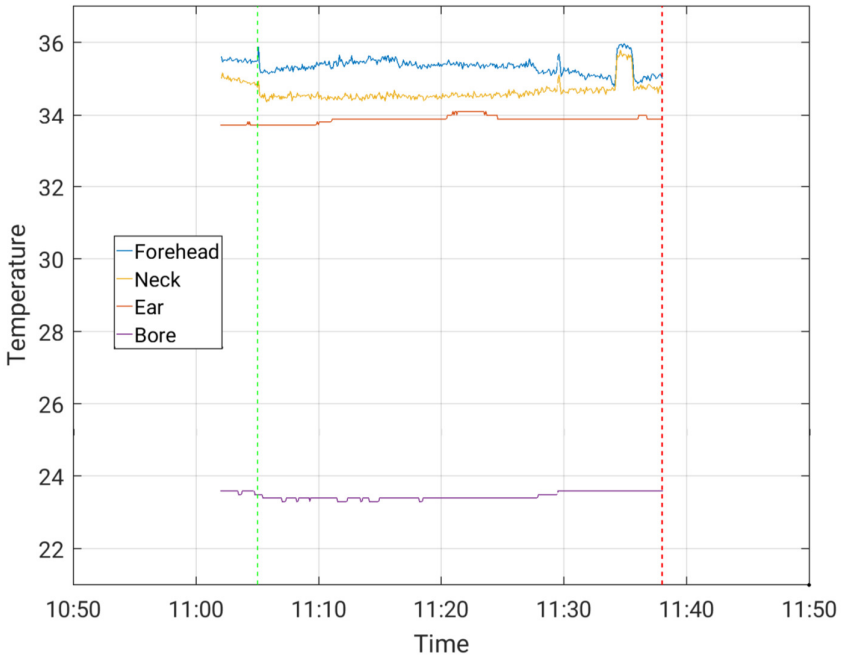


**Fig 6. Temperature measurement during a 30-minute EVI sequence with EEG cap on, in the Phillips Achieva scanner.**

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outside the MR scanner can serve as templates for algorithms searching for spikes in the EEGs recorded inside the MR-scanner [30]. A recent study described sensitivity advantages of concurrent HD-EEG-fMRI for mapping the epileptic networks [31]. However, other studies showed considerable decreases in the signal to noise ratio in fMRI due to susceptibility inhomogeneity, although no significant changes in task-based activation and resting state connectivity were detected [9] [10] [32]. This is consistent with our observation of trend level,

**Table 4. Summary of SAR values.**

| | | | SAR [%] | | |
|---|---|---|---|---|---|
| **Scanner** | **EEG System** | **Sequence / EEG cap** | **Mean** | **SD** | **Max** |
| Philips Achieva | Brain Products 64 channel | EPI_with_cap | 24 | 1 | 25 |
| | | EPI_without_cap | 25 | | |
| | | MB-EPI_with_cap | 18 | 2 | 21 |
| | | MB-EPI_without_cap | 17 | | |
| | | MS-EVI_with_cap | 13 | 3 | 17 |
| | | MS-EVI_without_cap | 14 | | |
| Siemens Prisma | EGI 256 channel | EPI_with_cap | 19 | 3 | 23 |
| | | EPI_without_cap | 8 | 0 | 8 |
| | | MB-EPI_with_cap | 16 | 3 | 18 |
| | | MB-EPI_without_cap | 7 | 1 | 8 |

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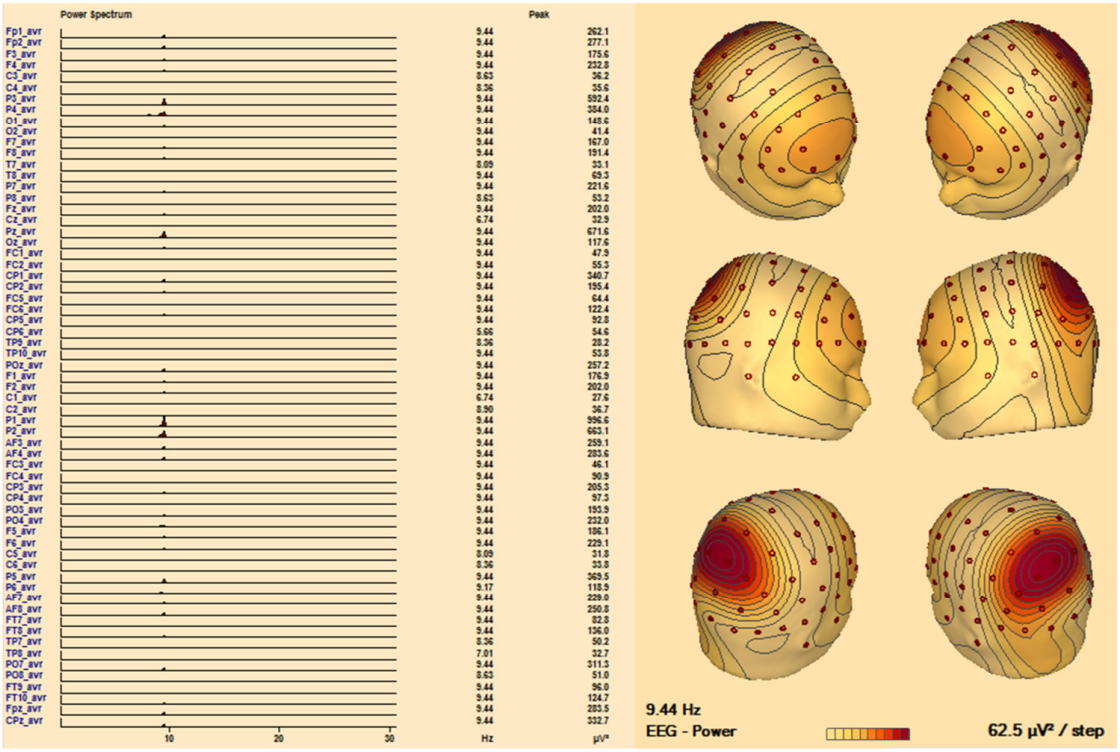


**Fig 7. Posterior dominant (alpha) rhythm in an EEG recorded in the MR scanner, during a high-speed sequence. Left:** Power Spectrum at EEG electrodes demonstrates a clear peak at 9.44 Hz, at the occipital electrodes. **Right:** power-map of alpha activity showing its 3D distribution.

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decreases in cortical SNR due to the presence of the 256 channel EEG cap, in contrast to the 64 channel cap, which showed no significant difference in SNR.

Another possible source of artifacts is RF noise that may be transmitted through the EEG leads. Further, EEG leads and electrodes may distort the transmit RF field (B1+) and the receive RF field (B1-) profiles, which causes regional flip angle variations and spatial variations in sensitivity, resulting in regional variation of fMRI signal intensity and degradation of the

**Table 5. EEG quality using conventional versus high-speed MR sequences and dependence on head motion.**

| | Conventional (EPI and MEPI) | High-speed (MS-EVI and MB-EPI) | Total |
|---|---|---|---|
| Number of scans | 30 | 20 | 50 |
| **EEG quality** (number (%) of poor ratings) | 18 (60%) | 11 (55%) | 29 (58%) |
| **Motion relative** (mm) | 0.1 (0.1) | 0.2 (0.1) † | |
| **Motion absolute** (mm) | 1.4 (1.1) | 0.9 (0.6) † | |

Relative and absolute motion are reported using mean and standard deviation.
EPI = Echo planar imaging. MEPI = Multi-echo planar imaging. MS-EVI = Multi-slab echo volumar imaging. MB-EPI = Multi-band echo planar imaging.
†Data from 4 scans missing.

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SNR [10]. However, fMRI at the typical voxel sizes used in clinical studies is dominated by physiological noise and as stated above, most previous studies have reported that the sensitivity of task-based and resting state fMRI is not significantly affected by the presence of the EEG cap [32] [10] [9].

Concurrent EEG-fMRI is a tool that is of considerable interest for many aspect of neuroscience, e.g., evoked potentials, sleep and epilepsy. Although the electrodes put some pressure on the skin, and especially for the electrodes the subjects were lying on, the use of the EEG cap in our study was well tolerated and did not limit the duration of the studies. Among the potential clinical use of concurrent EEG-fMRI should be mentioned selected patients with pharmacoresistant epilepsy where it is well documented that seizure freedom can be obtained after surgical removal of the epileptogenic tissue [1]. However, localizing the epileptogenic zone is often complex and challenging as both epileptic discharge and symptoms may spread during the attack. Therefore, pre-surgical evaluation of structure and function to localize the epileptogenic zone and adjacent eloquent cortex in these patients becomes a major goal for rendering as many patients as possible seizure free without neurological deficits. The approach is multimodal and in some patients invasive EEG is necessary with electrodes placed on the brain surface or inside the brain. In this context, concurrent acquisition of fMRI and EEG has emerged as a new potential tool for localizing the epileptogenic zone.

## Conclusions

This study demonstrates that high-density EEG can be safely implemented in conjunction with high-speed fMRI. Despite these encouraging results one should not forget that placing electrodes and wires into high field scanners that are equipped with high-power RF amplifiers requires constant attention for the safety and comfort of the subjects. We recommend performing temperature measurements with any new pulse sequence. High-speed fMRI does not adversely affect EEG data quality as visually evaluated by a trained expert. However, the deterioration of the EEG quality due to residual ballistocardiographic artifacts remains a significant constraint for routine clinical applications of concurrent EEG-fMRI.

## Supporting information

**S1 Fig. EEG cap with the respective temperature probes.** Electrode display in the 256-channel (left) and the 64-channel (right). The temperature probes were placed underneath the electrodes marked with the red circle, or underneath one of the neighboring electrodes. The ear temperature probe was placed on the left or the right side.
(TIF)

**S1 Data. From which Fig 2 was constructed.**
(CSV)

**S2 Data. From which Fig 3 was constructed.**
(CSV)

**S3 Data. From which Fig 4 was constructed.**
(CSV)

**S4 Data. From which Fig 5 was constructed.**
(CSV)

**S5 Data. From which Fig 6 was constructed.**
(CSV)

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Paper 4

# Clinical Utility of ESI in Presurgical Evaluation of Patients with Epilepsy (CUESIPE)

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## Abstract

### Purpose

To investigate the diagnostic added value of low-density (LD) and high-density (HD) EEG source imaging (ESI) in presurgical evaluation of patients with drug-resistant focal epilepsy. Previous clinical studies on EEG source imaging addressed the accuracy, but little is known about the clinical utility, defined as the added diagnostic value.

### Method

Eighty-two patients undergoing epilepsy surgery evaluation in Denmark between 2015 and 2018 were included. LD ESI was based on long-term video-EEG recordings with standard 25 electrodes, and an age-matched template head model. HD ESI was done using 90 minutes recordings with 256 electrodes array, digitized electrode positions and realistic head model using the patients' individual MRI. The multidisciplinary team made decisions in three steps: (1) based on all data except ESI; (2) adding LD ESI to the dataset; (3) adding HD ESI to the dataset. Changes in decision on patient-management options (stop / implantation of intracranial electrodes / alterations in implantation plan/ operation with perioperative electrocorticography/ operation/ extend of resection area) based on LD ESI and HD ESI were noted in the database.

### Results

Based on LD ESI the decision was changed in 16/82 patients (20%) and based on HD ESI in 23/82 patients (28%). This difference was significant ($p<0.001$).

### Conclusion

ESI using an HD array and individual MRI has significantly higher impact on the clinical decision making than ESI using LD EEG data ($p<0.001$), suggesting that HD ESI provides more, non-redundant information in the presurgical evaluation.

## 1. Introduction

Epilepsy surgery is a treatment option in patients with drug-resistant focal epilepsy. The goal is to render the patients seizure-free and increase their quality of life, but it requires that a focal epileptogenic zone (EZ) in the cortex is identified (1) (2). Despite technological development of imaging techniques this often remains a complicated task. Patients go through a multimodal presurgical workup, and the results are thoroughly evaluated at epilepsy surgery multidisciplinary team meetings (MDT) to assess agreement between modalities (3) (4). When semiology, long-term video electroencephalography (EEG) monitoring (LTM) and magnetic resonance imaging (MRI) are concordant surgery can be offered, provided the focus is not in the eloquent cortex. In case of discordance or when the MRI is normal or unrevealing, additional investigations such as photon emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG) are typically performed, followed by implantation of intracranial electrodes into the regions where the EZ is hypothesized (3) (5) (6).

Recently, electric source imaging (ESI) has gained ground in the presurgical evaluation program (3) (5) (6). ESI provides a non-invasive low-cost possibility of modelling where the electric signals recorded with a scalp EEG comes from within the cortex. In recent years the accuracy, including sensitivity, specificity and predictive value of ESI has been demonstrated with a high level of evidence (7) (8) (9) (10) (11). ESI based on HD EEG recordings (HD ESI) with multiple electrodes covering the 'whole head' are more accurate than ESI based on LD EEG recordings (LD ESI) (12). Applying a head model based on the individual MRI scan and individual electrode position measurement further improves the accuracy (10). Still, the time cost to perform ESI on HD EEG recordings with the individual MRI scan and electrode position measurement far exceeds that of ESI performed on LD EEG recordings with a template brain and template electrode position. Furthermore, it is difficult to apply HD arrays in LTM recordings. This limits the HD EEG recordings to a few hours compared to LD EEG recordings that last several days, lowering the opportunity to catch interictal discharges (IEDs) and especially ictal waves (ICs) (13) (14).

Many centres and clinicians still do not consider ESI as a routine investigation in the presurgical evaluation program (6) (15). The lack of evidence of the clinical utility of ESI might be the reason (5). Implementing a new diagnostic technique, besides its accuracy in localization, it is important to be acquainted with whether or not the technique has an added value in the clinical setting. Does it provide non-redundant information compared to already implemented modalities. The clinical utility of MSI has been investigated thoroughly (16) (17) (18) but that of ESI has not (14). One study evaluated the clinical utility of IC ESI in 31 patients but IEDs was not investigated (19). To fill the gap of knowledge, we tested whether LD ESI and HD ESI changed the surgical decision in a prospective, blinded, crossover study. At epilepsy surgery MDT meetings, a decision regarding surgery was made before and after presentation of LD ESI and HD ESI results respectively. Cases where LD ESI and HD ESI altered the decision were noted. This

allowed us to evaluate the combined and separate clinical utility of LD ESI and HD ESI and thus the role of these modalities in the presurgical program. The clinical utility being defined as the proportion of patients in whom the patient management plan was changed, based on the LD ESI and HD ESI respectively.

Finally, in the subgroup of investigated patients, with available follow-up data, we verified the usefulness of changes, i.e. if the localization provided by our ESI analysis, corresponds to results of intracranial EEG recordings and seizure outcome.

## 2. Methods

This study followed the protocol published at ClinicialTrials.gov May 23, 2018 (identifier: NCT03533530).

### *2.1. Patients*

A total of 82 patients (47 males, age range 68-10 years), have been prospectively investigated with LD ESI and HD ESI as a part of the Danish epilepsy surgery evaluation program between 2015 and 2018. The study was approved by the Ethics Committee of the Capital Region of Copenhagen Denmark (H-2-2013-038). All patients gave written informed consent before participation. The Danish epilepsy surgery evaluation program consists of LTM, MRI (3 T) and neuropsychological evaluation. In selected patients $^{18}$F-fluorodeoxyglucose PET, 99mTc-hexamethyl-propyleneamine oxime SPECT [subtraction ictalSPECT co-registered with MRI (SISCOM)] and MEG can be performed. When, based on these investigations, one main hypothesis can be formulated, the patient can be operated. In case of alternative hypothesis further, invasive, investigation with intracranial electrodes is offered. When there is no hypothesis or to many hypotheses the patient cannot be operated neither offered further investigation with intracranial electrodes (3). A flowchart is presented in Figure S1.

### *2.2. EEG recordings and head models*

LD ESI was based on LTM recordings with standard 25 electrodes (20), and an age-matched template head model (21). In HD ESI a minimum of 90-minute recordings was used with 256 electrodes array, digitized electrode positions and a realistic head model using the patients´ individual MRI in BESA MRI (BESAGmbH, Gräfelfing, Germany). In one patient the HD ESI was performed on an age-matched template head model due to technical problems with the individual MRI.

The template head models were made by non-linear averaging across real brains in age-ranges from infancy to adulthood, and from these 4-layer FEM models were constructed (21). The

individual electrode position file was made with the cerebral mapping system/ EEG geodesic photogrammetry system (GPS) in patients from Rigshospitalet and the Geoscan system (3D optical scanner) in patients from the Epilepsy Hospital in Dianalund. The MRI was a 3.0 Tesla T1 MPRAGE without contrast aiming to include the entire scalp. The MRI went through an automatic segmentation after three points (anterior commissure, rotation, posterior commissure), five brain stem markers, and three fiducials (nasion, left and right periauricular) were manually set. The electrode position file was co-registered to the MRI according to the three fiducials set at the MRI and three fiducials also manually set at the electrode position file. The co-registration was visualized and a range of settings were possible to adjust if electrodes in certain areas was hidden underneath the skin or there was an airgap between electrodes and skin. Manual adjustments were only done when strictly necessary.

### *2.3. Electric Source Imaging*

Interictal epileptiform discharges (IEDs) and ictal waves (IC) were visually identified by at least two of the authors (MTF, MF, SB). Whenever this was possible, an average of at least five IEDs of the same topography (cluster) was used as a template for automated pattern search with a threshold of 85 percent. Results of the automated search were visually evaluated and edited (discarded or accepted). If fewer than five IEDs was identified but the signal-to-noise ratio was acceptable an average of the few visual detected spikes was made and used without the step of the pattern search algorithm. All clusters were analysed. IC was analysed when a clear seizure onset pattern was recognised. All seizure onset regions were analysed. The negative peaks were averaged (typically over 1–3 s) (22).

To identify propagation, 1) sequential voltage maps were made on the rising phase of the averaged IEDs and IC waves, and 2) principal components analysis (PCA) was considered (23). When intra-discharge propagation was identified, the earliest time point with stable voltage distribution (onset) was analysed. In cases with no clear propagation, the middle third of the rising phase was analysed (24).

We used two different inverse solutions, the equivalent current dipole (ECD) and a distributed source model (DSM) constricted to the cortex, Cortical CLARA (25) .

Our entire ESI protocol is displayed in the supplementary material, Table S1.

### *2.4. Clinical utility*

The multidisciplinary team (MDT) made decisions in three steps: (1) based on all data from the Danish epilepsy surgery evaluation program except ESI; (2) adding LD ESI to the dataset; (3) adding HD ESI to the dataset. Changes in decision on patient-management options (stop / implantation of intracranial electrodes / alterations in implantation plan/ operation with

perioperative electrocorticography/ operation/ extend of resection area) based on LD ESI and HD ESI, compared with the initial decision (blinded to ESI) were noted in the database. Clinical utility was defined as the proportion of patients in whom the patient management plan was changed, based on the results of ESI.

For cases where ESI induced a change, patients were followed up to assess the utility of the changes (see below).

For cases where decision was not changed by ESI, it was evaluated if LD ESI and HD ESI supported the final decision made by the MDT or not. It was rated whether the ESI was concordant or discordant with the final decision. Concordance was registered when the ESI source was within the sublobar region of the EZ defined by the final MDT conclusions (26). The ESI source being either the CLARA or the dipole model and either the ictal or the interictal localization.

### *2.5. Follow-up*

In patients were ESI lead to a change in the final implantation plan for intracranial registration (ICR) or perioperative electrocorticography (ECoG), it was evaluated whether this change (e.g. extra electrode) lead to localization of the IZ or SOZ with either the dipole or the CLARA source model. Concordance was noted if the ESI pointed to the same sub-lobar region as the added change to the ICR (e.g. extra electrode) (26). If ESI lead to the addition of ECoG to the surgical approach it was evaluated whether any electrical discharges were recorded at the suggested ESI location. In patients where ESI lead to surgery, the ½-year seizure outcome was evaluated when available according to the ILAE classification (27). In some patients the MDT approval was not pursued, and this was registered.

### *2.6. Statistical analysis*

McNemars tests was used to compare the proportion of changes based on LD ESI with those based on HD ESI, taking $P < 0.05$ as significant.

Analyses were performed with SAS Enterprise Guide 7.1 for Windows.

## 3. Results

LD ESI changed the decision in 16/82 patients (20%), Fig 1. HD ESI changed the decision in 23/82 patients (28%), Fig 2. The number of patients in whom the decision was changed according to the HD ESI results was significantly higher compared to the number of changes according to the LD ESI results ($p<0.001$). In 11 of the 16 patients with changes based on LD ESI, changes were

also made based on HD ESI. In conjunction LD ESI and HD ESI lead to a change in decision in 28/82 patients (34%). Follow-up with ICR or ½-year postsurgical seizure outcome was possible so far in 5 patients with LD ESI changes (Fig 1) and in 10 patients with HD ESI changes (Fig 2).

For LD ESI, in 3 out of 4 cases ICR confirmed the usefulness of the change made. In one case where extension of the resected site was decided by the MDT based on LD ESI and HD ESI, the

**Fig. 1**. *Impact of low-density electrical source imaging (LD ESI) in the 82 included patients. ICR= intracranial registration. Stop= No operation nor any further evaluation. OP= operation. ECoG= perioperative electrocorticography. IZ= interictal zone SOZ= seizure onset zone. † HD ESI changed the decision to direct OP without ICR.*

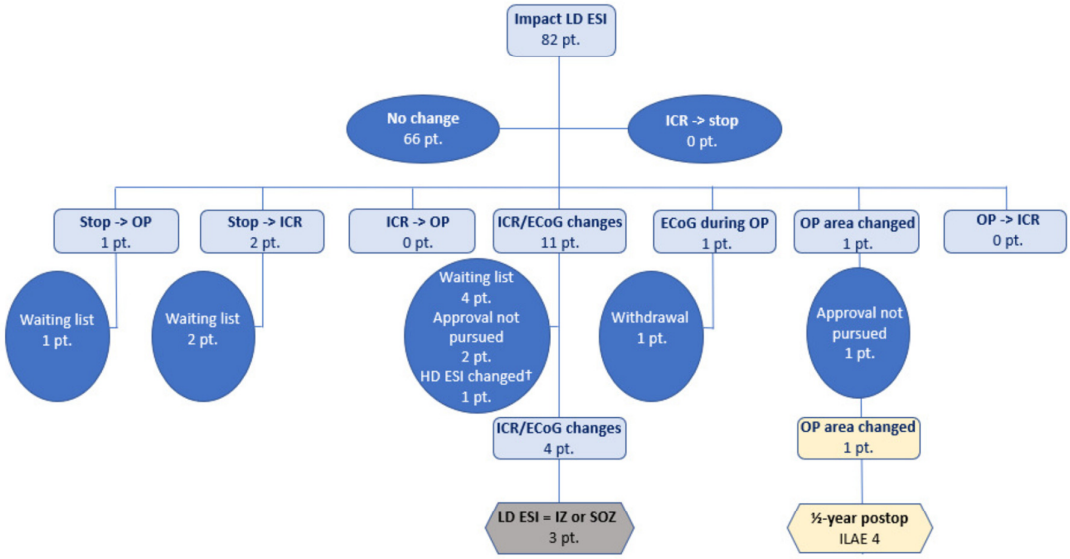
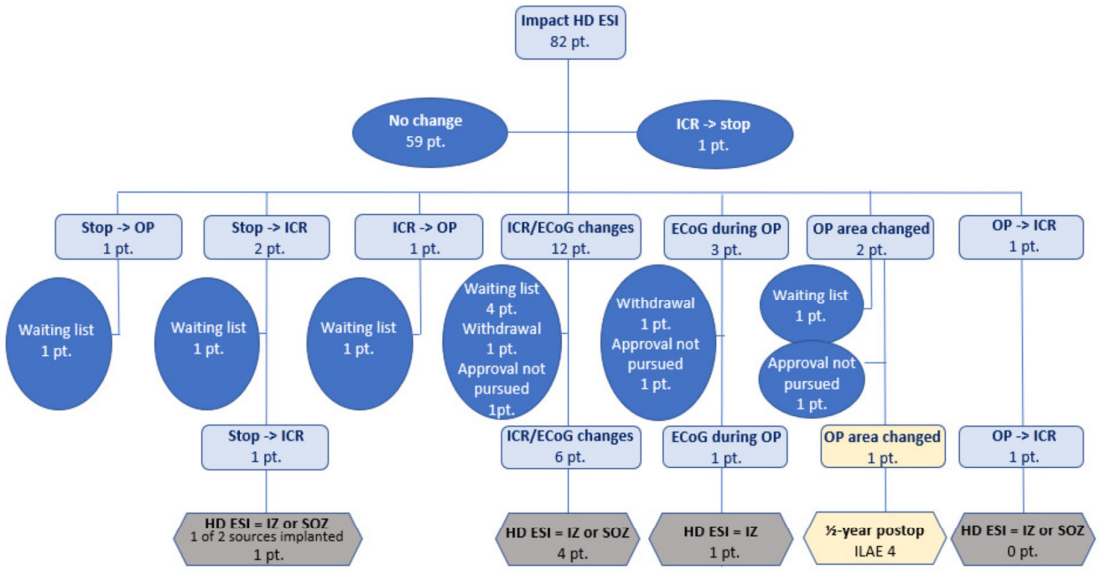



**Fig. 2**. *Impact of high-density electrical source imaging (HD ESI) in the 82 included patients. ICR= intracranial registration. Stop= No operation nor any further evaluation. OP= operation. ECoG= perioperative electrocorticography. IZ= interictal zone SOZ= seizure onset zone.*



surgeon decided not to follow this change, and the patient did not become seizure free. For HD ESI, usefulness was confirmed by the follow-up in 6 of the available 10 cases.

The distribution of concordant and discordant results in patients with "no change" in decision comparing LD ESI and HD ESI to the final MDT conclusion is displayed in table 2. Concordance was seen in 74% after LD ESI and 51% after HD ESI. The percentage of recordings with no epileptiform discharges was six in LD ESI and 27 in HD ESI. In the HD EEG recordings ictal waves was only identified in three patients. In two patients with no epileptiform discharges detected with LTM recordings, spikes were detected with HD EEG.

**Table 2.** *Concordance or discordance of respectively low-density electrical source imaging (LD ESI) and high-density electrical source imaging (HD ESI) with the final MDT decision in patients were ESI did not lead to a change.*

| No change | Patients | |
|---|---|---|
| | HD ESI | LD ESI |
| Source concordant with conference decision | **51 %** (30/59) | **74 %** (49/66) |
| Source discordant with conference decision | **22 %** (13/59) | **20 %** (13/66) |
| No epileptiform discharges | **27 %** (16/59) | **6 %** (4/66) |
| Total | 100 % (59) | 100 % (66) |

## 4. Discussion

The combined use of ESI, LD and HD, led to a change in the MDT conclusion in more than 1/3 of the patients. Therefore, we suggest that ESI is a clinical useful modality in epilepsy surgery evaluation. The number of changes made based on HD ESI was significantly higher than the number of changes made based on LD ESI ($p<0.001$), implying that the extra precision of HD ESI (high density EEG, individual MRI), results in an added value in the process of decision making. At present we await ICR results and postoperative seizure outcome in more patients to be able to draw a final conclusion.

With regard to number of recordings with "no epileptiform discharges" this was higher in HD ESI (27%) compared to LD ESI (6%) and ictal EEG activity was only observed in three patients during the HD EEG recordings. This difference can be explained by the longer duration of the LD EEG recordings (several days) compared to the HD EEG recordings (2 to 1½ hours). The longer recording time leads to a higher chance of catching interictal and especially ictal discharges. The recording time can also explain the lower number of HD ESI results (51%) being concordant

with the MDT conclusion compared to the LD ESI results (74%). In conjunction, these results have, in our group, led to the conclusion that LD ESI, which is based on data already available within the routine work-up, will be performed in all epilepsy surgery candidates whereas HD ESI will be performed in a selected subset of especially difficult cases.

The most frequent observed added clinical value of ESI was in the planning of ICR/ECoG. Sixty-nine percent (11/16) of changes based on LD ESI and 52% of changes based on HD ESI (12/23) was made at this step of the evaluation. However, changes from a total stop of further evaluation to either surgery or ICR was also observed. As well as changes towards a more reluctant approach adding either ICR to the evaluation, ECoG to the surgical procedure or a change from ICR to a total stop of further evaluation and in a few patients ESI resulted in a change of the resection zone.

*Follow-up and future development*

Outcomes of the Danish epilepsy surgery evaluation program has been found to be comparable to international standards (28) but the waiting time for ICR can be up to 1½ year which prolongs follow-up significantly. We will continue to evaluate results of ICR and seizure outcome when available in patients where ESI led to a change. However, using intracranial EEG as a golden standard regarding localization can be problematic because of the possibility of false positive or false negative localization compared to early surgical outcome (29). Our eventual goal is to compare the postsurgical resection zone identified on MRI in operated 1-year seizure-free patients with the ESI results.

In the future, experience and finetuning of hard- and software can potentially increase the added yield of ESI. At present there is a need for exact indications and contraindications of the application of ESI. Should the modality e.g. be avoided in patients treated with benzodiazepines in close approximation to the EEG recording and how many spikes should be present to provide a signal solid enough to justify an analysis.

*Protocol and implementation*

Many different approaches are currently used to solve the two fundamental problems of ESI, the forward and the inverse problem (15). In the present study, we chose to use the forward model with the highest known accuracy for the HD ESI (individual MRI, digitized electrode position) (10). In LD ESI we chose a model within the limits of data available from the routine work-up (age-matched template brain, template electrode position). To solve the inverse problem, we chose two different models, as currently recommended (30), the distributed source model CLARA and the equivalent current dipole model developed by BESA. We believe that it is important to use very strict and identical criteria in a centre if ESI is implemented in the epilepsy surgery evaluation and our ESI protocol is displayed in table S2.

Implementing ESI in the epilepsy surgery evaluation it is important to recognize that the method has the same fundamental limits as EEG i.e. the uncertainty of the exact conductivity of

brain tissue, skull and scalp (31). ESI results cannot be interpreted as an exact spot of the EZ but should be interpreted as a sublobar localization of the assumed origin of the epileptic discharge investigated. In this context it is important that members of the MDT are aware of differences in interpretation of diverse source models and their pros and cons (30). An updated review targeting this group of clinicians is requested.

## 5. Conclusion

The present study suggests that ESI is a clinical useful modality in epilepsy surgery evaluation. HD ESI based on individual MRI and digitized electrode position leads to changes in the MDT decision in a significantly higher proportion of patients than LD ESI based on age-matched template brain and template electrode position ($p<0.001$).

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***Figure S1.*** *The Danish epilepsy surgery evaluation program. EEG= Electroencephalography. MRI= Magnetic resonance imaging. MDT= Multidisciplinary team. PET= Photon emission tomography. SPECT= Single-photon emission computed tomography. MEG = Magnetoencephalography. ICR= Intracranial registration with electrodes.*

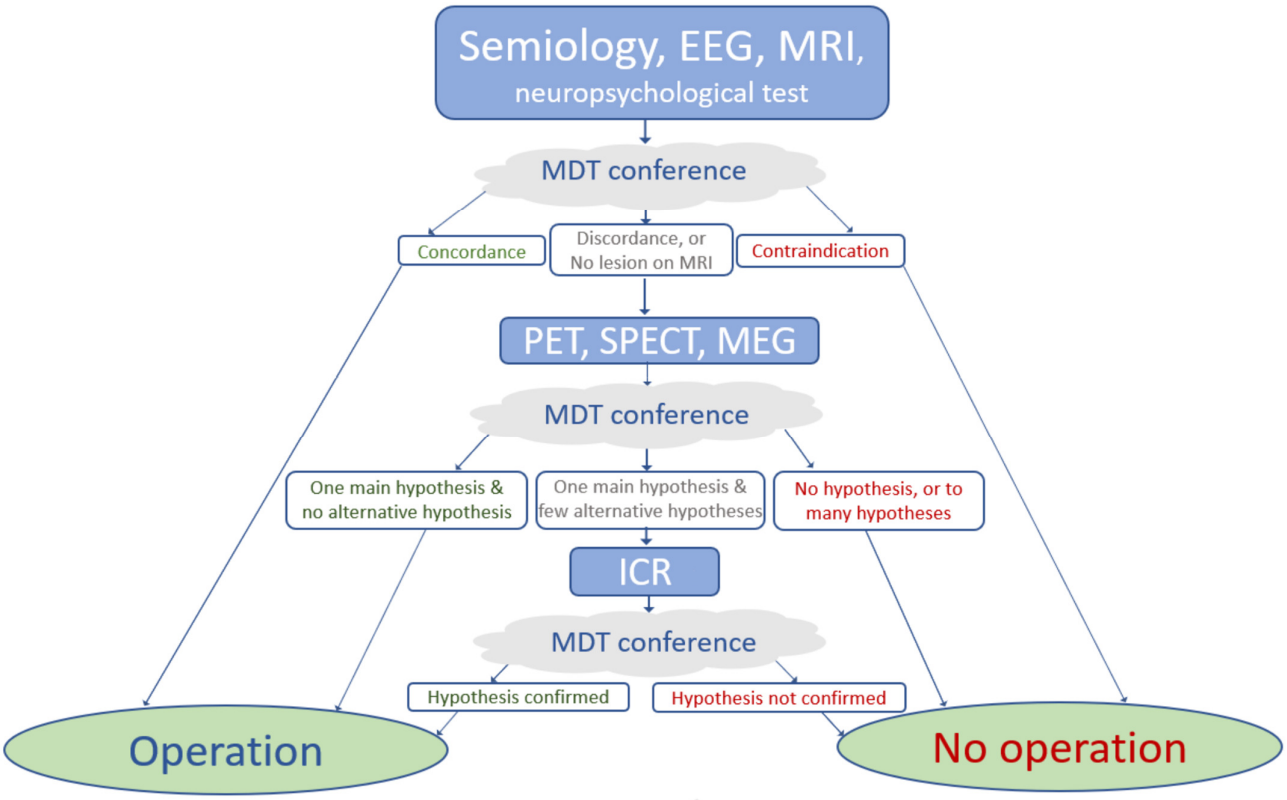

*Table S1. Electrical source imaging (ESI) analysis protocol.*
*IC= Ictal wave, LD= Low density, HD= High density, FEM= Finite Element Method.*

## 1. EEG inspection

- Use common average montage 33
- Choose 5-10 spikes for each focus

## 2. Averaging and template search

- "Average visually detected spikes". Document 'average spike' in power point according to step 3.
- If you analyze IC's or for other reasons wish to continue with the "averaged visually detected spikes", skip the following steps and go to step 3. If you want to search the EEG file for template matched spikes, continue with the next steps:
  - Set the filters to: 2-35 Hz in the 'average visual' file and the file to be search.
  - Apply a threshold of 85 % for the search.
  - After the search, check whether you have enough spikes detected (preferably 50), if to many (including erroneously ones) redo the search with a higher threshold, if to few spikes redo with a lower threshold, but not less than 75%.
  - "Average pattern searched spikes". Document 'average pattern spike' according to step 3.

## 3. Documentation

- Document the top view and voltage map of the peak in power point.
- Document the voltage distribution in power point.

## 4. Identification of onset

- Inspect the evolution in time of the sequence of the sequential voltage map, 0.0 ms should be in the right lowest corner.
- If you see an onset distribution different from the peak, note the time period of the onset, otherwise chose the onset to be at the middle third of the rising peak in the source analysis.

## 5. Source analysis

- Perform spike-fit for spike 1 according to the steps below. When done with spike 1, if more spikes: continue with spike 2, spike 3 etc. A filter of 5-40 Hz is applied.
  - In **LD ESI** choose the head model: "age appropriate template model" (the oldest 20-24 years, unless the patient is younger)
  - In **HD ESI** choose the head model: "individual FEM" (use the co-registered .sfh file)
  - Specify the time window for onset (using the period chosen under the sequential voltage maps). Check the principle component analysis (PCA), it should be higher than 95%. Check the residual variance (RV), it should be below 5 %.
  - Start the dipole fit. You will get one fit for onset (red) and one fit for peak (blue). Document with screen shots.
  - Start a Cortical CLARA fit, one for the onset chosen above and one for the peak. Document with screen shots.