Faculty of Medicine and Health Sciences

Department of Neurology

MMIND-E

MEG and MRI in the Diagnostics of Epilepsy

An explorative study in novel approaches of epilepsy diagnostics

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“Het is belangrijker om te weten wat voor soort persoon deze ziekte heeft, dan te weten wat voor soort ziekte deze persoon heeft”

Hippocrates, circa 400 voor Christus

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List of abbreviations

3T: 3 Tesla

7TI: 7 Tesla

ACoG: Acute CorticoGraphy

AED: Anti Epileptic Drugs

Cho: choline

Cr: Creatin

CT: Computer-assisted Tomography

CSI: Chemical Shift Imaging

CVA: Conventional Visual Analysis

DNET: Dysembryoplastic neuroepithelial tumor

DTI: Diffusion Tensor Imaging

ECD: Equivalent Current Dipole

EEG: ElectroEncephaloGraphy

EEG-SD: EEG after Sleep Deprivation

EMU: Epilepsy Monitoring Unit

FCD: Focal Cortical Dysplasia

FLAIR: FLuid Attenuated Inversed Recovery

fMEG: functional MEG

fMRI: functional MRI

GABA: Gamma-Aminobutyric Acid

IED: Interictal Epileptiform Discharges

ILAE: International League Against Epilepsy

IR: Inversed Recovery

LTM: Long Term Monitoring

MAP: Morphometric Analysis Program

MEG: Magnetic EncephaloGraphy

MRI: Magnetic Resonance Imaging

MRS: Magnetic Resonance Spectroscopy

NAA: N-acetylaspartate

NMR: Nuclear Magnatic Resonance

NPT: Neuropsychological Tests

MSI: Magnetic Source Imaging

PET: Positron Emission Tomography

PNES: Psychogenic Non-Epileptic Seizures

POST: Positive Occipital Sharp Transient

RF: Radio Frequent pulse

ROI: Region of Interest

SEEG: Stereo-EEG plus video

SNR: Signal to Noise Ratio

SPECT: Single Photon Emission Computed Tomography

SPM: Statistic Parametrical Mapping

SQUID: Superconducting Quantum Interference Device

SV-MRS: Single Voxel 1H-MRS

SWI: Susceptibility Weighted Imaging

TCD: Transcranial Duplex/Doppler

TE: echo time

TMS: Transcranial Magnetic Stimulation

TR: repetition time

V-EEG: surface Video-EEG

WHO: World Health Organization

CHAPTER 1:

Introduction

1.1 Epilepsy and epilepsy surgery

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is characterized by the occurrence of multiple unprovoked epileptic seizures ("at least 2 unprovoked or reflex seizures >24 hours apart" (Fisher 2014)). The addition of the criterion "multiple" is essential, as although epilepsy is a common brain disorder with an estimated prevalence of 0.4 to 1.4% (WHO 2015), non-febrile seizures anywhere during lifetime are estimated to occur in 2-6% of the population (Research Committee 1960, Annegers 1979, Goodridge 1983, Juul-Jensen 1983). However, this definition is too limited to reflect present insights and current knowledge. Therefor, in the present operational clinical definition of epilepsy described in the same article (Fisher 2014), "diagnosis of an epilepsy syndrome" is incorporated: *"*one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years". In order to predict a recurrence rate after a first seizure, a routine EEG is registered and often an EEG after sleep deprivation. Donselaar et al (1990) demonstrated that 2 years after a first unprovoked seizure the recurrence rate of seizures in untreated patients was 83% if epileptiform discharges (like interictal spikes and sharp waves) were present in routine-EEG or EEG after sleep deprivation. If both EEG's were

completely normal, the recurrence rate was 12%. Specificity of the combined EEG's was 91%. Stroink et al (1998) described a seizure recurrence rate of 71% in children in the first two years after a first seizure when epileptiform abnormalities were present on their EEG. Concluding, EEG is very helpful in predicting recurrence of seizures, but EEG's without abnormalities do not rule out the existence of epilepsy.

Finding a lesion on brain imaging can also indicate a higher chance of seizures recurrencing. In adults presenting on the emergency ward with a first seizure presence of an abnormality on CT scan had a positive predictive value of 78% for developing epilepsy (Sierra-Marcos et al 2011). Arthur et al (2008) demonstrated that in children the presence of a significant abnormality on MRI leads to a recurrence rate of 80%, with all first recurrences within 9 months. However, in a review that same year Pohlmann-Eden and Newton (2011) still conclude that "there is a striking lack of systematic studies using early EEG and MRI in order to better characterize epileptogenic areas and elucidate the mechanisms of seizure provocation". In 2011 Gaillard et al mention "the lack of high quality data reflecting fundamental weaknesses in many imaging studies but also limitations in the assumptions underlying evidence classification schemes". For MRI, however, there are numerous reports on patients in epilepsy surgery literature with "epileptogenic lesions", e.g. focal cortical dysplasia, DNET, cerebral infarct or bleeding, hamartoma, tumor, etcetera, thus highlighting the importance of MRI to demonstrate a possible underlying structural cause of epilepsy.

On the other side of the spectrum, it has been estimated that between 10 and 30% of patients referred to epilepsy centers have paroxysmal events that despite looking like epileptic episodes are in fact non-epileptic (Auxéméry 2011). There seems to be a trend that faster referral to a tertiairy center is more likely in the PNES (Psychogenic

Non-Epileptic Seizures)-group with more profound psychological complaints (Bodde 2012). Further improvement in differentiating and diagnosing epilepsy and non-epileptic fits would be beneficial in guiding treatment.

Once epilepsy is diagnosed, it has to be classified in order to guide further treatment. “With the avalanche of genetic, structural, and functional information, it has become abundantly evident that what we call the epilepsies are really complex neurological and even multisystem disorders that may involve cognitive, behavioral, motor, sleep, autonomic, and other systemic impairments and dysfunctions. Seizures are a facet, often a prominent one, of these disorders, but seizures are not disorders unto themselves“ (Berg 2016). This more detailed approach will help in investigating and understanding the different causes of epilepsy and to further tailor treatment. However, although finer classification is possible (Berg 2010), the major impact for the purpose of this thesis stems from the division between localization related epilepsy and the others. Although not advocated as the descriptions of first choice, Berg and Scheffer (2011) acknowledge that the term localization related epilepsy may still apply in some circumstances. Most of the surgically treatable epilepsies will be denominated structural.

Once the epilepsy has been classified, treatment with anti epileptic drugs can be started. As epilepsy in adults in most cases is a chronic condition, life long treatment is often necessary (Brodie 2012, Burakgazi 2016). In children, however, in 60% epilepsy is a transient condition, for which medication given over a limited number of years is sufficient. There is a negative correlation to age of onset of epilepsy, meaning that a negative prognostic factor to achieve complete remission (seizure and drug free) is an age of onset of over 10 years of age (Berg 2014). This is in line with the reviews of Beghi (2015) and of Walsh (2016) claiming that “most epilepsies

have a good prognosis for full seizure control and eventual discontinuation of AEDs", while the history of a high number of seizures at the time of diagnosis, intellectual disability, and symptomatic aetiology are negative predictors (for long-term prognosis)". However, in about 41% of newly diagnosed epilepsy patients, even with medication sustained seizure freedom is not reached according to Brodie (2012). The epilepsy will thus prove to be drug-resistant, also called refractory. In these patients with refractory epilepsy non-idiopathic epilepsy is about 3 to 4 times as prevalent as idiopathic epilepsy (according to modern terminology epilepsy of genetic or metabolic origin) (Brodie 2012). In those patients, epilepsy surgery must be considered. A Cochrane review showed that good post-operative outcome, over-all being 65%, ranges from 13,5% to 92.5% (West 2015), depending on duration of follow up, location of the epileptogenic focus, extend of the (possible) resection, used technique and underlying pathology. According to a Swedish cohort study, if a surgically removable focus can be found chances of post operative seizure freedom over the long term is about 62 % in adults and 50% in children (Edelvik 2013). In a review in 2015, Hu et al calculated a pooled post-operative seizure freedom in 73% of the operated patients. In patients with localization related epilepsy originating in the temporal lobe surgery is significantly better than drug therapy in improving quality of life (Fiest 2014). All together, surgery is the best available option for these patients. Therefor, it is worthwhile to put as much effort as possible in identifying good surgical candidates and targets.

In pre-surgical analysis, several definitions are used to clarify what is analysed exactly. The irritative zone (Talairach 1966) is defined as the region of cortex that generates interictal epileptiform discharges in the EEG or MEG (Lüders and Awad 1992). The epileptogenic zone is defined as the region of cortex that can generate

epileptic seizures. By definition, total removal or disconnection of the epileptogenic zone is necessary and sufficient for seizure freedom. These regions, however, do not necessary coincide with the seizure onset zone (the region where the clinical seizures originate), the ictal symptomatogenic zone (the region of cortex that generates the initial seizure symptoms), the functional deficit zone (the region of cortex that in the interictal period is functionally abnormal, as indicated by neurological examination, neuropsychological testing and functional imaging or non-epileptiform EEG or MEG abnormalities) or even the epileptogenic lesion (the structural lesion that is causally related to the epilepsy) (Lüders and Awad 1992). For this analysis, a thorough pre-surgical evaluation is necessary. The evaluation includes video-EEG seizure recordings (with simultaneous recording of semiology and ictal EEG-findings), state-of-the-art MRI, neuropsychologic testing and on indication PET, (f)MEG, SPECT, EEG-fMRI, fMRI, DTI, TCD, TMS, visual field analysis, intracranial recordings and testing, etcetera. Which tests are used is dependent on indication, availability and necessity. Throughout Europe there is no uniformity in the pre-surgical protocol (e.g. Mouthaan 2016).

One of the major factors in predicting successful epilepsy surgery is finding a structural lesion that corresponds with the other electro-clinical data (West 2015). At 1.5T, MRI provides images that show abnormalities that could account for the epilepsy in up to 83% of the patients with localization-related epilepsy within a pre-surgical evaluation (Ubach 2004). However, in a more recent study on 158 operated patients with frontal lobe epilepsy, of which 76% were lesional cases as seen on 1.5T or 3T MRI, only 44% were postoperatively seizure-free (Simasathien et al. 2013). Failure to reach seizure freedom in this group can partly be attributed to incomplete resection when the lesion/focus is too close to eloquent cortex. However, in many

cases (like in dysplastic lesions) the epileptogenic focus may not necessarily overlap completely with the visible structural anomaly. Furthermore, it is postulated that many of the “MRI-negative” patients actually suffer from Focal Cortical Dysplasia (FCD) (Bautista 2003). A Cleveland Clinic analysis of 95 operated “MRI-negative” epilepsy patients found FCD (in majority type I) at histopathology in 45% of cases (Wang 2013). FCD is highly associated with refractory epilepsy (Guerinni 2014). In formerly MRI-negative patients, re-evaluation of the MRI with all available data will show more abnormalities. Of the operated patients, in 22% of bottom-of-the-sulcus FCD’s the lesion can be missed on initial visual inspection of the MRI (Harvey 2015). Gain of MRI could be improved by improving scanning techniques (including higher field strength, Von Oertzen 2002) and by predefining a region of interest. Clinical symptoms of the seizures are strong localizers and reasonably strong lateralizers for the epileptogenic zone whereas ictal EEG is strongly lateralizing and reasonably localizing (Kotagal 2010). If MEG results are compatible with a plausible location of a possible epileptogenic zone they are also powerful indicators for the region of interest (Bagic 2016).

1.2 MEG

MEG is a non-invasive method to record brain activity, with a history in humans dating back to 1968 (Cohen 1968). Changes in the pericranial magnetic field, generated by the electrical currents in the brain, are measured. In order to be able to record these changes, which are of the magnitude of pico-Tesla, recordings must take place in a magnetically shielded room, using highly cooled super-conductant

sensors (SQUIDS (superconducting quantum interference devices), gradiometers or magnetometers). In contrast to EEG which depends mostly on the radial component of the electric currents produced by the neurons, MEG is mainly dependent on the tangential component. However, source depth, and not orientation, is the main factor that compromises the sensitivity of MEG to activity in the adult human cortex (Hillebrand 2002). At the convexity, about 3 to 4 cm^2 of synchronous active cortex produces a detectable MEG-signal, as compared to 6-10 cm^2 needed for a detectable EEG signal (Cooper 1965, Oishi 2002, Tao 2006). In analysing possible epilepsy patients interictal epileptiform discharges in the MEG, like spikes and spike-waves, support the diagnosis of epilepsy (this thesis).

If epileptiform discharges are recorded, in order to facilitate interpretation of MEG data for clinical use an attempt can be made to estimate its source. The results of source estimations (often equivalent current dipole (ECD) solutions) can be projected on the MRI of the same patient. This is called Magnetic Source Imaging (MSI) (Williamson 1991). MSI is a valuable tool in the presurgical work-up (Bagic 2016).

The mathematical exercise to calculate the source of a given spike starts from the presumption that the recorded activity originates from one single source or at most a very limited number of sources (the inverse problem). The most likely solution of the equations at hand will be the one best explaining most of the recorded signal. If no dipole can explain at least 70% of the signal, the solution is too weak to accept. Despite these caveats, there is a good correlation between recording of spikes and their location as measured simultaneously with Acute CorticoGraphy (ACoG) and MEG (Oishi 2002). One has to keep in mind that interictal sharp MEG-activity merely indicates the irritative zone, but not always the epileptogenic zone as well. Over the years MEG has proven to be a very powerful tool to determine the epileptogenic zone

or the irritative zone in patients who have enough spikes in their traces (e.g. Ossenblok 1999, Shiraishi 2001, Van ‘t Ent 2003, Iida 2005, Papanicolaou 2005, Ossenblok 2007). Higher ECD-clustering in a specific area correlates with a higher likelihood of indicating the seizure onset zone (Mamelak 2002). In non-lesional epilepsy surgery, MEG-source localization has proven to be of value to guide implantation of intracranial electrodes (Brodbeck 2011, Heers 2012). Complete removal of the area with clustered ECD’s leads to better outcome of epilepsy surgery and vise versa (Widjaja 2008, Wilenius 2013).

1.3 MRI

MRI is an imaging method based on Nuclear Magnetic Resonance (NMR). It is a non-invasive method using quantum mechanical properties of nuclei with an uneven number of protons to make images of structures and acquire information on the concentration of different molecular compounds. Applying the Bloch-equations, it is possible to describe the obtained reactions based on quantum mechanical principles with the more simple mechanical laws of physics. When a human body is submitted to the strong magnetic field of the MRI-scanner the tissues, like brain, acquire a small amount of measurable magnetism. Each type of tissue (e.g. white or grey matter) has different magnetic properties which can be shown in an image by applying property-specific radio-frequency pulses (RF) for contrast and time-varying magnetic gradients for localization. By changing the time sequence of successive RF pulses and their properties (e.g. duration, frequency, bandwidth), different tissue contrasts can be obtained. The most important iconic contrasts in MRI are T1 and T2 contrasts. Images depicting those contrasts are better know as T1- and T2-weighted images

(T1W, T2W). Other contrasts are related to other properties, like proton density and diffusion. The amount of signal that can be obtained is a complex function of the field strength. Generally the Signal-to-Noise-Ratio (SNR) in the images scales linearly with the field strength of the scanner. This is important for this thesis because imaging of epilepsy patients at a very high field strength of 7T is reported.
The beauty of MRI is that basic contrasts can be manipulated to accentuate certain tissues. FLAIR for example is such a manipulated T2W image, where the normal high water signal is suppressed, resulting in an improvement of the detection of FCD's. Several investigations emphasise that the gain of MRI in epilepsy patients can be enhanced by specific procedures. Not only, for example, are conventional low field strength MRI studies inferior to higher field strength studies such as 3T MRI (Winston 2013), but also the experience of the neuroradiologist plays an important role (Von Oertzen 2002). Scanning protocol, including slice-orientation can also play an important role (Meiners 1997).

For more extensive description of the MRI technology, several handbooks are available, e.g. Magnetic Resonance in Epilepsy, 2005 by Kuzniecky and Jackson and Neuroradiology: the requisites, 2010 by Zimmerman et al. Also recommended are the following articles: Bloch 1946, Purcell 1946, Hahn 1950, Bloch 1953, Purcell 1953, Vleck 1970, Lauterbur 1973, Mansfield 1977, Buxton 1987.

The theoretical basis of Nuclear Magnetic Resonance (NMR, the basis of MRI) was provided in 1924 by Wolfgang Pauli in mail correspondence with colleagues, demonstrating hyperfine splitting in atomic spectra and concluding that many nuclei possess both a magnetic moment and an angular momentum. In 1946 almost simultaneously both at Harvard and at Stanford University NMR phenomena were described by respectively Purcell and Bloch. Both showed how electromagnetic

waves could flip atomic nuclei that were aligned in a static magnetic field. Initially, this technique was used by physicists and chemists. In 1973, Lauterbur described how operator-controlled magnetic field gradients could be used to encode position-dependent information in the NMR signal. This suggested the possibility of generating cross-sectional anatomic images of human beings. The first reports of MRI used to acquire images in live human subjects were made in 1976 (Mansfield) and 1977 (Damadian). Major technical developments, like improvements on the coils, more elaborated sequences but also application of higher magnetic field strength, ameliorated the quality of the obtained images. Providing images with ever improving contrast resolution, MRI quickly became the gold standard in imaging in epilepsy patients. The first report on epilepsy patients with gliomas that were not seen on CT but detected with MRI was published in 1984 (Aaron). Focal cortical dysplasia is described on MRI in 1987 (Sellier). However, even with the present achievements, MRI will not show abnormalities in a substantial proportion of epilepsy patients. For example, MRI showed no abnormalities in over 40% of children with newly diagnosed epilepsy in a cohort of 259 subjects with (presumed) symptomatic focal epilepsy (Vecchi 2016).

1.4 MRS

Specific other MRI techniques have also been applied in epilepsy patients. One of them is Magnetic Resonance Spectroscopy (MRS), picturing metabolic compound concentrations, like N-acetylaspartate (NAA), choline (Cho) and Creatin (Cr), in the brain. For these compounds, 1H MRS is used. In different chemical compounds local magnetic field is influenced differently in function of the organization of the electrons surrounding the hydrogen proton. Their number and resulting relative electrode cloud

are different for different molecules, leading to different changes in local magnetic field. In response to the external B_0 electrons move to oppose this magnetic field, thus shielding the nucleus. In order to get the same local magnetic field, and thus resonance at the same frequency, the magnitude of B_0 therefor has to be increased. This increase is molecule-dependent and typically only a fraction of the original B_0. The change needed is expressed in ppm (parts-per-million): the percentage of change compared to the original B_0 to obtain a resonance multiplied by 10,000. In order to get reliable results, extra care has to be taken to make B_0 as homogeneous as possible. This can be achieved by “shimming”, an automated process in most MRS-sequences.

As each type of molecule has a different change, a spectrum can be recorded. For the brain, this spectrum for 1H-containing molecules is narrow: it spans a band of about 12 ppm. The H2O peak is high, compared to the other components; the concentration of H2O exceeds the concentration of the metabolites that are of interest by a factor 10,000+. Therefor, water suppression techniques are applied. After correcting for this H2O peak, NAA, Cho and Cr peaks are reasonably easy to distinguish. Myo-inositol (Ins), GABA and Glutamate are less easy to distinguish and require a shorter TE.

The intensity of the signal is linearly proportional to the number of 1H atoms at that specific magnetic field/resonance in the sample. A molecule with double the amount of hydrogen will therefor show a double magnitude on the spectrum as compared to the low hydrogen molecule if concentrations are equal (https://www2.chemistry.msu.edu/faculty/reusch/virttxtjml/spectrpy/nmr/nmr1.htm). Concentrations are usually expressed as ratio’s to Cr, as presence of Cr is reasonably stable throughout the brain. It is a marker for brain energy metabolism

(Rubaek Danielsen 1999). It is also possible to use absolute values but this is technically much more challenging (Janssen 2006).

NAA concentrations increase during maturation (Rubaek Danielsen 1999). Local decrease of NAA concentration is associated with neuronal loss and neuronal damage (Castillo 1996, Burtscher 2001).

Choline and choline containing compounds are markers of cell membrane turn-over. Increase of choline concentration is associated with tumors and with demyelination (Maheshwari 2000).

We used single voxel MRS (SV-MRS), where relative concentrations in a limited volume (the “voxel”) are determined. This is a time-efficient procedure with a relatively high SNR, partly due to the smaller volume that has to be shimmed. Alternative techniques are 2D-Chemical Shift Imaging (CSI) and 3D-CSI. These techniques require longer scanning times and have a lower SNR (Vigneron 2001, Janssen 2006),

1.5 MEG-guided MRI

Three studies highlight the importance of ROI guided MRI-analysis (Moore 2002, Funke 2011, Itabashi 2014). Summarizing, all find a gain of MEG-guided MRI re-evaluation of 20% in those MRI’s that were deemed to be normal before adding the MEG-information. No report of MEG-guided analysis of 7T MRI is available up to now.

1.6 SEEG

SEEG or Stereo-EEG is an intracranial EEG recording with multiple depth electrodes placed within the brain. Based on the work of Penfield and Jasper (1954) and the development of stereotactic devices (Spiegel 1947) the method was further developed and advocated by Talairach and Bancaud (Bancaud 1959, Talairach 1973). First, after the non-invasive pre-surgical analysis hypotheses are formulated about the epileptogenic zone and the spreading pattern. Guided by these hypotheses and based on an MRI with double dose of contrast to visualize the blood vessels to avoid, multiple depth electrodes with several contact points each are stereotactically placed within the brain. The electrodes are inserted through small burr holes (typically up to 2.3 mm in diameter) and fixated to the skull. After this surgical procedure, the patient will be transferred to the epilepsy monitoring unit (EMU). Subsequent recording of intracerebral EEG combined with video will take place to determine the seizure onset zone. Time spend on the EMU varies in function of the number of clinically different seizure types, seizure frequency and response to electrostimulation. SEEG allows for the recording of intracerebral EEG, thus reaching areas that cannot be sampled by subdural grids and/or strips. Also in the case of wide-spread hypotheses, SEEG has an advantage over subdural grids due to technical limitations of the latter (Lhatoo 2016).

Electrostimulation is a procedure where a current of several milli-amperes is delivered between two adjacent contact points, thus focally hampering brain function. This allows functional mapping in the regions where electrodes are placed, thereby giving the neurosurgeon an indication of the functional (eloquent) areas. Secondly,

stimulation is used to try to provoke seizures or part of the seizures, thus giving additional insight in the location of the epileptogenic zone and of the spreading pattern. For mapping purposes, on average subdural grids are more suited than SEEG.

When sufficient information is gathered the electrodes are removed and the data analyzed. If the epileptogenic zone can be identified and is not located within eloquent cortex, resection will follow several months later.

Compared to subdural recording (Wellmer 2012), SEEG is a relatively safe procedure. Complication rates of 2.4 to 4.5% (Guenot 2001, Almeida 2006, Cardinale 2015, González-Martínez 2016) have been reported. Reported complication rate, however is also dependent on the used definition of complications. In our own limited series on our first 23 SEEG implantations (Colon 2014) we reported a complication rate of 13% when including irritation of the skin at the entrance point of one of the electrodes. Looking at long lasting neurological deficit, only one patient (4%) experienced an aggravation of his pre-implantation already present afasia after subdural haemorrhage due to the implantation. This resolved spontaneously within 8 months. No other long lasting neurological deficits were noted.

CHAPTER 2:

Aim and outline of this thesis

This thesis is conceptualized having a patient in mind that comes to a tertiary epilepsy center after having tried several anti-epileptic drugs without any positive result. In such a case, the first question to resolve is whether or not the diagnosis of epilepsy is correct. If this is the case the next question is whether or not this patient is a candidate for epilepsy surgery, making of utmost importance not only the correct diagnosis, but also a correct lateralisation and localization of the epileptigenic zone and eloquent cortex (the what and the where). Diagnostic procedures are continuously developing, and the researches presented in this thesis are part of that development. Emphasis is put on those investigations that utilize magnetic fields. Therefor, the aim of this thesis is to investigate possible ameliorations of diagnostics in epilepsy, both in first line, e.i. diagnosing epilepsy, as in localizing the epileptogenic zone in case of presurgical analysis. The studies in this thesis examine possible roles for MEG and MRI in improving diagnostics in epilepsy, both alone and in combination.

The two articles that are comprised in chapter 3 describe the validity of MEG in diagnosing epilepsy; in the first article as compared to EEG after sleep deprivation, in the second article as compared to the long term diagnosis. Results in these patients are partly used to define the region of interest in the patients of chapter 4.

The three articles that are comprised in Chapter 4 describe MEG-guided single voxel magnetic MRS at 3 Tesla and MEG guided 7 Tesla MRI support in localizing an epileptogenic zone or lesion in epilepsy patients. As the most frequent “missed abnormalities” in MRI negative epilepsy patients probably are FCD’s (Bautista 2003, Wang 2013), prior to the study on MEG guided 7T MRI in 3T MRI negative patients an analysis is made of patients with known FCD to get an impression of the appearance of FCD on 7T MRI.

Chapter 5 is a synopsis of the conclusions formulated in the prior chapters.

Chapter 6 represents a more open interpretation of the impact on clinical practice in a tertiary epilepsy center of the studies described in chapters 3 and 4.

CHAPTER 3:

MEG in diagnosing Epilepsy

3.1 MEG in primary diagnostics

Use of Routine MEG in the Primary Diagnostic Process of Epilepsy

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Abstract: Purpose: At present, in epilepsy magnetoencephalography (MEG) is mostly used for pre-surgical evaluations. It has proven to be robust for detecting and localizing inter-ictal epileptiform discharges. Whether this is also true for first line investigation in the diagnosis of epilepsy has not yet been investigated. We present our data on the usefulness of MEG in the earliest phase of diagnosing epilepsy.

Methods: We examined 51 patients with suspicion of neocortical epilepsy and an inconclusive routine EEG. A method to integrate MEG in daily routine was developed. Results of visually assessed MEG recordings were compared, retrospectively, with clinical data and with results of EEG after sleep deprivation.

Results: After a negative routine EEG, routine MEG generated a gain in diagnostic value of 63 % as compared to “final” clinical diagnosis. This is comparable with the added value of EEG after sleep deprivation recorded previously in the same patients. MEG, however, is less of a burden for patient and hospital and has no association with risk of increase in seizure frequency.

Discussion: Routine MEG with visual assessment only is a reliable diagnostic tool in the routine diagnosis of epilepsy and may replace or precede EEG after sleep deprivation in daily clinical practice. Furthermore, MEG together with MRI enables magnetic source imaging (MSI) and, thus may provide additional information on the cortical localization of the epilepsy of a patient.

Key words: MEG, EEG, diagnosis, epilepsy

Introduction

The occurrence of epileptiform discharges in the electroencephalogram (EEG) is of great value for the clinician to confirm the clinical diagnosis of epilepsy and to classify the epilepsy syndrome (Commission on Classification and Terminology of the ILAE 1989).

Unfortunately, sensitivity of routine EEG is rather low, ranging from 40% (Walter, Hodge and Hutchinson 1951) to 49% (Binnie and Stefan 1999), increasing to 68% when recorded within 2 days after a seizure (Sundaram 1990). If routine EEG is not conclusive additional EEG examinations (e.g. EEG after sleep deprivation, ambulatory 24-hours EEG) should be performed. Subsequently, in 85 to 92% of all patients with epilepsy epileptiform or focal activity can be shown (Werkgroep richtlijnen epilepsie 2006, Leach 2006).

Sleep deprivation in patients with epilepsy has considerable disadvantages. Sleep deprivation can elicit seizures (Rajne and Veres 1993, Scalise 2006), has been reported as precipitating seizures from the days of Hippocrates (Lloyd 1983) and still is one of the three most important seizure precipitating factors mentioned by patients in questionnaires (Frucht 2000, Malow 2004, Nakken 2005, Tan 2005). Furthermore, to perform an EEG after sleep deprivation adequately a night of sleep deprivation is required. Despite all good intentions in the normal setting at home most patients have problems complying to the instructions. Therefor, in most cases hospitalisation should be performed. Moreover, sleep deprivation is a rather patient unfriendly procedure; having to stay awake during a night is hard for most people and can deregulate the diurnal rhythm for several days. Some patients have complaints that

remind them of “jet lag”. Finally, in most centres once again electrodes have to be applied, including the irritating scratching of the skin of the head to reduce impedance and gluing.

It is argued in this paper that magnetoencephalography (MEG) is an alternative and more patient friendly way to detect epileptiform discharges, potentially with great diagnostic value in this early stage of the diagnostic process. Currently, MEG is mainly used in pre-surgical workup, where it is very helpful in localizing epileptiform activity (e.g. Stefan 2003, Knowlton and Shih 2004, Pataraia 2004, Rampp and Stefan 2007). More recently automated procedures for classifying and localizing interictal epileptiform discharges (IED) were developed (Oishi 2006, Ossenblok 2007) that enable the use of MEG in the diagnostic process of epilepsy.

In these and other studies (e.g. Park 2004, Iwasaki 2005) of patients with neocortical localization related epilepsy as well as in theoretical model studies of, among others, de Jongh et al (2005) and Ramantani et al 2006 MEG has been shown to be more sensitive to the presence of epileptiform activity as compared to simultaneously recorded scalp EEG, each entity being complementary to the other. Especially in lateral (Lin 2003) and frontal (Ossenblok 2007) foci, MEG has been shown to be more sensitive than EEG. Aforementioned authors mostly compared MEG and EEG based on the analysis of single or clustered spikes. Knake et al (2006) and Kirsch, Mantle and Nagarajan (2007) however used another concept. They compared MEG and simultaneously recorded EEG based on the overall conclusion taking the entire study (either MEG or EEG) into account. Using this approach they showed more or less equal sensitivity between simultaneously recorded EEG and MEG. We intend to use the same conclusion driven approach when analysing our data. Our main goal, however, is to investigate whether MEG can be used in the primary diagnostic

process of epilepsy in patients suspected of having neocortical epilepsy. As routine EEG is readily available in all centers and independent of patient's cooperation, we place the comparison one step later in the diagnostic process. Based on the higher spike sensitivity of MEG as compared to EEG in neocortical epilepsy (de Jongh 2003) we hypothesized that visually analysed routine MEG after an inconclusive routine EEG would be able to prevent more unpleasant additional EEG-examination after sleep deprivation in a considerable percentage of patients. We therefor analysed the diagnostic gain of a routine MEG after a routine EEG. To allow an estimate of the influence of vigilance on outcome we determined presence or absence of sleep in the MEG-files and compared these data to the vigilance data retrieved from the EEG-reports of the same patients.

Furthermore, the procedures developed in this study will make it easier to apply MEG in every day clinical practice.

Methods

Patients

We included 51 patients referred to the out-patient clinic of Kempenhaeghe, a tertiary referral centre for epilepsy. The reasons for referral varied from uncertainty of diagnosis to lack of response to medication.

Inclusion criteria were age over 6 years, suspicion of neocortical localization related epilepsy and a non-conclusive routine EEG. As in our centre only patients with an inconclusive routine EEG undergo additional examinations directly after this EEG, the

presence of this combination was used as criterion to include the patients in the study.

Exclusion criteria were (very) high suspicion of non-epileptic seizures on clinical grounds, prior EEG with epileptiform discharges and medication change before routine MEG could be performed, presence of intracranial metals, pacemakers or pumps and inability to cooperate.

In 29 patients EEG examination was done in order to confirm the clinical diagnosis of epilepsy. Interestingly, in 8 of these patients anti-epileptic drugs had already been started. In the other 22 patients the main question concerned the localization of the irritative zone.

Semiology suggested epilepsy but left room for the diagnosis of non-epileptic “seizures” (PNES) in 5 patients. As PNES was not the primary differential diagnosis, these 5 patients were still selected. In 3 patients, history only mentioned nocturnal generalized tonic clonic seizures. In 8 patients, the referring clinicians did not describe a clear hypothesis on the origin of the complaints noted. In all other 35 patients description of the seizures led to a strong clinical suspicion of localization related epilepsy of neocortical origin. In 29 of these patients semiology led to a clinically more robust localization hypothesis.

Routine EEG performed in Kempenhaeghe before inclusion in the present study was strictly normal in only 15 patients. The abnormalities in the remaining 36 routine EEG’s were focal slow waves, sharp waves of low amplitude not fitting the ILAE-criteria of epileptiform discharges but recurring in more or less the same region, diffuse slowing and/or beta-activity and asymmetry of occipital rhythm.

The local medical ethical committee approved the study protocol. All patients signed an informed consent.

Gender	Age	Semiology suggested	Already treated	MRI
Male 26	Mean 43.4	Temporal neocortical 9	32 (59%)	Not available 7
Female 28	Range 16-72	Extratemporal 21		No abnormalities 31
		Unclear 24		Cortical abnormalities 7
				Only white matter abnormalities 9

Table 1. Patient characteristics.

Recordings

In the days after the EEG-recordings, patients meeting the criteria as stated above were asked to participate in this study. Those who signed the informed consent underwent a routine MEG within 2 to 5 weeks after the EEG. To prevent a change in frequency of interictal abnormalities due to the sleep deprivation MEG recordings were not to be made within the first 2 weeks after a sleep deprivation.

MEG was performed at the MEG-centre of the Free University (VU) medical centre in Amsterdam, The Netherlands. We did not co-register EEG nor did we synchronize video and MEG. The MEG recordings were carried out using a 151-channel whole head MEG system with a base length of 5 cm (VSM Inc., Vancouver, BC, Canada). Squid noise levels were below 10 fT/Hz. Recordings were made with third order gradiometer noise cancellation. The anti-aliasing filter of the CTF hardware system was set to 200 Hz and the data were sampled at 625 Hz.

All MEGs were recorded with the patient in supine position with a total patient examination time amounting up to 45 minutes. The procedure included after a test file of 5 min, periods of opening and closing eyes (10 min), eyes closed (5 min), making a left or right fist (5 min), hyperventilation (5 min) and finally a period of relaxation (15 min). These procedures match the procedures used during routine EEG recordings, except for photo stimulation. Furthermore, before each recording of a file, a head localization was performed using head coils located at three anatomical landmarks, impressions before the left and right ear and the nasion. This was done in order to be able to correlate the estimated equivalent current dipoles to an MRI if required.

Visual review and analysis

MEG data were visually analyzed at Kempenhaeghe in accordance to current clinical practice.

As this study aims at investigating clinical feasibility of MEG, for screening of the MEG we devised a basic derivation consisting of 31 sensors distributed all over the head plus ECG (our “Routine MEG”-derivation, fig 1). In this derivation all regions are visible without loosing details in the abundance of data. As all sensors are recorded

and stored, visual analysis was expanded with other sensors when needed. For example, if on clinical grounds a clear hypothesis on the location of the epileptogenic zone was present that region would be looked at in closer detail. We evaluated the robustness of this approach by complete visual review of at randomly chosen in total 10 files of 10 minutes in 10 different patients with all 151 channels visible instead of “only” the routine derivation. The ‘complete visual review’ did not reveal new abnormalities that changed the conclusion in the report. We therefor accepted this protocol as being sufficient for our purpose.

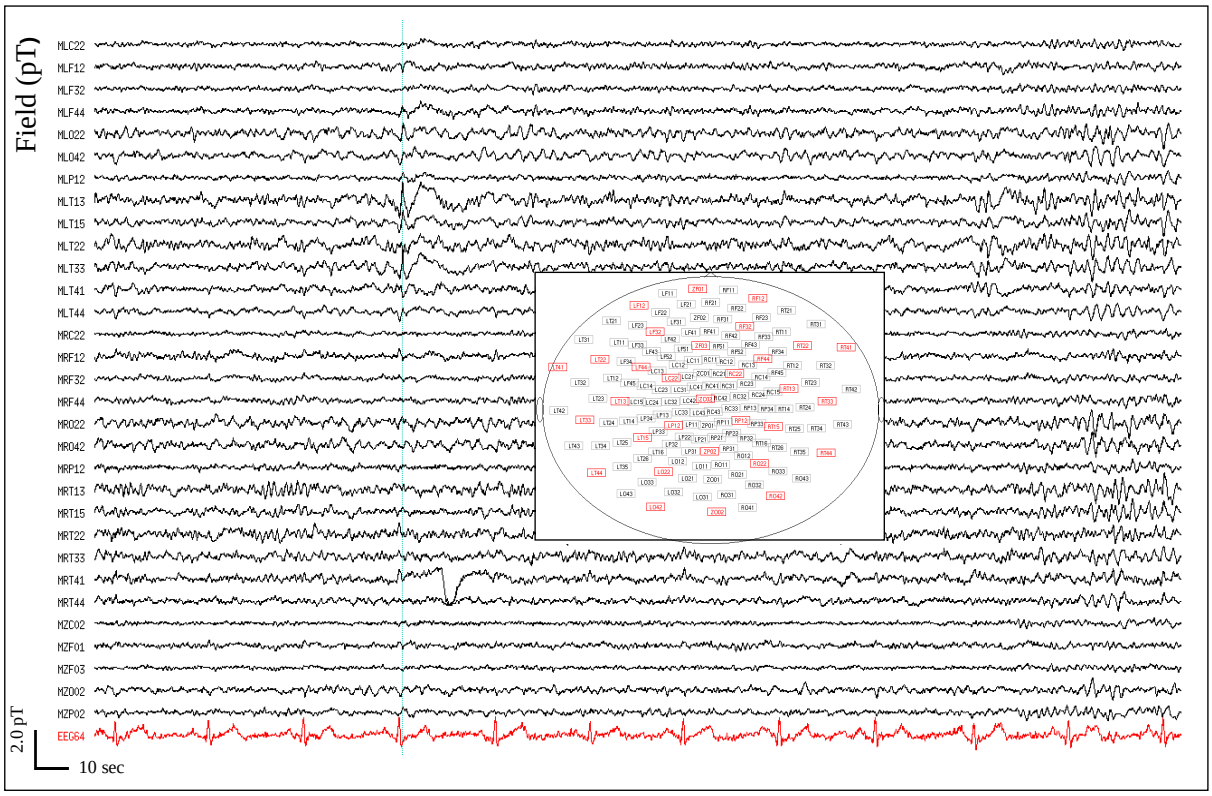

Figure 1. Example of “Routine MEG” showing a left temporal spike-wave with a spike maximum indicated by a vertical line. Insert: of all the recorded 151 sensors, as shown, in routine MEG only the sensors in red are shown on screen.

The MEG files were anonymized and were rated without a prior knowledge of the outcome of previous EEGs. Epileptiform activity was defined as a sharp transient different from background activity with an “epileptiform” morphology and a plausible spatial distribution, as is recommended for EEG by the International Federation of Clinical Neurophysiology (Cobb 1983). As MEG files were only available on a 10 seconds base we evaluated the presence of sleep on a 10 second epoch base. Vigilance was divided into wake, drowsy and sleep. If there was only one epoch in a row with sleep stage 1 or 2 this was scored as drowsy. Rating was performed visually both by a skilled technician (W.D. or E.J. for epileptiform transients, LH. for vigilance) and by a skilled certified clinical neurophysiologist (A.C. or L.N.) independently and thereafter discussed to reach consensus, as is our current clinical standard procedure in evaluation of EEG-recordings.

Results of the EEG after sleep deprivation of the same patients were obtained retrospectively from the patients charts, as were data on vigilance in routine EEG’s.

At last, for patients for whom the main question concerned the localization of the irritative zone magnetic source imaging (MSI) was performed, according to the protocol previously described for automated classification and localization of IEDs (Ossenblok 2007).

Study design

In order to formulate a hypothesis on the probable diagnosis semiology as described by the treating physician was studied, including localization and if possible lateralisation.

MEG findings were categorized as “epileptiform” (multiple spikes < 70 ms, clearly distinguishable from the background), “suggestive for epilepsy” (recurrent but less pronounced sharp activity, sharp-slow wave complexes), “other abnormalities” and “no abnormalities”. This is the same categorization that is used in Kempenhaeghe for visual EEG-coding. As in most cases the combination of history, including ictal data, and clinical neurophysiological findings being categorized either as “epileptiform” or “suggestive for epilepsy” is sufficient for the clinician to diagnose epilepsy, these two were grouped in the analysis.

MEG reports were sent to the referring physician, in concordance with every day clinical practice for EEG reports. The final diagnosis from the clinician based on all available information (that is, including the results from EEG and MEG) was taken from the patient chart and considered as the gold standard of diagnosis. The clinician’s assessments were categorized as “epilepsy” (including probable epilepsy, leading to the decision to start anti-epileptic drug treatment), “no epilepsy” and “uncertain”.

Results

Visual analysis of the MEG recordings of the 51 patients studied showed epileptiform discharges in 16 of the 51 patients. Another 16 MEG recordings showed sharp abnormalities suggestive for epilepsy, however, these were less pronounced. In 14 patients there were other non-specific abnormalities, while in 5 patients MEG did not reveal any abnormalities.

The results of the comparison of, respectively, MEG and EEG after sleep deprivation to clinical diagnosis are listed in table 2. The clinical diagnosis in the 16 patients with

epileptiform discharges was “epilepsy” in 15, “uncertain” in 1. In the group of 16 patients with MEG findings suggestive for epilepsy, the final conclusion was “epilepsy” in 12, “uncertain” in 4.

			Clinical diagnosis		
		No epilepsy	Diagnosis uncertain	Epilepsy	Total
	No abnormalities	1	1	3	5
MEG	Other abnormalities	2	5	7	14
	Supportive of epilepsy	0	4	12	16
	Epileptiform	0	1	15	16
	Total	3	11	37	51

			Clinical diagnosis		
		No epilepsy	Diagnosis uncertain	Epilepsy	Total
	No abnormalities	2	2	1	5
EEG	Other abnormalities	1	3	13	17
	Supportive of epilepsy	0	6	12	18
	Epileptiform	0	0	11	11
	Total	3	11	37	51

Table 2. Results of routine MEG and EEG after sleep deprivation vs clinical diagnosis

When pooling the groups with epileptiform discharges and with sharp abnormalities supportive of epilepsy, MEG was suggestive for the diagnosis of epilepsy in 32 of 51 patients (63%). In 7 of the 37 patients with the clinical conclusion of “epilepsy”, MEG did not support the diagnosis of epilepsy. In 2 patients, despite support from MEG findings, the clinician did not (yet) decide on the diagnosis of epilepsy. In the 51 EEG’s after sleep deprivation (that were made in all of these patients as it was one of the inclusion criteria) the conclusion of the clinical neurophysiologist stated “epileptiform” in 11 patients and “suggestive of the diagnosis of epilepsy” in 18 patients. If we compare these results to the MEG spike yield it appears that none of these patients had a normal MEG (table 3). In total 5 EEG’s after sleep deprivation showed “no abnormalities”. In the remaining 17 the conclusion was “other abnormalities”. These EEG’s were therefor supportive of the diagnosis of epilepsy in 29 of 51 patients (57%). In 11 of the 37 patients with the clinical conclusion of epilepsy EEG after sleep deprivation did not support the diagnosis of epilepsy.

The comparison between MEG category and clinical conclusion and the results of the EEG’s after sleep deprivation compared to those of the MEG and to the clinical conclusion are summarized in tables 2 and 3. Table 4 shows the vigilance state of the patients during the different recording modalities. In both routine EEG and routine MEG, about the same number of patients did not have an altered vigilance whatsoever, whereas almost all patients reached sleep during EEG after sleep deprivation.

			EEG			
		No abnormalities	Other abnormalities	Supportive of epilepsy	Epileptiform	total
	No abnormalities	4	1	0	0	5
MEG	Other abnormalities	1	13	1	0	14
	Supportive of epilepsy	0	3	12	1	16
	Epileptiform	0	1	5	10	16
	Total	5	17	18	11	51

Table 3. Results of routine MEG vs results of EEG after sleep deprivation

	wake	drowsy	Sleep
RT EEG	13	19	19
SD EEG	0	1	50
RT MEG	13	17	21

Table 4. Lowest vigilance during the recording. Noted the number of patients reaching a specific vigilance state. Wake: not even drowsy. Drowsy: no actual sleep. Sleep: actual sleep recorded. RT EEG: routine EEG. SD EEG: EEG after sleep deprivation. RT MEG: routine MEG

In the original subgroup of 29 patients primarily recorded to support the diagnostic process MEG findings supported the diagnosis in 15 (52%) of these patients. Interestingly, in the subgroup of 22 patients primarily recorded to localize the epileptic (or irritative) zone, in 2 patients the clinicians diagnosis changed from “very probable epilepsy” to “localization related epilepsy” based on the MEG results. This reflects the fact that the diagnosis of epilepsy does not mandatory requires the presence of EEG-abnormalities, but that a clinician does feel reassured in diagnosing epilepsy when neurophysiological data support this diagnosis. In the remaining 20 of these 22 patients the diagnosis remained unchanged, i.e. localization related epilepsy. In 15 of these 22 patients a sufficient number of spikes (10 or more) was obtained to enable the automated procedures for grouping and localizing of the spikes, as developed by Van ‘t Ent et al. (2003). These procedures yielded for 8 of these 15 patients a localized irritative zone, in the temporal regions for 3 patients and in the extratemporal regions for the other 5 patients. For example, for one of the patients with temporal lobe localization previous routine EEG as well as EEG after sleep deprivation in our centre did not show any specific epileptiform discharges either. Semiology of the seizures pointed to a probably left-sided, neocortical epileptogenic zone, possibly in the posterior temporal region or the temporo-parieto-occipital junction. MRI showed right (!) frontal gliotic tissue. For this patient, MEG played a pivotal role in fine tuning the diagnosis of this patient’s epilepsy. The interictal MEG shown in figure 1 and representation of the equivalent dipole analysis in fig 2 indicate that the epilepsy of this patient originates in the left temporal lobe, at a location bordering the transverse temporal gyrus.

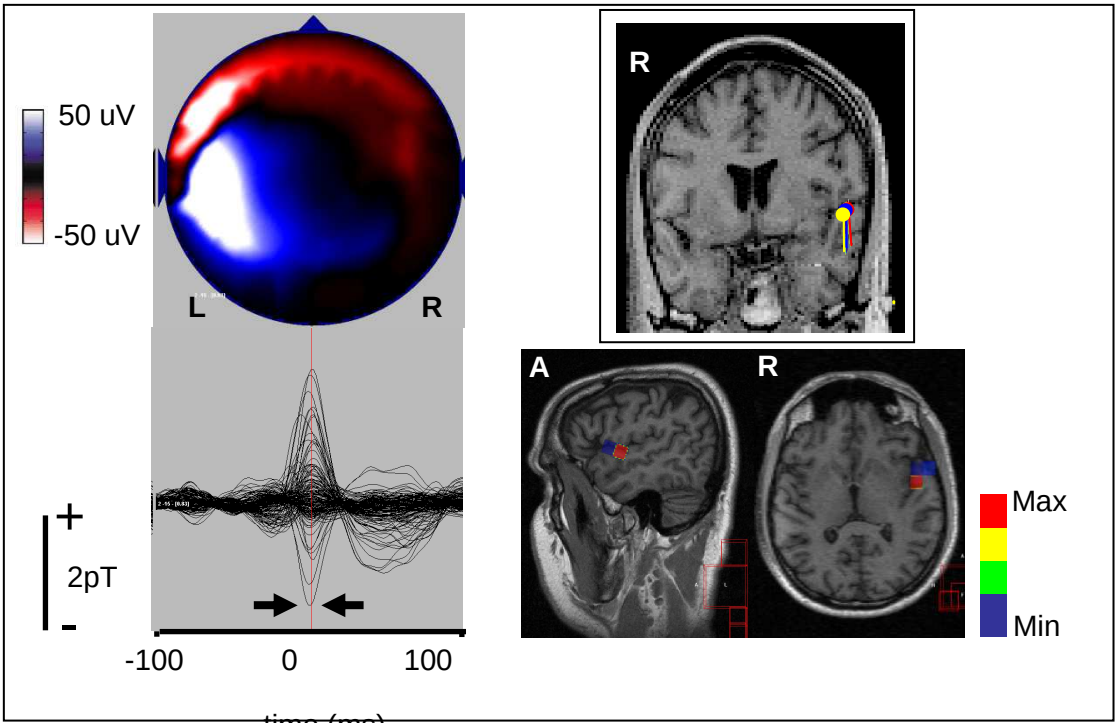

Figure 2. The density of the equivalent dipoles, fitted at an epoch across the maximum of the averaged spikes with similar field distribution (left), is plotted at the sagittal, coronal and axial MR-scans of the patient (bottom right). The vector representation (e.g. location and direction) of the equivalent dipoles (%err < 5) plotted at the coronal MR-scan of the patient (upper right)

Discussion

For a specified group of patients from the out-patient clinic of Kempenhaeghe, a tertiary referral center for epilepsy, with probable localization related neocortical epilepsy and with inconclusive standard EEG we found that MEG provided additional information leading to the diagnosis of epilepsy in 63% of the patients. Taking the clinical diagnosis as gold standard and excluding the 11 patients in whom the “final”

diagnosis was uncertain there were 27% false negatives and no false positives. This performance is in the range of EEG after sleep deprivation in the same patients, in whom we found a gain of 57% and with the same restriction 38% false negatives and no false positives. The absence of false positives probably partly is due to the trust clinicians have in clinical neurophysiologists. Therefor, it is of utmost importance that clinical neurophysiologists do not conclude too easily that a recording is epileptiform and in their conclusion correlate findings in the recordings with clinical data provided by the attending neurologist. We are very aware of this fact.

We consider routine MEG to be more patient friendly than EEG after sleep deprivation the way it is done in our center. Our procedure includes a night of hospitalization with a dedicated watch to ensure complete sleep deprivation followed by a recording of 4 hours. In most hospitals partial sleep deprivation is considered sufficient, whether or not during hospitalization with shorter recording. The underlying thought is that the most important goal of this procedure is to record EEG during sleep. There is, however, “a long-standing discussion on the usefulness of sleep and sleep deprivation as activating methods in electroencephalographic recordings” (Roupakiotis 2000) with a tendency to favor the specific activating role of sleep deprivation per se (Fountain, Kim and Lee 1998). e.g. Degen, Degen and Reker (1987) did not find a clinically useful difference between sleep EEG with or without 24 hour sleep deprivation. The first was achieved by administering promazine hydrochloride. They did, however, find significantly more epileptic discharges in the sleep EEGs after sleep deprivation.

Even accepting the fact that sleep deprivation in itself causes a rise of epileptiform discharges one can dispute the necessity of 24 hours of sleep deprivation. Unfortunately, even 24 hours of sleep deprivation does not ensure sleep during the

EEG the next day. After only partial sleep deprivation percentages of patients above 8 years reaching sleep during the subsequent EEG already range from 64% (Liamsuan 2000) to 91% (Peraita-Adrados 2001). In a review by Ellingson, Wilken and Bennett (1984) it is stated that “there is no good reason for not using it (partial sleep deprivation) routinely”. This, however, is not supported by any direct comparison between results after complete and partial sleep deprivation. Our percentage of patients reaching sleep after a night of sleep deprivation is considerably higher than the figures mentioned in the above mentioned literature. Partly this might be due to our policy of complete sleep deprivation during the night. Another factor could be the location of our EEG laboratory in the middle of the woods without major sources of noise in the vicinity. The most important factor, however, probably is the length of our recordings. Time to sleep onset varied between 0.5 and 49 minutes, indicating that a longer recording time will give a higher chance of reaching sleep. Accepting the evidence that sleep deprivation per se is an activating factor for epileptiform activity in the EEG we prefer a period of 24 hours of sleep deprivation above a partial sleep deprivation.

As the procedure in routine MEG mimics that in routine EEG we did not expect much difference on the level of vigilance. Indeed in this respect there was no difference between these two recordings. As the presence of sleep greatly enhances the chance of finding epileptiform phenomena in the EEG of patients with epilepsy (e.g. Gibbs and Gibbs 1947, Viteri 2007) this might also be true for MEG-recordings. Based solely on the covariant sleep the gain of routine MEG would be expected to be the same as of routine EEG. Also, in our EEG’s after sleep deprivation the percentage of patients achieving a considerable amount of sleep is quite higher than in MEG whilst the gain is comparable. Therefor, the gain of MEG cannot be due to

sleep alone. Therefor, if routine MEG does not support the diagnosis of epilepsy in a patient with high suspicion of epilepsy performing an MEG after sleep deprivation might even be more sensitive than an EEG after sleep deprivation. This, however, falls outside the scope of the present study.

Furthermore, routine MEG even is more patient friendly and less time consuming than any EEG recording, because application of electrodes might be unpleasant and preparation and cleaning time is much less for MEG than for EEG. In comparison, a routine EEG recording of one hour takes about two hours from starting the preparation to departure of the patient and EEG recording after sleep deprivation takes up to five hours in our center, whereas a complete routine MEG recording can be done within about 1 hour of patient time. Furthermore, using our protocol for analysis, MEG takes about as much time as thorough analysis of routine EEG and about half the time of analyzing an EEG after sleep deprivation. Apart from the benefits of patient friendliness, less time-consuming for technicians and patients there is the “free” extra of being able to perform localization if localization is of utmost importance, e.g. if the possibility of epilepsy surgery evaluation is considered. The automated procedures for classifying and localizing the interictal discharges (De Munck 2001; Van ‘t Ent 2003; Ossenblok 2007) immediately provides the clinician with an overview of the nature and if feasible the location of the sources underlying the interictal epileptiform discharges, as shown in figure 2. Especially, if the epileptiform discharges originate in an area bordering the sulcus in between temporal and frontal lobe (see figure 2) these are more easily demonstrated by MEG than by EEG (Ossenblok 2007). Thus, for this group of patients MEG can be of importance in case of presurgical evaluation. Manual detection of interictal epileptiform discharges in MEG is, however, time consuming, because the rater will need extra time to put

markers in the files, a 3D-MRI will have to be performed including extra time for classifying and localizing the interictal events. At the moment this might be somewhat overdone for every day clinical practice and should only be performed when the question of the clinician regards the location of the cortical origin of the epilepsy of the patient. Further development and implementation of automated detection of interictal events will probably allow localization on a more routine base in the future.

At the moment, however, MEG systems are still rather expensive and require a magnetic shielded room (comparable to the first MRI-systems) whereas a sophisticated EEG system is already present in most clinical settings (comparable to the presence of CT-systems in former days), at present using routine-MEG as primary diagnostic tool for epilepsy will be the privilege of epilepsy centers or centers who already posses or consider acquiring an MEG system for other purposes as well. On the other hand, depending on the local costs of factors like a night of hospitalization, a dedicated nurse or host to keep the patient awake during the night and some extra time for the technician and the frequency at which at present an EEG after sleep deprivation is recorded in a specific institute, acquiring MEG equipment might even be of financial benefit.

As Kempenhaeghe is a tertiary epilepsy centre, our patient group will not necessarily reflect the patient group as seen in other hospitals, since in a tertiary epilepsy centre the chances of diagnosing epilepsy are much higher than in other hospitals. Therefor, we expect that the gain of diagnostic tools in our centre might be higher than in normal hospitals. Combined with the exclusion criterion of high suspicion of non-

epileptic seizures, this also explains why the percentage of patients with epilepsy according to the final clinical assessment is so high.

There is no definite proof that the patients in our study with abnormalities in EEG or MEG supportive of the diagnosis actually have epilepsy. EEG and MEG can only increase the probability of this diagnosis. The diagnosis of epilepsy is a clinical one. Even in patients with definite epilepsy combined routine EEG and EEG after sleep deprivation show epileptiform discharges in only 85% of the patients (richtlijnen NVvN, guidelines national neurological society). Also, in perfectly healthy candidates for aircrew training unequivocal epileptiform discharges can be found in up to 0.5 %, almost half of them without photic stimulation (Gregory, Oates and Merry 1993). Therefor, clinical neurophysiologic data are supportive of the diagnosis at best. In our centre, the EEG is considered supportive if there is a clear epileptiform focus or pattern or if clinical features are concurrent with focal, preferably sharp abnormalities resembling epileptiform patterns. Therefor we pooled the groups with epileptiform discharges and with sharp abnormalities suggestive for epilepsy.

MEG as a routine tool in clinical neurophysiology is still under development. Brain activity appears to be sharper when measured with MEG (Fernandes 2005, Ossenblok 2007) and there still is debate on what the criteria should be for naming a grapho-element in MEG epileptiform (Zijlmans 2002). Therefor, we took a conservative approach to determining MEG grapho-elements “epileptiform”. Once criteria for naming a grapho-element epileptiform become clearer, the group in which epilepsy is thought to be proven might grow at the expense of the group with less specific features, e.g. “sharp abnormalities suggestive for epilepsy”. However, looking back at our data at the end of the data collection period we still discarded for several patients several visually detected phenomena as probably not being epileptiform but

more likely sharp mu rhythm, POSTs or benign epileptiform transients of sleep (BETS). These phenomena, identified initially as (suspicious of) interictal epileptiform events, appeared to be i.e. discordant with clinical suspicion, while in some of these patients the same phenomena were described in the routine EEG or EEG after sleep deprivation as being probably non-epileptic. Also, we encountered above mentioned phenomena in several patients in whom the localization of these phenomena were discordant with clinical suspicion while in the same patient there were also spikes that were concordant with clinical suspicion. Furthermore, in several patients MEG turned out to show a lot of activity that did not resemble EEG in the basal temporal regions. For example, in figure 1 apart from the spike and waves maximal at the left temporal lobe sensors sharp paroxysmal activity occurs, more or less symmetrically at the temporal and occipital lobe sensors of this patient. We learned from this study that whenever the sharp transients in the temporal regions either may indicate a left, right or symmetric temporal distribution for a small number of detected events one should be aware that these are false detections due to sharp MEG components, which may become apparent, especially, in the temporal regions. Acquiring a vast experience with “normal” MEG in the coming years will prove of utmost importance to better distinguish the physiological variants. As this is not the case yet, the authors cannot emphasize enough the caution a clinical neurophysiologist should apply before stating the MEG is epileptiform. Furthermore, in order to validate the outcome and give a more reliable estimation on sensitivity and specificity of the tests used, patients will be re-evaluated 8 years after enrollment in this study. They will be asked again to supply their medical history with special regard to the occurrence of seizures and the clinical diagnosis of epilepsy. This data will be correlated with the present results of the routine MEG-recordings.

Conclusion:

We have shown that routine MEG is a reliable diagnostic tool in the routine diagnosis of epilepsy when the first EEG is negative or inconclusive. None of the patients with findings on EEG after sleep deprivation supporting the diagnosis of epilepsy had a negative MEG. For the patients studied the diagnostic gain of MEG recorded routinely did not differ significantly from the diagnostic gain of EEG after sleep deprivation performed after a non-conclusive routine EEG examination. When taking other factors into account, like patient friendliness and duration of the examination MEG, when already available, and not EEG after sleep deprivation could be the investigation of first choice. Financial issues are still the major obstacles. However, one should keep in mind that a high degree of cooperation is required to perform a MEG as the patient is required not to move his or her head, making it inapt for long term monitoring and registration of restless or uncooperative patients.

3.2 Long-term reliability of MEG outcome

Evaluation of MEG vs EEG after sleep deprivation in epilepsy.

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Abstract

Objective: MEG and EEG after sleep deprivation (EEG-SD) are applied as diagnostic tools in the evaluation of patients with possible epilepsy. There is no gold standard to check whether the diagnosis based on these two modalities is correct. The best standard available is the long-term follow-up of patients. As follow-up of an earlier study in which the additional value of MEG vs EEG-SD diagnosis was evaluated, we investigated the long-term validity of MEG-based and EEG-SD-based diagnosis.

Materials and methods: Data collected from 46 patients were used in a comparative study of the last known diagnosis against the original one of 8 years ago.

Results: Long-term (3–8 years) sensitivity of sharp phenomena (combining spikes and sharp waves) in routine MEG and in EEG-SD for the diagnosis epilepsy is 71% and 62%, respectively. When compared to the original study, this hardly changed. Over time, uncertainty on diagnosis diminishes.

Conclusion: MEG as well as EEG-SD are robust long-term predictors for epilepsy.

Key words**:** EEG after sleep deprivation; epilepsy diagnosis; MEG; Validation

Introduction

Epilepsy has a profound and long-term impact on life. It can have a major impact on socio-economic factors (i.e. restrictions in work, restrictions in driving, social stigma (e.g. [Van Mil 2009, Taylor 2011, Jacoby 2014]) and can lead to lifelong use of medication. Therefor, it is of utmost importance to avoid an erroneous diagnosis. On the other hand, it is also important to correctly diagnose epilepsy in order to start the optimal treatment. To determine whether or not a particular patient has epilepsy, several tools are available. The most important of these is the medical history, including description of the alleged seizures and the changes in clinical symptoms over time. Further support for diagnosis can be found in video recordings, structural imaging (CT or MRI), and above all electrophysiological investigations. Routine electroencephalogram (EEG) and EEG after sleep deprivation (EEG-SD) are mostly used. Long-term video-EEG (LTM) capturing events are considered to provide the highest level of security on the diagnosis. It changes diagnosis in up to 58% of patients [Ghougassian 2004]. However, even in the highly selected population undergoing this time-consuming and expensive investigation in up to 5.2%, it neither helps to improve the diagnosis nor the management [Baheti 2011]. And LTM certainly is not a standard procedure applied in all diagnostic processes. Therefor, while in a limited number of cases an unequivocal diagnosis can be made, there is no gold standard proving that a person does not have epilepsy. Decades after the first description of the occipital alpha, rhythm producing a detectable magnetic field [Cohen 1968] magnetoencephalography (MEG) is also gaining ground, both in the primary diagnosis of epilepsy and in the presurgical evaluation of patients with drug-resistant epilepsy [Ossenblok 2007, Colon 2009, Heers 2010, De Tiege 2012].

Despite the prominent role of neurophysiologic investigations in diagnosing epilepsy, to our knowledge there are no studies addressing the long-term validation of EEG-SD, let alone of MEG as diagnostic tools for epilepsy. In an earlier study, we showed that for patients who all had a negative routine EEG, routine MEG was as supportive for diagnosing epilepsy as EEG-SD [Colon 2009]. In the present study, we examined the changes in diagnosis 3–8 years after the actual MEG and EEG-SD examinations.

Materials and methods

Included were all patients that participated in our earlier study on the use of MEG for primary diagnosis [Colon 2009]. Inclusion criteria for this study included age over 6 years, suspicion of neocortical extratemporal localization-related epilepsy, and an inconclusive routine EEG, including provocation trials of hyperventilation and photostimulation. Results of visually assessed MEG recordings were compared, retrospectively, with clinical data and with the results of EEG-SD. Encephalographies were considered supportive for the diagnosis of epilepsy if there was a clear epileptiform focus or pattern or clinical features were concordant with focal, preferably sharp abnormalities resembling epileptiform patterns. Therefor, groups with epileptiform discharges and with sharp abnormalities suggestive for epilepsy were pooled in the final analysis. MEG and EEG-SD examinations were performed in 2005 or 2006. In routine EEG as well as in EEG-SD, recording time was 1 h. In MEG, in total 45 min were recorded. Sleep deprivation was carried out clinically and lasted until 7 a.m. Results were compared to our ‘gold’ standard: the final diagnosis made by the treating epileptologist. This diagnosis therefor was an expert opinion, based on all the data deemed necessary or sufficient by this epileptologist to make a

diagnosis. For this study, the same patients were sent a questionnaire asking about their medical history in the past years, their present diagnosis, and present use of anti-epileptic drugs. They were asked, furthermore, permission to collect further information from the family physician or to use information available from our institute. Information of last follow-up, either via the returned questionnaire, by information from the family physician or available in our charts was added to the original database. Diagnosis at last follow-up by a neurologist was noted, plus reasons for chance of diagnosis (Table 1) if applicable.

Table 1. Reason of changed diagnoses in the eight patients in whom original diagnosis is thought to be false

Patient	Initial diagnosis	Diagnosis at last FU	Reason of change
1	Uncertain	Epilepsy	Tonic-clonic seizure
2	Uncertain	Epilepsy	Finding of MRI abnormality on plausible location by applying voxel-based morphology analysis
3	Uncertain	Epilepsy	Partial seizure during routine EEG
4	Uncertain	Epilepsy	Cell phone video of seizure
5	Uncertain	Not epilepsy	Without treatment abrupt cessation of seizures after explanatory talk
6	Uncertain	Not epilepsy	Proven Syncope (tilt-table test)
7	Epilepsy	Uncertain	Unclear from files. Probably the emerging psychiatric abnormalities
8	Epilepsy	Not epilepsy	Change of symptoms to bizarre semiology

Classification of the encephalographies was taken from the former study, and thus categorized as epileptiform (multiple spikes <70 ms, clearly distinguishable from the background [Cobb 1983, Pedley 1980]), ‘suggestive for epilepsy’ (recurrent but less-pronounced sharp activity of 70–200 ms, sharp–slow wave complexes), ‘other abnormalities’, or ‘no abnormalities’. In Table 2, the original diagnosis after review of the routine EEG, EEG-SD, and MEG is listed vs the results of the review. In comparison, Table 3 contains the same results of review of EEG-SD and MEG, but now listed vs the diagnosis at last follow-up.

In line with the original study, to obtain a sensitivity and specificity percentage, the encephalography results were pooled in two categories: epilepsy (Spikes plus sharp waves) and no epilepsy (other and no abnormalities). For specificity calculation, the diagnostic groups of epilepsy and uncertain were pooled as ‘other’, whereas for sensitivity calculation the diagnostic groups of uncertain diagnosis and no epilepsy were pooled as ‘other’ (Tables 4 and 5), thus eliminating the uncertain diagnoses from the equations.

Table 2. Results of routine MEG and EEG after sleep deprivation vs original clinical diagnosis

	Clinical diagnosis			
	No epilepsy	**Diagnosis uncertain**	**Epilepsy**	**Total**
MEG				
No abnormalities	1	1	3	5
Other abnormalities	2	5	7	14
Supportive of epilepsy	0	4	12	16
Epileptiform	0	1	15	16
Total	3	11	37	51
EEG				
No abnormalities	2	2	1	5
Other abnormalities	1	3	13	17
Supportive of epilepsy	0	6	12	18
Epileptiform	0	0	11	11
Total	3	11	37	51

Table 3. Results of routine MEG and EEG after sleep deprivation vs clinical diagnosis at last follow-up

	Last follow-up			
	No epilepsy	**Diagnosis uncertain**	**Epilepsy**	**Total**
MEG				
No abnormalities	1	0	3	4
Other abnormalities	3	2	7	12
Supportive of epilepsy	2	2	10	14
Epileptiform	0	2	14	16
Total	6	6	34	46
EEG				
No abnormalities	1	0	3	4
Other abnormalities	1	4	10	15
Supportive of epilepsy	4	1	11	16
Epileptiform	0	1	10	11
Total	6	6	34	46

Table 4. Specificity calculation at last follow-up. To be as pure as possible, 'other' includes patients in whom the diagnosis was 'epilepsy' plus those in whom the diagnosis was still uncertain

	Diagnosis 'other'	**Diagnosis no epilepsy**	**Total**
MEG			
Epilepsy	28	2	30
No epilepsy	12	4	16
Specificity		4/6*100 = 67%	
EEG-SD			
Epilepsy	23	4	27
No epilepsy	17	2	19
Specificity		2/6*100 = 33%	

Table 5. Sensitivity calculation at last follow-up. To be as pure as possible, 'other' includes patients in whom the diagnosis was 'no epilepsy' plus those in whom the diagnosis was still uncertain

	Diagnosis epilepsy	Diagnosis 'other'	Total
1. EEG-SD, EEG after sleep deprivation.			
MEG			
Epilepsy	24	6	30
No epilepsy	10	6	16
Sensitivity	24/34*100 = 71%		
EEG-SD			
Epilepsy	21	6	27
No epilepsy	13	6	19
Sensitivity	21/34*100 = 62%		

The local medical ethical committee approved this study. Consent was assumed if the patient returned the questionnaire.

Results

A total of 46 of the 51 questionnaires were returned. One patient died, but the relatives allowed use of the data. Follow-up in this patient was 3 years. Three patients returned the questionnaire supplying data but not allowing to contact the

family physician. Follow-up of these patients in our own institute was 5, 6, and 8 years, respectively. Follow-up in the remaining group was 8 years, in 29 patients based on information available in our institution and in an additional 13 patients also based on the information provided by the family physician. Follow-up of this last group in our own institute was 5–7 years.

In only one of the included patients, Long Term Monitoring (LTM) was performed. This patient underwent extensive presurgical analysis, resulting in a successful right frontal resection. Both in the original study as in this review, this patient was considered to have a definite diagnosis of epilepsy. In eight of the patients, diagnosis changed over the years: in four from ‘diagnosis uncertain’ to ‘epilepsy’, in two from ‘diagnosis uncertain’ to ‘not epilepsy’, in one from ‘epilepsy’ to ‘diagnosis uncertain’, and in one from ‘ epilepsy’ to ‘not epilepsy’. Reasons for change in diagnosis varied, as indicated in Table 1. In addition, four patients who now are diagnosed as having epilepsy developed a different event type next to the original, resulting in combined diagnoses of epileptic and non-epileptic seizures. In one of these four patients, this occurred after a cerebrovascular infarction.

When pooling the groups with epileptiform discharges (spikes) and with sharp abnormalities supportive of epilepsy, the original MEG conclusion corresponded with the latest diagnosis of epilepsy in 24 (52%) patients, as compared to 53% at initial diagnosis. For EEG-SD that was true in 21 (46%) patients as compared to 45%. Including the patients with an (as yet) uncertain diagnosis but excluding those in whom epilepsy was ruled out, the gain of MEG was 61%, as compared to 63% of positive MEG diagnoses in the original group. For EEG-SD, these numbers were 50%, coming from 57% initially. The percentage of uncertain diagnoses dropped over the 8-year follow-up from 22% to 13%. The percentage of patients with abnormalities

supportive of epilepsy but a diagnosis of no epilepsy, however, augmented during this follow-up from 0% to 4% for MEG and 9% for EEG-SD. There were no patients in our group with MEG or EEG-SD with spikes without a diagnosis of epilepsy.

In the group of eight patients in whom diagnosis changed, six changed from uncertain to a definite diagnosis. Four had no sharp or epileptiform activity in their MEG nor in their EEG-SD. Two of these had MEG and EEG-SD abnormalities supportive of epilepsy, one of them changing to a diagnosis of epilepsy, one to a diagnosis of not epilepsy. In the patient in who the diagnosis changed from ‘epilepsy’ to ‘not epilepsy’ MEG and EEG-SD were supportive of epilepsy, whereas in the patient whose diagnosis changed from ‘epilepsy’ to ‘uncertain’ both MEG and EEG-SD showed sharp waves but no spikes, thus supportive of epilepsy.

Sensitivity and specificity of EEG-SD and MEG for epilepsy are, respectively, 62% and 33% (EEG-SD) vs 71% and 67% (MEG) (Tables 4 and 5).

Discussion

Over a time period of 3–8 years, there was no significant change in the positive predictive value of routine MEG or EEG-SD in our group of patients. However, there seems to be a trend for spikes and sharp waves to be rather more robust long-term predictors for definite epilepsy in MEG than in EEG-SD. Unfortunately, the size of this study is insufficient to make solid conclusions on this observation. Looking at epileptiform discharges in the strictest sense (spikes), there were no definite false positives. However, looking at patients with only sharp waves in MEG or EEG-SD, over time a larger portion of them was diagnosed as not having epilepsy. For EEG, in the past there has been some debate whether or not there is a difference between

spikes and sharp waves in predicting or confirming epilepsy [Pedley 1980, Walczak 1997] This discussion seems to have ended by favoring the conclusion that both are equally supportive for diagnosing epilepsy (e.g. [Niedermeyer 1999]. Our present study including patients without epilepsy, albeit small, tends to favor the view that in the long-run spikes are more suggestive of epilepsy than sharp waves. Former studies were based on the first diagnosis or included only patients with an established diagnosis of epilepsy [Celesia 1976], whereas our study looks at the long-term consistency. In healthy adults, EEG can show sharp waves and spikes in 0 up to 6.6% of the subjects [Gibbs 1943, Kooi 1964, Jabbari 2000]. We are not aware of similar studies on MEG; however, it is very likely that a small portion of normal controls will present the same phenomena in MEG as well. In our study, we initially did not find patients with epileptiform abnormalities in their encephalography in whom a clear diagnosis of no epilepsy was reached. However, in the present long-term analysis, this was 4% (2/46) and 7% (4/26) for MEG and EEG-SD, respectively, in all cases presence of sharp waves. All in all, we therefor advocate re-evaluation of the predictive value of spikes vs sharp waves and at present differentiating between them in describing EEG and MEG abnormalities in the context of epilepsy diagnosis. And to do so even more vigorously for EEG-SD than for MEG. The adagio ‘it is no epilepsy if the EEG/MEG is normal’ is false as well as the adagio ‘it is epilepsy if EEG/MEG contains sharp transients’.

Diagnosis changed in 17% of the patients. In three quarters of them, over time the diagnosis changed from uncertain to certain. As there is no gold standard for diagnosing epilepsy, in some cases only time can tell. A change of diagnosis from epilepsy to no epilepsy has been described, mainly for PNES (psychogenic non-epileptic seizures) with a mean latency between onset of PNES and final diagnosis

as being non-epileptic and psychogenic of approximately 7 years [Bodde 2009] but also for other entities like syncope.

There is one study on long-term changes in EEG in epilepsy patients [Hughes 1985]. This study included only patients with ongoing seizures, thus excluding most of the group of patients of our study. However, changes in EEG pattern in this study occurred almost exclusively within 8 years. It is likely that possible changes in semiology would parallel a change in EEG pattern. We therefor believe that a period of 8 years is adequate to re-evaluate the patients included.

There is no gold standard for diagnosing epilepsy, LTM is the best option available. Unfortunately, even apart from the tremendous costs of this procedure making it impossible to apply it in every patient, it is only suitable for patients with a higher frequency of seizures or events. Therefor, as ‘best available standard’, we used the clinical diagnosis at last follow-up. This might overestimate, especially, the number of patients in whom the diagnosis of epilepsy did not change as challenging a once-made diagnosis of epilepsy is counterintuitive. In our center, it is standard procedure to re-evaluate a diagnosis every several years, even if clinical signs did not change. A follow-up of 8 years is long enough for all of our patients to have been re-analyzed. In the group of 13 patients, however, not still under our care we cannot guarantee the validity of the last diagnosis. As in this group there are six patients with the diagnosis of epilepsy and one with a still uncertain diagnosis this could influence our results. All changes in diagnosis took place while patients were under our care, including four patients that are part of this last group (three with a final diagnosis of ‘not epilepsy’, one with the diagnosis ‘epilepsy’). However, of the four patients in whom at present a mixed diagnosis of ‘epilepsy and non-epileptic seizures’ is noted, two have been

diagnosed outside of our center. This supports the notion that clinical changes influence diagnosis both in tertiary and secondary centers in the same way.

The population analyzed in this study is biased by the fact that we recruited from a tertiary epilepsy center. The *a priori* chance of having epilepsy is much higher in our patient group than in a standard neurology practice. The underrepresentation of patients without epilepsy might have influenced the results to overestimate the gain of our encephalographys. This, however, should hardly be true for the consistency of gain over time. Both EEG-SD and MEG show a remarkable consistency in gain in the patient group with diagnosed epilepsy, even though there is some decline in gain in the patient group with no epilepsy or a still uncertain diagnosis, a bit more pronounced in the EEG-SD's than in the MEGs. As the response rate of our study was 90%, we obtained a good representation of our original group. The calculated specificity cannot be interpreted as correct, seen the low number of patients in whom the diagnosis is NOT definite epilepsy. All in all we showed that the sensitivity of routine MEG in long term was 71%. The sensitivity of EEG-SD was 62%. For EEG-SD, the sensitivity is in line with the reported activation after sleep deprivation, ranging from 34% to 84% in the literature [Mattson 1965, Spadette 1971, Giorgi 2013]. However, these reports mainly are based on the appearance of spikes and sharp waves rather than diagnosis-specific sensitivity. In a recent comparison between primary generalized epilepsies and focal epilepsies [Renzel 2016], the sensitivity of EEG-SD for focal epilepsies was no higher than 17%. Inclusion criteria as well as recording time were almost equal to ours, so no good explanation for the difference can be found.

Conclusion

Epileptiform abnormalities in MEG are even more robust long-term predictors for epilepsy than these abnormalities in EEG-SD.

CHAPTER 4

MRI in Epilepsy

4.1 MEG-guided MRS

MRS-lateralisation index in patients with epilepsy and focal cortical dysplasia or a MEG-focus using bilateral single voxels

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Abstract

Purpose: To evaluate if single voxel proton magnetic resonance spectroscopy (SV-MRS) can help in lateralising and sometimes in localizing an epileptogenic focus. The assumption is that in MRI negative patients the underlying pathology most often is focal cortical dysplasia (FCD). Several studies have shown that in the presence of FCD there are also 1H-MRS abnormalities on the contralateral side. However, in most cases the studied group was not homogeneous and included different forms of dysplasias, including band heterotopias and polymicrogyria, and the studies used different spectroscopy protocols. In the present study, using bilateral SV-MRS we investigated the presence of a lateralisation index in two groups of patients with localization related epilepsy: patients with focal cortical dysplasia on MRI and patients without MRI abnormalities with a focus identified by MEG. Aim of the study was to show that in both groups the expected epileptogenic side shows more pronounced metabolic alterations, making MRS a possible screening tool for clarifying lateralisation questions in patients with cryptogenic localization related epilepsy. *Methods:* In ten patients a single voxel was placed over the FCD and in nine patients over the region of interest (ROI) as indicated by MEG. In all patients a voxel was also placed in the contralateral homologous location. We used metabolite concentrations as peak ratios relative to the creatine (Cr) peak to calculate a lateralisation index. *Results:* In both groups NAA/Cr was significantly lower on the affected side whereas the results for Cho/Cr were more diverse. There were no significant differences between the two groups. The limitations of the used methods and the implications of the findings are discussed.

Introduction

With the introduction of MRI in clinical practice the percentage of patients with cryptogenic localization related epilepsies diminished from 70% to 30%. However, despite the improvement of structural MRI techniques there are still a considerable number of patients with epilepsy left with a negative MRI study (von Oertzen 2002; Phal 2008). In case of intractable epilepsy of presumed extra-temporal origin this may prevent surgery or lower the chances of successful surgery in these patients. In most studies, the presence of a lesion on MRI and the possibility to resect the entire lesion are the major factors predicting successful outcome of surgery (e.g. Fauser 2004; Krsek 2009). Therefor, a lot of effort is put into improving imaging techniques. With an a priory hypothesis on the probable location of a lesion more lesions can be detected by reviewing the MRI (Moore 2002). MEG is a very powerful tool to determine the epileptogenic focus or the irritative zone in patients with enough spikes in their traces (e.g. Ossenblok 1999; Shiraishi 2001; Van ‘t Ent 2003; Iida 2005; Papanicolaou 2005; Ossenblok 2007). There are several alternative MRI techniques that are used or investigated in epilepsy, most notably MRS. Results of MRS largely depend on determining a ROI in advance. However, even if there is a priory information, for example an identified epileptogenic lesion, the results of MRS and the conclusions based on these results are currently conflicting, especially in case of extra-temporal epilepsy. This may partly be due to the inhomogeneity of the populations studied, while the methods and protocols used also differed. In extra-temporal epilepsy using MRS a decline of NAA concentration could be demonstrated in regions that were part of the epileptogenic or irritative zone (Guye 2005), according to intracerebral recordings. Six out of 12 patients in this study proved to have FCD at operation, 4 of them without abnormalities on conventional MRI, whereas 4 of the 12

patients were not operated upon. In another study in 12 out of 14 patients with frontal lobe epilepsy a decline of NAA concentration was seen in the epileptogenic focus (Lundbom 2001). According to structural MRI 4 had FCD (2 confirmed histological, 2 statistically significant), whereas 7 showed no abnormalities. In mesiotemporal sclerosis (MTS) MRS can show abnormalities before conventional MRI does (Hammen 2003), and if bilateral hippocampal changes are found the prognosis of operation is less favorable (Lee 2005). In 15 out of 20 patients with a neocortical temporal lobe epilepsy without abnormalities on MRI Shih et al. (2004) found MRS abnormalities in the region predicted by MEG. In summary, there is increasing evidence that MRS may be more sensitive than structural MRI in detecting lesions. Most cryptogenic epilepsies are believed to arise from FCD (Bautista 2003). FCD has been recognised increasingly as one of the most common causes of pharmacoresistant focal epilepsy (Widders-Walsh 2006). FCD is a developmental disorder in which cytoarchitectural derangements occur. Abnormal, immature cells remain present accompanied by a disruption of normal cortical and subcortical architecture (Palmini 2004). As MRS is a sensitive measure of both neuronal maturation (Kok 2002; Kreis 2002; Tkac 2003) and neuronal dysfunction (Cendes 1997; Tasch 1999) abnormalities are expected both in FCD and in epilepsy. As there is no support for a metabolic hemispheric asymmetry (Pouwels and Frahm 1998) when using MRS on patients their non-affected side can be used as control side in any given investigation. We investigated whether MRS-abnormalities in a focus as indicated by MEG in structural MRI negative epilepsy patients are comparable to MRS abnormalities in epilepsy patients with a FCD. Our goal was to determine whether SV-MRS could be supportive for localising an epileptogenic region and

eventually can be used in presurgical evaluation of epilepsy patients. This study is the first to do so for foci not confined to the temporal lobe.

Methods

All patients were outpatients of Epilepsy Centre Kempenhaeghe with localization related epilepsy. Two groups of patients were included in the study. In the first group (the FCD group) patients were included who on structural MRI had unilateral FCD. In group 2 (the MEG group) patients were included who already had an MEG-recording for another study (Colon 2009). Of these, patients in whom a plausible localization of the epileptiform activity within the grey matter could be determined using equivalent dipole modelling and in whom structural MRI showed no abnormalities were included. Exclusion criteria were the standard exclusion criteria for MRI investigations, a cerebral lesion on MRI that clearly was not FCD, inability to cooperate and age below 18. In the FCD group 10 patients were included, in the MEG group 9. Patients age ranged from 21 to 73 years. 10 women and 9 men were included. Localization of the ROI is described in Table 1. Permission for this study was obtained by the Local Medical Ethical Committee and all patients signed the informed consent.

	Age	sexe	EEG	MRI location FCD
1	44	m	Left	Left precentral sulcus
2	53	m	Left	Left precentral sulcus
3	22	m	Right	Right insula
5	24	m	Bilateral	Left frontal
6	32	f	Left	Left parietal
7	39	m	Left	Left parietal
8	22	f	Left	Left frontal
10	44	f	Left	Left frontal
11	24	m	Normal	Left occipital
12	30	m	Right	Right frontal
				MEG
20	21	m		Left peri-insular
21	58	f		Left insular, Right lateral temporal
22	52	f		Left angular
23	59	f		Left mesial fronto-parietal
24	73	f		Right temporo-occipital
25	22	f		Left parietal
26	34	m		Right temporal
27	35	f		Left insula
28	37	f		Right frontal

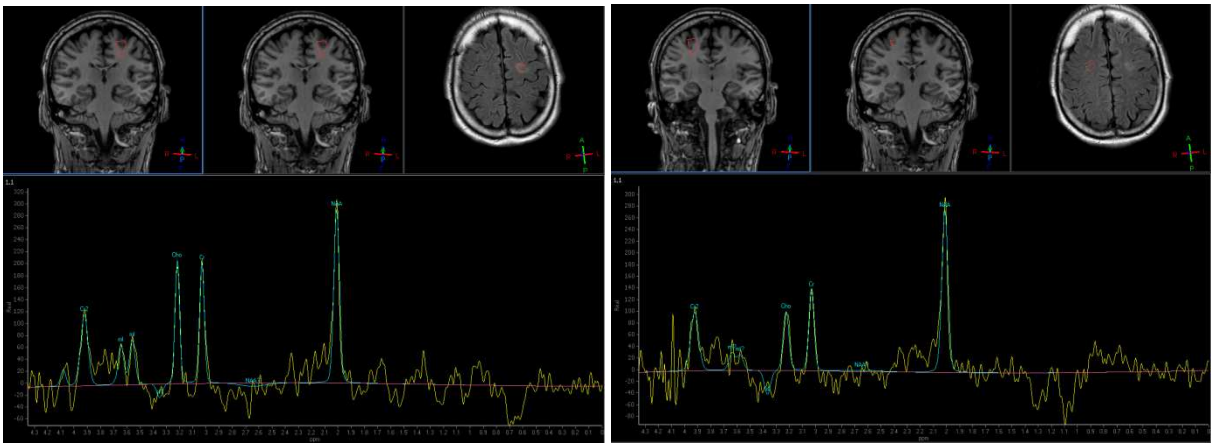
Table 1: Patient Characteristics FCD (1-12) and MEG (20-28) group, Age in years. Sexe: m: male f: female. EEG: predominant side of found abnormalities on EEG. MRI location FCD: side and lobe. MEG: the location (side and lobe) of the irritative zone as provided by the result of the automated cluster- and localization analysis procedures applied to the interictal MEG spikes.

In order to get the best possible signal-to-noise ratio we decided to use single voxel 1H-MRS (SV-MRS) and not chemical shift imaging (CSI). Even though CSI has the advantage of allowing a better spatial resolution and can be performed in a similar scan time as SV-MRS using SENSE parallel imaging, a CSI volume is more difficult to shim due to a larger shim volume. Better shimming provides smaller line widths and hence better SNR. SV-MRS spectra are therefor expected to be more robust, i.e. less variations over a large patient population. As there still is abundant discussion on the validity and on what reference to use of measuring absolute metabolite concentrations (Jansen 2006) we decided to express metabolite concentrations as peak ratios relative to the creatine (Cr) peak, to calculate a lateralisation index. In both groups bilateral SV-MRS was applied and a lateralisation index for the major metabolites was calculated. In all patients voxels of 1 cm×1cm×2 cm were placed. In the FCD group the location of the voxel was determined by the position of the FCD, including as much of the visible FCD as possible. In the MEG group the location of the voxel was determined by the source localization of clustered epileptiform activity in MEG (Ossenblok 2007). The contralateral voxel was placed over the corresponding gyri. We avoided inclusion of cerebro-spinal fluid (CSF) as much as possible, always less than 5% of the entire volume. MRI was performed with a 3 T Philips Intera MRI (Philips Healthcare, Best, The Netherlands). The MRI sequences consisted of 3D TFE in sagittal plane (TR 8.2 ms TE 3.7 ms, TI 1030 ms, flip angle 8, gap 0, resolution 1mm×1 mm), coronal FLAIR (TR 1100 ms, TE 128 ms, IR 2800 ms, 4.5mm slice thickness, gap −0.5) and two runs of 1H-MRS (one for each side) (TR 2000 ms, TE 37 ms, standard voxel size 1cm×1cm×2 cm, NSA 256). If at the initial quality control of the MRS sequence online the signal-to-noise ratio (SNR) of NAA was less than 5 or if the NAA, Cho and/or Cr peak could not be recognized, a

second run was performed. This was done either during the same session, only on the side where the problem appeared (n = 3), or double-sided on a separate session (n = 1). If a separate session was planned, the entire procedure was repeated. Post-processing was performed using the standard Philips SpectroView software installed on the scanner. Initial baseline substraction was set using 15 terms in the polynomial. Automated peak fitting for NAA, Cho, Cr and Ins was applied. No corrections for relaxation were performed. Manual baseline correction was performed in Real modus. The NAA/Cr and the Cho/Cr ratios were calculated for each voxel. These data were used to calculate a lateralisation index (voxel ratio affected side/voxel ratio contralateral side). A Mann-Whitney test with a two-tailed p value was performed to analyse relevancy of the results. As this study was intended as a pilot study, we estimated the normal values setting at 1 with a SD of 0.1 in 10 persons

Results

An example of the SV-MRI's in one patient is shown in Fig. 1.



A B

Figure 1: example of SV-MRS in one patient. Small MRI's on top showing the positioning of the voxel. As this is a rectangle with fixed dimensions but positioned in slightly different ways to ensure comparible percentages of CSF shape and size seems to differ in different MRI-slices.
MRS after baseline correction is depicted below including the peakfitting. A: affected side. B: healthy contralateral side

In 7 out of the 10 patients in the FCD group and in 6 out of the 9 patients in the MEG group the NAA/Cr ratio was decreased on the affected side as compared to the contralateral side. This resulted in a mean lateralisation index of 0.772 (p = 0.01) in the FCD group and 0.845 (p = 0.04) in the MEG group. The difference between the FCD and the MEG group was not significant (p = 0.37). In the FCD group of 2 of the remaining 3 patients and in the MEG group of 3 of the remaining 3 patients it was not possible to determine the peak of the NAA, Cho and Cr reliably on both sides because of the low signal-to-noise ratio of the MR spectrogram. The Cho/Cr ratios were much more diverse without statistical significant difference in both groups (p = 0.17 and 0.51 respectively) nor between both groups (p = 0.08). Results are shown in Table 2.

FCD group	side	NAA	Cho		MEG group	side	NAA	Cho
1	le	0.818	0.998		**20**	le	0.975	0.842
2	le	0.934	1.236		**21**		Noise	
3	ri	0.765	0.903		**22**	le	0.974	0.631
5	le	1.084	0.929		**23**	le	0.629	1.366
6	le	0.440	1.435		**24**	ri	Noise	
7	le	0.872	2.107		**25**	le	0.831	0.897
8	le	Noise	noise		**26**	ri	Noise	
10	le	0.585	0.782		**27**	le	0.885	0.873
11	le	Noise	1.745		**28**	ri	0.778	1.182
12	ri	0.681	2.457					
mean		0.772	1.399		**mean**		0.845	0.965
SD		0.203	0.589		**SD**		0.132	0.264

Table 2: MRS lateralisation indices in FCD and MEG groups

Lateralisation index: (Metabolite/Cr affected side)/(metabolite/Cr contralateral side): ratio of "lesioned"/contralateral relative metabolite concentration. Side: le: left. Ri: right. Noise: SNR of at least one of the measured metabolites < 5

Discussion

Our main finding for all of the patients studied (*n* = 19) is a significantly decreased NAA/Cr ratio in the pathologic hemisphere as compared to the healthy side, whereas there is less consistency in the Cho/Cr ratios for both groups. We found no statistically significant differences between the FCD group and the MEG group. To our knowledge this is the only study published on MEG guided MRS findings in MRI negative patients including patients with extra-temporal foci. An earlier study by Shih et al. (2004) dealt only with temporal lobe patients. In addition we compared our SV-

MRS data with SV-MRS data from patients with FCD visible at MRI. The present pilot study has limitations. Assessment of occurrence of seizures in the 24 h prior to the MRI was based on self-report. Therefor, we cannot be absolutely sure not to have recorded post-ictal changes. However, in the context of a pilot study it was not acceptable to hospitalize the patients 24 h prior to the MRI. Furthermore, even though Simister et al. (2007) found 1H-MRS to be sensitive to metabolite changes following epileptic seizures within the immediate post-ictal period the individual NAAt and NAAt/Cr levels did not change significantly between studies directly post-ictal as compared to 7 h post-ictal. We did not correct for age even though it is shown that concentrations and ratios change with age (Angelie 2001). We compared ipsi and contra lateral side in the same patient. As far as we could investigate patients have had no other brain injuries or diseases. Concentration changes due to aging are presumed to be symmetrical. Therefor, any asymmetry can be attributed to the epilepsy or the FCD. Concentrations of Cr are more or less equal in all brain regions including ‘‘epileptic’’ brain tissue and are stable, even in epilepsy (Peeling, 1992; Peeling and Sutherland 1993; Kauppinen and Williams 1994; Cross 1996; Cendes 1997). There are also indications that Cr concentration in grey matter is higher than in white matter (Pouwels and Frahm 1998). Furthermore, cerebrospinal fluid (CSF) is considered to provide negligible signal (Lynch 1993). Unfortunately, at present we are not able to perform segmentation on single voxel MRS data. While placing the voxels we took care to include as equal as possible amounts of all three components in each voxel within the same patient. Positioning of a voxel over the MEG indicated region means that most of the time the voxel is placed very close to the convexity of the brain. Closer to the convexity, however, it is more likely that there is an effect of the skull on the SV-MRS resulting in a lower SNR. Therefor, the gain of using a

single voxel instead of CSI could be lost again. In our MEG-group, despite a second recording (but not a third) we did not succeed in getting a reliable MRS-spectrum on both sides in 3 out of 9 patients. In FCD this is less of a problem as most in our group have a tail going from the dysplasia to the ventricle, allowing for a less lateralised positioning of the voxel. We choose to use the ratios to Cr as our standard. Quantitative analysis of concentration would give a better insight. There is, however, still too much uncertainty about the viability of the different methods of quantitative analysis (Jansen 2006). We therefor decided against using these methods at this stage. It is likely that results of SV-MRS in epilepsy patients will have a normal distribution. If this is so, the use of an unpaired *t*-test would be appropriate in this study, resulting in more outspoken significance levels. However, as our sample size is too small to prove a Gaussian distribution we decided to use the Mann—Whitney test, also resulting in significant results. It has been reported that in patients with temporal lobe epilepsy the temporal MRS spectrum ipsilateral to the seizure focus displays a significant increase in total Cr (and also Cho) (Connelly 1994). Similar conclusions were drawn in studies on frontal lobe epilepsy (Lundbom 2001). NAA concentration is considered to be a rather nonspecific marker of neuroaxonal integrity and is decreased in a wide range of diseases (Bizzi 2005). Combining these data the NAA/Cr ratio on the affected site is expected to decrease dramatically in epileptic patients. However, we found only a modest decrease in NAA/Cr lateralisation index. Our data does not support the aforementioned ipsilateral versus unilateral Cr decrease. Although we found a decreased lateralisation index in NAA/Cr ratio in the region of the FCD, which is in agreement with the findings of Munakata et al. (2003), the decrease is less pronounced than the decreases found by Munakata et al. A reason might be the distinct references used. Munakata et al. used a remote part of

the contralateral cortex. As there are regional differences we decided to use for control the homologue contralateral cortex. Even although we thoroughly screened for other regions displaying cortical dysplasia in our patients there might have been contralateral FCD below detection threshold. This statement, however, is highly speculative. Furthermore, none of the patients included in this study was recruited from the presurgical group, in order not to give them any false hope. We expect the differences found to be more outspoken in presurgical patients, because our patient group includes less severe epilepsies than in the presurgical group. The lower NAA/Cr ratio on the location where MEG predicts an epileptogenic lesion provides extra support for the localization of the epileptogenic focus. However, it does not prove there is FCD at the investigated region. Our findings do agree with an earlier study on metabolic disturbances in epileptic patients without MRI abnormalities and/or with a focal lesion (Lundbom 2001). It is an indication that there is neuronal damage in that region. Bearing in mind that metabolite changes in FCD are evidently less pronounced than in low grade gliomas (Vuori 2004), combined with the fact that there were no significant differences in lateralisation index profile in the FCD and MEG group it is appealing to postulate that our findings in MRI negative patients could suggest the presence of FCD. Further study of this method in MRI-negative patients in the presurgical evaluation will be carried out and will provide us with a correlation with a histopathological substrate. However, MEG guided SV 1HMRS does seem to be helpful in determining the presence of an epileptogenic focus.

Chapter 4.2

3T versus 7T

4.2.1 FCD

Detection superiority of 7T MRI protocol in patients with epilepsy and suspected focal cortical dysplasia.

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Abstract

In 11 adult patients with suspicion of Focal cortical dysplasia (FCD) on 1.5T (n=1) or 3T (n=10) magnetic resonance imaging (MRI), 7T MRI was performed. Visibility, extent, morphological features and delineation were independently rated and subsequently discussed by three observers. Additionally, head-to-head comparisons with corresponding 3T images were made in the eight patients with a previous 3T MRI and sustained suspicion of FCD. Comparison with histopathology was done in the five patients that underwent surgery. All lesions, seen at 1.5T and 3T, were also recognized on 7T. At 7T FLAIR highlighted the FCD-like lesions best, whereas T2 and T2* were deemed better suited to review structure and extent of the lesion. Image quality with the used 7T MRI setup was higher than the quality with the used 3T MRI setup. In 2 out of ten patients diagnosis changed, in one after re-evaluation of the images, and in the other based on histopathology.

With the used 7T MRI setup, FCD-like lesions can be detected with more confidence and detail as compared to lower field strength. However, concordance between radiologic diagnosis and final diagnosis seems to be lower than expected.

Keywords: 7T MRI, Focal Cortical Dysplasia, Epilepsy, human, misdiagnosis

Introduction

20-40% of epilepsy patients are drug resistant. In this group resective surgery, if possible, is the treatment of choice [Cockerell 1995, Kwan 2000]. Finding a lesion on Magnetic Resonance Imaging (MRI) is of clinical importance, as presence of a lesion is associated with a higher chance of developing drug resistant (refractory) epilepsy [Yoon 2011] and increased success rate of surgery [Bien 2009, Oster 2012, Rowland 2012]. Sensitivity of MRI for brain lesions partly depends on the system's magnetic field strength [Von Oertzen 2002, Knake 2005, Phal 2008, Strandberg 2008, Mellerio 2014, Tselikas 2015]. Higher field strength gives rise to higher signal-to-noise ratio, which allows for higher anatomical resolution and increased sensitivity for contrast mechanisms such as those based on iron [Li 2006, Kwan 2012, Fukunaga 2010, Conijn 2011, Yao 2012, Van Veluw 2013]. Most studies in epilepsy patients have been performed using 1.5 and 3T MRI systems. MRI systems operating at a magnetic field strength of 7T may have added value for epilepsy patients [Breyer 2010] especially because they may have a higher sensitivity for focal cortical dysplasia (FCD) and decrease the number of MRI-occult FCDs. In surgical series, FCD is a common pathologic finding with a reported presence in 8% [Alexiou 2009] to 53% of the operated epileptic patients [Piao 2010]. 20-30% of patients with postsurgical proven FCD were MRI-negative [Tassi 2002, Krsek 2008, Yoon 2011]. No systematic comparison between 3T MRI and 7T MRI appearance of FCD is available. On the other hand, MRI diagnosis of FCD can be erroneous. FCD's can be hard to distinguish from gliomas, with a preference for FCD on frontal locations or a lesser distinct high intensity on T2 weighted images than in case of glioma [Abdel Razek 2009].

The most frequently described MRI features of FCD include: increased cortical thickness, blurred grey/white matter junction, increased signal on T2, decreased signal on T1 of the subcortical white matter and gyration anomalies [Tassi 2002, Krsek 2008]. The most typical feature highly specific for FCD type II is alteration of white matter signal towards the ventricle, the “transmantle sign” [Colombo 2012]. Presence of a focal lesion (e.g. mesiotemporal sclerosis) combined with FCD defines FCD type III. FCD can be characterised by combinations of several of the above mentioned MRI features [Blümcke 2011]. In many patients only a subset of these MRI features are detected [Blümcke 2011].

As presentation of an abnormality can be dependent on the field strength, we wanted to study the presentation on 7T MRI of FCD’s previously described on lower field strength MRI. Furthermore findings on 3T MRI if available were compared to the appearance at 7T MRI and radiologic diagnosis was compared to histopathology in operated cases.

Methods

Ten adult patients, diagnosed with localization related epilepsy and presence of a lesion diagnosed as FCD on 3T (n=9) or 1.5T (n=1) MRI, were included (patient characteristics: table 1). An additional patient (Patient 5) was excluded from further analysis as due to technical failure on 7T MRI the signal-to-noise ratio was too low. All lesions were located extra-temporal, one with temporal extension and one with dual pathology. Standard MRI exclusion criteria were applied. Presence of a dental retainer wire was added as a 7T-specific MRI exclusion criterion. At present this is

not an exclusion criterion any more [Wezel 2014]. Informed consent was obtained from all individual participants included in the study. The study was approved by the Institutional Review Board of LUMC (Leiden Universitair Medisch Centrum).

patient	age	sexe	Location of FCD on previous MRI	semiology
1	34	M	Right frontal	Conscious, forced head version to right followed by secondary generalisation
2	22	M	Left parietal	Short lasting: light headedness, goosebumps, staring, incorrect answers, bilateral manual automatisms
3	25	V	left frontal	Stretching right arm and inability to speak
4	44	M	Left temporo-occipital	Lowered consciousness, automatisms, wandering
5	47	M	Left parietal	Nightly symmetric or asymmetric tonic contractions or very brief myoclonias
6	21	M	Right parietal	Visual hallucinations, lowered consciousness, hypermotor behaviour
7	47	V	Right hand knob	Pounding sensation left thumb, painfull contraction left hand
8	20	M	Left occipital	Sensation of mouth movement, inability to speak, problems with co-ordination. If secondary generalisation then post-ictal visual disturbances
9	34	M	Left parietal	Vibrating sensation right face, sensation of falling to the right (actually going to the left), raising right arm, staring. Fully conscious.
10	36	V	Left parietal	1) Sensation of jaw cramp, tingeling gums, hypersalivation, aphasia 2) short epigastric aura, tonic contraction right arm, secondary generalisation
11	43	V	Right frontal	1) cephalic sensation, fear, sensation of short of breath 2) during sleep head turning to left, orofacial automatisms and/or bipedaling and/or hypertonia left arm

Table 1: Patient characteristics of patients with signs of FCD on prior MRI.

7T MRI was performed on a Philips Achieva platform (Philips Healthcare, Cleveland, Ohio) using a 32 channel receive head coil with quadrature transmit. The following sequences were used: 3D T1 (TR 4.2 ms, TE 1.88 ms, voxel-size 0.9x0.9x0.9mm), 3D FLAIR (TR 7900 ms, TE 300 ms, TI 2200 ms, voxel-size 0.85x0.85x0.85mm), T2 TSE (TR 3000 ms, TE 58 ms, voxel-size 0.5x0.5x1mm) and T2* (TR 1764 ms, TE 25ms, voxel-size 0.24x0.24x1 mm). Total acquisition time was under one hour, which was considered acceptable for possible future use in clinical practice. The 3T MRI images were acquired using a 16 channel receive head coil and a state-of-the-art epilepsy protocol (3D-T1 (TR 8.1 ms, TE 3.7 ms, voxel 1x1x1 mm), T2 (TR 3000 ms, TE 80 ms, voxel 0.5x0.5x5 mm), T2* in the last 5 patients (TR 777 ms, TE 16 ms, voxel 0.9x1.1x5 mm), IR (TR 120 ms, TE 10 ms, TI 400 ms, voxel 0.4x0.6x2 mm), FLAIR (TR 8000 ms, TE 50 ms, TI 2400 ms, voxel 1.1x1.1x0.5 mm)) performed on a Philips 3.0T Achieva platform (Philips Medical systems, Best, Netherlands). Diagnosis of FCD was made by an experienced neuroradiologist in a tertiary epilepsy centre (PH). In one patient only 1.5T MRI, made in a referring hospital, was available; since this 1.5T MRI examination showed clearly an FCD, additional 3T MRI was deemed unnecessary.

Patient charts were examined by two neurologists (AC, LW), with experience in analysing patients for epilepsy surgery. Based on medical history, semiology, EEG, and if available seizure-recordings clinical estimation of the location of the epileptogenic focus was formulated. If the patient underwent surgery data on histopathology were noted. Data were compared to the MRI results.

Two experienced neuroradiologists (MvB, PH) and a neurologist (AC) visually inspected the images.

All observers were aware of the presence of a MRI-detectable lesion. Windowing was individually adapted to gain optimal contrast. Orientation of slides with the highest visibility of the abnormality was chosen separately for each field strength. Presence and characteristics of a possible FCD (see table 2) were noted using a predefined scoring system. Seven features were scored: blurring of the grey-white matter junction, focal thickening of the cortex, focal increased intensity, presence of a transmantle sign, clear demarcation of transition to normal cortex, gyral pattern and abnormal Internal structure. A flag-like appearance of the FCD was noted in several patients This characteristic was added to the study.

In 8 patients with a 3T MRI and a sustained pre-operatieve diagnosis of FCD the features of the FCD on T2 and FLAIR images were rated for visibility using a Likert scale from 1 to 3 [Likert 1932]: 1 indicating 7T superior to 3T, 2 equal quality, and 3 indicating 3T superior to 7T. Comparison was made between the same sequences using a Sign test (http://www.fon.hum.uva.nl/Service/Statistics/Sign_Test.html). Non-difference was set as the null hypothesis. As T2* was not available in all 3T MRIs no comparison between T2* on 7T and on 3T sequence was made.

Results

In none of the patients abnormalities were found on 7T MRI that were not observed at lower field strength and all lesions visible at lower field strength were visible at 7T.

In the ten analysed patients, both neurologists agreed that the stereotyped seizures were based on a single epileptogenic focus. In each patient one or more hypotheses on the possible locations of this epileptogenic focus could be postulated. Comparison between these hypotheses and the location of the lesion on MRI showed concordance in each individual patient.

By visual inspection in all patients the lesion was detected on 7T MRI without prior knowledge of the location as seen at lower field strength. In patient 1 the diagnosis changed from FCD to cavernoma based on the 7T MRI and re-evaluation of the 3T images. The treating physician was informed. Further visual analysis of the 7T MRI was done for the remaining nine patients.

On the T1-weighted images cortical thickening and blurring were most prominent (figure 1). A hypo-intense line at the grey-white matter junction was observed on T2 weighted images (figure 2) in eight patients creating a typical three layer flag-like appearance. Detection of the FCD was readily made on the FLAIR images (figure 3), whereas the abnormal internal structure of FCDs was most clearly seen on T2* (figure 4). Of the seven imaging features, four (blurring of grey-white matter, focal signal increase, visibility of transition to normal cortex, abnormal internal structure) were observed in all nine patients. Focal thickening was observed in eight patients, funnel shaped extension in and the presence of an abnormal gyral pattern in six patients (table 2). The flag-like appearance was noted in all but patient 3.

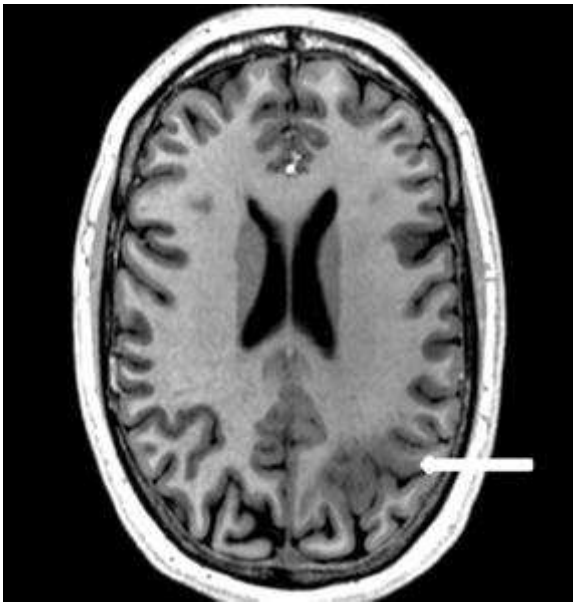


Fig. 1

7 T T1 image showing cortical thickening and blurring

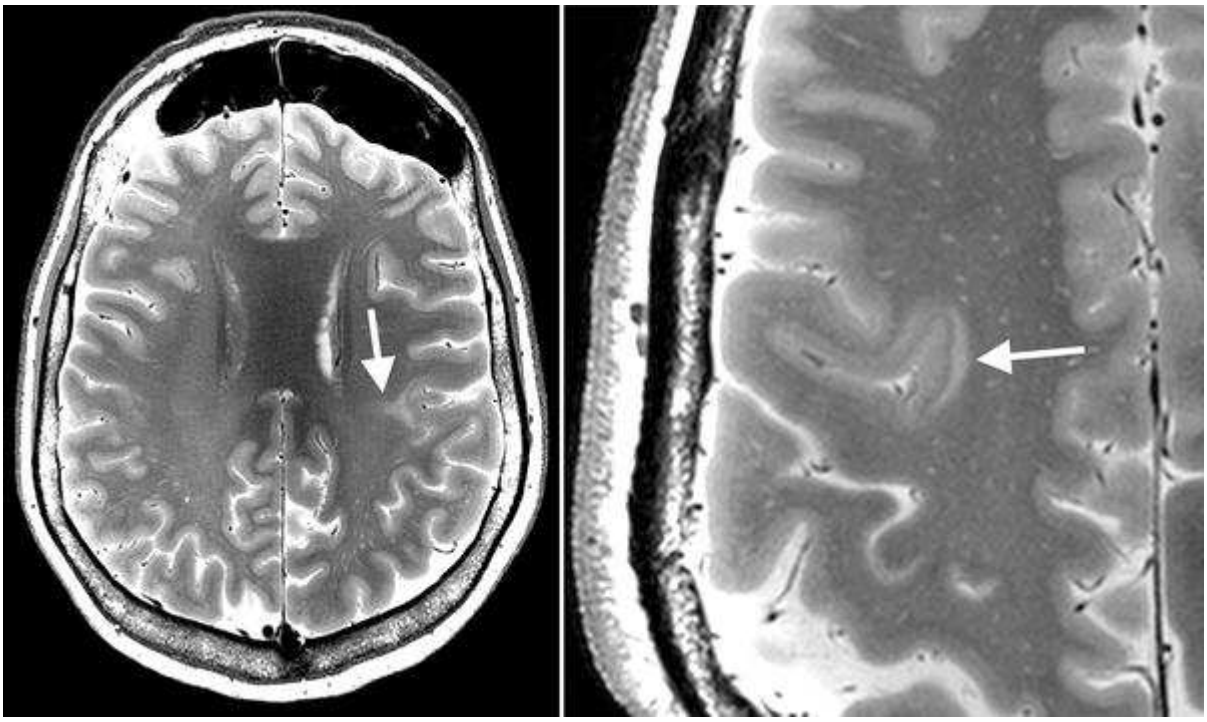


Fig. 2

7 T T2 image showing cortical thickning, transmantle sign (left) and flag-like appearence at the bottom of the sulcus in FCD (right more pronounced than left)

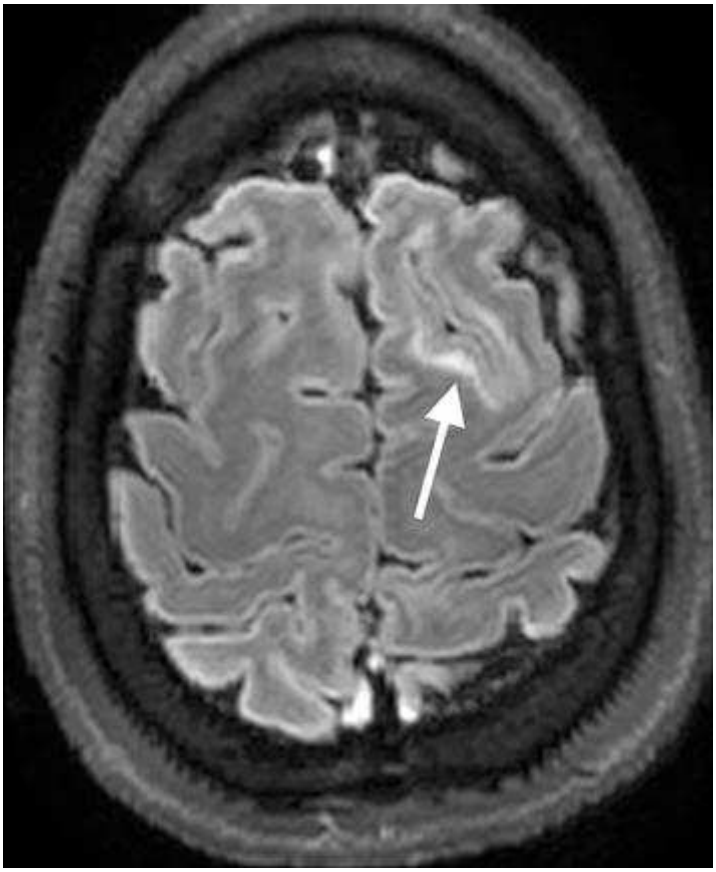


Fig. 3

7 T FLAIR image, showing highlighted FCD

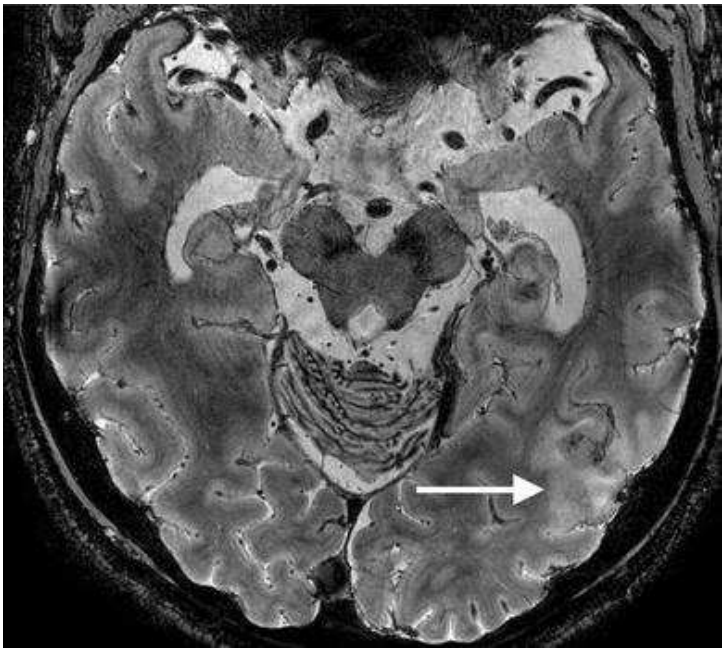


Fig. 4

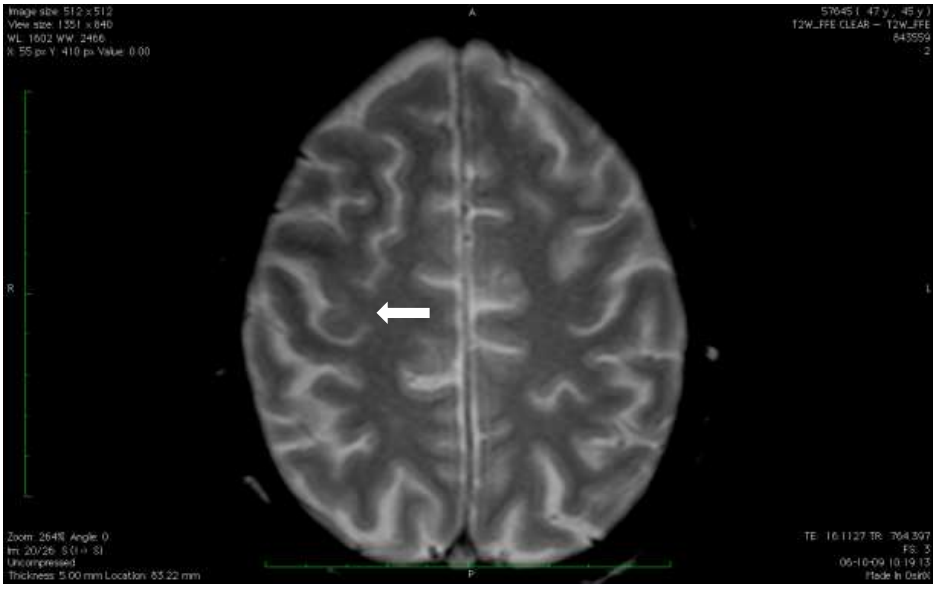
7 T T2* image showing abnormal internal structure of FCD

Patient	2	3	4	6	7	8	9	10	11	Overall
Blurring	+	+	+	+	+	+	+	+	+	9/9
Focal thickening	+	+	+	+	-	+	+	+	+	8/9
Focal increased intensity	+	+	+	+	+	+	+	+	+	9/9
Transmantle sign	-	+	-	-	+	+	+	+	+	6/9
Transition to normal cortex	v	s	s	s	v	s	s	s	s	2 vague, 7 sharp
Gyral pattern	norm	abn	abn	abn	norm	norm	abn	abn	abn	6/9
Abnormal Internal structure	+	+	+	+	+	+	+	+	+	9/9
Total	4/7	7/7	6/7	6/7	4/7	6/7	7/7	7/7	7/7	

Table 2: features of FCD recognized on 7T MRI, all sequences combined. +=present, -=not visible, v=vague, s=scharp, norm=normal, abn=abnormal

In the eight patients in whom 3T MRI was available, 7T MRI depiction scored significantly better than 3T MRI for blurring ($p<0.01$), abnormalities of internal structure ($p<0.01$) and demarcation of transition to normal cortex ($p<0.02$) (figure 5) on T2 and for abnormalities of internal structure ($p<0.04$) on FLAIR.

Although not statistically significant, 7T MRI tended to be superior to 3T on another 7 out of 14 scored items (2 sequences compared, with 7 features analysed in each comparison) 3T MRI tended to be superior to 7T on none of the 14 items (table 3). When combining all 7 analysed characteristics on T2 and FLAIR in each individual patient, 7T scored better than 3T (table 4).



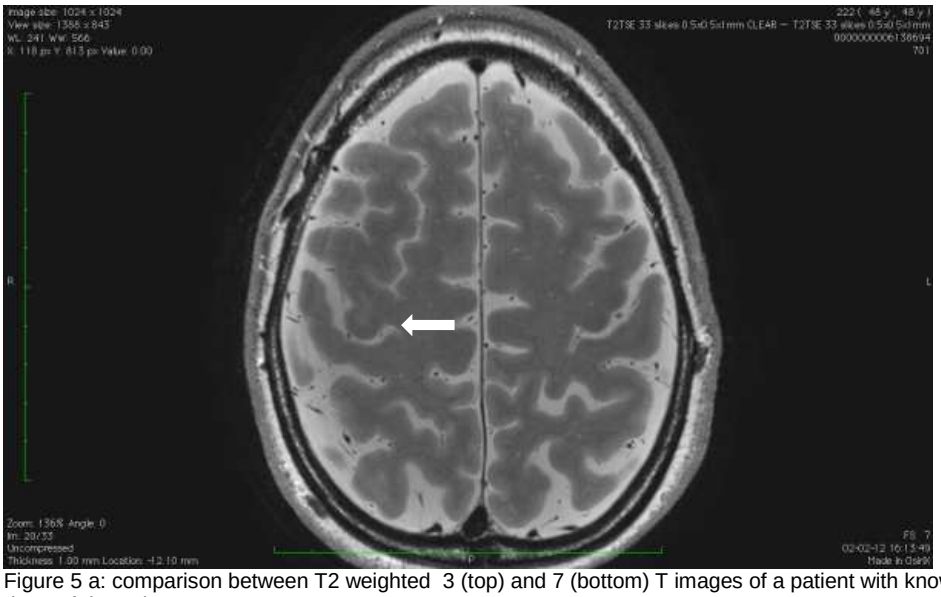


Figure 5 a: comparison between T2 weighted 3 (top) and 7 (bottom) T images of a patient with known FCD right hand knob to deep-of-the-sulcus

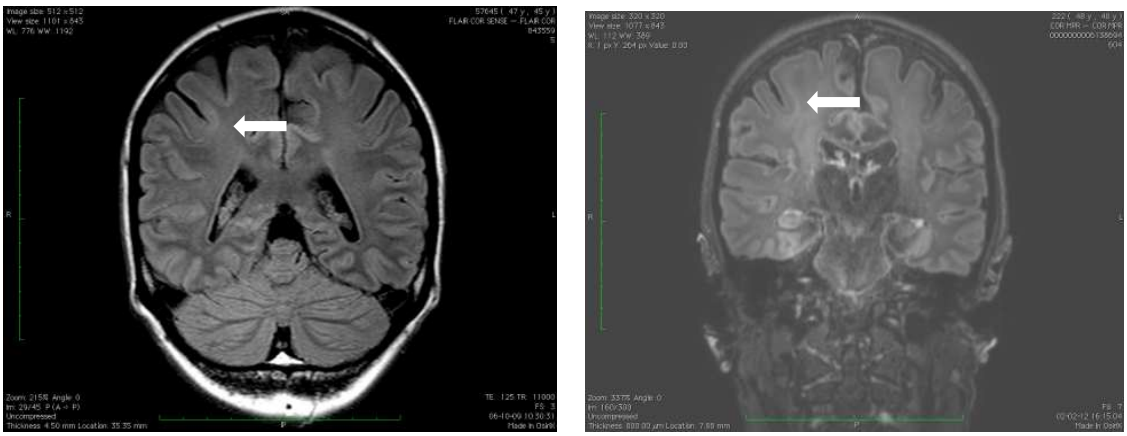


Fig. 5 b . same patient: comparison between FLAIR 3 (left) and 7 (right) T images of a patient with known FCD right hand knob to deep-of-the-sulcus

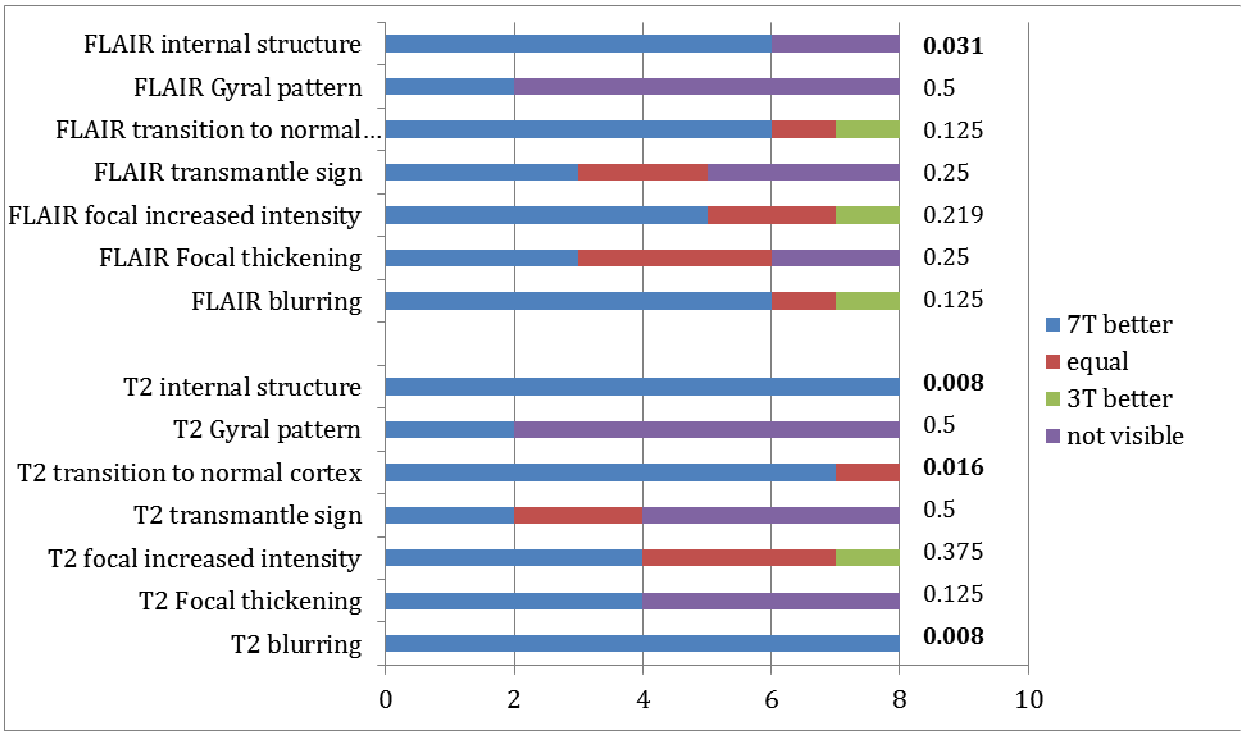


Table 3 : Conventional Visual Analysis of 3 vs 7 T images.

Blue: 7T superior to 3T. Red: 7T and 3T equal. Green: 3T superior to 7T. Purple: feature not visible.

Last column: p-values Sign Test, significant values in **fat**.

Patient	2	3	4	6	7	8	10	11	7T better:3T better
Blurring T2	1	1	1	1	1	1	1	1	8/8:0/8
Focal thickening T2	Na	0	1	1	Na	1	1	0	4/6 :0/6 (na :2)
Focal increased intensity T2	1	0	1	1	1	0	0	-1	4/8:1/8
Transmantle sign T2	Na	0	Na	Na	Na	0	1	1	2/4:0/4 (na: 4)
Transition to normal cortex T2	1	1	1	1	1	1	1	0	7/8:0/8
Gyral pattern T2	Na	Na	1	1	Na	Na	Na	Na	2/2 (na: 6)
Internal structure T2	1	1	1	1	1	1	1	1	8/8:0/8
Blurring FLAIR	-1	0	1	1	1	1	1	1	6/8:1/8
Focal thickening FLAIR	Na	0	1	1	Na	1	0	0	3/6:0/6 (na: 2)
Focal increased intensity FLAIR	-1	0	1	1	1	1	1	0	5/8:1/8
Transmantle sign FLAIR	Na	1	Na	Na	0	0	1	1	3/5:0/5 (na: 3)
Transition to normal cortex FLAIR	-1	1	1	1	1	1	1	W 7T, G 3T (1)	6*/8:1*/8
Gyral pattern FLAIR	Na	Na	1	1	Na	Na	Na	na	2/2 :0/2 (na: 6)
Internal structure FLAIR	na	Na	1	1	1	1	1	1	6/6 :0/6 (na: 2)
Total 7T better than 3T	4/7	5/11	12/12	12/12	8/9	9/12	10/12	6/11*	
Total 3T better than 7T	3/7	0/11	0/12	0/12	0/9	0/12	0/12	1/11*	
Total not applicable	7	3	2	2	5	2	2	2*	

Table 4: comparison between 3T and 7T MRI's combining all characteristic on T2 and FLAIR. -1: 3T better than 7T, 0: equaly visible on 3T and 7T, 1: 7T better than 3T, na: Not applicable as not visible on either 7T or 3T, W: white matter, G: gray matter. *: excluding patient 11 transition to normal cortex on FLAIR

Five of the six included patients that were also evaluated for epilepsy surgery were operated. In patient 3 histopathology showed a ganglioglioma WHO grade 1, patient 8 had FCD type IIIb (frontal infantile desmoplastic ganglioglioma with bordering FCD operated plus parietal FCD that we analysed in this study), patient 9 showed a FCD type IIa and patients 10 and 11 showed a FCD type IIb. The location of the lesion

was congruent between MRI and surgical specimen. The 3T MRI and 7T MRI images of the 2 patients in whom the diagnosis changed from FCD to respectively cavernoma and ganglioglioma are shown in figure 6.

One patient complained of profound nausea at entering the MRI. Slowing down the table movement reduced the symptoms. During the imaging this complaint was not present.

Discussion

The main finding of this study is that all observers agreed that on conventional visual analysis the lesions were easier detected and better detailed with the applied 7T MRI protocol than on lower field strength. None of the known lesions were missed on the 7T images. Using a semi-quantitative scale, overall our 7T MRI protocol tended to be superior to the previously applied 3T protocol. Statistical significance was reached for 4 out of 14 scored items. In two patients final diagnosis changed from FCD to respectively cavernoma and gangioglioma

As far as we know this is the first publication describing 7T MRI in a group of patients with suspicion of FCD using a standard clinical protocol.

In one patient, due to the 7T images diagnosis changed from FCD to cavernoma. There are several explanations possible for this change. First, due to slice thickness in the 3T images the small hemosiderin deposit could have been located exactly in between 2 slices, thus escaping detection. Due to the thinner slice thickness of the 7T images, the hemosiderin is more obvious. The images as depicted in figure 6 seems to substantiate this hypothesis. Second, the artefact effect of hemosiderin is

more pronounced on 7T MRI than on 3T MRI, thereby highlighting the cavernoma more evidently in 7T MRI. The sequence most sensitive for hemosiderin is SWI (susceptibility weighted imaging). However, in epilepsy the presence of small hemosiderin deposits is of minor relevance and therefor in the initial phase of our study this swquence was not part of our standard epilepsy protocol. This will have lowered the sensitivity for the detection of small haemorrhages on the 3T MRI more than the sensitivity of 7T MRI. Especially compared to 7T MRI, in which a T2* weighted sequence was part of the standard protocol. Third, there is a time delay of several months between these 3T and 7T MRI's. Although there were no additional clinical symptoms, it is possible that in between these time points the amount of blood surrounding the cavernoma increased. As the patient is no longer under our care we regrettably do not have access to a 3T MRI made after the 7T MRI.

In one of the five operated cases histopathology showed that the abnormality was a ganglioglioma instead of a FCD type II as the radiological diagnosis stated. Re-challenging of three pathologists and two radiologists with information on the opinion of the other specialist did not change their conclusions. Taking the diagnosis of the pathologists as gold standard, this proves that MRI can help giving an indication of the diagnosis. But visual inspection is not (yet) able to provide the definite diagnosis with 100% certainty. Noteworthy is the fact that in this patient (patient 3) *all* evaluated MRI-characteristics of FCD were present, including a transmantle sign (fig 6).

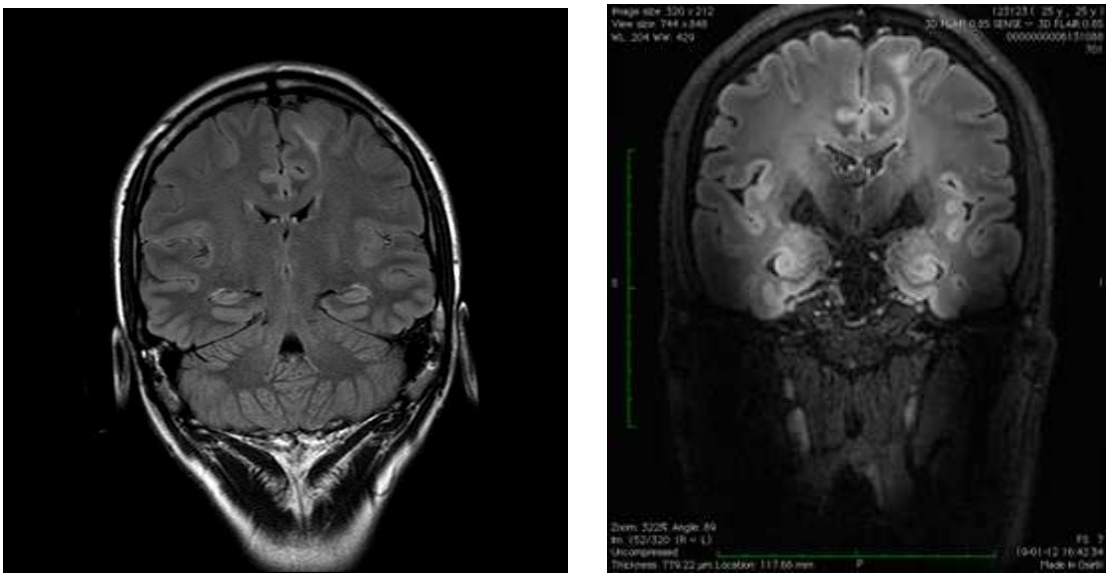


Fig 6: changed diagnoses from original (FCD) to ganglioma. left: 3T MRI. right: 7T MRI.

The frequency of the imaging features of FCDs as seen in our study is higher than reported for FCD in the literature for 1.5T and 3T studies. For example cortical thickening was seen in 50% [Krsek 2009] to 76% [Lerner 2009] whereas in our series it is 89%. Blurring ranged from 36% [Urbach 2002] to 87% [Colombo 2003], whereas in our series it is 100%. For transmantle sign this ranged from 19% [Besson 2008] to 81% [Urbach 2002], and in our series it is 67%. Most publications are based on histopathologically proven diagnoses of FCD, including patients without MRI abnormalities, whereas for our study the suspicion of a FCD on lower field strength MRI was an inclusion criterion. This explains the relative high frequency of the imaging features in our series. Quality of the 7T MRI images itself plays a role as well: signal-to-noise ratio scales approximately linear with magnetic field strength [Van der Kolk 2012, Versluis 2012]. Furthermore, it has also been observed that 7T MRI provides an increased contrast-to-noise ratio in FLAIR as compared to 1.5T and 3T [Li 2006, Zwanenburg 2010]. The smaller voxels that can be achieved with 7T MRI within a clinically applicable protocol will also provide better spatial resolution,

leading to the detection of thin abnormalities, such as blurring or the transmantle sign.

Other limitations of the current studies include the fact that, besides the magnetic field strength, the scanners differed with respect to other hardware such as the number of receive channels of the head-coil and that choices of sequence parameters were based on local expertise without an effort to homogenize these between the field strengths. Comparisons were made between acquisitions made on the scanners available to us, which led to inherent differences in receive and transmit coil properties, other hardware components as well as software. Using, for example, a 32-channel head coil for the 3 T might have improved image quality on that field strength. However, based on our experience with both field strengths we think that magnetic field strength is the main contributor to the improved image quality.

Applying visual analysis, in our series 7T MRI FLAIR was the sequence on which the lesions were most prominent. The flag-like three-layer appearance is easiest appreciated on T2. The middle hypo-intense line is accentuated by the bordering hyper-intense parts of the lesions. However, even though much less pronounced, looking at the homologue contralateral area this line often is bilaterally noticeable. The appearance of this line is not equally distributed in all different regions, which is in line with the findings of Zwanenburg et al [2012] who described similar regional differences (but no asymmetries) in the normal brain in 7T MRI. The line is located at the grey-white matter junction and is present in almost all regions, and therefor it does not represent the striae of Gennari [Gennari 1782]. Based on our small series, this line seems to be more prominent with rising age, even more in the FCD-like

region than in the other regions of the brain. We postulate that this line represents iron deposits which would explain an age-dependency [Hagemeier 2012]. Alternatively, this line could represent a low signal coming from the deepest cortical layer, seen on thin 7T slices but masked on thicker 3T slices. In 7T MRI this accentuated three-layer appearance on the T2 weighted images has the potential to be used as an imaging marker of FCD. The internal structure and extend of the lesions were best visible on T2 and especially T2* sequences. This is in line with expectations, as the T2* sequence provides high spatial resolution and sensitivity to the magnetic susceptibility properties of tissues, thus improving evaluation of the different components within the cortex. When in more cases histopathology will become available, this might help in differentiating between different pathological substrates, like the different types of FCD.

Although due to the nature of this study we did not co-register all the sequences of 3T and 7T study, visual inspection and interpretation support the notion that on 7T the lesion seemed often to extends beyond what is seen on 3T.

Because of the better delineation of lesions on 7T, if intracranial EEG recording is needed we would advise to use the T2 sequence to guide the implantation. Especially in case of multiple depth-electrodes (Stereo-EEG) where presurgical delineation of the abnormality is even more dependant on electrode placing than when using grids.

In epilepsy, abnormalities observed on MRI do not always reflect the epileptogenic focus. This is illustrated by the observation of Salmenpera et al [2007] that 9% of 3T

MRI-positive findings are not related to the epileptogenic lesion. Therefor, every positive MRI result should be interpreted with caution and in combination with the electro clinical findings. However, clinical assessment based on the intra-individual stereotyped semiology makes it likely that all our patients had a single epileptogenic focus, correlating well with the observed location of the lesion. Interpretation of MRI should only be done including all clinical information available. This holds true for all other modalities such as PET, MEG and intracranial EEG as well. Probably, multimodality fusion will increase insight in analysing difficult surgery cases. The limitation of our study is that we included only patients with a diagnosis of FCD based on 3T or 1.5T MRI and only three patients had a histologically proven diagnosis. Further studies will evaluate the additional value of 7T MRI in presurgical analysis in patients without abnormalities on 3T MRI. There is one study on the detectability of FCD's on 7T MRI in 21 patients without lesions on 3T or 1.5T MRI, showing a 29% diagnostic gain [De Ciantis 2016]. Agreement in imaging interpretation was reached through consensus-based discussions based on visual identification of structural abnormalities. Four out of the 6 patients with a thus detected lesion were operated, all showing a FCD on histopathology. These results are almost identical to our own results [Colon 2016].

Conclusion

7T brain imaging in vivo is feasible in epilepsy patients and can be beneficial. Lesions are well recognizable and details are better visible than at lower field strengths. The presence of typical FCD-characteristics on MRI, however, does not always reflect the final histopathological diagnosis.

4.2.2 MEG-guided 7T MRI in 3T MRI negative patients

MEG-guided analysis of 7T-MRI in patients with epilepsy

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Abstract

Aim: To study possible detection of structural abnormalities on 7T MRI that were not detected on 3T MRI and estimate the added value of MEG-guidance. For abnormalities found, analysis of convergence between clinical, MEG and 7T MRI localization of suspected epileptogenic foci.

Methods: In adult patients with well-documented localization-related epilepsy in whom a previous 3T MRI did not demonstrate an epileptogenic lesion but MEG indicated a plausible epileptogenic focus, 7T MRI was performed. Based on semiologic data, visual analysis of the 7T images was performed as well as based on prior MEG results. Correlation with other data from the patient charts, for as far as these were available, was analysed. To establish the level of concordance between the three observers the generalized or Fleiss kappa was calculated.

Results: In 3/19 patients abnormalities that, based on semiology, could plausibly represent an epileptogenic lesion were detected using 7T MRI. In an additional 3/19 an abnormality was detected after MEG-guidance. However, in these later cases there was no concordance among the three observers with regard to the presence of a structural abnormality. In one of these three cases intracranial recording was performed, proving the possible abnormality on 7T MRI to be the epileptogenic focus.

Conclusions: In 32% of patients 7T MRI showed abnormalities that could indicate an epileptogenic lesion whereas previous 3T MRI did not, especially when visual inspection was guided by the presence of focal interictal MEG abnormalities.

INTRODUCTION

Epilepsy has an estimated prevalence of 0.4 to 1.4% (WHO 2015). At least 61% of the patients diagnosed with epilepsy suffer from localization-related epilepsies (Browne 2000). Approximately 30% of patients with localization-related seizures suffer from refractory epilepsy (Kwan and Brodie 2000). In up to 74% of patients with localization-related seizures, MRI shows no abnormalities (Griffiths et al 2005). In children with epilepsy this is about one-third (Reijs et al 2007). Prognosis for seizure control following focal resection of the epileptogenic zone is excellent (Urbach et al 2002). Identification of a lesion on MRI is a major predictive factor for surgical outcome (Yun et al 2006, Noe et al 2013). The majority of patients suffering from focal seizures of unknown origin (Berg et al 2010) probably have a small focal cortical dysplasia (FCD) (Bautista et al 2003, Barkovich et al 2005). FCD's often escape detection with present imaging techniques (Wang et al 2014), may considerably vary in size and localization (Guerinni et al 2008) and are likely to be located at the bottom of sulci (Besson et al 2008). Using higher field strength MRI more abnormalities can be visualized (Von Oetzen et al 2002, Phal et al 2008). Therefor, 7 T MRI yields the promise of improving detection. In epilepsy patients, ex vivo (Zucca et al 2016) and in vivo 7T MRI examples of FCD in humans are available (De Ciantis et al 2016, Colon et al 2016, Veersema et al 2016).

When an MRI is re-analysed with an a-priori hypothesis more lesions are detected (Moore et al 2002, Itabashi et al 2014). Magnetoencephalography (MEG) is not only a reliable indicator of epilepsy (Colon 2016) but also a powerful tool to determine a

possible epileptogenic focus (Ossenblok 2007, Kharkara 2015) and is of growing presurgical importance in combination with MRI (MRS, magnetic source imaging) (Bagić 2016).

The present study explores the possible role of visual and of MEG-guided visual 7T MRI analysis in improving detection of a possible epileptogenic lesion. The levels of convergence between clinical data, MEG and 7T MRI findings are described.

Methods

Patients were prospectively recruited from the Academic Centre for Epileptology (ACE), location Kempenhaeghe, a tertiary epilepsy centre. Additionally, two patients were referred by another institution (SEIN) to participate in this study. Inclusion criteria included previously diagnosed focal epilepsy, MEG results showing epileptiform abnormalities concordant with semiology (“plausible”), and a 3T-MRI without showing abnormalities that could explain the seizures, despite availability of all other clinical data. Further inclusion criteria included age 18 or above and signed informed consent. Exclusion criteria included pregnancy and being incapacitated. Standard MRI-exclusion criteria applied, including body implants that are not (yet) proven safe at 7T MRI.

Although not an inclusion criterion, all but one patient were included during a period of pre-surgical analysis. Seizure description, MEG results and other auxiliary information on possible locations of the epileptic focus were gathered from the patient charts. If, after analysis of the 7T MRI, a patient was operated upon, data on results of surgery and histopathology were added to the database. The 7T MRI then was re-evaluated by two of the three observers.

Previously performed clinical MEG data (Neuromag 306, Elekta Oy, Helsinki, Finland) had been analysed in an experienced centre (VUmc, Amsterdam, Netherlands) and indicated a plausible epileptogenic focus in all patients. MEG recording time was at least one hour, including eye opening and closing, hyperventilation and rest. Obtaining a recording in sleep was not mandatory. No EEG co-registration was available. Used analysis methods included equivalent current dipole modelling and beamforming analysis. (Baillet 2001, Klink 2016)

The previously performed state-of-the-art 3T MRI (3.0 T Achieva, Philips, Best, The Netherlands) was analysed by an experienced neuroradiologist with special interest in epilepsy, aware of all available data including the MEG results. A voxel-based morphologic analysis program (MAP-07 (Huppertz et al 2008, Wang et al 2015)) was available during part of our study. During this time, patients were only included if MAP-07 did not indicate any abnormalities. In 14 out of the 19 included patients MAP-07 was applied. Used 3T MRI sequences included 3D-T1 (TR 8.1 ms, TE 3.7 ms, voxel 1x1x1 mm), T2 (TR 3000 ms, TE 80 ms, voxel 0.5x0.5x5 mm), T2* (TR 777 ms, TE 16 ms, voxel 0.9x1.1x5 mm), IR (TR 120 ms, TE 10 ms, TI 400 ms, voxel 0.4x0.6x2 mm) and FLAIR (TR 8000 ms, TE 50 ms, TI 2400 ms, voxel 1.1x1.1x0.5 mm) No abnormalities that could account for the particular epilepsy were found.

7T MRI was applied well within the limits of the American Food and Drug Administration (FDA) guidelines. Images were acquired on a Philips 7.0 T Achieva (Philips, Best, The Netherlands) using a 32-channel receive head coil at Leiden University Medical Center (LUMC). The protocol included: 3D T1 (TR 4.2 ms, TE 1.88 ms, voxel 0.9x0.9x0.9mm), 3D FLAIR (TR 8000 ms, TE 300 ms, TI 2200 ms, voxel 0.80x0.84x0.80mm), T2TSE (TR 3000 ms, TE 58 ms, voxel 0.5x0.5x1mm) and

T2* (TR 1764 ms, TE 25ms, voxel 0.24x0.24x1 mm). No specific correction or post-processing techniques were used.

The region of interest (ROI) was determined by semiological data and by localization of epileptiform abnormalities recorded during MEG, projected on a 3D T1 3T MRI.

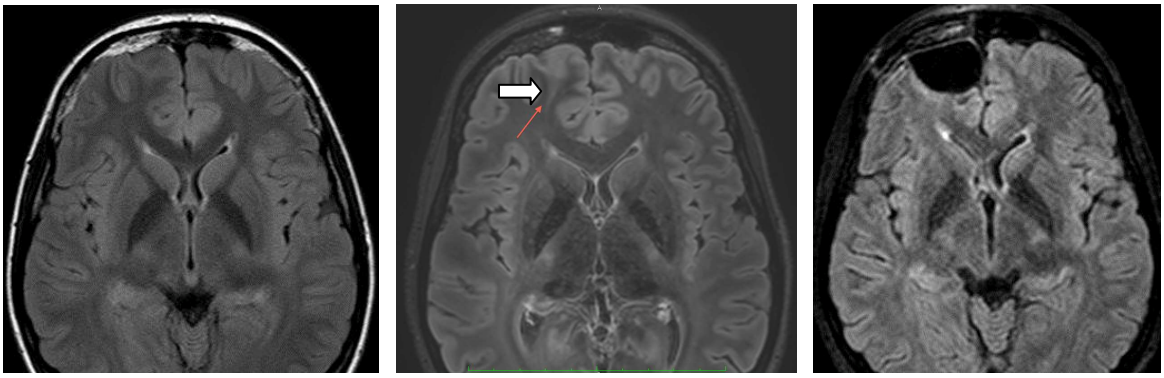
Images were visually assessed by two experienced neuroradiologists and one neurologist specialized in epilepsy. The first assessment was done by these 3 specialists independently of each other, while taking semiologic data into account but without knowledge of the MEG-results. A second assessment was based on visual guidance by MEG. Presence and location of MRI abnormalities were noted and compared to the contralateral site. Finally conclusions by the individual specialists were compared. To establish the level of concordance the generalized or Fleiss kappa was calculated.

In this study, one patient in whom an SEEG recording (Munari et al 1994) was performed before, and five patients in whom an SEEG recording was performed after the 7T MRI were included. In one patient intracranial recording using multiple subdural strips was carried out. Results of the intracranial recordings and results of surgery, when performed, were not available at the time of analysis of the MRI. However, surgical outcome and histological diagnosis were added in a later stage to the database in patients who underwent resective surgery. For patients without abnormalities on the first analysis of 7T MRI but a successful resection, two of the three observers re-evaluated the 7T MRI.

The medical ethical committee of LUMC approved the study protocol. All patients provided informed consent.

Results

Twenty patients were studied. Complete data were obtained in 19 patients (patient and seizure characteristics: table 1). 13 Patients did not show any new abnormalities on 7T MRI as compared to 3T MRI despite MEG-guidance. Of these 13 patients, however, patient 7 showed abundant extensive white matter hyper-intensities, hampering detailed interpretation of the images. In three of the remaining six patients new abnormalities were seen that fitted the clinical epilepsy symptoms by all three observers without prior knowledge of the MEG-findings. All three showed characteristics of FCD type II. In retrospect, one of these three patients also showed discrete signs of FCD on the 3T images (supplementary data fig S1).



Supplementary data Fig S1: Possible FCD after conventional visual analysis missed on 3T MRI (left), but seen on 7T MRI (middle). On the right the post-resection image. Transversal FLAIR images.

Further MEG-guided visual inspection of the 7T MRI data resulted in possible abnormalities in three more patients (fig 1). There was, however, no concordance among the observers in these patients as to the presence of an abnormality. Furthermore, no clear differential diagnosis could be given. Also, in one of the patients in whom semiology guided analysis showed a FCD MEG-guided analysis did

not point to the same location. The generalized or Fleiss kappa between the observers was 0.683.

Patient	gender	Age	Semiology
1	F	45	Undefinable feeling, orofacial automatisms, motionless. Clusters.
2	M	36	Abrupt hyperkinetic movements of all extremities.
3	F	31	1) short lasting unresponsiveness and freezing 2) painful sensation stomach 3) clusters of staring and automatisms.
4	M	33	Headache, orofacial automatisms , lowered consciousness, inconsistent version.
5	M	23	Sometimes auditive aura. Gasping for breath and fast eye blinking. Late in seizure turning to left and lowered consciousness. Provocation by specific sounds possible but not mandatory
6	F	34	Tingling left hand, cramp left hand, hyperkinesias left arm
7	M	65	Shout, bilateralhypertonia changing to clonias. Postictal incoherent speech.
8	M	19	Arousal, clonias both arms, head turning to right
9	M	56	Head version to left, tonic left arm, then leg and face. Preserved consciousness
10	F	49	Arms hyperkinetic, vocalisation, inadequate responses
11	M	29	Tingling right hand, cramp right hand
12	M	27	1) Sensations left arm, than leg, then lowered consciousness and automatisms 2) cramps left arm, secondary generalisation
13	M	32	Feeling warm, dreamy, cramps hands, orofacial automatisms, inability to react, lowered consciousness, fists, stretching arms. Mainly during sleep.
14	F		Strange feeling stomach, feeling of falling through the floor, inability to react
15	F	21	Head version to right, tonic right hemi face
16	M	46	Right arm turns backward while trembling.
17	F	33	1) No grip on her own thoughts 2) clonic movements eyes (sometimes also head) to the right.

18	M	19	1) up to 30s lowered conscience 2) nausea, loss of conscience, peri-oral cramps, making sounds, turning away eyes.
19	F	28	1) fear, turning red, incontinence. 2) Asymmetric cramp arms (L>R), torso flexed, tachypneu, followed by restlessness and manual automatisms
20	M	32	Pre-ictal hyperactive behaviour, then staring, perspiring, lowered conscience, restlessness. Sometimes leading to spastic movements, clonias, foaming mouth, hitting and kicking, tongue bite, grey skin.

Table 1: patient characteristics: gender, age, present semiology.

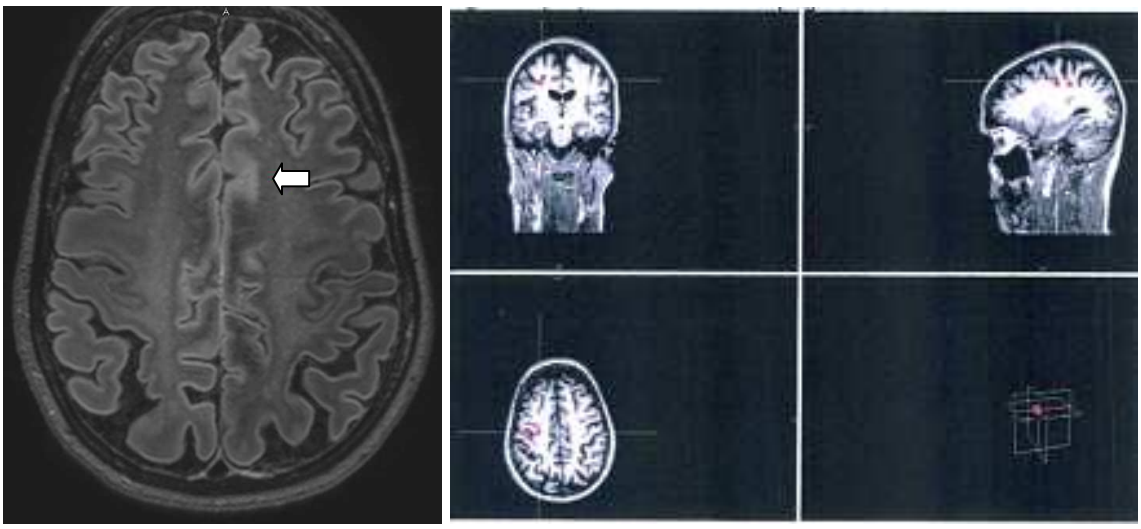


Fig 1: left: Discrete possible abnormality only seen after MEG guidance. Clinical representation (patients left is on the right of the image)

Right: representation on MRI of 5 MEG spikes. Attention: Physicist's representation (patients left is on the left of the image).

In the six patients with (possible) abnormalities on the 7T MRI perfect concordance was found between 7T MRI abnormality and regional location and lateralisation as predicted on clinical grounds. In other words: in these patients, the abnormality found with MRI was localized well within the clinically predicted region. In two patients MEG dipole localizations showed perfect concordance with the MRI abnormality. In three patients MEG dipoles and 7T MRI abnormalities were within each others vicinity but not exactly overlapping. In one patient MEG pointed at an area far away from the

abnormalities seen on 7T MRI. Other investigations, when present, gave mixed results (table 2).

patient	clinic	V-EEG	PET	SPECT	NPT	SEEG	MEG	7T MRI
1	T/F	R>L F/T	R/L T	R/L F/T	-	-	RO, LT	NA
2	LF	F	-	-	-	-	L F	NA
3	F/P/T/I	R	R C-P	-	-	Network, R PTO	R C-P R T	NA
4	T/F	R T	-	-	R	R T (amygdala)	R T	NA
5	R TPO/I	R F/T/I	R T	-	-	-	R T-P	?R I
6	R F-C	Extra-T	R F/T	-	diffuse	R F	R F	R F
7	F	-	-	-	-	-	L T	Multiple
8	L F	L P-O	L T		L	-	L T (F)	NA
9	R	R F-C	-	-	-	R F	R P	R F
10	F	R F	-	P	NA	-	R F L T	R F (old)
11	L F/P-C	-	-	-	-	-	L C	L C
12	R F/P/C/I	R T/C-P/I	R P	-	NA	-	R P	NA
13	F/T/othe rs	-	-	-	-	-	L T	NA
14	P/I/F/T	L T	L T	L F	NA	L F	L C	L F ? (n=1/3)

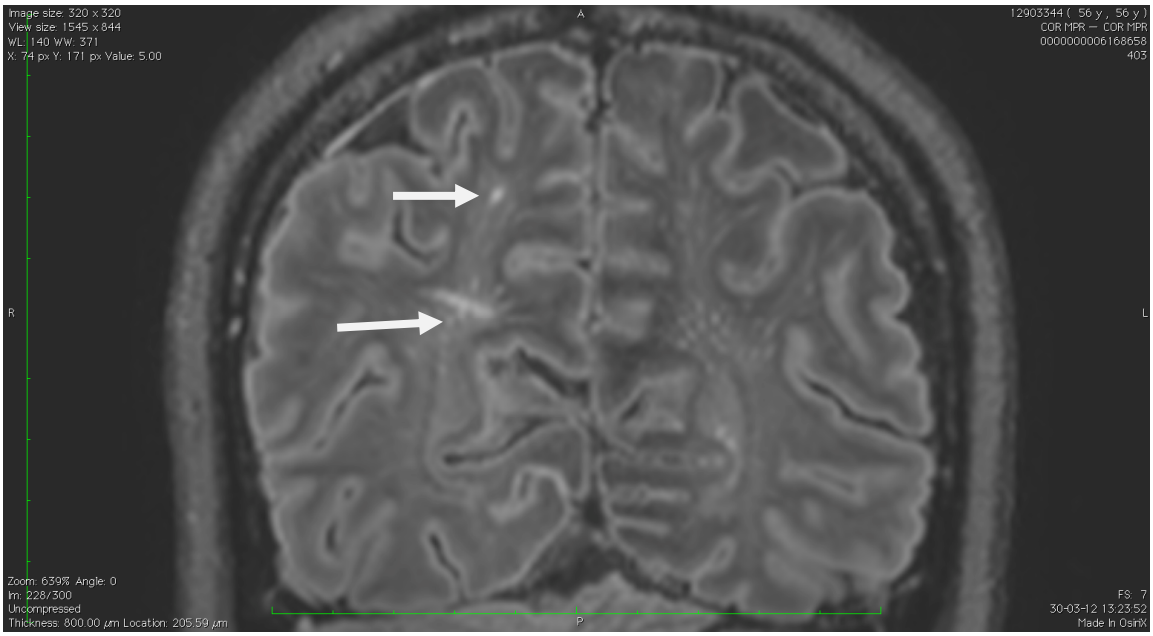
16	L C	L>R C	L I	-	NA	L F (post cingulum)	L C	NA
17	L F	L>R F	NA	LF	NA	-	L F	L F?
18	F	F	L T	-	(R) F	Strips: not on focus. bilateral F and O?	R F/T (associate-analysis: L P/O)	NA
19	F/I	F/O/I	NA	-	-	-	L F	NA
20	F/T/I	(R) F/T/P	NA	-	-	-	L T	NA

Table 2: concordance between localization based on clinical data, V-EEG, SEEG, PET, SPECT, MEG, NPT (neuropsychological testing) and 7T MRI (final conclusion). R: right, L: left, C: central, F: frontal, I: insular, O: occipital, P: parietal, S: parasaggital, T: temporal, TPO: Temporo-parieto-occipital junction, PA: histopathologic diagnosis, -: Not Available. NA: No Abnormalities. ?: no concordance between all 3 observers. Patient 15 did not complete the MRI and is therefor not listed in this table.

In one patient the location of the identified abnormality on 7T MRI influenced the decision not to proceed with presurgical analysis. In five patients MRI information was helpful in proposing an SEEG (n=2) and/or surgical planning, leading to resection in three. This resulted in seizure freedom for two patients and marked seizure reduction in one patient, whereas two patients refrained from continuing presurgical analysis.

Intracranial recordings to prove location of the epileptogenic focus were performed in eight out of the 19 patients: seven patients were analysed with implantation of multiple intracerebral electrodes (SEEG) and one patient with arrays of subdural strips (table 3). Due to the used neurosurgical approaches histopathologic diagnosis could not be obtained in all patients. Two of the SEEG implantations were performed

in patients with a FCD unanimously detected on 7T MRI. Both were operated upon, histopathology showed FCD type II. In one of these two patients SEEG was performed before the 7T MRI was made. Some of the trajectories of the removed electrodes were still visible (Supplementary Data fig S2).



Supplementary Data Fig S2: traces of depth electrodes that were removed 5 weeks before (pat 9)

MEG predicted a right posterior frontal focus, whereas SEEG showed the focus to be more anterior frontal. Subsequent 7T MRI showed possible abnormalities located antero-basal to the most anterior SEEG electrode. The resected area included both the SEEG region and the abnormal region on 7T MRI. One SEEG implantation was performed in a patient with an electrode within the area that was suspicious based on the 7T MRI. (fig 2). Histopathologic diagnosis could not be obtained.

patient	7T MRI	ICR	histopathology	Outcome
3	NA	SEEG: network R	Not available	Not operated
4	NA	SEEG: RT	NA	34 mo seizure free
6	RF	SEEG: RF	FCD IIb	46 mo seizure free
8	NA	SEEG: multifocal	Not available	Not operated
9	RF	SEEG: RF	FCD IIa? (quality of the material obtained was insufficient to make a firm statement)	27 mo seizure free
14	LF?	SEEG: LF	Not available	16 mo seizure free, then recurrence. Frequency and severity of the seizures are markedly less than before operation.
16	NA	SEEG: LF	FCD II? (quality of the material obtained was insufficient to make a firm statement)	15 mo seizure free
18	NA	Strips: bilateral F/O, onset not recorded	Not available	Not operated

Table 3: data of patients that underwent intracranial recording (ICR). FCD: Focal Cortical Dysplasia, F/O: Frontal to Occipital, LF: Left Frontal, mo: months, NA: No Abnormalities, R: Right, RF: right frontal, RT: Right Temporal, SEEG: stereo-EEG/multiple depth electrodes

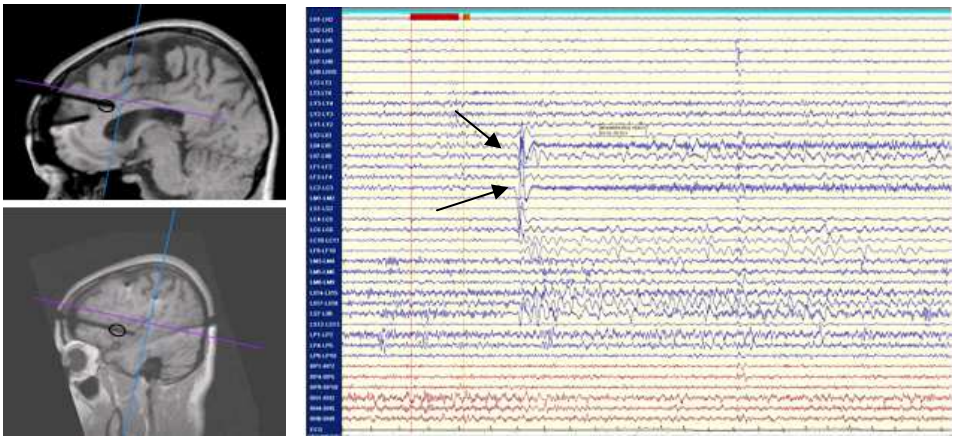


Fig 2: Left: 1.5T MRI with SEEG in situ. Top: contacts LC 1-4 encircled. Bottom: contacts LX 4-6 encircled. Right: bipolar SEEG traces at the beginning of a seizure. Seizure onset with high amplitude wave followed by gamma-activity on contacts LC 2-3 (left anterior cingulum) and contacts LX 4-5 (left anterior insula). Contacts LC 2-3 correspond with highlighted

Of the five patients with an undisputed normal MRI undergoing intracranial recordings, one patient had a clear-cut seizure onset zone demonstrated by SEEG in the posterior bank of the left cingulate gyrus. The electrical properties of the region as well as the local ictal SEEG pattern and the post-operative histopathology suggested the presence of FCD. Re-analysis of the 7T MRI still did not show any abnormalities in this region (fig 3). Resection resulted in seizure freedom.

One patient with signs of FCD in the left central region decided not to proceed with epilepsy surgery due to fear of complications.

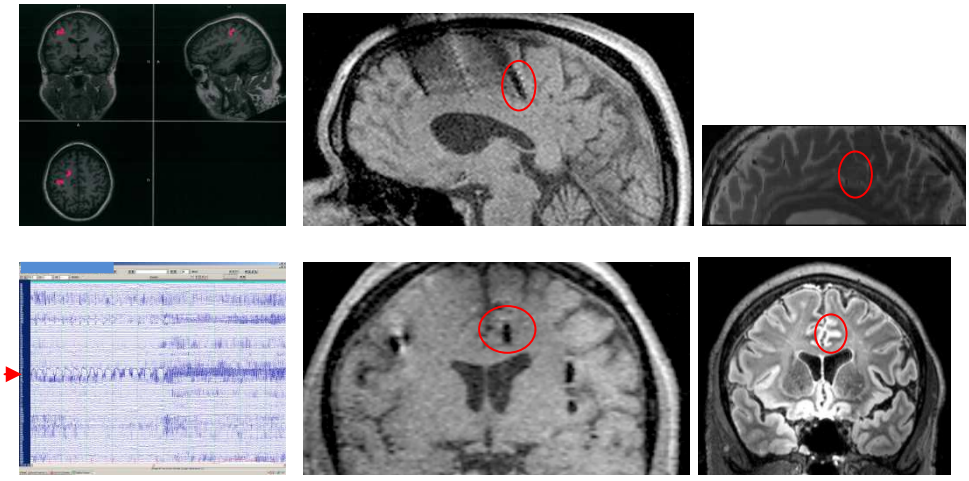


Fig 3: Re-evaluated region of epileptic focus as proved by SEEG that before SEEG were considered to be without anatomical abnormalities on visual inspection of the 7T MRI

Structural abnormalities that were believed to be unrelated to the epileptic seizures were described in five patients both on 3T and 7T MRI: once multiple hyperintensities, once traumatic lesions far anterior to the suspected epileptic focus but in the same right medial frontal gyrus, twice arachnoid cysts and SEEG post-implantation abnormalities in one patient.

In one patient examination was interrupted due to restlessness during the imaging session. One of the patients experienced several habitual short-lasting seizures of lowered consciousness and peculiar sensations without motor signs during the scanning, not intervening with the scanning procedure. No other adverse events were noted during MRI-examination.

Discussion

This study analysed semiology- and MEG-guided 7T MRI in patients with epilepsy in whom visual MEG-assisted 3T MRI analysis did not show abnormalities that could explain the epilepsy. In 3 out of 19 patients, a formerly unnoticed lesion with characteristics of an FCD was found. In 3 other patients the observers were not unanimous with regard to the visual analysis. In one of these, by using SEEG the possible abnormality proved to be the epileptogenic focus. In the other 2 patients there was no functional (SEEG) or histopathological proof available on the possible abnormalities as seen on the 7T MRI. Therefor, it is not possible to conclude whether the findings could have been of clinical importance in these 2 patients. However, detection of these abnormalities can influence the decision making process during pre-surgical evaluation, making it more likely that the patient is not (yet) rejected for epilepsy surgery. Therefor, this finding is of clinical importance.

This study was performed in a highly selected group of patients; all but one of the patients were undergoing pre-surgical analysis. Therefor, the level of confidence on the accuracy of the diagnosis of diagnosis of localization related epilepsy was high. The additional gain of 7T MRI compared to 3T MRI has clinical importance for this specific patient group. However, results of this study cannot easily be translated to a more general group of patients with epilepsy.

Recently, a comparable study was published on the detectability of FCD's on 7T MRI in 21 patients without definite lesions on 3T or 1.5T MRI, showing a 29% diagnostic gain (De Ciantis et al 2016). Agreement in imaging interpretation was reached through consensus-based discussions based on visual identification of structural abnormalities. Four out of the 6 patients with a thus detected lesion were operated, all showing FCD on histopathology. These results are almost identical to our own results, even without additional guidance by a pre-determined ROI. However, in 50% of their patients with an abnormality on 7T MRI a dubious region was already mentioned on visual inspection of lower field strength MRI. In our cohort even after re-examination of the lower field strength MRI's with knowledge of the outcome at 7T MRI in only 1 out of 6 cases a lesion could be detected on previous scans. In contrast to the study by De Ciantis et al, in our cohort all patients previously had a 3T MRI, which in each individual was inspected after MEG-results were available. Therefor, our inclusion criteria were much more vigorous. The above leads us to postulate that MEG-guided 7T MRI has higher additional value than 7T MRI sec. Also, the used sequences, although being of the same type, differed in scan-parameters. Without head-to-head comparison between the two protocols in the same patients we cannot estimate differences in additional value.

Earlier work on 7T MRI in refractory temporal lobe epilepsy (Henry et al 2011, Coras et al 2014, Derix 2014) showed the possibility to measure hippocampal subregions and border variability. Further analysis of 7T MRI along the lines of the study by Henri might provide even more additional value of 7T MRI in patients with suspicion of temporal lobe epilepsy.

In our study, using conventional visual analysis 7T MRI showed additional abnormalities even in the ¾ of patients in whom MAP07 of 3T MRI did not indicate abnormalities, with over-all abnormalities in up to 32% of 3T MRI negative patients. Voxel based morphology analysis of 7T MRI is under investigation (Seiger et al 2015).

Our study population is too small to define the definite number needed to diagnose for 7T MRI. However, comparison with literature on other modalities, mostly used in presurgical analysis, can help to give an indication of the relative benefit of the use of 7T MRI in this patient group.

For example, 1H-MRS (*Magnetic Resonance Spectroscopy*) is helpful in lateralisation of the abnormal temporal lobe in all patients with MRI-negative temporal lobe epilepsy (Xu et al 2015) as well as extra-temporal epilepsies (Colon et al 2010). MRS is much less helpful in localizing the epileptogenic focus in the abnormal hemisphere as MRS highlights network metabolic dysfunction rather than the epileptogenic focus (Pan et al 2012). The abnormalities found in our study also provide a clear cut localization, making 7T MRI more suitable for presurgical analysis than MRS.

For SPECT (*Single Photon Emission Computed Tomography)* sensitivity rates are reported to be ranging from 81% to 90% (Spencer 1994) for ictal SPECT. However, SPECT is performed in very selected cases and success is highly dependent on early ictal injection (Desai et al 2013). Due to the low temporal resolution, SPECT often highlights both the ictal onset zone and the propagation pathways (VanPaesschen et al 2007). Removal of an area with concordance between intracranial recording and SPECT leads to seizure freedom in only 66.7% of cases (Schneider et al 2013). These findings support the notion of SPECT as a marker of the epileptic network, whereas abnormalities on 7T MRI are more likely to represent the epileptogenic focus.

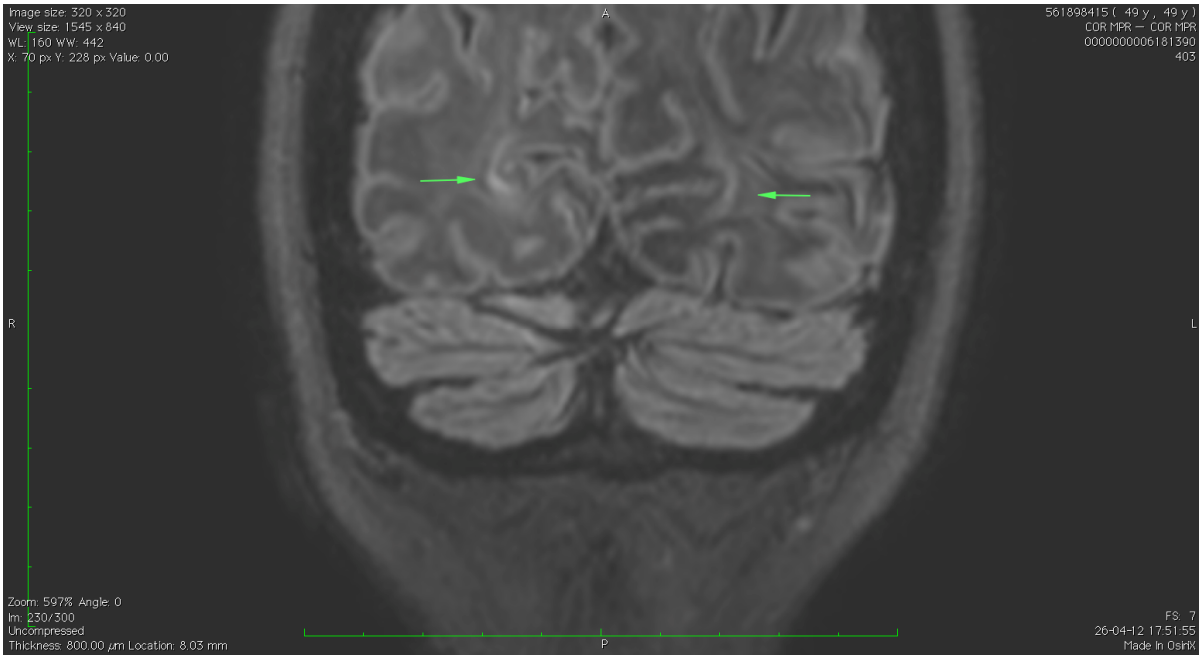
PET (*Positron Emission Tomography*) is mainly used in MRI negative patients, depicting metabolic activity of the brain. Especially in temporal lobe epilepsy a unilobar PET hypo metabolism is highly predictive of a good outcome (Yang et al 2014). However, PET tends to show more (sub)lobar hypo metabolism, rather than localised abnormalities (Komoto et al 2015). In current clinical practise, PET will only be applied if MRI does not give sufficient information.

Comparing 7T MRI to the modalities mentioned above, it has a potential additional role in pre-surgical analysis of epilepsy patients. In our study MEG guidance had added value when scoring the 7T MRI as compared to semiology alone as in three out of the six abnormal MRI's the abnormality was not detected based on semiology alone without MEG-guidance.

MEG abnormalities are described with FCD (Wilenius et al 2013) and can be used in daily practise (Colon et al 2016). In our cohort in five out of 19 patients 7T MRI abnormalities were found in concordance with MEG at the level of lobe and

lateralisation. However, in three of these 7T MRI and MEG localizations were not 100% overlapping. In one additional patient with MRI features of a FCD, MEG even seemed to be falsely localizing. This might reflect the intrinsic limitation of MEG analysis, being based upon determining the source of a signal using a mathematical model, trying to explain the recorded signal given a certain number of assumptions and limitations (Baillet 2001, Grave de Peralta 2009); the inverse problem (Helmholtz 1847). There are reports of convexity source localization errors of up to 2 cm using MEG (Sutherling et al 2001). In our patients some sources were located in deeper structures, making it likely that localization errors can even be larger (Hillebrand 2002). Another explanation could be that deeper sources can become visible on MEG after propagation of the activity to more superficial regions, thus highlighting this region instead of the epileptogenic focus. Last but not least, MEG records interictal epileptiform activity. This activity is an indication of the irritative zone, but does not necessarily reflects the epileptogenic zone.

High field MRI provides much more detailed images than 3T MRI. Some normal variants, as for example occipital extending ventricular walls, can be mistaken for FCD (Supplementary data, fig S3). On the other hand the discordance between MEG and MRI might point to false positive findings at 7T MRI. This might be true for the three out of six possible abnormalities found where there was no concordance among the observers. However, SEEG showed one out of these three to be the epileptogenic focus. In both other cases neither SEEG nor surgery has been performed. In case SEEG would have been planned, using the information gained by 7T MRI as well as by MEG would probably have impacted the implantation strategy.



Supplementary Data fig S3: occipital normal variant mimicking FCD

Use of the clinical MEG report, in combination with a representation of the MEG sources projected on MRI in three planes, sufficiently guides the eye of the radiologist. However, visual inspection of a 7T MRI without concordance with clinical signs and symptoms may lead to erroneous conclusions. Therefor we advocate that on request of 7T MRI epileptologists should incorporate clinical data and possible spreading patterns of epileptic activity including hypotheses on possible location in order to help the radiologists in their analysis and thus enable them to be *clinical* neuroradiologists in the true sense of the word. E.g. in our series there was 1 patient in whom semiology pointed towards a temporal epileptogenic focus but MEG indicated an occipital focus. This reflects a known spreading pattern and is therefor not incongruent. In this case MRI must thoroughly be inspected in the occipital regions.

Conclusion:

Semiology-guided visual analysis of 7T MRI has by itself already demonstrated a marking of possible epileptogenic abnormalities resembling FCD that were formerly not detected on MEG guided 3T MRI in 3 out of 19 of our patients. In an additional 3 out of 19 patients adding MEG-guidance lead to the detection of a possible lesion on 7T MRI. This is of clinical importance and especially in the pre-surgical work-up a valuable addition to current protocols.

CHAPTER 5

Synopsis

5.1 Summary

Epilepsy is one of the most frequent neurologic disorders, characterized by the occurrence of multiple unprovoked epileptic seizures (fits). If drug treatment is ineffective epilepsy surgery can be a good alternative.

To ameliorate diagnostics in epilepsy is an ungoing quest. Both in first line, e.i. diagnosing epilepsy, as in localizing the epileptogenic zone in case of presurgical analysis. The studies in this thesis examine possible roles for MEG and MRI in improving diagnostics in epilepsy, both alone and in combination.

The two studies in chapter 3 evaluate the possible role of MEG as primary diagnosticum for epilepsy. At present, history, semiology and EEG are the basis for diagnosis, often supplemented with MRI. If a routine EEG is insufficient to make a definite diagnosis, an EEG after sleep deprivation is asked for. This is a rather patient unfriendly procedure, in contrast to MEG. Chapter 3.1 describes a prospective study on diagnostic gain of MEG in 51 patients in whom routine EEG showed no abnormalities. A methodology to apply MEG as stand-alone investigation in daily practice is developed. Basis for analysis is final clinical diagnosis and conclusion of the report, NOT individual spike-hunting. The results are retrospectively compared to semiology and to outcome of EEG after sleep deprivation. No major differences are found between MEG and EEG after sleep deprivation, although there is a slight trend in favor of MEG showing a gain in diagnostic value of 63%.

As there is no literature proving that an original MEG or EEG conclusion is predictive of the diagnosis on the long run, chapter 3.2 describes the consistency over time of the diagnosis and its correlation with the original MEG and EEG after sleep deprivation. Information of 46 patients out of the 51 from the first study could be retrieved 8 years later, making it possible to examine the robustness of the original conclusion as compared to the last clinical diagnosis. In 8 of the 46 patients diagnosis changed. Both for MEG and for EEG after sleep deprivation the long-term correlation with the diagnosis diminished, for MEG from 63% to 61% and for EEG after sleep deprivation from 57% to 50%. Remarkably, spikes tend to be more predictive than sharp waves, albeit numbers are too small to make a firm statement on this observation. More specific to the positive results, sensitivity of sharp phenomena (combining spikes and sharp waves) in routine MEG and in EEG-SD for the long-term (3–8 years) diagnosis epilepsy is 71% and 62%, respectively.

Chapter 4 describes possible roles of MRS and of 7T MRI, partly based on previous MEG findings. Chapter 4.1 describes single voxel 1H-MRS in 19 patients, 10 with a known temporal FCD and 9 otherwise 3T MRI negative patients with temporal lobe epilepsy seeking for confirmation of the MEG-based hypothesis of lateralisation of epileptogenic zone. Relative concentrations of measured metabolites are calculated per voxel and compared to outcome in a mirror-voxel on the opposite side. In both groups NAA/Cr ratio is significantly lower on the affected side whereas the results for Cho/Cr ratios are more diverse. There are no significant differences between the two groups, making single voxel 1H-MRS a reliable predictor of lateralisation in case of an MRI-negative epilepsy patient.

Chapter 4.2.1 describes the appearance on 7T MRI of lesions already seen at lower field strength. This study is a preparation for chapter 4.2.2. Ten patients in whom previously a probable FCD was diagnosed on 1.5T (n=1) or 3T (n=9) MRI undergo a 7T MRI. The MRI characteristics of FCD are visually evaluated by three specialists, comparison between 3T and 7T images are made and radiologic diagnosis is compared to histopathology in the 5 cases where this is available. In 2 out of 10 patients the original diagnosis of FCD is changed. Image quality at 7T MRI is significantly higher than the quality at 3T MRI. At 7T, FLAIR turns out to be the sequence in which the abnormality is easiest detected, T2 and T2* are better suited to review structure and extent of the lesion, whereas T1-weighted images highlight cortical thickening and blurring most prominent. A hypo-intense line at the grey-white matter junction is striking on T2 weighted images creating a typical three layer flag-like appearance.

Chapter 4.2.2 describes findings of MEG-guided 7T MRI in a cohort of 19 patients with localization related epilepsy in whom a MEG-guided state-of-the-art 3T MRI did not reveal a structural lesion. This is the first publication on epilepsy patients undergoing MEG-guided 7T MRI in whom former MEG-guided 3T MRI analysis reported no abnormalities. In those cases where it is available other data from pre-surgical analysis and post-resection histopathology are compared to findings at MEG-guided 7T MRI. Three specialists visually analyse the 7T images. New abnormalities are detected by all three observers in 3 patients. Retrospectively, in one of these patients the abnormality was already visible on 3T MRI, but not in the other 2. Not unanimous, there are indications for another abnormality in 3 more patients, one of which is proven by depth recordings to be the epileptogenic focus.

The MRI of another patient with a focus found with depth recordings, showing a classical FCD-signal, stayed unremarkable at re-evaluation.

Findings are compared with the gain in MRI-negative patients of voxel based morphology, MRS, SPECT, and PET. This leads to the observation that MEG-guided 7T MRI provides a valuable added gain in pre-surgical analysis.

Concluding, MEG is a robust and reliable diagnosticum, not just in diagnosing epilepsy but also in guiding analysis of MRS and of 7T MRI. MRS in itself can indicate the lateralisation of an epileptogenic zone. Further, abnormalities are better (to anyway) visible on 7T MRI than on lower field strengths. Especially if the review is MEG-guided, making MEG-guided 7T MRI a welcome addition to the test possibilities in the pre-surgical analysis of patients with a refractory localization related epilepsy.

5.2 Samenvatting (dutch version of summary)

Epilepsie is een van de meest frequent voorkomende neurologische aandoeningen en wordt gekenmerkt door het spontaan optreden van meerdere epileptische aanvallen (toevallen). Als medicatie niet werkt kan epilepsie chirurgie een goed alternatief zijn.

Het is een voortdurende queeste om de diagnostiek voor epilepsie te verbeteren. Zowel initieel, oftewel bij het vaststellen dat er sprake is van epilepsie, als ook bij het lokaliseren van de epileptogene zone in geval van pre-chirurgische analyse. De onderzoeken in dit proefschrift onderzoeken of MEG en MRI mogelijk een rol kunnen spelen in de verbetering van de diagnostiek bij epilepsie, zowel losstaand als in combinatie.

De twee onderzoeken in hoofdstuk 3 evalueren de mogelijke rol van MEG als eerste lijns diagnosticum voor epilepsie. Momenteel is het zo dat voorgeschiedenis, semiologie en EEG de basis vormen voor de diagnostiek, vaak aangevuld met MRI. Als een routine EEG onvoldoende is om tot een definitieve diagnose te komen wordt vaak een EEG na slaapdeprivatie aangevraagd. Dit is een nogal patiënt-onvriendelijke methode, in tegenstelling tot MEG. Hoofdstuk 3.1 beschrijft een prospectief onderzoek naar de diagnostische opbrengst van MEG bij 51 patiënten waarbij routine EEG geen afwijkingen toonde. Een methode om MEG als losstaand onderzoek in de dagelijkse praktijk toe te kunnen passen is ontwikkeld. Analyse van de data is gebaseerd op het niveau van diagnose en conclusie in het verslag, NIET op het niveau van individuele pieken. De uitkomsten zijn retrospectief vergeleken met de semiologie en met de uitkomst van het EEG na slaapdeprivatie. Er zijn geen overweldigende verschillen gevonden tussen MEG en EEG na slaapdeprivatie, al bestaat er wel een trend ten faveure van MEG, waar een winst in diagnostische waarde van 63% wordt gevonden.

Aangezien er geen literatuur gevonden is die aantoont dat de uitkomst van een MEG of EEG voorspellend is voor de diagnose op langere termijn beschrijft hoofdstuk 3.2 de consistentie over de tijd van een gestelde diagnose en de relatie hiervan met de oorspronkelijke uitslag van MEG en EEG na slaapdeprivatie. Acht jaar na het eerste onderzoek kunnen gegevens over 46 van de oorspronkelijke 51 patiënten boven water gehaald worden, waarmee de consistentie van de originele conclusie vergeleken kan worden met de laatst beschikbare klinische diagnose. Bij 8 van de 46 patiënten veranderde de diagnosis. Bij zowel MEG als bij EEG na slaapdeprivatie verminderde op lange termijn de overeenkomst met de diagnose, voor MEG van 63%

naar 61% en voor EEG na slaapdeprivatie van 57% naar 50%. Opvallenderwijs lijken pieken een betere voorspeller van de definitieve prognose dan scherpe golven, al is de groep te klein om over deze observatie een harde uitspaak te kunnen doen. Meer toegespitst op de positieve uitslagen, gevoeligheid van scherpe fenomenen (pieken en scherpe golven bij elkaar genomen) in routine MEG en in EEG na slaapdeprivatie voor de diagnose epilepsie bedraagt op de langere termijn (3–8 jaren) respectievelijk 71% en 62%.

Hoofdstuk 4 beschrijft mogelijke rollen voor MRS en voor 7T MRI, gedeeltelijk gebaseerd op eerdere MEG-bevindingen. Hoofdstuk 4.1 beschrijft single voxel 1H-MRS in 19 patiënten, 10 bekend met een temporale FCD en 9 verder 3T MRI negatieve patiënten met temporaalkwab epilepsie waarbij gezocht wordt naar bevestiging van een op MEG-gebaseerde hypothese aangaande de lateralisatie van de mogelijke epileptogene zone. Relatieve concentraties van de gemeten metabolieten worden per voxel berekend en vergeleken met de uitkomsten vanuit een spiegel-voxel contralateraal. In beide groepen blijkt de NAA/Cr ratio significant lager aan de aangedane zijde, terwijl de uitkomsten voor Cho/Cr ratio veel diverser zijn. Er zijn geen significante verschillen tussen beide groepen en single voxel 1H-MRS is een betrouwbare voorspeller van lateralisatie, ook bij MRI-negatieve epilepsie patiënten.

Hoofdstuk 4.2.1 beschrijft het voorkomen op 7T MRI van bekende lesies die al op lagere veldsterkte zijn aangetoond. Deze studie dient als voorbereiding voor hoofdstuk 4.2.2. Tien patiënten bij wie in eerdere fase een FCD was vastgesteld, gebaseerd op 1.5T (n=1) of 3T (n=9) MRI ondergaan een 7T MRI. De MRI

karakteristieken van FCD worden door 3 specialisten visueel beoordeeld, een vergelijking tussen de 3T en de 7T beelden wordt gemaakt en de radiologische diagnose wordt vergeleken met de histopathologie in de 5 gevallen dat deze beschikbaar is. In 2 van de 10 patiënten verandert de oorspronkelijke diagnose FCD. Beeldkwaliteit is bij 7T significant hoger dan bij 3T. Bij 7T blijkt FLAIR de sequentie te zijn waarmee een afwijking het makkelijkst gezien wordt, T2 en T2* zijn geschikter om de structuur en uitgebreidheid van het afwijkende gebied te bekijken, terwijl T1-gewogen beelden corticale verdikking en vervaging van de wit/grijze stof demarcatie goed zichtbaar maken. Een hypo-intense lijn ter hoogte van de overgang van witte naar grijze stof valt vooral op op T2 gewogen beelden, aldus een typische 3-banen vlag-achtig beeld tonend.

Hoofdstuk 4.2.2 beschrijft bevindingen bij MEG-gestuurde 7T MRI in een cohort van 19 patiënten met localisatie gerelateerde epilepsie waarbij eerdere MEG-gestuurde state-of-the-art 3T MRI geen structurele lesie aan het licht bracht. Dit is de eerste publicatie over daadwerkelijke 3T MRI negatieve epilepsie patiënten die een MEG-gestuurde 7T MRI analyse ondergaan. Daar waar beschikbaar worden de bevindingen vergeleken met overige data uit de pre-chirurgische analyse en post-operatieve histopathologie. Drie specialisten voeren een visuele analyse van de 7T beelden uit. Alle 3 zijn ze het eens over nieuwe afwijkingen bij 3 patiënten. Terugkijkend was bij 1 van deze patiënten de afwijking al zichtbaar op de 3T MRI, maar niet bij de andere 2. Daarnaast zijn er bij nog 3 patiënten aanwijzingen voor afwijkingen die echter niet door alle 3 de specialisten gezien worden. Bij 1 hiervan toont een diepteregistratie aan dat dit ook het epileptogene focus is. De MRI van een andere patiënt waarbij diepteregistratie een focus aantoont met een klassieke FCD signatuur blijft ook bij herbeoordeling brandschoon.

De uitkomsten worden vergeleken met de opbrengsten van voxel based morphology, MRS, SPECT en PET bij MRI-negatieve patiënten. Dit leidt tot de observatie dat MEG-gestuurde 7T MRI een waardevolle aanvullende waarde heeft in de pre-chirurgische analyse.

Tot besluit kan worden gesteld dat MEG een robuust en betrouwbaar diagnosticum is, niet alleen ter vaststelling van epilepsie maar ook als richtingaanwijzer voor MRS en 7T MRI. MRS kan op zich al aanwijzingen geven over lateralisatie van een epileptogene zone. Verder zijn afwijkingen beter (tot überhaupt) zichtbaar op 7T MRI dan op lagere veldsterktes, vooral als er MEG-gestuurd naar de plaatjes gekeken wordt. Hiermee is 7T MRI een welkome aanvulling op het onderzoekspallet in pre-chirurgische analyse bij patiënten met een refractaire localisatiegebonden epilepsie.

CHAPTER 6

General discussion and future perspectives

The studies in this thesis were all concerned with questions on how diagnostic procedures in epilepsy can be improved. To that aim, possibilities and reliability of MEG, MRS and 7T MRI were explored, each showing specific advantages and disadvantages, both as stand alone investigation as in combination with each other. This is in line with experiences in daily practice of epilepsy and of epilepsy surgery: no investigation provides the answer in all patients and in (almost) no patient all investigations are positive. This might also be one of the reasons why there is no uniformity in the used methodology in presurgical evaluation amongst different experienced centers (Mouthaan 2016). The results of the studies presented here, however, have several implications.

First, MEG and EEG-SD have shown to be good predictors of the diagnosis of epilepsy if epileptiform activity was present in the encephalography. Interestingly, in contrast to the debates the past decades, the notion that in EEG spikes and sharp waves are equally strong markers for the diagnosis of epilepsy was not completely endorsed. In the upcoming years for both modalities we will enlarge the cohort in order to evaluate whether this observation should lead to a repraisal of the impact of spikes versus sharp waves in diagnosing epilepsy. Furthermore, routine MEG tended to be at least as sensitive as EEG-SD, which is in line with the evaluation of gain of MEG and EEG in a population of patients that underwent earlier EEG's without

epileptiform abnormalities as reported by Duez et al (2016). They describe an added value of MEG to EEG of 14 to 18%, which is even higher than our findings of 11% added value. The next step is to examine if MEG could replace EEG-SD *plus* routine EEG in the first-line diagnostic procedures. To answer that question we started a study based on the model of chapter 3.1, comparing conclusions of MEG, routine EEG and EEG-SD reports to the clinical diagnosis at the end of the diagnostic process. Furthermore, a medical technology assessment is carried out to evaluate practical and financial feasibility of implementing MEG in daily practice in the dutch setting. This will not only be based on gain from a medical and patient point of view, but also on cost-effectiveness. After all, almost every european hospital owns EEG-equipment but at present access to MEG is very limited. Furthermore, for MEG both costs of purchase and maintenance (e.g. costs of liquid helium) are higher than for EEG. On the other hand, whether costs of personnel are higher for EEG or for MEG is not clear yet. Although analysis time is much longer for MEG as compared to EEG, preparation and cleaning time are much shorter. Finally, in contrast to EEG, for MEG no additional equipment (such as caps or contact paste) is necessary.

A second advantage of implementing MEG early in the diagnostic process could be that IF a patient is refractory and becomes a possible candidate for epilepsy surgery, data to execute MSI are already present. De Tiege et al (2012) showed that MEG influences desicion making in the pre-surgical analysis when available during the final stage. However, at present it is unclear at what stage of the pre-surgical analysis the impact of this data could be highest. Therefor, a study has started comparing intra-individually the different impacts on decisions when MEG data become available in different phases of this process.

MRS seemed quite promising when the study started. It held the promise of being able to demonstrate focal metabolic abnormalities indicating the epileptogenic zone. As it turned out in recent years, MRS is a good lateralizer but is much less helpful in localizing the epileptogenic zone in the abnormal hemisphere as MRS highlights network metabolic dysfunction rather than the epileptogenic zone (Pan 2012). Therefor, MRS changes reflect changes in the epileptic network, much less of the epileptogenic zone. This zone is the holy grail of epilepsy surgery. After our first enthousiasm, in our center MRS tended to disappear into oblivion. As in several patients with temporal lobe epilepsy lateralisation is more of a problem than localization, based on our own research MRS deserves to be revitalized. Nevertheless, results should be met with caution: we presumed a lateralisation index to be correct if the results were concordant with visible abnormalities (FCD on MRI) and/or with physiological tests (MEG). This implies the risk of circular reasoning. Correlation with intracranial recordings and with outcome after surgery was not yet established. Furthermore, in patients with bilateral temporal lobe epilepsy there still could be an asymmetry, giving rise to a misleading lateralisation index. Finding an asymmetry should therefor urge the investigator to re-examine the original data.

During the last years there is some emerging evidence that finding a lesion on MRI is NOT the prognostic factor par excellence for success of epilepsy surgery, as success rates of resections in non-lesional cases can in highly selected cases be up to 88% as well (Chen 2016, Ryvlin 2014, Chassoux 2012, Hyslop 2012, Lee 2011). Unfortunately, to reach this success percentage in these cases very extensive pre-surgical workup is necessary. Therefor, the role of MRI remains highly important. 7T MRI is becoming more easily available, with more 7T machines installed every year. Seen the results presented in the literature this year and in this thesis, there is

definitely a place for 7T MRI in epilepsy diagnostics. During the 12-th European Congress on epileptology, September 2016, Prague, the group of Veersema presented their experiences with 7T MRI in formerly MRI-negative epilepsy surgery candidates. They described 8 lesions in 38 patients in whom former MRI was considered normal. Histopathology was not (yet) available for all 8 cases. This is in line with our findings of 6 abnormalities in 19 patients when adding localizing information based on a MEG-guided ROI. It is likely that the combination of 7T MRI with an adequately defined ROI will lead to improvement of outcome of epilepsy surgery or giving access to epilepsy surgery to more patients. To define the ROI, MEG can be helpful, as was shown in our study. However, MEG is not the only modality capable of indicating a reasonable ROI. Other modalities can indicate the ROI as well. Therefor, we extended our inclusion and started a 7T MRI study where all 3T MRI negative patients within the epilepsy surgery program in whom a robust and plausible hypothesis on location of the seizure onset zone can be formulated will be included. With time, this will also lead to more tissue specimens being available and more correlations being made between pathology and MRI findings. This, in turn, will lead to better understanding of the images themselves.

With the new ILAE proposal for “Terminology and concepts for organization of seizures and epilepsies” a more holistic approach of patients with epilepsy emerges. Integrating more different investigative modalities to analyse a patient fits this development. Finally, Hippocrates was right: “It is more important to know what kind of person has this disease than to know what kind of disease this person has”.

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Geachte professor Boon, beste Paul,

Zonder uw duwtjes in de juiste richting op de juiste momenten zou dit proefschrift er nooit gekomen zijn. Dit was al zo nog voor de officiële start van het promotie-traject. De introductie van het SEEG in Nederland voelde voor mij al als een proeve van bekwaamheid. En tijdens het promotietraject waren er ook meerdere momenten dat dagelijkse werkzaamheden een promotietraject dreigden onder te sneeuwen. Uw sturing op deze momenten was onmisbaar. Gelukkig zonder acute momenten.

Maar het meest heb ik misschien nog wel geleerd van je eindeloos positieve instelling, je vermogen om schijnbaar onoplosbare situaties tot een oplossing te brengen zonder ook maar één van de kemphanen het gevoel te geven miskend te worden. En het was heerlijk om een bourgondische levensinslag te delen. Ik hoop nog vele malen de dis met je te mogen delen.

Geachte professor Hofman, Beste Paul,

De rol van co-promotor kan niet worden overschat. Uw rol in de aanvang met de samenwerking met het LUMC, evenals in de afronding van de MRI-gerelateerde onderdelen van dit proefschrift kan niet anders dan als essentieel omschreven worden.

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Geachte dr Ossenblok, Beste Pauly,

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De afgelopen jaren heeft onze samenwerking zich geïntensiveerd en zijn er vele projecten waarbij jij mij ook betrokken hebt. Deze samenwerking mag wat mij betreft nog heel lang duren! Het is altijd weer een genoegen “ even” de tijd te nemen om nieuwe stappen te bespreken. Maar ook om “even” te roddelen over hoe de hazen lopen. En daar op de achtergrond de visie van Han in door te horen klinken. Jammer dat hij er nu niet meer bij kan zijn.

Esteemed members of the examination and reading board, prof dr M. Cools, Prof. dr P. Ryvlin, Prof. dr C. Dirven, Prof. dr E. Achten, Prof. dr D. Van Roost, Prof. dr K. Vonck and dr M. Vlooswijk, thank you for the time and effort you have put in reading and evaluating this thesis. Your valued comments made this booklet quite presentable.

Geachte dr Van Osch, Beste Thijs,

Wat was het interessant om via dit proefschrift de cultuurverschillen tussen de verschillende universiteiten van nabij mee te mogen maken. Vanuit LUMC was jij degene die het frequentst en het uitgebreidst reageerde. Ik hou van Socratiaans discussiëren, maar jij wist mij soms tot wanhoop te drijven. Na alles te laten bezinken waren al jouw commentaren echter altijd weer zinvol en grond voor verbetering. Ik beschouw jou voor een deel van deze promotie als een co-copromotor en wil jou in het bijzonder danken voor de energie die jij hierin gestoken hebt.

Geachte professor Stam,

Zeker in de beginfase van dit proefschrift heeft u veel invloed gehad op de opzet van zowel het MEG-onderzoek als hoe MEG als indicator voor een ROI gebruikt kan worden. Uw invloed is groter geweest dan de frequentie waarin uw naam in de auteurslijsten voorkomt doet vermoeden. Wat mij betreft ligt de oorzaak hiervan in uw bescheidenheid. Ik hoop van harte in de toekomst nog vaker met u de degens te mogen kruisen voor een vriendschappelijke trainingswedstrijd.

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Geachte dr Van der Grond,

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Geachte Drs. Wagner, beste Louis,

Geen enkel onderzoek hier beschreven, geen enkele stap van het promotietraject is zonder jouw welkome commentaar, en nog welkomere steun geweest. We hebben een goed epilepsie-chirurgieteam. Nu is het jouw beurt. Ik hoop dat de moeilijkheden die ik ben tegengekomen jou niet ontmoedigd hebben, en dat de dag van de promotie zelf jou inspireert. En ik hoop jouw proces van nabij mee te mogen maken. Succes!

Geachte professor De Louw, Beste Anton,

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Geachte dr Vredeveld, beste Jan-Willem,

Wat moet ik hier nou schrijven? Dat jij een goed klankbord geweest bent voor de KNF? Dat we enkele zeer fraaie plexus-onderzoeken gedaan hebben? Dat het net zo goed een plexus-promotie had kunnen worden, ware ik niet naar Kempenhaeghe gegaan? Dat ik het samen koken mis maar nog meer jouw maaltijden? Het is altijd een onderdrijving van de werkelijkheid. Dank voor een goede, spannende en inspirerende tijd.

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LUMC, VUmc, MUMC+, uzGent en Kempenhaeghe,

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Dear Heather,

So nice to have a neighbour that not only is a very pleasant and sofisticated person but also a native English speaker willing to help correct the most ridiculous mistakes. Time for a good glas of wine!

Beste Jan,

Met je schoonvader discusiëren over zo iets kleins als quarks en magnetisch moment… Wat kunnen we toch pietluttig zijn. Heerlijk.

Beste Emma,

Weinig promovendi zullen een eerste engelse correctie door hun pete-nicht kunnen laten doen. Het was enorm boeiend om dit proces mee te maken. Ik kijk ernaar uit jou ook als collega te mogen groeten.

Beste Gongers, Lamawaaiers, buurtgenoten, vrienden en familie,

Zelden zullen zoveel mensen zo vaak het excuus van “ geen tijd, moet promoveren” gehoord hebben. Ik voelde me meer dan gesteund en vooral ook geaccepteerd. Waar jullie geduld vandaan komt weet ik niet, maar het heeft me wel door de moeilijkste tijden heen geholpen. Mijn waardering voor jullie is gigantisch.

Oerol, Parade, Sonsbeek-festival, etcetera, enzovoorts,

Het leven is meer dan de alledaagse bezigheden. De bijzondere momenten zijn onderdeel van het evenwicht, zonder welke een promovendus autistisch wordt. Nederland kent vele opties, waarvan ik dankbaar gebruik gemaakt heb.

Lieve zus,

Jaja, het komt er echt van. Tijd om een andere running gag te gaan verzinnen.

Lieve ouders,

Alle ups en downs hebben jullie meegemaakt. Wonderlijke trajecten. Himmelhoch jauchtzend zum toden betrubt was het net niet, maar het zat er wel eens tegenaan. Zonder jullie steun en opvoeding en opvang en Calonge en enz, enz, enz betwijfel ik of dit proefschrift er was gekomen. Ik ben trots dit moment met jullie te mogen delen.

Lieve Laurien en Maarten,

Dit proefschrift draag ik aan jullie op. Bij tijd en wijle was dit proefschrift de reden dat jullie een minder aanwezige vader hadden. Jullie hebben er nooit over geklaagd. Sterker nog, jullie stimuleerden mij zo nu en dan als ik er even helemaal doorheen zat. Dank.

Ruscha, lieve Ruscha

Van ons allemaal heb jij het het zwaarst gehad. En heb jij het minst geklaagd. Niet over het feit dat ik veel buitenshuis was, niet over het feit dat ik thuis veel achter de computer zat, nauwelijks over het feit dat ik vaak moe was. Hoe je het hebt volgehouden is mij een raadsel, zeker met je eigen opleiding tot psychotherapeut er de laatste jaren naast. Eerder afgerond dan ik mijn promotie... In opvoeding en regelen van zaken vormen wij een prima team, maar belangrijker nog is de liefde die wij delen. We gaan er ook verder een mooie tijd van maken samen!

Curriculum Vitae

Albert Jozef Colon was born on august 29-th 1965 in Amsterdam. After secundary school (Canisius College-Mater Deï, Nijmegen) he studied medicine at the Radboud University Nijmegen (1983-1991). After several residencies (neurosurgery Groningen, Health technology assessement of lung transplantations Groningen, neurology Heerlen, Intensive care Enschede) he specialized in neurology in Atrium Medical Center in Heerlen (dr C. Franke, dr P. Koehler and dr J.W. Vredeveld). To obtain the degree of “hoofdvakker clinical neurophysiology” he followed over a year of specialized training in expertise-centrum Kempenhaeghe (dr J. Arends) and the academical hospital of Maastricht (prof. dr F. Spaans). After obtaining this degree (2000) he continued working in Kempenhaeghe, where he further specialized in the neurological aspects of epilepsy surgery (dr E. Veltman). In order to get a broader view, several visits of 1 to 2 months to different international epilepsy centers were made: MNI, Montreal, Canada (dr F. Dubeau and dr J. Gotmann), Lyon (prof. dr Ph. Ryvlin), Bonn (prof. dr Ch. Elger) and Gent (prof. Dr P. Boon). During these visits, he learned about stereo-EEG and started to promote this way of investigating selected patients in the Netherlands. After more thourough training in 2008 (Lyon prof. dr Ph. Ryvlin, Grenoble prof. dr Ph. Kahane and dr L. Minotti, Milano dr S. Francione) he started the intracranial SEEG program in the Academic Center for Epileptology Kempenhaeghe/MUMC+ (ACE) together with prof dr V. Visser van de Walle and dr O. Schijns. Recently he started with thermo-coagulation in epilepsy patients in collaboration with Drs. Wagner. He participates in the education of neurology residents and students from the Technical University Eindhoven. Meanwhile, in

pursuit of better indicators on how to best place the intracerebral electrodes, interest in other diagnostic investigations also grew, leading to this thesis.

Apart from being an epileptologist, Albert very much enjoys theater, dancing, coocking, food, wine, reading, delta-flying (vol libre), old Citroëns but above all his loved ones. He is married and has a daughter and a son who are (almost) as stubborn as he is.

Albert Jozef Colon is 29 august 1965 in Amsterdam geboren. Na de middelbare school (Canisius College-Mater Deï, Nijmegen) studeerde hij geneeskunde aan de Radboud Universiteit te Nijmegen (1983-1991). Na verscheidene assistentschappen (neurochirurgie Groningen, Health technology assessement van long transplantaties Groningen, neurologie Heerlen, Intensive care Enschede) specialiseerde hij tot neuroloog in Atrium Medisch Centrum in Heerlen (dr C. Franke, dr P. Koehler en dr J.W. Vredeveld). Om de titel van “hoofdvakker klinisch neurofysioloog” te behalen volgde hij meer dan een jaar gespecialiseerde opleiding in expertise-centrum Kempenhaeghe (dr J. Arends) en het academisch Ziekenhuis Maastricht (prof. dr F. Spaans). Na het behalen van deze titel (2000) bleef hij in Kempenhaeghe werken, waar hij zich verder specialiseerde in de neurologische aspecten van epilepsiechirurgie (dr E. Veltman). Om zijn blikveld te verruimen zijn verscheidene 1 tot 2 maanden lange bezoeken bij verschillende internationale epilepsiecentra afgelegd: MNI, Montreal, Canada (dr F. Dubeau en dr J. Gotmann), Lyon (prof dr Ph. Ryvlin), Bonn (prof. dr Ch. Elger) en Gent (prof. Dr P. Boon). Tijdens deze bezoeken kwam hij in aanraking met stereo-EEG waarna hij deze onderzoeksmethode voor daarvoor geïndiceerde patiënten in Nederland begon te promoten. Na een diepgaandere training in 2008 (Lyon prof. dr Ph. Ryvlin, Grenoble prof. dr Ph. Kahane and dr L. Minotti, Milano dr S. Francione) startte hij samen met prof dr V. Visser van de Walle en dr O. Schijns het intracraniële SEEG programma in het Academisch Centrum voor Epileptologie Kempenhaeghe/MUMC+ (ACE). Recent is hij samen met Drs Wagner gestart met thermo-coagulatie in epilepsie patiënten. Hij participeert in de opleiding aan arts-assistenten neurologie en aan studenten van de technische universiteit Eindhoven (TU/e). Ondertussen, al zoekende naar betere

indicatoren voor een optimale plaatsing van intracerebrale elektroden, groeide ook de interesse in ander diagnostisch onderzoek wat tot de huidige thesis heeft geleid.

Naast het zijn van een epileptoloog kan Albert enorm genieten van theater, dansen, koken, eten, wijn, lezen, delta-vliegen (vol libre), oude Citroëns maar boven alles zijn geliefden. Hij is getrouwd en heeft een dochter en een zoon die (bijna) net zo eigenwijs zijn als hij.

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