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Clinical Neurophysiology 131 (2020) 1711–1720

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Detection of interictal epileptiform discharges: A comparison of on-scalp MEG and conventional MEG measurements ☆

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ARTICLE INFO

Article history:
Accepted 30 March 2020
Available online 11 May 2020

Keywords:
Epilepsy
Interictal epileptiform discharges
Magnetoencephalography
High-critical temperature SQUIDs
Instrumentation

HIGHLIGHTS

- First ever on-scalp magnetoencephalography (MEG) measurement on an epilepsy patient.
- Twice as many interictal epileptiform discharges seen with on-scalp MEG.
- Indicates that on-scalp MEG detects more epileptic activity than conventional MEG.

ABSTRACT

Objective: Conventional MEG provides an unsurpassed ability to, non-invasively, detect epileptic activity. However, highly resolved information on small neuronal populations required in epilepsy diagnostics is lost and can be detected only intracranially. Next-generation on-scalp magnetencephalography (MEG) sensors aim to retrieve information unavailable to conventional non-invasive brain imaging techniques. To evaluate the benefits of on-scalp MEG in epilepsy, we performed the first-ever such measurement on an epilepsy patient.
Methods: Conducted as a benchmarking study focusing on interictal epileptiform discharge (IED) detectability, an on-scalp high-temperature superconducting quantum interference device magnetometer (high-Tc SQUID) system was compared to a conventional, low-temperature SQUID system. Co-registration of electroencephalopraphy (EEG) was performed. A novel machine learning-based IED-detection algorithm was developed to aid identification of on-scalp MEG unique IEDs.
Results: Conventional MEG contained 24 IEDs. On-scalp MEG revealed 47 IEDs (16 co-registered by EEG, 31 unique to the on-scalp MEG recording).
Conclusion: Our results indicate that on-scalp MEG might capture IEDs not seen by other non-invasive modalities.
Significance: On-scalp MEG has the potential of improving non-invasive epilepsy evaluation.

1. Introduction

Magnetoencephalography (MEG) has played a role in epilepsy care for almost thirty years, and is today widely regarded as an established clinical tool (De Tiège et al., 2012; Hari et al., 2018). Several studies have demonstrated that MEG detects interictal epileptiform discharges (IEDs) with unsurpassed sensitivity, detecting them in approximately 70–80% of all epilepsy patients as compared to a 60% detection rate in electroencephalography (EEG) (Stefan et al., 2003; Knake et al., 2006; De Tiège et al., 2017). MEG also plays a role in EEG-negative epilepsy cases, and adding MEG to the clinical evaluation of such patients increase the spike detection probability with almost 20% (Pataraia et al., 2004; Colon et al., 2009; Duez et al., 2016). Furthermore, since MEG source reconstruction is less affected by skull anatomy and

☆ The study was conducted at The National Research Facility for Magnetoencephalography (MEG), Karolinska Institute, Stockholm, Sweden.

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https://doi.org/10.1016/j.clinph.2020.03.041
1388-2457/

conductivity than EEG is, the localization of an epileptogenic zone is more accurate with MEG than what is possible with EEG (Hämäläinen et al., 1993; Jayakar et al., 2014). Also, using MEG to guide intracranial electrode placement increases the likelihood of a successful sampling of the seizure onset zone (Knowlton et al., 2006; Sutherling et al., 2008; Jung et al., 2013). Additionally, resection of findings localized with MEG increases the likelihood of post-surgery seizure freedom compared to surgery performed without MEG findings taken into account (Murakami et al., 2016; Rampp et al., 2019). For the above reasons, MEG has become a standard part of presurgical evaluation of epilepsy patients (De Tiège et al., 2017; Hari et al., 2018).

Despite these unique contributions in presurgical epilepsy evaluation, conventional MEG systems exhibit some inherent limitations, and addressing these might further enhance the utility of MEG in epilepsy research and clinical evaluations. Conventional MEG (hereafter called in-helmet MEG) sensors are cooled down to approximately 4 Kelvin (−269 °C) using liquid helium, which is why they must be housed behind thick layer of insulation (Heiden, 1991) within a fixed-size helmet. On adults, this solution results in a 20–40 mm sensor-scalp distance typically influencing distance to frontal and temporal cortices the most; the situation is even worse for children (Riaz et al., 2017). This distance has a detrimental influence on the signal-to-noise ratio of the cortical signal since the magnetic field strength weakens quickly with distance (Boto et al., 2016; Iivanainen et al., 2017). Spatial resolution depends on the sensor spacing. A smaller sensor-to-sensor distance results in a better ability to distinguish between neural sources, compared to a greater sensor-to-sensor distance (Boto et al., 2016; Riaz et al., 2017). To address both the problems of sensor-cortex distance and that of the fix in-helmet system, as well as improve both neuroscientific and clinical applicability of MEG, systems where the sensors are flexibly placed directly on the scalp are under development (Borna et al., 2018; Boto et al., 2018; Iivanainen et al., 2020; Pfeiffer et al., 2019). On-scalp MEG sensors comprise, amongst others, optically-pumped magnetometers (OPMs) (Budker and Romalis, 2007) and high-temperature superconducting quantum interference device magnetometer (high-Tc SQUID) (Zhang et al., 1993). Both of these on-scalp MEG sensor systems allow for a significant reduction of the sensor-cortex distance, as well as a rearrangement of the sensor layout geometry, thus increasing the signal-to-noise ratio and spatial resolution of the recorded neuronal activity. Furthermore, placing the sensors evenly distributed on the scalp enables a more even sampling of brain regions. (Schneiderman, 2014; Boto et al., 2016; Iivanainen et al., 2017). This has also been verified by several experimental studies (Andersen et al., 2017; Xie et al., 2017; Boto et al., 2018). Conclusively, the development of on-scalp MEG sensors holds the promise of improving the quality of non-invasive MEG measurements, potentially moving these towards the quality of intracranial registrations. Potentially, on-scalp MEG sensors could enable better non-invasive characterization of focal epileptic networks, seizure development and seizure onset zone, which today is only possible using invasive intracranial recordings (Stefan and Lopes da Silva, 2013; Jayakar et al., 2016; Bartolomei et al., 2017). Improving the spatial resolution of non-invasive neurophysiological measurements would thus be of great value both for neuroscientific and clinical applications.

We present the first-ever measurement on an epilepsy patient using on-scalp MEG sensors. We aimed to evaluate the potential added value of these sensors compared to in-helmet MEG with focus on IED detection. To this end, a benchmarking protocol with acquisition of both on-scalp and in-helmet MEG and co-registration of EEG from the same patient was utilized.

2. Method and material

2.1. E thical approval

The experiment was approved by the Swedish Ethical Review Authority (DNR: 2018/1337-31), and was performed in agreement with the Declaration of Helsinki.

2.2. MEG systems

2.2.1. On-scalp high-T_c-MEG system

The on-scalp high-Tc-MEG system (hereafter referred to as on-scalp MEG) consists of seven SQUID magnetometers, each with a pickup loop with dimensions 8.6 mm × 9.2 mm. The magnetometers are positioned with 12.0 mm center-to-center distance in a hexagonal array enclosed within a cryostat cooled with liquid nitrogen. The distance between the sensors and the participant's scalp can be as small as 1 mm. A detailed description of the system is found in Pfeiffer et al. (2019).

2.2.2. In-helmet MEG system

For in-helmet MEG recordings, an Elekta Neuromag TRIUX (Elekta Oy, Helsinki, Finland) with 102 sensor chips, each with one magnetometer with a pickup loop size of 21 mm × 21 mm and two orthogonal planar gradiometers, was used.

2.3. Patient and experimental procedure

In order for IEDs to be feasibly detected via on-scalp recordings, they need to be focal, reliably sampled by in-helmet MEG, and frequently occurring. Furthermore, in order to compare IED properties across MEG/EEG sensors, the IED configuration should be as simple as possible, preferably distinct, solitary sharp waves or spikes. To identify potential participants that met these criteria, scalp EEG of ten adult, cognitively intact epilepsy patients under optimal pharmacological treatment who had undergone long-term video EEG (with antiepileptic drugs withdrawn during registration) as part of an epilepsy evaluation at the department of clinical neurophysiology at the Karolinska University Hospital during 2017–2018 were screened. The six focal epilepsy patients fulfilling the inclusion criteriae and exhibiting the greatest number of IEDs were contacted. Their off medication IED rate resembled averaged number of IEDs per hour as seen in the literature (Iwasaki et al., 2005). Three of these agreed to be screened for inclusion in the benchmarking study. These three patients subsequently underwent an in-helmet MEG recording with co-registration of EEG, electrooculography (EOG), and electrocardiography (ECG). These recordings were used to identify patients with IEDs that are clearly visible on MEG. For EEG, a 10–20 montage with 21 channels was used. During measurements, patients were seated upright and instructed to try to stay awake. Data was recorded for one hour: 30 minutes with eyes closed and 30 minutes with eyes open. Two patients with prominent in-helmet MEG detected IEDs were invited to participate in further measurements involving both in-helmet and on-scalp MEG. One patient (female, 45 years old) agreed to further participation. This patient is diagnosed with left temporal lobe epilepsy and underwent epilepsy surgery in 1996, resulting in only a short period of seizure freedom. During a long-term video EEG registration off antiepileptic pharmacological treatment, this patient exhibited approximately 15 IEDs during 10 minutes of resting state recording. However, due to patient safety, the benchmarking study was performed with optimal pharmacological treatment, reducing the number of IEDs (Goncharova et al., 2016).

2.4. Benchmarking measurements and analysis

The main measurements involved consecutive in-helmet and on-scalp MEG measurements from the epilepsy patient and were conducted in accordance with the benchmarking protocol described by Xie et al., (Xie et al., 2017). In short, this protocol involves an initial measurement session using in-helmet MEG, from which the magnetic fields related to the brain activities of interest are projected to the scalp to guide the placement of the on-scalp MEG system, currently having a small and limited scalp coverage. The on-scalp MEG measurement was hereafter performed during a separate recording session.

2.4.1. In-helmet MEG session

2.4.1.1. Measurements. An initial measurement session of one hour was performed, involving in-helmet MEG with co-registered EEG, EOG, and ECG. EEG was recorded with the 21 electrodes previously mentioned, based on the 10–20 placement system. A total of 74 points of the head including the 21 EEG electrodes were digitized with a Polhemus Fastrak system. During the session, the patient was asked to rest with closed eyes, while remaining awake during measurements. Data was sampled at 5000 Hz, online low and high pass filtered at 1650 and 0.1 Hz, respectively. The EEG data was recorded together with the MEG data, using the TRIUX EEG channels.

2.4.1.2. Analysis. In-helmet MEG data was initially pre-processed using MaxFilter (Elekta Neuromag) signal-space separation (Taulu and Simola, 2006) (buffer length 10 s, cut-off correlation coefficient at 0.98). The EEG signal and the maxfiltered raw in-helmet MEG data was filtered using a 1–40 Hz Butterworth band-pass filter in order to allow visual inspection of the signal. IEDs were detected via visual inspection of the in-helmet MEG and co-registered EEG data by a physician (KW) trained in IED detection both in EEG and MEG data. IEDs were averaged across events and source localization was performed using software package MNE Python (Gramfort et al., 2013). Minimum norm estimates (MNE) (Hämäläinen and Ilmoniemi, 1994) was used to localize the IED origin (Fig. 1). To this end, the patient's clinical MRI (magnetic resonance imaging) was used to create a full head and brain segmentation using FreeSurfer (Dale et al., 1999; Fischl et al., 1999). The segmentation was used to determine skin, skull, and brain surface boundaries using the MNE-C software watershed algorithm (Gramfort et al., 2013). A source and single compartment volume conductor model based upon these were created using MNE-C. The locations of the peak positive and negative magnetic fields of the IEDs averaged across events were determined and plotted alongside the EEG electrode positions on a model of the patient's head that included the EEG cap and 74 digitalization points (Fig. 2). These projections and points were used to guide the positioning of the on-scalp MEG sensor array at the center of both the positive and negative peak field positions on the patient's head.

2.4.2. On-scalp MEG session

2.4.2.1. Measurements. Two consecutive one-hour on-scalp MEG sessions were performed with the high-T_c-MEG central sensor pointing at the center of each peak field position (Fig. 2). The patient was seated upright with closed eyes and asked to stay awake, similar to the in-helmet MEG measurements in Session 1. For each peak field position, co-registration of EEG was performed using the 10–20 system. During the positive peak field registration, one electrode was removed and two were slightly shifted; during the negative peak field registration, three electrodes were removed in order to make room for the on-scalp MEG system. Data from the on-scalp MEG was acquired through analog channels of the TRIUX. On-scalp MEG data and co-registered EEG was sampled and filtered as in the in-helmet session (see *2.4.1.1, In-helmet MEG session, Measurements).*

2.4.2.2. Analysis. EEG data was preprocessed as in the in-helmet MEG session. From the two on-scalp MEG recording sessions (one at the maximum field peak projected from the IEDs registered in the in-helmet MEG, one at the minimum field peak) only data from the maximum peak field recording was analyzed. Data from the minimum field peak was unfortunately rendered useless due to the removal of EEG electrodes in order to fit the cryostat, making inspection of the EEG difficult and IED detection unreliable, if not impossible. Any minimum peak on-scalp findings would hence be impossible to validate against EEG-recorded IEDs. In the data from the maximum field measurement, one high-T_c

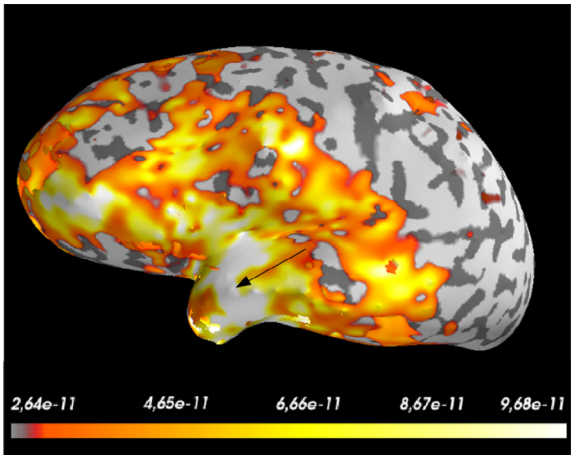


Fig. 1. Source localization of (interictal epileptiform discharges) IEDs. Source reconstruction using (minimum norm estimate) MNE (unit: amperemeter (Am)) of averaged IEDs found in the in-helmet MEG measurement. Peak of IED activity marked by arrow.

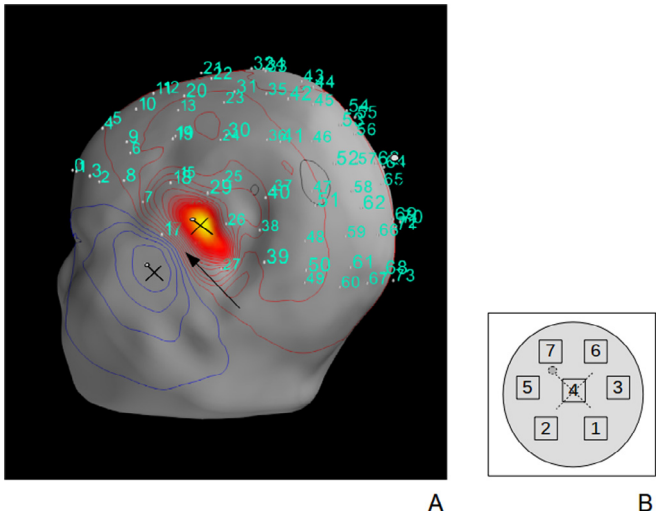
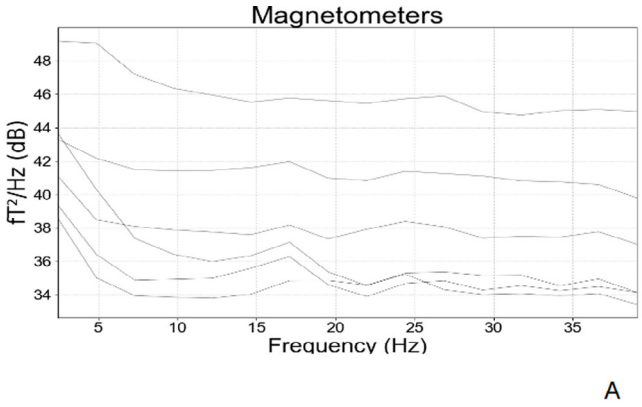


Fig. 2. Placement of on-scalp magnetencephalography MEG sensor system. On-scalp MEG recordings (sensor layout of the on-scalp MEG system as in 2B) were performed at maximum (red) and minimum (blue) peak magnetic fields of averaged interictal epileptiform discharges (IEDs) from the in-helmet MEG measurement. Peak IED activity indicated by arrow. Position of digitalized EEG electrodes in cyan (2A). The sensors were positioned as indicated by the hair cross.

sensor was excluded due to high noise. Internal noise levels of the remaining high-T_c sensors were 35–46 fT/Hz$^{1/2}$ across frequencies 1–40 Hz. The average amplitude of internal sensor noise was approximately 1000 fT in three sensors, and approximately 2000 fT in the remaining two sensors (Fig. 3A-B). Since continuous head position indicator coils cannot be used during the on-scalp MEG measurement session, head movement compensation cannot be performed. High-amplitude, low-frequency movement artifacts thus occur intermittently during the recording. Visual inspection of on-scalp MEG epochs locked to IEDs in the EEG recording (hereafter referred to as EEG-positive IEDs) revealed that some of these on-scalp IEDs were sharp, transient events easily distinguishable from the background activity, while some were obscured by artifacts (Fig. 4A-B). Importantly, beyond these EEG-positive on-scalp MEG IEDs, the on-scalp MEG data contained a large number of high-amplitude events visually resembling the EEG-positive IEDs (Fig. 5), but without any coinciding IEDs in the co-registered EEG to validate them. Thus, visually distinguishing which of these events that might be EEG-negative, on-scalp MEG-positive IEDs, and which might be artifacts or epilepsy-related, non-IED focal activity was not possible, and an alternative approach to IED detection in this data was developed. Inspection of the dataset was performed with bandpass filtering 1–40 Hz and 5–20 Hz. Frequency bands were chosen so as to optimize visual inspection of IEDs and reduce movement and muscular artifacts.



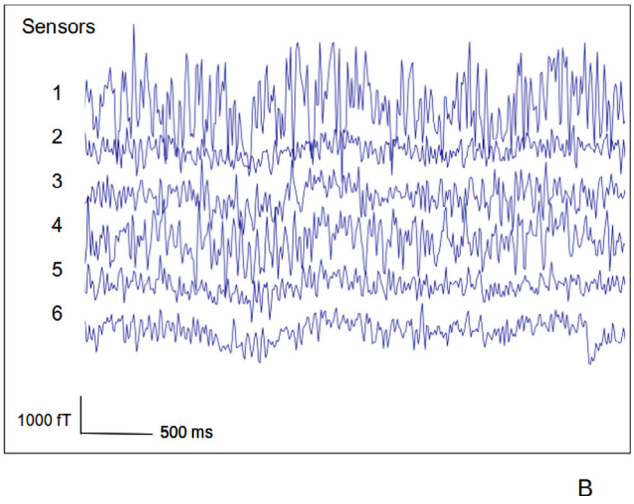


Fig. 3. Clearly visible EEG-positive on-scalp MEG interictal epileptiform discharge (IED). Raw on-scalp MEG data with IED also seen in co-registered EEG clearly standing out from the background activity. Data filtered 1–40 Hz. Numbering refers to sensor layout geometry (see Fig. 2).

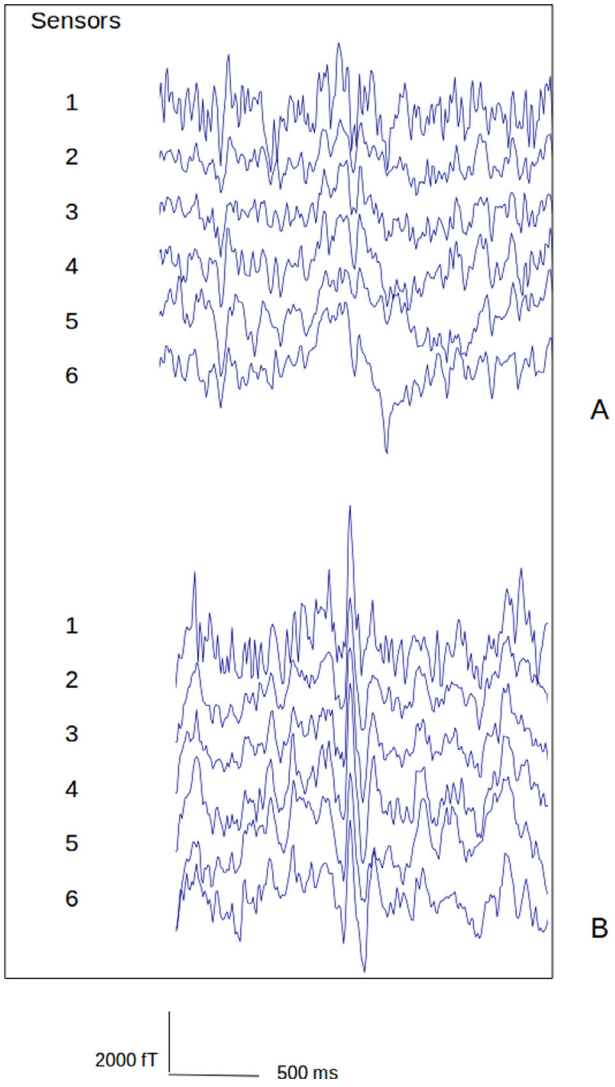


Fig. 4. EEG-positive on-scalp MEG interictal epileptiform discharge (IED) obscured by artifacts. Raw on-scalp MEG data epoch coinciding with an IED in the co-registered EEG. Data filtered 1–40 Hz. Numbering refers to sensor layout geometry as seen in Fig. 2.

2.5. Spike detection

2.5.1. In-helmet MEG session data

IED detection was performed as described in 2.4.1.2 *In-helmet MEG session, Analysis.*

2.5.2. On-scalp MEG session data

In order to reveal whether the on-scalp MEG raw data contained any EEG-negative IEDs, a detection algorithm based upon inherent data characteristics of the on-scalp MEG data was needed. However, it is not initially given what data parameters should be used to distinguish on-scalp IED events. Definitions of interictal activity are largely arbitrary descriptions of scalp EEG-IED morphology, which varies greatly between patients (Kane et al., 2017). In order to capture their appearance, IED-detection algorithms typically depend on feature extraction from a large number of IEDs followed by classification, which can be performed using machine learning, template matching, or independent component analysis, amongst others (Wilson and Emerson, 2002). Here, we aimed to employ a similar approach combined with anomaly detection. Due to the expected difference in on-scalp and in-helmet MEG data character-

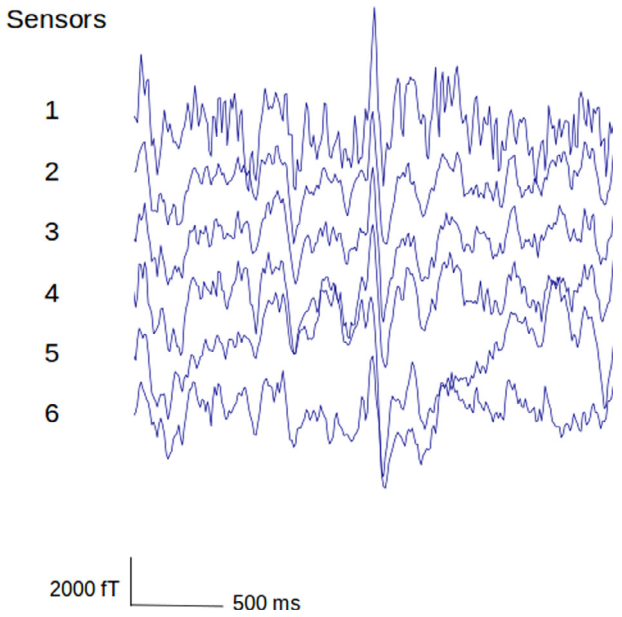


Fig. 5. On-scalp MEG high-amplitude event. High-amplitude event from on-scalp MEG raw data not coinciding with any IED in co-registered EEG. Data filtered 1–40 Hz. Numbering refers to sensor layout geometry (see Fig. 2).

istics, in-helmet MEG IEDs could not be used as templates. The one existing on-scalp recording (our current recording) therefore had to be used both for parameter extraction and spike detection validation. In order to minimize overfitting, a genetic algorithm (Mitchell, 1998) was used to create artificial data parameter vectors resembling the corresponding real on-scalp IED data parameters.

First, on-scalp MEG IEDs time locked to IEDs found by visual inspection of the EEG-recording were located. The parameters of Table 1 were extracted from these EEG-positive on-scalp MEG IEDs creating *IED feature vectors*. The genetic algorithm was used to generate *synthetic IED feature vectors* resembling these. *Non-IED feature vectors* were obtained by extraction Table 1 parameters from IED-free raw data. *Artificial IED feature vectors* and *non-IED feature vectors* were used to train the support vector machine (SVM) (Pedregosa et al., 2011). Secondly, the SVM was evaluated on the EEG-positive on-scalp MEG IEDs, calling correctly classified ones "true positives", and incorrectly classified ones "false negatives". Third, classification was performed on the remaining on-scalp MEG raw data set. Positive peaks of each wave constituted the center of an epoch from which a feature vector was extracted, and classification was performed upon these vectors. Thus, on-scalp MEG events with similar statistical properties as the EEG-positive on-scalp MEG IEDs will be found (and called *potential IEDs)*.

Since it is central to the IED definition that such an activity should stand out against the background activity, an IED can be considered a time series anomaly (Chandola et al., 2009; Kane et al., 2017). Only potential IEDs constituting discordant events should be kept. To this end, changes in the extracted parameters induced by the potential IEDs were quantified and only events exhibiting an equal or larger change than the smallest change exhibited by the EEG-positive on-scalp IEDs were kept. These were labeled *likely IEDs.* (For details, see Appendix.).

The spike detection algorithm was also applied to the in-helmet MEG measurement to evaluate its effectiveness.

Features extracted from EEG positive on-scalp MEG IEDs used to create artificial IED feature vectors used to train a support vector machine (SVM) for on-scalp MEG IED detection (for details, see Appendix).

Table 1
Features extracted from EEG positive on-scalp MEG interictal epileptiform discharges (IEDs).

Features extracted from EEG-positive on-scalp MEG IEDs
Standard deviation
Skewness
Mean
Kurtosis
Sum of points in time series
Maximum value of time series
Minimum value of time series
Range of time series
Energy of time series
Integral of time series
Duration of peak
Fractal dimension
Variance
Slope of peak

3. Results

3.1. In-helmet MEG session

3.1.1. EEG data

From the EEG data co-registered with the in-helmet MEG recording, a total of 16 IEDs were identified via visual inspection.

3.1.2. In-helmet MEG data

Visual inspection of the in-helmet MEG data revealed 24 IEDs. While 16 of these coincided with the EEG IEDs, the remaining eight in-helmet MEG IEDs were not visible in the EEG data. MNE source localization of averaged IEDs placed the epileptic focus of the MEG IEDs in the left temporal lobe (cf. Fig. 1). Amplitude of averaged IEDs was 2000 femtotesla (fT) IED duration was approximately 0.1–0.2 seconds.

3.2. On-scalp MEG session

3.2.1. EEG data

From the EEG data co-registered with the on-scalp MEG recording, a total of 16 IED events were detected in left temporal lobe channels, similarly to in the in-helmet MEG recording.

3.2.2. On-scalp MEG data

The 16 IEDs located in the co-registered EEG data could be identified upon averaging (see Fig. 6). These had an approximate amplitude of 4000 fT and a duration of approximately 0.2 seconds.

3.3. Spike detection algorithm

First, the combined genetic algorithm-support vector machine (GA-SVM) was evaluated on the 16 EEG-identified IEDs events in the on-scalp MEG data (see Fig. 4 for example of raw IEDs). Amplitude of averaged such EEG-identified on-scalp IEDs was 4000 fT. Of these, 11 events were correctly classified. Inspection of the 5 false negative epochs revealed that these on-scalp MEG events contained artifacts obscuring the IED. See Fig. 7 for an average of the true positive and false negative EEG-positive on-scalp MEG IEDs; see Fig. 4A for an example of a raw false negative event. Second, the GA-SVM was used to detect potential IEDs in the raw on-scalp MEG data. A total of 4623 epochs were extracted, as described in Appendix, from the part of the on-scalp MEG recording on which classification was performed. Out of these, 416 events were classified as *potential* IEDs. Third, the potential IEDs constitut-

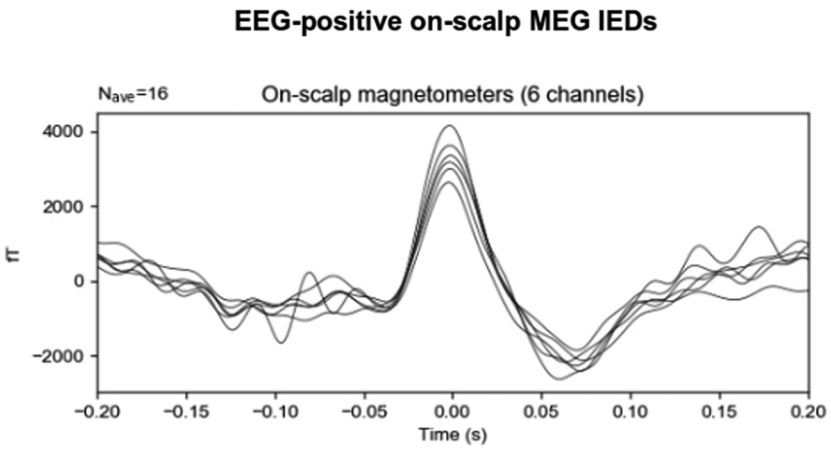


Fig. 6. EEG-positive on-scalp MEG interictal epileptiform discharge (IED)s. Average of all on-scalp MEG events coinciding with IEDs in co-registered EEG.

ing anomalies (see Appendix for details) were kept and considered as *likely IEDs*. The on-scalp MEG recording contained 31 such likely IEDs not seen by the co-registered EEG (see Fig. 8 for average of these, and Fig. 9 for examples of such events in raw data). Amplitude of the averaged likely IEDs was 3000 fT. Duration of these events was approximately 0.2 seconds.

Applying the spike detection algorithm on the in-helmet MEG data revealed that the algorithm correctly identified 20 out 24 IEDs, and no additional false positive events were located.

4. Discussion

We present the first-ever on-scalp MEG epilepsy study with the aim to investigate whether the sensor technology could improve non-invasive IED detection. Both on-scalp and in-helmet MEG, with co-registered EEG, was recorded consecutively from the same temporal lobe epilepsy patient. A novel on-scalp MEG IED-detection algorithm was also developed to help discern IEDs from the on-scalp MEG background activity. Below, the following

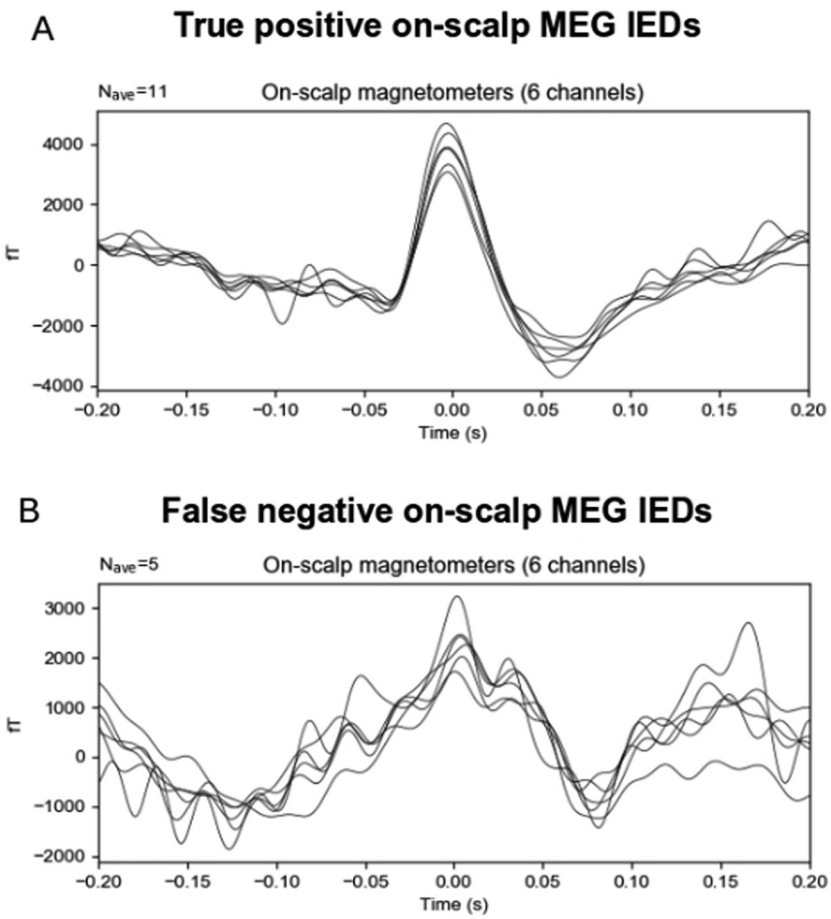


Fig. 7. Validation of genetic algorithm-support vector machine (GA-SVM) algorithm on EEG-positive on-scalp MEG interictal epileptiform discharge (IED)s. On-scalp MEG events coinciding with IEDs in co-registered EEG correctly classified as IEDs by the GA-SVM algorithm (7A), and on-scalp MEG events coinciding with IEDs in co-registered EEG not classified as IEDs (7B).

aspects are discussed separately: (4.1) the feasibility of benchmarking recordings on epilepsy patients and (4.2) registration and detection of IEDs.

4.1. Benchmarking protocol/on-scalp measurement

Data presented in this study rely on an initial careful screening of suitable epilepsy patients, and the development of a reliable benchmarking protocol. From the perspective of a study protocol, we deem on-scalp MEG recordings of epileptogenic foci activity feasible, but for now limited to patients capable of adhering to the benchmarking protocol. The temporal lobe epilepsy patient included herein exhibits relatively frequent IEDs, which enables source localization from the in-helmet MEG recording, and thus accurate placement of the on-scalp MEG system for sampling of the maximal field generated by the IEDs. However, epileptogenic foci that are difficult to localize by EEG or in-helmet MEG would hinder such optimal positioning of the on-scalp MEG system and provide poor benchmarking data, at least in studies using an on-scalp MEG array with limited coverage as we do here. A limited-coverage on-scalp MEG system is thus unlikely to be suited for measurements on patients with inconclusive non-invasive recordings, thus requiring intracranial measurements for localization (Gonzalez-Martinez et al., 2014; Jayakar et al., 2014).

4.2. Registration and detection of IEDs

EEG data was co-registered with MEG in both the in-helmet and on-scalp MEG recordings. From each EEG data set, we could successfully detect 16 IEDs using visual inspection, indicating that the occurrence rate of IEDs in the patient were the same during both recordings. From the in-helmet MEG data, we could independently detect the same 16 IEDs found in the EEG data, plus an additional 8 MEG-positive IEDs. This is in line with the literature on IEDs in MEG and EEG, where MEG typically demonstrates a higher sensitivity to IEDs (Stefan et al., 2003; Knake et al., 2006). While the IEDs in on-scalp MEG data could not be readily discriminated from other high-amplitude activities using visual inspection alone, we could guide the visual identification of the IEDs using the co-registered EEG data to validate on-scalp MEG IEDs. Leaning on EEG, we could thus identify 16 IEDs also in the on-scalp MEG data. When averaged, these on-scalp MEG IEDs revealed a prominent peak followed by hyperpolarization (Fig. 6). Duration of these events were similar to IEDs occurring in the in-helmet measurement. They showed typical characteristics of IEDs once we knew where they were, but were too difficult to reliably discern from other events in the data using vision alone.

To explore the on-scalp MEG data for additional IEDs, we therefore used an IED detection algorithm that focuses on the abstract statistical features of IEDs, rather than their characteristic visual appearance. Evaluation of this approach on in-helmet MEG data demonstrate that the algorithm successfully discriminates between IEDs and the background activity of the patient's epileptogenic focus. In the on-scalp MEG data, the EEG-positive IEDs not obscured by artifacts were detected, plus an additional 31 on-scalp MEG-unique events likely to be IEDs. In comparison to in-helmet MEG, where MEG data showed 8 IEDs in addition to the 16 IEDs also seen by EEG, this demonstrates a potential increase in IED detection compared to EEG from 50% using in-helmet MEG to almost 200% using on-scalp MEG. By definition, an IED is a transient event distinguishable from the background with a stereotypic peak, often with a higher amplitude than physiological cortical activity and a duration from 0.1 to 0.7 seconds (Kane et al., 2017). Visual inspection of such on-scalp MEG-unique events in Fig. 9 reveal that these requirements are fulfilled. Furthermore, these events are consistent across channels which would not have been the case had these events been randomly distributed noise. Neither do the raw noise data contain any sharp events resembling the patient's IEDs (Fig. 3). Our results thus demonstrate a feasibility in registering and detecting IEDs in on-scalp MEG data, but also show that the added complexity in on-scalp MEG data might require assistance from algorithms so pick up on the abstract statistical features of IED events.

Inspection of in-helmet MEG IEDs and EEG-positive on-scalp MEG IEDs reveal that the field magnitude of these on-scalp MEG IEDs were roughly two times larger than the amplitude of in-helmet MEG IEDs (4000 fT and 2000 fT, respectively). This increase is in accordance with modeling predictions of the field strength acquired through a one-channel system employing the same type of on-scalp sensor used here (Xie et al., 2015, 2017). The amplitude of the 31 additional on-scalp MEG IEDs on the other hand exhibit a lower amplitude (3000 fT, Fig. 8) than do the EEG-positive ones (Fig. 6). These amplitude differences may explain why on-scalp MEG can detect IEDs that are not identified by EEG. Tao et al., have reported that the majority of IEDs visible on scalp EEG arise from hypersynchronization of at least 10 cm^2 cortex, and no IED originating from cortical patches smaller than 6 cm^2 can be detected with scalp EEG. However, the majority of IEDs recorded intracranially arise from smaller areas and remain undetected by scalp EEG (Tao et al., 2005). Indeed, the region capable of generating

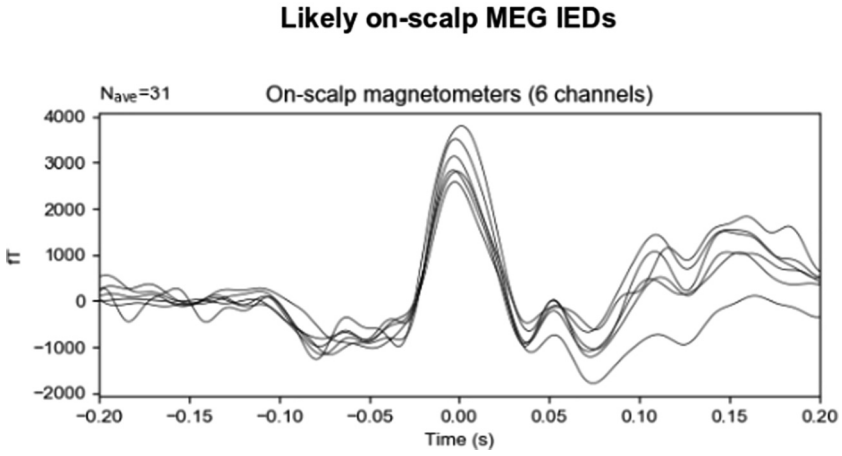


Fig. 8. Likely on-scalp MEG interictal epileptiform discharges (IEDs). Average of the 31 on-scalp MEG events deemed likely IEDs by the on-scalp MEG-specific IED detection algorithm.

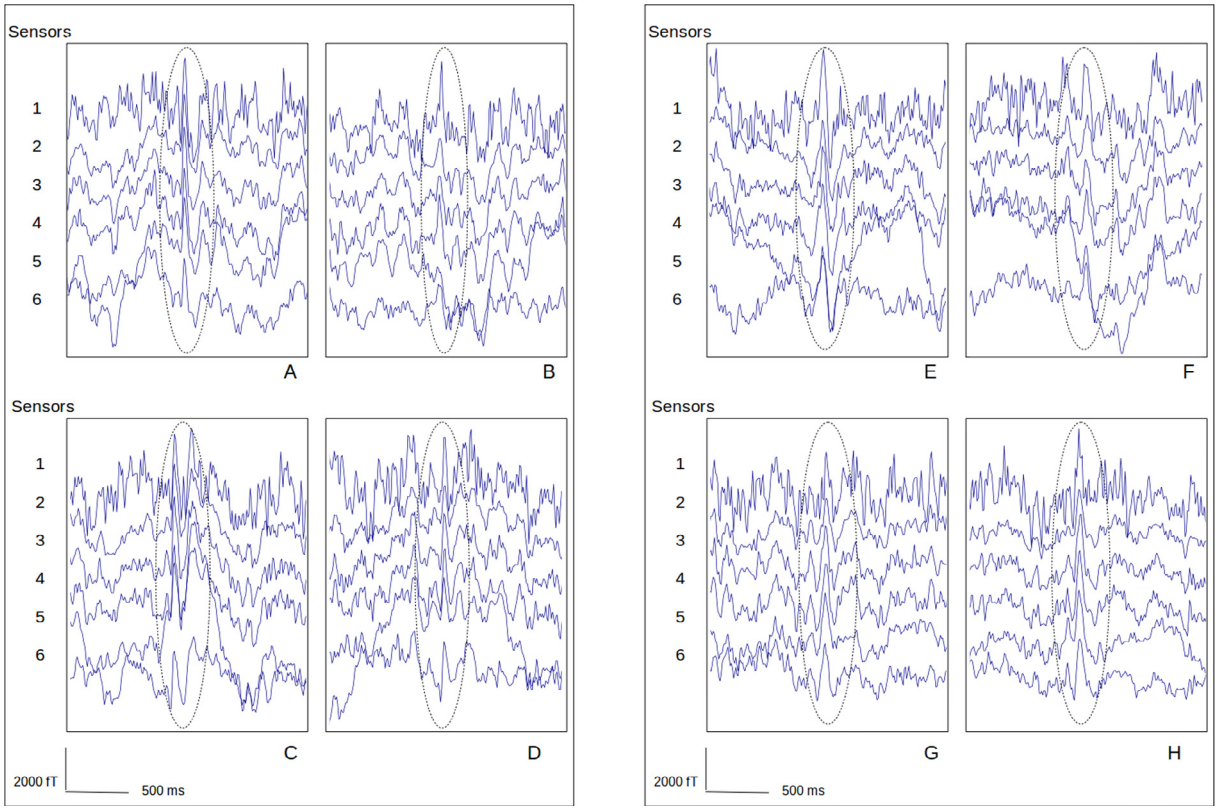


Fig. 9. Examples of likely interictal epileptiform discharges (IEDs) in raw on-scalp MEG data. Raw on-scalp MEG data containing events deemed as likely IEDs by the on-scalp MEG-specific IED detection algorithm.

IEDs, the irritative zone (Rosenow and Luders, 2001; Jehi, 2018), is organized in subregions which might independently generate epileptic activity (Keller et al., 2010; Wilke et al., 2011; Sabolek et al., 2012; Janca et al., 2018). It is thus possible that the additional IEDs detected in on-scalp MEG arise from such functional subunits of an epileptic network. Today, characterization of functional connectivity within a small region is impossible using EEG or in-helmet -MEG (Schoffelen and Gross, 2009). However, it is possible that the improved source separation and neural signal amplitude of the on-scalp MEG measurement (Boto et al., 2016; Riaz et al., 2017) would allow not only identification of such subunits, but also characterization of network dynamics. These are of course issues that need to be further explored in future on-scalp MEG measurements on epilepsy patients.

4.3. Challenges and limitations

There are several limitations to this study. The ultimate value of on-scalp MEG epilepsy recordings can be said to depend on the extent to which on-scalp MEG can acquire information that is not available to in-helmet MEG or other existing non-invasive technologies. We present a successful benchmarking protocol that may be used to demonstrate the identification of IEDs uniquely detected by on-scalp MEG. However, the data consist of just one session from a single patient using a relatively small on-scalp MEG sensor array. While we wish the reader to be aware of this limitation, we also wish to stress that studies with singleton subjects are often seen when new MEG instrumentation and methods are explored in novel applications, especially so on patients. Several published on-scalp MEG studies (e.g. Andersen et al., 2017; Xie et al., 2017; Boto et al., 2018) follow this tradition and present single subject studies. Such single-subject studies allow for a continuous development of study protocols alongside on-scalp MEG instrumentation development. Indeed, also in the early days of conventional MEG, the optimization of in-helmet MEG study design occurred through studies on singleton subjects (see e. g. Tiihonen et al., 1989; Chiarenza et al., 1991; Paetau et al., 1991; Ahlfors et al., 1992; Forss et al., 1995).

To further evaluate the potential usefulness of on-scalp MEG in epilepsy, as well as to evaluate the GA-SVM approach for IED detection, further studies are needed: preferably with larger-coverage (ideally whole-head) on-scalp MEG system, preferably on several epilepsy patients, and preferably with a higher-density co-registered EEG in both conventional and on-scalp MEG. The present study demonstrates that such studies are feasible, both from the perspective of screening suitable patients and from the perspective of a data recording protocol.

5. Conclusions

In this study, we present data from measurements on a temporal lobe epilepsy patient, where both on-scalp MEG data and in-helmet MEG data are obtained and compared. Using a benchmarking protocol aimed to quantify the amount of IEDs that are captured by on-scalp MEG, as compared to in-helmet MEG, we employed a novel automatic IED detection algorithm validated on the patient's in-helmet MEG recording. The results indicate that we were able to find almost twice as many IEDs in the on-scalp MEG recording (47 IEDs: 16 EEG positive IEDs and 31 MEG-only IEDs) as we did in the in-helmet MEG measurement (24: 16 EEG positive IEDs and 8 MEG-only IEDs). It is possible that the additional IEDs detected in on-scalp MEG stem from cortical sources that are too small to be reflected in EEG or in-helmet MEG, potentially indicating that the on-scalp MEG system can identify IEDs

that are not detectable by other non-invasive methods. Additional studies are needed to further evaluate the potential clinical usefulness of on-scalp MEG in epilepsy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.03.041.

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