Epilepsy Research 124 (2016) 23–33

Contents lists available at www.sciencedirect.com

Epilepsy Research

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

Preoperative evaluation using magnetoencephalography: Experience in 382 epilepsy patients

I.A. Nissen[a,*], C.J. Stam[a], J. Citroen[a,1], J.C. Reijneveld[b], A. Hillebrand[a]

[a] Department of Clinical Neurophysiology and MEG Center, Neuroscience Campus Amsterdam, VU University Medical Center, Postbus 7057, 1007 MB, Amsterdam, The Netherlands
[b] Brain Tumor Center Amsterdam & Department of Neurology, VU University Medical Center, Postbus 7057, 1007 MB, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 16 June 2015
Received in revised form 3 October 2015
Accepted 9 May 2016
Available online 10 May 2016

Keywords:
MEG
Refractory epilepsy
Epileptogenic zone
Source localization
Surgery

ABSTRACT

Objective: Identifying epilepsy patients for whom clinical MEG is likely to be beneficial avoids or optimizes burdensome ancillary investigations. We determined whether it could be predicted upfront if MEG would be able to generate a hypothesis about the location of the epileptogenic zone (EZ), and in which patients MEG fails to do so.
Methods: MEG recordings of 382 epilepsy patients with inconclusive findings regarding EZ localization prior to MEG were acquired for preoperative evaluation. MEG reports were categorized for several demographic, clinical and MEG variables. First, demographic and clinical variables were associated with MEG localization ability for upfront prediction. Second, all variables were compared between patients with and without MEG location in order to characterize patients without MEG location.
Results: Our patient group had often complex etiology and did not contain the (by other means) straightforward and well-localized cases, such as those with concordant tumor and EEG location. For our highly-selected patient group, MEG localization ability cannot be predicted upfront, although the odds of a recording with MEG location were significantly higher in the absence of a tumor and in the presence of widespread MRI abnormalities. Compared to the patients with MEG location, patients without MEG location more often had a tumor, widespread EEG abnormalities, non-lateralizing MEG abnormalities, non-concordant MEG/EEG abnormalities and less often widespread MRI abnormalities or epileptiform MEG activity. In a subgroup of 48 patients with known surgery outcome, more patients with concordant MEG and resection area were seizure-free than patients with discordant results.
Conclusions: MEG potentially adds information about the location of the EZ even in patients with a complex etiology, and the clinical advice is to not withhold MEG in epilepsy surgery candidates. Providing a hypothesis about the location of the EZ using MEG is difficult in patients with inconclusive EEG and MRI findings, and in the absence of specific epileptiform activity. More refined methods are needed for patients where MEG currently does not contribute to the hypothesis about the location of the EZ.

1. Introduction

Epilepsy is one of the most common neurological disorders (Hirtz et al., 2007; Siniatchkin and Koepp, 2009), affecting both children and adults. Currently, 65 million people throughout the world carry the diagnosis epilepsy (Thurman et al., 2011). The majority of patients is treated successfully with anti-epileptic drugs (AED), but approximately one third continues having seizures (Kwan and Brodie, 2000; Sander, 2003). A patient is considered pharmacoresistant (having refractory epilepsy) when two or more adequate trials of appropriately chosen and tolerated anti-epileptic drugs fail to achieve sustained seizure freedom (Kwan et al., 2010). In that case, the patient is a potential candidate for epilepsy surgery. For successful epilepsy surgery it is essential to accurately identify the epileptogenic zone (EZ) and delineate it from eloquent brain areas.

The EZ is defined as the area that needs to be resected to ensure seizure freedom (Luders et al., 2006; Rosenow and Lüders, 2001) and can only be confirmed postoperatively. Preoperative evaluation aims to develop a hypothesis about both the location of the EZ (Rosenow and Lüders, 2001) and whether resection of that

* Corresponding author at: Department of Clinical Neurophysiology, VU University Medical Center, Postbus 7057, 1007 MB, Amsterdam, The Netherlands.
E-mail addresses: i.nissen@vumc.nl, idaanissen@gmail.com (I.A. Nissen), cj.stam@vumc.nl (C.J. Stam), j.citroen@slaz.nl (J. Citroen), jc.reijneveld@vumc.nl (J.C. Reijneveld), a.hillebrand@vumc.nl (A. Hillebrand).
[1] Present address: Department of Neurology, Sint Lucas Andreas Hospital, Postbus 9243, 1006 AE, Amsterdam, The Netherlands.

http://dx.doi.org/10.1016/j.eplepsyres.2016.05.002
0920-1211/

area will cause functional impairment. Magnetoencephalography (MEG) is useful for both purposes (Ochi and Otsubo, 2008; Pataraia et al., 2004; Paulini et al., 2007; RamachandranNair et al., 2007; Seo et al., 2011; Tovar-Spinoza et al., 2008). Several studies have demonstrated that MEG has better temporal resolution than functional magnetic resonance imaging (MRI) (Dale et al., 2000; Zotev et al., 2008) and better spatial resolution than electroencephalography (EEG) (Ebersole and Ebersole, 2010). Structural lesions are detectable using MRI, but many epilepsy patients are MRI-negative (Berg et al., 2003; Semah et al., 1998) and the EZ may not always coincide with the structural lesion (Aubert et al., 2009; Cohen-Gadol et al., 2004; Otsubo et al., 2001; Paulini et al., 2007). MEG may therefore achieve localization of the EZ in cases where EEG (Pataraia et al., 2004; Paulini et al., 2007; Stefan et al., 2003) or MRI (Jung et al., 2013; Paulini et al., 2007; RamachandranNair et al., 2007; Wilenius et al., 2013) do not succeed. As a result, MEG increases the number of eligible patients for epilepsy surgery (Stefan et al., 2011). An emerging additional clinical application of MEG is to aid in the planning of invasive recordings with grids and/or depth electrodes (Knowlton et al., 2009; Stefan et al., 2011). In some cases non-invasive techniques fail to derive a clear hypothesis about the location of the EZ, and in these cases invasive recordings are needed for epilepsy surgery planning (Bulacio et al., 2012; Kim et al., 2010; Taimouri et al., 2014). However, intracranial electrodes have limited spatial coverage and MEG might enable placement near the hypothesized location of the EZ and thus improve the yield of this invasive procedure (Blount et al., 2008; Knowlton et al., 2009; Stefan et al., 2011).

Successful application of MEG in preoperative evaluation of epilepsy patients has been described in several studies, where agreement of MEG localization with the resected area correlated with postoperative seizure freedom (Bast et al., 2004; Fujiwara et al., 2012; Genow et al., 2004; RamachandranNair et al., 2007). It is not yet clear which patients benefit most from MEG recordings in clinical practice and which factors determine success or failure to provide a hypothesis about the location of the EZ using MEG. Identifying the patients for whom MEG is likely to be able to localize abnormal activity (epileptiform or non-epileptiform) avoids or improves the planning of other burdensome investigations and reduces risks and costs for these patients. For those patients for whom MEG is unable to localize abnormal activity we want to understand why this is the case, and what could be improved in current methodologies.

In this paper we report on a clinical database of 382 epilepsy patients, who underwent a clinical MEG recording. The key first question to be answered is whether it can be predicted upfront, on the basis of patient characteristics, medical history and ancillary investigations (e.g. MRI and EEG findings), whether MEG will be able to localize abnormal activity (epileptiform or non-epileptiform), i.e. provide a hypothesis about the location of the EZ. The second key question is what the clinical characteristics are of patients in whom MEG is unable to localize abnormal activity. The answer to the first question allows to optimize referrals for clinical MEG, whereas the answer to the second question gives ground for new research into optimizing recording and analysis strategies.

2. Methods

2.1. Patients

382 patients with epilepsy had a clinical MEG recording between January 1st 2010 and December 31st 2013 at the VU University Medical Center, Amsterdam, The Netherlands, as part of their preoperative evaluation. The VU University Medical Center is a tertiary referral center for epilepsy surgery. Patients were referred for clinical MEG by the three largest epilepsy centers in the Netherlands (Stichting Epilepsie Instellingen Nederland/VU University Medical Center; University Medical Center Utrecht; Kempenhaege/Maastricht University Medical Center). Of note, most patients were referred for MEG because previous workup through EEG and MRI was insufficient to generate a reliable hypothesis about the location of the EZ. The straightforward and well-localized cases, such as those with concordant tumor and EEG location, underwent surgery without getting a clinical MEG during their preoperative evaluation. Patients were not subjected to procedures and were not required to follow rules of behavior other than routine clinical care, hence approval for this study by the institutional review board and informed consent was not required according to the Dutch health law of February 26, 1998 (amended March 1, 2006), i.e. Wet Medisch-Wetenschappelijk Onderzoek met mensen (WMO; Medical Research Involving Human Subjects Act), division 1, Section 1.2.

2.2. MEG recordings

MEG recordings were acquired using a 306-channel whole-head MEG system (Elekta Neuromag Oy, Helsinki, Finland), containing 102 magnetometers and 204 gradiometers. The patients were in supine position inside a magnetically shielded room (Vacuumschmelze GmbH, Hanau, Germany). Recordings typically involved paradigms for the localization of eloquent cortex, such as voluntary movements and somatosensory stimulation (see Hillebrand et al. (2013)), as well as eyes-closed resting state recordings for the identification and localization of interictal epileptiform activity. Typically, three spontaneous datasets of 15 min each were recorded. The data were sampled at 1250 Hz, and filtered online with a 410 Hz anti-aliasing filter and a 0.1 Hz high-pass filter.

The head position relative to the MEG sensors was recorded continuously using signals from 4 or 5 head-localization coils. The head-localization coil positions and the outline of the scalp (roughly 500 points) were digitized with a 3D digitizer (3Space FastTrack, Polhemus, Colchester, VT, USA). The points on the scalp surface were used for co-registration with the anatomical MRI of the patient through surface-matching.

2.3. MEG analysis

The raw data were spatially filtered offline to remove artifacts using the temporal extension of Signal Space Separation (tSSS) (Taulu and Simola, 2006; Taulu and Hari, 2009) using MaxFilter software (Elekta Neuromag, Oy). A detailed description and parameter settings can be found in (Hillebrand et al., 2013). Instances of epileptiform activity were marked manually by trained MEG/EEG technicians. The sources of selected events were found by applying dipole fitting or beamformer analysis to the spatially filtered (tSSS) data. The outcome was visualized on the co-registered MRI of the patient.

A single equivalent current dipole model was fitted to each selected event with abnormal (usually epileptiform) activity. The dipole parameters were optimized according to the least-square error criterion, which minimizes the difference between the measured field and the field computed from the dipole model. A spherical head model based on the scalp surface obtained from the anatomical MRI was used as volume conductor. Typically, dipoles exceeding a goodness-of-fit of 70% were included. Sources of slow activity (delta waves) were found using beamformer analysis. The beamformer (Elekta Neuromag Oy, beamformer) reconstructs an index of neuronal activity for each voxel ($5 \times 5 \times 5$ mm) in a predefined grid covering the entire brain (see Hillebrand et al. (2012) for details). All clinical MEG recordings were discussed in multidisciplinary meetings involving MEG technicians, MEG physicists and