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Spatiotemporal mapping of interictal epileptiform discharges in human absence epilepsy: A MEG study

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ABSTRACT

Purpose: Although absence epilepsy is considered to be a prototypic type of generalized epilepsy, it is still under debate whether generalized 3 Hz spike-and-wave discharges (SWDs) might have a cortical focal origin. Here it is investigated whether focal interictal epileptiform discharges (IEDs), which typically occur in the electro- (EEG) and magnetoencephalogram (MEG) in case of focal epilepsy, are present in the MEG of children with absence epilepsy. Next, the location of the sources of the IEDs is established, and it is investigated whether the location is concordant to the earlier established focal cortical regions involved in the generalized SWDs of these children.

Methods: Whole head MEG recordings of seven children with absence epilepsy were reviewed with respect to the presence of IEDs (spikes and sharp waves). These IEDs were grouped into distinct clusters, in which each contribution to a cluster yields a comparable magnetic field distribution. Source localization was then performed onto the average signal of each cluster using an equivalent current dipole model and a realistic head model of the cortical surface.

Results: IEDs were detected in 6 out of 7 patients. Source reconstruction indicated most often frontal, central or parietal origins of the IED in either the left and or right hemisphere. Spatiotemporal assessment of the IEDs indicated a stable location of the averages of these discharges, indicating a single underlying cortical source.

Discussion: The outcome of this pilot study shows that MEG is well suited for the detection of IEDs and suggests that their estimated sources coincide rather well with the cortical regions involved during the spikes of the SWDs. It is discussed whether the presence of IEDs, classically seen as a marker of focal epilepsies, indicate that absence epilepsy should be considered as a focal type of epilepsy, in which changes in the network are evolving rapidly.

1. Introduction

The recurrent spontaneous seizures typical for various forms of absence epilepsy, commonly but not exclusively seen in children between 4 and 12 years (Loiseau et al., 2002), are still classified as generalized (Berg and Plioplys, 2012), although it is questioned whether there are fundamental differences between generalized and focal types of epilepsy (Lüders et al., 2009; Seneviratne et al., 2012; van Luijtelaar et al., 2014).

One of the reasons for the controversy is that recent electrophysiological studies in well validated and widely used genetic absence models have revealed a cortical origin of the spike-and-wave discharges (SWDs) accompanying the clinically observed absences (Meeren et al., 2002; Polack et al., 2007). Functional MRI (fMRI) studies confirmed not only a focal cortical driving origin, but also demonstrated that SWDs propagate to distinct cortical regions (Aghakhani et al., 2004; Blumenfeld, 2007; Carney et al., 2010; David et al., 2008; Gotman et al., 2005; Moeller et al., 2013a;

Abbreviations: CAE, childhood absence epilepsy; ECD, equivalent current dipole; IEDs, interictal epileptiform discharges; MEG, magnetoencephalography; SWDs, spike-and-wave discharges.

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Tenney et al., 2013). In addition, high-resolution EEG and MEG studies in children and adults with various types of absence seizures in combination with advanced signal analytical techniques have confirmed the existence of a preferential cortical origin of SWDs. Focal cortical regions with increased connectivity were detected either in the frontal cortex, orbito-frontal, medial temporal or parietal lobe (Amor et al., 2009; Holmes et al., 2004; Tenney et al., 2013; Westmijse et al., 2009). It is obvious that this challenges the dichotomy between focal and generalized epilepsy.

The localization of the origin of interictal epileptiform discharges (IEDs) plays a major role in the presurgical work-up of patients with focal refractory epilepsy, especially, using MEG (Englot et al., 2015; Knowlton, 2008; Ossenblok et al., 2007; Pataraia et al., 2004; Stefan et al., 2003) and more recently simultaneous EEG and fMRI (Thornton et al., 2010; Zijlmans et al., 2002). Nowadays the identification of the network underlying the IEDs is an auxiliary tool for the question where to place an intracortical grid or stereotactic depth electrodes for presurgical evaluation in refractory candidates (Pataraia et al., 2004; Schulz et al., 2000; van Houdt et al., 2013, 2012; Walczak et al., 1990). Furthermore, the presence of localized IEDs has been employed to differentiate between the type of epilepsy (focal or generalized) in relation with post surgical outcome (Holmes et al., 2000). The presence of IEDs in children with the diagnosis of childhood absence epilepsy (CAE) is another challenge to the dichotomy if these IEDs appear to be localized, comparable with focal spikes and intermittent sharp waves in the EEG of patients with complex partial epilepsy. Recently, more attention has been paid to investigate whether focal epileptiform events occur in the EEG of patients with absence epilepsy. It has been reported that focal EEG abnormalities were found in 14.7% of the children with typical CAE (Caraballo et al., 2008); in other routine EEG studies these findings amounted to 34% or 56% of the patients with primary generalized epilepsy (Lombroso, 1997; Matur et al., 2009). This percentage was even higher in a study of Lagae et al. (2001), which revealed that 80% of the children with frontal onset absences showed interictal, isolated epileptiform discharges in their EEG. The presence, specifically, of focal epileptiform spikes has been reported in a few EEG studies: Leutmezer et al. (2002) reported their presence in 35% of patients with idiopathic generalized epilepsy, and 40% of patients with absence epilepsy and Yoshinaga et al. (2004) found that 52% of the children diagnosed as CAE had isolated interictal focal epileptiform spikes with no statistical difference between those who responded to treatment (Valproic acid or Ethosuximide) and those who suffered from a relapse of IEDs despite being seizure free.

In this study, the presence of IEDs in children diagnosed as having absence epilepsy with typical 3 Hz SWDs concomitant to a transient decrease of consciousness was investigated using MEG. MEG has some advances over EEG: MEG signals are less attenuated and distorted by intervening tissue layers between the brain and the recording sensors than electric potentials. MEG also has a higher spatial resolution and is therefore better able to localize sources of events than EEG since solutions to the inverse problem are more accurate (Ray and Bowyer, 2010). Lastly, MEG spikes are more clearly distinguishable from background activity and appear to be sharper, leading to a higher spike sensitivity (Ossenblok et al., 2007). A disadvantage is that MEG is less sensitive to activity of deep lying sources than EEG (de Jongh et al., 2005).

Next to the presence of IEDs and their localization in local cortical regions it is additionally described whether the underlying cortical sources of the IEDs are related to the focal cortical regions involved in the ictal 3 Hz SWD itself, as described by Westmijse et al. (2009) and Gupta et al. (2011). The outcomes of this study contribute to the discussion whether these IEDs, which are classically seen as a biomarker of focal epilepsies, should be considered as a manifestation of a focal or a generalized type of epilepsy.

Table 2.1
Summary of patient information.

Patient	Gender	Age [y]	Seizure onset age [y]	Epilepsy type	#Seizures (SWDs)*
1	M	7	6	CAE	4
2	F	12	5	CAE	3
3	M	7	5	CAE	2
4	F	8	5	CAE	3
5	F	10	5	CAE	4
6	M	14	12	JAE	5
7	F	8	7	CAE	3

* Number of seizures >4 s, see Westmijse et al. (2009) for details.

2. Methods

2.1. Patients

Seven children diagnosed with absence epilepsy by neurologists of the Academic Center of Epileptology Kempenhaeghe & Maastricht UMC+ (Heeze, the Netherlands) were included in this study. The inclusion criteria, based on the criteria for absence epilepsy of the International League Against Epilepsy (ILAE), were 3 Hz SWDs in the EEG with a minimum duration of 4 s, impairment of consciousness, no other seizure types present (either at the time of measurement or in the past, with the exception of febrile seizures), not being seizure-free at the time of measurement (medication was allowed), no major myoclonic elements present during seizures, normal neurologic development, and the mental and physical ability to participate in the measurements. All patients had experienced standard EEG monitoring for diagnostic purposes prior to their participation in this study. The anatomical MRIs, as far as available, did not show visible abnormalities. The mean age of these children at the time of measurement was 9 years (range: 7–14 years) and the mean age of seizure onset was 6 years (range: 5–12 year). The clinical information of the patients is summarized in Table 2.1. All patients had a history of subsequent use of different antiepileptic drugs (AEDs), but were not seizure-free at the time of measurement. After approval of the Committee for Research in Humans of the region Arnhem/Nijmegen-the Netherlands, written informed consent for the recordings was obtained from the parents of the patients, and in the case of the 12-year old also from the patient herself.

2.2. Data acquisition

The MEG measurements were performed at the Donders Centre for Cognitive Neuroimaging in Nijmegen, the Netherlands. The MEG system used was the whole head system, with either 151 or 275 sensors (CTF Systems Inc., VSM MedTech Ltd., Coquitlam, BC, Canada). The MEG was measured with the children in a supine position. During the 50 min recording session, data were collected in consecutive files with a duration of 5 min. For more details the reader is referred to Westmijse et al. (2009). If no SWDs were seen in the MEG signal of the first five recorded files, 3 min of hyperventilation were issued in order to provoke generalized SWDs, which was required for three out of the seven patients included. The patients performed hand movements in one of the 5 min recording sessions, meant to obtain an anatomical landmark to localize the frontal lobe activity relative to the motor cortex.

Patients above the age of 8 years received a three-dimensional MRI (MPRAGE sequence with 1 mm isotropic resolution; Siemens, Erlangen, Germany) in order to relate the functional (MEG) data to the anatomy of the individual patient. The three reference points of the revised combinatorial nomenclature system were used to co-register the functional and anatomical data, i.e. the left and right preauricular points and the nasion.

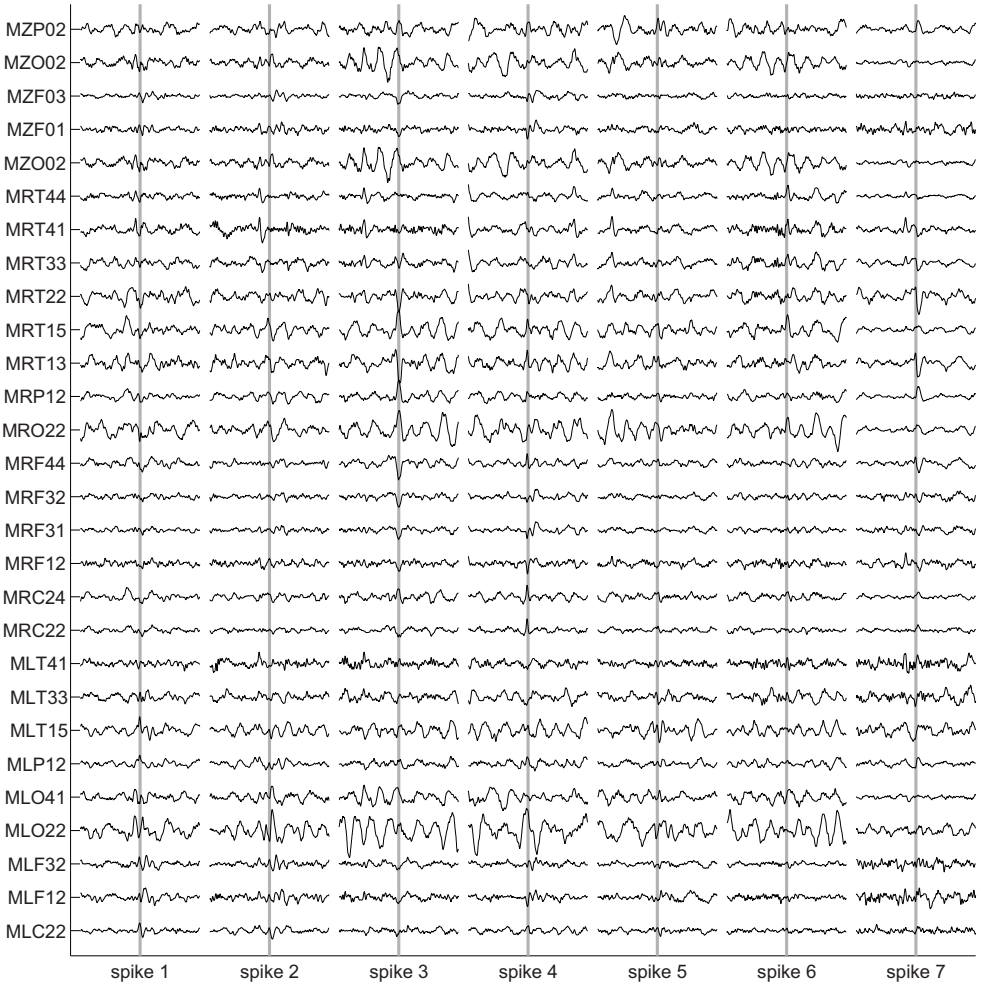

Fig. 2.1. Concatenation of several epochs containing interictal epileptiform activity as present in the raw MEG recordings of patient 1. The IEDs are visualized in epochs of 1 s, in which the IED itself is annotated in the center in gray.

The MEG recordings were visually reviewed according to the usual clinical procedures. An apparent 'abnormal' sharp transient that was clearly distinguishable from background activity was the discriminating factor. However, some sharp transients might look like interictal epileptiform discharges (IEDs), but actually are sharp transients involved in paroxysms or sharp transients within a delta wave. Therefore, only IEDs that did not occur during a rhythmic discharge or epileptic paroxysm but occurred isolated were included. Moreover, IEDs occurring in the MEG may differ in morphology from electrical ones, but because no standardized definition of magnetic epileptiform discharges currently exists (Zijlmans et al., 2002), the EEG criteria were used for the identification of the IEDs in the MEG. The identified IEDs were isolated interictal sharp transients clearly distinguishable from ongoing background activity, with either a duration of <70 ms (spike) or <200 ms (sharp wave) (see Fig. 2.1). These IEDs were considered to be focal discharges since the activity is limited to a small region of the brain, reflected in the records of only a number of channels. Sharp signals suspected of originating from heart beats, eye movements, physiological rhythmic discharges, or vertex sharp activities during sleep were excluded. Markers were placed at the maximum of the so defined IED, which allowed the concatenation of the epileptiform events from all sessions into one file. After trend-removal the signals were band-pass filtered between 3 and 70 Hz and the data were extracted (in 1 s time windows around the selected maximum of the IED, identified by the marker) and interpolated to a MEG grid corresponding to the average head position across the entire recording session (De Munck et al., 2001).

2.3. Clustering of epileptiform events

The automated clustering procedure as developed by Van't Ent et al. (2003) was applied to improve reliability and accuracy of source reconstruction by grouping the IEDs before averaging and source reconstruction. A computer based cluster algorithm was used to align and cluster the IEDs and to visualize the data focused around the marker (Ward, 1963). Next, the MEG data in epochs of 9.2 ms (11 samples given a 1200 Hz sampling rate) centered on the spike markers were analyzed using the hierarchical clustering algorithm. For more details the reader is referred to Van't Ent et al. (2003). Subsequently, spike averages and average field maps were computed for each cluster of IEDs. The IEDs were considered to be focal discharges, thus spike clusters with broad averaged magnetic field distributions (no clear dipolar distribution) and clusters containing less than three spikes were excluded from further analyses.

2.4. Source reconstruction

The underlying sources of all IED clusters were reconstructed using an equivalent current dipole model to describe the averaged magnetic field distribution of each spike cluster. First, a boundary element model of the cortical surface was constructed from

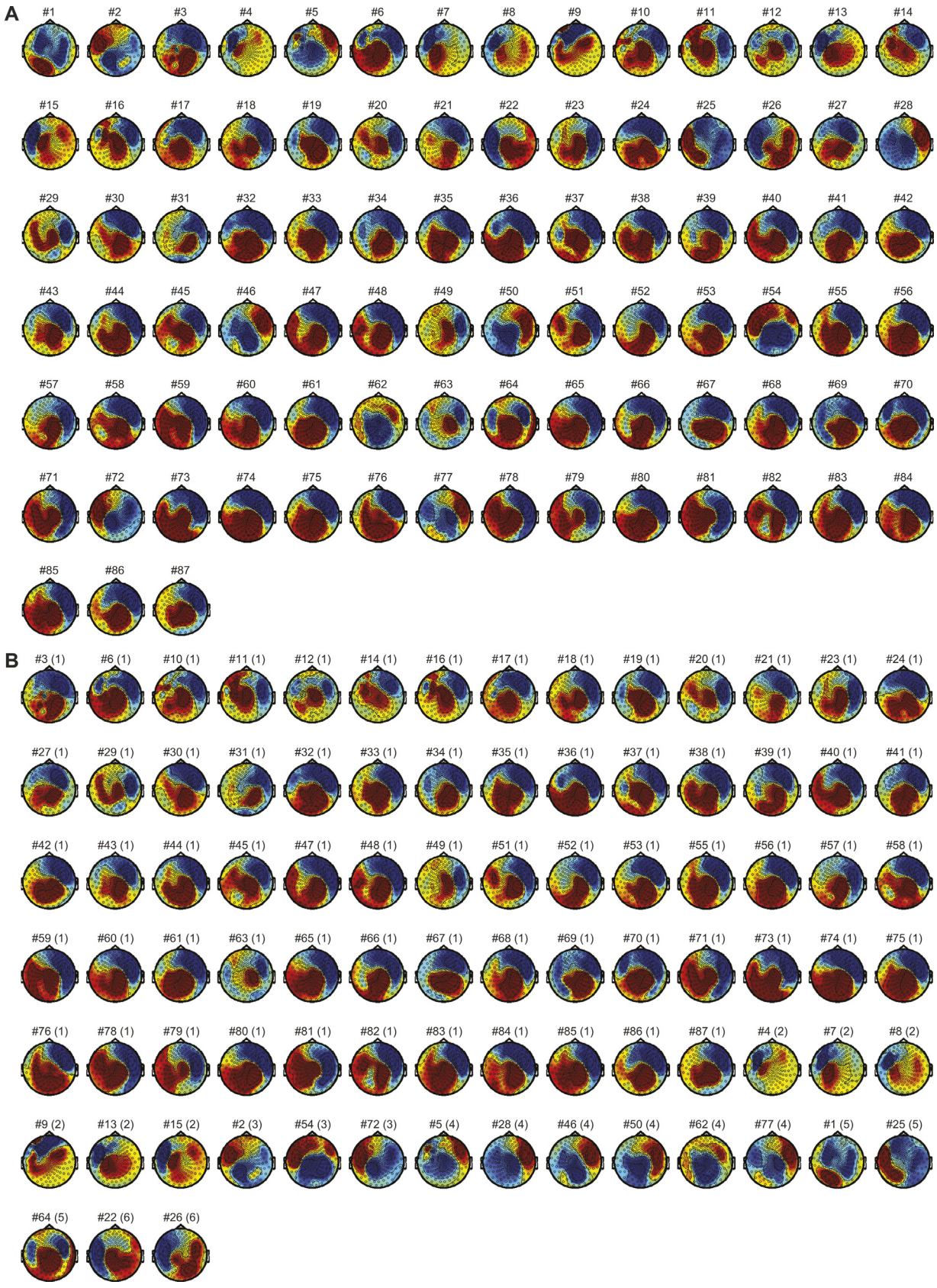

Fig. 3.1. Magnetic field distribution of each IED of patient 1. Panel (A) depicts the maps of the individual, ungrouped IEDs ($N = 87$), whereas panel (B) portraits the maps of the individual, grouped IEDs after they were clustered (resulting cluster numbers are indicated between brackets).

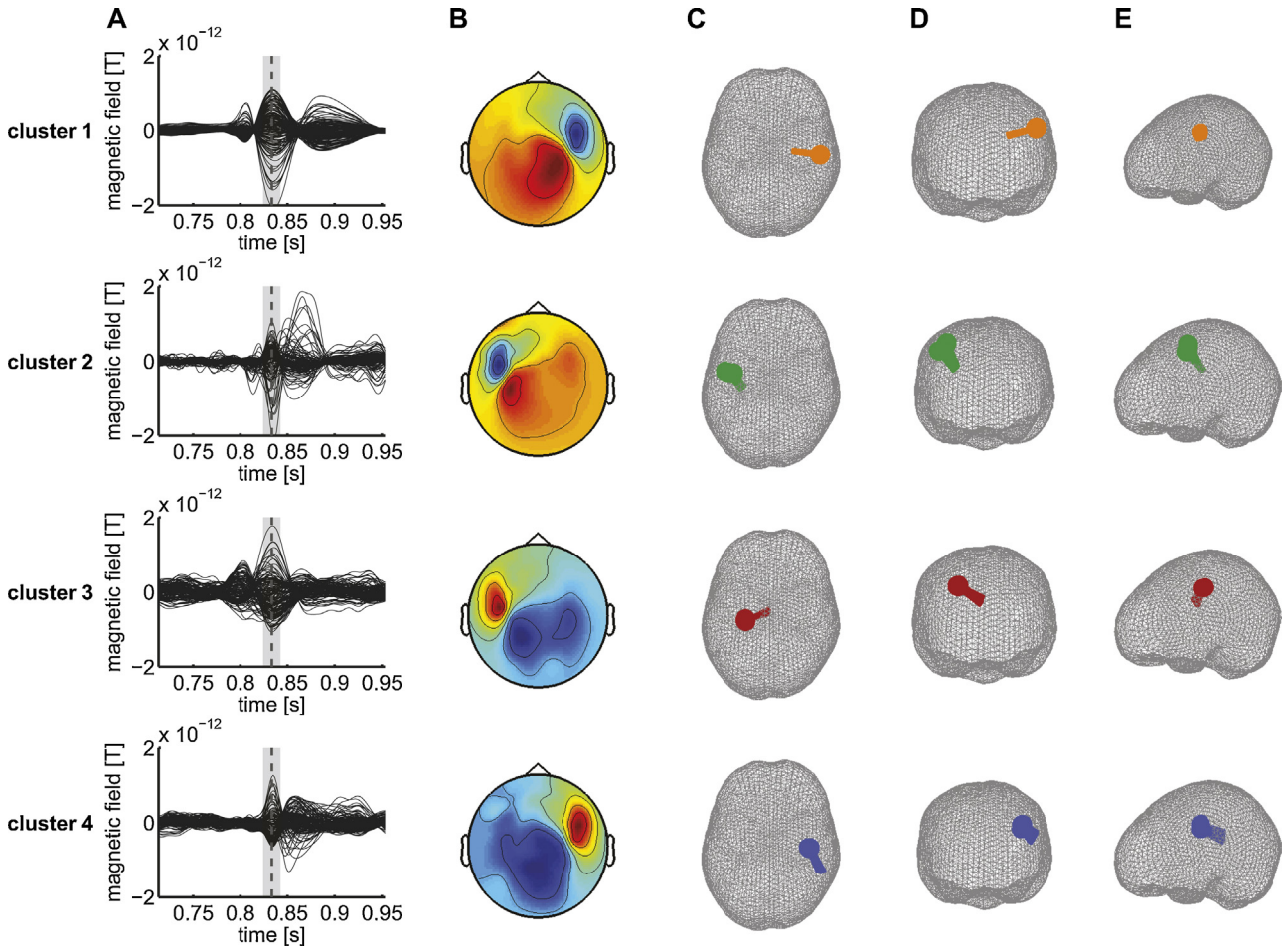

Fig. 3.2. Averaged IED signal as an overlay of all MEG channels, including the position of the spike marker (dashed line) and the epoch of 11 samples surrounding the spike marker (shaded area) on which source reconstruction was performed (A), corresponding averaged map of the measured magnetic field distribution (B) and the results of the source reconstruction procedure using an equivalent moving dipole model from an axial (C), coronal (D) and sagittal (E) view. The estimated location and orientation of the moving dipole source are projected onto the volume conduction model and resemble the averaged magnetic field map as depicted in panel B.

the anatomical MRI to co-register the functional and anatomical data using the three reference points: the left and right preauricular points and the nasion. The resulting realistic volume conduction model was used along with the equivalent current dipole model to localize the sources through a coarse grid scan in which initially the whole brain was scanned. During this iterative approach, the position (x, y, z) and moment (ϕ: azimuthal angle, θ: polar angle, r: radial distance) were iteratively re-estimated to obtain the optimal dipole configuration in which the difference between measured and modeled MEG topography has been minimized. Subsequently, a more precise non-linear search was performed (starting from the optimal location) to find the location and orientation at which the dipole model is best able to explain the measured MEG topography. The source reconstruction procedure was implemented in MATLAB (R2013b, The MathWorks, Natick, Massachusetts) and utilizes components of the Fieldtrip toolbox [Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, the Netherlands (http://www.ru.nl/neuroimaging/fieldtrip)] (Oostenveld et al., 2011) that is designed for EEG and MEG analysis. Brain regions were identified and classified according to the CTF sensor subdivision.

A stationary equivalent current dipole (ECD) model was used to estimate the (fixed) location of the dipole source responsible for the magnetic field distribution during the time interval (9.2 ms) surrounding the maximum of the averaged spike cluster, while the orientation of the dipole may change over time. This particular dipole model was used in case the location of the 'moving dipoles', estimated for each subsequent time point, did not change over time. Finally, a stationary dipole analysis over a time interval that included all the positive and negative deflections of the IEDs indicated that the activity underlying the spike clusters was generated by a single source.

Table 3.1
Overview of incidence of IEDs and resulting number of clusters.

Patient	#IEDs*	#Clusters
1	87 (116)	4
2	26 (24.0)	3
3	27 (32.4)	4
4	29 (34.1)	4
5	0 (0)	–
6	14 (28.5)	3
7	10 (16.5)	1

* The incidence rate is indicated between brackets as the number of IEDs per hour.

3. Results

Manual review of the MEG of the patients studied revealed that the number of IEDs occurring in the MEG is highly variable amongst the included patients (see Table 3.1). The incidence rate among patients from which IEDs were found, ranged from 16.5 to 116

spikes per hour (mean and SEM: 41.9 ± 36.8), while for one of the seven patients no clear IEDs could be identified.

3.1. Clustering results

The results of the source analysis procedures are illustrated for the first patient, whose MEG showed 87 IEDs. Fig. 3.1A shows the magnetic field distributions of the ungrouped interictal events indicating that distinct topologies of these distributions may exist. Clustering of the data of patient 1 results in 6 clusters with, respectively, 67, 6, 3, 6, 3 and 2 spikes, shown subsequently from left to right and top to bottom in Fig. 3.1B, indicating a typical topology of the magnetic field distribution for each individual cluster. The averages of the spikes and magnetic field distributions of each of the clusters of patient 1 are presented in Fig. 3.2A and B. Only 4 of the 6 obtained clusters were selected for source reconstruction, since the number of spikes was not sufficient for cluster 6 (<3), while the averaged field map of cluster 5 was widely distributed and not dipolar. The number of spike clusters obtained by the same procedures as described for clustering of the IEDs of the other five patients varied between 1 to 4 clusters per patients, see Table 3.1.

3.2. Source reconstruction

The results of the source reconstruction (for the selected clusters of patient 1) using a moving dipole model are displayed in Fig. 3.2C–E, in which the estimated sources are projected onto the volume conduction model. These results indicate that both the location and orientation of the estimated moving dipoles (%err < 10) are quite stable during the time interval centered around the maximum of the spike cluster, thus allowing the application of a stationary fixed dipole model. The high reproducibility of the moving dipole sources for each time point within the analysis interval of 9.2 ms indicates that a single stationary dipole is sufficient to reconstruct the underlying source activity of the spike clusters of patient 1, with an average residual error (%err) of 7.2 ± 4.5 for all selected clusters. The position of the estimated stationary dipole sources for all clusters of each patient are presented in Fig. 3.3 separately. The sources are projected onto the anatomical MRI slices that coincide with the average position of the reconstructed sources. The source reconstructions of the IEDs indicate the involvement of the bilateral central regions.

3.3. Spatiotemporal dipole analysis

So far the source reconstruction was performed for a time interval centered around the maximum of the IEDs. However, several spike clusters contained multiple peaks (maxima and minima at consecutive time points), as illustrated in Fig. 3.4A for spike cluster 1 of patient 1. A spatiotemporal analysis of the spike cluster over a time interval of 17.5 ms, which included all the positive and negative deflections of the spikes as indicated in Fig. 3.4A, was performed in order to explore whether the activity underlying these IEDs could be explained by multiple dipole sources. However, as indicated in Fig. 3.4B, the topologies of the magnetic field distributions over time are rather similar, indicating that these distributions are generated by a single source with a stable location and orientation over time. Interestingly, although the spatiotemporal analysis did not show propagation of activity, it did reveal reversal of polarity over time for this specific spike cluster. The reversal of the polarity was also found in all other patients from whom IEDs were recorded in their MEG.

3.4. Interictal versus ictal focal regions

The source reconstruction results indicated (see Fig. 3.3), sources in the frontal (patients 2 and 4) and central/parietal region (patients 1, 3,6, and 7) of either the left or right hemisphere with no outspoken preference for their presence in either hemisphere, see also Table 3.2. Note, furthermore, that there is a large inter-individual variability in the location of the source.

It can be questioned whether the regions of the identified sources of the spike clusters of all six children with clear IEDs occurring in their MEG coincide with at least one of the focal cortical regions involved in the generalized SWDs. In Table 3.2 both the focal regions involved in the IEDs and the focal regions involved during the generalized SWDs of the same 7 patients studied are listed. The focal cortical regions involved during the spikes of the SWDs (Gupta et al., 2011; Westmijse et al., 2009) is concordant for 4 of the 6 children from whom IEDs occurred in the MEG with the location of at least 2 spike clusters. In total, the location of the sources of 10 out of the 12 identified spike clusters is concordant at the lobe level with (one of) the focal regions of the generalized SWDs, as illustrated in Fig. 3.3.

4. Discussion

Results are presented of the occurrence, clustering and localization of the sources of focal IEDs in the MEG of children who all were diagnosed with absence epilepsy. The MEG of all patients, except one, reflected IEDs in a 45 min recording session, although their number varied extensively between these six patients (range: 10–87). It has been reported by, amongst others (Ossenblok et al., 2007) that MEG is more sensitive to the identification of IEDs for patients with focal epilepsy. The reason for the higher sensitivity of MEG compared to EEG is that IEDs in the EEG may be masked by the rapid propagation to more widely distributed brain regions or to regions within deep lying structures of the brain, while MEG is less sensitive to activity from distributed and deep lying brain structures (de Jongh et al., 2005). This might also explain the high number of IEDs in the MEG included in this study compared to earlier EEG reports, although it is acknowledged that a larger number of patients were included in the EEG vs our MEG study (Leutmezer et al., 2002; Yoshinaga et al., 2004).

Furthermore, clustering and localization of the IEDs indicated that the focal cortical regions which appear to be the origin of the discharges are comparable to the focal cortical regions involved in the spikes of the generalized SWDs of children with absence epilepsy, as reported by Westmijse et al. (2009) and Gupta et al. (2011).

4.1. IED clustering and localization

The IEDs identified by visual review were grouped into clusters based on similarity of field distribution with subsequent current dipole reconstruction of the sources underlying the averaged spike clusters. For each of the patients studied, except for one from whom there were no IEDs detected, we were able to reconstruct the current dipole sources underlying the epileptiform discharges. The MEG of five of the six patients reflected multifocal spike activity, leading to mostly 3 or 4 distinct spike clusters with distinct localizations in different cortical regions and/or in either the left or right hemisphere (see Table 3.2). The interictal spikes were preferentially found in the frontal and central/parietal regions without an outspoken difference between left and right hemisphere.

The ECDs appeared to be stable in location during the selected interval centered around the maximum of the IED, this indicated that it is allowed to localize each of these spike clusters within the time interval of analysis using a single stationary dipole model.

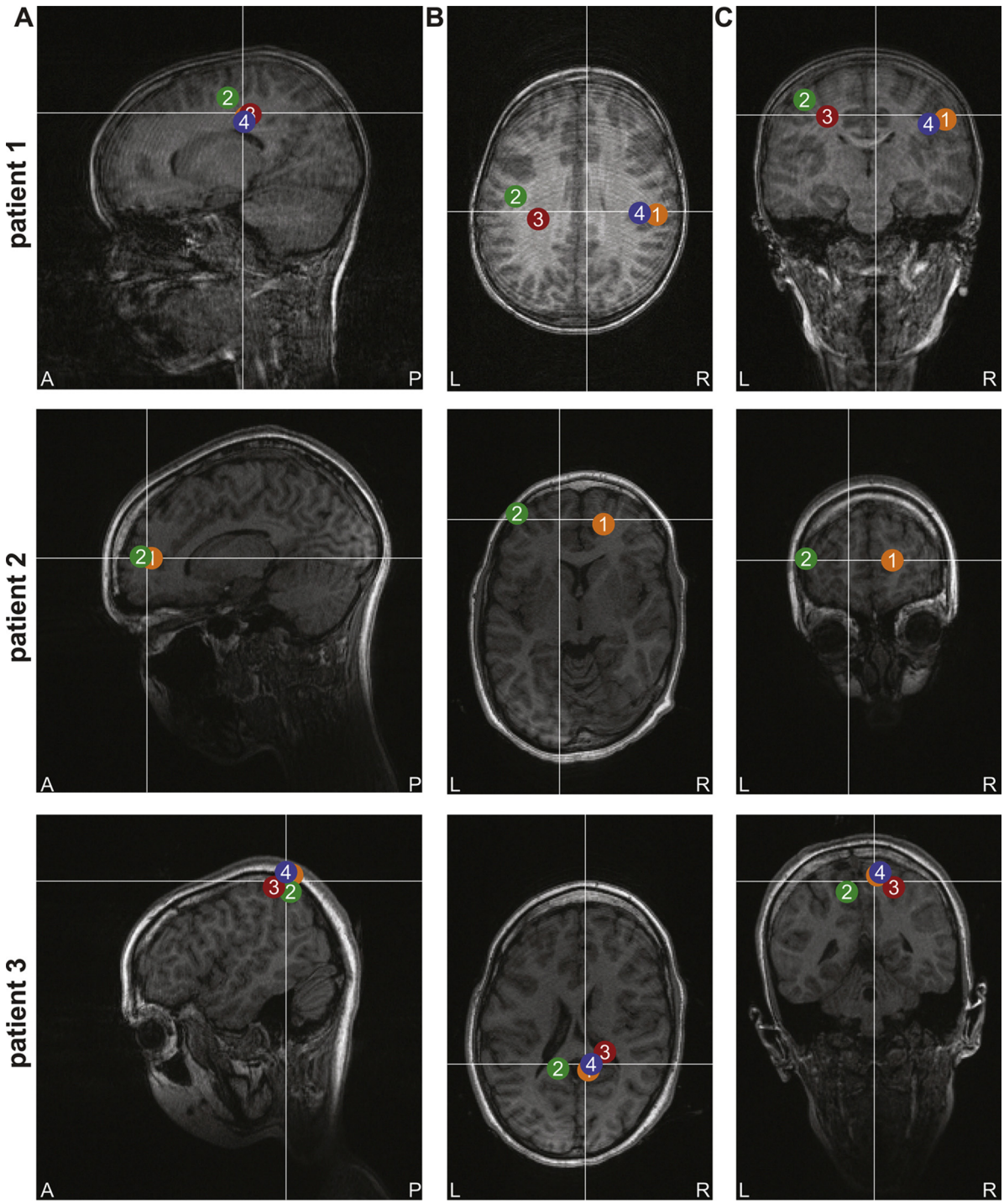

Fig. 3.3. Source reconstruction results using stationary equivalent dipole models depicted onto the anatomical MRI from a sagittal (A), axial (B) and coronal (C) point of view. The depicted slices coincide with the average position of the reconstructed sources (depicted by the white lines) for each patient separately. When no MRI was available, which was the case for patients 3, 6, 7, the MRI of patient 2 was used.

Further evidence for the accurateness of the dipole source solutions can be derived from the %err which always was less than 10%, varying for the distinct spike clusters, possibly because of the number of spikes that could be averaged for each cluster. A remaining source of error might be that for 3 of the patients studied (patients 3, 6 and 7) no patient-specific head model could be applied, because no anatomical MRI was available for these patients. Instead we used a head model from a patient similar in age and head size, which is still preferable to using a general single sphere head model (Hauk, 2009).

4.2. Similarity between ictal and interictal focal regions

Earlier MEG and EEG/fMRI studies of the 3 Hz SWDs of children with absence epilepsy revealed the involvement of a cortico–thalamo–cortical network during the evolvement of these ictal discharges (Amor et al., 2009; Moeller et al., 2013b; Ossenblok et al., 2010; Westmijse et al., 2009). According to these studies, the dynamics of the SWD indicates a sharp transition from the preictal to the ictal state in a period starting about 500 ms to 1 s before the first visible onset of the SWDs and about 500 ms onwards

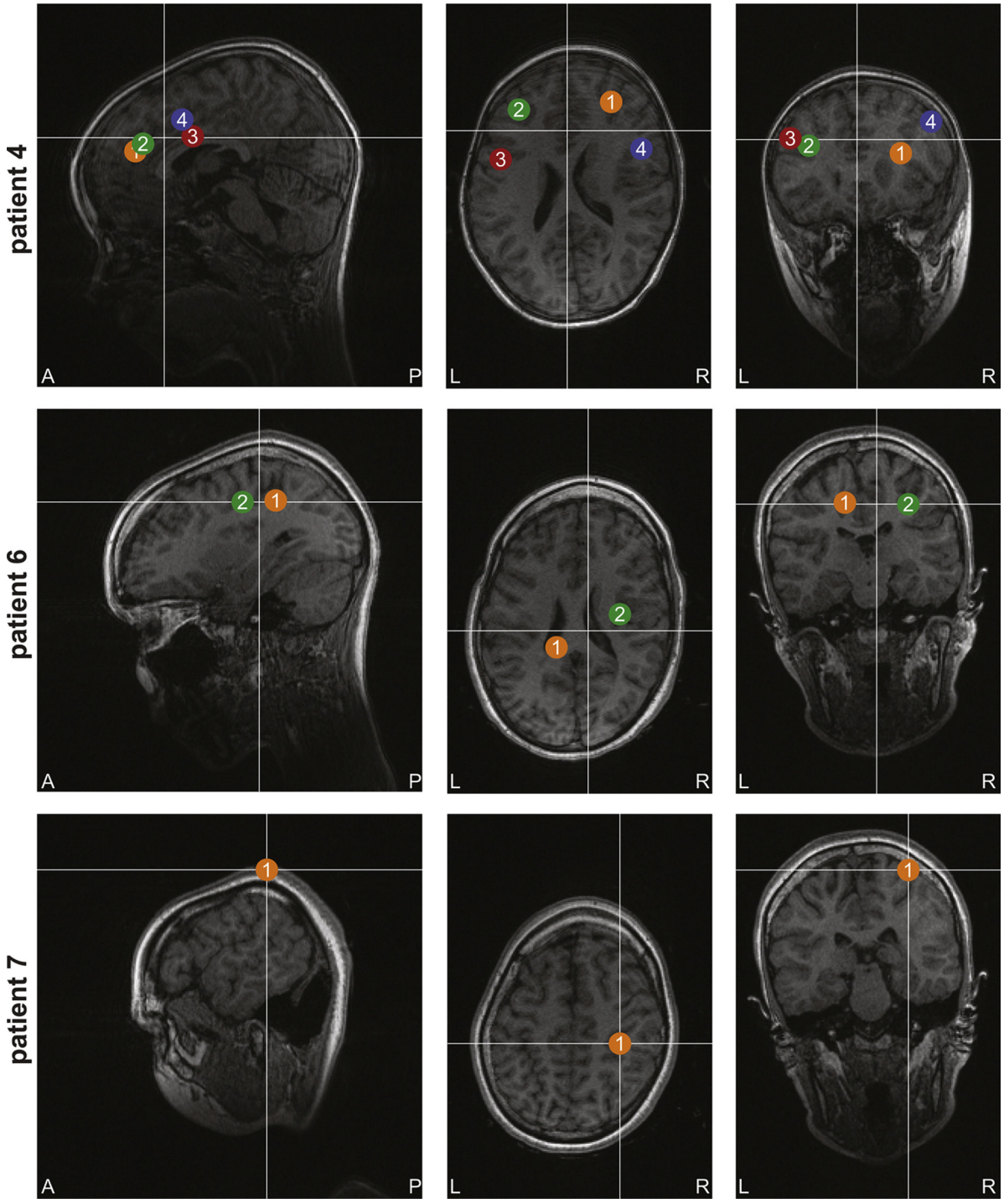

Fig. 3.3. (*Continued*).

(Gupta et al., 2011), followed by the 3 Hz bilateral synchronous rhythmic pattern starting at the first generalization of the SWDs (Ossenblok et al., 2010; Westmijse et al., 2009). After the initialization of the SWDs, a repetitive pattern of generalized bilateral synchronous activation during the waves alternated the bilateral focal frontal and parietal regions of activity during the spikes, which probably reflects the activity of the cortico–thalamo–cortical network (Ossenblok et al., 2010). Here it is proposed that the sources underlying the IEDs coincide with the nodes of the cortico–cortical and cortico–thalamo–cortical networks underlying the generalized SWDs and that the distinct spike clusters reflect the network activity of distinct cortical sources at different locations in either the left or right hemisphere. Similar processes have been described by, amongst others, Ossenblok et al. (2007) for the interictal MEG of patients with focal epilepsy: the IEDs, differing in morphology and topography, are not necessarily related to the early onset of the IEDs at the irritative zone, but they are expressions of the propagation of these discharges throughout the networks involved.

In this study the sources of the interictal spike clusters were preferentially found in the frontal and central/parietal regions with no outspoken difference between left and right hemisphere. From Table 3.2, it is evident that IEDs often arise from the same regions as

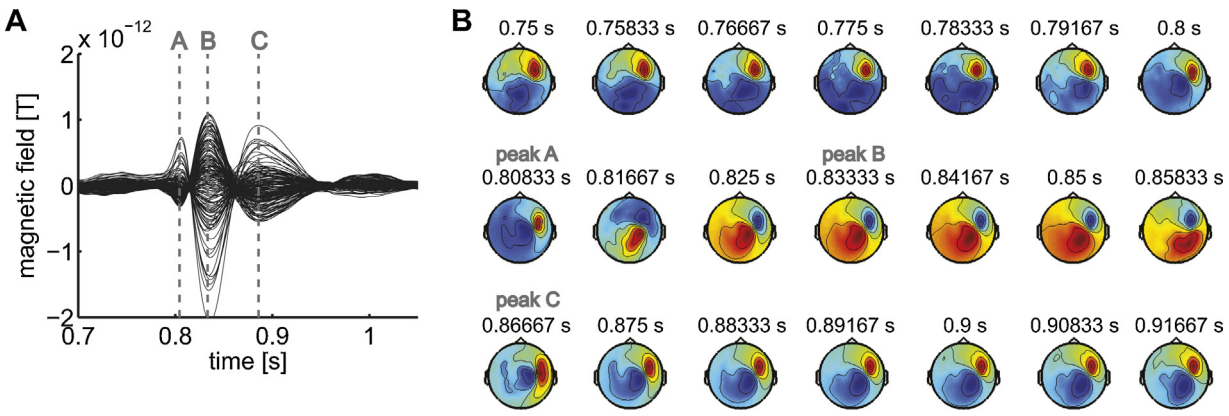

Fig. 3.4. Spatiotemporal analysis results of cluster 1 for patient 1. Panel (A) shows the averaged IED signal as overlay of all channels. The dashed lines indicate different maxima or peaks of the averaged IED, of which peak B was used for the source reconstruction as depicted in Fig. 3.2. Panel (B) visualizes the spatiotemporal behavior of the averaged magnetic field distribution over time, from left to right and from top to bottom.

Table 3.2
Comparison of the location of the ictal focal source (frontal, temporal, occipital, central/parietal) of the generalized SWDs as reported in Westmijse et al. (2009) and Ossenblok et al. (2010) and the location of the sources of the IEDs. The ictal sources of the spikes of the SWDs had been reconstructed using the SAM (g2) beamformer technique (Westmijse et al., 2009) and using nonlinear association analysis (Ossenblok et al., 2010). Entries highlighted in red imply an agreement regarding the involvement of the same brain region for the ictal and interictal source of the same patient.

Patient		Frontal		Temporal		Occipital		Central/parietal	
		L	*R*	L	*R*	*L*	*R*	*L*	*R*
1	Ictal	x	x					x	x
	Interictal							x	x
2	Ictal		x					x	x
	Interictal	x	x	x					
3	Ictal	x						x	x
	Interictal							x	x
4	Ictal	x	x					x	x
	Interictal	x	x						
5	Ictal	x		x			x	x	x
	Interictal								
6	Ictal	x	x	x			x	x	x
	Interictal							x	x
7	Ictal	x	x		x			x	x
	Interictal								x

the focal cortical regions involved during the spikes of the generalized SWDs. Here it is proposed that the sources of the distinct spike clusters coincide with the focal cortical regions involved during the spikes of the generalized SWDs at either the frontal or central/parietal regions in either the left or right hemisphere. It should be kept in mind that this does not imply that the source of the IEDs is the driving force for the generalized SWDs; it only indicates that the IEDs might arise from the same cortical regions as involved in the occurrence of the ictal SWDs and might be part of the same networks. Similar processes have been describes by, amongst others, Ossenblok et al. (2007) for the interictal MEG of patients with focal epilepsy: the IEDs, differing in morphology and topography, are not necessarily related to the early onset of the IEDs at the irritative zone, but they are expressions of the propagation of these discharges throughout the networks involved.

Whether there is also a coincidence between the sources underlying the IEDs and the driving sources of the ictal SWDs, at the transition period from the preictal to ictal evolvement of the SWDs (Gupta et al., 2011), needs further research in a larger patient cohort with longer lasting recordings thus acquiring more IEDs as well as more SWDs.

4.3. Concluding remarks

Despite the fact that CAE is classified as a generalized type of epilepsy, the majority of children (6 out of 7) of the children studied revealed isolated IEDs, which were clearly related to a localized dipolar pattern of activation. The presence of IEDs in the EEG or MEG of an epilepsy patient is in general considered as a characteristic of a focal type of epilepsy.

In this study, we were able to reconstruct the sources underlying the focal IEDs indicating involvement of focal frontal or central/parietal cortical regions in either the left or right hemisphere, which is concordant with the focal cortical regions that are involved in the spikes of the generalized SWDs. This finding might indicate that the underlying network is the same for both the interictal and the ictal epileptiform events.

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