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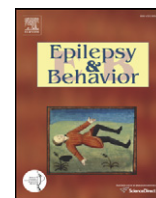
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Review

Magnetoencephalography in the study of epilepsy and consciousness



Elaine Foley ^{a,1}, Antonella Cerquiglioni ^{f,1}, Andrea Cavanna ^{c,d,e}, Mable Angela Nakubulwa ^a, Paul Lawrence Furlong ^a, Caroline Witton ^a, Stefano Seri ^{a,b,*}

^a School of Life and Health Sciences, Aston Brain Centre, Wellcome Trust Laboratory for MEG Studies, Aston University, Birmingham B4 7ET, UK

^b Department of Clinical Neurophysiology and Pediatric Epilepsy Surgery Programme, The Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK

^c Department of Neuropsychiatry, University of Birmingham, Birmingham, UK

^d BSMHFT, Birmingham, UK

^e Institute of Neurology, UCL, London, UK

^f Dipartimento di Scienze e Biotechnologie Medico-Chirurgiche, Developmental Neuropsychiatry Unit, "Sapienza" Università di Roma, Polo Pontino, Italy

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ABSTRACT

The neural bases of altered consciousness in patients with epilepsy during seizures and at rest have raised significant interest in the last decade. This exponential growth has been supported by the parallel development of techniques and methods to investigate brain function noninvasively with unprecedented spatial and temporal resolution. In this article, we review the contribution of magnetoencephalography to deconvolve the bioelectrical changes associated with impaired consciousness during seizures. We use data collected from a patient with refractory absence seizures to discuss how spike-wave discharges are associated with perturbations in optimal connectivity within and between brain regions and discuss indirect evidence to suggest that this phenomenon might explain the cognitive deficits experienced during prolonged 3/s spike-wave discharges.

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1. Introduction

Magnetoencephalography (MEG) is a noninvasive functional neuroimaging tool, which measures and maps the magnetic fields of the brain mainly generated by neurons tangentially oriented to the skull. It has been suggested that magnetic fields, and therefore MEG modeling, are less distorted by the conductivity and geometry of the skull and scalp than electroencephalography (EEG) and that this results in improved spatial resolution [1–3]. Magnetoencephalography has established itself as a useful technique in epilepsy, offering nonredundant diagnostic information in the presurgical evaluation of patients with drug-resistant epilepsy [4,5]. In these patients, MEG offers the unsurpassed temporal resolution that is necessary to deconvolve the rapidly spreading nature of paroxysmal epileptiform discharges combined with high spatial sampling and localization accuracy. These properties are also critical in characterizing the functional properties of the networks involved in the ictal epileptic discharges as well as those responsible for fundamental cognitive processes. In this paper, we will review analysis methods and recent literature to support its use in investigating epileptic networks during seizures affecting consciousness and present original data on childhood absence seizures from our laboratory.

2. MEG and connectivity in epilepsy

Recent models have conceptualized brain functioning as a complex interplay between “local networks” (responsible for modality-specific sensory processing) and “large-scale networks” enabling integrative processing with high degree of computational parallelism [6]. These networks are active independently from the presence of external stimuli and are, therefore, referred to as resting state networks (RSNs) and are the expression of functional integration between and within brain regions that go beyond that of the underlying anatomical connections [7]. One particular RSN is the so-called “default-mode” network (DMN), a set of brain regions that are active at rest and have the unique property of deactivating during active task states [8,9].

Magnetoencephalography has been used successfully to characterize the dynamics of these networks [10,11], and MEG connectivity analysis methods are starting to be applied in clinical studies [12–14]. Since epilepsy is associated with an abnormal expression of neural oscillations and their synchronization across brain regions, MEG is eminently suitable to measure connectivity patterns within the “epileptic region” and between this and other brain structures. Furthermore, MEG can offer significant advantages in resolving the frequency-domain aspects of the bioelectrical signal, since fMRI can only characterize coherent activity in frequency components of around 0.1 Hz. This low-frequency activity, although not directly corresponding to the brain electromagnetic activity, is thought to be the expression of the modulation of local field potentials responsible for the MEG and EEG signals [15]:

* Corresponding author at: Aston Brain Centre, Aston University, Aston Triangle, Birmingham B4 7ET, UK.

E-mail address: s.seri@aston.ac.uk (S. Seri).

¹ These authors have equally contributed to the study and the manuscript preparation.

this has been postulated as being the reason for the significant spatial overlap in studies using the two techniques [10,16]. At the microscopic level, the transition between the interictal and the ictal phase is associated with reduction in the level of coupling (desynchronization) preceding seizures or during their early stages and increased synchronization towards the end of a seizure [17]. However, whole-brain imaging studies have highlighted a macroscopic and stable decrease in the activity of the DMN during complex partial, generalized tonic-clonic, and absence seizures with impairment of consciousness [18]. The resilience of the DMN is confirmed by its persistent activity – albeit with significantly reduced connectivity – in patients in a vegetative state but not in brain-dead patients [19], supporting its potential role as a biomarker of integrity of conscious processes.

3. MEG source and connectivity analysis in epilepsy

Aston's Wellcome Laboratory for MEG studies has pioneered the development of analysis methods as well as applications of MEG in clinical settings. In our center, MEG data are recorded in a magnetically shielded room (VacuumSchmelze GmbH, Hanua, Germany) using a 306-channel system (Elekta Neuromag Triux) with 102 magnetometers and 204 planar gradiometers, at a sampling rate of 1250 Hz. An anti-aliasing filter and a high-pass filter of 410 Hz and 0.1 Hz, respectively, are applied. Artifacts are removed from the data with the MaxFilter software (Elekta Neuromag Oy, version 2.2.10), which adopts the temporal extension of signal space separation (tSSS) [20]. One bipolar EEG channel is dedicated to recording EKG and two for monitoring ocular movements in order to facilitate the identification and removal of physiological artifacts. Head localization is performed by attaching 5 coils on the patient's head in locations that are covered by the sensors. Each patient's MEG recording time ranges between 45 and 90 min. The MEG data are then coregistered with the patient's own T1-weighted anatomical MRI by means of surface-based alignment [21]. Recordings are performed in the awake state, and patients are asked to sit upright in the MEG scanner and view a centrally presented fixation cross while 5 min of data are recorded. During data acquisition, the location of the subject's head within the scanner is measured by energizing coils placed at the five fiducial points on the head. We collect a 5-minute recording in eyes-open and eyes-closed conditions, unless suggested otherwise based on the clinical presentation; hyperventilation is performed when indicated. Localization of interictal abnormalities is performed using a joint minimum-variance beamformer and spike-detection algorithm called SAM(g_2) [22,23]. First, the spatial filter estimates the strength of a dipolar source at each location within the brain volume as a function of time by suppressing contributions from temporally correlated noise sources (e.g., other active brain regions or external noise) and computes a unique set of sensor weights for each target location with an optimized orientation. The beamformer output at a target location has the same temporal resolution as the recorded MEG signals and is, therefore, often referred to as a *virtual electrode* and can be seen as a morphologic characterization of the regional electrical activity. For each patient, we compute measures for 40,320 voxels (virtual electrodes) with a 5-mm equal spacing covering the entire head. A second analysis step identifies abnormal transients from the estimated source data in terms of excess kurtosis, defined as $g_2 = \sum_{t=1}^T [S(t) - (-S)]^4 / (\sigma^4 T) - 3$ where σ is the standard deviation and T is the number of time samples. Source data are analyzed using an adaptive thresholding algorithm in the 20- to 70-Hz frequency range to provide optimal contrast for spike-like activity identification. A peak-to-rms ratio is computed across the time series as the ratio of the absolute value of the waveform to the rms(σ) at each time point; a marker is inserted when a threshold of 5 is exceeded. The time series of the virtual electrodes is visually inspected in the same window as the sensor-space data in the DC-100-Hz band to confirm or reject the marked event as an interictal epileptiform discharge. Images of the g_2 values corresponding to each voxel are finally produced and coregistered with the patient's own MRI.

For resting state analysis, activity is divided in the traditional frequency bands delta (0.5–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz) and analyzed in 6-second segments. Functional connectivity in the sensor space is assessed at rest and during paroxysmal ictal events using the phase lag index (PLI). The PLI measures the synchronization between time series by calculating the asymmetry of the distribution of (instantaneous) phase differences between two MEG signals, reflecting the consistency with which one signal is phase-leading or phase-lagging with respect to another signal [24]. Contrary to other measures of frequency-domain coupling between signals, PLI is not influenced by the effect of common sources. The connectivity analysis of sensor-space MEG data is performed using BrainWave version 0.9.111 (available at <http://home.kpn.nl/stam7883/brainwave.html>).

4. MEG and connectivity in refractory absences: case presentation

In our center, we have been able to investigate with MEG several patients with childhood absence epilepsy and systematically confirmed the published data on frontal lobe involvement in the early stages of 3/s spike-wave discharges. Here, we report on a 12-year-old patient with absences that failed to respond to antiepileptic medication over a 7-year period, including valproate, ethosuximide, lamotrigine, levetiracetam, topiramate, clobazam, and acetazolamide in monotherapy and in variable combinations. High-resolution MRI using T1- and T2-weighted and FLAIR sequences was normal. We recorded resting MEG in the eyes-open and eyes-closed conditions to localize the sources of spike-wave discharges and calculated whole-head connectivity measures using the PLI as described above in Section 3. Spike-wave discharges involved the frontal lobe bilaterally (Fig. 1A) with a constant right hemisphere lead ranging between 8 and 10 ms (Figs. 1B, C). Connectivity measures in the source space calculated on the spatially filtered data using the voxel with maximal activity in the right frontal lobe as seed showed strong coupling between the bilateral frontal and temporal regions and temporoparietal junction (Fig. 1D). Measures of PLI showed a significant increase in global mean PLI during the 3/s spike-wave discharges associated with absence seizures in the alpha (8–12 Hz) band, an expression of increased phase synchronization. When we analyzed the PLI within discrete brain regions, we observed that the highest contribution to the increased global PLI comes from the right frontal and occipital and bilateral temporal sensor clusters, whereas parietal sensor clusters show reduced phase synchronization (Fig. 2, above the red line). The analysis of PLI between regions of the two hemispheres shows global increase in the index, the largest of which involves the right and left frontal sensor clusters with bilateral temporal ones as well as right frontal and parietal ones (Fig. 2, below the red line).

A graphic representation of the data obtained in this patient suggests that absence seizures are associated with a significant increase in long-distance phase synchronization throughout the scalp, particularly in the right hemisphere and in the frontotemporal and frontoparietal regions, in accordance with the leading role of the right frontal lobe in the genesis of the spike-wave discharge. Furthermore, short-range connectivity within the parietal region is reduced, which could be a biomarker of impaired regional functioning (Fig. 3).

The global increase in connectivity is a striking feature in this patient, whose seizures may not be representative of typical absences, being refractory to antiepileptic medications. Abnormally high phase synchrony can itself lead to perturbation in the information-encoding process. While in neural systems entrainment of neuronal discharges can increase encoding efficiency [25], there is also evidence to suggest that in a population of neurons, synchrony reduces variability in neuron spiking and increases coding redundancy, with the net effect of reduced capacity of the network to encode information [26]. It has recently been suggested that the optimal amount of correlation is required for efficient information processing [27]. In this context,

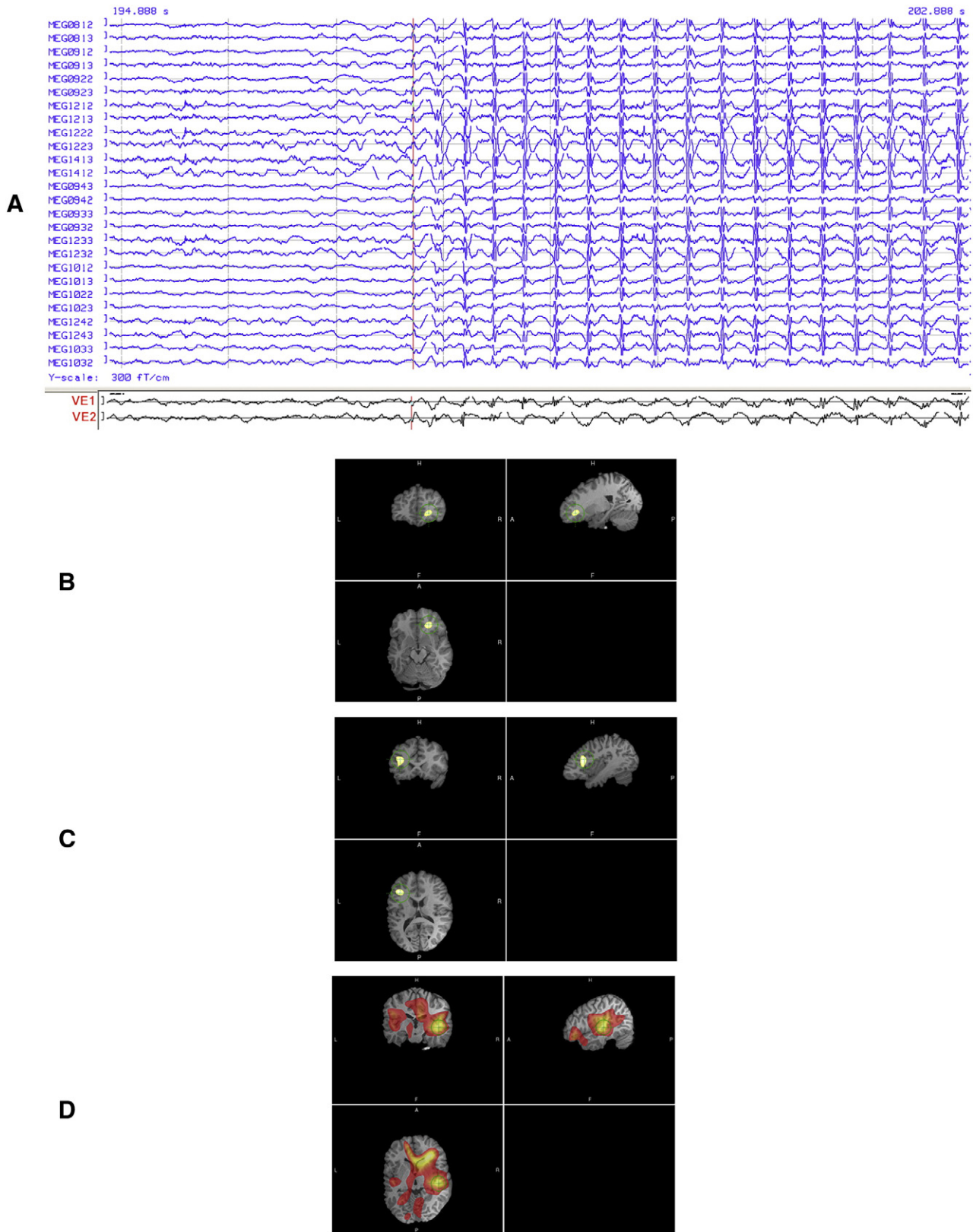


Fig. 1. Source analysis of MEG data during an absence seizure. Sensor level data and time series of reconstructed sources (A), leading and lagging sources (B and C) and strength of connectivity between the right frontal source and the rest of the cortex (D) displayed on the patient's MRI.

one could speculate that the abnormally high phase coherence between brain subsystems might reduce the efficiency of information processing and, if sufficiently widespread, might interfere with conscious experience.

5. Connectivity and consciousness in absence epilepsy

Absence seizures, with their associated typical 3/s spike-wave discharges and clinical correlate of loss of contact with the environment

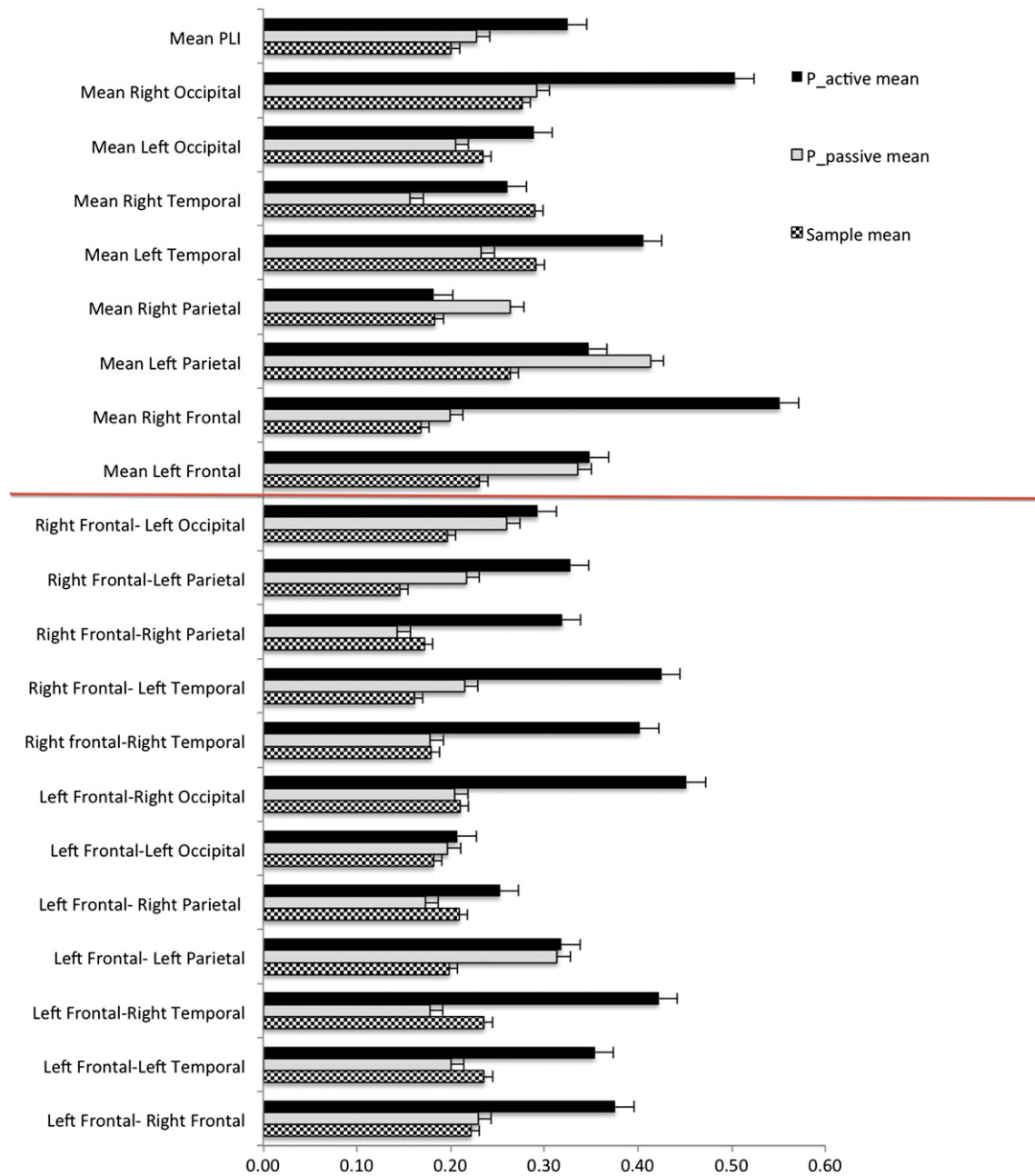


Fig. 2. Mean Phase Lag Index during the 3/s spike wave discharge (solid black, P_active), at rest (solid grey, P_passive) and in matched healthy controls (patterned, sample mean). Variability is expressed as SEM.

[28], have often been subject to controversy in the literature on disorders of consciousness in epilepsy. Behavioral evidence of impaired cognitive functions during absence seizures comes from relatively old studies and shows significant variability in the quantitative and qualitative aspects of cognitive and sensorimotor processing. Repetitive simple motor tasks such as finger tapping tend to be preserved during absence seizures; while this was initially interpreted as evidence of limited impairment of consciousness, recent evidence on the significant behavioral repertoire of the “zombie brain” suggests that even complex motor behavior can occur in conditions traditionally considered as characterized by impaired consciousness [29]. A recent review has proposed that impairment of consciousness is highly variable between subjects and between seizures in the same patient [30]. Moreover, absence seizures impair focal and not distributed brain functions, and there is a qualitative and/or quantitative difference in the impairment of consciousness between the beginning, the central part, and the end of an

absence seizure. Electrophysiological evidence from EEG and, more recently, MEG studies has identified local cortical onset of spike-wave discharges involving frontal and parietal regions at onset [31]. A recent study has also demonstrated sequential activation and progressive recruitment during a spike-wave train with frontal cortex and thalamic activation in the 50 ms prior to the start of the seizure, followed by involvement of the lateral frontal cortex and decreased thalamic localization at the time of the first spike, after which the localization becomes more widespread throughout the cortex [32]. This electrophysiological correlate could be seen as a biological equivalent of the time-varying pattern of cognitive impairment observed during absence seizures [30]. The role of slow-wave activity as an electrographic biomarker of ictal impairment of consciousness has been documented in focal interictal discharges [33] as well as ictal temporal lobe seizures [34], in which frontoparietal slow-wave activity is seen during seizures with impaired consciousness. While technically more difficult to

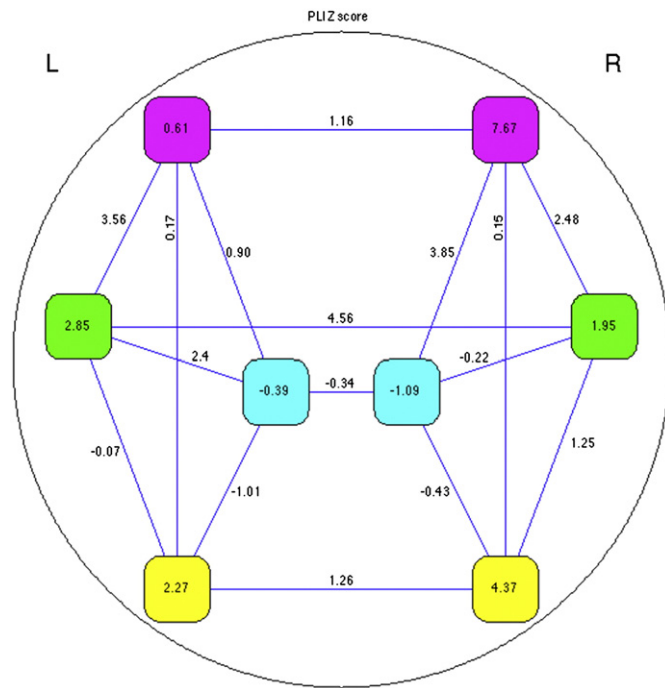


Fig. 3. Graphic representation of Phase Lag Index within and between sensor regions in one patient. Values represent Z scores obtained by comparing 10 seconds of MEG data during the absence seizure and four ten-second epochs of resting state data.

demonstrate in generalized spike–wave discharges, it is possible to hypothesize that thalamocortical hypersynchronization and the associated slow-wave component that dominates the frontoparietal scalp electrodes during an absence seizure could be responsible for a transient impairment of the DMN [35] and the consequent involvement of consciousness. The variability in the duration of spike–wave discharges and in the associated clinical manifestations would suggest that impaired consciousness in absence seizures is not an all-or-nothing phenomenon.

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