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Imaging brain synchrony at high spatio-temporal resolution: application to MEG signals during absence seizures

Frédérique Amor, David Rudrauf, Vincent Navarro, Karim N'diaye, Line Garnero, Jacques Martinerie, Michel Le Van Quyen*

Laboratoire de Neurosciences Cognitives et Imagerie Cérébrale, LENA,CNRS UPR 640, Hôpital de la Pitié-Salpêtrière, 47 Bd de l'Hôpital, 75651 Paris, Cedex 13, France

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Abstract

Imaging the dynamics of distributed phase synchrony across brain signals is of crucial importance for the study of large-scale interactions in the brain, and requires combining at the same time, wide coverage of the brain with high spatial and temporal resolution. Electro- and magneto-encephalography (EEG–MEG), which provide full head coverage measurements of the human brain activity, can potentially satisfy those needs. Nevertheless, EEG–MEG signals reflects the integration of separately generated brain processes on the scalp that typically overlap in space and give rise to spurious phase-locking between their signals. Moreover, current phase synchronization measures do not have a sufficient time resolution to capture very brief periods of phase locking between brain signals, because of their dependence on a window of time integration. We present here a new, non-invasive technique for characterizing the phase synchronization between brain regions at high spatial and temporal resolution. An efficient inverse problem algorithm was used to estimate, from the MEG signals and with the help of the anatomical MRI, the corresponding intracranial brain sources on the cortical surface. The synchronization analysis was then directly performed on the cortex by the characterization of common instantaneous frequencies between groups of cortical sources which preserve a fine temporal resolution. The proposed method was illustrated by its application to MEG data recorded during absence seizures in two epileptic patients. The technique visualizes local and short-lasting synchronization patterns leading to the seizure, thus providing new potential for understanding non-invasively the origin of epileptic discharges.

Keywords: MEG; Wavelets; Synchronization; Inverse problem; Epilepsy; Absence seizure

1. Introduction

Normal cognitive operations require the rapid integration of activities in numerous functional areas widely distributed in the brain and in constant interaction with each other [1–4]. Phase-locking

*Corresponding author. Tel.: + 33 1 42 16 11 71; fax: + 33 1 45 86 25 37.
E-mail address: lenalm@ext.jussieu.fr (M. Le Van Quyen).

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synchrony is an important candidate for such large-scale integration, mediated by neuronal groups that oscillate in specific frequency bands and enter into precise phase-locking over a limited period of time [4]. Large-scale cortical synchronization has been demonstrated in numerous electro- and magneto-encephalographic (EEG–MEG) studies [5,6]. EEG–MEG are particularly well suited for this type of exploration, as they provide full head coverage with a time resolution in the msec range. The quantification of synchrony between EEG–MEG signals is therefore of crucial importance for the study of these large-scale interactions. Measures of covariance or coherence have been extensively used to quantify brain synchronization [7,8]. These tools are however highly dependent on the stationarity of the measured signal, and do not disentangle amplitudes and phases while evaluating their interrelations. In order to overcome these limitations, and motivated by previous theoretical works on chaotic systems [9,10], methods of "phase" synchronization analysis were introduced in the neuroscience community by Tass et al. [11] and Lachaux et al. [12]. Phase synchrony measures the temporal adjustments of a pair of signals, within a given frequency band, whereas the amplitudes can remain uncorrelated. The local stability of the phase adjustment within the band is then characterized over a time window by means of various statistical parameters [13]. The relevant theoretical formalism was analysed in detail by Bruns [14]. Other techniques, such as adaptive phase estimation by ARMA modelling [15], have also been proposed in this context.

Although phase synchronization measures have been shown to be very useful for understanding large-scale dynamical properties of cognitive processes [5,6,16] or neurological disorders such as Parkinson's disease [11] or epilepsy [17–20], phase synchrony still faces two problems to be solved before becoming a robust method in brain imaging: (1) EEG–MEG signals do have sufficient time resolution to capture the macroscopic dynamics of brain activation and synchronization. Nevertheless, the projections on the scalp of separately generated brain processes typically overlap both in time and space, becoming inextricably mixed in recordings from scalp electrodes. This lack of a good spatial resolution of EEG/MEG may cause two separate electrodes to record from overlapping neural populations, which may lead to false detection of synchrony between electrodes not due to a coupling between brain structures but to volume conduction [21,22]. (2) It has been emphasized that classical phase synchronization methods may be insensitive to very brief periods of synchronization because of their use of a time integration window including several cycles of oscillation [23,24]. Otherwise, signals can be phase locked whereas their frequency of synchronization vary rapidly according to time, so that time integration within a given frequency band can mask events of synchronization [25].

The technique presented in this paper intends to overcome these limitations, and is based on a new combination of two recent developments: (1) Instead of proceeding to a temporal analysis in the sensor space, we estimated the cortical currents by resolving the inverse problem, and then performed a synchronization analysis in the source space [6,22]. An efficient source estimation algorithm was applied to the observed MEG signals to estimate intracranial brain sources with a high spatial resolution [26]. We used the inverse problem minimum norm method that constrains the locations of the sources on the cortical mantle on the basis of the anatomical MRI. (2) We then performed a distributed synchronization analysis directly on the cortical data using the method introduced in Rudrauf et al. [25]. This method is based on the classical equivalence between phase locking and frequency locking for narrow band signals. High-resolution time-frequency decompositions are used in order to reveal the instantaneous frequencies of possibly distinct spectral components [27,28]. Synchronized groups of cortical sources are identified as groups showing short periods of common instantaneous frequencies. Our procedure results in a spatiotemporal mapping on the structural MRI of the ongoing dynamics of synchronization among cortical sources.

We evaluate this new technique using MEG data recorded during absence seizures in two epileptic patients. Absence seizures are the most characteristic expression of non-convulsive generalized epilepsy. They consist of a sudden arrest of ongoing behaviour and impairment of consciousness associated with abrupt occurrence of bilateral, synchronous and three-per-second spike-and-wave discharges (SWD) in EEG signals over wide cortical areas [29]. Despite evidence that absence seizures imply a corticothalamic network, the mechanisms responsible for the initiation and generalization of the discharges is still not understood. The application of the proposed technique to the corresponding MEG data revealed cortical short-lasting and spatially restricted synchronization patterns leading to the seizures, thus providing helpful information for understanding, with non-invasive methods, the origin of epileptic discharges associated with absence epilepsy.

2. Material and methods

2.1. MEG source estimation

The temporal resolution of the MEG/EEG (on the order of a millisecond) allows one to measure in real-time the electromagnetic field on the scalp generated by underlying cortical neurons. The MEG recordings are totally non-invasive, but access only remote measures of brain activity and therefore offer a very limited spatial resolution. To overcome this limitation, the MEG/EEG inverse problem aims to estimate the current density of clusters of cortical neurons at the origin of the magnetic fields and electric potentials measured at the surface of the head [26]. We used the inverse problem method described in David et al. [21,30], that constrains the locations of the sources on the cortical mantle on the basis of the anatomical MRI. We first modelled the scalp potential and magnetic field given an internal current distribution, considering the physical properties of the head such as the electrical conductivity and its geometry (approached here by a single sphere). This lead us to the calculation of a gain matrix, which contains global information on the head model and basically links the source currents located on the cortex to the MEG sensors signals measured on the surface of the skull. Given the location and orientation of N cortical sources, T time samples of S MEG data measurements, one can model the measured magnetic field fluctuations using the following linear equation [31]:

$$\mathbf{M} = \mathbf{G} \cdot \mathbf{J} + \mathbf{B}, \tag{1}$$

where $\mathbf{M}$ is the $S\ x\ T$ matrix of MEG data, $\mathbf{J}$ is the $N\ x\ T$ matrix representing the contribution of each source to the scalp magnetic field, $\mathbf{G}$ is an $S\ x\ N$ gain matrix and $\mathbf{B}$ is an $S\ x\ T$ matrix modelling additive noise. The location of the sources is determined by using a mesh of white/grey matter interface, extracted from the anatomical MR image of the subjects: each dipole is placed at the node of a triangular tessellation of the cortical mantle surface computed with the Brainvisa software (http://brainvisa.info/). Given the high number of distributed sources (3–10 thousand) compared to the number of MEG sensors (less than 300), the inverse problem solution happens to be neither unique nor stable. One way to obtain a stable solution to Eq. (1) consists in using an estimator of the cortical current density, named $\hat{\mathbf{J}}$ [32,33]. We used here the classical minimum norm (MN) estimator, as its properties are well-known and it minimizes the amplitude of the source, thus preventing strong oscillations in the inverse problem resolution. In practice, it presents a unique solution and minimizes the L2-norm of the estimate $\hat{\mathbf{J}}$ of $\mathbf{J}$:

$$\hat{\mathbf{J}} = \mathbf{G}^{\mathrm{T}}(\mathbf{G}\mathbf{G}^{\mathrm{T}} + \alpha\mathbf{I})^{-1}\mathbf{M}, \tag{2}$$

where $\mathbf{I}$ is the identity matrix, and α is roughly linked to the signal to noise ratio. The resolution of the inverse problem finally results in the estimation of the time course of the cortical currents amplitude at each node of the white/grey matter interface from which the scalp magnetic field measured during MEG recordings originates. The inverse problem has been performed using Brainstorm Matlab Toolbox (http://neuroimage.usc.edu/brainstorm/).

2.2. Estimation of the instantaneous frequencies of the cortical sources using a ridge algorithm

The instantaneous frequency of a monocomponent signal, not corrupted by noise, can be estimated by well-known algorithms [27,34]. When the useful signal is multicomponent or is perturbed by additive noise, the estimation of the instantaneous frequencies is not trivial. Such an estimation can however be achieved computing the ridges of certain time-frequency decompositions of the signal [28,34]. We used here by the analytic wavelet transform (AWT), known to be well suited for studying non stationary data [12]. In the AWT, a family of time-scale wavelets of the form:

$$\psi_{u,s}(t) = \frac{1}{\sqrt{s}}\psi\left(\frac{t-u}{s}\right), \tag{3}$$

where ψ denotes the mother wavelet (a Gabor wavelet here), u and s the translation and scale parameters respectively. The convolution of the signal f(t) with the family of wavelets provides its wavelet transform $Wf(u,s)$. The squared modulus of $Wf(u,s)$, called the scalogram, is the power density of the signal in the time-scale plane:

$$Pf(u,s) = \left|\langle f, \psi_{u,s}\rangle\right|^2 = \left|Wf(u,s)\right|^2. \tag{4}$$

Assuming that the analysed signal can be approximated by a linear combination of analytic signals of the form $f(u) = a(u)e^{i\phi(u)}$, with $a(u)$ and $\phi(u)$ the instantaneous amplitude and phase of the signal's components, the instantaneous frequency (within a narrow band) can be defined from the *ridges* points of the normalized scalogram $s^{-1}Pf(u,s)$, corresponding to its local maxima [25,28,34]. The ridges points define curves in the (u, s) plan, called *wavelet ridges*. It must be noted that if the instantaneous frequencies of the components of a given signal are too close, the spectral curves interfere and the ridge extraction is not able to distinguish them properly. Noise artifacts are removed by neglecting the ridges corresponding to small amplitudes $a(u)$. The ridge algorithm results in a high resolution spatio-temporal binary map, with ones where a significant instantaneous frequency has been found in the signal and zeros otherwise. To compute the analytic wavelet transform and the associated ridges, we used the routines of the Matlab toolbox WaveLab (see http://www.stat.stanford.edu/~wavelab).

3. Results

3.1. Detecting synchronization by common instantaneous frequencies

In the classical sense of periodic, self-sustained oscillators, synchronization is usually defined as locking (entrainment) of the phases $\Delta\phi = n\phi_1 - m\phi_2 = const$ (a), where n and m are integers, and ϕ_1,ϕ_2 are the phases of the two oscillators. Condition (a) is valid for quasi-periodic oscillators only. The amplitudes of phase synchronized oscillations can be quite different and do not even need to be related [9]. For periodic oscillators, the condition of phase locking (a) is equivalent to the notion of frequency locking $nf_1 = mf_2$ (b), where $f = \langle d\phi/dt\rangle/2\pi$ and brackets mean time averaging. Synchronization of periodic oscillators thus means the appearance of phase locking and the adjustment of frequencies. When the useful signal contains several components or is perturbed by a small additive noise, the notion of frequency locking is more complicated. A solution is to define the instantaneous frequency based on a time-frequency deconvolution of the analyzed signal. Indeed, time-frequency distributions have two useful properties: (i) They have a very good concentration around the curve of the instantaneous frequency of the analysed signal [35]. (ii) They realize a diffusion of the perturbation noise's power in the time-frequency plane. Using AWT, we can associate a set of time-varying frequencies to the signal. As introduced in Rudrauf et al. [25], locating the instantaneous frequencies of several spectral components by the extraction of ridges (i.e., the local maxima with respect to the scale of the energy density in the time-scale plane), we can define a condition of frequency locking (c). An example of the operational mode of the proposed method is presented in Fig. 1. The ridges of three different artificial signals were added in the time-frequency plane. Their respective instantaneous frequencies $f_1(t)$, $f_2(t)$ and $f_3(t)$ superimpose during a period of synchronization, i.e., a common continuous trajectory in the time-frequency plane, reflecting 1:1 phase synchronization.

The relation between phase synchrony and the existence of common instantaneous frequency

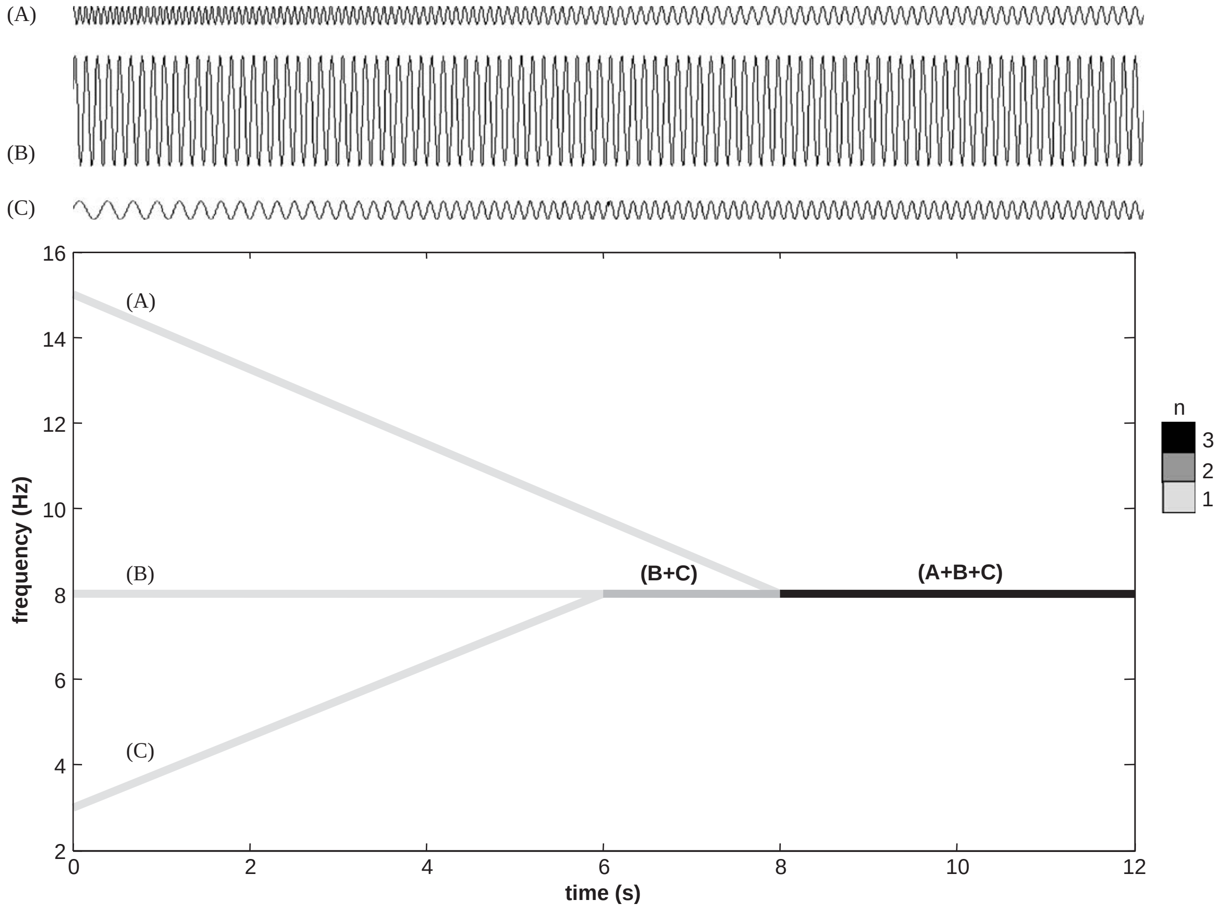
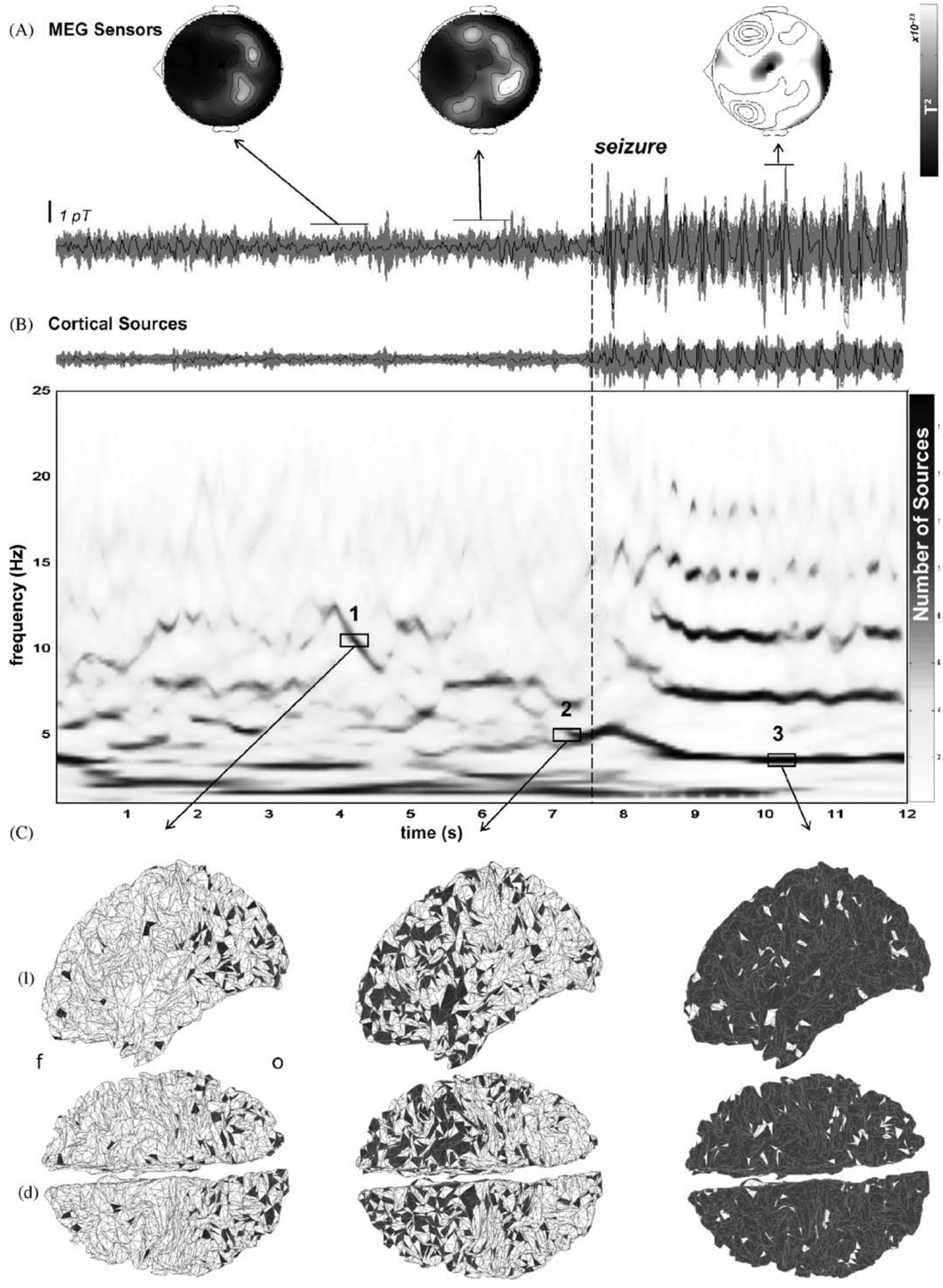


Fig. 1. Schematic presentation of the methodological approach followed in this study.A. An artificial signal (A) was simulated by a sinusoid with linearly decreasing frequency from 15 to 8 Hz.After 8 s, the signal presents a constant frequency of 8 Hz. A second sinusoidal signal (B) was simulated with a constant frequency of 8 Hz across the entire time window. Finally, a third signal (C) presents a linearly increasing frequency from 3 to 8 Hz and, after 6 s, a period of sustained 8 Hz frequency. B. The instantaneous frequencies of the signals are extracted by the ridge decomposition (local time-frequency maxima) in the time-frequency plane. The colour codes the number of ridge skeletons that superimpose in a local time-frequency window. The orange segment (B + C) shows the superposition of the instantaneous frequencies of signals (B) and (C) at 8 Hz.Finally, the red segment (A + B + C) shows the superposition of the time-frequency trajectories of the three signals. Due to the classical equivalence between phase locking and frequency locking for narrow-band signals, one can therefore assume phase synchronization between the corresponding signals. Note that the difference in amplitude between the signals does not affect the synchronization detection.

provides a direct bridge to the study of synchrony at the level of an arbitrary number of signals. If n oscillators are mutually phase-synchronous over a period of time, all oscillators will have the same instantaneous frequency in the time-frequency plane. Consequently, rather than computing $(n^2-n)/2$ synchronizations between pairs of signals, we can directly characterize synchronization between an arbitrary number of signals by detecting a common instantaneous frequency in n time-frequency representations. Using this simplification in what follows, we were able to study synchronous patterns of 7003 cortical sources over the cortical surface.


(A) MEG Sensors
seizure
1 pT
$x10^{-23}$
T^2
4.5
2.5
0.5
(B) Cortical Sources
frequency (Hz)
25
20
15
10
5
1
2
3
Number of Sources
1600
800
200
time (s)
1
2
3
4
5
6
7
8
9
10
11
12
(C)
(l)
f
o
(d)

3.2. Application to MEG data recorded during absence seizures

The synchronization analysis was applied to four spontaneous epileptic seizures recorded from two patients (3 and 1 seizures, respectively) suffering from intractable juvenile absence epilepsy, a subtype of non-convulsive generalised epilepsy. The MEG recordings were done on a 151-SQUID sensors CTF system (CTF System Inc., Port Coquitlam, BC, Canada) at the MEG Centre of the Hôpital de la Salpêtrière, in Paris, France. The experimental protocol was approved by the Hôpital de la Salpêtrière ethics committee (CCPPRB). The seizures spontaneously occurred during an eyes-closed resting condition. Their onsets were determined by the abrupt occurrence of spike-wave discharges (SWD) with a power spectral density peaking at 3 Hz, observed widespread on the MEG sensors (Fig. 2-A). After reconstruction of the current densities' time courses over the cortical mantle (about 7000 sources), AWTs of the signals and their associated ridges were computed between 1 and 25 Hz, and summed, in order to reveal regions of synchronization in the time-frequency plane (Fig. 2-B). In each analysed case (4/4 seizures), a sustained period of common instantaneous frequency between a large group of cortical sources (>500) was observed to precede the seizure onset by about 1–2 s. This synchronization mostly involved the alpha frequency band (between 5 and 10 Hz). The projection of the corresponding synchronized sources onto the cortex reveals two principal zones of concentration of synchronization, near frontal and pre-central areas. Such spatial patterns of synchronization were very reproducible across the four seizures we analyzed (Fig. 3). These observations suggested the existence of a cortical synchronization before the occurrence of SWDs associated with absence seizures. They support the importance of cortical activity in the initiation of absence seizures, as recently suggested by high-density EEG [36].

4. Discussion

We have presented a new, non-invasive method for imaging at high temporal and spatial resolution, the dynamics of synchronization over the human cerebral cortex. Instead of analyzing synchronization in the sensor space, which mixes signals originating from separately generated brain processes, we first estimated cortical current densities using an inverse procedure, and then performed a distributed synchronization analysis in the sources' space. The anatomies of the head and brain were used to guide the source estimation, and to display the synchronization on the

Fig. 2. Synchronization analysis of a typical absence seizure A. Superposition of from 151 MEG sensors recorded from 7.5 s before to 4.5 s after seizure onset. One sensor trace (black) was selected to show the sudden onset of characteristic 3 Hz SWD of amplitude three times larger than background inter-ictal MEG activity. The three head schemes show the projection of the mean spectral power (calculated using the Fourier Transform) of each sensor between 1 and 12 Hz, during inter-ictal, pre-ictal and ictal periods, respectively. The seizures were recorded during an eyes-closed resting condition and the background MEG major component consists of a sustained alpha band occipital activity (10–12 Hz). During the pre-ictal period, one can observe a more central and frontal activity pattern, whereas the ictal state displays a general activation over the whole head. B. *Top*. Superposition of signals from 7003 cortical sources. Overlaid in black, the signal associated with one channel. *Bottom*. Grand-average of the ridges maps associated with each cortical sources, computed between 1 and 25 Hz.The colours code the number of sources displaying synchronous activity. Around 1 s before the seizure, a period of common instantaneous frequency between a large group of cortical sources can be observed. During the seizure, a hyper-synchronous pattern at 3 Hz, associated with the SWD activity, can be seen. Note the presence of spurious harmonics of the 3 Hz component. C. Lateral (l) and dorsal (d) views of the projections onto the anatomical MRI of the synchronized sources during inter-ictal, pre-ictal and ictal periods (see selected windows 1–3 in the time-frequency plane in B), with f = frontal, o = occipital. The ridges of each cortical source were averaged within a specific frequency band across a window of time of 400 ms, and then projected onto the cortex. Sources having a ridge defined within the time-frequency windows of interest were coded in red. Sources that did not participate to the flow of common instantaneous frequency were coded in blue. For the interictal window (1), the projection of the synchronized sources shows an occipital 11 Hz synchronization corresponding to the physiological eyes-closed resting state. The preictal window (2) reveals a large frontal synchronization at 5 Hz, 500 ms before seizure onset. Finally, the projection of the synchronized sources during the seizure (window 3) illustrates a widespread hyper-synchronization of SWD.

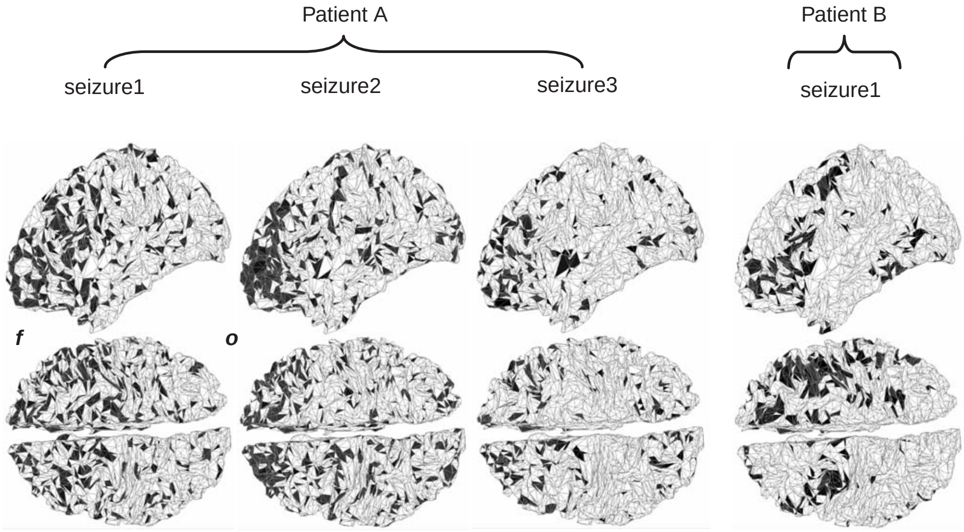


Fig. 3. Cortical networks of synchronous brain activation at the onset of four absence seizures from two patients. Lateral and dorsal view of the projections onto the anatomical MRI of the synchronized sources at pre-ictal periods, with f = frontal, o = occipital. The ridges of each cortical source at 3–5 Hz was averaged within a window of time of 400 and 350 ms before the seizures. In both patients, the technique allowed to localize a frontal and pre-central synchronization implicated early in the emergence of the absence seizures.

cortex directly. A similar use of anatomical MRI in order to constrain the estimation of synchronization to the cortical mantle has already been proposed elsewhere [6,22,37]. Nevertheless, we improved the temporal resolution of synchrony analysis by looking for continuous periods of common instantaneous frequencies, allowing direct estimations of synchronization among groups of signals. We used a robust estimation procedure for the extraction of the instantaneous frequency, based on the computation of the AWT of the signals, followed by the computation of a ridges skeleton, which provides a high resolution time-frequency representation.

The proposed method was applied to MEG data recorded during absence seizures. As MEG is most sensitive to cortical sources perpendicularly orientated to the brain surface, the reconstructed neuronal activity can plausibly be constrained to the cortical surface [26]. We reported here evidence from two patients that the method could provide relevant information about the anatomical origin of the bilateral synchronous SWD associated with absence seizures. In this context, there are experimental evidences that absence seizures are driven by a thalamocortical network, but the precise origin of generalized absence seizures is still unclear [29]. A recent hypothesis (called the “hot spot theory”) proposed that a cortical focus in the somatosensory cortex drives widespread thalamocortical networks during spontaneous absence seizures [36,38]. In a very similar way, we showed here a reproducible pattern of synchronization across several cortical locations in a low frequency range, just before the seizure. Changes in synchronous neuronal activities appeared within and between frontal and pre-central areas, suggesting that the cerebral cortex is critically involved in the occurrence of spike-wave discharges. It is yet too early to draw conclusions from the observed synchronizations because of the relatively small sample size. There are also known errors in source reconstructions associated with the use of cortical surfaces as anatomical constraints, which might limit the interpretability of the results [39]. Nevertheless, the reliability of the results across seizures and subjects suggests the potential interest of this technique for characterizing the involvement of the cerebral cortex in absence seizures triggering.

Our group is currently investigating this issue that will be the focus of an upcoming study.

Based on this application to MEG, we believe that a satisfactory measure of synchrony can be obtained by tracking continuous periods of identical instantaneous frequencies in time-frequency representations. Nevertheless, three points need to be stressed here:

(1) Our method uses the classical equivalence between phase locking and frequency locking for narrow band signals. This relationship applies only in cases in which the periods of phase synchrony are not affected by a high level of noise on the phases. Strong noise can indeed cause *phase slips,* i.e., rapid jumps of the relative phase, and systems might have the tendency to lock phase in a stochastic way but with strong instability due to random forces [10], leading to strong instabilities of the instantaneous frequency. Consequently, the proposed method can overlook such cases of *statistical phase locking*, i.e., cases in which the question of the presence of a phase locking can only be addressed in a stochastic sense. Nevertheless, as demonstrated by our results (see also [25]), the strong criterion of frequency locking is valid for certain brain signals at least, opening the possibility of directly generalizing phase synchrony analysis to the multivariate case.
(2) The use of this relationship depends on the ability to separate signal components that have a compact spectral representation; if not possible the instantaneous phase and frequency have no meaningful interpretation. It is well known that EEG-MEG recordings often exhibit a typical 1/f spectral distribution, and that there might be important information contained in broad-band signals [40,41]—Despite clear limitations in detecting these nonlinear structures and their interrelations, the proposed method, which uses an algorithm of characterization of the intrinsic modes of oscillations of the signals, has some advantages over conventional methods of phase synchronization analysis, which impose an arbitrary spectral decomposition of the signal using band-pass filtering [12,13]; discussed in [14]. Therefore, any event (trapping, transition, etc.) fluctuating in time on different frequencies is missed by these conventional methods. By contrast, our method allows tracking the rapid variations of instantaneous frequencies. Accordingly, it has been shown that instantaneous frequencies based on ridge decompositions reveal the low-dimensional phase space structures (resonance transitions, trappings, etc.) of chaotic systems [42]. Therefore, the proposed strategy permits a refinement of the synchronization measures, helping to track some nonlinearity and/or nonstationarity in the time-frequency domain.
(3) Another future research direction is the development of adequate statistical analyses for the method. The ridge extraction involves a statistics on the energy of the signal, although such a statistic is local and can track instantaneous frequency components with very low amplitude [28]. Nevertheless, in high frequencies, and, in particular, when signals show broad-band components, ridges can be more unstable, and very closely spaced spectral components in individual signals can lead to a local phenomenon of interference. Supplementary statistical criteria should contribute to a better definition of frequency-locking between groups of signals. For example, further developments may propose statistical criteria defining the minimum duration of common instantaneous frequencies or the minimum number of elements in the flow, as well as the continuity of the contribution of individual channels (see Rudrauf et al. [25]). Multivariate methods can here help to construct an ensemble of 'surrogate data' which share some properties with the original data, except for the synchronization [24,43].

In summary, the general framework outlined above allows a new examination of the ongoing dynamics of synchronous cortical sources, with a high spatial and temporal resolution. The main interests of this approach are, on the one hand, the use of the inverse problem to deconvoluate the brain dynamic at the cortical level and, on the other hand, the use of time-frequency approaches that allow imaging time-varying synchronizations in large arrays of signals, with a high temporal, spatial and frequency resolution. This synchrony method could be applied to other imaging technologies such as PET, optical imaging, and transcranial Doppler. In spite of a clear potential of the approach, in particular for epilepsy research, further investigations are needed to evaluate its general usefulness. Analyses are currently carried out on other types of data involving distributed brain activities. We are studying the behaviour of the method in signals including multiple modes of oscillations with close frequencies, as well as the influence of noise on the definition of multivariate instantaneous frequencies, and the extension of the method to broad-band signals for characterizing nonlinear behaviours.

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