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Interictal stereotactic-EEG functional connectivity in refractory focal epilepsies

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Drug-refractory focal epilepsies are network diseases associated with functional connectivity alterations both during ictal and interictal periods. A large majority of studies on the interictal/resting state have focused on functional MRI-based functional connectivity. Few studies have used electrophysiology, despite its high temporal capacities. In particular, stereotactic-EEG is highly suitable to study functional connectivity because it permits direct intracranial electrophysiological recordings with relative large-scale sampling. Most previous studies in stereotactic-EEG have been directed towards temporal lobe epilepsy, which does not represent the whole spectrum of drug-refractory epilepsies. The present study aims at filling this gap, investigating interictal functional connectivity alterations behind cortical epileptic organization and its association with post-surgical prognosis. To this purpose, we studied a large cohort of 59 patients with malformation of cortical development explored by stereotactic-EEG with a wide spatial sampling (76 distinct brain areas were recorded, median of 13.2 per patient). We computed functional connectivity using non-linear correlation. We focused on three zones defined by stereotactic-EEG ictal activity: the epileptogenic zone, the propagation zone and the non-involved zone. First, we compared within-zone and between-zones functional connectivity. Second, we analysed the directionality of functional connectivity between these zones. Third, we measured the associations between functional connectivity measures and clinical variables, especially post-surgical prognosis. Our study confirms that functional connectivity differs according to the zone under investigation. We found: (i) a gradual decrease of the within-zone functional connectivity with higher values for epileptogenic zone and propagation zone, and lower for non-involved zones; (ii) preferential coupling between structures of the epileptogenic zone; (iii) preferential coupling between epileptogenic zone and propagation zone; and (iv) poorer post-surgical outcome in patients with higher functional connectivity of non-involved zone (within- non-involved zone, between non-involved zone and propagation zone functional connectivity). Our work suggests that, even during the interictal state, functional connectivity is reinforced within epileptic cortices (epileptogenic zone and propagation zone) with a gradual organization. Moreover, larger functional connectivity alterations, suggesting more diffuse disease, are associated with poorer post-surgical prognosis. This is consistent with computational studies suggesting that connectivity is crucial in order to model the spatiotemporal dynamics of seizures.

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Abbreviations: EZ = epileptogenic zone; FCD = focal cortical dysplasia; NIZ = non-involved zone; PZ = propagation zone

Introduction

The human brain is a complex network connecting billions of neurons organized over several spatial scales and interacting over several time scales (Fornito *et al.*, 2015). Consequently, brain connectivity analyses coupled with graph-theory principles have attracted much effort in neuroscience research, leading to unprecedented understanding of normal brain network organization (Bullmore and Sporns, 2009; Stam, 2014). Recently, these approaches have been successfully applied to the study of neurological diseases such as epilepsy (van Diessen *et al.*, 2013).

Epilepsy is a serious and highly prevalent neurological disease, affecting 1% of the population worldwide (Fiest *et al.*, 2016). Pharmacoresistance to anticonvulsant therapy remains a major issue for about one-third of patients, who may benefit from epilepsy surgery when epilepsy is focal (Ryvlin *et al.*, 2014). Focal epilepsy is increasingly conceptualized as a network disorder with regards to spatial organization of epileptic cortices, pattern of seizure propagation, and brain network alterations (Bartolomei *et al.*, 2017). While numerous studies have shown modified brain synchrony during seizures, cerebral connectivity is also notably altered during interictal and resting states. These studies used structural or functional connectivity, MRI or electrophysiological recordings [scalp EEG, intracranial EEG, magnetoencephalography (MEG)], and in some cases used graph-theory analyses (Bernhardt *et al.*, 2013; Coito *et al.*, 2015; Englot *et al.*, 2015; Bartolomei *et al.*, 2017; Besson *et al.*, 2017). Even focal epilepsies are thus associated with large-scale connectivity alterations during interictal/resting state, possibly accounting for comorbidities such as cognitive dysfunction. Furthermore, conceptualization of the epileptic brain in terms of pathological networks could help identify the anatomical distribution of the epileptogenic process and help estimate efficiency of surgery. For example, a recent connectivity-based personalized brain model demonstrated good prediction of seizure propagation correlating with surgical outcomes (Hutchings *et al.*, 2015; Goodfellow *et al.*, 2016; Proix *et al.*, 2017; Sinha *et al.*, 2017; Steimer *et al.*, 2017).

Nevertheless, despite numerous studies on the subject, network organization in epilepsy remains incompletely understood (Richardson, 2012; Bernhardt *et al.*, 2013; Duncan *et al.*, 2016; Bartolomei *et al.*, 2017). A large

majority of literature has focused on MRI extracted connectivity (Bernhardt *et al.*, 2013; Duncan *et al.*, 2016) although the relationship between functional MRI and electrophysiological data is still incompletely understood (Béнар *et al.*, 2006; Bettus *et al.*, 2011; Coan *et al.*, 2016; Ridley *et al.*, 2017). Other studies used electrophysiological recordings (intracranial or not) to compute functional connectivity (Kramer *et al.*, 2011; Chu *et al.*, 2012; Kramer and Cash, 2012; van Diessen *et al.*, 2013; Yaffe *et al.*, 2015). These studies are essentially limited to temporal lobe epilepsy, although extra-temporal epilepsies are highly prevalent and represent complex cases in epilepsy surgery. Moreover, invasive recordings are mostly based on electrocorticography (ECoG) with some limitations compared to stereotactic-EEG. Stereotactic-EEG is a direct intracranial recording avoiding methodological issues in terms of source connectivity analysis, contrary to MEG or EEG that require an ill-posed inverse problem and are prone to source leakage (Schoffelen and Gross, 2009). Moreover, it is now clear that stereotactic-EEG and functional MRI data are not highly correlated (Bettus *et al.*, 2011; Ridley *et al.*, 2017). Despite the clear interest of stereotactic-EEG, stereotactic-EEG-extracted functional connectivity data from large cohorts of patients with extensive extra-temporal sampling remain scarce. One study included 10 patients with focal cortical dysplasia type II and showed in the gamma sub-band higher out-density and betweenness centrality within the lesion than in other brain areas (Varotto *et al.*, 2012). The present study aims at filling this gap and more specifically to correlate functional connectivity data with post-surgical outcome.

To this end, we investigated a cohort of 59 consecutive patients with malformations of cortical development using stereotactic-EEG. We chose this ‘model’ of focal epilepsy for three reasons: (i) malformation of cortical development is a common aetiology of intractable focal epilepsy (~30% of patients referred for presurgical evaluation) (Guerrini *et al.*, 2015; Cloppenborg *et al.*, 2016); (ii) malformation of cortical development lesions are known to be intrinsically epileptogenic (Aubert *et al.*, 2009; Guerrini *et al.*, 2015); and (iii) malformation of cortical development may be observed in different brain structures across patients (leading to wide brain sampling in our cohort). Based on stereotactic-EEG recordings, we defined three

zones of interest: the epileptogenic zone (EZ), propagation zone (PZ) and the non-involved zone (NIZ). We then computed functional connectivity from stereotactic-EEG signals across several frequency bands. We used non-linear correlation to calculate directed functional connectivity (Pijn and da Silva, 1993; Wendling *et al.*, 2010). Finally, we addressed four questions: (i) does the within-zone functional connectivity differ according to the zones? (ii) is there a particular pattern of functional connectivity coupling between zones? (iii) do certain zones drive others in term of directionality? and (iv) is there an association between functional connectivity and clinical variables, in particular post-surgical prognosis?

Materials and methods

Figure 1 summarizes the methods that were used in this study.

Patient selection

Among all patients (children and adults) who underwent stereotactic-EEG in our department from 2000 to 2016, we

reviewed 75 consecutive patients with pathologically proven focal cortical dysplasia (FCD) or neurodevelopmental tumours. An expert neuropathologist reviewed data and established the pathological diagnosis according to International League Against Epilepsy (ILAE) (Blümcke *et al.*, 2011) and WHO classifications (Louis *et al.*, 2016) according to a previous study (Lagarde *et al.*, 2016). We included patients with isolated FCD type I or type II, and patients with neurodevelopmental tumours. We excluded 16 patients: one patient in whom no seizure was recorded during stereotactic-EEG and 15 patients not fulfilling resting state stereotactic-EEG quality criteria. Thus, 59 patients were analysed. The institutional review board of the French Institute of Health (IRB15226) approved this study and written patient consent was obtained.

All patients had detailed evaluation including medical history, neurological examination, cognitive testing, cerebral ^{18}F -fluorodeoxyglucose-PET and MRI. In this study, all patients required invasive recordings after the non-invasive phase and stereotactic-EEG exploration was carried out as part of patients' usual clinical care. Stereotactic-EEG was indicated when the EZ was suspected to be larger than the lesion; and/or when extra-temporal structures were suspected to be involved in temporal lobe seizures; and/or when bilateralism was suspected; and/or when an eloquent area was suspected to be involved (Jayakar *et al.*, 2016). The placement

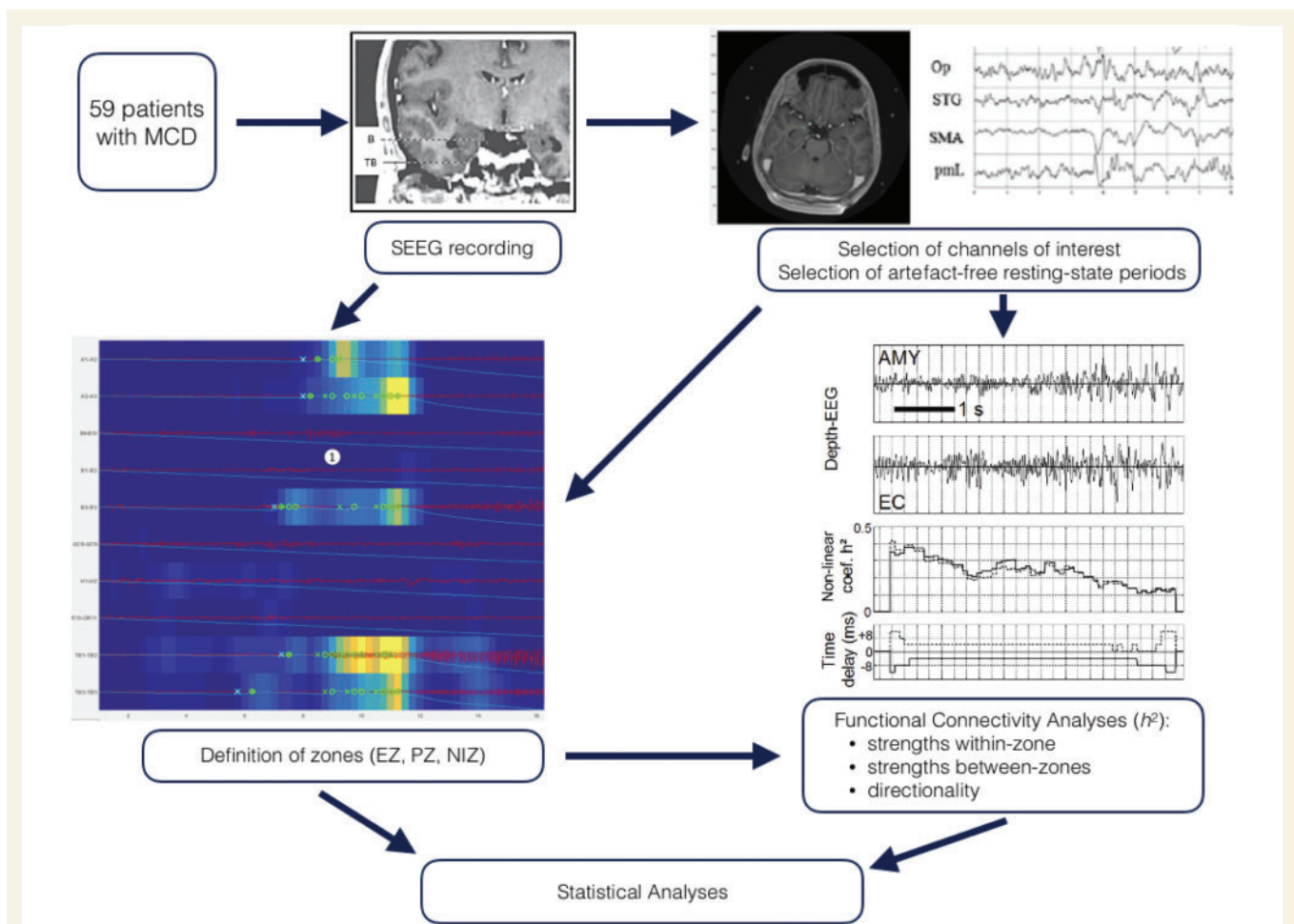


Figure 1 Summary of the analysis pipeline. For details see the 'Materials and methods' section. MCD = malformations of cortical development; Op = operculum; pml = premotor lateral cortex; STG = superior temporal gyrus.

of electrodes was defined in each patient based on non-invasive information providing hypotheses about the potential localization of the EZ.

Stereotactic-EEG recordings

Long-term video-stereotactic-EEG monitoring was performed to record several of the patient's usual seizures, following complete or partial withdrawal of antiepileptic drugs. The stereotactic-EEG exploration was performed using intracerebral multiple-contact electrodes (Dixi Medical or Alcis), consisting of 10–15 contacts with length 2 mm, diameter 0.8 mm, spaced by 1.5 mm; for details see Bartolomei *et al.* (2008). Signals were recorded on a 128- or 256-channel Natus system depending on the year of recording. They were sampled at 256, 512, or 1024 Hz, depending on the year of recording, and recorded on a hard disk (16 bits/sample) using no digital filter. Two hardware filters were present in the acquisition procedure: a high-pass filter (cut-off frequency = 0.16 Hz at –3 dB), and an anti-aliasing low-pass filter (cut-off frequency = 97 Hz for 256 Hz sampling rate, 170 Hz for 512 Hz sampling rate, or 340 Hz for 1024 Hz sampling rate).

The surgical outcome was assessed regularly during post-operative follow-up and coded according to Engel's classification (Engel, 1993). For analysis, we used the surgical outcome score at the latest available follow-up.

Definition of the three zones

Based on ictal activity, we labelled stereotactic-EEG contacts as belonging to the EZ, PZ or NIZ, according to previous studies and models (Bartolomei *et al.*, 2017; Besson *et al.*, 2017). We used the epileptogenicity index to define the EZ. The epileptogenicity index is a semi-automatic method to quantify the dynamic of the fast-activity genesis at the beginning of seizure. The epileptogenicity index is based on two important features of the transition from pre-ictal to ictal activity: (i) the redistribution of signal energy from lower frequency bands (theta, alpha) toward higher frequency bands (beta, gamma); and (ii) the delay of appearance of these high-frequencies. The epileptogenicity index (EI) is the energy ratio (ER) (averaged over time just after the detection by Page–Hinkley algorithm of the beginning of a rapid discharge) in signal s_i of a structure S_i , divided by the delay Δt_i of involvement of this structure with respect to time N_0 of the first detection of a rapid discharge among all channels:

$$EI_i = \frac{1}{N_{di} - N_0 + \tau} \sum_{n=N_{di}}^{N_{di}+H} ER[n], \tau > 0 \quad (1)$$

Where N_{di} is the detection time in signal s_i recorded from structure S_i , $ER = (E_\beta + E_\gamma)/(E_\theta + E_\alpha)$ (where E is the energy spectral density), and H is the duration over which $ER[n]$ is integrated. From this equation, it can be observed that: the sooner structure S_i becomes involved in the seizure, and the faster its ictal discharge, the higher its epileptogenicity index. Finally, to obtain normalized values per patient, ranging from 0 (no epileptogenicity) to 1 (maximal epileptogenicity), epileptogenicity index values were divided by the maximal value obtained in each patient (for more details regarding methodology see Bartolomei *et al.*, 2008; Marchi *et al.*, 2016). We defined the EZ as all brain areas with epileptogenicity index >0.3 . This

cut-off was chosen pragmatically because it allows the best separation between epileptogenic and non-epileptogenic areas, as demonstrated in previous reports (Bartolomei *et al.*, 2008; Marchi *et al.*, 2016). The PZ was defined by visual analysis as brain areas with an epileptogenicity index <0.3 but with sustained discharge during the seizure course (including rhythmic discharges with propagation delay and/or low frequency) (Proix *et al.*, 2017). The NIZ was defined as all other brain structures.

Functional connectivity analysis

We first selected a subset of all stereotactic-EEG channels. To this purpose, we co-registered pre-implantation MRI and post-implantation CT (using the maximization of normalized mutual information and trilinear interpolation) (Medina Villalon *et al.*, 2018) and visually defined the anatomical area using the Mai *et al.* (2015) atlas. First, we selected only the contacts within the grey matter, because the exact origin of the signal recorded in white matter is not well understood. Second, we chose only one bipolar channel (from two adjacent contacts) for one specific brain area, to limit volume conduction effects and to study only the relation between distant brain areas. Third, in case of more than two channels within the same brain area, we selected the channel without artefact and with the higher amplitude. To limit the influence of not completely inactive common reference and biases due to volume conduction effects, we choose a bipolar re-referencing (obtained from subtraction of monopolar signals recorded on two adjacent contacts in the structure) rather than monopolar signals (Bettus *et al.*, 2008; van Mierlo *et al.*, 2014).

The analysed stereotactic-EEG recordings corresponded to periods of time in which patients were instructed to stay at rest and awake (15 min, eyes closed, resting state, recording performed between 07:00 and 12:30). We selected interictal recordings that were temporally distant from the preceding and the following seizure by at least 2 h. In addition, recordings were chosen at least 2 days after the electrode implantation surgical procedure to limit possible effects of general anaesthesia (Bettus *et al.*, 2008). We visually inspected and selected only artefact-free periods.

As neuronal networks dynamic includes non-linear properties, especially in epilepsy (Jirsa *et al.*, 2014), we chose to estimate functional connectivity using a non-linear regression: b^2 (Pijn and da Silva, 1993; Wendling *et al.*, 2001). b^2 is a non-parametric analysis aiming at quantifying the amplitude correlation of a signal Y on a signal X, independently of the type of the relation between the two signals. This technique has been shown to be particularly suitable for the analysis of EEG/stereotactic-EEG signals in the context of epilepsy (review in Bartolomei *et al.*, 2017). In a sliding window, a piecewise linear regression is performed between each pair of signals. The b^2 is the coefficient of determination, which measures the goodness of fit of the regression (equivalent to the r^2 used in linear regression). The b^2 is bounded between 0 (no correlation) and 1 (maximal correlation) and is asymmetric. For each step, we shifted the time windows to obtain the time lag maximizing the b^2 . This time lag can be used to estimate the time delay between the two signals (for methodological details, see Wendling *et al.*, 2001). To optimize functional connectivity estimation (Wang *et al.*, 2014), we used the following parameters for b^2 analysis: 8 s sliding window, steps 4 s and a maximum lag of 0.1 s. We performed

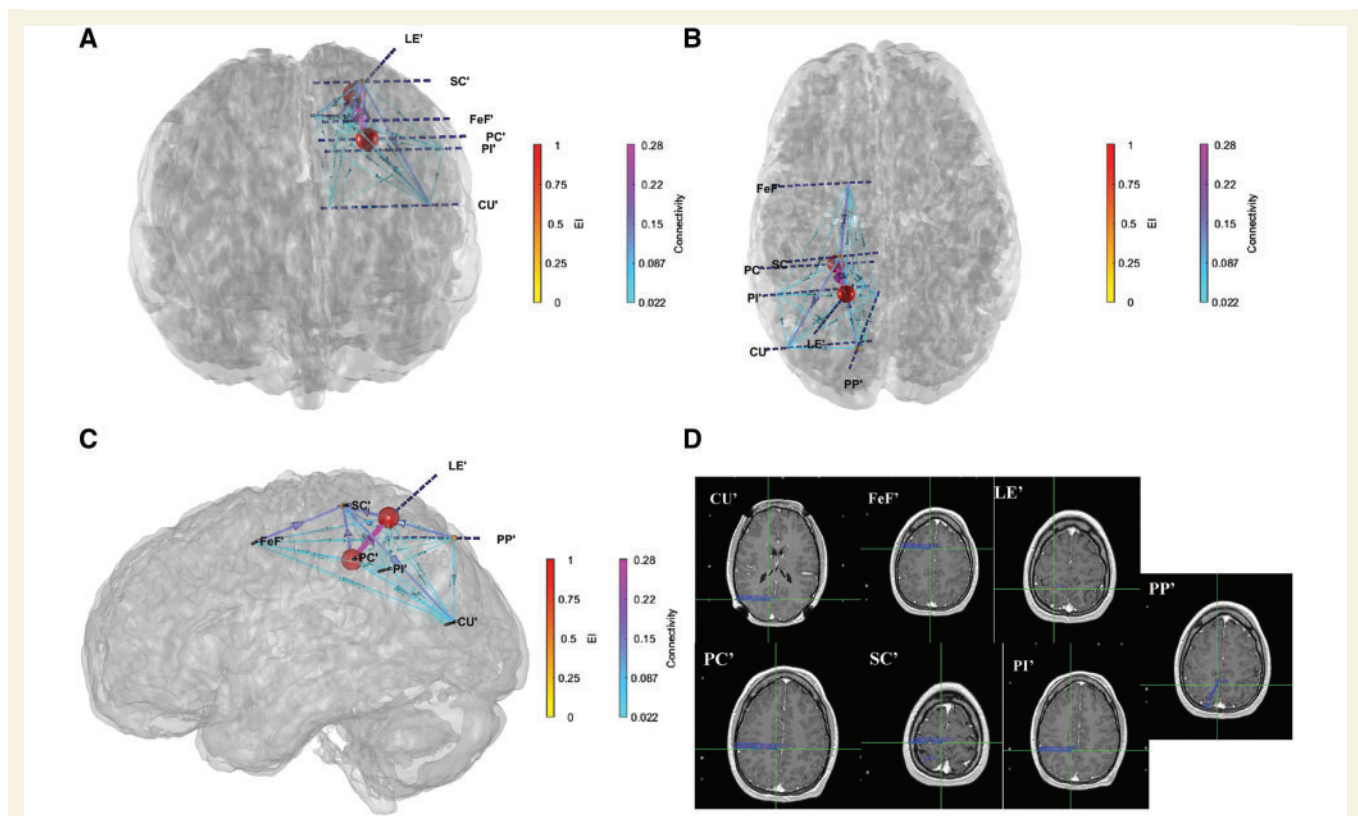


Figure 2 Example of connectivity results in a patient with FCD. 3D representation of the stereotactic-EEG electrodes in one patient with left post-central FCD. (A) Coronal view; (B) axial view; (C) sagittal view; and (D) view of the position of the electrodes superimposed on axial MRI. LE' explored the lesion; FeF' explored the premotor cortex; SC' explored the superior central cortex; PC' explored the inferior central cortex; PI' explored precuneus and inferior parietal lobe; PP' explored precuneus and superior parietal lobe; and CU' explored the cuneus and lateral occipital cortex. Red large spheres represent structures within-EZ and smaller orange spheres represent structures within-PZ, the other contacts belong to the NIZ. The coloured lines represent the functional connectivity between two structures. The arrows represent the directionality of these connections. Note that the highest non-linear correlation was within-EZ (L' and PC') and that medium non-linear correlation were within-PZ or between the EZ and PZ.

h^2 using the AnyWave open-source software (Colombet *et al.*, 2015) (available at <http://meg.univ-amu.fr/wiki/AnyWave>). In the present study, h^2 values were computed on broadband signals (providing a global estimation of non-linear interdependencies and used for statistical tests). For exploratory purposes, we also computed h^2 values on raw signals filtered in classically defined EEG sub-bands, namely delta (0.5–3.4 Hz), theta (3.4–7.4 Hz), alpha (7.4–12.4 Hz), beta (12.4–24 Hz) and gamma (24–80 Hz) (Bettus *et al.*, 2008). We applied a second-order Butterworth filter forward and backward to ensure zero-phase response (Colombet *et al.*, 2015). Figure 2 illustrates one example of connectivity graphs in a given patient.

To obtain the weighted connectivity matrix, we computed the median values across all time windows of h^2 values for a given pair of nodes (which we will refer to as 'node x' and 'node y' hereafter). As the h^2 measure is not symmetric ($h^2_{x \rightarrow y} \neq h^2_{y \rightarrow x}$), we took the higher median value across directions ($x \rightarrow y$ or $y \rightarrow x$).

Then, we computed the median of the connection weights linking all nodes of a same zone, resulting in a within-zone functional connectivity (i.e. EZ, PZ and NIZ functional connectivity); and between all the nodes linking two zones: inter-zone functional connectivity (i.e. EZ–PZ, EZ–NIZ and PZ–NIZ functional connectivity).

We also studied the directionality of the coupling between two zones, taking advantage of the time delay given by the h^2 computation. Since the time-delay matrix is asymmetric, we analysed the time delay of the edge whose median h^2 was higher. First, we performed a sign test on the time delays across all temporal windows for all selected edges to retain only links with consistent timing of coupling (null hypothesis of a median equal to 0 and threshold of $P < 0.05$). We then defined, only using edges with significant sign-test, the directionality as the percentage of edges between two zones going in one direction (e.g. EZ to PZ) minus the percentage of links going in the opposite direction (e.g. PZ to EZ).

Since distance between two channels may be a potential factor influencing the results of functional connectivity analysis (Warren *et al.*, 2010) we estimated the distances between all bipolar channels selected for functional connectivity analysis. We calculated the Euclidian distance between the centre of the two selected contacts of each bipolar channels (using the coordinates extracted from our co-registration tool).

Statistical analyses

To test the significance of directionality, we used a Wilcoxon signed rank test to examine if the proportion of links between

two zones was preferentially directed toward one direction (i to j) or the opposite direction (j to i). To take the effect of the distance between regions into account, we used an ANOVA with type of functional connectivity (e.g. within-EZ, between PZ–NIZ) as regressors of interest, controlling distance as covariate.

To estimate the association with clinical variables, we used a bivariate Pearson correlation test (for quantitative data such as epilepsy duration, age at stereotactic-EEG, age of epilepsy onset), Mann-Whitney U-test for two independent samples and a Kruskal-Wallis test for multiple independent samples (for qualitative data such as post-surgical outcome, histology, gender, visible lesion on MRI). For the post-surgical outcome, we compared the functional connectivity measures of the seizure-free patients (Engel class Ia) to those of the non-seizure-free patients (all others Engel classes). Wherever possible we reported statistical testing of data computed from broadband signals. The results of frequency sub-bands were reported only in case of significant variation according to the frequency band (otherwise see Supplementary material). We corrected significance for multiple comparisons using Bonferroni correction.

Statistical tests were performed with the software Statistical Package for the Social Sciences (SPSS) for Mac, version 22.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Patient characteristics

Fifty-nine patients (23 females, 36 males) were analysed in this study; their clinical features are summarized in Table 1. Mean age at epilepsy onset was 7 years (range 0–30); mean age at stereotactic-EEG was 24 years (range 2.75–56) and mean epilepsy duration before stereotactic-EEG was 16.9 years (range 1–56). The pathological diagnoses were the following: 14 FCD type I, 31 FCD type II, 14 neurodevelopmental tumours. Fifty-one patients had a visible lesion on MRI (20 in frontal lobe, 20 in temporal lobe, seven in parietal lobe, three in occipital lobe, and one with a fronto-parieto-insulo-occipital lesion) and eight were considered to be MRI-negative. The EZ was localized in the right hemisphere in 33 patients (55.9%). The surgical outcome was: Engel class I for 34 patients (57.6%), Engel class II for 10 patients (16.9%), Engel class III for four patients (6.8%), and Engel class IV for 11 patients (18.6%). The median follow-up duration after surgery was 10 years (ranging from 3 to 17 years).

A total of 76 distinct brain areas were sampled with a median of 13.2 (min–max: 6–25) per patient. All brain lobes were sampled including frontal (302 selected channels; 38.9% of all selected channels), temporal (256; 33%), parietal (126; 16.2%), occipital (48; 6.2%), insula (37; 4.8%) and thalamus was also sampled in seven patients (0.9%, more details about spatial sampling are available in Supplementary Table 1).

Table 1 Summary of patients' clinical features

Patients' clinical features	
Gender, female/male	23/36
Visible MRI lesion, n (%)	51 (86.4)
Median age at epilepsy onset, years (min–max)	7 (0–30)
Median age at SEEG, years (min–max)	24 (2.75–56)
Median epilepsy duration, years (min–max)	16.9 (1–56)
Lesion localization	
Frontal	20
Temporal	20
Parietal	7
Occipital	3
Hemispheric	1
Epileptogenic zone lateralization, right/left	33/26
Histological type	
FCD I	14
FCD II	31
NDT	14
Engel classes (%)	
I	34 (57.6)
II	10 (16.9)
III	4 (6.8)
IV	11 (18.6)
Median follow-up post-surgery (years, min–max)	4 (0.25–15)

SEEG = stereotactic-EEG.

Functional connectivity

There was a significant relationship between the distance and the functional connectivity value ($P < 0.001$, ANOVA), justifying taking into account this parameter in our statistical analysis. We found a significant difference in functional connectivity within-zone functional connectivity with a gradual decrease of the median functional connectivity within-zone functional connectivity from EZ and PZ to NIZ (Fig. 3). Within-EZ functional connectivity was significantly higher than within-NIZ functional connectivity and functional connectivity within-PZ was significantly higher than within-NIZ ($P < 0.001$, ANOVA, after Bonferroni correction). There was no significant difference between the functional connectivity within-EZ and within-PZ.

Second, we found that structures of EZ had higher functional connectivity within them than with NIZ ($P < 0.001$, ANOVA, after Bonferroni correction); and with-PZ than with-NIZ ($P < 0.001$, ANOVA, after Bonferroni correction) (Fig. 3).

Additionally, the inter-patient variability of the functional connectivity was high. The analysis in frequency sub-bands showed gradual decrease of functional connectivity values with the increase in frequency, and similar variation of functional connectivity within and between-zone in all frequency sub-bands (Supplementary Fig. 1).

Directionality

After statistical testing, no connection between zones had significant directionality as computed on broadband (Fig. 4A).

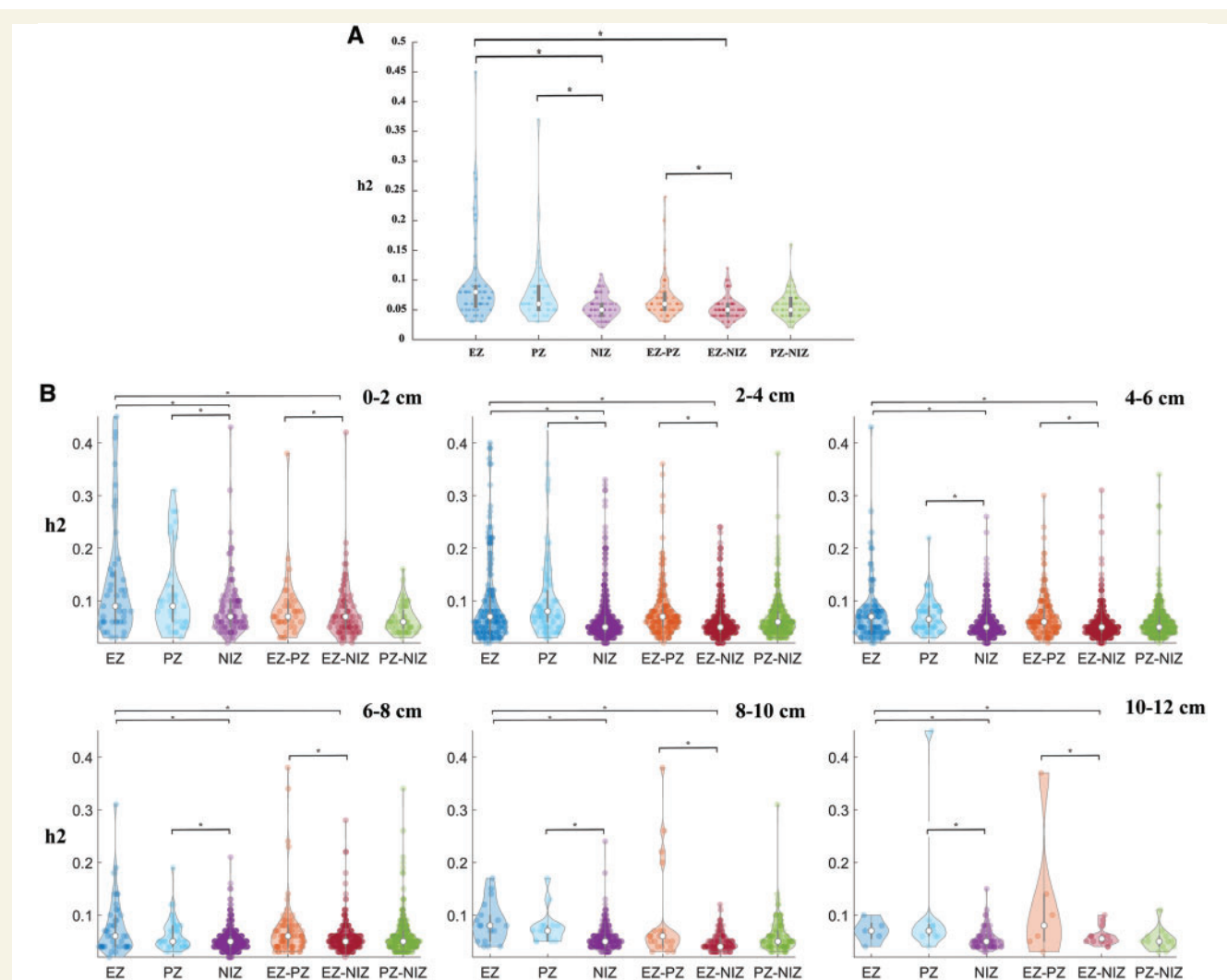


Figure 3 Within-zone and between-zone functional connectivity. (A) Plot showing within-zone and between-zone functional connectivity, as computed on broadband signals. (B) Plot showing within-zone and between-zone functional connectivity, as computed on broadband signals, according to subgroups of interchannel distances. The violin plots represent the kernel density plot (shape), the median (white circle), the interquartile range (inner grey line), and all individual values (median h^2 per patient in A, and h^2 per links in B, coloured circles). *Significant differences ($P < 0.05$, ANOVA). Functional connectivity was significantly higher within-EZ than within NIZ and between EZ–NIZ; within-PZ than within-NIZ; between EZ–PZ than between EZ–NIZ. EZ–PZ = connections between structures of EZ and PZ; EZ–NIZ = connections between structures of EZ and NIZ; PZ–NIZ = connections between structures of PZ and NIZ.

Notably, the directionality varied according to the frequency band under consideration (Fig. 4B). We found that the EZ was a significant driver of the NIZ in alpha and beta bands ($P = 0.001$ and $P < 0.001$, respectively, Wilcoxon signed rank test with Bonferroni correction for multiple tests), and that EZ was a driver of PZ in the beta-band only ($P = 0.001$, Wilcoxon signed rank test with Bonferroni correction for multiple tests). All other connections and frequency bands were not significant.

Association with clinical variables

There was a difference in the functional connectivity within-PZ according to the histological type ($P = 0.016$, Kruskal-Wallis

test) with higher functional connectivity for FCD I (Supplementary Fig. 2).

We did not find significant correlation or association between age at epilepsy onset, age at stereotactic-EEG, epilepsy duration, sex, or visible MRI lesion and functional connectivity measures (within-zone functional connectivity, inter-zones functional connectivity and directionality).

Association with post-surgical prognosis

There was no statistical difference in term of follow-up duration between seizure-free and non-seizure-free patients ($P \approx 1$, Mann-Whitney independent samples U-test).

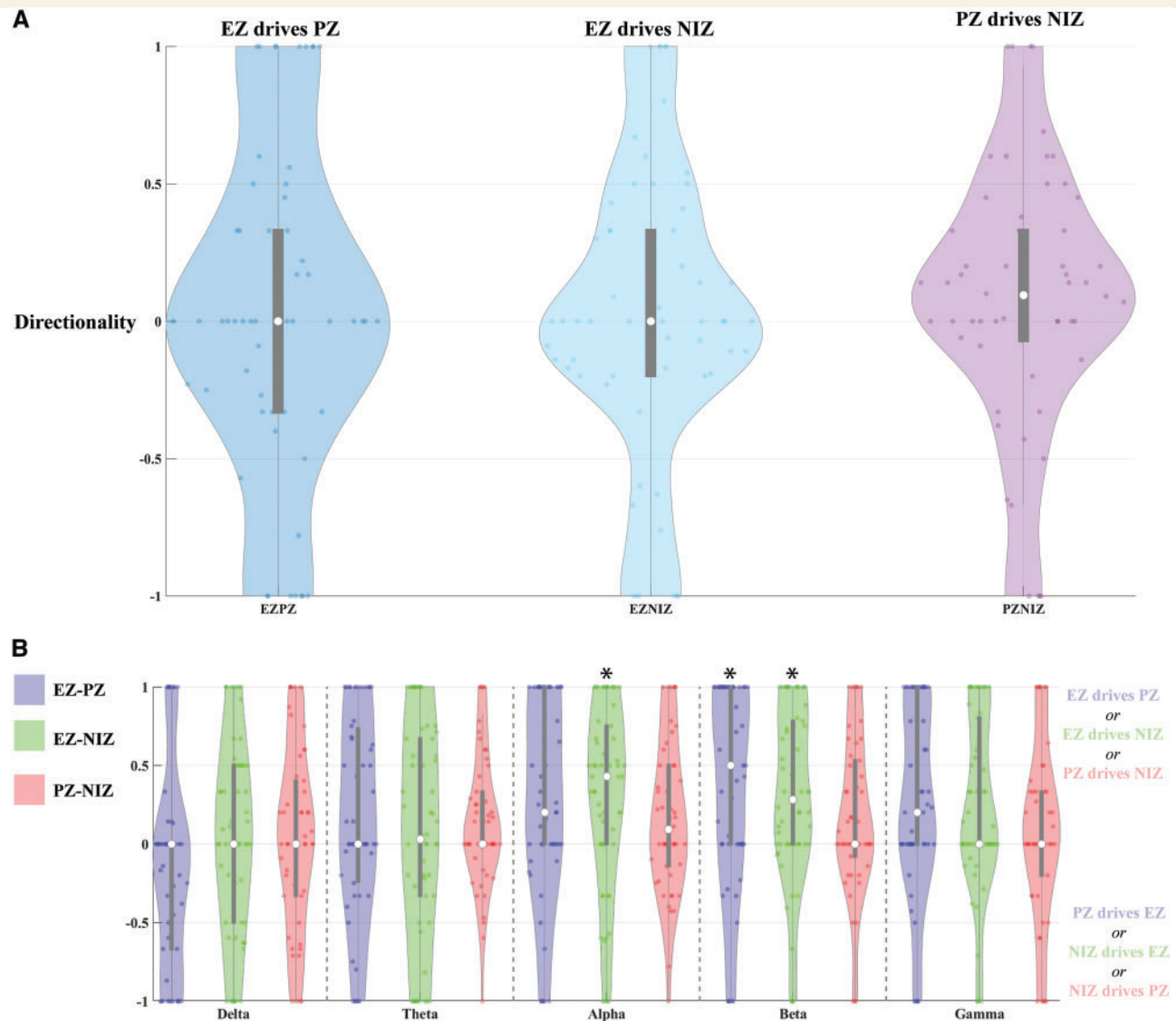


Figure 4 Plot showing the directionality in the connections between zones. Violin plots represent the kernel density plot (shape), the median (white circle), the interquartile range (inner grey line), and all individual values (coloured circles). Positive values indicate that the majority of links come from EZ to PZ (EZ drives PZ), or EZ to NIZ (EZ drives NIZ), or PZ to NIZ (PZ drives NIZ) (negative values mean the opposite, 0 value mean no drive). *Statistically significant (Wilcoxon signed rank test, Bonferroni's correction, $P < 0.002$). **(A)** In broad-band no directionality was statistically significant. **(B)** In alpha and beta, the EZ significantly drives NIZ; in beta, the EZ significantly drives PZ.

There was a difference between seizure-free versus non-seizure-free patients concerning the functional connectivity within the NIZ, and between NIZ-PZ ($P = 0.006$ for both, Mann-Whitney independent samples U-test with Bonferroni's correction for multiple test; Fig. 5). There was no significant difference in the other functional connectivity according to the post-surgical outcome (Supplementary Fig. 3).

Discussion

In this study, we used stereotactic-EEG data to perform large-scale functional connectivity analysis on the interictal period

in patients with malformation of cortical development. We focused on FCD and neurodevelopmental tumours, which are major causes of refractory focal epilepsies. Our study confirms that functional connectivity differs according to the studied zone (epileptogenic, propagation or non-involved). Figure 6 summarizes our significant findings, indicating that: (i) functional connectivity is higher within-EZ and within-PZ compared to within-NIZ; and (ii) a gradient of coupling is seen, with structures belonging to the EZ showing preferential coupling between them, followed by a lesser degree of coupling between the EZ and PZ.

Moreover, we found that the post-surgical outcome is linked to functional connectivity value of the NIZ

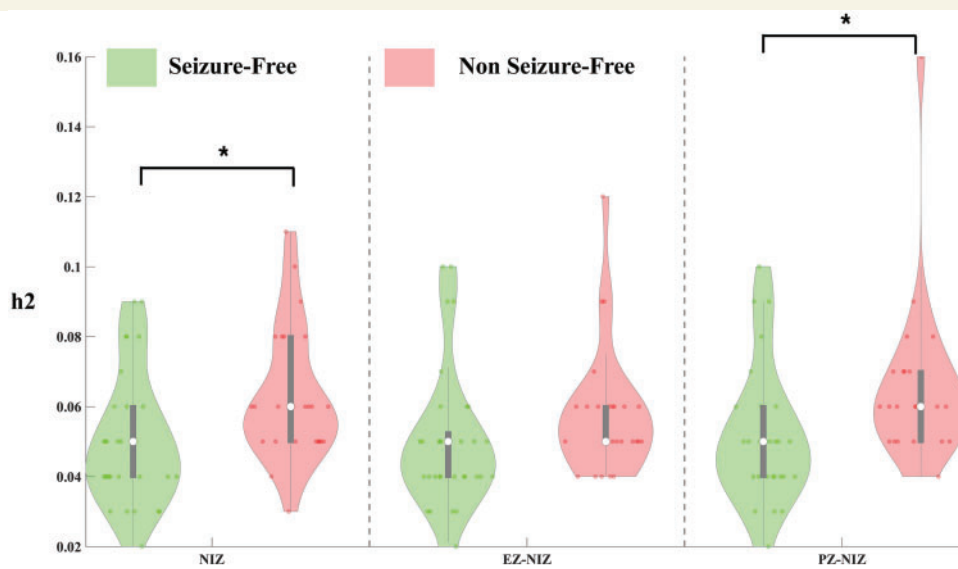


Figure 5 Plot showing functional connectivity within and from NIZ according to the post-surgical outcome, as computed on broadband. Violin plots represent the kernel density plot (shape), the median (white circle), the interquartile range (inner grey line), and all individual values (coloured circles). *Significant in the Mann-Whitney U-test after Bonferroni correction. Functional connectivity within-NIZ and between PZ-NIZ was significantly lower in seizure-free than non-seizure-free patients.

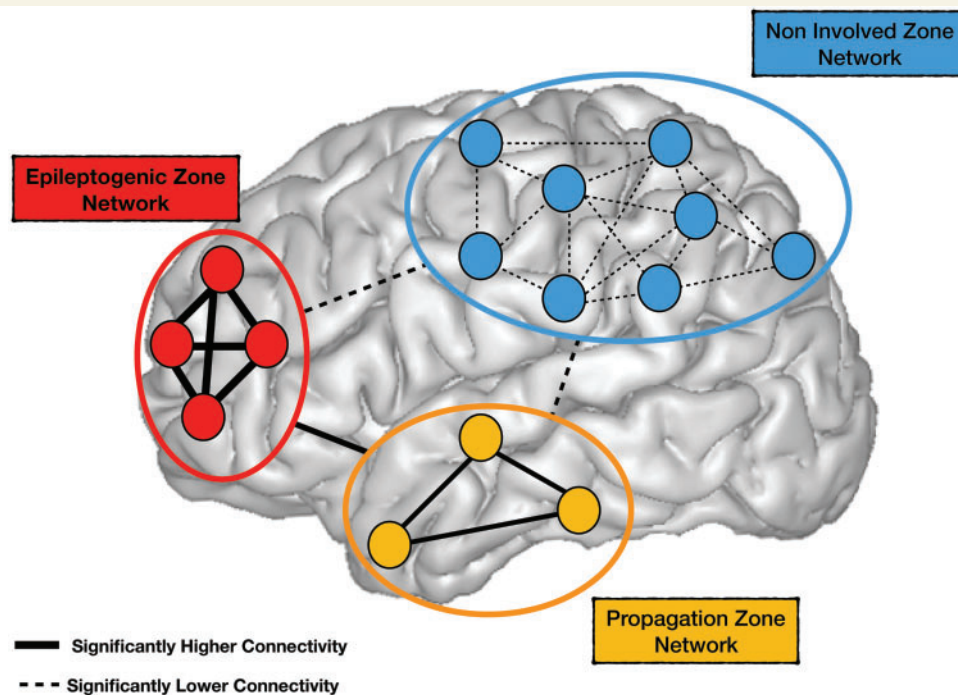


Figure 6 Summary of changes in functional connectivity (broadband analysis). Lines between small circles represent the functional connectivity within structures of a zone. The lines between large-circles represent the functional connectivity between zones. Plain lines represent significantly higher functional connectivity and the dashed lines represent lower functional connectivity. Concerning within-zone functional connectivity, the EZ and PZ have significantly higher functional connectivity than the NIZ. Concerning between-zone functional connectivity, the EZ and PZ have significantly higher functional connectivity between them than with the NIZ. The absence of arrows in the lines shows the lack of significant directionality in the functional connectivity between zones.

(within-NIZ functional connectivity, between NIZ–PZ functional connectivity).

Epileptogenic and propagation zones have higher interictal functional connectivity

It is now recognized that ‘focal’ epilepsies involve networks of varying scales across multiple brain areas (Bartolomei *et al.*, 2017). Hence, there is evidence of functional connectivity alteration during the interictal state. The majority of studies based on electrophysiological recordings used ECoG and found clusters of elevated local synchrony between areas of the EZ/SOZ (Arnhold *et al.*, 1999; Schevon *et al.*, 2007; Dauwels *et al.*, 2009), suggesting that increased short-range functional connectivity may be a marker of epileptogenic cortex. Furthermore, epileptogenic structures are functionally isolated from surrounding brain structures (Warren *et al.*, 2010). Nevertheless, these studies explored structures that were relatively spatially limited and thus addressed very local aspects of functional connectivity. In contrast, stereotactic-EEG allows for large-scale sampling including base of sulci (a preferential localization of FCD) as well as deep grey matter structures such as insular cortices and thalamus (known for its importance as a hub in brain network analysis) (Bartolomei *et al.*, 1999; Nieuwenhuys, 2012; Gonzalez-Martinez *et al.*, 2013; Nakajima and Halassa, 2017). A previous study from our group based on a limited number of patients also used stereotactic-EEG, and confirmed that temporal lobe structures exhibit higher interictal functional connectivity when they are involved during seizures than when they are not (Bettus *et al.*, 2008, 2011). In the particular case of malformation of cortical development, only one study using stereotactic-EEG confirmed that FCD type II exhibits higher functional connectivity (higher out-degree between 30 and 80 Hz) than other structures involved in the seizure (Varotto *et al.*, 2012). Importantly, our data highlight that not only the EZ but also the PZ exhibits increased functional connectivity in comparison with the NIZ; indeed, no difference was shown between the functional connectivity within the EZ and PZ. In summary, structures within either the EZ or PZ have short-range (as shown in ECoG studies) but may also have long-range increased functional connectivity (as shown in our stereotactic-EEG study).

Our data are in agreement with results in a rat kindling model, in which increase of functional connectivity was observed (Blumenfeld *et al.*, 2007), and with a model of cortical neuronal network in which greater connectivity among neurons without alteration of neuronal excitability was sufficient to confer an epileptogenic state (Traub *et al.*, 2001). A pathophysiological potential substrate of such functional connectivity alterations could be synaptic alterations as observed during secondary epileptogenesis (Khalilov *et al.*, 2003). Moreover, this particular network configuration could facilitate seizure occurrence and early

propagation (Wendling *et al.*, 2010; Proix *et al.*, 2014), since a reinforcement of couplings was observed during the pre-ictal state (Bartolomei *et al.*, 2004; Courtens *et al.*, 2016). Thus, reinforcement of functional connectivity during inter-ictal state in the EZ and PZ could be both the consequences (kindling) and the cause of the recurrence of seizure.

Structures of the epileptogenic zone have preferential coupling first between them, and second with the propagation zone

A previous study failed to find significant differences in the coupling between EZ and other zones in temporal lobe epilepsies (Bettus *et al.*, 2011). Moreover, a study on FCD type II showed no preferential connection of the lesional structures: between them or with other zones involved or not during ictal discharge (Varotto *et al.*, 2012). One study, comparing epileptic to non-epileptic patients, showed that structures within the seizure-onset zone were functionally disconnected from their neighbouring structures (Warren *et al.*, 2010). Our work goes further, showing that structures of the EZ present a unique pattern of connectivity, with higher coupling between them than with the structures outside the EZ.

On the other hand, we also found that EZ displays preferential coupling with the PZ. This is particularly interesting, knowing that such coupling is crucial in seizure propagation. Indeed, recent analyses of brain network models have shown that the propagation of seizure depends crucially on this coupling (Proix *et al.*, 2014). A clear and practical example is the good prediction of seizure propagation using individualized brain models based on structural connectivity (Proix *et al.*, 2017). This is also suggested by other studies, where brain connectivity, estimated with cortico-cortical evoked potentials, differs according to both structure epileptogenicity (Buser and Bancaud, 1983) and timing of seizure propagation (Lega *et al.*, 2015).

Directionality

If ‘undirected’ functional connectivity infers whether two brain areas are communicating or not, ‘directed’ functional connectivity estimates the directionality of this communication. Here, we analysed the directionality of coupling between zones, using time delay from non-linear correlation.

Previous studies have shown strong influence of the EZ on the NIZ in temporal lobe epilepsies using both stereotactic-EEG and functional MRI modalities (Bettus *et al.*, 2011). Moreover, in FCD II, the lesional zone also has a leading role (high out-degrees) over other zones (Varotto *et al.*, 2012). Here, we did not find significant directionality on broadband analysis (and low frequencies), but we showed a drive from EZ to NIZ and PZ on alpha and beta frequency bands. Furthermore, Courtens *et al.*

(2016) have shown also that the OUT strength during the pre-ictal state in the 15–40 Hz frequency band is a good marker of the structure's epileptogenicity.

Comparison with MRI data

There are two main aspects in comparing our results (as well as other functional connectivity data extracted from electrophysiological recordings) with data from MRI studies: (i) the relation with structural connectivity studies; and (ii) the relation with functional connectivity extracted from functional MRI.

Structural connectivity analysis in temporal lobe epilepsies have shown widely distributed structural connectivity disruption extending well beyond areas generating seizures (Bonilha *et al.*, 2012; Bernhardt *et al.*, 2013; Besson *et al.*, 2014) including large-scale networks such as default mode, salience and fronto-parietal networks (Besson *et al.*, 2017). Further studies suggested a predictive value of these structural connectivity alterations on surgical outcomes (Bonilha *et al.*, 2013; Munsell *et al.*, 2015; Keller *et al.*, 2017). Recently, our group focused on the link between the structural connectivity alterations according to the brain network involved during seizure as defined by stereotactic-EEG. We found that structural connectivity was significantly preserved within epileptic zones (epileptogenic and propagation zones) and decreased beyond epileptic structures (Besson *et al.*, 2017). The large-scale disruption of structural connectivity remote from seizure onset zone and the relatively normal structural connectivity within epileptic structures may actually indicate that these structures are pathologically hyper-connected at the expense of connectivity with the remainder of the brain (Taylor *et al.*, 2015; Besson *et al.*, 2017). We can summarize these structural connectivity MRI data with two main statements: (i) areas involved in seizure genesis and propagation (e.g. thalamus in temporal lobe epilepsy) have preserved structural connectivity (Bonilha *et al.*, 2012; Dinkelacker *et al.*, 2015; Besson *et al.*, 2017); and (ii) in addition, other remote areas have widely decreased structural connectivity (Besson *et al.*, 2014). This pattern of local 'hyperconnectivity' within epileptic structures combined with widespread 'hypoconnectivity' outside these areas is concordant with our findings and other studies on functional connectivity extracted from electrophysiological recording (Bettus *et al.*, 2008, 2011; Englot *et al.*, 2015). This similarity confirms both the tight relationships between structural and functional connectivity known to exist in healthy conditions (Honey *et al.*, 2007; Goni *et al.*, 2014), and the increased structural-functional correlation in epilepsy (Wirsih *et al.*, 2016).

The relationship between functional connectivity extracted from functional MRI and electrophysiological recordings is more complex. While some studies have confirmed similar network disruption on large-scale analysis, others have found an opposite pattern with functional connectivity alteration locally within epileptic zones. On the one hand, several studies found various, widespread and

complex patterns of increased and decreased functional connectivity, affecting key features of large scale networks such as the default mode (Pittau *et al.*, 2012; Voets *et al.*, 2012; Wirsih *et al.*, 2016) and salience networks (de Campos *et al.*, 2016). The functional connectivity from functional MRI has been described as locally decreased within the epileptogenic temporal lobe (Waites *et al.*, 2006; Bettus *et al.*, 2009). Moreover, the same patients explored by stereotactic-EEG and functional MRI (at different times) exhibit increased functional connectivity in stereotactic-EEG but decreased functional connectivity using BOLD signals within epileptic structures (Bettus *et al.*, 2011). A recent study confirmed this discrepancy in simultaneous recordings of functional MRI and stereotactic-EEG, demonstrating that intermodal connectivity correlation exists in non-epileptic structures but is altered in the epileptic zones (Ridley *et al.*, 2017). Thus, whereas increased EEG connectivity could be related to pathologically reinforced links between hyperexcitable structures, decreased functional MRI connectivity could be more likely related to metabolic/perfusion alterations (Bettus *et al.*, 2009). This view tends to support the complementarity of information from both modalities, rather than true discrepancy.

The extension of increased functional connectivity is associated with poorer prognosis

Clearly, the main factor influencing the post-surgical outcome is the completeness of the resection of the EZ (including the lesion and the area primarily involved during seizures). Some studies have also suggested a relation between the complete resection of areas exhibiting high local synchrony and surgical outcome (Schevon *et al.*, 2007; Antony *et al.*, 2013). Our findings showed similar results with higher functional connectivity within-NIZ, and from-NIZ being associated with a poorer surgical prognosis. This could reflect a wider extension of the epileptic process with failure to correctly identify 'epileptic' structures based only on seizure activity. Furthermore, several recent studies showed that connectivity data can help better predict post-surgical outcome (Bonilha *et al.*, 2013; Baker *et al.*, 2015; Munsell *et al.*, 2015; He *et al.*, 2017; Keller *et al.*, 2017; Proix *et al.*, 2017), notably using computational modelling (Hutchings *et al.*, 2015; Goodfellow *et al.*, 2016; Proix *et al.*, 2017; Sinha *et al.*, 2017; Steimer *et al.*, 2017).

These results demonstrate that the boundaries of epileptogenic zone in the brain are not easy to determine. A hierarchy of brain structures disclosing gradual decrease of epileptogenicity from the most epileptogenic (EZ) to the least epileptogenic (NIZ) has been proposed (Bartolomei *et al.*, 2008, 2017). This model clearly differs from the classical 'split' vision of these zones in focal epilepsies and is fully justified by modelling approaches showing

that epileptogenicity is a complex feature depending on excitability and connectivity (Proix *et al.*, 2014). In recognition of this, recent analyses of brain network models based on both epileptogenicity and coupling between structures have shown good performance in simulating the seizure course in a ‘Virtual Brain’ (Jirsa *et al.*, 2017; Proix *et al.*, 2017).

Methodological aspects and limitations

Stereotactic-EEG recordings are advantageous in the present study because this method allows sampling of distant brain areas including mesial structures better than ECoG, thus allowing relatively long-range connections analysis. Nevertheless, the sampled areas depend on the clinical hypotheses that determine electrode placement, with multiple areas of the brain necessarily remaining unsampled. Stereotactic-EEG does not guarantee in all patients a comprehensive spatial coverage of all the networks affected by epilepsy (in contrast with MEG or MRI studies for example). However, stereotactic-EEG permits direct intracerebral recording of electrophysiological signals, avoiding potential biases in the source-based connectivity reconstruction encountered in MEG or EEG studies (Malinowska *et al.*, 2014; Coito *et al.*, 2015, 2016). Moreover, as described above, functional MRI-based functional connectivity does not necessarily match stereotactic-EEG-based functional connectivity. In our study, placement and degree of spatial coverage of stereotactic-EEG electrodes were motivated by clinical indications, permitting to sample many brain areas across patients but leading to heterogeneity in our sample and variation in the distance within/between zones. To limit this bias, we performed paired statistical testing to compare functional connectivity according to the zones within each patient, and we included the distance between selected channels as a covariate of statistical analysis.

In our study, the definition of the EZ was based on the epileptogenicity index. This is a semi-automatic method built to help the interpretation of the spatio-temporal organization of seizures. The main advantage of epileptogenicity index is to estimate the epileptogenicity of structure within the seizure onset zone in a quantitative manner. The epileptogenicity index proved a good concordance and consistency compared to visual analysis (Gollwitzer *et al.*, 2016). Nevertheless, the epileptogenicity index has some limitations linked to the morphology of the seizure onset pattern (i.e. some very low amplitude fast activity could result in relatively low value of the epileptogenicity index), visual preselection of suitable seizures and channels is prerequisite, and good performance of the method requires some (semi-automatic) adjustments of parameters, requiring user expertise. Indeed, our EZ and PZ could overlap with the lesional and peri-lesional areas, but electrophysiological definitions did not limit these zones to the visible lesion and its surroundings, since more remote

structures were also included (such as an area involved in propagation, which could be many centimetres away from the lesion).

For the estimation of interictal functional connectivity we tried to control some factors influencing the resting state (proximity of general anaesthesia and/or seizures), nevertheless the effect of the anti-epileptic drugs tapering during the monitoring period is obviously variable across patients. As some studies demonstrated the effect of anti-epileptic drugs on functional connectivity (Wandschneider *et al.*, 2017), it could be a confounding variable. Moreover, the reproducibility of connectivity values across larger time-scales (e.g. days) is still unknown.

During the past decades, numerous methods (both linear and non-linear) have been developed for computing functional connectivity. Although results may differ from one method to another, comparative studies have shown that results are qualitatively similar (Ansari-Asl *et al.*, 2006) and that most methods could correctly reconstruct simulated connectivity (Wang *et al.*, 2014). In this study, we used non-linear correlation, a method known for its good performance in the computation of functional connectivity from intracranial EEG signal (Wendling *et al.*, 2009; Wang *et al.*, 2014) and which has proved its usefulness in numerous epilepsy studies (reviewed in Bartolomei *et al.*, 2017). Advantageously, this method does not require assumptions with regards to the linear or non-linear character of the relationships between signals (Lopes da Silva *et al.*, 1989). Nevertheless, as all functional connectivity methods, non-linear correlation also has its weakness: requirement of longer time series, some variation in performance according to the coupling strength, lower performance in case of distinct noise across studied signals and high computational time cost (Wang *et al.*, 2014). Notably, we chose our analysis parameters in accordance with recommendations from a systematic benchmark study (Wang *et al.*, 2014). Moreover, the presence of spikes has some impact in non-linear correlation estimation of inter-ictal functional connectivity. A previous study demonstrated that non-linear correlation value of background stereotactic-EEG decrease by ~5% after spikes removal, but without change in the difference of functional connectivity within epileptic versus within non-epileptic zones (Bettus *et al.*, 2008).

Graph theory is a powerful tool to capture the complexity of brain networks (Fornito *et al.*, 2015). Nevertheless, we did not use graph theory metrics (such as centrality, small-worldness, efficiencies) evaluation in our study to avoid over-interpretation. This was due to two factors: limited spatial sampling (less than 25 brain areas) hampering topology and centrality analyses, and variation in the structures sampled across patients preventing the comparison of the same areas/network involved or not in the EZ/PZ. Finally, we analysed directionality between pairs with a delay significantly different from zero, thus excluding zero-lag correlations (sign test in our methodology). This renders measures more robust to volume conduction

effects. It is also an important point because the behaviour of brain network (coupling oscillatory large-scale systems) is crucially determined by both connection strengths and signal transmission delays (Petkoski *et al.*, 2016).

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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