



**HAL**  
open science

# Parieto-premotor functional connectivity changes during parietal lobe seizures are associated with motor semiology

Davide Fonti, Stanislas Lagarde, Francesca Pizzo, Wala Aboubakr, Christian G. Bénar, Bernard Giusiano, Fabrice Bartolomei

## ► To cite this version:

Davide Fonti, Stanislas Lagarde, Francesca Pizzo, Wala Aboubakr, Christian G. Bénar, et al.. Parieto-premotor functional connectivity changes during parietal lobe seizures are associated with motor semiology. *Clinical Neurophysiology*, 2021, 132 (9), pp.2046-2053. 10.1016/j.clinph.2021.06.003 . hal-03620341

**HAL Id: hal-03620341**

**<https://hal.science/hal-03620341>**

Submitted on 25 Mar 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# **Parieto-Premotor functional connectivity changes during parietal lobe seizures are associated with motor semiology**

**Davide Fonti**<sup>1,2</sup>; **Stanislas Lagarde**<sup>3</sup>; **Francesca Pizzo**<sup>3</sup>, **Wala Aboubakr**<sup>4</sup>, **Christian Benar**<sup>4</sup>, **Bernard Giusiano**<sup>4</sup>, **Fabrice Bartolomei**<sup>3</sup>

1. APHM, Timone Hospital, Epileptology Department, Marseille, France
2. Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy.
3. Aix Marseille Univ, APMH, INSERM, INS, Inst Neurosci Syst, Timone Hospital, Epileptology Department, Marseille, France
4. Aix Marseille Univ, INSERM, INS, Inst Neurosci Syst, Marseille, France

## **Corresponding author:**

Prof Fabrice Bartolomei, MD, PhD; Epileptology Department, CHU Timone, 264 Rue Saint-Pierre, 13005, Marseille, France ; Tel: +33491385833 Fax: +33491385826; Email: [fabrice.bartolomei@ap-hm.fr](mailto:fabrice.bartolomei@ap-hm.fr)

## **Abbreviations**

PLS: parietal lobe seizures, PLE: parietal lobe epilepsy, FC: functional connectivity, SEEG: StereoElectroEncephalography, EI: epileptogenicity index, pmL: lateral pre-motor area , SPL: superior parietal lobule, IPL: inferior parietal lobule, SMA: supplementary motor area, pCG: posterior cingular gyrus, PoCg: post-central gyrus; OP: parietal operculum, SOZ: seizure onset zone, BG: background pre-ictal activity period, SO: seizure onset period, SP: seizure propagation period

**Acknowledgments**

We thank Prof Patrick Chauvel, Prof Martine Gavaret, Prof Maxime Guye, Prof Mathieu Milh, Prof. Agnes Trebuchon, Dr Aileen McGonigal, Dr Francesca Bonini, Dr Sandrine Aubert, Dr Geraldine Daquin, Dr Lisa Vaugier, Dr Anne Lépine, Dr Nathalie Villeneuve (Marseille) for the clinical management of some included patients; Prof Didier Scavarda, Dr Romain Carron, Prof Henry Dufour, Prof Jean-Claude Peragut, and Prof Jean Régis (Marseille) for surgical or SEEG procedures. We thank all the paramedical team of the epileptology unit, who allow optimal recordings and clinical testing of the patients explored by SEEG.

We thank Dr Rinki Singh for proofreading and correction of the manuscript.

**Authors have no conflict of interest to disclose**

## Abstract

Objectives: Parietal lobe seizures (PLS) are characterized by multiple clinical manifestations including motor signs. The mechanisms underlying the occurrence of motor signs are poorly understood. The main objective of this work was to estimate the functional coupling of brain regions associated with this clinical presentation.

Methods: We retrospectively selected patients affected by drug-resistant epilepsy who underwent Stereoelectroencephalography (SEEG) for pre-surgical evaluation and in whom the seizure onset zone (SOZ) was located in the parietal cortex. The SOZ was defined visually and quantitatively by the epileptogenicity index (EI) method. Two groups of seizures were defined according to the presence (“motor seizures”) or the absence (“non-motor seizures”) of motor signs. Functional connectivity (FC) estimation was based on pairwise nonlinear regression analysis ( $h^2$  coefficient). To study FC changes between parietal, frontal and temporal regions, for each patient, z-score values of 16 cortico-cortical interactions were obtained comparing  $h^2$  coefficients of pre-ictal, seizure onset and seizure propagation periods.

Results: We included 22 patients, 13 with “motor seizures” and 9 with “non-motor seizures”. Resective surgery was performed in 14 patients, 8 patients had a positive surgical outcome (Engel’s class I and II). During seizure onset period, a decrease of FC was observed and was significantly more important (in comparison with background period) in “motor” seizures. This was particularly observed between parietal operculum/ post-central gyrus (OP/PoCg) and mesial temporal areas. During seizure propagation, a FC increase was significantly more important (in comparison with seizure onset) in “motor seizures”, in particular between lateral pre-motor (pmL) area and precuneus, pmL and superior parietal lobule (SPL) and between inferior parietal lobule (IPL) and supplementary motor area (SMA).

**Conclusions:** Our study shows that motor semiology in PLS is accompanied by an increase of FC between parietal and premotor cortices, significantly different than what is observed in PLS without motor semiology.

**Significance:** Our results indicate that preferential routes of coupling between parietal and premotor cortices are responsible for the prominent motor presentation during PLS.

**Keywords:** parietal lobe seizures, motor semiology, Stereoelectroencephalography, functional connectivity.

**Highlights:**

- Motor manifestations are the most frequent signs in parietal seizures
- Parietal-frontal functional connectivity during seizure onset does not differ between patients with and without ictal motor manifestations
- Increase in parietal-premotor functional connectivity during seizure propagation is associated with ictal motor manifestations.

## 1. Introduction

Parietal lobe epilepsies (PLE) are defined by seizures originating from the posterior parietal cortex. PLE is a rare medical condition representing up to 6% of focal epilepsies in surgical series (Asadollahi et al., 2017; Bartolomei et al., 2011; Francione et al., 2015; V. Salanova et al., 1995a). Furthermore the incidence of PLE is probably underestimated due to misleading clinical and electrical features that can make differential diagnosis difficult from epileptic seizures arising from other lobes or even psychogenic nonepileptic seizures (Francione et al., 2015; Pilipović-Dragović et al., 2018; V Salanova et al., 1995; Sveinbjornsdottir and Duncan, 1993). Functionally, the parietal lobe is a multimodal cortex that receives and integrates somato-sensory, visual and auditory inputs and that participates in motor planning, attention, spatial representation, working and long-term memory, calculation and language processes (Orban et al., 2006). Posterior parietal cortex is strongly interconnected with sub-cortical and others cortical areas (Caspers and Zilles, 2018). Parietal areas are strongly connected with frontal areas for multiple aspects of motor planning, in particular posterior parietal lobe with pre-motor areas (supplementary motor area (SMA), pre-SMA) and pre-frontal areas (Andersen and Cui, 2009; Caspers and Zilles, 2018; Fogassi and Luppino, 2005; Luppino et al., 1993; Wise et al., 1997). The high connectivity of the parietal lobe explains the involvement during PLS seizures of many extra-parietal regions. Some authors have suggested that the variety of clinical signs observed in PLS could be due to the involvement of distinct systems in the propagation of ictal discharge (Francione et al., 2015; V. Salanova et al., 1995a).

One of the most striking features of parietal seizures are motor signs, which are reported in 75 to 88% of PLS (Asadollahi et al., 2017; Bartolomei et al., 2011; Francione et al., 2015; Kim et al., 2004; V. Salanova et al., 1995b; Sveinbjornsdottir and Duncan, 1993). The mechanisms

underlying the occurrence of motor signs are poorly understood and no study has specifically addressed this question. SEEG during presurgical evaluation for drug resistant epilepsy allows recording of the electrical activity of cerebral areas (including deep structures) and represents a unique way to study and quantify epileptogenic networks in focal epilepsies (Bartolomei et al., 2017). In a previous study, using the Epileptogenicity Index Method (EI), we observed that neural networks underlying PLS involved different subnetworks in the parietal lobe and that their complexity was higher when maximal epileptogenicity was in the precuneus or in Brodman area 7 (Bartolomei et al., 2011).

SEEG can also study epileptogenic networks through the estimation of functional connectivity (FC). FC allows an estimate of the functional coupling between brain regions in physiological and pathological brain processes (Bartolomei et al., 2017; Fornito et al., 2015; Guye et al., 2008). For example, in epilepsy FC is altered during both interictal and ictal periods (Bartolomei et al., 2017 *for review*; ). In the latter case, it provides insights into the modifications of brain networks during seizures (desynchronisation or hypersynchronisation depending on the features of the ictal discharge) and how these changes are involved in clinical manifestations (Bartolomei et al., 2019, 2017, 2016; Hagiwara et al., 2017).

In this study, we analyzed seizures recorded by SEEG originating from the posterior parietal cortex. Our main objective was to evaluate the changes in FC occurring at seizure onset and during seizure propagation and to correlate these changes to the clinical semiology. In particular we focused our work on motor semiology, which is one of the most frequent presentations of parietal seizures. For this purpose we compared the FC changes during PLS with and without motor semiology. We hypothesized that FC between parietal and extra-parietal frontal areas would be altered differently according to the generation or absence of

ictal motor symptoms. Moreover, the extension of epileptogenicity in extra-parietal regions can be the cause of some surgical failures (Ristić et al., 2012). Therefore, connectivity changes could be a reflection of the extension of epileptogenic networks. We also evaluated FC changes and surgical outcome as a secondary objective of our study.

## **2. Methods**

### **2.1. Patients**

We retrospectively selected 22 patients affected by drug-resistant focal epilepsy who underwent SEEG for pre-surgical evaluation between April 2005 and September 2019 at the epileptology department of the Timone Hospital, Marseille, France. The institutional review board of the French Institute of Health (IRB15226) approved this study and written patient consent was obtained. All patients had a seizure onset zone (SOZ) in the posterior parietal cortex. SOZ was established visually and quantitatively by the epileptogenicity index (EI) method as previously defined (Bartolomei et al., 2008). The EI is a semi-automatic method to quantify the dynamic of the fast-activity genesis at the beginning of a seizure. The EI is calculated from two important features of the transition from pre-ictal to ictal activity: (i) the redistribution of signal frequencies from lower frequency bands (theta, alpha) toward higher frequency bands (beta, gamma); and (ii) the time delay over which appearance of these high-frequencies occur at the seizure onset. EI values are normalized at the patients level by the maximum value, and then ranges from 0 (no epileptogenicity) to 1 (maximal epileptogenicity). A threshold  $> 0.3$  was chosen as an indicator of regions included in the SOZ. Indication for video-SEEG and the anatomical targeting of electrodes was established in each patient on the basis of non-invasive information and hypotheses about the SOZ. SEEG explorations were



done using intracerebral multiple contacts electrodes (5-18 contacts, length: 2 mm, 1,5 mm apart, diameter 0,8 mm, placed according Talairach stereotactic method or with frameless method (Skoch et al., 2017; Talairach J, Bancaud J, Szikla G, Bonis A, Geier S, 1974). A post implantation computerized tomography was done to exclude complications and for localisation of each electrode contact by using Gardel GUI (<https://meg.univ-amu.fr/wiki/GARDEL:presentation>) for fusioning with pre-implantation magnetic resonance imaging (Medina Villalon et al., 2018). SEEG signals were recorded with 256 channel Deltamed™, sampled at 256 Hz or 512 Hz and recorded on a hard disk (16 bit/ samples) without using a digital filter. A high-pass filter was used (cut-off 0.16 Hz at -3 db) to remove very slow variations that sometimes contaminate the baseline.

## **2.2. Clinical data**

For each patient included in the study one representative spontaneous seizure recorded during video-SEEG monitoring was selected. The semiology of each seizure was analysed, with particular attention to the presence of limb clonic, tonic/ dystonic phenomena or hypermotor semiology. According to this analysis two groups of seizures were determined : a “motor seizures” group , in which was present at least one of the aforementioned signs, and a “non-motor seizures” group, in which seizures occurred without motor signs.

## **2.3. Functional Connectivity (FC) analysis**

FC analysis was done using the software (<https://meg.univ-amu.fr/wiki/AnyWave>) (Colombet et al., 2015). In each SEEG seizure, we selected three temporal periods for FC analysis: Background (BG) representing pre-ictal activity, which could terminate up to one second before ictal discharges; Seizure onset (SO) representing seizure onset period and commencing

at the beginning of the ictal discharges, Seizure Propagation period (SP) which commenced at the end of SO, when ictal discharges propagated and became more rhythmic and of higher voltages. Each time period was of the same duration in each patient, averaging 16 s across the cohort (Standard deviation (SD) 11), depending on the total duration of each analysed seizure.

We selected eight areas sampled in all patients. 4 parietal areas: 1) precuneus, 2) superior parietal lobule (SPL), 3) inferior parietal lobule (IPL) or posterior cingular gyrus (pCG), 4) parietal operculum (OP) or Post-central Gyrus (PoCg); 2 frontal areas ( supplementary motor area (SMA) and lateral pre-motor area (pmL); and 2 temporal areas (mesial and lateral). For this purpose, we co-registered pre-implantation MRI and post-implantation CT (Medina Villalon et al., 2018) and visually defined the anatomical areas. We chose one bipolar channel (from two adjacent contacts) in grey matter for each specific brain area. As implantation schemes vary largely according to SOZ localisation hypothesis, not all regions were explored in all patients selected. To address the changes in functional connectivity occurring between parietal/temporal/frontal regions we studied 16 specific links as indicated in *Supplementary Figure 1*.

Interdependencies between bipolar SEEG signals were estimated by pairwise nonlinear regression analysis based on the  $h^2$  coefficient (Wendling et al., 2001), computed using the Anywave software (Colombet et al., 2015). Nonlinear regression analysis is aimed at estimating the degree of association between two signals X and Y independently from the linear or nonlinear nature of this association. The basic idea is to describe the amplitude of signal Y as a function of the amplitude of signal X using a nonlinear regression curve and to compute the variance of Y that is explained, or predicted, by X according to this regression

curve. This technique has been shown to be particularly suitable for the analysis of EEG/SEEG signals in the context of epilepsy (*review in* (Bartolomei et al., 2017) and achieves high accuracy in the setting of intracranial EEG recordings (Ansari-Asl et al., 2006; Wang et al., 2014; Wendling et al., 2009). In a sliding window, a piecewise linear regression is performed between each pair of signals. The  $h^2$  is the coefficient of determination, which measures the goodness of fit of the regression (equivalent to the  $r^2$  used in linear regression). The  $h^2$  is bounded between 0 (no correlation) and 1 (maximal correlation) and is asymmetric. We used a sliding window of 3 seconds with an overlap of 2 seconds and a maximum delay between signals of 100 ms. We used 0.5 Hz high pass filter in all analyses. Because  $h^2$  values are asymmetric, we symmetrised our connectivity matrix using the higher  $h^2$  value between two channels (chan1->chan2 and chan2->chan1). We thus obtained connectivity graphs, with each bipolar channel representing a node of the graph, and  $h^2$  values between two brain areas the edges. For each seizure, FC graphs of the different periods were compared (SO *versus* BG, SP *versus* BG, SP *versus* SO). For studying the FC changes between parietal, frontal and temporal regions, for each patient, a z-score values of 16 cortico-cortical interaction comparing the different above mentioned periods were obtained. We also regrouped interactions between parietal and temporal or frontal regions.

#### **2.4. Statistical analysis**

We looked at how the changes in FC may differ in seizures with and without motor manifestations. Firstly, we computed the z-scores of FC changes (measure of the difference between periods of seizure: BG, SO and SP) in parieto-extra-parietal interactions. The z-scores, obtained comparing FC graphs, were computed with the difference of  $h^2$  values derived from two different windows (SO *versus* BG, SP *versus* BG, and SP *versus* SO) and

between two specific cortical areas, normalized with SD. In this way z-scores represent a normalised index of FC changes for a given cortico-cortical interaction between different periods.

Finally, we analysed the relation between ictal FC changes and post-surgical seizure outcome. For this, we used the mean difference and permutation t-test for assessing statistical differences between motor and non-motor seizures and between patients with a positive surgical outcome (Engel's classes I and II) or an unfavourable surgical outcome (Engel's classes III and IV).

We also used  $\chi^2$  test, Fisher's exact test, Student's t test, Spearman's R for the other analyses. Statistical significance was established for  $p \leq 0.05$ . For Statistical analysis we utilised IBM®SPSS®STATISTICS software, 23th edition and Estimation statistics beta (<https://www.estimationstats.com/#/>) (Ho et al., 2019).

### 3. Results

We studied 22 patients with a SOZ localized in the parietal cortex (see Table 1). The SOZ was in the right hemisphere in 8 patients (36.4%), in the left hemisphere in 9 patients (40.9%) and bilateral or multifocal in 5 (22.7%). The mean age at epilepsy onset (SD) was 7.1 ( $\pm 4.3$ ) years (range 3 month- 14 years). The mean age at SEEG was 24.9 (SD 11.1) years (range 2.5 to 50 years). Parietal regions disclosing the maximal epileptogenicity were precuneus in 2 patients (9.1%), superior parietal lobule (SPL) in 9 patients (40.9%), post-central gyrus (PoCg) in 2 (9.1%), inferior parietal lobule (IPL) in 7 (31.8%), parietal operculum (OP) in one (4.5 %) and posterior cingulate gyrus (pCG) in one patient (4.5%). A resective surgery (lesionectomy, cortectomy, or lobectomy) was performed after SEEG exploration in 14 patients (63.6%). One patient was awaiting surgery, one had a long-term improvement after SEEG

thermocoagulation, surgery was contra-indicated in 5 cases (bilateral/ multifocal epilepsy, high risk of functional damage) (22.7%) and refused in one case (4.5%). The two main aetiologies were focal cortical dysplasia in 8 patients (36.4%) and a stroke in 7 patients (31.8%) (see Supplementary table 1)

In 14 patients who underwent a surgical intervention, outcome (with a mean follow of 7.9 years, range 9 months-15 years) was favourable (Engel class I and II) in 8 patients (57.1%) (Table 1). SEEG was performed with a mean number of 9.64 electrodes per patient (min 6, max 18).

### **3.1. Semiology of motor and non-motor seizures**

We analysed 22 SEEG recorded seizures, one for each patient. 13 seizures (59%) were classified as “motor seizure”, 9 (41%) as “non-motor seizure”. Age at SEEG, was younger (20.9 years  $\pm$  12.0) in the “motor-seizure” group than in “non-motor seizure” group, (30.8 years  $\pm$  6.2), (t test for independent samples,  $p= 0.035$ ). Age at epilepsy onset and epilepsy duration were not significantly different in the two groups. No significant correlation was found between the two groups of seizures for aetiology and surgical outcome. The clinical features are summarized in Table 1.

### **3.2. Functional connectivity (FC) analysis**

The figure 1 illustrates an example of PLS with motor semiology in patient 7.

At the group-level, during seizure onset (SO), most of parietal-extra-parietal links showed a decrease in FC. When looking at SO vs BG comparison, significant lower z-scores values were found in motor seizures (mean difference in z-scores= -0.918 (95% confidence interval (CI) - 1.5, -0.368);  $p= 0.0018$ ; Figure 2A), in particular between OP/PoCg and mesial temporal areas

(mean difference in z-scores= -2.52 (95% IC= -3.31,-1.52);  $p < 0.001$ ; Figure 2B). No other significant differences were found in the studied parietal-extra-parietal interactions.

In contrast, during seizure propagation (SP), most of parietal-extra-parietal links exhibited a tendency to an increase in functional connectivity. Overall, no significant difference was found in parietal-extra-parietal z-scores computed between SP and BG (mean difference in z-scores 0.53 (95% IC -0.179, 1.28);  $p = 0.149$ ). However, z-score computed between SP and BG windows were significantly higher in motor seizures only for SPL-pmL interaction (mean difference in z-scores 2.5 (95% IC 0.297, 4.46;  $p=0.037$ ). We also observed that “motor seizures” had a significantly higher FC increase in comparison with “non-motor seizure” between SP and SO (mean difference in z-scores 1.63 (95% IC 1.01, 2.27);  $p < 0.001$ ) (see Figure 3A). We observed in seizures with motor signs a significantly higher increase in FC during SP in comparison with seizures without motor signs in some specific links (see Figure 3B):

- Precuneus – Premotor Lateral (mean difference in z-score = 3.69 (95%IC 1.45, 5.95);  $p=0.0132$ );
- Superior parietal lobule – Premotor lateral (mean difference in z-score = 3.03 (95%IC 0.754, 5.44);  $p=0.0344$ );
- Inferior parietal lobule – SMA (mean difference in z-score = 1.97 (95%IC 0.699, 3.86);  $p=0.046$ ).

The difference for other links were not statistically significant (Supplementary Table 2). As “motor” and “non-motor” groups differ for age at SEEG, we tested if there was a correlation between age at SEEG and FC z-scores however no significant correlation was found (Spearman R test ,  $p = 0.47$  for SO *versus* BG z-scores, 0.07 for SP *versus* BG z-scores and 0.98 for SP *versus* SO z-scores).

### 3.3. Relation with post-surgical outcome

We analyzed z-scores of parietal-extra parietal links in patients who underwent resective surgery after SEEG (8 with favourable outcome (Engel's Classes I and II) and 6 with unfavourable outcome (Engel's classes III and IV). Overall, patients with unfavourable outcome showed a significantly higher FC changes between parietal-extra-parietal areas, overall, during SP (not during SO) (mean difference in z-scores -1.08 (95% IC -1.73, -0.415;  $p=0.0124$ ) (see figure 4). We did not find significant difference in FC changes at the level of links between each brain area, between patients with favourable versus those with unfavourable post-surgical outcome.

## 4. Discussion

The main purpose of this work was to study ictal changes of FC in patients with PLE and their relationship with ictal motor signs. Motor signs, including limb tonic, dystonic or clonic contractions or hyperkinetic manifestations, are the most frequent clinical signs of PLS, reported as habitual semiological features in 19 patients (86.4%) in our cohort, this is in agreement with 75-88% reported in previous studies (Asadollahi et al., 2017; Bartolomei et al., 2011; Francione et al., 2015; Kim et al., 2004; Salanova, 2012; Sveinbjornsdottir and Duncan, 1993). Our main result was that ictal FC is differently modified according to the presence (or the absence) of motor semiology. Overall, FC between parietal, frontal and temporal areas decreased at SO and increased during SP. During the period of SO we observed a more pronounced decrease of FC between parietal and extra-parietal areas in "motor" seizures, particular in the interaction between the most anterior part of parietal lobe

(OP/PoCg) and mesial temporal areas. In contrast, during the phase of SP, we observed an increased FC between parietal and premotor areas in “motor” parietal seizures. This pattern of FC changes is in agreement with previous studies, showing in particular that fast ictal onset discharges are associated with decreased synchronization (*for review see* Bartolomei et al., 2017). During seizures with motor manifestations, we observed a higher re-increase of FC during SP period between parietal cortex and premotor cortex, particularly the pmL and SMA, in comparison with seizures without motor signs. This result indicates that preferential routes from parietal cortex to frontal cortices are responsible of the prominent motor presentation during PLS.

By definition, our patients disclosed maximal epileptogenicity in the posterior parietal cortex, in particular, half of included patients had maximal epileptogenicity in the precuneus or in the SPL. These two regions are involved in important intrinsic brain networks such as the default mode and motor networks (Andersen and Cui, 2009; Bartolomei et al., 2011; Cauda et al., 2010; Cavanna and Trimble, 2006; Fogassi and Luppino, 2005; Wise et al., 1997) and are therefore highly connected with several brain areas. The posterior parietal cortex is anatomically and functionally well connected with the pmL and with the SMA (Andersen and Cui, 2009; Caspers and Zilles, 2018; Fogassi and Luppino, 2005; Rushworth et al., 2006, 2003; Wise et al., 1997). Evidence from studies in primates, showed that the pmL is highly connected with different parietal regions and most of its inputs arise from the SPL (Wise et al., 1997). Other studies showed a strong connectivity also between the IPL, particularly its rostral part, and the ventral premotor cortex and caudal ventrolateral prefrontal cortex (Caspers et al., 2011; Rushworth et al., 2006). As well as the IPL, the rostral part of intraparietal sulcus (IPS) is mainly connected to premotor and prefrontal areas (Caspers and Zilles, 2018; Rushworth et al., 2006; Uddin et al., 2010). Concerning the underlying structural connectivity, data from



human and primates demonstrate the important anatomical role of the superior longitudinal fasciculus with its subcomponents, which can also overlap with the arcuate fascicle. The first bundle creates a dense link between the medial, dorso-lateral SPL and premotor areas, pre-SMA, SMA and prefrontal cortex for body centred action and motor initiative, the second subcomponent links the IPL, anterior and middle IPS with posterior prefrontal and premotor cortices for perception and awareness and finally the third subcomponent links the posterior IPL with ventral premotor areas and with posterior temporal areas, probably involved in action imitation (Caspers and Zilles, 2018; Martino et al., 2013; Schmahmann et al., 2007). This strong underlying connectivity between parietal and premotor cortex may explain the preferential ictal coupling we observed in our study.

Our secondary objective was to analyse the association between ictal FC changes and the postsurgical seizure outcome. We found that patients with unfavourable post-surgical seizure outcome showed a higher FC increase between parietal-extra-parietal areas during SP. This result, although derived from ictal FC analysis, seems to be in accordance with interictal evidence that a higher FC between cortical areas involved during seizure propagation and those not involved, is associated with a poorer surgical prognosis (Lagarde et al., 2018). Other interictal studies suggested that more complex networks are associated with poorer surgical outcome in focal epilepsies (Antony et al., 2013; Bartolomei et al., 2008; Englot et al., 2015; Nissen et al., 2017; Schevon et al., 2007; Shah et al., 2019). Therefore, it seems that ictal FC could be a marker of the extension of epileptic networks and predict seizure outcome following resective surgery. Other studies are needed to better understand if some specific interactions between parietal and extra-parietal areas are particularly important for surgical prognosis and to establish if ictal and interictal FC analysis can represent a possible prognostic biomarker for outcome in epilepsy surgery.

There are some limitations in our study. SEEG has the advantage of directly studying brain activity in several brain regions. However, this technique is limited by sampling and the variability of implantations from one patient to another. We therefore selected the common regions available in our patients and limited our study to the interactions between these regions. We selected our sample by verifying that the maximum EI value was calculated in contacts positioned within the parietal lobe; this method, although semi-automatic, requires an adequate preselection of the SEEG channels and verification by an experienced user, and performs less well in seizure onset patterns without rapid discharge. Another limitation of our work is the variability of the spontaneous seizures selected for each patient, both in terms of the state in which they could occur (sleep, quiet wakefulness, during the execution of tasks) and in seizure duration. The state where seizures occur can influence the FC of the pre-ictal window (BG) and therefore potentially the z-score values computed.

In conclusion, we found that motor semiology observed during PLS is associated with an increase of synchronisation between parietal and premotor cortex during seizure propagation. It suggests that seizures follow underlying strong connectivity between these two cortices, reflecting underlying structural connections, and leading to a pathological over-synchronisation responsible for the emergence of motor semiology.

## References

Andersen RA, Cui H. Intention, Action Planning, and Decision Making in Parietal-Frontal Circuits.

*Neuron* 2009;63:568–83. <https://doi.org/10.1016/j.neuron.2009.08.028>.

Ansari-Asl K, Senhadji L, Bellanger J-J, Wendling F. Quantitative evaluation of linear and nonlinear methods characterizing interdependencies between brain signals. *Phys Rev E* 2006;74:031916.

<https://doi.org/10.1103/PhysRevE.74.031916>.

Antony AR, Alexopoulos A V., González-Martínez JA, Mosher JC, Jehi L, Burgess RC, et al. Functional connectivity estimated from intracranial EEG predicts surgical outcome in intractable temporal lobe epilepsy. *PLoS One* 2013;8:1–7. <https://doi.org/10.1371/journal.pone.0077916>.

Asadollahi M, Sperling MR, Rabiei AH, Asadi-Pooya AA. Drug-resistant parietal lobe epilepsy: clinical manifestations and surgery outcome. *Epileptic Disord* 2017;19:35–9.

<https://doi.org/10.1684/epd.2017.0893>.

Bartolomei F, Bettus G, Stam CJ, Guye M. Interictal network properties in mesial temporal lobe epilepsy: A graph theoretical study from intracerebral recordings. *Clin Neurophysiol* 2013;124:2345–53. <https://doi.org/10.1016/j.clinph.2013.06.003>.

Bartolomei F, Bonini F, Vidal E, Trébuchon A, Lagarde S, Lambert I, et al. How does vagal nerve stimulation (VNS) change EEG brain functional connectivity? *Epilepsy Res* 2016;126:141–6.

<https://doi.org/10.1016/j.epilepsyres.2016.06.008>.

Bartolomei F, Chauvel P, Wendling F. Epileptogenicity of brain structures in human temporal lobe

epilepsy: A quantified study from intracerebral EEG. *Brain* 2008;131:1818–30.

<https://doi.org/10.1093/brain/awn111>.

Bartolomei F, Gavaret M, Hewett R, Valton L, Aubert S, Régis J, et al. Neural networks underlying parietal lobe seizures: A quantified study from intracerebral recordings. *Epilepsy Res* 2011;93:164–76. <https://doi.org/10.1016/j.eplepsyres.2010.12.005>.

Bartolomei F, Lagarde S, Scavarda D, Carron R, Bénar CG, Picard F. The role of the dorsal anterior insula in ecstatic sensation revealed by direct electrical brain stimulation. *Brain Stimul* 2019. <https://doi.org/10.1016/j.brs.2019.06.005>.

Bartolomei F, Lagarde S, Wendling F, McGonigal A, Jirsa V, Guye M, et al. Defining epileptogenic networks: Contribution of SEEG and signal analysis. *Epilepsia* 2017;58:1131–47. <https://doi.org/10.1111/epi.13791>.

Bjellvi J, Olsson I, Malmgren K, Wilbe Ramsay K. Epilepsy duration and seizure outcome in epilepsy surgery: A systematic review and meta-Analysis. *Neurology* 2019;93:E159–66. <https://doi.org/10.1212/WNL.00000000000007753>.

Blumenfeld H, Rivera M, Vasquez JG, Shah A, Ismail D, Enev M, et al. Neocortical and thalamic spread of amygdala kindled seizures. *Epilepsia* 2007;48:254–62. <https://doi.org/10.1111/j.1528-1167.2006.00934.x>.

Caspers S, Eickhoff SB, Rick T, von Kapri A, Kuhlen T, Huang R, et al. Probabilistic fibre tract analysis of cytoarchitectonically defined human inferior parietal lobule areas reveals similarities to macaques. *Neuroimage* 2011;58:362–80. <https://doi.org/10.1016/j.neuroimage.2011.06.027>.

Caspers S, Zilles K. Microarchitecture and connectivity of the parietal lobe. *Handb. Clin. Neurol.*, vol. 151. 1st ed., Elsevier B.V.; 2018, p. 53–72. <https://doi.org/10.1016/B978-0-444-63622-5.00003-6>.

Cauda F, Geminiani G, D'Agata F, Sacco K, Duca S, Bagshaw AP, et al. Functional connectivity of the posteromedial cortex. *PLoS One* 2010;5:1–11. <https://doi.org/10.1371/journal.pone.0013107>.

Cavanna AE, Trimble MR. The precuneus: A review of its functional anatomy and behavioural correlates. *Brain* 2006;129:564–83. <https://doi.org/10.1093/brain/awl004>.

Colombet B, Woodman M, Badier JM, Bénar CG. AnyWave: A cross-platform and modular software for visualizing and processing electrophysiological signals. *J Neurosci Methods* 2015;242:118–26. <https://doi.org/10.1016/j.jneumeth.2015.01.017>.

Englot DJ, Hinkley LB, Kort NS, Imber BS, Mizuiru D, Honma SM, et al. Global and regional functional connectivity maps of neural oscillations in focal epilepsy. *Brain* 2015;138:2249–62. <https://doi.org/10.1093/brain/awv130>.

Fogassi L, Luppino G. Motor functions of the parietal lobe. *Curr Opin Neurobiol* 2005;15:626–31. <https://doi.org/10.1016/j.conb.2005.10.015>.

Fornito A, Zalesky A, Bullmore ET. *Fundamentals of Brain Network Analysis*. Academic Press; 2015.

Francione S, Liava A, Mai R, Nobili L, Sartori I, Tassi L, et al. Drug-resistant parietal epilepsy: Polymorphic ictal semiology does not preclude good post-surgical outcome. *Epileptic Disord* 2015;17:32–46. <https://doi.org/10.1684/epd.2015.0728>.

Guye M, Bartolomei F, Ranjeva J-P. Imaging structural and functional connectivity: towards a unified definition of human brain organization? *Curr Opin Neurol* 2008;24:393–403. <https://doi.org/10.1097/WCO.0b013e3283065cfb>.

Hagiwara K, Jung J, Bouet R, Abdallah C, Guénot M, Garcia-Larrea L, et al. How can we explain the frontal presentation of insular lobe epilepsy? The impact of non-linear analysis of insular seizures. *Clin Neurophysiol* 2017;128:780–91. <https://doi.org/10.1016/j.clinph.2017.01.022>.

Ho J, Tumkaya T, Aryal S, Choi H, Claridge-Chang A. Moving beyond P values: data analysis with estimation graphics. *Nat Methods* 2019;16:565–6. <https://doi.org/10.1038/s41592-019-0470-3>.

Kim DW, Lee SK, Yun C, Kim K, Lee DS, Chung C, et al. Parietal Lobe Epilepsy: The Semiology, Yield of

Diagnostic Workup, and Surgical Outcome. *Epilepsia* 2004;45:1–9.

Lagarde S, Roehri N, Lambert I, Trebuchon A, McGonigal A, Carron R, et al. Interictal stereotactic-EEG functional connectivity in refractory focal epilepsies. *Brain* 2018;141:2966–80.

<https://doi.org/10.1093/brain/awy214>.

Luppino G, Matelli M, Camarda R, Rizzolatti G. Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *J Comp Neurol* 1993;338:114–40.

<https://doi.org/10.1002/cne.903380109>.

Martino J, De Witt Hamer PC, Berger MS, Lawton MT, Arnold CM, De Lucas EM, et al. Analysis of the subcomponents and cortical terminations of the perisylvian superior longitudinal fasciculus: A fiber dissection and DTI tractography study. *Brain Struct Funct* 2013;218:105–21.

<https://doi.org/10.1007/s00429-012-0386-5>.

Medina Villalon S, Paz R, Roehri N, Lagarde S, Pizzo F, Colombet B, et al. EpiTools, A software suite for presurgical brain mapping in epilepsy: Intracerebral EEG. *J Neurosci Methods* 2018;303:7–15.

<https://doi.org/10.1016/j.jneumeth.2018.03.018>.

Nissen IA, Stam CJ, Reijneveld JC, van Straaten IECW, Hendriks EJ, Baayen JC, et al. Identifying the epileptogenic zone in interictal resting-state MEG source-space networks. *Epilepsia* 2017;58:137–48.

<https://doi.org/10.1111/epi.13622>.

Orban GA, Claeys K, Nelissen K, Smans R, Sunaert S, Todd JT, et al. Mapping the parietal cortex of human and non-human primates. *Neuropsychologia* 2006;44:2647–67.

<https://doi.org/10.1016/j.neuropsychologia.2005.11.001>.

Pilipović-Dragović S, Ristić AJ, Bukumirić Z, Trajković G, Sokić D. Long-term seizure outcome following epilepsy surgery in the parietal lobe: a meta-analysis. *Epileptic Disord* 2018;20:116–22.

<https://doi.org/10.1684/epd.2018.0960>.

Ristić AJ, Alexopoulos A V., So N, Wong C, Najm IM. Parietal lobe epilepsy: The great imitator among

focal epilepsies. *Epileptic Disord* 2012;14:22–31. <https://doi.org/10.1684/epd.2012.0484>.

Rushworth MFS, Behrens TEJ, Johansen-Berg H. Connection patterns distinguish 3 regions of human parietal cortex. *Cereb Cortex* 2006;16:1418–30. <https://doi.org/10.1093/cercor/bhj079>.

Rushworth MFS, Johansen-Berg H, Göbel SM, Devlin JT. The left parietal and premotor cortices: Motor attention and selection. *Neuroimage* 2003;20.  
<https://doi.org/10.1016/j.neuroimage.2003.09.011>.

Salanova V. Parietal lobe epilepsy. *Handb Clin Neurol* 2012;151:413–25.  
<https://doi.org/10.1016/B978-0-444-63622-5.00021-8>.

Salanova V, Andermann F, Rasmussen T, Olivier a, Quesney LF, Salanova, V., Andermann, F., Rasmussen, T., Olivier, A., Quesney LF. Parietal lobe epilepsy clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988. *Brain* 1995;118 ( Pt 3):607–27.

Salanova V., Andermann F, Rasmussen T, Olivier A, Quesney LF. Parietal lobe epilepsy clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988. *Brain* 1995a;118:607–27. <https://doi.org/10.1093/brain/118.3.607>.

Salanova V., Andermann F, Rasmussen T, Olivier A, Quesney LF. Tumoral Parietal lobe epilepsy Clinical manifestations and outcome in 34 patients treated between 1934 and 1988. *Brain* 1995b;118:1289-1304 Clinical. <https://doi.org/10.1093/brain/118.3.607>.

Schevon CA, Cappell J, Emerson R, Isler J, Grieve P, Goodman R, et al. Cortical abnormalities in epilepsy revealed by local EEG synchrony. *Neuroimage* 2007;35:140–8.  
<https://doi.org/10.1016/j.neuroimage.2006.11.009>.

Schmahmann JD, Pandya DN, Wang R, Dai G, D’Arceuil HE, De Crespigny AJ, et al. Association fibre pathways of the brain: Parallel observations from diffusion spectrum imaging and autoradiography. *Brain* 2007;130:630–53. <https://doi.org/10.1093/brain/awl359>.

Scholly J, Valenti MP, Staack AM, Strobl K, Bast T, Kehrli P, et al. Hypothalamic hamartoma: Is the epileptogenic zone always hypothalamic? Arguments for independent (third stage) secondary epileptogenesis. *Epilepsia* 2013;54:123–8. <https://doi.org/10.1111/epi.12456>.

Shah P, Bernabei JM, Kini LG, Ashourvan A, Boccanfuso J, Archer R, et al. High interictal connectivity within the resection zone is associated with favorable post-surgical outcomes in focal epilepsy patients. *NeuroImage Clin* 2019;23:101908. <https://doi.org/10.1016/j.nicl.2019.101908>.

Skoch J, Adelson PD, Bhatia S, Greiner HM, Rydenhag B, Scavarda D, et al. Subdural grid and depth electrode monitoring in pediatric patients. *Epilepsia* 2017;58:56–65. <https://doi.org/10.1111/epi.13685>.

Sveinbjornsdottir S, Duncan JS. Parietal and Occipital Lobe Epilepsy: A Review. *Epilepsia* 1993;34:493–521. <https://doi.org/10.1111/j.1528-1157.1993.tb02590.x>.

Talairach J, Bancaud J, Szikla G, Bonis A, Geier S VC. [New approach to the neurosurgery of epilepsy. Stereotaxic methodology and therapeutic results. 1. Introduction and history]. *Neurochirurgie* 1974;20 Suppl 1.

Uddin LQ, Supekar K, Amin H, Rykhlevskaia E, Nguyen DA, Greicius MD, et al. Dissociable connectivity within human angular gyrus and intraparietal sulcus: Evidence from functional and structural connectivity. *Cereb Cortex* 2010;20:2636–46. <https://doi.org/10.1093/cercor/bhq011>.

Wang HE, Bénar CG, Quilichini PP, Friston KJ, Jirsa VK, Bernard C. A systematic framework for functional connectivity measures. *Front Neurosci* 2014;8:1–22. <https://doi.org/10.3389/fnins.2014.00405>.

Wendling F, Ansari-Asl K, Bartolomei F, Senhadji L. From EEG signals to brain connectivity: A model-based evaluation of interdependence measures. *J Neurosci Methods* 2009;183:9–18. <https://doi.org/10.1016/j.jneumeth.2009.04.021>.

Wendling F, Bartolomei F, Bellanger JJ, Chauvel P. Interpretation of interdependencies in epileptic



signals using a macroscopic physiological model of the EEG. *Clin Neurophysiol* 2001;112:1201–18.

[https://doi.org/10.1016/S1388-2457\(01\)00547-8](https://doi.org/10.1016/S1388-2457(01)00547-8).

Wise SP, Boussaoud D, Johnson PB, Caminiti R. PREMOTOR AND PARIETAL CORTEX: Corticocortical Connectivity and Combinatorial Computations. *Annu Rev Neurosci* 1997;20:25–42.

<https://doi.org/10.1146/annurev.neuro.20.1.25>.

## Tables and Figures Legends

**Table 1. Comparison of clinical features of the motor and non-motor seizures groups.**

*N*, number of patients; %, percent; SEEG, Stereoelectroencephalography; SOZ, seizure onset zone; SD, standard deviation; NS, not significant; ANET, angiocentric neuroepithelial tumour; DNET, dysembryoplastic neuroepithelial tumour; FCD, focal cortical dysplasia; PMG, polymicrogyria; EI, epileptogenicity index; SPL, superior parietal lobule; IPL, inferior parietal lobule; pCG, posterior cingulate gyrus; OP, parietal operculum; PoCg, post-central gyrus; \*: one patient has no identified manual dominance because of very young age.

**Figure 1. Ictal Stereoelectroencephalography (SEEG) trace and functional connectivity (FC) changes graphs of patient 7 with hypermotor seizure.**

**A:** Ictal SEEG trace, bipolar 13 channels montage, pink parts represent the three periods of analysis: BG (background), SO (seizure onset) and SP (seizure propagation). In BG period, note the interictal spikes in post-central gyrus (PoCg) and inferior parietal lobule (SMG). In SO, this activity is replaced by low voltage rapid discharges that involved both parietal and frontal areas. During SP, slower rhythmic activities with higher voltage are seen.

**B:** Graphic representation of the FC changes (z-score) between the different periods, only significant changes are represented, blue links represents significant FC decreasing, yellow ones significant FC increasing. Between SO and BG, inferior parietal lobule (IPL), PoCg and supplementary motor area (SMA) show decrease of FC with temporal mesial area and central areas, FC increase is seen between pre-frontal area and contralateral superior parietal lobule (SPL). During SP, in comparison with BG and SO, an important FC increase is seen between parietal and frontal areas.

*PM1-PM2* sample medial prefrontal cortex (mPFC); *PM5-PM6* sample dorso lateral pre-frontal cortex (DLPFC); *SA1-SA2* sample supplementary motor area (SMA); *SA8-SA9* sample the dorso-lateral pre-motor area (pmL); *R1-R2* sample medial pre-central cortex (mCen); *R10-R11* sample lateral pre-central cortex (lCen); *PA1-PA2* sample precuneus (pCu); *PA9-PA10* sample

*superior parietal lobule (SPL(7)), GSM9-GSM10 sample supramarginal gyrus (SMG); PoC11-PoC12 sample post-central gyrus (PoCg); B1-B2 sample hippocampus (Hip); B11-B12 sample anterior medium temporal gyrus (aMTG); LP'11-LP'12 sample contralateral (left) SPL.*

**Figure 2: Differences in z-scores computed between Seizure onset period (SO) and pre-ictal period (BG) in all parietal-extra-parietal interactions studied, between “motor” and “non-motor” seizures**

The mean difference between non-motor seizures and motor seizures is shown in the above Gardner-Altman estimation plot. Both groups are plotted on the left axes; the mean difference is plotted on a floating axis on the right as a bootstrap sampling distribution. The mean difference is depicted as a dot; the 95% confidence interval (CI) is indicated by the ends of the vertical error bar. On the left are represented z-scores of all explored parietal-extra-parietal interactions (mean difference in z-scores= -0.918 (95% CI -1.5, -0.368);  $p= 0.0018$ ). On the right are represented z-scores computed between parietal operculum/ post-central gyrus (OP/PoCg) and mesial temporal areas (temp mes) (mean difference in z-scores= -2.52 (95% IC= -3.31, -1.52);  $p< 0.001$ ). *SO, seizure onset period; BG, pre-ictal period; OP/PoCg, parietal operculum/ Post central gyrus; Temp mes, mesial temporal areas.*

**Figure 3: Differences in z-scores computed between seizure propagation period (SP) and seizure onset period (SO) in all parietal-extra-parietal interactions studied, between “motor” and “non-motor” seizures**

The mean difference between Non-motor seizures and Motor seizures is shown in the above Gardner-Altman estimation plot. Both groups are plotted on the left axes; the mean difference is plotted on a floating axis on the right as a bootstrap sampling distribution. The mean difference is depicted as a dot; the 95% confidence interval (CI) is indicated by the ends of the vertical error bar. On the left **(A)** are represented z-score of all explored parietal-extra-parietal interactions (mean difference in z-scores 1.63 (95% IC 1.01, 2.27);  $p< 0.001$ ). On the right **(B)** are represented the significant differences between “motor” and “non-motor” seizures in z-scores computed between SP and SO at the level of brain structures interactions. On the left are represented z-scores of the interaction between Precuneus (PCUN) and lateral pre-motor

are (pmL) (mean difference in z-score = 3.69 (95%IC 1.45, 5.95);  $p=0.0132$ ), on the centre are represented z-scores of the interaction between superior parietal lobule (SPL) and pmL (mean difference in z-score = 3.03 (95%IC 0.754, 5.44);  $p=0.0344$ ), on the right are represented z-scores of the interaction between inferior parietal lobule (IPL)/posterior cingular gyrus (pCG) and supplementary motor area (SMA) (mean difference in z-score = 1.97 (95%IC 0.699, 3.86);  $p=0.046$ ). *SP*, seizure propagation period; *SO*, seizure onset period; *PCUN*, precuneus; *pmL*, lateral pre-motor area; *SPL*, superior parietal lobule; *IPL/pCG*, inferior parietal lobule/posterior cingular gyrus; *SMA*, supplementary motor area.

**Figure 4: Differences in z-scores computed between seizure propagation period (SP) and seizure onset period (SO) in all parietal-extra-parietal interactions studied, between patients with favourable surgical outcome (Engel's classes I and II) and unfavourable surgical outcome (Engel's classes III and IV).**

The mean difference between Negative Outcome and Positive Outcome is shown in the above Gardner-Altman estimation plot. Both groups are plotted on the left axes; the mean difference is plotted on a floating axis on the right as a bootstrap sampling distribution. The mean difference is depicted as a dot; the 95% confidence interval (CI) is indicated by the ends of the vertical error bar. Mean difference in z-scores is equal to -1.08 (95% IC -1.73, -0.415)

*SP*, seizure propagation period; *SO*, seizure onset period.





