Patient-specific network connectivity combined with a next generation neural mass model to test clinical hypothesis of seizure propagation

Moritz Gerster, Halgurd Taher, Jaroslav Hlinka, Maxime Guye, Fabrice Bartolomei, Anna Zakharova, and Simona Olmi

1 Institut für Theoretische Physik, Technische Universität Berlin, Hardenbergstr. 36, 10623 Berlin
2 Inria Sophia Antipolis Méditerranée Research Centre, MathNeuro Team, 2004 route des Lucioles-Boîte Postale 93 06902 Sophia Antipolis, Cedex, France
3 National Institute of Mental Health, Topolová 748, 250 67 Klecany, Czech Republic
4 Institute of Computer Science of the Czech Academy of Sciences, Pod Vodarenskou vezi 2, 18207 Prague 8, Czech Republic
5 Faculté de Médecine de la Timone, centre de Résonance Magnétique et Biologique et Médicale (CRMBM, UMR CNRS-AMU 7339), Medical School of Marseille, Aix-Marseille Université, 13005, Marseille, France
6 Assistance Publique - Hôpitaux de Marseille, Hôpital de la Timone, Pôle d’Imagerie, CHU, 13005, Marseille, France
7 Assistance Publique - Hôpitaux de Marseille, Hôpital de la Timone, Service de Neurophysiologie Clinique, CHU, 13005 Marseille, France
8 CNR - Consiglio Nazionale delle Ricerche - Istituto dei Sistemi Complessi, 50019, Sesto Fiorentino, Italy

Correspondence*: Simona Olmi
simona.olmi@inria.fr

ABSTRACT

Modulations of the neuronal subthreshold activity, giving rise to rhythms at high firing rate, represent the high signal complexity of the brain dynamic repertoire. Together with neural network oscillations, they are a fundamental mechanism for cognition, perception and consciousness. Consequently, perturbations of network activity play an important role in the pathophysiology of brain disorders. Here we combine structural information from non-invasive brain imaging with mathematical modeling, thus leveraging an in-silico platform for the exploration of causal mechanisms of brain function and clinical hypothesis testing. In particular we use a recently derived set of exact mean-field equations for networks of quadratic integrate-and-fire neurons to provide a comprehensive study of the effect of external drives or perturbations on neuronal networks exhibiting multistability in order to investigate the role played by the neuroanatomical connectivity matrix in shaping the emergent dynamics.

We demonstrate, along the example of 20 diffusion-weighted magnetic resonance imaging (MRI) connectomes of healthy subjects, that individual variations in structural connectivity, when linked
with mathematical dynamic models, have the capacity to explain changes in spatiotemporal organization of brain dynamics, as observed in network-based brain disorders. Moreover we studied patient-specific brain network models of 15 drug-resistant epilepsy patients with implanted stereotactic electroencephalography (SEEG) electrodes. Each personalized brain model was derived from structural data of MRI and diffusion tensor weighted imaging (DTI), while each patient’s virtual brain was further personalized through the integration of the clinically hypothesized epileptogenic zone (EZ), i.e. the local network where highly synchronous seizures originate. Across patients, it turns out that patient-specific network connectivity is predictive for the subsequent seizure propagation pattern thus opening the possibility of improving diagnosis and surgery outcome.

Keywords: Neural mass models, quadratic integrate-and-fire neuron, patient-specific brain network models, epileptic seizure

1 INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by occurrence and recurrence of seizures and it represents the third most common neurological disorder affecting more than 50 million people worldwide. Anti-epilepsy drugs are the first line of treatment for epilepsy and they provide sufficient seizure control in around two thirds of cases \cite{Kwan2000}. However, the seizures of about 30 to 40\% of epilepsy patients do not respond to drugs, a percentage that has remained relatively stable despite significant efforts to develop new antiepileptic medication over the past decades. For drug-resistant patients, a possible treatment is the surgical resection of the brain tissue responsible for the generation of seizures.

As a common procedure, epilepsy surgery is preceded by a qualitative assessment of different brain imaging modalities in order to identify the brain tissue responsible for seizure generation, i.e. the epileptogenic zone (EZ) \cite{Rosenow2001}, which in general represents a localized region or network where seizures arise, before recruiting secondary networks, called the propagation zone (PZ) \cite{Talairach1966, Bartolomei2001, Spencer2002}. Operation outcomes are positive whenever the patient has become seizure-free after surgical operation, thus meaning that surgeons have correctly inferred the EZ.

Intracranial electroencephalography (iEEG) is commonly used during the presurgical assessment to find the seizure onset zone \cite{David2011, Duncan2016}, which is assumed to be a marker of the EZ \cite{Rosenow2001}, the assumption being that the region where seizures emerge, is at least part of the brain tissue responsible for seizure generation. As a part of the standard presurgical evaluation with iEEG, stereotactic EEG (SEEG) is used to help correctly delineating the EZ \cite{Bartolomei2002}. Alternative imaging techniques such as structural MRI, M/EEG, and positron emission tomography (PET) help the clinician to outline the EZ. Recently, diffusion MRI (dMRI) started being evaluated as well, thus giving the possibility to infer the connectivity between different brain regions and revealing reduced fractional anisotropy \cite{Ahmadi2009, Bernhardt2013} and structural alterations in the connectome of epileptic patients \cite{Bonilha2012, Desalvo2014, Besson2014}. However epilepsy surgery is often unsuccessful and long-term positive outcome may be lower than 25\% in extra-temporal cases \cite{DeTisi2011, Najm2013}, thus meaning that the EZ has not been correctly identified or that EZ and seizure onset zone may not coincide.

In order to quantitatively examine clinical data and determine targets for surgery, many computational models have been recently proposed \cite{Hutchings2015, Goodfellow2017, Khambhati2016, Lopes2017, Sinha2017}, that use MRI or iEEG data acquired during presurgical workup to infer structural or functional brain networks. Taking advantages of recent advances in our
understanding of epilepsy, that indicate that seizures may arise from distributed ictogenic networks \cite{Richardson2012, Bartolomei2017, Besson2017}, phenomenological models of seizure transitions are used to compute the escape time, i.e., the time that each network node takes to transit from a normal state to a seizure-like state. Nodes with the lowest escape time are then considered as representative of the seizure onset zone and therefore candidates for surgical resection, by assuming seizure onset zone as a proxy for the EZ \cite{Hutchings2015, Sinha2017}. Alternatively different possible surgeries are simulated in silico to predict surgical outcomes \cite{Goodfellow2017, Lopes2017, Lopes2019} by making use of synthetic networks and phenomenological network models of seizure generation. Further attention has been paid to studying how network structure and tissue heterogeneities underpin the emergence of focal and widespread seizure dynamics in synthetic networks of phase oscillators \cite{Lopes2019, Lopes2020}.

More in general there is a vast and valuable literature on computational modeling in epilepsy, where two classes of models are used: 1) mean-field (macroscopic) models and 2) detailed (microscopic) network models. The mean field models have certain advantages over the more detailed models since they are suitable for looking into transitions from interictal to ictal states and for exploring EEG analysis from epilepsy patients, as the macroelectrodes used for EEG recordings represent the average local field potential arising from neuronal populations. Indeed, a big effort has been made so far to explain the biophysical and dynamical nature of seizure onsets and offsets by employing neural mass models \cite{DaSilva1974, Wendling2002, Kalitzin2010, Touboul2011, Kramer2012, Jirsa2014}. Since the mean field models remain relatively simple, they can also be employed to describe epileptic processes occurring in “large-scale” systems, e.g. the precise identification of brain structures that belong to the seizure-triggering zone (epileptic activity often spreads over quite extended regions and involves several cortical and sub-cortical structures). However, only recently, propagation of epileptic seizures started to be studied using brain network models, and was limited to small-scales \cite{Terry2012} or absence seizures \cite{Taylor2013}, while partial seizures have been reported to propagate through large-scale networks in humans \cite{Bartolomei2013} and animal models \cite{Toyoda2013}. All in all, even though neural mass models are in general easier to analyze numerically because relatively few variables and parameters are involved, they drastically fail to suggest molecular and cellular mechanisms of epileptogenesis. Therefore they result unable to model therapeutics targeting molecular pathways responsible for seizures.

On the other hand, the detailed network models are best suited for understanding the molecular and cellular bases of epilepsy and thus they may be used to suggest therapeutics targeting molecular pathways \cite{Destexhe1995, VanDrongelen2005, Turrigiano2008, Cressman2009, Ullah2009}. Due to the substantial complexity of neuronal structures, relatively few variables and parameters can be accessed at any time experimentally. Although biophysically explicit modeling is the primary technique to look into the role played by experimentally inaccessible variables in epilepsy, the usefulness of detailed biophysical models is limited by constraints in computational power, uncertainties in detailed knowledge of neuronal systems, and the required simplification for the numerical analysis. Therefore an intermediate “across-scale” approach, establishing relationships between sub-cellular/cellular variables of detailed models and mean-field parameters governing macroscopic models, would be a very useful strategy to cover the gaps between these two modeling approaches.

In view of developing a cross-scale approach, it is important to point out that large-scale brain network models emphasize the network character of the brain and merge structural information of individual brains with mathematical modeling, thus constituting in-silico platforms for the exploration of causal mechanisms of brain function and clinical hypothesis testing. In particular, in brain network models, a network region is
Gerster et al.

Patient-specific network connectivity

In this paper we have built brain network models for a cohort of 20 healthy subjects and 15 epileptic patients and we have systematically simulated the individual seizure propagation patterns, looking for the role played by the individual structural topologies in determining the recruitment mechanisms. Specific attention has been devoted to the analogies and differences among the self-emergent dynamics in healthy and epilepsy-affected subjects. Furthermore, for epileptic patients, we have validated the model against the presurgical stereotactic electroencephalography (SEEG) data and the standard-of-care clinical evaluation.

More specifically Sec. 2 is devoted to the description of the implemented model and the applied methods. In Sec. 3 are reported the results specific for healthy subjects, while in Sec. 4 is reported a detailed analysis performed on epileptic patients. Finally a discussion on the presented results is reported in Sec. 5.
2 METHODS

2.1 Network Model

The membrane potential dynamics of the $i$-th QIF neuron in a network of size $N$ can be written as

$$\tau_m \frac{d}{dt} V_i = V_i^2(t) + \eta_i + I_B + I_S(t) + \tau_m \frac{1}{N} \sum_{j=1}^{N} \tilde{J}_{ij}(t) S_j(t), \quad i = 1, \ldots, N \quad (1)$$

where $\tau_m = 20$ ms is the membrane time constant and $\tilde{J}_{ij}(t)$ the strength of the direct synapse from neuron $j$ to $i$ that we assume to be constant and all identical, i.e. $\tilde{J}_{ij}(t) = J$. The sign of $J$ determines if the neuron is excitatory ($J > 0$) or inhibitory ($J < 0$); in the following we will consider only excitatory neurons. Moreover, $\eta_i$ represents the neuronal excitability, $I_B$ a constant background DC current, $I_S(t)$ an external stimulus and the last term on the right hand side the synaptic current due to the recurrent connections with the pre-synaptic neurons. For instantaneous post-synaptic potentials (corresponding to $\delta$-spikes) the neural activity $S_j(t)$ of neuron $j$ reads as

$$S_j(t) = \sum_{t_j(k)<t} \delta(t - t_j(k)), \quad (2)$$

where $S_j(t)$ is the spike train produced by the $j$-th neuron and $t_j(k)$ denotes the $k$-th spike time in such sequence. We have considered a fully coupled network without autapses, therefore the post-synaptic current will be the same for each neuron apart corrections of order $O(1/N)$.

In the absence of synaptic input, external stimuli and $I_B = 0$, the QIF neuron exhibits two possible dynamics, depending on the sign of $\eta_i$. For negative $\eta_i$, the neuron is excitable and for any initial condition $V_i(0) < \sqrt{-\eta_i}$, it reaches asymptotically the resting value $-\sqrt{-\eta_i}$. On the other hand, for initial values larger than the excitability threshold, $V_i(0) > \sqrt{-\eta_i}$, the membrane potential grows unbounded and a reset mechanism has to be introduced to describe the spiking behaviour of a neuron. Whenever $V_i(t)$ reaches a threshold value $V_p$, the neuron $i$ delivers a spike and its membrane voltage is reset to $V_r$, for the QIF neuron $V_p = -V_r = \infty$. For positive $\eta_i$ the neuron is supra-threshold and it delivers a regular train of spikes with frequency $\nu_0 = \sqrt{\eta_i}/\pi$.

From this microscopic neural model, mean-field equations can be derived which lead to an exact description of the firing rate of a large number of neurons in the thermodynamic limit (Montbriò et al., 2015). The analytic derivation of the neural mass model can be performed when the excitabilities $\{\eta_i\}$ follow a Lorentzian distribution $g(\eta) = \frac{1}{\pi} \frac{\Delta}{(\eta - \bar{\eta})^2 + \Delta^2}$. (3) centred at $\bar{\eta}$ and with HWHM $\Delta$.

2.2 Neural Mass Model

For the heterogeneous QIF network with instantaneous synapses (Eqs. (1)-(2)), an exact neural mass model has been derived in Montbriò et al. (2015). The analytic derivation is possible for QIF spiking networks thanks to the Ott-Antonsen Ansatz Ott and Antonsen (2008) applicable to phase-oscillators networks whenever the natural frequencies (here corresponding to the excitabilities $\{\eta_i\}$) are distributed...
accordingly to a Lorentzian distribution with median $\bar{\eta}$ and HWHM $\Delta$. In particular, this neural mass model allows for an exact macroscopic description of the population dynamics, in the thermodynamic limit $N \to \infty$, in terms of only two collective variables, namely the mean membrane voltage $v(t)$ and the instantaneous population rate $r(t)$, as follows

$$\tau_m \dot{r}(t) = \frac{\Delta}{\tau_m \pi} + 2r(t)v(t) \quad (4a)$$

$$\tau_m \dot{v}(t) = v^2(t) + \bar{\eta} + I_B + I_S(t) - (\pi \tau_m r(t))^2 + \tau_m J(t)r(t) \quad ; \quad (4b)$$

where the synaptic strength is assumed to be identical for all neurons and for instantaneous synapses in absence of plasticity $J(t) = J$. However, by including a dynamical evolution for the synapses and therefore additional collective variables, this neural mass model can be extended to any generic postsynaptic potentials, see e.g. [Devalle et al. (2017)] for exponential synapses or [Coombes and Byrne (2019)] for conductance based synapses with $\alpha$-function profile.

### 2.3 Multipopulation Neural Mass Model

The discussed neural mass model can be easily extended to account for multiple interconnected neuronal populations $N_{\text{pop}}$. In the following we consider personalized brain models derived from structural data of magnetic resonance imaging (MRI) and diffusion tensor weighted imaging (DTI), thus implementing different structural connectivity matrices for healthy subjects and epileptic patients. For healthy subjects cortical and volumetric parcellations were performed using the Automatic Anatomical Atlas 1 (AAL1) [Tzourio-Mazoyer et al. (2002)] with $N_{\text{pop}} = 90$ brain regions: each region will be described in terms of the presented neural mass model. For epileptic subjects cortical and volumetric parcellations were performed using the Desikan-Killiany atlas with 70 cortical regions and 17 subcortical regions [Desikan et al. (2006)] (one more empty region is added in the construction of the structural connectivity for symmetry). In this case the structural connectivity matrix is composed, for each epileptic patient, by 88 nodes equipped with the presented region specific neural mass model capable of demonstrating epileptiform discharges.

The corresponding multi-population neural mass model can be straightforwardly written as

$$\tau_m \dot{r}_k(t) = \frac{\Delta_k}{\tau_m \pi} + 2r_k(t)v_k(t) \quad k = 0, 1, \ldots, N_{\text{pop}} \quad (5a)$$

$$\tau_m \dot{v}_k(t) = v_k^2(t) + \bar{\eta}_k + I_B + I_S^{(k)}(t) - (\pi \tau_m r_k(t))^2 + \tau_m \sigma \sum_{l=0}^{N_{\text{pop}}} J_{kl}r_l(t), \quad (5b)$$

where $\sigma$ is the synaptic strength and $J_{kl}$ represents the connectivity matrix among the populations. The synaptic couplings $J_{kl}$ depend on the population indices $k$ and $l$ but not on the neuron indices; therefore we assume that the neurons are globally coupled both at the intra- and inter-population level. The connectivity matrix entries $\tilde{J}_{kl}$, extracted from empirical Diffusion Tensor Imaging (DTI) topologies, are real numbers rescaled with the maximal entry value and normalized in the range $[0, 1]$, while $\tilde{J}_{kk} = 0$. Since intra-coupling is usually stronger than inter-coupling, we can assume that the entries of each structural connectivity matrix can be rescaled such as

$$J_{kl} = \begin{cases} 5 \tilde{J}_{kl} & \text{if } k \neq l \\ 20 & \text{if } k = l \end{cases} \quad (6)$$

This is a provisional file, not the final typeset article
Hence, all connections are in a range $J_{kl} \in [0, 5]$ for $k \neq l$ and the intra-coupling is set to $J_{kk} = 20$. The time dependent stimulus current $I_{S}^{(k)}(t)$ is population specific and a single population at a time is generally stimulated during a numerical experiment. The delivered stimulus $I_{S}^{(k)}(t)$ consists of a rectangular pulse of height $I_{S}$ and duration $t_I$; the dependence on amplitude and duration is studied in this paper to support the generality of the results. The parameter value $\Delta = 1$ is kept fixed for all the simulations reported in this paper.

### 2.4 Topologies

As a first set of data, we have selected 20 diffusion-weighted magnetic resonance imaging connectomes of healthy subjects (mean age 33 years, standard deviation 5.7 years, 10 females, 2 left-handed) that participated in a study on schizophrenia as a control group (Melicher et al., 2015). All subjects were recruited via local advertisements and had none of the following conditions: Personal lifetime history of any psychiatric disorder or substance abuse established by the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Lecrubier et al., 1997), any psychotic disorder in first or second-degree relatives. Further exclusion criteria included current neurological disorders, lifetime history of seizures or head injury with altered consciousness, intracranial hemorrhage, neurological sequelae, history of mental retardation, history of substance dependence, any contraindication for MRI scanning.

The scans were performed on a 3T Siemens scanner in the Institute of Clinical and Experimental Medicine in Prague, employing a Spin-Echo EPI sequence with 30 diffusion gradient directions, $TR = 8300$ ms, $TE = 84$ ms, $2 \times 2 \times 2\text{mm}^3$ voxel size, $b$-value $900\text{s/mm}^2$. The diffusion weighted images (DWI) were analyzed using the Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006), part of FMRIB’s Software Library (FSL) (Smith et al., 2004). Image conversion from DICOM to NIfTI format was accomplished using dcm2nii. With FMRIB’s Diffusion Toolbox (FDT), the fractional anisotropy (FA) images were created by fitting a tensor model to the raw diffusion data and then, using the Brain Extraction Tool (BET) (Smith, 2002), brain-extracted. FA identifies the degree of anisotropy of a diffusion process and it is a measure often used in diffusion imaging where it is thought to reflect fiber density, axonal diameter, and myelination in white matter. A value of zero means that diffusion is isotropic, i.e. it is unrestricted (or equally restricted) in all directions, while a value of one means that diffusion occurs only along one axis and is fully restricted along all other directions. Subsequently the FA images were transformed into a common space by nonlinear registration IRTK (Rueckert et al., 1999). A mean FA skeleton, representing the centers of all tracts common to the group, was obtained from the thinned mean FA image. All FA data were projected onto this skeleton. The resulting data was fed into voxel-wise cross-subject statistics. Prior to analysis in SPM, the FA maps were converted from NIfTI format to Analyze.

The brains were segregated into 90 brain areas according to the Automated Anatomical Labeling Atlas 1 (AAL1) (Tzourio-Mazoyer et al., 2002). The anatomical names of the brain areas for each index $k$ is shown in Tab. 1. In each brain network, one AAL brain area corresponds to a node of the network. The weights between the nodes were estimated through the measurement of the preferred diffusion directions, given by a set of $n_s = 5000$ streamlines for each voxel. The streamlines are hypothesized to correlate with the white-matter tracts. The ratio of streamlines connecting area $l$ and area $k$ is given by the probability coefficient $p_{lk}$. Then, the adjacency matrix $J_{kl}$ is constructed from this probability coefficient. The DTI processing pipeline has been adopted from Ref. (Cabral et al., 2013).

Besides the healthy connectomes, we selected 15 connectomes (9 females, 6 males, mean age 33.4, range 22-56) of patients with different types of partial epilepsy that underwent a presurgical evaluation. The scans were performed at the Centre de Résonance Magnétique et Biologique et Médicale (Faculté de
Médecine de la Timone) in Marseille. Diffusion MRI images were acquired on a Siemens Magnetom Verio 3T MR-scanner using a DTI-MR sequence with an angular gradient set of 64 directions, $TR = 10700$ ms, $TE = 95$ ms, $2 \times 2 \times 2mm^3$ voxel size, 70 slices, b-value $1000s/mm^2$.

The data processing to import structural and diffusion MRI data in The Virtual Brain has been done using SCRIPTS. This processing pipeline makes use of various tools such as FreeSurfer (Fischl, 2012), FSL (Jenkinson et al., 2012), MRtrix3 (Tournier, 2010) and Remesher (Fuhrmann et al., 2010), to reconstruct the individual cortical surface and large-scale connectivity. The surface was reconstructed using 20,000 vertices. Cortical and volumetric parcellations were performed using the Desikan-Killiany atlas with 70 cortical regions and 17 subcortical regions (Desikan et al., 2006). The final atlas consists of 88 regions since one more empty region is added in the construction of the structural connectivity for symmetry. After correction of the diffusion data for eddy-currents and head motions using eddy-correct FSL functions, the Fiber orientation was estimated using Constrained Spherical Deconvolution (Tournier et al., 2007) and improved with Anatomically Constrained Tractography (Smith et al., 2012). For tractography, $2.5 \times 10^6$ fibers were used and, for correction, Spherical-Deconvolution Informed Filtering of Tractograms (Smith et al., 2013) was applied. Summing track counts over each region of the parcellation yielded the adjacency matrix. Here, the AAL2 was employed for brain segmentation leading to 88 brain areas for each patient, see Tab. 2.

2.5 Network Measures

Topological properties of a network can be examined by using different graph measures that are provided by the general framework of the graph theory. These graph metrics can be classified in measures that are covering three main aspects of the topology: segregation, integration and centrality. The segregation accounts for the specialized processes that occur inside a restricted group of brain regions, usually densely connected, and it reveals eventually the presence of a dense neighborhood around a node which results to be fundamental for the generation of clusters and cliques capable to share specialized information. Among the possible measures of segregation, we have considered the clustering coefficient, which gives the fraction of triangles around a node and it is equivalent to the fraction of node’s neighbors that are neighbors of each other as well. In particular the average clustering coefficient $C$ of a network gives the fraction of closed triplets over the number of all open and closed triplets, where a triplet consists of three nodes with either two edges (open triplet) or three edges (closed triplet). The weighted clustering coefficient $C^w$ (Barrat et al., 2004) considers the weights of its neighbors:

$$
C^w_i = \frac{1}{s_i(k_i - 1)} \sum_{j,h} \frac{w_{ij} + w_{ih}}{2} a_{ij}a_{ih}a_{jh}, \tag{7}
$$

where $s_i$ is the node strength, $k_i$ the node degree, $w_{ij}$ the weight of the link, and $a_{ij}$ is 1 if the link $i \rightarrow j$ exists and 0 if node $i$ and $j$ are not connected. The average weighted clustering coefficient $C^w$ is the mean of all weighted clustering coefficients: $C^w = \frac{1}{N} \sum_i C^w_i$.

The measures of integration refer to the capacity of the network to rapidly combine specialized information from not nearby, distributed regions. Integration measures are based on the concept of communication paths and path lengths, which estimate the unique sequence of nodes and links that are able to carry the transmission flow of information between pairs of brain regions. The shortest path $d_{ij}$ between two nodes is the path with the least number of links. The average shortest path length of node $i$ of a graph $G$ is the mean of all shortest paths from node $i$ to all other nodes of the network: $L(G, i) = \frac{1}{N-1} \sum_{j \neq i} d_{ij}$. The average shortest path length of all nodes is the mean of all shortest paths (Boccaletti et al., 2006): $L(G) = \frac{1}{N} \sum_{i \neq j} d_{ij}$.
in a weighted network, the weights represent the distance of a node. If a weight between two adjacent nodes is doubled, their shortest path is cut by half: \( L(G) = \frac{1}{N-1} \sum_{i,j \in N, i \neq j} d_{ij}. \)

Centrality refers to the importance of network nodes and edges for the network functioning. The most intuitive index of centrality is the node degree, which gives the number of links connected to the node; for this measure connection weights are ignored in calculations. In this manuscript, we employ the network measure node strength \( s_i \), which corresponds to the weighted node degree of node \( i \) and equals the sum of all its weights: \( s_i = \sum_{j \in N} w_{ij}. \) Accordingly, the average node strength \( S = \frac{1}{N} \sum_i s_i. \) All finite networks have a finite number of shortest paths \( d_{ij} \) between any pair of nodes \( i, j \). The betweenness centrality \( c_B(s) \) of node \( s \) is equal to all pairs of shortest paths that pass through \( s \) divided by the number of all shortest paths in the network: \( c_B(s) = \frac{\sum_{i,j \in N} d(i,j)s}{d(i,j)}. \) For the weighted betweenness centrality, the weighted shortest paths are used.

### 2.6 EEG and SEEG data

As already discussed in Sec. 2.4, 15 drug-resistant patients, with different types of partial epilepsy accounting for different Epileptogenic Zone (EZ) localizations, were considered. All patients underwent a presurgical evaluation (see Supplementary Tables 3, 4). For each patient a first not invasive evaluation procedure is foreseen that comprises of the patient clinical record, neurological examinations, positron emission tomography (PET), and electroencephalography (EEG) along with video monitoring. Following the non-invasive evaluation, potential EZs are identified by the clinicians. Further elaboration on the EZ is done in a second, invasive phase, which consists of positioning stereotactic EEG (SEEG) electrodes in or close to the suspected regions. These electrodes are equipped with 10 to 15 contacts that are 1.5 mm apart. Each contact is 2 mm of length and 0.8 mm in diameter. Recordings were obtained using a 128 channel DeltamedTM system with a 256 Hz sampling rate and band-pass filtered between 0.16 Hz and 97 Hz by a hardware filter. All patients showed seizures in the SEEG starting in one or several localized areas (EZ), before recruiting distant regions, identified as the Propagation Zone (PZ). Precise electrode positioning was performed by either a computerized tomography or MRI scan after implanting the electrodes.

Two methods were used for the identification of the propagation zone (see Supplementary Table 4). First, the clinicians evaluated the PZs subjectively on the basis of the EEG and SEEG recordings gathered throughout the two-step procedure (non-invasive and invasive). Second, the PZs were identified automatically based on the SEEG recordings: For each patient, all seizures were isolated in the SEEG time series. The bipolar SEEG was considered (between pairs of electrode contacts) and filtered between 1-50 Hz using a Butterworth band-pass filter. An area was defined as a PZ if its electrodes detected at least 30% of the maximum signal energy over all contacts, and if it was not in the EZ. In the following, we call the PZs identified by the subjective evaluation of clinicians PZ\(_\text{Clin}\) and the PZs identified through SEEG data PZ\(_\text{SEEG}\).

### 3 HEALTHY SUBJECTS

#### 3.1 Phase and Bifurcation Diagrams

The analysis of firing rate equations ([4]), performed in ([Montbrió et al., 2015]), has revealed that there are three qualitatively distinct regions, when considering the phase diagram of the system as a function of the mean external drive \( \bar{\eta} \) and synaptic weight \( J \), in absence of external forcing \( (I(t) = 0) \): (1) a single stable node corresponding to a low-activity state, (2) a single stable focus (spiral) generally corresponding to a high-activity state, and (3) a region of bistability between low and high firing rate. In particular, in the
region where the stable focus is observable, the system undergoes oscillatory decay to the stable fixed point. The presence of damped oscillations at the macroscopic level reflects the transitory synchronous firing of a fraction of the neurons in the ensemble. While this behavior is common in spiking neuron models, it is not captured by traditional firing-rate models [Schaffer et al., 2013; Taher et al., 2020].

![Graphs showing equilibrium firing rates](image)

**Figure 1.** A1-A3 Equilibrium firing rates $\langle r^* \rangle$ vs. $\bar{\eta}$ for the up-sweep (blue dots) and down-sweep (orange squares). For each $\bar{\eta} \in [-50, 10]$ in steps of $\Delta \bar{\eta} = 1.5$ the system is initialized using the final state of the previous run and evolves for 2 s after which the average network firing rate in the equilibrium state is determined. Different panels correspond to different $\sigma$ values: $\sigma = 1.5$ (A1), $\sigma = 1$ (A2), $\sigma = 0.5$ (A3). The solid (dashed) black line corresponds to the stable (unstable) equilibria in the single-node case. Maps of regimes as a function of $\sigma$ and $\bar{\eta}$ showing the network average $\langle r^* \rangle$ color coded for up- (B) and down-sweep (C), obtained by following the same procedure as in A1-A3 for $\sigma \in [0, 2]$ in steps of $\Delta \sigma = 0.05$. The black line indicates the single-node map of regimes like in [Montbrió et al., 2015]. Parameter values: $N_{\text{pop}} = 90$, $\tau_m = 20$ ms, $\Delta = 1$, $J_{kk} = 20$, $J_{kl} = 5 \tilde{J}_{kl}$ $\forall k \neq l$.

When considering the multipopulation neural mass model [5], the corresponding phase diagram (shown in Fig. 1B) is qualitatively the same as the one shown in Fig 1 in [Montbrió et al., 2015], since the same attractors are observable. The single node bistability pretty much reflects the hysteretic transition in the network when changing $\bar{\eta}$: This is not surprising since the diagonal elements of the connectivity matrix $J$ are the leading weight components, while the non-diagonal entries, representing inter-connections among the nodes, are much smaller. However inter-connections play a relevant role in determining the minimum $\bar{\eta}$ value required to reach the multistable regime while they are less relevant in determining the maximum $\bar{\eta}$ at which almost all nodes reach the high-activity state.

The bifurcation diagrams shown in panels A1-A3 for increasing $\sigma$ values are obtained by performing an adiabatic analysis along two different protocols: up-sweep and down-sweep. Following the up-sweep protocol, the system’s state variables $r_k, v_k$ are initialized at $\bar{\eta} = -50$ with the values $r_k = 0, v_k = 0$; then the excitability is increased in steps $\Delta \bar{\eta} = 1.5$ until the maximal value $\bar{\eta} = 0$ is reached. At each step, the initial conditions for mean firing rates and mean membrane potentials correspond to the final conditions obtained for the previous $\bar{\eta}$ value. Note that the average firing rate increases for increasing $\bar{\eta}$ values, both for the single node and for the network. Once the maximum $\bar{\eta}$ value is reached, the reverse
procedure is performed, thus following the down-sweep protocol. This time the initial state corresponds to the high-activity state system at $\bar{\eta} = 0$, while the excitability is adiabatically decreased in steps $\Delta \bar{\eta} = 1.5$, until we approach again a low-activity state at $\bar{\eta} = -50$. For both protocols, the investigation of the nature of the dynamics emerging at each time step is done by using the same procedure: the system is simulated for a transient time $T_R = 2$ s, until it has reached a quiescent state, followed by an investigation period $T_W = 2$ s, during which the average values of the firing activity is calculated and the final state is registered.

The transition from low-activity (LA) to high-activity (HA) regime is hysteretic: the system doesn’t follow the same path during the up-sweep and the down-sweep protocol. When the system is initialized in the low activity regime, it remains there until a critical excitability value $\bar{\eta}_{HA}$ is reached. For further increase of the excitability, the average firing rate exhibits a rapid jump to higher values. However, when the system is initialized in the high-activity regime, this regime survives for a large $\bar{\eta}$ interval until it collapses toward a low-activity state at $\bar{\eta} < \bar{\eta}_{LA}$, where $\bar{\eta}_{LA} < \bar{\eta}_{HA}$. There is a considerable difference between the critical excitability values required to lead the system to a high-activity or a low-activity regime and the difference increases for increasing coupling strength $\sigma$. While the up-sweep protocol (blue dots) is well approximated by the bifurcation diagram of the single node, represented in panels A1-A3 by the black (dashed and continuous) curve, this is no more true for the down-sweep protocol, where the coupling plays a role in determining the transition at the multipopulation level (orange squares). This results in different phase diagrams for the two protocols: the maps of regimes is dominated by the low-activity (high-activity) state when following the up-sweep (down-sweep) protocol. Merging together these results we observe that the region of bistability is still identifiable by the original boundaries found for the single node in [Montbrió et al., 2015] (see red curve in panels B, C), even though, for the multipopulation system, the region is wider. The up (down) state stops existing only for few nodes when crossing the curved (vertical) red line for decreasing (increasing) $\bar{\eta}$ values; however the transition from one state to the other turns out to be quite sharp.

### 3.2 Seizure Recruitment in Dependence of Perturbation Site and $\bar{\eta}$

To analyze the response of the multipopulation system to time-varying stimuli, we stimulate one population with a step function $I_S(t)$ of amplitude $I_S = 10$ and duration $t_I = 0.4$ s. The system is initially ($t < 0$) in a bistable regime and set in the low-activity state. We start stimulating a single node for $\bar{\eta} = -9.54$: the perturbed brain area abandons the bistable region due to the applied current and approaches, with damped oscillations, the high-activity state, which is a stable focus (see Fig. 2 A2). When the current is removed, the system converges, showing again damped oscillations, to the new location of the (focus) fixed point, which clearly coexists with the stable node where it was originally placed at $t < 0$.

When the perturbation of a single node has no consequences on the dynamics of the other populations, as shown in Fig. 2 A2, A3), we are in the presence of an asymptomatic seizure, where the activity is limited to the epileptogenic zone (here represented by the stimulated node) and no propagation takes place. For higher excitability values ($\bar{\eta} = -6.3$), the perturbation of a single node gives rise to a different response dynamics. In this case other brain areas are “recruited” and not only the perturbed node, but also other populations reach the high-activity regime by showing damped oscillations (see panels B2, B3). In terms of epileptic seizures, the seizure originates in the EZ (as a results of the stimulation) and propagates to the PZ, identified by the other regions where fastly propagates the oscillatory activity. The recruitment of the regions in the propagation zone can happen either by independent activation of the single areas, or by activating multiple areas at the same time, until the propagation involves almost all populations (generalized seizure).
Figure 2. Spectrograms of mean membrane potentials for subject sc0. (A1-B1) Stimulation current $I^k_S$, (A2-B2) population firing rates $r_k$ and (A3-B3) mean membrane potentials $v_k$ for the EZ (orange) and other populations (black). The blue curves show the network average firing rate and membrane potential. Non-stimulated node dynamics is plotted as transparent gray curves: some of the nodes adapt their voltage to the stimulation of the EZ and change during stimulation. However they do not reach the high-activity state regime. (A4-B4) Spectrogram of the network average membrane potential and (A5-B5) of the $v_k$ of the EZ. Column A shows an asymptomatic seizure event for $\bar{\eta} = -9.54$, column B a generalized seizure for $\bar{\eta} = -6.3$. In both cases the EZ node 46 is stimulated. Parameter values: $N_{\text{pop}} = 90$, $\tau_m = 20$ ms, $\Delta = 1$, $J_{kk} = 20$, $\sigma = 1$, $J_{kl} = 5J_{kl}$ $\forall k \neq l$.

The transition of a single population to the high-activity regime, upon stimulus onset, is characterized by a transient activity in the $\delta$ band ($< 12$ Hz) and a sustained activity in the $\gamma$ band (40-80 Hz), present for all the duration of the stimulus, as shown in panels A4-A5, where are reported the spectrograms of the mean membrane potentials averaged over the network population and for the single stimulated population respectively. When more populations are recruited at higher excitability values, in addition to the former activity, it is possible to observe $\gamma$ activity at higher frequencies (see panels B4-B5). High-frequency oscillations, between 80 and 500 Hz, can be recorded with EEG and reflect the seizure-generating capability of the underlying tissue, thus being used as markers of the epileptogenic zone (Jacobs et al., 2012). Moreover the $\delta$ band is clearly associated to the recruitment mechanism of a single population.
leading to the appearance of the same frequency in the spectrogram. Similar results have been obtained for all the other investigated subjects (results not shown).

Figure 3. Number of recruited brain areas as a function of the excitability parameter $\bar{\eta}$ for 5 exemplary healthy subject connectomes A-E. Color coding is the following: grey corresponds to the asymptomatic threshold (one area seizing); red represents 90 seizing areas (generalized threshold); light blue to purple indicate intermediate recruitment values, white marks no recruitment. When performing a vertical cut, all nodes are characterized by the same $\bar{\eta}$ for panels (A1-E1). At the contrary, in panels (A2-E2), $\bar{\eta}_G$ represents the mean value of a Gaussian distribution with standard deviation 0.1. Therefore, when perturbing one brain area at a time, excitabilities are distributed and not uniform in the latter case; the results are averaged over 10 repetitions with different Gaussian excitability distributions. A), B), C), D), and E) correspond to patients 0, 4, 11, 15, and 18. Parameters: $N = 90$, $\Delta = 1$, $\sigma = 1$, $I_S = 10$, $t_I = 0.4$ s.

In the following we report a wide analysis of the impact of the perturbation site on the recruitment effect, for different excitability values. In particular we stimulate one population at a time with a step function $I_S(t)$, whose amplitude $I_S = 10$ and duration $t_I = 0.4$ s are kept fixed during the analysis. For each stimulated area, we count the number of recruitments, i.e. the number of populations that pass from the low-activity state to the high-activity state following the single-node stimulation. All the 90 brain areas of the healthy subject connectomes are stimulated, one after the other, and we repeat the procedure varying $\bar{\eta}$ in a range $[-15, -4]$, with steps of $\Delta \bar{\eta} = 0.1$. The results for five exemplary subjects are shown in Fig. 3 (A1)-E1).

If the perturbed area jumps back to the low-activity state when the external input current is removed, no brain area results in the high-activity state: the color code corresponding to this case is white. If the perturbed area remains in the high-activity state without recruiting other areas, we are in presence of an asymptomatic seizure, which corresponds to the color code grey. For every further recruited brain area, the color code changes from light blue to purple. If all brain areas are recruited, we observe a generalized seizure (coded as red). For $\bar{\eta} < -9$, most of the perturbed brain areas do not leave the fixed point at low activity when the perturbation ends while, for $\bar{\eta} \approx -9$, we generally observe asymptomatic seizures for
all the subjects and for most of the perturbation sites. For increasing $\bar{\eta}$ values, the probability of larger recruitments increases and the system exhibits generalized seizures for $\bar{\eta} > -6$. However, some notable differences between brain areas and among the different subjects are observable. Brain area 72, for example, corresponding to the rh-CAU, exhibits asymptomatic seizures at $\bar{\eta} > -11$ for most of the patients, thus suggesting that the rh-CAU is much more likely to favour asymptomatic seizures than other brain areas. On the other hand, some brain areas are less likely to cause generalized seizures, when stimulated, than others: Brain area 40, for example, the rh-PHIP, causes no generalized seizure for any $\bar{\eta} > -5$. Note that, for very large $\bar{\eta}$ values, the system doesn’t find itself anymore in the bistability regime and enters the stable focus regime corresponding to high firing rate. This usually happens for $\bar{\eta} \in [-5.7, -4.9]$, depending on the subject.

The scenario remains unchanged when we take into account heterogeneous excitabilities, as shown in Fig. 3[A2]-E2). In this case the populations are stimulated one after the other, keeping fixed the mean value $\bar{\eta}_G$ of a Gaussian distribution, thus mimicking the variability present in a real brain. As before, $\bar{\eta}_G$ is varied in a range $[-15, -4]$, keeping fixed the standard deviation of the Gaussian distribution, that we set to 0.1. For larger standard deviations, most of the nodes enters the stable focus characterized by a high-activity regime, thus impeding the analysis of the impact of the external perturbation. The shown results are obtained averaging over 10 Gaussian distribution realizations of the $\bar{\eta}$ parameter; slightly more variability becomes apparent especially when considering the threshold in $\bar{\eta}$ to observe generalized seizures.

An overview over all the investigated subjects is possible when looking at Fig. 4[A), where is reported the average, over all subjects, of the data shown in Fig. 3[A1]-E1) for five exemplary subjects only. The average operation smears out the transition contours and, while the region of generalized seizures shrinks, it becomes wider the region of accessibility of partial seizures, where a small percentage of nodes ($\sim 20\%$) are recruited. In panel B are reported the smallest $\bar{\eta}$ values for which an asymptomatic seizure occurs, and the smallest $\bar{\eta}$ values for which a generalized seizure occurs, for all the stimulated nodes and for all the subjects. The $\bar{\eta}$ values that identify the thresholds for asymptomatic and generalized seizures, averaged over all the subjects, are identified, for each brain area, as blue and red circles, respectively. Grey dots indicate the individual thresholds for each of the 20 subjects. Across all brain areas, the averaged asymptomatic and generalized seizure thresholds are $\bar{\eta}_{asy} = -9.36 \pm 0.43$ and $\bar{\eta}_{gen} = -6.04 \pm 0.38$. Brain areas 72, 73, 67, and 3 have lower thresholds for asymptomatic seizures, areas 40, 86, and 82 have larger thresholds for generalized seizures and do not fall within a standard deviation. The variability in the response among the different areas is more evident for $\bar{\eta}_{gen}$ values with respect to the $\bar{\eta}_{asy}$ ones: the threshold values to obtain an asymptomatic seizure are very similar among the areas and among the subjects, while the threshold values to obtain a generalized seizure strongly depend on the stimulated area and on the subject.

### 3.3 The Role Played by Brain Area Network Measures on Enhancing Recruitment

As shown in Fig. 4[B), the asymptomatic seizure threshold value does not vary significantly among the subjects and among the brain areas; it mainly occurs in the range $\bar{\eta}_{asy} \in [-10, -9]$, with just few nodes (72, 73, 67, and 3) showing smaller $\bar{\eta}_{asy}$ values. Since each brain area is characterized by its own network measure, the first hypothesis that we aim testing, is the role played, on the identification of the threshold, by the different network measures. In particular we investigate the dependency of the threshold for asymptomatic seizures on the node strength, clustering coefficient, shortest path length, and betweenness centrality of the corresponding brain area, as shown in Fig. 5. A very strong correlation between asymptomatic threshold and node strength becomes apparent: Brain areas that are strongly connected need a smaller excitability to pass from the low-activity to the high-activity regime (panel A).
Figure 4. A) Number of recruited brain areas as a function of the excitability parameter $\bar{\eta}$, as shown in Fig. 3 A1)-E1), averaged across all subjects. B) $\bar{\eta}$ threshold values for asymptomatic and generalized seizures. Grey dots show the thresholds for each brain area and each patient. Blue and red dots show the averaged asymptomatic and generalized seizure thresholds across all subjects. The blue and red cross at the bottom show the average value and its standard deviation for both thresholds across all patients and across all areas. Parameters as in Fig. 3.

The same holds true for the clustering coefficient, even though the relationship is less sharp (panel B). Moreover it is possible to observe a direct correlation between $\bar{\eta}_{asy}$ and shortest path length (i.e. shortest is the path smallest is the threshold value), while betweenness is smaller for higher threshold values (panels C and D respectively).

Figure 5. Threshold for asymptomatic seizures as a function of node measures: A) Node strength, B) clustering coefficient, C) average shortest path length, D) betweenness centrality. The relationship between $\bar{\eta}_{asy}$ and the corresponding network measure is performed independently over all 90 brain areas, for each subject, and then averaged over all 20 subjects. Parameters as in Fig. 3.

When considering the threshold for generalized seizure, we face a higher variability among different nodes (as shown in Fig. 4B, $\bar{\eta}_{gen}$ varies mainly between $-6.5$ and $-5.5$). The dependency of $\bar{\eta}_{gen}$ on the node strength reveals a strong correlation: Areas with very small node strengths are characterized by large thresholds and are less likely to cause generalized seizures. On the other hand, for large node strengths, $\bar{\eta}_{gen}$ saturates at a value $\approx -6.5$ (see Fig. 6 A)). The clustering coefficient, shown in Fig. 6 B), shows a similar relationship as the node strength, even though more scattered. This is not surprising since
Figure 6. Threshold for generalized seizures as a function of node measures: A) Node strength, B) clustering coefficient, C) average shortest path length, D) betweenness centrality. For each panel, the thresholds are calculated for all 90 brain areas and averaged over all 20 patients. Parameters as in Fig. 3.

Node strength and clustering coefficient are strongly correlated with each other (the Pearson Correlation coefficient in this case is $r = 0.75$, as shown in Fig. 1 of the Supplementary Material), thus explaining the similarity between the analyses reported in panels A) and B). Moreover, regarding the integration measure, it turns out that the average shortest path length correlates positively with the threshold for generalized seizure (see Fig. 6 C)). Brain areas that are characterized, on average, by a short path to all the other areas are more likely to cause generalized seizures. Finally, the betweenness centrality correlates negatively with the generalized threshold (panel D). This means that brain areas that are crossed by many shortest path lengths (large betweenness centrality) are more likely to cause generalized seizures. For increasing values of node strength, clustering coefficient and betweenness centrality, we observe a saturation toward $\bar{\eta}_\text{gen} \approx -6.5$, that corresponds to the critical excitability value, during the upsweep simulation, at which the system jumps to the high-activity state (Fig. 1 A2).

To better explore the causal mechanisms of brain function and understand the sequential mechanism of seizure recruitment, we investigate the timing at which different brain areas are recruited. To ensure complete recruitment of all nodes, the excitability parameter $\bar{\eta}_k$ of the perturbed brain area $k$ is set to the threshold value $\bar{\eta}_k^\text{gen}$ (for $k = 1, ..., 90$). The results shown in Fig. 7 are obtained by averaging over different perturbed nodes and different subjects: for each subject, all brain areas are subsequently stimulated with an external step function $I_S(t)$ of amplitude $I_S = 10$ and duration $t_I = 0.4$ s; for each stimulated area the recruitment time of all the other areas is registered. The stimulated brain area stands in for the EZ. The brain areas are sorted by their recruitment times in ascending order and, following the same order, are registered the different node measures of the corresponding areas. The weight and shortest path values taken into account are divided in two types: those related to the nodes outgoing the EZ, and those related to the connections between the recruited area and all the other nodes except the EZ. Therefore, for the first case, if a certain recruited area is not directly connected to the EZ, its corresponding weight is equal to 0. The values for recruitment time (panel A), weight of a connection between a single area and the EZ (panel B) and shortest path (panel C) are finally obtained averaging over all the stimulated nodes and all the subjects (i.e., the average is performed over 1800 simulations across all 90 brain area perturbations times all 20 subject). The same average procedure has been employed to obtain the data shown in panels D-G. However, in this case, the node measures are evaluated over all the connections of the recruited node minus the connection to the EZ. While ignoring the link to the excited area (EZ), are reported the overall network measure for connection weights (panel D), clustering coefficient (panel E), shortest path (panel F), betweenness centrality (panel G).
Gerster et al.

Figure 7. A) Recruitment times reported in descending order: Brain area 1 is the brain area which is recruited first and brain area 90 is the last recruited brain area. B) Connection weights between the recruited brain area and the EZ, ordered according to their recruitment time, thus following the indexing of panel A). C) Shortest path between the recruited area and the EZ, ordered according to their recruitment time. D) Connection weights between the recruited brain area and all the nodes except EZ, ordered according to their recruitment time. E) Clustering coefficient between the recruited brain area and all the nodes except EZ, ordered according to their recruitment time. F) Shortest path between the recruited area and all the other nodes except EZ, ordered according to their recruitment time. G) Betweenness centrality between the recruited brain area and all the nodes except EZ, ordered according to their recruitment time. The excitability $\bar{\eta}_k$ is set to the subject-specific threshold $\bar{\eta}_k^{gen}$, according to Fig. 3 B) for each patient separately. Data are averaged over all subjects and all the stimulated areas. Parameters: $N = 90$, $\Delta = 1$, $\sigma = 1$, $I_S = 10$, $t_I = 0.4$ s as in Fig. 3.

On average, the first recruited brain area (labelled as 1) is connected to the EZ with a weight equal to 0.25 (1/4 of the maximum possible weight) and it is characterized by an average shortest path length to the EZ of less than 4.7. Moreover the area is recruited within an average time of less than 156 ms (calculated after the onset of the external perturbation current). However the first recruited area has, not only the strongest weight and the shortest path to the EZ but it also has, in general, the largest node strength, largest clustering coefficient, shortest average path length and largest betweenness centrality. Clearly, the seizure spreads rapidly along the brain areas with strongest connection weights outgoing from the EZ; to the stronger weights are associated the shortest paths from the EZ. More in general, a region well connected is a region well recruited; this is related to the log-normal distribution of the weights (see Supplementary Fig. 2): few connections per node have a strong weight, thus allowing for fast recruitment. Note that the results for one exemplary subject and just one perturbed brain area per time (i.e. not averaged over all the brain areas and over all subjects) are comparable, even though the corresponding relationships are characterized by more variability (data not shown).

If we vary the strength of the perturbation current, the recruitment time will vary accordingly, decreasing for increasing $I_S$. In particular in Fig. 8 we show an exemplary case, obtained from the stimulation of one brain area (45), for a specific subject (results are similar for other trials). Irrespectively of the recruitment order, the time needed by the first ten recruited brain areas to pass from the low-activity to the high-activity state decreases slightly for increasing current strengths. However, this decrease reaches a saturation at a current value $I_S \approx 40$ already. The order of recruitment varies little: we observe some exchanges between the 4-th and 5-th and between the 9-th and 10-th recruited areas. For example, for a current strength
Gerster et al.  
Patient-specific network connectivity

$I_S = 15$, the 9-th recruited area (dark blue circles) gets recruited earlier than the 10-th area (pink dots) while, for very strong currents ($I_S = 100$), the 9-th area gets recruited latest. On the other hand we do not observe a significative change in the recruitment time and order if we increase the amplitude of the external current $I_S$ (see Supplementary Fig. 3).

Figure 8. Recruitment times of the first 10 recruited areas as a function of the input current $I_S$. The strength of the input current is varied between 0 and 100 on the x-axis. The order of the recruitment is color coded for each current strength and it changes slightly with different current strengths. Parameters: $N = 90$, $\Delta = 1$, $\sigma = 1$, $t_I = 0.4$ s, $\bar{\eta} = -6$, stimulation site: brain area 45 of subject 0.

4 EPILEPTIC PATIENTS

4.1 Phase and Bifurcation Diagrams

Following the analysis shown in Sec. 3.1 we present here the phase and bifurcation diagrams for the multipopulation neural mass model, where we employ the structural connectivity matrices of epileptic patients. As detailed before, the bifurcation diagrams shown in Fig. 9 (A1)-A3) for increasing $\sigma$ values are obtained by performing an adiabatic analysis along the up-sweep and down-sweep protocols. The system is initialized at $\bar{\eta} = -50$ with state variables $r_k = 0$, $v_k = 0$, then it is evolved until it has reached a quiescent state; finally its final state is registered in terms of average firing rate and average membrane potential. The successive step consists in increasing the excitability value and performing the same analysis: $\bar{\eta}$ is increased in steps $\Delta \bar{\eta} = 1.5$ until the maximal value $\bar{\eta} = 0$ is reached. At each step, the initial conditions for mean firing rates and mean membrane potentials correspond to the final conditions obtained for the previous $\bar{\eta}$ value. Equivalently, when performing the down-sweep protocol, the system is initialized in the high-activity state system at $\bar{\eta} = 0$, then the excitability is adiabatically decreased in steps $\Delta \bar{\eta} = 1.5$, until we approach again a low-activity state, registering at each step average firing rate and average membrane potential of the multipopulation system.

The transition is hysteretic and, as shown for the healthy subjects, $\bar{\eta}_{LA} < \bar{\eta}_{HA}$. However in this case, the width of the hysteretic transition is bigger, especially for larger $\sigma$ values. The width of the hysteretic transition can be translated in terms of the extension of the bistability region in the bifurcation diagram (see

This is a provisional file, not the final typeset article
Figure 9. Phase and bifurcation diagrams for patient FB. A1-A3 Equilibrium firing rates $\langle r^* \rangle$ vs. $\bar{\eta}$ for the up-sweep (blue dots) and down-sweep (orange squares). For each $\bar{\eta} \in [-50, 10]$ in steps of $\Delta \bar{\eta} = 1.5$ the system is initialized using the final state of the previous run and evolves for 2 s after which the average network firing rate in the equilibrium state is determined. Different panels correspond to different $\sigma$ values: $\sigma = 1.5$ (A1), $\sigma = 1$ (A2), $\sigma = 0.5$ (A3). The solid (dashed) black line corresponds to the stable (unstable) equilibria in the single-node case. Maps of regimes as a function of $\sigma$ and $\bar{\eta}$ showing the network average $\langle r^* \rangle$ color coded for up- (B) and down-sweep (C), obtained by following the same procedure as in A1-A3 for $\sigma \in [0, 2]$ in steps of $\Delta \sigma = 0.05$. The black line indicates the single-node map of regimes like in (Montbrió et al., 2015). Parameter values: $N_{\text{pop}} = 88$, $\tau_m = 20$ ms, $\Delta = 1$, $J_{kk} = 20$, $J_{kl} = 5\tilde{J}_{kl}$ $\forall k \neq l$.

Fig. 9 B, C), which turns out to be slightly bigger than before, thus suggesting that, for epileptic patients, the high-activity state can be reached for smaller excitability values than for the healthy subjects.

While the phase diagram is obtained investigating the system in absence of the external forcing, in the following we analyze the response of the multipopulation system to time-varying stimuli. We stimulate one population with a step function $I_S(t)$ of amplitude $I_S = 10$ and duration $t_I = 0.4$ s. The system is initially $(t < 0)$ in a bistable regime and set in the low-activity state. For small $\bar{\eta}$ values ($\bar{\eta} = -14$), when a single node is stimulated, it abandons the bistable region due to the applied current and approaches, with damped oscillations, the high-activity state, which is a stable focus (see Fig. 10 A2, A3). The other brain areas, non perturbed by the transition of the stimulated node, remain in the low-activity regime. For higher excitability values ($\bar{\eta} = -7.5$), the perturbation of a single node gives rise to a cascade of recruitments, where other brain areas, initially not perturbed, reach the high-activity regime by showing damped oscillations (panels B2, B3). With respect to the recruitment features observed in Fig. 2, we observe here a faster emergence of the generalized seizure: once a brain area is stimulated, the other react, in substantial number, quite immediately.

Looking at the spectrograms, the transition of the stimulated population to the high-activity regime is characterized by a transient activity at low frequency ($< 20$ Hz) and a sustained activity in the $\gamma$ band (50-180 Hz), observable for all the duration of the stimulus, as shown in panel A5, where is reported the spectrogram for the single stimulated population. Regarding the spectrogram of the mean membrane potentials averaged over the network population (panel A4), it turns out that the low frequency activity in
Figure 10. Spectrograms of mean membrane potentials for patient FB. (A1-B1) Stimulation current $I_{S}^k$, (A2-B2) population firing rates $r_k$ and (A3-B3) mean membrane potentials $v_k$ for the EZ (orange) and other populations (black). The blue curves show the network average firing rate and membrane potential. (A4-B4) Spectrogram of the network average membrane potential and (A5-B5) of the $v_k$ of the EZ. Column A shows an asymptomatic seizure event for $\bar{\eta} = -14$, column B a generalized seizure for $\bar{\eta} = -7.5$. In both cases the EZ node 46 is stimulated. Parameter values: $N_{pop} = 88, \tau_m = 20 \text{ ms}, \Delta = 1, \sigma = 1.25, J_{kk} = 20, J_{kl} = 5J_{kl} \ \forall k \neq l$.

the $\delta, \theta$ bands is present, while the activity at high frequency simply reflects the activity of the stimulated area. When recruitment events are present at higher excitability values, it is possible to observe $\gamma$ activity at higher frequencies (see panels B4-B5), which is enhanced with respect to the situation where an asymptomatic seizure is present. Moreover, comparing the spectrograms in Fig. 10 and those reported in Fig. 2 we see that the activity takes place at higher frequency ranges in epileptogenic patients and the activity is mainly concentrated in the EZ. The last statement may be qualified, however, by recent studies proposing high frequency oscillations (80–500 Hz) recorded not only at seizure onset but also between seizures (the interictal period), as a putative new marker of the epileptogenic focus [Jacobs et al., 2012]. More specifically fast cortical ripples superimposed to interictal epileptiform discharges were correlated with the seizure onset zone and primary propagation area in neocortical epilepsy [Khadjevand et al., 2017]. Moreover neocortical ripples also were found to be more specifically confined to the seizure onset and propagation regions, and thus a better marker compared to interictal epileptiform discharges alone [Wang, 2012].
et al. (2013). High frequency oscillations, shown in Fig. B4, B5, are much more frequent in the seizure onset zone than outside, where they are often totally absent. The rather empty spectrograms of mean membrane potentials for patient FB are a result of rather rapid recruitment of a majority of nodes, thus giving rise to a strong signal change, immediately upon recruitment, which suppresses the rest of the signal in the spectrogram. At the same time the damped oscillations are all compressed within a narrow time window, and not very elongated in time as it happens for healthy subjects (see Fig. 2). In other words, if the generalized seizure is rapid, all the signals overlap, and this is especially clear looking at the strong low frequency bands. A fast generalized seizure event, in absence of high frequency oscillations outside the EZ, can be obtained for healthy subjects only increasing the excitability parameter: for higher $\bar{\eta}$ values, the recruitment is more sudden, as shown in the Supplementary Fig. 22.

### 4.2 Temporal Recruitment of Clinically and SEEG Predicted Propagation Zones

![Recruitment times of seizing brain areas for all epileptic patients.](image)

**Figure 11.** Recruitment times of seizing brain areas for all epileptic patients. The boxplots consist of the recruitment times of all brain areas for each patient. Patients are identified according to their initials on the y-axis. The median is represented as a green vertical line, the boxes contain the second and third quantile of the distribution, and the whiskers have 1.5 the length of the boxes. The grey dots represent the recruitment times for each brain area. The red $\times$ shows the recruitment of a brain area clinically predicted to be part of the propagation zone $\text{PZ}_{\text{Clin}}$. The blue + represents the recruitment of a brain area which is part of the propagation zone according to the SEEG measurements $\text{PZ}_{\text{SEEG}}$. The recruitment time, reported on the x-axis, identifies the time needed by a brain area to jump to the high-activity regime after the application of the perturbation current. Parameters: $N_{\text{pop}} = 88$, $\Delta = 1$, $\sigma = 1.25$, $I_S = 10$, $t_I = 0.4$ s, $\bar{\eta} = -7.5$ (except for patients AC ($\bar{\eta} = -6$) and ML ($\bar{\eta} = -6.5$)).

A general overview on the recruitment times of all brain areas, for all patients, is shown in Fig. 11. As perturbation sites, the EZs, identified by clinical doctors via presurgical invasive evaluation, are used for all
patients. The perturbation current is applied, to each perturbation site, in correspondence of the dashed vertical black line. The parameters are identical for almost all patients and are chosen such that at least 90\% of the brain areas are recruited while avoiding the stable focus regime. For each patient (identified via his/her initials on the y-axis), the recruitment time of each brain area is reported: The grey dots represent the time values for each brain area. Superimposed on the grey dots are red $\times$ and blue $+$ marks that identify the brain areas belonging to the PZ, according to the non invasive ($\text{PZ}_{\text{Clin}}$) or invasive ($\text{PZ}_{\text{SEEG}}$) presurgical evaluation, respectively. The average recruitment time is identified, for each patient, by a green vertical line, while the boxes contain the second and third quantile of the distribution, and the whiskers have 1.5 the length of the boxes. For all patients the predicted propagation zones turn out to be the first recruited brain areas. However the temporal dynamics vary for all patients, with GC and AC having late recruitments.

Looking at the first ten recruited brain areas for each patient (reported in detail in the Tables 5-7 in the Supplementary Material) we notice that most of the areas, identified by clinicians as belonging to the PZ, are actually recruited. For patients CV, ET, FB, IL, SF all the areas belonging to $\text{PZ}_{\text{Clin}}$ are recruited among the first ten recruitments in our numerical simulations, while the same holds true for patients CJ, CM, FB if we consider the area identified by the stereotactic EEG analysis as belonging to the propagation zone ($\text{PZ}_{\text{SEEG}}$). In general a large number of the first ten recruited areas, as revealed by our simulations, coincides with the areas that are supposed to be crucial in the seizure spreading according to the medical doctors (e.g. for patients CJ, CM, JS, PC, PG, RB).

To evaluate the dependence of the shown results on the chosen parameters, with the idea in mind of going towards a more biologically realistic framework, we have repeated the previous numerical experiment by employing a random Gaussian distribution of the excitability parameter $\bar{\eta}$ (see Fig. 12). The distribution is centered in $\bar{\eta}_0 = -7.5$ with standard deviation 0.1 for all patients except AC and ML. For the latter patients it has been necessary to use a stronger excitability value in order to get a sufficient number of recruitments when the EZ is stimulated. In all cases the results are averaged over 10 different random realizations of this distribution. For larger standard deviations than the one employed, the system would frequently enter the stable focus regime, highlighting the system sensitivity to small parameter changes. However, for the chosen distribution, the results are comparable with the ones obtained with a $\delta$-peaked $\bar{\eta}$ distribution, shown in Fig. 11. For patients CJ, CM, CV, ET, FB, IL the predicted propagation zones are always the first ones to be recruited. Moreover most of the areas are usually recruited in the first half of the recruitment process, fastly increasing in number, once the areas in the propagation zones have been recruited (thus giving rise to a peak in the histogram). As a general remark, view the distributed nature of the excitabilities, recruitment events at longer times with respect to the former case with a $\delta$-peaked $\bar{\eta}$ distribution may now take place.

For patients with many nodes in the EZ the recruitment process may result to be more complex, as it happens for patients RB and JS whose histograms are less peaked and widely distributed. However this cannot be taken as a general rule, since comparable histograms are obtained for patients PG (1 node in the EZ) and GC (2 nodes in the EZ), while for SF and PC (with both 4 nodes in the EZ) the histograms result to be very peaked, thus denoting a fast recruitment process of most of the nodes. This can be justified in part by the fact that each patient has a specific connectome with peculiar characteristics and in part by the analysis that we have proposed by choosing similar $\bar{\eta}$ values for all the patients. In this way we have preferred to have a general look on the multiple self-emergent dynamics in a group of patients, instead of fine-tuning the excitability parameter in order to obtain similar collective behaviors. What we observe here is strictly related to what we have presented in Sec. 4.1 regarding Fig. 10: Fast generalized seizure events...
Figure 12. Histograms of recruitment times for all epileptic patients. For each patient (identified by his/her initials), the recruitment times of all the brain areas are collected, once the EZ is stimulated. The EZ is chosen according to the presurgical evaluation (see Table 4 of the Supplementary Material) and vary from one patient to the other. Parameters as in Fig. 11 except for $\bar{\eta} = -6.5 \pm 0.1$ (for AC $\bar{\eta} = -6 \pm 0.1$, for ML $\bar{\eta} = -6.5 \pm 0.1$). Results are averaged over 10 repetitions of different random Gaussian distributions.

Moreover, for one exemplary patient, CJ, we show in detail the impact of different random Gaussian distributions on the recruitment times of the brain areas (see Fig. 13). In particular space-time plots and histograms are shown for 6 different realizations of random Gaussian distributions, all centered in $\bar{\eta}_0 = -7.5$ with standard deviation 0.1. Due to the analogy among the results obtained for 10 different realizations of Gaussian distributions, we have considered to be sufficient showing just a part of them, without loss of generality. Spacetime plots of the average firing rates (panels A1-F1) give an immediate visualization of the recruitment events for each brain area and the pattern of recruitment does not change substantially for different realizations of the excitability distributions. The EZ is localized in the area lh-LOCC, that corresponds to the node 20: The firing rate activity of this node increases immediately
Figure 13. Recruitment times for patient CJ obtained for 6 different random Gaussian distributions of $\bar{\eta}$. (A1-F1) Spacetime plots of the average firing rates of all brain areas. (A2-F2) Histograms of the recruitment times. Red (blue) bins identify those recruited area that belong to $PZ_{Clin}$ ($PZ_{SEEG}$). (A3-F3) Cumulative histograms of the recruitment times. Purple bin: EZ. Red bins: first 10 recruited areas. Parameters as in Fig. 11.

after the stimulation, thus giving rise to the recruitment mechanism. The brain areas in the PZ are fastly recruited: In general the first 10 areas are always recruited in less then 0.1 s (panels A3-F3), followed by a continuous increase of the recruited nodes. Finally it is worth noticing that the first recruited areas correspond to those predicted clinically (panels A2-F2).

4.3 Relationship Between DTI Network Structure and Temporal Seizure Recruitment

In order to understand the mechanism underlying the recruitment events, we evaluate the relationship between the network structure, in terms of topological measures, and the recruitment times of the first 10 recruited brain areas. For simplicity, we consider patients with only one brain area in the EZ and we report, in Fig. 14 the EZ (purple dot) and the first 10 recruited areas in a graph representation. The first recruited areas are ordered according to their recruitment times in clockwise order. Moreover we indicate in blue the areas belonging to the PZ, as identified according to the presurgical invasive evaluation ($PZ_{SEEG}$). Black lines identify the weighted connections between all areas and their thickness is proportional to their weight. The sizes of the circles representing each brain area are proportional to their inverse recruitment...
Figure 14. Graph plot of the first 10 recruited areas, ordered clockwise according to their recruitment times. Node circle size corresponds to the inverse recruitment time (A1-D1), to the inverse shortest path length to the EZ (A2-D2) and to the connection strength to the EZ (A3-D3). The purple dot identifies the EZ and its size remains fixed. Blue dots distinguish a recruited area to belong to the PZ\textsubscript{SEEG}, i.e. the PZ identified according to the presurgical invasive evaluation. Results are obtained for patients CJ (panels A1-A3), CM (panels B1-B3), FB (panels C1-C3), PG (panels D1-D3). Parameters as in Fig. 11.

Since in (A1-D1) the node size is proportional to the inverse recruitment time, large circles indicate early recruitment while small circles indicate late recruitments: Hence the circles become clockwise smaller. In panels (A2-D2), the node size is proportional to the weight connecting each area to the EZ and it turns out that, for all patients, the first recruited area has the strongest connecting weight. However, after a few recruitments this does not hold true anymore. There are many examples in which areas with a strong weight to the EZ (see e.g. area 85 for patient PG) are recruited much later than areas with very small weights (e.g. area 67 for PG). The seizure propagates as a chain reaction and, therefore, the strongest connecting weight to the EZ is only decisive for the very first recruited area. Later, strong connections to other early recruited areas play a decisive role, as it is the case for area 67 in PG which has a weak connection weight to the EZ.

However, through its strong connection to area 61, its weighted shortest path length to the EZ is quite short, thus meaning that the weighted shortest path length to the EZ cannot be underestimated in order to find the recruitment ordering. Indeed, in (A3-D3) one can see the good predictability of the shortest path: the node size, proportional to the inverse shortest path length to EZ, decreases in general with later recruitment. This is expected, given the fact that the average shortest path to the EZ considers all connections in the network, not just the connections subgraph outgoing the EZ. An example of the high predictability of the shortest
path is given by the node 38 in patient CJ, which has a shorter path length to the EZ than node 18. Node 38 is recruited before node 18 irrespectively of its strong connection to node 16 and a connection strength to the EZ comparable with the one of node 38.

For later recruitments, the prediction becomes even more difficult because one needs to account for the temporal order of the seizing brain areas. As shown before, the area which is first recruited, is the one with the strongest connection to the EZ. However, depending on the strength of the connection, the recruitment time changes and it increases for decreasing strength. In the case of patient CJ the recruitment of the second area is determined, more by the strength of the connections to the EZ (i.e. area 20) than by the connection to area 16, while, for the recruitments of the third and forth areas, are fundamental the strong connections of node 18 to 16 and of node 17 to 38, i.e. the first and second recruited nodes. On the other hand, when the first recruited areas have strong connections to the EZ, as for example area 74 in patient FB, the successive recruitments are strongly influenced by the the first recruited area, whose outgoing graph reveals areas that are recruited with high probability. Thus the connection to area 74 turns out to be, for the second, third, and fourth recruitment almost as important as the connection to the EZ (i.e. area 76). Finally, if we compare two late recruited areas that are characterized by the same shortest path length to the EZ, but with a path to the EZ that crosses very different nodes, we observe that the area with the path going through earlier recruited nodes is recruited earlier. The longer the seizure propagates, the less important the shortest path length to the EZ becomes and the more important the path lengths to other recruited nodes become. This underlines the difficulty of predicting the seizure propagation in complex networks.

To confirm the importance of the shortest path length and the strength of the connections outgoing the EZ in determining seizure recruitments, we report in Fig. 15 the recruitment time values as a function of the shortest path and the connection weights for the patients with a single node as EZ (panels A, B) and for all 15 epileptic patients (panels C, D). While in panel B the recruitment time is plotted over the logarithm of the weight, in panel C (D) the values of the recruitment time, plotted as a function of the shortest path (connection weight), are ordered according to their recruitment order. In particular the order for recruitment, shortest path, and weight to EZ is ascending from small values to large values. This means that, in panel D, the areas with the strongest weights (87th, 86th, etc.) correspond to the areas that are recruited earliest (1st, 2nd, etc.). The ordering has been preferred to the specific values of the shortest path and connection weight when reporting data for all 15 patients, in order to obtain a better visualization. For patients CJ, CM, PG, FB, the recruitment time grows almost linearly with the shortest path, while it decreases for increasing weights. This analysis is confirmed in Fig. 23, reported in the Supplementary Material, where a regression fit is performed over the data shown in panel A, thus underlying the approximately linear relationship between the shortest path length and the recruitment time for larger $t_{reg}$. The relationship is not anymore so evident when we consider different cases of Ezs, that are composed of more that one area. However, in this case, it is still possible to affirm that the earliest recruitments are associated with the shortest path lengths and the strongest weights, while the nodes corresponding to $\text{PZ}_{\text{SEEG}}$ or $\text{PZ}_{\text{Clin}}$ that, according to our simulations, were recruited late, have very long shortest path lengths to the Ezs or very small weights.

In general the recruitment mechanism is not completely defined by the shortest path length and the connection weight, therefore it is not possible to match the pre-surgical predictions in terms of $\text{PZ}_{\text{SEEG}}$ and $\text{PZ}_{\text{Clin}}$ if we try to identify the nodes belonging to the PZ by calculating the first recruited nodes according to their shortest paths length or their connection weights. In particular it turns out that the $\text{PZ}_{\text{SEEG}}$ areas are well predicted by the investigated model if the shortest path length between the predicted PZ and the EZ is short, as shown in Fig. 16A). However, for patients GC and JS, the recruitments of the nodes belonging to $\text{PZ}_{\text{SEEG}}$ happen much later when compared to brain areas of other patients with a similar
Figure 15. Relationship between network measure and recruitment time for four patients with one EZ: A) Shortest path to EZ; B) Logarithmic value of the weight to EZ. In A) all four EZs are shown at (0, 0) while in B) the EZs are omitted. The recruitment time is calculated, in seconds, after the perturbation current has started. In C), D) the recruitment time values are plotted according to their order, as a function of shortest path to EZ (C) and weight to EZ (D) for all 15 patients. In D) the x-axis was inverted for better comparison. Parameters as in Fig. 11.

Figure 16. Recruitment times $t_{rec}$ of the areas belonging to PZ$_{SEEG}$ (A) and PZ$_{Clin}$ (B) as a function of the shortest path length to EZ, for all patients. Parameters as in Fig. 11.

shortest path length. Equivalently in panel B) it is possible to observe that, for short values of the shortest path length ($< 5$), there is a linear correspondence between short recruitment times and PZ$_{Clin}$ areas that are characterized by small values of the shortest path. However the areas belonging to PZ$_{Clin}$ are still not identifiable, in terms of topological measures, for patient GC.

To conclude this Section on the influence of single connectome topology in determining seizure spreading and area recruitment, we elaborate the data reported in Fig. 11 by sorting, from top to bottom, the patients...
Figure 17. Recruitment times of all brain areas and all patients. The patients are sorted from top to bottom according to their median shortest path length, calculated by listing all the shortest path lengths of all areas to the EZ and then locating the number in the centre of that distribution. Grey dots and diamonds show individual recruitments (we use two different symbols to highlight those values that are beyond one standard deviation); boxes cover the 2nd and 3rd quantile and whiskers extend 1.5 times the interquantile range. Parameters as in Fig. 11.

According to their median shortest path length, calculated on all areas with respect to the EZ. In Fig. 17 are shown the recruitment times of all brain areas for all patients. Since patients are ordered according to their median shortest path length, the brain areas of CV have, on average, the shortest paths to the EZ and the areas of AC the longest. In general, it is possible to detect a slight trend, for the overall recruitment events, to delay with longer average shortest path lengths. More in detail, JS and GC show both very long and very short recruitment times, thus confirming the results obtained in Fig. 12 for Gaussian-distributed excitabilities. The scattering of the recruitment times for these patients determines the fact that, on average, their recruitment times are longer with respect to the other patients. However the mean recruitment times are comparable with those of ML, AC, that show comparatively late recruitments irrespectively of the fact that are characterized by a longer median shortest path. A common characteristic that brings together patients JS, GC, ML, AC is the weak connection among the EZ and the first recruited area, that slows down the recruitment time (as already mentioned when discussing about Fig. 14), thus suggesting that is the interplay between connection strength and shortest path to determine the efficacy of seizure spreading and not the single topology measure alone.
Figure 18. Recruitment times of the first 10 recruited areas as a function of the input current $I_S$ for the epileptic patients A) CJ, B) CM, C) FB and D) PG. The strength of the input current is varied between 0 and 100 on the x-axis while its duration is kept unchanged at $t_I = 0.4$ s with respect to the previous numerical experiments. The order of the recruitment is color coded for each current strength (i.e. blue dots indicate the recruitment of the EZ, green dots indicate the first recruited area, red the second, etc.) and it hold the same for all investigated patients. Parameters as in Fig. 11.

4.4 Recruitment Differences Among Patients: The Impact of the Input Current Strength

Following what shown in Fig. 8 for a healthy subject, we present here an analysis on the impact of the input current strength on the recruitment mechanism. In particular in Fig. 18 are shown the recruitment times of the first 10 recruited areas for different current strengths. The analysis has been performed for patients CJ (panel A), CM (panel B), FB (panel C) and PG (panel D), thus integrating the information on the dependency on topological measures presented in the previous section. As expected, the recruitment times decrease for larger current strengths, even though the order of recruitment does not substantially change when increasing the input current strength. This means that, whenever we increase the current strength or the excitability value, the recruitment mechanism remains unaffected and the same populations are involved in the seizure spreading in the same order. What changes is the velocity of the seizure spreading and the time necessary to observe a generalized seizure event which is smaller for stronger currents. As a general remark the brain areas that are recruited after the first ones (i.e. the 5th, 6th,...,10th recruited areas), tend to be recruited at the same time for increasing current strength, thus determining possible changes in the recruitment order. This can be appreciated especially for patient CJ: For a current strength $I_S = 20$, for example, the 10th brain area (pink) gets recruited later than the 9th area (darkblue), while for a very strong currents ($I_S = 100$) the darkblue area gets recruited latest whereas the pink area gets recruited earlier.

On the other hand if we vary the current duration $t_I$ keeping fixed the current strength $I_S$ (the numerical experiment has been done for $I_S = 15$), we do not observe any change in the recruitment times of the
first 10 recruited areas, analogously to what already observed for a healthy subject in Fig. 21 of the Supplementary Material. Contrary to other experiments with this model (e.g. the numerical experiments on competing items in working memory shown in [Taher et al. (2020)]), the duration of the external stimulus does not influence the recruitment mechanism and does not lead to any form of competition or abandonment of high-activity state, that would result here in escaping from recruitment. Results not shown.

5 DISCUSSION

Neural mass models have been actively used since the 1970s to model the coarse grained activity of large populations of neurons and synapses [Wilson and Cowan (1972); Zetterberg et al. (1978)]. They have proven especially useful in understanding brain rhythms [Da Silva et al. (1974, 1976); Sotero et al. (2007)], epileptic dynamics [Wendling et al. (2016); Jirsa et al. (2014)], brain resonance phenomena [Spiegler et al. (2011)], resting state activity [Deco et al. (2011)], neurological and psychiatric disorders [Bhattacharya and Chowdhury (2015)] and are very popular in the neuroimaging community [Valdes-Sosa et al. (2009); Moran et al. (2013)]. Moreover, the desire to understand large scale brain dynamics as observed using EEG, MEG and fMRI has prompted the increasing use of computational models [Bojak and Breakspear (2014)] and, among these approaches, we find The Virtual Brain project [Sanz-Leon et al. (2015)] which makes use of networks of interconnected neural mass models.

However, although motivated by neurobiological considerations, neural mass models are phenomenological in nature, and cannot hope to recreate some of the rich repertoire of responses seen in real neuronal tissue. In particular their state variables track coarse grained measures of the population firing rate or synaptic activity. At best they are expected to provide appropriate levels of description for many thousands of near identical interconnected neurons with a preference to operate in synchrony, but they cannot reproduce the variation of synchrony within a neuronal population which is believed to underlie the decrease or increase of power seen in given EEG frequency bands. Importantly, unlike its phenomenological counterpart, the next generation neural mass model we have implemented in this paper, is an exact macroscopic description of an underlying microscopic spiking neurodynamics, and is a natural candidate for use in future large scale human brain simulations. The alternative method to heuristic neural mass models employed so far consists in performing large numerical simulations. Since the next generation neural mass model allows to overcome the limitations in the maximal affordable number of simulated neurons, it solves also the problems that are usually encountered in the analysis of spiking neural circuits addressed through numerical simulations, i.e. the limited available numerical resources.

In addition to this, the inability of a single neural mass model to support event-related desynchronisation/synchronisation [Flurtscheller and Da Silva (1999)] or to capture the onset of synchronous oscillations in networks of inhibitory neurons [Devalle et al. (2017)], reminds us that these phenomenological models could be improved upon. While building more detailed biophysically realistic models of neurons would increase the computational complexity and the difficulties to interpret the behaviour of very high dimensional models in a meaningful way, the next generation neural mass models here applied, are very much in the original spirit of neural mass modelling, yet importantly they can be interpreted directly in terms of an underlying spiking model. This exact derivation is possible for networks of quadratic integrate-and-fire neurons, representing the normal form of Hodgkin’s class I excitable membranes [Ermentrout and Kopell (1986)], thanks to the analytic techniques developed for coupled phase oscillators [Ott and Antonsen (2008)]. This new generation of neural mass models has been recently used to describe the emergence of collective oscillations in fully coupled networks [Devalle et al. (2017); Laing (2017); Coombes and Byrne (2019); Dumont and Gutkin (2019) as well as in balanced sparse networks [di Volo and Torcini (2018)].
Furthermore, it has been successfully employed to reveal the mechanisms at the basis of theta-nested gamma oscillations [Segneri et al. (2020); Ceni et al. (2020)] and the coexistence of slow and fast gamma oscillations [Bi et al. (2020)]. Finally it has been recently applied to modelling electrical synapses [Montbrió and Pazó (2020)] and working memory [Taher et al. (2020)].

In this paper we have extended the single next generation neural mass model derived in [Montbrió et al. (2015)] to a network of interacting neural mass models, where the topology is determined by structural connectivity matrices of healthy and epilepsy-affected subjects. In this way we coped not only with the macroscopic dynamics self-emergent in the system due to the interactions among nodes, but also with the various differences related to the patient-specific analyses.

In absence of external forcing, the phase diagram of the system as a function of the mean external drive \( \bar{\eta} \) and synaptic weight \( J \) resembles this of the single neural mass model, since the same distinct regions can be observed: (1) a single stable node corresponding to a low-activity state, (2) a single stable focus (spiral) generally corresponding to a high-activity state, and (3) a region of bistability between low and high firing rate. However, when the system is subject to external forcing the scenario is completely different, being ruled by the interactions among different nodes. In this case, for low excitability values, a single stimulated node abandons the bistable region due to the applied current and it approaches, with damped oscillations, the high-activity state, which is a stable focus. On the other hand, for sufficiently high excitabilities, the single node stimulation leads to the recruitment of other brain areas that reach, as the perturbed node, the high-activity regime by showing damped oscillations. This mechanism can be interpreted, in terms of epileptic seizures, as seizure generation, propagation and recruitment: the seizure originates in the EZ (as a result of the stimulation) and propagates to the PZ, identified by the other regions that fastly propagates the oscillatory activity.

The spectrogram analysis has revealed that the recruitment process is characterized by high frequency gamma oscillations, thus reproducing the high-frequency (gamma band) EEG activity typical of electrophysiological patterns in focal seizures of human epilepsy. Many hypotheses have been formulated on the origin of this fast activity: (i) the behaviour of inhibitory interneurons in hippocampal or neocortical networks in the generation of gamma frequency oscillations [Jefferys et al. (1996); Whittington et al. (2000)]; (ii) the nonuniform alteration of GABAergic inhibition in experimental epilepsy (reduced dendritic inhibition and increased somatic inhibition) [Cossart et al. (2001); Wendling et al. (2002)]; (iii) the possible depression of GABA_{A,fast} circuit activity by GABA_{A,slow} inhibitory postsynaptic currents [White et al. (2000); Banks et al. (2000)]; iv) the out of phase patterns of depolarizing GABAergic post-synaptic potentials onto pyramidal cells, generated by feed-forward activation of cortical interneurons [Shamas et al. (2018)]. In any case high-frequency EEG waves originating from one or several brain regions are the most characteristic electrophysiological pattern in focal seizures of human epilepsy and can be observed, in our numerical experiments, both for healthy subjects and epileptic patients, though with a distinction: for the same excitability value, the activity takes place at higher frequency ranges in epileptogenic patients and it is mainly concentrated in the EZ. Moreover the recruitment process turns out to be faster in epileptic patients, for which it is possible to observe, in general, generalize seizure events for smaller values of the excitability parameter \( \bar{\eta} \). In particular, when comparing the results obtained for healthy subjects and epileptic patients, it turns out that the time necessary to recruit areas in the PZ is usually smaller for epileptic patients. However, the first recruited area is, in general, the area with the stronger connection to the EZ, independently of the considered structural connectivity matrix. The recruitment time in both cases is influenced by the strength of the external perturbation \( I_S \), and decreases for increasing strength, while no dependence is shown on the duration of the external perturbation.
More specifically for healthy subjects we have investigated the dependence of the recruitment mechanism on the single subject, in terms of the position of the eventual EZ and in terms of the topological measures of the single connectome. Brain network models of healthy subjects comprise 90 nodes equipped with region specific next generation neural mass models and each subject is characterized by a specific structural large-scale connectivity amongst brain areas. The smallest $\bar{\eta}$ values for which an asymptomatic seizure occurs do not vary significantly from one subject to the other and do not show a relevant dependence on the stimulated area, while the smallest $\bar{\eta}$ values for which a generalized seizure occurs, show fluctuations in the interval $(-7, -5)$ for all stimulated nodes and for all the subjects. Nonetheless we have found many similarities at the level of topological measures, since there is always a strong correlation between $\bar{\eta}_{asy}$ ($\bar{\eta}_{gen}$) and node strength, clustering coefficient and shortest path, thus meaning that a region well connected is a region well recruited.

For epileptic patients, we have systematically simulated the individual seizure propagation patterns and validated the numerical predictions of the PZ against clinical diagnosis and SEEG signals. Patient-specific brain network models of epileptic patients comprise 88 nodes equipped with region specific next generation neural mass models and, for this set-up, we have studied the role of the large-scale connectome based on diffusion MRI, in predicting the recruitment of distant areas through seizures originating from a focal epileptogenic network. We have demonstrated that simulations and analytical solutions approximating the large-scale brain network model behavior significantly predict the propagation zone as determined by SEEG recordings and clinical expertise, with performances comparable to previous analyses on this set of data Proix et al. (2017); Olmi et al. (2019), thus confirming the relevance of using a large-scale network modeling to predict seizure recruitment networks.

Most computational models of seizure propagation focus on small continuous spatial scales Hall and Kuhlmann (2013); Ursino and La Cara (2006); Kim et al. (2009) or population of neurons Miles et al. (1988); Golomb and Amitai (1997); Compte et al. (2003); Bazhenov et al. (2008); Lopes et al. (2019); Gerster et al. (2020) while only small networks are commonly used to investigate the role of the topology and localization of the epileptogenic zone Terry et al. (2012). However functional, volumetric and electrographic data suggest a broad reorganization of the networks in epileptic patients Lieb et al. (1987, 1991); Cassidy and Gale (1998); Rosenberg et al. (2006); Bettus et al. (2009), thus laying the foundations for a different approach based on large-scale connectomes to identify the recruitment networks. The large-scale character of partial seizure propagation in the human brain has been only recently investigated, using patient-specific diffusion MRI data to systematically test the relevance of the large-scale network modeling in predicting seizure recruitment networks Proix et al. (2014, 2017, 2018); Olmi et al. (2019). In this framework of large-scale network modeling we can also place the results presented in this paper, since we have confirmed the importance of patient-specific connectomes to identify the recruitment process. As shown above, the topological characteristics of connection strength and shortest path play a non-trivial role in determining the seizure spreading, together with the localization of the epileptogenic zone, while the next generation neural mass model, here employed for the first time to study seizure spreading, allows us to construct patient-specific brain models via a multiscale approach: the variability of brain regions as extracted from the human brain atlas can be introduced in the mean-field parameters thanks to the exact correspondence between microscopic and macroscopic scales guaranteed by the model itself. Improving the predictive power of the model by the means of anatomical data (available e.g. in the BigBrain and human brain atlas) will be the scope of further research.
CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Moritz Gerster and Halgurd Taher performed the simulations and data analysis, writing original software and investigating the results. Data Curation is contributed by Maxime Guye, Fabrice Bartolomei and Jaroslav Hlinka. All the authors validated the research and participated to the drafting process. Simona Olmi was responsible for conceptualization, supervision, state-of-the-art review and the paper write-up.

FUNDING

S. O. received financial support from Campus France - programme PHC PROCOPE 2019 - Numero de projet : 42511TA. A. Z. received financial support from the Deutsche Akademische Austauschdienst (DAAD, German Academic Exchange Service) - Projektkennziffer - 57445304 - PPP Frankreich Phase I. This work was also supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) - Projektnummer - 163436311 - SFB 910.

DATA AVAILABILITY STATEMENT

All relevant data are within the paper and its Supporting Information files.

REFERENCES

Ahmadi, M. E., Hagler, D., McDonald, C. R., Tecoma, E., Iragui, V., Dale, A. M., et al. (2009). Side matters: diffusion tensor imaging tractography in left and right temporal lobe epilepsy. American journal of neuroradiology 30, 1740–1747
Banks, M. I., White, J. A., and Pearce, R. A. (2000). Interactions between distinct gabaa circuits in hippocampus. Neuron 25, 449–457
Barrat, A., Barthélemy, M., Pastor-Satorras, R., and Vespignani, A. (2004). The architecture of complex weighted networks. Proc. Natl. Acad. Sci. U.S.A. 101, 3747–3752. doi:10.1073/pnas.0400087101
Bartolomei, F., Guye, M., Gavaret, M., Regis, J., Wendling, F., Raybaud, C., et al. (2002). The presurgical evaluation of epilepsies. Revue neurologique 158, 4S55–64
Bartolomei, F., Guye, M., and Wendling, F. (2013). Abnormal binding and disruption in large scale networks involved in human partial seizures. EPJ Nonlinear Biomedical Physics 1, 4
Bartolomei, F., Lagarde, S., Wendling, F., McGonigal, A., Jirsa, V., Guye, M., et al. (2017). Defining epileptogenic networks: contribution of seeg and signal analysis. Epilepsia 58, 1131–1147
Bartolomei, F., Wendling, F., Bellanger, J.-J., Régis, J., and Chauvel, P. (2001). Neural networks involving the medial temporal structures in temporal lobe epilepsy. Clinical neurophysiology 112, 1746–1760
Bazhenov, M., Timofeev, I., Fröhlich, F., and Sejnowski, T. J. (2008). Cellular and network mechanisms of electrographic seizures. Drug Discovery Today: Disease Models 5, 45–57
Bernhardt, B., Hong, S.-J., Bernasconi, A., and Bernasconi, N. (2013). Imaging structural and functional brain networks in temporal lobe epilepsy. Frontiers in human neuroscience 7, 624
Besson, P., Bandt, S. K., Proix, T., Lagarde, S., Jirsa, V. K., Ranjeva, J.-P., et al. (2017). Anatomic consistencies across epilepsies: a stereotactic-eeg informed high-resolution structural connectivity study. *Brain* 140, 2639–2652

Besson, P., Dinkelacker, V., Valabregue, R., Thivard, L., Leclerc, X., Baulac, M., et al. (2014). Structural connectivity differences in left and right temporal lobe epilepsy. *Neuroimage* 100, 135–144

Bettus, G., Guedj, E., Joyeux, F., Confort-Gouny, S., Soulier, E., Laguitton, V., et al. (2009). Decreased basal fmri functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. *Human brain mapping* 30, 1580–1591

Bhattacharya, B. S. and Chowdhury, F. N. (2015). *Validating neuro-computational models of neurological and psychiatric disorders*, vol. 14 (Springer)

Bi, H., Segneri, M., di Volo, M., and Torcini, A. (2020). Coexistence of fast and slow gamma oscillations in one population of inhibitory spiking neurons. *Physical Review Research* 2, 013042

Boccaletti, S., Latora, V., Moreno, Y., Chavez, M., and Hwang, D.-U. (2006). Complex networks: Structure and dynamics. *Physics reports* 424, 175–308

Bojak, I. and Breakspear, M. (2014). Neuroimaging, neural population models for

Bonilha, L., Nesland, T., Martz, G. U., Joseph, J. E., Spampinato, M. V., Edwards, J. C., et al. (2012). Medial temporal lobe epilepsy is associated with neuronal fibre loss and paradoxical increase in structural connectivity of limbic structures. *Journal of Neurology, Neurosurgery & Psychiatry* 83, 903–909

Cabral, J., Fernandes, H., Van Hartevelt, T., James, A., and Kringelbach, M. (2013). Structural connectivity in schizophrenia and its impact on the dynamics of spontaneous functional networks. *Chaos* 23, 046111

Cassidy, R. M. and Gale, K. (1998). Mediodorsal thalamus plays a critical role in the development of limbic motor seizures. *Journal of Neuroscience* 18, 9002–9009

Ceni, A., Olmi, S., Torcini, A., and Angulo-Garcia, D. (2020). Cross frequency coupling in next generation inhibitory neural mass models. *Chaos: An Interdisciplinary Journal of Nonlinear Science* 30, 053121

Compte, A., Sanchez-Vives, M. V., McCormick, D. A., and Wang, X.-J. (2003). Cellular and network mechanisms of slow oscillatory activity (¡ 1 hz) and wave propagations in a cortical network model. *Journal of neurophysiology* 89, 2707–2725

Coombes, S. and Byrne, A. (2019). Next generation neural mass models. In *Nonlinear Dynamics in Computational Neuroscience*, eds. F. Corinto and A. Torcini (Springer). 1–16

Cossart, R., Dinocourt, C., Hirsch, J., Merchán-Perez, A., De Felipe, J., Ben-Ari, Y., et al. (2001). Dendritic but not somatic gabaaergic inhibition is decreased in experimental epilepsy. *Nature neuroscience* 4, 52–62

Cressman, J. R., Ullah, G., Ziburkus, J., Schiff, S. J., and Barreto, E. (2009). The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: I. single neuron dynamics. *Journal of computational neuroscience* 26, 159–170

Da Silva, F. L., Hoeks, A., Smits, H., and Zetterberg, L. (1974). Model of brain rhythmic activity. *Kybernetik* 15, 27–37

Da Silva, F. L., Van Rotterdam, A., Barts, P., Van Heusden, E., and Burr, W. (1976). Models of neuronal populations: the basic mechanisms of rhythmicity. In *Progress in brain research* (Elsevier), vol. 45. 281–308

David, O., Blauwblomme, T., Job, A.-S., Chabardès, S., Hoffmann, D., Minotti, L., et al. (2011). Imaging the seizure onset zone with stereo-electroencephalography. *Brain* 134, 2898–2911

De Tisi, J., Bell, G. S., Peacock, J. L., McEvoy, A. W., Harkness, W. F., Sander, J. W., et al. (2011). The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *The Lancet* 378, 1388–1395
Deco, G., Jirsa, V. K., and McIntosh, A. R. (2011). Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nature Reviews Neuroscience* 12, 43–56

DeSalvo, M. N., Douw, L., Tanaka, N., Reinsberger, C., and Stufflebeam, S. M. (2014). Altered structural connectome in temporal lobe epilepsy. *Radiology* 270, 842–848

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., et al. (2006). An automated labeling system for subdividing the human cerebral cortex on mri scans into gyral based regions of interest. *Neuroimage* 31, 968–980

Destexhe, A. and Sejnowski, T. J. (1995). G protein activation kinetics and spillover of gamma-aminobutyric acid may account for differences between inhibitory responses in the hippocampus and thalamus. *Proceedings of the National Academy of Sciences* 92, 9515–9519

Devalle, F., Roxin, A., and Montbrió, E. (2017). Firing rate equations require a spike synchrony mechanism to correctly describe fast oscillations in inhibitory networks. *PLoS computational biology* 13, e1005881

Di Volo, M. and Torcini, A. (2018). Transition from asynchronous to oscillatory dynamics in balanced spiking networks with instantaneous synapses. *Physical review letters* 121, 128301

Dumont, G. and Gutkin, B. (2019). Macroscopic phase resetting-curves determine oscillatory coherence and signal transfer in inter-coupled neural circuits. *PLoS computational biology* 15, e1007019

Duncan, J. S., Winston, G. P., Koepp, M. J., and Ourselin, S. (2016). Brain imaging in the assessment for epilepsy surgery. *The Lancet Neurology* 15, 420–433

Ermentrout, G. B. and Kopell, N. (1986). Parabolic bursting in an excitable system coupled with a slow oscillation. *SIAM Journal on Applied Mathematics* 46, 233–253

Fischl, B. (2012). Freesurfer. *Neuroimage* 62, 774–781

Fuhrmann, S., Ackermann, J., Kalbe, T., and Goesele, M. (2010). Direct resampling for isotropic surface remeshing. . 9–16

Gerster, M., Berner, R., Sawicki, J., Zakharova, A., Škoch, A., Hlinka, J., et al. (2020). Fitzhugh–nagumo oscillators on complex networks mimic epileptic-seizure-related synchronization phenomena. *Chaos: An Interdisciplinary Journal of Nonlinear Science* 30, 123130

Golomb, D. and Amitai, Y. (1997). Propagating neuronal discharges in neocortical slices: computational and experimental study. *Journal of neurophysiology* 78, 1199–1211

Goodfellow, M., Rummel, C., Abela, E., Richardson, M. P., Schindler, K., and Terry, J. R. (2017). Computer models to inform epilepsy surgery strategies: prediction of postoperative outcome. *Brain* 140, e30–e30

Hall, D. and Kuhlmann, L. (2013). Mechanisms of seizure propagation in 2-dimensional centre-surround recurrent networks. *PLoS One* 8, e71369

Hutchings, F., Han, C. E., Keller, S. S., Weber, B., Taylor, P. N., and Kaiser, M. (2015). Predicting surgery targets in temporal lobe epilepsy through structural connectome based simulations. *PLoS computational biology* 11, e1004642

Jacobs, J., Staba, R., Asano, E., Otsubo, H., Wu, J., Zijlmans, M., et al. (2012). High-frequency oscillations (hfos) in clinical epilepsy. *Progress in neurobiology* 98, 302–315

Jefferys, J. G., Traub, R. D., and Whittington, M. A. (1996). Neuronal networks for induced ’40 hz’ rhythms. *Trends in neurosciences* 19, 202–208

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., and Smith, S. M. (2012). Fsl. *Neuroimage* 62, 782–790

Jirsa, V., Sporns, O., Breakspear, M., Deco, G., and McIntosh, A. R. (2010). Towards the virtual brain: network modeling of the intact and the damaged brain. *Archives italiennes de biologie* 148, 189–205
Gerster et al.  Patient-specific network connectivity

Jirsa, V. K., Jantzen, K. J., Fuchs, A., and Kelso, J. S. (2002). Spatiotemporal forward solution of the eeg and meg using network modeling. *IEEE transactions on medical imaging* 21, 493–504

Jirsa, V. K., Stacey, W. C., Quilichini, P. P., Ivanov, A. I., and Bernard, C. (2014). On the nature of seizure dynamics. *Brain* 137, 2210–2230

Kalitzin, S. N., Velis, D. N., and da Silva, F. H. L. (2010). Stimulation-based anticipation and control of state transitions in the epileptic brain. *Epilepsy & Behavior* 17, 310–323

Khadjevand, F., Cimbalkin, J., and Worrell, G. A. (2017). Progress and remaining challenges in the application of high frequency oscillations as biomarkers of epileptic brain. *Current opinion in biomedical engineering* 4, 87–96

Khambhati, A. N., Davis, K. A., Lucas, T. H., Litt, B., and Bassett, D. S. (2016). Virtual cortical resection reveals push-pull network control preceding seizure evolution. *Neuron* 91, 1170–1182

Kim, J., Roberts, J., and Robinson, P. (2009). Dynamics of epileptic seizures: evolution, spreading, and suppression. *Journal of theoretical biology* 257, 527–532

Kramer, M. A., Truccolo, W., Eden, U. T., Lepage, K. Q., Hochberg, L. R., Eskandar, E. N., et al. (2012). Human seizures self-terminate across spatial scales via a critical transition. *Proceedings of the National Academy of Sciences* 109, 21116–21121

Kwan, P. and Brodie, M. J. (2000). Early identification of refractory epilepsy. *New England Journal of Medicine* 342, 314–319

Laing, C. R. (2017). Phase oscillator network models of brain dynamics. *Computational models of brain and behavior*, 505–517

Lecriubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K. H., et al. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *Eur. Psychiatry* 12, 224–231

Lieb, J. P., Dasheiff, R. M., Engel, J., Genton, P., and Genton, P. (1991). Role of the frontal lobes in the propagation of mesial temporal lobe seizures. *Epilepsia* 32, 822–837

Lieb, J. P., Hoque, K., Skomer, C. E., and Song, X.-W. (1987). Inter-hemispheric propagation of human mesial temporal lobe seizures: a coherence/phase analysis. *Electroencephalography and clinical neurophysiology* 67, 101–119

Lopes, M. A., Goodfellow, M., and Terry, J. R. (2019). A model-based assessment of the seizure onset zone predictive power to inform the epileptogenic zone. *Frontiers in computational neuroscience* 13, 25

Lopes, M. A., Junges, L., Woldman, W., Goodfellow, M., and Terry, J. R. (2020). The role of excitability and network structure in the emergence of focal and generalized seizures. *Frontiers in neurology* 11, 74

Lopes, M. A., Richardson, M. P., Abela, E., Rummel, C., Schindler, K., Goodfellow, M., et al. (2017). An optimal strategy for epilepsy surgery: Disruption of the rich-club? *PLoS computational biology* 13, e1005637

Melter, T., Horacek, J., Hlinka, J., Spaniel, F., Tintera, J., Ibrahim, I., et al. (2015). White matter changes in first episode psychosis and their relation to the size of sample studied: a DTI study. *Schizophr. Res.* 162, 22–28

Miles, R., Traub, R. D., and Wong, R. (1988). Spread of synchronous firing in longitudinal slices from the ca3 region of the hippocampus. *Journal of Neurophysiology* 60, 1481–1496

Montbrió, E. and Pazó, D. (2020). Exact mean-field theory explains the dual role of electrical synapses in collective synchronization. *Phys. Rev. Lett.* 125, 248101. doi:10.1103/PhysRevLett.125.248101

Montbrió, E., Pazó, D., and Roxin, A. (2015). Macroscopic description for networks of spiking neurons. *Phys. Rev. X* 5, 021028

This is a provisional file, not the final typeset article
Moran, R. J., Pinotsis, D. A., and Friston, K. J. (2013). Neural masses and fields in dynamic causal modeling. *Frontiers in computational neuroscience* 7, 57

Najm, I., Jehi, L., Palmini, A., Gonzalez-Martinez, J., Paglioli, E., and Bingaman, W. (2013). Temporal patterns and mechanisms of epilepsy surgery failure. *Epilepsia* 54, 772–782

Olmi, S., Petkoski, S., Guye, M., Bartolomei, F., and Jirsa, V. (2019). Controlling seizure propagation in large-scale brain networks. *PLoS computational biology* 15, e1006805

Ott, E. and Antonsen, T. M. (2008). Low dimensional behavior of large systems of globally coupled oscillators. *Chaos: An Interdisciplinary Journal of Nonlinear Science* 18, 037113

Pfurtscheller, G. and Da Silva, F. L. (1999). Event-related eeg/meg synchronization and desynchronization: basic principles. *Clinical neurophysiology* 110, 1842–1857

Proix, T., Bartolomei, F., Chauvel, P., Bernard, C., and Jirsa, V. K. (2014). Permittivity coupling across brain regions determines seizure recruitment in partial epilepsy. *Journal of Neuroscience* 34, 15009–15021

Proix, T., Bartolomei, F., Guye, M., and Jirsa, V. K. (2017). Individual structural connectivity defines propagation networks in partial epilepsy. *Brain* 140, 641–654

Proix, T., Jirsa, V. K., Bartolomei, F., Guye, M., and Truccolo, W. (2018). Predicting the spatiotemporal diversity of seizure propagation and termination in human focal epilepsy. *Nature communications* 9, 1–15

Richardson, M. P. (2012). Large scale brain models of epilepsy: dynamics meets connectomics. *Journal of Neurology, Neurosurgery & Psychiatry* 83, 1238–1248

Rosenberg, D. S., Mauguière, F., Demarquay, G., Ryvlin, P., Isnard, J., Fischer, C., et al. (2006). Involvement of medial pulvinar thalamic nucleus in human temporal lobe seizures. *Epilepsia* 47, 98–107

Rosenow, F. and Lüders, H. (2001). Presurgical evaluation of epilepsy. *Brain* 124, 1683–1700

Rueckert, D., Sonoda, L. I., Hayes, C., Hill, D. L., Leach, M. O., and Hawkes, D. J. (1999). Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans. Med. Imaging* 18, 712–721

Sanz-Leon, P., Knock, S. A., Spiegler, A., and Jirsa, V. K. (2015). Mathematical framework for large-scale brain network modeling in the virtual brain. *Neuroimage* 111, 385–430

Schaffer, E. S., Ostojic, S., and Abbott, L. F. (2013). A complex-valued firing-rate model that approximates the dynamics of spiking networks. *PLoS Comput Biol* 9, e1003301

Segneri, M., Bi, H., Olmi, S., and Torcini, A. (2020). Theta-nested gamma oscillations in next generation neural mass models. *Frontiers in Computational Neuroscience* 14, 47

Shamas, M., Benquet, P., Merlet, I., Khalil, M., El Falou, W., Nica, A., et al. (2018). On the origin of epileptic high frequency oscillations observed on clinical electrodes. *Clinical Neurophysiology* 129, 829–841

Sinha, N., Dauwels, J., Kaiser, M., Cash, S. S., Brandon Westover, M., Wang, Y., et al. (2017). Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling. *Brain* 140, 319–332

Smith, R. E., Tournier, J., Calamante, F., and Connelly, A. (2012). Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. *Neuroimage* 62, 1924–1938

Smith, R. E., Tournier, J., Calamante, F., and Connelly, A. (2013). SIFT: Spherical-deconvolution informed filtering of tractograms. *Neuroimage* 67, 298–312

Smith, S. (2002). Fast robust automated brain extraction. *Hum. Brain Mapp.* 17, 143–155
Smith, S., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31, 1487–1505

Smith, S., Jenkinson, M., Woolrich, M., Beckmann, C., Behrens, T., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23, S208–S219

Sotero, R. C., Trujillo-Barreto, N. J., Iturria-Medina, Y., Carbonell, F., and Jimenez, J. C. (2007). Realistically coupled neural mass models can generate eeg rhythms. *Neural computation* 19, 478–512

Spencer, S. S. (2002). Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia* 43, 219–227

Spiegler, A., Knösche, T. R., Schwab, K., Haueisen, J., and Atay, F. M. (2011). Modeling brain resonance phenomena using a neural mass model. *PLoS Comput Biol* 7, e1002298

Taher, H., Torcini, A., and Olmi, S. (2020). Exact neural mass model for synaptic-based working memory. *PLoS Computational Biology* 16, e1008533

Talairach, J. and Bancaud, J. (1966). Lesion,” irritative” zone and epileptogenic focus. *Stereotactic and Functional Neurosurgery* 27, 91–94

Taylor, P. N., Goodfellow, M., Wang, Y., and Baier, G. (2013). Towards a large-scale model of patient-specific epileptic spike-wave discharges. *Biological cybernetics* 107, 83–94

Terry, J. R., Benjamin, O., and Richardson, M. P. (2012). Seizure generation: the role of nodes and networks. *Epilepsia* 53, e166–e169

Touboul, J., Wendling, F., Chauvel, P., and Faugeras, O. (2011). Neural mass activity, bifurcations, and epilepsy. *Neural computation* 23, 3232–3286

Tournier, J. (2010). Mrtrix package. *Brain Research Institute, Melbourne, Australia, https://github.com/jdtournier/mrtrix3. Available at: https://github.com/jdtournier/mrtrix3*

Tournier, J., Calamante, F., and Connelly, A. (2007). Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. *Neuroimage* 35, 1459–1472

Toyoda, I., Bower, M. R., Leyva, F., and Buckmaster, P. S. (2013). Early activation of ventral hippocampus and subiculum during spontaneous seizures in a rat model of temporal lobe epilepsy. *Journal of Neuroscience* 33, 11100–11115

Turrigiano, G. G. (2008). The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* 135, 422–435

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289

Ullah, G., Cressman Jr, J. R., Barreto, E., and Schiff, S. J. (2009). The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: II. network and glial dynamics. *Journal of computational neuroscience* 26, 171–183

Ursino, M. and La Cara, G.-E. (2006). Travelling waves and eeg patterns during epileptic seizure: analysis with an integrate-and-fire neural network. *Journal of theoretical biology* 242, 171–187

Valdes-Sosa, P. A., Sanchez-Bornot, J. M., Sotero, R. C., Iturria-Medina, Y., Aleman-Gomez, Y., Bosch-Bayard, J., et al. (2009). Model driven eeg/fmri fusion of brain oscillations. *Human brain mapping* 30, 2701–2721
Van Drongelen, W., Lee, H. C., Hereld, M., Chen, Z., Elsen, F. P., and Stevens, R. L. (2005). Emergent epileptiform activity in neural networks with weak excitatory synapses. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 13, 236–241

Wang, S., Wang, I. Z., Bulacio, J. C., Mosher, J. C., Gonzalez-Martinez, J., Alexopoulos, A. V., et al. (2013). Ripple classification helps to localize the seizure-onset zone in neocortical epilepsy. *Epilepsia* 54, 370–376

Wendling, F., Bartolomei, F., Bellanger, J., and Chauvel, P. (2002). Epileptic fast activity can be explained by a model of impaired gabaergic dendritic inhibition. *European Journal of Neuroscience* 15, 1499–1508

Wendling, F., Benquet, P., Bartolomei, F., and Jirsa, V. (2016). Computational models of epileptiform activity. *Journal of neuroscience methods* 260, 233–251

White, J. A., Banks, M. I., Pearce, R. A., and Kopell, N. J. (2000). Networks of interneurons with fast and slow γ-aminobutyric acid type a (gabaa) kinetics provide substrate for mixed gamma-theta rhythm. *Proceedings of the National Academy of Sciences* 97, 8128–8133

Whittington, M. A., Traub, R., Kopell, N., Ermentrout, B., and Buhl, E. (2000). Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *International journal of psychophysiology* 38, 315–336

Wilson, H. R. and Cowan, J. D. (1972). Excitatory and inhibitory interactions in localized populations of model neurons. *Biophysical journal* 12, 1–24

Zetterberg, L., Kristiansson, L., and Mossberg, K. (1978). Performance of a model for a local neuron population. *Biological cybernetics* 31, 15–26

**SUPPLEMENTARY MATERIAL**
| Label | Region | Abbreviation | Label | Region | Abbreviation |
|-------|--------|--------------|-------|--------|--------------|
| 1     | Precentral Gyrus | PRE | 46    | Cuneus | Q |
| 2     | Precentral Gyrus | PRE | 47    | Lingual Gyrus | LING |
| 3     | Superior Frontal Gyrus | F1 | 48    | Lingual Gyrus | LING |
| 4     | Superior Frontal Gyrus | F1 | 49    | Superior Occipital Gyrus | O1 |
| 5     | Superior Frontal Gyrus Orbital Part | F1O | 50    | Superior Occipital Gyrus | O1 |
| 6     | Superior Frontal Gyrus Orbital Part | F1O | 51    | Middle Occipital Gyrus | O2 |
| 7     | Middle Frontal Gyrus | F2 | 52    | Middle Occipital Gyrus | O2 |
| 8     | Middle Frontal Gyrus | F2 | 53    | Inferior Occipital Gyrus | O3 |
| 9     | Middle Frontal Gyrus Orbital Part | F2O | 54    | Inferior Occipital Gyrus | O3 |
| 10    | Middle Frontal Gyrus Orbital Part | F2O | 55    | Fusiform Gyrus | FUS1 |
| 11    | Inferior Frontal Gyrus Opercular Part | F3OP | 56    | Fusiform Gyrus | FUS1 |
| 12    | Inferior Frontal Gyrus Opercular Part | F3OP | 57    | Postcentral Gyrus | POST |
| 13    | Inferior Frontal Gyrus Triangular Part | F3T | 58    | Postcentral Gyrus | POST |
| 14    | Inferior Frontal Gyrus Triangular Part | F3T | 59    | Superior Parietal Gyrus | P1 |
| 15    | Inferior Frontal Gyrus Orbital Part | F3O | 60    | Superior Parietal Gyrus | P1 |
| 16    | Inferior Frontal Gyrus Orbital Part | F3O | 61    | Inferior Parietal Gyrus | P2 |
| 17    | Rolandic Operculum | RO | 62    | Inferior Parietal Gyrus | P2 |
| 18    | Rolandic Operculum | RO | 63    | Supramarginal Gyrus | SMG |
| 19    | Supplementary Motor Area | SMA | 64    | Supramarginal Gyrus | SMG |
| 20    | Supplementary Motor Area | SMA | 65    | Angular Gyrus | AG |
| 21    | Olfactory Cortex | OC | 66    | Angular Gyrus | AG |
| 22    | Olfactory Cortex | OC | 67    | Precuneus | PQ |
| 23    | Superior Frontal Gyrus Medial | F1M | 68    | Precuneus | PQ |
| 24    | Superior Frontal Gyrus Medial | F1M | 69    | Paracentral Lobule | PCL |
| 25    | Superior Frontal Gyrus Medial Orbital | F1MO | 70    | Paracentral Lobule | PCL |
| 26    | Superior Frontal Gyrus Medial Orbital | F1MO | 71    | Caudate Nucleus | CAU |
| 27    | Gyrus Rectus | GR | 72    | Caudate Nucleus | CAU |
| 28    | Gyrus Rectus | GR e | 73    | Putamen | PUT |
| 29    | Insula | IN | 74    | Putamen | PUT |
| 30    | Insula | IN | 75    | Pallidum | PAL |
| 31    | Anterior Cingulate and paracingulate gyri | ACIN | 76    | Pallidum | PAL |
| 32    | Anterior Cingulate and paracingulate gyri | ACIN | 77    | Thalamus | THA |
| 33    | Median Cingulate and paracingulate gyri | MCIN | 78    | Thalamus | THA |
| 34    | Median Cingulate and paracingulate gyri | MCIN | 79    | Heschl Gyrus | HES |
| 35    | Posterior Cingulate Gyrus | PCIN | 80    | Heschl Gyrus | HES |
| 36    | Posterior Cingulate Gyrus | PCIN | 81    | Superior Temporal Gyrus | T1 |
| 37    | Hippocampus | HIP | 82    | Superior Temporal Gyrus | T1 |
| 38    | Hippocampus | HIP | 83    | Heschl Gyrus | HES |
| 39    | ParaHippocampal Gyrus | PHIP | 84    | Temporal Pole: superior temporal gyrus | T1P |
| 40    | ParaHippocampal Gyrus | PHIP | 85    | Temporal Pole: superior temporal gyrus | T1P |
| 41    | Amygdala | AMYG | 86    | Temporal Mid | T2 |
| 42    | Amygdala | AMYG | 87    | Temporal Mid | T2 |
| 43    | Calcarine fissure and surrounding cortex | V1 | 88    | Temporal Pole: middle temporal gyrus | T2P |
| 44    | Calcarine fissure and surrounding cortex | V1 | 89    | Middle Temporal Gyrus | T2 |
| 45    | Cuneus | Q | 90    | Inferior Temporal Gyrus | T3 |

**Table 1.** Cortical and subcortical regions, according to the Automated Anatomical Labeling atlas 1(AAL1) [Tzourio-Mazoyer et al. (2002)]. Uneven/even numbers correspond to the left/right hemisphere.
| Label | Region | Abbreviation | Label | Region | Abbreviation |
|-------|--------|--------------|-------|--------|--------------|
| 1     | Unknown |              | 46    | Right-Cerebellum Cortex |              |
| 2     | Brain-Stem |              | 47    | Right-Thalamus Proper |              |
| 3     | Left-Cerebellum Cortex | lh-Th | 48    | Right-Caudate |              |
| 4     | Left-Thalamus Proper | lh-Cd | 49    | Right-Putamen |              |
| 5     | Left-Caudate | lh-Pu | 50    | Right-Pallidum |              |
| 6     | Left-Pallidum | lh-Pal | 51    | Right-Hippocampus |              |
| 7     | Left-Hippocampus | lh-Hi | 52    | Right-Amygdala |              |
| 8     | Left-Amygdala | lh-Amg | 53    | Right-Accumbens Area |              |
| 9     | Left-Accumbens-Area |              | 54    | Right-unknown |              |
| 10    | Left-unknown |              | 55    | Right-bankssts |              |
| 11    | Left-bankssts |              | 56    | Right-Caudal Anterior Cingulate | lh-CACC |
| 12    | Left-Caudal Anterior Cingulate | lh-CACC | 57    | Right-Caudal Middle Frontal | lh-CMFG |
| 13    | Left-Caudal Middle Frontal | lh-CMFG | 58    | Right-Cuneus | lh-Cun |
| 14    | Left-Cuneus | lh-Cun | 59    | Right-Entorhinal Cortex | lh-EntC |
| 15    | Left-Entorhinal Cortex | lh-EntC | 60    | Right-Fusiform Gyrus | lh-FuG |
| 16    | Left-Inferior Parietal Cortex | lh-IPC | 61    | Right-Inferior Parietal Cortex | lh-IPC |
| 17    | Left-Inferior Temporal Gyrus | lh-ITG | 62    | Right-Inferior Temporal Gyrus | lh-ITG |
| 18    | Left-Isthmus Cingulate Cortex | lh-ICC | 63    | Right-Isthmus Cingulate Cortex | lh-ICC |
| 19    | Left-Lateral Occipital Cortex | lh-LOCC | 64    | Right-Lateral Occipital Cortex | lh-LOCC |
| 20    | Left-Lateral Orbito Frontal Cortex | lh-LOFC | 65    | Right-Lateral Orbito Frontal Cortex | lh-LOFC |
| 21    | Left-Linguual Gyrus | lh-LG | 66    | Right-Linguual Gyrus | lh-LG |
| 22    | Left-Lateral Temporal Gyrus | lh-MTG | 67    | Right-Medial Orbito Frontal Cortex | lh-MOFC |
| 23    | Left-Medial Orbito Frontal Cortex | lh-MOFC | 68    | Right-Medial Temporal Gyrus | lh-MTG |
| 24    | Left-Medial Temporal Gyrus | lh-MTG | 69    | Right-Parahippocampal Gyrus | lh-PHiG |
| 25    | Left-Parahippocampal Gyrus | lh-PHiG | 70    | Right-Paracentral Cortex | lh-PaC |
| 26    | Left-Paracentral Cortex | lh-PaC | 71    | Right-Pars Opercularis | lh-Pop |
| 27    | Left-Pars Opercularis | lh-Pop | 72    | Right-Pars Orbitalis | lh-POr |
| 28    | Left-Pars Orbitalis | lh-POr | 73    | Right-Pars Triangularis | lh-PT |
| 29    | Left-Pars Triangularis | lh-PT | 74    | Right-Pericalcarine | lh-PC |
| 30    | Left-Pericalcarine | lh-PC | 75    | Right-Postcentral Gyrus | lh-PoG |
| 31    | Left-Postcentral Gyrus | lh-PoG | 76    | Right-Posterior Cingulate Gyrus | lh-PCG |
| 32    | Left-Posterior Cingulate Gyrus | lh-PCG | 77    | Right-Precentral Gyrus | lh-PrG |
| 33    | Left-Precentral Gyrus | lh-PrG | 78    | Right-Precuneus Cortex | lh-PCunC |
| 34    | Left-Precuneus Cortex | lh-PCunC | 79    | Right-Rostral Anterior Cingulate Cortex | lh-RACC |
| 35    | Left-Rostral Anterior Cingulate Cortex | lh-RACC | 80    | Right-Rostral Middle Frontal Gyrus | lh-RMFG |
| 36    | Left-Rostral Middle Frontal Gyrus | lh-RMFG | 81    | Right-Supercingulate Gyrus | lh-RSFG |
| 37    | Left-Supercingulate Gyrus | lh-RSFG | 82    | Right-Supercingulate Gyrus | lh-RSP |
| 38    | Left-Superior Frontal Gyrus | lh-SF | 83    | Right-Supereor Temporal Gyrus | lh-ST |
| 39    | Left-Superior Parietal Cortex | lh-SPC | 84    | Right-Supremaordinary Gyrus | lh-SMG |
| 40    | Left-Superior Temporal Gyrus | lh-SMG | 85    | Right-Frontal Pole | lh-FP |
| 41    | Left-Supremeordinary Gyrus | lh-FP | 86    | Right-Frontal Pole | lh-TP |
| 42    | Left-Frontal Pole | lh-TP | 87    | Right-Superior Temporal Gyrus | lh-TMP |
| 43    | Left-Superior Temporal Pole | lh-TMP | 88    | Right-Transverse Temporal Pole | lh-TTmP |
| 44    | Left-Transverse Temporal Pole | lh-TTmP | 89    | Right-Insula | lh-Ins |

**Table 2.** Cortical and subcortical regions, according to the Desikan-Killiany atlas [Desikan et al. (2006)].
| Patient | Gender | Epilepsy duration (years) | Age at seizure onset (years) | Epilepsy type | Surgical procedure | Surgical outcome | MRI | Histopathology | Side |
|---------|--------|--------------------------|-------------------------------|---------------|-------------------|-----------------|-----|----------------|------|
| AC      | F      | 14                       | 8                             | Temporo-frontal | Sr                | III             | Anterior temporal necrosis | Gliosis | R         |
| CJ      | F      | 14                       | 9                             | Occipital      | Sr                | III             | N              | FCD type 1 | L         |
| CM      | M      | 35                       | 7                             | Insular        | GK                | I               | N              | NA            | L         |
| CV      | F      | 18                       | 5                             | SMA            | Sr                | I               | N              | FDC type 2   | L         |
| ET      | F      | 23                       | 7                             | Parietal       | Sr                | I               | FCD SPC        | FCD type 2   | L         |
| FB      | F      | 16                       | 7                             | Premotor       | Th                | II              | N              | NA            | R         |
| FO      | M      | 45                       | 11                            | Temporo-frontal | Jr                | I               | FCD F          | FCD type 2   | R         |
| GC      | M      | 5                        | 28                            | Temporal       | Sr                | III             | Temporopolar hypersignal | FCD type 1   | R         |
| IL      | F      | 18                       | 20                            | Occipital      | N                 | NO              | N              | NA            | R         |
| JS      | M      | 11                       | 18                            | Frontal        | Sr                | I               | Frontal necrosis (post-trauma) | Gliosis     | R         |
| ML      | F      | 10                       | 17                            | Temporal       | Gk                | II              | Hypocampal sclerosis | NA          | R         |
| PC      | M      | 15                       | 14                            | Temporal       | N                 | NO              | N              | NA            | R         |
| PG      | M      | 29                       | 7                             | Temporal       | Sr                | III             | N              | Cavernoma     | Cavernoma   | R         |
| RB      | M      | 28                       | 35                            | Temporal       | Sr                | III             | Gliosis        | L            |           |
| SF      | F      | 24                       | 4                             | Occipital      | N                 | NO              | PVH            | NA            | R         |

**Table 3.** Clinical characteristics of the patients. N, normal; L, left; R, right; Th, thermocoagulation; Gk, Gamma knife; Sr, surgical resection; NO, not operated; PVH, periventricular nodular heterotopia; FCD, focal cortical dysplasia; SPC, superior parietal cortex; F, Frontal; NA, not available.

| Patient | EZ location | PZ location | SEEG | PZ clinical prediction |
|---------|-------------|-------------|------|------------------------|
| AC      | rLOFC, rTmP | rRMFG, rFMFG | rRMFG, rMOFC, rPOr, rIns | rPu, rPT, rAccumbens |
| CJ      | ILOCC       | IFuG, IPC, ISPC | IFuG, ISPC, IITG, IIPC, IPC, ILgG | IPu, ILOFC, ISMG, IPG, IPop, IPoG |
| CM      | lIns        | lPoG        | lRMFG, lPrG, lSPG, lCA, lIpC, lPaC | lIpG, lIPoG |
| CV      | IPCG, ICMFG, ISFG | lPrG, lISPC, lIPG | lIPoG, lIIPC | lIICC, lIIPC, lISP |
| ET      | IPCG, IPCunC | lPoG, IIPC | lIPoG, lIIPC | lIICC, lIIPC, lISP |
| FB      | rPrG        | lCMFG, rCMFG, rPOp, rSFG | rPrG, rCMFG, rPOp, rSFG | rTh, rPu, rPC, rSMG |
| FO      | rAmg, rTmP, rLOFC | rFuG, rLOFC, rIPHiG, rITG | rFuG, rLOFC, rIPHiG, rITG | rTmP, rIns, rPu, rMOFC, rPOr, rRMFG |
| GC      | rAmg, rHi   | rITG, rTmP, rPOp | rITG, rTmP, rPOp | rPrG, rEntC, rTmP, rFuG, rPaL, rTh |
| IL      | rLgG, rPHiG | rHi, rFuG, rPC, rLOCC, rSPC, rITG | rHi, rFuG, rPOp, rMTG, rLOFC | rIPoG, rPRG, rCD, rPOp, rPu |
| JS      | rMOFC, rFP, rRMFG, rPOr | rPop, rMTG, rLOFC | rPOp, rMTG, rLOFC | rTH, rLOFC, rRA, rIns |
| ML      | rHi, rAmg  | rLOFC, rMTG | rLOFC, rMTG | rTh, rLOFC, rRA, rIns |
| PC      | rHi, rFuG, rEntC, rTmP | IFuG, rITG | IFuG, rITG | rITG, rLOCC, rLgG, rPHiG, rAmg |
| PG      | rFuG       | rEntC, rPC, rHi | rITG, rLOCC, rTmP | rITG, rLOCC, rTmP |
| RB      | rAmg, rHi, rEntC, rFuG | rMTG, rMTG, rInns | rITG, rLOCC, rIPHiG, rLgG | rITG, rLOCC, rIPHiG, rLgG |
| IITmF, rEntC | rCerebellum | rFuG, rIPc, rITG, rMTG, rSPC | rFuG, rIPc, rITG, rMTG, rSPC |

**Table 4.** Results of Propagation zone prediction for each patient. Abbreviations are given in Supplementary Table 2.
Figure 19. Network measure correlations of healthy subjects. Panels A-F are obtained plotting independently all node values for all the subjects (90*20=1800 data points). Panel G: Data are averaged over all 20 subjects. The single node values are averaged over the different subjects and afterwards, the correlation between node strength and clustering coefficient is estimated. Infinite values were excluded. The Pearson correlation of clustering coefficient and node strength of the averaged healthy DTI topology is $r = 0.9$ and much stronger compared to the average of all individual topologies $r = 0.75$ from panel A.

Figure 20. Weight Distribution of the DTI graphs. The weight distribution with weights on the x-axis in ascending order. a) Weight distribution, b) the inverse weight distribution, c) and the logarithmic weight distribution of the healthy averaged DTI graph. Note that c) matches the curve of recruitment times in Figure 7(a).
Figure 21. Input Current Duration Variation. The duration of the input current is varied between 0 and 100 on the x-axis. The strength is kept constant at 15. The y-axis shows the recruitment times of the first 10 recruited areas for each current strength. Blue is the EZ, green is the first recruited area, red the second, etc. The recruitment times are independent of the pulse duration. Parameters: $N = 90$, $\sigma = 1$, $\Delta = 1$, $\eta = -6$, $I_S = 15$, stimulation site: brain area 45 of healthy patient 0.
Figure 22. Spectrograms of mean membrane potentials for healthy subject sc2. (A1-B1) Stimulation current \( I_k^S \), (A2-B2) population firing rates \( r_k \) and (A3-B3) mean membrane potentials \( v_k \) for the EZ (orange) and other populations (black). The blue curves show the network average firing rate and membrane potential. Non-stimulated node dynamics is plotted as transparent gray curves: some of the nodes adapt their voltage to the stimulation of the EZ and change during stimulation. However they do not reach the high-activity state regime. (A4-B4) Spectrogram of the network average membrane potential and (A5-B5) of the \( v_k \) of the EZ. Column A shows an asymptomatic seizure event for \( \bar{\eta} = -9.20 \), column B a generalized seizure for \( \bar{\eta} = -5.3 \). In both cases the EZ node 46 is stimulated. Parameter values: \( N_{\text{pop}} = 90 \), \( \tau_m = 20 \text{ms} \), \( \Delta = 1 \), \( J_{kk} = 20 \), \( \sigma = 1 \), \( J_{kl} = 5 \tilde{J}_{kl} \quad \forall k \neq l \).
| Patient | Recruitment order | Recruitment time (s) | Type | Region |
|---------|-------------------|---------------------|------|--------|
| AC 0    | 0.0               | EZ                  | rh-LOFC |
| AC 1    | 0.0005            | EZ                  | rh-TmP  |
| AC 2    | 0.123             | PZ$_{SEEG}$, PZ$_{Clin}$ | rh-RMFG |
| AC 3    | 0.1324            | PZ$_{Clin}$          | rh-Pu   |
| AC 4    | 0.1546            | other               | rh-SFG  |
| AC 5    | 0.1587            | PZ$_{Clin}$          | rh-Ins  |
| AC 6    | 0.1718            | other               | rh-Pal  |
| AC 7    | 0.1747            | other               | rh-PrG  |
| AC 8    | 0.175             | other               | rh-MOFC |
| AC 9    | 0.1769            | other               | rh-Cd   |
| AC 10   | 0.1797            | other               | rh-SFG  |
| AC 11   | 0.1801            | other               | rh-PoG  |
| CJ 0    | 0.0               | EZ                  | lh-LOCC |
| CJ 1    | 0.0255            | PZ$_{SEEG}$, PZ$_{Clin}$ | lh-FuG  |
| CJ 2    | 0.0294            | PZ$_{SEEG}$, PZ$_{Clin}$ | lh-SPC  |
| CJ 3    | 0.0333            | PZ$_{Clin}$          | lh-ITG  |
| CJ 4    | 0.0354            | PZ$_{SEEG}$, PZ$_{Clin}$ | lh-IPC  |
| CJ 5    | 0.045             | other               | lh-MTG  |
| CJ 6    | 0.046             | other               | lh-SMG  |
| CJ 7    | 0.0466            | other               | lh-PcunC |
| CJ 8    | 0.0479            | PZ$_{Clin}$          | lh-LgG  |
| CJ 9    | 0.0482            | other               | lh-PoG  |
| CJ 10   | 0.0521            | other               | lh-PrG  |
| CM 0    | 0.0               | EZ                  | lh-Ins  |
| CM 1    | 0.0224            | PZ$_{Clin}$          | lh-Pu   |
| CM 2    | 0.0369            | other               | lh-SFG  |
| CM 3    | 0.0394            | PZ$_{Clin}$          | lh-LOFC |
| CM 4    | 0.04              | PZ$_{Clin}$          | lh-PrG  |
| CM 5    | 0.0438            | PZ$_{SEEG}$, PZ$_{Clin}$ | lh-PoG  |
| CM 6    | 0.0446            | other               | lh-RMFG |
| CM 7    | 0.0451            | other               | lh-Th   |
| CM 8    | 0.0453            | other               | lh-CMFG |
| CM 9    | 0.0459            | other               | rh-SFG  |
| CM 10   | 0.0465            | PZ$_{Clin}$          | lh-Pop  |
| CV 0    | 0.0               | EZ                  | lh-SFG  |
| CV 1    | 0.0016            | EZ                  | lh-CMFG |
| CV 2    | 0.0026            | EZ                  | lh-PCG  |
| CV 3    | 0.007             | PZ$_{SEEG}$, PZ$_{Clin}$ | lh-PrG  |
| CV 4    | 0.0085            | PZ$_{Clin}$          | lh-RMFG |
| CV 5    | 0.0122            | PZ$_{SEEG}$          | lh-PoG  |
| CV 6    | 0.0126            | PZ$_{Clin}$          | lh-SFG  |
| CV 7    | 0.0155            | PZ$_{Clin}$          | lh-PaC  |
| CV 8    | 0.0168            | other               | lh-Pop  |
| CV 9    | 0.0168            | other               | lh-Pu   |
| CV 10   | 0.0175            | other               | lh-Th   |
| CV 11   | 0.0211            | other               | lh-SMG  |
| CV 12   | 0.0212            | PZ$_{Clin}$          | lh-CACC |
| ET 0    | 0.0               | EZ                  | lh-PcunC |
| ET 1    | 0.0006            | EZ                  | lh-PCG  |
| ET 2    | 0.0181            | PZ$_{Clin}$          | lh-SPC  |
| ET 3    | 0.0219            | PZ$_{Clin}$          | lh-ICC  |
| ET 4    | 0.0244            | PZ$_{SEEG}$, PZ$_{Clin}$ | lh-IPC  |
| ET 5    | 0.0284            | other               | lh-SFG  |
| ET 6    | 0.0318            | other               | lh-LOC  |
| ET 7    | 0.0345            | other               | rh-SFG  |
| ET 8    | 0.0363            | other               | lh-Cun  |
| ET 9    | 0.0364            | other               | lh-SMG  |
| ET 10   | 0.0366            | other               | lh-Th   |
| ET 11   | 0.0374            | other               | rh-PrG  |

**Table 5.** List of the first 10 recruited brain areas for each patient. The column “Type” indicates whether the recruited area belongs or not to the PZ estimated via presurgical invasive (PZ$_{SEEG}$) or non-invasive (PZ$_{Clin}$) evaluation.
| Patient | Recruitment order | Recruitment time (s) | Type        | Region  |
|---------|-------------------|----------------------|-------------|---------|
| FB      | 0                 | 0.0                  | EZ          | rh-FrG  |
| FB      | 1                 | 0.0146               | PZClin      | rh-PoG  |
| FB      | 2                 | 0.02                 | PZClin      | rh-SFG  |
| FB      | 3                 | 0.0287               | PZ_{SEEG}, PZ_{Clin} | rh-CMFG |
| FB      | 4                 | 0.0342               | PZClin      | rh-SMG  |
| FB      | 5                 | 0.0369               | PZClin      | rh-Pop  |
| FB      | 6                 | 0.038                | other       | lh-SFG  |
| FB      | 7                 | 0.0382               | PZClin      | rh-Th   |
| FB      | 8                 | 0.0396               | other       | rh-RMFG |
| FB      | 9                 | 0.0417               | PZClin      | rh-PaC  |
| FB      | 10                | 0.042                | PZClin      | rh-Pu   |
| FO      | 0                 | 0.0                  | EZ          | rh-LOFC |
| FO      | 1                 | 0.0012               | EZ          | rh-TmP  |
| FO      | 2                 | 0.0012               | EZ          | rh-Amg  |
| FO      | 3                 | 0.0379               | PZClin      | rh-Ins  |
| FO      | 4                 | 0.0516               | PZClin      | rh-Pu   |
| FO      | 5                 | 0.0875               | other       | rh-SFG  |
| FO      | 6                 | 0.0949               | other       | rh-PrG  |
| FO      | 7                 | 0.0954               | other       | rh-Pal  |
| FO      | 8                 | 0.098                | PZClin      | rh-RMFG |
| FO      | 9                 | 0.1027               | other       | rh-PoG  |
| FO      | 10                | 0.1031               | other       | rh-CMFG |
| FO      | 11                | 0.1034               | other       | lh-SFG  |
| FO      | 12                | 0.1067               | other       | rh-Th   |
| GC      | 0                 | 0.0                  | EZ          | rh-Hi   |
| GC      | 1                 | 0.0003               | EZ          | rh-Amg  |
| GC      | 2                 | 0.3184               | PZClin      | rh-PHiG |
| GC      | 3                 | 0.3735               | PZClin      | rh-FuG  |
| GC      | 4                 | 0.3905               | PZ_{SEEG}   | rh-ITG  |
| GC      | 5                 | 0.3965               | other       | rh-LOCC |
| GC      | 6                 | 0.3999               | other       | rh-MTNG |
| GC      | 7                 | 0.4027               | other       | rh-LgG  |
| GC      | 8                 | 0.4097               | other       | rh-IPC  |
| GC      | 9                 | 0.4106               | other       | rh-STG  |
| GC      | 10                | 0.4137               | other       | rh-PC   |
| GC      | 11                | 0.4179               | other       | rh-bnks |
| IL      | 0                 | 0.0                  | EZ          | rh-LgG  |
| IL      | 1                 | 0.0006               | EZ          | rh-PHiG |
| IL      | 2                 | 0.0128               | PZ_{SEEG}, PZ_{Clin} | rh-FuG |
| IL      | 3                 | 0.0181               | PZ_{SEEG}, PZ_{Clin} | rh-Hi |
| IL      | 4                 | 0.0205               | PZ_{SEEG}, PZ_{Clin} | rh-LOCC |
| IL      | 5                 | 0.0217               | PZ_{SEEG}   | rh-ITG  |
| IL      | 6                 | 0.0264               | PZClin      | rh-PC   |
| IL      | 7                 | 0.0408               | PZ_{SEEG}   | rh-IPC  |
| IL      | 8                 | 0.0417               | other       | rh-MTNG |
| IL      | 9                 | 0.0453               | PZ_{SEEG}   | rh-SPC  |
| IL      | 10                | 0.0483               | other       | rh-Th   |
| JS      | 0                 | 0.0                  | EZ          | rh-RMFG |
| JS      | 1                 | 0.0006               | EZ          | rh-MOFC |
| JS      | 2                 | 0.0008               | EZ          | rh-FP   |
| JS      | 3                 | 0.0008               | EZ          | rh-PoR  |
| JS      | 4                 | 0.0414               | PZClin      | rh-SFG  |
| JS      | 5                 | 0.0745               | PZClin      | rh-PrG  |
| JS      | 6                 | 0.0882               | other       | rh-PoG  |
| JS      | 7                 | 0.0894               | other       | rh-CMFG |
| JS      | 8                 | 0.0957               | other       | rh-SMG  |
| JS      | 9                 | 0.1035               | other       | rh-SPC  |
| JS      | 10                | 0.1103               | PZ_{SEEG}, PZ_{Clin} | rh-PoG |
| JS      | 11                | 0.1119               | other       | rh-IPC  |
| JS      | 12                | 0.1155               | other       | rh-PaC  |

Table 6. Continued from Table 5.
| Patient | Recruitment order | Recruitment time (s) | Type       | Region       |
|---------|-------------------|----------------------|------------|--------------|
| ML 0    | 0.0               | EZ                   | rh-Hi      |
| ML 1    | 0.0003            | EZ                   | rh-Amg     |
| ML 2    | 0.158             | PZ<sub>Clin</sub>    | rh-Th      |
| ML 3    | 0.185             | PZ<sub>Clin</sub>    | rh-Cd      |
| ML 4    | 0.19              | other                | rh-SFG     |
| ML 5    | 0.1993            | other                | rh-RMFG    |
| ML 6    | 0.2006            | other                | BS         |
| ML 7    | 0.2015            | PZ<sub>Clin</sub>    | rh-Pu      |
| ML 8    | 0.2035            | other                | rh-Pal     |
| ML 9    | 0.2072            | other                | rh-PrG     |
| ML 10   | 0.2084            | other                | lh-SFG     |
| ML 11   | 0.2123            | other                | rh-CMFG    |
| PC 0    | 0.0               | EZ                   | rh-FuG     |
| PC 1    | 0.0006            | EZ                   | rh-Hi      |
| PC 2    | 0.0014            | EZ                   | rh-EntC    |
| PC 3    | 0.0016            | EZ                   | rh-TmP     |
| PC 4    | 0.008             | PZ<sub>Clin</sub>    | rh-LOCC    |
| PC 5    | 0.0137            | PZ<sub>SEEG</sub>, PZ<sub>Clin</sub> | rh-ITG |
| PC 6    | 0.0202            | PZ<sub>Clin</sub>    | rh-LgG     |
| PC 7    | 0.0215            | other                | rh-MTG     |
| PC 8    | 0.0243            | other                | rh-SPC     |
| PC 9    | 0.0267            | other                | rh-IPC     |
| PC 10   | 0.0288            | other                | rh-PC      |
| PC 11   | 0.0298            | PZ<sub>Clin</sub>    | rh-PHiG    |
| PC 12   | 0.0324            | other                | rh-PCunC   |
| PC 13   | 0.0325            | other                | rh-SMG     |
| PG 0    | 0.0               | EZ                   | rh-FuG     |
| PG 1    | 0.035             | PZ<sub>Clin</sub>    | rh-LOCC    |
| PG 2    | 0.0375            | PZ<sub>Clin</sub>    | rh-ITG     |
| PG 3    | 0.062             | other                | rh-ITG     |
| PG 4    | 0.0683            | PZ<sub>SEEG</sub>    | rh-IPC     |
| PG 5    | 0.0742            | other                | rh-SPC     |
| PG 6    | 0.084             | other                | rh-STG     |
| PG 7    | 0.0864            | other                | rh-SMG     |
| PG 8    | 0.0903            | other                | rh-bnks    |
| PG 9    | 0.0907            | other                | rh-PrG     |
| PG 10   | 0.0922            | other                | rh-PoG     |
| RB 0    | 0.0               | EZ                   | lh-Hi      |
| RB 1    | 0.0               | EZ                   | lh-FuG     |
| RB 2    | 0.0008            | EZ                   | lh-EntC    |
| RB 3    | 0.0008            | EZ                   | lh-TmP     |
| RB 4    | 0.0008            | EZ                   | lh-EntC    |
| RB 5    | 0.0008            | EZ                   | lh-Amg     |
| RB 6    | 0.016             | PZ<sub>Clin</sub>    | lh-ITG     |
| RB 7    | 0.0166            | PZ<sub>Clin</sub>    | lh-PHiG    |
| RB 8    | 0.0266            | PZ<sub>Clin</sub>    | lh-LOCC    |
| RB 9    | 0.0336            | PZ<sub>SEEG</sub>    | lh-MTG     |
| RB 10   | 0.0391            | PZ<sub>Clin</sub>    | lh-LgG     |
| RB 11   | 0.0474            | other                | lh-STG     |
| RB 12   | 0.0504            | other                | lh-IPC     |
| SF 0    | 0.0               | EZ                   | rh-LOCC    |
| SF 1    | 0.0003            | EZ                   | rh-PC      |
| SF 2    | 0.0003            | EZ                   | rh-LgG     |
| SF 3    | 0.0008            | EZ                   | rh-Cun     |
| SF 4    | 0.0095            | PZ<sub>Clin</sub>    | rh-FuG     |
| SF 5    | 0.021             | PZ<sub>Clin</sub>    | rh-IPC     |
| SF 6    | 0.024             | PZ<sub>Clin</sub>    | rh-SPC     |
| SF 7    | 0.0253            | PZ<sub>Clin</sub>    | rh-ITG     |
| SF 8    | 0.0272            | PZ<sub>SEEG</sub>    | rh-PCunC   |
| SF 9    | 0.0293            | PZ<sub>Clin</sub>    | rh-MTG     |
| SF 10   | 0.0338            | other                | rh-SMG     |
| SF 11   | 0.0361            | other                | rh-bnks    |
| SF 12   | 0.0374            | other                | rh-PoG     |
Figure 23. Recruitment time and Shortest Path. The recruitment times $t_{rec}$ as a function of the shortest path to the EZ are shown for four patients and all brain areas. Same as Fig. 15 A, with a regression fit that underlines the approximately linear relationship between the shortest path length and the recruitment time. Parameters as in Fig. 15.