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Personalized Recommendations for Neurodegenerative Disease

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Public deliverable report

D3.6: Group level SEEG brain dynamics measures and analysis pipeline

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Dissemination level	**public**
Website	www.VirtualBrainCloud-2020.eu

This project has received funding from the **European Union´s Horizon 2020** research and innovation programme under **grant agreement No 826421**

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1. Introduction

We here present the release of a series of advanced electrophysiological features computed on a full cohort of *N* = 22 adults (average age 40.5 years) that showed no clinically observable indications of dementia and were investigated with invasive intra-cerebral stereo-EEG (SEEG) for pre-surgical evaluation after a diagnosis of intractable focal epilepsy. These data will give a comprehensive view of the dynamics of the human brain in the context of criticality and the communication through coherence framework. The former look at the brain as a complex system poised near a critical regime where its dynamics are balanced between excitation and inhibition. The latter postulate that neuronal communication is favored when presynaptic inputs align with specific phase of excitatory cycle of the target cells (Fries 2015). Combining the two theoretical and experimental frameworks, we provide observations (i.e. metrics) that comprehensively quantify phase synchronization and criticality indices in the same anatomical space with very high signal-to-noise ratio (SNR).

SEEG is an electrophysiological recordings technique used in focal epilepsy patients in order to identify the epileptogenic zone (EZ) that is the cortical mass underlying seizure generation. EZ is formally defined as: “the minimal amount of removed cerebral cortex to produce seizure freedom”. The intracerebral nature of SEEG yields close coupling of the electrodes with meso-scale neuronal populations and thereby SEEG yields a superior SNR and anatomical accuracy compared to non-invasive electrophysiological techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) that acquire electric potential and magnetic field, respectively, signals from scalp level.

Focal epilepsy is a particular subgroup of all the epilepsies, where seizures originate within a single EZ and, in general, cannot be controlled by commercially available drugs. As only a single location displays pathological activity, SEEG data are nowadays *de facto* the gold standard for human invasive recordings as healthy activity can be clearly identified and accurately isolated from the pathological ones. Then, any metric derived from SEEG data if coming from just the healthy tissue, can provide important insights about the physiological dynamics of the human brain. Thus, the set of data we here deliver will help foster a complete overview of the physiological dynamics in the context of dynamical oscillations and criticality. In particular, multiple metrics computed on the same data capturing different aspects of physiological brain dynamics could be used as prior inputs on brain modelling to constraint parameter space to mimic data driven observations. Hence, in our view, could play a key role in advancing and expanding current modelling results.

2. Partners involved

1. University of Genoa, *Lead*
2. Neuroscience Centre, HiLife, University of Helsinki

3. Description of work performed

3.1. SEEG pre-processing

We acquired monopolar (with shared reference in the white matter far from the putative epileptic zone) local field potentials (LFPs) from brain tissue with platinum–iridium, multi-lead electrodes. Each penetrating shaft has 8 to 15 contacts, and the contacts were 2 mm long, 0.8 mm thick and had an inter-contact border-to-border distance of 1.5 mm (DIXI medical, Besancon, France). We acquired an average of 10 minutes of uninterrupted spontaneous activity with eyes closed with a 192-channel SEEG amplifier system (NIHON-KOHDEN NEUROFAX-110) at a sampling rate of 1 kHz.

We excluded electrode contacts that demonstrate non-physiological activity from analyses. We employed a novel referencing scheme for SEEG data where electrodes in grey-matter were referenced by the contacts located in the closest white-matter (CW). This referencing scheme is proven optimal for preserving phase relationship between SEEG contact data.

Prior to the main analysis, SEEG time series were filtered 30 Morlet filter with omega=5 and centered in frequencies ranging from 3 up to 500Hz. We excluded all 50 Hz line-noise harmonics using a band-stop equi-ripples FIR filter with 1 % of maximal band-pass ripples and 3 up to 8Hz width for the stop band parameters.

In SEEG clinical settings, channel position are usually localized by means visual investigation of super-imposed pre-implant and post-implant imaging. In this work, we used rigid co-registration algorithm that maximizes the shared mutual information between the two images by applying an affine transform with 12 degrees of freedom. Cortical pial and grey-white matter surfaces were extracted from pre-implant T1-weighted MRI volume with Freesurfer. We developed a semi-automated segmentation algorithm that uses the planned insertion coordinates (i.e. entry and target points) and the known physical dimensions of each implanted electrode (i.e. number of contacts and inter-contact distances) to identify the contact positions from post-implantation CT imaging data.

3.2. Phase synchronization (PLV/iPLV)

We estimated inter-areal phase-phase interactions at individual subject level using the Phase Locking Value (PLV). Defining $x'(t) = x(t) + i\mathrm{H}[x(t)]$ as the analytical representation of the signal $x(t)$, where H[··] denotes the Hilbert transform, complex PLV (cPLV) is computed as:

$$cPLV = \frac{1}{T}\sum_{t=1}^{T} \frac{x\prime(t)}{|x\prime(t)|}\frac{y'^{*}(t)}{|y'(t)|} \qquad (1)$$

where T is the sample number of the entire signal (i.e., ~10 minutes), and * is complex conjugate. The PLV is the absolute value of complex cPLV ($PLV = |cPLV|$), and it is a scalar measure bounded between 0 and 1 indicating absence of phase and full phase synchronization, respectively.

Additionally, we used imaginary part of cPLV ($iPLV = Im(cPLV)$), a metric insensitive to zero-lag interactions caused by volume conduction(Nolte et al. 2004; Palva et al. 2018; Palva and Palva 2012), for verification. For both PLV and iPLV connectivity, the fraction of significant edges (*K*) is the number of significant edges divided by the total possible edge number. Since one same white-matter contact can be used for referencing multiple cortical contacts, we rejected derivations with shared reference.

We estimated the null-hypothesis distributions of interaction metrics with surrogates that preserve the temporal autocorrelation structure of the original signals while abolishing correlations between two contacts. For each contact pair, we divided each narrow band time series into two blocks with a random time point k so that $x_1(t) = x(1 \dots k)$ and $x_2(t) = x(k \dots T)$, and constructed the surrogate as $x_{surr}(t) = [x_2, x_1]$. We computed surrogate PLV across all channel pairs and assembled the surrogate interaction matrix, and its mean and standard deviation was later used in hypothesis testing.

3.3. Cross-frequency coupling

Cross-frequency Synchronization (CFS) and Phase-amplitude coupling (PAC) were computed between all low- (LF) and high-frequency (HF) frequency pairs at ratios of *n:m* (LF:HF) from 1:2 to 1:7, and for each contact-pair c_a, c_b of non-epileptic contacts. Frequency pairs were chosen so that the ratio of their center frequencies lay within 5% deviation of the desired integer 1:*m* ratio.

CFS was computed as:

$$PLV_{CFS,a,b,m} = \frac{1}{N}\left|\sum_t \exp\left[\mathrm{i}\cdot\left(m\cdot\theta_{a,LF} - \theta_{b,HF}\right)\right]\right| \qquad (3)$$

where $\theta_{a,LF}$ and $\theta_{b,HF}$ are the phases of the time series of contact /parcels. $\theta_{a,LF}$ was upsampled to match the sampling rate of the HF signal and then 'phase-accelerated' by multiplication with m. Local CFS (CFS_{loc}) was obtained where $a = b$ and inter-areal CFS where $a \neq b$.

The strength of PAC was quantified with as:

$$PLV_{PAC,a,b} = \frac{1}{N}\left|\sum_t \exp\left[\mathrm{i}\cdot\left(\theta_{a,LF} - \theta^{env}_{b,HF,LF}\right)\right]\right| \qquad (4)$$

where $\theta^{env}_{b,HF,LF}$ is the phase of the amplitude envelope of the HF signal filtered with a Morlet filter at LF, and downsampled to match the LF signal's sampling rate. Local PAC was obtained where $a = b$, inter-areal PAC where $a \neq b$.

For both CFS and PAC, we obtained, for each frequency pair, surrogate values for each contact pair c_a, c_b by rotating $\theta_{b,HF}$ or $\theta^{env}_{b,HF,LF}$ and then calculated the means over contact pairs ($PLV_{CFS,surr\_mean}$, $PLV_{PAC,surr\_mean}$). this was done separately for inter-areal ($a \neq b$) and local CFC ($a = b$).

Connections with a ratio PLV_{meas}/PLV_{surr} of 2.42 or higher were identified as significant at alpha level 0.01.

In order to correct for potentially spurious observations of inter-areal PAC and CFS arising from non-sinusoidal or non-zero-mean signals, we used a novel method based on graph theory (Siebenhühner et al. 2016, 2020). The rationale, in brief is, that inter-areal CFC can only be spurious if the signal at f_{low} in a and the signal at f_{high} in b are also connected otherwise, namely by local CFC and inter-areal synchronization between a and b. Thus, observations of inter-areal CFC were discarded if we observed either significant local $f_{low}:f_{high}$ CFC in p and significant inter-areal synchronization at f_{high}, or significant local $f_{low}:f_{high}$ CFC in q and significant inter-areal synchronization at f_{low}.

3.4. Avalanches dynamics

We identified neuronal avalanches from SEEG time series and quantified their statistical properties as follows. Using z-transform, we normalized the broadband-filtered time series (1– 40 Hz) by subtracting their mean and dividing by their SD. We then detected amplitude peaks exceeding multiple thresholds T that ranged from 1.5 to 5.25 with step 0.25 and binarized the corresponding time-series. These binary sequences (or sequences of events) were then converted into avalanche time series by summing the events across the electrodes in different time bins (t, ranges from 4 to 80 ms with step 4 ms) (Yang et al. 2012). A neuronal avalanche is defined as cluster of events (i.e. amplitude samples exceeding T) in successive time bins surrounded by at least one empty time bins. The total number of events and the number of time bins represent the avalanche size and life-time duration, respectively

3.5. Long-range temporal correlations

We used detrended fluctuation analysis (DFA) to assess the scaling exponents of Long-range Temporal Correlations (Linkenkaer-Hansen et al. 2001; Palva et al. 2013). We filtered LFPs using Morlet's wavelets with the logarithmically spaced central frequencies (from 3 to 40 Hz). We then applied DFA on the amplitude envelopes (i.e. module of the wavelet transformed signals) of neuronal time series. The analysis can be represented as a two stage procedure. In the first stage, time series X is normalized to 0 mean and cumulatively integrated over time-samples, then we segmented into time windows of various length. At the second stage, each segment of integrated data is locally fitted to a linear function and the mean-squared residual is computed. The scaling exponent ß is defined as the slope of linear regression of the fitted function log-log space.

4. Results

4.1. Data Structure

We here present a set of group-level metrics estimated from SEEG recordings of focal epileptic adult patients. As BIDS specification for connectivity is still being constantly updated and heavily under development we here adopt the current version of the specification document [BEP017].

This release contains:

1. crosspy/DFA/
    a. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.tsv
    b. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.json
2. crosspy/avalanches
    a. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.tsv
    b. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.json
3. crosspy/PLV/
    a. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.tsv
    b. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.json
4. crosspy/CFC-CFS/
    a. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.tsv
    b. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.json
5. crosspy/CFC-PAC/
    a. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.tsv
    b. group_ses-01_run-01_conndata-network_atlas-schaefer2018200P17N_connectivity.json

5. Conclusion, next steps

Here we provide a comprehensive set of metrics that capture different aspects of brain dynamics computed on StereoEEG data. In our view, these data could be of paramount importance in guiding future development of whole-brain modeling initiatives. This release include multiple metrics, harmonized in a common anatomical space that could serve as initial state variable to constraint model evolution in parameter space driving its evolution in even more biologically-realistic way. The full package containing the release is available from the authors.

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