2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Effect of segment length, sampling frequency, and imaging modality on the estimation of measures of brain meta-state activation: an MEG/EEG study

Pablo Núñez, Víctor Rodríguez-González, Víctor Gutiérrez-de Pablo, Carlos Gómez, *IEEE Senior Member*, Yoshihito Shigihara, Hideyuki Hoshi, Roberto Hornero, *IEEE Senior Member*, and Jesús Poza, *IEEE Senior Member*

***Abstract*— The main objective of this study was to examine the influence that recording length, sampling frequency, and imaging modality have on the estimation and characterization of spontaneous brain meta-states during rest. To this end, a recently developed method of meta-state extraction and characterization was applied to a subset of 16 healthy elderly subjects from two independent electroencephalographic and magnetoencephalographic (EEG/MEG) databases. The recordings were segmented into the first 5, 10, 15, 20, 25, 30, 60 and 90-s of artifact-free activity and meta-states were extracted. Temporal activation sequence (TAS) complexity, which characterizes the complexity of the metastateactivation sequences during rest, was calculated. Then, its stability as a function of segment length, sampling frequency, and imaging modality was assessed. The results showed that, in general, the minimum segment length needed to fully characterize resting-state meta-state activation complexity ranged from 15 to 25 seconds. Moreover, it was found that the sampling frequency has a slight influence on the complexity measure, and that results were similar across EEG and MEG. The findings indicate that the proposed methodology can be applied to both EEG and MEG recordings and displays stable behavior with relatively short segments. However, methodological choices, such as sampling frequency, should be carefully considered.**

I. INTRODUCTION

Human brain function is governed by electrochemical processes that are inherently dynamic across time and space: networks of neurons evolve constantly, forming and dissolving assemblies that interact in complex ways [1]. The field known as *dynamic functional connectivity* (dFC) studies the time-varying behavior of interactions between neuronal ensembles [2]. In particular, there has recently been a focus on characterizing the formation and dissolution of repeating brain network patterns with specific topologies that activate in sequence in a metastable way (meta-states), acting as attractors that pull the functional network with varying strength [1], [3].

We recently conducted a study in which a novel method to detect meta-states by means of a measure of instantaneous functional connectivity, recurrence plots (RPs), and community detection algorithms was presented and tested on a database of healthy controls, patients with mild cognitive impairment, and patients with dementia due to Alzheimer's disease (AD) [4]. With the aforementioned method, we were able to successfully extract meaningful meta-states at the individual- and group-level from all subject groups, and to characterize their activation patterns. However, there were several methodological choices, such as the sampling frequency (200 Hz) and the length of the segment (60 seconds), that could have an influence on the results. Moreover, the choice of neuroimaging technique (EEG in the aforementioned study) could also have an impact on the estimations, due to the effects of volume conduction [5].

On the basis of the previous issues, the present study was aimed at characterizing the influence of three factors (i.e., segment length, sampling frequency, and neuroimaging technique) on the estimation of both meta-states and a metric that captures the structural richness of their activation sequences (i.e., temporal activation sequence (TAS) complexity) [4]. To this end, we compared this measure across segment lengths and sampling frequencies with a subset of healthy elderly subjects from two independent databases (with EEG and MEG recordings). The specific objectives of the study were: (i) to determine the minimum segment length needed to achieve stability in the estimations; and (ii) to evaluate whether this length is also influenced by the sampling frequency and neuroimaging technique.

II. MATERIALS

A. Participants

The study sample was composed of 16 cognitively healthy elderly subjects from two independent databases, with no history of psychiatric or neurological disorders. Five minutes of eyes-closed resting-state activity were recorded for both databases. The EEG database was composed of 5 females

This research was supported by 'Ministerio de Ciencia e Innovación - Agencia Estatal de Investigación' and 'European Regional Development Fund' (FEDER) and 'Ministerio de Ciencia, Innovación y Universidades' under projects PGC2018-098214-A-I00, the 'European Commission' and FEDER under project 'Análisis y correlación entre el genoma completo y la actividad cerebral para la ayuda en el diagnóstico de la enfermedad de Alzheimer' and 'Análisis y correlación entre la epigenética y la actividad cerebral para evaluar el riesgo de migraña crónica y episódica en mujeres' ('Cooperation Programme Interreg V-A Spain-Portugal POCTEP 2014–2020'), and by CIBER-BBN (ISCIII) co-funded with FEDER funds.

P. Núñez was in receipt of a predoctoral scholarship 'Ayuda para contratos predoctorales para la Formación de Profesorado Universitario (FPU)' grant from the 'Ministerio de Educación, Cultura y Deporte' (FPU17/00850). V. Rodríguez-González was in receipt of a PIF-UVa grant from the 'University of Valladolid'.

P. Núñez, V. Rodríguez-González, J. Poza, C. Gómez and R. Hornero are with the Biomedical Engineering Group, University of Valladolid, Valladolid, Spain (corresponding author's e-mail: pablo.nunez@gib.uva.es

Y. Shigihara and H. Hoshi are with Hokuto Hospital, Obihiro, Japan.

and 3 males, of median age 77 years (interquartile range 73.5 to 83 years). The MEG database was composed of 3 females and 5 males, of median age 72.5 years (interquartile range 70 to 75 years).

The study was carried out according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants gave written informed consent and the study protocol was approved by the Ethics Committees of the University of Porto (Portugal) and Hokuto Hospital (Obihiro, Japan).

B. Electroencephalographic and magnetoencephalographic recordings

Signals from the EEG database were recorded from a 19-channel EEG system (Nihon Kohden Neurofax JE-921A) with a sampling frequency of 500 Hz and common average reference, following the international 10-20 system (electrodes: Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1, and O2). Signals from the MEG database were recorded by means of a 160-channel axial gradiometer MEG system (MEG Vision PQ1160C, Yokogawa Electric) with a sampling frequency of 1000 Hz.

C. Signal preprocessing

Five minutes of M/EEG activity were recorded for each subject, which were then preprocessed with the same three-step procedure for both databases: (i) artifact rejection by means of independent component analysis. For the MEG database, an additional artifact rejection was performed by means of the SOUND algorithm [6] (ii) finite impulse response (FIR) filtering (Hamming window) to limit spectral content to the wide frequency band of 1-70 Hz, and to remove 50 Hz noise; and (iii) visual rejection of remaining artifacts, selecting the first 90 consecutive seconds of artifact-free activity [7]. The MEG database was resampled to 500 Hz after this final step.

III. METHODS

In the following section, the methodology applied in [4] to detect meta-states and compute the TAS complexity is briefly described. The main method aims to extract repeating brain meta-states during the resting-state under different conditions (sampling frequency, segment length, and imaging modality), and compute a measure of complexity from their activation (TAS complexity). Afterwards, the stability of the measure under the different parameters is assessed.

A. Study protocol: community detection of brain meta-states

1) All recordings were reconstructed at the source level by means of standardized low resolution brain electromagnetic tomography (sLORETA) [8]. A 15000 source head model was used as source space. The source-reconstructed time series were then averaged into 68 cortical regions of interest (ROIs) according to the Desikan-Killiany atlas [9].
2) The 90-s M/EEG recordings were subsampled to sampling frequencies of 200, and 100 Hz. The segments were subdivided into the first 5, 10, 15, 20, 25, 60, and 90 s of activity. All the following steps were performed for each individual segment length and sampling frequency (500, 200, and 100 Hz) in the following frequency bands: delta (δ, 1-4 Hz), theta (θ, 4-8 Hz), alpha (α, 8-13 Hz), beta-1 ($\beta 1$, 13-19 Hz), and beta-2 ($\beta 2$, 19-30 Hz).
3) A tensor of instantaneous functional connectivity of size 68 ROIs $\times$ 68 ROIs $\times$ (number of sampling frequencies (3) $\times$ number of types of segments (5)) was built by means of the instantaneous amplitude correlation (IAC).
4) Recurrence plots (RPs) were built from the IAC matrices and data-driven windows were obtained from them to reduce their size by averaging the IAC over time.
5) Community detection was performed on the aggregated RPs to extract the meta-states that appeared in the segment.
6) The TAS, a representation of the temporal sequencing of the meta-states, was obtained and its complexity (TAS complexity) was computed.
7) An exploratory stability analysis was performed to determine the minimum segment length needed to characterize meta-states for each sampling frequency, and imaging modality.

The individual methods used in each step are briefly described in the following sections. For a detailed explanation, please refer to [4].

B. Instantaneous amplitude correlation (IAC)

The IAC is a high temporal resolution measure of functional connectivity (FC) based on the amplitude envelope correlation [10] and can be seen as its instantaneous counterpart [10]. It is calculated as the Hadamard product between the amplitude envelopes of two ROIs [10]:

$$IAC_{ij}(t) = \hat{E}_i(t) \circ \hat{E}_j(t), \tag{1}$$

where $\circ$ represents the Hadamard product and $\hat{E}(t)$ is the amplitude envelope of a normalized (z-score) time-series. The M/EEG recordings were pairwise orthogonalized to prevent spurious correlations due to spatial leakage [2].

C. Construction of recurrence plots (RPs)

RPs are two-dimensional plots that can characterize the emergence and dissolution of states in dynamical systems and help to visualize periodicity patterns [11]. They are symmetric $N \times N$ arrays (where N represents the time points) that indicate how the system returns to previous states [11]: In the present study, the Spearman correlation between the IAC FC time-series, instead of the norm, is used for the RP construction, to avoid the selection of an arbitrary threshold [10].

$$\mathbf{R}_{n,m} = \mathrm{corr}[IAC(n), IAC(m)]. \tag{2}$$

where $IAC(n)$ is the instantaneous connectivity at time n. Hence, an RP that displays how the functional network returns to similar configurations is obtained.

The RPs can be employed to display points in time where the system transitions to other states by calculating the gradients, where the local maxima in the gradient matrix expose transitions to other states. These points are used as boundaries for data-driven windows [10]. The IAC was temporally averaged over these windows and a smaller RP was computed with the windowed IAC.

D. Meta-state extraction

If one interprets the RPs as weighted graphs where each window is a node and each correlation between windows is an edge, community detection algorithms can be applied to find the windowed connectivity matrices that are highly correlated. By doing this, clusters of repeating patterns of connectivity can be extracted [4]. In the present study, the Louvain GJA community detection algorithm was used to detect repeating meta-states due to its ability to be robust in the presence of poorly defined communities [12]. The meta-states were computed as the average of the connectivity matrices that were assigned to the same community.

E. Meta-state temporal activation sequence

After obtaining the meta-states from the RPs, each IAC connectivity matrix in the original time-series is assigned to the closest meta-state (Spearman correlation distance). This procedure yields a symbolic sequence, called the TAS were the value of each temporal sample represents the currently active meta-state [4].

F. TAS complexity

The TAS complexity is a measure that characterizes the underlying structural complexity of the TAS. It is computed as the Lempel-Ziv complexity (LZC) of the TAS [4]. The LZC is directly related to the amount of distinct substrings in the sequence and how often they occur, indicating the level of complexity of the said sequence [13].

G. Measure normalization by means of surrogate data

In order to evaluate whether the TAS complexity measure is due to genuine dFC and not due to random fluctuations, surrogate data normalization was performed [14]. Surrogate versions of each M/EEG recording were constructed by means of the amplitude adjusted Fourier transform (AAFT), using the same sequence of random numbers for every ROI to preserve static FC. [4], [14]. All the TAS complexity values were normalized by dividing them by the average values obtained from 100 surrogate time series [4].

IV. RESULTS AND DISCUSSION

The main objective of the study was to determine the minimum segment length needed to adequately characterize meta-state activation, while also taking into account the influence of sampling frequency and imaging modality. To this end, the stability of the normalized TAS complexity as a function of segment length was assessed for each combination. The elbow criterion was used to determine the point in which the average TAS complexity values reached stability.

Figure 1 shows the grand-average normalized TAS complexity values for each database, frequency band, and sampling frequency. Following the elbow criterion, it was observed that that TAS complexity values tend to stabilize at a length of around 15 to 25 s, with a slight dependence on sampling frequency on lower frequency bands (delta and theta). The neuroimaging modality does not seem to influence the minimum recording length. Thus, we hypothesize that a minimum length of around 15-25 s is needed to obtain stable and reproducible results when characterizing meta-state activation during the resting-state.

The aforementioned minimum segment length could be due to multiple factors. In a previous study, we found that the amount of brain meta-states that appear during rest is not dependent on the frequency band [4]. Thus, it could be plausible that the faster nature of EEG activity in higher frequency bands displays the whole range of meta-state sequences in less time. We hypothesize that the minimum segment length could be related to the time it takes for the brain to display the full range of meta-states before a new "cycle" of activation begins. Nonetheless, this could also be due to inherent limitations of the community detection algorithm, as they usually perform better with larger graph sizes [12]. Lower frequency bands have less nodes in their RPs due to the fact that data-driven windows are larger, as at they must have a length of at least one-cycle of the frequency band [10]. Hence, this is a factor that must be taken into account.

Moreover, it can be observed that, in general, TAS complexity values show less variation with sampling frequency for higher frequency bands, and they do not seem to converge to a single average value in delta and theta for the sizes explored in the study. Thus, even though TAS complexity stabilizes at similar recording lengths, it could be the case that longer segments are needed until they converge for all sampling frequencies. Therefore, higher sampling frequencies should be selected when available if one wishes to use shorter segments, for example to reduce computational time, as the Louvain GJA algorithm runs in $O(n \log 2(n))$ time, where n is the number of nodes in the network [15].

The study has two main limitations. The first is the size of the database. Due to the computational time needed to perform the surrogate analysis, a small selection of healthy subjects was used for this study. However, both databases consist of subjects with mild cognitive impairment and dementia due to Alzheimer's disease, in addition to cognitively healthy controls. Therefore, a thorough analysis should be performed, including subjects from all groups, in order to improve statistical power and assess the influence of these neurodegenerative diseases on the minimum length needed for each sampling frequency and band. The second limitation is that only one measure from the array of possible meta-state activation measures was assessed [4]. Ideally, a similar procedure should be performed for all of them, as the lower limit could be different for some due to the properties they characterize.

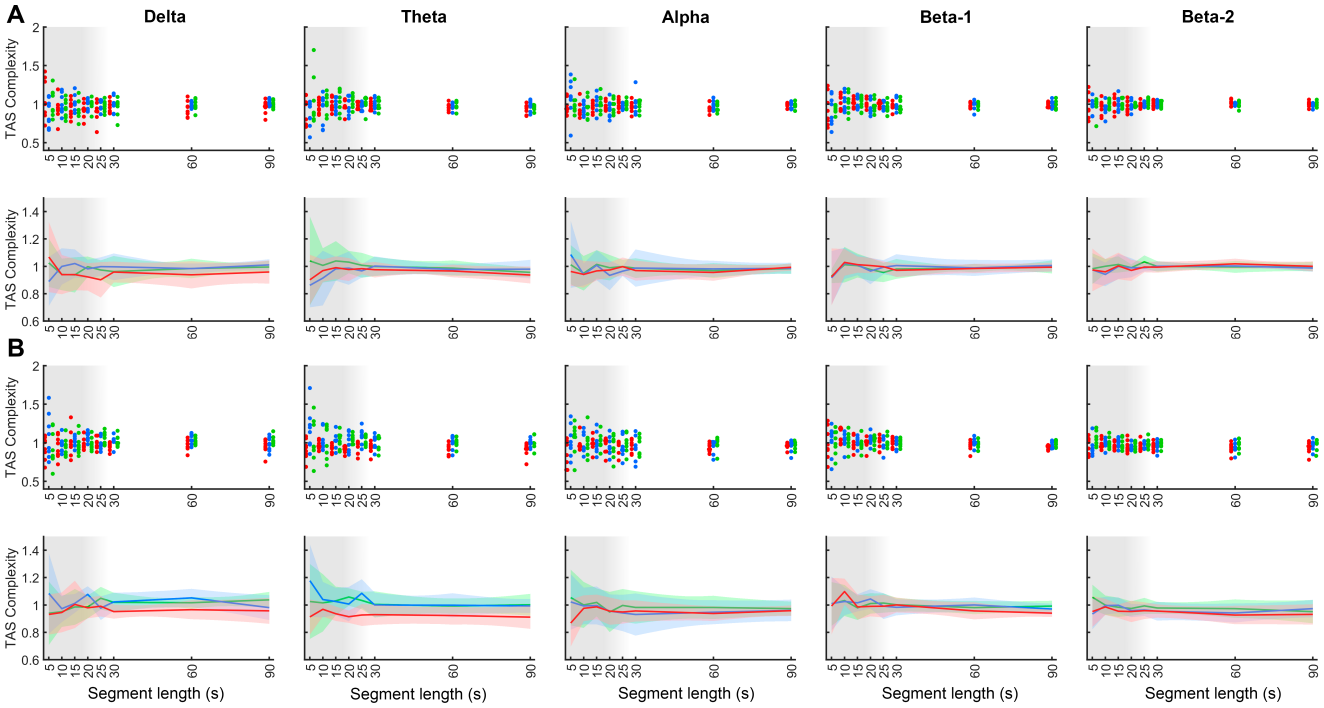

Fig. 1. Normalized TAS complexity values across frequency bands and sampling frequencies for (A) the EEG database and (B) the MEG database. For each frequency band, the upper panel represents the distribution of the normalized TAS complexity values, the bold lines in the lower panel represent the mean normalized TAS complexity values, while the shaded area marks the standard deviation. The red lines correspond to values obtained for a sampling frequency of 500 Hz, the blue lines correspond to values obtained for a sampling frequency of 200 Hz, and the green lines correspond to values obtained for a sampling frequency of 100 Hz. In both panels, the gray area represents the range of segment lengths in which the TAS complexity values do not exhibit stable behavior for all sampling frequencies.

V. CONCLUSIONS

The influence of M/EEG recording length on a measure of complexity of meta-state activation in the brain was assessed. We have demonstrated that a relatively short length (i.e., 15-25 s) could be considered enough to fully characterize the variety of resting-state activation sequences in healthy controls, while acknowledging that sampling frequency and the frequency band under study should be carefully selected to avoid running into limitations of the community detection algorithm. These results suggest that the healthy brain could go through "cycles" of meta-state activation during rest that are of relatively short duration. Moreover, useful information could be extracted from small segments of M/EEG activity, optimizing computational time and the viability of its potential use in a clinical setting.

REFERENCES

[1] E. Tognoli and J. A. S. Kelso, The Metastable Brain, Neuron, vol. 81, no. 1, pp. 35–48, 2014.

[2] G. C. O'Neill, P. Tewarie, D. Vidaurre, L. Liuzzi, M. W. Woolrich, and M. J. Brookes, Dynamics of large-scale electrophysiological networks: A technical review, Neuroimage, vol. 180, pp. 559–576, 2018.

[3] J. Vohryzek, G. Deco, B. Cessac, M. L. Kringelbach, and J. Cabral, Ghost Attractors in Spontaneous Brain Activity: Recurrent Excursions Into Functionally-Relevant BOLD Phase-Locking States, Front. Syst. Neurosci., vol. 14, no. April, pp. 1–15, 2020.

[4] P. Núñez et al., "Abnormal meta-state activation of dynamic brain networks across the Alzheimer spectrum," Neuroimage, vol. 232, p. 117898, 2021.

[5] M. Lai, M. Demuru, A. Hillebrand, and M. Fraschini, A comparison between scalp- and source-reconstructed EEG networks, Sci. Rep., vol. 8, no. 1, pp. 1–8, 2018.

[6] V. Rodríguez-González et al., "Consistency of local activation parameters at sensor- and source-level in neural signals," J. Neural Eng., vol. 17, no. 5, p. 056020, 2020.

[7] P. Núñez et al., Characterizing the fluctuations of dynamic resting-state electrophysiological functional connectivity: reduced neuronal coupling variability in mild cognitive impairment and dementia due to Alzheimer's disease, J. Neural Eng., vol. 16, no. 5, p. 056030, Sep. 2019.

[8] R. D. Pascual-Marqui, Standardized low-resolution brain electromagnetic tomography (sLORETA): Technical details, Methods Find Exp Clin Pharmacol., vol. 24, no. Suppl D, pp. 5–12, 2002.

[9] R. S. Desikan et al., An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest, Neuroimage, vol. 31, no. 3, pp. 968–980, 2006.

[10] P. Tewarie et al., Tracking dynamic brain networks using high temporal resolution MEG measures of functional connectivity, Neuroimage, vol. 200, pp. 38–50, 2019.

[11] N. Marwan, M. Carmen Romano, M. Thiel, and J. Kurths, Recurrence plots for the analysis of complex systems, Phys. Rep., vol. 438, no. 5–6, pp. 237–329, 2007.

[12] K. M. Gates, T. Henry, D. Steinley, and D. A. Fair, A Monte Carlo Evaluation of Weighted Community Detection Algorithms, Front. Neuroinform., vol. 10, 2016.

[13] D. Abásolo, R. Hornero, C. Gómez, M. García, and M. López, Analysis of EEG background activity in Alzheimer's disease patients with Lempel-Ziv complexity and central tendency measure, Med. Eng. Phys., vol. 28, no. 4, pp. 315–322, 2006.

[14] R. Hindriks et al., Can sliding-window correlations reveal dynamic functional connectivity in resting-state fMRI?, Neuroimage, vol. 127, pp. 242–256, 2016.

[15] A. Lancichinetti and S. Fortunato, "Community detection algorithms: A comparative analysis," Phys. Rev. E, vol. 80, no. 5, p. 056117, 2009.