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Time changes of involvement indexes in a cohort of epileptic patients during a working memory task

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Abstract:
Working memory (WM) is the mental ability to encode, keep, and manipulate information over a short period of time. It can be noninvasively investigated by electroencephalography (EEG) and implies a certain level of mental involvement that can be evaluated by computing involvement indexes based on the spectral power of EEG rhythms. WM impairment is known to be present in epileptic patients. Thus, this study aims to evaluate if (and how) EEG-derived involvement indexes change over time in a population of epileptic patients during a WM task. The population analyzed comes from a public dataset, acquired and organized by Boran et al. EEG data were recorded while patients were performing a verbal WM task, which included 50 trials of about 8 s each. The EEG signals were analyzed for the preprocessing and extraction of normalized involvement indexes according to the definition presented in the review by Marcantoni et al. (2023). Starting from the spectral power energy of the EEG-derived rhythms, 37 involvement indexes were computed recursively along the EEG for each patient. Results showed that involvement indexes change throughout the WM task, according to the cognitive engagement elicited in its phases. Changes of involvement indexes with respect to the resting cognitive status of patients were most heightened in the frontal region. Moreover, most indexes increase during the task and the indexes that showed a decrease with respect to resting cognitive status are those having high-frequency rhythms (α, β, γ) at the denominator in their definition. In the population here considered, only the patients affected by brain contusion and hippocampal sclerosis seem to deviate from the physiological paradigm. This study has to be intended without the purpose of generalizing the obtained outcomes, which are preliminary and may be confirmed in further studies on more homogeneous and larger epileptic populations.

Keywords: Involvement index, Working memory, Epilepsy.

1. Introduction: Working memory in epilepsy

Working memory (WM) is defined as the ability to encode, keep, and manipulate information in mind over a short period of time. It is often conceptualized as a mental workspace where information is actively processed. Being one of the main components of information processing, WM plays a crucial role in several cognitive tasks, such as language comprehension, mathematical reasoning, decision-making, spatial processing, learning, and planning (Myatchin, 2011).

Given its role, WM involves the coordinated activity of multiple brain regions and neural networks, as shown noninvasively with electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Evidence from fMRI studies demonstrated that WM relies on oscillatory interactions within and between large-scale functional networks. The most involved is the frontoparietal central executive network, which interacts with other networks during WM tasks, such as the salience network, and the default mode network. From EEG studies, it has been observed that neural oscillations assume specific roles in WM tasks according to their frequency. Indeed, based on the EEG frequency range (0.1-100 Hz), five EEG frequency bands, also known as EEG rhythms, can be derived: delta, theta, alpha, beta, and gamma. These rhythms, distributed along the EEG frequency range, are widely recognized even if the frequency thresholds of each band are not uniquely defined. Among EEG rhythms, theta and alpha are the most studied rhythms during WM tasks, but also gamma rhythm, sometimes coupled with theta or alpha, has been evaluated (Chai, 2018; Arski, 2021). Specifically, theta rhythm exhibits power increases associated with greater levels of mental effort in the frontal brain regions, while power in the alpha band is often seen to decrease under conditions of greater mental effort, especially in posterior brain regions (Meltzer, 2007; Brzezicka, 2019). The level of mental involvement in a task can be also evaluated by computing involvement (or engagement) indexes based on the spectral power of EEG rhythms, as reported by Marcantoni et al. (Marcantoni, 2023).

WM impairment is well-documented in both children and adults with epilepsy. Indeed, it is a common comorbidity of epilepsy (Chai, 2023). It has been observed in generalized epilepsy (Myatchin, 2009), as well as in temporal lobe epilepsy (Stretton, 2012; Bolocan, 2021), and frontal lobe epilepsy (Caciagli, 2023). Many factors contribute to WM impairment in epilepsy, including epileptogenic substrate, recurrent seizures, interictal epileptic activity, and anti-epileptic drugs. Given the multifactorial causes, there is an unmet need to better understand WM impairment to develop treatments targeting WM function in individuals with epilepsy (Arski, 2021).

In this context, the present study aims to evaluate if (and how) EEG-derived involvement indexes change over time in a population of epileptic patients during a WM task in accordance with their cognitive engagement.

2. Literature Review

According to the aim of this study, a literature review was conducted in Scopus. Studies that consider epileptic patients while performing a WM task were taken into account. Some of them, like the study of Bolocan et al, simply evaluated the answers of WM tasks performed by epileptic patients (without taking into account EEG or fMRI data) to demonstrate their WM deficits. Other studies evaluated fMRI data to better understand the brain regions involved in WM tasks or the role of specific brain regions, like the hippocampus, in such tasks (Boran, 2019a; Qin, 2023). Among the studies that analyzed EEG data, none of them evaluated involvement indexes during a WM task. Most of them evaluated only theta and alpha rhythms, pointing out that both rhythm changes are common during WM tasks. However, instead of having an increased theta power during the WM task (as in healthy subjects), the theta power seems to be reduced in epileptic patients (Brzezicka, 2019; Tuladhar, 2007; Boran, 2019a; Qin, 2023; Arski, 2021). The study of Qin et al. demonstrated also an unbalance between activation and deactivation networks during the WM process, which may indicate the pathophysiological mechanism of cognitive dysfunction in generalized epilepsy (Qin, 2023).

3. Material: Database description

The population analyzed in the present study comes from a public dataset that can be downloaded at https://doi.gin.g-node.org/10.12751/g-node.d76994/ (Boran, 2019b). It includes scalp EEG data recorded according to the 10-20 system with the NicoletOne system (0.3–100 Hz passband, Natus®, https://neuro.natus.com) from a population of 9 epileptic patients. The sampling frequency of the system was 200 Hz and the number of EEG channels recorded was not the same for all the patients. Details about patients' age, gender, type of epilepsy, and EEG channels recorded are reported in Table 1.

EEG data were recorded while the patients were performing a verbal WM task which included 50 trials of about 8 s each. Thus, the database included 50 EEG signals (about 8 s long) for each patient. The WM task used was a modified Sternberg task, where encoding of memory items, retention, and recall were temporally separated. In particular, each trial started with a 1-s period in which a fixation dot was displayed on the screen (fixation period). After that, a set of consonants (stimulus) was presented for 2 s at the center of the screen and patients were required to retain them in memory for 3 s (retention period). All stimuli contained 8 consonants. Of these, the middle 4, 6 or 8 letters were the memory items. When the size of the memory set was 4 or 6, the outer positions were filled with X which was never a memory item. Thus, the physical size and the visual content of the stimulus were always the same, independently from the size of the memory set. After the 3-s retention period, the probe letter was displayed on the screen and patients were asked to indicate whether the probe letter was part of the stimulus by pressing a button on a joystick (recall). After the response, the probe was turned off and patients received acoustic feedback whether their response was correct or incorrect. Trials with different sizes of the memory set were presented in random order (Boran, 2019b; Michels, 2008).

4. Methods: Computation of involvement indexes

The EEG signals were analyzed in MATLAB R2022b using EEGLAB. The preprocessing included band-pass filtering between 0.5 Hz and 100 Hz, baseline removal, powerline removal using CleanLine, and noise removal by independent component analysis (ICA). This last preprocessing phase was performed by exploiting a specific plugin of EEGLAB that provided an estimation of the probability that the extracted independent components belonged to 6 possible classes. The considered classes depended on the physiological or

Table 1 – Characteristics of the study population.

Patient	Age (years)	Gender	Pathology	EEG channels recorded
1	24	Female	Xanthoastrocytoma WHO II	F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, A1, A2
2	39	Male	Gliosis	F3, F4, C3, C4, O1, O2, A1, A2
3	18	Female	Hippocampal sclerosis	F3, F4, C3, C4, O1, O2, A1, A2
4	28	Male	Brain contusion	F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, A1, A2
5	20	Female	Focal cortical dysplasia	Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T4, T5, T6, Fz, Cz, Pz, A1, A2
6	31	Male	Hippocampal sclerosis	Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2
7	47	Male	Hippocampal sclerosis	F3, F4, C3, C4, O1, O2, A1, A2
8	56	Female	Hippocampal sclerosis	F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, A1, A2
9	19	Female	Hippocampal sclerosis	F3, F4, C3, C4, O1, O2, A1, A2

(Boran, 2019b)

extra-physiological source contributing to the components and were: “brain”, “muscle”, “eye”, “heart”, for the physiological sources; “line noise”, “channel noise”, for extra-physiological sources; “other”, for unrecognized sources. The probability that a component belonged to a given class was automatically computed by a pre-trained classifier implemented within the plugin. Then, based on these probabilities, components were removed from the EEG signal if the percentage of “brain” source was lower than 10% or if the percentage of at least another class (*i.e.*, “muscle”, “eye”, “heart”, “line noise”, “channel noise”, “other”) was higher than 90%. After that, for each patient, EEG signals of all trials were averaged channel by channel, and the mean EEG signal obtained was recursively windowed. Specifically, 3-s EEG windows were extracted every second until the end of the signal was reached. Then, for each EEG channel, EEG rhythms were extracted from each EEG window by applying a 6^{th}-order bidirectional Butterworth filter. Specifically, the filter passing band was defined in the frequency range 8–12 Hz for alpha rhythm (α), 13–30 Hz for beta rhythm (β), 30–90 Hz for gamma rhythm (γ), 0.5–4 Hz for delta rhythm (δ), 4–7 Hz for theta rhythm (θ), and 12–15 Hz for somatosensory rhythm (SMR). After that, the power spectral density of each extracted EEG rhythm was computed for each EEG window and channel using the Welch’s overlapped segment averaging estimator. Then, only the common EEG channels among patients were further analyzed singularly. The area under each power spectral density was computed and referred to as spectral power energy. Starting from the spectral power energy of the previously defined EEG rhythms, 37 involvement indexes were computed for each EEG window and for each patient. The definition of such indexes is provided in the systematic review by Marcantoni et al. (Marcantoni, 2023). Values of each index were then normalized by the maximum value reached (by the same index) over the EEG windows considered.

Overall evaluations were performed only for patients having the same kind of pathology. Specifically, indexes of those patients were averaged (median) channel by channel.

Distributions of the 37 involvement indexes in each EEG window were averaged over EEG channels belonging to the same cortical region and compared against the first EEG window (fixation period) by the Wilcoxon signed rank test, setting the statistical significance (p) to 0.05.

5. Results

After EEG windowing, 6 EEG windows were analyzed for each patient. Thus, each involvement index was described by 6 consecutive values, computed considering the spectral power energy of EEG rhythms in the consecutive EEG windows. The EEG channels resulted common among patients were: F3, F4 (frontal region), C3, C4 (central region), O1, O2 (occipital region). Overall evaluation was performed only over patients 3, 6, 7, 8, and 9, who were all affected by hippocampal sclerosis, while patients 1, 2, 4, and 5 were evaluated singularly since they were affected by different pathologies. Results relative to patients 1, 2, 4, and 5 are displayed in Figure 1, 2, 3, and 4, respectively, while those relative to the overall evaluation of patients 3, 6, 7, 8, and 9 are displayed in Figure 5. Each figure is divided into 37 panels, one per index. Each panel contains 6 coloured lines, one per EEG channel. Each line represents the trend of the involvement index over the time instants considered, since it connects the values the index has assumed in the recursively-extracted EEG windows. Such values are represented with a star marker placed at the central time instants of the considered windows, and refer to different phases of the WM task, which are confined by dotted lines in each panel. Specifically, the first value refers to the initial fixation period, the last value refers to the final recall period, while all the others refer to the stimuli and retention period. A minimum or a maximum in the index trend indicates that the index changes over time during the WM task, while a flat index trend indicates minor changes during the WM task. The line’s colour varies according to the cortical region covered by the EEG channels considered: F3 and F4 were represented in red, C3 and C4 were

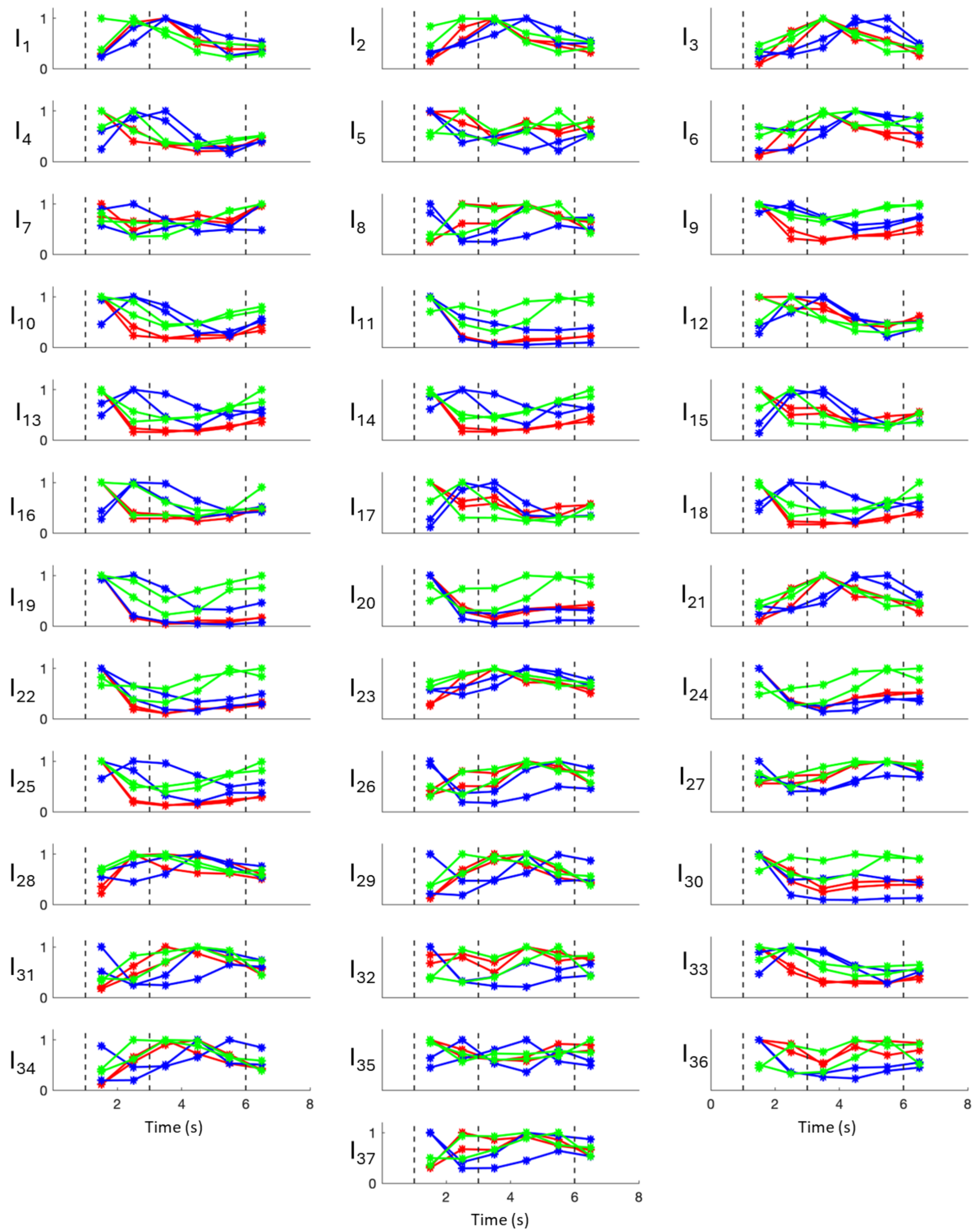

Figure 1 – Involvement indexes over time related to patient 1 (axes limits were reported only on the first panels of each row/last panels of each column, referring to the entire row/column).

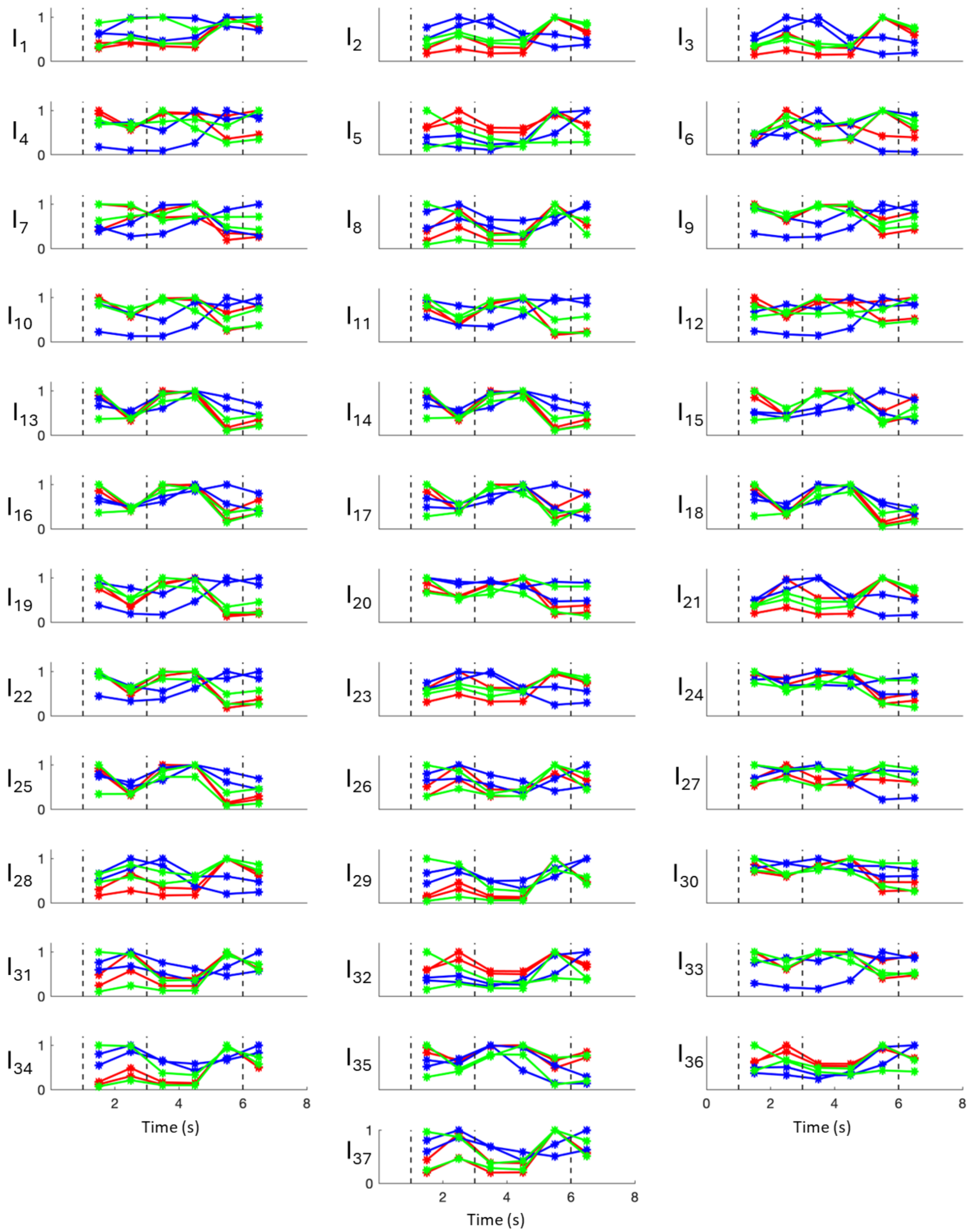

Figure 2 – Involvement indexes over time related to patient 2 (axes limits were reported only on the first panels of each row/last panels of each column, referring to the entire row/column).

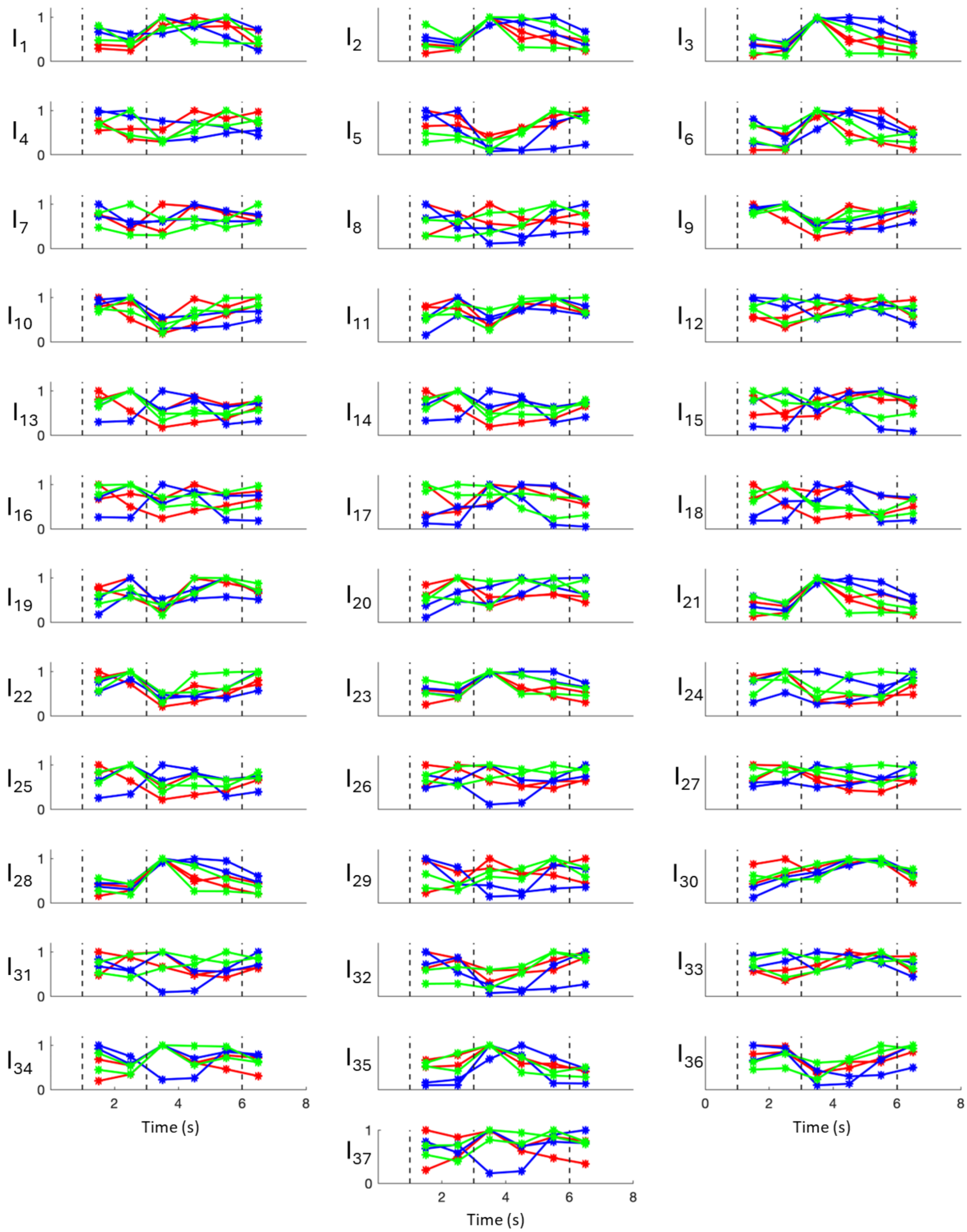

Figure 3 – Involvement indexes over time related to patient 4 (axes limits were reported only on the first panels of each row/last panels of each column, referring to the entire row/column).

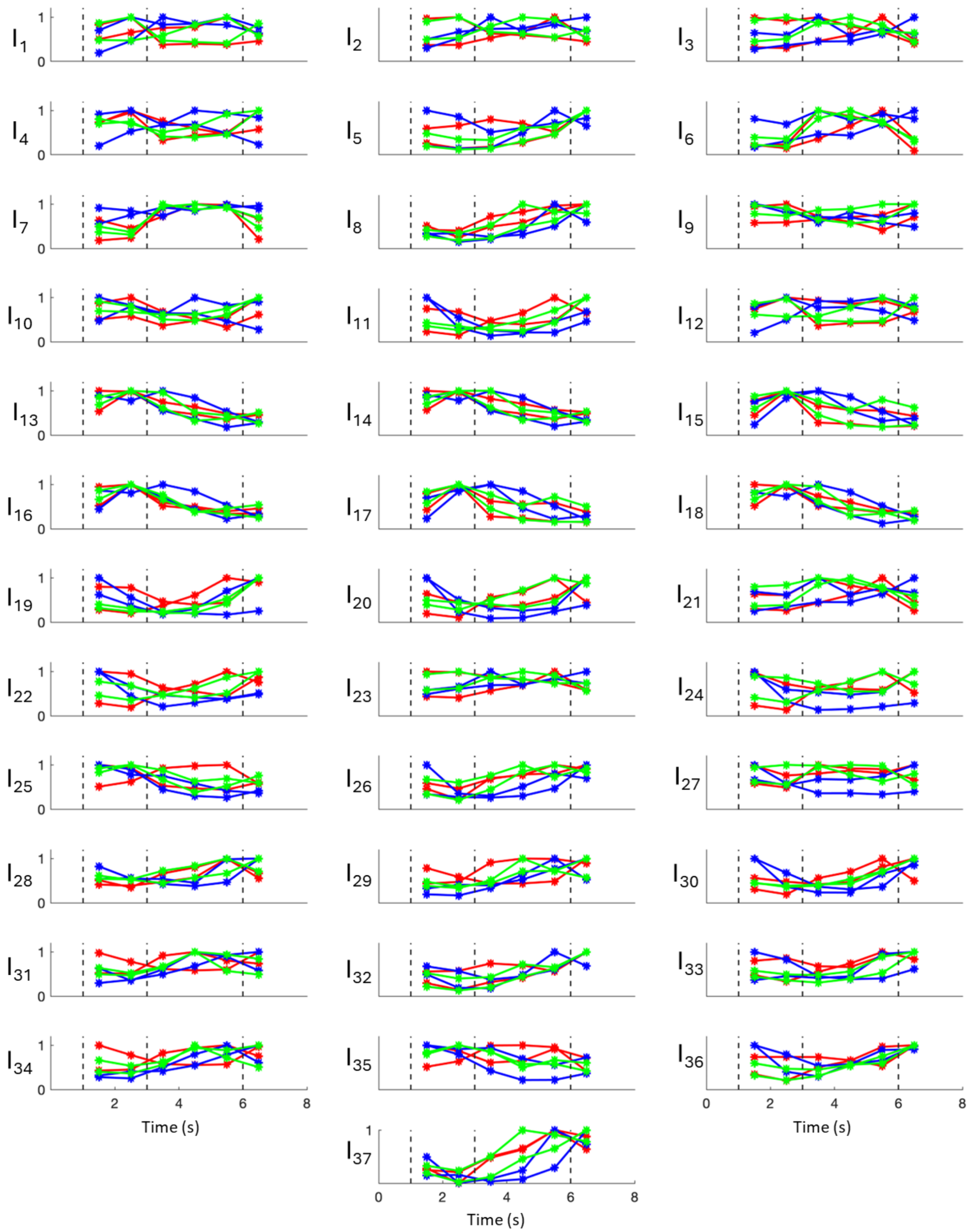

Figure 4 – Involvement indexes over time related to patient 5 (axes limits were reported only on the first panels of each row/last panels of each column, referring to the entire row/column).

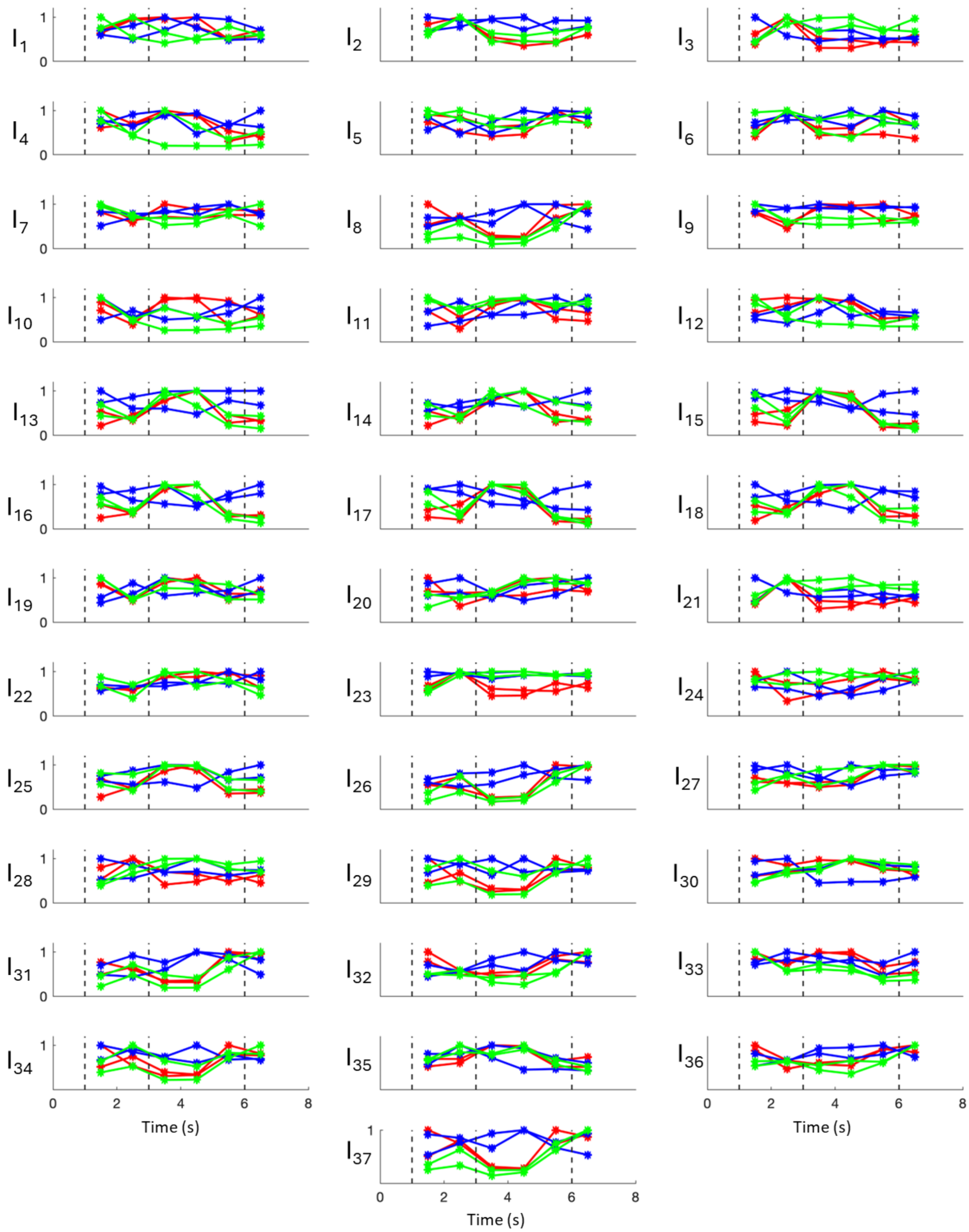

Figure 5 – Involvement indexes over time related the overall evaluation of patients 3, 6, 7, 8, 9 (axes limits were reported only on the first panels of each row/last panels of each column, referring to the entire row/column).

represented in blue, while O1 and O2 were represented in green. Overall, most involvement indexes had the tendency to increase during the WM task. However, indexes I_4, I_9 –I_{20}, I_{22}, I_{25}, I_{33}, I_{35} decreased their values with respect to the first EEG window (first star marker). From Figure 5, it can be noticed that in EEG channels located in the central region, some indexes, in particular I_9 and I_{23}, do not change during the WM task.

Results about the statistical difference of index distributions in each EEG window confirmed which changes were meaningful and showed that:

- For patient 1: in the frontal region all comparisons resulted statistically different; in the occipital region only the 3rd window.
- For patient 2: in the frontal region all comparisons resulted statistically different but the 3rd window; in the central region only the 4th window; in the occipital region all comparisons but the 3rd and 4th windows.
- For patient 4: in the central region only the 3rd and 4th windows resulted statistically different.
- For patient 5: in the frontal region only the 3rd window resulted statistically different.
- For patients 3, 6, 7, 8, 9 (averaged together): in the frontal region all comparisons resulted statistically different but the 2nd window; in the central region only the 1st window; in the occipital region only the last window.

6. Discussion

This study evaluated if (and, in case how) EEG-derived involvement indexes change over time during a WM task in an epileptic population. To reach this aim, the dataset of Boran et al., containing simultaneous scalp EEG and intracranial EEG recordings during a verbal WM task, was considered. This dataset was suitable for a comparison of EEG-derived involvement indexes between the resting cognitive status (initial fixation period) and each of the other phases of the WM task performed by the epileptic patients, having different pathological conditions (xanthoastrocytoma WHO II, gliosis, hippocampal sclerosis, brain contusion, focal cortical dysplasia). This study took into account only scalp EEG data, but further studies may investigate also intracranial EEG-derived involvement indexes for comparative analysis. The choice of this dataset was justified by the fact that the protocol applied (modified Sternberg task) involved repetition of the same task many times (50) allowing to have a common task-dependent pattern among the trials, that could be highlighted by computing the mean. On the other side, some drawbacks have to be considered: the database contained data from only 9 patients, having different pathologies (only patients 3, 6, 7, 8, 9 had the same pathology) and moreover a different number of EEG channels were acquired. Thus, patients 1, 2, 4, and 5 had to be considered singularly, since the analysis could have different outcomes according to the pathology. In addition, only common EEG channels were analyzed for the involvement indexes computation.

Figures show that involvement indexes change throughout the WM task, reflecting EEG-rhythm changes, which are dependent from the cognitive engagement elicited by the different phases of the WM task. Involvement index changes with respect to the patient’s resting cognitive status (fixation period) were most heightened in frontal regions, where most differences between index values over time resulted to be statistically significant. Along with frontal regions, also occipital regions showed some significant involvement index changes. Indeed, despite the inherent subjective nature of mental processes, which may result in the activation of different brain regions from subject to subject, the literature has widely recognized frontal and occipital regions as physiologically related to analytical reasoning and decision-making. These mechanisms may be different in pathophysiological conditions like epilepsy, which could imply cognitive dysfunctions reflecting on the EEG. However, in the population here considered, only the patient affected by brain contusion seems to deviate from this physiological paradigm.

The indexes that showed a decrease with respect to the resting cognitive status are those having high-frequency rhythms (α, β, γ) at the denominator in their definition. Thus, our outcomes on the epileptic population considered seem to be in accordance with the literature in which intense high-frequency EEG rhythms and suppressed low-frequency EEG rhythms are associated with higher cognitive engagement. However, a deviation from this paradigm was observed for patients affected by hippocampal sclerosis (Figure 5).

Based on our literature review, there are no studies evaluating time changes of EEG-derived involvement indexes during a WM task, but simply time changes of single EEG rhythms. Thus, only a qualitative comparison with the literature was possible and was performed as an additional remark. It would be interesting to consider also a healthy population and a pathologic population with different conditions, because this would allow to emphasize any possible difference that could be attributed only to the epileptic condition. Nevertheless, this would imply the availability of databases in which all participants (healthy subjects and patients) are performing a WM task with the same protocol. As far as we know, these databases are not available; thus, a real statistical and quantitative inter-population comparison was not feasible for our results.

This study has to be intended as the observation of a small cohort of epileptic patients without the purpose of generalizing the obtained outcomes. Indeed, the limited dimension of the population and the lack of a homogeneous clinical profile prevent statistically significant evaluations. Future works should perform an analogous analysis of the involvement indexes on larger databases in order to possibly confirm our preliminary results and benefit from them as a valid term of comparison.

7. Conclusions

This study suggests that involvement indexes are able to reflect changes of cognitive engagement during WM tasks in case of epilepsy. Even if some results highlighted a deviation from the physiological condition, overall they confirm what was already observed in healthy subjects in relation to the role of the frontal region as the cortical area mostly involved in cognitive tasks.

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