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A fusion scheme of EEG epoch durations for an improved Alzheimer’s disease detection

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Abstract* – Electroencephalography (EEG) has been exploited since a long time for Alzheimer’s disease (AD) diagnosis. Several studies in the literature investigated functional connectivity to distinguish between AD patients and Healthy controls. In this work, we investigate the impact of analyzing EEG signals with different epoch durations on classification performance, when discriminating AD patients from Subjective Cognitive Impairment (SCI) subjects, using Phase-Lag Index (PLI) to quantify functional connectivity. We find that the PLI measurement is more reliable to distinguish between SCI and AD epochs, when it is estimated on large epochs. Then, going towards the classification of AD and SCI patients, we average the classifier output scores of epochs, for each epoch duration. Results show that fusing the output scores of epochs allows achieving better classification performance, compared to the obtained results on separate epochs. The best classification performance of AD and SCI patients is obtained with epochs of 4 seconds (AUC=0.825, Accuracy=82%). Finally, we propose a new framework based on the fusion of classification results at different epoch durations. Experiments show that this proposal leads to an improvement of classification performance, reaching an AUC of 0.93 and an Accuracy value of 90%, with a good balance between Specificity and Sensitivity.

Keywords: Electroencephalography; Alzheimer’s disease; epoch duration; score fusion; classifier probabilistic scores.

I. INTRODUCTION

Alzheimer’s disease (AD) is a chronic, neurodegenerative disease caused by changes in the nerve cells of the brain. The causes of the disease are not totally identified; however, some medical studies have linked AD to the accumulation of amyloid plaques and neurofibrillary tangles in the brain, which disrupts the brain dynamics and leads to the death of neurons [1]. Other studies have identified other potential causes, which involve immune [2], inflammatory [3], and infectious phenomena [4].

The disease at its early stage generally affects memory, language and reasoning functions [5]. AD is clearly distinct from ageing and its incidence increases sharply after age 65 [6]. AD accounts for about 70% of dementia cases in the world. It is estimated that AD affected 25 million people worldwide in 2010, and this number is rising sharply particularly in Western countries due to the unprecedented level of aging [5,6], thus imposing a highly health care costs.

The disease progresses over several years to decades. It consists of a pre-symptomatic stage, during which some characteristic changes of AD are already taking place in the brain, but the subjects have no symptom of AD and appear normal and unaffected. Then, subjects may go through a preclinical stage during which they may experience cognitive impairment, with very subtle cognitive changes that are not detectable with current memory and cognitive tests. This is the stage of Subjective Cognitive Impairment (SCI) [7]. There is a growing interest in detecting SCI subjects, because at this stage the developed therapeutics may have the greatest chance of success. Then, patients progress to a more advanced stage where memory and cognitive deficits start to be noticeable by close family and friends, but without making the patient dependent. This is the stage of Mild Cognitive Impairment (MCI). The patients then progress to the Mild AD stage, on which they exhibit more marked cognitive deficits, such as memory and learning impairments. These deficits become more severe in the moderate and the final stage of the disease. Such progression of the disease differs among patients, but it is inexorable and leads to a complete loss of autonomy [5].

The diagnosis of AD is based on a battery of clinical tests, including neurological tests and medical recordings. Neuroimaging techniques, like Magnetic Resonance Imaging (MRI), are also used to investigate the brain damage. Usual medical imaging tools are expensive, not portable, and require complex facilities and protocols. Moreover, they are unsuitable to follow-up the ongoing brain dynamics.

Electroencephalography (EEG), on the other hand, is an inexpensive and non-invasive technique that can be performed in clinical or outpatient setting. It offers the possibility to study the functional brain dynamics thanks to its high temporal resolution. Many studies have exploited resting-state EEG to distinguish AD patients from healthy controls (HC) by investigating functional connectivity, since AD is considered as a disconnection syndrome [8]. Different measures have been proposed to quantify functional connectivity [9,10], among them Phase-Lag Index [10-12], Phase Coherence [9], Mean Square Coherence [13], and Mutual Information [10,14]. To distinguish between HC and AD patients, functional connectivity values are computed between pairs of EEG signals; the common paradigm in the literature is to average the obtained connectivity values per EEG electrode, or to gather electrodes into regions and to average the connectivity values calculated between pairs of EEG signals per region [9,15]. The obtained average connectivity values are used as discriminative features for AD detection.

Our present work exploits Phase-Lag Index (PLI), as a measure of functional connectivity, to distinguish between SCI and AD patients (a classification problem). We have chosen to aggregate the electrodes into regions and compute one PLI value per region, in order to reduce the computational complexity and to deduce a comprehensive trend on brain activity.

The complete EEG signal recorded with each electrode of one person is split into small segments called “epochs” for further analysis. In the literature, there is a great variability in the duration of the studied EEG signals, ranging from 0.3s to 70s per epoch [8]. Also, there is a high variability in the number of epochs used for EEG analysis, ranging from 1 to 500 [8]. There is often no clear explanation about the chosen epoch duration or the number of epochs. To our knowledge, no study has investigated the impact of varying the epoch duration on the classification performance with functional connectivity.

By the way, in this work, we aim at filling this gap. First, by studying the impact of analyzing EEG signals with different epoch durations on classification performance, when discriminating AD patients from SCI subjects, using PLI to quantify functional connectivity. Then, by proposing a new framework for EEG analysis based on the fusion of classification results at different epoch durations. We will show that this proposal leads to a significant improvement of performance.

II. MATERIAL AND METHODS

A. *Description of the database*

In this work, we analyze resting-state EEG data of 22 SCI patients and 28 AD patients, recorded in real-life conditions at Charles-Foix Hospital (Ivry-Sur-Seine, France). Subjects who complained of memory impairment were referred to the outpatient memory clinic of the hospital to undergo a battery of clinical and neuropsychological tests for brain disorders.

The diagnosis was performed on the basis of the clinical assessment, brain imaging, psychometric findings, interviews and neuropsychological tests, in agreement with the standard diagnostic criteria: DSM-IV, NINDS, Jessen criteria for SCI [16]. Patients with epilepsy were excluded and EEG was not used to establish the diagnosis.

This retrospective study was approved by the institutional review board of the local Ethics Committee Paris 6. Table I shows information about demographic and clinical characteristics of the patients.

TABLE I: Clinical characteristics of the cohort. MMSE: Mini-Mental State Examination; BZD: benzodiazepine.

	SCI (n=22)	AD (n=28)
Age (mean ± SD)	68.9 ± 10.3	80.8 ± 10.5
Female (%)	81.8%	67.8%
MMSE (mean ± SD)	28.3 ± 1.6	18.3 ± 6.1
BZD use (%)	4 (18.2%)	8 (28.6%)
Antidepressant use (%)	2 (9%)	12 (42.8%)
Neuroleptic use (%)	0	5 (17.8%)
Hypnotic use (%)	5 (22.7%)	7 (25%)

The acquisition of EEG signals was done at rest with eyes closed, and by making sure that the patients were not falling asleep. The raw EEG data duration is at least 20 minutes per patient.

EEG signals were acquired with a frequency sampling of 256 Hz, using 30 electrodes positioned over the whole head according to the 10-20 international system: Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FC7, FC4, FT8, T3, C3, Cz, C4, T4, TP7, CP3, CPz, CP4, TP8, T5, P3, Pz, P4, T6, O1, Oz, and O2.

The EEG data were pre-processed off-line and continuous signals of 20 seconds, free from artifacts (ocular, muscular, instrumental) were selected manually after a visual inspection by an expert. Then, the obtained EEG signals were band-pass filtered in the frequency range [1-30] Hz with a third-order Butterworth filter.

B. *Methodology used to analyze EEG data*

In this work, we evaluate the classification performance between AD and SCI populations using Support Vector Machine (SVM) classifier [17], and considering as input features the PLI connectivity values computed between pairwise EEG signals of different durations. From our past experience on the use of EEG connectivity measures, PLI has proven to be efficient because of its robustness to head volume conduction, which is a common issue in EEG recordings [10,12,18].

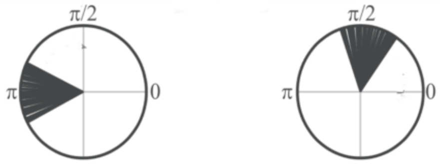
For each patient, we split his/her whole EEG signal of 20s into epochs of different durations: 10s, 5s, 4s, and 2s. Thereby, we evaluate the classification performance between AD and SCI patients considering, separately, the 20s-signal, the two epochs of 10s, the four epochs of 5s, the five epochs of 4s, and the ten epochs of 2s.

For each of these epoch durations, we compute the PLI between pairs of EEG signals, as follows:

$$PLI = |\langle sign(\Delta\phi(t_k))\rangle| \qquad (1)$$

where $|.|$ represents the absolute value, $\langle . \rangle$ indicates the mean (over index k), "sign" denotes the signum function and $\Delta\phi(t_k)$ is the phase difference between two time series at time t_k.

PLI quantifies the non-zero lags between the two EEG signals. More precisely, it quantifies the asymmetry of the distribution of the phase differences between two EEG signals over many trials above or below 0 degree. PLI values range between 0 and 1. A zero value indicates either no coupling or coupling with a phase difference centered around 0 mod π (see Fig. 1.a). A PLI equals to 1 indicates a perfect phase locking at a value of $\Delta\emptyset$ (see Fig. 1.b). The higher is this nonzero phase locking, the higher is the PLI.



(a) (b)

Figure 1. Effects of time lag matching on phase-based connectivity [19].

This measure is not very sensitive to volume conduction since the instantaneous variations in the two EEG signals due to noise give a phase difference close to zero, which results in an equal proportion of negative and positive signs, thus having little effect on the whole distribution [12,18,19].

We define 8 brain regions for PLI computation: frontal/prefrontal (Fp1, Fp2, Fz), frontal left (F7, F3, FT7, FC3), frontal right (F4, F8, FC4, FT8), central (FCz, C3, CZ, C4), temporal left (T3, TP7, CP3, T5), temporal right (T4, CP4, TP8, T6), parietal (P3, Pz, P4), and occipital (O1, Oz, O2) region, as shown in Figure 2.

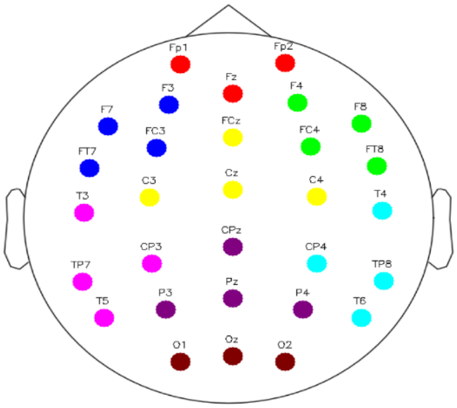


Figure 2. Visualization of the electrodes aggregated into 8 brain regions.

To estimate the functional connectivity of a brain region, we average the PLI values computed between all pairs of EEG signals associated to such region. For example, for the frontal/prefrontal region, we take the average of the PLI values computed between Fp1 and Fp2, Fp1 and Fz, Fp2 and Fz. We also estimate the connectivity inter-regions by taking the average of the PLI values computed between all pairs of EEG signals associated to such regions. For example, for the connectivity between the prefrontal/frontal region and the occipital one, we take the mean of the PLI values computed between Fp1 and O1, Fp1 and Oz, Fp1 and O2, Fp2 and O1, Fp2 and Oz, Fp2 and O2, Fz and O1, Fz and Oz, Fz and O2.

Therefore, for each patient and for each signal duration, we obtain a feature vector containing 36 average PLI values: 8 intra-region PLI values and 28 inter-regions PLI values.

To discriminate between AD and SCI populations, we perform a 10-folds SVM classifier (RBF kernel, default parameters in the Python library Sklearn), and estimate the posterior probabilities of AD and SCI using Platt's estimation method [20]. Note that each patient has all his/her EEG epochs in the same fold. This is carried out in order to overcome the issue of bias when evaluating the classification performance.

To reduce the dimension of the input feature vector for the SVM classifier, we select the most relevant features, among the computed 36 features, with the Forward Orthogonal Regression (OFR) method [21,22]. This process is conducted for each time configuration (i.e. epoch duration).

Finally, for each patient, we obtain one probabilistic score associated to the 20s-signal, two SVM probabilistic scores associated to the two 10s-epochs, five scores for the 4s-epochs, four scores for the 5s-epochs, and ten scores for the 2s-epochs.

III. EXPERIMENTAL RESULTS

In this section, we present the obtained classification results for each EEG epoch duration. We first analyze the classification performance of SCI and AD epochs, independently of the patient, and then we analyze the classification performance of SCI and AD patients by averaging the output SVM scores of epochs for each patient. This is carried out considering separately, the 20s-signal, 10s-epochs, 5s-epochs, 4s-epochs and 2s-epochs. Hence, we analyze the performance with five individual systems.

After that, we present the classification performance of SCI and AD patients, when fusing the individual systems, by averaging the output SVM scores of different epoch durations.

A. *Classification of SCI and AD epochs*

Figure 3 shows the ROC curves of the individual SVM classifiers obtained for different EEG epoch durations, when discriminating AD from SCI epochs. Each epoch is assigned to the label of the corresponding patient.

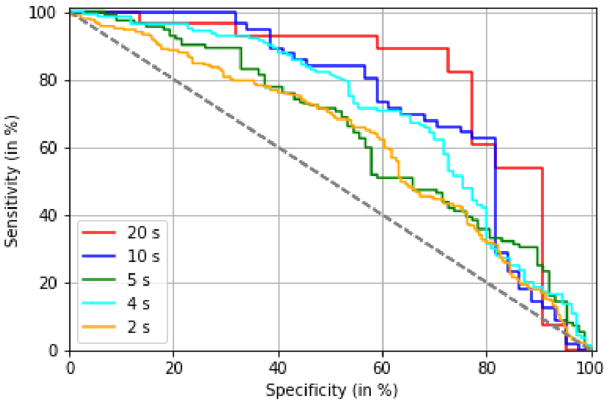


Figure 3. ROC curves for AD and SCI epochs classification, with different epoch durations: 20s, 10s, 5s, 4s and 2s.

We report in Table 2 the classification performance, in terms of Area Under the Curve (AUC), best Accuracy, Specificity (percentage of SCI epochs well classified) and Sensitivity (percentage of AD epochs well classified) values.

TABLE II: Classification results when discriminating AD from SCI epochs, with different epoch durations.

Epoch length	AUC	Accuracy (%)	Sensitivity (%)	Specificity (%)
20s	0.804	82	89.3	72.7
10s	0.734	72	83.9	56.8
5s	0.640	64.5	89.3	33
4s	0.699	68	81.4	53.6
2s	0.616	61.8	63.9	59.1

We first observe that we obtain good classification performance of AD and SCI epochs when estimating the PLI overall the 20s-signal, reaching an accuracy value of 82% and an AUC value 0.804. The performance is degraded when computing the functional connectivity on shorter epochs. Such degradation of performance is progressive, from 20s-signal to 5s-epochs, as indicated by the AUC (from 0.804 to 0.64), the Accuracy (from 82% to 64.5%), and particularly the Specificity (from 72.7% to 33%).

By considering shorter epochs of 4s and 2s, the degradation of performance is also observed, particularly for 2s-epochs in which both Specificity and Sensitivity measures are much degraded. However, with 4s-epochs, an AUC value of 0.699 and an Accuracy of 68% are obtained, which are slightly higher than those obtained with 5s-epochs. This result highlights the difficulty of predicting the information content of EEG signals at different epoch durations. This may be explained by the fact that EEG signal is non-stationary and it contains naturally an intrinsic noise that is difficult to characterize.

B. *Classification of AD and SCI patients*

In this section, we go towards the classification of AD patients from SCI patients, based on the SVM scores previously obtained on epochs, as presented in Section III.A.

For each epoch duration, we estimate the score of a patient by averaging the probabilistic SVM scores of his/her epochs. For example, in case of 5s-epochs, we average the probabilistic scores of the four epochs of 5s to obtain an average score per patient.

Figure 4 and Table III show the obtained classification results on patients, based on PLI measurement at different epoch durations. For a comparative analysis, we also report the results of 20s-signal, even there is no fusion since we consider the whole EEG signal of 20s. Specificity indicates the percentage of SCI patients well classified; Sensitivity indicates the percentage of AD patients well classified.

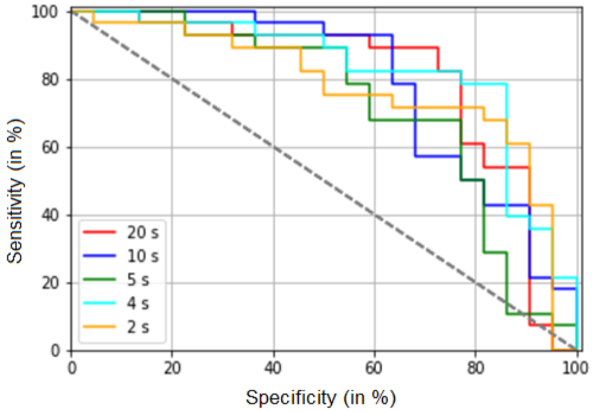


Figure 4: ROC curves for AD and SCI patient classification, with different epoch durations: 20s, 10s, 5s, 4s and 2s.

TABLE III: Classification results when discriminating AD from SCI patients, with different epoch durations.

Epoch length	AUC	Accuracy (%)	Sensitivity (%)	Specificity (%)
20s	0.804	82	89.3	72.7
10s	0.789	80	92.9	63.6
5s	0.724	74	89.3	54.5
4s	0.825	82	78.6	86.4
2s	0.774	76	71.4	81.8

We clearly observe that fusing the SVM scores of epochs leads to better classification performance, compared to the obtained results on separate epochs (see Fig. 3 and Table II). Indeed, for all epoch durations (except 20s of course), the AUC and the Accuracy values are significantly improved, particularly when PLI is computed on shorter epochs: the improvement of the Accuracy is between 8% (from 72% to 80%) with 10s-epochs and 14% (from 68% to 82%) with 4s-epochs. We also observe a significant improvement of Specificity, particularly with 4s-epochs, reaching 86.4% against 53.6% on separate epochs.

Moreover, we notice that the classification performance of patients using the whole 20s-signal or the five epochs of 4s is similar in terms of the Accuracy value (82%), as reported in Table III. However, we notice an inverse behavior in Specificity and Sensitivity. Actually, the fusion of the scores of the five 4s-epochs increases the detection of SCI patients, considered as healthy controls, at the price of a decrease in Sensitivity, comparatively to 20s-signal. Nevertheless, in case of 4s-epochs, there is more balance between Specificity and Sensitivity, and on the associated ROC curve, we note that at a Sensitivity value of 78.6%, Specificity varies between 77.3% and 86.4%, while on the ROC curve of the 20s-signal, we see that at a Sensitivity value of 89.3%, Specificity is between 59% and 72.7%.

Although the classification performance of patients is better when fusing the scores of different epochs, no clear trend emerges on the relationship between performance and epoch duration. Indeed, the performance decreases for the 10s-epochs, and even more for the 5s-epochs, then increases at 4s-epochs, and decreases again with 2s-epochs but is better than at 5s-epochs.

Given this fact, we propose to go a step forward in our fusion scheme, by combining the SVM scores of epochs of different durations. We present in following the obtained results.

C. *Fusion of the scores of different epoch durations*

We calculate a SVM probabilistic score per patient by averaging the obtained scores of all the epochs of such patient extracted at different durations. For example, to make the fusion of the 20s and 10s, we average the output score associated to the 20s-signal and the two scores associated to the two epochs of 10s. Then, relying on the average scores computed for all patients, we analyze the classification performance to discriminate AD from SCI patients.

In Table IV, we report the obtained results for different fusion configurations. Specificity indicates the percentage of SCI patients well classified; Sensitivity indicates the percentage of AD patients well classified.

In Figure 5, we plot only four ROC curves associated to the 20s-signal and three fusion configurations to facilitate the readability.

We clearly observe that the fusion of the SVM scores obtained at epochs of different durations allows to highly improving the classification performance of AD and SCI patients, compared to individual systems that have been fused (i.e. considering each epoch duration separately). Indeed, in Section III.B, the best performance is obtained with 4s-epochs duration (AUC=0.825, Accuracy=82%); whereas, when fusing the scores of epochs of different durations, we notice that better performance is obtained for all fusion combinations.

Besides, we observe that the fusion gives better results when we combine the whole signal with shorter epochs in a progressive manner. By the way, when fusing the scores of 20s-signal, 10s-epochs, 5s-epochs (or 4s-epochs) and 2s-epochs, we obtain the best classification performance with an AUC value of 0.93, and an Accuracy of 90%. We also notice a good balance between Specificity (81.8%) and Sensitivity (96.4%).

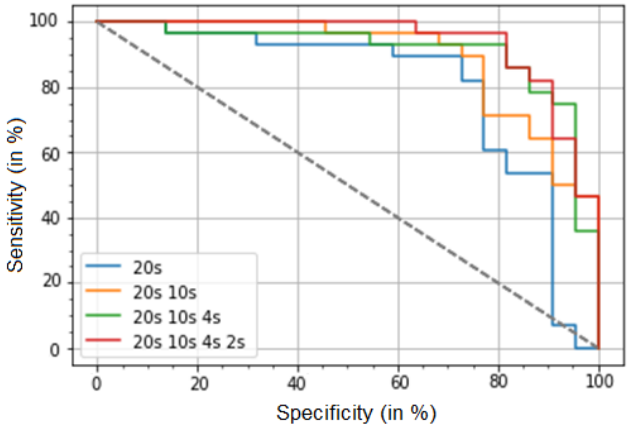


Figure 5: ROC curves for AD and SCI patient classification, when fusing the output SVM scores at different epoch durations.

Table IV: Classification results when discriminating AD from SCI patients, based on the fusion of time durations.

Epoch lengths	AUC	Accuracy (in %)	Sensitivity (in %)	Specificity (in %)
20s – 10s	0.894	84	89.3	77.3
20s – 5s	0.878	86	85.7	86.4
20s – 4s	0.878	86	85.7	86.4
20s – 2s	0.846	80	92.9	63.6
10s – 5s	0.813	82	96.4	63.6
10s – 4s	0.872	82	85.7	77.3
4s – 2s	0.857	82	100	59.1
20s – 10s – 4s	0.909	88	92.9	81.8
20s – 10s – 5s	0.904	88	100	72.7
10s – 4s – 2s	0.904	86	100	68.2
20s – 10s – 4s – 2s	0.938	90	96.4	81.8
20s – 10s – 5s – 2s	0.937	90	96.4	81.8

Finally, even we obtained different results with individual systems based on 4s-epochs and 5s-epochs (see Section III.B), we see that both systems contribute in the same way when they are fused with other systems.

IV. DISCUSSION AND CONCLUSION

The classification performance of SCI and AD epochs obtained with different EEG epoch durations show that good performance is obtained when estimating the PLI on the whole 20s-signal (AUC=0.804, Accuracy=82%). The performance decreases progressively on shorter epochs of 10s, 5s and 2s. On

4s-epochs, we notice a slight improvement of performance comparatively to those obtained on 5s-epochs. The results show that the PLI measurement is more reliable to distinguish between SCI and AD populations, when it is estimated on large epochs of 20s. Actually, when we consider shorter epochs, the Specificity decreases but the Sensitivity still maintained, but at 2s-epochs (the shortest epoch configuration) both Specificity and Sensitivity are degraded. The predictive capabilities of PLI diminishes with the reduction of the signal length on which it is estimated.

Then, going towards the classification of AD and SCI patients, we average the output SVM scores of epochs, for each epoch duration. Hence, we analyze the classification performance with five individual systems, considering separately 20s-signal, 10s-epochs, 5s-epochs, 4s-epochs and 2s-epochs. Results show that fusing the output scores of epochs allows achieving better classification performance, compared to the obtained results on separate epochs. The best discrimination between AD and SCI patients is obtained with 4s-epochs (AUC=0.825, Accuracy=82%).

Since the score fusion shows an improvement of performance, we propose to go a step forward in our fusion scheme, by averaging for each patient the SVM scores of all the epochs extracted at different durations. This proposal leads to a significant improvement of performance, outperforming the case when the 20s-signal is used. Indeed, when PLI is estimated on the whole 20s-signal, we obtain an AUC value of 0.804 and an Accuracy of 82%; when combining the scores of 20s-signal and 10s-epochs, we obtain an AUC of 0.894 and an Accuracy of 84%. Such performance increases progressively when combining more shorter epochs. Indeed, we reach the best performance (AUC=0.93, Accuracy=90%) when fusing the scores of 20s-signal, 10s-epochs, 5s-epochs (or 4s-epochs) and 2s-epochs.

These preliminary results first highlight that the EEG signal duration has an impact on the classification performance. This could explain in part the difference of results in the state of the art. Therefore, it is important to clarify in scientific articles the epoching process, such as the number and length of epochs.

Besides, our preliminary results demonstrate the effectiveness of analyzing the EEG signal at different epoch durations and fusing the classification scores of the extracted epochs. This framework allows a refine characterization of the brain dynamics across time by computing the functional connectivity on short epochs, while taking into account all the available information in the whole EEG signal. Our proposal is novel, since in the literature, we observe that the EEG epoch length is quite consistent across studies, using 5s-epochs or 2s-epochs [8].

In the near future, we will conduct further analyses to confirm these results. We plan to investigate the effectiveness of our fusion scheme to discriminate between SCI, AD and MCI patients, in different frequency bands (delta, theta, alpha, and beta) and using other functional connectivity measures.

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