Diagnosis of Alzheimer's Disease from EEG by Means of Synchrony Measures in Optimized Frequency Bands

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***Abstract*—Several clinical studies have reported that EEG synchrony is affected by Alzheimer's disease (AD). In this paper a frequency band analysis of AD EEG signals is presented, with the aim of improving the diagnosis of AD using EEG signals. In this paper, multiple synchrony measures are assessed through statistical tests (Mann–Whitney *U* test), including correlation, phase synchrony and Granger causality measures. Moreover, linear discriminant analysis (LDA) is conducted with those synchrony measures as features. For the data set at hand, the frequency range (5-6Hz) yields the best accuracy for diagnosing AD, which lies within the classical theta band (4-8Hz). The corresponding classification error is 4.88% for directed transfer function (DTF) Granger causality measure. Interestingly, results show that EEG of AD patients is more synchronous than in healthy subjects within the optimized range 5-6Hz, which is in sharp contrast with the loss of synchrony in AD EEG reported in many earlier studies. This new finding may provide new insights about the neurophysiology of AD. Additional testing on larger AD datasets is required to verify the effectiveness of the proposed approach**.

I. Introduction

Alzheimer's disease (AD) is a brain disease that is characterized by a progressive loss of structure or function of neurons, including death of neurons. It is the most common form of dementia; third most expensive disease and sixth leading cause of death in the United States. In particular, it affects more than 10% of Americans above the age of 65, roughly 50% of people older than 85, and it is expected that the number of AD cases will triple within the next 50 years [1, 2].

The electroencephalography (EEG) is considered as a promising diagnostic tool for AD because of its non-invasive, safe, and easy-to-use properties. EEG has the potential to complement or replace some of the current traditional AD diagnostic methods. However, diagnosing AD in EEG signals remains a challenging problem [3, 4].

Medical studies have shown that many neurophysiological diseases, such as AD, are often associated with abnormalities in neural synchrony. It has frequently been reported that AD causes signals from different brain regions to become less correlated [5]. In this paper, we investigate the efficacy of EEG synchrony measures within different frequency bands to distinguish mild AD patients from healthy subjects. As a result, we identify several narrow EEG frequency ranges that improve the diagnosis of AD compared to the wider range of 4−30Hz.

Several earlier studies [6, 7] have applied a variety of synchronous measures to EEG data of patients with AD. Those studies indicated a statistically significant loss in EEG synchrony between patients with AD and healthy subjects. In an earlier study [6], multiple synchrony measures were applied to study the statistical significance of EEG synchrony loss due to Mild AD in the frequency range [4,30 Hz]. Here we consider the same data set, but systematically explore narrower frequency bands. Surprisingly perhaps, we observe that in mild AD patients, EEG synchrony significantly increases in *narrow* frequency bands (e.g., 5-6Hz).

In earlier work, we have used relative power of EEG in optimized frequency bands to detect mild AD [8]. We observed in that study that several narrow-band frequency ranges (4-7Hz, 8-15Hz and 19-24Hz) improve the detection accuracy.

This paper is structured as follows: in Section II the EEG data set is described (Mild AD), and in Section III the synchrony measures used in this paper are briefly reviewed; in Section IV we discuss the methodology used to distinguish AD patients from healthy subjects; in Section V we present our results, and we offer concluding remarks in Section VI.

II. EEG Data Set

We consider EEG data of mild-AD patients and age-matched control subjects. The EEG data set has been analyzed in previous studies [9-11]; the data was obtained using a strict protocol from Derriford Hospital, Plymouth, U.K., and had been collected using standard hospital practices [10]. EEGs were recorded during a resting period with various states: awake, drowsy, alert and resting states with eyes closed and open. All recording sessions and experiments proceeded after obtaining the informed consent

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of the subjects or the caregivers and were approved by local institutional ethics committees. EEG dataset is composed of 24 healthy Ctrl subjects (age: 69.4±11.5 years old; 10 males) and 17 patients with mild AD (age: 77.6±10.0 years old; 9 males). The patient group underwent full battery of cognitive tests (Mini Mental State Examination, Rey Auditory Verbal Learning Test, Benton Visual Retention Test, and memory recall tests). The EEG time series were recorded using 21 electrodes positioned according to Maudsley system, similar to the 10-20 international system, at a sampling frequency of 128 Hz. EEGs were band-pass filtered with digital third-order Butterworth filter (forward and reverse filtering) between 0.5 and 30 Hz. The recordings were conducted with the subjects in an awake but resting state with eyes closed, and the length of the EEG recording was about 5 minutes, for each subject. The EEG technicians prevented the subjects from falling asleep (vigilance control). After recording, the EEG data has been carefully inspected. Indeed, EEG recordings are prone to a variety of artifacts, for example due to electronic smog, head movements, and muscular activity. For each patient, an EEG expert extracted one segment of 20 seconds that is most informative. The EEG expert was blinded from the results of the present study. These extracted 20-second segments are used in the analysis, as described below.

III. Synchrony Measures

We briefly review the various families of synchrony measures investigated in this paper: cross-correlation coefficient, phase synchrony , and Granger causality; we describe those measures in more detail in [7]. We optimize the parameters of the synchrony measures and the window length, following the same procedures as in [7].

A. Cross-Correlation Coefficient

The cross-correlation coefficient *r* measures the similarity of two signals *x* and *y*. If *x* and *y* are not similar, not linearly correlated, *r* is close to zero. Conversely, if both signals are identical, then *r* = 1[12] . A window length of 20 seconds was used.

B. Phase Synchrony

Phase synchrony refers to the interdependence between the instantaneous phases ϕ_x and ϕ_y of two signals x and y; the instantaneous phases may be strongly synchronized even when the amplitudes of *x* and *y* are statistically independent. The instantaneous phase ϕ_x of a signal *x* may be extracted as [7]:

$$\phi_x(k) = \arg[x(k) + i\tilde{x}(k)] \quad (1)$$

where $\tilde{x}$ is the Hilbert transform of *x*. The phase synchrony index γ for two instantaneous phases ϕ_x and ϕ_y is defined as [7]:

$$\gamma = |e^{i(n\phi_x - m\phi_y)}| \in [0,1] \quad (2)$$

where n and m are integers (usually $n=1=m$). A window length of 20 seconds was used.

C. Granger Causality

Granger causality[1] refers to a family of synchrony measures that are derived from linear stochastic models of time series; they quantify to which extent different signals are linearly interdependent. Non-linear extensions of Granger causality exist, but we do not consider them here since they are less common. Whereas the above linear interdependence measures are bivariate, i.e., they can only be applied to pairs of signals, Granger causality measures are multivariate, they can be applied to multiple signals simultaneously.

Assume that we are given *n* signals $X_1(k), X_2(k), \ldots X_n(k)$, each one is stemming from a different EEG channel. Those signals are modeled as a multivariate autoregressive (MVAR) model, which is a linear model that captures the statistical dependencies among the *n* signals. The Granger causality measures are defined in terms of coefficients of the MVAR model, both in time and frequency domain. Two symmetric Granger measures are:

- Granger coherence $|K_{ij}(f)| \in [0,1]$ describes the amount of in-phase components signals *i* and *j* at the frequency *f*. A second order model with a window length of 1 second was used.
- Partial coherence (PC) $|C_{ij}(f)| \in [0,1]$ describes the amount of in-phase components in signals *i* and *j* at the frequency *f* when the influence (i.e., linear dependence) of the other signals is statistically removed. A fourth order model with a 20-second window length.

The following asymmetric ("directed") Granger causality measures capture causal relations:

- DTF $\gamma_{ij}^2(f)$ quantifies the fraction of inflow to channel *i* stemming from channel *j*. A seventh order model with a window length of 1 second was used.
- Full frequency directed transfer function (ffDTF)

$$F_{ij}^2(f) = \frac{|H_{ij}(f)|^2}{\sum_f \sum_{j=1}^m |H_{ij}(f)|^2} \in [0,1] \quad (3)$$

is a variation of γ_{ij}^2 with a global normalization in frequency. A second order model with a window length of 1 second was used.

- Partial directed coherence (PDC) $|P_{ij}(f)| \in [0,1]$ represents the fraction of outflow from channel *j* to channel *i*. A second order model with a window length of 1 second was used.
- Direct directed transfer function (dDTF) $\chi_{ij}^2(f) = F_{ij}^2(f) C_{ij}^2(f)$ is non-zero if the connection between channel *i* and *j* is causal (non-zero $F_{ij}^2(f)$) and direct (non-zero $C_{ij}^2(f)$). A second order model with a window length of 20 second was used.

[1] Granger causality measures are implemented in the BioSig library: http://biosig.sourceforge.net

IV. METHODOLOGY

Our aim is to use EEG synchrony measures for diagnosis of AD. Our approach consists of three steps: feature extraction, separability tests, and classification.

A. Feature Extraction

The synchrony measures are computed in frequency bands [*F:(F+W)*] Hz as follows:

1) *Bandpass filter*: is applied to each EEG channel to extract the EEG data in specific frequency band [*F:(F+W)*]Hz. Butterworth filters were used (of third order) as they offer good transition band characteristics at low coefficient orders; thus, they can be implemented efficiently [13].

2) *Synchrony measures*: computes the EEG synchrony by aggregating the EEG signals into 5 zones, as discussed in [7]. Calculating the synchrony between those 5 different regions, using each synchrony measure, has been discussed in Section III.

B. Separability Test

After calculating the averages of EEG synchrony [7] for each subject, in all frequency band [*F:(F+W)*]Hz, the average of each population (MiAD and Control) is calculated and denoted by μ_{AD} for AD patients, and μ_{Ctr} for control subjects. Likewise, standard deviation is computed for both populations, denoted by σ_{AD} and σ_{Ctr} respectively.

The linear separability criterion *J* is then computed:

$$J(F,F+W)=\frac{\left|\mu_{Ctr}(F,F+W)-\mu_{AD}(F,F+W)\right|}{(\sigma_{Ctr}(F,F+W)+\sigma_{AD}(F,F+W))}. \quad (4)$$

We calculate the index *J(F,F+W)* over a range of frequency bands, i.e., F =1, 2, …, 30Hz and W = 1, 2, …, 30 Hz, corresponding to 900 different frequency bands within [1,30Hz]; we depict the value *J* as a function of *F* and *W*.

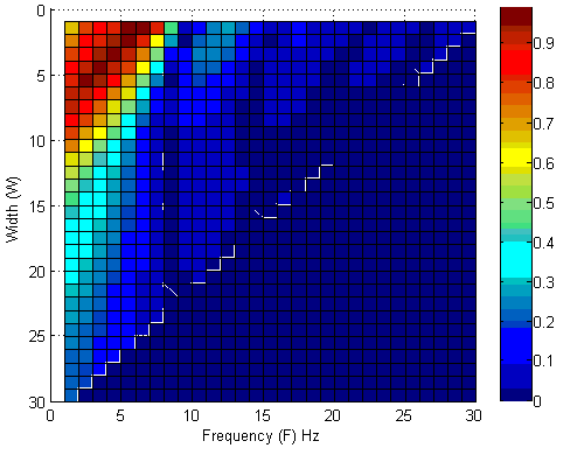

Fig. 1. 2D representation of the linear separability value *J* for the DTF measure between MiAD patients and healthy subjects, calculated over frequency bands [*F,F+W*]. The x-axis represents frequency *F*, the y-axis represents the witdh *W*, while the color represents the linear separability *J*.

Figure 1 shows the linear separation *J* for DTF between Mild Alzheimer patients and Healthy subjects, calculated over frequency bands [*F,F+W*]. Interestingly, a few peaks in *J* can be seen, representing the largest linear separation *J* between MiAD patients and Control subjects. The *J* index was computed similarly for the other synchrony measures.

C. Mann-Whitney U Test

The Mann-Whitney statistical test allows us to investigate whether the EEG statistics at hand (synchrony measures of various frequency bands) take different values between the two subject populations. Low *p*-values indicate large difference in the medians of the two populations. The Mann-Whitney U Test was computed for all synchrony measures in all the frequency bands between [1,30Hz].

D. LDA

It is a linear classifier to distinguish MiAD patients from healthy subjects. LDA has been used earlier for diagnosis of AD from EEG [11, 14-18]. The classification performance was evaluated through leave-one-out (LOO) cross-validation.

The weight vector w of the linear classifier is determined from a subset of the data (training set) and LDA is then assessed on the remaining data (test set). Each learning set is created by taking all the samples except one, and the corresponding test set is the sample left out. Thus, for n samples, we have n different training sets (each yielding a coefficients vector w) and n different test sets. This procedure was conducted for all synchrony measures, in the frequency ranges that correspond to the largest values of *J*.

V. RESULTS

The largest *J* –values, corresponding p-values and lower classification error are presented in Table I. The *J* value obtained for DTF measure is presented in Figure 1, as mentioned earlier. As can be seen, small *p*-value (p<0.005) are obtained for all synchrony measures except for cross-correlation. The highest *J* index and the lowest *p*-value have been achieved by the PDC synchrony measure.

TABLE I. LARGEST INDEX J FOR EACH MEASURE. *P* VALUES FROM MANN-WHITNEY TEST

Synchrony measure	***J* value**	**Optimized frequency range (Hz)**	***p*-value**
Cross-Correlation	0.3276	22-23	0.0378
Phase Synchrony	0.5832	9-10	0.00005
Coherence	0.8850	1-2	0.00003
PC	0.5069	3-4	0.0027
DTF	0.9875	6-7	3×10^{-6}
ffDTF	0.9741	1-2	3×10^{-6}
PDC	1.0282	1-4	2×10^{-6}
dDTF	0.8263	3-4	9.5×10^{-5}

TABLE II. ERROR RATE CALCULATED BY LOO CROSSVALIDATION

Synchrony measure	***Optimal frequency ranges (Hz)***	***Error Rate %***
Cross-Correlation	23-24	31.71
Phase Synchrony	9-10	19.51
Coherence	1-2	17.07
PC	3-4	31.71
DTF	5-6	4.88
ffDTF	1-2	19.51
PDC	1-4	19.51
dDTF	2-4	21.95

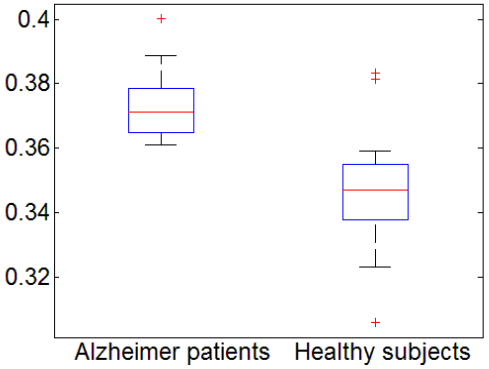

Fig. 2. Boxplot shows the DTF measure for healthy subjects and Mild Alzheimer patients in the optimised frequency range 5-6Hz.

Table II represents the classification error obtained by LDA, calculated by leave-one-out crossvalidation, for all synchrony measures introduced in section IV. It is clear that DTF for the band range 5-6Hz achieved the smallest error classification rate among all measures, with a value of 4.88%. This result is in agreement with the results of Table I, as DTF has the second smallest *p*-value (after PDC). Figure 2 shows a boxplot of the DTF values in the optimized frequency range 5-6Hz, for MiAD patients and control subjects.

In Figure 3, we show a EEG signals from an MiAD patient and control subject in the 5-6Hz. Clearly, the narrow-band EEG signals in MiAD patients have higher amplitude and are more coherent compared the healthy subject. The increased amplitudes are due to the slowing effect MiAD. That observation is in agreement with earlier studies. However, the finding of increased correlation among the 5-6Hz waves in MiAD patients is fascinating, since it is in disagreement with the often documented observation of loss in EEG synchrony in AD patients. It is noteworthy though that a few studies have reported increased EEG synchrony in AD patients (see [7] for a review).

In Table III, we list statistics of the synchrony measures, including the average computed across the entire subject groups and the standard deviation.

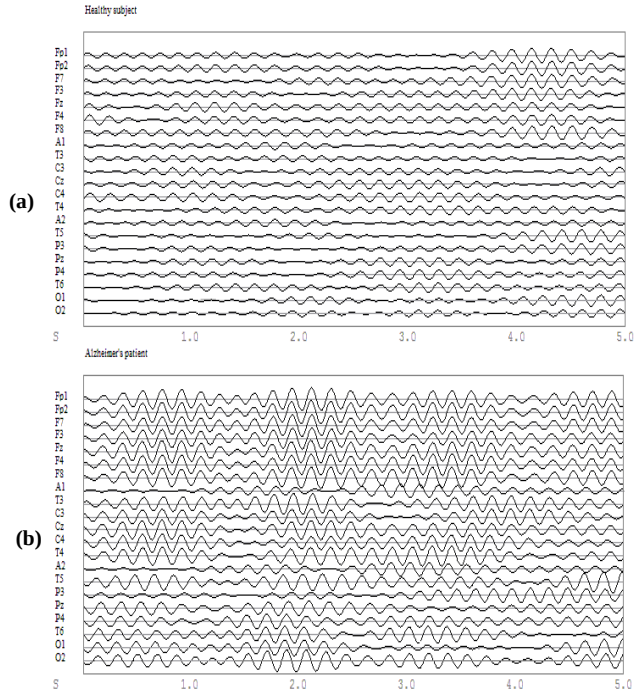

Fig. 3. Examples of EEG signals in frequency range 5-6Hz. (a) Healthy subject, (b) Alzheimer patient.

TABLE III. MEAN AND STANDARD DEVIATION VALUES OF CROSS-CORRELATION, PHASE SYNCHRONY AND SYNCHRONY MEASURES. *P* VALUES FROM MANN-WHITNEY TEST

	Traditional Frequency Band 4-30Hz			**Optimized Frequency Band 5-6 Hz**		
Measure	**AD**	**Control**	***p*-value**	**AD**	**Control**	***p*-value**
Cross-Correlation	0.28±0.13	0.26±0.08	0.78	0.27±0.10	0.26±0.09	0.84
Phase Synchrony	0.18±0.08	0.20±0.06	0.14	0.23±0.07	0.19±0.04	4.6×10^{-2}
Coherence	0.50±0.10	0.46±0.05	0.20	0.59±0.06	0.53±0.05	2.1×10^{-3}
PC	0.42±0.09	0.43±0.10	0.86	0.56±0.12	0.48±0.12	5.5×10^{-2}
DTF	0.36±0.02	0.36±0.01	0.66	0.37±0.01	0.35±0.02	2.6×10^{-6}
ffDTF	0.05±0.01	0.05±0.00	0.01	0.26±0.01	0.24±0.02	4.3×10^{-5}
PDC	0.28±0.04	0.29±0.03	0.22	0.37±0.02	0.32±0.03	6.4×10^{-6}
dDTF	0.02±0.01	0.02±0.01	0.61	0.14±0.04	0.09±0.04	5.0×10^{-4}

We report the Mann-Whitney *p*-values. The Mann-Whitney test allows us to investigate whether the statistics at hand (EEG measures) take different values between two subject populations, as discussed in section IV.

As shown in Table III, the results for the narrow frequency band (5-6Hz) are more consistent compared to the standard frequency band of 4-30Hz, which has often been considered in previous studies. For example, in the latter frequency band, cross-correlation, DTF, and Granger coherence have high values for MiAD. On the other hand, PDC, dDTF, ffDTF, and partial coherence measures are lower in MiAD patients compared to control subjects. This inconsistency has to some extent been documented in literature. Interestingly, in the 5-6Hz frequency range, *all* synchrony measures have high values for MiAD patients

compared to control subjects. In other words, EEG synchrony is enhanced in MiAD patients in 5-6Hz, which is part of the standard theta band (4-8Hz), as indicated consistently by a large variety off synchrony measures. This new finding may provide new insights about the neurophysiology of Alzheimer's disease.

VI. Discussion and Conclusion

This study demonstrates the discriminative power of EEG synchrony for diagnosing Alzheimer's disease. Narrow frequency bands between 4 and 30Hz are systematically tested, besides the standard wide frequency band (4–30Hz), for evaluating multiple synchrony measures. Assessment has been done through statistical tests (Mann–Whitney *U* test) and LDA (leave-one-out crossvalidation).

The best classification results were obtained by directed transfer function (DTF) Granger causality measure (4.88% classification error). Interestingly, the corresponding optimized frequency range is 5-6Hz that lies within the classical theta band (4-8Hz).

Surprisingly perhaps, our results for the data set at hand show that EEG of AD patients is more synchronous than in healthy subjects within the optimized range 5-6Hz. It would be interesting to speculate on the origin of the enhanced synchrony.

Of course, it is important to point out that the data set at hand is fairly small. A larger sample size and a more diverse data set are needed in order to generalize the findings of this study. Multiple types of dementia and other neurological disorders can also be analysed through our technique, which may further validate our results. The ultimate objective of this line of research is to determine the most appropriate EEG frequency bands for diagnosing AD (and potentially other neurodegenerative diseases) with synchrony measures.

In addition, it seems to be promising to combine synchrony measures with each other or with other EEG features, such as relative power.

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