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DIAGNOSIS OF ALZHEMERS DISEASE BY PDM USING EEG DATA:A REVIEW

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ABSTRACT

We examine whether modeling of the causal dynamic relationships between frontal and occipital electroencephalogram (EEG) time-series recordings reveal reliable dif-ferentiating characteristics of Alzheimer's patients versus control subjects in a man-ner that may assist clinical diagnosis of Alzheimer's disease (AD). The proposed modeling approach utilizes the concept of principal dynamic modes (PDMs) and their associated nonlinear functions (ANF) and hypothesizes that the ANFs of some PDMs for the AD patients will be distinct from their counterparts in control sub-jects. To this purpose, global PDMs are extracted from 1-min EEG signals of 17 AD patients and 24 control subjects at rest using Volterra models estimated via Laguerre expansions, whereby the O1 or O2 recording is viewed as the input sig-nal and the F3 or F4 recording as the output signal. Subsequent singular value decomposition of the estimated Volterra kernels yields the global PDMs that rep-resent an e cient basis of functions for the representation of the EEG dynamics in all subjects. The respective ANFs are computed for each subject and characterize the speci c dynamics of each subject. For comparison, signal features traditionally used in the analysis of EEG signals in AD are computed as benchmark. The results indicate that the ANFs of two speci c PDMs, corresponding to the delta, theta and alpha bands, can delineate the two groups well.

I. INTRODUCTION

A. Alzheimer's disease (ad) and elec- troencephalogram (eeg)

Alzheimer's disease (AD) is the most common neurodegenerative disorder in the western world and the number of patients is expected to double approximately every 20 years because of the aging population . AD is characterized by the accumulation of amyloid plaques and neurobrillary tangles in the patient's brain and loss of corti-cal neurons and synapses . These pathological changes cause memory loss and other cognitive and behavioral impairments that progressively a ect the patient's ability to live independently . The guidelines for clinical diagnosis of AD are based on the exclusion of other causes for the symptoms. However, a denite diagnosis of AD can only be made by necropsy and AD pathology is hypothesized to start years before the rst symptoms appear. The patient's quality of life already a ected by the time clinical diagnosis is made . Thus, there is a need for objective, non-invasive and a ordable meansto support clinicians in the detection and monitoring of AD. One of such potential means is the analysis of electroencephalogram (EEG) recordings

The analysis of EEG time series has been explored previously for its diagnostic potential in AD, based on the notion that the EEG signals represent uctuations of aggregate brain activity in the respective brain regions and, therefore, may be able to reveal di erences in brain function under di erent clinical conditions . Many previous studies have explored this question through the computation of diverse signal features from EEG recordings . Spectral features, including both spectral indices such as median frequency and relative power values, have revealed a spectral slowdown of the brain activity in AD . Nonlinear features provide additional points of view in the inspection of the EEG signals. Features such as Sample Entropy have been applied to the EEG recordings of patients . The results indicate that AD a ects the nonlinear characteristics of the EEG signals, making them more regular and predictable. AD is hypothesized to be a disconnection syndrome .

Therefore, there is increasing interest in the inspection of the connectivity of EEG recordings. This is often evaluated by measuring the (linear or nonlinear) dependencies between two signals in di erent spectral bands . This is particularly important in AD as the disease may cause opposing changes in di erent frequency ranges . Traditional ap-proaches to measure the connectivity between EEG signals are limited by a number of factors. To start with,

spurious results could appear due to the volume conduction e ects , because nearby channels are likely to record activity from identical sources. Ideally, the connectivity evaluation should also inform about the causality of the interactions between signals . While some techniques have been recently developed to address these issues (e.g., phase lag index in , their use is limited perhaps due to a less straightforward interpretation than other techniques. As an alternative, the present study focuses on the modeling and analysis of the possible causal relationship between occipital recordings (viewed as the \input" signal) and frontal recordings (viewed as the\output" signal) frontal recordings (viewed as the \output" signal) in order to generate model-based indices to characterize the EEGs of AD patients.

To this purpose, we apply the Volterra modeling approach using Laguerre expansions of the kernels and employ the concept of Principal Dynamic Modes (PDM), which our group has pioneered . This reduces signicantly the required number of free pa-rameters in the model and enables estimation of reliable linear or nonlinear dynamic models under conditions of low

SNR. This modeling methodology has been recently applied to many different physiological domains, including the cerebral hemodynamics in AD patients . The results to date corroborate the potential and efficiency of this modeling approach. The proposed diagnostic indices in this study are generated through the use of the Associated Nonlinear Functions (ANFs) that correspond to each PDM of each subject. Our aim is to examine whether the estimated PDMs exhibit spectral characteristics in line with the neural rhythms naturally occurring in the brain (delta, theta, alpha, beta, and gamma) and whether the ANFs obtained for each subject can be used as descriptors of disease. It is posited that these ANFs may constitute useful \features" for the classification and differentiation of overall cognitive function in AD patients versus controls.

II. LITERATURE REVIEW

A. Regional coherence evaluation in mild cognitive impairment and alzheimer's disease based on adap-tively extracted magnetoencephalo- gram rhythms

MEG recordings are composed of numerous channels and it may be helpful to group them into regions. In this study, the channels are grouped into left central (LC), an-terior (LA), lateral (LL) and posterior (LP); and right central (RC), anterior (RA), lateral (RL) and posterior (RP)regions. This distribution considers the difference be-tween left and right channels. Mid-line sensors are not considered c(f) is computed with two different approaches. The rst one consists of calculating c(f) for all pairs of channels resulting in a large number of pairwise values.

Then, the results are averaged considering the region to which each channel belongs to estimate the inter-regional c(f) in (14 Hz), (48 Hz), (813 Hz) and (1330 Hz) bands.In the second approach, the MEG inter-regional c(f) is assessed by means of a novel adaptive procedure to characterize each region and band with a single signal. This approach where the MEG channels appear on top of the diagram. An EMD is applied to each single channel to obtain the intrinsic mode functions (IMFs) Afterwards, all IMFs from channels in the same scalp region are combined into a pool of single-channel rhythms. Subsequently, a k-means is used to automatically select reference signals representative of the, and bands from the pool of IMFs. Then, these references guide a cBSSto extract one activity signal that simultaneously characterizes all channels in the region for every band. Finally, c(f) is calculated between extracted signals of different regions to assess the connectivity.

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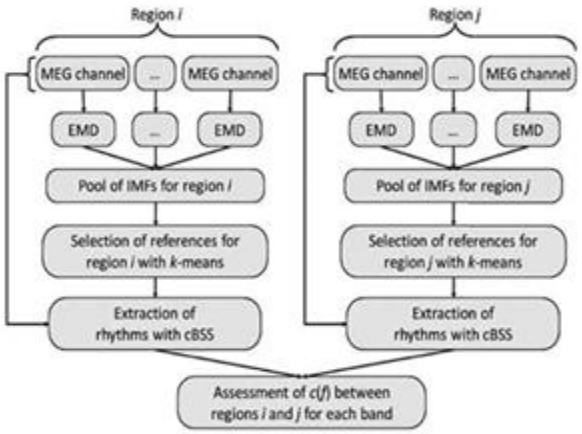

Figure 2.1: Regional coherence evaluation using MEG block diagram

B. Graph theoretical analysis of mag-netoencephalographic functional connectivity in alzheimers disease

Graph analysis

As a filtering process, offline frequency analysis is performed on the raw data, using a Fourier transformation. In the obtained frequency spectrum all frequencies outside the studied bands are set to zero, and using an inverse Fourier transformation the filtered signal is then obtained, with preservation of all phase information of the original data. For the subsequent off-line processing the recordings were converted to ASCII files and down-sampled to 312.5 Hz. For each subject care was taken to find and select exactly three artifact-free epochs of 4096 samples (13.083 s) by two of the investigators (BFJ and IM). MEG registrations were converted to datafiles with a coded filename before epoch selection, so the investigators were blind to the subjects' diagnosis during this process. Typical artifacts were due to (eye) movements, drowsiness or technical issues. Visual inspection and selection of epochs was realized with the DIGEEGXP software (CS). Epochs were band-pass filtered for the commonly used frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–13 Hz), beta (13–30 Hz) and gamma (30–45 Hz), and all further analyses were performed for these bands separately.

In principle, networks can be represented by graphs, which are sets of vertices and corresponding sets of edges (Boccaletti et al., 2006; Stam and Reijneveld, 2007c). One may say that an edge or connection either exists or not but one may also assign a certain weight to an edge that reflects the importance or strength of the relation between two vertices. While the first one yields unweighted graphs in that edges have values of either 0 or 1, the latter produces so-called weighted graphs. To define the corresponding weights a matrix of correlations between signals recorded at different electrodes is generally suitable. We denote the matrix' coefficients as wij, i.e. they connect vertex i with vertex j and specified their values using the afore-explained PLI. That is we defined a network of 149 vertices (matching the 149 available MEG channels) and used the matrix of PLI values between all pairs of MEG channels as edge weights. Graphs can be characterized by various measures. Two fundamental ones are the clustering coefficient, which denotes the likelihood that neighbours of a vertex will also be connected to each other, and the average path length, i.e. the average number of edges of the shortest path between pairs of vertices (Fig. 1). Well ordered networks

are strongly clustered and show large path lengths. In contrast, random networks are weakly clustered with small path lengths. Neither ordered nor random networks are good candidates for real networks like the human brain. Hence, Watts and Strogatz suggested a new type of networks, so-called small-world networks, which have both large clustering coefficients as well as small path lengths. Interestingly, these networks can be designed to be scale-free by having very short path lengths and a power law degree distribution (Baraba´si and Albert, 1999). Both small-world and scale-free networks are optimal in the sense that they allow efficient information processing with a minimal number of connections. By now it has been shown that many types of network ranging from metabolic and

genetic to social are either small-world or scale-free i will also be connected to each other. This notion can be adopted for use with weighted graphs in various ways (Boccaletti et al., 2006). Here we propose a simple definition, closely related to the proposal of The clustering index Ci of a vertex i generally represents the likelihood that other vertices j that are connected to the vertex Onnela et al. (2005), which only requires symmetry (wij = wji) and that 04wij41 holds. Indeed, both conditions are readily fulfilled when using PLI as weight definition. The (weighted) clustering index of vertex i is then defined as

$$C_i = \frac{\sum_{k\neq i}\sum_{l\neq i,k} w_{ik}w_{il}w_{kl}}{\sum_{k\neq i}\sum_{l\neq i,k} w_{ik}w_{il}} \qquad (1)$$

Notice that in all sums in (1) terms with k = i, l = i or k = l are skipped. In the special case in which wij equals either 0 or 1, this definition is equivalent to the classical definition for unweighted graphs. For isolated vertices, i.e. vertices that do not have any connections, all weights wij vanish, and the clustering index is defined as Ci = 0. The mean clustering coefficient of the entire network can be determined via (1) as

$$C_w = \frac{1}{N}\sum_{i=1}^{N} C_i \qquad (2)$$

In detail, we define the length of an edge as the inverse of the aforementioned edge weight, i.e. Lij = 1/wij if wij 6¼ 0, and Lij = +1 if wij = 0; recall that wij is positive because we use the PLI as edge weight. The length of a weighted path between two vertices is then defined as the sum of the lengths of the edges of this path. The shortest path lij between two vertices i and j is the path between i and j with the shortest length. Analogously to definition (2) the average weighted path length of the entire graph is computed as

$$L_w = \frac{1}{(1/N(N-1))\sum_{i=1}^{N}\sum_{j\neq i}^{N}(1/L_{ij})} \qquad (3)$$

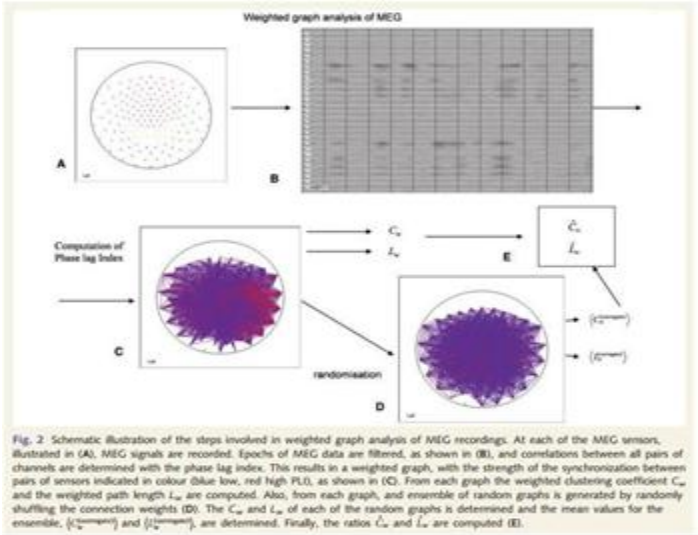

Fig. 2 Schematic illustration of the steps involved in weighted graph analysis of MEG recordings. At each of the MEG sensors, illustrated in (A), MEG signals are recorded. Epochs of MEG data are filtered, as shown in (B), and correlations between all pairs of channels are determined with the phase lag index. This results in a weighted graph, with the strength of the synchronization between pairs of sensors indicated in colour (blue low, red high PLI), as shown in (C). From each graph the weighted clustering coefficient C_w and the weighted path length L_w are computed. Also, from each graph, and ensemble of random graphs is generated by randomly shuffling the connection weights (D). The C_w and L_w of each of the random graphs is determined and the mean values for the ensemble, $\langle C_w^{random}\rangle$ and $\langle L_w^{random}\rangle$, are determined. Finally, the ratios $\hat{C}_w$ and $\hat{L}_w$ are computed (E).

III. PROPOSED METHOD

A. Data collection and pre-processing

This study involves 24 control subjects (42% male; average age: 69.4_11.5 years, mean standard deviation, SD) and 17 AD patients (53% male; average age: 77.6_10.0 years) who voluntarily participated and signed the Informed Consent Form according to institutional guidelines The EEG recordings were obtained for patients at rest and with their eyes closed using the traditional 10_20 system in a Common Reference montage using a sampling rate of 256 Hz. The signals were down sampled to 128Hz offline. The data were obtained under a strict protocol from Derisory Hospital, Plymouth, UK, and had been collected using normal hospital practices. The patients were referred to the hospital EEG department from a specialist memory clinic where all patients undergo a battery of psychometric tests before referral. The results from the psychometric tests were scored and interpreted by a specialist psychologist. Each patient was given a diagnosis at the memory clinic on the basis of the clinical and psychometric endings' and discussions held by a multidisciplinary team. Each patient was then referred to the hospital for EEG assessment. All age-matched controls were healthy volunteers and had normal EEGs (confirmed by a Consultant Clinical Neurophysiologist). For each subject, continuous epochs of 60 seconds were simultaneously extracted from the left frontal (F3), right frontal (F4), left occipital (O1) and right occipital (O2) channels. The selection of these electrodes is supported by the fact that AD is hypothesized to affect long-range connectivity as a result of the loss of long corticoid-cortical association bers, which may play an important role in functional interactions .

Moreover, selecting nearby channels would probably result in all of them picking up identical sources, which may lead to spurious connectivity levels rejecting simple volume conduction rather than true functional connectivity. The positions of the selected electrodes minimize possible effects of ocular activity. The epochs of 60s were selected for having a small presence of artifacts. They were then band-pass filtered in the range of 1 to 40 Hz with a band-pass Hamming window FIR filter with order 200. The data were then demeaned and scaled by a factor of 1/100 for computational/numerical convenience. Fig. 1 shows illustrative pre-processed

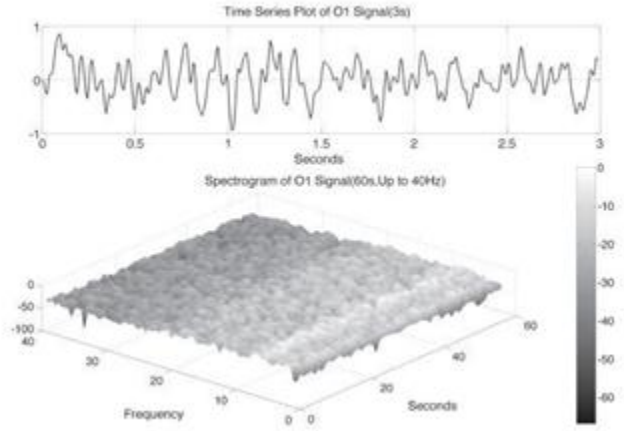

Fig.2: illustrative time-series data over 3 sec from the O1 EEG signal of AD patient #1. Bottom panel: the spectrogram over 60 sec of the time-series data up to 40Hz for this patient.

Time-series data over 3 sec and the respective spectrogram for the O1 EEG signal of an AD patient. The spectral properties of this data segment seem stationary

B. Modelling methodology

The proposed modeling approach utilizes the concept of Principal Dynamic Modes (PDM) that has been pioneered by our group and applied successfully over the last 10 years to various physiological systems . In this approach, we seek to determine from input-output data a set of basis functions (the PDMs) that represent an ef_cient ``coordinate system'' for the representation of the Volterra kernels of a given class of systems. Static nonlinear functions

associated with each PDM (termed ANF: Associated Nonlinear Functions) describe the (possible) nonlinearities of the system. The PDM modeling approach relies on an ef_cient methodology for the estimation of Volterra kernels using Laguerre expansions . To reduce the complexity of the obtained PDM-based models and facilitate comparisons between different cohorts, we seek to determine the ``global'' PDMs of a given system from the estimated kernels of a cohort. This is accomplished through singular value decomposition (SVD) of a rectangular matrix containing all estimated Volterra kernels in the cohort. We note that the computation of the global PDMs must be based on all subjects because they represent a common frame of reference for all subjects who are subsequently classifed according to their

respective ANFs. The global PDMs correspond to the selected ``significant'' singular vectors by applying a selection criterion on the respective singular values. In this study, we analyze the causal relationship between two EEG signals, in which the frontal signal is taken as the ``output'' and the occipital signal is taken as the ``input''.

Using the Laguerre expansion technique, we start with linear modeling (1st order Volterra kernel only) and proceed with nonlinear modeling estimating the 2nd-order Volterra kernels as well. These kernel estimates are used to compute the global PDMs of these cohorts via SVD of a rectangular matrix that contains either all the 1st order kernels (Method 1) or the 1st and 2nd order kernels (Method 2) for all subjects (patients and controls). The resulting PDMs are used to

obtain nonlinear models of 5th order. The key to the model estimation problem is the use of the Laguerre expansion technique that keeps the number of free parameters manageable for all models. A detailed description of this methodology is given in the monograph . We summarize below the methodology of PDM-based modeling. The 1st order (linear) Volterra model is:

$$y(n) = k_0 + \sum_{m=0}^{M-1} k_1 \quad (m)x(n-m) \qquad (4)$$

where

- x(n) is the input (occipital) signal
- y(n) is the output (frontal) signal
- {k0; k1} are the zeroth order kernel (constant) and the first order kernel respectively
- M is the system memory (M=70 here)

IV. CONCLUSION

The previous study showed that resting-state functional connectivity of MEG is decreased in Alzheimer's disease patients in the lower alpha and beta bands using a recently developed measure, the PLI that appears invariant against volume conduction. This finding supports the concept of

Alzheimer's disease as a disconnection syndrome. Moreover, changes in functional connectivity in Alzheimer's disease patients did not involve all brain regions to the same extent, suggesting a heterogeneous disruption of overall network structure. This idea was confirmed by graph analysis of the functional connectivity data, which revealed lower normalized clustering coefficients and path lengths in the Alzheimer's disease group in the lower alpha band.

This type of change suggests that brain networks in Alzheimer's disease patients are closer to random networks than those of non-demented control subjects. The modelling results suggest that this change was brought about by a preferential decrease of connections between high degree nodes ('hubs'), rather than a non-specific decrease of connection strength. We have presented a methodology for input-output modeling of the dynamic relationships between EEG recordings in AD patients and control subjects that can be used for diagnostic delineation of the two groups. The methodology is based on the concept of Principal Dynamic Modes (PDMs) and their associated nonlinear functions (ANFs) that has been recently developed and applied successfully to various physiological systems.

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