Using Static and Dynamic Canonical Correlation Coefficients as Quantitative EEG Markers for Alzheimer's Disease Severity*

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***Abstract*— We analyzed the relation between Alzheimer's disease (AD) severity as measured by Mini-Mental State Examination (MMSE) scores and quantitative electroencephalographic (qEEG) markers that were derived from canonical correlation analysis. This allowed an investigation of EEG synchrony between groups of EEG channels. In this study, we applied the data from 79 participants in the multi-centric cohort study PRODEM-Austria with probable AD. Following a homogeneous protocol, the EEG was recorded both in resting state and during a cognitive task. A quadratic regression model was used to describe the relation between MMSE and the qEEG synchrony markers. This relation was most significant in the δ and θ frequency bands in resting state, and between left-hemispheric central, temporal and parietal channel groups during the cognitive task. Here, the MMSE explained up to 40% of the qEEG marker's variation. QEEG markers showed an ambiguous trend, i.e. an increase of EEG synchrony in the initial stage of AD (MMSE>20) and a decrease in later stages. This effect could be caused by compensatory brain mechanisms. We conclude that the proposed qEEG markers are closely related to AD severity. Despite the ambiguous trend and the resulting diagnostic ambiguity, the qEEG markers could provide aid in the diagnostics of early-stage AD.**

I. INTRODUCTION

Quantitative electroencephalogram (qEEG) measures have been used to investigate EEG alterations in the course of Alzheimer's disease (AD). EEG changes include frequency slowing, reduced complexity and altered synchrony [1][2].

Several studies have analyzed resting state qEEG synchrony markers between AD patients, subjects with mild cognitive impairment (MCI), and healthy controls, e.g. coherences [3][4] and phase synchrony measures [5][6][2]. Most of these studies have suggested a decrease of resting state EEG synchrony for AD patients as compared to the controls. Additionally, a small number of studies has investigated EEG synchrony during cognitive tasks (e.g. coherences in [7][8][9] and synchronization likelihood in [6]). Increased EEG synchrony has been reported for MCI subjects as compared to the controls [8][10][11], often attributed to compensatory brain mechanisms [6][12]. However, only few studies correlate qEEG synchrony markers with AD severity: coherences in [3][10], synchronization likelihood in [5][6][13], and global field synchronization [14].

In this study, we analyzed EEG synchrony between EEG channel groups by means of both static and dynamic canonical correlation analysis [15][16]. Canonical correlation is a multivariate concept that allows to investigate the dependence between groups of variates – in our case groups of EEG channels. The change of canonical correlations with AD severity has – to the best of our knowledge – not been reported before. The main focus of our analysis was whether the qEEG markers were capable of explaining AD severity quantified by Mini-Mental State Examination (MMSE) scores [17].

II. MATERIALS AND METHODS

A. Study Subjects

For this study, only data from subjects diagnosed with probable AD according to NINCDS-ADRDA [18] criteria were employed. Subjects were participants in the multi-centric cohort study PRODEM-Austria of the Austrian Alzheimer Society. In compliance with a homogeneous study protocol, clinical assessments were conducted at the Medical Universities of Graz, Innsbruck, Vienna, and the General Hospital Linz. We used the clinical assessments of 79 subjects (50 female, 29 male) aged between 52 and 88 years with a duration of probable AD ranging from 2 to 120 months. Each subject's highest completed level of education was classified on a scale of 1 (primary school) to 6 (tertiary institution). Cognitive deficits were quantified by MMSE scores. On the MMSE scale of 0 to 30 – lower scores indicate more severe cognitive deficits – the study subjects achieved scores between 15 and 26.

B. EEG Recordings

The EEG recordings were conducted from 19 gold cup electrodes placed according to the International 10-20 System [19] with connected mastoids as reference and ground electrode located between electrodes FZ and CZ. In addition,

*Research supported by Austrian Research Promotion Agency FFG, project no. 827462, including financial contributions from Dr. Grossegger & Drbal GmbH, Vienna, Austria.

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978-1-4244-7929-0/14/$26.00 ©2014 IEEE

electrodes above and below the left eye and at the outer corners of both eyes recorded the vertical and horizontal electrooculogram (EOG) respectively. The electrocardiogram (ECG) was acquired by using wrist clip electrodes. The signals were amplified, bandpass (0.3–70 Hz), and notch (50 Hz) filtered by an AlphaEEG amplifier (alpha trace medical systems) and digitized at 256 Hz with a resolution of 16 bits. Impedances were kept below 10 kΩ.

The EEG paradigm consisted of two phases. In the *resting phase*, the subjects sat in upright position in armchairs with integrated neck support in resting but awake condition with closed eyes (180 seconds). The *cognitive phase* included a face-name encoding task with open eyes where subjects were asked to memorize three faces and corresponding names shown on a computer screen and recall the names while only the faces were presented (130 seconds). Thus, AD-specific deficits including episodic memory and processing of complex stimuli were targeted.

C. EEG Preprocessing

EEG recordings – and, thus, any analysis based on them – are generally corrupted by artifacts from non-neurological sources including physiological sources (e.g. eye movements, blinking, muscular contractions, movement, transpiration, cardiac acitivy, and talking) and technical sources (e.g. spurious noise from medical equipment, induction from the mains supply, and poor electrode contacts). In order to remove these artifacts, we applied the following preprocessing procedure:

EEG segments containing irremovable artifacts, e.g. from poor electrode contacts, were excluded from further analyses by visual inspection. Thus, 22 out of 180 seconds (≈12%) in the resting phase and 44 out of 130 seconds (≈34%) in the cognitive phase were rejected. EEG, EOG, and ECG signals were then – in order to remove non-neuronal trends and low-frequency artifacts – digitally high-pass filtered using a stable, direct-form finite impulse response (FIR) filter with linear phase and cut-off frequency of 2 Hz. Cardiac artifacts were removed by applying the modified Pan-Tompkins algorithm that makes use of the ECG channel [20]. Eye and blinking artifacts were removed by making use of the EOG channels. However, as the EOG captures high-frequency neuronal signals as well, the EOG channels were first low-pass filtered using a stable, direct-form FIR filter with linear phase and cut-off frequency of 12 Hz. Subsequently, ocular artifacts were removed by applying static linear regression of each EEG channel on the filtered EOG channels. Finally, in order to remove high-frequency artifacts from e.g. muscle tension, the EEG signals were digitally low-pass filtered using a stable, direct-form FIR filter with linear phase and cut-off frequency of 15 Hz.

In general, brain dynamics and, consequently, EEG signals are non-stationary [21]. However, since this study's methods rely on (wide-sense) stationarity of the signals, the EEG was divided in "quasi-stationary" 4-second segments with 2-second overlap. All analyses were carried out on these artifact corrected and band-pass filtered (2–15 Hz) 4-second EEG segments.

D. Covariance and Spectral Density Function

In this study, an EEG segment was interpreted as a realization of a 19-dimensional (i.e. the number of EEG channels) stationary stochastic process $(x_t)_{t\in\mathbb{Z}}$ with $\mathbb{E}x_t = 0\ \forall t$. Assuming absolutely summable covariances $\gamma(s) = \mathbb{E}x_{t+s}x_t'$ where $s \in \mathbb{Z}$, the spectral density at (normalized) frequency $\lambda \in [-\pi,\pi]$ exists and is defined as $f(\lambda) = (2\pi)^{-1}\sum\gamma(s)\ e^{-i\lambda s}$. Note that both $\gamma = (\gamma_{ij})$ and $f = (f_{ij})$ are matrices with $i,j = 1,\ldots,19$ where the diagonal elements γ_{ii} and f_{ii} are the auto-covariance and auto-spectrum of subprocess i, and γ_{ij} and f_{ij} are the cross-covariance and cross-spectrum between subprocesses i and j.

E. Static Canonical Correlation Coefficients

Hotelling introduced the concept of canonical correlation analysis for the investigation of the relation between two groups of variables in [15]. Let $y_t \in \mathbb{R}^p$ and $z_t \in \mathbb{R}^q$ be subprocesses of (x_t). The idea is to find time-invariant linear transformations $a_1 \in \mathbb{R}^p$ and $b_1 \in \mathbb{R}^q$ that maximize $\rho_1 = corr(a_1'y_t, b_1'z_t)$. Next, the $a_2 \in \mathbb{R}^p$ and $b_2 \in \mathbb{R}^q$ maximizing $\rho_2 = corr(a_2'y_t, b_2'z_t)$ with side conditions $a_2'y_t \perp a_1'y_t$ and $b_2'z_t \perp b_1'z_t$ have to be determined. Repeating this procedure $r = \min p,q$ times defines the static canonical correlation coefficients $\rho_1 \ldots \rho_r$. It can be shown (cf. [15]) that the $\rho_1 \ldots \rho_r$ are the eigenvalues of

$$\gamma_{yy}^{-\frac{1}{2}}\gamma_{yz}\gamma_{zz}^{-1}\gamma_{zy}\gamma_{yy}^{-\frac{1}{2}} \tag{1}$$

where γ_{yy} and γ_{zz} are the auto-covariance functions and $\gamma_{yz} = \gamma_{zy}'$ is the cross-covariance function of y_t and z_t. Any norm of $(\rho_1 \ldots \rho_r)$, e.g. the maximum or the Euklidean norm, is a measure for the static dependence between y_t and z_t.

F. Dynamic Canonical Correlation Coefficients

Brillinger introduced the concept of dynamic canonical correlation analysis in [16]. The dynamic canonical correlation coefficients are defined as the maximum correlation between the convolutions $\sum_s a_i(t-s)'y_t$ and $\sum_s b_i(t-s)'z_t$ where $a_i \in \mathbb{R}^p$ and $b_i \in \mathbb{R}^q$. Analogously to the static case, it can be shown that the dynamic canonical correlation coefficients are the eigenvalues $\rho_1(\lambda)\ldots\rho_r(\lambda)$ of

$$f_{yy}^{-\frac{1}{2}}(\lambda)f_{yz}(\lambda)f_{zz}^{-1}(\lambda)f_{zy}(\lambda)f_{yy}^{-\frac{1}{2}}(\lambda) \tag{2}$$

where $f_{yy}(\lambda)$ and $f_{zz}(\lambda)$ are the auto-spectra and $f_{yz}(\lambda) = \overline{f_{zy}'}(\lambda)$ is the cross-spectrum of y_t and z_t (cf. [16]). Any norm of $(\rho_1(\lambda)\ldots\rho_r(\lambda))$ is a frequency-wise measure for the dynamic dependence between y_t and z_t.

G. Statistical Evaluation

The covariances of each 4-second EEG segment x_t were estimated by the empirical auto-covariance function

$$\widehat{\gamma}(s) = \frac{1}{T}\sum_{t=\max(1,1-s)}^{\min(T,T-s)} x_{t+s}x_t'. \tag{3}$$

For estimating the spectral density, an indirect estimation procedure was applied: at first, $\widehat{\gamma}$ was multiplied component-wise with a Parzen lag-window $w(s)$ with a truncation point

of 255 sample points [22]. The tapered empirical auto-covariance function was then Fourier transformed, resulting in the estimate

$$\widehat{f}(\lambda) = \frac{1}{2\pi} \sum_{s=-255}^{255} w(s)\widehat{\gamma}(s)\ e^{-i\lambda s}. \qquad (4)$$

Using a Parzen window guaranteed that $\widehat{f}$ was positive semi-definite. The truncation point of 255 sample points was determined by window closing.

The static and dynamic canonical correlation coefficients between two groups of EEG signals were computed by substituting the auto- and cross-covariances in (1) and auto- and cross-spectra in (2) by the estimates (3) and (4) respectively. As measure for the dependence between the two groups, we used the Euklidean norm of the coefficients as it was more robust (i.e. less influenced by single EEG channels) than the maximum.

On each 4-second EEG segment, a total of six measures for dependence between groups of EEG signals were computed: the norm of the static canonical correlation coefficients, and the norm of the dynamic canonical correlation coefficients within the frequency-bands δ (2-4 Hz), θ (4-8 Hz), α (8-13 Hz), β_0 (13-15 Hz), and overall (2-15 Hz). Thereby, the coefficients were calculated frequency-wise and then averaged within each band (the respective lower frequency-limit was included, the upper limit excluded from the bands). The arithmetic mean of the Euklidean norm of canonical correlation coefficients over all 4-second segments within resting phase and cognitive phase respectively were then used as qEEG markers.

The following groups of EEG signals were investigated (cf. [12]): Anterior (FP1, FP2, F3, F4), Central (FZ, C3, CZ, C4, PZ), Posterior (P3, P4, O1, O2), Temporal/Left (F7, T7, P7), and Temporal/Right (F8, T8, P8). The approximate electrode positions and the electrode groups on the human scalp (from above) are illustrated in Figure 1.

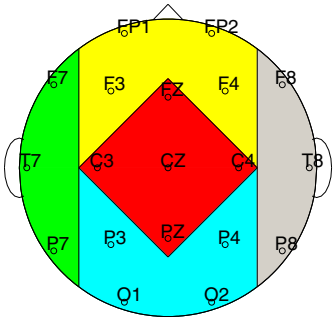

Fig. 1. Electrode groups: Anterior (yellow), Central (red), Posterior (cyan), Temporal/Left (green), and Temporal/Right (gray) (cf. [12]).

The change of the qEEG markers in the course of AD was estimated by quadratic regression models with the MMSE as independent and each qEEG marker as dependent variables. The demographics age, sex, completed level of education, and duration of AD were used as co-variables. The regression fit was evaluated by the coefficient of determination R^2 and the corresponding p-value of Fisher's F-test. Since multiple qEEG markers were computed from the same data and, thus, multiple hypotheses were tested, we used Bonferroni correction for controlling the familywise error rate.

III. RESULTS

Table I displays the p-values of Fisher's F-test for each qEEG marker in both resting and cognitive phase. The table-rows correspond to the pairs of EEG channel groups (cf. Figure 1). Statistically significant results, i.e. $p<0.0083$ after Bonferroni correction, are shown in bold font. In these cases, the quadratic regression model was able to accurately describe the relation of MMSE and qEEG marker.

In the resting phase, the most significant results were observed for the dynamic qEEG marker in the "slow" frequency bands δ and θ. In θ, maximum R^2-values of 0.23 (Central-Temporal/Left and Posterior-Temporal/Right) and 0.25 (Posterior-Temporal/Left) were observed; the MMSE described thus up to 25% of the qEEG marker's variation. We found no significant relation between static qEEG marker or dynamic marker in α and β_0 and MMSE scores.

In the cognitive phase, however, highly significant results for all qEEG markers were observed for Central-Temporal/Left, exhibiting R^2-values of 0.40 for the static qEEG marker and 0.39 for the dynamic marker in θ. The group combination Posterior-Temporal/Left showed highly significant results for all qEEG markers but in δ with coefficients of determination of around 0.30.

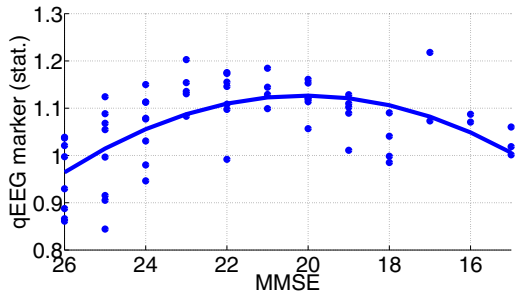

Fig. 2. qEEG marker vs. MMSE: norm of the static canonical correlation coefficients between Central and Temporal/Left during the cognitive phase.

Figure 2 shows a scatter plot with MMSE scores on the abscissa and the static qEEG marker for Central-Temporal/Left during the cognitive phase. Each dot corresponds to the qEEG marker value of one patient. Low MMSE scores (further right in the plot) correspond to more severe cognitive deficits. The curve shows the values of the quadratic regression model with MMSE as independent variable, qEEG marker as dependent variable, and the former described demographic characteristics as co-variables. For MMSE scores from 26 to about 20, an increase of qEEG marker values and, thus, of EEG synchrony can be observed. Only for MMSE scores below 20, a decrease of synchrony was apparent. The model was highly significant with $R^2 = 0.40$.

TABLE I

RELATION OF QEEG MARKERS AND MMSE SCORES: P-VALUES OF FISHER'S F-TEST FOR QUADRATIC REGRESSION. SIGNIFICANT RESULTS (P<0.0083 AFTER BONFERRONI CORRECTION) ARE SHOWN IN BOLD FONT.

	Resting phase						Cognitive phase					
	stat.	dyn.(all)	dyn.(δ)	dyn.(θ)	dyn.(α)	dyn.(β_0)	stat.	dyn.(all)	dyn.(δ)	dyn.(θ)	dyn.(α)	dyn.(β_0)
An.-Ce.	0.171	0.373	0.023	0.024	0.909	0.800	0.034	0.060	0.038	0.032	0.132	0.099
An.-Po.	0.312	0.215	0.047	**0.002**	0.524	0.364	**0.002**	**0.005**	0.094	**0.001**	0.092	0.034
An.-Te/L.	0.077	0.132	0.018	**0.002**	0.703	0.862	**0.001**	**0.001**	0.057	**6.76e-05**	0.012	0.089
An.-Te/R.	0.120	0.209	**0.005**	**0.007**	0.460	0.640	0.125	0.061	0.033	**0.004**	0.356	0.042
Ce.-Po.	0.061	0.010	**0.005**	**0.001**	0.099	0.030	**0.002**	0.009	0.040	**0.001**	0.065	0.022
Ce.-Te/L.	0.013	0.021	**0.004**	**3.26e-04**	0.298	0.522	**2.28e-07**	**3.45e-05**	**0.004**	**4.54e-07**	**0.002**	**0.008**
Ce.-Te/R.	0.062	0.012	**0.001**	**0.001**	0.094	0.027	**0.001**	**0.001**	**0.004**	**0.001**	**0.005**	0.028
Po.-Te/L.	0.026	**0.002**	0.026	**1.43e-04**	0.054	0.040	**3.49e-05**	**6.58e-05**	0.077	**1.09e-04**	**1.92e-04**	**1.23e-04**
Po.-Te/R.	0.012	**0.006**	**0.005**	**2.80e-04**	0.289	0.394	**2.43e-05**	**0.001**	0.016	**3.89e-04**	0.012	**0.001**
Te/L.-Te/R.	0.106	0.120	0.009	**0.003**	0.194	0.187	0.011	0.022	0.048	0.013	0.098	0.178

IV. DISCUSSION AND CONCLUSION

In this study, we analyzed the relation between qEEG markers derived from canonical correlations with AD severity measured by MMSE scores. This relation was observed to be most significant in δ and θ in the resting phase, and for Central-Temporal/Left and Posterior-Temporal/Left in the cognitive phase. Here, the MMSE explained up to 40% of the qEEG marker's variation. The qEEG markers showed an increase of EEG synchrony in the initial stage of AD (MMSE>20) and a decrease in later stages. This effect was most prominent during the cognitive task and it adds to related reports about compensatory brain mechanisms [12]. The quadratic regression model was well suited to model this ambiguous EEG synchrony trend whereas a linear model would be inappropriate. This could explain why no significant changes of EEG synchrony were reported in related studies that applied linear analyses, e.g. [3][10].

In conclusion, this study indicates that the proposed qEEG markers relate closely to AD severity (i.e. MMSE scores). However, the quadratic trend of EEG synchrony with decreasing MMSE causes diagnostic ambiguity. Even so, this ambiguous trend of EEG synchrony could contribute to the understanding of neuronal changes in AD. Future studies need to determine whether a combination of our qEEG markers with other markers for synchrony, but also for slowing and reduced complexity, could provide aid in both diagnosis and prognosis of AD.

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