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EEG Dominant Frequency Peak Differentiates Between Alzheimer's Disease and Frontotemporal Lobar Degeneration

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Abstract. We investigated the power of EEG as biomarker in differential diagnosis of Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). EEG was recorded from 106 patients with AD or FTLD, of which 37 had a definite diagnosis, and 40 controls. Dominant frequency peaks were extracted for all 19 channels, for each subject. The average frequency of the largest dominant frequency peaks (maxpeak) was significantly lower in AD than FTLD patients and controls. Based on ROC analysis, classification could be made with diagnostic accuracy of 78.9%. Our findings show that quantitative analysis of EEG maxpeak frequency is an easy and useful measure for differential dementia diagnosis.

Keywords: Alzheimer's disease, biomarkers, differential diagnosis, electroencephalography, frontotemporal lobar degeneration

INTRODUCTION

Clinical diagnosis of both Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) is mainly based on the exclusion of other diseases, and this results at best in a diagnosis of probable AD or probable FTLD. Moreover, it is difficult to distinguish between these disorders on a clinical level, as up to 25% of clinical FTLD is actually due to atypical presentation of AD pathology [1, 2]. At the same time, patients might be misdiagnosed with AD while having an underlying FTLD pathology but presenting with memory difficulties [3]. This two-way association between FTLD and AD shows there is a clear need for tools that allow early and reliable differential diagnosis. Diagnostic accuracy could be increased by the use of biomarkers [4].

Electroencephalography (EEG) is an easy-to-use, non-invasive technique capable of picking up

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functional changes in the brain [5]. As such, it can be used to investigate the disruption of brain connectivity as a result of neurodegeneration associated with dementia. Trained clinicians routinely use visual analysis of EEG to support clinical dementia diagnosis, but this is a subjective measure and therefore difficult to reproduce. To objectively assess EEG recordings and pick up more subtle differences, quantification of EEG characteristics is more useful. Recent advances in recording and analysis of EEG showed an added value for EEG in the differentiation between AD and FTLD [6, 7]. However, to our knowledge no studies have been performed where (subgroups of) patients had a confirmed type of dementia. Therefore, it can be assumed that classification of patients has so far been biased toward clinical symptoms. Since clinical symptoms mostly reflect affected brain regions, generated results are not specific for underlying brain pathology. In this study, we aim to differentiate between AD and FTLD based on straightforward computational analysis of EEG recordings from both clinical and definite dementia patients.

MATERIALS AND METHODS

Subjects

The study cohort comprised age-matched groups of 55 (19 definite) AD dementia, 51 (19 definite) FTLD patients, and 40 neurologically healthy controls (Table 1). Patients were selected from the Memory Clinic of Hospital Network Antwerp [8, 9]. Controls had diagnoses of headache, dizziness, or syncope, not suggestive of epileptic fits. To ensure high evidence of dementia subtypes for patients without definite diagnosis, only patients with extensive clinical follow-up were included. All patients underwent (among others) neuropsychological testing including Mini-Mental State Examination (MMSE), and had routine AD biomarker analyses ($A\beta_{42}$, tau, and phosphorylated tau proteins) in cerebrospinal fluid [10]. Diagnosis of probable AD was based on IWG-2 criteria [4] and included these biomarkers. Diagnosis of probable FTLD was based on criteria described by Neary [11]. Subgroups of definite dementia patients were defined by genetic carrier status and/or postmortem confirmation of brain pathology [12–14]. This study was approved by the ethics committee of University of Antwerp, Antwerp, Belgium.

EEG Recordings

EEG data was recorded using OSG digital equipment (BrainLab/BrainRT) with the international 10–20 system used for electrode placement [15]. ECG was recorded in a separate channel. Recordings were exported in EEGLab format [16] for offline analysis and each file contained continuous data in 19 channels. During recording, subjects were seated upright and were asked to alternate between eyes closed and eyes open to stay awake. EEG data was processed manually using BrainRT. Artifact-free epochs during the eyes-closed condition were flagged. This flag consisted of start latency of the useable part and its duration, both in milliseconds. No epileptiform activity was observed in any of the EEG recordings.

EEG Processing

Extraction of epochs

For each subject, the first 12 epochs that showed 2,048 ms (512 samples at a sampling frequency of 250 Hz) of continuous artifact-free EEG signal were selected.

Transformation to frequency spectrum

The number of data points per epoch was set at 512. This is a power of two, ensuring optimal performance of the Fast Fourier Transform in Matlab [17], which was used for transformation to the frequency spectrum. Every epoch was transformed separately to its spectrum, after which these spectra were averaged into one average spectrum as described by Welch [18]. An important advantage of this method is that the variance decreases as the number of periodograms increases [19]. This resulted in one spectrum for each channel for each subject.

Extraction of dominant frequency peaks

In the obtained spectra, dominant frequency peaks (DFPs) were detected. This peak was defined as a transition from a rising edge to a falling edge in the frequency interval [5–15] Hz. For each channel, a DFP was extracted. The DFP with the largest amplitude along all channels for a specific subject (maxpeak) was also saved separately, with its frequency and its channel of occurrence. Group averages and standard deviations were calculated.

The resulting dataset contained, for each subject: the frequency spectrum in each channel; the amplitude and frequency of the DFP in each channel; and the amplitude, frequency and channel of the maxpeak.

Table 1
Demographic information and maxpeak characteristics

	Controls	AD	FTLD	*p*-value
Gender (%male/female) (n)	38/62 (40)	44/56 (55)	71/29 (51)	**0.003**
Age at EEG (years)	67.4 ± 11.2	71.9 ± 7.7	68.9 ± 9.7	0.062
Age at onset (years)	n.a.	68.9 ± 9.7	64.9 ± 10.2	**0.028***
MMSE (0–30) (n)	n.a.	18.3 ± 5.8 (44)	21.0 ± 8.0 (39)	0.088
Maxpeak frequency (Hz)	8.94 ± 1.43	7.80 ± 1.44	8.57 ± 1.34	**<0.001***$
Maxpeak amplitude	5.70 ± 4.67	3.86 ± 2.01	5.45 ± 3.93	**0.027**
Definite subgroups				
Gender (%male/female) (n)		47/53 (19)	68/32 (19)	0.324
Age at EEG (years)		69.3 ± 8.5	64.9 ± 9.9	0.144
Age at onset (years)		66.5 ± 9.6	61.4 ± 9.2	0.100
MMSE (0–30) (n)		16.5 ± 6.8 (14)	19.5 ± 9.1 (12)	0.347
Maxpeak frequency (Hz)		7.22 ± 1.11	8.92 ± 1.23	**<0.001***
Maxpeak amplitude		3.58 ± 2.10	4.47 ± 2.50	0.242

Values are mean ± SD, percentage (%) or number (n). Definite subgroups are defined by genetic and/or postmortem neuropathological confirmation. In the AD group, three patients had a mutation in either *PSEN1* or *APP* and 16 were pathologically confirmed (time between EEG and autopsy = 0.8 [0.5–1.7] years). In the FTLD group, 9 patients had a mutation in *MAPT*, *GRN*, *C9orf72*, *VCP*, or *TBK1* and 13 (including four mutation carriers) were neuropathologically confirmed (time between EEG and autopsy = 2.2 [0.7–2.9] years). Statistically significant *p*-values (<0.05) are marked in bold. *Significant difference between AD and FTLD. $Significant difference between AD and controls.

Statistical testing

Statistical analyses were performed using IBM SPSS Statistics 23 and Matlab. To describe our study cohort, Student's *t*-tests were performed. Categorical variables were analyzed with a Chi-square test. Analysis of Variance (ANOVA) was performed to compare each of the characteristics of the DFPs (frequency, amplitude and power), between groups and between channels, the latter having 15 levels, since the maxpeak was not found for any subject in 4 of the 19 channels. Pearson's r was calculated to determine correlations. Receiver operating characteristic (ROC) curves were used to determine optimal cut-off values to differentiate between AD and FTLD (i.e., maximizing the Youden index). ROC curves were compared using area under the curve (AUC) values. For all analyses, *p*-values below 0.05 were considered statistically significant.

RESULTS

Demographic and clinical data of the study cohort as well as values for average maxpeak frequency and maxpeak amplitude in the control, AD and FTLD patient groups are presented in Table 1. A significant difference was found in average frequency of the maxpeak (largest DFP), being lower in AD than in FTLD patients and controls (Fig. 1a). More importantly, the difference in DFP frequency was visible on each separate electrode and indeed no significance was found for channel as a factor in ANOVA analysis.

To our knowledge, this is the first report where a large proportion of patients (35%) from both AD and FTLD groups had a definite dementia diagnosis. When analyzing only the definite subgroups our main finding was consolidated, as the gap in maxpeak frequency became larger (Table 1).

Based on ROC curve analysis, maxpeak frequency reached an AUC of 0.656 in differentiating between AD and FTLD with diagnostic accuracy of 61.3% (sensitivity: 49.1%; specificity: 74.5%) at a cut-off of 7.32 Hz. Analysis of the definite subgroups again increased clinical significance of our findings, reaching an AUC of 0.835, and a diagnostic accuracy of 78.9% (sensitivity: 94.7%; specificity: 63.2%) at a cut-off of 8.79 Hz (Fig. 1b).

DISCUSSION

The aim of this study was to use quantitative EEG analysis to differentiate between AD and FTLD patients. A substantial subset of patients had a definite dementia diagnosis established by genetic carrier status and/or neuropathological confirmation. Clinical follow-up contributed to diagnostic certainty of clinical AD and FTLD groups, and AD diagnoses were biomarker-based. We found a significant difference in frequency of the dominant frequency peaks, being lower in the AD than in the FTLD group. This difference was even more pronounced in the definite subgroup.

In research, visual analysis of EEG has almost completely been replaced by quantitative analysis

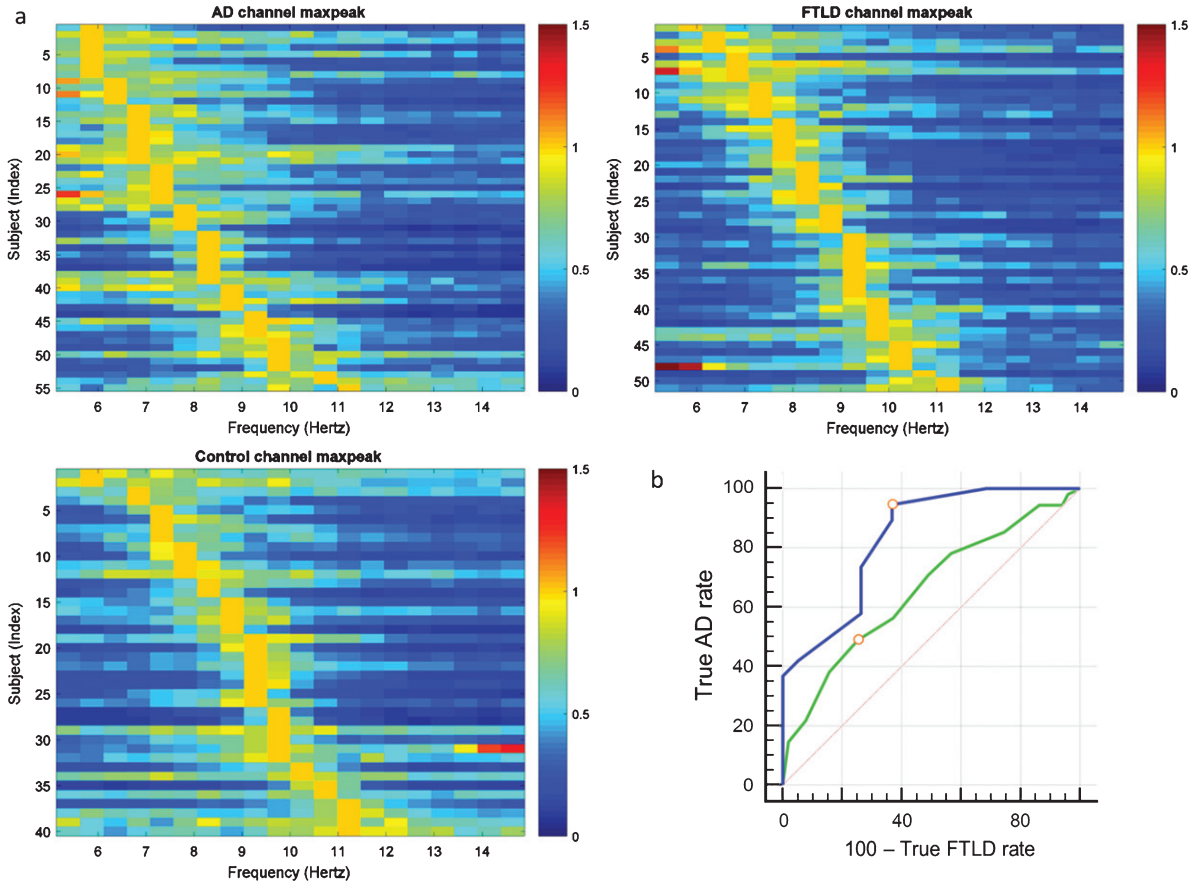

Fig. 1. maxpeak frequency differentiates between AD and FTLD. Panel (a) shows a generally lower maxpeak frequency in AD patients (upper left) than in FTLD patients (right) and controls (bottom left). For each patient, the frequency spectrum from the channel containing the patient's largest DFP (maxpeak) is plotted. This channel can be different for different patients. Patients are ordered according to their maxpeak frequency in this spectrum from lowest to highest. Every row's amplitudes have been divided by the amplitude of its maxpeak, fixing the maxpeak value at 1. As a result, one can clearly see the maxpeak frequencies appear as a downward sloping line along the figures. Only the [5–15] Hz band is shown in the plot. (b) ROC curve analyses determined optimal maxpeak frequency cut-off to differentiate between AD and FTLD. AUC value for the complete patient subgroup was 0.656 (green), and AUC value for the definite subgroups was 0.835 (blue). Orange markers correspond to the maximized Youden's index for each ROC curve.

and several papers have used EEG to differentiate between AD and FTLD. However, each study used different methods and thus different useful measures are reported, making inter-study comparison difficult [6, 7, 20–24]. The aim of the present study was to use a straightforward measure that is easily determined from a short EEG, recorded from subjects at rest. Since we aimed to describe general changes in EEG, we chose to not limit ourselves to the conventional frequency ranges but calculated the DFP in the entire EEG spectrum, for each subject and for each channel.

Our results show that the DFP frequency is lower in AD than FTLD patients and controls. In the AD group, the low DFP frequency in each channel corresponds to a mean frequency slowing, which is considered the general EEG abnormality in AD [25, 26]. These EEG abnormalities are supposedly dependent on the severity of disease and indeed we found a correlation with MMSE score (Supplementary Table 1). In the FTLD group, the DFP frequency was only slightly lower than that of controls. This was expected as there is no 'general' EEG abnormality in FTLD. On the contrary, EEG recordings in patients with FTLD are indeed considered relatively normal and this finding is even used as an item in the clinical diagnostic criteria of Neary [11]. However, researchers have reported both normal and abnormal EEG on visual inspection in FTLD patients, and this again would mostly depend on disease severity

[21, 23, 27]. For this FTLD patient group, no significant correlation was found between DFP characteristics and MMSE score, but MMSE is known to perform poorly in FTLD and to be a bad predictor of disease severity [28].

Observed differences in correlations (Supplementary Material) between AD and FTLD groups may point toward disease-specific effects on maxpeak amplitude and frequency, respectively. These findings should be replicated and validated in a prospective study that consists of an independent cohort of AD and FTLD patients, with at least probable clinical diagnoses.

In summary, our results show that EEG maxpeak frequency is an easy and useful measure with an added value in the differentiation between AD and FTLD, with a diagnostic accuracy of up to 78.9%.

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SUPPLEMENTARY MATERIAL

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