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Quantitative EEG Differences in Subtypes of Frontotemporal Dementia

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Abstract

Background: Frontotemporal dementia (FTD) is the second most common group of neurodegenerative disorder following Alzheimer's Disease (AD); and characterized by degeneration of frontal and/or temporal lobes. FTD can be classified as behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA). The aim of this study is to investigate electrophysiological differences in bvFTD and nonfluent/agrammatic PPA (naPPA), one of three forms of PPA.

Methods: Twelve patients with bvFTD and 15 patients with naPPA were included in the study. EEG was recorded from 19 electrode sites based on international 10-20 system. Each participant's data were averaged across the recording epochs for each electrode, and the mean absolute power values were computed for delta, theta, beta and alpha frequency bands.

Results: For all frequency bands, inter-hemispheric and intrahemispheric coherence were calculated. In absolute power; increased theta power at all regions was found in naPPA group as compared to bvFTD group. Regarding coherence; increased alpha coherence at inter-hemispheric frontal region was found in bvFTD as compared to naPPA group.

Conclusions: Our findings suggest that subtypes of FTD vary in resting-state EEG especially indexed by the decreased theta power reflecting bvFTD.

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INTRODUCTION

Frontotemporal dementia (FTD) is a group of neuropathologically and clinically heterogeneous disease characterized by changes in personality and behavior or aphasia accompanied by degeneration of the frontal or temporal lobes, or both. FTD spectrum generally has two clinical presentations, as behavioral variant FTD (bvFTD) and three forms of primary progressive aphasia (PPA). The bvFTD is the most common variant of FTD and presented by progressive change in personality, behavior, and cognition. First two variants of PPA are nonfluent/agrammatic (naPPA) and semantic.(1) The third variant, logopenic variant, often neuropathologically differs from PPA spectrum, and usually, it has had similar neuropathology with AD [1]. The hallmark of PPA is a gradual progression of language impairment with relative sparing of memory and other cognitive functions, at least in the early stage of the disease course.

Quantitative EEG (qEEG) is defined by American Academy of Neurology as the mathematical processing of digitally recorded EEG in order to highlight specific waveform components, transform the EEG into a format or domain that elucidates relevant information, or associate numerical results with the EEG data for subsequent review or comparison [2] Since it is possible to increase EEG sensitivity through the mathematical procedures implemented in qEEG, the background neural activity can be quantified using power and coherence variables [3].

Even though EEG is not typically considered as a diagnostic tool for FTD including variants, EEG may show asymmetric mild focal slowing usually in the atrophic region of the brain [3-6]. However, identifying possible qEEG related biomarkers distinguishing subtypes dementia, can possibly facilitate the diagnosis procedure and help practitioners to follow the patient during treatment. Furthermore, taking its common, practical, economic use into account, qEEG can be preferred as compared to other diagnostic techniques such as fMRI. There are few studies in the literature that compared qEEG findings of FTD with having contradictory

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results. While plenty of studies reported decreased alpha and beta power in FTD without any change in slow wave activities, some other studies reported increased theta power [7]. Based on the previous literature, the aim of the present study was to explore possible electrophysiological variations among two types of FTD, bvFTD and naPPA.

METHODS

Participants

14 patients with the diagnosis of bvFTD and 17 patients with the diagnosis of naPPA were identified retrospectively from NPIstanbul Brain Hospital databases. Diagnosis were obtained by clinical history, neurological examination, cranial magnetic resonance imaging (MRI) and neuropsychological evaluation. All patients meets the criteria of probable bvFTD, and naPPA according to Rascovsky and Gorno-Tempini.(1, 6) The EEG data of **3** participants was discarded as a result of too many artifacts in EEG recording. Finally, 12 patients with bvFTD and **16** patients with naPPA were included in the study. The exclusion criteria were a history of psychiatric disorder, presence of any cranial vascular lession or hemorrhage on MRI, leukoaraiosis, suspected hydrocephalus or any other neurodegenerative disease and any medical disorder that may affect cognition. Gender distribution among the groups was different at borderline significance (x^2 *(1, N = 28)* = 3.88, p = .05*)*. In terms of age, bvFTD group (*M* = 68.38 ±8.37) was significantly older than naPPA group (*M* = 61.83 ±5.98), $t(26) = 2.30$, $p < .05$. Patients' mental state was assessed by MMSE and no significant difference was found between naPPA group *(M = 25.83 ±1.02)* and bvFTD group *(M = 25.78 ± .80), p* > .05. The study protocol was in compliance with the Helsinki Declaration of Human Rights and was approved by the Ethics Committee of Üsküdar University (B.08.6.YÖK.2.ÜS.0.05.0.06/2018/ 908).

Electrophysiological Data Collection

EEG was recorded from 19 electrode sites based on the international 10-20 system, using 19 electrodes for 3 minutes. During the recording, participants sat in a quiet room with their eyes closed. The data sampling rate was 250 Hz and the acquired signals were filtered with a band - pass filter of 0.15-70 Hz. EEG impedances were kept below 10 kΩ (monitored online with SCAN software). Horizontal eye movements (HEOG) were recorded with electrodes placed on the outer canthi of the eyes and vertical eye movements (VEOG) were recorded from an electrode placed below the left eye. Prior to comparison analysis, data was automatically corrected for eye blinks and ocular artifacts. Artifact rejection criteria were set to ±100 μV. The data analysis was completed using the Neuroguide Deluxe 2.5.1 software (Applied Neuroscience, St Petersburg, FL).

Absolute Power

Each participant's data were averaged across the recording epochs for each electrode, and the mean absolute power values were computed for each of the following frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz). A natural log transform was computed for all EEG power variables. Data were then lognormalized.

We limited the number of regions by grouping electrodes and creating 4 main regions of interest to perform statistical analyses: medial prefrontal (Fp1, Fz, Fp2), frontal (F3, F4, F7, F8), parietal (P3, P4, T5, T6,), and central (Cz, C3, C4).

Coherence

For all frequency bands, inter-hemispheric and intra-hemispheric coherence were calculated. Intra-hemispheric coherence was measured across electrode pairs F3-C3, F3-P3, F3-T5, C3-P3, C3-T5, P3-T5 on the left hemisphere, and F4-C4, F4-P4, F4-T6, C4- P4, C4-T6, P4-T6 on the right hemisphere. Inter-hemispheric coherence was measured across electrode pairs F3-F4, C3-C4 and P3-P4.

Statistical Analysis

Group comparisons were carried out via repeated measures of ANOVA. Significant interaction effects were followed by t-tests. All statistical analyses were conducted Statistical Package for the Social Sciences (SPSS, version 20) and statistical significance was set at $p \leq .05$ (2-tailed). For multiple comparisons Benjamini - Hochberg corrected p values were reported.

RESULTS

Absolute Power

A 4 × 4 x 2 mixed ANOVA with frequency (alpha, beta, theta, delta) and region (frontal, central, prefrontal, parietal) as within-subject factors and group (naPPA, bvFTD) as between-subject factor revealed a significant main effect of region ($F(3, 78) = 3.91$, $p = .01$, $\eta p^2 = 0.13$); and frequency ($F(3, 78) = 147.4$, $p < .001$, $\eta p^2 = 0.85$). The 2 way interaction between the frequency and region was also significant ($F(9, 234) = 21.86$, $p < .001$, $\eta p^2 = 0.46$). The 3 way interaction between frequency, group and region ($F(9, 234) = 1.33$, *NS*) and the 2 way interaction between region and group ($F < 1$, *NS*) were not significant. However, 2 way interaction between frequency and group reached significance ($F(3, 78) = 3.24$, $p < .05$, $\eta p^2 = 0.11$).

The 2 way interaction between frequency and group was followed by post-hoc analyses regardless of the region. These analyses showed that groups significantly differed in the theta band ($t(26)=3.04$, $p < .01$, $d = 1.20$ all other *t*s > 1.62, *NS*). This result was significant after Benjamini-Hochberg correction as well (Benjamini-Hochberg corrected p value = 0.02). Further exploratory analyses showed groups differed in theta band frequency at all regions (prefrontal, $t(26) = 2.55$, $p < .05$, $d = 1.01$; frontal, $t(26) = 2.89$, $p < .01$, $d = 1.12$; central, $t(26) = 2.92$, $p < .01$, $d = 1.14$; parietal, $t(26) = 2.75$, $p = .01$, $d = 1.08$; see Table 1 for mean scores and SDs). The mean scores indicated that naPPA group had increased theta absolute power as compared to bvFTD.

Table 1. Means (and standard deviations in parenthesis) of EEG absolute power values in different regions and frequency for bvFTD (behavioral variant of frontotemporal dementia) and naPPA (nonfluent/agrammatic primary progressive aphasia) groups separately.

Frequencies	Theta		Beta		Delta		Alpha	
Region / Group	bvFTD	naPPA	bvFTD	naPPA	bvFTD	naPPA	bvFTD	naPPA
Prefrontal	0.34 (0.15)	0.55 (0.24)	-0.46 (0.14)	-0.33 (0.25)	0.88 (0.37)	1.04 (0.33)	0.43 (0.32)	0.25 (0.22)
Frontal	0.32 (0.12)	0.56 (0.26)	-0.44 (0.17)	-0.35 (0.24)	0.73 (0.27)	0.88 (0.26)	0.45 (0.35)	0.32 (0.24)
Central	0.26 (0.14)	0.48 (0.21)	-0.40 (0.17)	-0.35 (0.22)	0.68 (0.27)	0.79 (0.23)	0.45 (0.36)	0.37 (0.21)
Parietal	0.18 (0.18)	0.41 (0.23)	-0.41 (0.16)	-0.39 (0.19)	0.53 (0.23)	0.75 (0.28)	0.58 (0.42)	0.49 (0.27)

Coherence

Intra-Hemispheric Coherence

According to the results of 4 x 12 x 2 mixed ANOVA with frequency (alpha, beta, theta, delta) and region (F3-C3, F3-P3, F3-T5, C3-P3, C3-T5, P3-T5, F4-C4, F4-P4, F4-T6, C4- P4, C4-T6, P4-T6) as within-subject factors and Group (naPPA, bvFFT) as between-subject factor, there was a significant main effect of frequency ($F(3, 78) = 125.47$, $p < .001$, $\eta p^2 = 0.82$) and region ($F(3, 78) = 80.90$, $p < .001$, $\eta p^2 = 0.76$). Furthermore, there was a significant region and group $F(11, 286) = 2.25$, $p < .05$, $\eta p^2 = 0.08$; region and frequency, $F(33, 858) = 55.36$, $p < .001$, $\eta p^2 = 0.68$) region, group and frequency interaction $F(33, 858) = 2.22$, $p < .001$, $\eta p^2 = 0.08$. Frequency and group interaction was not statistically significant ($F < 1$, *NS*).

Following the 3 way interaction, post-hoc analyses revealed groups only differed in Beta band at left central-parietal region (C3-P3; $t(26) = 2.06$, $p = .05$, $d = 0.80$). Accordingly, naPPA group ($M = 5.38$, $SD = 2.71$) had significantly decreased beta coherence at left central-parietal region as compared to bvFTD ($M = 7.34$, $SD = 2.17$). All other *t*s were < 1.7, *NS*. After the Benjamini-Hochberg correction this difference was not significant anymore.

Inter-Hemispheric Coherence

4 x 3 x 2 mixed ANOVA with frequency (alpha, beta, theta, delta) and region (F3-F4, C3-C4, P3-P4) as within-subject factors and Group (naPPA, bvFTD) as between-subject factor showed that there was a significant main effect of frequency $F(3, 78) = 58.93$, $p < .001$, $\eta p^2 = 0.69$; main effect of region, $F(2, 52) = 21.22$, $p < .001$, $\eta p^2 = 0.45$; frequency and region interaction, $F(6, 156) = 20.92$, $p < .001$, $\eta p^2 = 0.45$. Furthermore there was a significant 3-way interaction effect among group, frequency band and region $F(6, 156) = 2.71$, $p < .05$, $\eta p^2 = 0.09$ (other *F*s ≤ 1, *NS*).

In post-hoc analyses, it was found that groups significantly differed in beta coherence ($t(26) = 2.11$, $p < .05$, $d = 0.79$); and alpha coherence ($t(26) = 3.11$, $p < .01$, $d = 1.19$) at frontal region (F3-F4). naPPA group (for beta $M = 3.51$, $SD = 1.60$; for alpha $M = 2.18$, $SD = 0.92$) had significantly lower frontal inter-hemispheric beta and alpha coherence as compared to bvFTD (for beta $M = 4.95$, $SD = 2.01$; for alpha $M = 3.27$, $SD = 0.91$). All other *t*s were < 1.8, *NS*. After the Benjamini-Hochberg correction only alpha coherence at the frontal region was significantly different for two groups (corrected *p* value = 0.05).

DISCUSSION

Since the classical EEG has been found to be unsuccessful even in the discrimination of FTD and AD which have different pathophysiological course qEEG has started to be considered as a more sensitive tool for the evaluation of dementia subtypes [5]. It is important to note that qEEG should be regarded as a supplemental electrodiagnostic tool following classical EEG which is still standart tool for diagnosis and differential diagnosis in neurologic diseases.

The main finding of this study was the increased theta absolute power in the naPPA group at all regions in comparison to the bvFTD group. In literature, increased slow wave activity (delta & theta) has been generally associated decreased cognitive decline; though there are also few studies indicating decreased theta power in healthy cognitive aging [8-10]. Since we only included patients with an MMSE score higher than 25, we suggest that alteration in slow wave activities in naPPA may have a predictive value for the cognitive decline before MMSE can measure it. Also, the qEEG pattern of naPPA seems to be more similar to AD, as the literature shows increased theta power in AD [11].

The second important finding of the study was the decreased inter-hemispheric alpha coherence at the frontal region in the naPPA group. Similar to the absolute power finding, our results for coherence are consistent with the previous literature. Namely, studies show that there is decreased alpha coherence in AD at temporoparietal region, decreased alpha coherence at left temporal region, decreased alpha and beta coherence at frontal regions [8, 12-14]. Therefore, it can be inferred that our naPPA group demonstrated a more AD-like electrophysiological pattern as compared to the behavioral variant FTD. Also, it is not surprising to acquire decreased beta coherence at the left central-parietal region, since naPPA has a left hemisphere dominant symptomatology.

The relatively small sample size was the first major limitation of the study. However, since it is not easy to find FTD patients in the clinic, the number of patient can be acceptable. The lack of a wide neuropsychological

evaluation was also an important limitation of the study. It would be plausible to compare the 2 subtypes of FTD in terms of different cognitive functions and associate those functions with qEEG findings. Finally, a significant age difference was present between the groups which may affect the findings. However, as the younger group (naPPA) displayed a qEEG pattern more representative for cognitive decline, it is even possible to think that age-matched groups could strengthen the results especially regarding the increased slow-wave activity in naPPA group.

To conclude, this was the first study which compared primary progressive aphasia with the behavioral variant of FTD in terms of qEEG parameters. Our findings suggest that naPPA and bvFTD have different qEEG patterns and especially alterations in theta power might reflect a predictive value for AD-like cognitive decline. Future studies are needed to establish a more concrete distinction between different types of FTD, where a detailed neuropsychological evaluation is also combined with electrophysiological data.

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