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Anterior EEG slowing in Dementia with Lewy Bodies: a multicenter European cohort study.

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Running title: anterior EEG slowing in DLB

Abbreviations

AD = Alzheimer's disease; DF = dominant frequency; DFV = dominant frequency variability; DLB = Dementia with Lewy Bodies; FP = frequency prevalence; MMSE= Mini Mental State Examination; PD= Parkinson's Disease; RBD= REM sleep Behaviour Disorder; UPDRS-III= Unified Parkinson's Disease Rating Scale-III.

Abstract

EEG slowing with pre-alpha dominant frequency (DF) in posterior derivations is a supportive biomarker for Dementia with Lewy Bodies (DLB) diagnosis, with high predictive value for the differential diagnosis with Alzheimer's Disease (AD). However, an intra-subject re-evaluation of original data showed that in the group of DLB, DF recorded on anterior derivations was slower than in posterior derivations.

We hypothesize that the intra-subject evaluation could arise different involvement of anterior and posterior areas in DLB.

EEG was recorded in 144 DLB, 116 AD and 65 controls from 7 Centers of the European DLB Consortium. Spectra, divided into delta, theta, pre-alpha, alpha frequency bands were described by DF, DF variability (DFV), frequency prevalence (FP).

In DLB mean DF was in the pre-alpha band in both anterior and posterior derivations, but it was lower in anterior derivations ($p<0.001$). In both AD and controls mean DF was lower in anterior than in posterior derivations ($p<0.001$) but was constantly in the alpha band. In 14% of DLB patients, pre-alpha was dominant in anterior while alpha was still dominant in posterior derivations.

EEG abnormalities in DLB patients were found to be correlated with cognitive impairment.

In DLB EEG abnormalities were more prominent in anterior derivations. A longitudinal study should address if EEG abnormalities appear earlier in anterior than in posterior leads during the disease course.

Keywords: dementia with Lewy bodies; EEG rhythms; thalamo-cortical dysfunctions.

1. Introduction

Prior studies have demonstrated the power of quantitative electroencephalography (EEG) as diagnostic tool in dementia (Garn et al., 2017; Snaedal et al., 2012). The most prominent eyes-closed resting state finding in dementia patients is that of EEG slowing, i.e. a shift of the dominant frequency (DF) towards lower frequency bands, outside the alpha band. The DF is defined as the frequency with the highest power in the EEG spectrum and typically occurs between 3 and 12 Hz (Niedermeyer and Lopes da Silva, 2005). In dementia with Lewy bodies (DLB), DF shifts from the alpha frequency range towards a fast-theta (pre-alpha) rhythm with neurodegenerative progression (Bonanni et al., 2008). A pre-alpha DF, either stable along the recording or intermixed with DF in alpha or theta or delta bands in posterior derivations (Bonanni et al, 2008), is now considered a supportive biomarker for the diagnosis of DLB (McKeith et al., 2017).

The appearance of a pre-alpha rhythm in the cortex is considered to be linked to a dysfunctional thalamo-cortical connection, the so called thalamocortical dysrhythmia (Llinás et al., 1999; Llinás and Steriade, 2006).

In the original work (Bonanni et al., 2008), the most reliable diagnostic index, which separated with 100% sensitivity and specificity DLB patients from Alzheimer's disease (AD) , resulted to be the EEG pre-alpha DF recorded from posterior derivations.

This is because, as expected in eyes-closed relaxed wakefulness, in posterior derivations the power of alpha rhythm was maximal in healthy controls and AD (Niedermeyer and Lopes da Silva, 2005), allowing a strong differentiation with DLB where alpha in posterior derivations was much less represented, due to substitution with slower DF (Bonanni et al., 2008).

However, an intra-subject re-evaluation of original data showed that in the group of DLB, the DF recorded on anterior derivations were constantly slower (in frequency bands lower than alpha) than in posterior derivations, suggesting a more prominent thalamocortical dysrhythmia involving the anterior cortical regions.

Thalamocortical dysrhythmia in anterior cortical regions has been implicated in the appearance of altered conscious and sleep states, including fluctuating cognition, REM sleep behaviour disorder, hallucinations (Antelmi et al., 2016; Fiset et al., 1999; Foucher et al., 2004; Llinás et al., 1999;Volkow et al., 1995; Ward, 2011) all symptoms which are listed among the clinical core features of DLB (McKeith et al., 2017).

With the present study we aim to test, in a multicentre cohort, the hypothesis that the thalamocortical dysrhythmia with consequent appearance of pre-alpha rhythm in DLB could primarily involve the anterior cortical regions, with the aforementioned potential pathophysiological implications. The same intra-subject analysis was also performed in AD patients and healthy controls to test the hypothesis that the thalomocortical dysrhythmia was specific to DLB pathology.

2. Materials and Methods

2.1. Subjects and diagnostic criteria

We analyzed EEG traces of 144 patients with probable DLB (McKeith et al., 2005), confirmed applying a posteriori the last released criteria (McKeith et al., 2017), 116 AD patients, diagnosed according to the international criteria (McKhann et al., 2011) and matched for education with DLB patients and 65 age and education-matched healthy control subjects (controls), recruited from 7 different European Centers involved in the European DLB Consortium (E-DLB): 1) Department of Neuroscience, Imaging and Clinical Science, and Aging Research Centre, G. d'Annunzio University, Chieti, Italy; 2) Clinical Neurology Unit, Department of Neuroscience (DINOGMI), University of Genoa, Italy; 3) Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK; 4) Department of Clinical and Experimental Sciences, University of Brescia, Italy; 5) Alzheimer's Epidemiology and Rehabilitation in Alzheimer's disease Operative Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; 6) Department of Neurology, University Medical Centre, Ljubljana, Slovenia: 7) Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Clinical Geriatrics, Karolinska

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Each Center converted each recording to EDF file and shared it to Center 1 for the analysis.

The proportion of DLB, AD and controls were different among Centers is reported in the table of the supplementary material.

As previously described (Bonanni et al., 2016) demographics and clinical procedures were not harmonized across Centers, but at all Centers the clinical assessments included a detailed history with questions on previous diseases and physical and neurological examinations using standardized scales such as the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Routine blood tests, brain imaging and neuropsychological testing were available, including assessment of REM sleep Behavior Disorder (RBD) (World Health Organization, 1992), Clinician Assessment of Cognitive Fluctuations (Walker et al., 2000) and Neuropsychiatric Inventory (Cummings et al., 1994). Drug treatments reported in detail in table 1 were withdrawn before EEG recordings, according to their pharmacokinetic properties.

Dopamine transporter SPECT scans were performed in 48 (33%) DLB patients, and in 46 (96%) were rated as abnormal. Cognition was assessed using the Mini-Mental State Examination (MMSE). Local ethics committees at the individual Centers approved the study. The study was performed according to the Declaration of Helsinki and all subjects signed an informed consent.

2.2. EEG recordings

Quantitative EEGs were recorded in the morning with Ag/AgCl disk scalp electrodes from 19 scalp derivations placed according to the international 10–20 system, or with 128 scalp derivations and two additional electrodes placed on A1 and A2. Recordings were acquired continuously with subjects resting comfortably, with their eyes closed. Patients' wakefulness was ascertained every

two minutes inviting them to open their eyes and checking block reactions. A simultaneous electrooculogram was recorded and muscular or tremor artefacts were controlled for with supplementary derivations. Two pairs of bipolar recording channels for respiration and electrocardiogram were also applied.

2.3. Data analysis

EEG was acquired as a continuous signal for 30 min and visually inspected for current clinical interpretation or detection of artefacts and stored in order to be epoched in off-analysis setting as series of 2 seconds-long epochs. Twelve electrodes from anterior (Fp1, Fp2, Fz, F3, F4, F7, F8) and posterior derivations (P3, P4, Pz, O1, O2) were considered for the analysis.

Ninety blocks of artifact-free 2-second-long epochs appearing consecutively were selected off-line by visual inspection. Fast Fourier Transform was applied on each epoch allowing a frequency resolution of 0.5 Hz. The obtained spectra values were then processed in order to compute a mean Power Spectrum for each channel and divided automatically into 4 frequency bands ([3–3.5] Hz (delta), [4–5.5] Hz (theta), [6–7.5] Hz (pre-alpha), [8–12] Hz (alpha)) (Bonanni et al., 2008). EEG traces were quantified by the following mathematical descriptors: DF, i.e., the frequency where the spectral power value was greatest, was evaluated for each epoch; DFV expressing the variability of DF across the 90 analyzed epochs; FP, i.e. percent of epochs where a dominant frequency band was observed (1-100%) (Bonanni et al., 2008). To test the hypothesis that EEG slowing appeared to be more severe in anterior than in posterior derivations, we first compute the DF for all patients, then we divided the DLB groups according to the results on DF (see results and Figure 1).

2.4. Statistical analysis

Statistical comparisons among groups were performed by means of analysis of variance (ANOVA) on continuous demographic and clinical variables that passed normality testing by Kolmogorov-Smirnov test and Levene's test for equality of variances among groups. Bonferroni test was used for

post hoc analysis. Non-parametric statistics were applied for the comparison of dychotomic variables and demographic or clinical variables which did not pass normality testing by Kolmogorov-Smirnov test. Specifically, chi square test was performed to compare DLB and AD groups, Kruskal-Wallis test was applied for the comparison of the three groups.

Wilcoxon signed rank test for paired samples was used in the comparison between EEG variables (DF, DFV, FP delta, FP theta, FP pre-alpha, FP alpha) in anterior and posterior derivation for each group separately. For all statistical comparisons the level of statistical significance was adjusted for multiple comparisons.

Spearman correlation was performed between MMSE and EEG variables for all subjects on each group separately.

3. Results

The final analyses were performed on 137 DLB, 111 AD and 63 controls. Seven DLB patients, 5 AD and 2 controls were excluded due to the presence of ocular/muscular artefacts. Demographic, clinical and pharmacological data and statistical results are reported in Table 1.

3.1. DLB

Mean DF was in the pre-alpha band in both anterior and posterior derivations, but appeared to be lower in anterior derivations than in posterior derivations, thus supporting our hypothesis. In addition, DFV, FP delta and FP theta values were higher in anterior than in posterior derivations; as a consequence, due to the prevalence of delta/theta activity in anterior derivations, FP pre-alpha and FP alpha values were lower in anterior than in posterior derivations. All values and statistical comparisons results were reported in Table 2.

3.2. Anterior-posterior DF patterns (APDF)

Based on differences between DF values in anterior vs. posterior derivations (never higher in anterior) it was possible to distinguish 5 anterior-posterior DF patterns (APDF) in DLB patients.

APDF 1: DF in alpha band in both anterior and posterior derivations.

APDF 2: DF in pre-alpha band in anterior derivations and alpha band in posterior derivations.

APDF 3: DF in pre-alpha band in both anterior and posterior derivations.

APDF 4: DF in theta band in anterior derivations and in pre-alpha in posterior derivations.

APDF 5: DF in theta band in both anterior and posterior derivations.

Figure 1 shows the flow chart of the distribution of DLB patients into the 5 APDF patterns.

The majority of DLB patients belonged to APDF3 having DF in pre-alpha band in both anterior and posterior derivations, confirming the association of the presence of pre-alpha with the diagnosis of DLB.

Kruskal-Wallis test applied for the comparison of the MMSE scores in the five APDF pattern showed significant differences ($p=0.008$). MMSE values were significantly lower for APDF 5 than APDF 1 ($p=0.003$).

3.3. AD and controls

In both AD and controls mean DF was in the alpha band (lower in anterior derivations). In addition, DFV in AD was higher in anterior as compared to posterior derivations. In both AD and controls FP delta, theta and pre-alpha values were higher in anterior than in posterior derivations, whereas FP alpha values were lower in anterior than in posterior derivations. All values and statistical results were reported in Table 2.

Figure 2 reports an example of a normalized power spectrum performed of one EEG epoch of a representative subject from each group. DF in posterior and anterior derivations is shown. The DLB patient presents with a pre-alpha DF in both anterior and posterior derivations. The AD patient and controls present with alpha DF in both anterior and posterior derivations.

3.4. Correlations

For DLB patients significant correlations were found between MMSE score and DF and FP theta in both anterior (DF ρ=0.3, p=0.002; FP theta ρ= -0.2, p=0.02) and in posterior derivations (DF ρ=0.2, p=0.01, FP theta ρ= -0.2, p=0.01). MMSE correlated with FP alpha only in anterior derivations FP (ρ= 0.2, p=0.04). Figure 3 shows correlations. For AD patients significant correlation was found between MMSE and FP alpha in anterior (ρ= 0.2, p=0.03) derivation (ρ= 0.2, p=0.02).

4. Discussion

EEG in DLB is characterized by specific abnormalities, represented by the appearance of a pre-alpha band [6-7.5] Hz which distinguishes it from other neurodegenerative conditions (Bonanni et al., 2008, 2015, 2016; McKeith et al., 2017). Even though the highest statistical yields for differential diagnostic purposes with AD was found in the appearance of a dominant pre-alpha rhythm in posterior derivations (Bonanni et al., 2008, 2015, 2016; McKeith et al., 2017), the present study showed that an intra-subject evaluation on DLB patients reveals that EEG DF was slower in anterior derivations and specifically represented by the appearance of the pre-alpha rhythm.

The appearance of the dominant pre-alpha rhythm in anterior derivations was specific of DLB (APDF2 pattern). Even though a slowing of the DF in the anterior derivations was shared by AD patients and controls, these two groups always presented with an intra-band slowing of the alpha rhythm which was always dominant in both anterior and posterior derivations.

The presence of a distinction between frontal and occipital alpha, as determined by DF defining a ‘‘fast’’ (in posterior derivations) and ‘‘slow’’ (in anterior derivations) alpha has been found to occur in the healthy population (Chiang et al., 2008), and arise naturally in a theoretical model of the generation of the alpha rhythm (Robinson et al., 2003). This cannot be assimilated to the shift of the DF to a pre-alpha band, which has a different electrophysiological significance as compared to the alpha rhythm.

The appearance of a pre-alpha rhythm in the cortex is considered to be linked to a dysfunctional thalamo-cortical connection, the so called thalamocortical dysrhythmia (Llinás et al., 1999; Llinás and Steriade, 2006).

In the original model of thalamocortical dysrhytmia normal resting-state alpha activity [8–12 Hz] slows down to pre-alpha/theta frequencies [4–7.5] Hz in states of deprived thalamic input. The underlying idea is that deprivation leads to a thalamocortical column-specific decrease in information processing, which permits the slowing of resting-state thalamocortical activity from alpha to theta frequencies (Llinás et al., 1999; Llinás and Steriade, 2006).

Thalamocortical dysrhythmia in anterior cortical regions has been implicated in the appearance of altered conscious and sleep states, including clouding of consciousness (fluctuating cognition), sleep disturbances (mind-body dissociation), hallucinations (within-mind dissociation) (Antelmi et al., 2016; Fiset et al., 1999; Foucher et al., 2004; Llinás et al., 1999;Volkow et al., 1995; Ward, 2011), all symptoms which are listed among the clinical core features of DLB (McKeith et al., 2017).

The hypothesis that thalamic dysfunction is implicated in DLB has been demonstrated by several structural, functional and molecular imaging studies (Kenny et al., 2013; Delli Pizzi et al., 2015a; Delli Pizzi et al., 2015b; Delli Pizzi et al., 2014; Pilotto et al., 2019).

With the present study we suggest that the thalamocortical dysrhythmia with consequent appearance of pre-alpha rhythm, involving the anterior cortical regions, could play a role in DLB pathophysiology.

Furthermore, our findings suggest future research studies on possible correlations between the presence of pre-alpha rhythms and the appearance of DLB clinical features, including fluctuating cognition, hallucinations, somatic symptoms, to understand whether these symptoms are preceded or mirrored by the frontal thalamocortical-dysrhythmia.

This hypothesis is also supported by earlier pharmaco-EEG studies, showing that the administration of cholinesterase inhibitors, which considerably reduces cognitive fluctuations in DLB (Perry et al.,

1999), also reduces the pre-alpha/theta activity in DLB (Onofrj et al., 2003), whereas anticholinergic drugs induce both fluctuating cognition and EEG theta rhythms (Niedermeyer and Lopes da Silva, 2005).

It is therefore conceivable that pharmacological interventions on neurotrasmitters (Acetylcholine, Gamma-amino-butyric acid) (Llinás et al., 1999; Llinás and Steriade, 2006) involved in thalamic circuitry may provide a possible treatment of specific DLB clinical features (fluctuating cognition, RBD and hallucinations) (Llinás et al., 1999).

With our study we were also able to clusterize patients in patterns based on a graduation of appearance of slower rhyrthms in anterior derivations as compared to posterior derivations, The pre-alpha rhythm appeared in DLB patients with mild cognitive impairment as a pseudoperiodic inscription on alpha resting state background activity (APDF 1 and 2) in the anterior derivations. In APDF 2, in particular, pre-alpha appeared to be dominant in anterior derivations, while alpha rhythm was still dominant in posterior derivations. Pre-alpha became diffusely dominant on all scalp derivations when dementia was overt (APDF 3).

In patients with moderate dementia (APDF 4 and 5), the pre-alpha rhythm became less clearly distinguishable, as it was concealed by slower (delta – theta) arrhythmic activities, which are deemed to be generated directly in the cortex (idiocortical) (Llinás et al., 1999; Llinás and Steriade, 2006).

In our patient population represented by DLB at mild to moderate cognitive impairment stage (mean MMSE 22±5), we found a high FP in the pre-alpha band in both anterior and posterior derivations (APDF 3, 58%), while a more disrupted EEG patterns, represented by FP in slower frequency bands (theta in both anterior and posterior derivations, APDF 5) was found in only 9% of patients, who had lower MMSE scores than APDF 1.

In line with reports on cognitive impairment in parkinsonism (Caviness et al., 2007; Cozac et al., 2016), EEG abnormalities specific of DLB were correlated with MMSE scores, confirming that greater cognitive impairment was linked to higher EEG pattern disruption. It is noticeable however

that anterior EEG abnormalities were already evident at high MMSE scores. This was particularly evident in APDF 2, where, with a mean MMSE of 22, a pre-alpha band was already prevalent in anterior derivations (while alpha was still prevalent in posterior derivations).

The findings of the five APDF patterns allow to hypothesise that EEG slowing may appear earlier in anterior derivations. We could not demonstrate such a hypothesis with the present cross-sectional study and this is the main limitation of our study.

A longitudinal study, ideally involving DLB patients from the prodromal stage (e.g. MCI- DLB patients), would be needed to thoroughly evaluate this hypothesis.

Disclosure

The authors report no conflict of interest.

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Figure legends

Fig. 1. Flow-chart of the subdivision of the DLB patients in anterior-posterior patterns according to DF values (APDF).

Fig. 2. Normalized power spectrum performed of one EEG epoch of a representative subject from each group.

Fig. 3. Significant correlations between EEG variables and MMSE scores in DLB patients.

Table 1

Table 1 Demographic and clinical variables for all groups. Variables are reported as mean ± S.D. or percentage.

	DLB (n=137)	**AD (n=111)**	**Controls (n=63)**	**P value**
Age	76±6	78±6	74±9	0.1
Gender (male %)	60	33	42	<0.001 a
Education (years)	9±4	8±4	9±4	0.2
Disease duration (months)	25±22	33±23	n.a.	0.02 a
MMSE	22±5	23±4	29 ±2	<0.001 b,c
Fluctuating cognition (%)	43	1	n.a.	<0.001 a
RBD (%)	60	4	n.a.	<0.001 a
L-dopa (%)	53	1	n.a.	<0.001a
Antidepressants (%)	33	47	n.a.	0.1 a
Benzodiazepines (%)	25	9	n.a.	<0.01 a
Cholinesterase inhibitors (%)	58	45	n.a.	0.1 a
Antipsychotics (%)	20	5	n.a.	0.001a

n.a.= not applicable
a= statistical comparison between DLB and AD
b= statistical comparison between DLB and controls
c= statistical comparison between AD and controls
Age and Education were compared among the three groups by means of parametric ANOVAs (critical p value=0.025)
Disease duration was compared by means of parametric ANOVA (critical p value=0.05).
The percentage of male gender and MMSE scores were compared among groups by means of Kruskal-Wallis non parametric ANOVA test for independent samples (critical p value=0.025).
Chi square test was applied on the comparison between DLB and AD group for the percentages (critical p value=0.007)

Table 2

Table 2 EEG variables (mean ± S.D.) and statistical results in the comparison between EEG variables in anterior and posterior derivations for DLB, AD and control group.

	DF	DFV	FP delta	FP theta	FP pre-alpha	FP alpha
DLB						
ANTERIOR	6.7±1.1	2.1±2.0	18.0±10.2	16.1±11.8	48.1±18.6	17.8±17.2
POSTERIOR	7.0±1.3	1.1±1.5	11.0±9.0	13.2±12.4	51.0±22.2	24.8±24.2
P value	<0.001	<0.001	<0.001	<0.001	0.02	<0.001
AD						
ANTERIOR	8.4±1.5	1.4±2.2	24.2±12.2	8.6±7.0	19.7±10.3	47.5±25.7
POSTERIOR	8.8±1.6	0.3±0.7	15.6±6.8	5.0±6.0	16.7±13.5	62.7±28.0
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Controls						
ANTERIOR	9.4±1.3	1.5±1.1	20.9±12.7	11.3±7.6	12.8±9.7	55.0±23.6
POSTERIOR	10.0±1.3	1.3±0.9	9.7±9.2	5.0±5.1	7.9±7.8	77.4±17.7
P value	<0.001	0.2	<0.001	<0.001	<0.001	<0.001

Critical p value was reduced to $p<0.008$.

Figure 1

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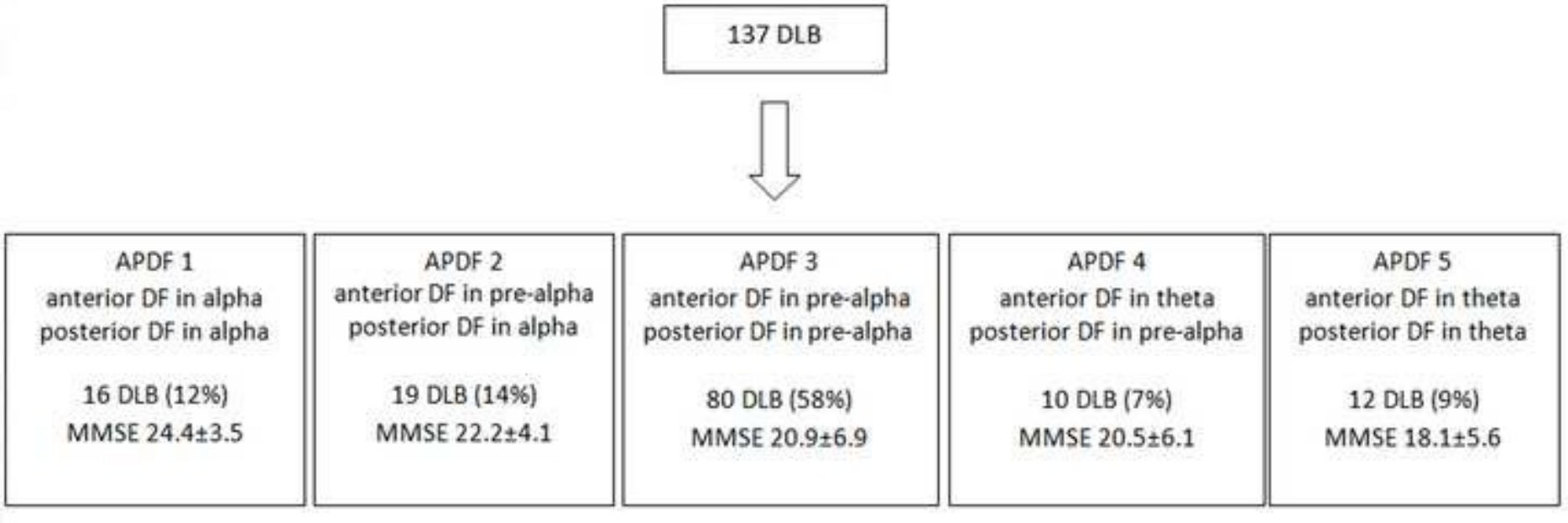

Figure 2

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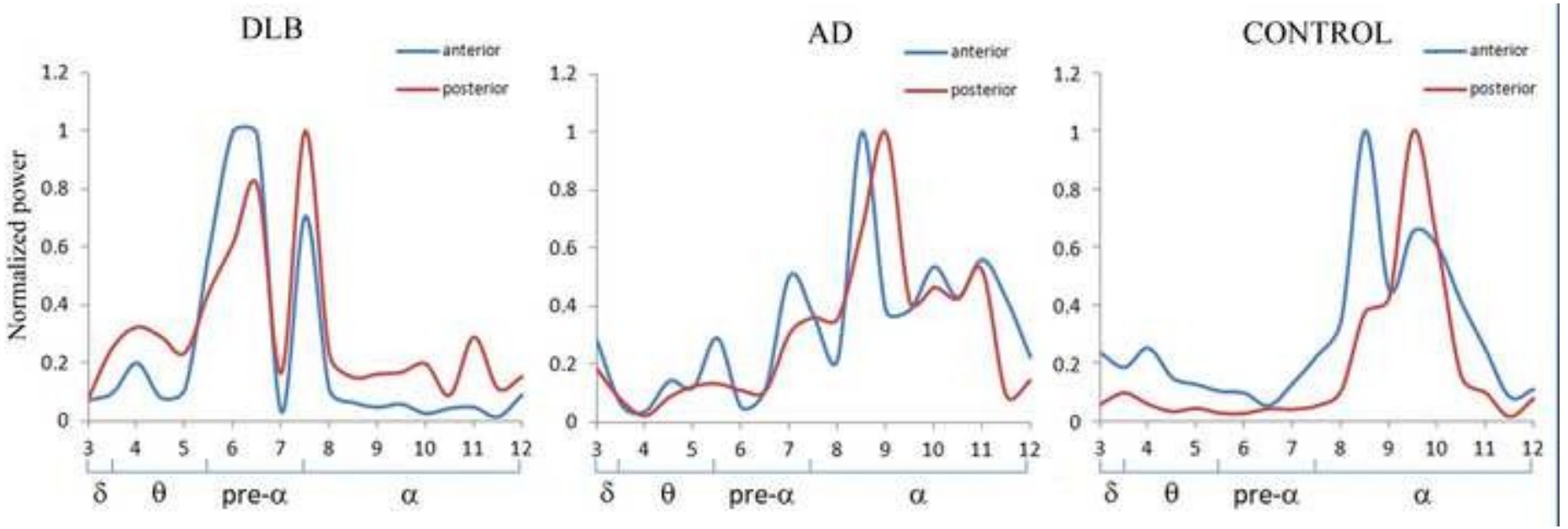

Figure 3

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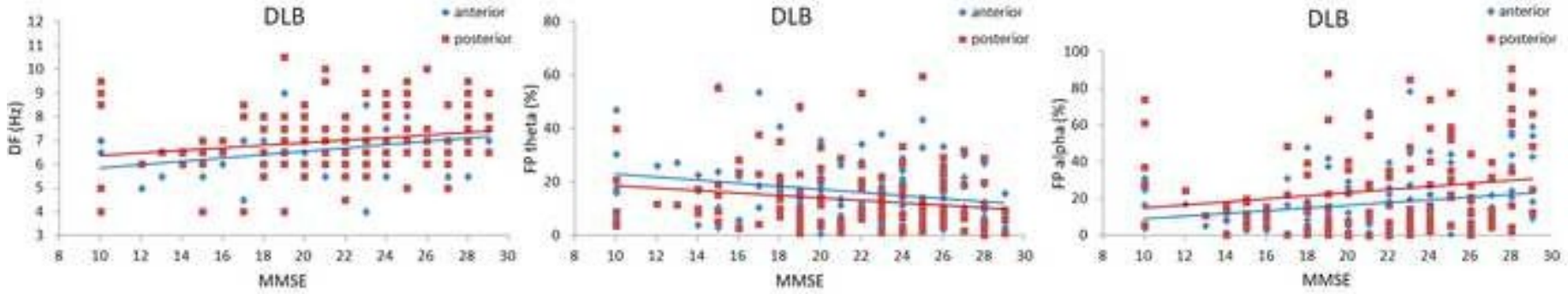

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***Highlights (for review)**

EEG dominant frequency recorded in anterior was slower than in posterior derivations.

In DLB patients EEG abnormalities were more prominent in anterior derivations.

In DLB pre-alpha rhythm is dominant in anterior leads, while alpha prevails behind.

CRediT author statement

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