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EEG variability in dementia with Lewy bodies, Alzheimer's disease and controls.

Short title: EEG in DLB, AD and controls.

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Abstract

Background/Aim: Dementia with Lewy bodies (DLB) is probably still underdiagnosed in the clinical setting. Previous studies have suggested a relationship between fluctuations in attention and EEG measures. Since fluctuation in attention is a core symptom of DLB, we sought to further explore whether EEG measures could help differentiate DLB from Alzheimer's disease (AD) and healthy controls. **Methods:** The EEGs of 20 patients with DLB, 64 patients with AD and 54 elderly controls were assessed in regard to frequencies, coherence, and variability. **Results:** Greater variability was seen in delta power over 2-sec intervals in parietal electrodes of DLB patients. The DLB group had a higher degree of overall coherence in the delta band and a lower degree of overall coherence in the alpha band than the other groups. Finally, EEG measures could distinguish DLB patients from AD patients and controls with areas under the ROC curves ranging between 0.75-0.80 and 0.91-0.97, respectively. **Conclusions:** We suggest that the difference in variability may be associated with the fluctuating cognition seen in DLB. This might have clinical implications as guidance in the diagnosis of DLB. The EEG analysis is simple enough to be possible to apply in clinical practice.

Keywords: EEG, dementia, Lewy body disease, fluctuating cognition.

Introduction

Dementia with Lewy bodies (DLB) is considered to be the second most common neurodegenerative dementia after Alzheimer's disease (AD). In population based studies the prevalence of DLB is up to 21.9% of all dementia cases [1]. At autopsy DLB constitutes about 20% of patients with dementia [2]. The three core clinical diagnostic features are fluctuating cognition (FC), visual hallucinations and parkinsonism. Moreover, a number of suggestive and supportive features, such as REM sleep behaviour disorder, neuroleptic sensitivity and repeated falls, are used to reach a diagnosis in accordance with a consensus statement [3-5]. The specificity of these diagnostic criteria is high but sensitivity needs improvement [6].

How to best identify and characterize fluctuations of attention in DLB is an important but poorly investigated issue. Fluctuating cognition is a symptom most often evaluated solely through medical history or different types of assessment scales, such as "The Clinician Assessment of Fluctuation" and "The One Day Fluctuation Assessment Scale" [7]. The distinguishing features of FC in DLB have been shown to be "daytime drowsiness and lethargy, daytime sleep of 2 or more hours, staring into space for long periods, and episodes of disorganized speech" [8]. These fluctuations impair activities of daily living [9]. Walker *et al* have in two articles investigated the characteristics of FC in DLB and its possible correlation with greater variability in electrocortical rhythms [10,11]. They found that fluctuations occur from second to second in patients with DLB as opposed to patients with AD or vascular dementia. They also showed that mean cortical EEG frequencies fluctuated more in DLB than in patients with other dementias. The variability was expressed as the standard deviation (SD) from the mean spectral frequency over a 90 s period [10]. The

variability in average delta power across 1 hour was also greater in patients with DLB than in patients with AD or elderly controls. This measure of fluctuation in slow electrocortical activity was significantly associated with clinical FC scores[11].

The cholinergic system is important for wakefulness, attention and alertness. Since the cholinergic deficit is greater in DLB [12] than in AD, the greater variability seen may be a consequence of this deficit. In DLB, EEG measures have previously shown slowing in wakefulness [13]. This is displayed as a loss of alpha activity as the dominant rhythm, slow wave transient activity in the temporal lobe areas [14], an increase in theta activity [15], frontal rhythmic intermittent delta activity [16] and an increase in EEG power density in the delta and theta bands [17]. EEG coherence, which can be interpreted as a measure of the functional interaction between cortical regions, shows an increase in the delta and theta bands in the fronto-temporo-central regions in DLB compared to AD [17].

Since it is difficult to distinguish between AD and DLB, especially in the early stages of the diseases, we aimed to further explore the differences in EEG patterns in the two diseases. Fluctuating cognition is an important feature of DLB and has been shown to correlate to variability in EEG. Therefore, our aim was to find a more simple method for analyzing the variability of EEG in order to increase the diagnostic precision of EEG analysis for the distinction between AD and DLB. To achieve this we used shorter time intervals and looked at variability between 2-sec epochs. The specific aims of the study were the following: (1) to resolve whether there are differences in the frequency analysis between DLB, AD and controls; (2) to study whether there are differences in the variability, expressed as the SD from the total power delta, between DLB, AD and controls over as short time intervals as

seconds-to-seconds; (3) to investigate whether there are any differences in overall coherence between DLB, AD and controls.

Methods

Participants

EEGs from 20 patients with DLB and 64 patients with AD were analysed. All the patients attended the Neuropsychiatric Clinic, Malmö University Hospital, Malmö, Sweden between 1999-2003 and were evaluated with a detailed clinical investigation of cognitive function. The complete investigation included medical history, physical and neuropsychiatric examinations, tests of cognitive function (Mini Mental State Examination (MMSE) [18] and Alzheimer's Disease Assessment Scale (ADAS-cog) [19]), blood and cerebrospinal fluid sampling, brain CT, EKG and blood pressure measurements. The diagnosis was given prospectively, using operationalized diagnostic criteria (NINCDS-ADRDA [20] for probable AD and the DLB consensus criteria for probable DLB [4]).

The controls (n=54) were recruited through advertisements. Volunteers went through a physical examination and cognitive testing. Inclusion criteria were absence of memory complaints or any other cognitive symptoms, preservation of general cognitive functioning and no active neurological or psychiatric disease. Individuals with other medical conditions that did not affect cognition were not excluded.

EEG

EEG was recorded for 20 minutes with a Nervus (Viasys Healthcare Inc, Madison WI) equipment from 19 electrodes, according to the 10-20 system and a sampling frequency of 256 Hz, high pass filter 0.16 Hz and low pass filter at 500 Hz. In order to certify that the

analysis was performed on EEG recorded with the patient fully awake, 10 sec epochs of artefact free EEG were selected in the eyes-closed situation within 20 sec after interaction with the patient either by verbal communication, or following eye closure on command. Quantification of the EEG data reconstructed in CA mode, 2 sec epochs (Hamming filter), was performed by using commercially available software (Nervus Reader 3.4, Viasys Healthcare Inc Madison, WI). By FFT analysis, peak frequency of posterior dominant activity, log absolute power and relative power of delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-32 Hz) were calculated for each quadrant of the skull: left anterior (F3,F7,T3, C3), right anterior (F4, F8, T4,C4), left posterior (P3,T5,O1), right posterior (P4,T6,O2). In this study only average values for all four quadrants were presented. The coherence values for each frequency band for each electrode combination among the 19 electrodes were calculated over 10 sec epochs (extended coherence function of Nervus reader). The average coherence among all electrode combinations for each frequency band was presented as extended coherence. For analysis of EEG variability FFT data (delta total power) from electrodes P3 (parietal left) and P4 (parietal right) (common average montage) over 2 sec epochs were exported from the trend monitor function. These electrodes were chosen because they reflect the posterior activity. The variability was expressed as the SD of the mean total power delta over the 2 sec epochs.

The study was approved by the ethical committee, Lund University. All patients gave informed consent to participate.

Statistics

Statistical analysis was performed with use of The Statistical Package for Social Sciences (SPSS) software version 14.0.1. T-tests were used to detect significant group differences. For

non-normally distributed variables non-parametric statistics (Kruskal-Wallis and Mann-Whitney U test) were used. Binary variables were compared using Chi-Square Tests. Sensitivity and specificity were calculated using receiver operating characteristic (ROC) curves. A linear regression analysis was performed to investigate if diagnosis, age, gender, MMSE score or medication were independent cofactors of the frequency distribution.

Results

Patient characteristics

In this study, EEGs from 20 clinically diagnosed DLB patients, 64 clinically diagnosed AD patients and 54 controls were analysed. There were no significant differences in age, sex or mean MMSE score between the DLB and the AD patients. The controls had a significantly higher MMSE score than the demented patients. (Table 1) The use of antidepressants was more prevalent among AD and DLB patients compared to the controls. The use of benzodiazepines and neuroleptics also differed between the groups (Table 2). The inappropriate use of neuroleptics among the DLB patients reflects the fact that the EEGs were performed prior to diagnosis. Primary care doctors had in most cases prescribed these medications.

EEG analysis

The frequency analysis showed that peak frequencies became progressively lower from the controls to AD and DLB (Table 3). The spectral analysis showed that delta and theta activity progressively increased from the controls, through AD and to DLB (Table 3). When using relative values there was also a decrease in alpha and beta activity in DLB as compared to AD and controls. (Table 3)

Since neuroleptics have earlier been shown to increase delta and theta activity and decrease alpha and beta activity [21] we performed a linear regression analysis for each of the frequency bands including diagnosis, age, gender, antidepressants, neuroleptics and benzodiazepines as cofactors. For log delta the significant independent cofactors were diagnosis (B 0.315, $p < 0.001$) and MMSE score (B -0.041, $p = 0.007$). For log theta the independent cofactors were diagnosis (B 0.380, $p < 0.001$) and age (B 0.022, $p = 0.044$). For log alpha the only significant independent cofactor was diagnosis (B 0.175, $p = 0.03$) while the only independent cofactor was gender for log beta (B (-0.315, $p = 0.013$).

To assess the EEG variability the SD of the mean total power delta was calculated. The variability differed significantly between the studied groups and increased progressively from the controls, through AD to DLB. (Figure 1) The number of two-sec epochs did not differ significantly between the groups. ($p = 0.259$)

In the coherence analysis, differences between the groups were found in the alpha and delta bands. The DLB group had a higher degree of coherence in the delta band and a lower degree of coherence in the alpha band compared to the other groups. (Figure 2)

Diagnostic utility of EEG

Further, we analysed the utility of EEG for diagnosing DLB. We found that four different EEG parameters could be used to discriminate DLB patients from AD patients and controls with areas under the ROC curves (AUC) ranging between 0.75-0.80 (Figure 3A, The AUC was 0.77 for the SD of the mean total power delta (P4); 0.80 for the SD of the mean total power delta (P3); 0.75 for log Theta; and 0.79 for log Delta.) and 0.91-0.97 (Figure 3B, The AUC was 0.91 for the SD of the mean total power delta (P4); 0.94 for the SD of the mean

total power delta (P3); 0.93 for log Theta; and 0.97 for log Delta.), respectively. The SD of the mean total power delta (P3) resulted in a sensitivity of 75 % and a specificity of 75 % for detection of DLB subjects among the demented patients, using the optimal cut-off value 2.3 as identified by Youden's index [22]. Moreover, the SD of the mean total power delta (P3) could differentiate DLB patients from controls with a sensitivity of 85% and a specificity of 93%, when an optimal cut-off value of 1.8 was used (Figure 3B). Since ROC-analysis should preferably be used on groups equal in size, the analysis was also performed with 20 AD patients matched to the DLB patients by age, gender and MMSE score. The four different EEG parameters could then discriminate between the AD and DLB patients with areas under the ROC curves ranging between 0.81-0.87. (AUC 0.81 for the SD of the mean total power delta (P4); 0.87 for the SD of the mean total power delta (P3); 0.81 for log Theta; and 0.86 for log Delta.) The SD of the mean total power delta (P3) resulted in a sensitivity of 75 % and a specificity of 80 % for detection of DLB subjects among the demented patients, using the optimal cut-off value 2.1 as identified by Youden's index.

Discussion

In this study we found that patients with DLB had an increase in delta and theta activity and a decrease in alpha and beta activity compared to patients with AD and controls. Greater variability was seen in delta power over 2-sec intervals in parietal electrodes. The DLB group had a higher degree of coherence in the delta band and a lower degree of coherence in the alpha band than the other groups. Furthermore, EEG measures could discriminate DLB patients from AD patients and controls with areas under the ROC curves ranging between 0.75-0.80 and 0.91-0.97, respectively.

The patient material was well investigated and diagnosed according to standard criteria. One potential limitation of the current study is that no clinical scale to evaluate FC was used in the investigation. However, as a part of the prospective diagnosis according to DLB consensus criteria [4], FC was present in 16 of the 20 DLB patients. The groups were homogenous concerning demographic factors. The use of antidepressants, benzodiazepines and neuroleptics differed between the groups, with neuroleptics being more prevalent in the DLB group and benzodiazepines in the AD group. To investigate the effect of this medication on the EEG we performed a linear regression analysis. It did not detect medication as independent cofactors for either log delta, log theta, log alpha or log beta. Thus, it seems unlikely that the observed differences could be explained solely by the differences in medication. One AD patient was treated with a cholinesterase inhibitor (ChEI) at the time of EEG recording. All other patients started ChEI medication after the EEG recording. This might otherwise have influenced the EEG [17]. The EEGs were performed at the patients' first visit at the clinic, prior to diagnosis. Their primary care doctors had already prescribed the neuroleptic medication. It is not surprising that many DLB patients were on neuroleptic medication as visual hallucinations are a core feature of the disease. The fact that the EEGs were performed prior to diagnosis also explains why only one patient was receiving an acetylcholinesterase inhibitor at the time of the recording.

The frequency analysis of the present investigation confirmed findings from earlier studies, specifically loss in alpha activity combined with an increase in delta and theta activity in DLB [14-17]. In our analysis of variability we sought to both confirm previous findings from Walker *et al* as well as to investigate if DLB had greater variability over intervals as short as 2-sec epochs. It has been postulated that the fluctuations in DLB occur on a sec-to-sec basis [10] and in this study we found that variability in delta power was increased in the DLB group

even during these short epochs. Coherence analysis has been used to estimate the functional connectivity among cortical areas. The coherence can be averaged over all electrode pairs for each frequency band as a global measure of connectivity [23]. Our findings are in concordance with findings in earlier studies that have found an increased coherence in the delta band in DLB compared to AD, although not as a global measure [17]. A study comparing coherence in AD and DLB over short and long distances, as well as between hemispheres found no significant differences, however. [24]. It has been suggested that alpha coherence is related to alterations in cortico-cortical connections, whereas the delta coherence increase could be related to lack of influence of subcortical cholinergic structures on cortical electrical activity [25]. It has earlier been proposed that since the increase in delta and theta activity is greater in DLB than in AD then the functional disorder of the ascending cholinergic system may be stronger in DLB than in AD patients [17].

It is difficult to objectively assess FC. In current clinical practice there are several assessment scales in use but there is no other way of visualizing the fluctuations. We suggest that the difference in variability in delta power between DLB and AD may be associated with the FC seen in DLB. Our findings, using commercially available software for quantitative EEG analysis may have clinical implications as guidance in the diagnosis of DLB. The EEG analysis is simple enough to be possible to apply in clinical practice. We would recommend that a frequency analysis is performed to find slowing of the EEG and that an analysis of delta variability is used to aid in the differentiation between DLB and AD.

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Disclosure statement

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Figure legends

Figure legend of Figure 1:

Median, interquartile range (IQR), acceptable range (1.5 times IQR), outliers (1.5-3 times IQR) and extreme outliers (>3 times IQR).

P3: $p < 0.001$ DLB vs AD and DLB vs controls, $p = 0.001$ AD vs controls.

P4: $p < 0.001$ DLB vs AD, DLB vs controls and AD vs controls.

Figure legend of Figure 2:

Median, interquartile range (IQR), acceptable range (1.5 times IQR), outliers (1.5-3 times IQR) and extreme outliers (>3 times IQR).

Delta: $p = 0.004$ DLB vs AD, $p = 0.007$ DLB vs controls.

Alpha: $p = 0.011$ DLB vs AD, $p = 0.016$ DLB vs controls.

Figure legend of Figure 3:

Panel A depicts the receiver operating characteristic (ROC) curves of four different EEG parameters for differentiation of DLB patients from AD patients. Panel B shows the ROC curves of the EEG parameters for discrimination of DLB patients from controls.

Tables

Table 1, demographics

	DLB	AD	Controls	DLB vs	DLB vs	AD vs
	(n=20)	(n=64)	(n=54)	AD, <i>p</i>	controls, <i>p</i>	controls, <i>p</i>
Median age	77	75	72	0.305	0.090	0.072
(range)	(54-85)	(52-85)	(60-94)			
Women, n (%)	10 (50)	43 (67)	34 (63)	0.261	0.458	0.775
Mean MMSE	22±4	23±5	29±1	0.564	<0.001	<0.001
score ± SD						

Table 2, medication

	DLB (n=20)	AD (n=64)	Controls (n=54)	DLB vs AD, <i>p</i>	DLB vs controls, <i>p</i>	AD vs controls, <i>p</i>
Antidepressants, n (%)	10 (50)	25 (39)	3 (6)	0.544	<0.001	<0.001
Benzodiazepines, n(%)	0 (0)	12 (19)	1 (2)	0.084	1.000	0.009
Neuroleptics, n (%)	10 (50)	9 (14)	0 (0)	0.002	<0.001	0.012

Table 3, frequency analysis

	DLB	AD	Controls	DLB vs	DLB vs	AD vs
	(n=20)	(n=64)	(n=54)	AD, <i>p</i>	controls, <i>p</i>	controls, <i>p</i>
Peak frequency (mean±SD)	7.30±1.26	8.44±1.32	9.87±1.47	0.001*	<0.001***	<0.001***
log Delta	2.19±0.84	1.29±0.82	0.53±0.49	<0.001**	<0.001***	<0.001***
log Theta	2.30±0.61	1.53±0.97	0.48±0.93	<0.001**	<0.001***	<0.001***
log Alpha	1.65±0.80	1.70±0.83	1.20±1.00	0.820	0.073	0.004
log Beta	0.90±0.80	0.95±0.68	0.71±0.66	0.797	0.294	0.055
rel Delta	33.75±15.85	22.89±9.95	20.37±10.84	0.005	0.001*	0.088
rel Theta	34.67±11.05	28.07±12.24	19.05±10.87	0.029	<0.001***	<0.001***
rel Alpha	21.38±14.48	32.54±12.94	36.43±13.10	0.001*	<0.001**	0.087
rel Beta	10.20±5.83	16.50±8.55	24.13±9.57	0.001*	<0.001***	<0.001***

*, **, ***: Significance level when corrected for multiple analyses.

Figure 1 Variability

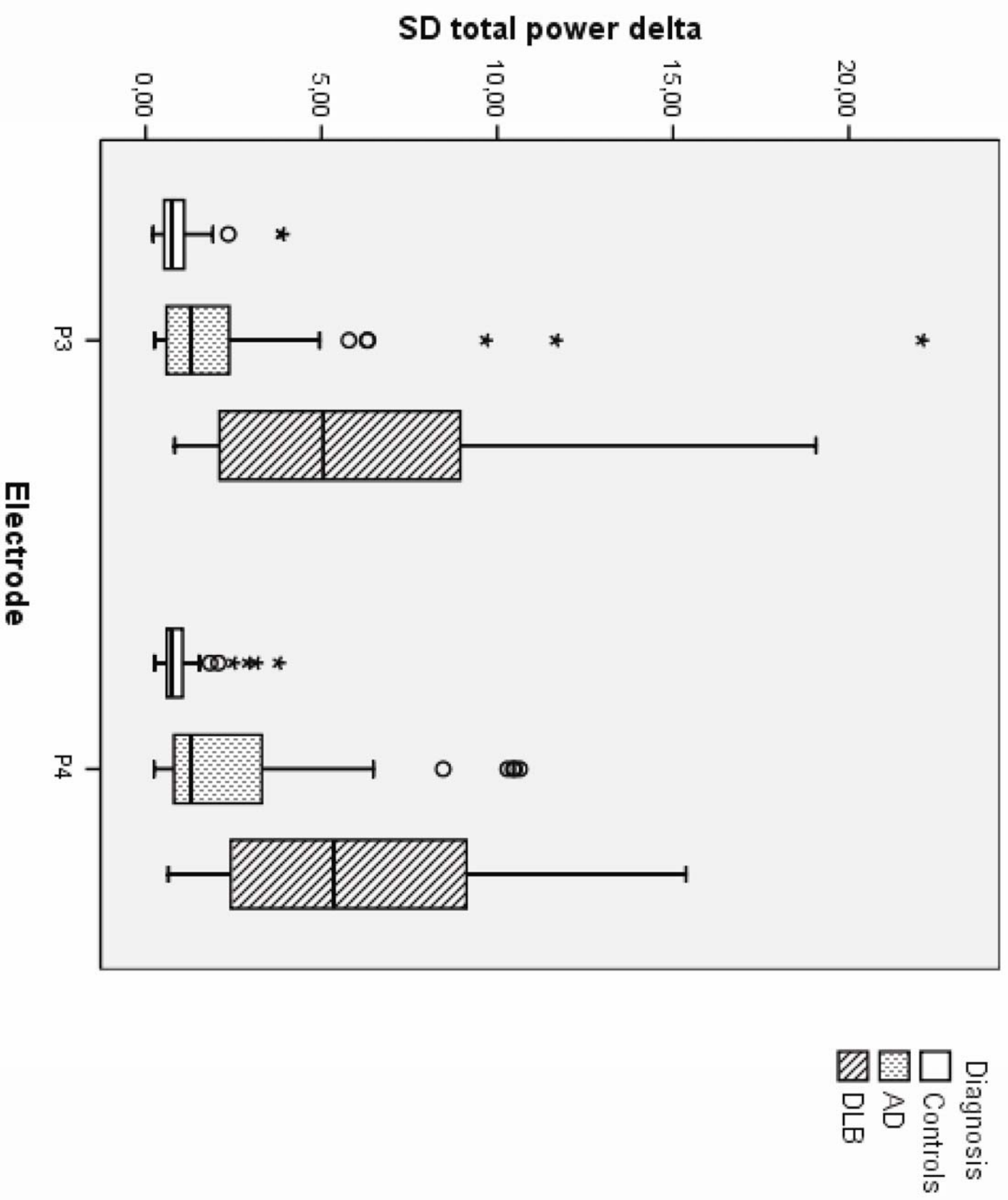
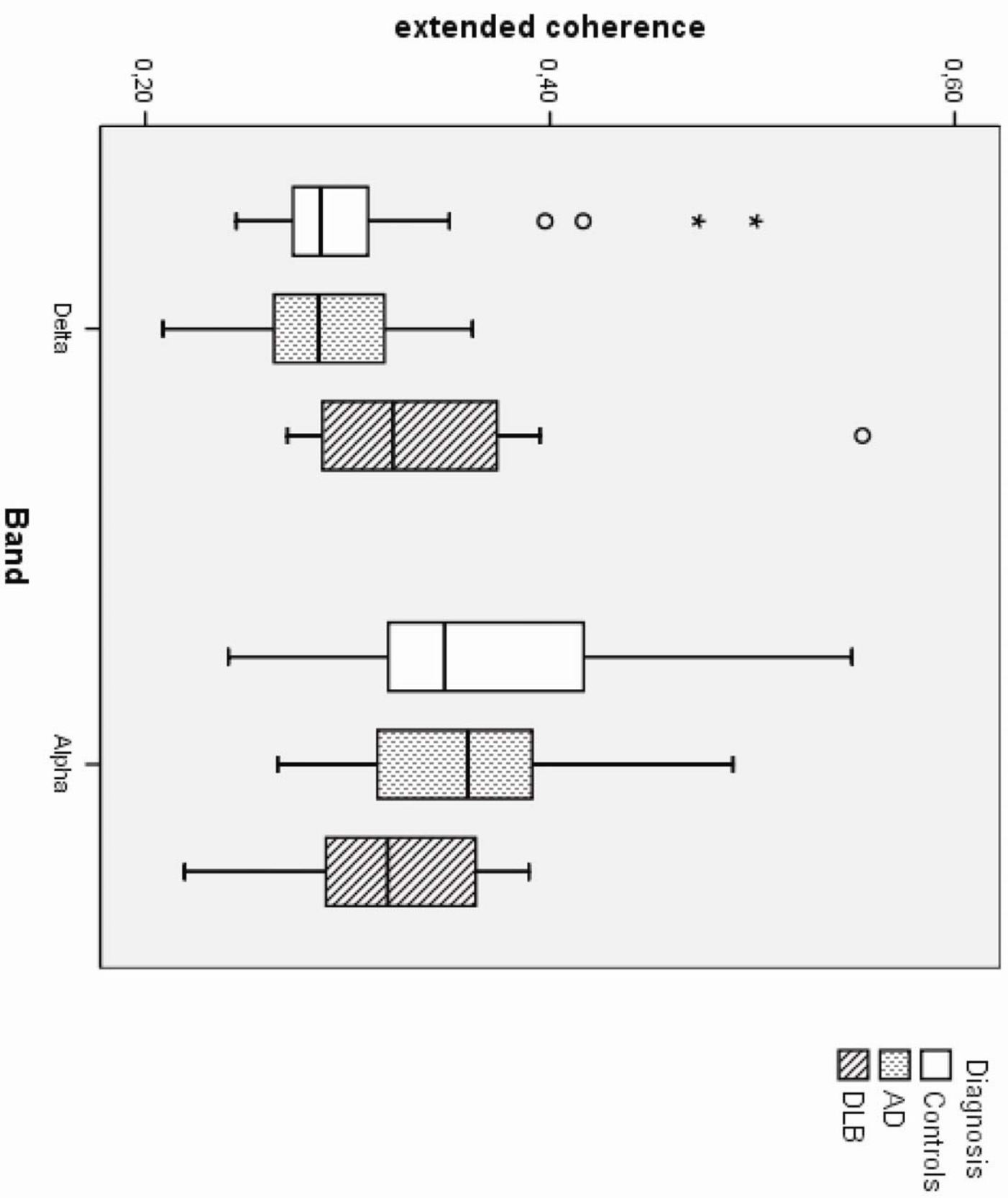
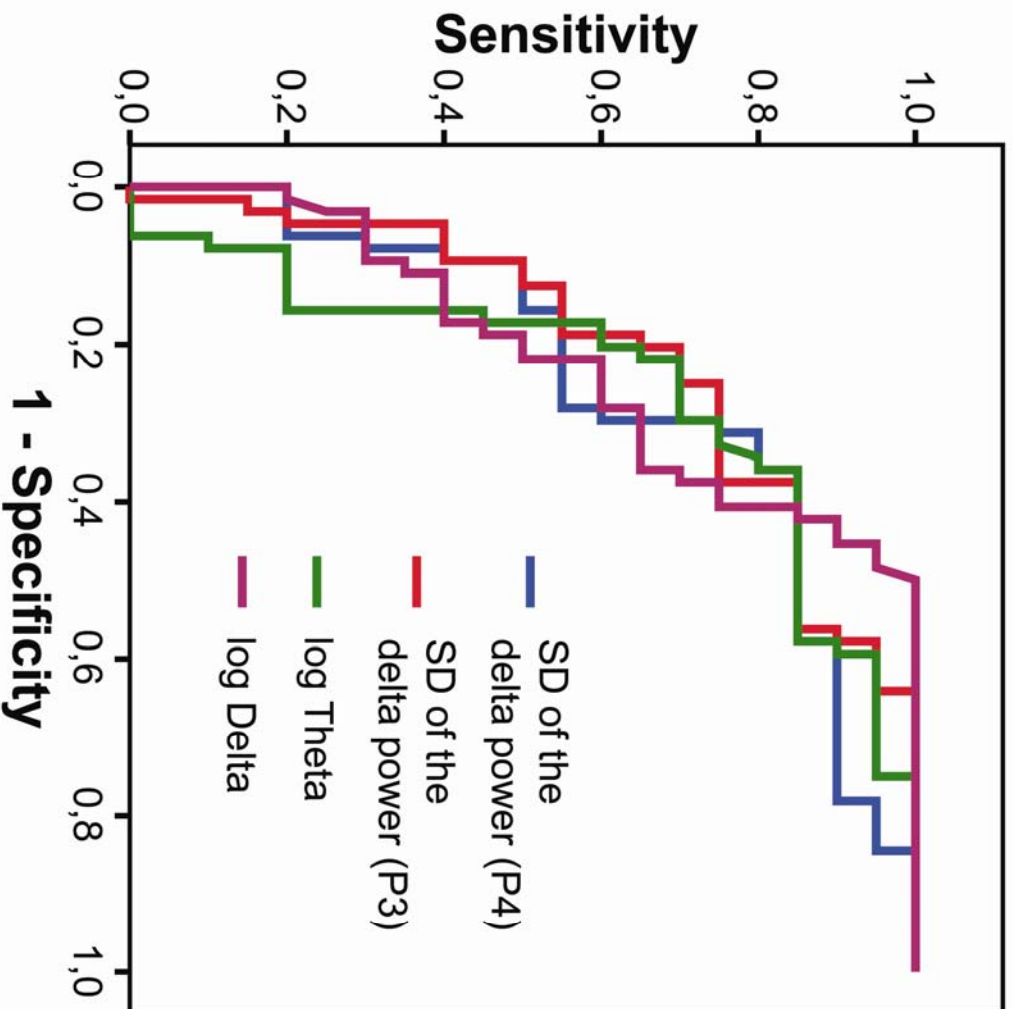


Figure 2 Extended coherence



A DLB vs AD



B DLB vs Controls

