

EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up

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EEG abnormalities have been reported for both dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). Although it has been suggested that variations in mean EEG frequency are greater in the former, the existence of meaningful differences remains controversial. No evidence is as yet available for Parkinson's disease with dementia (PDD). The aim of this study was to evaluate whether EEG abnormalities can discriminate between DLB, AD and PDD in the earliest stages of dementia and to do this 50 DLB, 50 AD and 40 PDD patients with slight cognitive impairment at first visit (MMSE \geq 20) were studied. To improve clinical diagnostic accuracy, special emphasis was placed on identifying cognitive fluctuations and REM-sleep behaviour disorder. EEG variability was assessed by mean frequency analysis and compressed spectral arrays (CSA) in order to detect changes over time from different scalp derivations. Patients' initial diagnoses were revised at a 2-year follow-up visit with neuroimaging evaluation. Initial diagnoses were confirmed in 36 DLB, 40 AD and 35 PDD patients. The most relevant group differences were observed between the AD and DLB patients in EEGs from posterior derivations ($P < 0.001$). Dominant frequencies were 8.3 ± 0.6 Hz for the AD group and 7.4 ± 1.6 Hz for the DLB group, in which most of the patients (88%) exhibited a frequency band of 5.6–7.9 Hz. Dominant frequency variability also differed between the AD (1.1 ± 0.4 Hz) and DLB groups (1.8 ± 1.2 Hz, $P < 0.001$). Of note, less than a half (46%) of the patients with PDD exhibited the EEG abnormalities seen in those with DLB. Graded according to the presence of alpha activity, five different patterns were identified on EEG CSA from posterior derivations. A pattern with dominant alpha bands was observed in patients with AD alone while, in those with DLB and PDD, the degree to which residual alpha and 5.6–7.9 bands appeared was related to the presence and severity of cognitive fluctuations. At follow-up, EEG abnormalities from posterior leads were seen in all subjects with DLB and in three-quarters of those with PDD. Of interest, in four patients initially labelled as having AD, in whom the occurrence of fluctuations and/or REM-sleep behaviour disorder during the 2-year follow-up had made the diagnosis of AD questionable, the initial EEG was characterized by the features observed in the DLB group. If revised consensus criteria for DLB diagnosis are properly applied (i.e. emphasizing the diagnostic weight of fluctuations and REM sleep behaviour disorder), EEG recording may act to support discrimination between AD and DLB at the earliest stages of dementia, since characteristic abnormalities may even precede the appearance of distinctive clinical features.

Keywords: Dementia with Lewy Bodies; Alzheimer's disease; Parkinson's disease with dementia; quantitative electroencephalography; compressed spectral array

Abbreviations: AD = Alzheimer's disease; CAF = clinician assessment of fluctuation; CSA = compressed spectral arrays; DF = dominant frequency; DLB = Dementia with Lewy bodies; FP = frequency prevalence; MFV = mean frequency variability; PDD = Parkinson's disease with dementia; RBD = REM Sleep Behaviour Disorder

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Introduction

Dementia with Lewy bodies (DLB) has been reported to be the second most common neurological cause of dementia after Alzheimer's disease (AD). Clinically, fluctuations in attention, visual hallucinations and extrapyramidal signs (including bradykinesia and rigidity, but not resting tremor) have been indicated as cardinal features of DLB (McKeith *et al.*, 1996). However, while neuropathologic series have demonstrated high accuracy for the clinical diagnosis of AD (Kosunen *et al.*, 1996), the accuracy of the clinical diagnosis of DLB has been less satisfactory (Litvan *et al.*, 1998; Lopez *et al.*, 1999; Hohl *et al.*, 2000) because, some of the 'core' clinical features of DLB may not invariably appear even during the entire course of disease (Merdes *et al.*, 2003) or may overlap to some extent with AD (Walker *et al.*, 2007). As a result, DLB tends to be underdiagnosed during life and mostly misdiagnosed as AD. It is important, however, to differentiate between these diseases in the earliest stages of dementia because, compared with patients with AD, those with DLB may be considerably more sensitive to adverse effects of neuroleptics (Ballard *et al.*, 1998) and may exhibit faster disease progression (Olichney *et al.*, 1998) and different responses to acetylcholinesterase inhibitors (Levy *et al.*, 1994). In light of the limitations on the level of accuracy that can be achieved by making a diagnosis of DLB only on the grounds of clinical history and examination, great emphasis has recently been placed on methods evaluating the uptake of either dopamine transporter (DAT) in basal ganglia (Walker *et al.*, 2002; O'Brien *et al.*, 2004) or metaiodobenzylguanidine (MIBG) in the myocardium (Yoshita *et al.*, 2006). These methods, respectively exploring the integrity of the nigrostriatal dopaminergic system and of postganglionic sympathetic cardiac innervation, have been suggested to improve clinical diagnostic accuracy of DLB, but there is a clear need of other markers to assist with accurate identification of this entity during life.

Unlike the distinction between DLB and AD, that between dementia superimposed on Parkinson's disease (Parkinson's disease with dementia, PDD) and AD poses considerably less challenge to the clinician's diagnostic ability since, in patients with PDD, parkinsonism is by definition invariably present and precedes the onset of dementia whereas, in those with AD, extrapyramidal signs are variable and, if present, usually follow the onset of cognitive deterioration. Such an order of presentation of cognitive and motor features is also typical of DLB. However, since this diagnosis applies equally well to cases with extrapyramidal signs preceding dementia, the clinical distinction between PDD and DLB may be blurred.

Several electroencephalographic studies on dementia (Coben *et al.*, 1983; Giaquinto and Nolfé, 1986; Breslau *et al.*, 1989) were performed in the years preceding the identification of DLB as a widespread dementing disorder (Coben *et al.*, 1983; Rae-Grant *et al.*, 1987; Breslau *et al.*, 1989). Correlations between electroencephalographic

spectral measures and severity of cognitive impairment were reported by some authors (Rae-Grant *et al.*, 1987; Leuchter *et al.*, 1993), but not by others (Hughes *et al.*, 1989; Prinz and Vitiello, 1989), as summarized in a recent review (Jeong, 2004). In the latest revision of clinical diagnostic criteria for DLB (Mc Keith *et al.*, 2005), prominent slow wave activity on EEG with temporal lobe transient sharp waves was regarded as a supportive feature for its diagnosis (Mc Keith *et al.*, 2005). However, this statement is largely based on anecdotal reports (Bonanni *et al.*, 2006), since only two studies (Walker *et al.*, 2000a; Kai *et al.*, 2005) showed statistical differences between quantitative EEG (QEEG) recordings of DLB and AD patients, while in three studies (Briel *et al.*, 1999; Barber *et al.*, 2000; Londos, 2003) no significant group differences were found. It is not unlikely, however, that different EEG quantification methods or clinical assessments insufficiently focused on more recent DLB diagnostic core or supportive criteria may have contributed to failures.

Since their first formulation, consortium clinical diagnostic criteria for DLB (McKeith *et al.*, 1996; Mc Keith *et al.*, 2005) have been based on a set of core and supportive features. Among those now regarded as highly suggestive of DLB is REM Sleep Behaviour Disorder (RBD), whose specificity to synucleinopathies has been highlighted in several papers (Boeve *et al.*, 2001; Braak *et al.*, 2003). Conversely, cognitive fluctuations (described as disorders of consciousness, ranging from reduced arousal to stupor) have long been considered central to DLB identification (McKeith *et al.*, 1996), but structured methods for their detection have been proposed only recently (Walker *et al.*, 2000b). The clinician assessment of fluctuation (CAF), for example, evaluates fluctuating confusion over a month prior to the clinician's interview with an informant (Walker *et al.*, 2000b). Although fluctuations are also described in patients with vascular dementia and AD, this scale has been reported to have good sensitivity and specificity to DLB (Ballard *et al.*, 2001; Walker *et al.*, 2000b), revealing not only quantitative (frequency and severity), but also qualitative differences between this and other dementing disorders (Bradshaw *et al.*, 2004; Serrano and Garcia-Borroguero, 2004). An early seminal study (Walker *et al.*, 2000a) examined characteristics of fluctuations as related to mean QEEG frequency variability across 90 s in DLB, AD and normal control subjects. The greatest variation in mean EEG frequency was noted in the DLB group, where a close relationship was found between EEG variability and CAF scores. An important implication of these findings is that clinicians might reliably capture weekly or monthly changes in attention and vigilance by simply analysing EEG recordings of just a few seconds. In fact, a DLB patient with the maximal CAF score, indicating particularly severe fluctuations over the month before the interview, was shown to have a particularly unstable, second-to-second fluctuating rhythm of activation during the whole 90 s period. Whether DLB patients with less severe fluctuating cognition can

display such a distinctive EEG pattern has not been equally clear, however.

Even though PDD is now often considered to overlap with DLB, but for the onset of motor disturbances (Braak *et al.*, 2003; Mc Keith *et al.*, 2005), the presence of fluctuating cognition has previously been described in one study alone, in which fluctuating attention was assessed using reaction time measurements (Ballard *et al.*, 2002).

The aim of the present study was to investigate whether EEG abnormalities in patients with clinically diagnosed AD, DLB, or PDD had distinctive characteristics from the earliest stages of deterioration (primary endpoint). To explore this, analyses were based on EEG recordings at first referral to our tertiary clinic, provided that the interval between the first visit and estimated onset of dementia did not exceed 1 year and global cognitive impairment was relatively mild (Mini-Mental-State- Examination ≥ 20). CAF scales and RBD assessments were used among other supportive elements for diagnosis. EEGs were analysed with the same methods used in previous controversial literature. (Briel *et al.*, 1999; Barber *et al.*, 2000; Londos, 2003; Kai *et al.*, 2005) and with methods focused on EEG variability assessment over time, such as mean frequency, mean frequency variability (MFV) as used by Walker MP (Walker *et al.*, 2000b) and compressed spectral arrays (CSA), by which even changes in single EEG derivations can be detected (Karnaze *et al.*, 1982; Yli-Hankala *et al.*, 1989; Wang and Wieser, 1994).

The second endpoint of this study was to evaluate whether EEG differences are merely statistical or might express cut-off levels dependent on methods of evaluation. The third endpoint was to understand whether PDD patients present with EEGs similar to those recorded in DLB or early AD patients and therefore to investigate whether DLB and PDD are overlapping entities.

Differentiating patients with DLB from those with AD can be extremely challenging, especially in early-stage dementia because, in this phase, the full spectrum of clinical features supporting a diagnosis of DLB may yet be expressed incompletely. For this reason, after enrolment in the study, each patient was prospectively followed up for at least 2 years, during which the appropriateness of initial diagnostic categorization was carefully re-evaluated.

Methods

Patients

The study sample was recruited from two case register cohorts: one consisting of 1400 consecutive referrals to our Memory Clinic, the other one consisting of 1016 consecutive referrals to our Movement Disorder Centre. A total of 140 people were enrolled in the study, representing a small minority of all those who came to both Services between 2001 and 2004. To be included in the current analysis, patients had to be at initial presentation, had not to be taking antidepressants, anticonvulsants, benzodiazepines, typical or atypical antipsychotics, or anticholinergic drugs, and their first clinical examination had to have occurred during the

earliest stages of dementia (as required by an initial Mini Mental State Examination (MMSE) score of at least 20 and an interval between estimated dementia onset and first visit no longer than 12 months).

The diagnosis of a chronic dementing disorder was based on progressive cognitive and functional deterioration in the preceding 12 months, in the absence of reversible causes of dementia and in the presence of a history of normal intellectual function prior to the onset of cognitive decline (American Psychiatric Association, 1994). The diagnosis of probable AD was based on National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann *et al.*, 1984). Specifically, patients were diagnosed as having AD in the presence of all cardinal features (Part I) and at least two supportive features (Part II and III). The diagnosis of DLB was based on more restrictive criteria than those recently recommended by the Consortium on DLB (McKeith *et al.*, 1996; Mc Keith *et al.*, 2005). In fact, a diagnosis of probable DLB was given to patients with at least two of the three core features (fluctuations, visual hallucinations and parkinsonism), but not to those with only one core and one suggestive feature. A diagnosis of PDD was given to patients with a history of dementia preceded by PD for at least 24 months. In this group, idiopathic PD was diagnosed 4.7 ± 3.2 years prior to the inclusion in the study, while criteria for dementia were fulfilled 3.6 ± 0.3 years after PD diagnosis. All PDD patients were on L-dopa (mean daily dosage 650.2 ± 50.7 mg), 30 PDD patients received also dopaminomimetics. They were neurophysiologically and neuropsychologically evaluated in 'ON' state and in the absence of dyskinesias.

There were 50 patients clinically diagnosed as having DLB who met all of the requirements for inclusion. Fifty patients with AD were matched one-to-one with the DLB patients according to initial MMSE score and level of education, while less than one match was available for those with PDD (Fig. 1). Finally, 50 subjects with age, gender, education and (past or current) occupational level comparable with those of DLB patients were recruited from our non-demented case register cohort and included in the study as a control group.

During follow-up, 17 patients (14 with DLB and 3 with PDD) dropped out of the study and clinical diagnoses changed in 12 cases (10 with an initial diagnosis of AD and 2 initially labelled as having PDD). As a result, 40 clinically confirmed AD, 36 DLB and 35 PDD patients entered final analyses (Fig. 1).

Procedures

Clinical assessment

Before being enrolled in the study, which was approved by our local ethical committee and was carried out according to the declaration of Helsinki and subsequent revisions (Declaration of Helsinki, 1997), all subjects (or their caregivers) signed a written informed consent. Global tests of cognition included Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) (Rosen *et al.*, 1984) and dementia rating scale-2 (DRS-2) (Jurica *et al.*, 2001). Presence and severity of extrapyramidal signs were rated using the unified Parkinson's disease rating scale (UPDRS) (Fahn and Elton, 1987) and the Hoehn/Yahr scale (H/Y) (Hoehn and Yahr, 1967). The presence of hallucinations or other psychotic symptoms was assessed by the neuropsychiatric inventory (Cummings *et al.*, 1994). The presence of frontal dysfunction

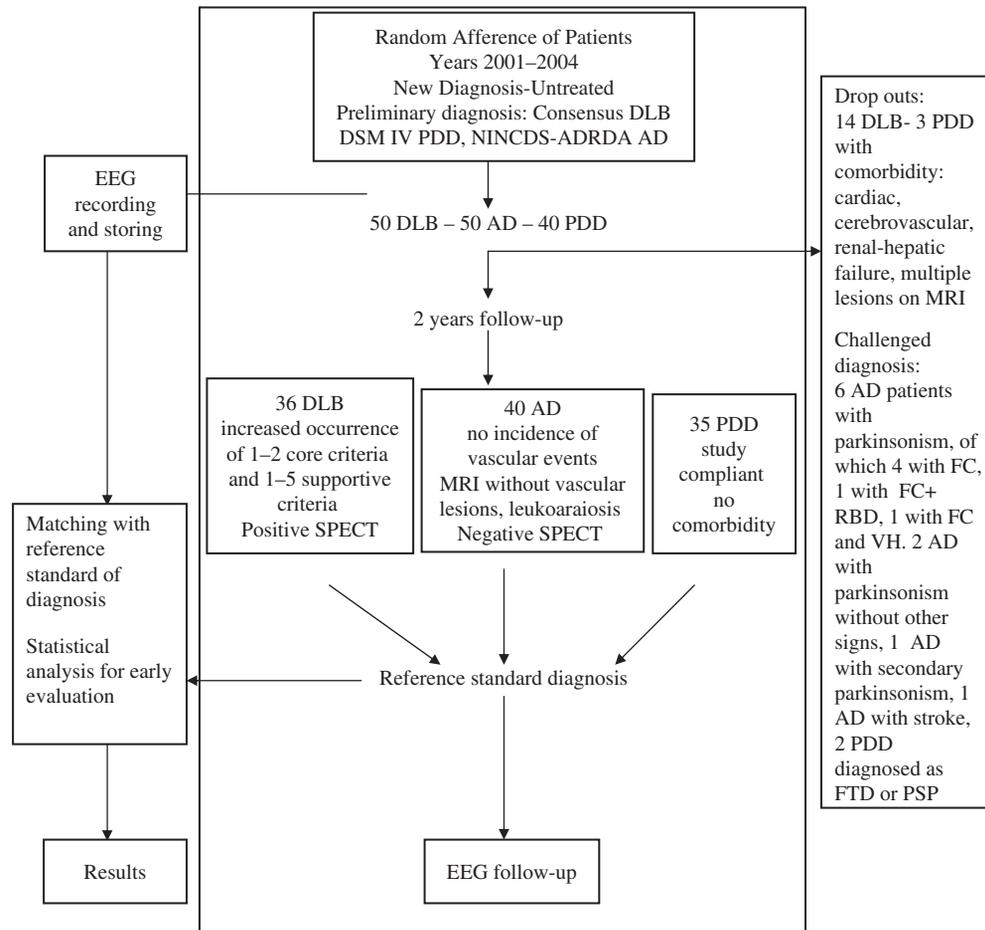


Fig. 1 Study design flow chart. DLB: Dementia with Lewy Bodies; AD: Alzheimer's Disease; PDD: PDD-F: Parkinson's Disease with Dementia with cognitive fluctuations; PDD-NF: Parkinson's Disease with Dementia without cognitive fluctuations; FTD: Fronto-Temporal Dementia; PSP: Progressive Supranuclear Palsy; CSA: Compressed Spectral Array; SPECT: Single Photon Emission Computerized Tomography; MRI: Magnetic Resonance Imaging; FC: fluctuating cognition; RBD: REM Sleep Behaviour Disorder; VH: Visual Hallucinations.

was assessed by the frontal assessment battery (FAB) (Dubois *et al.*, 2000). Presence and severity of cognitive fluctuations were evaluated using CAF (Walker *et al.*, 2000b). Although, in the study in which this scale was originally proposed, fluctuations were also reported for non-DLB dementing disorders, a cut-off of 5 was shown to have high sensitivity and specificity to DLB. However, since our patients were, on average, considerably less impaired at presentation than those included in that study, we felt that such a cut-off would be too restrictive, unacceptably sacrificing sensitivity on the altar of specificity. Thus, in our analysis, a CAF score of at least 1 was considered sufficient to regard fluctuating cognition as present. Patients and caregiver interviews were rated following indications for qualitative assessment of reported fluctuations (Bradshaw *et al.*, 2004; Serrano and Garcia-Borroguero, 2004), Supplementary Material 1. The quality of cognitive fluctuations was assessed by one-day assessment of fluctuations (ODFA) (Walker *et al.*, 2000b). The presence of RBD was evaluated according to minimal international classification of sleep disorders (ICSD) criteria (World Health Organization, 1992) and confirmed by polysomnographic recordings, as reported in a prior paper from our institution (Onofrij *et al.*, 2003).

Each patient underwent a CT scan and/or MRI at least twice, firstly within 6 months of inclusion in the study and secondly

during the 2-year follow-up. All DLB and AD patients were also scanned with dopaminergic presynaptic ligand ioflupane SPECT (DAT scan) during the 2-year follow-up.

All demented and non-demented subjects were evaluated with a comprehensive neuropsychological battery, EEG and QEEG every 4–8 months for 2 years. Caffeine, nicotine and alcohol were not allowed for at least 48 h prior to neuropsychological and neurophysiological assessment. During follow-up treatments including L-Dopa (all patients with PDD, 31 patients with DLB), dopaminergic agonists (26 patients with PDD), rivastigmine (all patients), quetiapine (12 DLB, 13 PDD, 16 AD) and clonazepam (16 DLB, 12 PDD with RBD) were allowed and adjusted according to patients needs, but treatment was discontinued for 12 h (L-Dopa-Dopaminergic agonists-Clonazepam) or 48 h (rivastigmine, quetiapine) before both EEG and neuropsychological assessment.

EEG and quantitative electroencephalography (QEEG) assessments

Nineteen Ag/AgCl disk scalp electrodes, placed according to the international 10–20 system, recorded EEG from Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, Pz, P3, P4, T3, T4, T5, T6, O1 and O2. Two additional electrodes were placed on A1 and A2. EEG activity

was analysed from single or multiple leads grouped to define the following scalp regions: anterior (Fz, Fp2, F7, Fp1, F3, F4, F8), central (Cz, C3, C4), posterior (Pz, P3, P4, O1, O2), temporal (T3, T4, T5, T6), peripheral (Fp1, Fp2, F8, T4, T6, O1, O2, T3, T5, Fz) and internal (F3, F4, Fz, C3, Cz, C4, P3, Pz, P4). Recordings were obtained with subjects resting comfortably, with their eyes closed. Patients' wakefulness was ascertained every 2 min 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. 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 s-long epochs. EEGs interpreted with classical visual inspection, corresponding to categories reported in previous literature (Briel *et al.*, 1999; Barber *et al.*, 2000; Londoño *et al.*, 2003) were defined as classic interpretation methods (CIM) and reported in Supplementary Material 2. The computer collected 10 min of EEG recorded with closed eyes, digitized at 1024 Hz with a low filter at 0.5 Hz and high filter at 70 Hz (decay constant 12 dB) with a 50 Hz notch filter in each channel. Blocks of artefact-free 2 s-long epochs appearing consecutively for 20–40 s were selected off-line by visual inspection after pre-programmed automatic blink reduction and muscle and tremor artefact rejection system and were compared with the remaining artefact-free epochs in order to avoid possible discrepancies among acquired sets. A total of 90 epochs per patient were processed by an automatic transforming programme present in the NEUROSCAN SynAmps System performing a fast fourier transform (FFT) on each second of EEG acquisition, allowing a frequency sensitivity = 0.05 Hz. The obtained spectra values were then processed in order to compute a mean power spectrum for each epoch and for each channel and expressed in square μV (μV^2). The mean power spectrum was divided automatically into four frequency bands [1–3.9 Hz (delta), 4–5.5 Hz (theta), 5.6–7.9 Hz (fast theta or pre-alpha), 8–12 Hz (alpha)]. These bands were defined after the *post hoc* analysis with the purpose of facilitating identification of differences, in the description of results, as statistical differences were showed when theta band was halved in two parts (4–5.5 Hz, theta and 5.6–7.9 Hz pre-alpha).

The FFT-QEEG programme expressed power values automatically after a log transform ($\log[x/(1-x)]$) and indicated the dominant frequency (DF) of the entire power spectrum of each epoch, i.e. the specific frequency where the maximum power for a single epoch or a sum of multiple epochs was contained.

Mean relative power spectra (percentage of the global mean power spectrum of each frequency band) were computed and log transformed (Rodríguez *et al.*, 1999) to normalize the data, automatically calculated and expressed in numeric percentages for each one of the single epochs obtained from each scalp derivation. EEG power spectra were represented as scalp maps of band amplitudes measured on the 180 s total analysis (total power) and analysed as mean frequency (MF), indicating the average frequency for the 90 epochs and as MFV, representing changes of mean frequency during the 90 epochs. Single channel power spectra were also represented as CSA showing the sequences of absolute or relative power spectra in each one of the 90 analysed epochs.

CSA is the epoch-to-epoch representation of EEG FFT, for each derivation. It shows peaks of amplitudes, corresponding

to frequencies in a single epoch (Bickford *et al.*, 1973). These peaks of amplitude appear as salient patterns and could either be relatively stable through time or change (i.e. different frequencies could have the highest amplitude through time). CSA can be quantified by the following mathematical descriptors: (i) DF, expressing the mean frequency where the maximum power was represented in the sum of the 90 epochs; (ii) DF range, expressing the range of dominant frequencies in the 90 epochs; (iii) frequency prevalence (FP), i.e. percent of epochs where prevalence of a DF band was observed (1.11–100%); (iv) band inscription, i.e. the percent of epochs where a peak of frequency was identified with a total amplitude above the mean amplitude of random peaks (noise); (v) frequency ratio, i.e. band powers of pre-alpha or alpha versus delta, theta, pre-alpha or alpha; (vi) DF variability (DFV), expressing the variability of DF across the 90 analysed epochs. Measurements performed on MF topographic displays and on CSA displays are exemplified in Fig. 2. An interrater reliability test was also performed on the different modalities of EEG representation, methods and results, with results of coherence measurements are reported in Supplementary Material 3.

Statistics

Differences between groups [AD, DLB, PDD Fluctuators (PDD-F), PDD Non Fluctuators (PDD-NF) and controls] were tested using ANOVA with Bonferroni correction (checked with Kruskal Wallis statistics) for continuous variables; Fisher exact test for categorical variables. As the main outcome, attempts were made to use polytomous logistic regression to test the differences across groups in each EEG characteristics adjusting for potential confounders. However, the presence of clear cut-offs, fully predicting the outcome for most EEG characteristics, made unfeasible any multivariate analysis that may produce estimates of the strength of the association between EEG patterns and type of disease.

Significance probability mapping based on *t*-test statistic (Duffy *et al.*, 1981) was used to define regional differences between the scalp distribution of power of each frequency band for the different groups of patients. To investigate whether frontal, temporal and posterior EEG recordings produced different results, we used Wilcoxon matched-pairs signed-ranks test to compare the median of delta frequency pattern in AD patients resulting from the frontal derivation with the delta median in the same patients coming from temporal recordings. We used the same approach to test the difference between frontal and posterior derivation results, as well as temporal and posterior recordings, repeating all analyses for any other frequency pattern (theta, pre-alpha and alpha) in any group of patients.

The EEG variables MF, MFV, relative power, DF, DFV, FP from posterior derivations were included in a k-means cluster analysis (Supplementary Material 4) to verify results of CSA visual analysis. All analyses were carried out using STATA statistical software, version 9.0 (Stata Corp., Texas Station, TX, 2006).

Results

Patient demographics, neuropsychological and clinical features are shown in Table 1. Concordant with their match on initial MMSE, DLB, PD and AD patients exhibited no differences at presentation on other global test of cognition

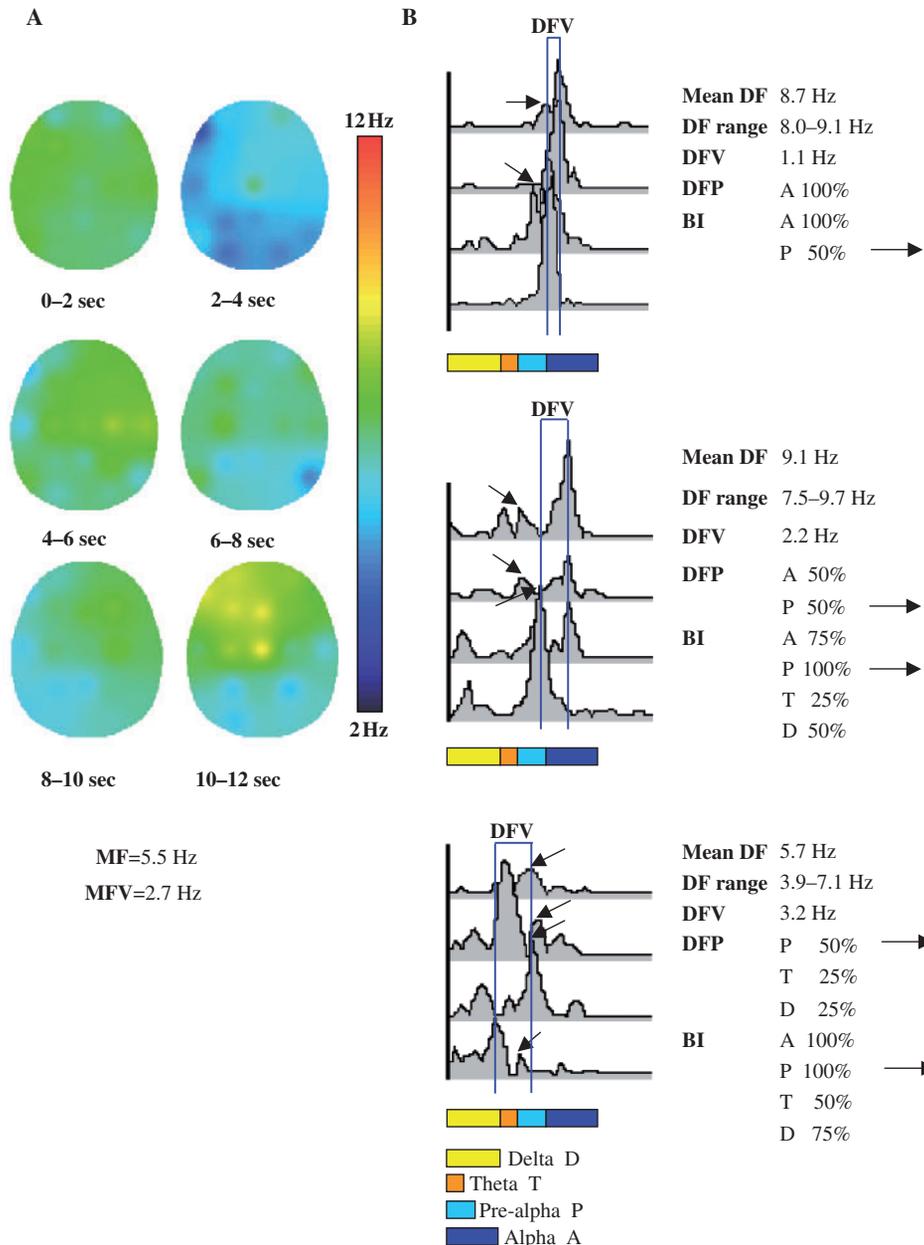


Fig. 2 (A) Examples of EEG variability measurements. Scalp map sequences showing Mean Frequency (MF) and MF Variability (MFV) in Six consecutive 2 s epochs. Colour maps should be matched with colour bar indicating frequencies (2–12 Hz). In the example, MF is in the theta band, MFV is visually evident because of variability of map colour distributions from epoch to epoch. Measurements are expressed by computer calculations (5.5 and 2.7 Hz). **(B)** CSA recorded from a single scalp lead, only four consecutive compressed spectra of 2 s epochs are shown in order to exemplify measurements. The frequency scale is 0–16 Hz, and frequency bands are indicated by colours. Variables are: Mean Dominant frequency (Mean DF), DF Variability (DFV), DF range, Frequency Prevalence (FP) and Band Inscription (BI) (% of epochs). DF range and DFV indicate the frequency variability of peaks of maximum power, in the different analysed epochs. In the top sequence Mean DF and DF range are in the alpha band, DFV is 1.1 Hz. In the middle sequence peaks of maximum power, change conspicuously from epoch to epoch, from 7.5 Hz (first epoch from bottom) to 9.7 Hz (third and fourth epoch from bottom), DFV is 2.2 Hz. In the bottom sequence DF peaks are different in each epoch and appear in the delta (first epoch from bottom), pre-alpha (second epoch), theta (third epoch). DF range is 3.9–7.1 Hz, DFV is 3.2 Hz. Further measurements can be performed: FP, expressing the relative (%) presence of a DF in the total of epochs, can indicate that the DF is always inside the same band, or shifts to other bands. In the top sequence DF is always alpha (FP alpha 100%). In the middle sequence the DF in part of epochs is in the alpha band (50%) and in part of epochs is in the pre-alpha band (50%). In the bottom sequence FP measurements show that pre-alpha is dominant in 50% of epochs, theta in 25% and delta in 25% of epochs. Band inscription (BI) is also a relative (%) measurement, indicating the percentage of epochs where power appears in a frequency band (being or not the maximum power for the epochs). BI in the top sequence indicates that pre-alpha appears in 50% of epochs, although it is never dominant). In the middle sequence non dominant theta or pre-alpha appear, in the bottom sequence pre-alpha can be identified in 75% of epochs. Mean DF is expressed by computer calculation. As the power peaks and their shift from epoch to epoch are salient, a visual inspection of traces can identify a stable or variable pattern. Arrows point to pre-alpha peaks of power.

Table 1 Demographic, clinical and neuropsychological data at admission to the study and after 2 years of follow-up

Variables	Phase	AD (n = 40)	DLB (n = 36)	PDD (n = 35)	Controls (n = 50)
Age, years	Admission	71.5 (4.5)	70.4 (4.9)	70.0 (4.0)	71.3 (4.4)
Male gender (in percentage)	–	37%	53%	54%	52%
Educational level, years	–	8.1 (4.4)	9.0 (4.1)	9.1 (5.0)	8.2 (4.0)
Mini Mental State Examination (MMSE)	Admission	22.3 (1.4)	22.8 (1.3)	22.9 (1.5)	28.9 (0.8)
	Follow up	17.1 (2.9)	17.2 (3.5)	17.6 (2.6)	28.4 (0.9)
Alzheimer Disease Assessment Scale – cognitive subscale (ADAS-cog)	Admission	21.6 (5.1)	22.0 (5.5)	22.1 (4.5)	12.0 (1.8)
	Follow up	25.3 (7.0)	29.4 (5.4)	28.6 (4.9)	13.0 (2.0)
Neuropsychiatry Inventory (NPI)	Admission	12.9 (2.9)	21.0 (1.7)	16.9 (4.0)	4.1 (2.1)
	Follow up	21.6 (3.5)	28.8 (3.1)	25.1 (2.9)	5.0 (2.3)
Frontal Assessment Battery (FAB)	Admission	15.1 (1.2)	14.4 (1.6)	15.0 (2.1)	17.8 (0.5)
	Follow up	13.7 (2.8)	11.5 (2.5)	11.4 (3.6)	17.5 (0.9)
Dementia Rating Scale – 2 (DRS-2)	Admission	100.9 (9.5)	103.1 (16.0)	103.5 (13.1)	137.4 (2.9)
	Follow up	77.4 (13.1)	80.1 (18.1)	81.4 (15.2)	135.7 (3.6)
Clinician Assessment of Fluctuation (CAF)	Admission	0.0	5.6 (2.0)	2.6 (3.1)	0.0
	Follow up	0.0	9.3 (1.5)	6.4 (4.3)	0.0
One-Day Fluctuation Assessment (ODFA)	Admission	0.2 (0.5)	4.1 (2.3)	2.7 (2.7)	0.0
	Follow up	1.8 (2.4)	7.6 (3.4)	3.9 (4.5)	0.2 (0.6)
Unified Parkinson's Disease Rating Scale – subscale III (UPDRS-III)	Admission	0.9 (1.0)	13.1 (6.6)	31.2 (7.4)	n.a.
	Follow up	0.8 (0.2)	17.5 (2.9)	49.4 (8.3)	n.a.
Hoehn/Yahr Staging (H/Y)	Admission	0.0	1.5 (0.9)	2.7 (0.6)	n.a.
	Follow up	0.0	1.9 (0.4)	2.9 (0.6)	n.a.
REM sleep Behavior Disorders (RBD)	Admission	2.5%	61.1%	40.0%	0.0%
	Follow up	0.0%	94.0%	63.0%	0.0%

When not differently stated, data are presented as mean (standard deviation).

AD = Alzheimer Disease; DLB = Dementia with Lewy Bodies; PDD = Parkinson's Disease with Dementia; n.a. = not applicable.

(ADAS-cog and DRS-2). However, frontal dysfunction (as assessed by FAB) was greater in DLB than AD patients ($P=0.05$). DLB patients also had, on average, the highest initial neuropsychiatric inventory score, indicating increased frequency and/or severity of behavioural disturbances at presentation (DLB > PDD > AD; $P < 0.001$ for each comparison). Conversely, severity of parkinsonism (as assessed by the UPDRS-motor subsection) was greatest in the PDD group (PDD > DLB > AD; $P < 0.001$ for each comparison).

Fluctuations (as assessed by CAF) were reported for all of the DLB patients and almost a half of the PDD patients, but for none of the AD patients. Specifically, in the DLB group, 22 patients were assigned a CAF score of 6–8, while the others had a CAF score between 2 and 5. Conversely, in the PDD group, the distribution of CAF scores included: 0, $n=19$; 1, $n=1$; 2, $n=1$; 4, $n=4$; 6–8, $n=10$; thus, 19 PDD patients (54.3%) were categorized as non-fluctuating (NF) and the remaining 16 PDD patients (46.7%) as fluctuating (F). Consistent with the results obtained using CAF, there also were significant group differences using ODFA, with patients with DLB having, on average, the highest score and approximately one-third of those with PDD with a score in the same range as that of DLB patients. As expected, within the PDD group, there were significant differences in ODFA between PDD-F and PDD-NF.

Even though 34 of the 36 DLB patients presented with some signs of parkinsonism, only 19 patients scored

at least 2 on items 22, 28, 29 or 31 of UPDRS III motor subscale (rigidity, posture, gait, bradykinesia). None of the AD patients had resting tremor or rigidity score above 1 as assessed with UPDRS III motor subscale items 22–26. None of the AD patients scored >0 at items 27, 28, 29, 31.

26 (72%) DLB patients complained of at least one episode of visual hallucinations. In 12 (33.3%) patients these were reported as recurrent. Six of them also presented psychotic episodes. 28 PDD patients suffered from recurrent complex visual hallucinations and 3 PDD patients from delusions. RBD was documented in 14 (40%) of the PDD patients. Conversely, none of the AD patients had visual hallucinations or RBD at presentation, even though sleep disorders not including nightmares were present in 6 (15%). In Supplementary Material 5, Table 1A details P -values for demographic and neuropsychological data in the comparison between each group of subjects.

EEG

Classic interpretation methods (CIM)

As shown in Table 2 although differences were observed between the three groups of patients, statistical comparison could be based only on chi-square test, not expressing cut-offs. In particular, significant differences were observed in the posterior derivations, with all of the AD and control

Table 2 Percentage of patients presenting with the different EEG patterns evaluated through classic interpretation methods (CIM)

		AD (n = 40)	DLB (n = 36)	PDD (n = 35)	Controls (n = 50)
Alpha frequency in posterior derivations ^a	Admission	100.0	66.7	68.6	100.0
	Follow-up	90.0	5.6	28.6	100.0
Theta/delta in anterior-temporal derivations ^b	Admission	5.0	11.1	5.7	0.0
	Follow-up	10.0	94.4	20.0	0.0
Theta/delta in posterior derivations	Admission	0.0	63.9	31.4	0.0
	Follow-up	10.0	94.4	51.4	0.0
Intermittent delta activity ^b	Admission	2.5	13.9	5.7	0.0
	Follow-up	7.5	25.0	11.4	0.0
Sharp transients ^b	Admission	2.5	5.6	0.0	0.0
	Follow-up	5.0	11.1	5.7	0.0

^aAlpha on posterior derivations is classified as unstable if faster (beta, >12 Hz) or slower (theta, 4–7.9) frequencies were detected.

^bTheta/delta, intermittent delta and sharp transients were positively reported when present on the traces, independently of relative predominance or sporadic appearance.

AD = Alzheimer Disease; DLB = Dementia with Lewy Bodies; PDD = Parkinson's Disease with Dementia.

subjects exclusively exhibiting an alpha rhythm and almost two-thirds of the DLB and one-third of the PDD displaying a theta/delta rhythm (Table 2 and Table 2A of the Supplementary Material 5). Supplementary Material 2 reports detailed analysis and examples of classic EEG traces for each group.

EEG total and relative power

Measurements of total powers showed differences only when significance probability mapping *T*-score statistics were applied, and only powers of a frequency band between 5.6 and 7.9 Hz were higher in DLB and PDD-F patients in comparison with controls and AD subjects (all $P = 0.01$ – 0.05). Therefore, the theta band was further separated into two bands, slow theta (4.0–5.5 Hz) and fast theta or pre-alpha (5.6–7.9 Hz). Mean relative power spectra showed that the pre-alpha band amplitude was higher in DLB in comparison with control, AD and PDD-NF subjects ($P \leq 0.01$) and that alpha band amplitude were higher in AD compared with DLB and PDD-F subjects ($P \leq 0.05$). In addition, pre-alpha relative amplitude was higher in patients with PDD-F than those with PDD-NF ($P = 0.05$).

Table 3 shows results of mean relative power spectra; statistical details of total and relative powers analysis are reported in Supplementary Material 6. Table 3A of the Supplementary Material 5 shows *P*-values for relative powers in the comparison between each group of subjects.

Mean frequency and MFV

Mean frequency values of the total 90 epochs were in the alpha range in controls, AD and PDD-NF and in the pre-alpha range in DLB and PDD-F patients. The EEG mean frequency value separated controls from all patient groups ($P < 0.05$). Table 3 shows mean frequencies. Table 3A of the Supplementary Material 5 shows *P*-values for MF in the comparison between each group of subjects.

Mean frequencies on scalp could be analysed on each single epoch, thus showing the MFV (Fig. 2).

In 75% of DLB and 35% PDD subjects (all from the PDD-F subgroup) mean frequency varied across time, with erratic representation of frequencies in the theta/pre-alpha and alpha range in posterior derivations of the two hemispheres. AD patients showed a stable pattern of mean frequency across the 180 s period, predominantly in the alpha range (DLB versus AD $P < 0.001$, PDD-F versus AD $P < 0.05$, DLB versus PDD-F n.s.).

Supplementary Material 7 show a comparison of mean frequency cartooning in patients affected by AD, DLB and PDD. Table 3 reports MFV during the 90 epochs. Table 3A of the Supplementary Material 5 shows *P*-values for MFV in the comparison between each group of subjects.

Compressed spectral array (CSA)

Table 4 shows DF, DFV, DF range, FP from grouped derivations of patients and controls. *P*-values are detailed in Table 4A of the Supplementary Material 5.

The highest statistical yields were obtained in the comparison of DF, DFV and FP measured on recordings from posterior derivations (AD versus DLB $P < 0.001$).

FP showed that alpha was present in 60% or more epochs recorded in 100% of AD patients with an amplitude ratio of 8.0 ± 2.8 in comparison with every other frequency. In DLB patients alpha was dominant in 32% or fewer epochs and absent in 66.7% of patients. Pre-alpha was prevalent in 40% or more epochs in 100% of DLB patients and in 11% or fewer epochs in 100% of AD patients. Statistical comparisons are summarized in Supplementary Material 4.

Pre-alpha/alpha band power ratio (mean band power ratio from all scalp derivations) was 3.2 ± 3.3 in DLB and 2.3 ± 1.2 in PDD-F, 0.1 ± 0.03 in AD, 0.1 ± 0.03 in PDD-NF (DLB versus AD, $P < 0.002$).

Table 3 Relative power spectra from all derivations, Mean Frequency (MF) and MF variability (MFV) at admission and at 2 years follow-up

		Phase	AD (n = 40)	DLB (n = 36)	PDD-NF (n = 19)	PDD-F (n = 16)	Controls (n = 50)
Q relative	delta (1.0–3.9 Hz)	Admission	94 (3.7)	94 (3.4)	94 (3.2)	95 (3.6)	74 (1.4)
		Follow up	6.0 (4.5)	10.8 (4.6)	8.9 (4.7)	10.1 (4.9)	4.7 (1.9)
	theta (4.0–5.5 Hz)	Admission	97 (3.5)	22.0 (11.7)	97 (1.9)	21.4 (5.8)	6.8 (2.0)
		Follow up	198 (5.6)	25.8 (5.7)	18.5 (3.1)	23.6 (4.6)	15.9 (4.9)
	Pre-alpha (5.6–7.9 Hz)	Admission	8.5 (2.0)	42.1 (13.6)	8.7 (1.8)	41.4 (9.0)	7.4 (1.5)
		Follow up	26.7 (8.4)	27.6 (12.8)	26.8 (6.5)	27.8 (11.7)	24.2 (5.6)
	alpha (8.0–12.0 Hz)	Admission	65.4 (4.3)	19.9 (10.0)	67.7 (3.8)	21.1 (7.1)	74.3 (2.3)
		Follow up	39.4 (10.9)	26.8 (4.5)	40.4 (8.4)	25.5 (5.8)	44.2 (5.8)
MF	Admission	8.0 (1.2)	7.1 (2.2)	8.4 (1.5)	7.0 (1.7)	8.1 (1.4)	
	Follow up	8.0 (1.8)	6.8 (2.1)	8.1 (1.4)	6.7 (1.6)	8.0 (1.4)	
MFV	Admission	1.2 (0.8)	1.9 (1.1)	0.9 (0.5)	1.7 (1.2)	1.0 (0.4)	
	Follow up	1.3 (1.1)	1.7 (1.2)	1.0 (0.7)	1.6 (1.1)	1.1 (0.5)	

Values are reported as mean (standard deviation).

AD = Alzheimer Disease; DLB = Dementia with Lewy Bodies; PDD-F = Parkinson's Disease with Dementia Fluctuators, PDD-NF = Parkinson's Disease with Dementia Non Fluctuators.

Alpha/theta ratio separated DLB and PDD-F from control, AD and PDD-NF subjects ($P < 0.001$). Alpha/delta ratio separated DLB and PDD-F from controls, AD and PDD-NF ($P < 0.001$).

Based on mean DF, DFV, on FP expressing the percentage of epochs where dominant alpha, pre-alpha, or theta-delta frequencies were found, and on the percentage of epochs where alpha, pre-alpha, theta-delta activities were detected (Band Inscription, BI), five patterns of EEG activity could be classified in the 90 epochs recorded from each derivations of patients or controls.

The first pattern corresponded to dominant alpha in 60% or more of analysed epochs (DF ≥ 8 Hz, FP alpha $\geq 60\%$), DFV of alpha below 0.6 Hz, mean DFV of all epochs below 1.6 Hz, Band Inscription of pre-alpha, theta or delta activities below 30% of epochs: this pattern could be defined Stable alpha, Pattern 1. The second pattern consisted of dominant alpha (≥ 8 Hz) in $< 50\%$ of epochs, mean DFV above 2 Hz, dominant pre-alpha or theta (< 8 Hz) in 40% of more of epochs (FP pre-alpha $> 40\%$, BI of pre-alpha-theta-delta 50%): this pattern was defined unstable alpha with pre-alpha or theta/delta, pattern 2. The third pattern consisted of absence of alpha, stable pre-alpha (DF ≤ 7.9 Hz), in 70% of more of analysed epochs, DF range 5.6–7.9 Hz, DFV of the analysed epochs below 1.0 Hz; this pattern was defined stable pre-alpha, pattern 3. The fourth pattern consisted of absence of alpha, dominant pre-alpha in $< 70\%$ of analysed epochs, dominant theta or delta in 40% or more of epochs, DFV above 2.0 Hz; this pattern was defined unstable pre-alpha with theta/delta, pattern 4. The last pattern consisted of absence of alpha, absence of alpha/pre-alpha dominant activity in more than two subsequent epochs with DFV above 4 Hz. This pattern was defined as unstable low frequency, pattern 5.

CSA sequences were classified as pattern 1 in 100% of controls and in 100% of recordings from posterior

derivations of AD patients and PDD-NF. CSA sequences in DLB and PDD-F were classified only in patterns 2, 3, 4, 5.

Table 4 summarizes results and Table 4A of the Supplementary Material 5 shows P -values. The five patterns, as power peaks corresponding to frequencies could be matched on frequency scales and could be stable or unstable, appeared also salient at visual inspection of CSAs, as shown in Fig. 3.

Visual inspection could rely on presence of alpha in the majority of epochs and shifts of DF below 1.6 Hz, appearance of frequencies other than alpha in less than one-third of epochs (pattern 1); on presence of pre-alpha in half of epochs or more and shifts of dominant frequencies (pattern 2); on presence of pre-alpha in the majority of epochs with slower frequencies in less than one-third of epochs (pattern 3); on presence of pre-alpha in less than half of epochs, absence of alpha and presence of dominant power peaks with slower frequencies in more than one-third of epochs (pattern 4); on absence of alpha and pre-alpha in more than two-third of epochs (pattern 5), corresponding to pattern 1–5 categorized by means of CSA variables.

The reliability of pattern classifications was confirmed by the k -means cluster analysis grouping Mean Frequency, EEG power and CSA variables in five clusters, corresponding to the five EEG CSA patterns (Spearman $\rho = 0.95$). Only 5 subjects of the 161 taking part to the study were misclassified. Results and methods of cluster analysis are reported in Supplementary Material 4.

Visual inspection evidenced also that pattern 2 activity could be characterized by pseudo-cyclicity of alpha and pre-alpha activities, consisting of stable alpha for 4–12 s, followed by 4–8 s of pre-alpha or theta/delta, or followed by change of alpha frequency (2.0 ± 0.6 Hz) for 2–4 s and pre-alpha or theta/delta for 4–8 s.

In pattern 3 CSAs the peak frequency of pre-alpha appeared asymmetrical on homologous derivations in 5 of

Table 4 Dominant frequency (DFV), DF variability (DFV), DF range, frequency prevalence (FP)/Band inscription (BI) for each frequency band, CSA patterns from frontal, temporal, parieto-occipital derivations from EEGs recorded at admission to the study

EEG variables	AD (n = 40)	DLB (n = 36)	PDD-NF (n = 19)	PDD-F (n = 16)	Controls (n = 50)
DF	8.0 (1.2)	7.0 (1.6)	8.2 (1.3)	7.4 (1.1)	9.0 (1.2)
DFV	1.7 (1.3)	2.8 (1.6)	1.3 (1.0)	2.1 (1.2)	0.5 (0.3)
DF range	3.0–10.0	5.0–11.0	3.0–9.1	5.8–10.0	8.0–12.0
FP/BI					
F Alpha	69 (6)/81 (2)	25 (11)/35 (15)	68 (8)/75 (3)	25 (8)/31 (9)	86 (3)/90 (2)
Pre-alpha	8 (3)/11 (3)	53 (10)/75 (11)	9 (3)/14 (3)	51 (7)/68 (10)	6 (2)/6 (2)
Theta	13 (4)/15 (5)	8 (4)/11 (4)	10 (4)/12 (5)	9 (7)/9 (3)	4 (1)/5 (2)
Delta	8 (5)/9 (5)	10 (4)/10 (4)	8 (5)/10 (4)	10 (3)/11 (4)	3 (2)/3 (3)
CSA Pattern					
1-Stable alpha	75.0	0.0	73.7	0.0	100.0
2-Unstable alpha+ pre-alpha	10.0	25.0	10.5	25.0	0.0
3-Stable pre-alpha	0.0	36.1	0.0	31.3	0.0
4-Unstable pre-alpha+theta/delta	10.0	27.8	10.5	31.3	0.0
5-unstable theta or delta	5.0	11.1	5.3	12.5	0.0
DF	8.0 (0.8)	6.8 (1.6)	8.1 (1.2)	7.8 (1.0)	8.7 (1.1)
DFV	1.3 (0.6)	1.9 (1.2)	1.1 (0.2)	1.8 (1.1)	0.4 (0.3)
DF range	6.0–10.0	3.5–9.0	5.5–10.0	6.5–10.0	8.0–12.0
FP/BI					
T Alpha	69 (5)/75 (6)	24 (7)/29 (8)	66 (5)/78 (6)	26 (10)/31 (11)	87 (3)/90 (3)
Pre-alpha	8 (3)/10 (5)	54 (8)/60 (9)	9 (1)/11 (2)	53 (8)/58 (10)	4 (2)/4 (2)
Theta	13 (2)/16 (3)	8 (4)/10 (5)	14 (2)/17 (4)	10 (6)/10 (6)	3 (2)/3 (2)
Delta	8 (3)/8 (3)	9 (6)/10 (6)	8 (3)/8 (3)	10 (6)/11 (6)	5 (1)/5 (1)
CSA Pattern					
1-Stable alpha	80.0	0.0	78.9	0.0	100.0
2-Unstable alpha+ pre-alpha	5.0	25.0	10.5	31.3	0.0
3-Stable pre-alpha	5.0	33.3	5.3	37.5	0.0
4-Unstable pre-alpha+theta/delta	5.0	30.6	5.3	31.3	0.0
5-unstable theta or delta	5.0	11.1	0.0	0.0	0.0
DF	8.3 (0.6)	7.4 (1.6)	8.8 (1.1)	7.5 (1.1)	8.6 (1.0)
DFV	1.1 (0.4)	1.8 (1.2)	0.9 (0.3)	1.9 (1.2)	0.4 (0.3)
DF range	7.9–11.0	4.8–11.0	8.0–12.0	5.8–10.0	8.0–12.0
FP/BI					
P Alpha	74 (6)/75 (8)	19 (5)/20 (7)	74 (10)/77 (11)	19 (7)/21 (9)	86 (3)/89 (4)
Pre-alpha	6 (3)/8 (3)	61 (8)/63 (8)	6 (1)/7 (3)	61 (7)/64 (9)	5 (2)/5 (3)
Theta	11 (4)/11 (5)	10 (4)/11 (5)	12 (2)/13 (4)	9 (6)/11 (7)	3 (2)/3 (2)
Delta	6 (2)/6 (3)	7 (3)/7 (3)	6 (3)/6 (3)	6 (4)/7 (4)	3 (1)/3 (2)
CSA pattern					
1-Stable alpha	100.0	0.0	100.0	0.0	100.0
2-Unstable alpha+ pre-alpha	0.0	33.3	0.0	62.5	0.0
3-Stable pre-alpha	0.0	25.0	0.0	25.0	0.0
4-Unstable pre-alpha+theta/delta	0.0	30.6	0.0	12.5	0.0
5-Unstable theta or delta	0.0	11.1	0.0	0.0	0.0

F = frontal derivations; T = temporal derivations; P = parieto-occipital derivations. DF = Dominant frequency; DFV = dominant frequency variability; FP = frequency prevalence; BI = Band Inscription; CSA = Compressed Spectral Array. DF, DFV and DF range are expressed in Hz; FP and BI are expressed as mean (standard deviation) and are approximate to the unit; CSA patterns are expressed as percentage of patients for each group. AD = Alzheimer Disease; DLB = Dementia with Lewy Bodies; PDD-F = Parkinson's Disease with Dementia Fluctuators, PDD-NF = Parkinson's Disease with Dementia Non Fluctuators.

9 DLB patients, with a difference by 0.3–0.9 Hz. Also in pattern 4 at pseudo-cyclicity appeared at visual inspection in 4 of 19 DLB patients, with 4–12 s of pre-alpha followed by 4–8 s of slower theta/delta. Supplementary Material 8 shows examples of CSA recordings in several patients.

Cut-offs

Cut-offs separating AD and DLB groups were only found with MFV evaluation and CSA analysis. MFV expressed a cut-off level of 1.3 Hz, separating controls, AD and PDD-NF patients (90% below) from DLB and PDD-F

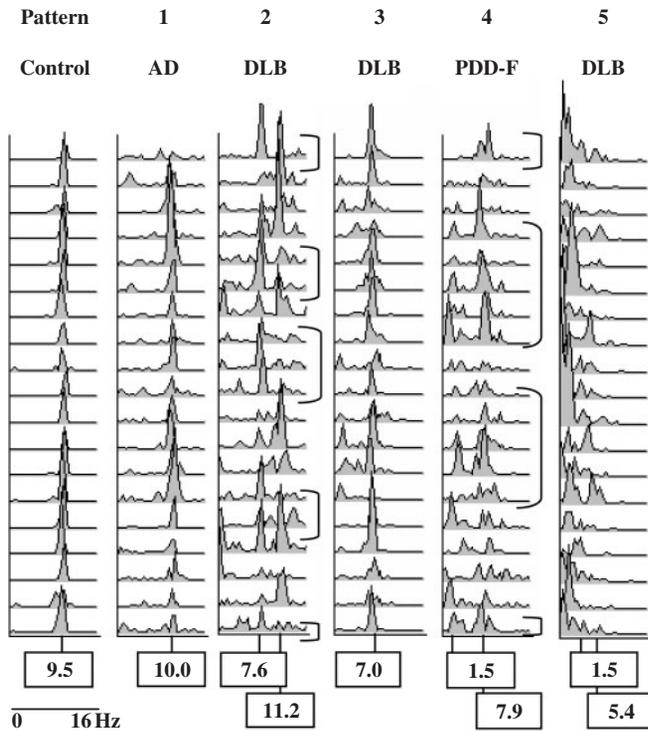


Fig. 3 CSA of EEG recording from occipital derivations in a control and five patients, showing the five patterns observed in patients at first assessment and at follow-up. Pattern 1: dominant frequency (DF) in the alpha range with stable alpha frequency recorded in an AD patient. FP 100%. Pattern 2: notice variability of the dominant frequencies shifting from alpha (9.0–11.5 Hz) for 2–4 s to dominant pre-alpha (6.9–7.6 Hz). Brackets indicate epochs with pre-alpha dominant frequency. DLB patient. Pattern 3: notice stable DF at 7.7 Hz, DLB patient. Pattern 4: DF variability, with the fastest frequency at 7 Hz and inscription of lower frequencies at 2–4 Hz, PDD-F patient. Brackets indicate pre-alpha dominant frequency. Pattern 5: Degraded EEG pattern with fastest frequencies slower than 5 Hz, and delta activity at 1–4 Hz, recorded in a DLB patient. Under each trace numbers in frames indicate the frequencies (in Hz), corresponding to power peaks.

patients (75% above). With CSA evaluations, DF measurements in posterior derivations expressed a cut-off corresponding to 8.0 Hz: this limit placed 95% of AD patients above the level and 88.9% of DLB patients below. DFV expressed a cut-off of 1.2 Hz on posterior derivations, separating 90% AD patients (below) and 75% of DLB patients (above).

By coupling DF and DFV measurements from posterior derivations, 97.2% of DLB and only 15% of AD patients had a DF < 8 Hz and a DFV > 1.2 Hz. The analysis of FP allowed to set a cut-off level for alpha and pre-alpha. As shown in Fig. 4, a pre-alpha FP \geq 40% with an alpha FP \leq 32% identified all of DLB and PDD-F patients, while a pre-alpha FP \leq 11% with an alpha FP \geq 55% identified all of AD and PDD-NF patients. Interrater reliability reached 100% only when CSA pattern categorization was applied to posterior leads, MF and MFV were correctly

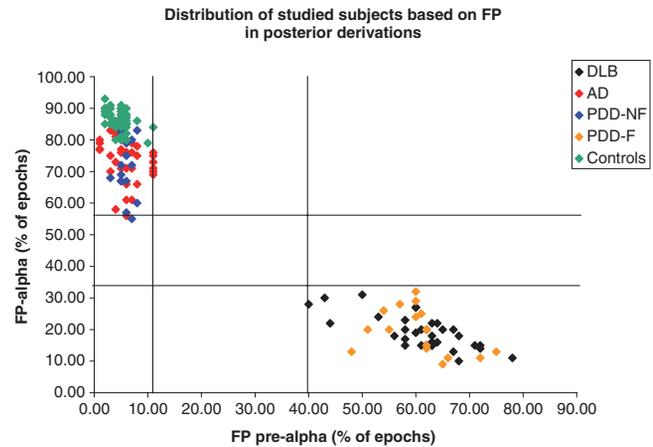


Fig. 4 Scatter plot distribution of all studied subjects based on cut-offs defined from CSA Frequency Prevalence (FP) measurements in posterior derivations. All the DLB and PDD-F patients situate above a pre-alpha FP of 40% of epochs and under an alpha FP of 32% of epochs. A pre-alpha FP under 11% with an alpha FP above 55% clustered all AD, PDD-NF patients and controls.

interpreted in 82% of AD and 92% of DLB. EEG evaluated with CIM was successfully classified in 70% of AD and 50% of DLB.

Follow-up

During follow-up several clinical and neuropsychological findings confirmed the initial diagnosis of possible or probable AD or DLB.

Clinical examination and neuropsychological tests

RBD appeared in 12 more patients initially classified as DLB; in 8 patients severe hypersensitivity to neuroleptic drugs, administered against our suggestions (olanzapine, risperidone, thietilparazine), was characterized by rigidity and increment of extrapyramidal symptoms. Twelve more patients experienced recurrent visual hallucinations and 16 patients reported episodes of delirium. None of these symptoms occurred in any AD patient. RBD appeared in 8 more and visual hallucinations in 4 more PDD patients. Delusional ideation appeared in 14 DLB patients and in 5 AD patients. In DLB patients, the CAF score increased by 2.2 ± 2.0 and in 12 of them, axial dystonia with camptocormia (7 patients) or lateral axial dystonia (5 patients) appeared. Consistent with the initial diagnosis of DLB, both UPDRS score and H/Y stage also increased (Table 1).

In PDD patients, the CAF score increased and in 10 PDD-NF patients who scored 0 at the onset, CAF scores rose (range 2–8). In the AD group selected for the study, CAF score did not change. In none of the AD patients did visual hallucinations or RBD occur during the 2-year follow-up. SPECT with ioflupane was normal in all AD patients and abnormal in all DLB patients.

Table 5 Dominant Frequency (DF), DF variability (DFV), CSA patterns from posterior derivations at 2 years follow-up.

EEG variables	AD (n = 40)	DLB (n = 36)	PDD-NF (n = 9)	PDD-F (n = 26)	Controls (n = 50)
Dominant Frequency (DF)	8.0 (1.9)	6.8 (2.7)	8.1 (1.4)	6.9 (2.4)	8.5 (1.2)
Dominant Frequency Variability (DFV)	1.1 (0.5)	1.8 (1.1)	1.0 (0.3)	1.8 (1.2)	0.4 (0.4)
CSA pattern					
1-Stable alpha	72.5	0.0	100.0	0.0	100.0
2-Unstable alpha + pre-alpha	10.0	5.6	0.0	26.9	0.0
3-Stable pre-alpha	2.5	38.9	0.0	26.9	0.0
4-Unstable pre-alpha + theta or delta	10.0	41.7	0.0	34.6	0.0
5-Unstable theta or delta	5.0	13.9	0.0	11.5	0.0

For DF and DFV values are expressed as mean (SD). Mean Dominant Frequency was measured as the average of dominant frequencies recorded in CSA of posterior derivations and Dominant Frequency Variability of CSA (expressing the range of dominant frequencies). For CSA pattern (from posterior derivations) values are expressed as percentage of patients per each group. AD = Alzheimer Disease; DLB = Dementia with Lewy Bodies; PDD-F = Parkinson's Disease with Dementia Fluctuators, PDD-NF = Parkinson's Disease with Dementia Non Fluctuators.

Table 1 shows results of neuropsychological tests and clinical scores at the end of the 2 years follow-up. Table 1A of the Supplementary Material 5 shows *P*-values for neuropsychological and clinical data at follow up in the comparison between each group of subjects.

EEG

Results of EEG CIM at follow-up are reported in Supplementary Material 2 and summarized in Table 2. Follow-up measurements of mRP, MF, MFV are reported in Table 3. Pre-alpha relative power differences observed at admission in the comparison between DLB and AD patients was lost. MF statistically separated AD from DLB patients (*P*=0.03) but MFV was not different here, and the definite cut-off observed at onset of symptoms was lost (Table 4A of the Supplementary Material 5).

DF and DFV on posterior leads separated DLB and PDD-F from AD and PDD-NF (*P*<0.05), Table 5 and Table 5A of the Supplementary Material 5. CSA sequences classification of patterns showed that pattern 1 was observed in posterior derivations of 72.5% of AD patients and in 70% of patients in anterior derivations, while in temporal derivations, only 11 (27.5%) AD patients had pattern 1 activity.

Alpha activity appeared sporadically in posterior derivations, with pattern 2 sequences only in 2 DLB patients (5.6%); all other DLB patients presented with CSA patterns 3, 4, or 5 (Table 5). In anterior and temporal derivations DLB presented only with 3, 4 or 5 CSA patterns.

In PDD patients, EEG alterations corresponding to patterns 2, 3 or 4, appeared in 26 patients (74.4%). In 10 of the 19 patients who had pattern 1 EEG at onset, the EEG was characterized by pattern 2, 3 or 4. In 16 patients only patterns 3 and 4 were observed (Table 5). In 3 patients (two had pattern 3, one pattern 4 at onset) pattern 5 was observed in posterior derivations. Table 5A shows *P*-values for CSA patterns at follow-up in the comparison between each group of subjects. Fig. 5 shows the evolution after

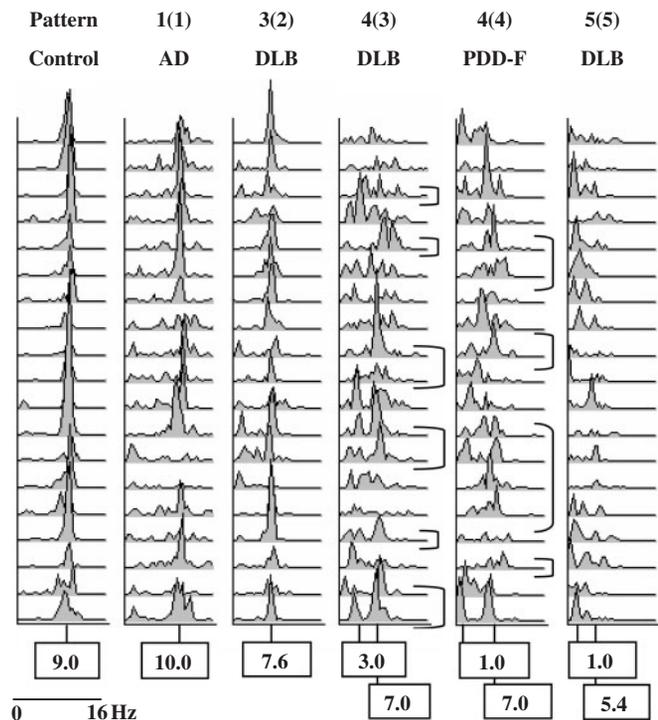


Fig. 5 CSA of EEG recordings from occipital derivations in the control and five patients, whose CSAs at first assessment were presented in Fig. 3, showing the 5 patterns observed at follow-up. Notice that CSA pattern 2 has become a pattern 3, in bracket CSA pattern at first assessment; CSA pattern 3 at first assessment is now a pattern 4. In brackets: sequences of pre-alpha DF.

the 2 years follow-up of CSA EEG representation of the 5 patients presented in Fig. 3.

Correlations

MMSE, ADAS-cog, DRS-2 and FAB scores and educational level correlations with mean relative power spectra of EEG recorded from different electrode locations did not reach statistical significance (Spearman rho<0.4). The power of delta or theta activity in frontal regions was highest in patients with lowest FAB scores (ΔV 60% of power,

FAB 11–13; ΔV 30% of power, FAB 14–18) but the results did not reach statistical significance.

CAF scores were correlated with DF and DFV scores and with the five patterns of EEG abnormalities shown by CSA analysis (Supplementary Material 9). In DLB patients at onset CAF scores (0 to 8) were significantly correlated with CSA patterns graded 1–5, Spearman $\rho = 0.8$. At follow up ρ was 0.6. In DLB and PDD patients worst FAB scores were significantly correlated with EEG pattern 3–4 in anterior derivations ($P = 0.04$ – 0.05). In all patients the worst MMSE, DRS-2, ADAS-cog were observed in patients with EEG pattern 5.

EEG findings in challenged diagnoses

Six AD patients were excluded from the randomized group because of the occurrence of parkinsonism, of which four with positive CAF scores, one with RBD and a CAF score of 2 and one with visual hallucinations and a CAF score of 2–6 during follow-up. Two more AD patients were excluded because of the occurrence of parkinsonism without other signs, one because of severe secondary parkinsonism induced by amisulpiride (50 mg/day) administration, one because of a stroke.

Analysis of CSA patterns of excluded patients showed that EEG abnormalities were already present at admission to the study in 7 out of 10 patients. In five of the six patients with positive CAF scores and parkinsonism, in one patient with parkinsonism only and in the patient with secondary parkinsonism, EEG recorded at admission from posterior derivations consisted of CSA pattern 2 (five patients) or pattern 3 (two patients). Only two AD patients who lately developed parkinsonian signs without RBD had EEG CSA pattern 1 at admission. Fourteen DLB patients were excluded from the study because of the occurrence of cardiac, cerebrovascular, renal/hepatic comorbidity. EEG recordings performed at admission to the study showed the presence of pattern 2 in three patients, of pattern 3 in four patients, pattern 4 in five patients, pattern 5 in two patients. Three PDD patients were excluded due to cardiac comorbidity. At admission to the study one of them had EEG CSA pattern 2, the other 2 had EEG CSA pattern 1. Two PDD patients were excluded from the study, because the diagnosis had changed at follow-up. One patient was diagnosed as a fronto-temporal dementia and one patient as Progressive Supranuclear Palsy. EEG recordings from both patients performed at admission and after 6 months from the end of the study showed a CSA pattern 1.

Discussion

The different EEG variables analysed in our study showed some distinct and specific patterns in patients affected by DLB or PDD-F. When EEGs were interpreted with the classic visual inspection methods, an alpha rhythm in posterior derivations was observed in all of the patients

with AD, but only in approximately two-thirds of those with DLB. In the PDD group, an alpha rhythm was observed in almost three-quarters of the patients. Although intermittent delta and sharp transients, as described in previous studies (Briel *et al.*, 1999; Mc Keith *et al.*, 2005), occurred more frequently in DLB than AD patients (13.9% versus 2.5% and 5.6% versus 2.5%, respectively), these findings were rare, and therefore scarcely useful for diagnostic purposes. Other group differences went unnoticed with visual inspection, but were appreciated with QEEG methods.

Our first relevant finding was the identification of slow activities (5.6–7.9 Hz) in posterior derivations of all DLB patients, which significantly differentiated these patients from those with AD. This activity was defined pre-alpha because it was suppressed by eye opening. Two prior studies (Fantini *et al.*, 2003; Massicotte-Marquez *et al.*, 2005), quantifying EEG characteristics during polysomnography in patients with RBD and DLB/PDD compared with normal controls, had shown differences between these two groups in the same EEG frequency band. Our study highlights differences between patients with DLB/PDD and those with AD. The variability of EEG dominant and mean frequency activity was our second most relevant finding leading to the identification of specific EEG patterns in DLB or PDD-F ($P < 0.001$). Confirming earlier suggestions from a previous study (Walker *et al.*, 2000a), MFV correctly categorized 90% of AD patients and 75% of DLB patients. The variability of the EEG frequencies in relaxed waking conditions emerged however more clearly by using the CSA method of representation that, previously, had only been used to assess coma, anaesthesia levels and background EEG activity of epileptogenic zones (Karnaze *et al.*, 1982; Yli-Hankala *et al.*, 1989; Wang and Wieser, 1994). Showing that dominant frequencies (DF) in DLB were either in the pre-alpha band or varied across time with pseudocyclic patterns of delta-theta/pre-alpha or theta-pre-alpha/alpha, this method was particularly useful in differentiating DLB from AD patients, as well as PDD patients with cognitive fluctuations (PDD-F) from those without (PDD-NF). Specifically, CSA representation allowed to evidence changes of EEG activities in single derivations. Assessing local variability, CSA, unlike total QEEG analyses and MF evaluations, clarified that the most significant group differences were present in posterior leads. Even more important, CSA analysis on posterior leads produced cut-offs that allowed the correct identification of all patients.

CSA showed that the variability of dominant activity could be separated in five patterns, describing presence and dominance of delta-theta-pre-alpha and alpha frequency bands. These patterns were also salient at visual inspection of the sequence of traces and classifications based on visual inspection were overlapping with classifications obtained by scoring CSA mathematical variables or by cluster analysis. The first pattern, with dominant stable alpha, was only

observed in early AD and in 54.3% of PDD (only non-fluctuators), while the other patterns, differently grading the DFV and pre-alpha presence, were only observed in posterior derivations of early DLB and PDD-F.

The abnormal patterns consisted either of a stable dominant activity at 5.6–7.9 Hz, encountered in 25% of DLB and 11.4% of PDD, but never in AD patients, or of unstable activities, all encompassing the presence of the 5.6–7.9 Hz activity and significant variations of the DF across time. Therefore, these EEG abnormalities, when observed in a patient with initial signs of cognitive decline, i.e. MMSE \geq 20, are highly suggestive of a diagnosis of DLB.

When EEGs were recorded 2 years later, further alterations were observed which differentiated groups of patients, even though the administration of drugs not allowed at baseline could have partly marred the results. In DLB patients and in 74.3% of PDD patients EEGs were similar, with a stable pre-alpha activity or unstable DF over time, with variability above 3 Hz, consisting of the presence of unstable alpha, pre-alpha, theta and delta activities. In 72.5% of AD patients and in 25.7% of PDD patients (all PDD patients without cognitive fluctuations) DFV was below 3 Hz and alpha activity was present.

Therefore both endpoints one and two were reached, statistical differences and cut-offs for MFV, DF with DFV could be shown. Furthermore, CSA patterns could be recognized by visual inspection of traces sequences. As CSA representation is available in the majority of digitalized EEG systems, this method of interpretation could be used in the majority of EEG laboratories.

Analyses focused on the third endpoint showed that PDD in its early course can apparently be separated into two groups: one with fluctuating cognition elements and EEG pattern abnormalities similar to those observed in early DLB and a group with EEGs similar to that of AD patients and without fluctuating cognition.

With follow-up, however, the majority of PDD patients (74.3%) had increased CAF scores and displayed the same EEG abnormalities characterizing those with DLB. The presence of two different clusters in early PDD suggests a variable distribution of neuropathological abnormalities in different patients, cumulating however across time to show, at follow-up, clinical and EEG patterns similar to those observed in DLB.

We would make further considerations. It is likely that our findings reflect a patient selection method particularly focused on the presence of fluctuating cognition (as assessed by CAF and ODFA scales) and RBD, which prominently characterize DLB (Mc Keith *et al.*, 2005). The rarity of both these features in early AD as compared with DLB has only recently been highlighted in the literature (Merdes *et al.*, 2003; Tiraboschi *et al.*, 2006). It might be, therefore, that the greater EEG abnormalities observed by others in less recent 'AD series' (Coben *et al.*, 1983; Rae-Grant *et al.*, 1987; Breslau *et al.*, 1989; Hughes *et al.*, 1989; Prinz and Vitiello, 1989; Leuchter *et al.*, 1993) depend

in part on heterogeneity of patient populations and, in particular, may reflect the inclusion of a variable number of DLB cases misdiagnosed as having AD. In support of this interpretation is the observation that, in the most recent literature (Mattia *et al.*, 2003; Jeong, 2002; Kai *et al.*, 2005; Ab'asolo *et al.*, 2006; Franciotti *et al.*, 2006), EEG alterations reported for AD patients were modest and consistent with those shown in our study. Therefore, by emphasizing the diagnostic weight of cognitive fluctuations, RBD and SPECT abnormalities, we were able to observe specific EEG abnormalities, that accurately distinguished DLB from AD patients. In fact, in the present study, all of the patients clinically diagnosed at presentation as having DLB had a positive CAF score and, in most of them, this score increased during the 2-year follow-up period despite the administration of cholinesterase inhibitors (allowed only after baseline examination). Conversely, in the AD group, none of the patients had a positive CAF score at presentation and the few in whom the CAF score became positive at follow-up (10%) were excluded from primary analysis.

In the DLB group, RBD was observed in 61% of the patients at admission and 94% of the patients at follow-up. In the AD group, none of the patients had RBD at admission, although few developed RBD at follow-up. Altogether, of the 50 patients clinically diagnosed as having AD at presentation, the 10 who developed RBD, parkinsonism, cognitive fluctuations, or visual hallucinations during the 2-year follow-up period were excluded from main analysis because their initial diagnosis was felt to have become questionable. Of interest, initial EEG abnormalities corresponding to patterns 2 and 3 were observed in seven of these patients, suggesting that, in the earliest stages of dementia, an EEG CSA pattern other than 1 may be regarded as a reliable negative predictor of a diagnosis of AD even when clinical features of dementing diseases other than AD and deemed typical of DLB have not yet appeared.

We would also highlight that, based on consensus criteria for the diagnosis of DLB (McKeith *et al.*, 1996), the frequency of core features in our patient population was higher than that usually reported in the literature. A possible explanation is that our patient population was prospectively followed, and thereby strictly evaluated for the presence of distinctive features of DLB, especially because our patients were enrolled beginning from 2001, when 5 years had passed since the scientific world started posing a special emphasis on investigating the presence of these features.

Even though a putative pre-mortem diagnosis of dementia subtypes might be extremely difficult (Walker *et al.*, 2007), in conclusion our study shows methods of analysis and quantitative comparisons supporting the suggestion that EEG might be helpful in the diagnosis of DLB (Mc Keith *et al.*, 2005).

Because EEG abnormalities are positively associated with frequency and severity of fluctuations and EEG activity

in posterior derivations is regulated by thalamic activity (Steriade, 2006), further hypotheses could be suggested on the pathophysiology behind cognitive and electrophysiological fluctuations. Recent studies, showing that a dorsal fronto-parietal network subserves attention (Corbetta *et al.*, 2005) and that parietal areas express basal attention (Hon *et al.*, 2006), suggest that this network might be altered in patients affected by dementia. The network is based on direct pathways or relays in thalamic nuclei (Treisman and Gelade, 1980). Furthermore, a recent neuropathological study evidences thalamic cholinergic alterations in DLB patients (Ziabreva *et al.*, 2006).

We suggest that this network should be studied in patients with DLB or PDD, and that, as previous studies showed anatomical degeneration of basal ganglia in DLB (Cousins *et al.*, 2003), also a possible degeneration of thalamic nuclei should be investigated by means of quantitative neuroimaging.

Supplementary material

Supplementary material is available at *Brain* online.

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