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Is There a Place for Clinical Neurophysiology Assessments in Synucleinopathies?

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1. Introduction

Parkinson Disease (PD), Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA) are characterized by deposition of Lewy Bodies (LB), consisting of eosinophilic intracellular (intraneural in PD and DLB and intragial in MSA) inclusions of α -synuclein and allowing the three disorders to be categorized as synucleinopathies. The identification in the last two decades of specific clinical features of synucleinopathies has been a major breakthrough in Neurology, as it prompted a reconsideration of diagnostic and therapeutic approaches to dementia and parkinsonism. The recognition of synuclein and ubiquitin markers in dementia resulted in the reclassification of patients previously considered as affected by Alzheimer Disease (AD) and Vascular Dementia (VaD), and there is now agreement that DLB is the second most common cause of dementia in elderly population: its prevalence is reported to be in the 25-43% range in different studies.

DLB is clinically characterized by the presence of prominently dysexecutive dementia (frontal lobe or subcortical dementia according to earlier classification [1]), cognitive fluctuations, consisting of remitting-relapsing episodes of blunted conscience reaching levels of stupor, by the occurrence of visual hallucinations and delusions, by parkinsonian motor signs and hypersensitivity to neuroleptic treatment, ranging from worsening of parkinsonism to the possible lethal neuroleptic-malignant syndromes [2]. Yet, variances of presentation and overlapping symptoms with AD and Fronto-Temporal lobe Degeneration (FTD), could be misleading in the process of addressing a clinical diagnosis with consequent therapeutic risks (e.g. introducing neuroleptic treatments in patient with DLB), or economic costs (e.g. addressing patients with DLB to treatment protocols dedicated to AD patients, based on vaccines or antibodies against β amyloid proteins, a neuropathological feature of AD).

It is evident the stringent need for improvement of reliable diagnostic tools (u.e. biomarkers) to differentiate the diseases associated with dementia. In 2010 the National Institute of Health, NIH, held a symposium focused on the development of possible biomarkers for DLB. Among the different suggested biomarkers, neurophysiological assessments were reconsidered, as a large amount of neurophysiological studies had been devoted to AD and PD, whose characteristics are shared by DLB.

We contributed to several studies on this argument along the years, and in the present chapter we discuss the role of clinical neurophysiological studies in DLB in comparison with other disorders. The essential background of our original studies laid in the fact that most historical studies were performed when the DLB clinical entity was unknown and therefore some of the past results were marred by absent recognition of this clinical entity.

2. Synucleinopathies: Dementia with lewy bodies

Synucleinopathies comprise a diverse groups of neurodegenerative proteinopathies that share common pathological lesions composed of aggregates of conformational and posttranslational modifications of alpha-synuclein in selected populations of neurons and glia. Abnormal filamentous aggregates of misfolded alpha-synuclein protein are the major components of LB, dystrophic (Lewy) neurites and the Papp-Lantos filaments in oligodendroglia and neurons linked to degeneration of affected brain regions. The synucleinopathies (see table 1) include Lewy Body disease (Parkinson Disease (PD), DLB, Multiple System Atrophy (MSA)) and neurodegeneration with brain iron accumulation type I, (NBIIA), formerly Hallervorden-Spatz disease. The pathological diagnosis of Lewy body disease is established by validated consensus criteria based on semi-quantitative assessment of subcortical and cortical LB as their common hallmarks. They are accompanied by subcortical multisystem degeneration with neuronal loss and gliosis with or without AD pathologic features. LB deposition also occur in numerous other disorders, including pure autonomic failure, neuroaxonal dystrophies and their presence is also evident in various amyloidoses and tauopathies. MSA, a sporadic, adult-onset degenerative movement disorder of unknown cause, is characterized by alpha-synuclein-positive glial cytoplasmic and rare neuronal inclusions throughout the central nervous system associated with striatonigral degeneration, olivopontocerebellar atrophy and involvement of medullar and spinal autonomic nuclei. In NBIIA alpha-synuclein is present in axonal spheroids and glial and neuronal inclusions. While the identity of the major components of LB suggests that a pathway leading from normal soluble to abnormal misfolded filamentous proteins is central for their pathogenesis, regardless of the primary disorder, there are conformational differences in alpha-synuclein between neuronal and glial aggregates, showing no uniform mapping for its epitopes. Despite several cellular and transgenic models, it is not clear whether inclusion body formation is an adaptive/neuroprotective or a pathogenic reaction process generated in response to different, mostly undetermined, functional triggers linked to neurodegeneration. From a clinicopathological point of view, recognizable differences appear along the spectrum of the synucleinopathies. In fact PD is characterized by subcortical and rare cortical LB associated with degeneration of the dopaminergic nigrostriatal and other subcortical systems while more extensively distributed LB accompanied by striatonigral degeneration and variable extents of AD pathologic states typify DLB which, depending on the severity and extent of neuritic AD pathologic conditions, can be divided into two subgroups: “pure” DLB and DLB variant of AD. Finally, LB may also occur in AD, which is defined by the presence of neocortical neuritic pathologic findings (β amyloid plaques and neurofibrillary tangles). Among the synucleinopathies DLB represents the second most frequent cause of dementia in the elderly after AD [3].

SYNUCLEINOPHATIES	LESION/COMPONENTS	LOCATION
PARKINSON’S DISEASE	LB/DYSTROPHIC NEURITIS	INTRACYTOPLASMIC
LEWY BODY DEMENTIA	LB/DYSTROPHIC NEURITIS	INTRACYTOPLASMIC
LEWY BODY VARIANT OF ALZHEIMER DISEASE	LB/DYSTROPHIC NEURITIS Aβ-PLAQUES TANGLES PHF/TAU	INTRACYTOPLASMIC EXTRACELLULAR INTRACELLULAR
PURE AUTONOMIC FAILURE	LB	INTRACYTOPLASMIC
ALZHEIMER’S DISEASE	PLAQUES (Aβ AMYLOID) TANGLES PHF/TAU LB/α-SYNUCLEIN	EXTRACELLULAR/ INTRACYTOPLASMIC
MULTIPLE SYSTEM ATROPHY	CYTOPLASMATIC GLIAL INCLUSION	INTRACYTOPLASMIC
HALLERVORDEN-SPATZ DISEASE	LB/CYTOPLASMATIC GLIAL INCLUSION	INTRACYTOPLASMIC
NEUROAXONAL DYSTROPHY	AXONAL SPHEROIDS	
AMYOTROPHIC LATERAL SCLEROSIS	UBIQUITIN, INCLUSION SOD 1, LB	INTRANUCLEAR, INTRACYTOPLASMIC
OTHER: DOWN SYNDROME MOTOR NEURON DISEASE		INTRACYTOPLASMIC

Table 1. Sinucleinopathies and LB location.

The central clinical feature of DLB is progressive dementia prominently characterized, in the early phases of the disease, by deficits in attention, executive function and visuospatial ability, at difference with AD where memory impairment is the main early feature of dementia. Fluctuations in attention and alertness, recurrent complex visual hallucinations and parkinsonism represent the core features for the diagnosis. Suggestive clinical features are REM sleep behavior disorder, severe sensitivity to neuroleptics and low dopamine transporter uptake in the basal ganglia demonstrated by single photon emission computerized tomography (SPECT) or Positron Emission Tomography (PET) imaging. Supportive features are often present and are represented by repeated falls and syncopes, transient and unexplained loss of consciousness, severe autonomic dysfunction (e.g., orthostatic hypotension, urinary incontinence), hallucinations in other modalities than visual, systematized delusions, depression, relative preservation of medial temporal lobe structures on CT or MRI scans, generalized low uptake on SPECT/PET perfusion scans with low occipital activity, abnormally low uptake on ¹²³I-metaiodobenzilguanidine (¹²³I-MIBG) myocardial scintigraphy [2].

In this last revision of criteria for the diagnosis of DLB, electroencephalography (EEG) abnormalities with transient slow waves or sharp waves were also reported as supportive features for the diagnosis[2,4].

We performed a prospective study evaluating the incidence and characteristics of EEG abnormalities in patients affected by AD, DLB and PD with Dementia at their first

presentation in a tertiary clinic, not later than 1 year from the onset of dementia [5]. Supportive elements for the diagnosis came from Clinical Assessment of Fluctuations (CAF) scale, polysomnography (PSG) and Mayo Sleep Questionnaire for the assessment of REM sleep Behaviour Disorder (RBD). CAF is a neuropsychological test [6] able to evidence, on the basis of patient and caregivers interviews, the presence of fluctuating consciousness. The questionnaires are able to discriminate 85% of DLB patients, as confirmed by autopsy [7]. Cognitive fluctuations are considered a clinical feature typical of DLB, described in 70-80% of these patients, only in 14-20% of AD patients and in 15-30% of VaD subjects [8].

3. Visual Evoked Potentials (VEPs)

PD and parkinsonism are associated with a variety of visual signs and symptoms summarized in table 2.

OCULAR ASPECT	CHANGE IN PD	REFERENCES
PRIMARY FUNCTION VISUAL ACUITY VISUAL FIELD COLOR VISION	POOR, ESPECIALLY AT LOW CONTRAST INCREASE IN GLAUCOMATOSE VISUAL FIELD DEFECTS VISION BLURRED FOR COLOURED STIMULI/PROGRESSIVE DETERIORATION	Repka et al., 1996 Bayer et al., 2002 Price at al., 1992/ Diederich et al., 2002
EYE MOVEMENTS SACCADIC GAZE SACCADIC EYE MOVEMENT SMOOTH PURSUIT OPTOKINETIC NYSTAGMUS	SLOWER THAN NORMAL HYPOMETRIA AFFECTED EARLY IN DISEASE PROCESS ABNORMAL IN SOME PATIENTS	Shibasaki et al., 1999 Crawford et al., 1989 Bares et al., 2003 Shibasaki et al., 1999
BLINK REFLEX FREQUENCY HABITUATION	REDUCED NOT OBSERVED	Garland et al., 1952 Garland et al., 1952
PUPIL REACTIVITY CONTRACTION AMPLITUDE LIGHT REFLEX	REDUCED LONGER LATENCY	Biousse et al., 2004 Miceli et al., 1991
VEP FLASH ERG PATTERN ERG CORTICAL VEP CHROMATIC VEP	REDUCED AMPLITUDE OF b WAVE with PHOTIC E SCOTOPIC STIMULI REDUCED AMPLITUDE, DELAYED P50 DELAYED P100, CHANGING TO NORMAL WITH L-DOPA INCREASED LATENCY AND REDUCED AMPLITUDE	Gottlob et al., 1987 Gottlob et al., 1987 Bodis-Wallner et al., 1982 Sartucci et al., 2006
COMPLEX VISUAL FUNCTION VISUO-SPATIAL ORIENTATION VISUAL HALLUCINATIONS	SEVERE IMPAIRMENT IMPAIRED CHRONIC IN 30-60% TREATED CASES	Davidsdottir et al., 2005 Trick et al., 1994 Diederich et al., 2005

Table 2. Abnormal visual symptoms in PD

Recent epidemiological studies have shown an association between visual impairments and visual hallucinations in patients with PD [9]. Neuropsychological studies have revealed visuoperceptual impairments in PDD and DLB patients with visual hallucinations [10]. Additionally, recent radiological studies have demonstrated decreased blood flow in the posterior temporal and occipital regions in hallucinatory PD and DLB patients [11]. Taking these findings together, it is possible to speculate that visual information processing functions are selectively impaired in DLB and PDD.

Impairment of achromatic as well as chromatic vision in PD has been extensively proven using clinical, psychophysiological and electrophysiological methods (ERGs and VEPs) and attributed to dopaminergic deficiency at the retina level.

Some studies demonstrated a significant difference between PD patients and well matched control subjects in the amplitude of VEP, of flash (ERG) and pattern electroretinogram (PERG: retinal response evoked by viewing an alternating checkerboard or grating) [12]. The VEP, PERG and flash ERG originate from different parts of the retina and central nervous system and reflect different physiological processes. The changes in these potentials in PD may reflect the widespread nature of the biochemical disorder affecting both retina and central nervous system. Indeed PD patients have also been shown to have abnormal auditory evoked potentials [13]. Abnormal VEPs were described in patients with PD: the percentage of VEP delays and the amount of latency increments detected in PD patients are dependent on the spatial frequency (that is a parameter of the stimulating pattern). The VEP latency increases as a function of increasing spatial frequency [14] in normal subjects, and our results [15] show that this latency increase is enhanced in PD and also when dopamine blockers are administered. Delayed responses, consisting of increased latencies of the P100 component evoked by patterned stimuli of degree to 7.5' elements (spatial frequency of 0.5 to 4 cycles per degree) were observed in PD patients and the delays disappeared together with clinical symptoms when L-Dopa was administered [15,16,17]. The evidence of VEP delays in PD were concomitant with the identification of dopaminergic cells (amacrine and horizontal cells) in the retina, both evidences reciprocally supporting the idea that the cause of delays was dependent on retinal dopamine cell deficiencies. In these studies retinal and occipital visual evoked potentials and event-related potentials (P300) have been recorded in normal human subjects before and after the administration of the dopaminergic receptor antagonist, haloperidol, and/or the dopaminergic precursor L-DOPA. The data show that either retinal or occipital visual potentials and P300 are delayed by haloperidol. These findings are consistent with the hypothesis that haloperidol in healthy subjects mimics the electrophysiological abnormalities observed in PD. On the other hand, L-Dopa does not generally modify these latencies in controls, while it is known to decrease the same parameters in PD patients. This is in accord with the involvement of a specific mechanism in the recovery observed in PD patients during L-Dopa therapy. Data confirm that the alterations of visual and cognitive potentials observed in PD are closely related to the impairment of dopaminergic transmission. The results of our study [15] on haloperidol administration in non-PD patients showed that this dopamine receptor blocking drug increased the latency of VEPs obtained with 2 and 4 cpd stimuli, while the effect on 0.5 cpd and 1 cpd VEPs was less consistent. This finding supports the hypothesis that dopamine modifies the processing of VEPs by acting at the synaptic level. The specific sensitivity of VEP changes to the spatial frequency of stimulation in PD and haloperidol treated subjects, which is evident in our results, might suggest that the VEP abnormalities found in our study

are dependent on the impairment of dopaminergic neural structures which regulate spatial frequency sensitivity. VEP findings were robustly confirmed in studies performed in animal models of PD [18, 19]. Despite the interest for the finding, only few confirmative studies were provided [15-17], most studies come from few laboratories devoted to this experimental approach. Guidelines for the use of VEPs in clinical practice only rarely suggested a role of VEPs in PD studies and VEPs were finally confined to the assessment of Multiple Sclerosis. Although the increased latency of the VEP in multiple sclerosis has in general been attributed to demyelination in the visual pathways, other mechanisms such as humoral factors, synaptic malfunction or changes in dendritic potentials may play a part. Such mechanisms may also be relevant to central nervous system disorders other than multiple sclerosis which have abnormal VEPs. Although the major clinical manifestations of PD involve the motor systems and the responsible pathology is located in the basal ganglia, there is evidence of more widespread disease, both pathologically, electrophysiologically and clinically. Only two studies explored the possible use of VEPs for the assessment of DLB [20,21] yet no comparison were presented with other forms of dementia. In MSA the visual system is believed to be spared and dopamine deficiency has been hypothesized to be less pronounced than in PD [22], even though the data in the literature are scarce and not unanimous and nothing on retinal dopamine content has been reported. Little information is available on VEPs and PERGs in MSA patients [22]. The main interest for studying responses elicited by patterns with pure chromatic contrast is that they allow recording of specific responses from colour-opponent pathways, anatomically and physiologically distinct from the achromatic ones at the retinal as well as the geniculate and cortical levels. A more recent study [23] showed that PERGs are virtually unaffected in MSA, whereas in early PD they are clearly impaired, suggesting different pathogenic retinal mechanisms and a useful simple tool for distinguishing MSA from PD. The strongest objection against the use of VEPs for the assessment of synucleinopathies derived from the technical constraints of VEP recordings: VEPs are altered by abnormalities of optic nerve and visual pathways, VEPs recordings require the adequate collaboration of patients who must focus attention on stimuli [24-26], VEP variable (amplitude, latency) are dependent on laboratories settings and must be adjusted according to each laboratory statistics of distribution.

The characteristic of VEP cannot be simply shared by different laboratories and differences in equipments might sustain variability which are far wider than variability observed in patient and control populations.

With the introduction of digital and led stimulating screen this condition worsened rather than improving [27].

In the age range of AD, DLB and PDD optic and visual abnormalities (cataracts, maculopathies, retinopathies, ischemic lesions) are frequent and might mislead possible diagnoses. In DLB, fluctuations of cognition (i.e. defective attention and collaboration to the task) are common and might impair the diagnostic yield of VEP recordings. It has been suggested that the discrepancies between different reports on VEP in Parkinson's disease may be due to the greater sensitivity of grating patterns compared to checkerboard patterns and, if so, this might in part account for our normal PD VEP latencies. The grating subtense used is about one third of that for the checkerboard, and the retinal field stimulated is predominantly foveal for the grating whereas for the checkerboard it extends beyond the perimacula. This could explain the observed differences rather than the pattern form, per se. We suggest that VEP recordings might still represent a "niche" research tool, but do not provide sufficient robustness in order to constitute a biomarker.

4. P 300 abnormalities

In an event related potential (ERP) the P300 is a positive deflection peaking at approximately 300 ms after a stimulus. It is supposed to be an endogenous response, mainly depending on the processing of stimulus context, involving registration, evaluation and memory of stimuli, and categorization (decision/closure) and impinging on attention and arousal [28]. P300 can reliably be elicited with relatively simple paradigms, such as the “oddball paradigm”, which requires the detection of a rare (“target”) stimulus within a train of frequent irrelevant “non target” stimuli. Other complex paradigms include the administration of multiple stimuli, dichotic stimuli, multisensory modalities, in order to evaluate responses evoked from anterior brain regions. We recently performed a P300 study on patients with DLB in comparisons with patients with AD matched for dementia severity and age and with age matched control subjects [29] to look for differences of P300 responses in the two dementia subtypes and for possible correlations between P300 recordings and EEG, as abnormal EEG variability was described in DLB [5].

P300 responses were recorded with Ag/AgCl electrodes from 19 derivations corresponding to Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Cz, Fz, Pz positions of the 10-20 International System with supplementary A1 and A2 derivations. Care was taken to avoid recordings if variations of body temperature, recent food ingestion, or previous-night sleep disturbances were present [30]. A classical auditory “oddball” paradigm was used. The stimuli were 500 Hz and 1000 Hz tones, designated as the “non-target” and “target” stimuli, respectively, and delivered by STIM System Headphones. Patients were instructed to count only “target” stimuli, aloud in a preliminary trial and mentally in subsequent trials. The presentation ratio of “non target/target” tones for training was 4/1-8/1 and during recording purposes 5/1. The intensity of the tone was 75 dBnHL, the duration of the stimulus was 150 ms (rise-fall and the plateau times 5 and 140 ms, respectively). The presentation rate was random with a minimum inter-stimulus interval of 1.1 seconds and a maximum interval of 4 seconds. Digital filters was set at 0.15 Hz and 100 Hz, and averaged with a dwell time of 0.5 ms, 2000 Hz sampling rate, 100 ms of pre-stimulus baseline recording. An artifact rejection system was calibrated on four supplementary derivations placed on eyebrows and inferior orbital ridges; the rejection system blocked the acquisition when eye movement exceeded 100 μ V. As the mean reference is known to distort P300 distribution one earlobe was used as online reference, with offline averaging with the other earlobe [31].

In each recording session, the correspondence between the counted and delivered stimuli was checked as described in previous studies [32] and stored on the hard disk. Sets where two or more targets had not been recognized or sets impaired by attention defects or false recognitions were discarded from analysis.

In each patient and control 120 responses to non-target and target stimuli were averaged in a single Final Average (FA). Four Sub-Averages (SA) of only 30 responses to target stimuli were preliminarily obtained in order to assess reliability of P300 among the recording sessions. Finally, inter-subject Grand Averages (GA) were obtained in DLB, AD and control groups. N100, N200, and P200 were detected at the Fz, Cz and Pz electrode for each subject separately. Peak latencies of each component were measured from stimulus onset to the point of maximum voltage in the range of 50-150 ms and 150-250 ms respectively. P300 was identified, in a time window of 300-500 ms, according to the operating definition based on

its scalp distribution (central-parietal amplitude gradient), probability and sequence of preceding components. For every electrode location the following P300 variables were analyzed: amplitude (voltage difference between pre-stimulus baseline and the largest positive-going peak of the ERP waveform within a latency range of 300-500 ms), latency (time from the stimulus onset to the point of maximum positive amplitude within 300-500 ms time window: latencies were considered delayed if the peak latency was at least 2SD longer than the controls mean value. 2SD was chosen because previous studies showed that more restrictive criteria, 3SD from the mean, are insensitive to detect differences between controls and patients populations [33]), inter-electrode (Fz-Cz; Fz-Pz; Cz-Pz) latency and amplitude distribution gradients (difference in latency or amplitude of P300 responses between each pair of leads). The use of 3SD in defining normative limits for P300 was discharged as being at risk of excluding an excessive number of patients from investigative categorization. Studies on P300 scalp distribution and topography showed that peak latency changes across the scalp i.e., it is shorter over anterior cortical regions and longer over parietal areas [34], which allows to identify an earlier anterior, and a late posterior P3 component. Whether anterior and posterior P3 components recorded with a simple oddball paradigm originate from the same generators as those proposed for the P3a and P3b components obtained with the three-stimuli “novel” paradigm is yet unclear, however studies evaluating P3 scalp distribution suggested that early P3 component and late P3 component have separate origins: anterior superior temporal gyrus [35], prefrontal cortex [36], and anterior cingulate or supplementary motor area [37] for the early component vs temporo-parietal junction for the late one [38]. P300 studies in dementia were originally based on recordings from midline scalp derivations (the three leads Fz, Cz, Pz). Recordings in patients with dementia were compared with normative data obtained through P300 measurements in age-matched control populations. In demented patients, comparisons between ranges of different widths evidenced that, for P300 latency, the 2SD criterion had the greatest sensitivity in the detection of dementia [39]. Thus, if recordings in patients exceeded the 95% odds ratio, corresponding to normal $\text{mean} \pm 2\text{SD}$, these recordings were considered abnormal and related to the cognitive disorder. By inference, delayed P300 latencies (by 2SD) or reduced P300 amplitudes were considered features of dementia, and thus useful diagnostic tools [40]. Based on this method, several studies found delays or amplitude decreases of P300 recorded from posterior (Pz) derivations in patients with putative AD [41], subcortical dementia [42], metabolic disorders [43] e PDD [44]. Yet, dementia categorization in the last ten years has been revolutionized by the identification of DLB, representing from 25 to 43% of all dementia cases. Therefore, one can assume that a discrete percentage of patients classified as AD patients in earlier studies, were instead affected by DLB. Because of cognitive ERPs were less investigated in DLB than other types of dementia, we examined the rates and qualitative features of P300 abnormalities in DLB vs AD patients. As EEG abnormalities are prevalent and linked to variability in DLB, the possible identification of correlations with EEG frequencies might support or challenge recent hypotheses suggesting that P300 is, or is not, the result of EEG phase resetting, due to orientation of attention to stimuli [45]. As our P300 recordings were obtained from a multielectrode montage covering the scalp, we could extend our analysis to further measurements, including topographic distribution of P300. Earlier topographical studies on P300 distribution were focused on AD patients, yet the same possible diagnostic flaws underlined above could be reported for topographic studies, and results were in some cases inconclusive with abnormal distributions described in anterior or in posterior derivations

[34], in the, supposedly, same kind of patients. The “classic” evaluation method was however encouraged by methodological guidelines [30] even after that topographic studies had been developed. The numerous clinical P300 studies suggest that this ERP component, elicited by auditory, visual, olfactory or somatosensory stimuli may be clinically useful as an index of such cognitive functions as attention and working memory. This assumption suggests that specific alterations should be found in DLB, where the cognitive disturbance is mainly characterized by fluctuating alterations of arousal and vigilance. Due to frontal dysexecutive dysfunction, DLB patients would be expected to express prevalent alterations of the anterior P3 component with a fronto-central scalp topography, whereas AD patients, with their early hypometabolism in the temporo-parietal junction, would be expected to show prevalent alterations in the parietal P3b response. If we restrict P300 measurements to classic assessment of P300 latencies in posterior (parietal) derivations, our study [32] shows that delayed latency and reduced amplitude, present in both dementia groups, can distinguish DLB from AD group, even though it is not possible to infer the applicability of these measures to an individual patient-to-patient analysis. The use of an active task did not allow us to investigate possible differences between groups in the mismatch negativity response, but we made sure that patients kept constant their attention during recordings, as P300 amplitude is sensitive to the amount of attention resources engaged during the task. In every group, N200 latencies were correlated with P300 latencies, confirming previous studies that showed prolonged N200 and P300 latencies in patients with dementia [46]. Topographical analysis of P300 recordings including all scalp leads did not add information about possible differences between patient groups, confirming that study of P300 topography could be limited to midline electrodes. Topographical differences, as latency distribution gradient, emerged and showed that P300 is different in DLB as compared to AD (figure 1): DLB patients had a more delayed P300 in anterior than in posterior derivations, while in all but two AD patients the latency was increased in posterior leads as compared to anterior leads, same as in controls. The normal latency distribution gradient consisting of increased latency in posterior leads as compared to anterior leads was reversed in DLB. Also the amplitude distribution gradients were reversed and thus different in DLB patients compared to AD or controls. The amplitude of P300 was prominent in frontal leads in DLB and in parietal leads in AD and controls. The finding of reversed amplitude gradient, with higher amplitude in frontal leads and smaller amplitude in posterior leads in DLB patients is apparently counterintuitive, as reduced amplitudes would be expected in a disease characterized by early frontal lobe involvement. Yet, delayed P300 latencies are also prominent in anterior leads of DLB patients and the two findings together seem compatible with the early frontal involvement of DLB. These findings suggest abnormal activity in anterior cortical areas of DLB patients, as compared with AD and controls. The correlation between P300 frontal delay and neuropsychological test scores exploring frontal lobe functions (FAB, NPI) supports this hypothesis. A possible interpretation might suggest that, in the early course of their disease, DLB patients need to increase efforts in frontal areas involved in recognition-attention tasks. P300 amplitude increment with delayed latency is correlated to increments of encoding loads in experimental paradigms [47].

An alternative hypothesis could be that altered topographical P300 distribution in DLB represents a constant interference of the frontal P3a component, which is normally evoked by “novel” stimuli. According to this hypothesis DLB patients might produce frontal P300 component as the target stimuli will be interpreted as novel because DLB patients could not act and decide on these stimuli (i.e. match and encode in the target category). Further

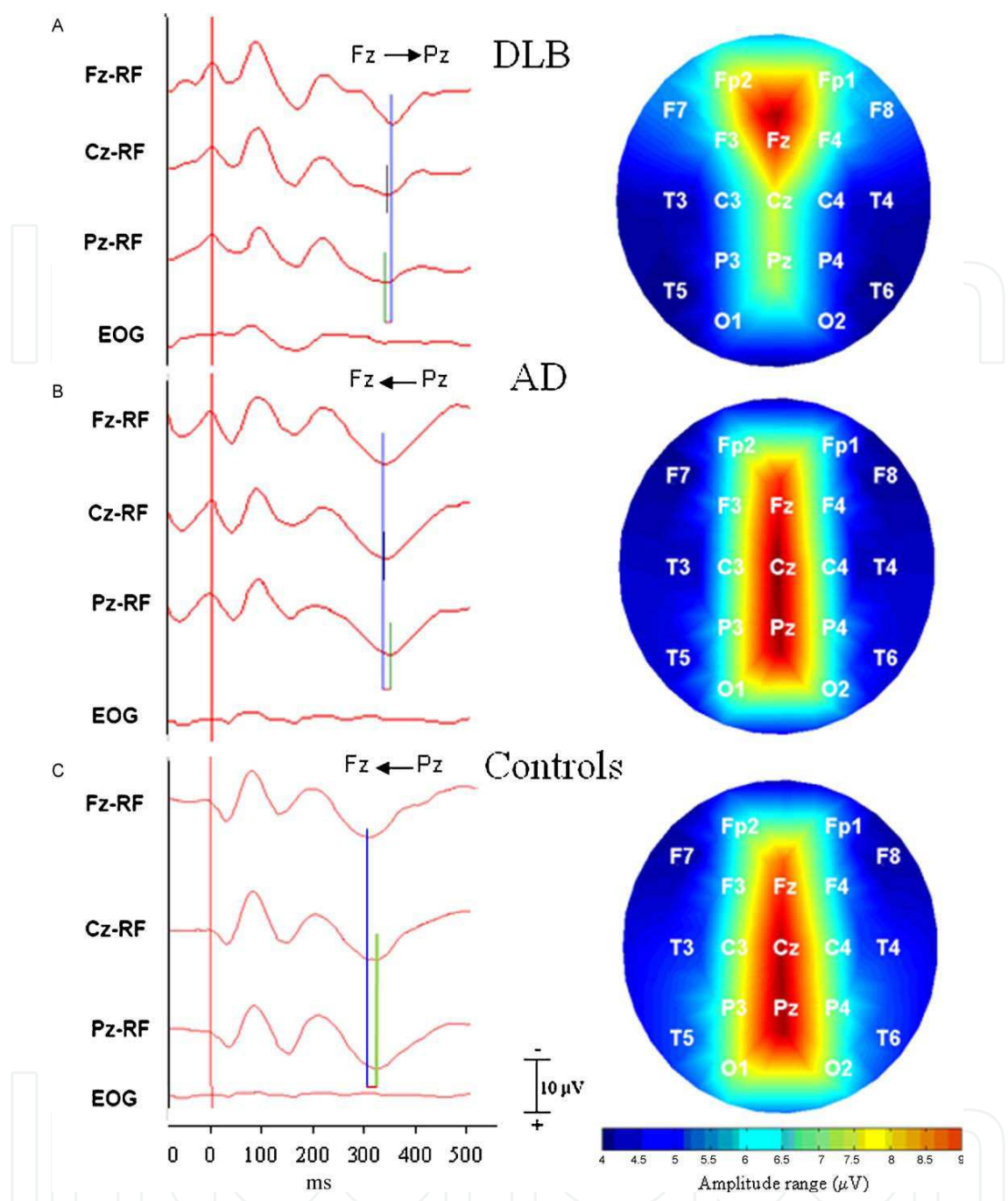


Fig. 1. Grand averages and amplitude maps of P300 response in the three groups of subjects. A. Left. Grand averages of P300 responses in the DLB group. Vertical lines mark peak latency. U-shaped bars mark the difference in latency between Fz and Pz leads, same or shorter latency in Pz. Right. Amplitude map of P300 distribution throughout the scalp (at the maximum amplitude recorded) in DLB group. Notice anterior-to-posterior (reversed) amplitude distribution gradient. B. Left. Grand Averages of P300 responses in AD group. Vertical lines mark peak latency. U-shaped bars mark the difference in latency between Fz and Pz leads, longer in Pz. Right. Amplitude map of P300 distribution throughout the scalp (at the maximum amplitude recorded) in the AD group. Notice a posterior to anterior amplitude distribution gradient. C. Traces and distribution in controls. EOG: electrooculogram; DLB: Dementia with Lewy Bodies; AD: Alzheimer’s Disease.

studies, in which infrequent distractor stimuli, will be inserted into the sequence of target and non target stimuli, should be carried out in order to evaluate the P3a and P3b components in AD and DLB patients. Indeed novel stimuli produce P3a component that is generally largest over the anterior and central recording sites and reflects frontal lobe function. On the other hand temporo-parietal pathway contributes to P300 from the target stimuli (P3b). Anyhow, the clinical utility of P300 recordings in differentiating DLB from AD was evidenced, in the patient populations with reliable P300 response, by sensitivity reaching 70% and specificity of 97%. Due to high specificity, when a reliable P300 is recorded in a patient with early dementia, and its gradients of latency and of amplitude across the scalp are reversed, i.e. anterior-to-posterior instead of the normal posterior to anterior distribution, P300 might have value to address diagnosis of DLB. Conversely, finding that P300 responses, although delayed and with reduced amplitude compared to controls, reach maximum amplitude and longer latencies in posterior leads suggests that the diagnosis of DLB is unlikely. The study of correlations between P300 recordings and neuropsychological test scores showed that increased latency and reduced amplitude were correlated with test scores assessing the presence of frontal lobe dysfunction (FAB), behavior abnormalities (NPI), fluctuating cognition (CAF). Topographical redistribution of P300 latency and amplitude, evidenced as distributions gradients were correlated with the presence of fluctuating cognition (positive CAF scores), typical symptom of DLB patients (figure 2). These correlations evidenced that the differences between groups are related to dementia and not to neuropsychiatric differences. A correlation between the performance of frontal lobe function in standardized neuropsychological tests and maximal P300 scalp distributions were also found in a previous study on a group of old adults [48]. Specifically, subjects who showed frontal-maximal P3 had lower performance than those elderly subjects who showed posterior-maximal scalp topographies. P300 measurements were also correlated with EEG descriptors (figure 2): latency and amplitude anterior to posterior distribution gradients were correlated with the DFP pre-alpha and with abnormal CSA patterns (CSA Patterns 2 to 4, see next on the test), typical of DLB, confirming the specificity of topographical redistribution of P300 in DLB patients.

5. Blink reflex abnormalities

Patients with PD exhibit a reduced frequency of blinking leading to a staring appearance [49]. Reduced blink rate can cause an abnormal tear film, dry eyes and reduced vision. A characteristic ocular sign may be the blink reflex, elicited by a light tap on the glabella above the bridge of the nose: successive taps in normal individuals produce less and less response as the reflex habituates but in PD subjects the blink reflex does not disappear on repeated tapping. Habituation may improve after treatment with L-dopa or amantadine. Blink duration and excitability appear to be increased in PD and as in VEP latency may reflect loss of dopamine neurons [50]. The electric Blink Reflex (BR) is a neurophysiological technique exploring pontine structures through a reflex arc connecting nuclei of the 5th to the nuclei of the 7th cranial nerve. The Blink reflex consists of three separate responses: R1, R2, R3. The first one is generated in the trigemino-facial reflex arc, the second and third one are generated in polysynaptic pathways involving the brainstem reticular formation [51]. Clinically, the BR is used to evaluate brainstem lesions and it has been applied in clinical and neurophysiological studies of brainstem lesions and neurodegenerative disorders [52-54].

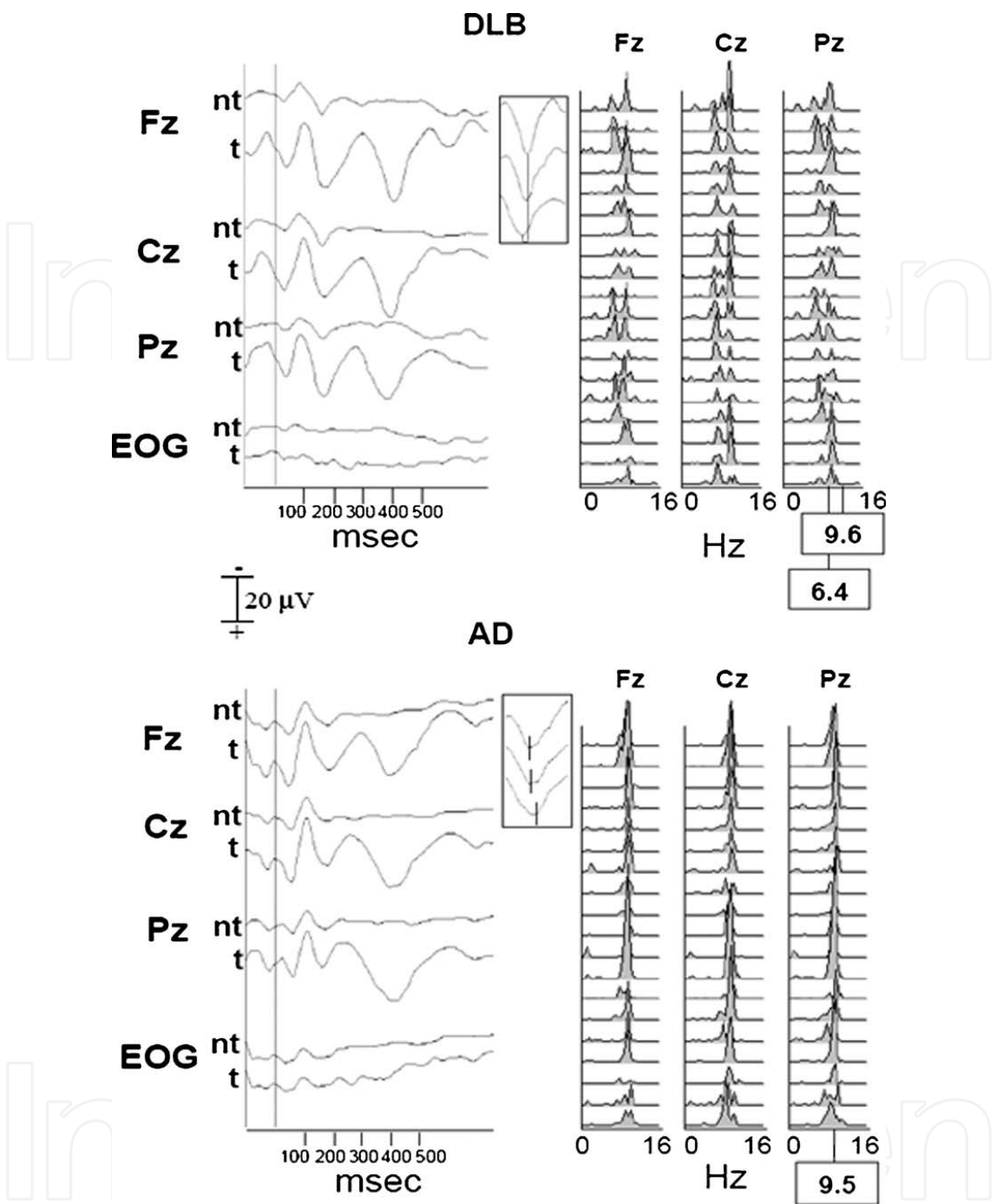


Fig. 2. Examples of P300 and CSA traces in one DLB and one AD patient. Top. Example of recordings in a DLB patient. Left. P300 recording. P300 response appears delayed (420 ms) with no latency inter-electrode distribution gradient and has a higher amplitude in frontal derivations (26.7 uV) compared to posterior derivations (21.0 uV) (inset, U-shaped bars mark the anterior-to-posterior (reversed) latency distribution gradient in the responses to target stimuli). Fz: frontal derivation, Cz: central derivation, Pz: posterior derivation, EOG: ocular derivation. Nt: non-target stimuli, t: target stimuli. Right. Quantitative EEG of the same patient represented as Compressed Spectral Array (CSA), i.e. arrays of traces are the representation of EEG power distribution in consecutive 2-second epochs. Peaks of power (amplitude) are found in variable frequencies shifting from alpha (9.6 Hz) to pre-alpha (6.4

Hz), corresponding to EEG CSA pattern 2 observed only in DLB patients [5]. Bottom. Example of neurophysiological recordings in an AD patient. Left. P300 recording. P300 response is delayed (410 ms) with posterior to anterior latency distribution gradient. Amplitude is higher in posterior derivations (14.9 uV) compared to anterior derivations (14.5 uV) (inset, I-shaped lines mark peak latencies in the responses to target stimuli). Fz-RF: frontal derivation, Cz-RF: central derivation, Pz-RF: posterior derivation, EOG: ocular derivation. Right. CSA of the same patient, with stable alpha dominant frequency at 9.5 Hz. EOG: electrooculogram; nt: non target stimuli, t: target stimuli; DLB: dementia with Lewy bodies; AD: Alzheimer's disease.

We performed a study of the blink reflex in patients with PD, DLB, MSA, AD and Progressive Supranuclear Palsy (PSP).

The subjects were comfortably sitting on an armchair in a quiet room, with eyes gently closed. The recordings took place in a temperature-controlled room (at about 25°C) in half-light. The cathode was placed over the supraorbital foramen and the anode 2cm rostrally. Surface electrodes were placed on the inferior part of the orbicularis oculi muscles on each side, recording ipsilateral R1, and ipsilateral and contralateral R2 and R3. Ground electrode was placed under the chin. Stimuli of 0,1ms of duration with intensity of 5-10 mA elicited stable R1 in repeated trials. Because surface electrodes lay only few centimetres away from the cathode, R1 tended to overlap the stimulus artifact, which could last more than 10ms. A special amplifier with a short blocking time (0.1ms) and low internal noise (0.5 uV at a bandwidth of 2kHz) minimized the problem of stimulus artifact. Signals were amplified and filtered (bandwidth 20-2000Hz), to avoid habituation the interstimuli intervals must be of at least 7 sec, 5-10 responses per site were elicited and stored. BR recording were previously described in MSA, PSP and PD patients: all reports showed R2 latencies inside the 2 SD of the mean and only evidenced enhancement or inhibition of R1-R2 in excitability-duration curve paradigms [52,53,55] in untreated PD. Recently we studied the BR in parkinsonism [56]: in all PD, MSA, PSP and AD patients we found normal R1 and R2 latencies inside the 2SD of the control mean independently of the presence of RBD. Only in DLB patients we found R2 latencies clustering in the upper limits of normality or definitely above the limits (figure 3). All findings were statistically significant. Thus, BR recordings might reveal brainstem dysfunction in DLB, but not in other parkinsonisms where different yet definite brainstem abnormalities are also described. According to the pathophysiological hypothesis [6] our data suggested that in DLB the brainstem is the site of initial lesions, consisting of α -synuclein deposits. Synucleinopathy is ascending from the brainstem, progressively involving the lower brainstem and inducing the appearance of REM Sleep Behaviour Disorder (RBD), then the mesencephalus, inducing the occurrence of parkinsonism and finally involving limbic structures, inducing hallucinations and psychosis, and cortical areas, inducing cognitive disorders. R2 latency delay might be attributed to the ascending synucleinopathy inducing the appearance of RBD, but our findings suggest that this possible correlation is controversial, as normal R2 latencies were observed in PD and MSA patients presenting with RBD, while delayed R2 latencies were recorded in 5 DLB patients who did not present with RBD. Our findings suggest instead that R2 latency delay in DLB is independent of the presence of RBD. The correlation with scores assessing cognitive fluctuations suggests that R2 abnormalities might evidence dysfunction of reticular brain stem pathways involved in vigilance regulation.

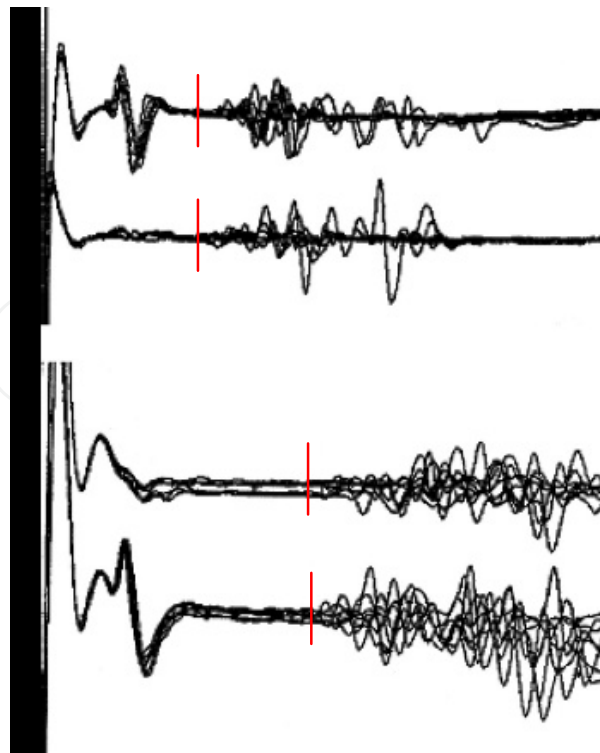


Fig. 3. Example of a blink response in a control subject (top: about 30msec) and in a patient with DLB (bottom: about 45msec). Note the delayed R2 response in the DLB patient in both the ipsilateral and contralateral recordings.

Current interpretations of BR neurophysiology [51,57] suggest that R2 abnormality should be ascribed to disruption of the afferent pathway when it is evident in ipsilateral and contralateral responses to stimuli of one side and efferent when the abnormality is observed in ipsilateral or contralateral responses of only one side, independently of the site of stimulation. Only in 3 of the DLB patients presenting with R2 delays, discrepant latencies on the two sides of stimulation were found [8], yet ipsilateral and contralateral responses were always overlapping, thus it is likely that the afferent pathway is prominently involved in DLB. In a successive study we tested the supposition that BR alterations present in DLB patients are sensitive to cholinergic modulation. It is known indeed, that choline acetyltransferase enzyme levels are lower in DLB compared with AD [58] whereas high muscarinic receptor density has been found in DLB [59]. Alterations of this cortical network are the pathophysiological correlate of cognitive impairment and attention deficit in DLB and are accompanied by abnormal electrocortical arousal [8,60] with alteration of electroencephalogram, event-related potential and choice reaction time. Administration of donepezil has been shown to significantly improve cognitive scores as well as electroencephalogram and event-related potential alterations in patients with fluctuating cognition [12] as a result of improvement of attentional participation in tested activities [60-63]. So we assessed whether BR alterations present in DLB patients are sensitive to cholinergic modulation [64]. We evaluated 26 patients affected by DLB and 20 patients affected by AD: for each patient, we performed BR recordings before and after 1 and 2 weeks of treatment with donepezil. The correlation between R2 abnormalities and score assessing cognitive fluctuations suggest that R2 latency delay might evidence dysfunctions

of brain stem reticular pathways involved in vigilance regulation. The administration of donepezil significantly improved BR response in DLB patients, with a mean reduction of 8.2%. R2 mean latency reduction was highly correlated with R2 mean latency delay at baseline, with a 46% of patients showing no difference between R2 mean latency at baseline and after treatment. Thus, the reduction of R2 latency was evident only in patients who had delayed R2 at baseline. A possible explanation is a “bottom effect” of R2 mean latency reduction, meaning that the correction of brain stem dysfunction by ChEI treatment is mostly evident when the alteration of subcortical cholinergic networks is so conspicuous to be evidenced by a BR response alteration. Another possible explanation is that 2 subpopulation of DLB patients can be recognized: responders and not responders to ChEI treatment. No correlation between R2 latency reduction and MMSE scores was found, as expected because of the short test-retest interval and learning effect [65]. However, at baseline, a high correlation between R2 abnormalities and CAF and ODFA scores was found, suggesting that responders are those patients with the worst grade of cognitive fluctuations. In our study, CAF scores were not significantly modified by the 2-week treatment, again as expected, because CAF scores track behaviors, reported by caregivers, of the last month. However, ODFA scores were significantly different after treatment compared with baseline. Our study suggests therefore that ChEI effect is mediated by correction of dysfunction of the brain stem reticular pathways involved in vigilance regulation. A previous study [66] had shown the correlation between improvement of attentional activities and improvement of neuropsychological scores after ChEI therapy and the finding was confirmed by following reports [60,62,67]. The lack of BR response alterations and subsequent absence of R2 latency modification by ChEI in AD patients suggest that due to the lower cholinergic functioning in DLB, a greater potential improvement from these drugs than that seen in AD might be expected, at least in the early phases of DLB pathophysiology, when a prevalent brain stem involvement is called into cause [6]. Furthermore, the presence of fewer neurofibrillary tangles and neuritic plaques and of less neuronal loss in DLB than AD [68,69] suggests that neurons in DLB are more viable than those in AD and could be more responsive to cholinergic stimulation [70-72]. These data suggest that the presence of alterations of neurophysiological responses tracking brain stem reticular formation might also predict the response to ChEI in DLB, as concluded in previous studies [67,73] about the efficacy of ChEI on cognitive impairments and psychiatric symptoms, and foster further studies on the long-term effect of ChEI and identification of responders.

6. Quantitative eeg:q EEG

Quantitative Electroencephalography (QEEG) is the measurement, using digital technology, of electrical patterns at the surface of the scalp which primarily reflect cortical activity or “brainwaves”. A multi-electrode recording of brain wave activity is recorded and converted into numbers by a computer. These numbers are then statistically analysed and are converted into a colour map of brain functioning. Digital EEG techniques have grown rapidly in both technology and popularity since the early 1980's for recording, reviewing and storing EEG data. Compared to other systems, QEEG is a non-invasive procedure and offers a superior temporal (time) resolution compared with fMRI, SPECT and PET imaging

techniques. MEG systems, though providing a high temporal and spatial resolution, are a relatively expensive means of monitoring the brain as compared with QEEG. Recently we had designed a QEEG study in a cohort of patients affected by early AD and DLB, whose diagnoses were confirmed by laboratory methods and by a 2-year follow-up, which allowed confirming or discarding earlier diagnoses, and thus reaching the best possible level of certainty on the classification of these two disorders [5]. As specific EEG abnormalities reflecting the presence of cognitive fluctuations (superimposition of pre-alpha/theta activity on alpha dominant frequency, or of theta/delta activity on dominant pre-alpha frequency) were evidenced in early DLB [5,74-76] while alpha dominant activity was more stable in early AD [1], we evaluated possible correlations between P300 and EEG characteristics in AD and DLB. Several electroencephalographic studies on dementia were performed in the years preceding the identification of DLB as a widespread cognitive disorder. Slowing of the rhythms and reduced coherence among brain regions, increased theta and delta activity, in parallel with reduction of alpha and beta rhythms were observed in patients affected by putative AD [76]: computerized EEG spectral analysis showed an increase in delta and theta power in AD patients compared to controls mainly in the left temporal area. EEGs were recorded with Ag/AgCl disk scalp electrodes placed on 19 derivations corresponding to Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Cz, Fz, Pz positions of the 10-20 International System with supplementary A1, A2 derivations. Derivations were grouped in order to define 5 scalp regions: anterior (Fz, Fp2, F7, Fp1, F3, F4, F8), central (T3, C3, Cz, C4, T4), posterior (T5, P3, Pz, P4, T6, O1, O2) and peripheral (Fp1, Fp2, F8, T4, T6, O1, O2, T5, T3, Fz) or internal (F3, F4, Fz, C3, Cz, C4, P3, Pz, P4). Reference was the mean (mean reference) of recordings from all scalp leads, A1, A2 signals were also stored for digitalized derivation reconstruction. Ground was placed at FpZ. Impedance was below 5 KOhm. The patients were seated in a quiet room on a comfortable armchair, awake with closed eyes under continuous control (Video EEG); wakefulness of the patients was verified every 2 min by asking to open eyes and checking block reactions; 2 supplementary derivations monitored electro-oculography (vertical and horizontal), two derivations monitored possible interference of tremor and two pairs of additional bipolar recording channels for the respiration and electrocardiogram were applied. EEG was acquired as a continuous signal for 30 min and visually inspected for current clinical interpretation or detection of artifacts and stored in order to be epoched in off-analysis setting as series of 2 seconds-long epochs. EEGs interpreted with classical visual inspection, corresponding to categories reported in previous literature [77,78] were defined as Classic Interpretation Methods (CIM) in results. The computer collected 10 minutes 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 artifact-free 2 seconds-long epochs appearing consecutively for 20-40 sec were selected off-line by visual inspection after pre-programmed automatic blink reduction and muscle and tremor artifact rejection system and were compared with the remaining artifact-free epochs in order to avoid possible discrepancies among acquired sets. A total of 90 epochs per patient were processed by an automatic transforming program present in the NEUROSCAN SynAmps System performing a fast Fourier Transform 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 (mPS) for each epoch and for each channel and expressed in square uV (μV^2). The

mPS was divided automatically into 4 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 to facilitate identification of differences, in the description of results, as statistical differences were evidenced when theta band was halved in two parts (4-5.5 Hz, theta and 5.6-7.9 Hz pre-alpha). Fast Fourier transform-QEEG program 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 (mRPS: percentage of the global mPS of each frequency band) were computed and log transformed [79] 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 sec total analysis (Total Power) and analyzed as Mean Frequency (MF), indicating the average frequency for the 90 epochs, and as mean frequency variability (MFV), representing changes of mean frequency during the 90 epochs. Single channel power spectra were also represented as Compressed Spectral Arrays (CSA) showing the sequences of absolute or relative power spectra in each one of the 90 analysed epochs. mRPS from all the scalp derivations were averaged in order to obtain a single Global Mean RPS representative of the frequency band powers in each patient expressing the average distribution of powers recorded from all the derivations. Eventually, in each epoch, mean band power in each of the three groups of patients (AD, DLB, PDD) as well as in the control group was then computed by averaging the values of subjects in each group.

Our EEG study [5] completed and detailed results of a preliminary study performed with Magneto-Encephalography (MEG) recordings [80] suggesting that activities in parietal and occipital areas differentiate early DLB from early AD. MEG technique excluded a reference effect, showed differences in reactivity of alpha rhythms between groups of patients, and explored coherence: therefore the present study was focused on waking-closed eyes condition and on methods evidencing differences. The different EEG variables analysed in our study showed some distinct and specific patterns in patients affected by DLB or PDD with cognitive fluctuations (PDDF). When EEGs were interpreted with the classic visual inspection methods, absent alpha in posterior derivations was observed in 63.9% of DLB and in none of AD patients. In PDD absent alpha was observed in 25.7% of patients (all from PDDF group). Intermittent delta and sharp transients, described in previous studies [2,4,9], occurred more frequently in DLB patients compared to AD (13.9% vs 2.5% and 5.6% vs 2.5%) yet these findings were rare, and therefore scarcely useful for diagnostic purposes. Visual inspection was not sufficient to evidence other differences which were observed with QEEG methods: the first relevant finding was the identification of slow activities in posterior derivations, with a frequency of 5.6-7.9 Hz, which were observed in all DLB patients and significantly separated DLB patients from AD. This activity was defined pre-alpha because it was suppressed by eye opening. Two studies [81,82] quantified EEG characteristics during polysomnography (PSG) in patients with RBD and DLB/PDD and indicated differences with controls in the same EEG frequency band. QEEG was analyzed with different methods. Total power and mRPS showed that pre-alpha activity on posterior derivations expressed the highest statistical difference between AD or PDD without cognitive fluctuations (PDDNF) and DLB or PDDF patients ($p < 0.01$). The study of MFV

showed that variability of EEG activity was the second most relevant finding leading to the identification of specific EEG patterns in DLB or PDDF ($p < 0.001$) as reported in a previous study [83]. The variability of the EEG frequencies in relaxed waking conditions was best evidenced by using the CSA method of representation, 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, differentiating DLB or PDDF patients from AD or PDDNF patients. CSA representation had only been previously used to assess coma or anaesthesia levels [83], and in the present study it allowed to evidence changes of EEG activities in single derivations. It allowed therefore to evaluate local variability, at contrary with total QEEG analyses and MF evaluations, and to evidence that significant differences among groups of patients were prevalent in posterior leads. CSA showed that changes of dominant activity could be separated in five patterns, salient at visual inspection of the sequence of traces: one, with dominant stable alpha, was only observed in early AD and in 54.3% of PDD (PDDNF), while the other patterns, differently grading the dominant frequency variability and pre-alpha presence, were only observed in posterior derivations of early DLB and PDDF. 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, or of unstable activities, all encompassing the presence of the 5.6-7.9 Hz activity and significant variations of the dominant frequency across time. When these EEG abnormalities are observed in a patient with initial signs of cognitive decline, i.e. MMSE < 24, they support a diagnosis of DLB. Therefore our study clarifies and quantifies the suggestion that EEG might support the diagnosis [2]. When EEGs were recorded two years later [5], further alterations were observed which differentiated groups of patients, even though the administration of current therapies 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 across 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 DFV was below 3 Hz and alpha activity was present. At follow-up patterns 2-4 were observed prominently in posterior derivations of DLB and PDDF patients, while only 27.5% of AD patients presented with similar EEG abnormalities. Pattern 5 was observed at follow-up in patients with severe cognitive deteriorations (5 DLB, 2 AD, 3 PDD), suggesting therefore that this degraded pattern is aspecific. In our experience we recorded pattern 5 activity also in cases of severe Progressive Supranuclear Palsy and Fronto-temporal dementia. In conclusion we would add two further considerations. First, PDD in its early course can be apparently separated in two different groups: one with fluctuating cognition elements and EEG pattern abnormalities akin to the ones observed in early DLB and a group with normal EEG akin to the AD patients and without fluctuating cognition. With follow-up, however, the majority of PDD patients (74.3%) presents with the same EEG abnormalities characterizing DLB. The presence of two different clusters in early PDD suggests that the distribution of neuropathological abnormalities might have different patterns in different patients, cumulating however across time to show, at follow-up, clinical and EEG patterns similar to the ones observed in DLB. Second, in AD we found less EEG abnormalities than previously reported [76]. We suggest that this finding depends on patients selection methods used in our study. In this study the selection was focused on elements of fluctuating cognition (CAF-ODFA scales) and presence of RBD, prominently

characterizing DLB [2]: the occurrence of positive CAF scores and of RBD during follow-up supported the categorization of patients. Patients diagnosed as affected by AD, who did not show evidence of fluctuating cognition or RBD, had rare EEG abnormalities. Yet, recent reports [84] showed that power spectra abnormalities in AD patients are characterized only by an increase in theta and a decrease in alpha and beta rhythms at rest and mostly limited to the temporal, and centro-parietal regions, or showed that entropy of EEG, expressing the irregularity and variability of EEG patterns, is reduced, rather than increased, in AD.

In conclusion, the definite presence of EEG abnormalities early in the course of DLB, with a core feature evidencing marked variability of dominant frequencies in posterior derivations, occurring every few seconds, or with the substitution of alpha with frequencies at 5.6-7.9 Hz, suggests that centers regulating EEG rhythms in parieto-occipital areas are affected in the early course of this disease.

7. Other investigations and future prospectives

Syncope associated to orthostatic hypotension, urinary incontinence and constipation is common symptoms in demented patients, mainly in DLB and in PDD. AD and FTD show less frequently autonomic dysfunction. There are non invasive tests including standard cardiovascular tests, ^{123}I -MIBG cardiac scintigraphy, urodynamic tests, gastrointestinal motility studies, sweating reflexes and pupillary responses that assess autonomic dysfunction in these patients.

^{123}I -MIBG is an analogue of the sympathomimetic amine guanethidine, which is used to determine the location, integrity, and function of postganglionic noradrenergic neurons [85]. Patients with PD can exhibit reduced cardiac ^{123}I -MIBG-derived radioactivity without other evidence of autonomic failure, whereas those with DLB can have reduced cardiac ^{123}I -MIBG-derived radioactivity without evidence of parkinsonism [86]. ^{123}I -MIBG may have the potential to differentiate PD from other causes of parkinsonism. For example, MSA and PSP pose a difficult diagnostic challenge.

In PD and DLB, LB are encountered in extracranial tissues, notably in autonomic ganglia [87]. Cardiac sympathetic degeneration can be demonstrated early in the disease process before motor symptoms. In 2005, the DLB Consortium concluded that diminished uptake of ^{123}I -MIBG on cardiac scintigraphy was a “supportive” clinical feature that required more study [2].

Positron emission tomography (PET) utilizes biologically active molecules in micromolar or nanomolar concentrations that have been labelled with short-lived positron-emitting isotopes. The physical characteristics of the isotopes and the molecular specificity of labeled molecules, combined with the high detection efficacy of modern PET scanners, provide a sensitivity for human in vivo measurement of indicator concentrations that is several orders of magnitude higher than with the other imaging techniques. Whereas the very short half-lives of O^{15} (2 min) and C^{11} (20 min) limit their use to fully equipped PET centres with a cyclotron and radiopharmaceutical laboratory, F^{18} labelled tracers (half-life 110 min) can be produced in specialized centres and distributed regionally to hospitals running a PET scanner only. Clinical use of PET is now well established in clinical oncology and it is therefore becoming widely available in major hospitals. In addition to its use in research, brain PET also provides diagnostically relevant information mainly in neurodegenerative disorders, focal epilepsy and brain tumors. In dementia, the measurement of cerebral

glucose metabolism by 18F-2-fluoro-2-deoxy-Dglucose (FDG) and specific molecular imaging techniques involving tracers for amyloid and major neurotransmitters are of diagnostic interest. Brain PET using FDG is a firmly established technique for demonstration of regional functional impairment in neurodegenerative disease. AD is associated with typical regional impairment of posterior cortical association areas that allow very early diagnosis before clinical manifestation of dementia and monitoring of progression and treatment effects. DLB additionally involves metabolic impairment of the primary visual cortex. Predominant impairment of the frontal and anterior temporal regions is seen in FTD, primary progressive aphasia and semantic dementia. New perspectives are opened by tracers for imaging amyloids, which appear to be very sensitive for detecting even preclinical AD cases, although confirmation of the specificity remains to be demonstrated. Tracers for measuring local AChE activity and the binding capacity of nicotinic and serotonergic receptors address neurotransmitter deficits in dementia. Impairment of dopamine synthesis that is characteristic for DLB can be demonstrated by 18F-fluorodopa PET. Pittsburgh compound-B (PIB)-PET imaging is a sensitive and specific marker for underlying β amyloid deposition and represents an important investigative tool for examining the relationship between amyloid burden, clinical symptoms and structural and functional changes in dementia. Amyloid imaging may also be useful for selecting patients for anti-amyloid therapies. However, studies have identified PIB-positive cases in otherwise healthy older individuals (10–30%), limiting diagnostic specificity. Development of biomarkers for investigating other aspects of dementia pathology, i.e. soluble β amyloid, tau protein, synuclein deposition and brain inflammation would further inform our understanding and assist in studying disease-modifying and preventive treatments in dementia. Both DLB and PDD are characterized at autopsy by the presence of subcortical and/or cortical Lewy bodies. It has been well established that often there is also a substantial burden of amyloid pathology, though, compared to AD, plaques are more often diffuse than dystrophic neurites [88]. A limited number of PET studies have examined the amyloid burden in DLB and PDD in vivo [89] and showed that in DLB mean brain PIB uptake was significantly higher than in controls, while uptake in PDD was comparable to controls and PD without dementia. In particular, 85% of DLB patients had significantly increased amyloid load in one or more cortical regions, whereas 83% of PDD patients had 'normal' PIB uptake. None of the PD patients showed any evidence of increased cortical amyloid deposition. A report by Gomperts and colleagues [90] revealed that cortical amyloid burden as measured by PIB was higher in DLB than in PDD, but similar to AD. The findings suggest that global cortical amyloid burden is high in DLB but low and infrequent in PDD. An increased amyloid burden could contribute to the rapid progression of dementia in DLB [89] while it may also play a role in the timing of dementia relative to the motor symptoms of Parkinsonism in DLB and PDD [88,90]. Either PET or SPECT can be employed to provide functional imaging of the nigrostriatal dopaminergic system in vivo. SPECT has the advantage of being more readily available and somewhat easier to organize and undertake, and the majority of the reported studies of imaging of the dopaminergic system in DLB have been SPECT studies, even though PET has produced equivalent results [91]. The first ligand used in SPECT was [123I]-2b-carbomethoxy-3b-(4-iodophenyl) tropane (b-CIT). Subsequently, [123I] N-x-fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane (FP-CIT) became available. FP-CIT was preferable because the time interval

between injection and scanning was just 3 hours, making the procedure possible on a single outpatient visit. Both ligands are cocaine analogues, which bind the dopamine reuptake and transporter molecule found in the presynaptic cell membrane of dopamine producing nigrostriatal nerve terminals in the striatum (caudate and putamen). Reduced binding reflects dysfunction or loss of nerve terminals, usually associated with loss of the neuronal cell bodies in the substantia nigra. Clearly, the test is not specific with regard to the nature of the pathology in the substantia nigra, but Lewy body pathology is the commonest cause of major bilateral loss of substantia nigra neurones, with loss of about 50% of neurones being necessary before parkinsonism becomes clinically detectable [92]. These studies show consistently and convincingly that in subjects with a clinical diagnosis of probable DLB, there is reduced binding of ligand in the putamen and caudate, and that in AD, the ligand binding is not significantly different from controls, suggesting strongly that FP-CIT SPECT would be effective in distinguishing DLB cases from AD cases when the distinction cannot be confidently made on clinical grounds. FP-CIT scans were abnormal in DLB cases without parkinsonism, as well as in cases with parkinsonism [93].

The weakness of all the studies is that the diagnoses of DLB and AD were clinical, and therefore subject to error. An autopsy diagnosis has to be the gold standard, notwithstanding the uncertainties involved in the neuropathological diagnosis of both AD and DLB and the difficult issue of the coexistence of neuropathological features in both disorders. In applying the consensus clinical diagnostic criteria for probable DLB proposed by the consortium on DLB at their first international workshop, the greatest accuracy when compared with subsequent autopsy diagnosis was achieved by the Newcastle upon Tyne group (83% sensitivity, 95% specificity). The estimated sensitivity and specificity of FP-CIT SPECT scan abnormality for a diagnosis of DLB versus AD will obviously be affected by the extent to which patients are wrongly categorized clinically. Ideally every patient with dementia deserves a diagnosis as accurate as possible. Accordingly, in any patient whose dementia diagnosis is uncertain and who could possibly have DLB a dopamine transporter SPECT scan should be considered. Most such patients will fulfill clinical diagnostic criteria for "possible DLB" (dementia plus one core feature; or dementia plus one or more "suggestive" features, obviously excluding abnormal dopamine transporter scan which is currently one of the suggestive features). The effectiveness of FP-CIT in contributing to the diagnosis of DLB has recently been convincingly shown [94]. Most patients with clinically typical DLB do not need a FP-CIT scan. However, there are patients who fulfill diagnostic criteria for probable DLB, but are also affected by complicating medical issues such as cerebrovascular disease or are on medication with extrapyramidal adverse effects, and in such situations, a dopamine transporter scan can clarify the diagnosis. Finally, there are patients who have mild cognitive impairment (not dementia) and in addition have features raising the possibility of DLB (such as visual hallucinations, fluctuating cognition, and neuroleptic sensitivity). In these cases, recurrent delirium may be a concern, leading to repeated investigations. An abnormal FP-CIT scan can be diagnostically helpful and possibly cost worthy.

Although there is a large and increasing body of knowledge on the genetic, molecular and cellular mechanisms of neurodegenerative disorders, the exact cause is unknown, except for a few rare genetic variants. Neurophysiological understanding could guide early differential diagnosis, and may suggest new ways to monitor treatment response. Since a few years the availability of whole-head MEG systems has expanded the scope of such studies. MEG can

record brain activity directly, and has several advantages compared to conventional EEG recordings. In contrast to EEG, MEG is hardly affected by the skull, and does not require a reference electrode. Therefore, MEG may provide a more accurate image of ongoing brain activity. In addition, significant advances have been made in neuroscience concerning the understanding of oscillatory and synchronized brain activities. In particular it is now assumed that synchronization of neural activity between different brain regions may reflect functional interactions between these regions [95]. Such synchronization processes can be measured at the level of the scalp with EEG and even better with MEG. Interesting patterns of abnormal oscillatory activity and interregional synchronization have now been described in various brain disorders, including PD and AD [96].

One of the first MEG studies in PD was aimed at auditory evoked magnetic fields [97]; they suggest that this might reflect the combined effect of basal ganglia disease and auditory cortex degeneration. MEG studies were stimulated by the observation that PD may be associated with an increase in EEG coherence in the beta band, possibly due to the failure of a normal basal ganglia/thalamic drive to the cortex [98]. These changes were reversible after either dopaminergic treatment or deep brain stimulation. Functional connectivity was studied in the same large cohort of non-demented PD patients mentioned above using the synchronization likelihood [99]. In untreated, early phase PD patients a diffuse increase in functional connectivity in the lower alpha band was found. This abnormally high connectivity extended to other frequency bands, in particular the theta, upper alpha and beta bands, with progression of the disease. Disease severity was associated with abnormal connectivity in theta and beta bands. Cognitive perseveration was correlated with inter-hemispheric alpha band synchronization. In contrast to spectral changes, functional connectivity in PD does respond to treatment with L-dopa. Again, changes in demented PD patients are qualitatively different from those in non-demented PD patients. Demented PD patients showed a loss of functional connectivity, especially between the frontal and temporal areas within each hemisphere, and between the temporal areas of both hemispheres, in the alpha band [100]. Connectivity changes in dementia thus are on the decrease rather than on the increase trend, and a distribution that is more fronto-temporal compared to the central dominance of connectivity changes in non-demented PD. The overall pattern of connectivity changes in demented PD shows a similarity patterns found in studies on AD [101]. Although the number of MEG studies in PD is still very small, a consistent pattern of changes in local band power and interregional synchronization is becoming clear. Slowing of background activity (increased theta; decreased beta) and increased alpha band connectivity occur early in non-demented, drug naïve PD patients; with disease progression the spectral changes keep constant, whereas increased connectivity extends to other bands. Dopamine affects connectivity, but does not influence power. With the advent of dementia, slowing occurs in different frequency bands (increased delta power; loss of alpha power), and lower rather than higher connectivity is seen mainly in the alpha band. Changes in demented PD may be reversible after cholinergic rather than dopaminergic treatment. This characteristic pattern of progressive neurophysiological changes in non-demented and demented PD patients could reflect the progressive involvement of different neurotransmitter systems, as well as subcortical and cortical Lewy body pathology, during the course of the disease [102].

The advent of whole-head MEG systems, and the improvements in the understanding of oscillatory and synchronized brain activity, have opened up the way to study disturbances

in large-scale brain networks in neurodegenerative disorders such as PD and AD. Many MEG studies, most of which were conducted in the last five years, have confirmed and extended findings from previous EEG work. It is becoming clear that PD and AD show characteristic patterns of abnormal brain function, both locally as manifested by changes in spectral power, as well as at the scale of functional networks, manifested by changes in interregional synchronization. These changes may reflect abnormalities in specific networks and neurotransmitter systems, and could become useful in differential diagnosis and treatment monitoring. While MEG may be superior to EEG especially for functional connectivity studies, its high cost and the impossibility to combine it directly with structural MRI remain important obstacles. In this respect the development of ultra low field MRI (ULF MRI) could be a very interesting new approach [103]. If this technology can be further developed high quality integrated structural and functional studies of brain networks may become feasible. However, improvements on the acquisition side alone may not be sufficient for a better understanding of normal and disturbed brain networks. There is a urgent need for a proper theoretical framework for the analysis and interpretation of the data obtained with advanced functional imaging techniques. One attempt to deal with this problem is the application of graph theory to functional neuroimaging data [104]. This approach provides a theoretical framework for describing the structure and function of complex networks. Further studies along these lines, could help to advance our knowledge of disrupted brain networks in neurodegenerative disease.

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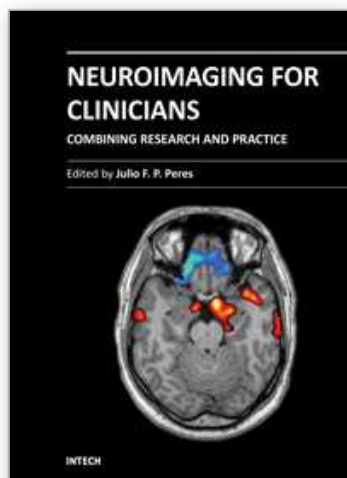
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Neuroimaging for clinicians sourced 19 chapters from some of the world's top brain-imaging researchers and clinicians to provide a timely review of the state of the art in neuroimaging, covering radiology, neurology, psychiatry, psychology, and geriatrics. Contributors from China, Brazil, France, Germany, Italy, Japan, Macedonia, Poland, Spain, South Africa, and the United States of America have collaborated enthusiastically and efficiently to create this reader-friendly but comprehensive work covering the diagnosis, pathophysiology, and effective treatment of several common health conditions, with many explanatory figures, tables and boxes to enhance legibility and make the book clinically useful. Countless hours have gone into writing these chapters, and our profound appreciation is in order for their consistent advice on the use of neuroimaging in diagnostic work-ups for conditions such as acute stroke, cell biology, ciliopathies, cognitive integration, dementia and other amnesic disorders, Post-Traumatic Stress Disorder, and many more

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