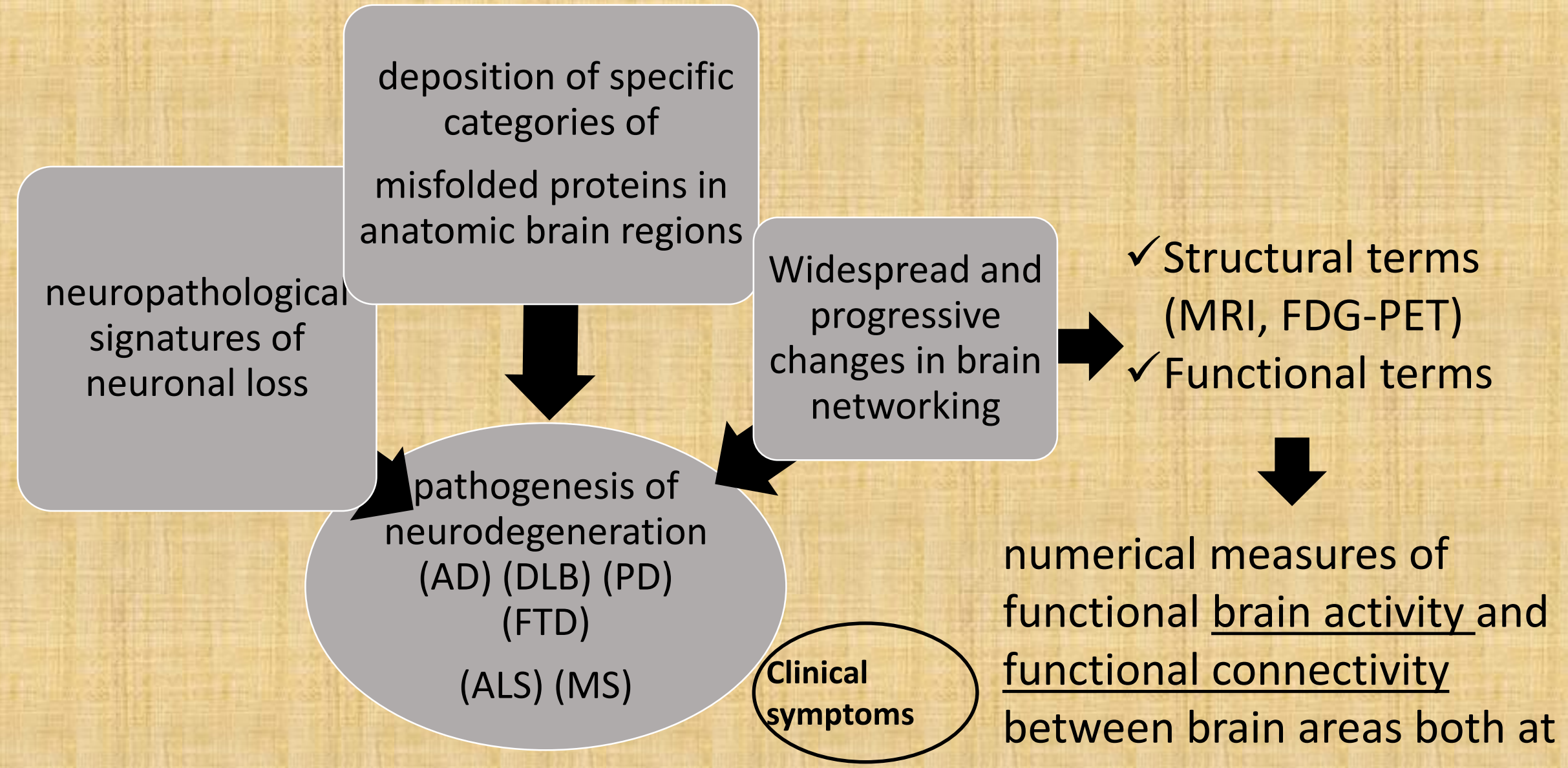
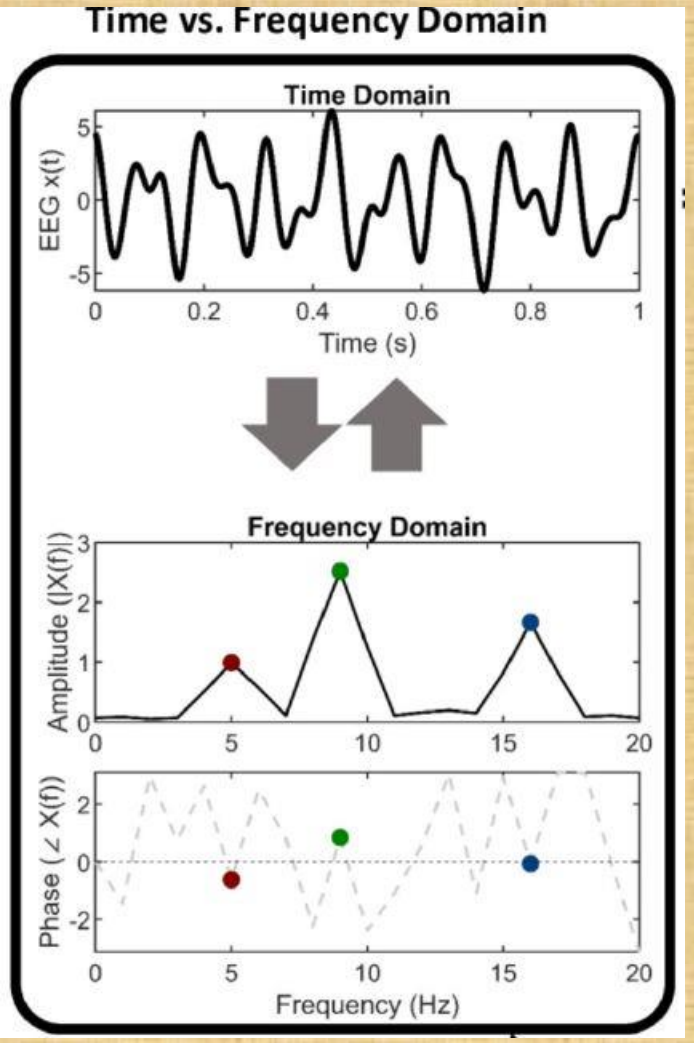
Neurofisiologia

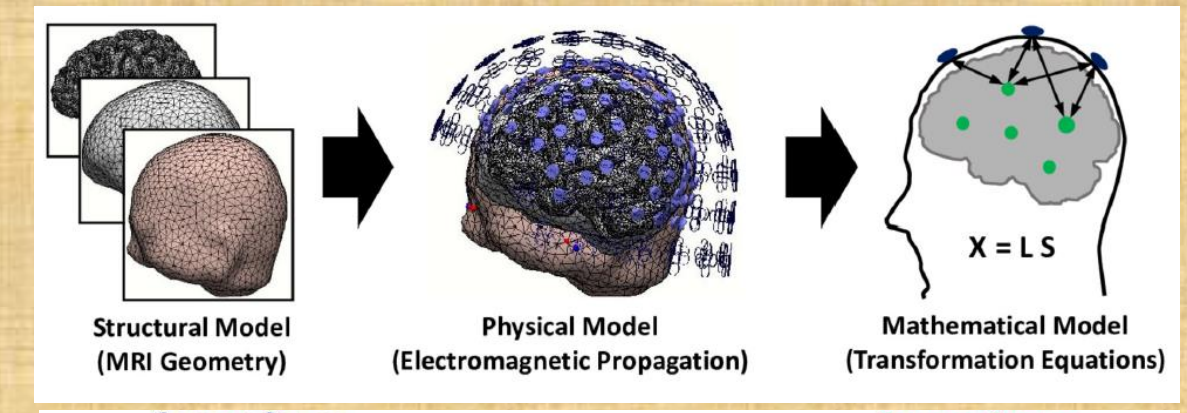
Francesco Famà
DiNOGMI
Università di Genova

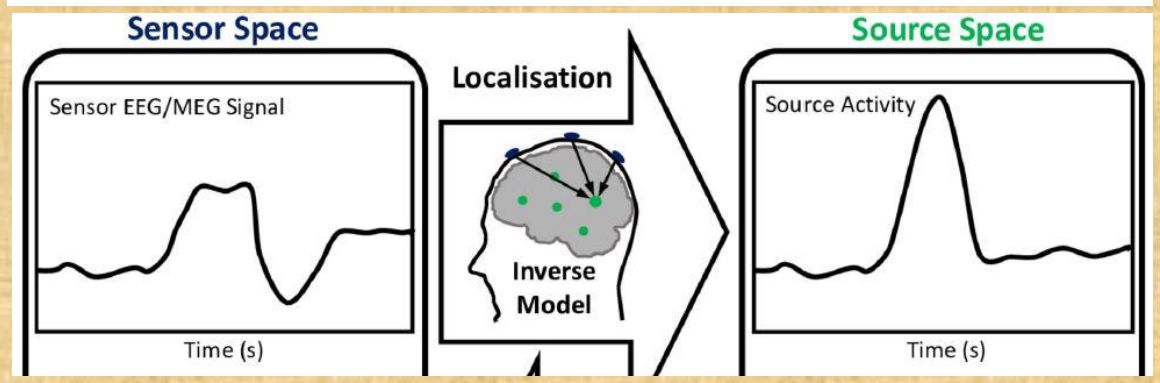

deposition of specific categories of
misfolded proteins in anatomic brain regions
neuropathological signatures of neuronal loss
Widespread and progressive changes in brain networking
✓Structural terms (MRI, FDG-PET)
✓Functional terms
pathogenesis of neurodegeneration
(AD) (DLB) (PD) (FTD)
(ALS) (MS)
Clinical symptoms
numerical measures of functional brain activity and functional connectivity between brain areas both at **rest** and during specified tasks

Evoked or event-related potentials (EPs/ERPs) :investigating ***latency*** and ***amplitude*** of a sequence of EEG voltage peaks and the underlying cortical source activity

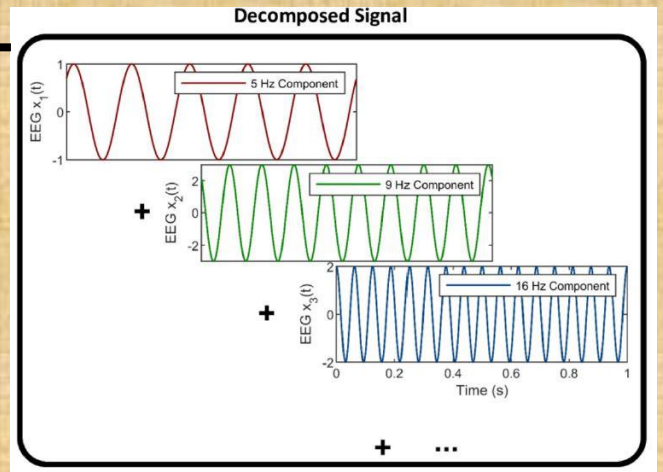


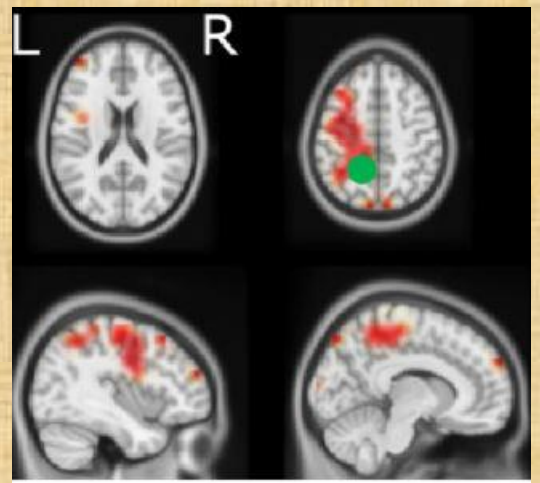
In the absence of event "resting-state" EEG signals: by linear (discrete Fourier transformation) or nonlinear techniques : to quantify brain neural oscillatory activity in terms of ***peak frequency***, ***magnitude (power density***) and ***phase***, either at sensory or brain source level.

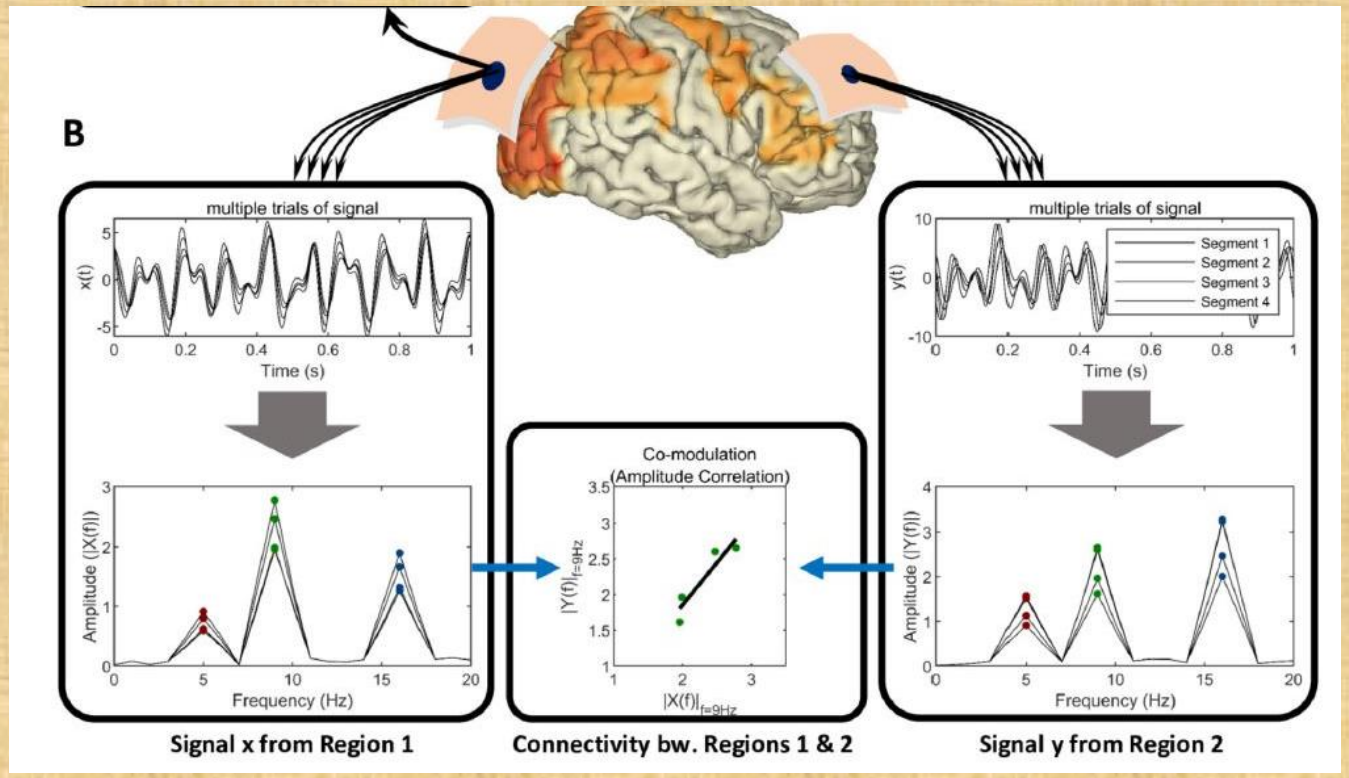




Low Resolution Electromagnetic Brain Tomography (LORETA): source estimation of EEG signals







EEG coupling between electrode pairs

→ functional and effective brain connectivity

↙ **Spectral coherence**

↘ **Granger causality**

(Babiloni et al., 2009; Rossini et al. 2007)

Cortical neural synchronization is typically indexed by EEG power density

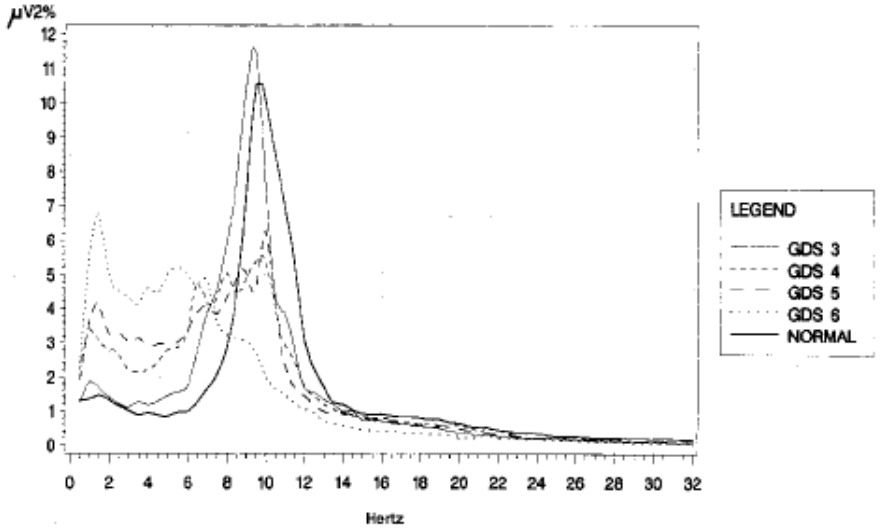
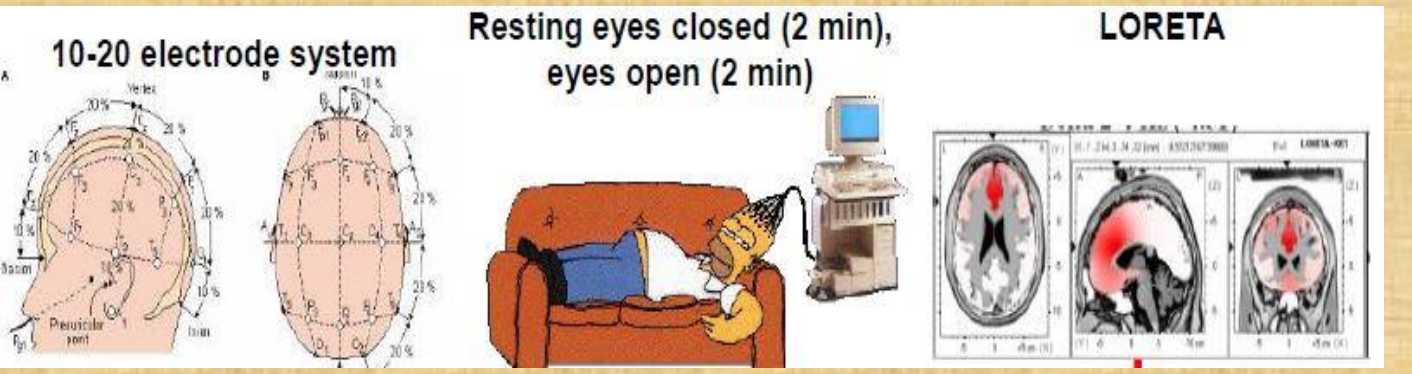


Fig. 1. Mean quantitative EEG spectral profiles of AD patients and healthy controls. Mean qEEG spectral profiles are shown for control group and the 4 patient groups, according to the legend on the right side of the figure. Graphics are drawn by the computation of mean values of 64 0.5 Hz frequency bands (0.5–32 Hz) in the left parietal channel. GDS 3 group shows a normally shaped but shifted-to-the-left spectral profile; in GDS 4 and 5 groups normal background activity is reduced and slower frequency powers are increased at various extent; in the GDS 6 group, the so called 'exponential asymptotic' profile can be appreciated, with the highest power in the lowest frequencies.

***EEG spectral profile to stage Alzheimer's disease. Clinical Neurophysiology* 110 (1999) 1831-7 G Rodriguez, F Copello, P Vitali, G Perego, F Nobili**



resting state eyes-closed electroencephalographic **(rsEEG)** rhythms: quiet wakefulness (eyes closed, no sleep) **non-invasive**, **cost-effective**, available worldwide, and **repeatable** even in severe dementia.

RsEEG markers in AD at the group level reflect

”Synchronization” markers

- ADD groups: **lower** power density in posterior cortical **alpha** and **beta** rhythms ; **higher** power density in widespread **delta and theta** rhythms

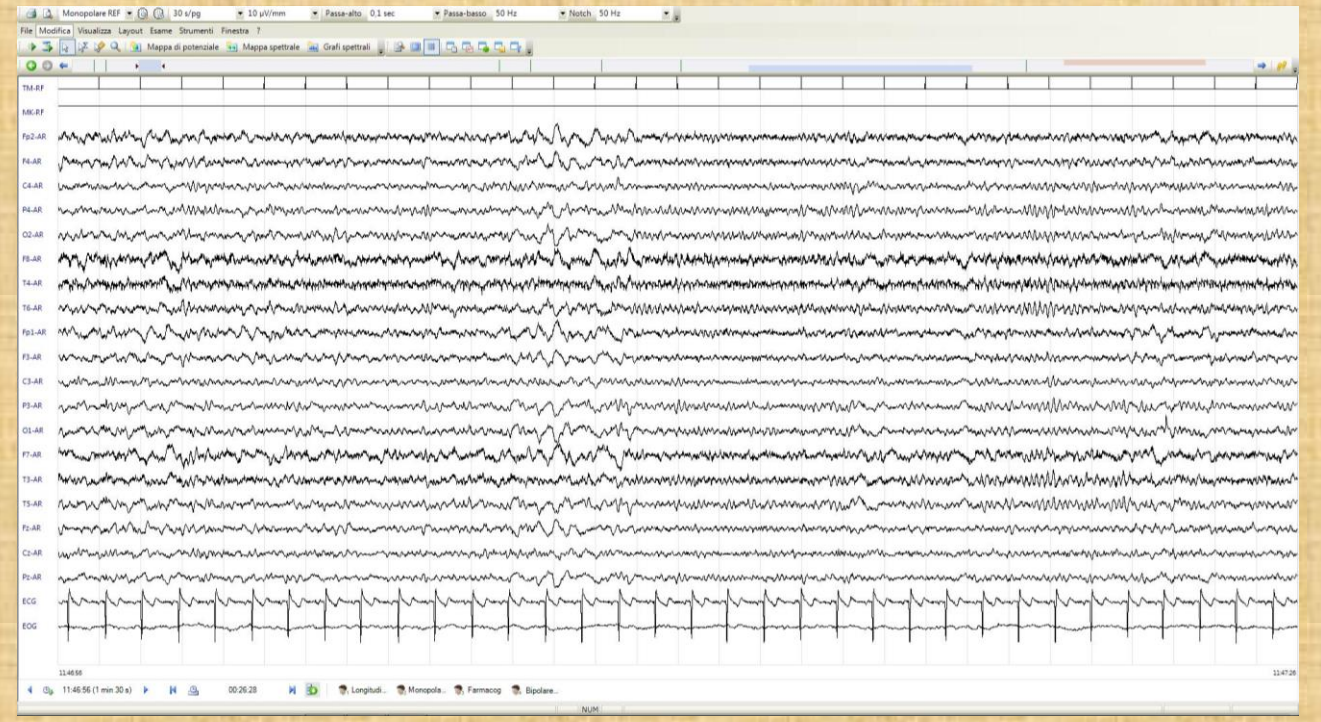
”Connectivity” markers

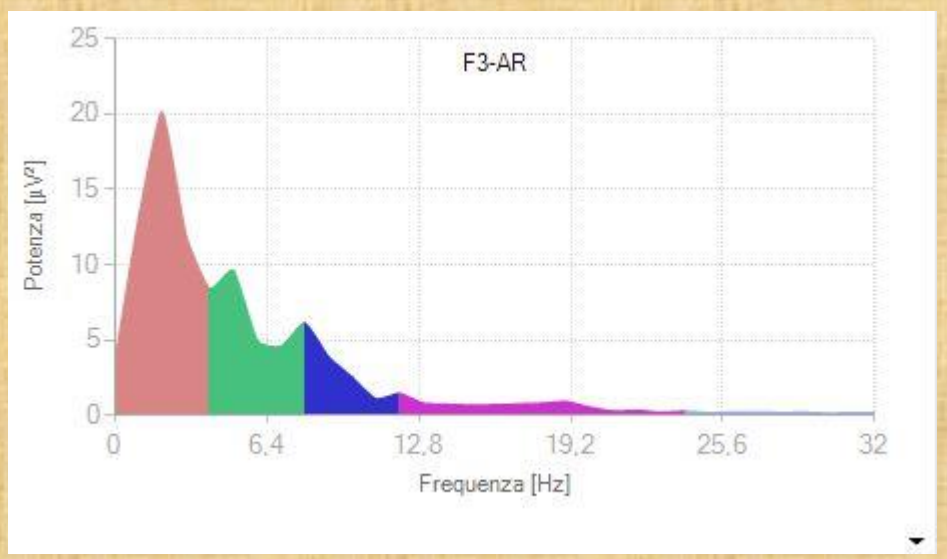
- ADD groups: abnormally lower **spectral coherence** in alpha and beta rhythms between **posterior electrode pairs**

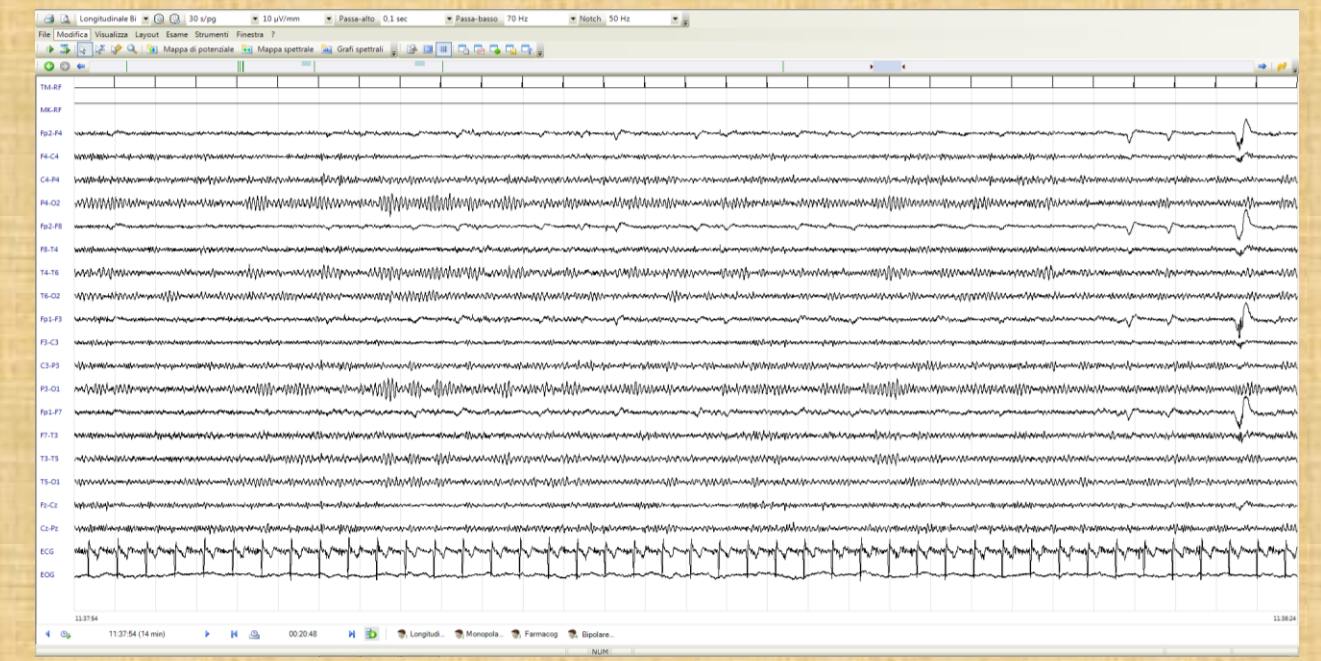
RsEEG markers in AD at the individual level: classification accuracy and predictions

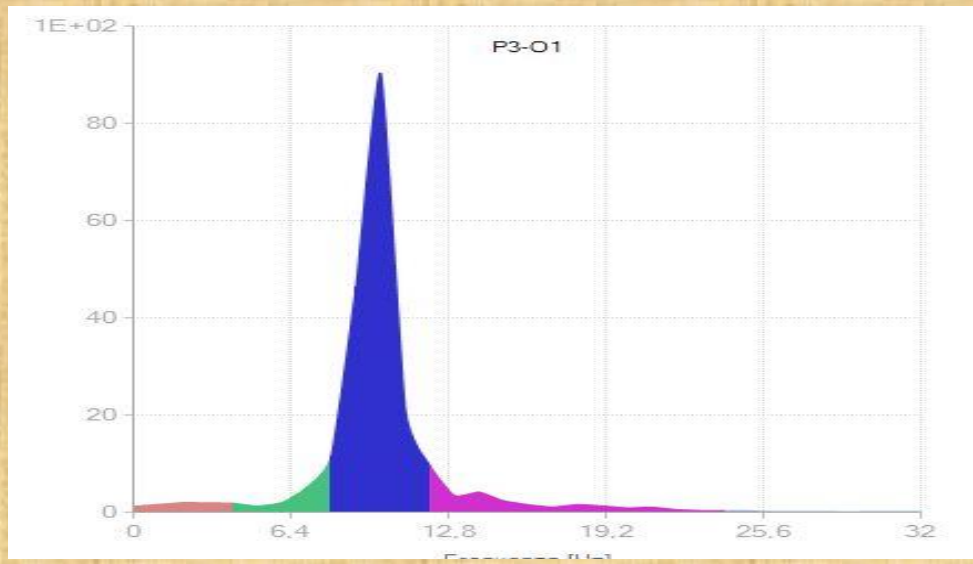
Established neurophysiological changes in neurodegeneration, their clinical utility and discrimination ability

Neurodegeneration	Method	Neurophysiological change	Clinical application	Discrimination statistics	References
Alzheimer's disease Dementia with Lewy bodies	EEG/ MEG	▶ ↓ Posterior α power ▶ ↑ Parietal δ and θ power	▶ Prodromal differential diagnosis ▶ Diagnostic biomarker ▶ Differential diagnosis of AD and DLB	▶ Sensitivity –78.3% ▶ Specificity - 66.7% ▶ AUROC – 72% ▶ AUROC=0.97 (log δ) and 0.93 (log θ) ▶ AUROC=0.879 (log δ) and 0.75 (log θ)	Andersson *et al*, Babiloni *et al*[36 43]




F3-AR
Potenza [µV²]
25
20
15
10
5
0
0
6,4
12,8
19,2
25,6
32
Frequenza [Hz]




P3-O1
1E+02
80
60
40
20
0
0
6,4
12,8
19,2
25,6
32

Journal of Alzheimer's Disease 54 (2016) 1649–1657
DOI 10.3233/JAD-160435
IOS Press

EEG Markers of Dementia with Lewy Bodies: A Multicenter Cohort Study

Laura Bonanni[a,*], Raffaella Franciotti[a], Flavio Nobili[b], Milica G. Kramberger[c], John-Paul Taylor[d], Sara Garcia-Ptacek[e], N. Walter Falasca[f], Francesco Famà[b], Ruth Cromarty[d], Marco Onofrj[a], Dag Aarsland[g] and on behalf of the E-DLB study group*

- ✓ the accuracy of the clinical diagnosis of DLB is less satisfactory because some of the core clinical features may not appear during the entire course of DLB or may overlap with AD
- ✓ high prevalence of amyloid load in DLB patient populations

90 analyzed epochs, FFT with fr of 0,5 Hz

Mean power spectrum :

- delta:3-4 Hz
- Theta: 4,5-5,5 Hz
- Pre-alpha: 6-7,5 Hz
- Alpha: 8-12 Hz

DF=Dominant Frequency

FP= Frequency Prevalence

DFV= Dominant Frequency Variability

	DLB ($n=79$)	AD ($n=133$)	p value
Age	75 ± 1	78 ± 1	0.005
Male gender (%)	66	37	0.01
Education	10 ± 1	8 ± 0	n.s.
MMSE	22.9 ± 0.5	22.7 ± 0.2	n.s.
NPI-total	9 ± 1	6 ± 2	n.s.
UPDRS-III	18 ± 1	2 ± 0	0.00001

EEG variables	DLB ($n=79$)	AD ($n=133$)	Statistical results	
		Anterior derivations		
DF	5.9 ± 0.2	7.3 ± 0.2	$F(1,210) = 19.8$	$p < 10^{-4}$
DFV	1.4 ± 0.2	1.5 ± 0.2	$F(1,210) = 0.1$	n.s.
FP delta	24 ± 1	19 ± 1	$F(3,630) = 47.0$	n.s.
FP theta	16 ± 1	10 ± 1		n.s.
FP pre-alpha	45 ± 2	28 ± 2		$p < 10^{-9}$
FP alpha	15 ± 2	42 ± 2		$p < 10^{-9}$
		Temporal derivations		
DF	6.7 ± 0.1	8.3 ± 0.1	$F(1,210) = 55.9$	$p < 10^{-6}$
DFV	0.7 ± 0.1	0.7 ± 0.1	$F(1,210) = 0.0$	n.s
FP delta	11 ± 1	9 ± 1	$F(3,630) = 69.98$	n.s
FP theta	11 ± 1	7 ± 1		n.s
FP pre-alpha	59 ± 2	33 ± 2		$p < 10^{-12}$
FP alpha	19 ± 2	52 ± 2		$p < 10^{-12}$
		Posterior derivations		
DF	6.9 ± 0.1	8.7 ± 0.1	$F(1,210) = 71.5$	$p < 10^{-6}$
DFV	0.7 ± 0.1	0.4 ± 0.1	$F(1,210) = 4.0$	$p < 0.05$
FP delta	11 ± 1	7 ± 1	$F(3,630) = 85.8$	n.s
FP theta	13 ± 1	7 ± 1		n.s
FP pre-alpha	54 ± 2	27 ± 2		$p < 10^{-12}$
FP alpha	22 ± 3	60 ± 2		$p < 10^{-12}$

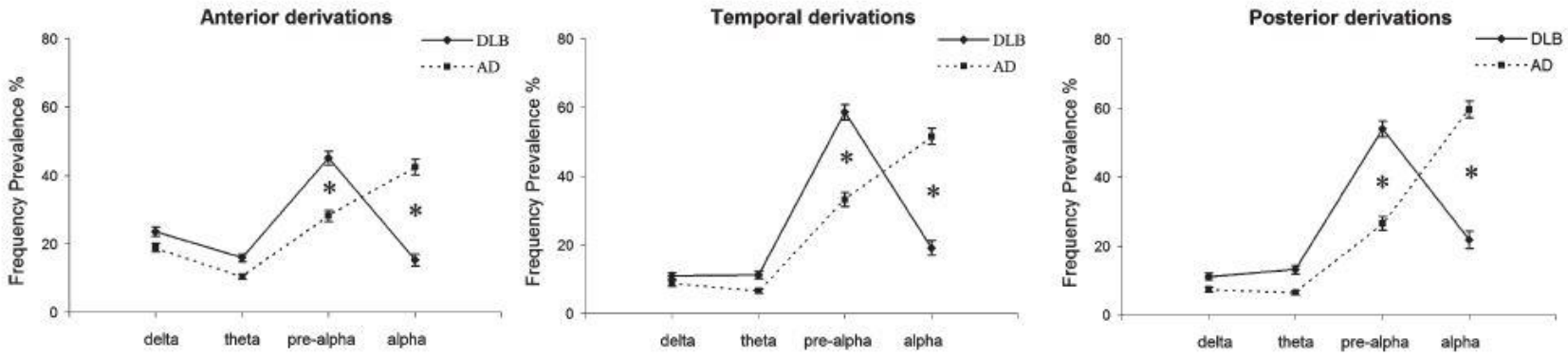
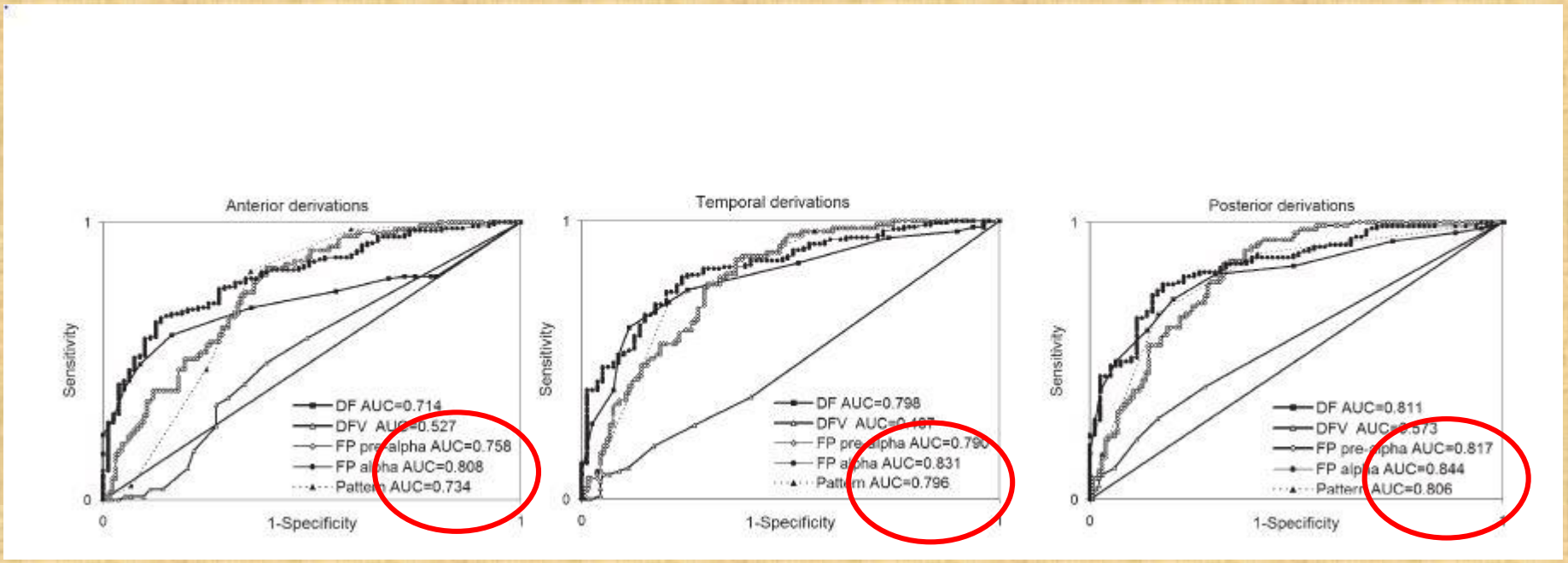


Fig. 1. Frequency Prevalence for delta, theta, pre-alpha, and alpha bands from anterior, temporal, and posterior derivations in DLB and AD groups. Significant differences between the two groups were found for pre-alpha and alpha band (*).



all the EEG variables
DF <7.8 Hz
DFV >2.2 Hz
FP pre-alpha >32.7 %
FP alpha <40.7 %
CSA pattern >2)
Sensitivity **90%**
Specificity **64%**
DLB vs AD patients

Linear discriminant analysis: the best discriminating variable between DLB and AD patients was **FP in alpha band** in all the derivations explored

Cut-off values provided by ROC analysis in all derivations

Cut-off values	Sens	Spec	PPV	NPV
Anterior derivations				
DF <7.3 Hz	84%	59%	55%	86%
DFV >1.3	42%	66%	42%	66%
FP pre-alpha >29.4%	84%	61%	56%	86%
FP alpha <27.6%	86%	65%	60%	89%
CSA pattern >2	97%	41%	49%	96%
Temporal derivations				
DF <7.8 Hz	89%	62%	58%	90%
DFV >3.3Hz	9%	95%	50%	64%
FP pre-alpha >36.8Hz	86%	63%	58%	88%
FP alpha <27.9%	76%	80%	69%	85%
CSA pattern >2	71%	79%	67%	82%
Posterior derivations				
DF <7.8 Hz	80%	72%	63%	86%
DFV >2.2 Hz	9%	97%	64%	64%
FP pre-alpha >32.7%	85%	68%	61%	88%
FP alpha <40.7%	82%	77%	68%	88%
CSA pattern >2	67%	83%	71%	81%

The highest sensitivity was found in **anterior derivations**

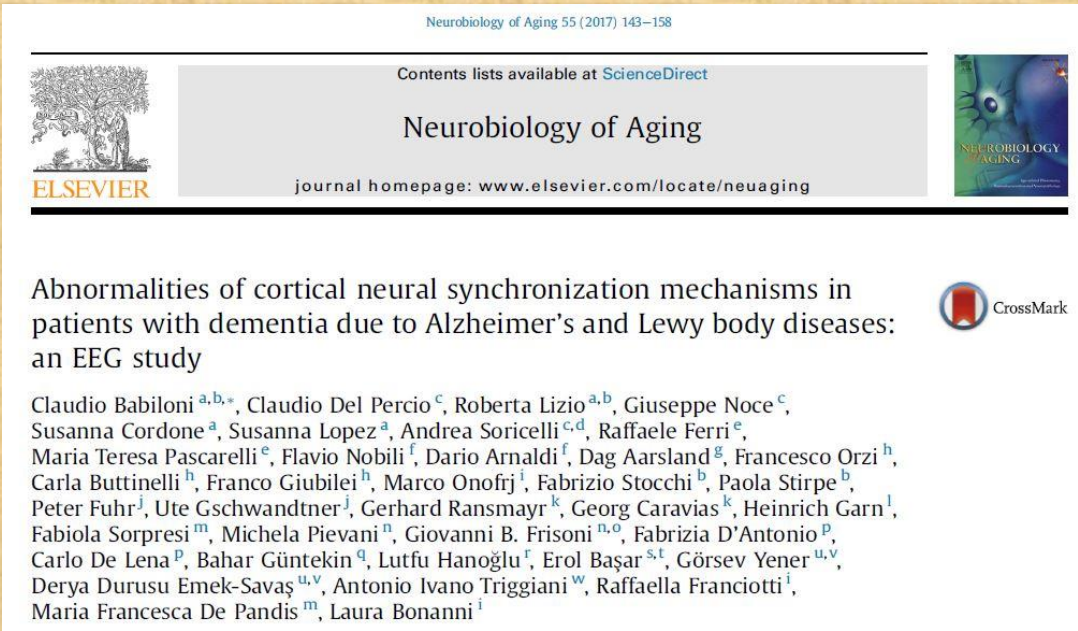
EEG variables values from **posterior derivations** were more specific

By combining EEG with 123I-FP-CIT SPECT scan, the percentage of DLB patients correctly classified **reached 100%.**

- ✓ Decreased in the **alpha** band: alterations in **cortico-cortical connection**
- ✓ Increased in the low frequency acticity (**pre-alfa**, **theta** and **delta** band): **Lack of influence** of subcortical cholinergic structures on cortical electrical activity

The functional disorder of the **ascending cholinergic system** may be stronger in DLB than in AD patients

qEEG discriminant value: **early stages** of DLB (frequency of patients presenting core symptoms is low)



Neurobiology of Aging 55 (2017) 143–158

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Abnormalities of cortical neural synchronization mechanisms in patients with dementia due to Alzheimer's and Lewy body diseases: an EEG study

Claudio Babiloni [a,b,*], Claudio Del Percio [c], Roberta Lizio [a,b], Giuseppe Noce [c], Susanna Cordone [a], Susanna Lopez [a], Andrea Soricelli [c,d], Raffaele Ferri [e], Maria Teresa Pascarelli [e], Flavio Nobili [f], Dario Arnaldi [f], Dag Aarsland [g], Francesco Orzi [h], Carla Buttinelli [h], Franco Giubilei [h], Marco Onofrj [i], Fabrizio Stocchi [b], Paola Stirpe [b], Peter Fuhr [j], Ute Gschwandtner [j], Gerhard Ransmayr [k], Georg Caravias [k], Heinrich Garn [l], Fabiola Sorpresi [m], Michela Pievani [n], Giovanni B. Frisoni [n,o], Fabrizia D'Antonio [p], Carlo De Lena [p], Bahar Güntekin [q], Lutfu Hanoğlu [r], Erol Başar [s,t], Görsev Yener [u,v], Derya Durusu Emek-Savaş [u,v], Antonio Ivano Triggiani [w], Raffaella Franciotti [i], Maria Francesca De Pandis [m], Laura Bonanni [i]

- ✓ rsEEG rhythms at scalp electrodes :reference electrode and head volume conduction effects ***(Nunez, 1995)***
- ✓ LORETA(low-resolution brain electromagnetic tomography) : analytical procedures for the estimation of cortical sources of eyes-closed rsEEG rhythms. ***(Pascual-Marqui et al., 1994)***

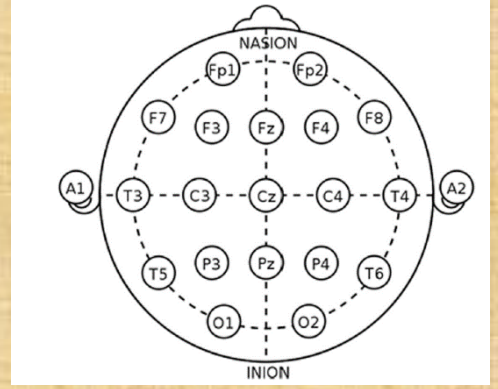
✓2 frequency landmarks in each individual PDD, ADD, DLB and Nold

- Transition Frequency **(TF)**: between the theta and the alpha bands
- Individual Alpha Frequency peak **(IAF)**: max power density peak in the alpha range

TF and IAF: delta, theta, and alpha frequency band ranges on an **individual basis**

	Nold	ADD	PDD	DLB	Statistical analysis
n	40	42	42	34	
Age	72.9 (±1.1 SE)	73.3 (±1.0 SE)	74.1 (±1.1 SE)	75.1 (±1.1 SE)	ANOVA: n.s.
Gender (M/F)	16/24	17/25	18/24	11/23	Kruskal-Wallis: n.s.
Education	8.5 (±0.6 SE)	8.1 (±0.8 SE)	7.0 (±0.6 SE)	7.4 (±0.8 SE)	ANOVA: n.s.
MMSE	28.7 (±0.2 SE)	18.9 (±0.6 SE)	18.8 (±0.7 SE)	18.6 (±0.8 SE)	Kruskal-Wallis: $H = 88.7$, $p < 0.00001$ (Nold > ADD, PDD, DLB)

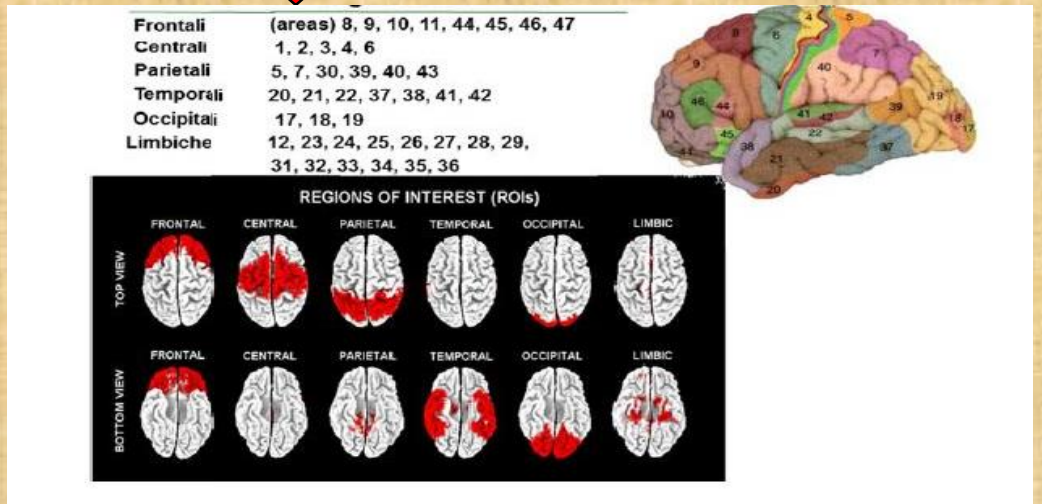
Key: M/F, males/females; MMSE, Mini–Mental State Evaluation; n.s., not significant ($p > 0.05$).



Power spectrum analysis: FFT with 0,5 frequency resolution
In the EEG power density spectrum for each subject :

TF= transition frequency between the theta and alpha bands defined as the minimum of the rsEEG power density between **3 and 8 Hz** (delta and the alpha power peak).

IAF = maximum power density peak between **6 and 14 Hz**



δ delta **from TF-4 Hz to TF-2 Hz**
θ theta **from TF-2 Hz to TF**
α1 e α2(low-frequency alpha band) **from TF to IAF**
α3(high-frequency alpha band) **from IAF to IAF+2 Hz**

standard fixed frequency ranges for

β1 (beta) **from 14 to 20 Hz**
β2 (beta 2) **from 20 to 30 Hz**

"exact LORETA" (eLORETA): linear estimation of the cortical source activity of rsEEG rhythms (*Pascual-Marqui, 2007*).

Statistical analysis

✓ *eLORETA solutions*

ANOVA

- regional normalized eLORETA solutions (normalized current density at all voxels of a given ROI) as a **dependent variable** ($p < 0.05$)
- Individual **TF** and the **IAF** were used as **covariates**
- ANOVA factors : **Group** (Nold, ADD, PDD, DLB)**-- Band** (delta, theta, alpha1, alpha2, alpha3, beta1, beta2, and gamma) **--ROI** (frontal, central, parietal, occipital, temporal, and limbic).

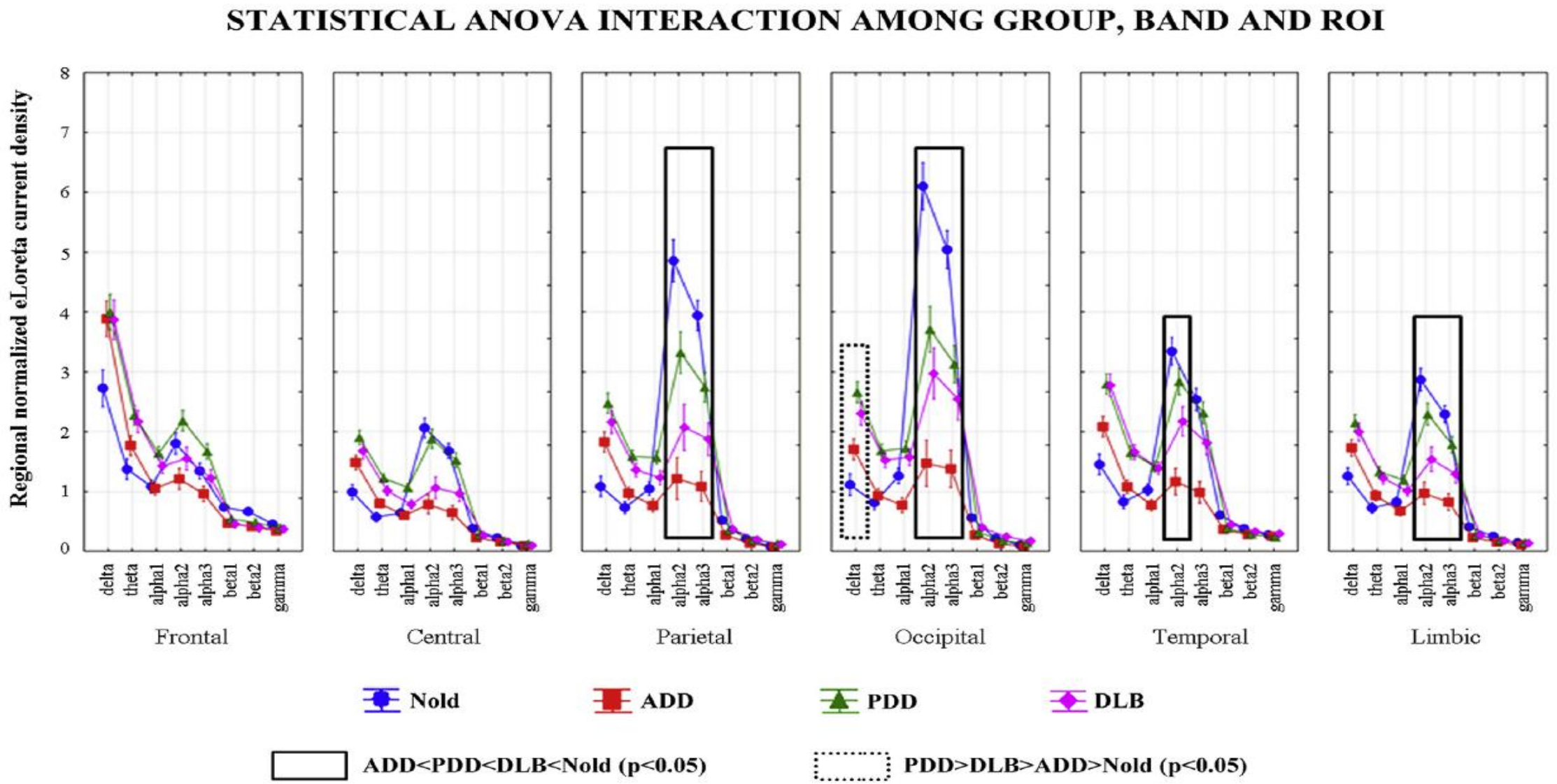
Post hoc testing

- a statistical **3-way interaction effect including the factors Group, Band and ROI** ($p < 0.05$)
- statistically **significant differences** of the regional normalized eLORETA solutions with the pattern **Nold ≠ ADD ≠ PDD ≠ DLB** (Duncan test, $p < 0.05$).

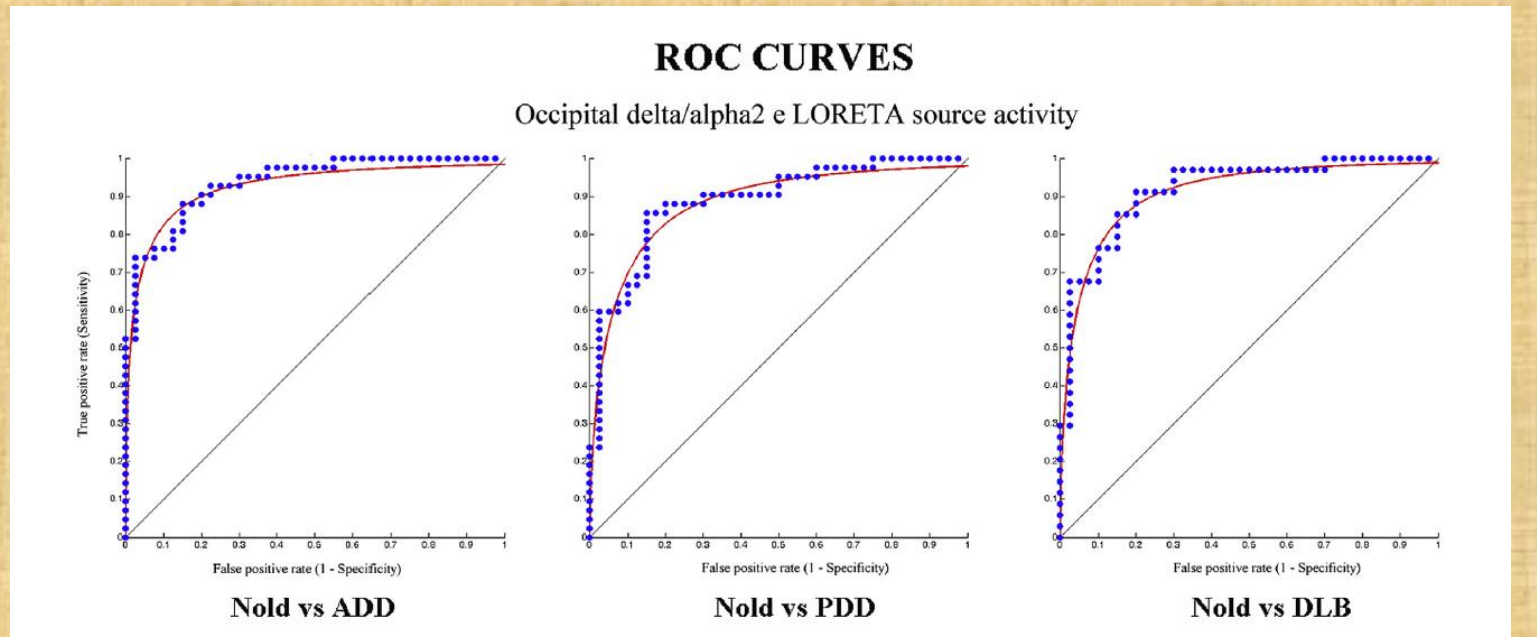
✓ *Accuracy of the rsEEG source activity in the discrimination between Nold, ADD, PDD, and DLB individuals*

Mean values (±SE) of transition frequency (TF) and individual alpha frequency peak (IAF) of the rsEEG power density spectra for the groups (i.e., Nold, ADD, PDD, DLB)

	Nold	ADD	PDD	DLB	Statistical analysis
TF	5.9 (±0.2 SE)	5.4 (±0.2 SE)	4.8 (±0.1 SE)	4.9 (±0.1 SE)	ANOVA: $F = 10.4$, $p < 0.00001$ (Nold > ADD > PDD, DLB)
IAF	9.0 (±0.2 SE)	8.0 (±0.3 SE)	7.3 (±0.2 SE)	7.2 (±0.2 SE)	ANOVA: $F = 14.9$, $p < 0.00001$ (Nold > ADD > PDD, DLB)



	eLORETA sources	Sensitivity	Specificity	Accuracy	AUROC (>0.75)
Nold versus ADD	Occipital delta	—	—	—	—
	Occipital alpha 2	83.3%	85.0%	84.1%	0.91
	Occipital delta/alpha 2	**88.1%**	**85.0%**	**86.6%**	**0.94**
Nold versus PDD	Occipital delta	81.0%	85.0%	82.9%	0.87
	Occipital alpha 2	—	—	—	—
	Occipital delta/alpha 2	**85.7%**	**85.0%**	**85.4%**	**0.89**
Nold versus DLB	Occipital delta	79.4%	80.0%	79.7%	0.86
	Occipital alpha 2	—	—	—	—
	Occipital delta/alpha 2	**85.3%**	**85.0%**	**85.1%**	**0.92**
ADD versus PDD	Occipital delta	—	—	—	—
	Occipital alpha 2	**81.0%**	**81.0%**	**81.0%**	**0.84**
	Occipital delta/alpha 2	—	—	—	—
ADD versus DLB	Occipital delta	—	—	—	—
	Occipital alpha 2	**64.7%**	**73.8%**	**69.7%**	**0.75**
	Occipital delta/alpha 2	—	—	—	—
PDD versus DLB	Occipital delta	—	—	—	—
	Occipital alpha 2	—	—	—	—
	Occipital delta/alpha 2	—	—	—	—



Occipital–parietal alpha 2 source activity **reduction**

Nold → ADD → DLB → PDD

Occipital delta source activity **increase**

Nold → PDD → DLB → ADD

Alteration of complex network regulating the cortical arousal and vigilance in quite wakefulness (glutamatergic and cholinergic neurons, thalamocortical high-threshold, GABAergic interneurons, thalamocortical relay-mode, cortical pyramidal neurons

Abnormal interaction between thalamic and cortical pyramidal neural populations

↓

loss of functional connectivity

↓

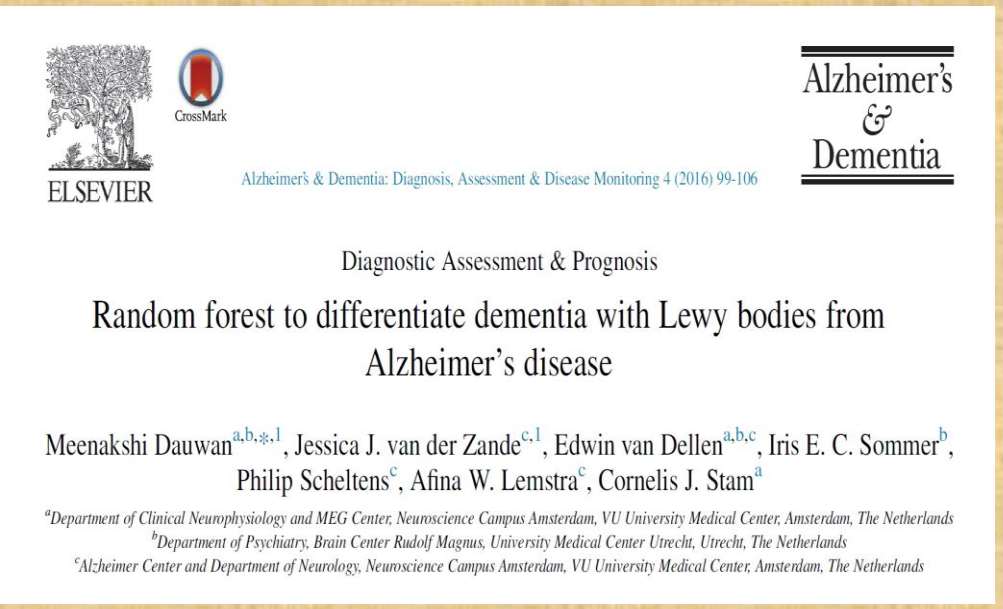
functional isolation

close to **90%** classification of Nold vs patients with dementia

Occipital delta/alpha2 e LORETA source activity

accuracy around 85% classification of ADD versus PDD patients
around 70% e 75% for ADD versus DLB individuals.

Occipital alpha2



ELSEVIER

CrossMark

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 4 (2016) 99-106

Alzheimer's & Dementia

Diagnostic Assessment & Prognosis

Random forest to differentiate dementia with Lewy bodies from Alzheimer's disease

Meenakshi Dauwan[a,b,*,1], Jessica J. van der Zande[c,1], Edwin van Dellen[a,b,c], Iris E. C. Sommer[b], Philip Scheltens[c], Afina W. Lemstra[c], Cornelis J. Stam[a]

[a]Department of Clinical Neurophysiology and MEG Center, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[b]Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands
[c]Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

	DLB	AD	Control
N	66	66	66
Age, y	70 (9)	70 (9)	70 (7)
Sex, female	14 (21%)	14 (21%)	14 (21%)

Random Forest classifier to:

- discriminate between DLB, AD, and controls
- quantify the importance of (combinations of) different types of diagnostic features

clinical
neuropsychological
EEG
CSF
neuroimaging

→ **specific focus on the role ofEEG.**

	DLB	AD	Control
N	66	66	66
Age, y	70 (9)	70 (9)	70 (7)
Sex, female	14 (21%)	14 (21%)	14 (21%)
Disease duration, y	2.9 (2.2)	3.3 (2.2)	3.6 (4.8)
CNS medication*†	16 (24.2%)	6 (9.1%)	6 (9.1%)
Rivastigmine	6 (9.1%)	4 (6.1%)	1 (1.5%)
Haloperidol	1 (1.5%)	1 (1.5%)	1 (1.5%)
Clozapine	2 (3%)	0 (0%)	0 (0%)
Quetiapine	2 (3%)	0 (0%)	0 (0%)
AED	3 (4.5%)	1 (1.5%)	2 (3%)
Other CNS medication	3 (4.5%)	0 (0%)	2 (3%)
MMSE‡	23 (5) (n = 59)	21 (5) (n = 63)	28 (1) (n = 66)
VAT‡	7.9 (3.5) (n = 47)	5.6 (4.3) (n = 60)	11.5 (.8) (n = 62)
TMT-A‡, se	123 (86) (n = 47)	87 (63) (n = 54)	43 (15) (n = 63)
Digit span forward§	11.5 (2.5) (n = 50)	10.5 (3.2) (n = 61)	12.4 (3.0) (n = 64)
Digit span backward‖	6.5 (2.8) (n = 49)	6.6 (3.0) (n = 60)	9.3 (2.9) (n = 64)
Hallucinations‡	16 (37.2%) (n = 43)	3 (5.8%) (n = 52)	0 (0%) (n = 40)
Extrapyramidal signs	32 (72.7%) (n = 44)	7 (13.5%) (n = 52)	4 (9.1%) (n = 44)
Bradykinesia‡	26 (59.1%) (n = 44)	2 (3.8%) (n = 52)	1 (2.3%) (n = 44)
Rigidity‡	26 (59.1%) (n = 44)	2 (3.8%) (n = 52)	3 (6.8%) (n = 44)
Tremor	6 (13.6%) (n = 44)	4 (7.8%) (n = 51)	2 (4.5%) (n = 44)
RBD	23 (88.5%) (n = 26)	NA	NA
Cognitive fluctuations	42 (91.3%) (n = 46)	NA	NA
CSF			
$A\beta_{42}$‡	677.7 (236.7) (n = 47)	503.6 (218.2) (n = 48)	835.0 (245.0) (n = 37)
Tau†§	341.4 (187.9) (n = 47)	601.7 (338.1) (n = 48)	326.2 (156.2) (n = 37)
p-Tau†§	56.7 (26.4) (n = 47)	86.9 (39.7) (n = 48)	52.1 (19.0) (n = 37)
Neuroimaging			
MTA score‡	1.0 (0.25–1.5) (n = 45)	1.5 (1.0–2.0) (n = 59)	0.5 (0.0–1.0) (n = 59)
GCA score‡	1.0 (1.0–2.0) (n = 45)	1.0 (1.0–2.0) (n = 59)	1.0 (0.0–1.0) (n = 59)
Fazekas score	1.0 (0.0–1.0) (n = 45)	1.0 (0.0–2.0) (n = 59)	1.0 (0.0–1.0) (n = 59)
Power			
Delta band*†	0.42 (0.16)	0.29 (0.12)	0.27 (0.11)
Theta band‡	0.32 (0.12)	0.22 (0.11)	0.14 (0.07)
Alpha1 band‡	0.11 (0.07)	0.17 (0.10)	0.23 (0.14)
Alpha2 band*†	0.05 (0.03)	0.11 (0.07)	0.12 (0.07)
Beta band*†	0.08 (0.04)	0.16 (0.07)	0.18 (0.07)
Peak frequency‡	7.02 (0.91)	8.06 (1.17)	8.84 (0.91)
Theta/alpha ratio‡	0.67 (0.15)	0.45 (0.18)	0.30 (0.13)

*Significantly different between DLB and controls.

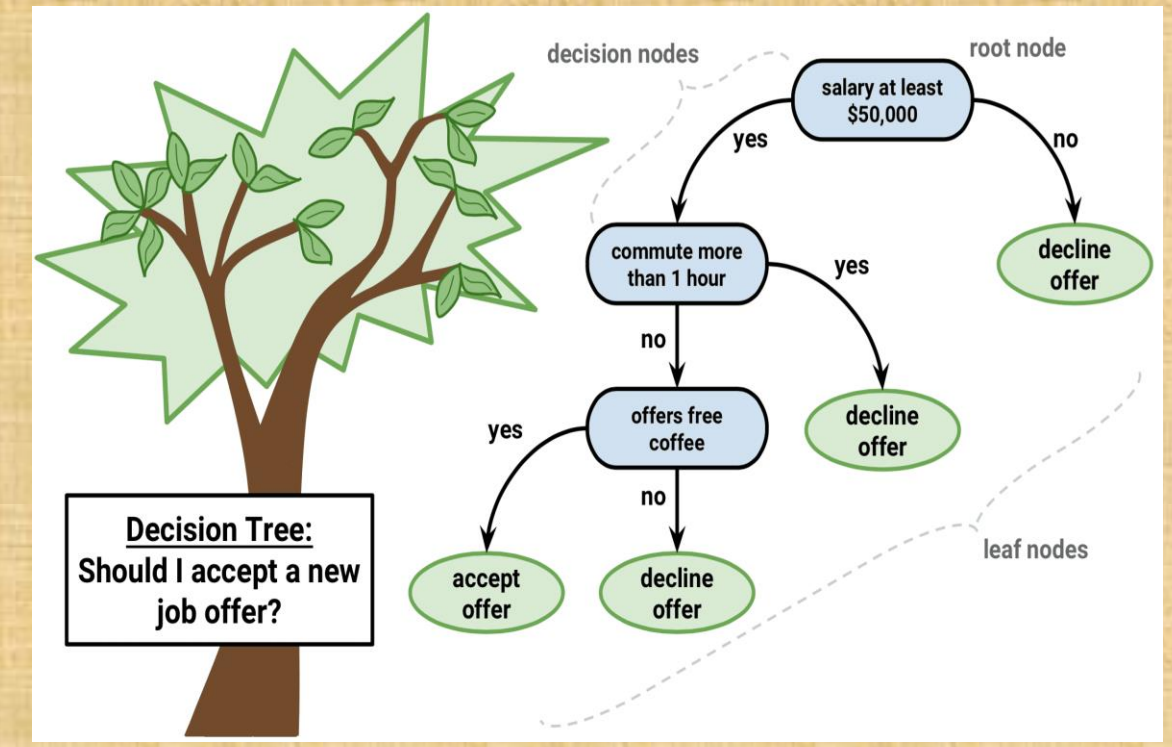
†Significantly different between AD and DLB.

‡Significantly different between all groups ($P < .05$).

§Significantly different between AD and controls.

‖Significantly different between the two dementia groups and controls ($P < .05$).

Decision Tree algorithm : supervised learning algorithms



Flowchart-like structure:

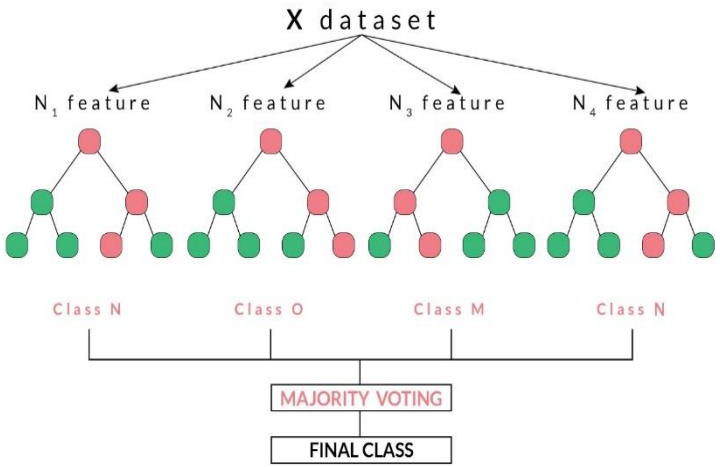
- ✓ each internal node represents a **"test" on an attribute**
- ✓ each branch represents the **outcome of the test**
- ✓ each leaf node represents a **class label** (decision taken after computing all attributes).

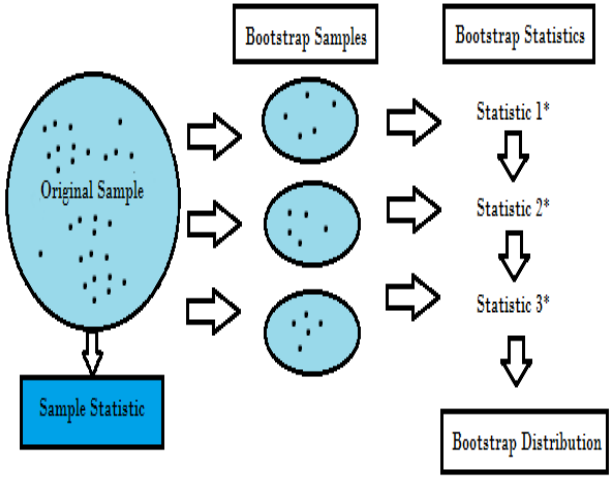
The paths from root to leaf represent classification rules

- regression and classification problems

- **Individually** predictions made by decision trees may **not be accurate**

Feature number	Feature name	Feature number	Feature name
Quantitative EEG			
1	Lowest delta power	36	Mean PTE alpha1 band
2	Mean delta power	37	Highest PTE alpha1 band
3	Highest delta power	38	Lowest PTE alpha2 band
4	Lowest theta power	39	Mean PTE alpha2 band
5	Mean theta power	40	Highest PTE alpha2 band
6	Highest theta power	41	Lowest PTE beta band
7	Lowest alpha1 power	42	Mean PTE beta band
8	Mean alpha1 power	43	Highest PTE beta band
9	Highest alpha1 power		
10	Lowest alpha2 power	Clinical data	
11	Mean alpha2 power	44	Hallucinations
12	Highest alpha2 power	45	Extrapyramidal signs
13	Lowest beta power	Neuropsychological data	
14	Mean beta power	46	MMSE score
15	Highest beta power	47	VAT total score
16	Lowest peak frequency	48	TMT-A score
17	Mean peak frequency	49	Digit span forward
18	Highest peak frequency	50	Digit span backward



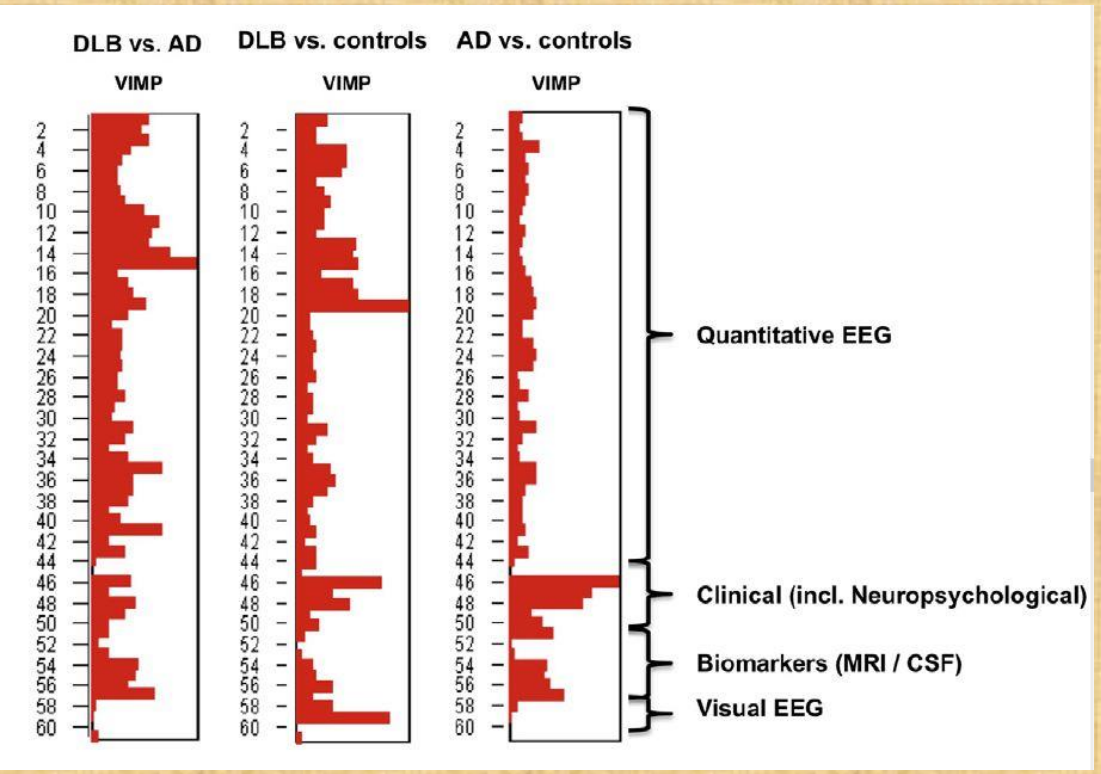


mTry : the number of input variables randomly chosen at each split **8**

nTree : the number of trees to grow for each forest)= **500**

no need for a **separate test set** to estimate the generalization error of the training set

- ✓ In every classification, each feature receives a variable importance (VIMP) score between 0 and 1
- ✓ 3 performance metrics: accuracy, sensitivity, and specificity: to assess the performance of the random forest in discriminating DLB, AD, and controls



Classifier results

Group and feature selection	Accuracy (%)	Sensitivity (%)	Specificity (%)
DLB vs. AD			
All features	87	88	86
Only clinical features	66	65	67
Clinical features + biomarkers	71	71	70
Clinical features + biomarkers + visual EEG	78	76	80
Quantitative and visual EEG	85	86	84
Only quantitative EEG	85	86	85
DLB vs. controls			
All features	94	95	92
Only clinical features	89	92	86
Clinical features + biomarkers	86	87	85
Clinical features + biomarkers + visual EEG	90	87	94
Quantitative and visual EEG	91	93	89
Only quantitative EEG	92	95	89
AD vs. controls			
All features	91	92	91
Only clinical features	90	93	88
Clinical features + biomarkers	93	94	92
Clinical features + biomarkers + visual EEG	93	93	92
Quantitative and visual EEG	63	62	64
Only quantitative EEG	62	63	62

DLB vs AD, DLB vs controls, and AD vs controls :reasonable diagnostic accuracies (>85%) **all preselected diagnostic variables**

DLB vs AD and DLB vs controls : **qEEG features**.

AD vs controls : **cognitive tests (e.g., MMSE)**

(q)EEG **did not have additional value for this discrimination**.

Power			
Delta band*†	0.42 (0.16)	0.29 (0.12)	0.27 (0.11)
Theta band‡	0.32 (0.12)	0.22 (0.11)	0.14 (0.07)
Alpha1 band‡	0.11 (0.07)	0.17 (0.10)	0.23 (0.14)
Alpha2 band*†	0.05 (0.03)	0.11 (0.07)	0.12 (0.07)
Beta band*†	0.08 (0.04)	0.16 (0.07)	0.18 (0.07)

DLB vs AD :Beta power as discriminative value

- Medication ?? muscle artifacts ??
- Overall shift in EEG activity from higher to lower frequency bands in DLB
- Dopaminergic networks defective in DLB and intact in AD
- Cholinergic system and the beta band have been related to the processes of attention

Theta/alpha ratio‡	0.67 (0.15)	0.45 (0.18)	0.30 (0.13)

AD vs. controls			
All features	91	92	91
Only clinical features	90	93	88
Clinical features + biomarkers	93	94	92
Clinical features + biomarkers + visual EEG	93	93	92
Quantitative and visual EEG	63	62	64
Only quantitative EEG	62	63	62

AD vs controls:

- accuracy of 91%
- Neuropsychological tests and CSF biomarkers have high VIMP scores
- low accuracy (63%) when including only EEG features

DLB vs controls:

- theta power is higher, and alpha power is lower than in AD and controls
- theta/alpha ratio was the most important discriminating feature.

Nat Med. 2017 June ; 23(6): 678–680. doi:10.1038/nm.4330.

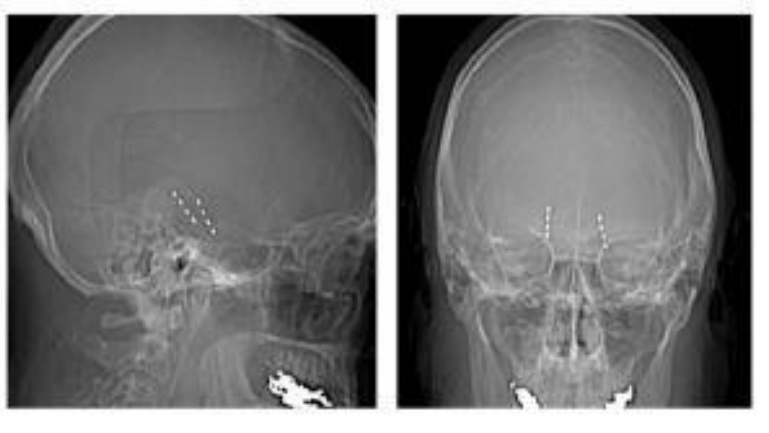
Silent Hippocampal Seizures and Spikes Identified by Foramen Ovale Electrodes in Alzheimer's Disease

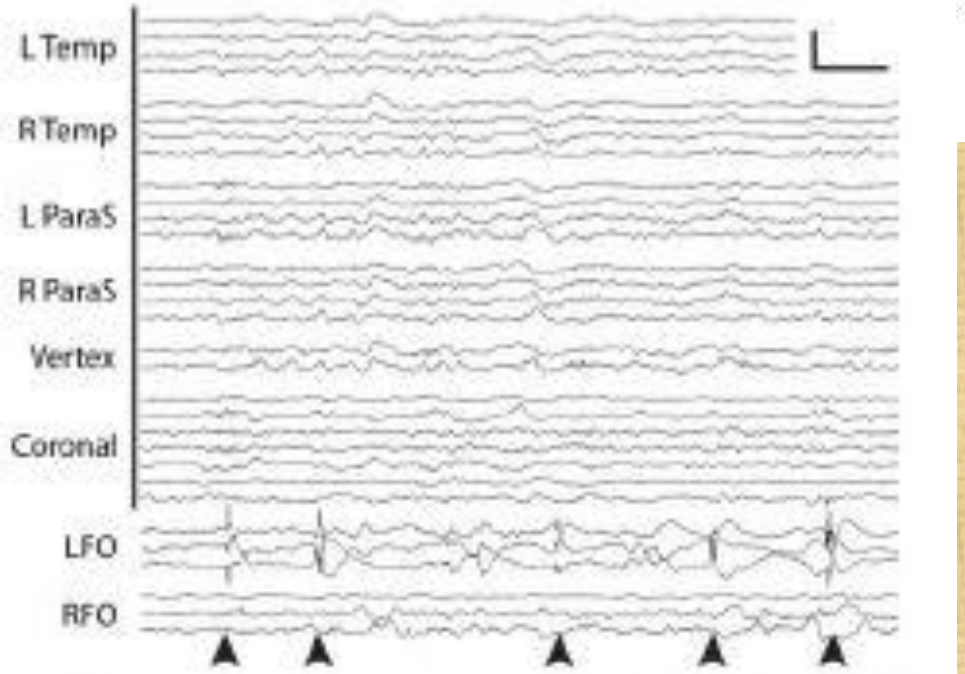
Alice D. Lam, M.D., Ph.D[1], Gina Deck, M.D.[1], Alica Goldman, M.D., Ph.D[2], Emad N. Eskandar, M.D.[3], Jeffrey Noebels, M.D., Ph.D.[2], and Andrew J. Cole, M.D.[1]

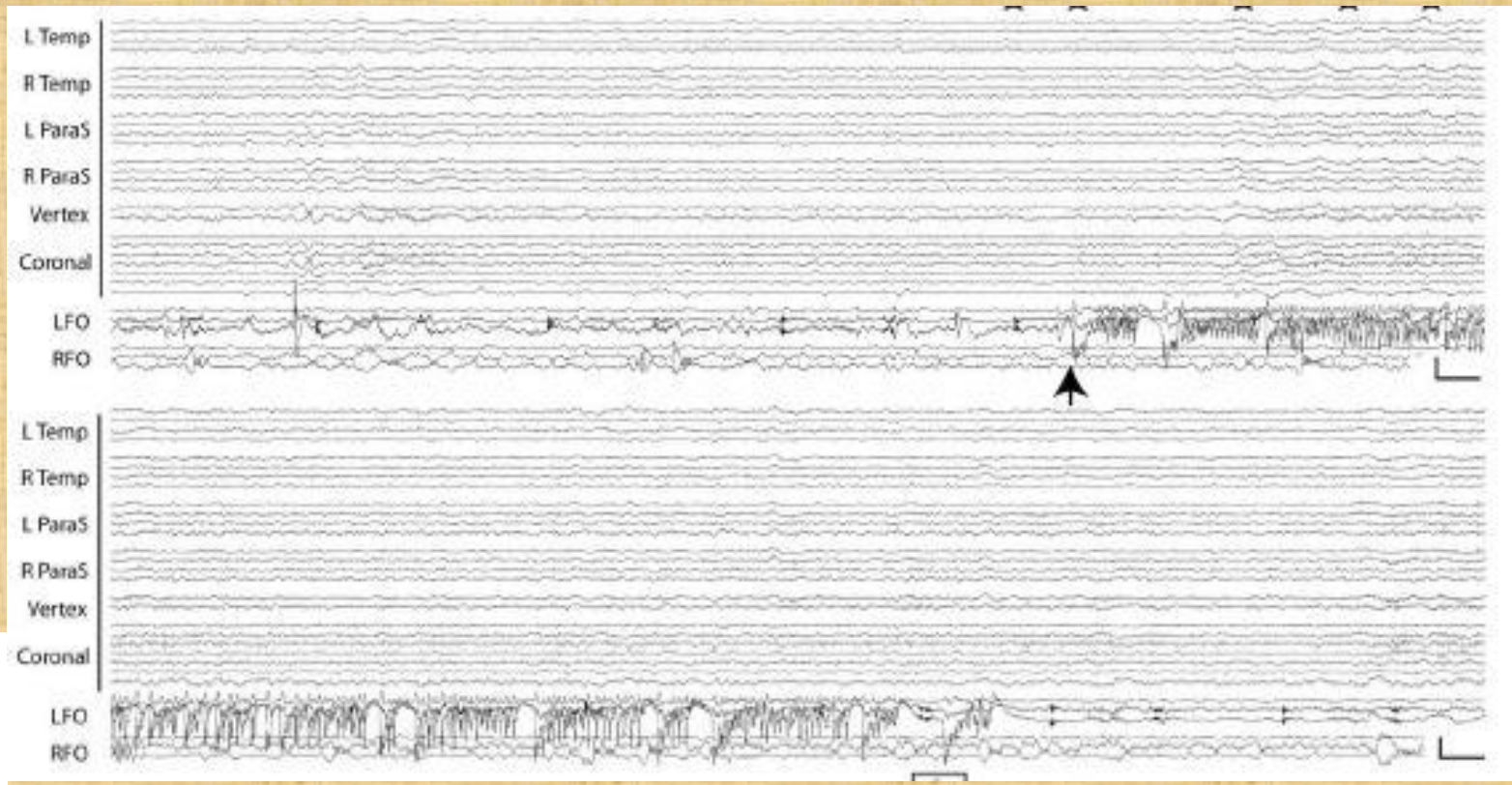
Patient #1

- 67 year-old woman with no seizure history
- Cognitive decline over one year(confusional episodes described as hours of repetitive questioning and garbled speech)
- Neuropsychological testing : aMCI
- Brain MRI :diffuse atrophy
- 18FDG-PET: left temporo-parietal hypometabolism
- CSF analysis: amyloid-tau index of **0.44** (<1.0 abnormal) ; phosphorylated tau level of **95.9 pg/mL** (>61 abnormal) consistent with a diagnosis of **AD**
- 35-minute scalp EEG during sleep: no evidence of focal slowing or epileptiform discharges, normal sleep architecture (including spindles and K-complexes)
- Continuous video-EEG monitoring: **left temporal sharp waves** at a rate of ~2/hour (wakefulness) and ~40–70/hour (sleep). Rare right temporal sharp waves during sleep (~5/hour)

high index of suspicion for occult seizures, the patient







reduce hippocampal hyperactivity in humans with amnestic mild cognitive impairment11. Levetiracetam binds to SV2A12, a synaptic vesicle protein that regulates neurotransmitter release, though the exact mechanism of levetiracetam's anticonvulsant effect is unknown. After starting levetiracetam (1500mg/day), no further seizures were captured on FO electrodes over the following 48 hours prior to their removal, and spike frequency was reduced by 65%. Twelve months later, she reported one spell of confusion following several consecutively missed doses of levetiracetam. Repeat neuropsychological testing showed mild progression of her

- ✓ epilepsy **not** occurs only as a late sequela of neurodegeneration in AD
- ✓ mTL epileptiform abnormalities are common or rare in AD?
- ✓ define a hyperexcitable subtype of AD (with specific treatment implications)?
- ✓ Subclinical seizures and spikes can cause significant cognitive impairments
- ✓ mTL seizures and spikes were activated during sleep, a period critical for memory consolidation, which may further increase their pathogenic impact

Grazie per l'attenzione