Cortical Electroencephalographic Oscillatory Activity Reflects Neurodegenerative Processes in Alzheimer's Disease

The challenge of the European PharmaCog and DECIDE projects

Claudio Babiloni [1,2] on behalf of the PharmaCog and DECIDE Consortia

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2. **Department of Clinical and Experimental Medicine, University of Foggia, Italy; IRCCS San Raffaele Pisana and Cassino, Italy**

Alzheimer's Disease (AD) is a social plaque

- Most common form of irreversible dementia
  - About 70% of all dementias are Alzheimer's
  - Over 4 million Europeans (EU27) have Alzheimer's
  - About 60% of all nursing home residents have Alzheimer's disease
  - In EU27 the total cost of Alzheimer's disorders (2008) was estimated to more than 100 billion Euro

AD symptoms are multi-dimensional

Cognition

- Memory
- Learning
- Language
- Praxic Function
- Abstract thinking
- Psycho-motor speed

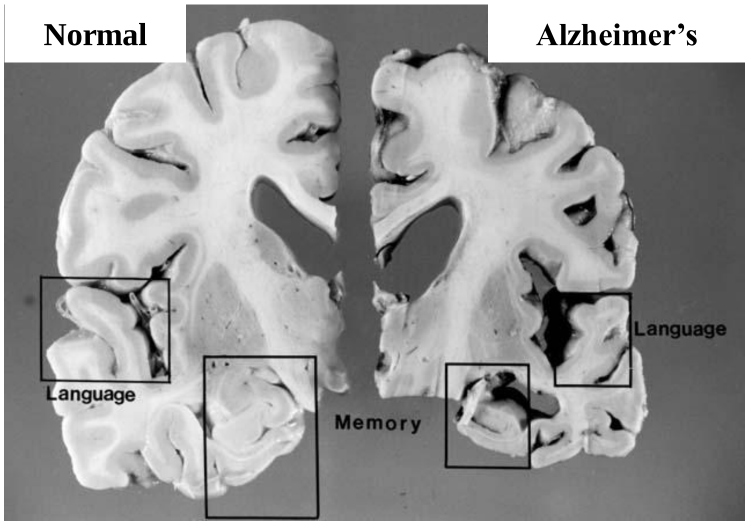
Behavior

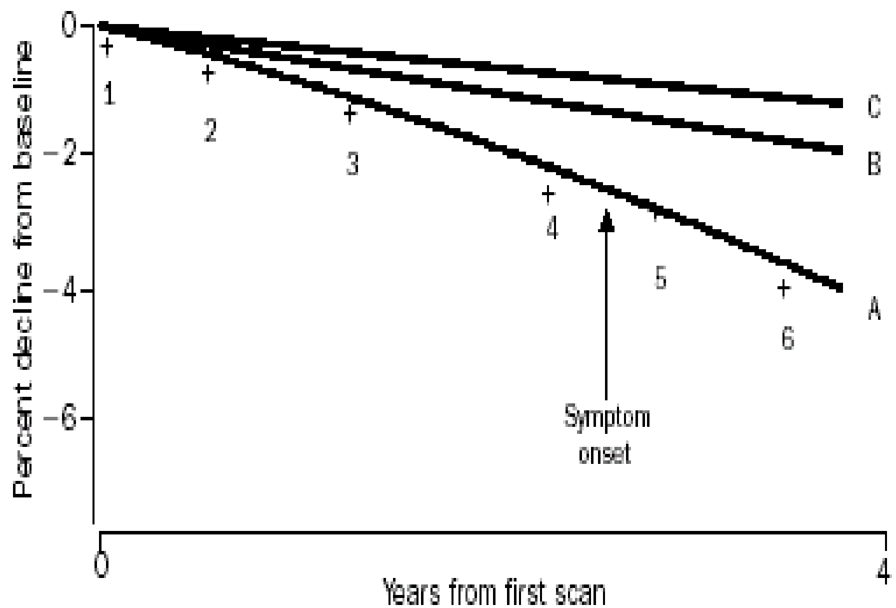
- Communi-cation
- Safety
- Personal care deteriorates
- Lapses in clarity
- Hallucina-tions
- Delusions

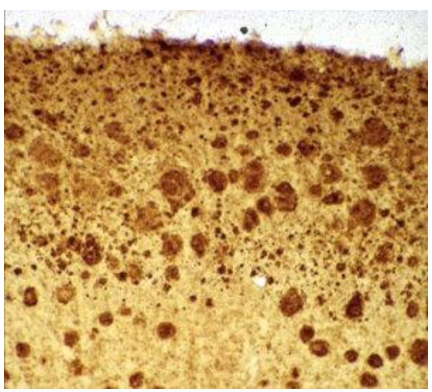
Emotion

- Disregulated
- Disorganized
- Apathy (loss of energy, willingness)
- Lability (moods change)

The neuropathological markers of the AD





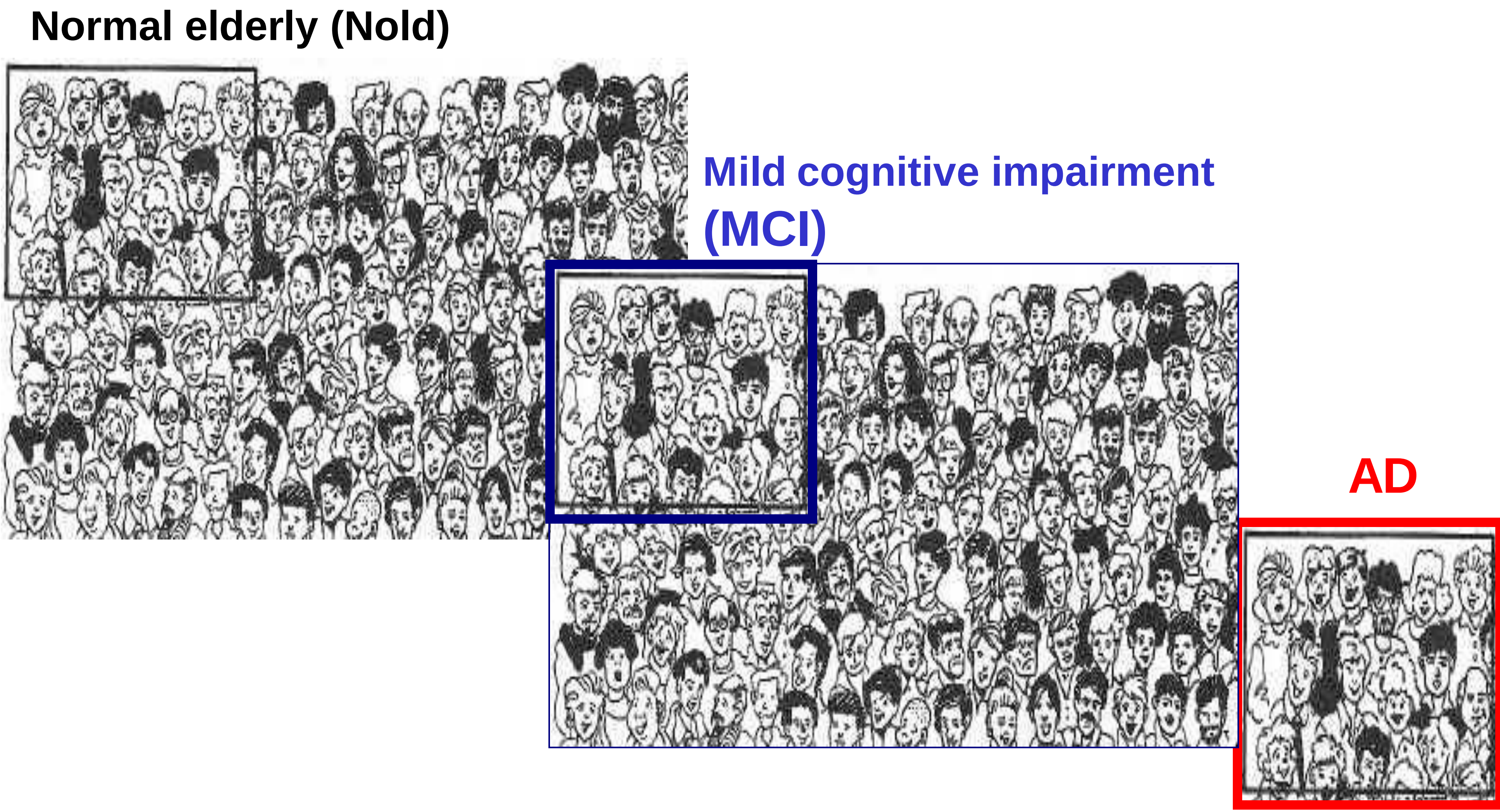


Extracellular Aβ plaques

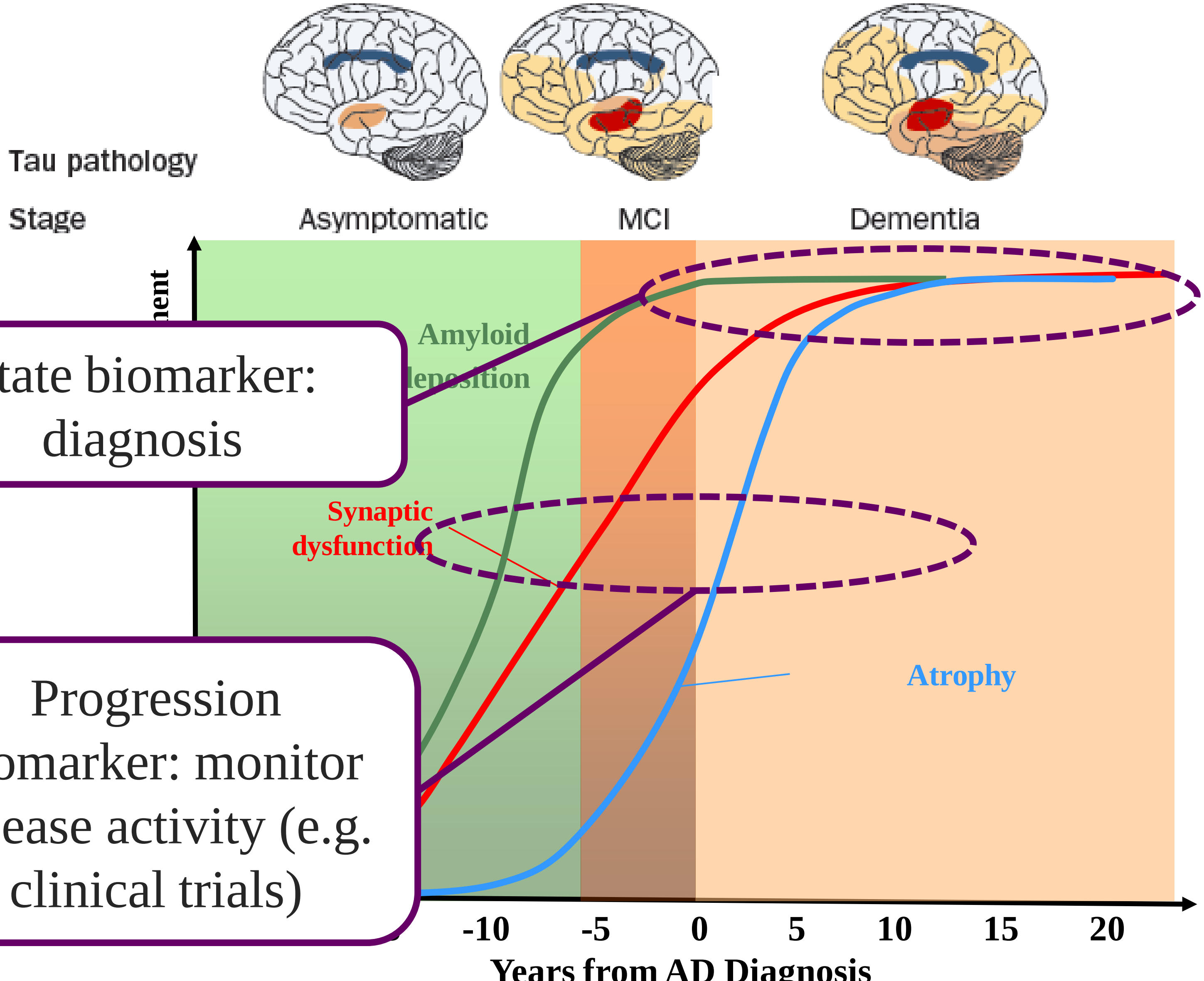
Intracellular tangles

Fox, Lancet (2004)

Which instrumental markers ("biomarkers") for early diagnosis, prognosis, disease monitoring, and drug discovery?



Alzheimer's biomarkers for diagnosis



State biomarker: diagnosis

Progression biomarker: monitor disease activity (e.g. clinical trials)

Courtesy by Frisoni GB et al. *Nat Rev Neurol* 2010

Alzheimer's & Dementia ■ (2011) 1–13

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o], Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison-Bogorad[r], Molly V. Wagster[r], Creighton H. Phelps[r]

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup

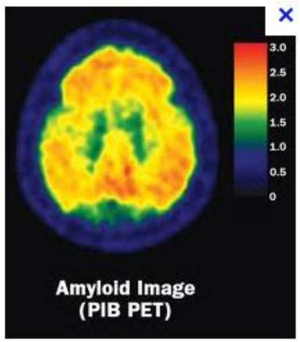
Marilyn S. Albert[a,*], Steven T. DeKosky[b,c], Dennis Dickson[d], Bruno Dubois[e], Howard H. Feldman[f], Nick C. Fox[g], Anthony Gamst[h], David M. Holtzman[i,j], William J. Jagust[k], Ronald C. Petersen[l], Peter J. Snyder[m,n], Maria C. Carrillo[o], Bill Thies[o], Creighton H. Phelps[p]

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

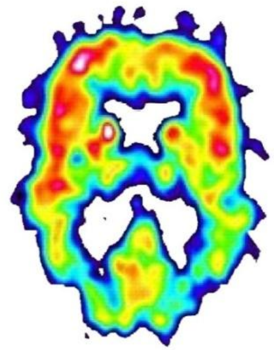
Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f], Clifford R. Jack, Jr.[g], Claudia H. Kawas[h,i,j], William E. Klunk[k], Walter J. Koroshetz[l], Jennifer J. Manly[m,n,o], Richard Mayeux[m,n,o], Richard C. Mohs[p], John C. Morris[q], Martin N. Rossor[r], Philip Scheltens[s], Maria C. Carillo[t], Bill Thies[t], Sandra Weintraub[u,v], Creighton H. Phelps[w]

The matrix of neurophysiologic and neuroimaging AD biomarkers: from topography to network disease

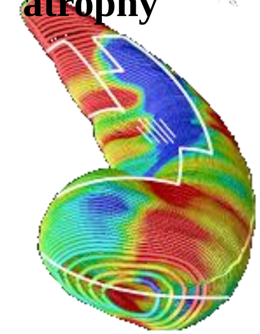
Molecular: PET-PIB amyloid deposition



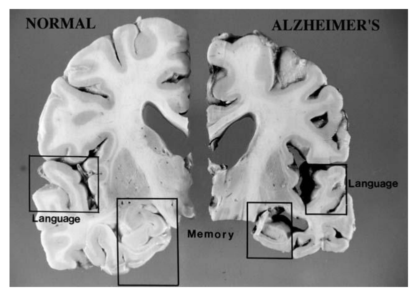
Molecular: PET-FDG hypo-metabolism



Structural: MRI cortical and hippocampus atrophy

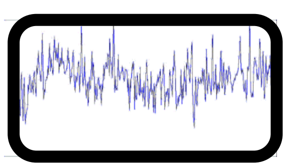


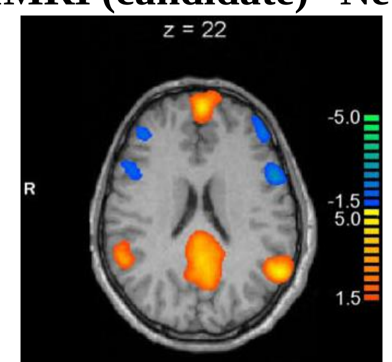
Normal



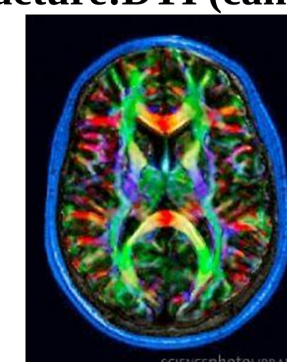
Alzheimer

Network function: resting EEG and fMRI (candidate)





Network structure:DTI (candidate)



Prediction of Cognitive Properties of New Drug Candidates for Neurodegenerative Diseases in Early Clinical Development : A Joint Industrial Academic Venture

EC Call: Innovative Medicine Initiative (IMI) “Neurodegenerative disorders” 2008
Duration: 60 months (January 2010-December 2014)
Coordinators:
Dr. Jill Richardson, Glaxo Smith Klaine (GSK)
Prof. Regis Bordet, University of Lille (France)

PharmaCog Consortium

Public

Regulators:
EMA

Patient Group:
Alzheimer Europe

Academic Institutions:
University of Marseille (Co-coordinator), France
University of Barcelona, Spain
University of Lille, France (Co-coordinator)
University of Leipzig, Germany
University of Murcia, Spain
University of Duisburg-Essen, Germany
CNRS, France
INSERM, France
University of Verona, Italy
IRCCS FBF, Brescia, Italy
University of Foggia, italy
Mario Negri Institute, Milan, Italy

Small and Medium Enterprises (SMEs):
Qualissima
AlzProtect
ExonHit
Innovative Health Diagnostics
ICDD (Innovative Concepts in Drug Development)

Private

GSK (Co-coordinator)
Astra Zeneca
Boehringer Ingelheim
Eli Lilly
Novartis Pharma
Servier
UCB Pharma
Merck Serono
Janssen Pharmaceuticals
Roche
Lundbeck
Eisai

Start date: 1/1/2010
Duration: 5 years
Total cost: €27.7M

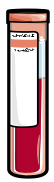
PharmaCog : focus on innnovation, translation and harmonisation

Preclinical Models ⟷ Clinical Models

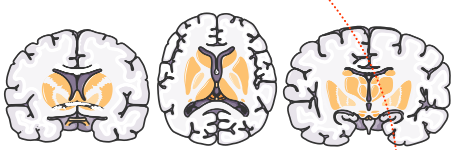
Develop laboratory based models and clinical models that mimics aspects of the disease and help to predict treatment efficacy

Develop markers using these models to predict effective dose ranges and prioritise new medicines

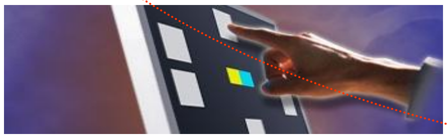
Develop Alzheimer's markers sensitive to the disease progression and drug treatment



Blood analysis



Brain scans



Cognitive testing

Core biomarker set

Brain talk (EEG)

Diagnostic enhancement of confidence by an international distributed environment

EC Call: FP7-INFRAS-2010-2 – VRC
“Neurodegenerative disorders” 2008
Contract n: RI-261593 _ Project type: CP-CSA
Duration: 30 months (September 2010- February 2013)
Coordinator: Dr. Fulvio Galeazzi, GARR (Italy)

DECIDE Consortium

Public

Patient Group:
Alzheimer Europe

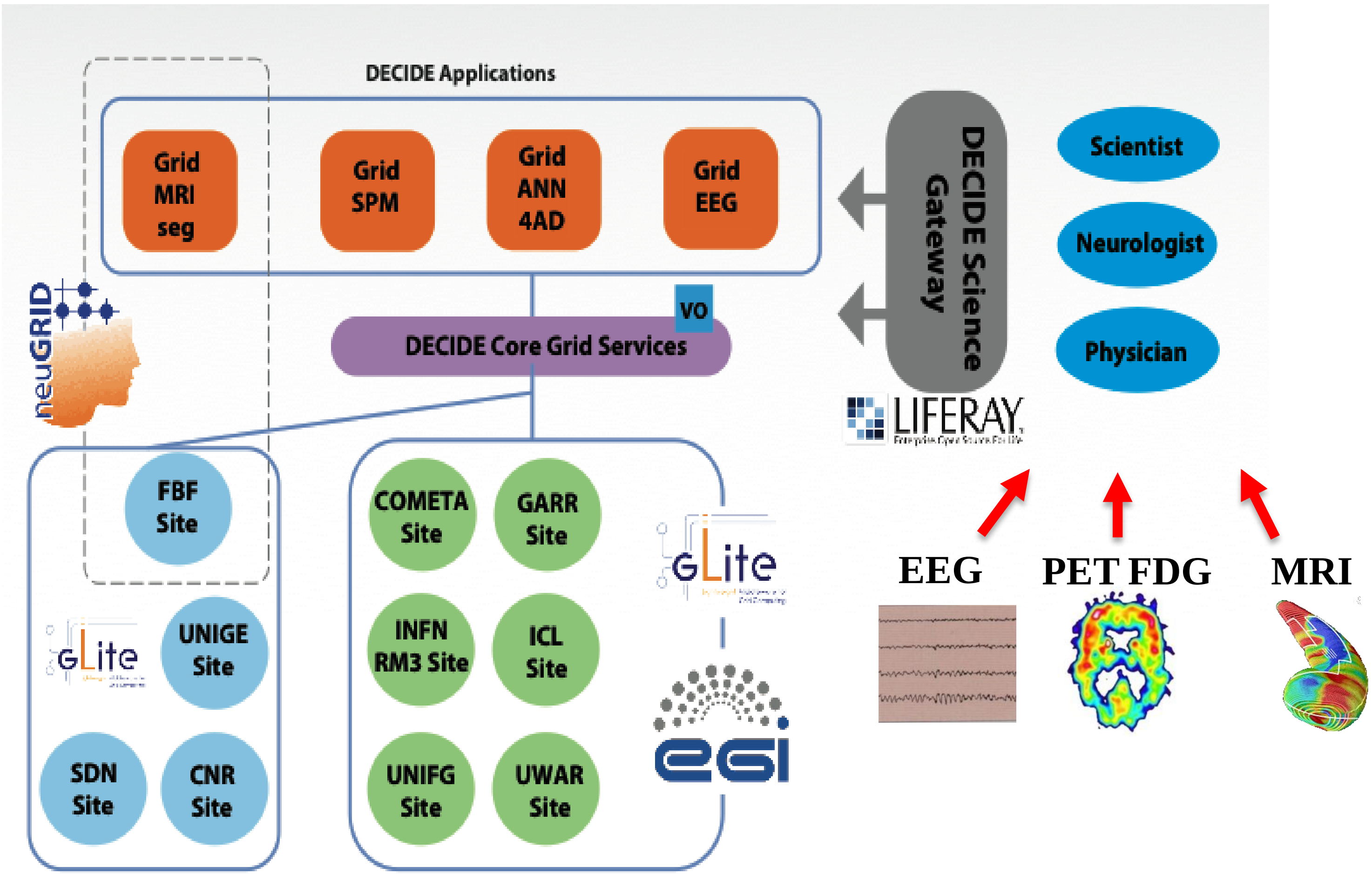
Academic Institutions:
GARR (Co-coordinator), Rome, Italy
University of Milan Vita-Salute San Raffaele, Italy
CNR of Milan, Italy
University of Foggia, Italy
University of Genova, Italy
University of Warrsaw, Poland
Imperial College, London UK
Centre hospitalier universitaire de Toulouse, Toulouse - France

Private

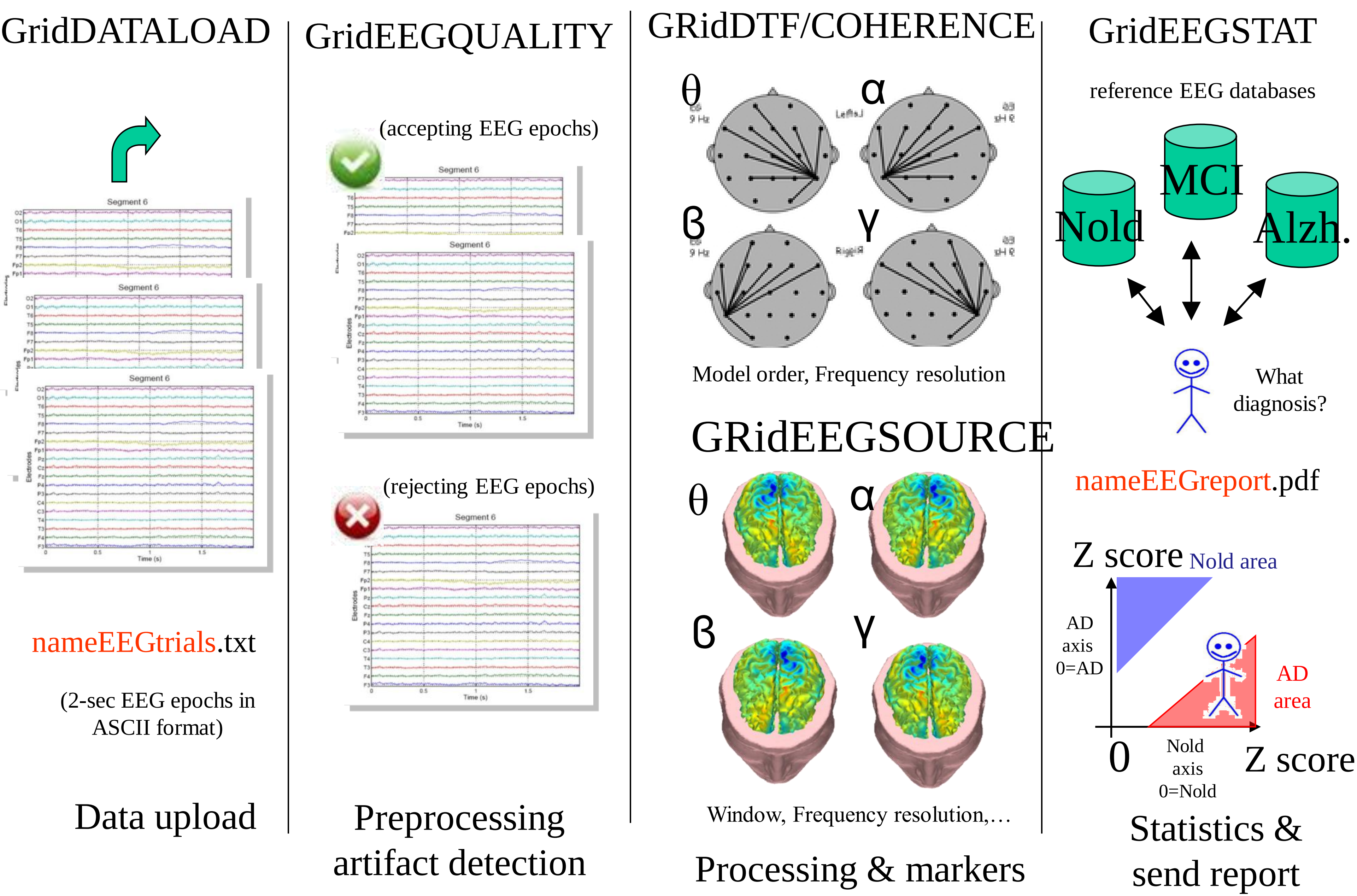
Small and Medium Enterprises (SMEs):
IRCCS Fatebenefratelli Brescia, Italy
IRCCS SDNi Naples, Italy
MAAT G, Gevneve, Ch

Start date: 9/1/2010
Duration: 30 months
Total cost: € 2.4 M €

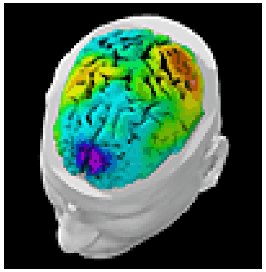
DECIDE service for early diagnosis of AD



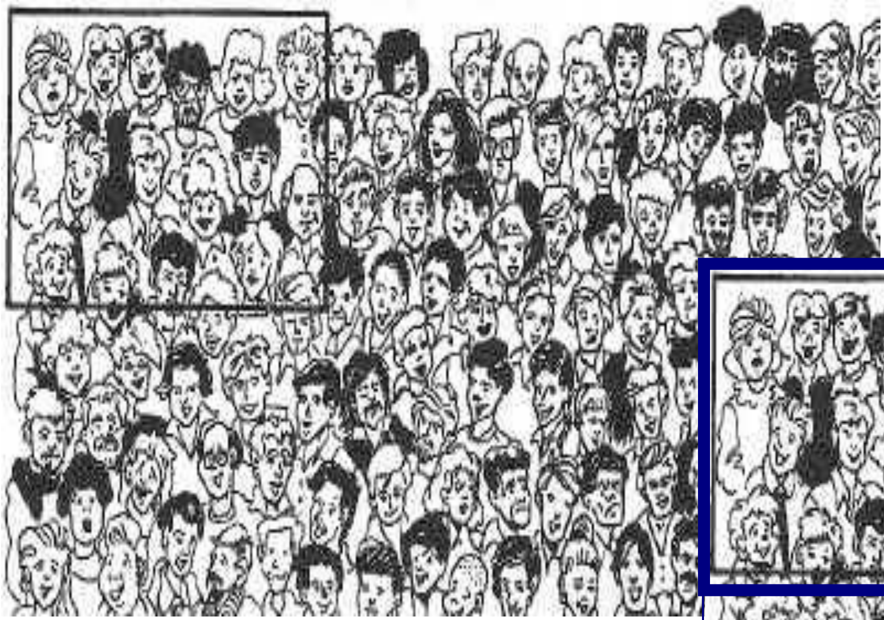
EEG facilities for the early diagnosis of AD in the DECIDE e-infrastructure



Which qEEG markers for early diagnosis, prognosis, disease monitoring, and drug discovery?



Normal elderly (Nold)



Mild cognitive impairment (MCI)

AD

Which qEEG markers for early diagnosis, prognosis, disease monitoring, and drug discovery?

PharmaCog

Clin Neurophysiol. 2012 Oct 22. pii: S1388-2457(12)00655-4. doi: 10.1016/j.clinph.2012.09.017. [Epub ahead of print]

Effects of acetylcholinesterase inhibitors and memantine on resting-state electroencephalographic rhythms in Alzheimer's disease patients.

Babiloni C, Del Percio C, Bordet R, Bourriez JL, Bentivoglio M, Payoux P, Derambure P, Dix S, Infarinato F, Lizio R, Triggiani AI, Richardson JC, Rossini PM.

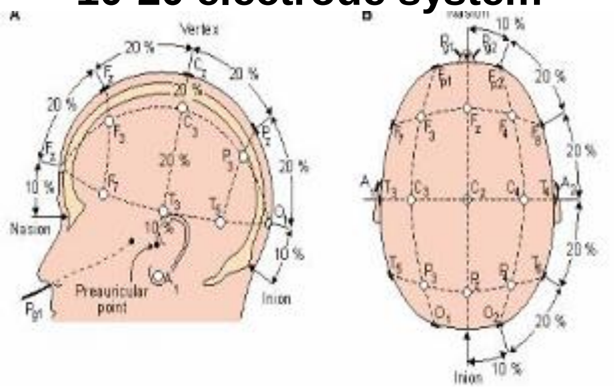
Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy; Department of Neuroscience, IRCCS San Raffaele Pisana, Rome, Italy. Electronic address: c.babiloni@unifg.it.

Abstract

Acetylcholinesterase inhibitors (AChEIs) are the most widely used symptomatic treatment for mild to severe Alzheimer's disease (AD) patients, while N-methyl-d-aspartic acid (NMDA) receptor antagonist memantine is licensed for use in moderate to severe AD patients. In this article, the effect of these compounds on resting state eyes-closed electroencephalographic (EEG) rhythms in AD patients is reviewed to form a knowledge platform for the European Innovative Medicine Initiative project "PharmaCog" (IMI Grant Agreement No. 115009) aimed at developing innovative translational models for drug testing in AD. Indeed, quite similar EEG experiments and the same kind of spectral data analysis can be performed in animal models of AD and in elderly individuals with prodromal or manifest AD. Several studies have shown that AChEIs affect both resting state EEG rhythms and cognitive functions in AD patients. After few weeks of successful treatment, delta (0-3Hz) or theta (4-7Hz) rhythms decrease, dominant alpha rhythms (8-10Hz) increase, and cognitive functions slightly improve. Beneficial effects of these rhythms and cognitive functions were also found in AD responders to the long-term successful treatment (i.e. 6-12months). In contrast, only one study has explored the long-term effects of memantine on EEG rhythms in AD patients, showing reduced theta rhythms. The present review enlightens the expected effects of AChEIs on resting state EEG rhythms in AD patients as promising EEG markers for the development of translational protocols both within the PharmaCog project and for wider use.

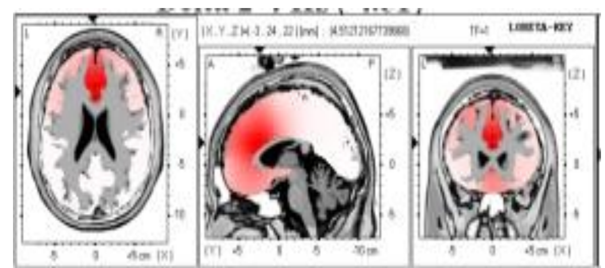
Basic methodology: 10-20 electrode montage and LORETA for source analysis of resting eyes-closed EEG

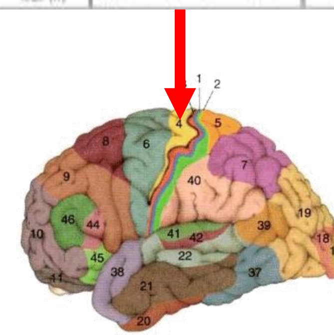
10-20 electrode system



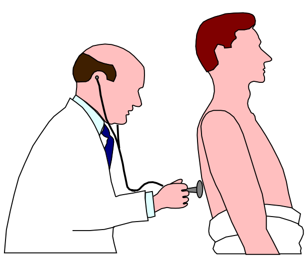
Resting eyes closed (2 min), eyes open (2 min)

LORETA



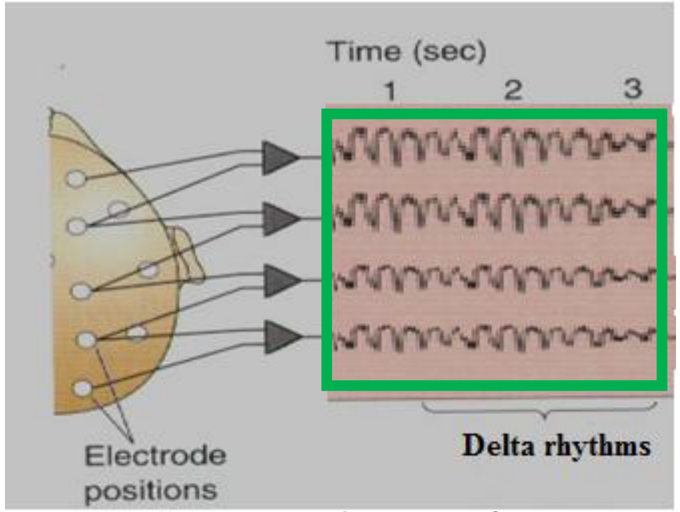


LORETA solutions averaged with cortical lobes (frontal, central, parietal, temporal, occipital, limbic)

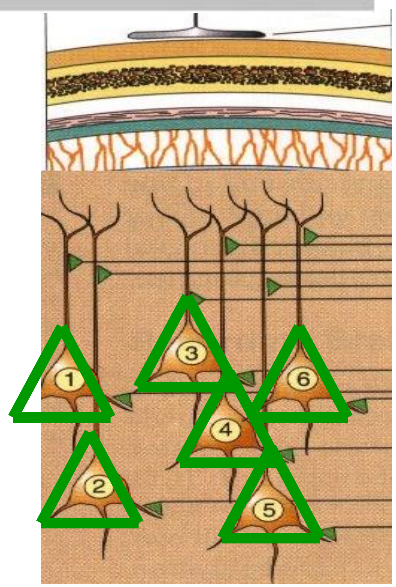


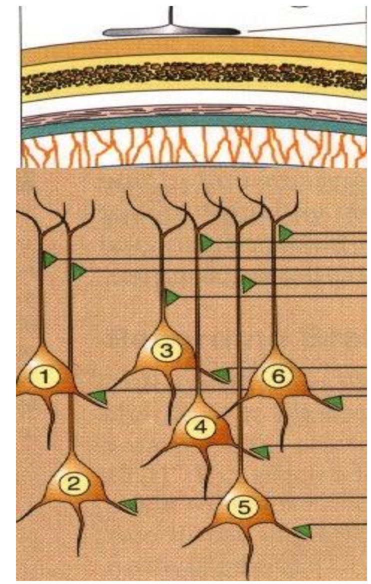
Psychometric testing and neurological evaluation

ISOLATED CORTEX



Spontaneous delta rhythms of cerebral cortex when disconnected from cortical and sub-cortical inputs





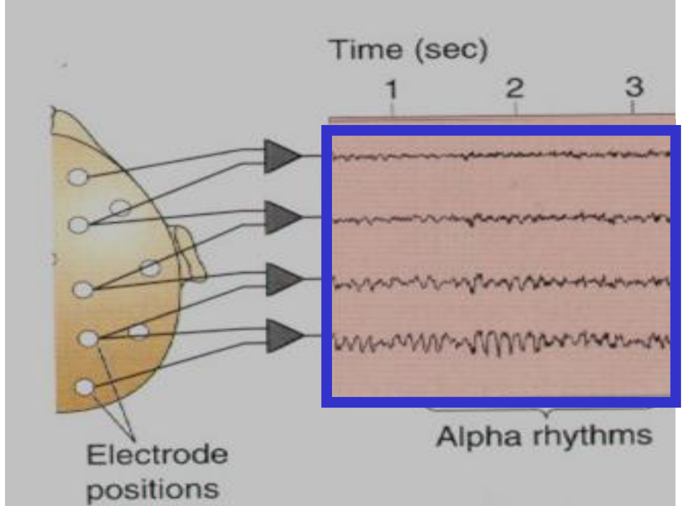
pyramidal neurons oscillating at synchronized delta frequencies (around 1 Hz)

△ **=All neurons synchronized at around 1 Hz**

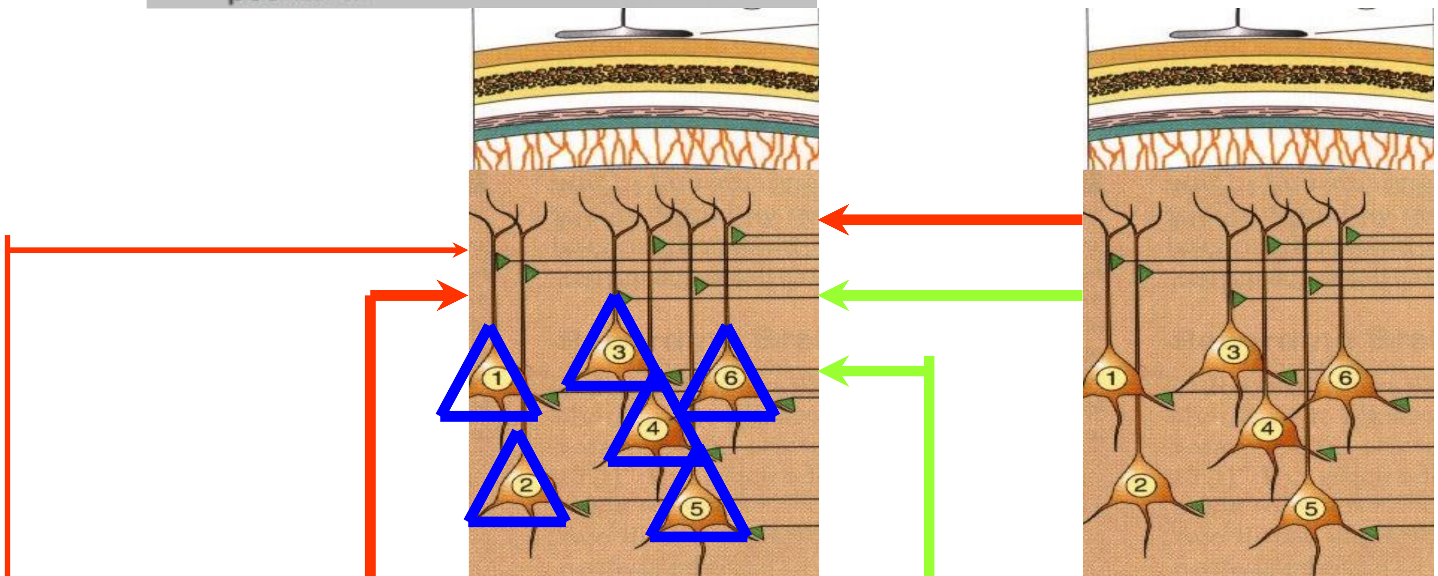
Reticular neurons **Relay neurons**

BRAIN STEM **THALAMUS**

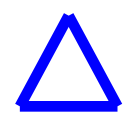
RESTING EYES CLOSED



Dominant resting (eyes-closed) alpha rhythms are synchronous and coherent over wide cortical areas and corresponding thalamic nuclei



pyramidal neurons oscillating at synchronized alpha frequencies (around 10 Hz)



=All neurons synchronized at around 10 Hz

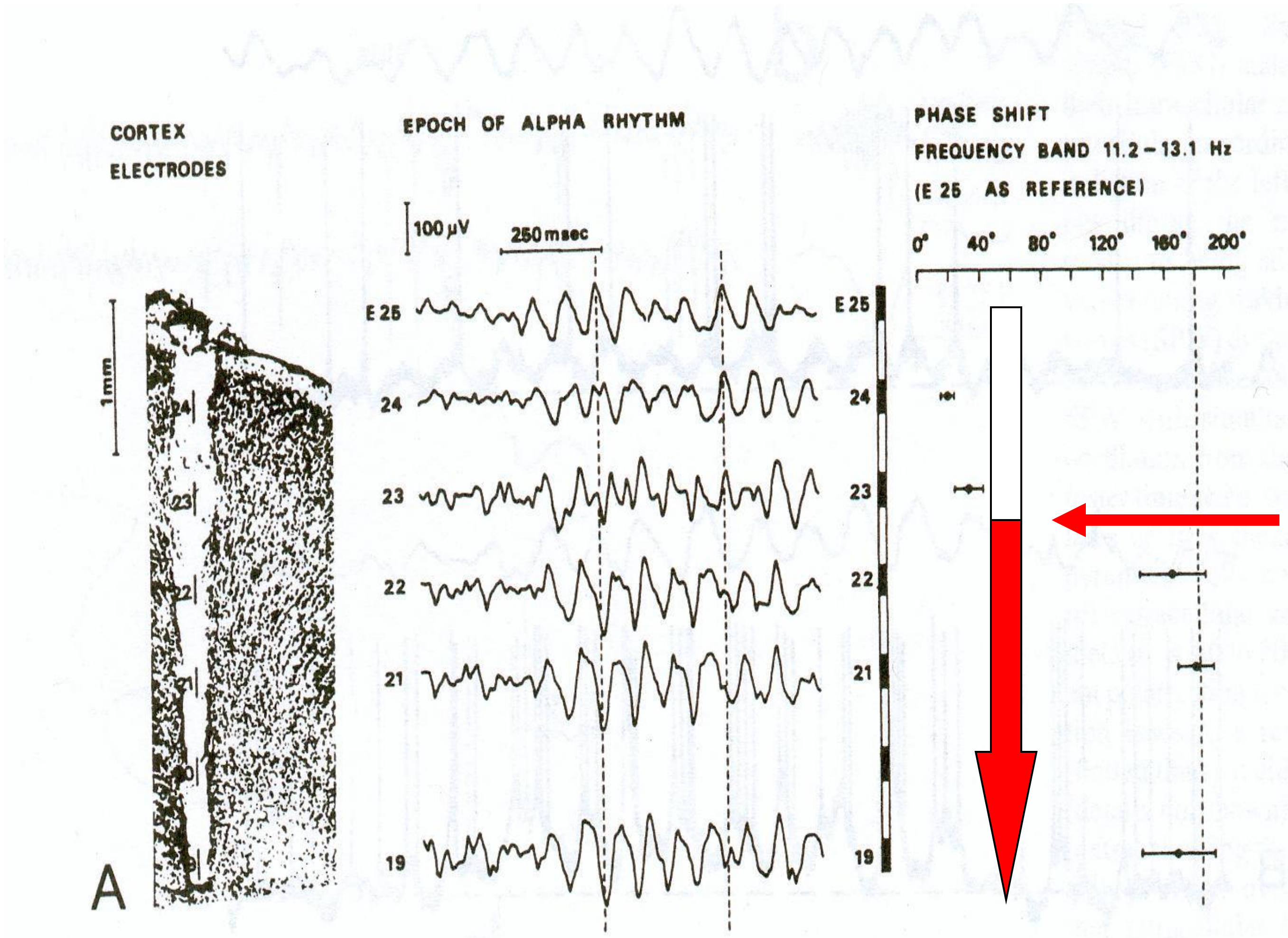
Reticular neurons

Relay neurons

BRAIN STEM

THALAMUS

Alpha rhythms recorded from the visual cortex of dog

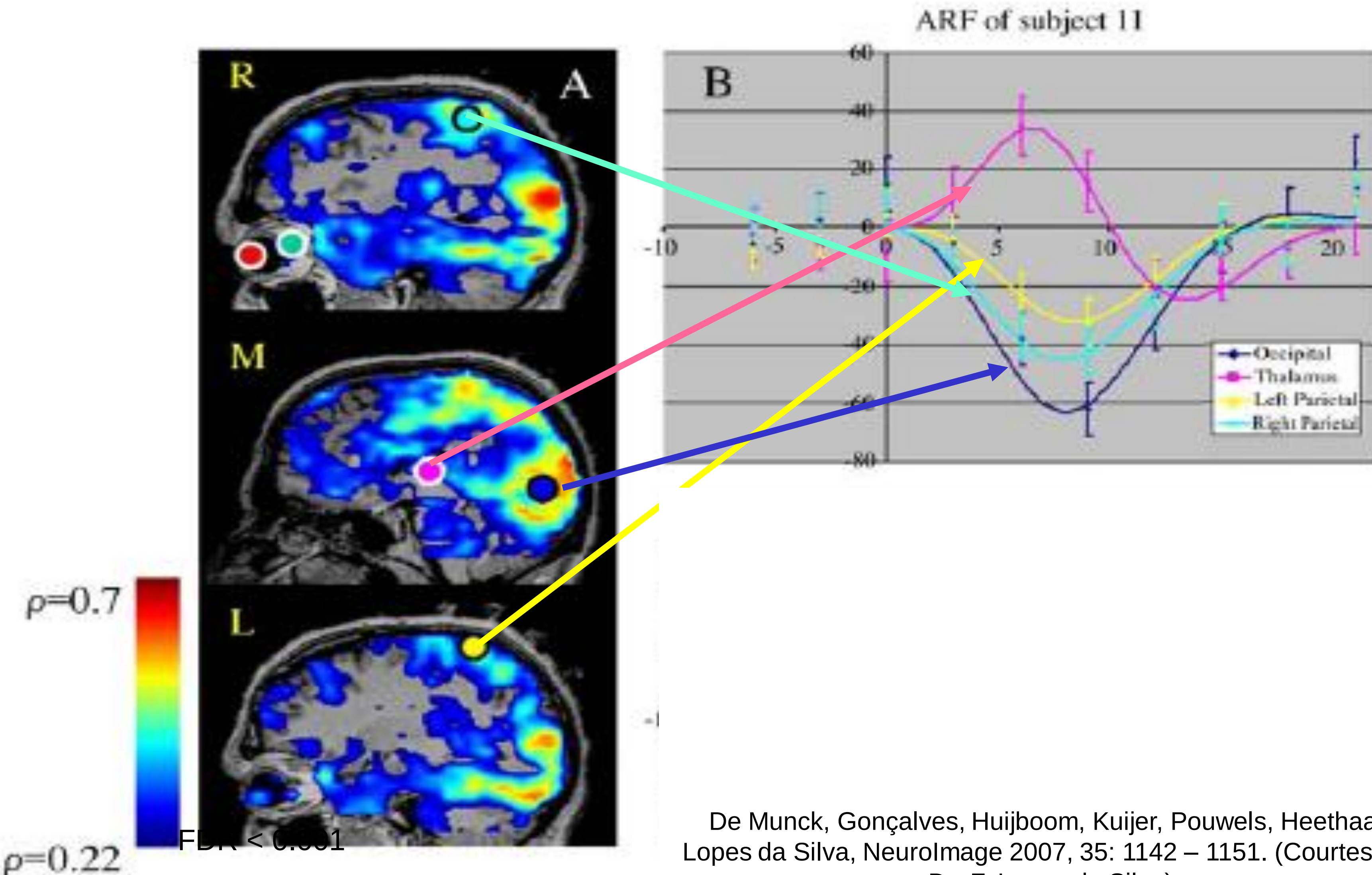


Cortical deep profile shows a polarity reversal across **cortical layers** reflecting a ***dipolar field.***

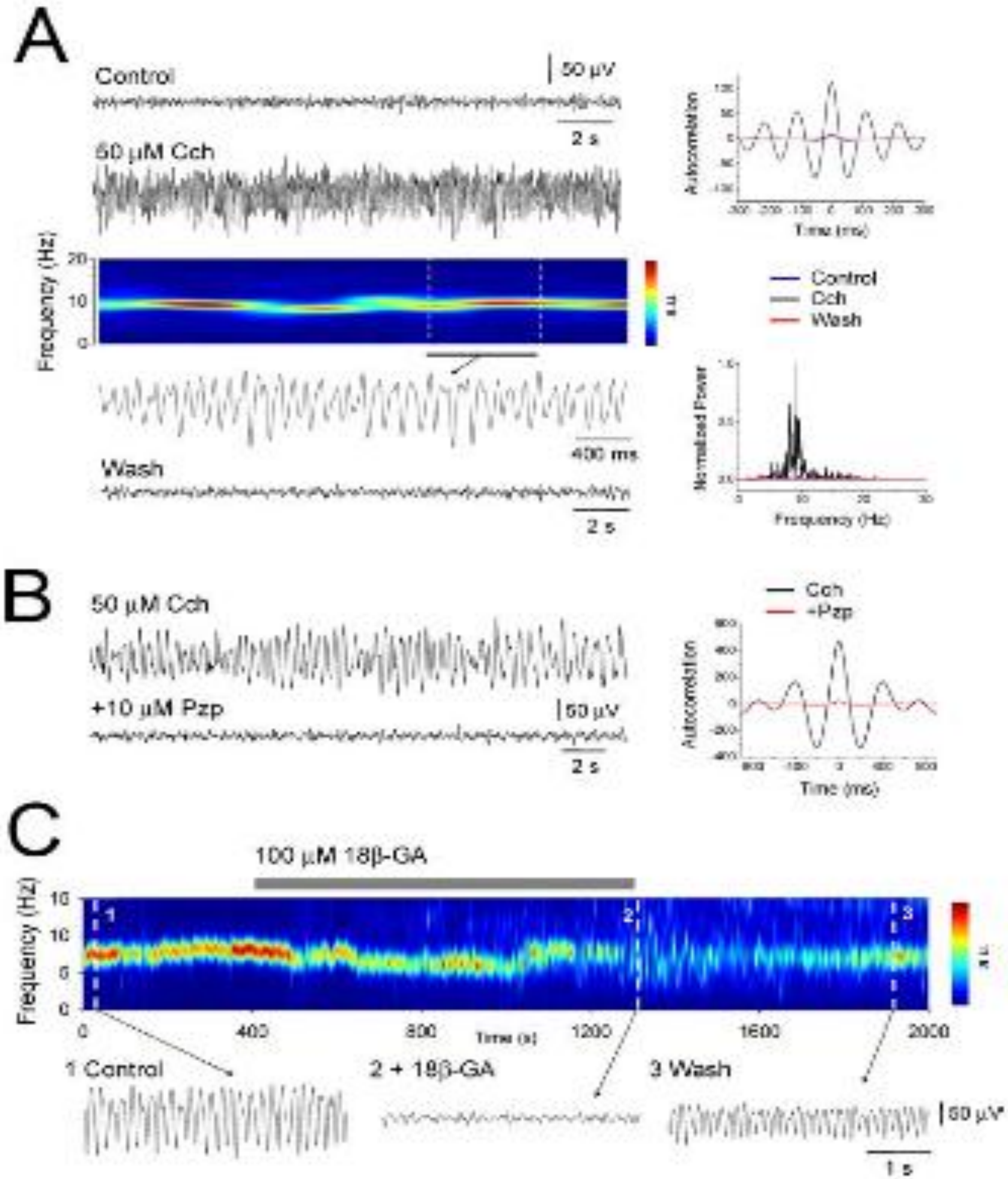
Lopes da Silva, and Storm van Leeuwen, 1977.
Courtesy by Dr. F. Lopes da Silva

Cortical alpha rhythms are negatively correlated with hemodynamic signals (BOLD) in parietal and occipital cortex

Cortical alpha rhythms are positively correlated with hemodynamic signals in thalamus



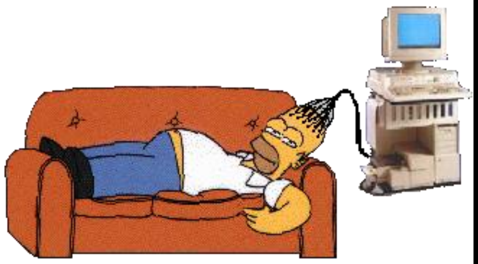
De Munck, Gonçalves, Huijboom, Kuijer, Pouwels, Heethaar, Lopes da Silva, NeuroImage 2007, 35: 1142 – 1151. (Courtesy by Dr- F. Lopes da Silva)



Cholinergic elicited alpha oscillations *in vitro* in the Thalamus - LGN and VB. Alpha abolished by M1-M3 receptor antagonist Pzp, and by Gap junction blocker 18β-GA. (Lorincz , Crunelli and Hughes, J Neurosci 2008)

- **qEEG markers of physiological aging:** **cortical resting EEG rhythms characterizing normal elderly (Nold) subjects compared to normal young subjects (physiological aging)**

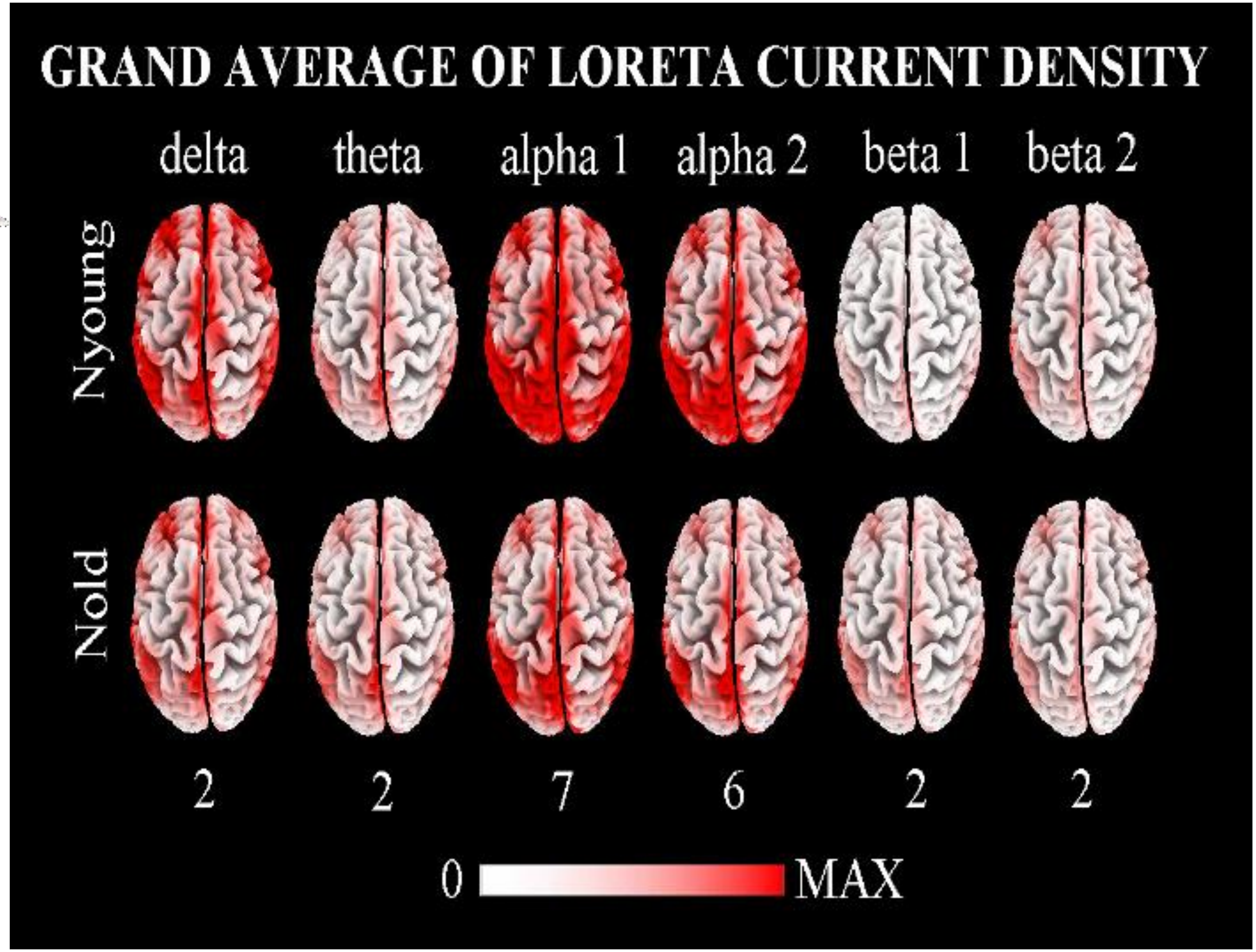
Posterior sources of resting alpha rhythms were lower in power in normal elderly than young subjects, despite similar degree of global cognition.



Resting EEG data

108 Nyoung

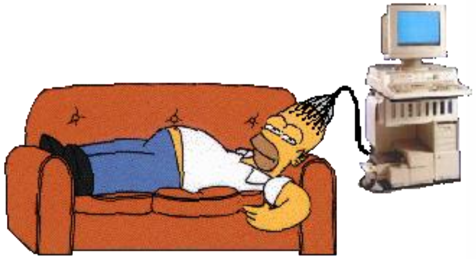
107 Nold



Babiloni C, Binetti G, Cassarino A, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Frisoni G, Galderisi S, Hirata K, Lanuzza B, Miniussi C, Mucci A, Nobili F, Rodriguez G, Romani GL, and Rossini PM. Sources of cortical rhythms in adults during physiological aging: a multi-centric EEG study. *Human Brain Mapping* 2006 Feb;27(2):162-72..

- **qEEG markers for differential diagnosis: cortical resting EEG rhythms characterizing mild AD compared to cerebrovascular dementia (VaD) and Parkinson disease with dementia**

Posterior sources of resting alpha rhythms were lower in power in mild AD than VaD subjects, despite similar degree of global cognition.

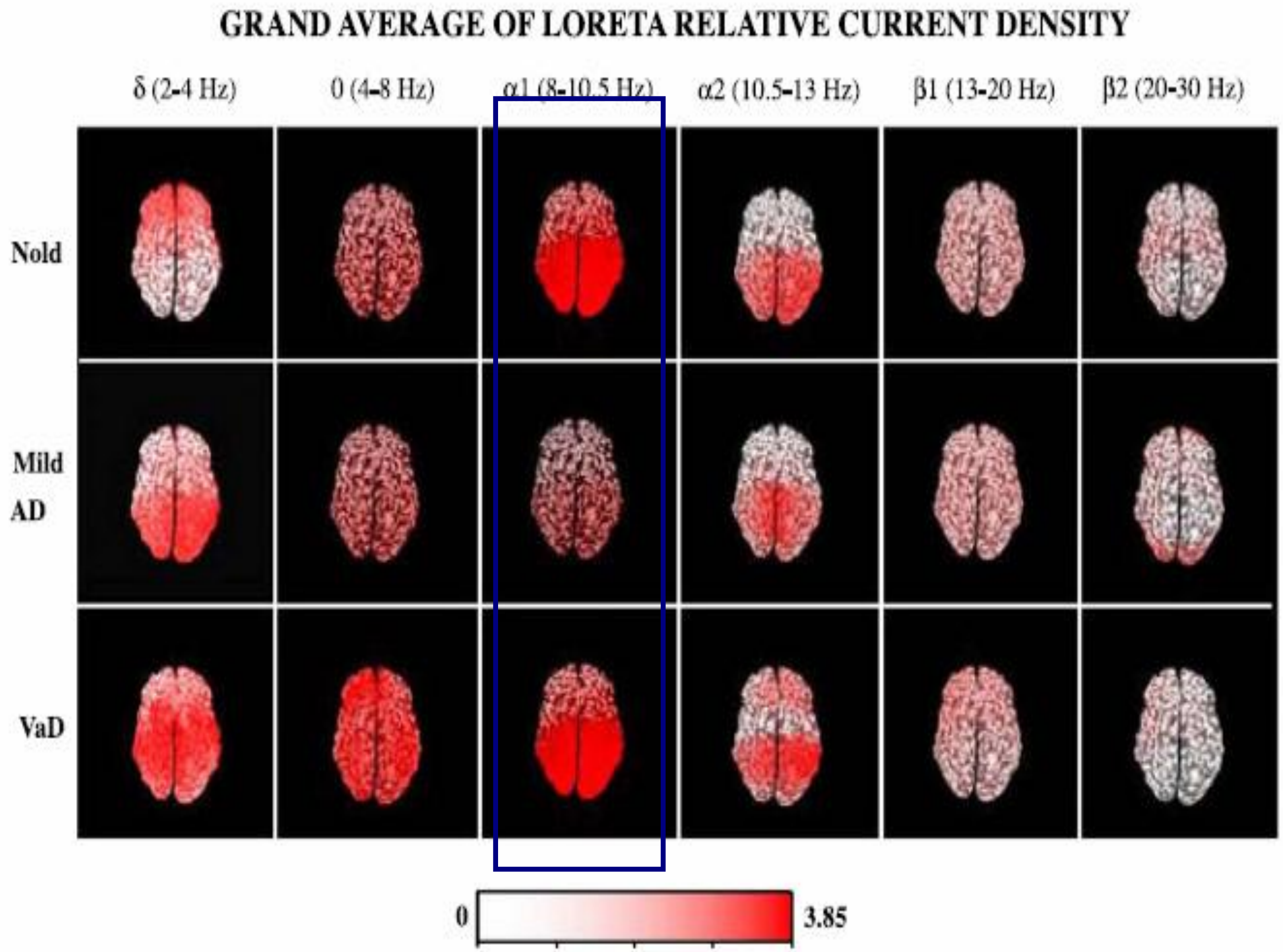


Resting EEG data:

38 Nold

48 mild AD

20 VaD



Babiloni C, Binetti G, Cassetta E, Cerboneschi D, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Lanuzza B, Miniussi C, Moretti DV, Nobili F, Pascual-Marqui RD, Rodriguez G, Romani GL, Salinari S, Tecchio F, Vitali P, Zanetti O, Zappasodi F, Rossini PM. Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multicentric EEG study. Neuroimage. 2004; 22(1): 57-67.

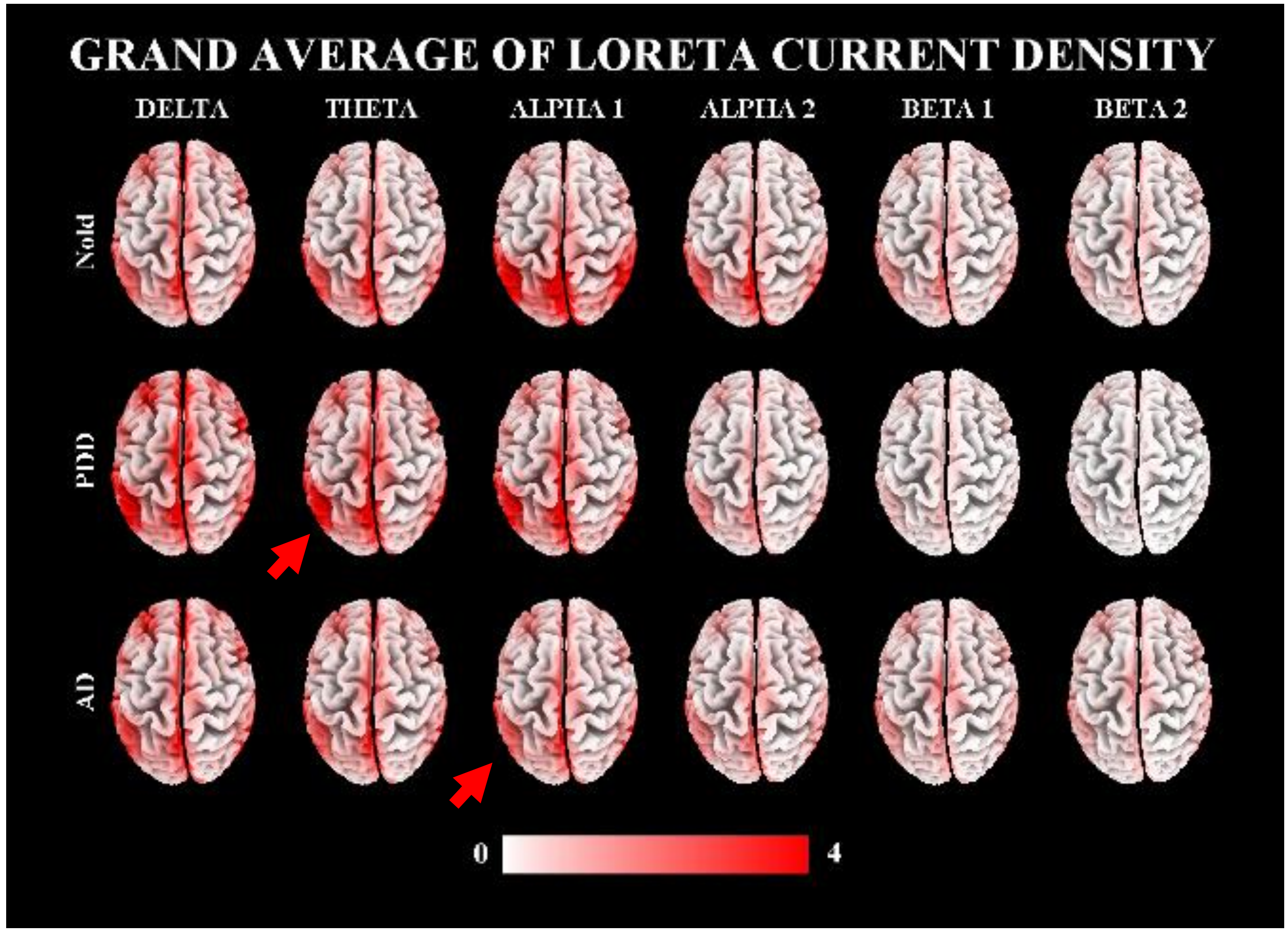
Posterior sources of resting alpha rhythms were lower in power in mild AD than PDD subjects but the opposite was true for widespread theta rhythms

Resting EEG data:

20 Nold

13 PDD

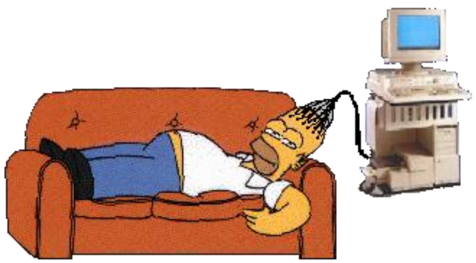
20 mild AD



Babiloni Claudio, De Pandis Francesca, Vecchio Fabrizio, Buffo Paola, Sorpresi Fabiola, Frisoni Giovanni B. and Rossini Paolo M. Cortical sources of resting state electroencephalographic rhythms in Parkinson's disease related dementia and Alzheimer's disease (Clinical Neurophysiology, 2011)

- qEEG markers for preclinical diagnosis of AD: cortical resting EEG rhythms characterizing mild cognitive impairment (MCI) and subjective memory complaint (SMC)

Posterior sources of resting delta and alpha rhythms gradually change in amplitude along Nold, MCI, and mild AD continuum

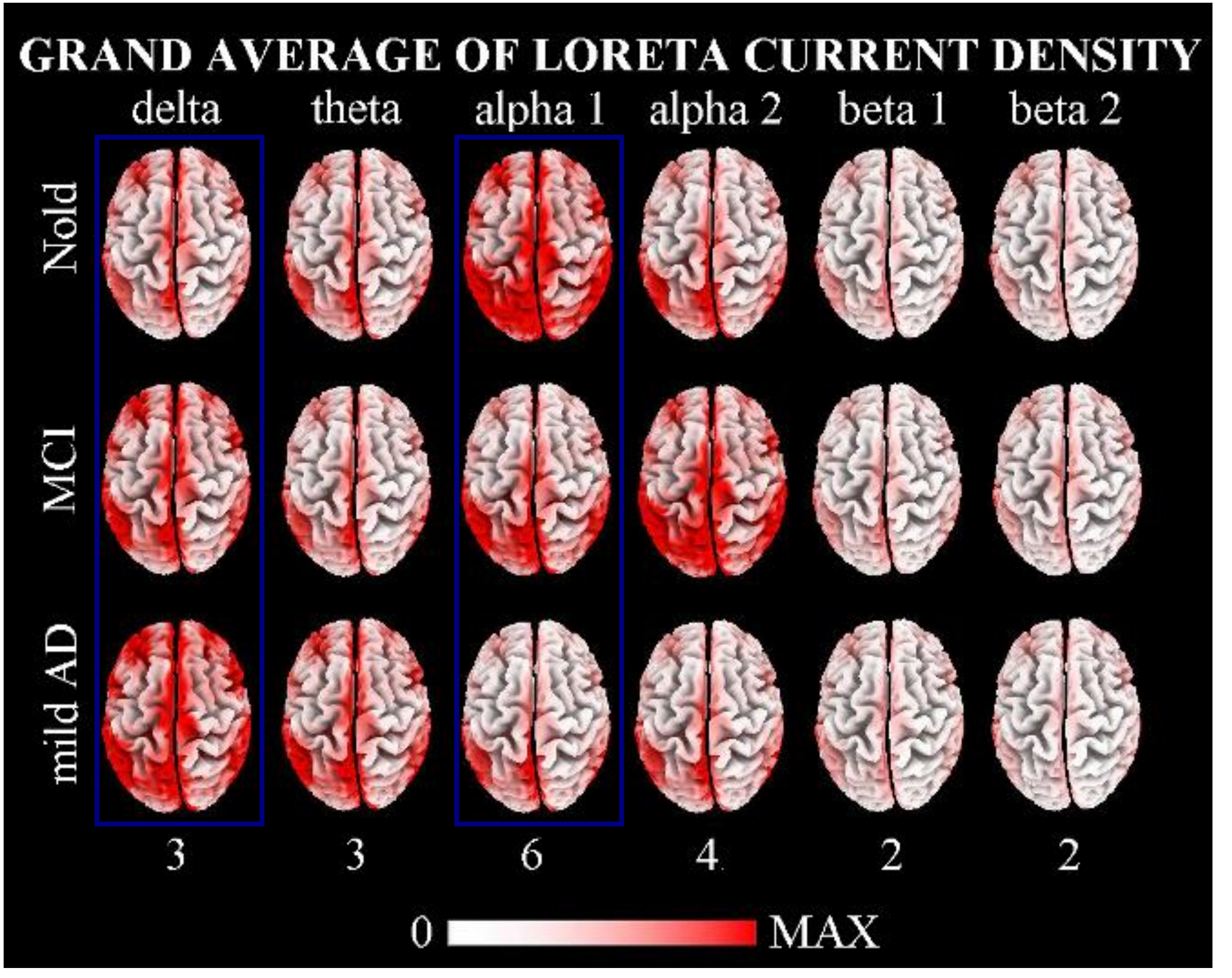


Resting EEG data:

126 Nold

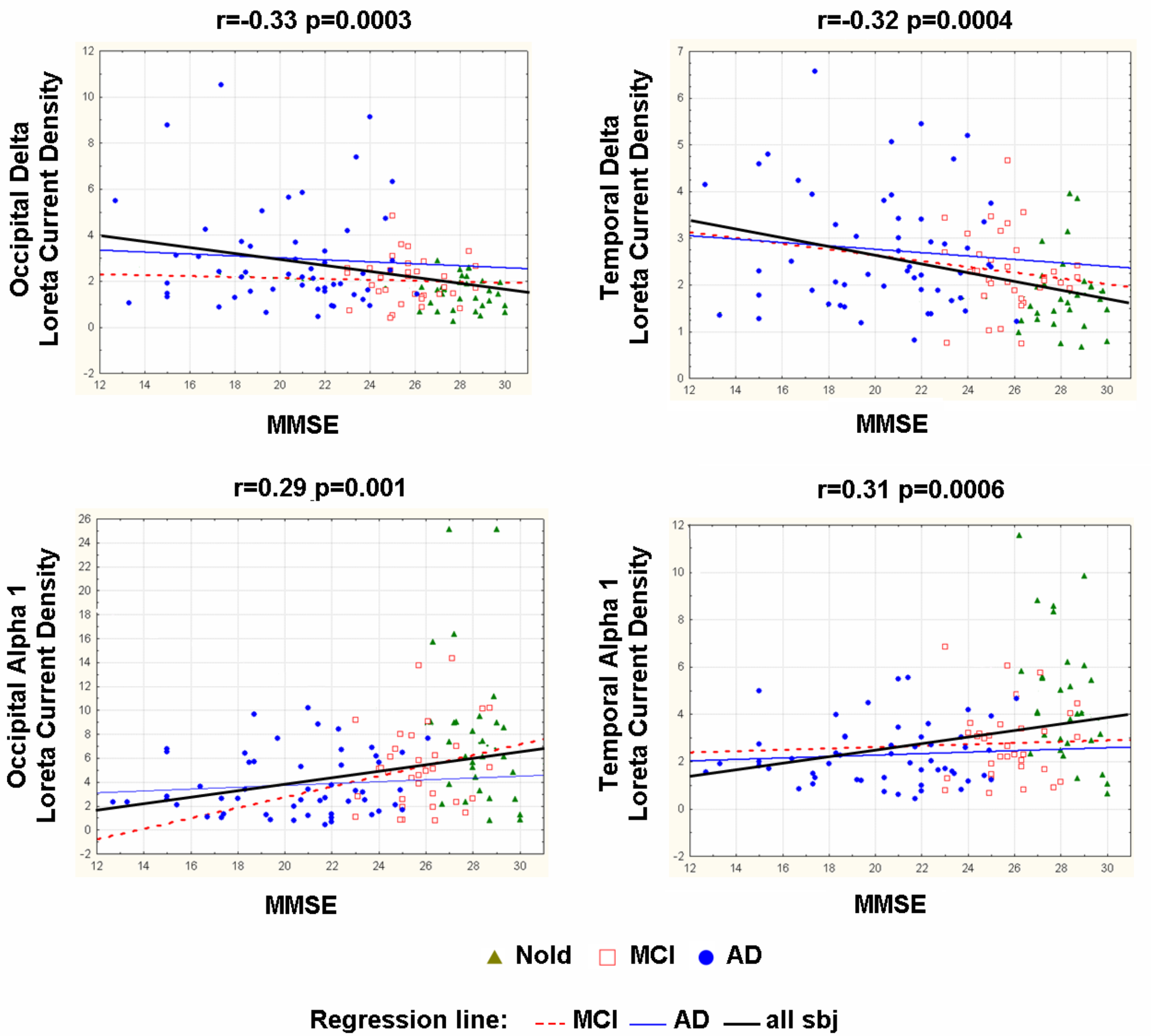
155 MCI

193 mild AD



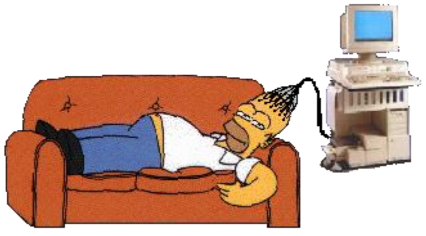
Babiloni C, Binetti G, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Frisoni G, Hirata K, Lanuzza B, Miniussi C, Moretti DV, Nobili F, Rodriguez G, Romani GL, Salinari S, and Rossini PM Sources of cortical rhythms in subjects with mild cognitive impairment: a multi-centric study Clinical Neurophysiology 2006

SCATTERPLOT: MMSE AND LORETA CURRENT DENSITY



Babiloni Claudio, Cassetta Emanuele, Binetti Giuliano, Tombini Mario, Del Percio Claudio, Ferreri Florinda, Ferri Raffaele, Frisoni Giovanni, Lanuzza Bartolo, Nobili Flavio, Parisi Laura, Rodriguez Guido, Frigerio Leonardo, Gurzì Mariella, Prestia Annapaola, Eusebi Fabrizio and Rossini Paolo M. Resting EEG sources correlate with attentional span in mild cognitive impairment and Alzheimer's disease European Journal of Neuroscience, 2007.

Posterior sources of resting alpha rhythms are higher in amplitude in the Nold than in the SMC and MCI subjects, and in the amnesic than in the non amnesic MCI



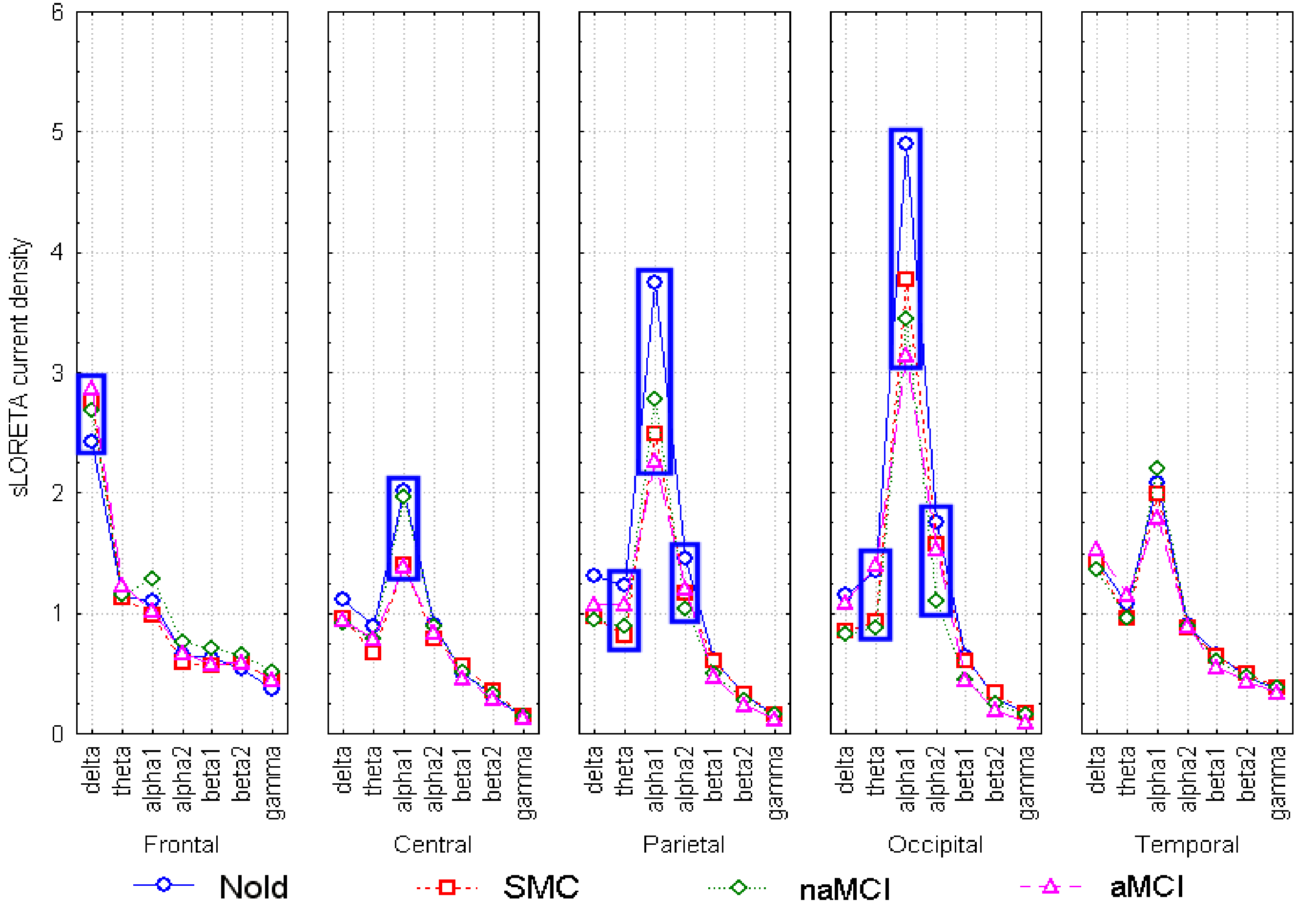
Resting EEG data:

74 Nold (Normal elderly)

29 SMC (Subjective Memory Complaint)

30 naMCI (Non Amnesic MCI)

57 aMCI (Amnesic MCI)



$0.000001 \leq p \leq 0.04836$

C Babiloni; PJ Visser, G Frisoni, D Colombo, PP De Deyn, L Bresciani, V Jelic, G Nagels, G Rodriguez, PM Rossini, F Vecchio, F Verhey, LO Wahlund, F Nobili. Cortical sources of resting EEG rhythms in mild cognitive impairment and subjective memory complaint. Neurobiology of Aging 2009 NETWORK OF EXCELLENCE "DESCRIPA"

- **qEEG markers related to AD neurodegeneration: cortical resting EEG rhythms associated to structural MRI (hippocampus and cortical atrophy) and functional PET-FDG markers in MCI and AD subjects**

Posterior sources of resting alpha rhythms gradually change in amplitude along MCI and mild AD continuum as a function of hippocampal atrophy

Resting EEG data:

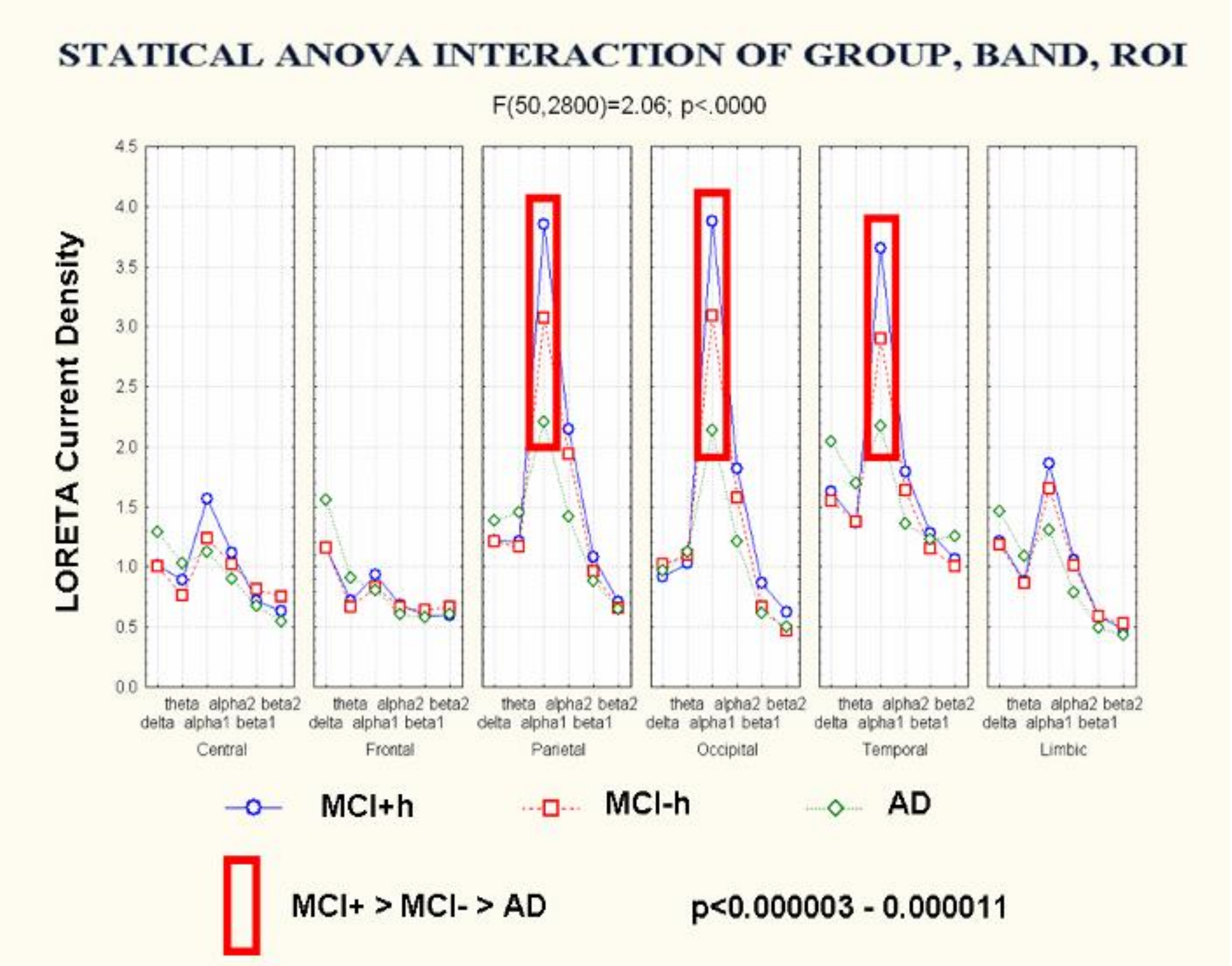
40 MCI

+ hippocampal volume (+h)

40 MCI

- hippocampal volume (-h)

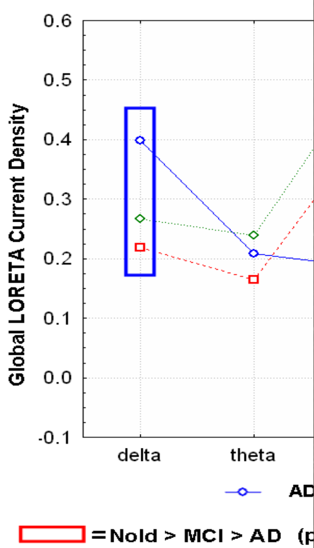
35 mild AD

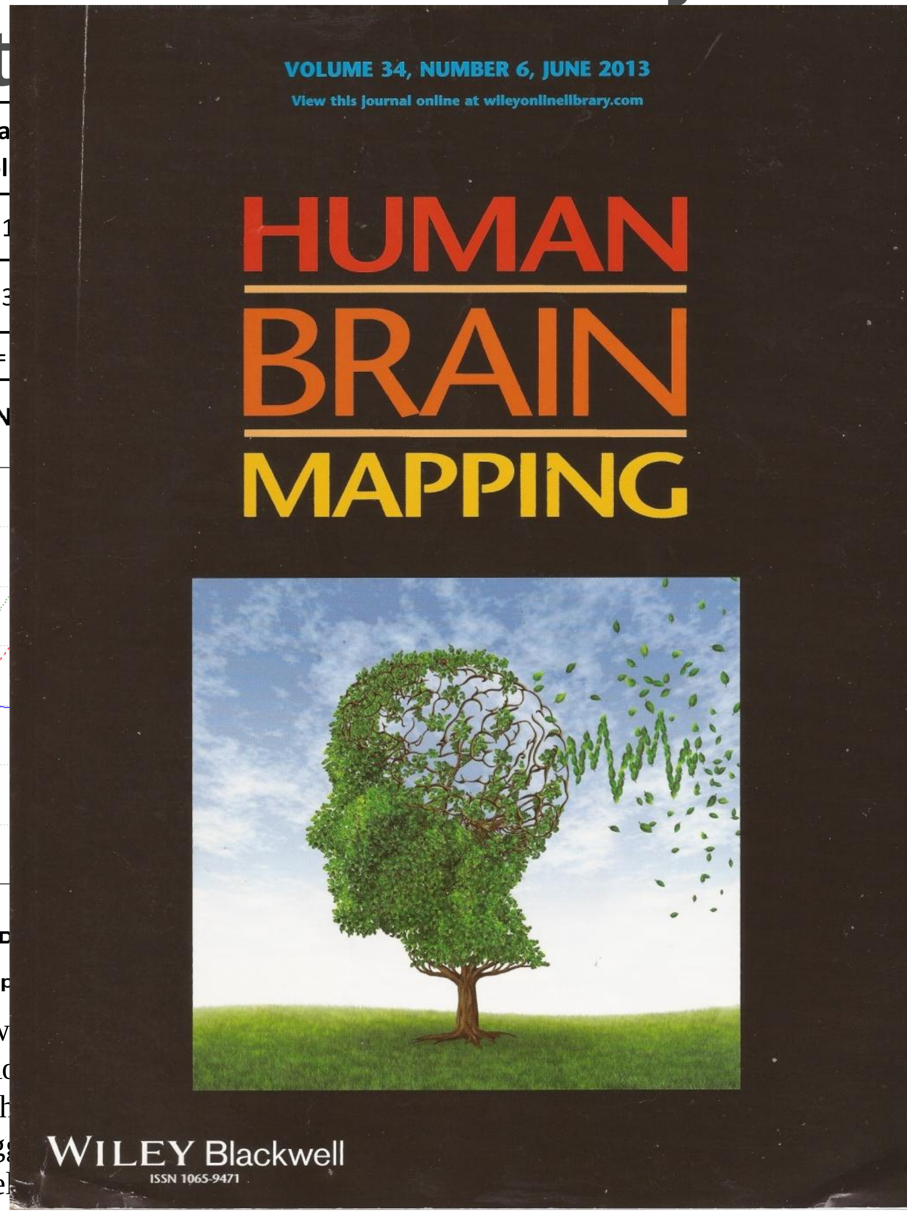


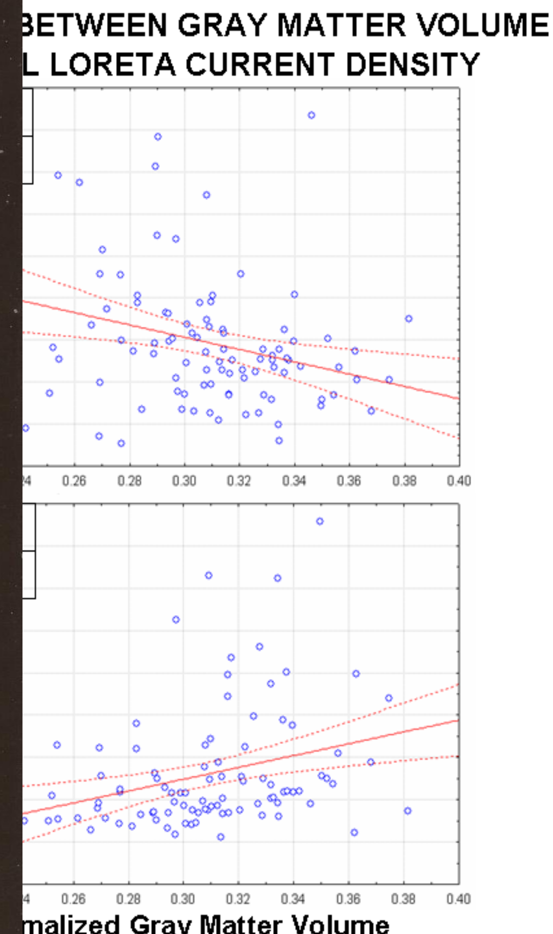
Babiloni C, Frisoni GB, Pievani M, Vecchio F, Lizio R, Geroldi C, Fracassi C, Eusebi F, and Rossini PM. Hippocampal volume and cortical sources of EEG alpha rhythms in mild cognitive impairment and Alzheimer disease. Neuroimage 2009

Resting state cortical EEG rhythms are related to gray mat ... D patients

	Subjects	Gra... Vol...
AD	108	498.1...
MCI	102	566.3...
MCI≠AD		p=...





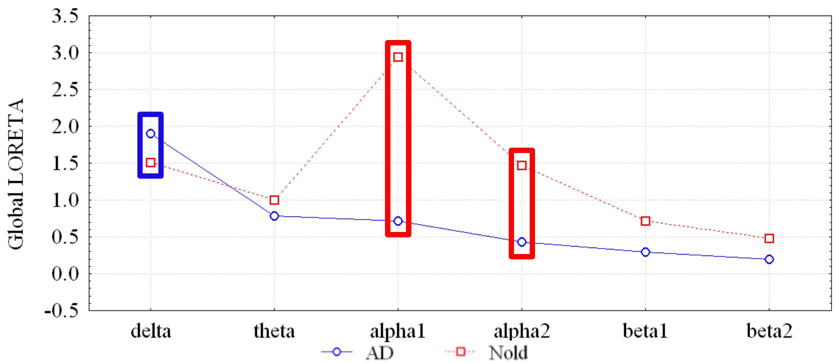


In the MCI and AD subjects as a w... the higher the delta sources, the lo... better the score to cognitive tests th... the alpha sources. These results sugg... cortical EEG rhythms are strictly rel...

Babiloni C, Carducci F, Lizio R, Vecchio F, Baglieri A, Bernardini S, Boccardi M, Bozzao A, Buttinelli C, Esposito F, Giubilei F, Guizzaro A, Marino S, Montella P, Quattrocchi C, Redolfi A, Soricelli A, Tedeschi G, Triggiani I, Rossi-Fedele G, Parisi L, Vernieri F, Rossini PM, and Frisoni GB- Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive impairment and Alzheimer's disease: an ADNI project. Human Brain Mapping 2011

Resting state cortical EEG rhythms correlate with PET markers in AD patients

	Subjects	Gender	Education	MMSE	Age (years)
AD	20	11 F, 9 M	9.7± (1.1 SE)	19.5± (1.1 SE)	67.4± (1.7 SE)
Nold	35	22 F, 13 M	9.8± (0.8 SE)	28.2± (0.2 SE)	69.5± (0.9 SE)

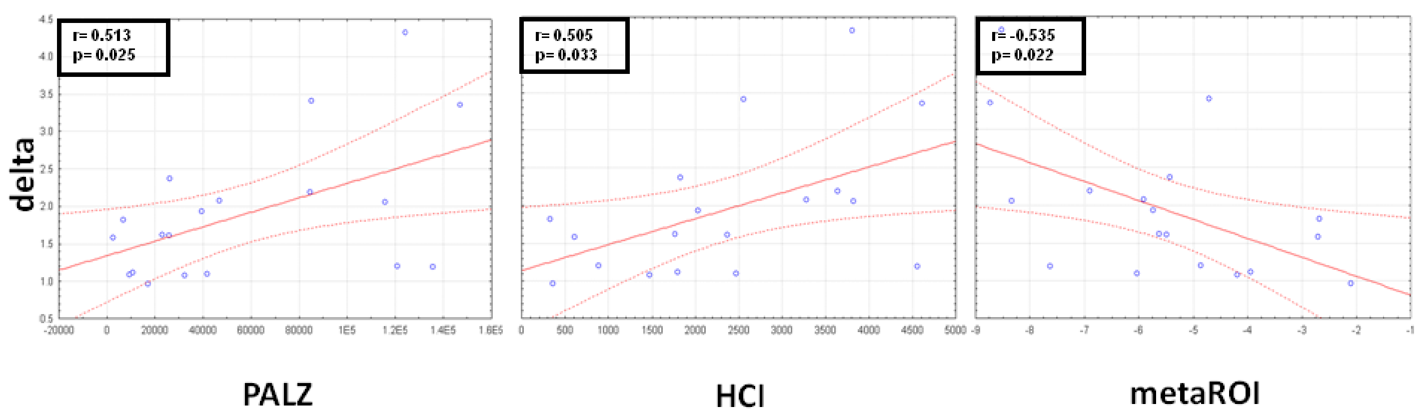


Alpha 1 and alpha 2 sources were higher in amplitude in the Nold than in the AD group; these results disclosed the pattern Nold>AD for the alpha sources. Furthermore, the <u>delta sources were lower in amplitude in the Nold than in the AD groups</u>, in line with the pattern Nold≠ AD

In the AD patients, magnitude of the global delta sources correlated with cortical metabolic damage as revealed by PALZ, HCI and metaROI indices of PET-FDG. <u>The higher the cortical metabolic damage, the higher the pathological delta sources.</u> These results reflect relevant pathological processes in these patients

AD> Nold (blue)

Nold> AD (red)



Babiloni C, Lizio R, Marzano N, Del Percio C, Soricelli A, Salvatore E, Caroli A, Cavedo E, Tedeschi G, Montella P, Guizzaro A, Esposito F, Frisoni GB, Rossini PM. Resting state cortical electroencephalographic rhythms are related to cerebral hypometabolism in subjects with Alzheimer's disease. Neurobiology of Aging, 2013 (in preparation)

Correlation between global delta/alpha 1 rhythms and FA values of DTI in mild AD patients.

ALPHA1

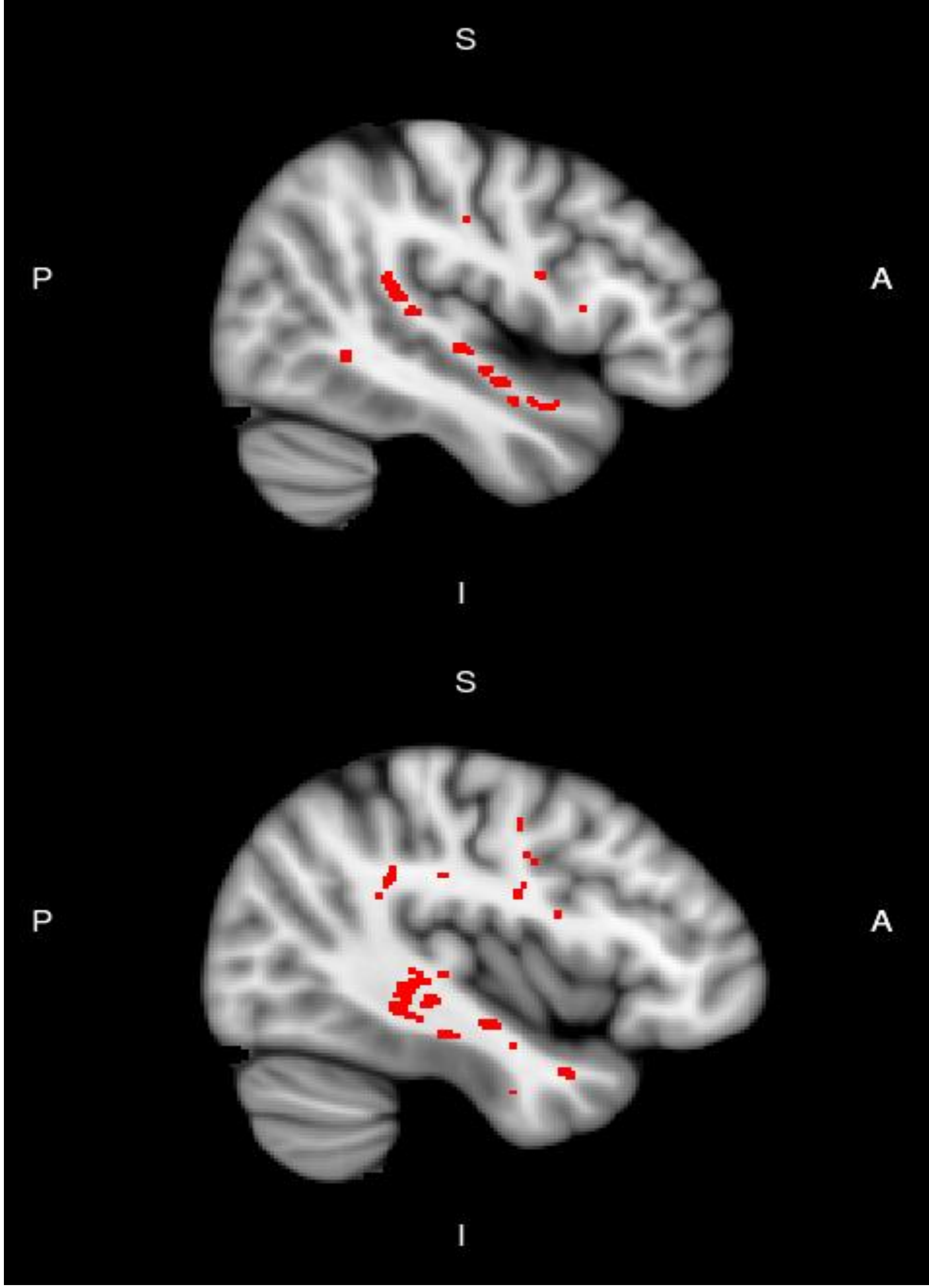
Anterior thalamic radiation L/R
Cingulum (cingulate gyrus) L/R
Corticospinal tract L/R
Forceps major
Forceps minor
Inferior fronto-occipital fasciculus L/R
Inferior longitudinal fasciculus L/R
Superior longitudinal fasciculus temporal part R
Superior longitudinal fasciculus L/R

Uncinate fasciculus L/R

Resting EEG data:
20 mild AD

THETA

Anterior thalamic radiation L/R
Corticospinal tract L/R
Forceps major
Forceps minor
Inferior fronto-occipital fasciculus L/R
Inferior longitudinal fasciculus L/R
Superior longitudinal fasciculus (temporal part) L
Superior longitudinal fasciculus L
Uncinate fasciculus L/R



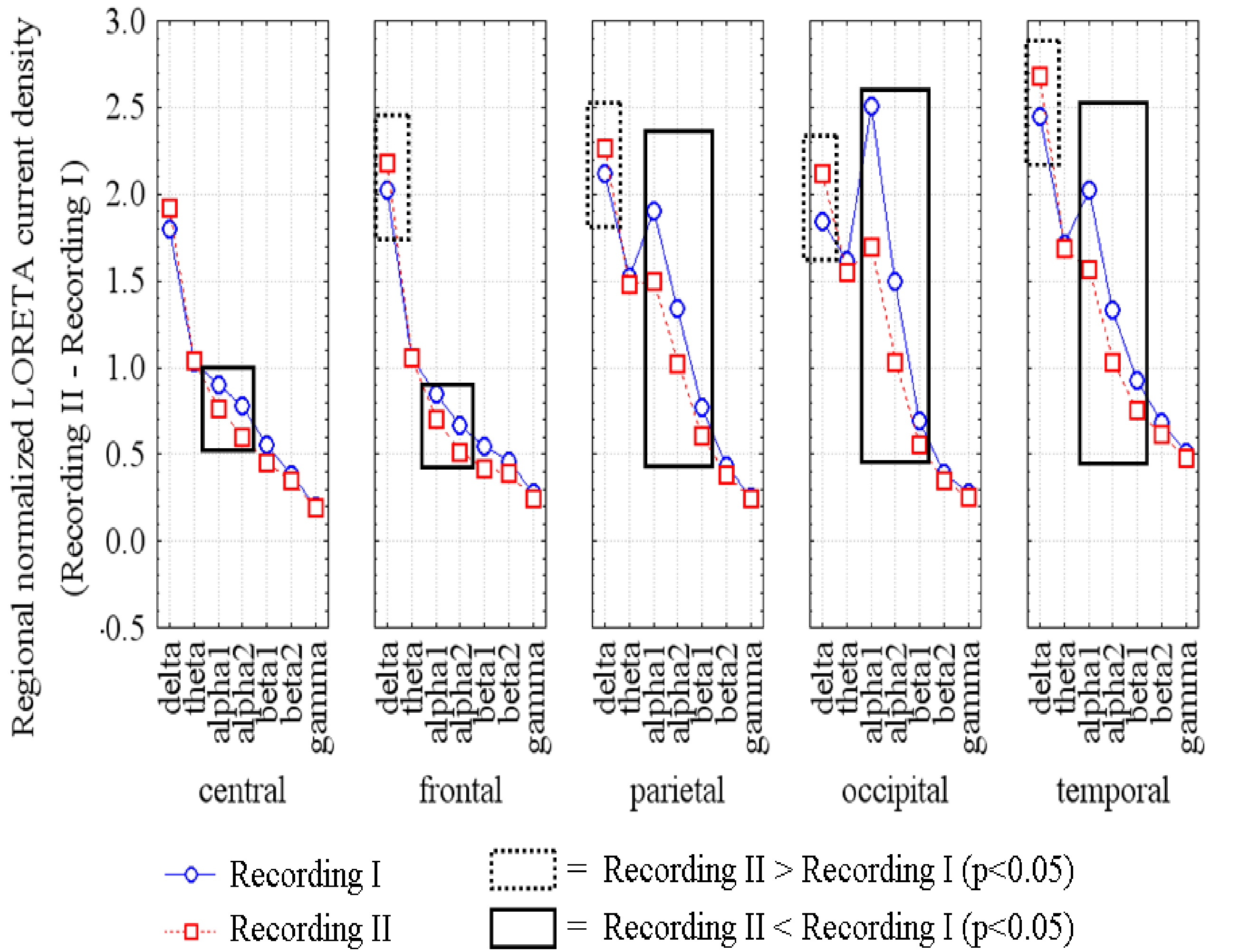
Babiloni C, Carducci F, Lizio R, Vecchio F, Baglieri A, Bernardini S, Boccardi M, Bozzao A, Buttinelli C, Esposito F, Giubilei F, Guizzaro A, Marino S, Montella P, Quattrocchi C, Redolfi A, Soricelli A, Tedeschi G, Triggiani I, Rossi-Fedele G, Parisi L, Vernieri F, Rossini PM, and Frisoni GB- Resting state cortical electroencephalographic rhythms are related to fractional anisotropy (DTI) of white matter tracts in subjects with Alzheimer's disease. 2013 (in preparation)

- **qEEG markers for the prediction of AD:** **cortical rhythms related to the conversion from MCI to AD**

Resting state EEG markers of disease progression at 1 year follow up in 88 mild AD patients

Widespread Increased power of delta and decreased power of alpha and posterior beta 1 sources over 1 year. Size effect in the table.

Variable	Partial Eta squared	Cohen's d
MMSE	0.178	0.5
Parietal Alpha 1	0.077	-0.29
Occipital Alpha 1	0.123	-0.42
Temporal Alpha 1	0.131	-0.38
Parietal Alpha 2	0.101	-0.34
Occipital Alpha 2	0.133	-0.43
Temporal Alpha 2	0.142	-0.42

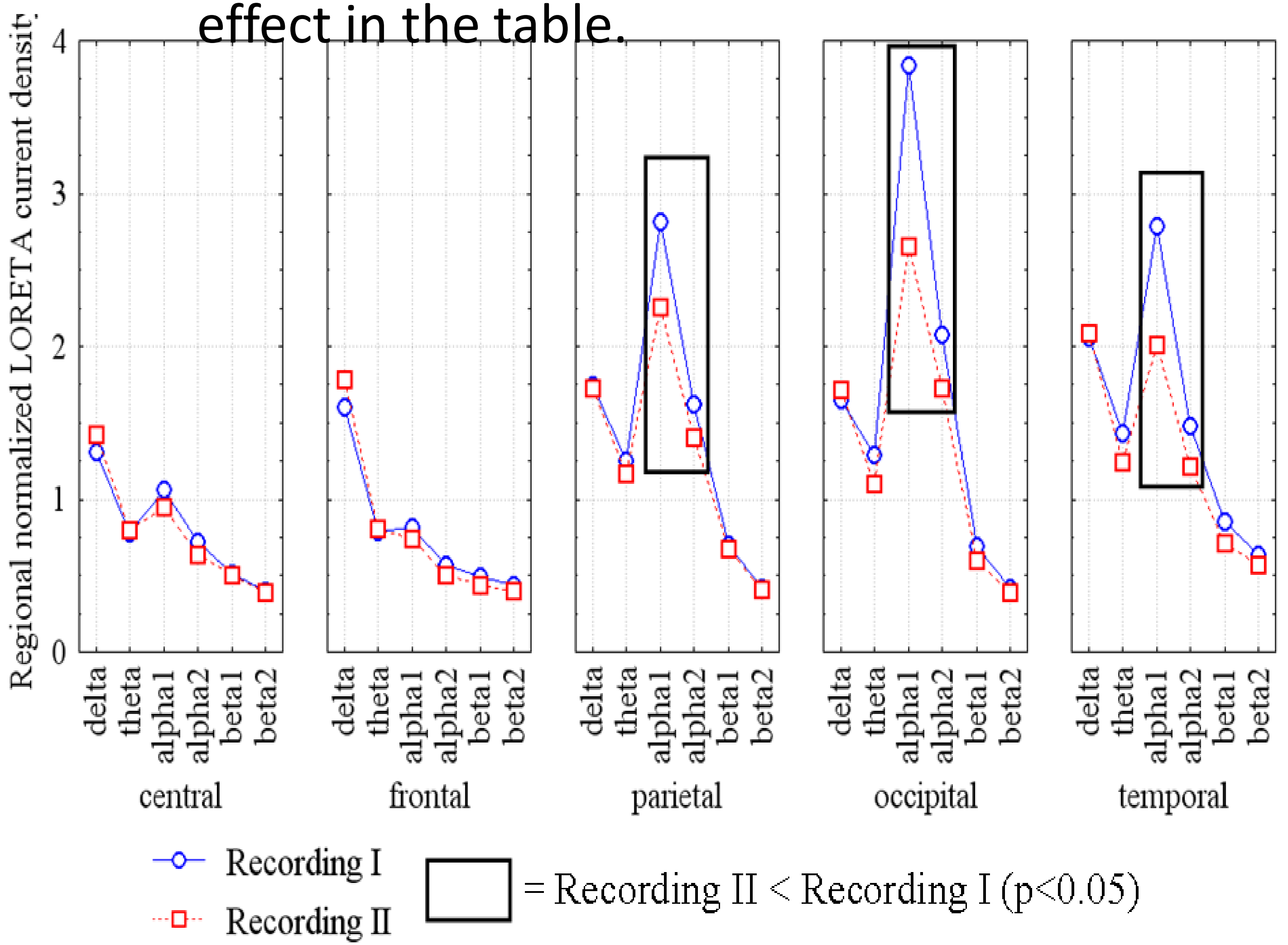


Babiloni C, Lizio R, Del Percio C, Marzano N, Soricelli A, Salvatore E, Ferri R, Cosentino F, Tedeschi G, Montella P, Marino S, Rodriguez G, Nobili F, Vernieri F, Ursini F, Mundi C, Richardson J, Frisoni GB, and Rossini PM. Cortical sources of resting state EEGrhythms are sensitive to the progression of Alzheimer's disease at early stage. Journal of Alzheimer Disease 2012

Resting state EEG markers of disease progression at 1 year follow up in 54 amnesic MCI patients

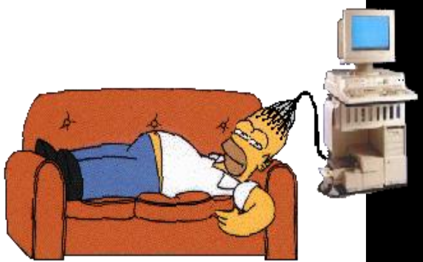
Decreased power of posterior alpha 1 and 2 sources over 1 year. Size effect in the table.

Variable	Partial Eta squared	Cohen's d
MMSE	0.262	0.59
Parietal alpha 1	0.131	-0.36
Occipital alpha 1	0.184	-0.4
Temporal alpha 1	0.234	-0.43
Parietal alpha 2	0.047	-0.19
Occipital alpha 2	0.036	-0.18
Temporal alpha 2	0.102	-0.29



Babiloni C, Del Percio C, Lizio R, Marzano N, Soricelli A, Salvatore E, Ferri R, Tedeschi G, Montella P, Marino S, Rodriguez G, Nobili F, Vernieri F, Ursini F, Mundi C, Frisoni GB, and Rossini PM. Cortical sources of resting state eeg alpha rhythms deteriorate across time in subjects with amnesic mild cognitive impairment. Neurobiology of Aging 2013

Posterior sources of resting delta, theta, and alpha rhythms at baseline recording were unselectively higher in amplitude in MCI subjects who will progress to AD (MCI converted) than in MCI subjects who will remain stable (MCI stable) after 1 year

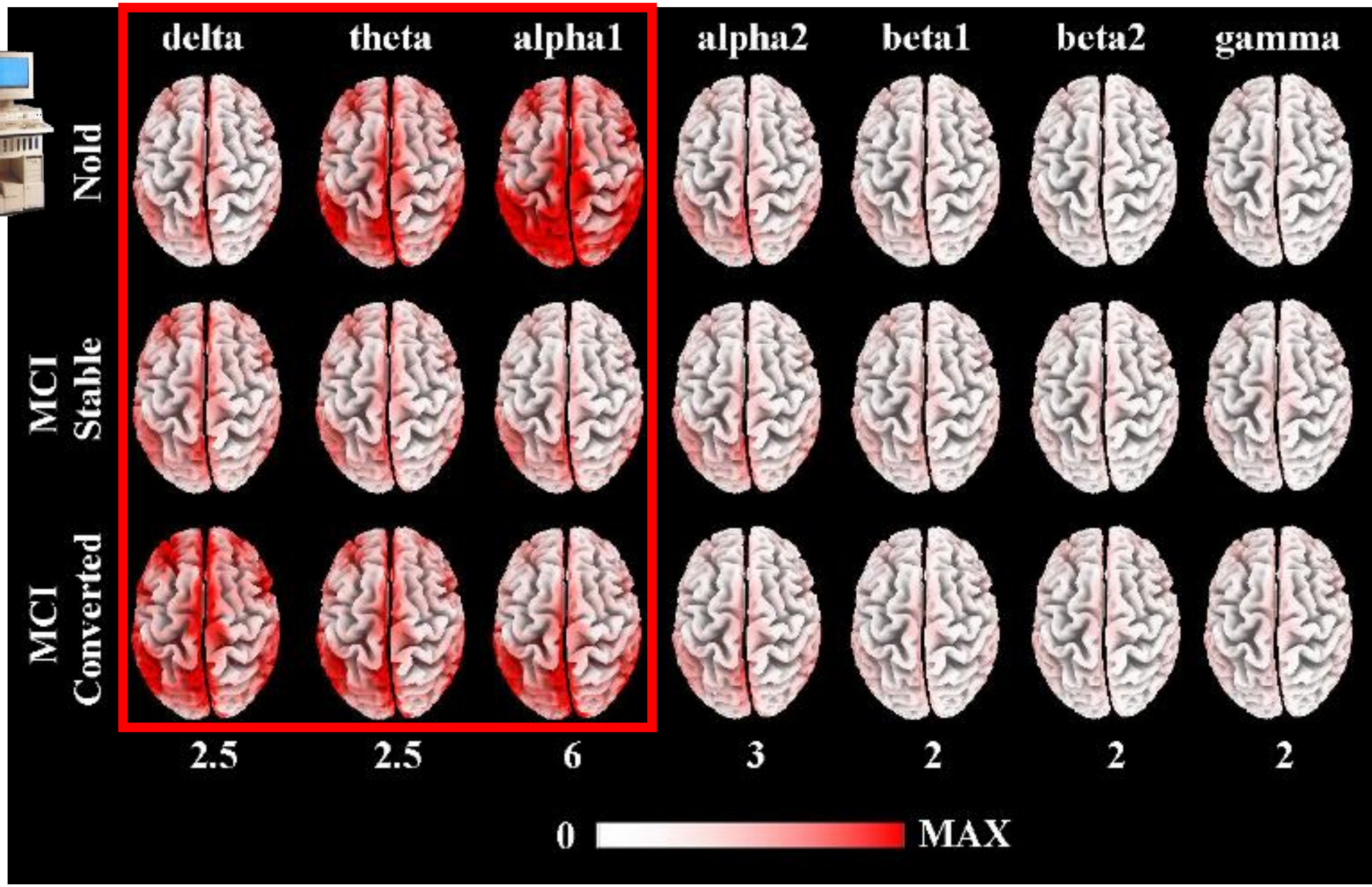


Resting EEG data:

45 MCI stable

24 MCI converted

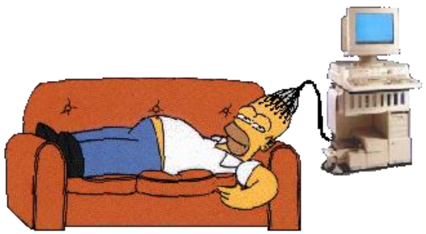
50 Nold



Rossini PM., Del Percio C, Pasqualetti P, Cassetta E, Binetti G, Dal Forno G, Ferreri F, Frisoni G, Chiovenda P, Miniussi C, Parisi L, Tombini M, Vecchio F, Babiloni C. Conversion from MCI to Alzheimer's disease is predicted by sources and coherence of brain EEG rhythms. Neuroscience 2006 Dec;143(3):793-803. Epub 2006 Oct 13.

- **qEEG markers for therapy monitoring and drug discovery in AD: cortical resting EEG rhythms characterizing response to Donepezil and Ibuprofen**

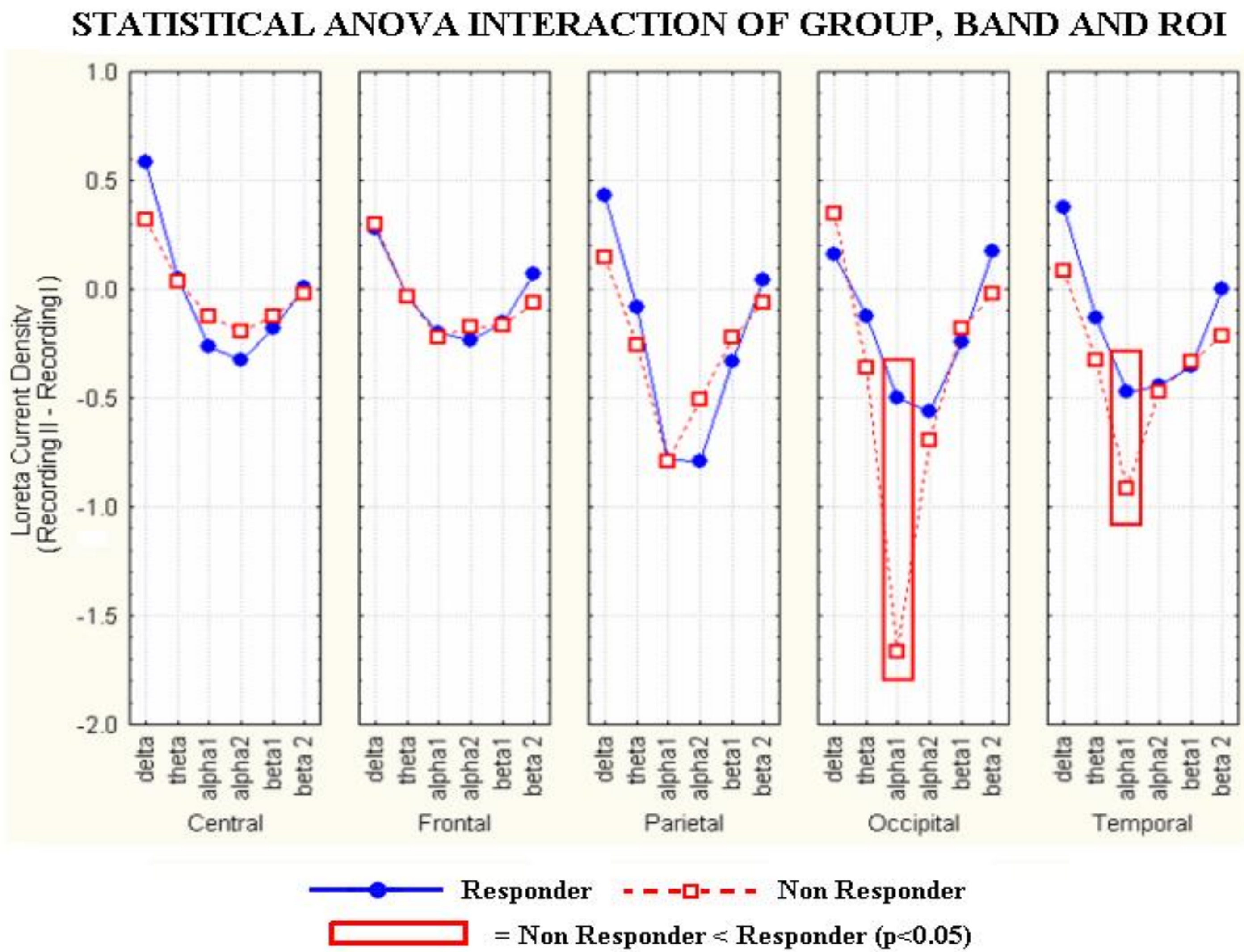
Long-term (1 year) cholinergic therapy reduces (i.e. it does not stop) the decline of occipital-temporal alpha sources in Alzheimer Responders when compared to Non-responders. Graphs illustrate the power of the EEG sources at baseline (before the therapy) minus follow up



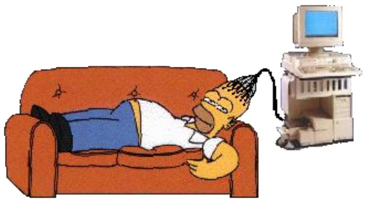
Resting EEG data:

28 Non Responder

30 Responder



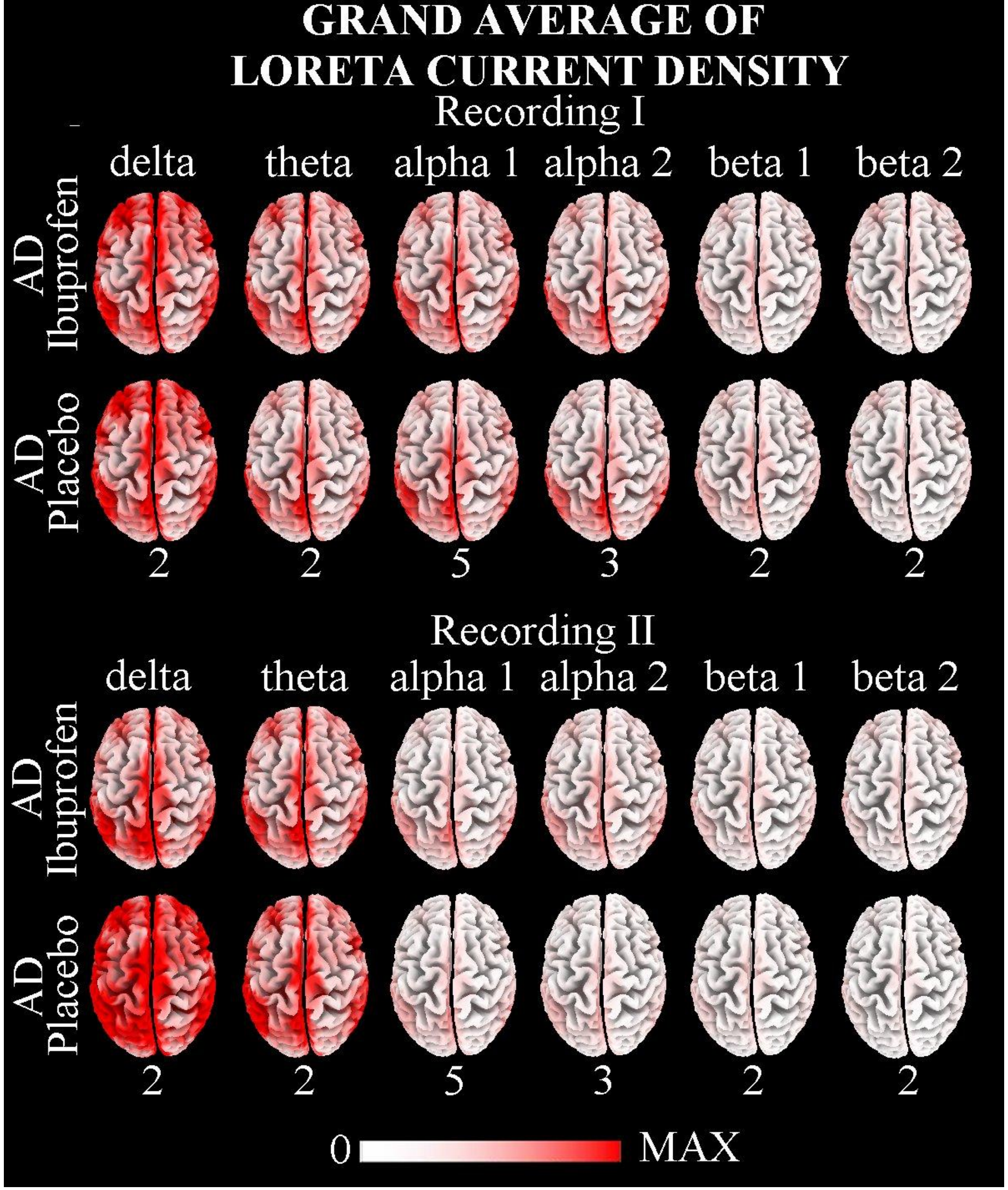
Babiloni C, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Lanuzza B, Miniussi C, Moretti DV, Nobili F, Pascual-Marqui R, Rodriguez G, Romani GL, Salinari S, Zanetti O, and Rossini PM. Donepezil effects on sources of cortical rhythms in mild alzheimer's disease: responders vs. non responders. NeuroImage 2006



Resting EEG data:

13 AD ibuprofen

10 AD placebo



Babiloni C, Frisoni GB, Del Percio C, Zanetti O, Bonomini C, Cassetta E, Pasqualetti P, Miniussi C, De Rosas M, Valenzano A, Cibelli G, Eusebi F, Rossini PM. Ibuprofen treatment modifies cortical sources of EEG rhythms in mild Alzheimer's disease. Clin Neurophysiol. 2009 Apr;120(4):709-18. Epub 2009 Mar 25.

Higher brain functions depend upon the rapid creation and dissolution of ever changing synchronous thalamo-cortical cell assemblies (neural networks)

Stam CJ, de Bruin EA.Scale-free dynamics of global functional connectivity in the human brain. Hum Brain Mapp. 2004 Jun;22(2):97-109.

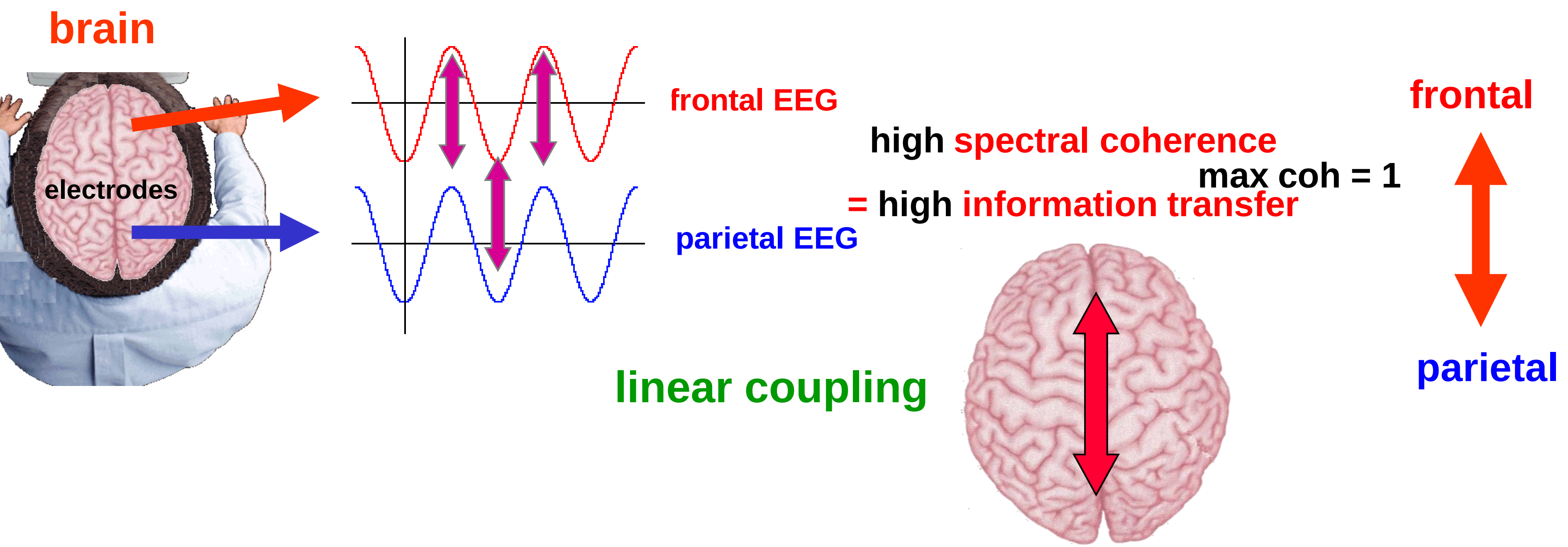
Neural networks integrate their activity by functional coupling of EEG rhythms

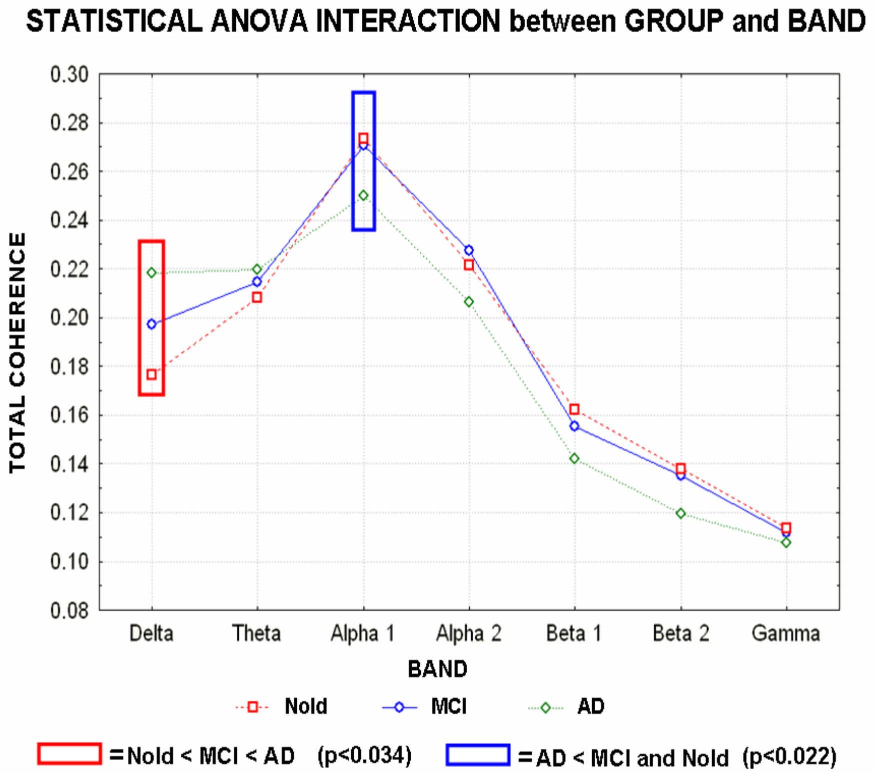
Linear coupling

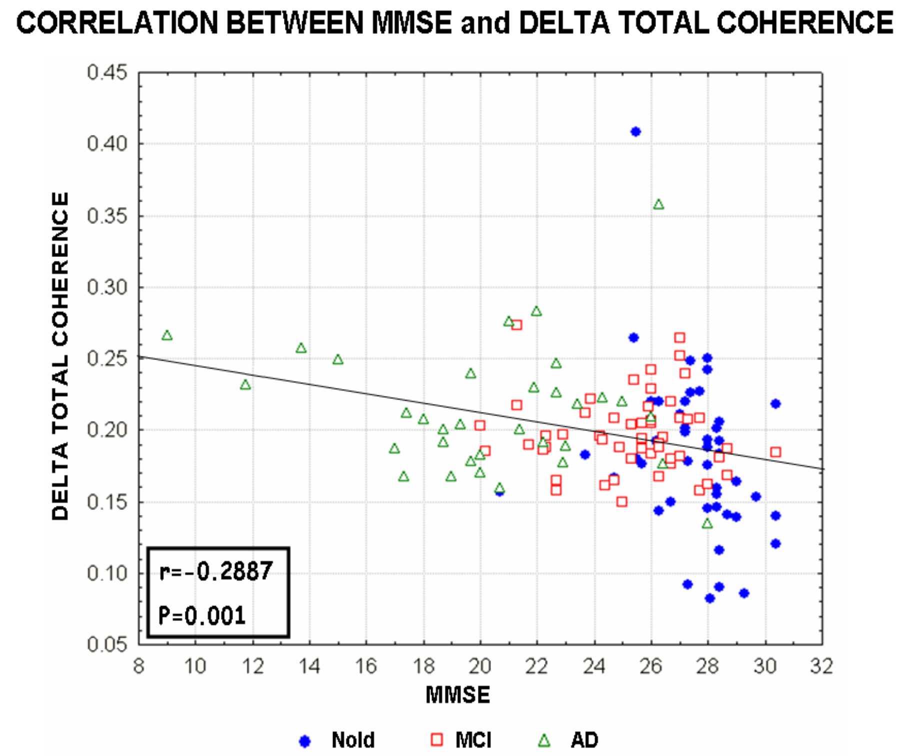
Non-linear coupling

Both should be considered

Linear temporal synchronization (coherence) of EEG rhythms at electrode pairs as an index of functional cortico-cortical coupling (information transfer)





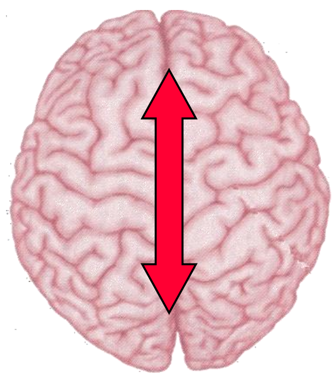


Resting EEG data:

33 Nold

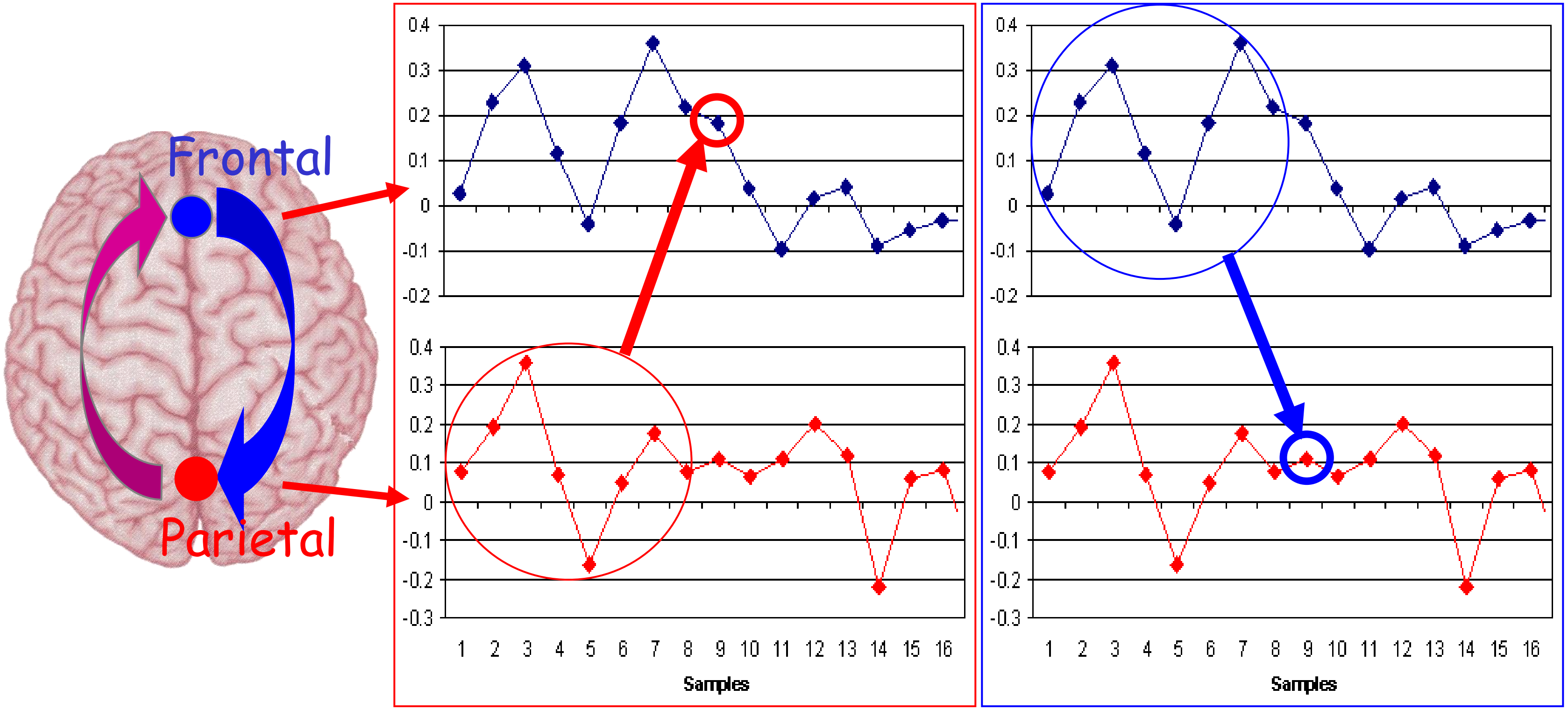
52 MCI

47 AD



Babiloni Claudio, Frisoni Giovanni B, Vecchio Fabrizio, Pievani Michela, Geroldi Cristina, De Carli Charles, Ferri Raffaele, Lizio Roberta, and Rossini Paolo M. Global functional coupling of resting EEG rhythms is abnormal in mild cognitive impairment and alzheimer's disease: a multicentric EEG study. Journal of Psychophysiology

“Directionality” (directed transfer function, DTF) of EEG rhythms at electrode pairs reflects fluxes of information within cortico-cortical coupling

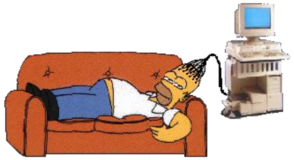


$$DTF_{ij}(F) = \frac{\left|H_{ij}\right|^2}{\sum_{m=1}^{L}\left|H_{im}(f)\right|^2}$$

MVAR model estimates “direction” of information flow by DTF

Kaminski MJ, Blinowska KJ. A new method of the description of the information flow in the brain structures. Biol Cybern. 1991;65(3):203-10.

Parietal to frontal direction of the information flux within EEG functional coupling (DTF) was stronger in Nold than in MCI and/or AD subjects



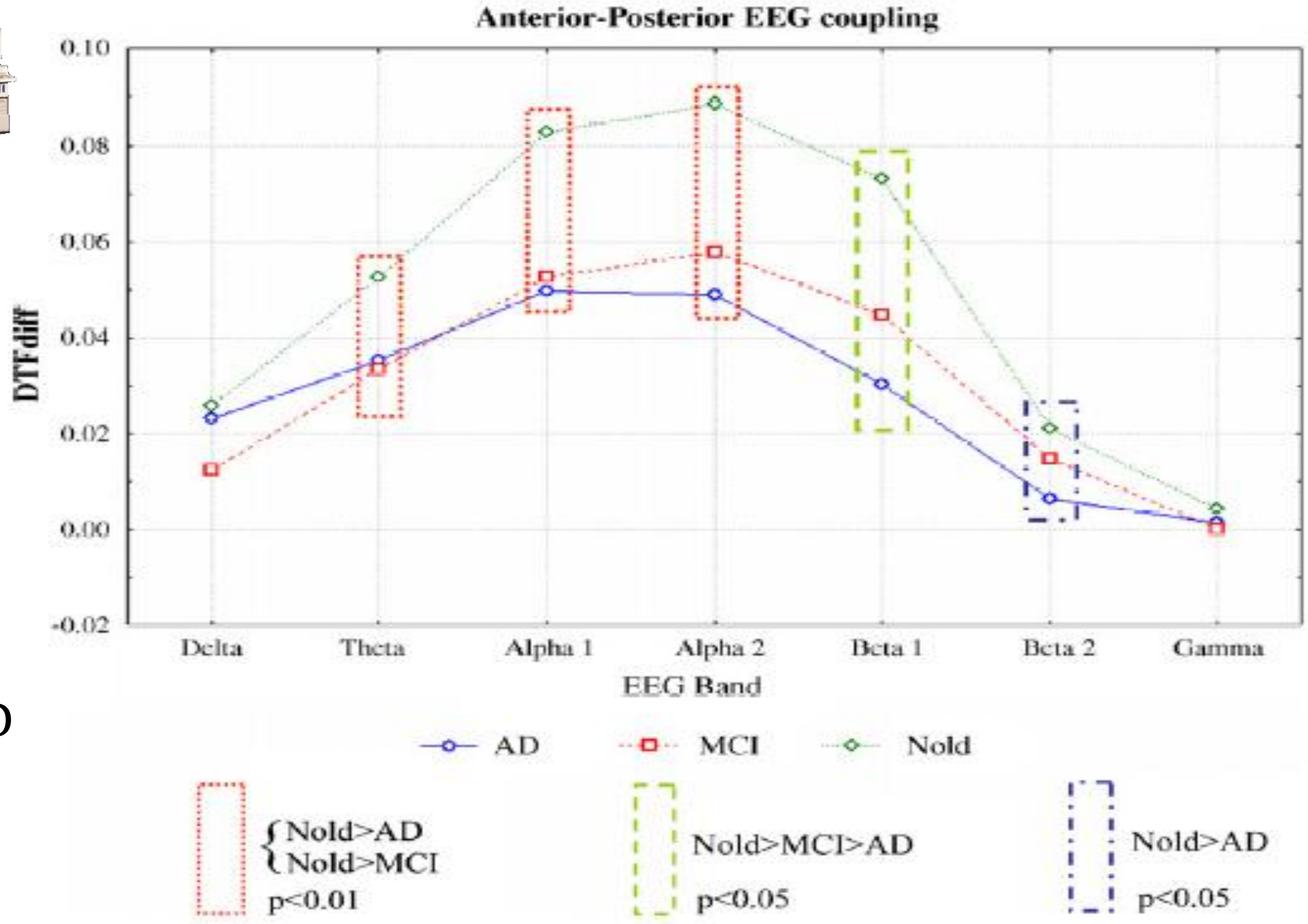
Resting

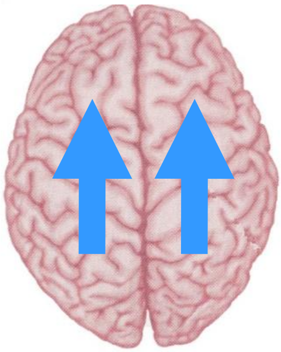
EEG data:

64 Nold

67 MCI

73 mild AD

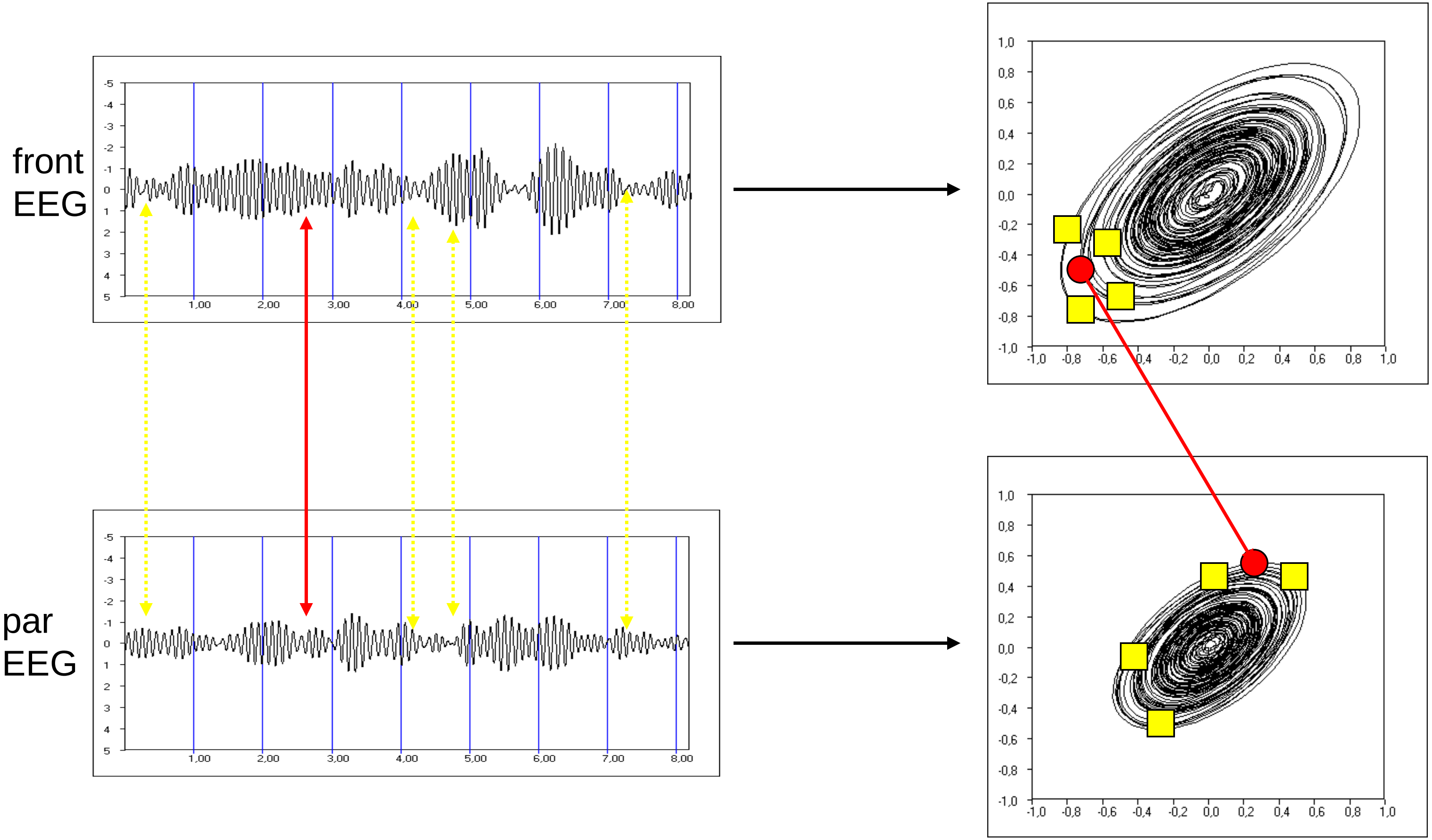




Claudio Babiloni, Raffaele Ferri, Giuliano Binetti, Fabrizio Vecchio, Giovanni B. Frisoni, Bartolo Lanuzza, Carlo Miniussi, Flavio Nobili, Guido Rodriguez, Francesco Rundo, Andrea Cassarino, Francesco Infarinato, Emanuele Cassetta, Serenella Salinari, Fabrizio Eusebi, and Paolo M. Rossini, Directionality of EEG synchronization in Alzheimer's disease subjects. Neurobiology of aging, 2007

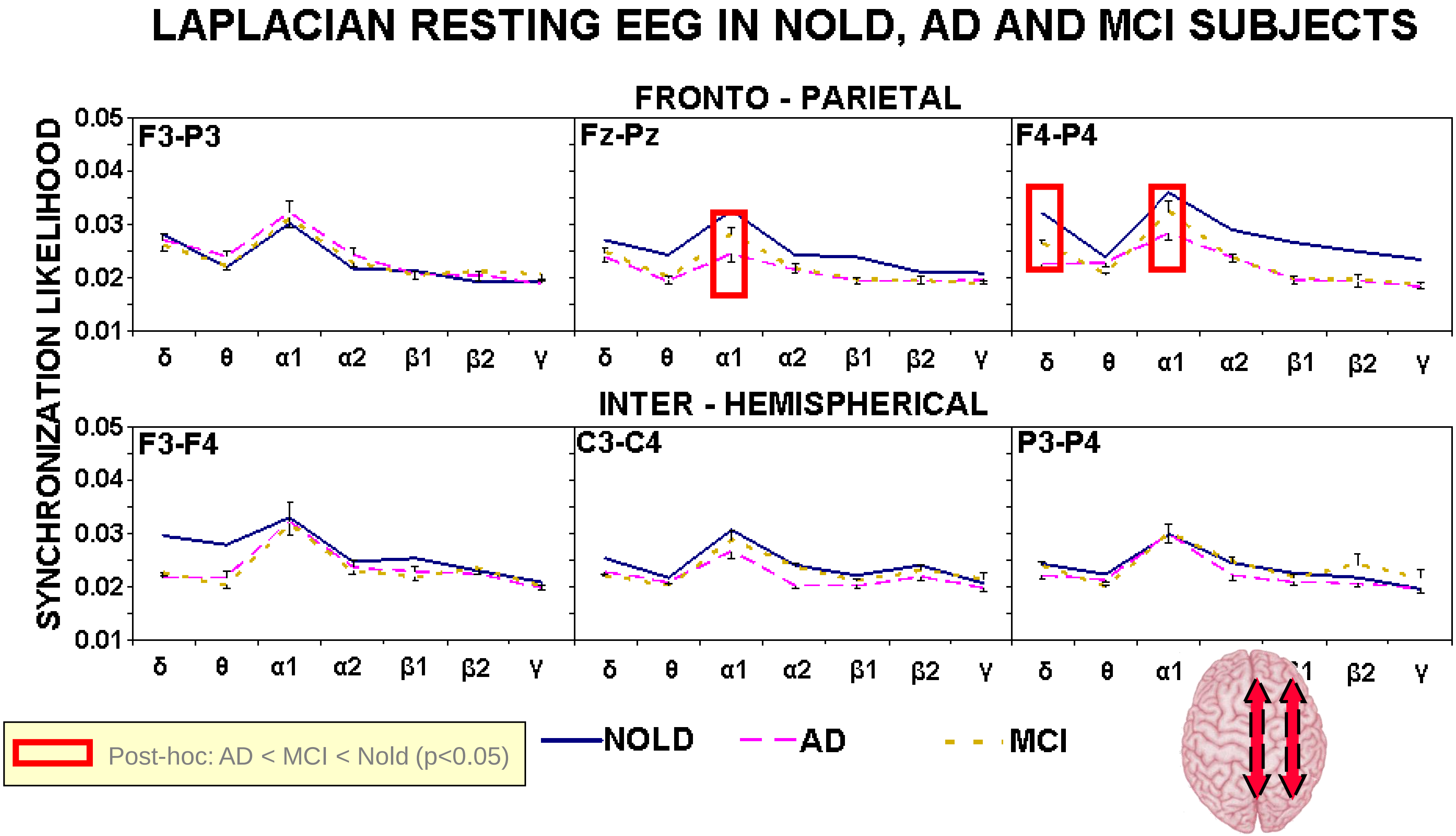
Synchronization likelihood measures linear plus non-linear functional coupling of EEG rhythms

Measure of the synchronization between two signals sensitive also to nonlinear coupling



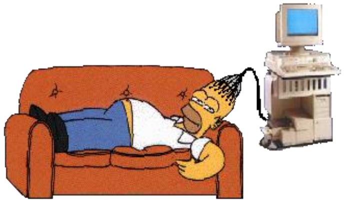
Stam, C.J., van Dijk, B.W., 2002. Synchronization likelihood: An unbiased measure of generalized synchronization in multivariate data sets. Physica D, 163: 236-241.).

Synchronization likelihood

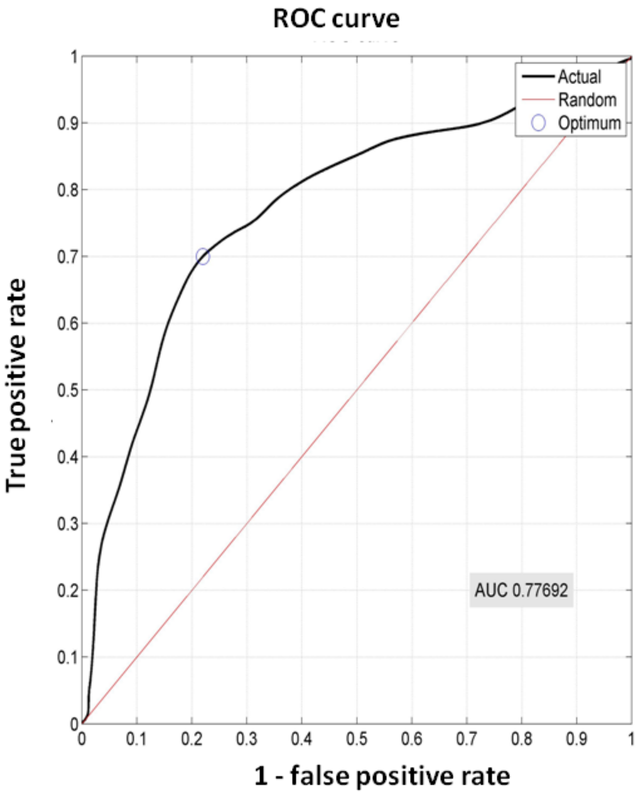


Babiloni C, Ferri R, Binetti G, Cassarino A, Dal Forno G, Ercolani M, Ferreri F, Frisoni GB, Lanuzza B, Miniussi C, Nobili F, Rodriguez G, Rundo F, Stam CJ, Musha T, Vecchio F, Rossini PM. Fronto-parietal coupling of brain rhythms in mild cognitive impairment: a multicentric EEG study. Brain Res Bull. 2006 Mar 15;69(1):63-73.

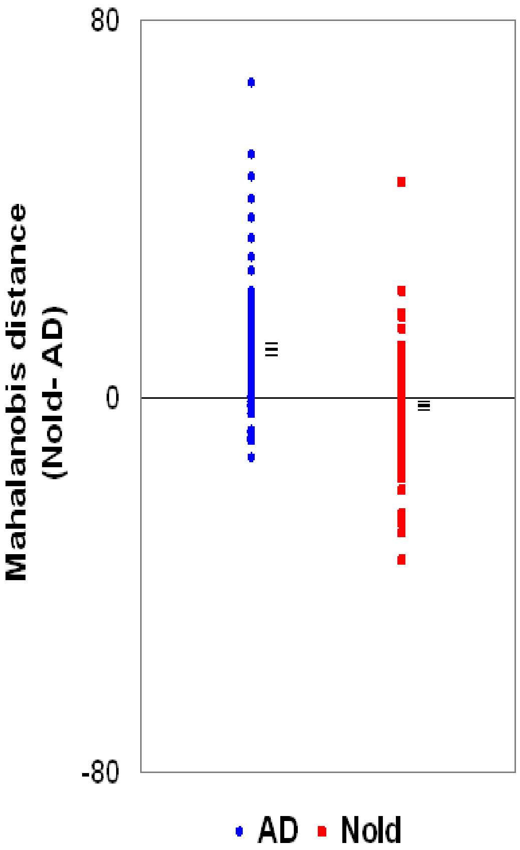
Validation of EEG markers: Diagnostic Accuracy



	Subjects (N)	Gender (M/F)	Age (years)	Education (years)	MMSE (score)	IAF (Hz)
Nold	85	38/47	62.6 (± 1.2 SE)	10.3 (± 0.6 SE)	28 (± 0.2 SE)	9.9 (±0.2SE)
AD	100	38/62	71.9 (± 0.9 SE)	7.1 (± 0.4 SE)	19.4 (± 0.5 SE)	8.7 (±0.2 SE)



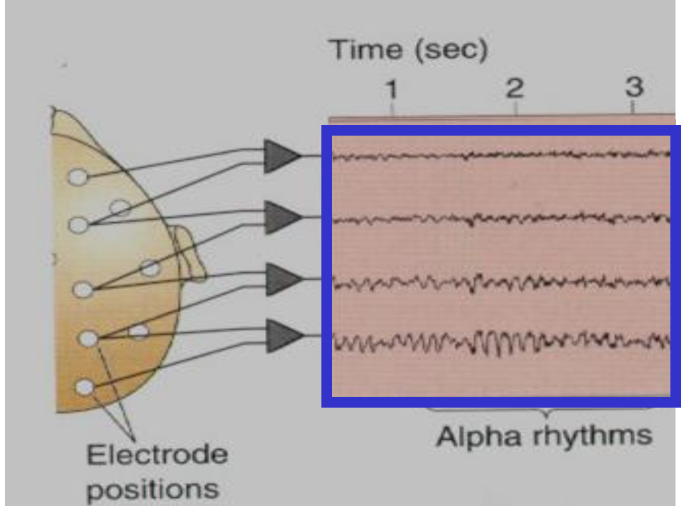
Results showed 80.2% of mean sensitivity, 61.8% of mean specificity, and 71.8% of mean accuracy of the EEG markers. Area under ROC curve was of 0.78. These results suggest that the combination of low-cost and non-invasive EEG markers allows a moderate classification of Nold and AD individuals.



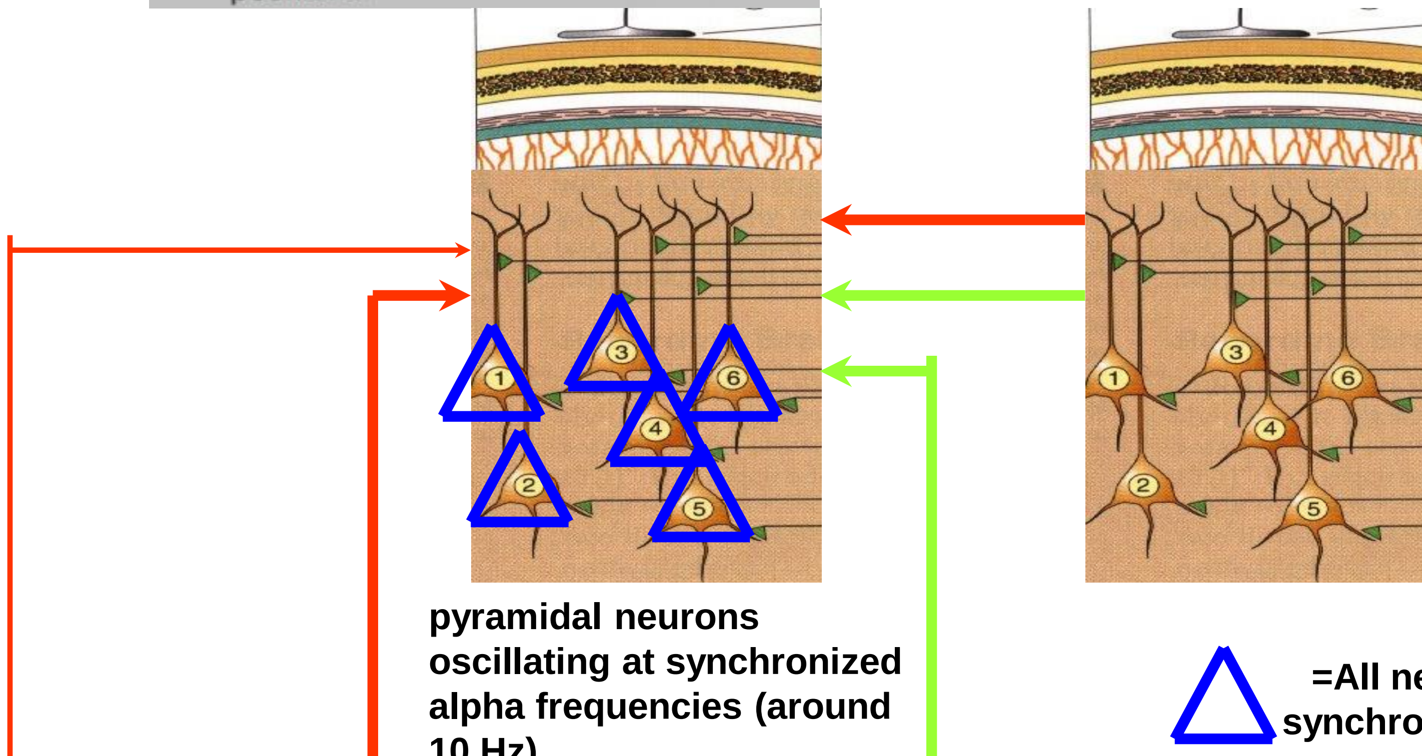
Babiloni C, De Vico Fallani F, Lizio R, Vecchio F, Del Percio C, Vernieri F, Babiloni F, Frisoni GB, and Rossini PM. Accuracy of resting state electroencephalographic markers in the discrimination of Alzheimer's disease and normal elderly subjects. JAD, under revision

- **qEEG markers of cortical arousal for translational purposes: comparison between "active" vs. "passive" conditions in humans and animal models**

RESTING EYES CLOSED



Dominant resting (eyes-closed) alpha rhythms are synchronous and coherent over wide cortical areas and corresponding thalamic nuclei

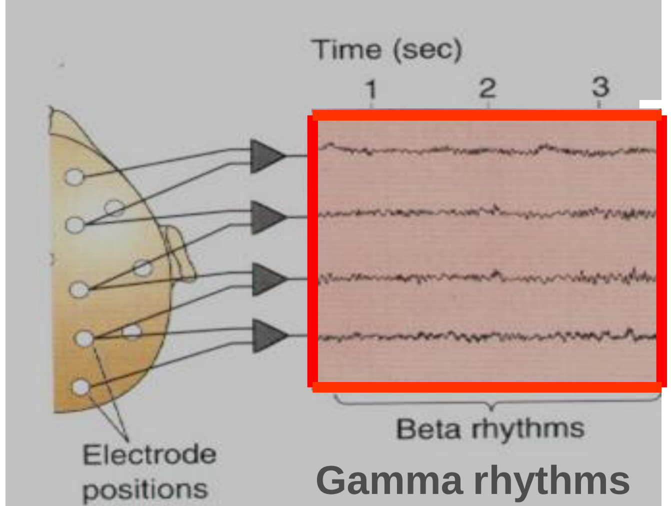


△ =All neurons synchronized at around 10 Hz

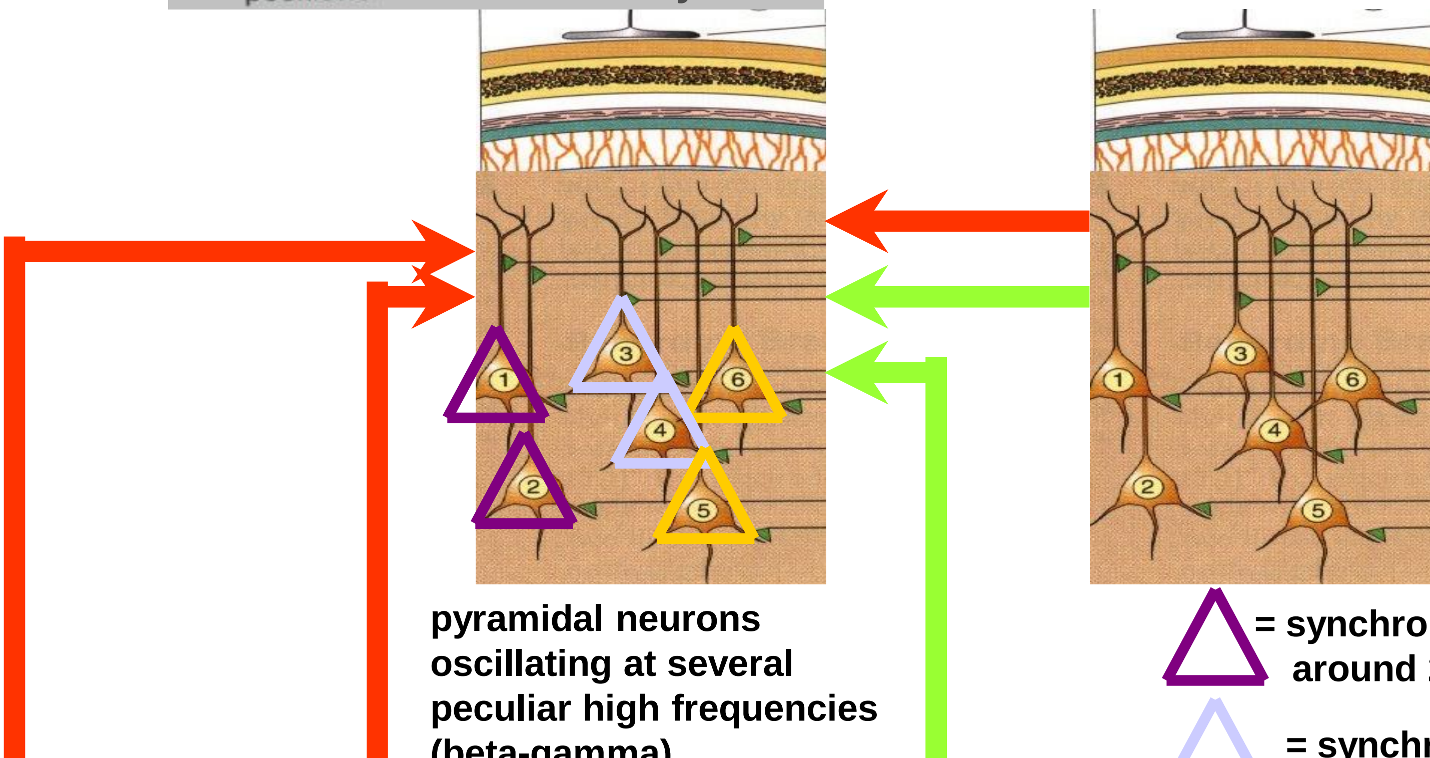
Reticular neurons **Relay neurons**

BRAIN STEM **THALAMUS**

EVENT



High-frequency EEG rhythms (20 to 100 Hz or highest) substitute alpha rhythms during eyes opening. These rhythms are coherent over small cortical areas and corresponding thalamic nuclei, and different sub-populations show different frequencies for opening their communication channel.



pyramidal neurons oscillating at several peculiar high frequencies (beta-gamma)

= synchronous at around 20 Hz

= synchronous at around 40 Hz

= synchronous at around 100 Hz

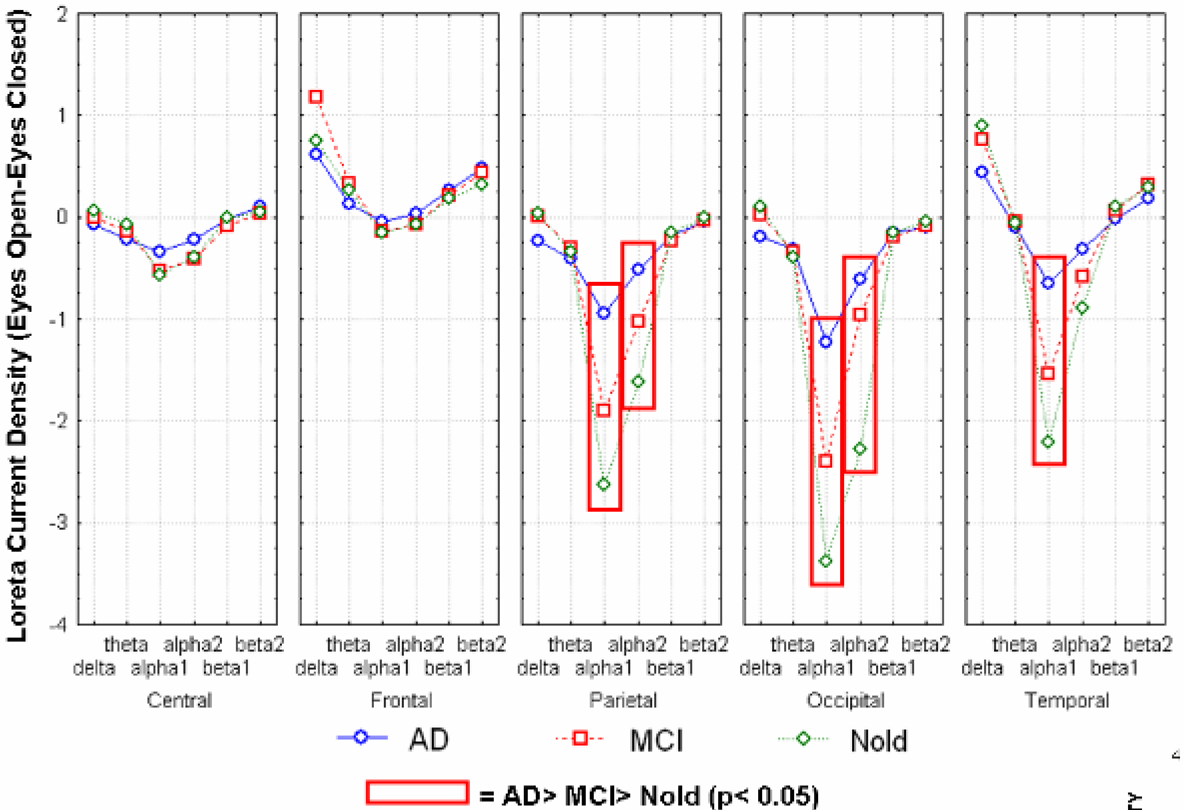
Reticular neurons

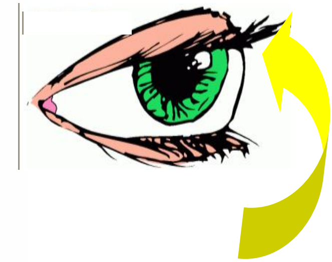
Relay neurons

BRAIN STEM

THALAMUS

STATISTICAL ANOVA INTERACTION of GROUP, BAND and ROI





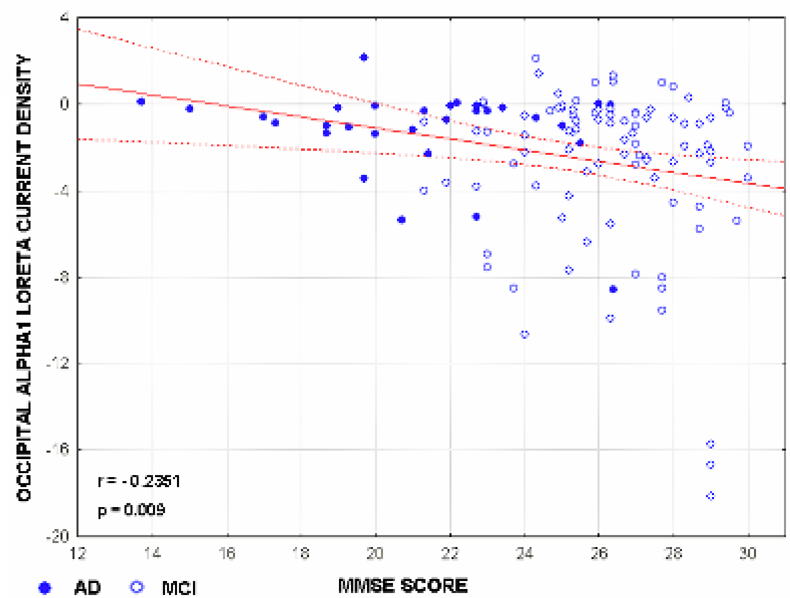
Resting EEG data:

96 MCI

31 mild AD

36 Nold

Reactivity to the eyes-open condition showed posterior alpha 1 and alpha 2 (10.5-13 Hz) sources was high in the Nold, intermediate in the MCI, and low in the AD subjects.



Babiloni Claudio, Frisoni Giovanni B, Vecchio Fabrizio, Lizio Roberta, Pievani Michela, Geroldi Cristina, Claudia Fracassi, Ferri Raffaele, Lanuzza Bartolo, and Rossini Paolo M.Reactivity of cortical alpha rhythms to eye opening in mild cognitive impairment and Alzheimer disease: an EEG study. Journal of Alzheimer's disease 2010

Which preclinical qEEG markers for drug discovery?

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ELSEVIER FULL-TEXT ARTICLE

Clin Neurophysiol. 2012 Oct 4. pii: S1388-2457(12)00581-0. doi: 10.1016/j.clinph.2012.07.023. [Epub ahead of print]

Effects of pharmacological agents, sleep deprivation, hypoxia and transcranial magnetic stimulation on electroencephalographic rhythms in rodents: Towards translational challenge models for drug discovery in Alzheimer's disease.

Babiloni C, Infarinato F, Aujard F, Bastlund JF, Bentivoglio M, Bertini G, Del Percio C, Fabene PF, Forloni G, Herrero Ezquerro MT, Noè FM, Pifferi F, Ros-Bernal F, Christensen DZ, Dix S, Richardson JC, Lamberty Y, Drinkenburg W, Rossini PM.

Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy; IRCCS San Raffaele Pisana, Rome, Italy. Electronic address: c.babiloni@unifg.it.

Abstract

Different kinds of challenge can alter spontaneous ongoing electroencephalographic (EEG) rhythms in animal models, thus providing paradigms to evaluate treatment effects in drug discovery. The effects of challenges represented by pharmacological agents, hypoxia, sleep deprivation and transcranial magnetic stimulation (TMS) on EEG rhythms are here reviewed to build a knowledge platform for innovative translational models for drug discovery in Alzheimer's disease (AD). It has been reported that antagonists of cholinergic neurotransmission cause synchronisation of spontaneous ongoing EEG rhythms in terms of enhanced power of EEG low frequencies and decreased power of EEG high frequencies. Acetylcholinesterase inhibitors and serotonergic drugs may restore a normal pattern of EEG desynchronisation. Sleep deprivation and hypoxia challenges have also been reported to elicit abnormal synchronisation of spontaneous ongoing EEG rhythms in rodents. The feasibility and reproducibility of TMS have been demonstrated in rodents but information on a consistent modulation of EEG after TMS manipulation is very limited. Transgenic mice over-expressing human amyloid precursor protein complementary DNAs (cDNAs) harbouring the 'Swedish' mutation and PS-1 cDNAs harbouring the A264E mutation, which recapitulate some of the pathological features of AD, exhibit alterations of spontaneous ongoing EEG rhythms at several low and high frequencies. This does not appear, however, to be a consequence of beta-amyloid deposition in the brain. The present review provides a critical evaluation of changes of spontaneous ongoing EEG rhythms due to the experimental manipulations described above, in order to stimulate the promote more adherent models fitting dynamics in humans.

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Related citations in PubMed

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Review [Selective stimulations and lesions of the rat brain nuclei [Glas Srp Akad Nauka Med. 2011]

New perspectives in transcranial magnetic stimulation: Epilepsy, consc [Behav Neurol. 2012]

EEG, activity, and sleep architecture in a transgenic AβPPswe/PS [J Alzheimers Dis. 2010]

Review Neuroprotective approaches in experimenta [Prog Neuropsychopharmacol Biol...]

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SPECTRAL EEG MARKERS OF MOTOR ACTIVITY IN TASTPM MICE

Transgenic AD mouse overexpressing human mutant amyloid precursor protein (hAPP695swe) and presenilin-1 (M146V)

AND PDAPP MICE

Transgenic mice overexpressing APP intracellular domain

In cooperation with Janssen, Lundbeck, Mario Negri Institute, and UNIFG-Foggia

Innovative Medicines Initiative

AIM

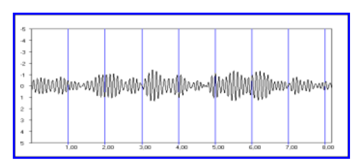
• To evaluate spectral **EEG marker of motor activity** (gross movements, exploratory movements or locomotor activity) in **wild type (WT) C57 and TASTPM mice**

•**TASTPM** mice
Transgenic AD mouse overexpressing human mutant amyloid precursor protein (hAPP695swe) and presenilin-1 (M146V)

ANIMALS

- **60 wild type (WT) C57 mice** by **Mario Negri Institute (MNI)**, **Lundbeck**, and **UNIVR**

UNIT	N	Gender (M/F)	Age
MNI	23	23/0	6 months (N=7), 12 months (N=3), 14 months (N=6), 24 months (N=7), monopolar parietal rec
Lundbeck	34	20/14	4.5 months (N=12), 15 months (N=14), 24 months (N=8), monopolar parietal rec
UNIVR	3	3/0	12 months (N=3), monopolar parietal rec
Total	**60**	**46/14**	**4.5 months (N=12), 6 months (N=7), 12 months (N=6), 15 months (N=14), 14 months (N=6), 24 months (N=15), monopolar** parietal rec
JANSSEN	12	7/5	12 months. bipolar frontoparietal rec



EEG RECORDING AND DATA ANALYSIS

EEG recording

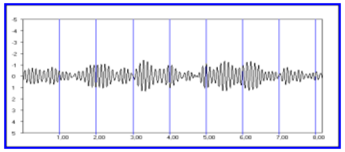
• EEG recordings in monopolar parietal area. Lundbeck, MNI, and UNIVR researchers selected 2-5 minutes of artifact-free EEG segments during wake “active” state (gross movements, exploratory movements or locomotor activity) and “passive” state (no sleep) on the basis of animal behavior according to the PharmaCog procedures

•EEG recordings in bipolar frontoparietal area by Janssen unit.

• Data analysis by UNIFG unit focused on these artifact free wakeful on-going EEG data according to the mentioned scoring (of note, the scoring at the local units was performed in blind with respect to EEG spectral data analysis performed by UNIFG). UNIFG researchers performed spectral EEG data analysis by a standard FFT algorithm using Welch technique and Hanning windowing function with 1 Hz frequency resolution.

Conditions

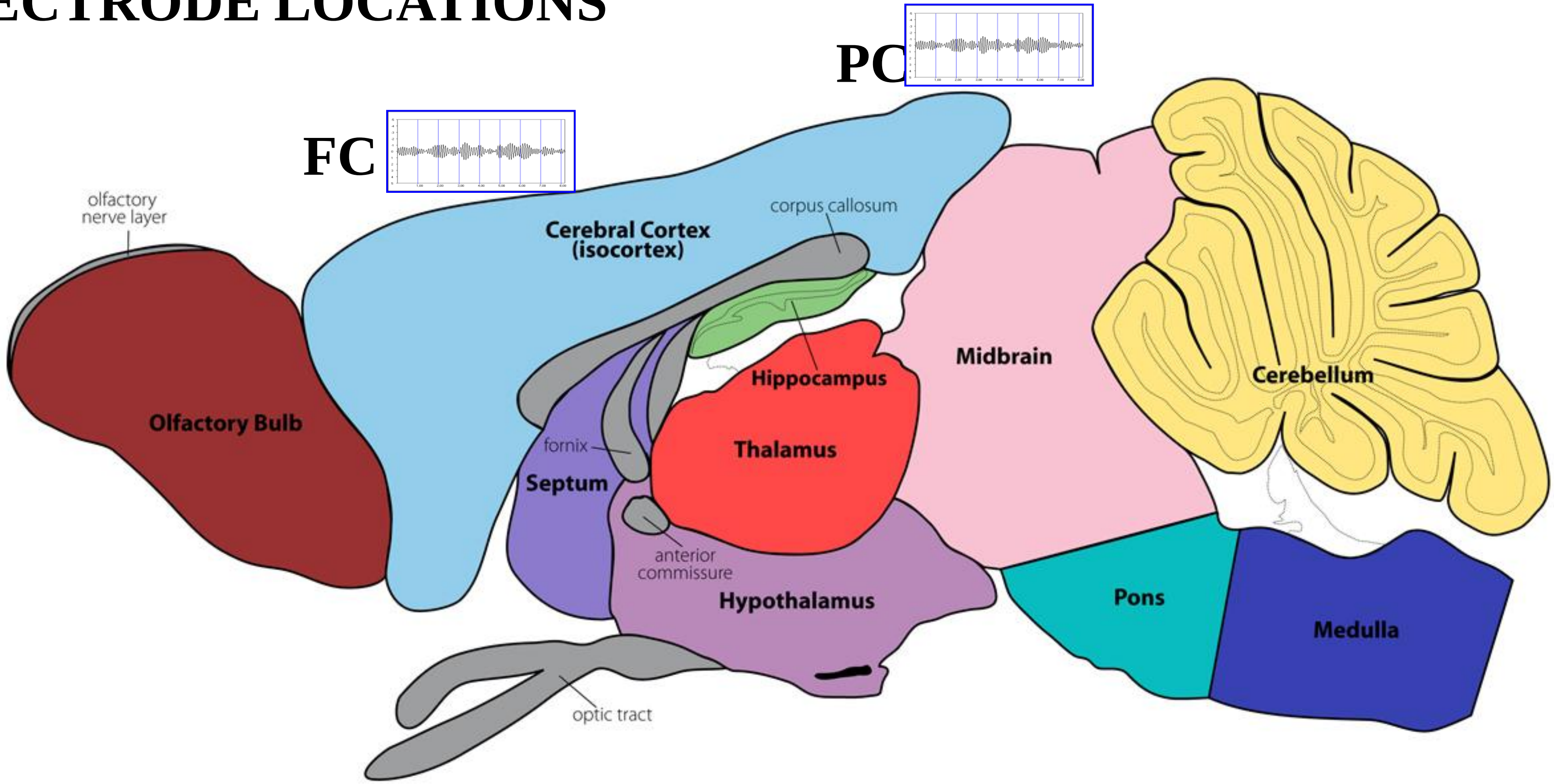
• Wakeful on-going EEG during passive state (no sleep)
• Wakeful on-going EEG during active state (movements)



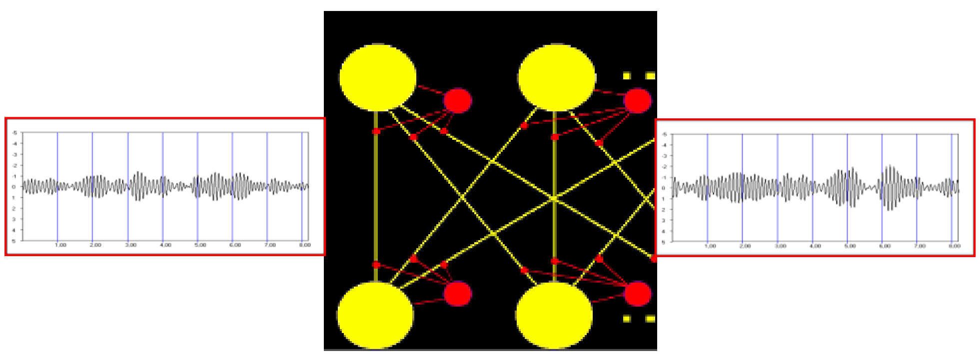
Analysis of EEG power density

• Active state vs. passive state

ECTRODE LOCATIONS

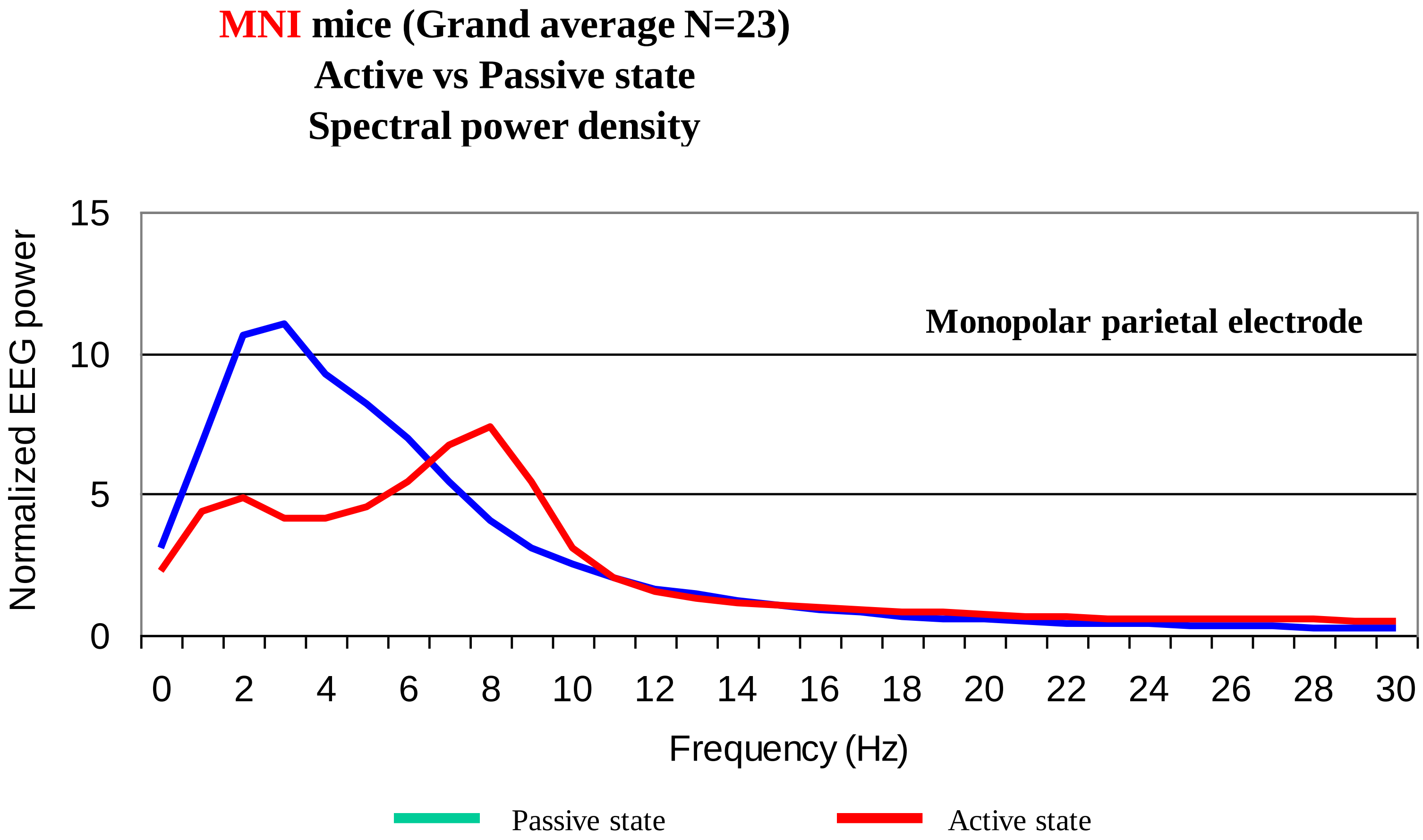


frontal (FC)



parietal PC

MNI WT mice: active vs passive

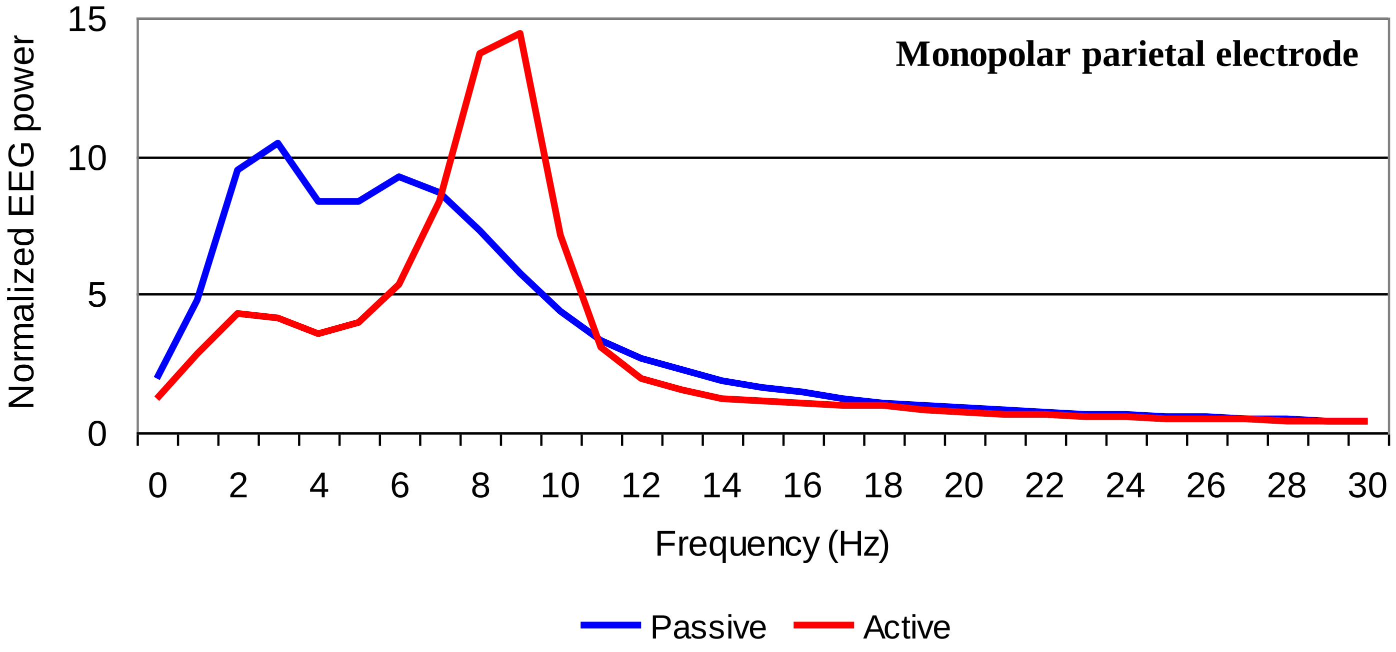


Unit	N	Gender (F/M)	Age
MNI	23	0/23	6 months (7 mice), 12 months (3 mice), 14 months (6 mice), 24 months (7 mice)

- **ACTIVE vs. PASSIVE state: N=23 MNI mice.** More 1-6 Hz power in passive than active state. More 8-10 Hz power in active than passive state.

Lundbeck WT mice: active vs passive

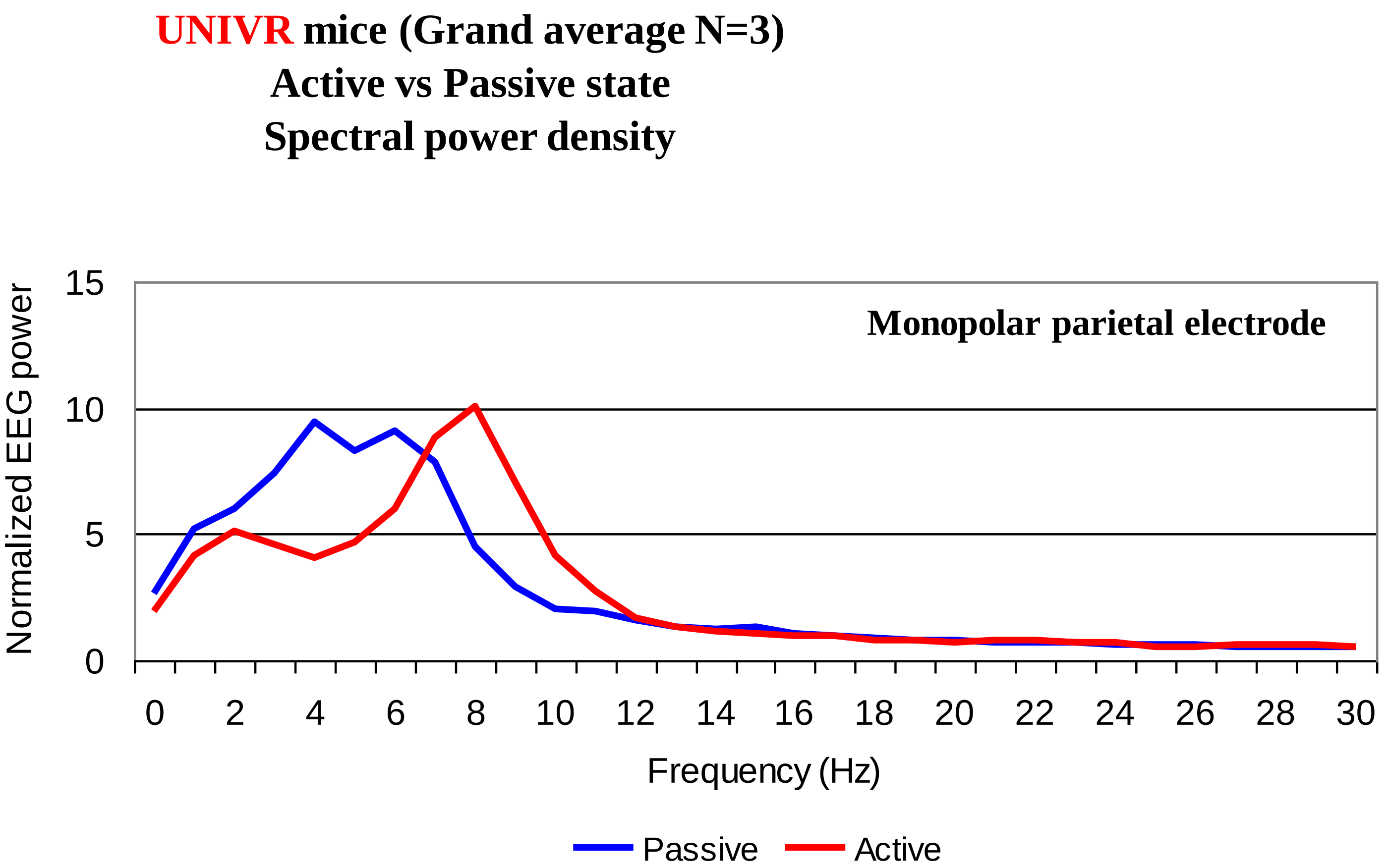
Lundbeck mice (Grand average N=20)
Active vs Passive state
Spectral power density



Unit	N	Gender (F/M)	Age
Lundbeck	20	0/20	4.5 months (12 mice), 24 months (8 mice)

• **ACTIVE vs. PASSIVE state: N=20 Lundbeck mice.** More 1-6 Hz power in passive than active state. More 8-10 Hz power in active than passive state.

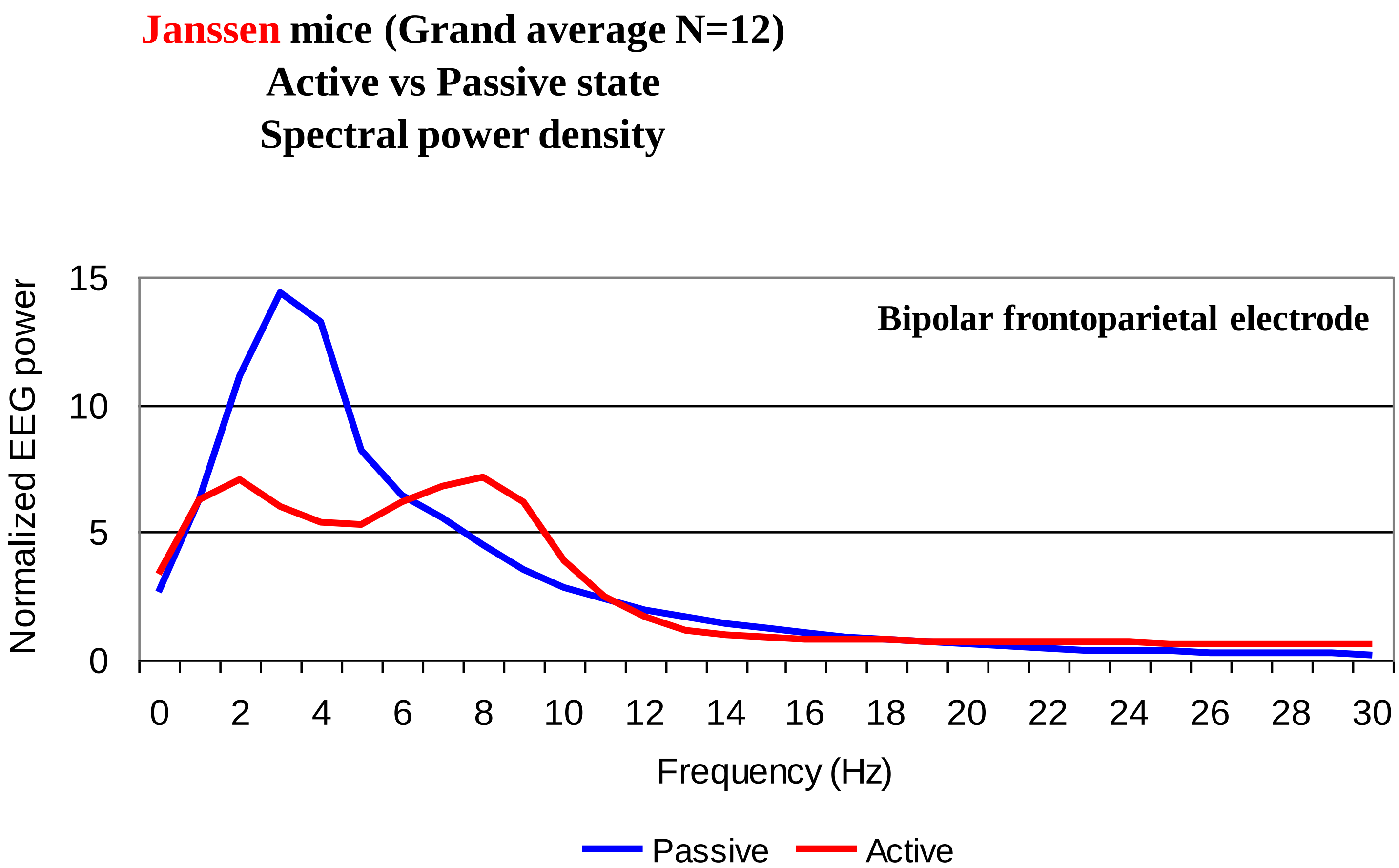
UNIVR WT mice: active vs passive



Unit	N	Gender (F/M)	Age
UNIVR	3	0/3	12 months (3 mice)

- **ACTIVE vs. PASSIVE state: N=3 UNIVR mice.** More 2-6 Hz power in passive than active state. More 8-10 Hz power in active than passive state.

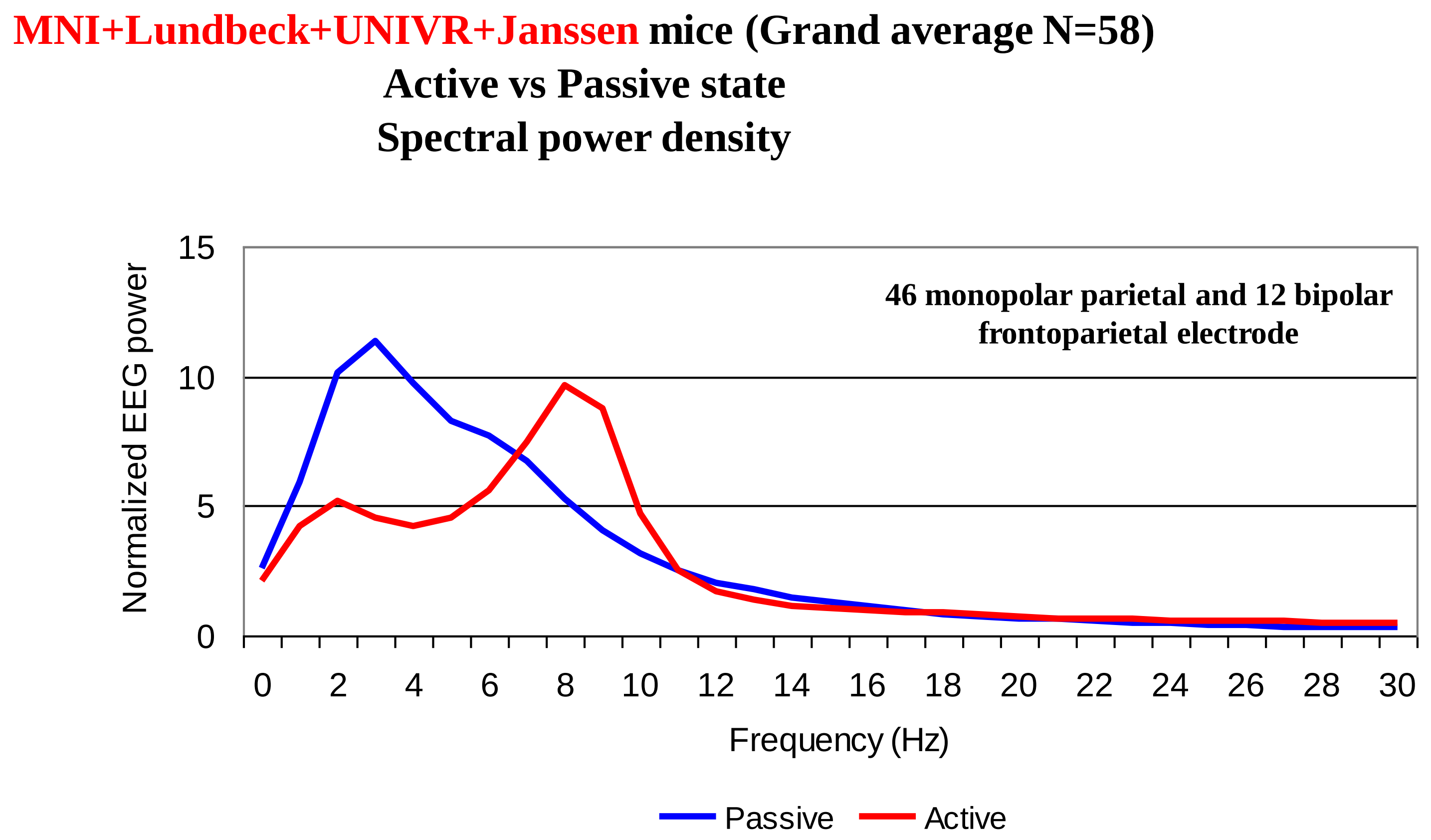
Janssen WT mice: active vs passive



Unit	N	Gender (F/M)	Age
Janssen	12	5/7	12 months (12 mice)

- **ACTIVE vs. PASSIVE state: N=12 Janssen mice.** More 1-6 Hz power in passive than active state. More 6-10 Hz power in active than passive state.

MNI+Lundbeck+UNIVR+Janssen WT mice: active vs passive

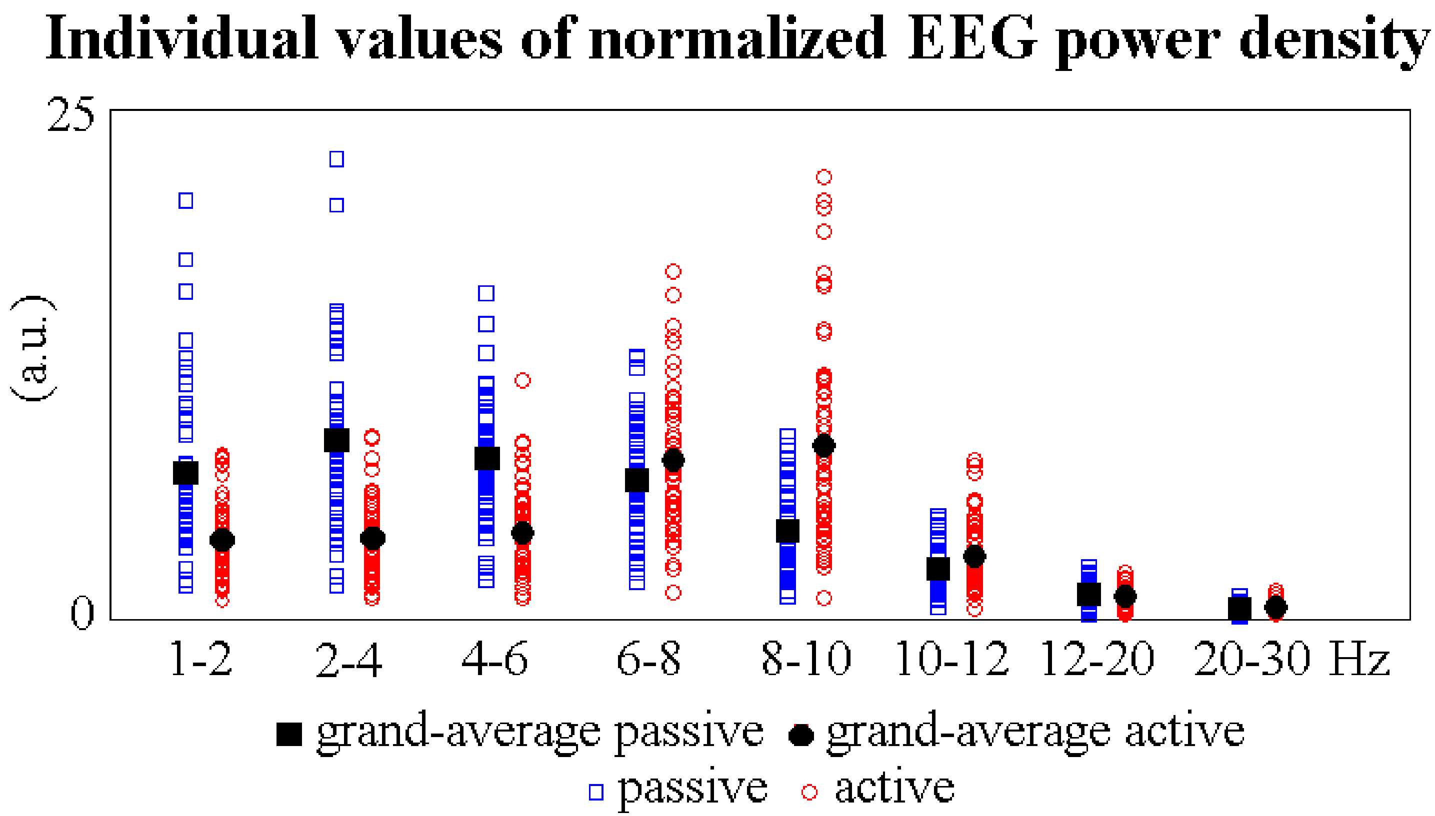


N	Gender (F/M)	Age
58	5/53	4.5 months (12 mice), 6 months (7 mice), 12 months (18 mice), 14 months (6 mice), 24 months (15 mice)

- **ACTIVE vs. PASSIVE state: N=58 MNI+Lundbeck+UNIVR+Janssen mice.** More 1-6 Hz power in passive than active state. More 6-10 Hz power in active than passive state.

Results: active vs passive

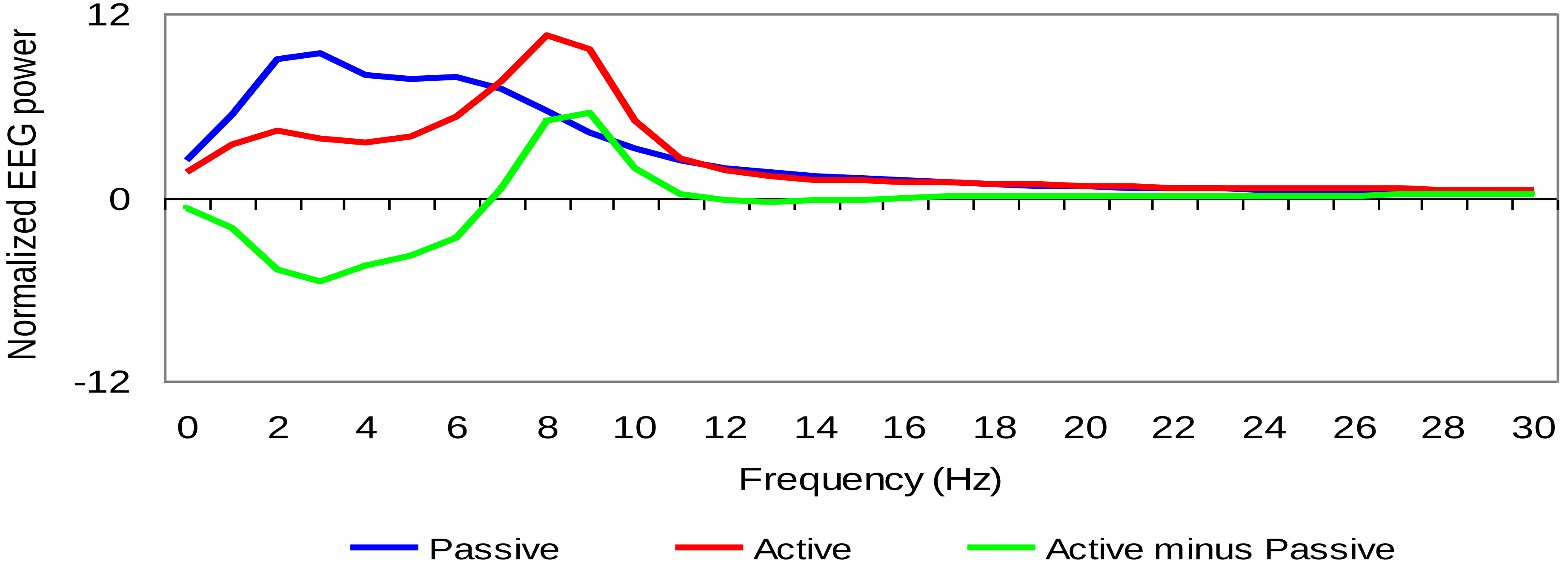
- **ACTIVE vs. PASSIVE state: N=60 mice parietal rec.**



Any blue circle or red square corresponds to an individual EEG data set. The distributions did not show remarkable outliers.

Update on the most significant EEG data

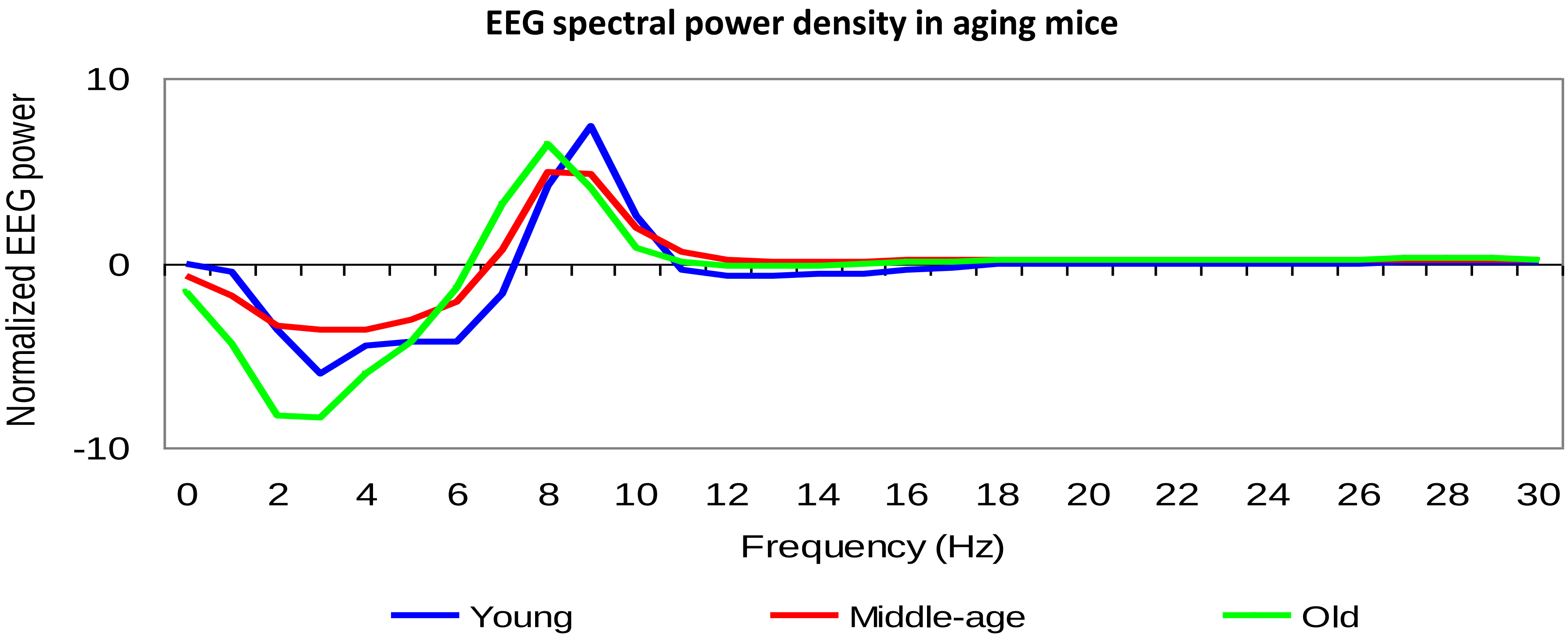
UNIFG, UniVR, Lundbeck, Mario Negri Institute



Grand-average (N=19 young, N=26 middle age, and N=15 old WT mice) of the normalized EEG power density (active minus passive) for parietal cortex. Compared to the young and middle age WT mice, the old WT mice are characterized by higher amplitude of 1-4 Hz power density during the passive state and higher amplitude of 6-8 Hz power during the active state. .

Update on the most significant EEG data

UNIFG, Lundbeck, Mario Negri Institute, UniVR, Janssen



Grand-average (N=19 young, N=26 middle age, and N=15 old WT mice) of the normalized EEG power density (active minus passive) for parietal cortex. Compared to the young and middle age WT mice, the old WT mice are characterized by higher amplitude of 1-4 Hz power density during the passive state and higher amplitude of 6-8 Hz power during the active state. Age: young (4.5-6 months), middle age (12-14 months), and old (24 months).. Gender /**14F/46M.**

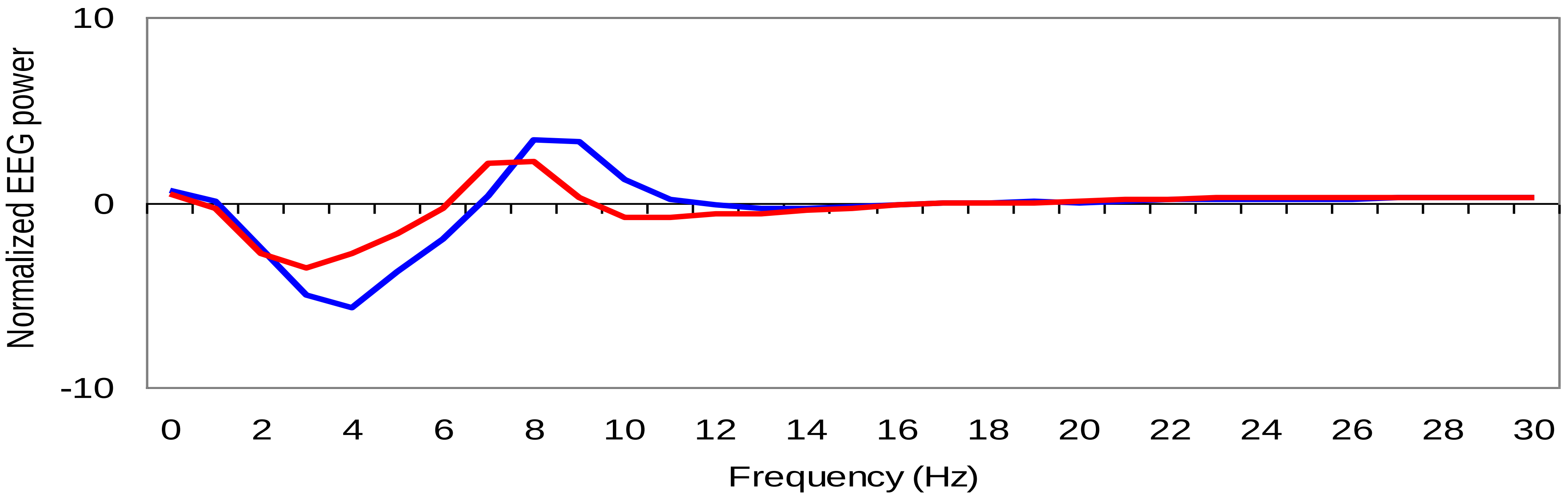
EEG recordings in Tg mice in PharmaCog

Research Unit	Kind of animals	N of animals	Description	Condition
Lundbeck	**Mice**	**34**	**11 TASTPM (female, 15 months) 12 PDAPP (male, 24 months) 11 Tg4510 (male, 4.5 months)**	**Passive and active wake**
Mario Negri	**Mice**	**13**	**7 TASTPM (male; 14 months) 6 PDAPP (male, 12-24 months)**	**Passive and active wake, passive auditory stimuli**
Janssen	**Mice**	**30**	**9 TASTPM (5 male; 12 months) 21 TauPS2APP (male, 17-18 months; 11 Vehicle, 10 donepezil 0.5 mg/Kg)**	**Passive and active wake, sleep, donepezil administration**

Update on the most significant EEG data

Lundbeck, Mario Negri Institute, Janssen

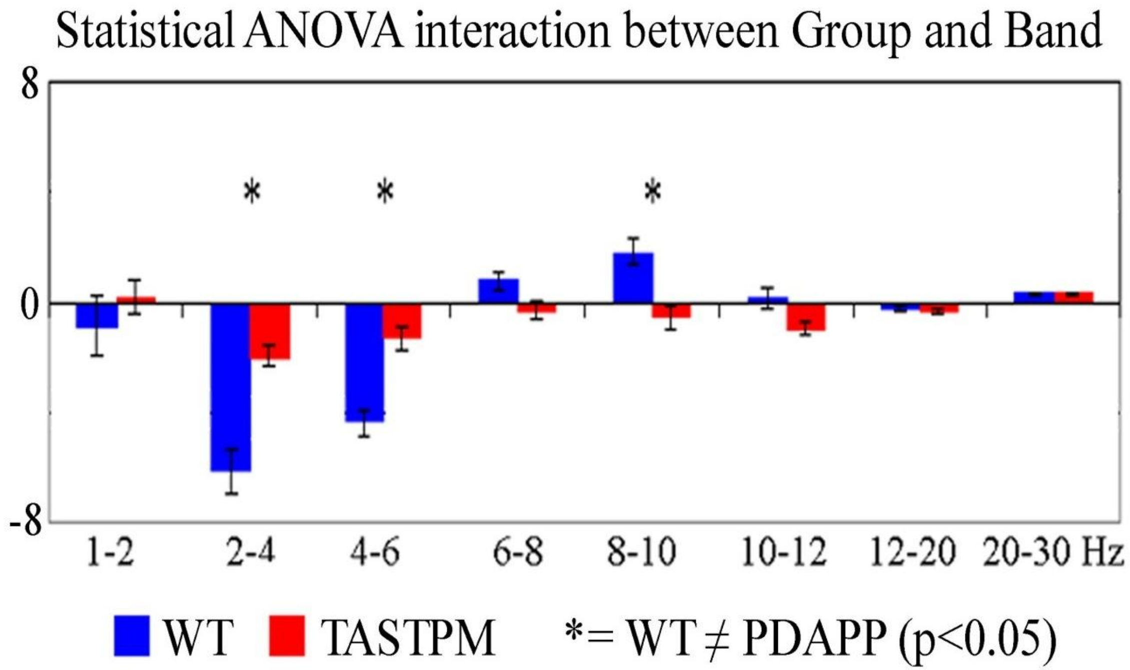
EEG spectral power density in WT Vs. TASTPM mice



Grand-average (N=27 WT and N=24 TASTPM mice) of the normalized EEG power density (active minus passive) for frontoparietal cortex. Compared to the WT mice, the TASTPM mice are characterized by: (1) lower 2-6 Hz power during the passive state, and (2) lower 6-8 Hz power during active state. Age: 12-15 months. Gender: **15F/12M**

WT (N=14, 5 females, 12-14 months) vs. TASTPM (N=15, 4 females, 12-14 months)

•**WT vs. TASTPM mice**. We performed two ANOVAs (light OFF, light ON) having normalized EEG power as a dependent variable and Group (WT, TASTPM), and Band (1-2 Hz, 2-4 Hz, 4-6 Hz, 6-8 Hz, 8-10 Hz, 10-12 Hz, 12-20 Hz, 20-30 Hz) as factors.



active minus passive: zero values mean no difference in power density between active and passive conditions

• The ANOVA showed statistically significant interaction between the factors Group and Band ($F(7,189)=117.3$; $p<0.0001$). Duncan planned post-hoc testing showed that: (1) the amplitude of 2-4 Hz ($p=0.00001$) and 4-6 Hz ($p=0.00002$) power was lower in the TASTPM compared to the WT mice during the passive; (2) the amplitude of 10-12 Hz ($p=0.002$) power was lower the TASTPM compared to the WT mice during the active state

CONCLUSIONS

• In the PharmaCog experiments, WT C57 mice show a power increase at 1-6 Hz during passive state and a power increase at 7-10 Hz during the motor activity (active state).

•Along **physiological aging**, WT C57 mice show a power increase at 1-6 Hz and a power decrease at 7-10 Hz in older mice than in younger mice

•Compared to WT C57 mice, **TASTPM mice** show a power decrease at 1-6 Hz and a power decrease at 7-10 Hz

Conclusions

Integration (correlation, fusion, and classification) of neurophysiologic and neuroimaging markers is a promising approach to cross-validate modal markers and to test hypotheses on the brain dis-function and dis-connection from early to severe stages of AD

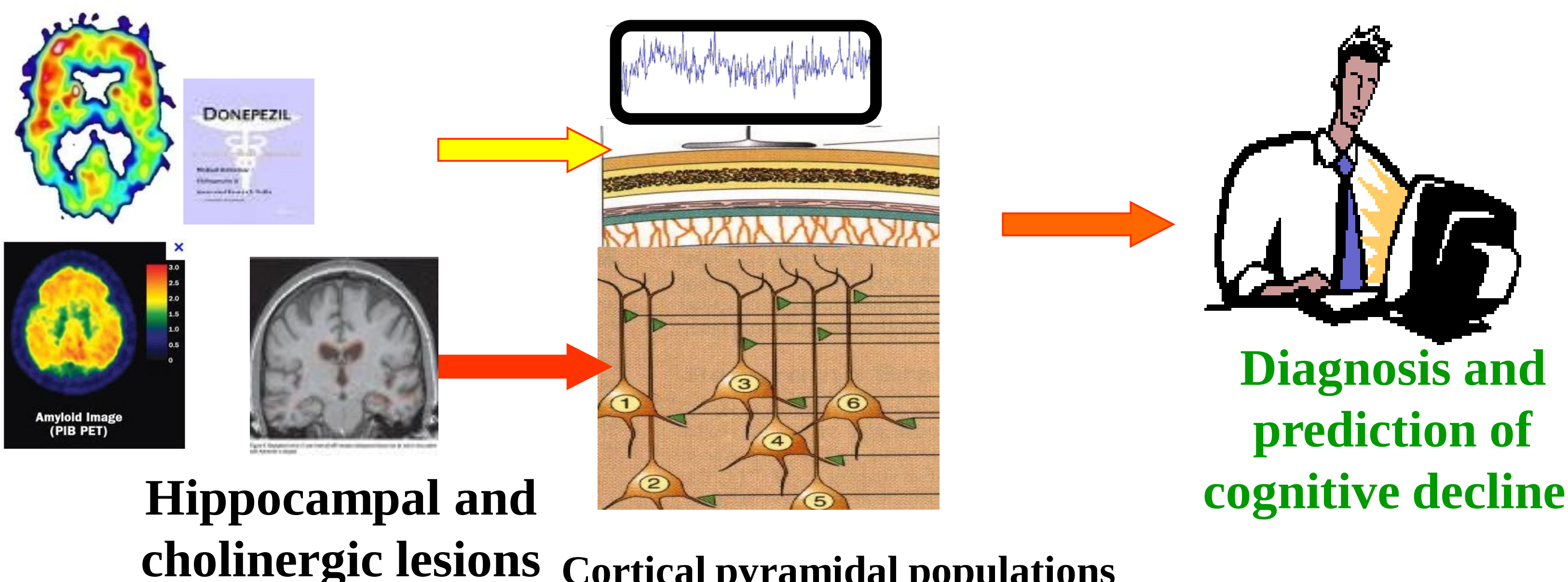
Mild cognitive impairment (MCI) and Alzheimer's disease (AD) are characterized by power reduction of resting alpha sources as opposed to cerebrovascular dementia and parkinson disease with dementia

Amnesic MCI and AD are characterized by power reduction of resting alpha or delta sources related to cortical atrophy and hippocampal volume as signs of neurodegenerations

Cholinergic therapy in AD (Donepezil) just slows down the power reduction of alpha rhythms and cognition in Responders, and is ineffective in Non Responders

FANS therapy in AD (Ibuprofen) slows down the power increment of pathological delta rhythms in correlation with daily ability

EEG markers of cortical arousal can be observed in rodent models of aging and in transgenic models of AD



Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development.

PHARMA-COG 2010-2014

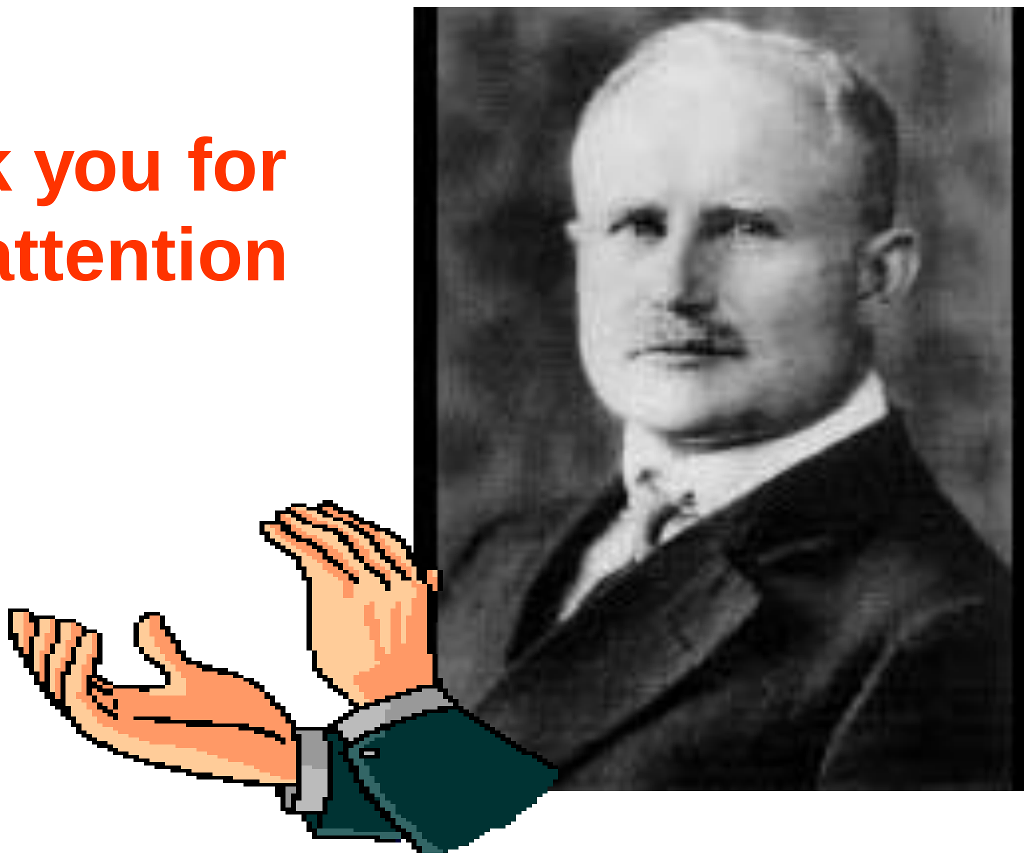
IMI Call topic: IMI_Call_2008_1_11: Neurodegenerative Disorders

Diagnostic Enhancement of Confidence by an International Distributed Environment

DECIDE-2010-2

Call fp7 infrastructures-Proposal Number 261593

Thank you for your attention



The father of EEG: H. Berger