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

1. Department of Physiology and Pharmacology, University of Rome “La Sapienza”
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

<table>
<thead>
<tr>
<th>Cognition</th>
<th>Behavior</th>
<th>Emotion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>Communication</td>
<td>Disregulated</td>
</tr>
<tr>
<td>Learning</td>
<td>Safety</td>
<td>Disorganized</td>
</tr>
<tr>
<td>Language</td>
<td>Personal care deteriorates</td>
<td>Apathy (loss of energy, willingness)</td>
</tr>
<tr>
<td>Praxic Function</td>
<td>Lapses in clarity</td>
<td>Lability (moods change)</td>
</tr>
<tr>
<td>Abstract thinking</td>
<td>Hallucinations</td>
<td></td>
</tr>
<tr>
<td>Psycho-motor speed</td>
<td>Delusions</td>
<td></td>
</tr>
</tbody>
</table>
The neuropathological markers of the AD


Extracellular Aβ plaques
Intracellular tangles
Which instrumental markers ("biomarkers") for early diagnosis, prognosis, disease monitoring, and drug discovery?

Normal elderly (Nold)

Mild cognitive impairment (MCI)

AD
Alzheimer’s biomarkers for diagnosis

State biomarker: diagnosis

Progression biomarker: monitor disease activity (e.g. clinical trials)
Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer’s Association workgroup


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, Steven T. DeKosky, Dennis Dickson, Bruno Dubois, Howard H. Feldman, Nick C. Fox, Anthony Gamst, David M. Holtzman, William J. Jagust, Ronald C. Petersen, Peter J. Snyder, Maria C. Carrillo, Bill Thies, Creighton H. Phelps

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

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)

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

Private

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

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

Start date: 1/1/2010
Duration: 5 years
Total cost: €27.7M
PharmaCog: focus on innovation, translation and harmonisation

Preclinical 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

Clinical Models

Core biomarker set

Blood analysis

Brain scans

Cognitive testing

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 Warsaw, 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

**GridDATALOAD**
- **Data upload**
  - **nameEEGtrials.txt**
  - (2-sec EEG epochs in ASCII format)

**GridEEGQUALITY**
- **Preprocessing artifact detection**
- **(accepting EEG epochs)**
- **(rejecting EEG epochs)**

**GRidDTF/COHERENCE**
- **Model order, Frequency resolution**
- **θ, α, ϒ, γ**

**GRidEEGSOURCE**
- **Window, Frequency resolution,…**

**GridEEGSTAT**
- **reference EEG databases**
- **MCI, Alzh.**
- **What diagnosis?**
- **nameEEGreport.pdf**
- **Z score**
- **Nold area**
- **AD area**
- **AD axis 0=AD**
- **Nold axis 0=Nold**
- **Statistics & send report**
Which qEEG markers for early diagnosis, prognosis, disease monitoring, and drug discovery?
Which qEEG markers for early diagnosis, prognosis, disease monitoring, and drug discovery?

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

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. 115008) 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.

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

Psychometric testing and neurological evaluation
Spontaneous delta rhythms of cerebral cortex when disconnected from cortical and sub-cortical inputs

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

Reticular neurons

Relay neurons

BRAIN STEM

THALAMUS

= All neurons synchronized at around 1 Hz
pyramidal neurons oscillating at synchronized alpha frequencies (around 10 Hz)

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

RESTING EYES CLOSED

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

Reticular neurons

Relay neurons

BRAIN STEM

THALAMUS

= All neurons synchronized at around 10 Hz
Alpha rhythms recorded from the visual cortex of dog

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


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 \textit{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.
qEEG markers for differential diagnosis: cortical resting EEG rhythms characterizing mild AD compared to cerebrovascular dementia (VaD) and Parkinson disease with dementia
Resting EEG data:

38 Nold
48 mild AD
20 VaD

<table>
<thead>
<tr>
<th>GRAND AVERAGE OF LORETA RELATIVE CURRENT DENSITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ (2-4 Hz)</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Nold</td>
</tr>
<tr>
<td>Mild AD</td>
</tr>
<tr>
<td>VaD</td>
</tr>
</tbody>
</table>

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.

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

GRAND AVERAGE OF LORETA CURRENT DENSITY

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)

\[ 0.000001 \leq p \leq 0.04836 \]

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

Resting state cortical EEG rhythms are related to gray matter volume in MCI and AD patients

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Gray Matter Volume (ml)</th>
<th>White Matter Volume (ml)</th>
<th>Cerebrospinal fluid (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>108 498.1 (±6.0 SE)</td>
<td>406.7 (±6.0 SE)</td>
<td>766.9 (±13.2 SE)</td>
</tr>
<tr>
<td>MCI</td>
<td>102 566.3 (±7.5 SE)</td>
<td>432.5 (±5.8 SE)</td>
<td>652.1 (±11.2 SE)</td>
</tr>
<tr>
<td>MCI≠AD</td>
<td>p= 0.00001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the MCI and AD subjects as a whole group, the lower the cortical gray matter volume (GMV), the higher the delta sources, the lower the alpha 1 sources. Furthermore, we observed that the better the score to cognitive tests the higher the GMV, the lower the delta sources, and the higher the alpha sources. These results suggest that abnormalities of resting state cortical EEG rhythms are strictly related to neurodegeneration and cognition.

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

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 delta sources were lower in amplitude in the Nold than in the AD groups, 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. The higher the cortical metabolic damage, the higher the pathological delta sources. These results reflect relevant pathological processes in these patients.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Gender</th>
<th>Education</th>
<th>MMSE</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>20</td>
<td>11 F, 9 M</td>
<td>9.7± (1.1 SE)</td>
<td>19.5± (1.1 SE)</td>
</tr>
<tr>
<td>Nold</td>
<td>35</td>
<td>22 F, 13 M</td>
<td>9.8± (0.8 SE)</td>
<td>28.2± (0.2 SE)</td>
</tr>
</tbody>
</table>

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

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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial Eta squared</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.178</td>
<td>0.5</td>
</tr>
<tr>
<td>Parietal Alpha 1</td>
<td>0.077</td>
<td>-0.29</td>
</tr>
<tr>
<td>Occipital Alpha 1</td>
<td>0.123</td>
<td>-0.42</td>
</tr>
<tr>
<td>Temporal Alpha 1</td>
<td>0.131</td>
<td>-0.38</td>
</tr>
<tr>
<td>Parietal Alpha 2</td>
<td>0.101</td>
<td>-0.34</td>
</tr>
<tr>
<td>Occipital Alpha 2</td>
<td>0.133</td>
<td>-0.43</td>
</tr>
<tr>
<td>Temporal Alpha 2</td>
<td>0.142</td>
<td>-0.42</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial Eta squared</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.262</td>
<td>0.59</td>
</tr>
<tr>
<td>Parietal alpha 1</td>
<td>0.131</td>
<td>-0.36</td>
</tr>
<tr>
<td>Occipital alpha 1</td>
<td>0.184</td>
<td>-0.4</td>
</tr>
<tr>
<td>Temporal alpha 1</td>
<td>0.234</td>
<td>-0.43</td>
</tr>
<tr>
<td>Parietal alpha 2</td>
<td>0.047</td>
<td>-0.19</td>
</tr>
<tr>
<td>Occipital alpha 2</td>
<td>0.036</td>
<td>-0.18</td>
</tr>
<tr>
<td>Temporal alpha 2</td>
<td>0.102</td>
<td>-0.29</td>
</tr>
</tbody>
</table>

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
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.

STATISTICAL ANOVA INTERACTION OF GROUP, BAND AND ROI


Resting EEG data:
- 28 Non Responder
- 30 Responder
Resting EEG data:
13 AD ibuprofen
10 AD placebo

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

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

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

MVAR model estimates “direction” of information flow by DTF.

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

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

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

Synchronization likelihood

LAPLACIAN RESTING EEG IN NOLD, AD AND MCI SUBJECTS

Validation of EEG markers: Diagnostic Accuracy

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.

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

qEEG markers of cortical arousal for translational purposes: comparison between “active” vs. “passive” conditions in humans and animal models
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)

Reticular neurons

Relay neurons

BRAIN STEM

THALAMUS
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)

Reticular neurons = synchronous at around 20 Hz

Relay neurons = synchronous at around 40 Hz

Relay neurons = synchronous at around 100 Hz
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.

Which preclinical qEEG markers for drug discovery?


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.
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
AIM

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

• TASTTPM 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

<table>
<thead>
<tr>
<th>UNIT</th>
<th>N</th>
<th>Gender (M/F)</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>MNI</td>
<td>23</td>
<td>23/0</td>
<td>6 months (N=7), 12 months (N=3), 14 months (N=6), 24 months (N=7), monopolar parietal rec</td>
</tr>
<tr>
<td>Lundbeck</td>
<td>34</td>
<td>20/14</td>
<td>4.5 months (N=12), 15 months (N=14), 24 months (N=8), monopolar parietal rec</td>
</tr>
<tr>
<td>UNIVR</td>
<td>3</td>
<td>3/0</td>
<td>12 months (N=3), monopolar parietal rec</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>46/14</td>
<td>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</td>
</tr>
<tr>
<td>JANSSEN</td>
<td>12</td>
<td>7/5</td>
<td>12 months. bipolar frontoparietal rec</td>
</tr>
</tbody>
</table>
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
ELECTRODE LOCATIONS

Frontal (FC) and Parietal PC
MNI WT mice: active vs passive

MNI mice (Grand average N=23)
Active vs Passive state
Spectral power density

- **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.
- **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

UNIVR mice (Grand average N=3)
Active vs Passive state
Spectral power density

- **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.

<table>
<thead>
<tr>
<th>Unit</th>
<th>N</th>
<th>Gender (F/M)</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNIVR</td>
<td>3</td>
<td>0/3</td>
<td>12 months (3 mice)</td>
</tr>
</tbody>
</table>
**Janssen WT mice: active vs passive**

**Janssen mice (Grand average N=12)**

Active vs Passive state
Spectral power density

- **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

**MNI+Lundbeck+UNIVR+Janssen** mice (Grand average N=58)

Active vs Passive state
Spectral power density

- **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**

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.
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

<table>
<thead>
<tr>
<th>Research Unit</th>
<th>Kind of animals</th>
<th>N of animals</th>
<th>Description</th>
<th>Condition</th>
</tr>
</thead>
</table>
| **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.

  - 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.

Diagnosis and prediction of cognitive decline!

Hippocampal and cholinergic lesions Cortical pyramidal populations
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