Multimodal Databases and EEG—the key to translational Brain Mapping

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Brain Mapping has hit the news recently

US BRAIN Project: >110 millones $USD 1 year

European Brain Project: >1 Billion Euros in 10 years
European Brain Project: >1 Billion Euros in 10 years

Main features:
- Top down
- Theory driven
- Focus on ICT
- 1 Billion Euros 10 years

ICT Platforms
- Neuroinformatics
- Brain Simulation
- Medical Informatics
- Neuromorphic Comput.
- Neurorobotics

Future:
- Neuroscience
- Medicine
- Computing

Mouse data

Human data

Cognitive Architect

Math & Theory

Training
- Neuroethics

HBP_flagship_report_for_Europe_2012
US Brain Research through Advancing Innovative Neurotechnologies (BRAIN)

Main features:
- Bottom up
- Data driven
- Focus on NT

Cell Census
Human data
Collect Human data

NT platforms
- Large Scale Network Recording
- Circuit manipulation tools
- Mechanisms of Human Neuroimaging
- Neuroinformatics

Link Neuronal Activity to Behavior

Theory, Modeling, Statistics, and Comput. with Experiments

Training
Neuroethics

NIH Brain Interim report 2013
The Second Cuban Human Brain Mapping Project imitated multimodal data gathering in 1989.
qEEG is based on the extraction of Descriptive parameters from the EEG and the constructions of norms.

128 channel EEG recording

Descriptive EEG Spectral parameters

Topographic Maps

Normative databases

High resolution quantitative EEG analysis. Szava et al (1994) Brain Topog. 6/3 211-219
Individual descriptive parameters can be “z-transformed” in a metric relative to the normative database.

\[ Z = \frac{x - \mu}{\sigma} \]

Age and other covariates avoid false positives.

\[ Z = \frac{x - \mu(\text{age})}{\sigma(\text{age})} \]

Individual Topographic Maps may be then compared to the normative data as “z-score topographies”

\[ z = \frac{x - \mu(\text{age})}{\sigma(\text{age})} \]

DP correlations must be corrected for with the Mahalanobis Distance improving accuracy

\[ D^2 = \frac{[x - \mu(\text{age})]^2}{\Sigma(\text{age})} \]

Multivariate statistical brain electromagnetic mapping. Galan et al (q9949 Brain Top 7/1 17-28)
In Cuba qEEG has been introduced into the Public Health system

Through the creation a national network of clinical neurophysiology

And subject to quality assessment by means of the area under the ROC curves: AUC

Sensitivity = \( P(TP) \)

Lack of specificity = \( P(FP) \)

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>TN</td>
<td>FP</td>
</tr>
<tr>
<td>Patient</td>
<td>FN</td>
<td>TP</td>
</tr>
</tbody>
</table>
A double blinded study of most of the Advisory Board of ISBET gave surprising results.

qEEG in a Public Health System. Valdes-Sosa et al. Brain Topography 4, 4 1992
The name ‘statistical parametric mapping’ was chosen carefully for a number of reasons. First, it acknowledged the TLA of ‘significance probability mapping’, developed for EEG. Significance probability mapping involved creating interpolated pseudo-maps of p-values to disclose the spatiotemporal organization of evoked electrical responses.
Brain Electrical Tomography picks a particular solution to the undetermined EEG inverse Problem

\[ \nu_1 = k_1 \cdot j_1 + k_2 \cdot j_2 \]
VARETA was applied to the EEG spectrum to determine the sources of EEG rhythms.

128 channel EEG recording

Descriptive EEG Spectral parameters

Source Spectra found using VARETA

Topographic Maps
The EEG of each individual is processed by an automatic pipeline that produced a source EEG atlas (norms).

This work relied on the adult MNI structural atlas to create an EEG atlas.
A VARETA EEG atlas was obtained for the Cuban population from ages 5-97

3D statistical parametric mapping of EEG source spectra by means of variable resolution electromagnetic tomography (VARETA) Bosch et al. (2001) Clinical EEG, 32/2 47-61
Developmental changes show specific spatial patterns for this age range

Topography of regression coefficients of spectral power with age
quantitative Tomographic EEG had higher diagnostic accuracy than scalp EEG based qEEEG

Babies with brain disorders

Normal test group

AUC

Diagnostic accuracy

qEEGt  qEEG-AV  qEEG-Lap
Neurometrics Science Paper

Mastousek Petersen
NYU-Cuba

EEG only

With EEG

Cuban HBM 1

78/2004
Cuban HBM 2

ICBM

Allen

Human Connectome
Brannetome
HBP
BRAIN

Without EEG

ADNI1

ADNI2
The Second Cuban Human Brain Mapping Project imitated multimodal data gathering in 2004
This project was initiated by sampling clinical, MRI, DWI images and EEG from the general population.

Sample

Blood(ADN)

N = 1864

Clinical

EEG

MRI

N = 539

N = 530

N = 394
The data base has been enhanced with data from a number of national studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial random sample of ages 15-80</td>
<td>2109</td>
</tr>
<tr>
<td>Cognitve Endophotypes of schizophrenia</td>
<td>797</td>
</tr>
<tr>
<td>Addtional Elderly Controls</td>
<td>40</td>
</tr>
<tr>
<td>Study of violent subjects</td>
<td>140</td>
</tr>
<tr>
<td>Special Cognitve study of normals</td>
<td>88</td>
</tr>
<tr>
<td>Pres-school Children</td>
<td>100</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50</td>
</tr>
<tr>
<td>School children</td>
<td>26200</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>29524</strong></td>
</tr>
</tbody>
</table>
The data of each individual is processed by a totally automatic pipeline that produces multimodal atlas (norms).
A patient with prosopagnosia was analyzed with mutimodal imaging and compared to atlases.

He retained only covert recognition of faces.

Severe damage to bilateral FA areas.

EEEG N400 showed some activation fin OFA as did fMRI with additonal prefrontal activation.
In silico lesions of subjects allowed testing of intact tracts sustaining covert recognition

Inferior longitudinal (ILF)

Normal subjects

An fMRI seeded tractography atlas allowed analysis of single subjects

Inferior fronto-occipital (IFOF)

Post→Ant

Ant

Post
The Cuban national study of Violent Behavior has shown that combinations of modalities improve accuracy in characterizing psychopaths.

Qualitative and quantitative EEG abnormalities in violent offenders with antisocial personality disorder. Calzado & Amador J. of Forensic and legal Medicine (2009) 16/2, 59-63
Predictive Neuroinformatics Needs for Falsifiable Theories and a Good Example: Nunez Global Theory of Brain Waves

\[ \omega_l \propto \sqrt{l(l+1)} \frac{v}{R}, \quad l = 1, 2, 3, \ldots \]

- \( v \): Conduction velocity
- \( R \): Radius of (spherical cortex)

Head size is inversely proportional to the peak of the alpha rhythm.
Which has been falsified by data

Surface area (Nunez) ?  

Conduction velocity in thalamo-cortica loops ?

\[
\omega_l \propto \sqrt{l(l+1)} \frac{v}{R}, \quad l = 1, 2, 3, \ldots
\]

Área Corteza Inc. Proportional Alfa
Nunez (1989)

No relation area and alpha

Relation between FA and alpha

\[
t = \frac{L}{v(D, f)}
\]

\[
C = N \propto fB^2
\]
This fact was used to model EEG/fMRI relations using a large scale neural mass model based on realistic connectivity

Model: differential-integral Random Differential Equation

\[ \ddot{g}(x,t) = f(\dot{g}, g, x, t) + \int \limits_{\text{brain}} c(x, X) S\left[ g(X, \tau(x, X)) + p(X, \tau(x, X)) \right] dX \]

Delay

\[ \tau(x, X) = t - \frac{x - X}{v} \]

Delay estimated from graph theoretical connectivity parameters
Which served as the basis of a principled predictive modeling of EEG/fMRI correlations

Current models integrate EEG-fMRI, DWI, MRI with massively parallel neural mass models (10^4)

Random Differential Algebraic Equations

Model driven EEG/fMRI fusion of brain oscillations. Valdes-Sosa et al. (2009) Human Brain Mapping, 30 2701
A major concern of countries is the preservation of its Mental Capital

The mental wealth of nations
Countries must learn how to capitalize on their citizens’ cognitive resources if they are to prosper, both economically and socially. Early interventions will be key.
How will Neuroscience impact on the Global Burden of Brain Disease?

- Neuroscience
  - Neurotechnology
    - Diagnosis
    - Treatment
      - Tertiary health level
      - Primary health level
        - Global Burden of Brain Disorders

Translational research
The Global Burden of Brain Disorders is simply Stagerring
The high burden of Brain Disorders goes together with the need for Neurotechnology

High Prevalence: needs actions at primary level

CONTRADICTION

Need and usefulness of technology including NeuroImages:
- Scarce Resources
- Geographic dispersion
- Difficult access
The solution to this contradiction is using Stratified Active Screening.
CNEURO has developed the AUDIX system to carry out early detection of hearing loss

A patented bone/air conduction technique avoids false positives, for example due to liquid in the auditory canals

Children detected since 1983 have better achievement in language and general IQ
The early detection effects were promissory...

Early detection of hearing loss improved cognitive development in children with hearing impairment.
For example we have helped the Republic of Ecuador to carry out in the past 2 years a population based screening program.

Coverage for 24 provinces

A total of 971 medical devices installed

Training of more than 998 professionals

More than 450 thousand screened!!!
Program for Prevention of Neurodevelopmental Disorders at School Age

International Health Conference “Cuba Health 2012”
More than 5% of school-age children suffer some kind of Neurodevelopmental Disorders in Cuba

**Universal Screening**
Centro Habana Study
Universe of school-age children
11,836

**Risk Factor Screening**
National Study 2006
270 Schools all the country
16,097

### Prevalences

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Universal Screening</th>
<th>Risk Factor Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental Dyscalculia</td>
<td>3.17</td>
<td>5.9</td>
</tr>
<tr>
<td>Developmental Dyslexia</td>
<td>4.27</td>
<td>2.57</td>
</tr>
<tr>
<td>Arithmetic Learning Disabilities</td>
<td>7.19</td>
<td>8.17</td>
</tr>
<tr>
<td>Reading Learning Disabilities</td>
<td>6.35</td>
<td>14.8</td>
</tr>
</tbody>
</table>
Basic skills predict reading and mathematical achievement

Basic skills assessment: magnitude comparison and lexical decoding

Achievement: Reading and arithmetic fluency assessment

Early evaluation of basic skills allow to select the best intervention program
Brain morphometric abnormalities in children with Dyscalculia

MaxiMat

Length SHSH: Dyscalculia > Normals

Centro de Neurociencias de Cuba
CNEURO has technology for implementing a program for prevention of neuro-developmental disorders at school-age children.

- Basic research
- Neuropsychological Evaluation (basic skills)
- Active Screening at school

Diagram:

- Computerized Behavioral Screening Tools
- Training
- Neurocognitive Tools
- At Risk
- No Risk

Intervention
Higher life expectancies leads to population aging, increasing cognitive impairment and dementia

In 2010, there was 18% (2 million) of persons with 60 years and older.

In 2035, will be 33.9% of persons > 60 years old.

In the next 20 years, Cuba become the most aged country of Latin America and the Caribbean.

Estimation of AD in Cuban population

Dementia’s prevalence 8.2 - 10.2 % (150,000 cases)

Incidence rate 21.7 per 1000/year (28,760 new cases/year)

Mortality rate 195.5 per 1000/year
EEG source z Images proved predictive in 5 extended families affected by early-onset AD due to an E280A Presenilin-1 mutation

AD (N=12)
With Mutation
Mild symptoms

ACr (N=9)
With Mutation
No symptoms

N (N=9)
Without Mutation
No symptoms
qEEG-t proved predictive in by early-onset AD due to an E280A Presenilin-1 mutation.

qEEG-t 5.4 Hz
Arterial Hypertension is one of the most prevalent diseases of the older adult

Prevalence:

- Global: 20-30 %
- Cuba: 26,2 %
- CHBMP: 28,2 %

68 % > 50 años
Hypertension leads to damage in target organs

Large vessels

Clinical diagnosis
(Overt symptoms)

Kidney: failure
Heart: Infarct
Brain: Ictus

Small vessels

Diagnosis with technology
(Daño subclínico)

Kidney: Microalbuminuria, creatinine
Heart: EKG, Echocardiogram
Brain: ¿MRI?

✓ BAJA Low availability
✓ High cost
A pilot study of hypertensive subjects was carried out to identify biomarkers for brain vascular damage from hypertension.

N=50 patients
Average age: 44 years
Average time of Hypertension evolution: 11 years

"Early markers for brain damage in asymptomatic hypertensive patients" pilot study (Cuban Human Brain Mapping Project)
MRI abnormalities are correlated with cognitive performance

Non classical vascular lesion

which declines with degree of severity from 0 - 3

$\text{WAIS-III}$

$p=0.014$
The brain was the earliest and most damaged organ by hypertension.

78% of patients had brain vascular damage.

20% of cases had no demonstrable cardiorrenal damage and they would have classified as “without Hypertensive target-organ damage” if the brain damage would have remained undetected.
qEEG tomographic maps showed a clear lesion type effect that predicts MRI lesion load.
ROC curves for ordinal data evaluated candidate “surrogate biomarkers” for MRI abnormality

Delta and alpha1 voltage (qEEG)
Dipper (ABPM)
Picture completion (WAIS-III)
GTE score (visual EEG)
Body mass index
Intima-media thickness (DC)
PIQ (WAIS-III)
Fundoscopy
Dd Rv (Echocardiogram)
MMSE
HDL cholesterol
Resistive index (TCD)
EKG

AMYLOVIS is a versatile radiotracer of β-amyloid plaques, it can adjust to the available equipment in the health installations (SPECT, PET or MRI).

SPECT $^{99m}$Tc-AMYLOVIS crosses the BBB

An Amylovis compound interact with folded Aβ$_{17-42}$ fragment

PET $^{18}$F-AMYLOVIS

Healthy animals

Transgenic animal

Aβ$_{17-42}$ segment fibrils
We propose a multistage prognostic screening model with innovative methods to ensure a high diagnostic efficiency and rational use of resources.
Stratified Active Screening combines Neurotechnology with Public Health to protect Mental Capital
Instead of averaging the MRIs to get a brain atlas, average the inverse solutions for different head models.

Bayesian Model Averaging

Figure 3. Simulated source in the occipital pole recovered by the average model, the true model and the BMA model with interpolation.
CNEURO is working with Peter Hersics (UltraSmart Ltd, Hungary) to develop a portable EEG device for use in active screening.
Development of SPM

PET years
fMRI years
EEG-MEG years