From Physics to Daily Life

Online Environments for Research and Care in Neurodegenerative Diseases

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University Hospitals and University of Geneva
IRCCS Fatebenefratelli, The National Centre for Alzheimer’s Disease, Brescia
Summary

Dementia and Alzheimer’s

Address the data deluge in cognitive neurosciences

Provide diagnostic tools to ordinary clinicians
Summary

Dementia and Alzheimer’s

Address the data deluge in cognitive neurosciences

Provide diagnostic tools to ordinary clinicians
Address the data deluge in the neurosciences

What’s dementia?

William Utermolhen (1933-2007)

1967 – 34 yrs

2000 – 67 yrs
Dementia is a syndrome, not a disease
Neurodegenerative dementias and their molecular cause

<table>
<thead>
<tr>
<th>ALZHEIMER</th>
<th>LEWY BODIES</th>
<th>FRONTO-TEMPORAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-amyloid tau</td>
<td>α-synuclein</td>
<td>tau TDP43 FUS</td>
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</tbody>
</table>
Summary

Dementia and Alzheimer’s

Address the data deluge in cognitive neurosciences

Provide diagnostic tools to ordinary clinicians
Address the data deluge in the neurosciences

Clinical neuroimaging studies in 2004: small groups and crude measures

Subcortical Vascular Lesions Predict Functional Recovery After Rehabilitation in Patients with L-Dopa Refractory Parkinsonism

Fabio Guerini, MD, Giovanni B. Frisoni, MD, Catherine Bellward, MD, Roberta Rossi, Psy, Giuseppe Bellelli, MD, and Marco Trabucchi, MD

JAGS 52:252–256, 2004
© 2004 by the American Geriatrics Society
Higher atrophy rate of entorhinal cortex than hippocampus in AD

A.T. Du, MD; N. Schuff, PhD; J.H. Kramer, PsyD; S. Ganzer, MD; X.P. Zhu, MD, PhD; W.J. Jagust, MD; B.L. Miller, MD; B.R. Reed, MD; D. Mungas, PhD; K. Yaffe, MD; H.C. Chui, MD; and M.W. Weiner, MD

Address the data deluge in the neurosciences

Clinical neuroimaging studies in 2004: small groups and crude measures
Address the data deluge in the neurosciences

Clinical neuroimaging studies in 2014: X-large groups...

<table>
<thead>
<tr>
<th>STUDY</th>
<th>sMR</th>
<th>dMR</th>
<th>rest fMRI</th>
<th>EEG</th>
<th>FDG-PET</th>
<th>Amy PET</th>
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<tbody>
<tr>
<td>EU-ADNI/Pharmacog (IMI)</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>US ADNIs</td>
<td>13'500</td>
<td>1’550</td>
<td>3’950</td>
<td>---</td>
<td>3’750</td>
<td>250</td>
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<tr>
<td>Japanese ADNI</td>
<td>3’500</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1’000</td>
<td>500</td>
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<tr>
<td>AddNeuroMed (IMI)</td>
<td>3’500</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Australian ADNI/AIBL</td>
<td>1’800</td>
<td>1’800</td>
<td>---</td>
<td>---</td>
<td>300</td>
<td>450</td>
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<tr>
<td>1000 connectomes</td>
<td>---</td>
<td>1350</td>
<td>700</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>OASIS</td>
<td>2’000</td>
<td>---</td>
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<td>---</td>
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<tr>
<td>LADIS (5th FP)</td>
<td>1’200</td>
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<tr>
<td>EMIF-AD (IMI)</td>
<td>15’000</td>
<td>5’000</td>
<td>5’000</td>
<td>---</td>
<td>2’000</td>
<td>1’000</td>
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<tr>
<td>AD Without Borders (It MH)</td>
<td>3’000</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>200</td>
<td>---</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>44’400</strong></td>
<td><strong>10’600</strong></td>
<td><strong>10’550</strong></td>
<td><strong>900</strong></td>
<td><strong>7’250</strong></td>
<td><strong>2’200</strong></td>
</tr>
</tbody>
</table>
Clinical neuroimaging studies in 2014: X-large groups and sophisticated measures

Address the data deluge in the neurosciences

**STRUCTURAL (GM damage)**
- MR Cortical thickness mapping
- MR Automated segmentation
- MR Voxel-based statistics

**MICROSTRUCTURAL (WM damage)**
- MR Tensor-based morphometry
- MR Tract-based spatial statistics

**FUNCTIONAL (network damage)**
- MR Activation fMRI (with task)
- MR Rest fMRI network extraction
Address the data deluge in the neurosciences

Alzheimer’s: biomarkers: the dynamic biomarker hypothesis

Mark abnormality

Deposits of cerebral amyloid

Amyloid PET

Years after diagnosis of dementia

% abnormality of biomarkers

Early neurodegeneration (synaptic dysfunction)

Cortical hypometabolism on PET

Late neurodegeneration (neuronal loss, atrophy)

Volumetrie de l’hippocampe en IRM

Frisoni GB et al. Nat Rev Neurol 2010

CERN

26/09/2014 From Physics to Daily Life 12
Address the data deluge in the neurosciences

**Clinical neuroimaging studies in 2014: X-large groups and sophisticated measures**

- 185 ADNI-1 subjects X
- 2 B2B 1.5T scans X
- 3 time points (BSL, M12, M24)
- 1110 total scans

Processing tools:
- CIVET
- FREESURFER
- VIP

**COMMON DATASET OF ANALYSIS:**
- 185 subjects X
- 1 scan (MPRAGE or MPRAGE-REPEAT) X
- 3 time points (BSL, M12, M24)

Redolfi et al., 2014 submitted
Address the data deluge in the neurosciences

Clinical neuroimaging studies in 2014: X-large groups and sophisticated measures

Redolfi et al., 2014 submitted
Address the data deluge in the neurosciences

Clinical neuroimaging studies in 2014: X-large groups and sophisticated measures

Redolfi et al., 2014 submitted
Address the data deluge in the neurosciences

A multimodal model of the biomarker progression of Alzheimer’s disease

Frisoni GB et al. Nat Rev Neurol 2010

Marker abnormality

Ans depuis le diagnostic de démence

\[ \frac{d^3 y}{dt^3} + 2 \frac{dy}{dx} \cdot y = \sin(x) \]
Address the data deluge in the neurosciences

neuGRID: a grid-based environment for high throughput neuroimage analyses
Address the data deluge in the neurosciences

**neuGRID: a grid-based environment for high throughput neuroimage analyses**

**Algorithm pipelines for marker extraction**

\[
\left(\frac{d^3y}{dx^3}\right)^4 + 2 \frac{dy}{dx} = \sin x
\]

**Vast computational resources**

<table>
<thead>
<tr>
<th>Node</th>
<th>Storage (MB)</th>
<th>CPUs (n)</th>
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<tbody>
<tr>
<td>Sweden</td>
<td>3,557</td>
<td>40</td>
</tr>
<tr>
<td>Italy</td>
<td>3,170</td>
<td>40</td>
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<tr>
<td>France</td>
<td>4,095</td>
<td>2,600</td>
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<tr>
<td>Maat</td>
<td>1,268</td>
<td>8</td>
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<tr>
<td>Brazil</td>
<td>0</td>
<td>128</td>
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<tr>
<td>EGI</td>
<td>71,793</td>
<td>1,912</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>83,883</strong></td>
<td><strong>4,728</strong></td>
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**Help & Training**

<table>
<thead>
<tr>
<th>Help desk</th>
<th>Home</th>
<th>Progetti</th>
<th>Aluto</th>
<th>neuGRID4you Help Desk</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Panoramica</td>
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<tr>
<td>21-12-2012</td>
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<tr>
<td>23:18</td>
<td>Support #797: desktop fusit</td>
<td>If you have any problem, try to put the or</td>
<td>Try to start FF from a termina...</td>
<td>Jérôme Revillard</td>
</tr>
<tr>
<td>21:29</td>
<td>Support #797: desktop fusit</td>
<td>Hi Jerome, both gateways. But it’s not a problem</td>
<td></td>
<td>Luigi Antelmi</td>
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<td>Support #797: desktop fusit</td>
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Summary

Dementia and Alzheimer’s

Address the data deluge in cognitive neurosciences

Provide diagnostic tools to routine clinicians
...pour le diagnostic précoce...

Phase de déficit cognitif léger (MCI)

Marker abnormality

Ans depuis le diagnostic de déméence

Frisoni GB et al. Nat Rev Neurol 2010
Why study brain structure and function with MR in Alzheimer’s disease?

Provide diagnostic tools to ordinary clinicians

---

<table>
<thead>
<tr>
<th>Analisi</th>
<th>Risultato</th>
<th>Unità</th>
<th>Intervallo di riferimento</th>
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</thead>
<tbody>
<tr>
<td>S-COLESTEROLO TOTALE</td>
<td>196</td>
<td>mg/dL</td>
<td>&lt; 200</td>
</tr>
<tr>
<td>S-COLESTEROLO HDL</td>
<td>62</td>
<td>mg/dL</td>
<td>&gt; 35</td>
</tr>
<tr>
<td>S-COLESTEROLO LDL</td>
<td>120</td>
<td>mg/dL</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>S-TRIGLICERIDI</td>
<td>101</td>
<td>mg/dL</td>
<td>&lt; 200</td>
</tr>
<tr>
<td>P-GLUCOSIO</td>
<td>124 &gt;</td>
<td>mg/dL</td>
<td>60 - 110</td>
</tr>
<tr>
<td>Sg-EMOGLOBINA GLICATA (unità DCCT)</td>
<td>6.0 &gt;</td>
<td>%</td>
<td>4.0 - 5.6</td>
</tr>
<tr>
<td>Sg-EMOGLOBINA GLICATA (unità IFCC)</td>
<td>42 &gt;</td>
<td>mmol/mol</td>
<td>20 - 38</td>
</tr>
</tbody>
</table>

Nota: il valore decisionale per la diagnosi di diabete è 6.5% oppure 48 mmol/mol secondo l'intervallo di riferimento indicato.
Provide diagnostic tools to ordinary clinicians

The change of a biological marker with age: the case of growth curves
The change of a biological marker with age: the case of growth curves

ACM-AdaBoost Results

Model: DECIDE Standard Model

Left Volume: 2462 mm³
Right Volume: 2945 mm³

Figure 1: Segmentation of the brain scan registered to the ICBM-152 template. The letter “R” identifies the Right direction. (a) Axial view. (b) Coronal view. (c) Sagittal view centered on the Right Hippocampus. (d) Sagittal view centered on the Left Hippocampus.
Summary

Computational neuroscience will make increasing use of grid/cloud resources

These will soon impact also on routine clinical procedures for the diagnosis of Alzheimer’s and other neurodegenerative diseases
Clinical neuroimaging studies in 2004: small groups and crude measures
Clinical neuroimaging studies in 2004: small groups and crude measures
Clinical neuroimaging studies in 2004: studies of cortical thinning
neuGRID in the HBP

Medical Informatics Platform

1. MIP1: Cloud based system for handling distributed clinical data
2. MIP2: Federated, privacy controlled, data access across 100 hospitals
3. MIP3: Predictive medical informatics on federated data to derive biological signatures of disease
4. MIP4: Biological signatures of any brain disease and personalized medicine

Timeline:
- Y1
- Y2
- Y3
- Y4
- Y5
- Y6
- Y7
- Y8
- Y9
- Y10
### Figures

**Epidemiology of Dementia in Geneva**

François R. Herrmann\(^a\), Jean-Jacques Mermod\(^b\), Scott Henderson\(^c\), Jean-Pierre Michel\(^a\)

<table>
<thead>
<tr>
<th>Year</th>
<th>1995</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>397.340</td>
<td>476.006</td>
</tr>
<tr>
<td>Population 65+</td>
<td>55.898</td>
<td>78.032</td>
</tr>
<tr>
<td>Affected by dementia</td>
<td>3.785</td>
<td>4.994</td>
</tr>
<tr>
<td></td>
<td>2.822 F, 963 M</td>
<td></td>
</tr>
</tbody>
</table>
The population with dementia in the canton of Geneva could fill 9 municipalities (yellow).
Alzheimer’s disease is not “brain aging”: neuropathological, genetic, and epidemiological human studies

Peter T. Nelson · Elizabeth Head · Frederick A. Schmitt · Paulina R. Davis · Janna H. Neltner · Gregory A. Jicha · Erin L. Abner · Charles D. Smith · Linda J. Van Eldik · Richard J. Kryscio · Stephen W. Scheff
The biological course of disease: the instance of hepatitis B

- **Phase with no symptoms**
- **Symptomatic phase**
- **Chronic or recovery phase**
...for early diagnosis...

Phase with no symptoms
...for staging...
…and follow-up