Automatic Morphological Analysis of the Medial Temporal Lobe

Neuroimaging analysis applied to the diagnosis and prognosis of the Alzheimer’s disease.

Andrea Chincarini, INFN Genova
Clinical aspects of the Alzheimer’s disease

Neuroimaging as diagnosis tools
Global prevalence of dementia:

Cleusa P Ferri, Martin Prince, Carol Brayne, Henry Brodaty, Laura Fratiglioni, Yueqing Huang, Anthony Jorm, Colin Mathers, Paulo R Menezes, Elizabeth Ruff, Philip R Wild, on behalf of the Global Burden of Disease Study 2004 Dementia Collaborators. Lancet. 2005; (366); pp. 2112-17

Summary

Background 100 years after the first description, Alzheimer's disease and other dementias are now among the most common health conditions worldwide. We used the Delphi consensus method to estimate prevalence rates for dementia by WHO world region.

Methods 12 international experts were provided with a systematic review of prevalence rates from WHO collaborating centres for populations aged 60 years and over (from 10 WHO world regions) and asked to provide prevalence estimates for every WHO world region, in the four WHO age groups (65–69 years, 70–74 years, 75–79 years, 80+ years), and for those aged 85 years and over. The Delphi consensus process was used to estimate numbers of people with dementia in 2001, 2020, and 2040. We estimated incidence rates for 2020, and 2040. We estimated incidence rates from 2000-2020. We estimated incidence rates for 2000-2020.

Findings Evidence from well-planned, representative epidemiological surveys is scarce in many regions. We estimate that 24·3 million people have dementia today, with 4·6 million new cases of dementia every year. The number of people affected will double every 20 years to 81·1 million by 2040. Most people with dementia live in developing countries (60% in 2001, rising to 71% by 2040). Rates of increase are not uniform; numbers in developed countries are forecast to increase by 100%, between 2001 and 2040, but by more than 300% in India, China, and their south Asian and western Pacific neighbours.

Lancet, 2005; (366); pp. 2112-17
Alzheimer’s disease typical progression

- Incipient
- Mild
- Severe

Cognitive symptoms
Behavioral disorder
Self-sufficiency loss
Hospitalization
Death

Overall cognitive ability vs. Decades
0 5 10 years
Neuropsychology in diagnosis

- Memory tests change relatively early in the disease course (1) and soon reach a plateau at high levels of impairment (2).

- They are useful for diagnosis at the MCI stage, but are less useful for tracking later disease progression (3).

- Verbal comprehension tests start to change later in the disease course: during MCI they show mild or no impairment (4), and are of limited use in diagnosis.

- These markers become more sensitive at the dementia stage, when the slope of change steepens (5).

Nature Neur., (6), 2010
What is meant by the term MCI: the syndromic level

- **Mild Cognitive Impairment:**
  a transitional stage between normal condition and dementia…

- …and then it is an important syndromic diagnosis, because part of MCI patients will develop dementia… but another substantial part will not!

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**MCI Original Criteria**

1. Memory complaint, preferably qualified by an informant
2. Memory impairment for age
3. Preserved general cognitive function
4. Intact activities of daily living
5. Not demented


**Current diagnostic algorithm for diagnosing and subtyping MCI**

- [Diagram showing the diagnostic algorithm]

  - **MCI = Mild Cognitive Impairment**
Imaging the brain

Physics, mathematics and computer science at work
What information?

- **Molecular imaging:**
  - Amyloid PET
  - FDG-PET

- **Structural MRI:**
  - Hippocampus
  - Entorhinal cortex
  - Medial Temporal Lobe

- **Biochemistry:**
  - CSF (*Celebro-Spinal Fluid*)
  - Tau/\(\alpha\beta\)

- **Other techniques:**
  - DTI (*Diffusion Tensor Imaging*)
  - EEG (*Electroencephalography*)
  - MEG (*Magnetoencephalography*)
  - fMRI-BOLD (*Blood Oxygen Level Dependent signal*)
  - ...
Brain atrophy

Neuroimaging tools to rate regional atrophy, subcortical cerebrovascular disease, and regional cerebral blood flow and metabolism: consensus paper of the EADC

G B Frisoni, P H Scheltens, S Galluzzi, F M Nobili, N C Fox, P H Robert, H Soininen, L-O Wahlund, G Waldemar, E Salmon

J Neural Neurosurg Psychiatry 2003;74:1371-1381

Fig. 5. Volumetric analysis for the three different diagnostic groups. The error bars represent standard errors of the mean. Percent differences are tabulated in Table 8.

Validation of a fully automated 3D hippocampal segmentation method using subjects with Alzheimer's disease mild cognitive impairment, and elderly controls

Jonathan H. Morra a, Zhuowen Tu a, Liana G. Apostolova a,b, Amity E. Green a,b, Christina Avedissian a, Sarah K. Madsen a, Neelroop Parikhshak a, Xue Hua a, Arthur W. Toga a, Clifford R. Jack Jr. a, Michael W. Weiner a,b, Paul M. Thompson a,b

Neuroimage 43 (2008) 59-68

A. Chincarini, the MAGIC-5 collaboration
The posterior cingulate and precuneus are early affected by $^{18}$FDG-PET hypometabolism in Apo E ε4 positive NORMAL middle-age subjects.

Amyloid PET imaging: $^{11}$C-PIB PET

Normal subject

AD patient

Normal subject

AD patient

Summary

The posterior cingulate and precuneus are early affected by $^{18}$FDG-PET hypometabolism in Apo E ε4 positive NORMAL middle-age subjects.

References

Longitudinal studies

MCI Patients Declining and Not-Declining at Mid-Term Follow-Up: FDG-PET Findings

M. Pagani1,4,*, B. Dessì2, S. Morbelli3, A. Brugnolo2, D. Salmaso1, A. Piccioni2, D. Mazzei2, G. Villavecchia1, S.A. Larsson1, G. Rodriguez1 and F. Nobili1

Fig. (3). Statistical parametric maps showing the regions of significant decrease in metabolism in MCI DECL patients compared with MCI NOD DECL, obtained by SPM2 analysis.

J. Nucl. Med. 2002; 43; 304-11

Fig. (4). SPM8 corrected for multiple comparisons (P = 0.05). Dual-color display of surface-rendered standard MR images from 8 viewpoints shows significantly lower (P = 0.001) gray matter volume (red) and rCBF (green) in AD patients, in comparison with those in healthy volunteers. Areas of overlap are indicated by yellow.

Longitudinal Evaluation of Both Morphologic and Functional Changes in the Same Individuals with Alzheimer’s Disease

Hiroshi Matsuda, MD1; Noriuki Kitayama, MD2; Takashi Otsubo, MD; Takashi Asada, MD; Seigo Nakano, MD; Shigeki Sakamoto, MD; Etsuko Inabayashi, MD; and Asako Kato, MD

Società Italiana di Fisica
XCVI Congresso Nazionale
Bologna, 20 - 24 Settembre, 2010

M. Chincarini, the MAGIC-5 collaboration
Latest diagnosis criteria

Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria

Panel 2: Diagnostic criteria for AD
Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria
A. Presence of an early and significant episodic memory impairment that includes the following features:
   1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
   2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
   3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features
B. Presence of medial temporal lobe atrophy
   - Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)
C. Abnormal cerebrospinal fluid biomarker
   - Low amyloid β₄₂ concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
   - Other well validated markers to be discovered in the future
D. Specific pattern on functional neuroimaging with PET
   - Reduced glucose metabolism in bilateral temporal parietal regions
   - Other well validated ligands, including those that foreseeably will emerge such as Pittsburgh compound B or FDDNP
E. Proven AD autosomal dominant mutation within the immediate family
The MAGIC-5 collaboration

- More than 40 researchers involved in the project
- 6 sites in Italy: TO, GE, PI, NA, BA, LE
- Activities:
  - Tools development for medical imaging applications
  - Structure segmentation and classification
  - Computer Aided Diagnostics
- Targets:
  - Pulmonary CT (nodules hunting)
  - Neuroimaging (neurodegenerative diseases)

- Genoa Group (Neuroimaging)
  - INFN/Università di Genova
    - A. Chincarini, G. Gemme
    - S. Squarcia, P. Calvini
    - M.A. Penco, P. Boccacci
    - R. Monge, M. Corosu
    - L. Rei, M. Esposito, P. Bosco

- Neurofisiologia Clinica (Università di Genova):
  - G. Rodriguez, F. M. Nobili

- Member of the European Alzheimer’s Disease Consortium (EADC)
MRI processing

From raw images to structural indexes
What should we aim at?

Index for discriminating Normalcy vs Pathology

- “Continuous” index: used for follow-ups, decline rate, subject ranking, …

Some considerations:

- **Signal**
  - is “unknown”: it must be deduced through group comparison
  - is complex: brain is greatly interconnected, structure and function are not yet fully understood

- **Noise**
  - Scanner noise (“real” noise)
  - Scanner non idealities (B-field inhomogeneities, …)
  - Image artifacts (reconstruction, subject movements during acquisition, etc)

- Inter-individual differences can be more significant than normalcy vs pathology (is it a noise at all?)
- Subject clinical assessment may not be 100% sure (group mixing)
- Comorbid pathologies (group purity)
- Information degradation due to sub-optimal processing
Image processing – MRI

- **Initial quality check**
  - Image artifacts
  - Voxel size and aspect ratio
- **Noise removal**
  - Steerable pyramid de-noising
  - Automatic threshold, 3D
- **Spatial registration**
  - 3-way scalable (7 d.o.f.) + affine (12 d.o.f.)
  - Mutual information and normalized correlation metric
- **Intensity normalization**
  - CSF/GM/WM segmentation
  - VOI-based histogram match
- **Region (VOI) extraction**
  - Template matching, rigid (6 d.o.f.) registration
  - Automatic quality control
- **Feature computation**
  - 4 different neighborhoods
  - Intensity & texture based filtering
- **Classification**
  - Random Forest (RF) important variable map
  - Support Vector Machine (SVM) classifier
Noise reduction, image normalization

- The steerable pyramid filter performs a polar-separable decomposition in the frequency domain, thus allowing independent representation of scale and orientation.

- Noise threshold is automatically computed as a dependent on the inflection point in the SSI function.

- A combined 7 d.o.f and 12 d.o.f. transformation is computed to minimize a given metric, mapping the MRI onto a reference image.

- Histogram normalization via CSF/GM/WM segmentation ensures consistency among the many scanners and acquisition protocols.

\[
SSIM(x, y) = \frac{(2\mu_x\mu_y + c_1)(2\sigma_{xy} + c_2)}{(\mu_x^2 + \mu_y^2 + c_1)(\sigma_x^2 + \sigma_y^2 + c_2)}
\]
VOI extraction

11 regions are automatically segmented from each MRI

Extraction and segmentation is performed by template matching and 3D rigid (6 par.) registration

Regions are passed onto the Random Forest (RF) and then to the Support Vector Machine (SVM) classifier
Subject diagnosis: features and Classification Index

- Each VOI is processed with intensity & texture filters
- Feature space: $K_{voi} \times N_{voxels/VOI} \times F_{filters} \approx 10^7$
- A RF algorithm selects those who most likely discriminate between Controls/AD, creating a subset of the original features
- A SVM classifier takes the feature subset from the RF and outputs the distance between the input set and the discriminating hypersurface (CI).
PET/MRI combined analysis

Adding functional information
Accurate PET/MRI co-registration is a non-trivial task
- Curvelet filter (MRI) + 7 d.o.f registration with mutual information metric
- More than 200 PET have been successfully registered

PET signal normalization
- Cerebellum volume automatically segmented
- Cerebellum PET counts used for normalization
VOI extraction, functional features

- PET images VOIs are extracted after accurate alignment on the corresponding MRI.

- VOI position and size (saved for each MRI) is used to sample the same region on the PET.

- Once PET counts are normalized, intensity information is taken “as is” and fed directly into the SVM classifier.

- Partial Volume Effect reduction (on PET) could boost local intensity information.
Results

(preliminary: single VOI)
Selected features (hippocampus)

- Selected feat. driven by Random Forest classification
  - Only the selected features are fed to the SVM classifier
  - Clinical regions are finely pinpointed.
  - Asymmetry is expected
Cohort discrimination (MRI)

- Cohort description:
  - 135 Normal subjects (75.5 ± 5.7) y
  - 247 aMCI (75.0 ± 7.0) y
  - 150 AD (76.8 ± 7.3) y
  - MMSE score (23.2 ± 4.0)

- 89 MCI converted to AD in t ≈ 2 years

ROC auc
- Norm / AD: 0.98
- Norm / MCI-conv: 0.90
- MCI-nc / MCI-conv: 0.70

"Application of Automated Medial Temporal Lobe Atrophy Scale to Alzheimer Disease"
Arch Neur. 2007; 64

Age matched controls
Non-converters [yet ?]
Converted in 0 < t < 2y
Alzheimer’s

A. Chincarini, the MAGIC-5 collaboration
Cohort discrimination (PET)

- **Cohort description:**
  - 26 Normal subjects
  - 67 aMCI
  - 29 AD

- PET scores are still preliminary. Analysis is ongoing

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**ROC auc**

<table>
<thead>
<tr>
<th>Group</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norm / AD</td>
<td>0.96</td>
</tr>
<tr>
<td>Norm / MCI</td>
<td>0.86</td>
</tr>
</tbody>
</table>

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**Principal component analysis of FDG PET in amnestic MCI**

Flavio Nobili, Dario Salmaso, Silvia Morbelli, Nicola Girtler, Arnoldo Piccardo, Andrea Bragagnolo, Barbara Desi, Stig A. Larsson, Guido Rodriguez, Marco Pagani
Computational tools

Implementing the infrastructure for automatic analysis
Tools for easy and efficient processing

- MAGIC-5 @ GE computing infrastructure
  - 48 cores, 2 GB/core memory
  - 6 TB of high available, high performing, scalable storage infrastructure (completely redundant FC SAN, IBM GPFS file system, ~60 TB total)
  - Reliable data center (UPS with battery backup)
  - Fast deployment of new nodes (completely automatic installation and configuration)
  - Currently up to 100 Mb/s GARR link
  - Managed by INFN-Genova computing service staff

- Software tools:
  - MATLAB
  - Insight ToolKit (ITK)
  - LONI pipeline
  - SUN Grid Engine (batch system)
A link to the clinical world

- **WWW site for neurologist (MTL analysis results)**
  - help diagnosis
  - easy & appealing
  - marketable
  - tapping into external funding

- **requirements**
  - needs very clear project specification
  - outstanding reliability and maintainability
  - data security & privacy
  - scalability

- **features**
  - multimodal analysis of same region (PET)
  - hippocampus segmentation (will be implemented in a later phase)

**PET analysis of the same extracted volumes can be easily performed with the same pipeline**

A. Chincarini, the MAGIC-5 collaboration
Conclusions

... plus some items on the “to do” list
Clinical potential

- Structural imaging based on magnetic resonance is an integral part of the clinical assessment of patients with suspected Alzheimer dementia.

- The ability to detect changes in structural and functional markers from preclinical to overt stages of Alzheimer disease is radically changing how the disease is diagnosed and will influence its future treatment.

- Rates of whole-brain and hippocampal atrophy are sensitive markers of neurodegeneration, and are increasingly used as outcome measures in trials of potentially disease-modifying therapies.

- Large multicenter studies are currently investigating the value of other imaging and non-imaging markers as adjuncts to clinical assessment in diagnosis and monitoring of progression.

- The utility of both structural and functional imaging will be increased by the development of robust algorithms for automated assessment.
Ongoing work

- MAGIC-5 Neuroimaging group future efforts:
  - Full MRI/PET combined analysis
  - Longitudinal studies
  - Classification Index blind validation
  - Relevant structures automatic segmentation (hippocampus, amygdala, caudate nuclei, …)
  - More efficient computational tools
  - WWW access to the clinical world
Thank you!