Multi-modality Imaging of dementia

Robert Lavayssière (IPN Sarcelles)
Anne-Elizabeth Cabée (RMX-Paris XV, CIMH Neuilly)
Overview
Objectives

- Definition/Time bomb: worldwide burden
- Normal aging brain
- Abnormal brain aging
- Imaging of dementia
  - Everyday practice: "basic" MRI
  - Other methods/advanced
- Conclusion/Take Home
Dementia?
Umbrella term

* **Used to describe the symptoms that occur when the brain is affected by specific diseases and conditions.** Symptoms of dementia include cognitive disorders (aphasia, apraxia, agnosia) and loss of memory (AD).

* **Many different types, named according to the condition that has caused the dementia:**
  * Alzheimer’s disease = n°1, about 60% of all forms
  * Vascular disease
  * Dementia with Lewy bodies
  * Fronto-temporal dementia
  * Dementia associated with other diseases (MS, Parkinson, Steel-R…)
  * Infectious: CJ, HIV…
Time bomb ? Worldwide burden

- Age related +++
- 2050: 2 billions > 60 yo
- Worldwide: x 2 every 20 y
  - 2010: 35.6 millions
  - 2030: 65.7 millions
  - 2050: 115.4 millions
  - = 7.7 millions new cases every year
- Cost: $ 604 billions *
  - Global: 85 %
  - Medical care: 15 %
  (* 90 % in developed countries)
- France: 1 million with dementia

Source: OMS/WHO 2012
Making proper diagnosis? Defining biomarkers

Biomarkers changes may precede clinically detectable changes

Biomarkers assist in identifying the underlying pathology

- **Biomarkers**? Characteristics that are **objectively measured and evaluated** as indicator of pathological processes

- **Diagnostic, Prognosis, Treatment evaluation**

- **Existing tools:**
  - CSF: $\alpha\beta_{1-42}$, Tau, P Tau
  - Imaging (MRI, NM): measures?

- **Projects:** on going…

Human Brain Project

ADNI
Is imaging recommended?

- **HAS 2008**: brain imaging is mandatory
  - Other cause: Tumours, Hydrocephalus, Stroke
  - Associations: atrophy, chronic vascular diseases

- **MRI first, if possible**
  - T1, T2, T2*, FLAIR, coronal views (or 3D +++)
  - IV, if needed

- **CT without IV as an alternative** (MRI not available, CI for MRI)

- **Nuclear medicine**: perfusion/metabolism

Importance of clinical symptoms
MRI & Multiples tools

**Standard MRI 1.5 T/ 3T**
- 3D T1 and/or STIR:
  - Commissuro-mammillary plane
  - Oblique coronal
- « visual » quantification
- FLAIR: parenchyma/WM
- T2*: haemorrhage ?
- Diffusion: ischemia ?
- Blade © or Propeller ©

**Advanced MRI**
- ASL
- Volume calculation
- Diffusion/Fiber Tracking
- Functional MRI
- Spectroscopy
- (3 T vs 1.5 T)
- Very high field
Normal brain aging
Life-course approach

- Hypercholesterolemia
- Alcohol misuse
- Unhealthy diet
- Hypertension
- Smoking
- Obesity
- Diabetes
- Vascular insults
- Neuronal damage
- Physical activity
- Mental and social activity
- Brain reserve
- APOE
- Other genes

Adapted from S. Gauthier
Update on AD, Montreal 11/2012
“Normal” brain aging

**Macroscopic**
- > 50 yo: weight loss = 2%/10 y
- Cortex « Atrophy » frontal & temporal

**Microscopic**
- Apoptosis: frontal et temporal cortex amygdala, locus niger
- Lipofuschin increase: 10 to 15 % of cellular volume
- Senile Plaques: cell debris & amyloid substance within intercellular space

Cellular loss + senile plaques

**Neurochemistry**
- Dopaminergic System: neurotransmitter & receptor decrease
- Cholinergic System: choline-acétyl transférase decrease
- Gabaergic System: glutamate decarboxylase decrease, receptors modification

**Vascular**: blood flow (slightly)

**Performance decrease**
- Reasoning
- Acquisition (memory)/learning
- Execution speed/response

Influence of sociocultural, psychoaffective and sensorial conditions
**Cerebral « atrophy »**

- **Atrophy**
  - Cortex: 3 cm$^3$/y
  - Cisternal & sulci enlargement
  - White matter: 3 cm$^3$/y
  - Vulnerable regions
    - Pre-frontal cortex
    - Anterior Cingular Gyrus
    - Parietal Inferior Lobule
    - Precuneus
    - Superior Temporal Gyrus
    - Insula

- ≥ 50, frequent at 60, not constant

- « Harmonious » phenomenon

**Great variations**

- No link to function

**Morphology**

- Homogenous atrophy (W and GM, lobes)
- No or little temporal atrophy

**Beware!**

Caution in reporting…
Virchow-Robin Space

- Peri-vascular space dilatation
  - Extension of sub-arachnoid space
  - Signal = CSF: hyper T2, hypo Flair
  - Neat borders

- Clinical consequences?
  - Incidence increases with age
  - Fortuitous discovery
  - Associated with cognitive disorders?
Other changes

**Basal ganglia**

* Iron load increase
  * > 25 yo:
    * Pallidum
    * Nucleus ruber
    * Locus niger
    * Nucleus dentata
  * > 65 yo: Putamen

* Calcifications

**Vessels**

* Arterial wall thinning
  * thinning of the inner elastic layer
  * media fibrosis

* Atherosclerosis

27 yo  
56 yo  
Neurospin (7T)
Abnormal brain aging

- **Dementia**
  - Global deterioration of cognitive function, *normal conscience*
  - Progressive onset and evolution, non reversible
  - Pre-clinical phase, variable, unknown duration (MCI)
  - Alzheimer = 60 % of dementia
  - Memory impairment +++
  - Evaluation methods
    - Simple (Folstein ou MMSE)
    - Specialised (Day care hosp)

- **Other dementia**
  - Vascular +++
  - Fronto-temporal dementia (Pick, < 70)
  - Sub-cortical and cortico-sub-cortical dementia:
    - Lewy’s body
    - Parkinson
    - Progressive SN palsy
  - Traumatic...
Grid & structured report
(need for)

- Leukoencephalopathy (Fazekas/Walhund) ?
- Fronto-temporal atrophy (Kipps) ?
- Parietal atrophy (Barkhof) ?
- Hippocampus atrophy (Scheltens) ?
- T2*: µbleed, bleed ?
- Diffusion ?
- Hydrocephalus ?
White Matter lesions

Age-Related White Matter Changes

- “Leukoencephalopathy”...
- Variable (grading Fazekas/Walhund)
- Common in aging subjects:
  - 95% > 60
  - Age, Hypertension
- Clinical consequences???
  - Associated with some risk of cognitive impairment and dementia, but limited predictive value.
- REPORT: in practice
  
  « White matter high signal lesions indicating the need for cardiovascular risk factors exploration »
Quantification/classification?

**Fazekas**
- **Periventricular (PVH)**
  - 0: none
  - 1: horns
  - 2: halo
  - 3: irregular, extensive
- **Deep (DWMH)**
  - 0: none
  - 1: focal
  - 2: confluence
  - 3: large confluence
- **Sub-cortical (SC)**
  - 0: none
  - 1: patchy
  - 2: multiple
  - 3: diffuse

**Walhund**
- **White matter**
  - 0: normal
  - 1: periventricular hyperintensity + small high signal foci
  - 2: periventricular hypertensity, extended, with confluent high signal zone
  - 3: confluent periventricular and major sub-cortical lesions
- **Basal ganglia**
  - 0: normal
  - 1: one lesion > 5 mm
  - 2: more than one focal lesion
  - 3: confluent lesions

**HS vascular**
- DWMH > 2 ou SC > 2

**HS non vascular**
- DWMH < 2 et SC < 2

1 = normal > 35 y
2 = normal > 70 y
3 = abnormal (any age)
White Matter
Fiber loss and diffusion decrease

✦ 3 major types of sub-cortical fibers
✦ Association (cortex to cortex)
✦ Peri-callous (cortex to hemisphere through CC)
✦ Projection (cortex to thalamus, midbrain & medulla)

✦ Age:
✦ Projection fibers degradation > global WM decrease
✦ Diffusion modification, variable according to fibers

Stadlauer Radiology 2008
Atrophy: classification?

Kipps: f-temporal atrophy

Barkhof: parietal atrophy

0 to 5

0 to 4
Neuro-degenerative Dementia

Pre frontal: Fronto-temporal lobe

Sub cortical Brainstem: Lewy’s body, SN progressive palsy (SRO)

Pericentral and parietal: apraxia, dystonia, Parkinson’s, corticobasal degenerescence

Inner/medial temporal Hippocampus: Episodic Memory, Alzheimer’s
Alzheimer disease (AD)

Criteria

A. Multiple cognitive deficit
   1. Memory loss
   2. Cognitive malfunction:
      * Aphasia (language)
      * Apraxia (motricity)
      * Agnosy (identification)
      * Executives function (projects, organization, planification, abstraction)

B. A1 + A2: behavioural alteration (social and/or professional)

C. Progressive onset (MCI phase), continuous cognitive decline

Misbehaviour? Yes/No

D. Rule out
   - Other diseases ???
     * Vascular
     * Parkinson
     * SDH, NPH, Tumour (Imaging methods)
   - General:
     * Hypothyroidism
     * B12/Folates
     * HIV...
     * Toxic

E. NO consciousness disorder

F. No Psychiatric disease (schizophrenia, depression)

Two sub-types:
- Onset ≤ 65
- Onset ≥ 65
Alzheimer disease (AD)

New criteria

- Memory impairment/loss (not long term memory)

- **CRITERIA (one or more)**
  - MRI: hippocampus atrophy
  - PET-FDG: decreased metabolism
  - CSF markers
  - Genes


7 T/NRI, Gachon, South Korea (Siemens)
Alzheimer disease (AD)

«in the centre of an apparently normal cell (...) one or a more fibrillar structures caracterized by their thickness and particular staining»

Extra cellular senile plaques

**Amyloïd deposit**: peptide $\alpha\beta$

Accumulation

Fibrillar degeneration, within neurons: *Tau* protein

= Tubule associated unit (gene 17p21)
Lesion Progression

- AD lesions are similar to lesion encountered in normal aging (JJ Hauw)
- Progressive increase (« hierarchical »)
- Over a certain topographic and quantitative threshold, evolution toward AD.
- Genetic and environment factors
Hippocampus

- Complex, located on medial side of temporal circonvolution T5 bulging into temporal horn of the lateral ventricle.
- Belongs to the limbic system (memory, emotion, Broca), sharing numerous connections (Papez).
- Hippocampus alteration often associated with limbic and/or extra-limbic alterations

Essential role in memory formation, events memory or explicit or declarative memory, opposed to knowledge/know how, or implicit or procedural memory, depending upon other brain structures (basal ganglia).
Quantification

* Normal temporal « Atrophy » in aging subjects
  * Temporal « Atrophy » but normal hippocampus
  * Individual variations +++
  * Evolution ? : follow-up +++ need for reproducible MRI studies

* Analysis
  * Visual : “subjective”
  * Quantitative :
    * Volumetry,
    * Morphometry….

From E. Sibleau
Table 4.1-4. Visual assessment of medial temporal lobe atrophy according to Scheltens et al. (1992) (↑ increase; ↓ decrease; N normal)

<table>
<thead>
<tr>
<th>Score</th>
<th>Width of choroid fissure</th>
<th>Width of temporal horn</th>
<th>Height of hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>2</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>4</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>
Sensitivity : 95 %
Specificity : 96 %

Scheltens P et al. J Neurol 1999
Wahlund LO et al. JNNP 2000
Wahlund LO et al. Psych Research 1999
Hippocampus atrophy
non specific

- **Normal:** 1.5% per year

- **Other dementia**
  - Vascular
  - Parkinson, with or without dementia
  - Lewy’s body dementia

- **Atrophy rate is increased in**
  - Alzheimer disease:
    - Normal/MCI before conversion = 3/3.5%
    - AD = 3/3.5%
  - Vascular dementia
  - Lewy’s body dementia

- **Follow-up +++**

F. Bonneville Neuro-Imagerie des démences 2009 2012
Automatic analysis
Volumetry/Morphometry

Segmentation Automatique Compétitive de l’Hippocampe et de l’Amygdale
Chupin et al, ISMRM 2009 à 7T

Morphometric Analysis Gerardin et al. NeuroImage 2009

Cortex thickness measurement (Mc Gill, Harvard)
Results

- AD detection: healthy vs AD
  - Voxel based and surfacic methods: good overall performances
  - Hippocampus analysis: lower specificity

- Prodromal AD: healthy vs MCI
  - Low sensitivity of all methods

- Conversion prediction: no method = hazard!
Enthorinal cortex atrophy

(not easy to measure!)

Early stage

Advanced

MR in dementia, Jaap Valk, Springer ed
Association
Bleeds

- T2*
- 7% > 65
- Correlated with diabetes, Hypertension
- Amyloid angiopathy ???

Vascular risk marker: increased risk
- Spontaneous hematoma
- Hematoma under anticoag. therapy (beware of Acetyl salicylic acid!)
- Haemorrhagic transformation of stroke

REPORT, in practice: « chronic microbleeds indicating the need of blood pressure check/control »
Other dementia
not only AD !!!

∗ Vascular dementia: 2° cause
  ∗ Cardio-vascular context
  ∗ CV disease
  ∗ Risk factors (HTA, diabetes, smoking,...)
  ∗ Focal symptoms
  ∗ MR (CAT scan) lesions
∗ Time course
  ∗ Onset 3 months > stroke
  ∗ Cognitive impairment step by step or brutal, not continuous
∗ Genes? (CADASIL)
∗ Amyloïd Angiopathy
∗ Association to AD

∗ Other neuro-degenerative dementia...
  ∗ Neurological symptoms
  ∗ No memory loss
  ∗ No temporal atrophy (but...)

∗ « Treatable » disease:
Advanced...

PartiallyClips

I KNOW I HAVE TO KEEP TALKING TO YOU, DOCTOR. BUT I'M AFRAID I'M DISTRACTING YOU OR SOMETHING.

IT'S PART OF THE PROCEDURE, MR. BILLINGS. I HAVE TO MAP THE REGIONS OF YOUR BRAIN. JUST KEEP TALKING, ABOUT ANYTHING AT ALL.

OH, OK. UH, DID YOU WATCH THE RAMS GAME?

YES! AND I CAN'T BELIEVE THEY COULDN'T BEAT THE SPREAD! I HAD $200 BUCKS ON THOSE—OOPS.

‘OOPS!’

IT'S NOTHING, GO ON.

OH. WELL, THEY COULD HAVE HAD A SMURFDOWN ON THAT FOURTH AND ONE SMURFUATION, IF SMURF WARNER HAD JUST THROWN THE SMURFBALL, INSTEAD OF SMURFING OFF TO MARSHALL SMURF...

YIKE. THIS IS EITHER A LAWSUIT OR AN ARTICLE IN JAMA, DEPENDING ON HOW I PLAY IT.
Other methods/advanced

DTI

Spectroscopy

Pit compound

[11C]PIB

Control Subject  AD Patient

Min Max

University of Pittsburgh PET Amyloid Imaging Group

ASL

RBF Perfusion

F MRI

Healthy  Alzheimer  Lewy’s body

NM  123I-FP-CIT SPECT (DAT scan)
Local perfusion decrease

Control subjects (A, B) and AD patients (C, D) All four patients were diagnosed correctly by both readers using both modalities. 

**Comparing**
- Structural magnetic resonance imaging images (T1 and fluid-attenuated inversion recovery)
- Arterial spin labeling magnetic resonance imaging (ASL-MRI), - FDG-PET).

White arrows highlight areas of concordant hypometabolism on FDG-PET and hypoperfusion on ASL-MRI.

Erik S. Musiek & al
Alzheimer’s & Dementia 24 Oct 2011
Spectroscopy

- Valid for large groups
- Not valid for a specific individual
- Distinction AD – Healthy

NAA decrease (N-Acetyl Aspartate) Correlated with MMSE*

Lehéricy, Eur Radiol 2007
Diminution of apparent diffusion coefficient predominant in hippocampus, gyrus cingularis, parietal cortex.

### TABLE 2
ADCs and Between-Group Comparison of ADCs in Control, MCI, and Alzheimer Disease Subjects

<table>
<thead>
<tr>
<th>ROI Location*</th>
<th>Control n = 55</th>
<th>MCI n = 19</th>
<th>Alzheimer Disease n = 21</th>
<th>Control vs MCI</th>
<th>Control vs Alzheimer Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal WM</td>
<td>793 ± 44</td>
<td>791 ± 46</td>
<td>807 ± 61</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Parietal WM</td>
<td>745 ± 42</td>
<td>755 ± 50</td>
<td>774 ± 51</td>
<td>NS</td>
<td>P = .004</td>
</tr>
<tr>
<td>Occipital WM</td>
<td>743 ± 30</td>
<td>749 ± 36</td>
<td>760 ± 50</td>
<td>NS</td>
<td>P = .047</td>
</tr>
<tr>
<td>Temporal stem</td>
<td>812 ± 53</td>
<td>823 ± 39</td>
<td>840 ± 56</td>
<td>NS</td>
<td>P = .014</td>
</tr>
<tr>
<td>Anterior cingulate WM</td>
<td>736 ± 52</td>
<td>739 ± 50</td>
<td>764 ± 59</td>
<td>NS</td>
<td>P = .053</td>
</tr>
<tr>
<td>Posterior cingulate WM</td>
<td>733 ± 32</td>
<td>748 ± 40</td>
<td>765 ± 61</td>
<td>NS</td>
<td>P = .001</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>857 ± 44</td>
<td>888 ± 47</td>
<td>899 ± 56</td>
<td>P = .016</td>
<td></td>
</tr>
<tr>
<td>Right thalamus</td>
<td>800 ± 46</td>
<td>805 ± 66</td>
<td>811 ± 69</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Left thalamus</td>
<td>783 ± 46</td>
<td>805 ± 58</td>
<td>804 ± 65</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note.—Data are the mean ADCs ± SD (×10⁻⁶ mm²/sec). NS = not significant (P > .05).
* Analyses of the ADC were made with the right and left hemisphere ROIs together, except for the right and left thalamic ROIs, which were analyzed separately owing to higher right than left thalamic ADC in control subjects (P < .01). There were no other side-to-side differences in ADC for the homologous ROIs in control subjects.
DTI

- Diminution in anisotropy fraction of association fibres (wallerian degeneration?)
- Early stage, before atrophy?

MCI  Alzheimer

Blue : isotropy
Red : anisotropy

Naggara O. JFR 2008
fMRI

* Functional disconnection between posterior cingular cortex and hippocampus: network default mode altered (posterior cingular cortex, prefrontal cortex, lateral cortex, hippocampus).

High resolution

Fatterpekar, 2002

Neurospin
Amyloïd plaques imaging

7T Clinical Scanner
Siemens
23.4 x 23.4 x 90 μm³
Tacq = 13 hours 50 min
Sequence: GRE
Neurospin
NM & Molecular Imaging

1990
Perfusion SPECT
HMPAO/Neurolite

2000
Metabolism
FDG PET

PET MRI

1990-2006
Dopamine Transporter
DaT Scan
123I-FP-CIT SPECT

2013
Amyloid Plaques
Florbetapir
Florbetaben
Flutemetamol

HAS 2008
Atypical dementia:
Perfusion
Metabolism
Lewy’s body:
DaTSCAN
Metabolism/perfusion

- Atypical AD
- **Non AD dementia**: Fronto-temporal D, Progressive Primary Aphasia, Lewy’s body dementia
- At risk population screening: MCI, genetic risk (presenilin, amyloïd precursor protein, progranline, APOEe4)
- Follow-up
- Treatment evaluation
Perfusion decrease:
- Diffuse: posterior associative cortex (parieto-temporal+++)
- Local: medial temporal area
Fronto-temporal dementia

- Decreased perfusion of fronto-temporal cortex
- Normal posterior cortex:
  Antero-posterior gradient = FTD
AD or Lewy’s body dementia ???

Normal Dopamine uptake 123I-FP-CIT SPECT (DAT scan)

Perfusion decrease
- Associative cortex (temp et occip)
- Inner prefrontal and dorsolat D
- Right hippocampus
Question ???

Advanced imaging techniques in MCI & Alzheimer's disease: how much imaging is enough?
From early phase to dementia

AD PROGRESSION USING BIOMARKERS

Conclusion/Take Home

- **Dialogue**: patient, family, other MDs
- **Basic imaging = MRI (HAS)**
  - Treatable disease...
  - Diagnosis orientation
  - Early detection
  - Follow-up
    - Evolution
    - Occurrence?
- **Numerous works**
  - Quantification
  - Advanced MRI
  - Functional
  - Nuclear Medicine

**General radiologist should be familiar**

- With normal brain aging
- With abnormal brain aging

**Report**

- Structured
- Practical: strategy, recommendation
- Beware of words: «atrophy», etc...

![DWI Image]
Note of Thanks

* Dr Marie-Thérèse Iba-Zizen
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* Dr Emmanuel A. Cabanis
* Dr Johan Le Guilloux
* Dr Jean-Luc Sarrazin
* Mr Julien Gervais
Study participants who spent time learning digital photography showed gains in memory.