Imaging the Brains of Centenarians

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Overview

1. How does the brain change with ‘normal’ ageing up to the 10th and 11th decades of life?
   a. Volumes of brain structures, both cortical and subcortical
   b. Brain networks
2. What does neuroimaging tell us about the accumulation of pathology in the ageing brain?
   a. White matter abnormalities
   b. Cerebral infarctions
   c. Cerebral microbleeds
   d. Alzheimer-type pathology, esp. with amyloid imaging
   e. Hippocampal sclerosis
3. Present data from the Sydney Centenarian Study on brain imaging
4. How does brain pathology on neuroimaging relate to brain function?
MRI - Atrophy

Brain changes with age:
- Atrophy of gyri
- Widened sulci
- Enlarged ventricular system

Brain weight shrinks:
- 5% by 70 years
- 10% by 80 years
- 20% by 90 years
MRI – White Matter Hyperintensities (WMH)

A 40 year old  A 60 year old  A 100 year old
101 years F, 11 years education, MMSE 19/30 (unadjusted), ACER 58/100
101 years F, 6 years education
MMSE 29/30, ACER 85/100
A non-parametric smoothing spline approach to delineate cross-sectionally estimated age-trajectories of the volume of 17 neuroanatomical structures in 1100 healthy adults (18–94 years).
Scatterplots of age - ventricular system relationships

Estimated age-trajectories and critical ages
A hypothetic model for discontinuous change in rate of atrophy
• No sex differences in age trends except for the caudate were observed.

• No evidence of neuroprotective effects of larger brain size or educational attainment.
Scatter plots of mean thickness in selected cortical areas

The strongest effects were seen in the superior and inferior frontal gyri, as well as superior parts of the temporal lobe.
Cross-sectional estimates of yearly differences in lobar brain volumes as a percentage of head size for men and women of the Framingham Heart Study. Significant differences are seen for Frontal and Temporal lobar brain volumes, but not Parietal or Occipital.
Heritability of 40,962 pointwise cortical phenotypes in 838 subjects.

Brain Imaging Behav. 2014 June; 8(2): 143–152.
Cross-sectional MRI Study

• Objective: brain changes in aging and in dementia

• Subjects
  – Sydney Centenarian Study: 95-103 years
  – Sydney Memory and Ageing Study: 71-94 years

• Dementia consensus

• Brain MRI: T13D and FLAIR

Sachdev et al. 2010, 2013
# Non-demented

Demographics of participants in different decades of age.

<table>
<thead>
<tr>
<th>Age range, years</th>
<th>70-79</th>
<th>80-89</th>
<th>90-99</th>
<th>100+</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-demented, N</td>
<td>134</td>
<td>73</td>
<td>65</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>High-functioning %</td>
<td>58.2%</td>
<td>53.4%</td>
<td>58.5%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>75.9 ± 2.3</td>
<td>83.7 ± 2.6</td>
<td>94.9 ± 3.1</td>
<td>101.4 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female %</td>
<td>50.7%</td>
<td>56.2%</td>
<td>50.8%</td>
<td>20%</td>
<td>0.446</td>
</tr>
<tr>
<td>MMSE (mean ± SD)</td>
<td>28.4 ± 1.4</td>
<td>27.8 ± 1.6</td>
<td>27.2 ± 2.0</td>
<td>28.4 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APOE ε4 carriage %</td>
<td>25%</td>
<td>22.2%</td>
<td>16.1%</td>
<td>0%</td>
<td>0.380</td>
</tr>
</tbody>
</table>

\( p \) value of Fisher’s Exact Test or analysis of variance.
Relationship of age with total brain volumes from 71 to 103 years

Group comparison of brain volumetrics between the young old (YO, 70-89 years) and oldest old (OO, 90+ years).
Surface analysis of age effects on cortical thickness

### Demographics of participants in different decades of age.

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<tr>
<th>Age range, years</th>
<th>70-79</th>
<th>80-89</th>
<th>90-99</th>
<th>100+</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>16</td>
<td>10</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>78.1 ± 1.5</td>
<td>86.6 ± 2.0</td>
<td>94.9 ± 2.5</td>
<td>101.5 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female %</td>
<td>50.0%</td>
<td>37.5%</td>
<td>70%</td>
<td>100%</td>
<td>0.100</td>
</tr>
<tr>
<td>MMSE (mean ± SD)</td>
<td>24.4 ± 2.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22.6 ± 4.1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>22.1 ± 2.9</td>
<td>16.5 ± 4.2&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>0.005&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>APOE ε4 carriage %</td>
<td>50.0%</td>
<td>37.5%</td>
<td>11.1%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.219</td>
</tr>
</tbody>
</table>

<sup>a</sup>p value of Fisher's Exact Test or analysis of variance.
Cortex, hippocampus and deep WMHs

<table>
<thead>
<tr>
<th>Logistic Regression</th>
<th>OR (95% CI) at 80 years</th>
<th>OR (95% CI) at 95 years</th>
<th>p-value (age*MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex, Z</td>
<td>12.26 (4.65 – 32.38)</td>
<td>7.57 (2.61 – 21.91)</td>
<td>0.320</td>
</tr>
<tr>
<td>Hippocampus, Z</td>
<td>6.37 (3.13 – 12.98)</td>
<td>3.39 (1.15 – 7.45)</td>
<td>0.204</td>
</tr>
<tr>
<td>Deep WMHs, 5%</td>
<td>5.21 (2.45 – 11.07)</td>
<td>1.70 (1.02 – 2.84 )</td>
<td>0.010*</td>
</tr>
</tbody>
</table>
Brain network construction

Brain anatomical network. Each node (red ball) here represents a cortical region and each line represents a connection between two regions and the color indicates the number of fibres for that particular connection.
Age - anatomical networks

Global efficiency vs. Age: considering the connectivity of the whole brain
n = 210; 20–89 y
Amyloid imaging
Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status

Individual records were provided for 2914 participants with normal cognition, 697 with SCI, and 3972 with MCI aged 18 to 100 years from 55 studies

Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status and Apolipoprotein E (APOE) Genotype
Test scores at baseline versus average cortical SUVr in non-demented participants from The 90+ Study

Longitudinal trajectories of neuropsychological tests in Aβ- and Aβ+ non-demented participants

Mean cognitive performance by Aβ-status groups (6SE) estimated from mixed models at discrete timepoints, showing patterns of change over time:

(A) steeper decline in semantic verbal fluency in the Aβ+ compared to Aβ- group;
(B) practice effects over time on phonemic verbal fluency in both groups;
(C) practice effects on verbal learning in both groups until approximately 2.5 years before neuroimaging, then decline in the Aβ+ but continued practice effect in the Aβ- group;
(D) similar rates of decline in inhibitory control in both groups, with consistently lower performance in the Aβ+ group.

Neurology; 2013;80:1378–1384
Bilateral hippocampal sclerosis

Prevalence of HS:
No other pathology 2-4%
Vascular/degen path 12-20%
Prevalence of MRI infarction by decade of life among subjects of the Framingham Heart Study.
<table>
<thead>
<tr>
<th>Age Range</th>
<th>No. of Persons</th>
<th>Cerebral Microbleeds, N (%)</th>
<th>Multiple Cerebral Microbleeds, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–50 yr</td>
<td>413</td>
<td>27 (6.5)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>1696</td>
<td>195 (11.5)</td>
<td>57 (3.4)</td>
</tr>
<tr>
<td>60–69 yr</td>
<td>1350</td>
<td>227 (16.8)</td>
<td>66 (4.9)</td>
</tr>
<tr>
<td>70–79 yr</td>
<td>377</td>
<td>109 (28.9)</td>
<td>56 (14.9)</td>
</tr>
<tr>
<td>&gt;80 yr</td>
<td>143</td>
<td>51 (35.7)</td>
<td>32 (22.4)</td>
</tr>
<tr>
<td>Total</td>
<td>3979</td>
<td>609 (15.3)</td>
<td>214 (5.4)</td>
</tr>
</tbody>
</table>
Figure 1: Distribution of single and multiple pathologies in oldest-old participants without (A) and with (B) dementia.

Non-demented

- AD: 28%
- Microinfarcts: 51%
- HS: 2%
- SAE: 2%
- CAA: 1%
- LBD: 0%
- Other: 1%
- Macroinfarcts: 0%
- Mixed: 14%

Demented

- AD: 23%
- Microinfarcts: 6%
- HS: 4%
- SAE: 4%
- CAA: 3%
- LBD: 1%
- Other: 1%
- Macroinfarcts: 0%
- Mixed: 45%

N=104
Age 90-107

Kawas et al., Neurology 2015
CONCLUSIONS

1. With ageing, there is a decline in volumes of brain volumes that continues into the 11th decade of life.
2. The reduction is linear in some structures. In other structures, there is stability followed by decline in later life.
3. There are critical ages for decline, esp for the hippocampus and the cerebral white matter.
4. These changes occur in both sexes, and big brain size and education do not appear to moderate the decline.
5. Cortical thinning continues to occur into the 11th decade, and the effect is strongest in the frontal and superior temporal regions.
6. The change in brain volumetrics has a strong genetic component.
7. WMHs increase through life, with an increasing trajectory later in life.
8. The difference between demented and non-demented individuals in brain volumetrics is much less in the old-old cf. the young-old. The structure-function relationships become weaker in very late life.
9. Brain network efficiency continues to decline with age. Healthy ageing is also associated with decreased specialization in brain function.
10. The older brain appears to compensate for the structural changes by recruiting additional regions/networks.
11. Amyloid positivity increases steadily from the 3rd decade, with a marked rise after 60 years. E4+ individuals are more at risk and positivity is related to poorer cognitive function, even in the very old.
12. Amyloid positivity is common in non-demented elderly. The presence of 2 or 3 pathologies (Ab+, hippo vol, WMH) increases the odds of having dementia.
13. Other pathologies that increase with age are hippocampal sclerosis, infarcts, microbleeds etc.