Ageing: issues, trends and technological challenges

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BA, MD, FRCPsych, FRANZCP
NARI Director & The University of Melbourne
Professor of Ageing and Health
Who are we and what do we do?

Why does ageing matter?

An example of the use of technology to address ageing issues

Q and A
NATIONAL AGEING RESEARCH INSTITUTE Ltd (NARI)

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Parkville

Staffing
- Total number of staff & students (56)
- Total number of research-only staff (37.23 EFT )
- Level & type (PhD, Masters & Hons) (25)
- Honoraries (24)
- Visiting Fellows (2-3 pa)
• **Research Areas**
  - **Dementia** – first memory clinic in Melbourne 1988, AIBL study, FABS II, AIBL active
  - **Late life depression** – collaboration with beyondblue
  - **Pain** research (Prof Gibson)
  - **Falls** research (Prof Hill)
  - **OATS** study
  - **Carers and Exercise** (Dr Dow)
  - **COPD** and **CBT** (Prof Doyle)
  - **WHAP** project (A/Prof C Szoeke)
  - 5 current **NHMRC & ARC** grants (CS; BD/DA; NL x 2; SG/DA) and CIs on another 6 grants

• **Major Discovery**
  - **Inauguration of ACAS teams** 1984 entirely due to NARI research by Dr Anna Howe
  - Set up **first outpatient multi-disciplinary clinics in Australia** for older persons (memory, pain, falls) under Prof Robert Helme
  - Cognitive Dementia and Memory Clinics (**CDAMS**)
  - **New questionnaire measures** for falls assessment, pain, dementia etc
  - **Altered** pain neuroplasticity in older persons, age-specific **beliefs** and **attitudes** regarding pain
  - **National Physical Activity Guidelines** for older people
LIFE

• A sexually transmitted terminal condition
A TRUE REVOLUTION

• 1900  1/10 expect to live to 65

• 2000  9/10 expect to live to 65
## WORLD POPULATION INCREASE 1975-2000

<table>
<thead>
<tr>
<th>Ages</th>
<th>Developed Countries</th>
<th>Less Developed</th>
<th>World Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>20.2%</td>
<td>72.6%</td>
<td>57.6%</td>
</tr>
<tr>
<td>65 - 74</td>
<td>33.2%</td>
<td>104.2%</td>
<td>68.9%</td>
</tr>
<tr>
<td>75 - 79</td>
<td>53.4%</td>
<td>121.2%</td>
<td>84.3%</td>
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<tr>
<td>80+</td>
<td>64.7%</td>
<td>138.0%</td>
<td>91.7%</td>
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</table>
LIFE EXPECTANCY AUSTRALIA
2003-2005

• Birth - male 78.5 - female 83.3

• Age 65 - male 83.1 - female 86.4
AUSTRALIA CHARACTERISED BY

• RAPID AGEING

• DISTANCE

• URBANISATION

• MULTICULTURALISM

• DISTINCTIVE HEALTH AND WELFARE SERVICES

• UNIQUE NATIONAL ATTITUDES – MATESHIP AND THE FAIR GO?

• RELATIVE ECONOMIC DECLINE?
• We live in a rapidly *ageing* world

• The most rapid gains in life expectancy since the 1970s have been amongst the old-old
  ‘*The ageing of the aged*’

• Community perceptions about the ageing process tend to be inaccurate and negative
'The crazy fool — you can't take Dead Man's Bend at that speed.'
‘No, you can’t be a lawyer. It’s handbag or shoes, that’s it.’

THE SPECTATOR 26 July 2003
The Grim Reaper called today.
You were out.
He will be in your area next week.
He hopes this will be convenient.
'Not your day, is it?"
• The challenge for old age to be regarded as a positive developmental stage
  Integrity
  Wisdom

• We now have a challenge to minimise the morbidity related to old age
  Neurodegenerative diseases
  Physical dependency
  Social isolation
  Depression
Nevertheless

• There are increasing rates of mortality and morbidity with ageing
• Geriatric syndromes include cognitive impairment, falls/instability, pain, slow wound healing, continence issues, frailty
AGEING

• both intrinsic and extrinsic to the organism

• universal

• biological

• psychological

• social
As a consequence of our ageing population there will be.....

• An increase in the incidence of dementia and other neurodegenerative conditions

• An increase in the number of people with pre-existing psychiatric disorders who survive into old age

• An increase in the number of people who develop a psychiatric disorder, esp depression, later in life

• An increase in disability from comorbid physical and psychological problems
What factors influence how we age?

- Genetic potential
  - Intelligence    Longevity    Familial diseases
- Personality
- Environmental opportunities
  - Education    Exposure to diversity    toxins
- LUCK
  - ‘Random walk hypothesis’
Psychological & Health Outcomes Affected by

- Not smoking
- Not abusing alcohol
- Mature psychological defenses
- Healthy weight
- Stable marriage
- Taking some exercise

(Vaillant, 2002)
Senile Dementia? - Isn't that when elderly clients disagree with you about what's best for them?
DEMENTIA

Dementia is an acquired decline in multiple higher mental functions (memory, intellect, personality) occurring in an alert patient which interferes with social or occupational functioning and is usually irreversible and progressive.
Dementia

Figure 5.2  Lifetime risk for dementing diseases (moderate–severe) according to data from the Lundby study, 1957–1972.
OLD MOTHER HUBBARD WENT TO THE CUPBOARD...

NOW WHAT DID I COME HERE FOR?
The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing

aibl
OVERVIEW: AIBL is the most comprehensive, longitudinal study of its kind in Australia, and aims to discover a way to develop biomarkers, diagnose patients earlier and prevent disease onset.

**COHORT**
N = 1,112 (aged 60+ yrs)

- Healthy Controls
- Subjective Memory Complainers
- Mild cognitive Impairment
- Alzheimer’s Disease

**METHODOLOGY**

- Cognitive and clinical assessment
- Biomarkers
- Vascular
- Diet & Lifestyle
- Neuroimaging
AIBL: Longitudinal cohort

Baseline

(1,112)
Psychometrics
Bloods
MRI/PET
Lifestyle
Genotype

18M
(972)
Psychometrics
Bloods
MRI/PET

36M
(824)
Psychometrics
Bloods
MRI/PET

Non-Return: 112
Deceased: NMC 2
SMC 4
MCI 5
AD 17

Non-Return: 120
Deceased: NMC 3
SMC 3
MCI 4
AD 34

Non-Return: (33)
Deceased: (16)

See AAIC poster P3-093 on Tuesday 1 – 3.30pm. Ellis et al.
Blood test for Alzheimer’s disease?

• Two panels of biomarkers were selected from a dataset of 224 biomarkers
  – Set A – panel of 18 biomarkers
  – Set B – panel of 8 biomarkers

• Set A performed with a Sens./Spec. of 85% in the AIBL cohort
  – Validation in ADNI at 77%

• Set B performed with a Sens./Spec. of 83% in the AIBL cohort
  – Validation in ADNI at 80%
11C-PIB – Image Quantification

Regions

Neocortical SUVR$_{40-70}$

= cortical activity / cerebellar grey matter activity from 40 to 70 minutes post injection

Negative is <1.5

Follow-up PiB co-registered to baseline and saved prior ROI set used.

Single operator for all PiB scans.
### Imaging Cohort Demographics

<table>
<thead>
<tr>
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<th>HC (n=195)</th>
<th>MCI (n=92)</th>
<th>AD (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>47%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>MMSE</td>
<td>29</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>CDR</td>
<td>0.0</td>
<td>0.5 ± 0.2</td>
<td>1.0 ± 0.5</td>
</tr>
<tr>
<td>CDR SOB</td>
<td>0.06 ± 0.2</td>
<td>1.25 ± 0.9</td>
<td>4.36 ± 1.7</td>
</tr>
<tr>
<td>% ApoE ε4</td>
<td>41%</td>
<td>61%</td>
<td>65%</td>
</tr>
<tr>
<td>Years of Education</td>
<td>13.4</td>
<td>12.5</td>
<td>12.4</td>
</tr>
</tbody>
</table>
% of Healthy who are PiB+ve

4% 12% 32% 52%

< 60 yrs data from Washington University

Years of age

50-59 60-69 70-79 80+

e4- e4+

Austin Health

aibl
% PiB+ HC vs Age (by decade)

(PiB+ when SUVR >1.5)

Prevalence of plaques in HC

(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

Prevalence of AD

(Tobias, 2008)

% PiB+ HC

ε4 corrected AIBL data

12% 32% 52%

15 yrs
PiB neocortical SUVR in AIBL+

Neocortical SUVR

- **HC**: 1.40 ± 0.4
  - (n = 195)
- **MCI**: 1.91 ± 0.6
  - (n = 92)
- **AD**: 2.30 ± 0.4
  - (n = 79)

31% 68% 99%

*Statistically significant results compared to controls (p < 0.0001)
Aβ vs Memory

HC

MCI

AD

Episodic Memory

Upper left:

$r = -0.20 \ (p = 0.13)$

Upper middle:

$r = -0.53 \ (p < 0.0001)$
Aβ deposition over time
3-5 year follow-up
(n=158)

Neocortical SUVR<sub>cb</sub>

Mean SUVR AD+ (2.35)

2.9%/yr
(95% CI 2.5-4.0%/yr)

Mean SUVR HC- (1.17)

19.6 yr
(95% CI 14-23 yrs)

14 yr
(95% CI 13-17 yrs)

Villemagne et al, Kinetics of Aβ deposition, AAIC, 2012
Average rate of atrophy over one year in HC PiB- vs PiB+.
Relation between baseline Aβ burden and memory decline in healthy controls
(36 months follow-up)

$r = 0.38 \ (p = 0.0005)$
Higher Mediterranean Diet (MeDi) Score is associated with lower PiB SUVR.

Controlling for age, APOE genotype, gender and years of education.

Rainey-Smith et al. manuscript in preparation.
PiB SUVR cut-point 1.5
3 year clinical progression

HC
(n=194)

<table>
<thead>
<tr>
<th>Positive Aβ (n=60)</th>
<th>Negative Aβ (n=134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%* to MCI/AD</td>
<td>6% to MCI/AD</td>
</tr>
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</table>

MCI
(n=92)

<table>
<thead>
<tr>
<th>Positive Aβ (n=64)</th>
<th>Negative Aβ (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66%* to AD</td>
<td>7% to AD</td>
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Hazard Ratio 3.6 (OR 4)
*(p= 0.016)
Corrected for age, gender, education

Hazard Ratio 11 (OR 25)
*(p< 0.0001)
Summary

• Aβ deposition is slow and of similar rate in PiB+ HC and MCI (3% SUVR per year).

• A plateau occurs with advancing dementia.

• Aβ is common in older HC
  11% if 60-69
  32% if 70-79
  51% if 80+ years

and strongly related to genetics i.e. ApoE-ε4 status (risk 2-3X)
Over 3 Years

• Aβ in HC is associated with faster cognitive decline and grey matter atrophy.

• 20% of PiB+ HC develop MCI/AD (c.f. 6% of PiB-)

• 74% PiB+ MCI develop AD c.f. 16% of PiB-

Odds Ratio = 25 (but 20% PiB- develop other dementias)

• Combination of biomarkers provides better prediction (e.g. if PiB+ and hippocampal atrophy = 86% accuracy, PPV 78%).
Parallel studies

**ROCS**

Characterize the cognitive performance of a group of 205 healthy older adults, and adults with MCI, and AD over short test-retest intervals (10 times over 18-months).

**ACTIVE**

RCT of physical activity to delay the progression of white matter hyperintensities on MRI in older adults at risk of cognitive decline.

**WHAP**

Prospective data from midlife, 3 cognitive timepoints over 20 years prior. 100 participants seen so far 80% retention from 2002 cognitive test.
Acknowledgements and thanks

AIBL is a large collaborative study and a complete list of contributors can be found at www.aibl.csiro.au

This research is funded in part by the Science and Industry Endowment Fund.

We thank all who took part in the study.
Meanwhile, in Darwin...

Euthanasia is just a simple operation like circumcision Mr. Jones. In fact it's very much like circumcision. At the end of your life there's a little bit which serves no real purpose and can cause a bit of irritation so we just nip it off for you. You won't feel a thing.

...I've had a prick of a life so I might as well...
"It may well bring about immortality, but it will take forever to test it."