Dementia: the next big thing is now

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Director
Dementia Collaborative Research Centre – Assessment and Better Care

Translating dementia research into practice
Why BIG?
Projections of a tripling of world’s dementia population by 2050

World Alzheimer Report, ADI, 2009
Quadrupling in Australia

Access Economics for Alzheimer’s Australia, 2009

Translating dementia research into practice

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Dementia

- 3<sup>rd</sup> leading cause of death - already
- Leading cause of disease burden – with 5 yrs
- GDP 0.8% $\rightarrow$ 1.8%
Cost of dementia

Cost of aged care (HACC, community care, RACF)

Why BIG?

Broad canvas
Broad canvas

- Epidemiology
  - Planning
  - Prevention
  - ID people @ risk
- Aetiology
- Pathology
- Diagnosis
  - Hi tech – PET, CSF
  - Lo tech – GPs, screen
  - Neuropsychology
- Drug treatment
- Cog rehab
- Neurorestorative
- Service planning
- BPSD
- Nursing homes
- Models of care
- Environment
- Palliative care
- Workforce
- Policy
What’s new in epidemiology?
Environment and AD

• Up to 50% of population attributable risk of AD cases from 7 environmental factors
• If 25% lower prevalence of these risk factors → 3 million fewer AD cases worldwide

Barnes D & Yaffe K, 2011
How much AD can be attributed to environmental factors?

- 2% diabetes mellitus (type 2)
- 2% midlife obesity*
- 5% midlife hypertension
- 10% depression
- 13% physical inactivity*
- 14% smoking
- 19% cognitive inactivity/education#

Barnes & Yaffe, 2011
Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL)

- Prospective longitudinal study of ageing
- Aims: to improve understanding of causes & diagnosis of Alzheimer’s disease & prevention of AD
- Sample: N = 1112, 60+ yo
- Includes patients with AD, MCI and healthy volunteers
Sydney Memory & Ageing Study (MAS)

• What predicts of cognitive decline and maintenance? What are rates of MCI?
• What is incidence/prevalence of MCI?
• What is incidence of dementia?
• Longitudinal, population based study
  – Non-demented, community dwelling
  – N = 1037, 70-90 yrs, eastern Sydney

Brodaty H, Sachdev P et al.
Sydney Memory & Ageing Study (MAS)

• Clinical, neuropsych, informant interviews
• MRI, bloods, genetics
• Falls, balance, vascular measures
• 0 √, 2y√, 4y√ and 6y (Wave 4) start now

Brodaty H, Sachdev P et al.
Older Australian Twins Study (OATS)

- Longitudinal study on healthy brain ageing in MZ and DZ twins ≥ 65 y.o.
- What influences cognition with ageing?
  - Environmental (lifetime physical & mental activity, socioeconomic status)
  - Biological (hypertension, genes)
- >150 MZ pairs + 150 DZ pairs √
- Sydney, Brisbane, Melbourne

Sydney Centenarian Study

- Fastest growing age group world wide
  - Models of ‘successful ageing’
- Which factors contribute to longevity?
- What is normal in very old?
- >250 people aged 95+ recruited

Sachdev P et al.
What’s new in prevention?
Physical activity = protective

• Several studies show physical activity protective against cognitive decline, dementia, Alzheimer’s, vascular dementia
• More is better – puffed, weights
• At least 3x per week; > 150 mins/wk
• Check with your doctor

Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease: A Randomized Trial

Nicola T. Lautenschlager, Kay L. Cox; Leon Flicker; et al.

JAMA 2008;300(9):1027-1037 (doi:10.1001/jama.300.9.1027)

N = 138 memory complainers

Lautenschlager et al (2008) JAMA; 300(9):1027-1037
Study of Mental & Regular Training (SMART)

• Aim: Does increased mental activity lead to decreased dementia risk?
• Intervention: 3 days/wk for 6 months
  – Memory series + stretching/callisthenics
  – Memory series + strength exercise
  – Memory & thinking exercises + stretching/callisthenics
  – Memory & thinking exercises + strength
• Follow up after 1 year to test for lasting benefits
The power of physical activity

Erickson et al., 2011
Mind your brain: Accumulating evidence for mental exercise/cognitive training
Mental Activity & Dementia ¹,²

- Meta-analysis of 22 studies, 29,000 people
- *Lifetime*: Education, occupation, IQ, leisure each reduce risk by about half
- *Late life*: ↑ complex mental activity ↓ risk of dementia by half
- Dose - response relationship evident
- Complex patterns of mental activity in early, mid- and late-life associated with ↓ dementia

Mind your diet

- Mediterranean diet
- Antioxidants
Nutrition / Supplements

- Alcohol ? moderate
- Fish/Seafood/ω3 ?
- Vitamin D ?
- Caffeine ??
- Vitamin E x
- Vitamin C x
Smoking and AD

• Current smoking
  – increase risk for AD
• Previous smoking
  – Risk not significantly increased

Anstey K. Am J Epidem 2008
Mind your health checks

- Blood pressure
- Sugar
- Cholesterol
Metabolic syndrome & dementia risk

- Diabetes/ raised fasting sugar
- Abdominal obesity
- High cholesterol
- High blood pressure
- 23% increased dementia risk for each component of metabolic syndrome

- 4895 older women
- 497 with metabolic syndrome

**BrainyApp:** developed by Alzheimer’s Australia to raise awareness of AD/dementia risk factors
What’s new in cause of Alzheimer’s disease
AD: a progressive CNS disorder with a characteristic pathology

Katzman, 1986
Cummings and Khachaturian, 1996
Best target for disease-modifying drug?

• γ-secretase inhibitor?
• β-secretase inhibitor?
• Aβ oligomer?
• Aggregated fibrillar Aβ?
• Aβ clearance mechanism?
• APP/ Aβ processing?
• Zn / Cu interactions with Aβ (Ashley Bush)

Slide courtesy of Colin Masters
Best target for disease-modifying drug?

• \( \gamma \)-secretase inhibitor?
• \( \beta \)-secretase inhibitor?
• \( \alpha \)\( \beta \) oligomer?
• Aggregated fibrillar \( \beta \) ?
• \( \alpha \)\( \beta \) clearance mechanism?

But anti-amyloid treatments not yet successful????

• \( \alpha \)\( \beta \) clearance mechanism?
• APP/ \( \alpha \)\( \beta \) processing?
Jürgen Götz

Tau and beta amyloid – a toxic pas de deux

First tau transgenic mouse

Support for amyloid cascade hypothesis *in vivo* (Science 2001)

(AD-like somatodendritic localisation of tau in human tau transgenic mice)

(Stereotaxic injection of Aβ induces tau tangles)
Jürgen Götz

Tau and beta amyloid – a toxic pas de deux

Paradigm shift: Aβ toxicity depends on dendritic tau (Cell 2010)

Tau axis hypothesis in AD (Nature Rev Neurosci 2011)

(Genetic and pharmacological approaches fully rescue clinical features of Aβ-depositing APP23 mice – disrupting NMDAR/PSD95 and Fyn/tau interaction for therapeutic intervention?

(Published in Cell - amyloid-β and tau – a toxic pas de deux in AD)
What’s new in diagnosis?
Advances in biomarkers

- Cerebrospinal fluid
  - Amyloid β Protein (Aβ42) ↓
  - Tau Protein (τt and τp) ↑
- MRI scans – serial, fMRI
- SPECT scans + dopamine label
- PET Scans + amyloid ligands

From the online newspaper of Prof Yasser Metwally
PiB-PET Scans: AD vs MCI vs control

From the online newspaper of Prof Yasser Metwally
Default mode network (DMN) significantly disrupted in MCI

In healthy individuals, DMN active during rest and deactivated during task performance

Posteromedial cortex (PMC) – consisting of medial precuneus, posterior cingulate and retrosplenial cortex = major node of the DMN

Varied reported alterations in task-induced deactivation in regions of the PMC during performance of memory tasks
fMRI & Functional Decline

- Posteromedial cortex (PMC) is one of the earliest affected regions in AD
  - Under high working memory load, greater deactivation of PMC in MCI¹
- Can this deactivation predict functional decline?²

¹Kochan et al. (2010). Dement Geriatr Cog Disord, Dementia & Geriat Cog Disorders, 30 (6)
Method: fMRI

- N = 30 MCI, fMRI data acquired
  - While performing Working Memory task
- WM load increased during the task
  - Manipulated by altering number of targets
- WM Load = low, medium, high
  - calibrated for each P so that
    - medium = 75-85% accuracy
    - high = 60-70% accuracy
Kochan et al. (2011). Cortical Responses to a Graded Working Memory Challenge Predict Functional Decline in Mild Cognitive Impairment
Results: fMRI

- Individuals with MCI followed for 2 yrs
- Results:
  - greater PMC deactivation predicted greater decline in IADL

Welcome to the official website of the GPCOG (The General Practitioner assessment of Cognition). The GPCOG is a screening tool for cognitive impairment. It has been designed for the primary care setting (i.e. general practitioners, primary care physicians, family doctors, etc.). This website is available in different languages. To select your language please use the drop down menu at the top of the start page.

Start Test
Learn more about the test
Read national guidelines for dementia and standard investigations

Disclaimer: Every attempt is made to ensure that all information is correct. However responsibility for investigations and further management remains in the clinician's responsibility.
GP diagnosis & management

- 4-site NHMRC-funded study
- Newcastle (Dimity Pond
- Sydney, Melbourne, Bendigo
- Can training GPs improve practice?
- Against nurse 1-hour standard GPs miss up to 50% and over diagnose ≤ 20%
Drug Trials
Current medications approved have modest benefits and are symptomatic:

4 drugs approved - all symptomatic:
- Aricept (donepezil)
- Exelon (rivastigmine)
- Reminyl (galantamine)
- Ebixa (memantine)

(Others under trial)
Disease modification

- 953 drug trials listed
- 294 trials recruiting participants
  www.clinicaltrials.gov (16.08.11)
- All promising at some stage
Cures for AD?

Potential
- $\beta$ & $\gamma$ secretase inhibitors
- Vaccines
  - Active
  - Passive (antibodies)
- Metals
- Stem cells

Failed trials
- Trimiprosate (Alzhemed)
- Flurbiprofen (tarenflurbil)
- Anti-inflammatory
- Rosiglitazone
- Statins
- Leuprolide
- Semagacestat ($\gamma$-secretase inhibitor)
Etanercept – anti TNF
Reducing BPSD & Improving QoL in RACFs
Caring for the Aged Dementia Residents Study - CADRES

- Prospective RCT comparing 3 groups:
  - Dementia Care Mapping (DCM)
  - Person-centred care (PCC)
  - Usual care (UC)
- Primary outcome = Cohen-Mansfield Agitation Inventory
Effects of DCM and PPC on CMAI

Chenoweth et al. Lancet Neurology 2009
Costs per CMAI point averted...

<table>
<thead>
<tr>
<th></th>
<th>After intervention</th>
<th>At Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCC</td>
<td>$ 8.01</td>
<td>$ 6.43</td>
</tr>
<tr>
<td>DCM</td>
<td>$ 48.95</td>
<td>$ 46.89</td>
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Chenoweth et al. Lancet Neurology 2009
ElderClowns -> Humour therapists
Sydney Multisite Intervention of LaughterBosses and ElderClowns (SMILE)

- **Primary aim**: To evaluate the effects of humour therapy on mood, quality of life, agitation & behavioural disturbance of residents in aged care
- **Assessments**:
  - Before intervention (baseline)
  - After 12 week intervention (post) – did it work?
  - At 26 wks (follow-up) – were results sustained?

Lee-Fay Low, Peter Spitzer, Belinda Goodenough, Anne Nicole Casey
Results

• Significant *decrease* in agitation in humour group compared to controls at post and follow-up
• No significant differences between groups over time
  – depression
  – quality of life (self or proxy rated)
  – social engagement
  – neuropsychiatric symptoms
Clinically significant?

- 20% reduction in agitation symptoms in SMILE
- The same effect size as is achieved by antipsychotic medications used to treat agitation
The Three Country Study (3CS)

Prof M Mittelman, New York

Prof A Burns, Manchester

Prof H Brodaty, Sydney

Investigator initiated study
Sponsored by Pfizer International Inc
Results on CG depression

Mittelman, Brodaty, Burns (2008) AJGP

BDI II Score

Control group

Counselling group

5 sessions of counselling

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<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Control</th>
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<tr>
<td><strong>AUS</strong></td>
<td>13 (50%)</td>
<td>6 (23%)</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td>12 (44%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td>19 (73%)</td>
<td>20 (77%)</td>
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**χ²: df=1, p=0.044**

**χ²: df=1, n.s.**
Some other studies ‘at’ DCRC

- Younger onset dementia (BD)
- Alcohol dementia (BD, AW)
- Dementia in hospitals (BD, AIHW)
- Aborigines and dementia (TB, RC, BD)
- CALD communities and dementia (LFL)
- Consumer Directed Care (LFL)
- Quality indicators in community care (LFL, MG)

Brian Draper, Lee-Fay Low, Adrienne Withall, Tony Broe, Robert Cumming, Australian Institute of Health and Welfare, Meredith Gresham
Research on dementia in Australia

• Broad canvas & exciting developments
• Although research funding lags behind diabetes, cancer, heart disease
  – Set to become research priority
  – Alzheimer’s Australia → >$1m 2011
• Opportunities for emerging researchers
• DCRC advertising PhD in Health Economics
Thank you

- Took up fencing, aged 85
- Rode bicycle till 100
- Lived alone till 110
- Poured olive oil on food and rubbed onto her skin
- Port wine, 2 cigs/day, 1Kg chocolate every week
- Died 122 without dementia

Jeanne Calment
1875-1997


www.dementiaresearch.org.au