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# Dementia: the next big thing is now



**Professor Henry Brodaty**  
**Director**

**Dementia Collaborative Research Centre – Assessment and Better Care**





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# Why BIG?



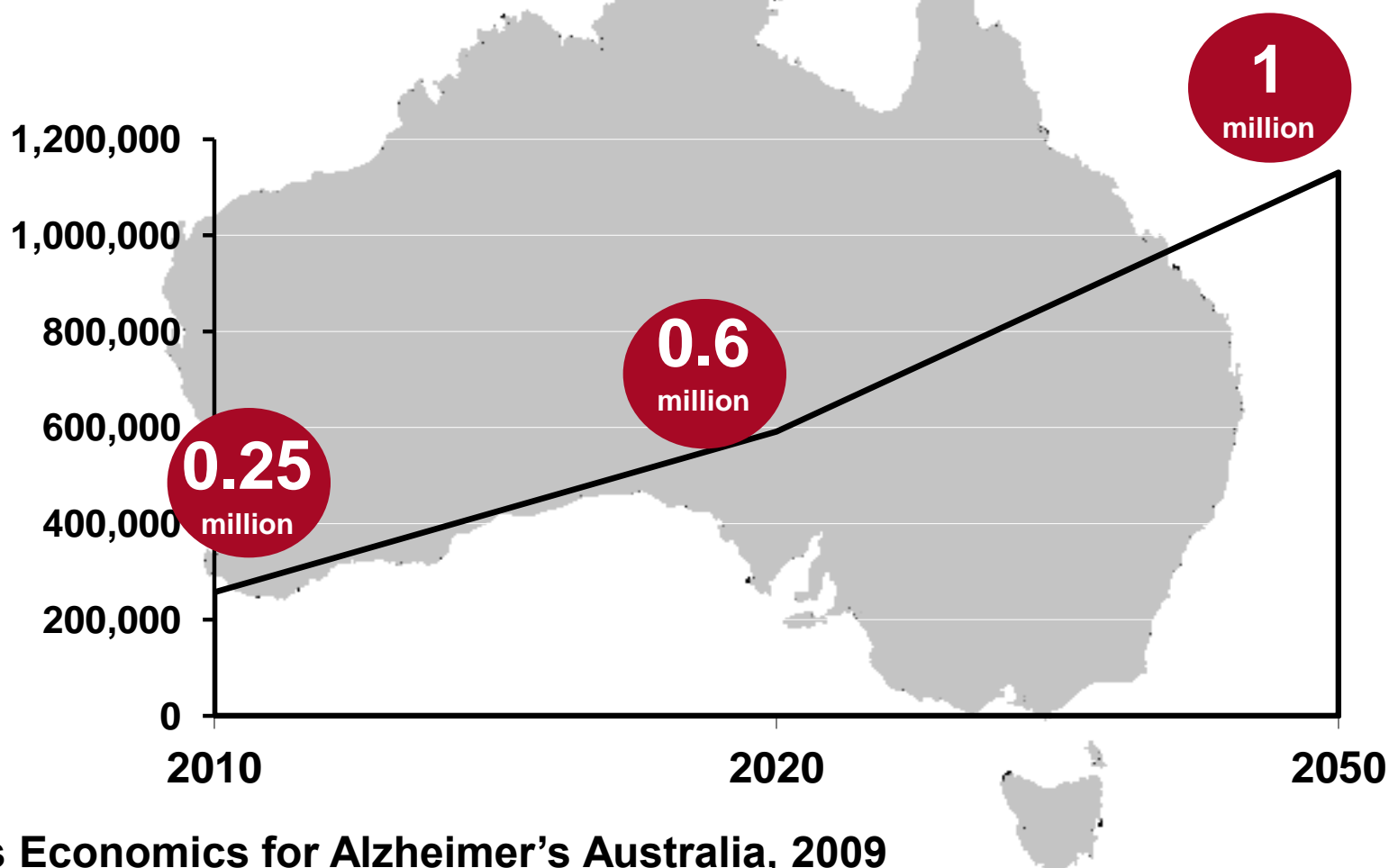
# Projections of a tripling of world's dementia population by 2050



**World Alzheimer Report, ADI, 2009**



# Quadrupling in Australia



Access Economics for Alzheimer's Australia, 2009



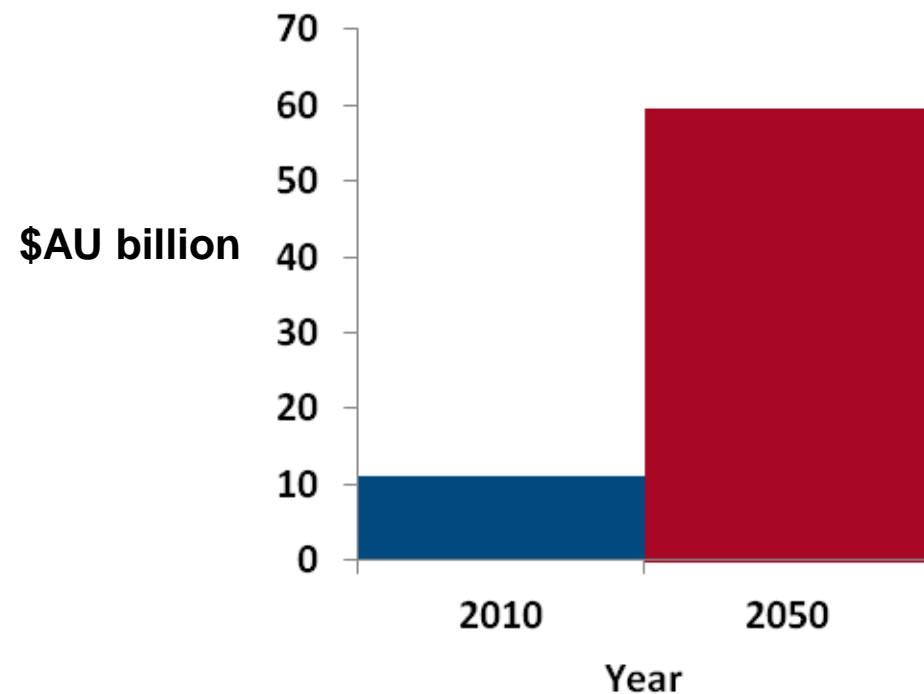
# Dementia

- **3<sup>rd</sup> leading cause of death - already**
- **Leading cause of disease burden – with 5 yrs**
- **GDP 0.8% → 1.8%**

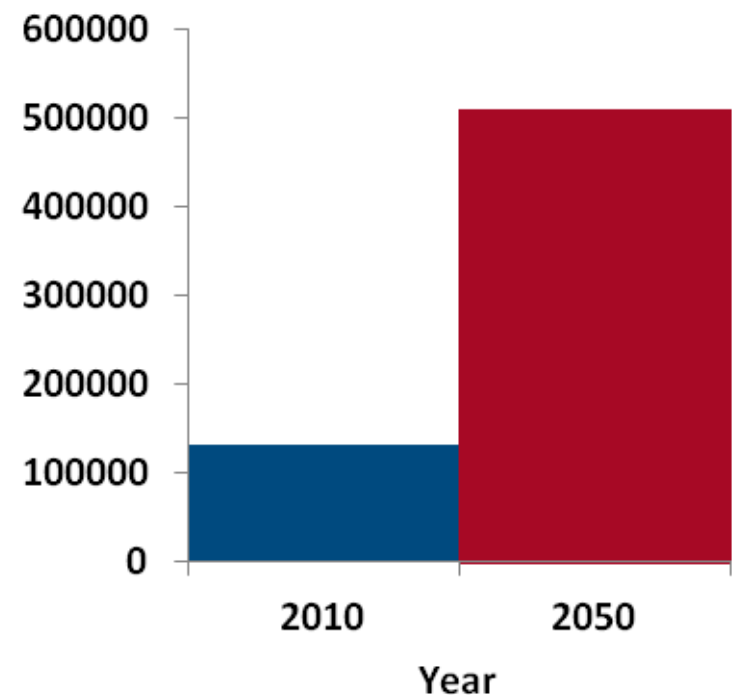


# Cost of dementia

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



**Number of RACF places**



# 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**





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# 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 y, 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  $\geq 65$  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.**



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# 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



<sup>1</sup>Jedrzejewski et al (2007). Alz Dem; 3:98-108; <sup>2</sup> Lautenschlager et al (2008) JAMA; 300(9):1027-1037; <sup>3</sup>Ravaglia et al (2007) Neurology; <sup>4</sup>Larson et al (2006) Ann Intern Med; 144:73-81; <sup>5</sup>Laurin et al, Arch Neurol 2001;58:498-504; <sup>6</sup>Middelton et al, PLoS ONE 2008;3(9):e3124



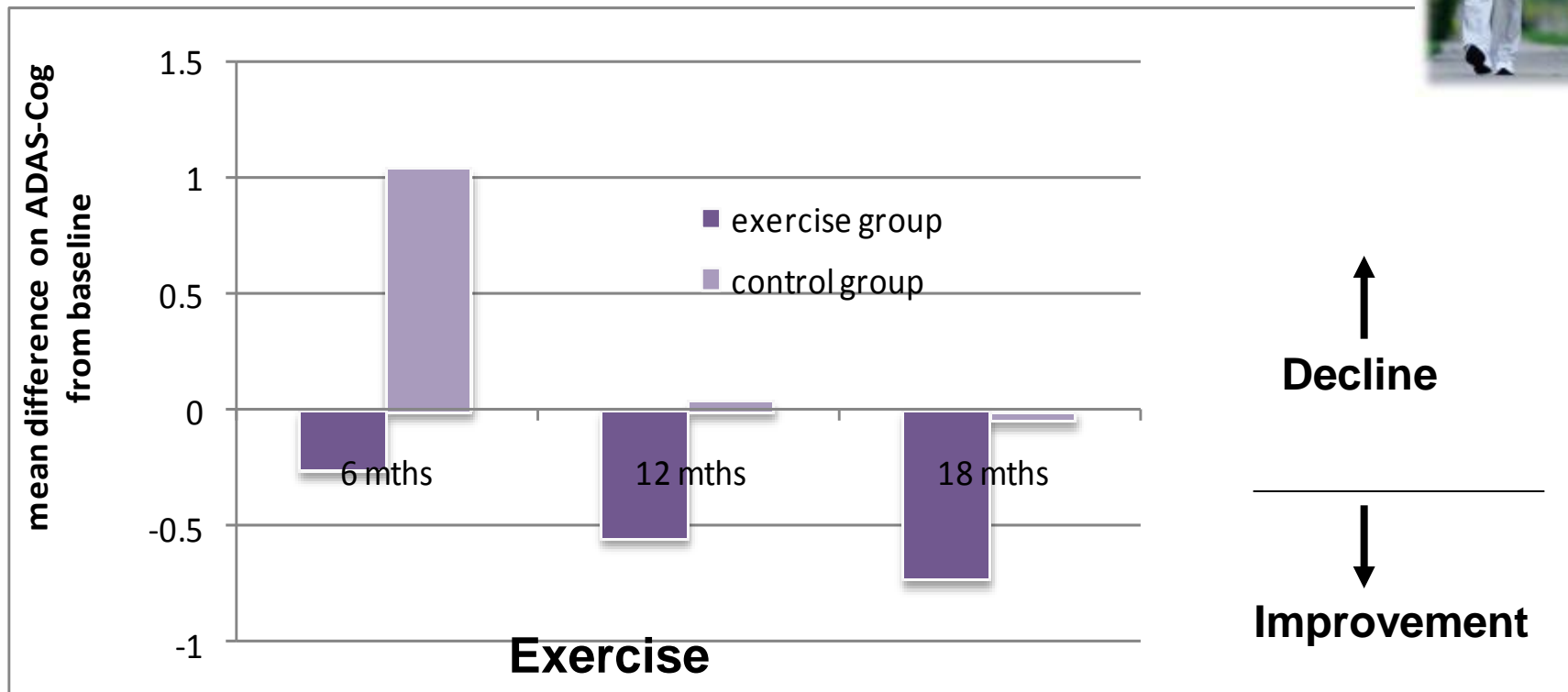
**JAMA**<sup>®</sup>

Online article and related content  
current as of September 2, 2008.

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

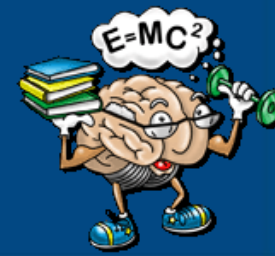
Nicola T. Lautenschlager; Kay L. Cox; Leon Flicker; et al.

*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)

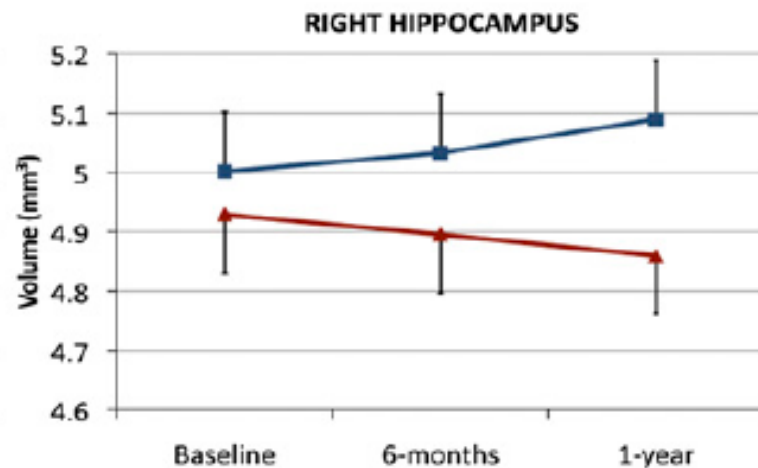
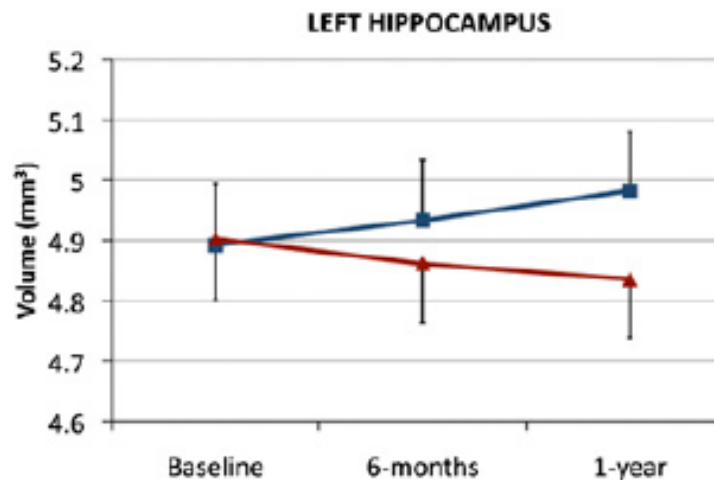
- **Aim: Does increased mental activity lead to decreased dementia risk?**
- **Intervention: 3 days/wk for 6 months**
  - Memory series + stretching/callisthenics
  - Memory series + strength exercise
  - Memory & thinking exercises + stretching/callisthenics
  - Memory & thinking exercises + strength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



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# The power of physical activity

## Hippocampus



Erickson et al., 2011



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# **Mind your brain: Accumulating evidence for mental exercise/ cognitive training**





# Mental Activity & Dementia <sup>1,2</sup>

- 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

<sup>1</sup>Valenzuela MJ. Sachdev P. (2006). Psychol Med. 36(4): 441-454;

<sup>2</sup>Valenzuela MJ. Sachdev P. (2006) Psychol Med. 36(8): 1065-1073



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# Mind your diet

- Mediterranean diet
- Antioxidants



# Nutrition / Supplements



- Alcohol ? **moderate**
- Fish/Seafood/ $\omega$ 3 ?
- 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 Epidemiol 2008



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# Mind your health checks

- ✓ Blood pressure
- ✓ Sugar
- ✓ Cholesterol

# Metabolic syndrome & dementia risk



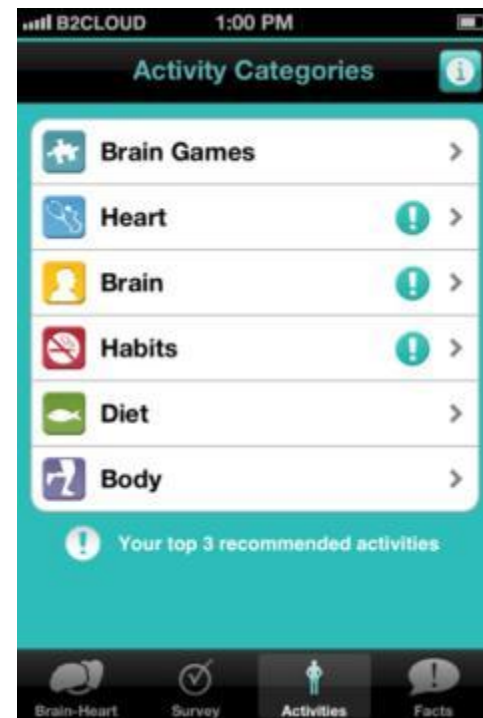
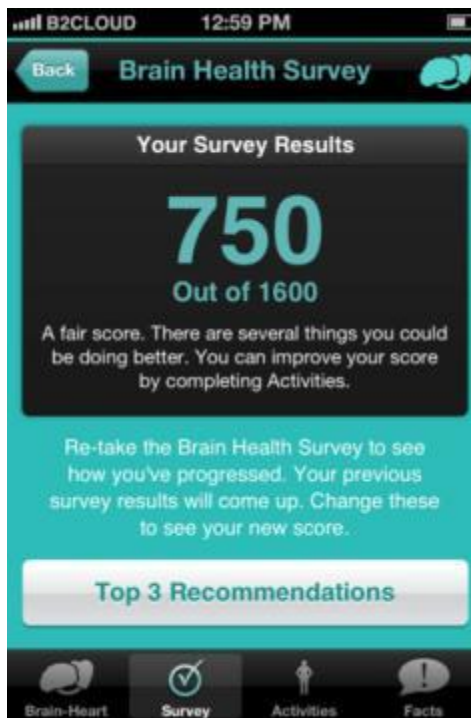
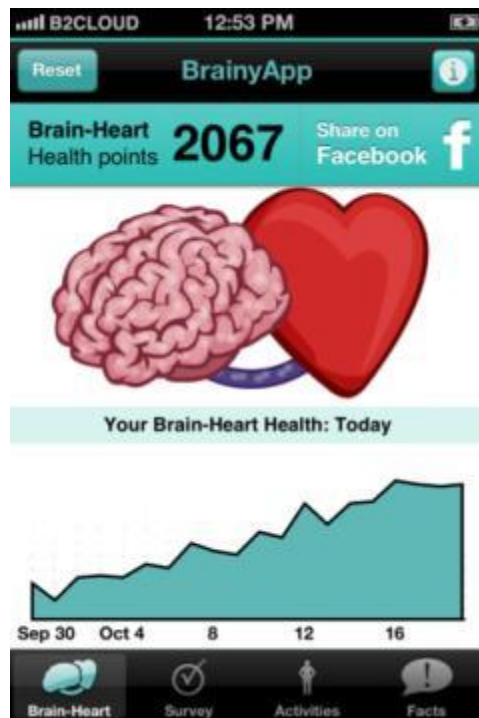
- Diabetes/ raised fasting sugar
- Abdominal obesity
- High cholesterol
- High blood pressure
- 23% increased dementia risk for each component of metabolic syndrome

- 4895 older women
- 497 with metabolic syndrome

Yaffe et al (2009) *Arch Neurol.* 66(3):324-328



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***BrainyApp*: developed by Alzheimer's Australia to raise awareness of AD/dementia risk factors**

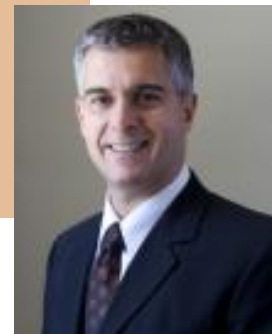




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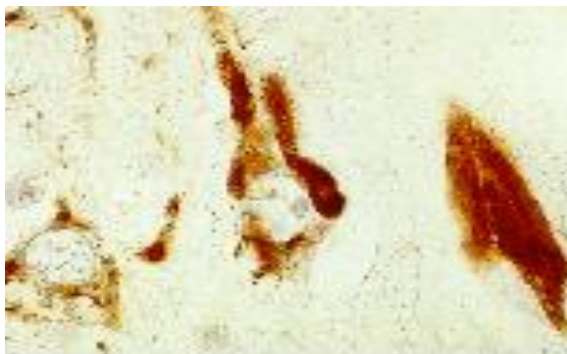
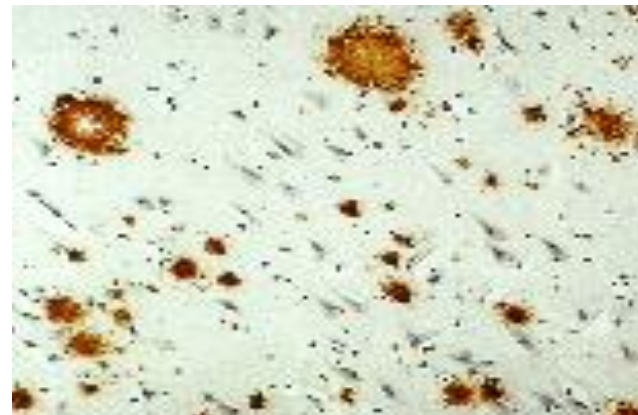
# What's new in cause of Alzheimer's disease





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# AD: a progressive CNS disorder with a characteristic pathology



Katzman, 1986

Cummings and Khachaturian, 1996

# Best target for disease-modifying drug?

- $\gamma$ -secretase inhibitor?
- $\beta$ -secretase inhibitor?
- **A $\beta$  oligomer?**
- Aggregated fibrillar A $\beta$  ?
- A $\beta$  clearance mechanism?
- APP/ A $\beta$  processing?
- **Zn / Cu interactions with A $\beta$  (Ashley Bush)**

Slide courtesy of Colin Masters

# **Best target for disease-modifying drug?**

- $\gamma$ -secretase inhibitor?
- $\beta$ -secretase inhibitor?

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

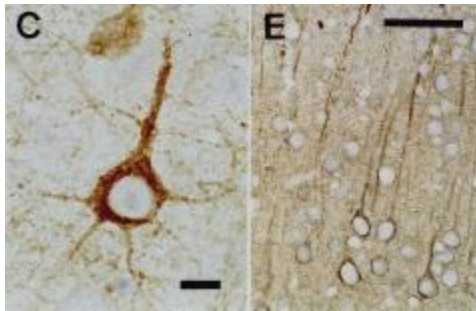
- $A\beta$  clearance mechanism?
- APP/  $A\beta$  processing?

Slide courtesy of Colin Masters

# Jürgen Götz

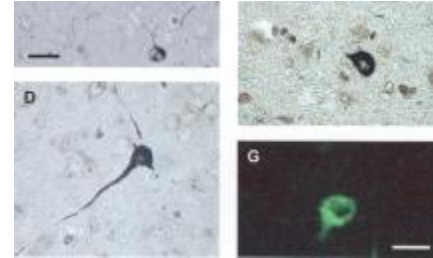
## Tau and beta amyloid – a toxic pas de deux

First tau transgenic mouse  
(EMBO J 1995,  
Acta Neuropathol 2000)



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

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

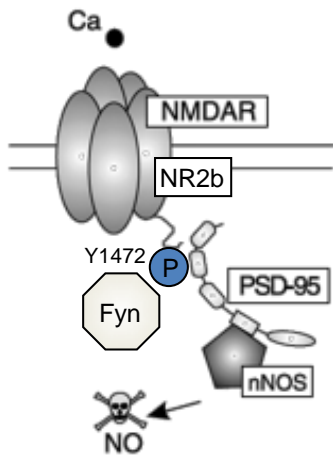


(Stereotaxic injection of A $\beta$   
induces tau tangles)

# Jürgen Götz

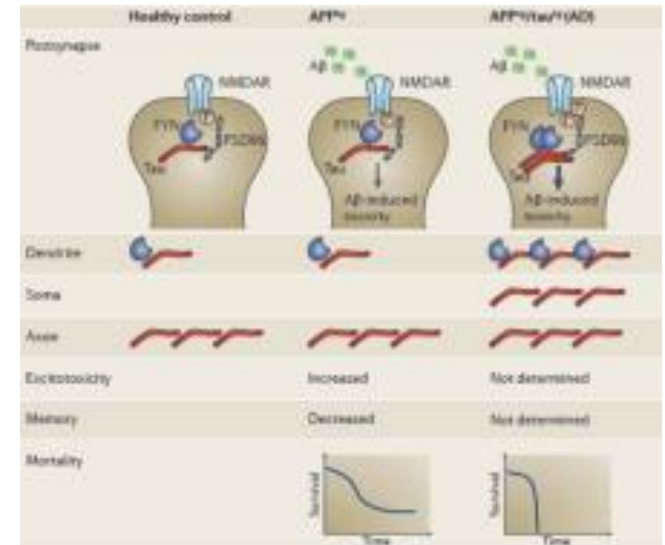
## Tau and beta amyloid – a toxic pas de deux

Paradigm shift: A $\beta$  toxicity depends on dendritic tau  
(Cell 2010)



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

Tau axis hypothesis in AD  
(Nature Rev Neurosci 2011)



(Published in Cell - amyloid- $\beta$  and tau – a toxic *pas de deux* in AD)



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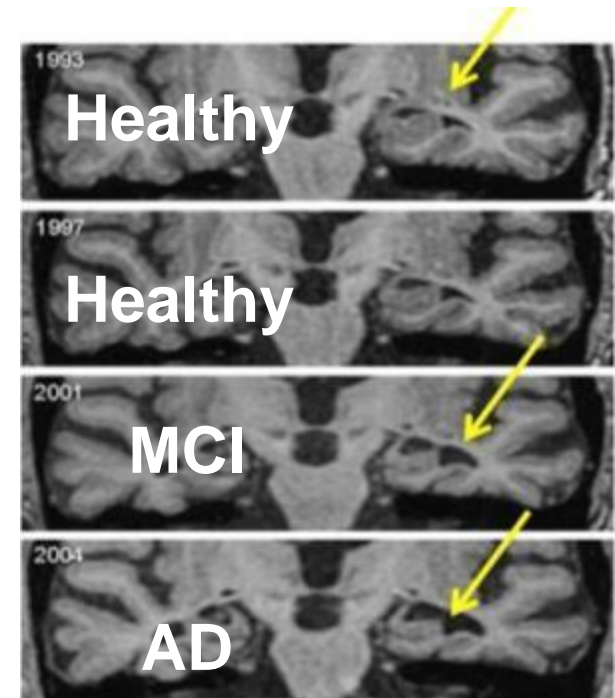
# What's new in diagnosis?





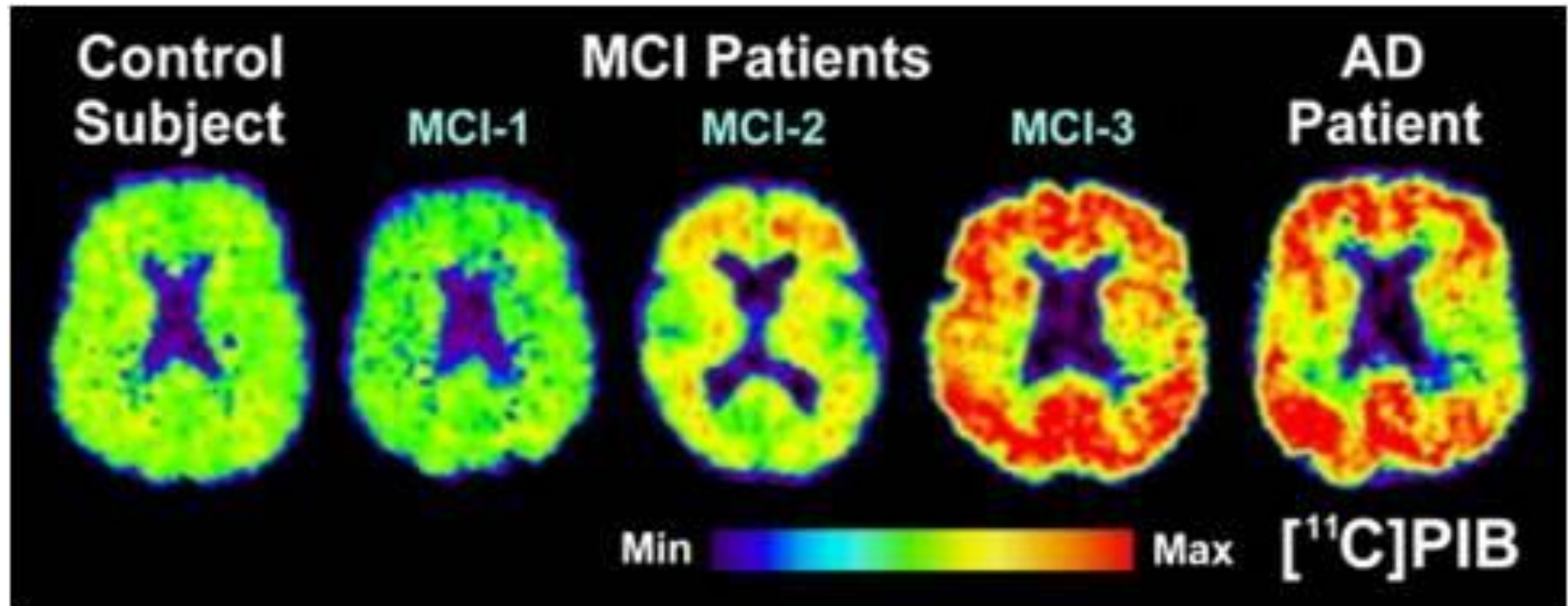
# Advances in biomarkers

- **Cerebrospinal fluid**
  - Amyloid  $\beta$  Protein ( $A\beta_{42}$ )  $\downarrow$
  - Tau Protein ( $\tau_t$  and  $\tau_p$ )  $\uparrow$
- **MRI scans – serial, fMRI**
- **SPECT scans + dopamine label**
- **PET Scans + amyloid ligands**





# PiB-PET Scans: AD vs MCI vs control

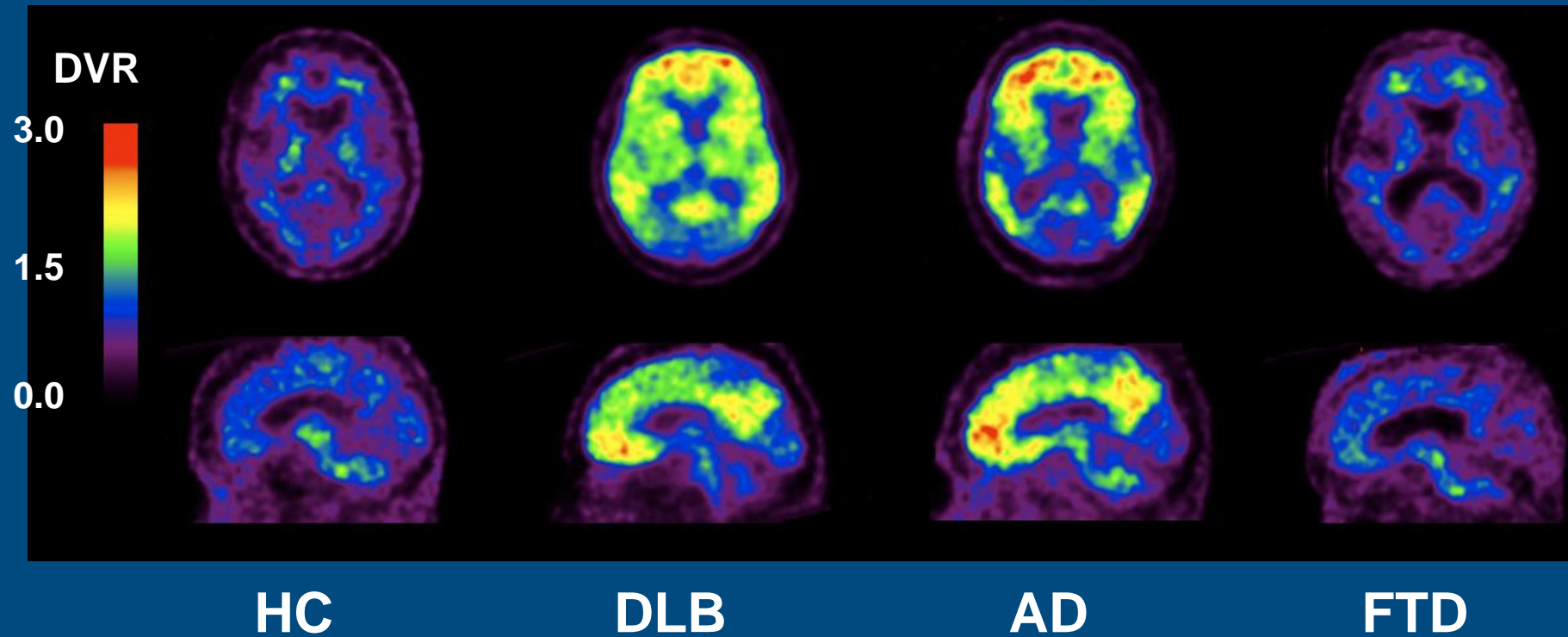


From the online newspaper of Prof Yasser Metwally  
<http://yassermetwally.wordpress.com/dementia-alzheimer-type-and-others/neuroimaging-of-dementia/>



# Rowe CC, et al. Imaging $\beta$ -amyloid burden in aging and dementia. Neurology 2007.

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tia Collaborative  
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- **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 MCI<sup>1</sup>
- **Can this deactivation predict functional decline?<sup>2</sup>**

<sup>1</sup>Kochan et al. (2010). *Dement Geriatr Cog Disord*, Dementia & Geriatr Cog Disorders, 30 (6)

<sup>2</sup>Kochan et al. (2010). Cortical Responses to a Graded Working Memory Challenge Predict Functional Decline in Mild Cognitive Impairment. *Biological Psychiatry*, 70 (2)



# 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

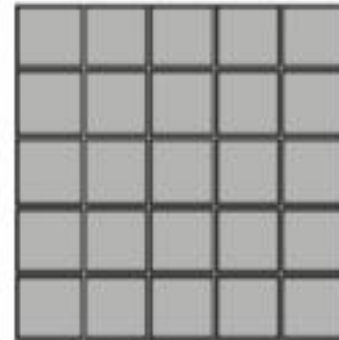
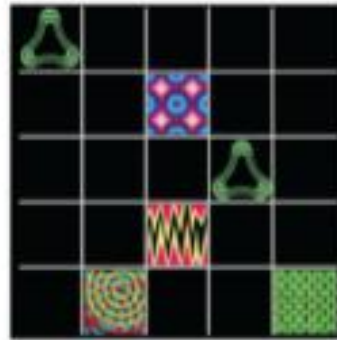
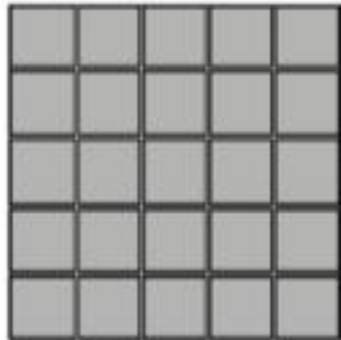




**STUDY  
screen**

**RESPONSE  
screen**

Remember  
the pictures  
and their  
positions



**Instruction**  
2, 4, 6s

**Pre- encoding**  
2s

**Encoding**  
6s

**Maintenance**  
8s

**Retrieval**  
6s



## **Results: fMRI**

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





[www.gpcog.com.au](http://www.gpcog.com.au)

## The General Practitioner assessment of COGnition

[Home](#)[Start Test](#)[National Guidelines](#)[GPCOG Information](#)[Downloads](#)[English](#)

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  $\leq 20\%$**



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# 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](http://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 )



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# Etanercept – anti TNF







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# **Reducing BPSD & Improving QoL in RACFs**



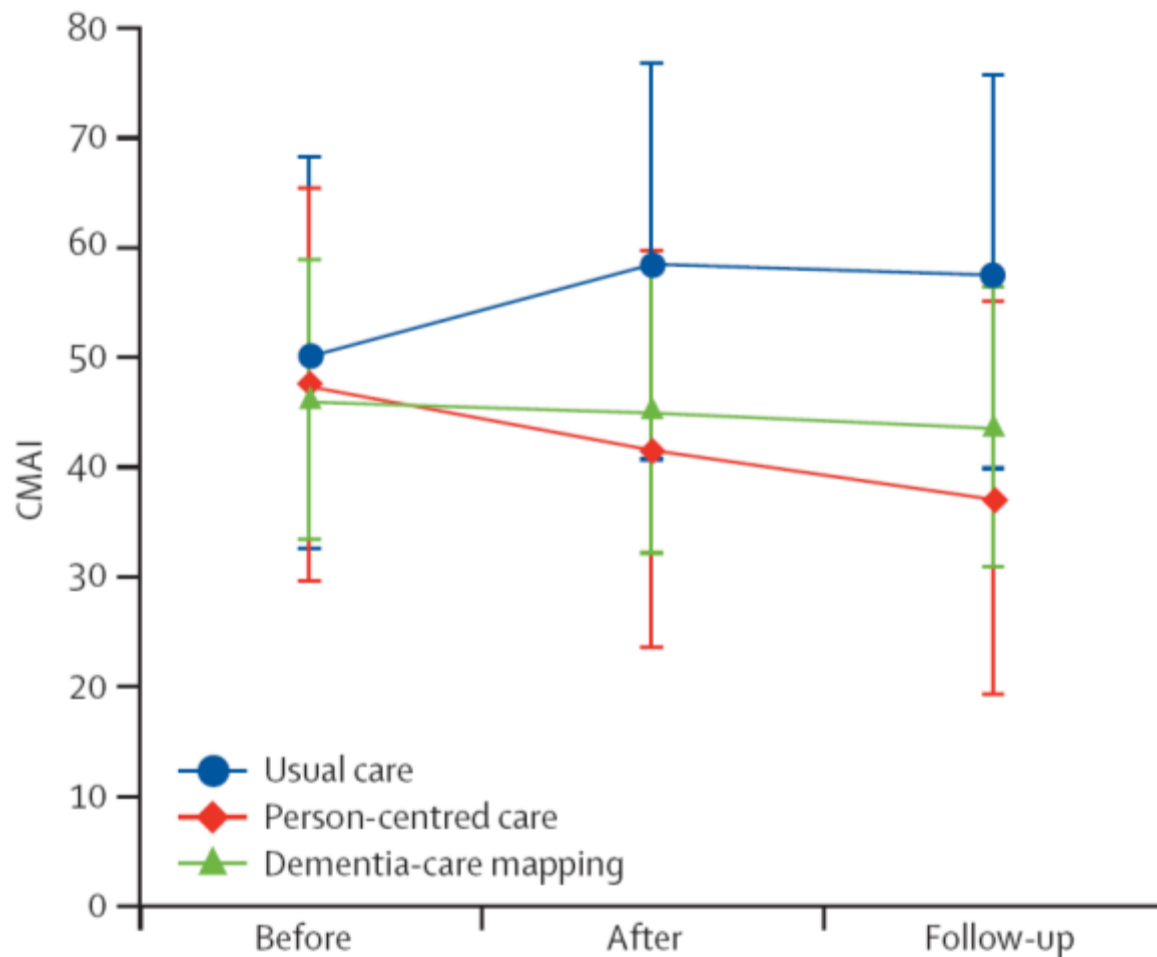


# **Caring for the Aged Dementia Residents Study - CADRES**

- **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...

	After intervention	At Follow-up
<b>PCC</b>	<b>\$ 8.01</b>	<b>\$ 6.43</b>
<b>DCM</b>	<b>\$ 48.95</b>	<b>\$ 46.89</b>

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 betw<sup>n</sup> 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



OR





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# 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



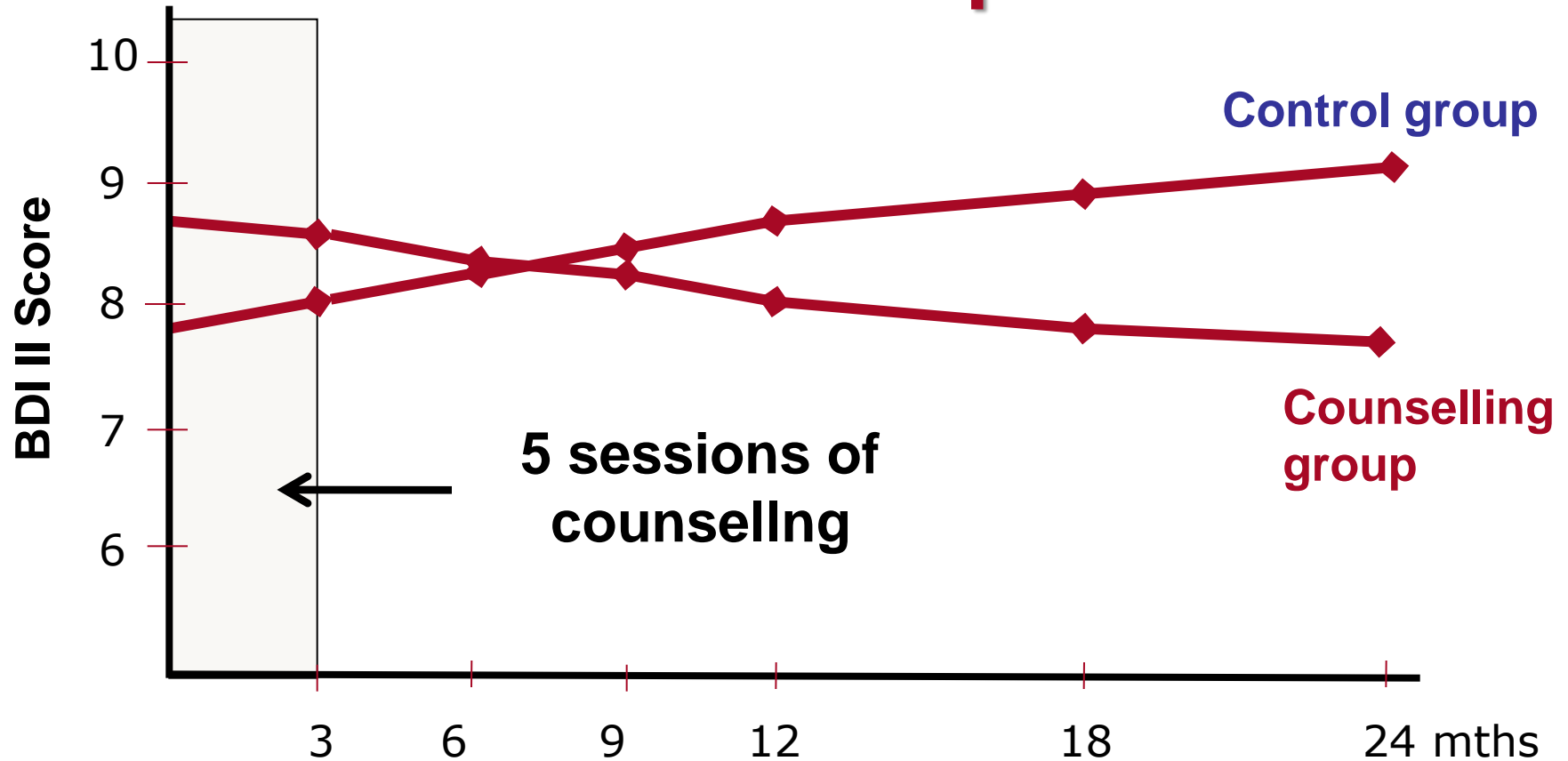


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## Results on CG depression



Mittelman, Brodaty, Burns (2008) AJGP

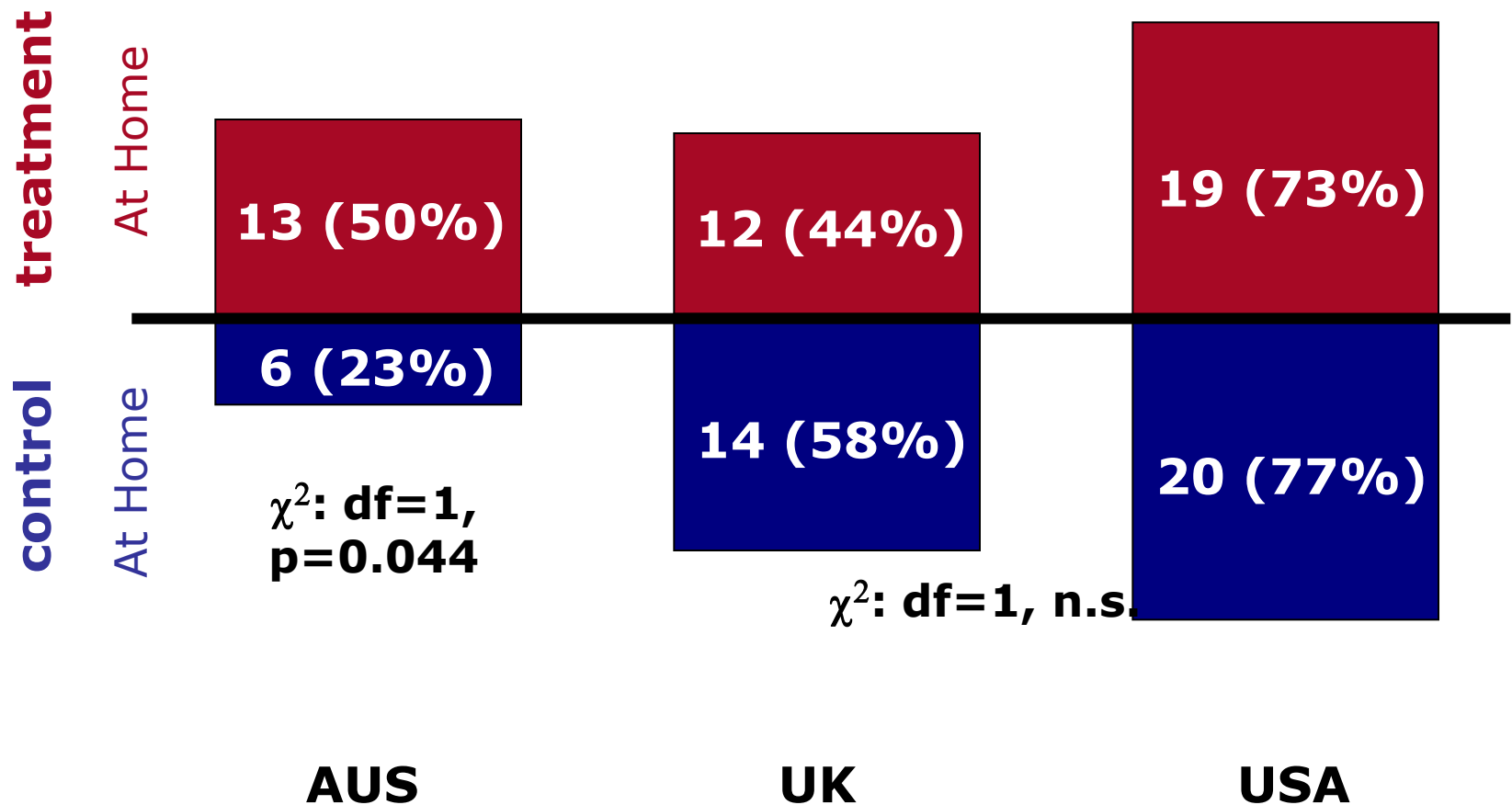


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# PWD still at home in AUS, UK & USA ( $\leq 5y$ )





## **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**



# 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



**Jeanne Calment**

**1875-1997**

- 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

**[www.dementiaresearch.org.au](http://www.dementiaresearch.org.au)**