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# Ten years of research at Swinburne University on CDRI08

Prof Con Stough

NICM Collaborative Research  
Centre in Neurocognition





**NICM**  
THE NATIONAL INSTITUTE OF  
COMPLEMENTARY MEDICINE

Collaborative Centre for Neurocognition

Collaborative Centre for Neurocognition

**Director**      **Co-director**  
Con Stough    Andrew Scholey

**Clinical Trials Co-ordinator**  
Marni Kras

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Pat Johnston [neuroimaging]  
(David Crewther)

**Post-docs**  
Lauren Owen [glucose, insulin]  
David Camfield [imaging]  
Vanessa Cropley [polyphenols]  
Jerome Sarris [psychiatry]  
Talitha Best [saccharides]

**PhDs**  
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Christina Kure [heart and brain h  
Vanessa Bilog [anti-oxidants]  
Helen MacPherson [anti-oxidants]  
Liz Harris [vitamins]  
Renee Rowsell [vitamins]  
Chris Neale [bacopa, neuroimaging]  
Rita Brien [oxytocin]  
Naomi Perry [phytoestrogens]  
Isabelle Bauer [fish oils]  
Rachel Gold [fish oils]  
Michaela Pascoe [fish oils]  
Matt Pase [heart-brain axis]  
Natalie Grima  
James Kean [ADHD]  
Melissa Wines [EGCG]

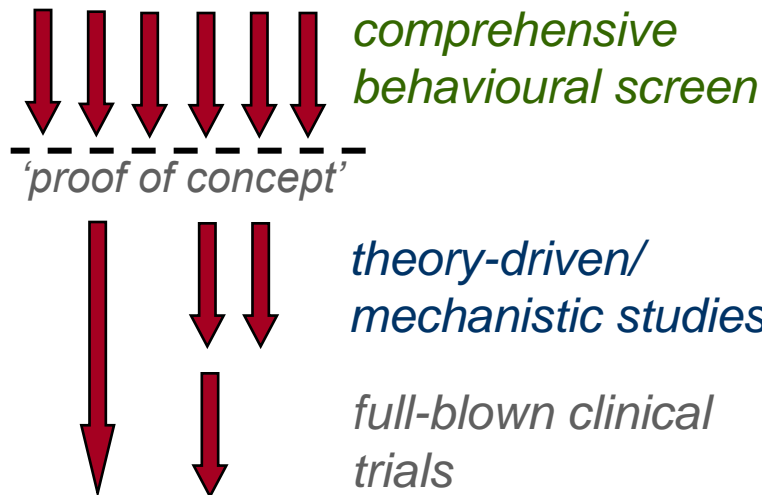
**RAs**  
Amy Gibbs  
Karen Nolidin



**Key collaborators**  
Kevin Croft (UWA)  
Frank Rosenfedlt (Alfred Hospital)  
Denis Chang (UWS)  
Peter Howe (UniSA)  
Stephen Myers (Southern Cross)

# Top down strategy: stage i. capturing behavioural effects in humans

- Focus on 'safe' treatments/interventions thought to improve mood and/or cognition from
  - history/tradition
  - anecdote
  - market



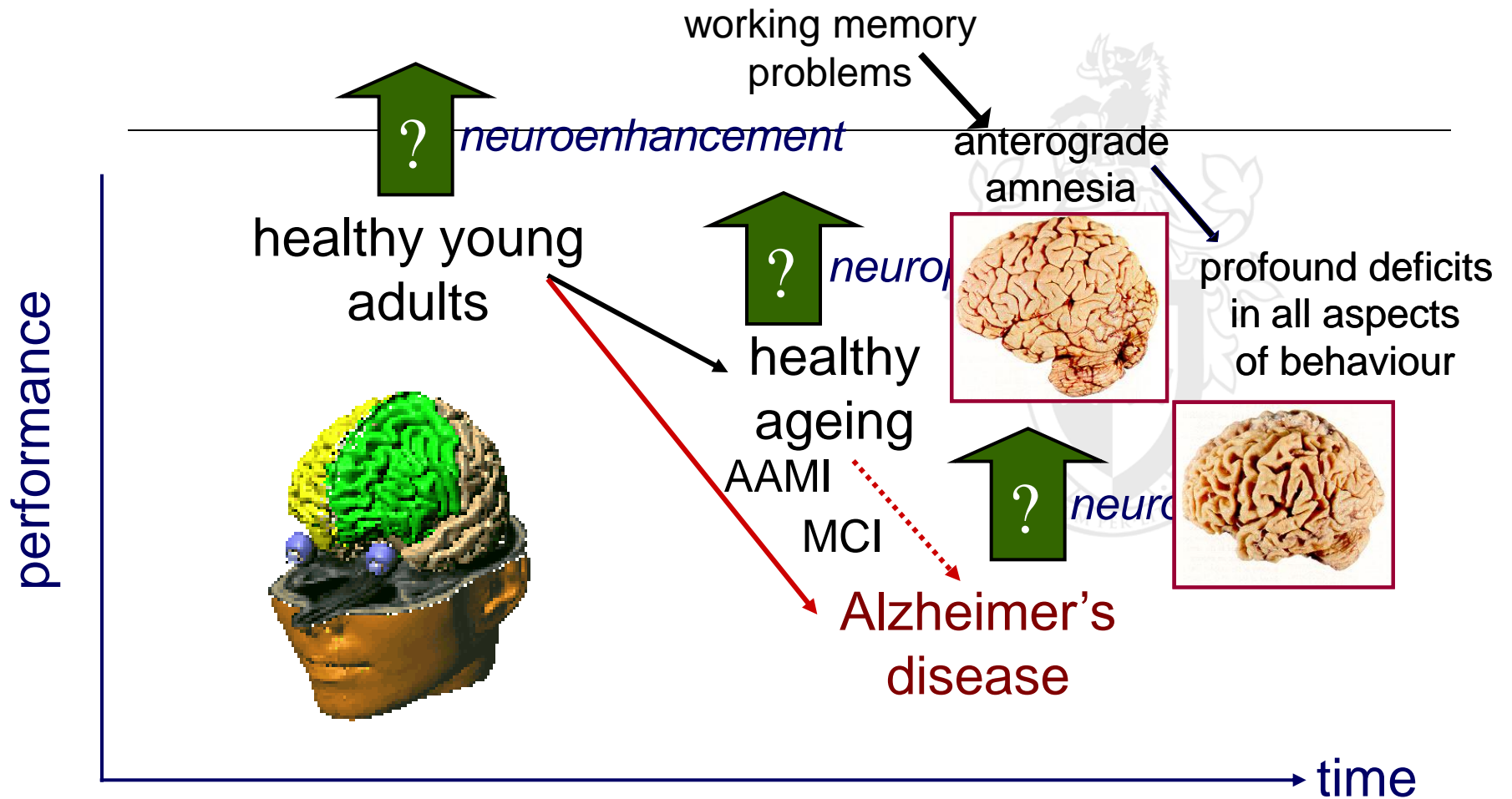
## PLANT EXTRACTS

- *Ginkgo biloba*
- *Panax ginseng*\*
- *Ginseng quinquefolius*\*
- *Ginkgo-ginseng combination*
- *Melissa officinalis*\*
- *Salvia officinalis*\*
- *Salvia lavandulaefolia*\*
- *Valerian*
- *Guaraná*\*
- *Ginkgo-phosphatidylserine*\*
- Cocoa polyphenols\*
- *Bacopa monnieri*\*
- Pycnogenol\*
- Enzogenol\*
- EGCG

## OTHERS

- oxygen\*
- glucose
- aromatherapy oils
- caffeine
- theanine
- water
- chewing gum\*
- alcohol [low dose]
- DHA
- multivitamins

\*first controlled human study [11/14]



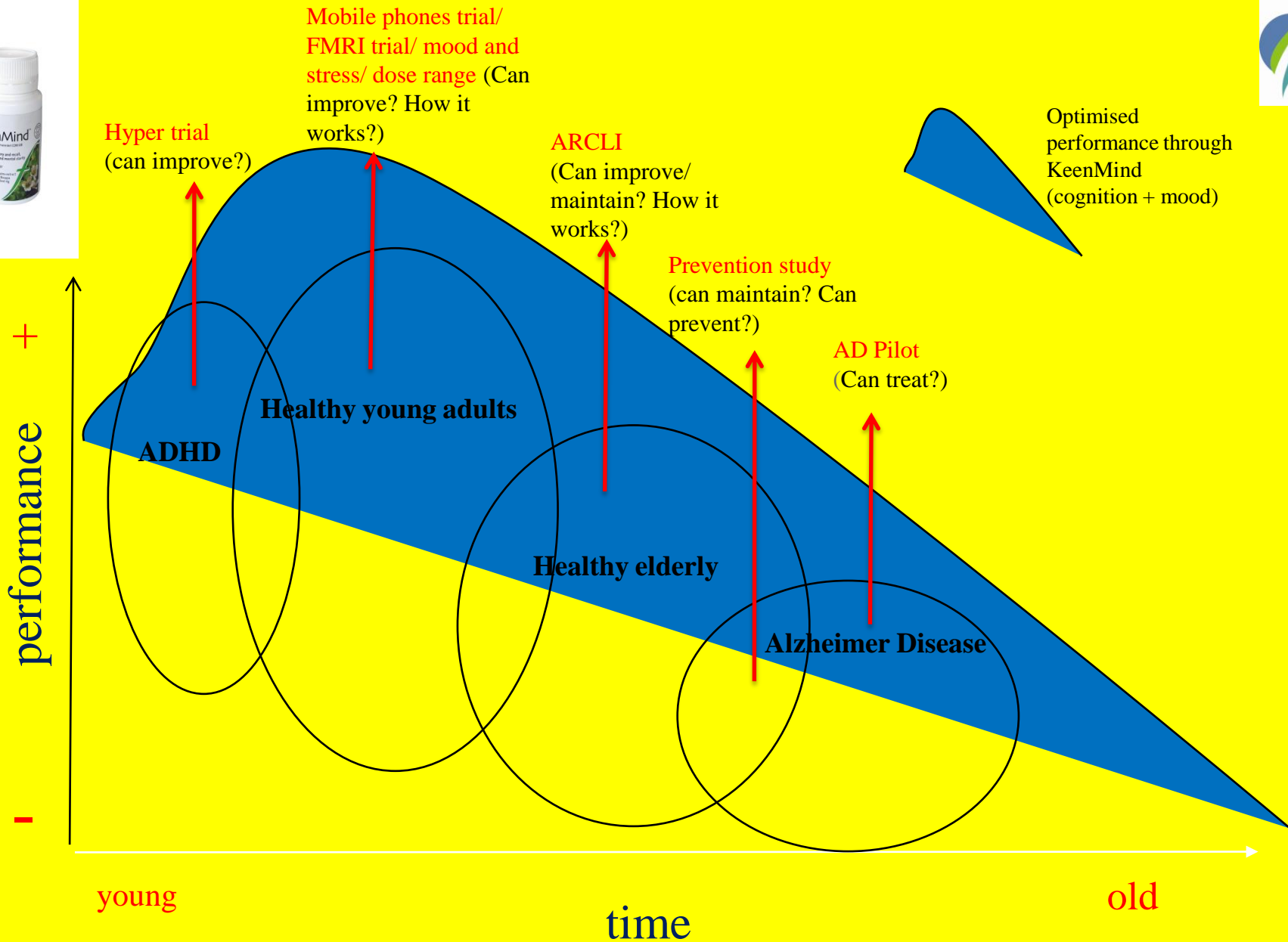
# Story of Adam Ritson- cognitive damage restored by CDRI08 Professional Rugby League Player



# Research on CDRI08

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1. The Past (animal and in vitro; chronic ageing)
2. The Present (acute memory enhancing; ADHD)
3. The Future (large scale, neuroimaging)



# KeenMind Brain Health Lifetime Clinical Trials Program

# The Past

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- 50 years of in vitro research in India
- Chronic trials
- Mechanisms of CDRI08 seemed to map appropriately to many putative cognitive systems
- Excellent animal and in vitro work already conducted in India

# Historical Use

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- inflammation,
- pain,
- pyrexia,
- epilepsy,
- and memory

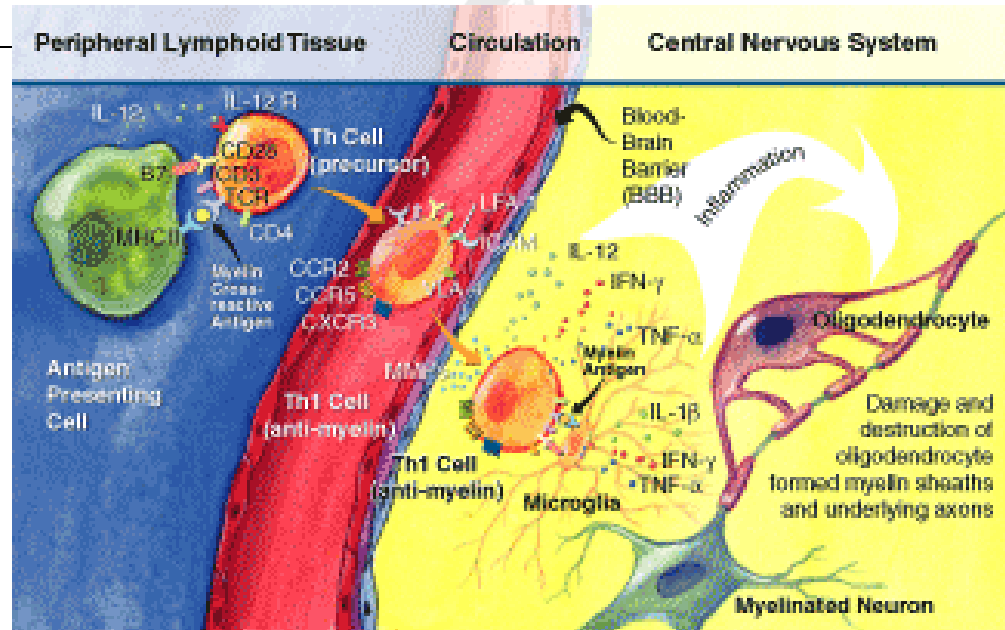
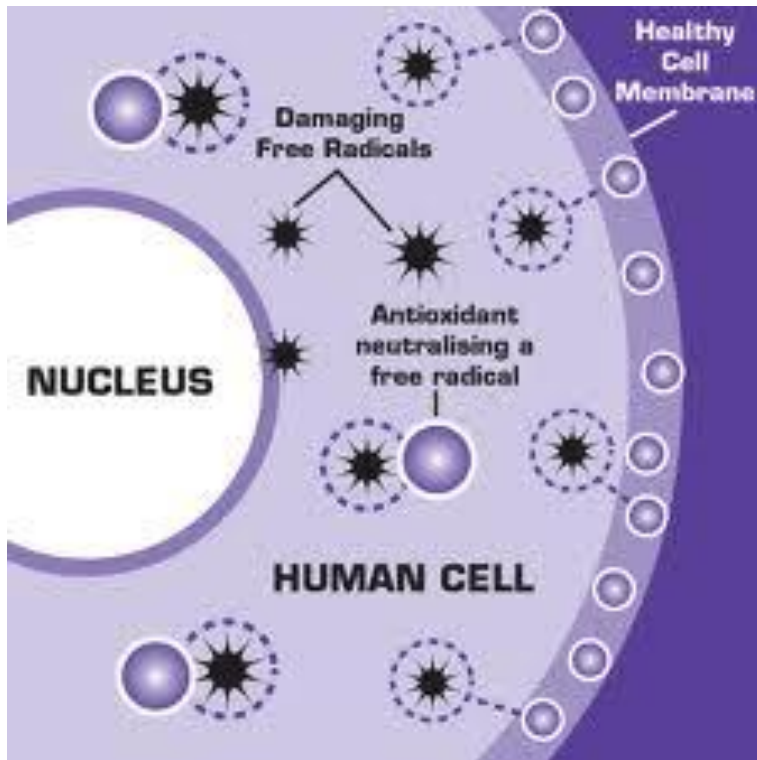


# Mechanisms-Indian research

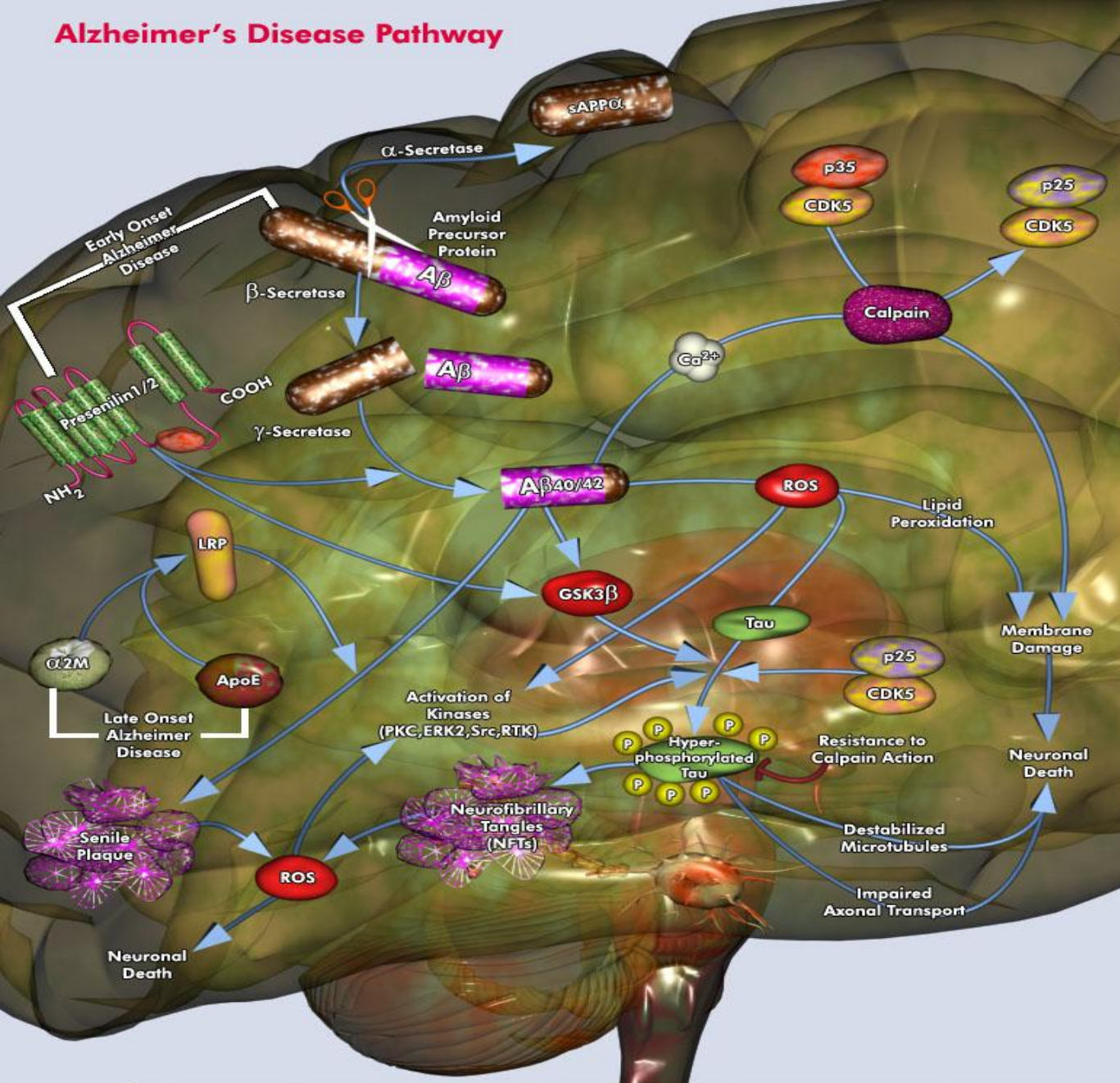
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- modulate the cholinergic system, Bhattacharya 1999
- have antioxidant and metal chelating effects Agrawal 1993
- anti inflammatory properties Jain 1994
- relaxant properties in blood vessels Dar & Channa 1999
- anxiolytic Bhattacharya & Ghosal 1998
- antidepressant Sairam 2002

# Mechanisms



# Alzheimer's Disease Pathway



# AD and Ageing Pathways

# Bacopa research

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- 2010-
- Scopus “Bacopa M”
- 108 published studies many on mechanisms



# Parkinsons Research Jadiya et al 2011

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- Neurodegenerative Parkinson's disease (PD) is associated with aggregation of protein alpha synuclein and selective death of dopaminergic neurons.
- *B. monnieri* reduces alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in nematodes

# Effects on brain: Vollalla et al 2011

- The current study examined the effects of standardized extract of *Bacopa monniera* on the dendritic morphology in adult rats of hippocampal CA3 neurons, one of the regions concerned with learning and memory.
- Subjected to spatial learning (T-maze) and passive avoidance tests. Brains were removed and hippocampal neurons were impregnated with silver nitrate (Golgi staining).

# Increased dendrites

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- The results showed improvement in spatial learning performance and enhanced memory retention in rats treated with BM extract.
- Increase in the dendritic intersections and dendritic branching points along the length of both apical and basal dendrites in rats treated with BM extract for four and six weeks.
- Growing neurons!

# Cardiovascular effects Kamkaew et al 2011

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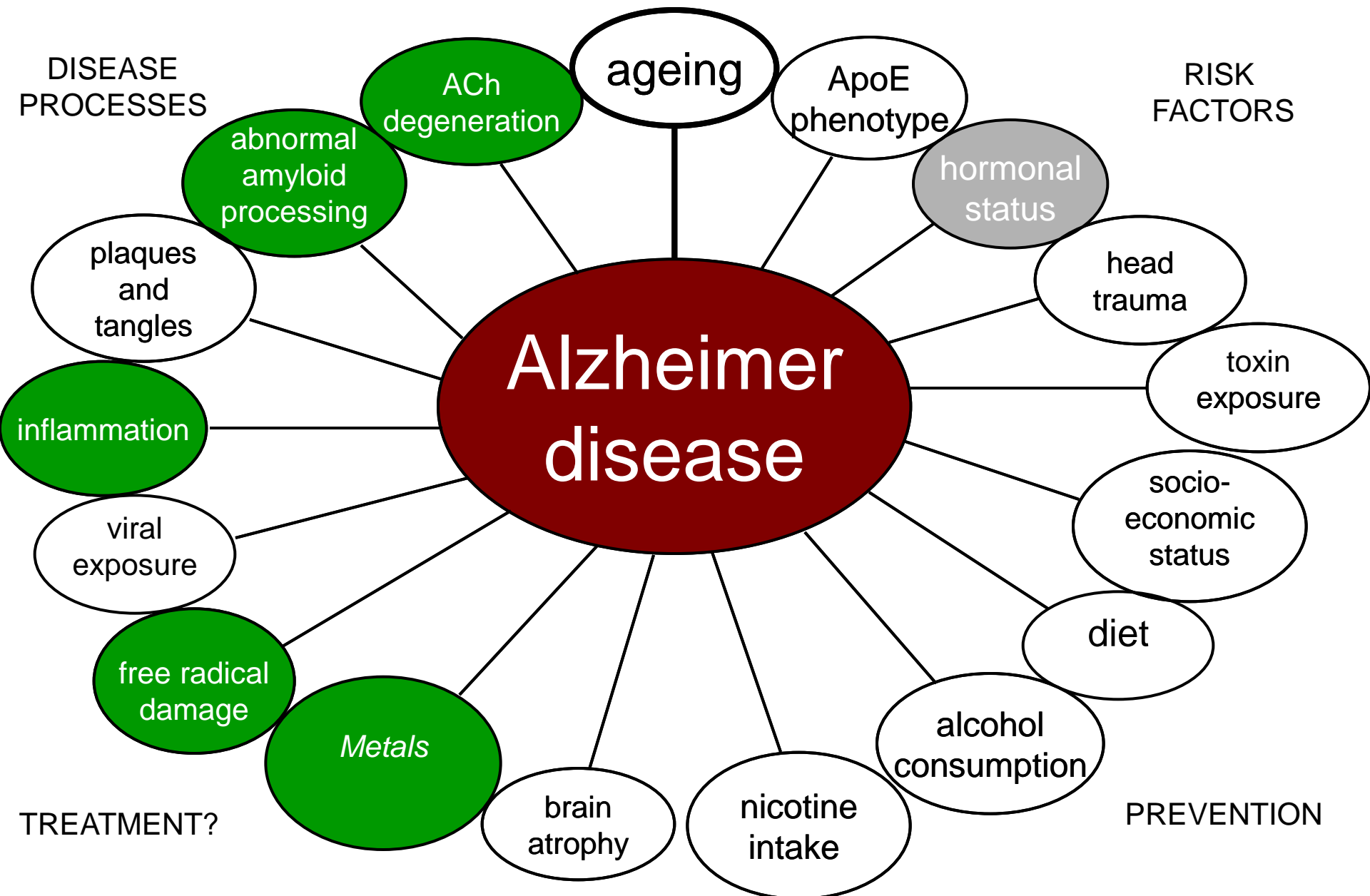
- Little is known about the cardiovascular actions of Brahmi.
- Intravenous Brahmi (20-60 mg/kg) was tested on arterial blood pressure and heart rate of anaesthetized rats. In vitro vasorelaxation was assessed in arteries.

# Cardiovascular effects?

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- Brahmi reduced blood pressure partly via releasing nitric oxide from the endothelium, with additional actions on vascular smooth muscle  $Ca^{2+}$  homeostasis.
- Some Brahmi ingredients could be efficacious antihypertensives
- Vasodilation could account for some medicinal actions (acute effects?)

# Bacopa properties



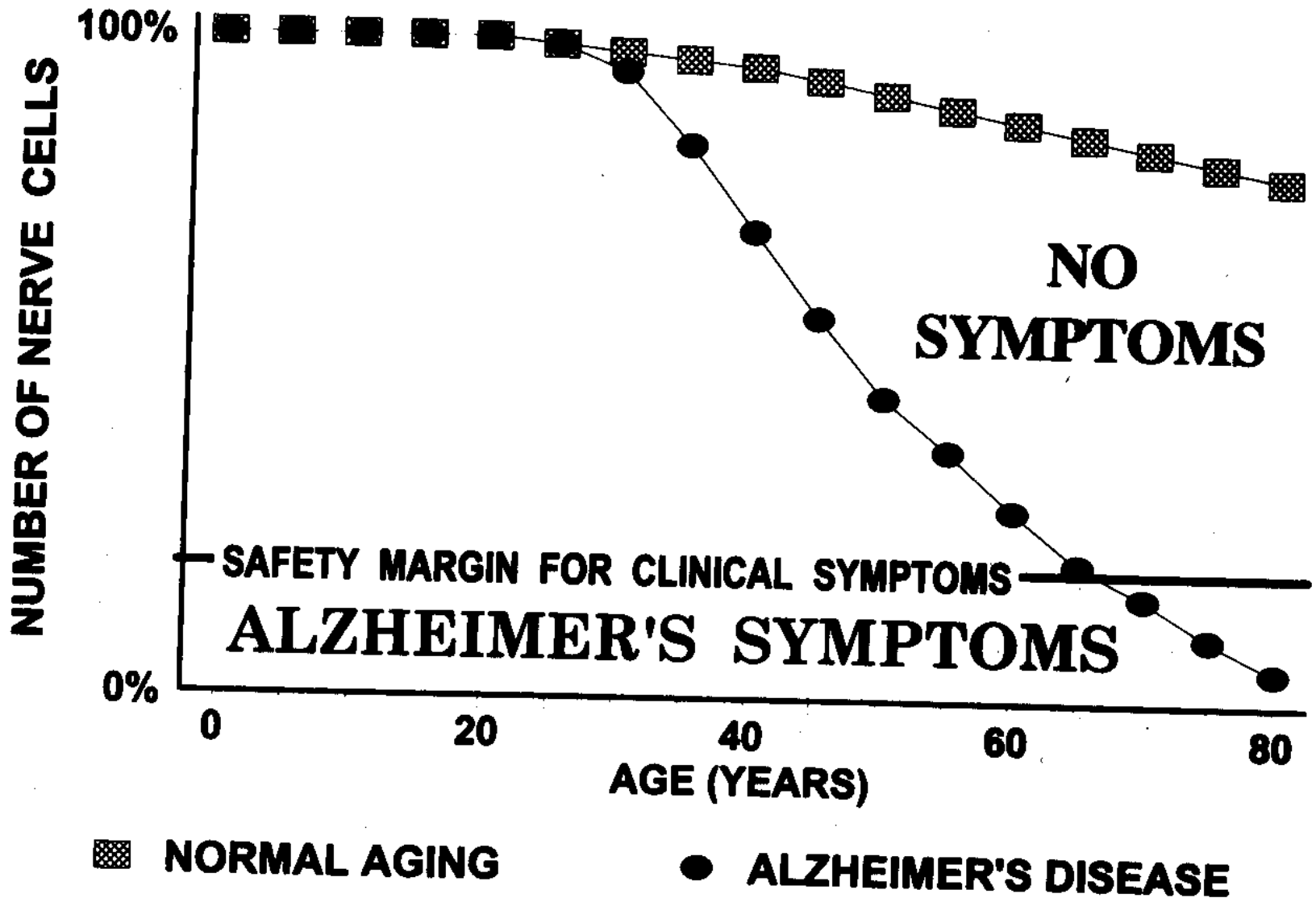
# CDRI08

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- CDRI08 extract has been highly researched for more than 50 years in India
- Sourced from the same place in India, same extract, same growing conditions
- Same quality assurance and same amount of bacosides

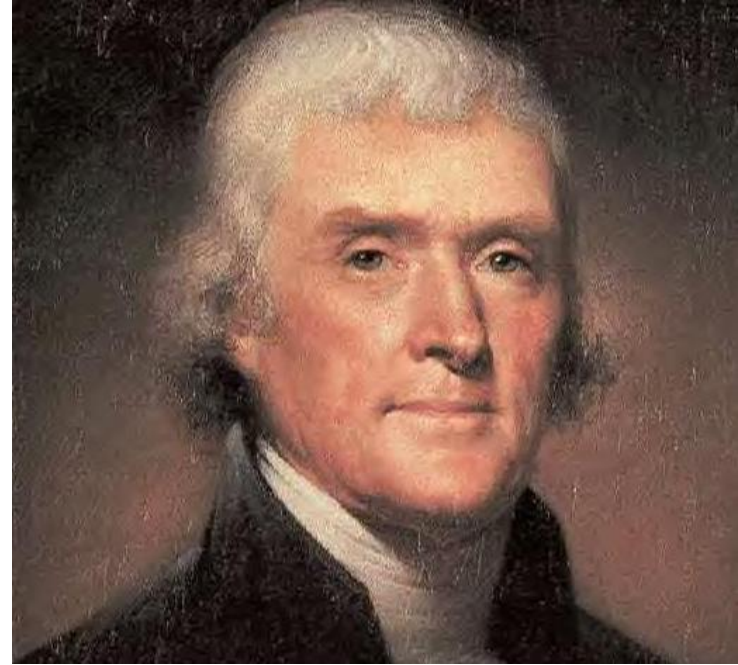
# CEREBRAL NERVE CELL LOSS

ALZHEIMER'S DISEASE vs. NORMAL AGING



# Thomas Jefferson..

Bodily decay is  
gloomy in prospect,  
but of all human  
contemplations the  
most abhorrent is  
body without mind.



# Cost of ageing...

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- Most people don't want to get older....
- In pure economic terms the costs of ageing reflects ***decreased productivity*** as well as ***increased levels of reliance on public services to health and social support*** but this also has obvious ramifications for our ***ability to lead fulfilling lives.***



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# Human Trials



# Clinical trials-chronic

1. Barbhaiya et al (2008) *Journal of Pharmacology and Toxicology*
2. Stough et al (2008) *Phytotherapy Research*
3. Calabrese et al (2008) *JACM*
4. Roodenrys et al (2002) *Neuropsychopharmacology*
5. Stough et al (2001) *Psychopharmacology*
6. Nathan et al (2004) *Human Psychopharmacology*
7. Morgan & Stevens (2010) *JACM*
8. Raghav et al. (2006) Age associated memory Imp

Systematic review (in press *JACM*)

Author/ Year	Dosage	n	Sample	Trial Design	Outcome Measures	Results	Effect Size	Q /10
Stough et al. (2001)	KM 300mg daily BC: min 55%	46 23(B) 23(P)	18-60 yrs	12-week DB, PC	Full cognitive testing battery inc: IT, AVLT, reaction time, digit span	BM significantly improved Speed of visual information processing (IT), learning rate and memory consolidation on AVLT	VP & A <sup>1</sup> : 0.25 L & M <sup>1</sup> : 0.27 L & M <sup>2</sup> : 0.52 L & M <sup>3</sup> : 1.01	8
Nathan et al. (2001)	KM 300mg single dose BC: min 55%	38 18 (B) 20 (P)	18-60 years	0 and 2 hours DB, PC	No effect on any measure	No acute effects of BM on a battery of measures	N/S	8
Roodenrys et al. (2002)	KM 300mg (ppts < 90kg) 400mg (ppts 90kg+) BC:55%	76 37 (B) 39 (P)	40 – 65 years	0 and 3 months DB, PC	Cognitive testing battery including story recall, word pairs, general knowledge	Positive effects on retention of new information	L & M <sup>9</sup> : 0.23	6
Raghav et al. (2006)	CDRI 250mg daily BC: min 55%	40 20 (B) 20 (P)	55+ years Participants had AAMI	0 and 12 weeks DB, PC	WMS	Significant improvements on mental control <sup>b</sup> , logical memory <sup>b</sup> , paired associate learning <sup>b</sup> (all from WMS)	WM & EF: 0.83 L & M <sup>7</sup> : 1.56 L & M <sup>8</sup> : 0.12	7
Stough et al. (2008)	KM 300mg daily BC: min 55%	62 33 (B) 29 (P)	18-60 years	0 and 90 days DB, PC	CDR Testing Battery	Significant Working Memory <sup>a</sup> and RVIP improvements <sup>a</sup>	WM & EF <sup>2</sup> : 0.47 VP & A <sup>2</sup> : 0.30	9
Calabrese et al. (2008)	MH 300mg daily BC: min 50%	44 24 (B) 24 (P)	65+ years	0 and 12 weeks DB, PC	AVLT, Stroop, DAT, WAIS letter digit test	Significant AVLT <sup>a</sup> and Stroop <sup>a</sup> improvements.	L & M <sup>4</sup> : 0.36 WM & EF <sup>3</sup> : 0.32	9
Barbhaiya et al. (2008)	BM 450mg daily BC: bacoside A <sub>3</sub> > 5% w/w	44 23 (B) 21 (P)	50 – 75 years MMSE 24+	0, 12 and 24 weeks DB, PC Treatment 0 – 12 wks	Cognitive testing battery @12 weeks treatment and 24 week follow up.	Significant improvements in digit cancellation and visual retention @12 week. Comparisons not between treatment groups but change from baseline in each group	N/A	9
Morgan & Stevens (2010)	BM 300mg daily BC: 40 – 50%	81 36 (B) 45 (P)	55+ years	0 and 12 weeks DB, PC	Multiple cognitive measures: AVLT, CFT, TMT, MAC-Q	Significant improvements on verbal learning, memory acquisition and delayed recall AVLT measures No significant differences on CFT, TMT or MAC- Q	L & M <sup>4</sup> : 0.95 L & M <sup>5</sup> : 0.53 L & M <sup>6</sup> : 0.57	10



Psychopharmacology (2001) 156:481–484  
DOI 10.1007/s002130100815

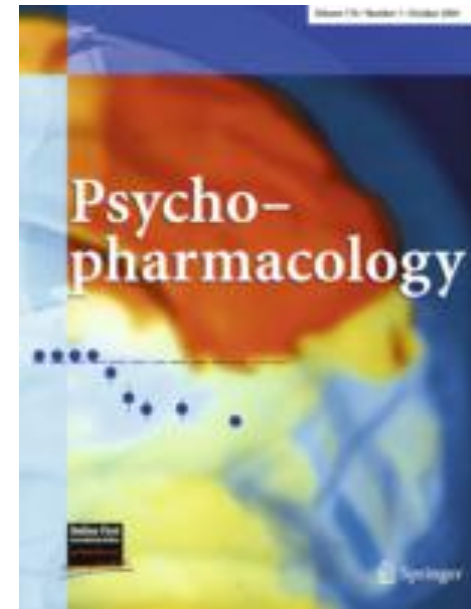
RAPID COMMUNICATION

C. Stough · J. Lloyd · J. Clarke · L. A. Downey  
C. W. Hutchison · T. Rodgers · P. J. Nathan

**The chronic effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy human subjects**

# Stough et al 2001

- 46 participants ages 18-60 years
- (1 and 90 days)
  
- Neuropsychological tests; anxiety
- Inspection Time/Reaction Time
- Auditory Verbal Learning Test (AVLT)
- Digit Span/ Digit Symbol
- Trail Making Test/ STAI/POMS



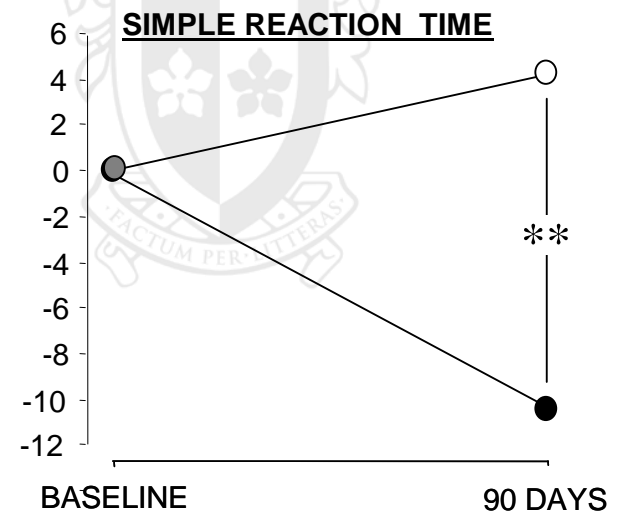
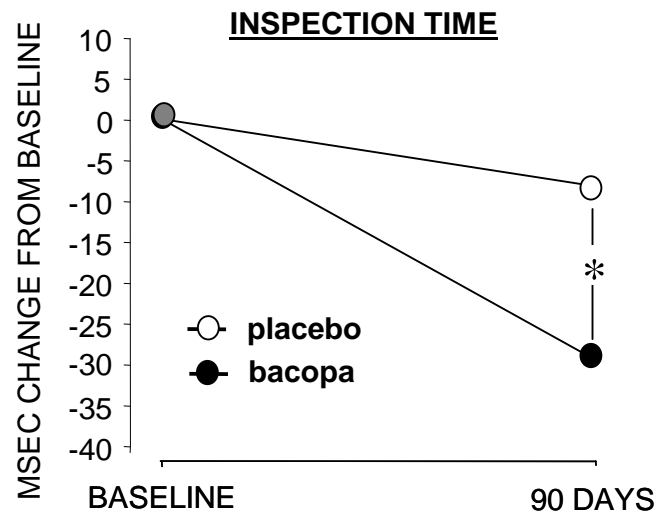


# *Auditory Verbal Learning Test*

List A Trial 1	List A Trial 2	List A Trial 3	List A Trial 4	List A Trial 5	List B Trial 6	List A Trial 7	List A Trial 8 *
DRUM	DRUM	DRUM	DRUM	DRUM	DESK		
CURTAIN	CURTAIN	CURTAIN	CURTAIN	CURTAIN	RANGER		
BELL	BELL	BELL	BELL	BELL	BIRD		
COFFEE	COFFEE	COFFEE	COFFEE	COFFEE	SHOE		
SCHOOL	SCHOOL	SCHOOL	SCHOOL	SCHOOL	STOVE		
PARENT	PARENT	PARENT	PARENT	PARENT	MOUNTAIN		
MOON	MOON	MOON	MOON	MOON	GLASSES		
GARDEN	GARDEN	GARDEN	GARDEN	GARDEN	TOWEL		
HAT	HAT	HAT	HAT	HAT	CLOUD		
FARMER	FARMER	FARMER	FARMER	FARMER	BOAT		
NOSE	NOSE	NOSE	NOSE	NOSE	LAMB		
TURKEY	TURKEY	TURKEY	TURKEY	TURKEY	GUN		
COLOUR	COLOUR	COLOUR	COLOUR	COLOUR	PENCIL		
HOUSE	HOUSE	HOUSE	HOUSE	HOUSE	CHURCH		
RIVER	RIVER	RIVER	RIVER	RIVER	FISH		

# Stough et al (2001) *Psychopharmacology*

- First study by our group ...



# Stough et al 2001

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- Results indicated improvement in information processing, memory consolidation and reduction in state anxiety after 90 days of Bacopa monniera administration (Stough *et al.*, 2001)

# Roodenrys et al (2002)

## *Neuropsychopharmacology*

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- Improvement in memory



# Calabrese et al (2008)

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- Used same methodology as Stough et al 2001
- Showed the same results in verbal learning and speed of processing

# Nathan, Stough et al (2004)

Human Psychopharmacology:  
Clinical & Experimental

- Combined Ginkgo and Bacopa
- No changes in cognitive functioning
- Not CDRI extract
- 1 month administration only
- Recent Indian rat study 2 weeks did not grow neurons

# Stough et al (2008)

- Double-blind placebo controlled design
- 81 healthy participants (52 females and 29 males) aged between 18 and 60 years were randomly allocated to either placebo or treatment group



# Method - *Procedure*

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- Baseline testing
  - 60 minute battery of cognitive tests from the Computerised Drug Research (CDR)
- Two tablets consumed daily for 90 days
- Participants retested on same battery of cognitive tests (alternate form) after 90 days
- 300Mg 55% standardised bacosides

# The CDR System

In use in worldwide clinical trials since 1984-900 trials



# **CDR DOMAINS & TESTS**

## **ATTENTION, CONCENTRATION, VIGILANCE**

Simple Reaction Time

Choice Reaction Time

Digit Vigilance

## **WORKING(SHORT-TERM ) MEMORY**

Articulatory Loop

Spatial Working Memory

## **EPISODIC (LONG-TERM) MEMORY**

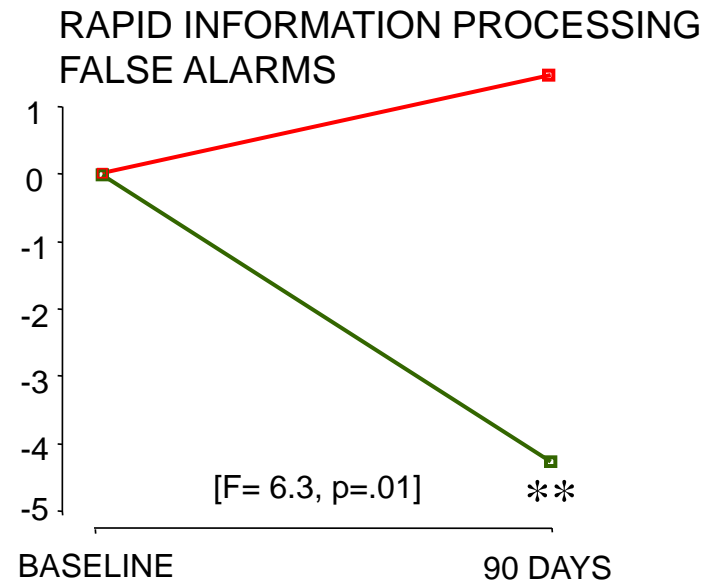
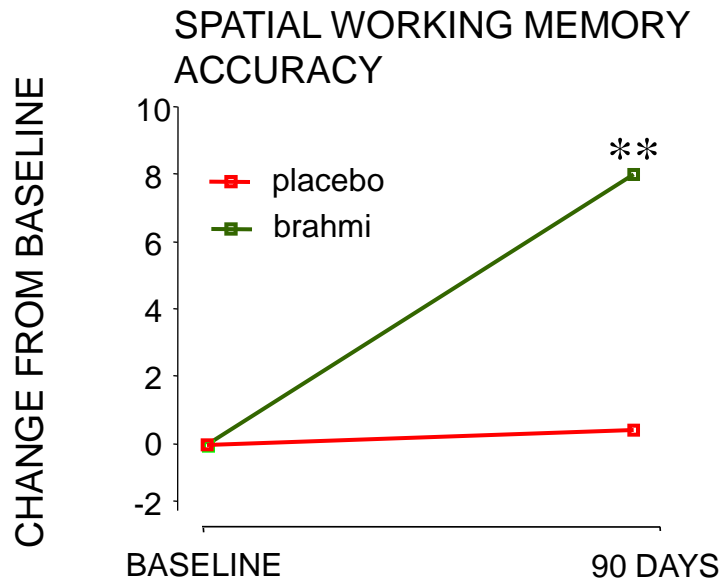
Immediate Word Recall

Delayed Word Recall

Word Recognition

Picture Recognition

# Effects of 90 day supplementation with *Bacopa monniera* (Stough et al, 2008)



# Results

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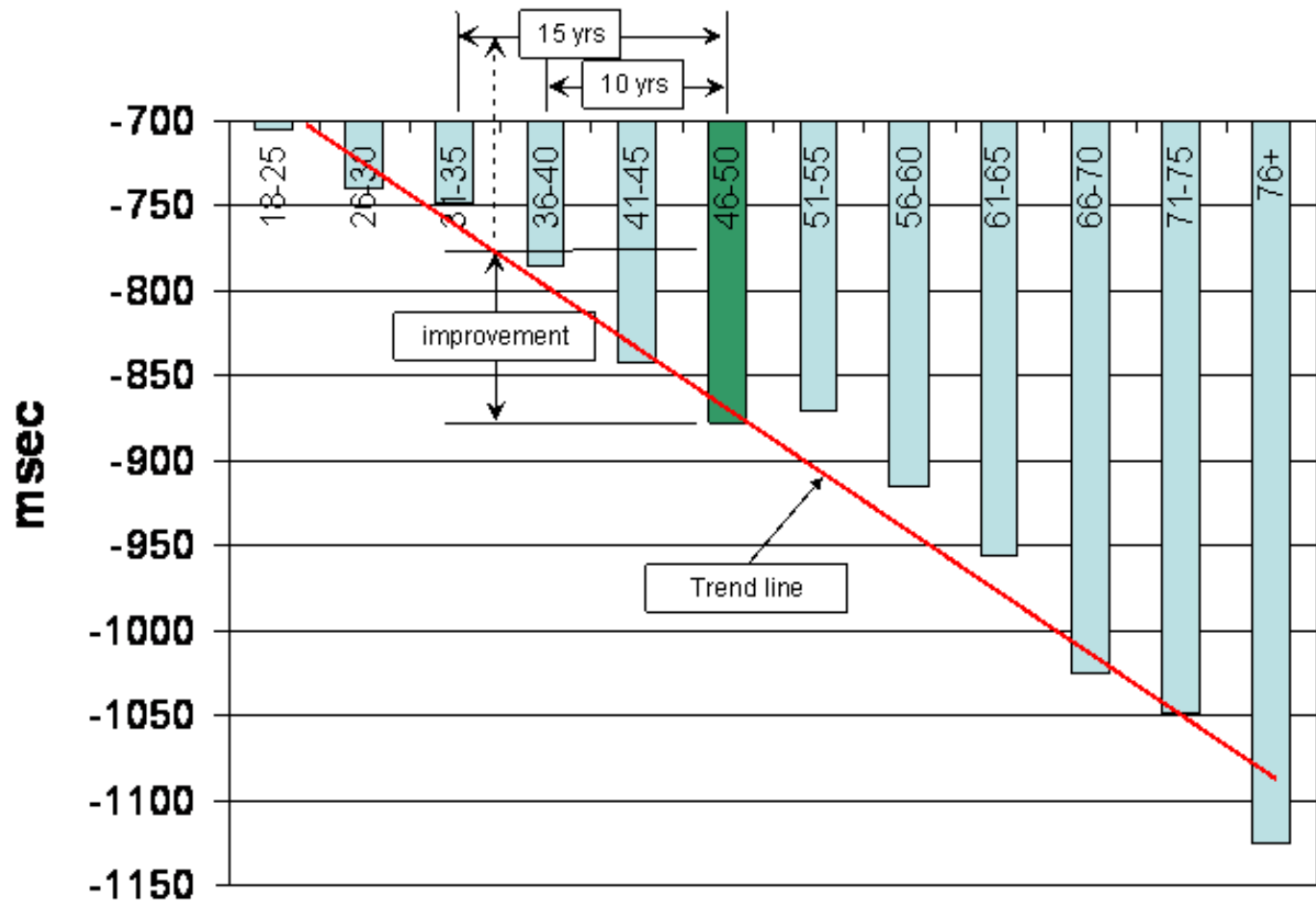
- Bacopa monniera significantly improved ( $p < .05$ ):
  - Accuracy in the logical memory task
  - Simple reaction time
  - Rapid visual information false alarms
  - Spatial working memory accuracy
- No significant improvements in any variables that could be attributed to the placebo treatment

# Clinical relevance...

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- Improvements in Memory consolidation and retrieval
- Improvements in cognitive speed
- THE two factors underpinning cognitive ageing

# Improving Cognitive Ageing



# Conclusions-CDRI08

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Treatment duration? 90 days but what about longer....

In our first study there were no changes after 1 and 2 months, but some changes after 3 months....

Implications for the **future**...but now to the **present**...

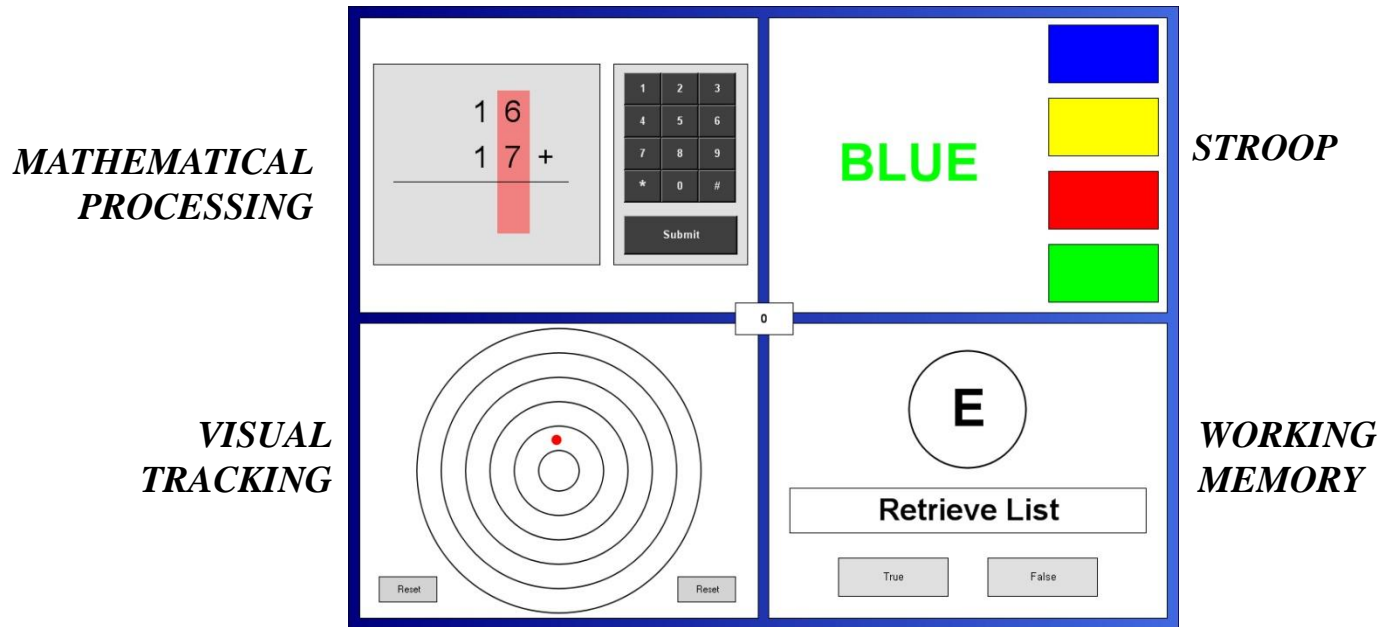
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# Recent acute dose- ranging study

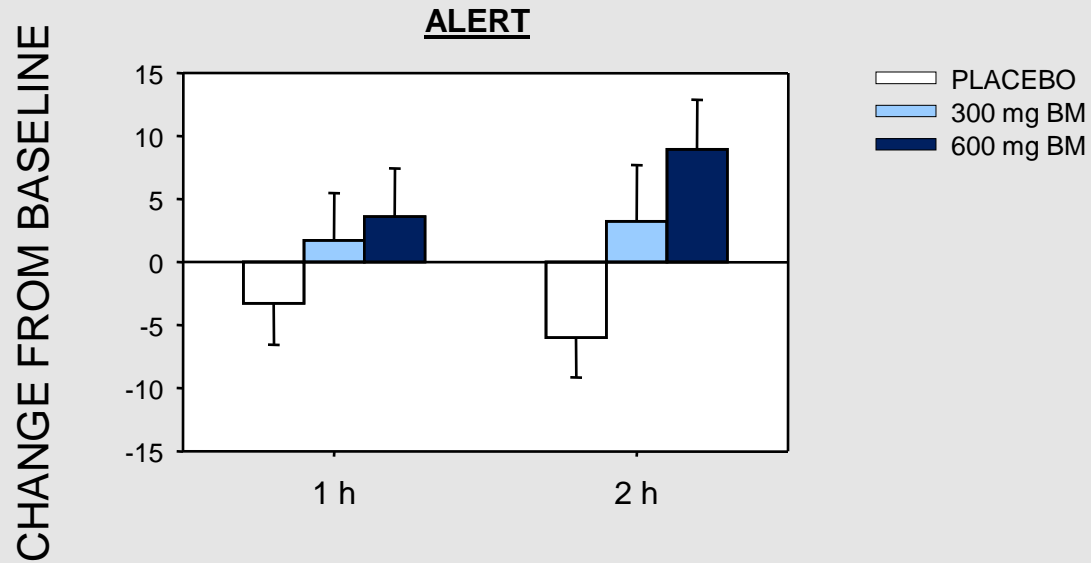


# Acute effects of bacopa: preliminary findings

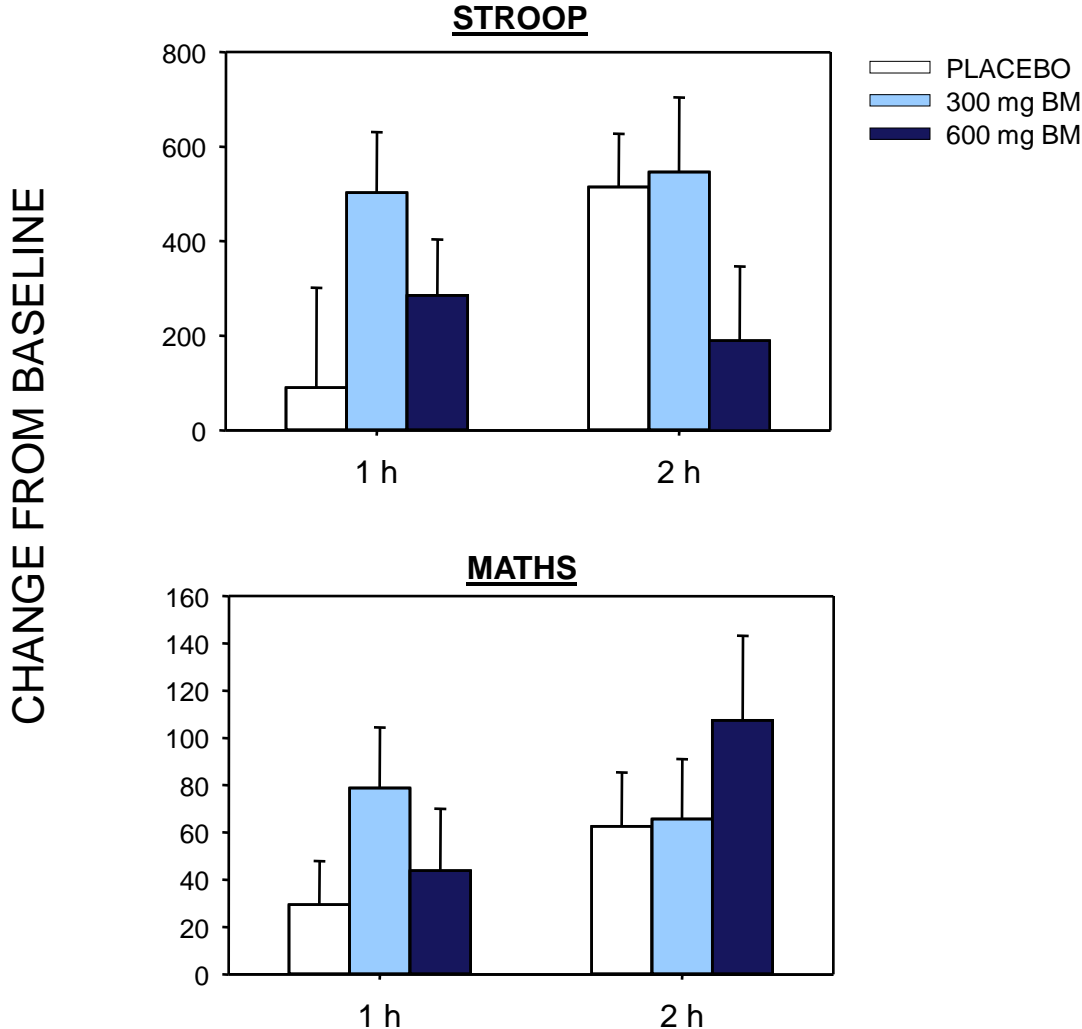


- multi-tasking in twenty min blocks (N = 17)
- baseline => 1 hr, 2 hr
- placebo, 300 mg BM, 600 mg BM
- assess
  - performance: maths, stroop, working memory, tracking
  - mood: alert, calm, content, anxiety, fatigue

# Acute effects of bacopa: mood effects



# Acute effects of bacopa: performance



# Acute data

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- Showing that even single high dose 600mg can improve:
  - Attention
  - Information processing
  - Next week add additional N=20

# CDRI08 3T fMRI (MEG 2012)

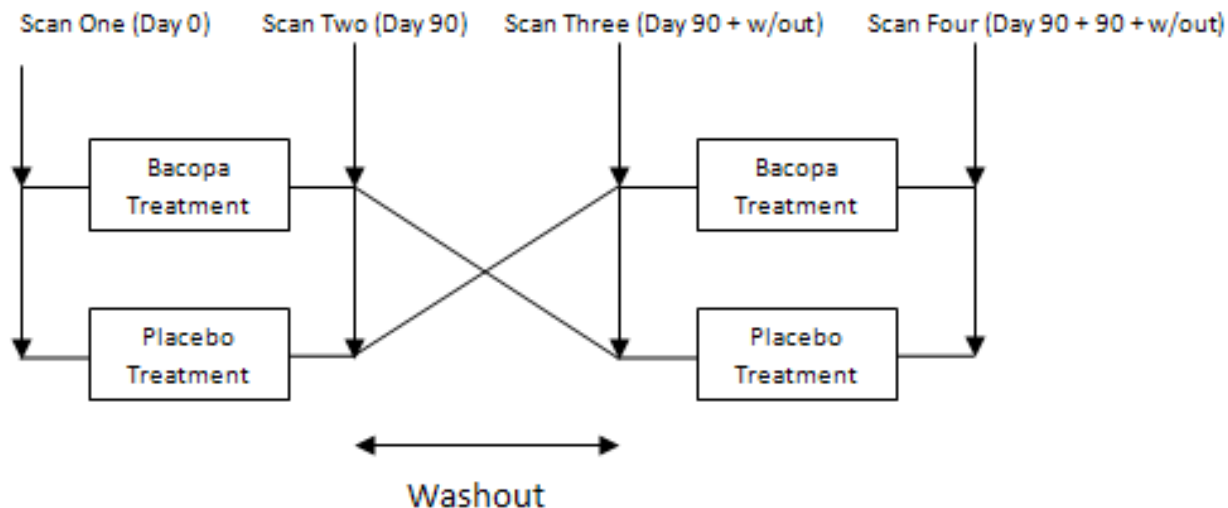
Currently in data collection stage (Chris Neale)

- Placebo controlled crossover design (10 month)
- 20 participants – 3 month intervention of CDRI08 or placebo separated by 4 month washout period.



# Bacopa fMRI Project

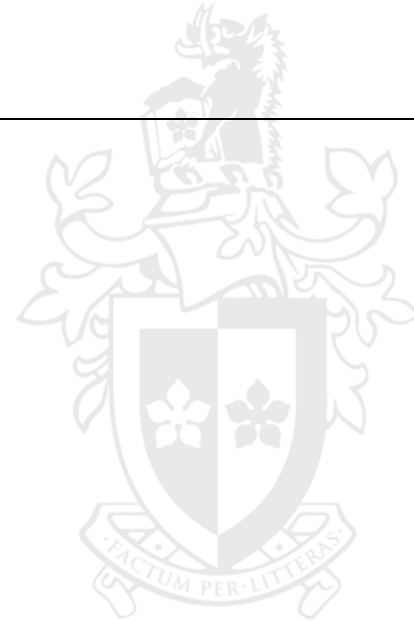
- Double blind, placebo controlled crossover trial.
- 90 day intervention of both placebo and Bacopa separated by a 120 day washout.
- MRI scans bookend each 90 day intervention
- Two tasks; RVIP and IT



# The Future

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- Next few years.....





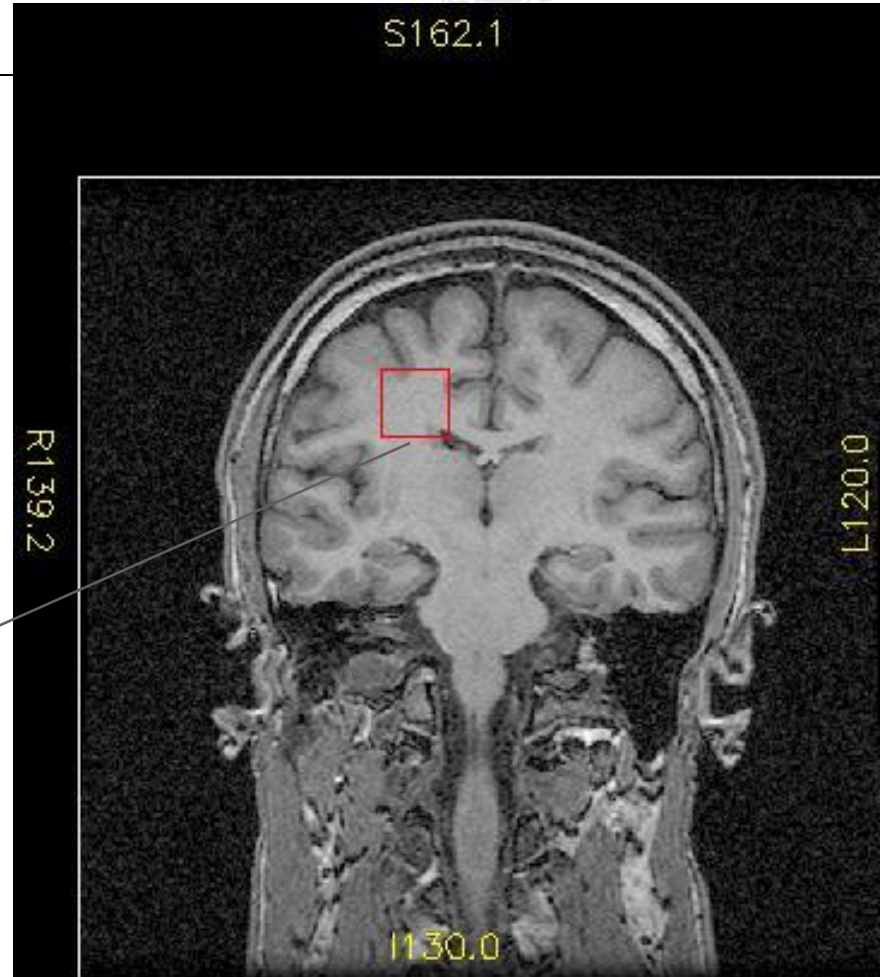
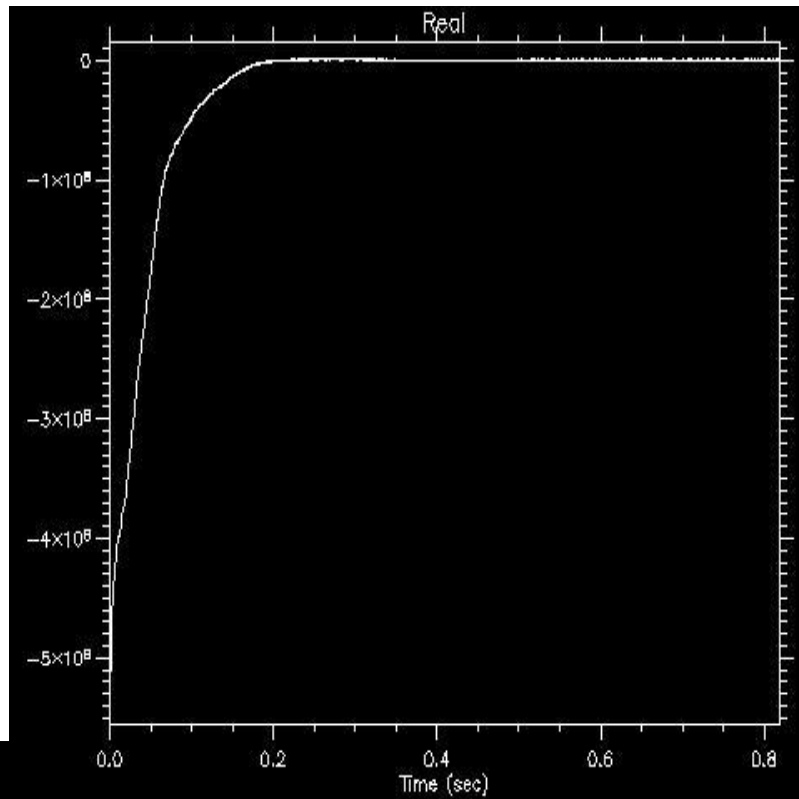
# **Australian Government**

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## **Australian Research Council**

- N=450 70+years participants (RCT)
- 12 month administration
- Cognitive and mood testing every 3 months
- Neuroimaging
- Biochemistry
- Genetics

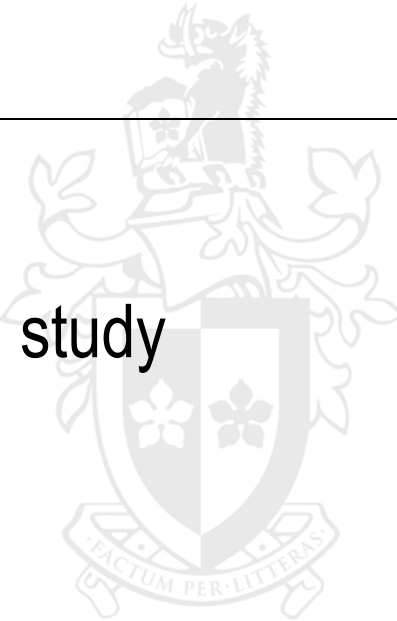
# Frontal left gyrus (MRS)



# On our radar...

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- 5 Year neuro-protective CDRI08 study
- Track 70+ year olds for 5 years
- Examine conversion to MCI or AD



# CDRI08 and Children

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- Kalra et al (2002)
- Sharma et al (1987)
- Agrawal et al (1993)
- Negi et al (2000)
- Abhang (1993)
- James Kean (PhD)



# CDRI08 and Children

- Has been used traditionally to improve memory, cognition, concentration in children
- Pharmaceutical alternatives increase dopamine or speed up the brain and increase memory processes
- CDRI08 may work in a different brain mechanism (Ach) but produce the same result