





Older Australian Twins Study (OATS)




Ageing Well Ageing Productively
AAG Nov 22, 2007



Overview

- Twin pairs > 65, MZ, DZ + sibs (NSW, Vic, Qld)
- Aims to determine the relative contribution of environmental and genetic factors to brain ageing and cognition
- Comprehensive & longitudinal assessment in multiple domains:
 - Neuropsychiatric
 - Neuropsychological
 - Lifestyle, physical health
 - Brain imaging
 - Bloods: biochemical, endocrine, inflammatory and genetics assessments


3



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4



Background

- Near-perfect natural experiment
- Other twin studies of the elderly
 - Swedish Adoption/Twin Study of Ageing (SATSA) (Nancy Pedersen)
 - Danish Twin Study (Christensen)
 - NAS-NRC Twin Registry (de Carli et al, 1999)
 - Smaller studies (Karlinsky et al, 1992; Barak, 2003)

5



Why twins?

Unique Environment (E) Shared Environment (C) Additive Genetic (A) Dominant Genetic (D)

Phenotype

$$P = eE + aA + cC + dD$$

6

Genetic Epidemiology

- Establishing the role of genes and environment in variation in disease and complex traits
- Finding those genes

7

Designs to disentangle G + E

Resemblance between relatives caused by:

- shared Genes (G = A + D)
- environment Common to family members (C)

Differences between relatives caused by:

- nonshared Genes
- Unique environment (U or E)

8

Designs to disentangle G + E

- Family studies – G + C confounded
- MZ twins alone – G + C confounded
- MZ twins reared apart – rare, atypical, selective placement ?
- Adoptions – increasingly rare, atypical, selective placement ?
- MZ and DZ twins reared together
- Extended twin design

9

Complex Trait Model

The diagram illustrates the Complex Trait Model. At the center is a grey circle labeled 'Disease Phenotype'. To its left is an orange circle labeled 'Marker', connected by a double-headed arrow labeled 'Linkage Association'. Above the 'Disease Phenotype' are two orange circles: 'Gene¹' and 'Gene²'. 'Gene¹' is connected to 'Marker' by a double-headed arrow labeled 'Linkage disequilibrium'. 'Gene¹' is connected to 'Disease Phenotype' by an arrow labeled 'Mode of inheritance'. 'Gene²' is also connected to 'Disease Phenotype' by an arrow. Below 'Disease Phenotype' are three teal circles: 'Individual environment', 'Common environment', and 'Polygenic background', each with an arrow pointing towards the 'Disease Phenotype'. 'Gene³' is another orange circle to the right, also with an arrow pointing towards the 'Disease Phenotype'.

10

What have twins told us so far about ageing and dementia?

- Twins studies estimate that the concordance of AD in MZ twins is 80%, suggesting high heritability
- NHLBI study:
 - brain size, CSF and WMH volumes strongly heritable
 - hippocampus appears to be more influenced by environmental factors
- In late life, heritability of cognitive ability decreases and environmental factors become more important

11

Heritability of WMHs

The graph plots Heritability (y-axis, 0 to 1) against Age Group (x-axis, 40, 50, 60, 70). Three lines represent different groups: 'All' (solid line with squares), 'Females' (dashed line with circles), and 'Males' (dotted line with triangles). Heritability is highest at age 40 and generally decreases as age increases, particularly after age 60.

Heritability of WMHs in the Framingham Study (Atwood et al, 2004)

Women	0.78
Men	0.52
All	0.55

12

Objectives

Short-term

1. To establish a well-characterised cohort of elderly MZ-DZ twins and their siblings for longitudinal study
2. To discover new genes related to healthy ageing and neurodegenerative disorders
3. To determine G and E factors and GxE and rGE which promote 'healthy brain ageing'
4. To determine G and E factors and GxE and rGE which trigger, modify or protect against neurodegenerative disease (cognitive and motor) in the elderly
5. To determine factors influence burden of disease and health-seeking behaviour in the elderly

13

Objectives –cont'd

Medium-term

To determine G and E factors and GxE and rGE in relation to decline in cognition and changes in brain morphology

Long-term

To link into an existing brain donor program for definitive tissue diagnosis and molecular studies to consolidate the findings and provide new insights into pathophysiology

14

Strengths

- Collaboration
- Multiple phenotypes
- Strong genetics, proteomics, biochemistry, environmental data
- Cutting edge neuroimaging
- Detailed cognitive assessment

15

Collaborations

Metabolic & Inflammatory Markers

Lesley Campbell, Katherine Samaras- Garvan
Bernhard Baune- James Cook

Genetics of Atrial Fibrillation

Diane Fatkin- Victor Chang

Linguistics

Alison Wray- Cardiff University

Falls

Stephen Lord- POWMRI

16

Phenotypes

Ageing related

- Successful ageing
- Physical health variables
- GM, WM, CSF and hippocampal volumes
- Cognitive function
- Personality dimensions

Disease related

- Mild cognitive impairment (MCI)
- Dementia/ Parkinson's Disease
- Cognitive decline
- Brain morphological change
- White matter hyperintensities

17

Specific Hypotheses

1. The extent and rate of progression of WMHs are highly heritable, with gender differences
2. Cerebrovascular risk factors (hypertension, diabetes, smoking) interact with genetic factors (e.g., Apo E4 and novel genes) in their association with WMHs
3. The heritability of cognitive functions (episodic memory, working memory, frontal-executive function, information processing speed) decreases with increasing age
4. Mental activity (e.g., brain reserve) interacts with genetic factors (e.g., Apo E4) in its association with 'successful ageing' and MCI

18

Specific Hypotheses – cont'd

5. Nutritional factors (e.g., calorie intake, antioxidant intake, plasma antioxidant measures, folic acid intake) account for a significant proportion of cognitive and motor discordance in MZ twins
6. Personality dimensions (novelty seeking, harm avoidance, reward dependence, and persistence) continue to have high heritability in old age
7. Phenotypic discordance in elderly MZ twins is related to global and locus-specific differences in DNA methylation

19

Research Plan

Sample

- 150 pairs each of MZ and DZ, and 1 or 2 sibs (Total n=1000)
- >65 years

Exclusion

- Life-threatening illness
- Inadequate English
- Acute psychosis

20

Promotion

- UNSW Media Release: TV; Radio interviews
- Advertising: SMH; Local Papers
- ATR

21

Assessment

- Clinical
- Neuropsychological
- Informant interview
- Nutrition
- Physical & mental activities
- Successful ageing questionnaire
- Blood collection
- Medical records
- MRI and other imaging
- Resource utilisation
- Brain collection

22

Protocol - Participants

Year 1

- Telephone interview
- Stage 1 - Questionnaires
- Stage 2 – Face-to-face assessment, MRI & blood collection/analysis
- Stage 3 – Questionnaires

Yearly

- Telephone interview

Year 2 & 4

- Face-to-face assessment, MRI & blood collection/analysis

23

Participants – Interview Admin Assistant

- Access database
 - Demographics
 - Work
 - Education
 - Memory (general)
 - Informant details
- Arrange face-to-face assessment
- Mail Stage 1 questionnaires, confirmation letter, Information Statement and Consent forms, Medicare Consent

24

Participants – Questionnaires

Stage 1: completed by participants in their own time

- Contact person
- Medical history
- Current medications
- Family history
- Questions about being a Twin
- K-10
- Successful Ageing Questionnaire
- Memory Screening Questionnaire
- Geriatric Depression Scale (GDS)
- Positive and Negative Affect Schedule (PANAS)

25

Participants – Questionnaires

Stage 1 : Variables

- Medical history
 - Stroke/TIA/heart problems
 - High BP/ high cholesterol/ Diabetes
 - other heart/blood vessel problems
 - Other serious illnesses
 - Thyroid problems
 - Fits
 - CNS infections
 - Smoking
 - Emotional/nerves
- Medications (incl OTC)

26

Participants – Questionnaires

Stage 1 : Variables – cont'd

- Family history
 - Parents' age of death
 - Cause of death
 - History of dementia
 - Memory loss
 - Stroke/TIA
 - Huntington's disease or other neurological
 - Psychiatric illnesses
 - Other

27

Participants – Questionnaires

Stage 1 : Variables – cont'd

- Questions about being a Twin
 - Birth order
 - Medical information
 - Lifestyle
 - Contact with Twin

28

Participants – Questionnaires

Stage 1 : Variables – cont'd

	Anxiety	Depression	Moods	Memory	Lifestyle/ activities	Life Satisfaction
K-10	✓	✓	✓	✓	✓	✓
Successful Ageing			✓	✓	✓	✓
Memory Screening				✓		
PANAS			✓			
GDS		✓	✓			

29


Participants - Face to Face Ax

Stage 2: by research psychologist

Collection of:

- Main consent form - consent to each part:
 - Face to face assessment
 - Bloods: collection option
 - MRI: best days; safety questionnaire
- Medicare consent form
- Completed questionnaires (from Stage 1 mail-out)

30




Participants - Face to Face Ax Stage 2: cont

Details recorded in the Access database (on laptop)

- Demographics
- Language/country of birth
- Education
- Work
- GP details

31




Participants - Face to Face Ax Stage 2: cont

Medical history

- Stroke/TIA/heart problems
- High BP/ high cholesterol/ Diabetes
- Head injury/disease that affects the brain
- Migraines/chronic lung disease/ arthritis/ thyroid/ autoimmune, etc
- Cancer/Leukemia
- Alcohol/smoking
- Mental health
- Vision/hearing
- Weight/height
- Exposure to pesticides
- Driving
- Sleep
- Dentist/teeth


32



Participants - Face to Face Ax Stage 2: cont

- Current medications
- Mini-Mental State Exam (MMSE)
- GP-Cog

33




Participants - Face to Face Ax Stage 2: cont

- Traditional neuropsychological assessment & SENSUS

Cognitive domains assessed:

- Concentration/attention
- Premorbid intelligence
- Verbal memory
- Visual memory
- Frontal/executive
- Confrontation naming
- Visuo-spatial/ constructional
- Psychomotor/processing speed
- Fine motor speed
- Reaction time


34



Participants - Face to Face Ax Stage 2: cont

- Medical examination
 - BP (2 sitting, 1 standing)
 - Height/weight
 - Hip/waist
 - Lateral stability
 - Rigidity
 - Sit to Stand Test
 - 6m walk - posture & gait
 - Motor assessment
 - Visual acuity
- Motor assessment:
 - body brady/hypokinesia
 - speech
 - facial expression
 - tremor at rest
 - action or postural tremor of hands

35



Participants - Face to Face Ax Stage 2: cont

- B-SIT (Brief Smell Identification Test)
- Goldberg Anxiety Scale
- Major Service Utilisation
 - Emotions/nerves
 - Memory/thinking
- CDR
- Spirometry

36

Participants - Face to Face Ax Stage 2: cont

- Modified Structured Clinical Interview DSM-IV (SCID)
 - Major Depressive Episode (current/ever)
 - Manic/Hypomanic Episode
 - Dysthymic Disorder (past 2 years)
 - Panic Disorder (with agoraphobia)
 - Generalised Anxiety Disorder
 - PTSD
 - Social and Specific Phobia

37

Participants - Face to Face Ax Stage 2: cont

- Screening Q's for Psychotic Disorders
- Personality Disorder Screen
- Sibling demographics/letter of invitation
- Stage 3 Questionnaires given to participant

38

Bloods: Logistics

- Logistics
- Study site
- Remote collections
- Separation
- Storage
- Processing

4.5 ml Li Hep for immediate analysis & participant feedback
Cholesterol, TGs, LDL, Fasting Glu, Creatinine, eGFR, Urate, CRP

9ml Serum
2ml x 2 serum for endocrine, inflammatory & metabolic markers

9ml Li Heparin
2ml plasma vitamins, 1ml plasma anticholinergic assay, 1ml plasma allantoin, inflammatory & metabolic markers

9ml EDTA
2ml EDTA plasma, 1ml EDTA Plasma, 1ml EDTA Plasma antioxidants
Remaining packed cells to POWMRI for buffy coat

9ml EDTA
Cell lines

39

MRI

Protocol: 45 mins

- T1 3D x 2
- T2 FLAIR
- 32 Direction DTI x 2
- Single voxel posterior cingulate MRS

40

3D T1 weighted (structural MRI)

To measure structures, both shapes and volumes, e.g.,

- cortical thickness
- total intracranial volume
- GM/WM/CSF volumes
- volumes of various structures such as hippocampus etc
- cortical thickness of structures such as cingulate etc

41

3D T1 weighted (structural MRI) – cont'd

42

Twin 1 Twin 2

Female
66 years
MZ

43

Twin 1 Twin 2

Male
77yrs
DZ
hypertension &
hypercholesterolemia

44

FLAIR

White matter hyperintensities (WMHs)

45

DTI 32 – directional

(b=800) – cont'd

- T2-weighted MRI
- ACD map (apparent diffusion coefficient)
- FA map (fractional anisotropy)
- Fibre tracking

Software:
FSL, CATNAP etc.

46

1H single-voxel MRS

(posterior cingulate only)

To measure

- brain chemistry such as NAA (N-acetyl aspartate)
- Cho (choline)
- Cr (creatine)
- ml (myo-inositol)

Software:
MRUI

47

1H single-voxel MRS

(posterior cingulate only) – cont'd

48

Participants – Questionnaires

Stage 3: completed by participants in their own time

- Significant Life Events Questionnaire
- Social Networks Questionnaire
- Satisfaction with Life Scale (SWLS)
- Assessment of Quality of Life (AQoL)
- World Health Organisation Disability Assessment Schedule – II (WHODAS-II)
- Life Experience Questionnaire
- Dietary Questionnaire
- NEO- FFI

49

Participants – Questionnaires

Stage 3: Variables

	QoL	Stress/ Disability	Lifestyle/ activities	Life Satisfaction	Personality
Significant Life Events		✓			
Social Networks			✓		
SWLS				✓	
AQoL	✓				
WHODAS-II		✓			
Life Experience			✓		
Diet			✓	✓	
NEO-FFI					✓

50

Informant – Questionnaires

mailed before informant telephone interview

- Information Statement & Consent form
- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) → Cognitive decline
- CICAQ → Cognitive decline
- Sleep Questionnaire → snoring/excessive day somnol/sleep apnoea + Rx/acting out in dreams

51

Informant – Interview

conducted by research psychologist

- GP-Cog → Cognitive decline
- Clinical Dementia Rating (CDR) → Cognitive decline
- Activities of Daily Life 1 (ADLs 1) → Everyday activities
- Activities of Daily Life 2 (ADLs 2) → Physical self maintenance
- NPI → delusions/hallucinations/aggression/depression/anxiety/elation/apathy/disinhibition/irritability/aberrant motor behaviour/sleep/appetite

52

Assessment Stats: Individuals

	NSW	QLD
• RA Interviews - completed	94	0
• RA Interviews - booked	12	0
• AA interviews - completed	104	0
• Interested (ATR, promo)	47	66
• Bloods	79	0
• MRIs	60	0
• Suspended	7	0
• Withdrawn	7	0

53

as of 26 October 2007

Issues

- Protocol
- Participant numbers
- Participant retention
- Sibling recruitment
- Informant recruitment
- MRI protocol
- Bloods: logistics

54

