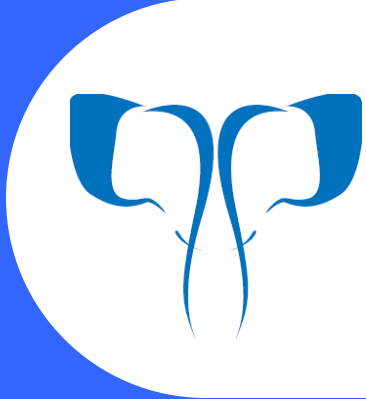


# Twins, Genetics and the Ageing Brain

Julian Trollor





# **Disentangling Genetic & Environmental Influences on Ageing**



## Disentangling Genetic & Environmental Influences on Ageing

- Establishing the role of genes and environment in variation in disease and complex traits
- Finding those genes
- Finding modifiable environmental or medical factors
- Intervention to reduce risk



## Disentangling Genetic & Environmental Influences on Ageing

### **Resemblance between relatives caused by:**

- shared Genes
- environment Common to family members

### **Differences between relatives caused by:**

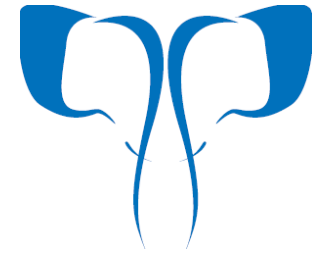
- nonshared Genes
- Unique environment



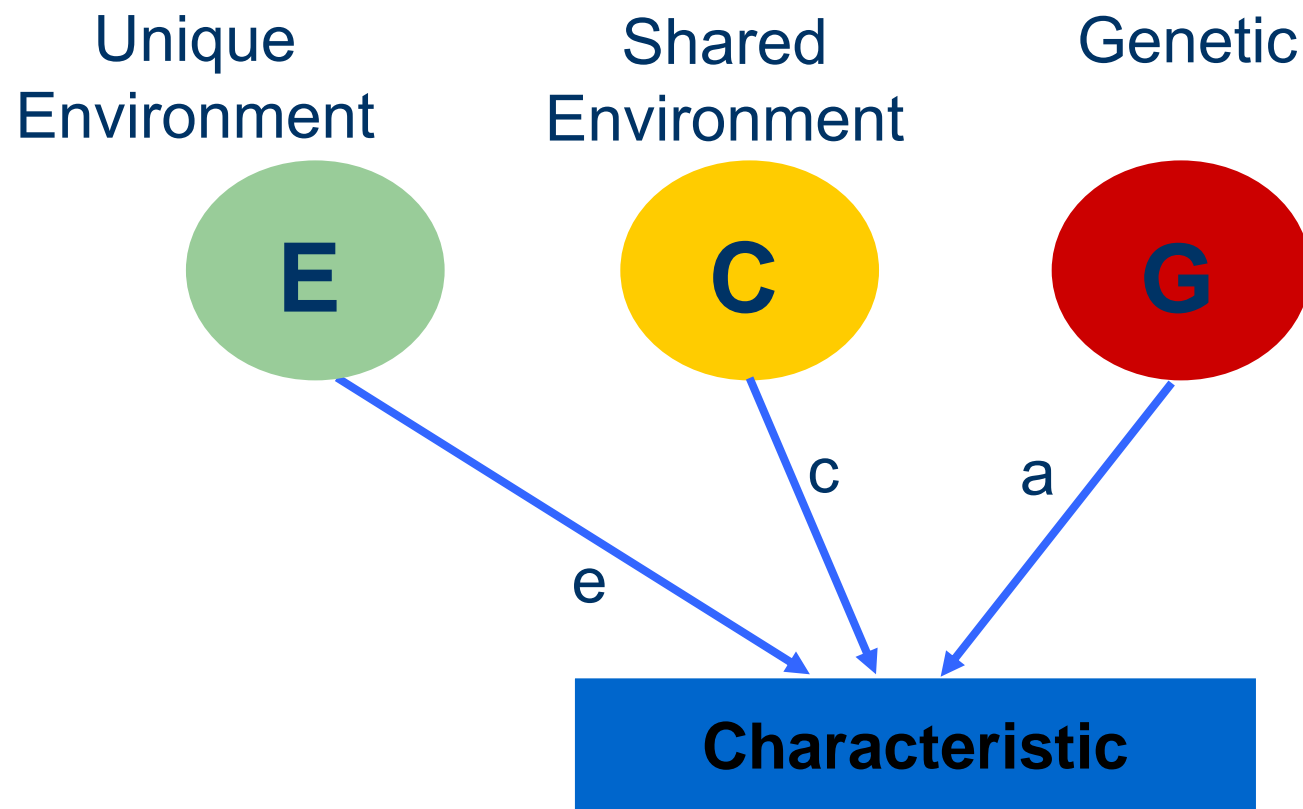
## Why Twins?

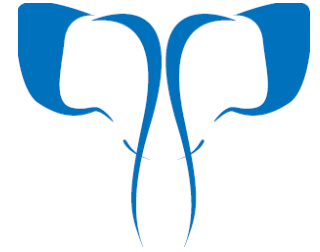
- Near-perfect natural experiment
- Identical (monozygotic) twins share the same DNA
- Non-identical (dizygotic) twins, like siblings, share about half of their DNA

*Allows investigation of genes, environment and how they interact*



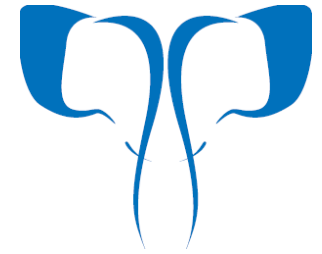
# Why twins?





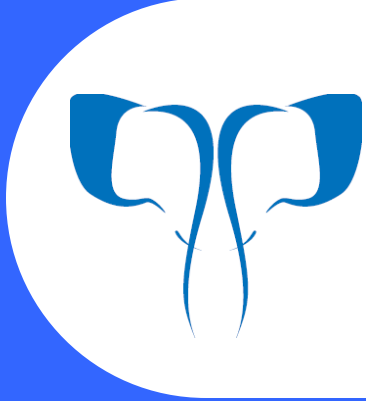
# What Questions Can Answered?

- Are there genes influencing this trait?
  - Heritability: the degree to which the variability in a particular characteristic is due to genetic factors
- Where are those genes?
- What are those genes?
- What are the effects of known genes?



# Twinning

- 2 major forms
  - **monozygotic** (from one fertilised egg and a single spermatozoa)
  - **dizygotic** (from two eggs fertilised by two different spermatozoa).



# **Genes and Dementia**



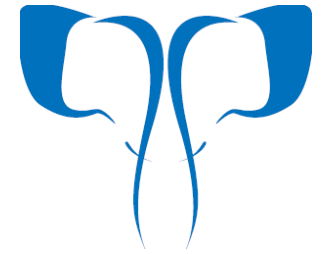
# Genetics of Alzheimer Disease

- mutations in 3 genes (chr 21, 14, 1) causative
- Variation in 1 gene (APOE) is a risk factor
- Only about 20% of the total genetic influence is currently explained



# APOE & Alzheimer Disease

- Gene pairs
- $\epsilon 2$ ,  $\epsilon 3$ ,  $\epsilon 4$
- $\epsilon 4$  x 1: increased risk 2-3x
- $\epsilon 4$  x 2: increased risk 5x
- About 20% of population have one or more  $\epsilon 4$



## APOE & Longevity

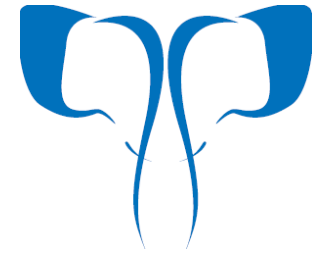
- $\epsilon 2$ : decreased ad & cardiovascular risk, increased longevity
- $\epsilon 3$ : neutral ad & cardiovascular risk, no effect on longevity
- $\epsilon 4$ : increased ad & cardiovascular risk, reduced longevity

Blacker & Lovestone 2006, J Ger Psych Neurol



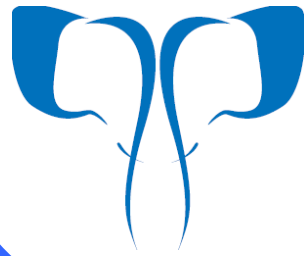
## Genetics of Frontotemporal Dementias

- 30-50% of cases are familial
  - A small proportion of those with familial FTD (10-30%) have an abnormality on chromosome 17
- Frontotemporal dementia associated with amyotrophic lateral sclerosis
  - Abnormal gene on chromosome 9



## Limitation of Current Knowledge

- We currently know enough to explain only about 20% of the total genetic contribution to causes of Alzheimer disease
  - ie 80% remains undiscovered!



# **Genes and Brain Structure & Function**



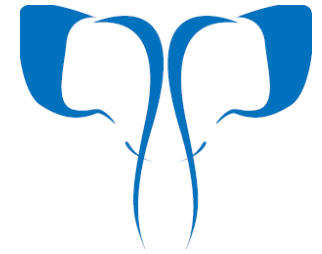
# Genes and Cognitive Function

- Genetic factors seem to be important for some cognitive functions in late life
  - High heritability of tests of higher level thought (80%)
  - Heritability decreases with advancing age



# Genes and Brain Structure

- In late life, genetic factors have strong influence over:
  - amount of brain shrinkage (atrophy) in some areas
  - Amount of abnormal white matter
  - Size of fluid filled spaces (CSF)



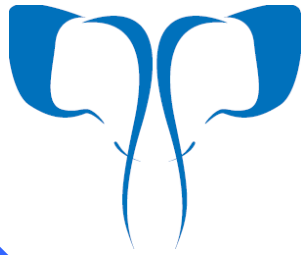
## Genes and Day to Day Functional Ability

- About 20% of the influence on day to day function appears to be determined by genetic factors



# Genes Modify Longevity and Physical Illness

- Stress Response Genes
- Proinflammatory Genes
- Genes that regulate glucose and insulin metabolism

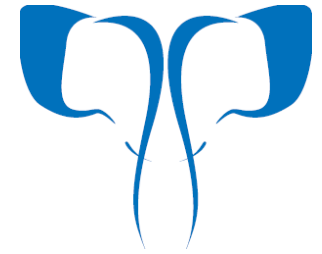


**Genes: Not the Be All and End All**



## Genes Interact with Other Factors

- Some genetic factors only influence outcome under particular conditions
  - APOE & hypertension in white matter hyperintensity volume
  - APOE & head injury in risk of AD



# Genes and Risk of Dementia

- Long established role of some genes in the dementias



# Genes and Risk of Dementia

- But:
  - Known genetic factors account for a small proportion of cases of common dementias



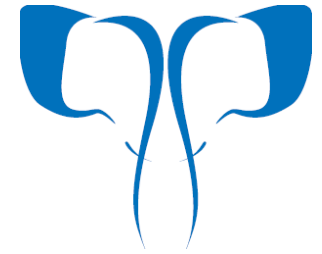
## Genes and Risk of Dementia

- Twin studies suggest that heritability of Alzheimer's disease is high. For example, in about 80% of identical twins, where 1 twin is affected, the other one is also



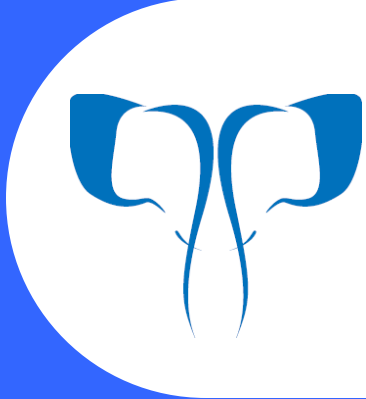
## BUT

- Identical twins can differ, with one being affected by dementia and the other not
- Or....may develop dementia at different times



## Suggesting

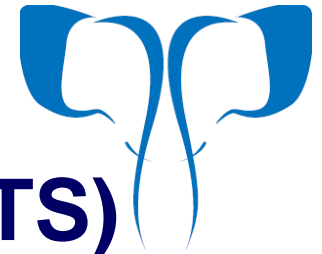
- Myriad other genes influence the development of Alzheimer's disease
- A role for other (environmental) effects in modifying the risk.



# Older Australian Twins Study (OATS)



# Older Australian Twins Study (OATS) Team



- UNSW
  - Perminder Sachdev
  - Julian Trollor
  - Henry Brodaty
  - Wei Wen
  - Teresa Lee
  - Tony Broe
- POWMRI
  - Peter Schofield
  - Glenda Halliday
- QIMR (Brisbane)
  - Margie Wright
  - Nick Martin
- NARI (Melbourne)
  - David Ames



## Older Australian Twins Study (OATS)

- Twin pairs > 65 years and siblings
- NSW, VIC, QLD
- Detailed initial assessments & follow-up
- Aims to determine the relative contribution of environmental and genetic factors to brain ageing and cognition

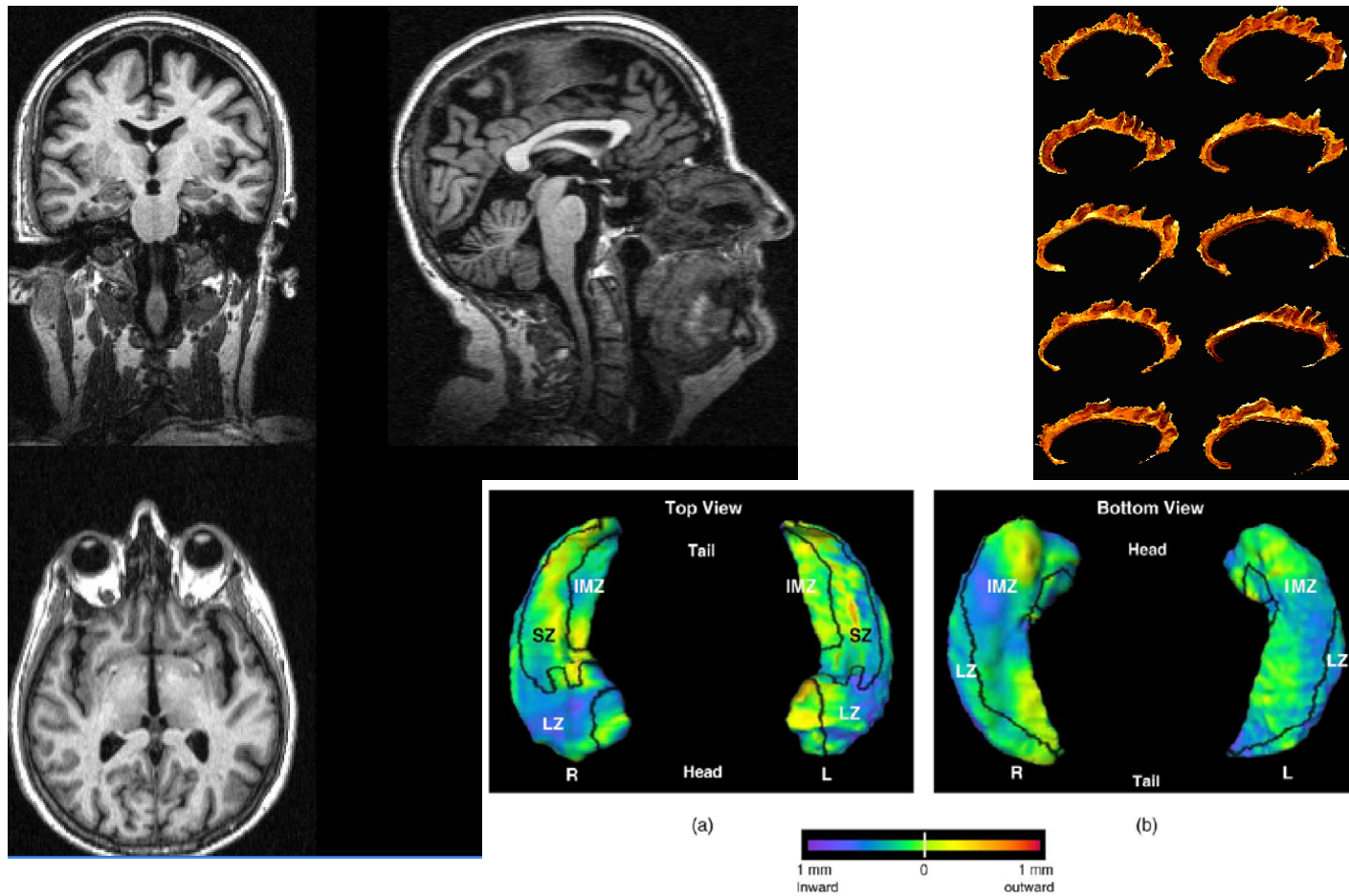


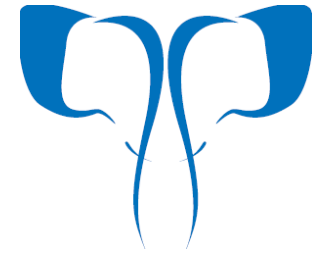
# Assessment

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

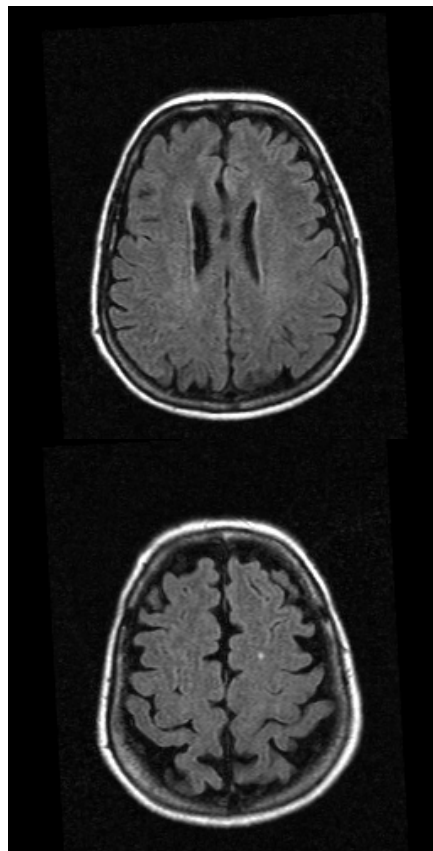


# 3D T1 weighted (structural MRI) – cont'd

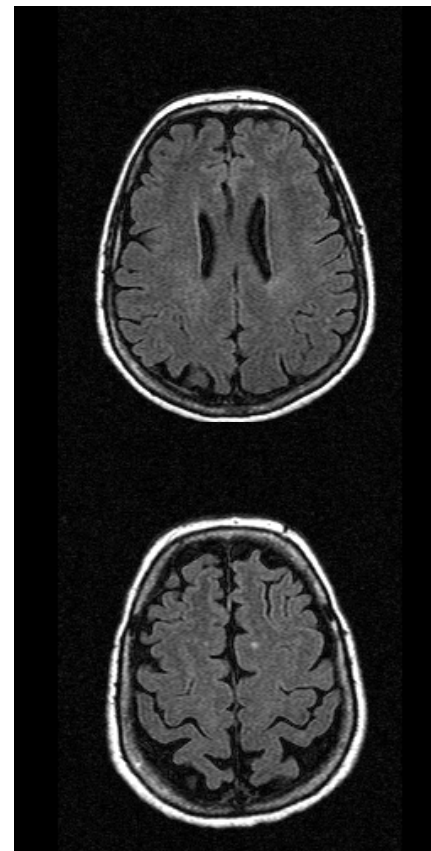




Twin 1



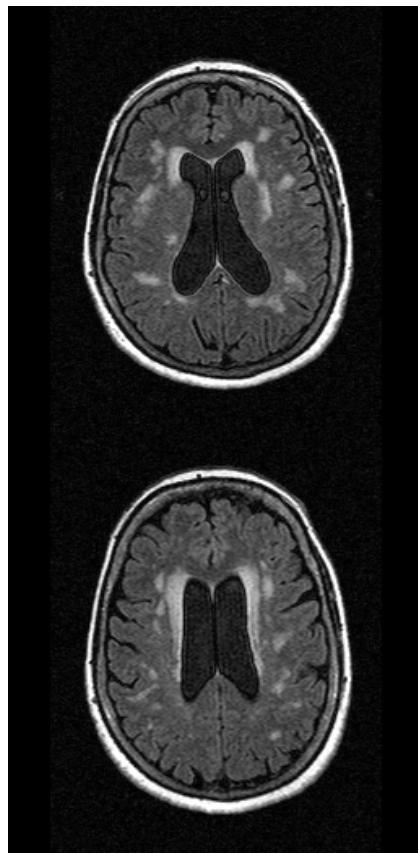
Twin 2



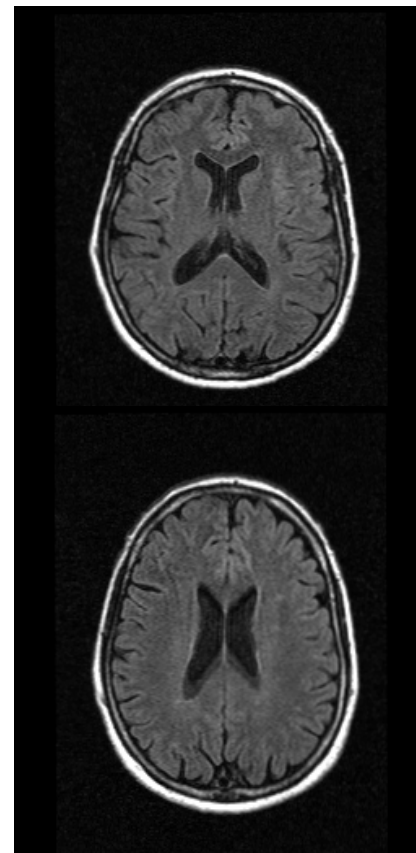
Female  
66 years  
MZ



Twin 1



Twin 2



Male  
77yrs  
DZ  
hypertension &  
hypercholesterolemia

