

# Down's syndrome, ageing and the risk of Alzheimer's disease

*Holland A.J., Ball S.L.,  
Huppert F.A.*



UNIVERSITY OF  
CAMBRIDGE



D O W N ' S  
S Y N D R O M E  
A S S O C I A T I O N



# Outline of talk

- **Background**
- **Life-expectancy**
- **Diagnosis, prevalence, and presentation of dementia in people with DS**
- **'Frontal-like' dementia**
- **Ageing**
- **Clinical implications and conclusions**

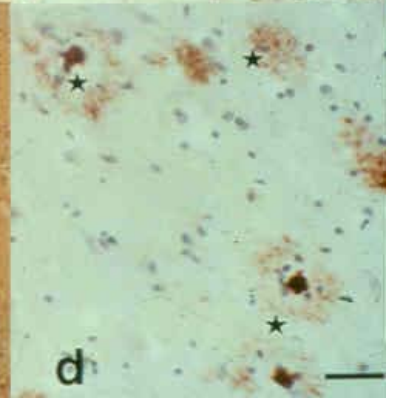
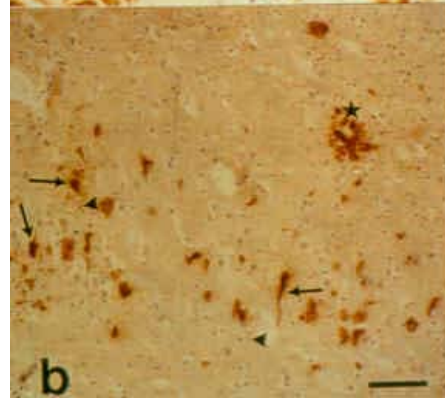
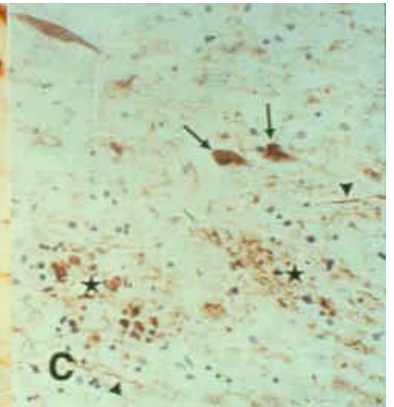
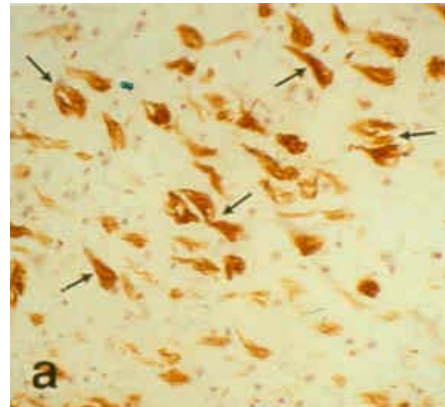
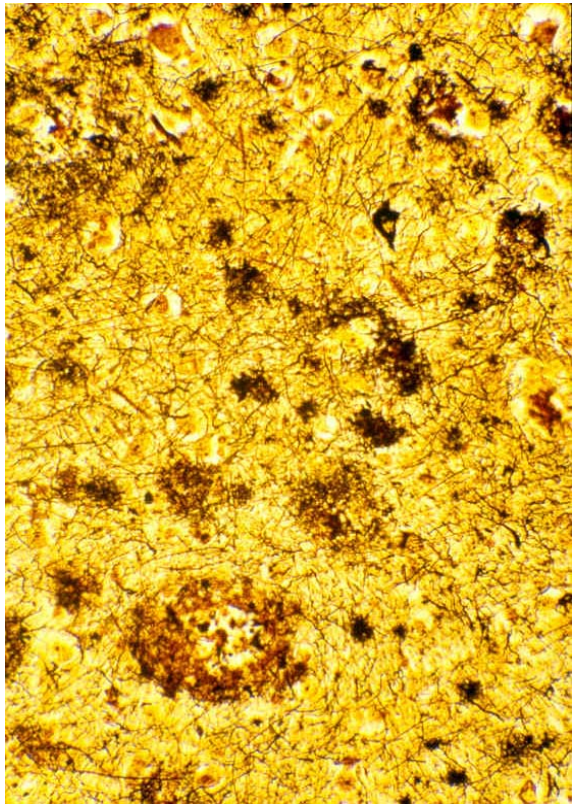
# Background

- **Neuropathological findings**
- **Anecdotal clinical observations**
- **Cross sectional studies**
- **Longitudinal studies**
- **Biological markers/mechanisms**
- **Treatment**

# Mean life expectancy (years)

	1901		2002	
	male	female	male	female
Gen. Pop	45	49	81	84
People with DS	9		55	

# Down syndrome: Neuropathological Hallmarks



# Down's syndrome and Alzheimer's disease

- People with DS have an increased risk of AD because of the extra copy of the APP gene (on chr 21) due to having trisomy 21
- Excess cerebral amyloid deposition leads to a chain of 'cerebral events' over time and to cerebral atrophy.

## Problems

- Not all people with trisomy 21 get AD
- Differences in ages of onset
- Does not explain decreased life expectancy?

## CAMDEX-DS Cambridge University Press, 2005

- Informant interview to identify presence or not of a deterioration in cognitive and functional abilities
- Structured assessment to identify possible causes for observed decline
- Cognitive assessment to identify specific problems and to track changes over time (CAMCOG-DS)
- Diagnostic criteria for dementia and other disorders
- Summary of advice if dementia present

Ball, S.L et al . (2004) The modified CAMDEX informant interview is a valid and reliable tool for use in the diagnosis of dementia in adults with Down's syndrome. *JIDR*, 48(6):611-620

# CAMDEX-DS Informant interview

## Memory

- Does he/she forget where he/she has left things?
- Does he/she forget the names of close relatives?
- Does he/she have difficulty remembering recent events?
- Does he/she have difficulty finding the way about the home?

## Prevalence of dementia in people with Down's syndrome (Holland et al, *Brit. J. Psych*, 1998; 172: 493-498)

	Age (years)				Total
	30-39 (n=29)	40-49 (n=29)	50-59 (n=15)	60+ (n=2)	
AD	1 (3%)	3 (10%)	6 (40%)	0	10 (7%)
Frontal -like	6 (21%)	3 (10%)	0	0	9 (12%)

## *Prevalence* (Lai and Williams, 1989, Arch. Neurol.46, 849)

Cohort: n=96, over 35 years of age

Overall prevalence rate of dementia 49/96 (50%)

Average age of onset 54.2 yrs

Average length of illness (n=23) 4.6 yrs

Age specific prevalence rates (n=53)

35 – 49 years 8%

50 – 59 years 55%

>60 years (n=8) 75%

## *DS Incidence study*

*Holland et al. JIDR, 2000: 44. 138-146.*

Reported changes:

- Personality/behaviour 30 years +
- Change in several domains 40 years +

Peak incidence of dementia

- Frontal-like 30s & 40s
- Alzheimer disease 50s

## *Frontal lobe hypothesis*

- Early 'undetected' cognitive decline leading to reduction in coping abilities
- Impairment of 'frontal lobe functions' due to small 'reserve capacity' of frontal lobes.

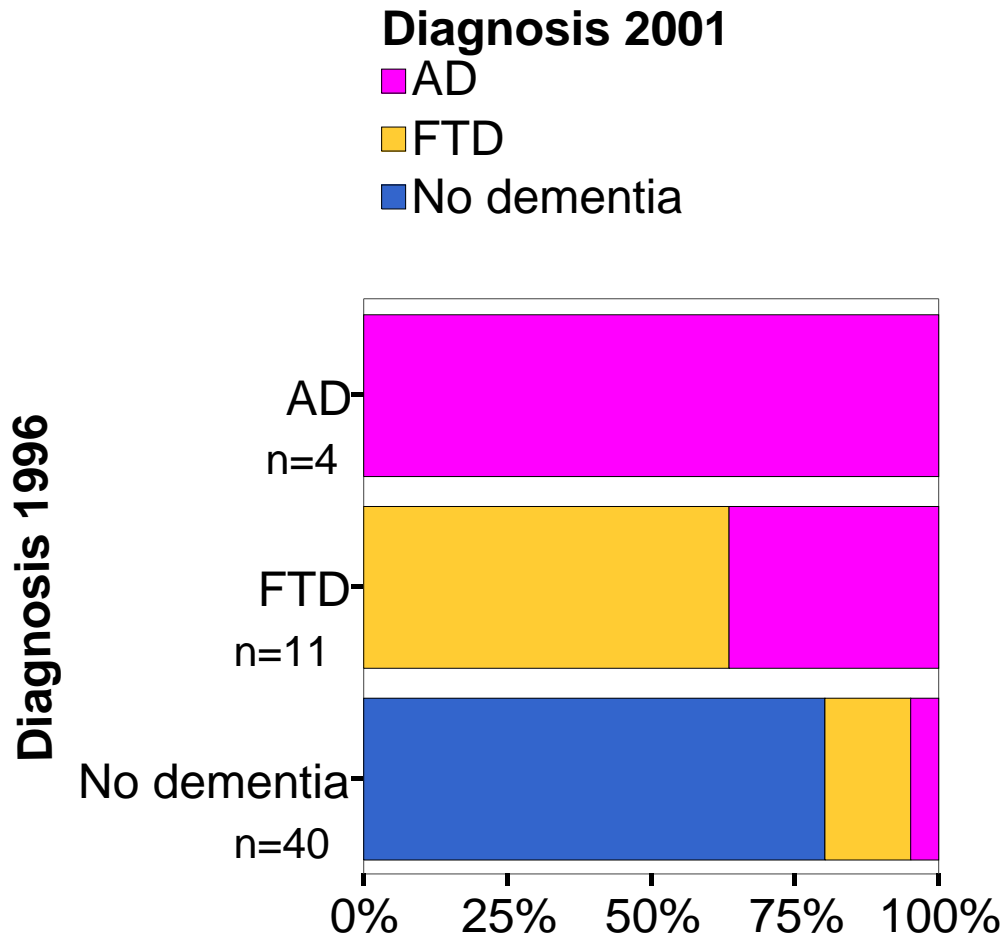
# What questions can we ask in order to test the frontal lobe hypothesis?

1. Do personality and behaviour changes mark an early stage in the development of AD in people with DS?
  - Longitudinal observation of progression in dementia diagnosis over time.
2. If so, are these changes associated with impaired performance on neuropsychological tasks measuring frontal lobe functioning (but not those measuring memory)?
  - Cross-sectional comparison of performance on tasks measuring executive function and memory, across diagnostic categories

# Progression in Diagnosis

- N = 55 (36 male) and main carers
- Total population of people with DS aged 30+ years on 01/07/1994 in Cambridgeshire health district
- Mean age at 1996 assessment 43 years (31-67)
- Modified CAMDEX informant interview conducted with each participant's main carer (1996 and 2001)
- Consensus diagnosis - blind to participants' previous diagnostic status, age, gender and neuropsychological test performance
- Diagnosis made using CAMDEX criteria for Alzheimer's Disease and Gregory and Hodges (1993) criteria for Frontal Type Dementia

# 1. Progression in Diagnosis: *Results*



36% of participants who met criteria for FTD in 1996 had developed AD by 2001 (vs. only 5% of those without FTD)

$p = 0.015$  (Fisher's exact)

Odds Ratio = 10.8  
(95% CI = 1.7 to 71.5)

# Cognitive Test Performance: *Hypotheses*

## 1. **FTD vs. Non FTD**

Participants with FTD will show:

- **impaired** performance on EF tasks
- **no difference** in performance on memory tasks

## 2. **AD vs. Non AD**

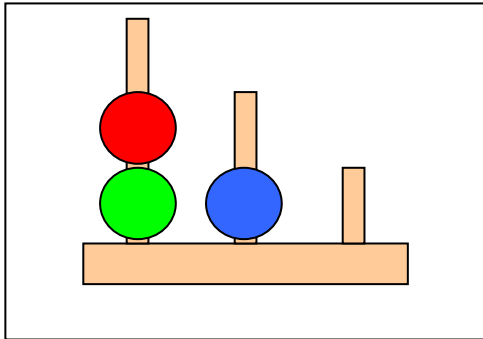
Participants with AD will show:

- **impaired** performance on EF tasks
- **impaired** performance on memory tasks

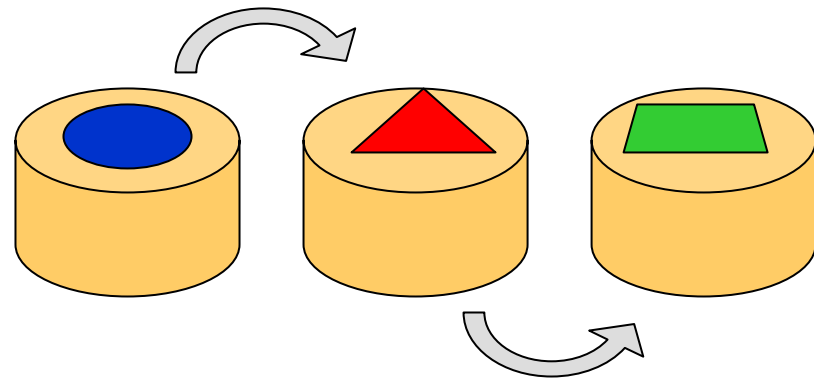
# **Cognitive Test Performance: *A set of EF tasks suitable for use with people with DS***

<b>Process</b>	<b>Task</b>
<b>Planning</b>	<b>Tower of London - shortened version</b>
<b>Attentional set shifting</b>	<b>WEIGL sorting test</b>
<b>Working memory</b>	<b>Scrambled Boxes</b>
<b>Inhibition of response</b>	<b>Cats and Dogs</b>
<b>Sequencing</b>	<b>Bead Threading Task</b>
<b>Reversal learning</b>	<b>Spatial Reversal Task</b>
<b>Verbal fluency</b>	<b>Category Fluency for Animals</b>

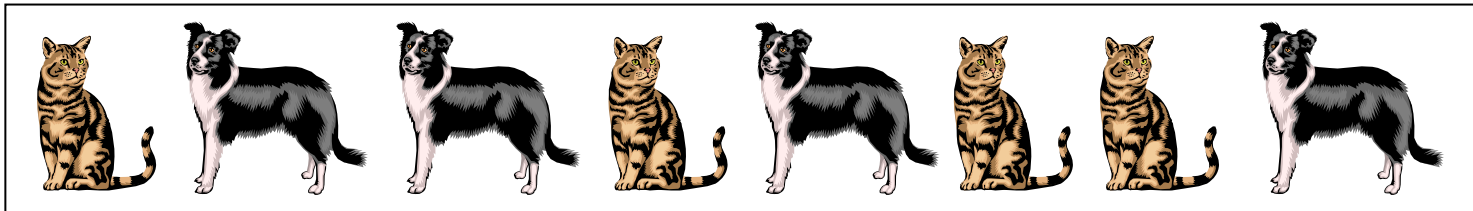
# Executive Function Tasks



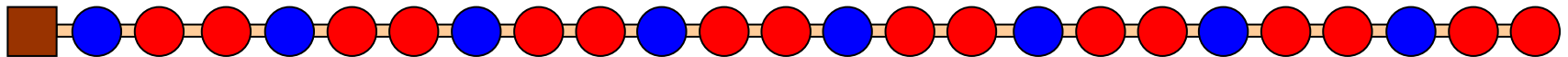
Tower of London -  
planning



Scrambled boxes – working memory



Cats and dogs - Inhibition



Bead threading - sequencing

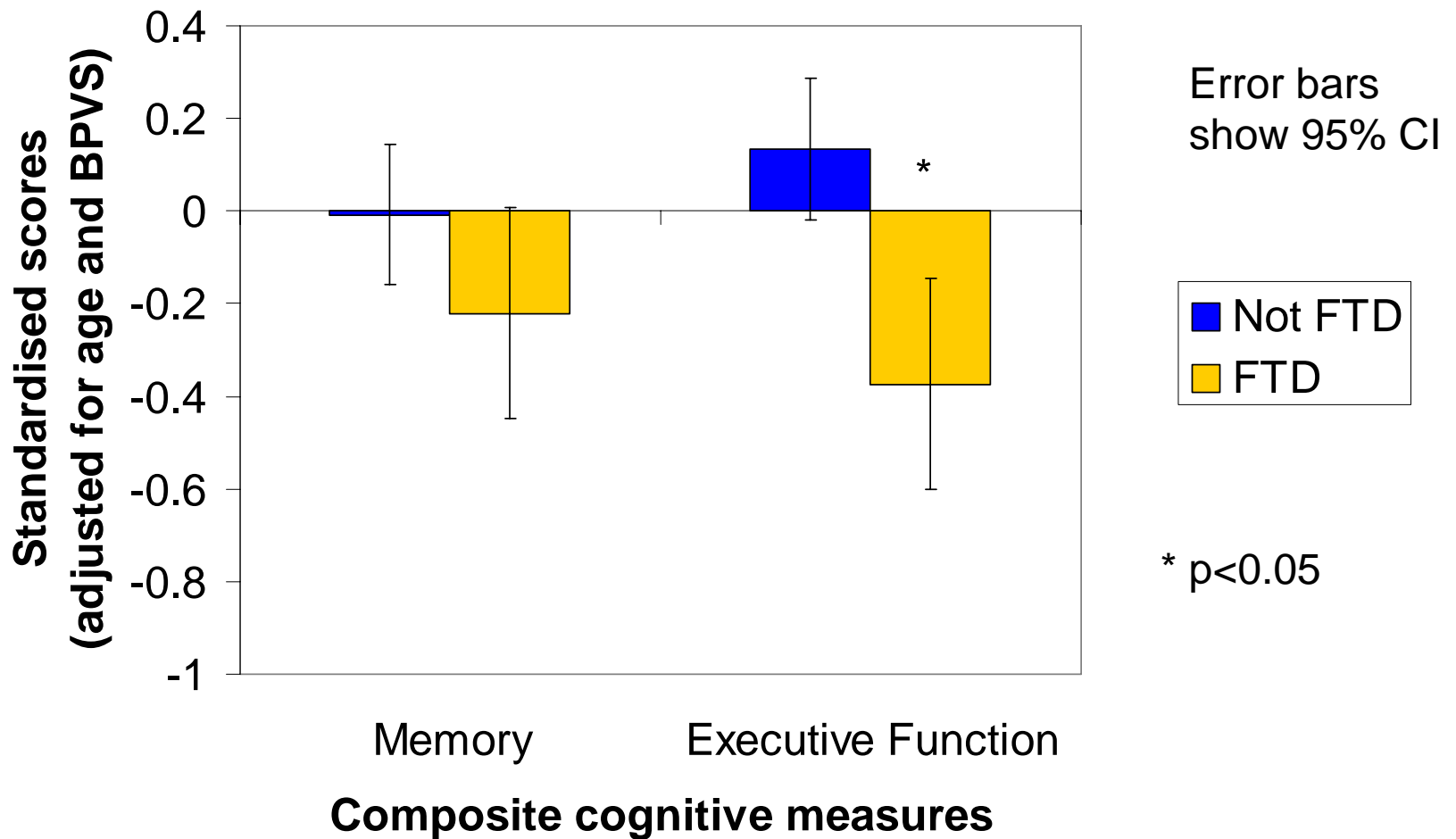
## Cognitive Test Performance: *Participants*

- 122 participants (71 male) from Cambridgeshire and neighbouring health districts – and their main carers
- All born before 01/07/1964
- Mean age at assessment 49 years (36-72)
- 43 mild, 60 moderate, 19 severe learning disability (ICD 10)

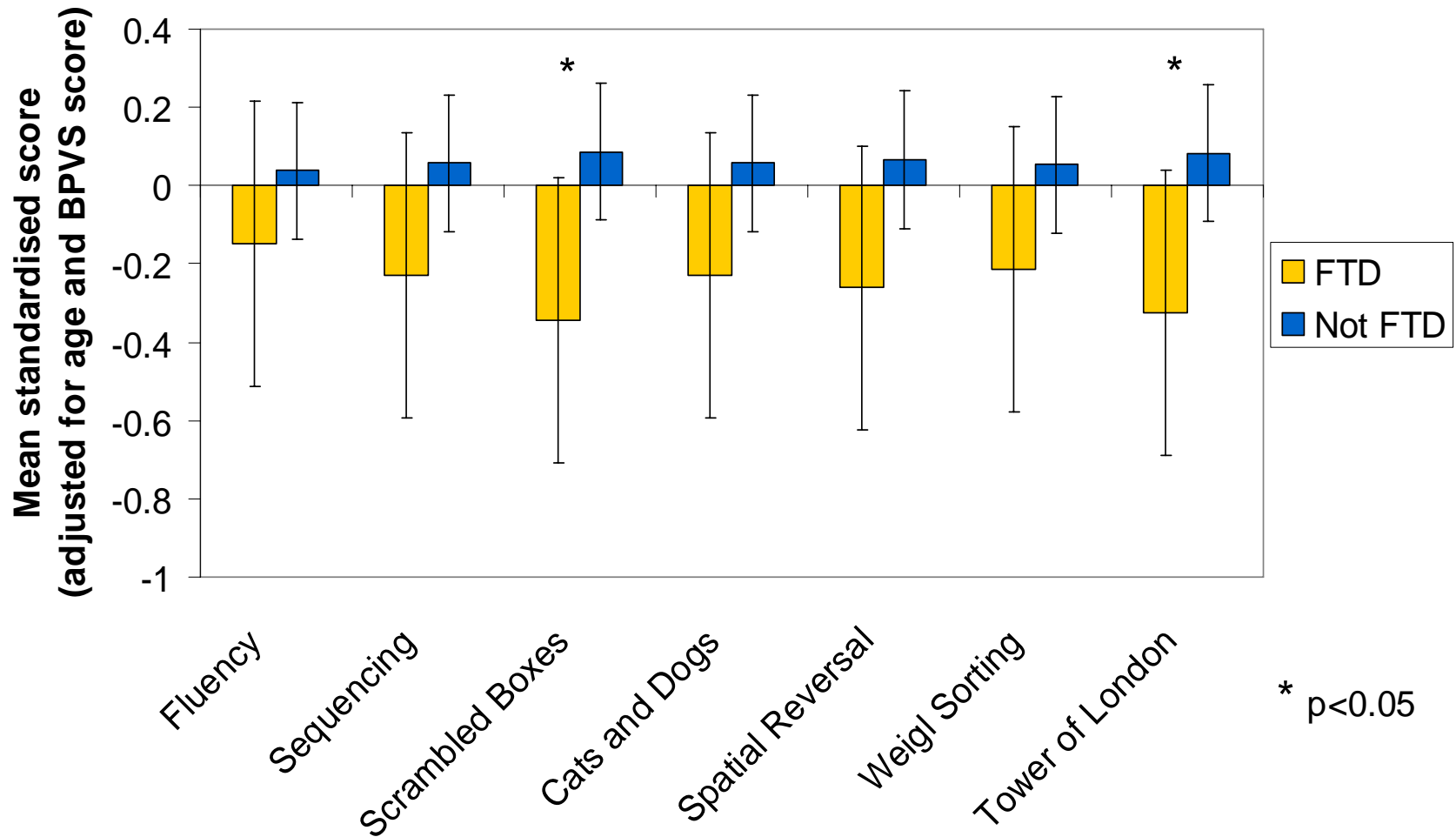
# Cognitive Test Performance: FTD vs. non FTD – Group Characteristics

	FTD	Non FTD	
<b>N</b>	19	75	
<b>Mean age (range)</b>	45 (36-57)	48 (36-72)	non significant
<b>% Male</b>	74	56	non significant
<b>Severity of Learning Disability (ICD 10)</b>			
<b>% Mild</b>	16	40	
<b>% Moderate</b>	73	41	* p<0.05
<b>% Severe</b>	11	19	
<b>Mean BPVS raw score</b>	30	51	* p<0.05

# Cognitive Test Performance: *FTD vs. non FTD - Results*



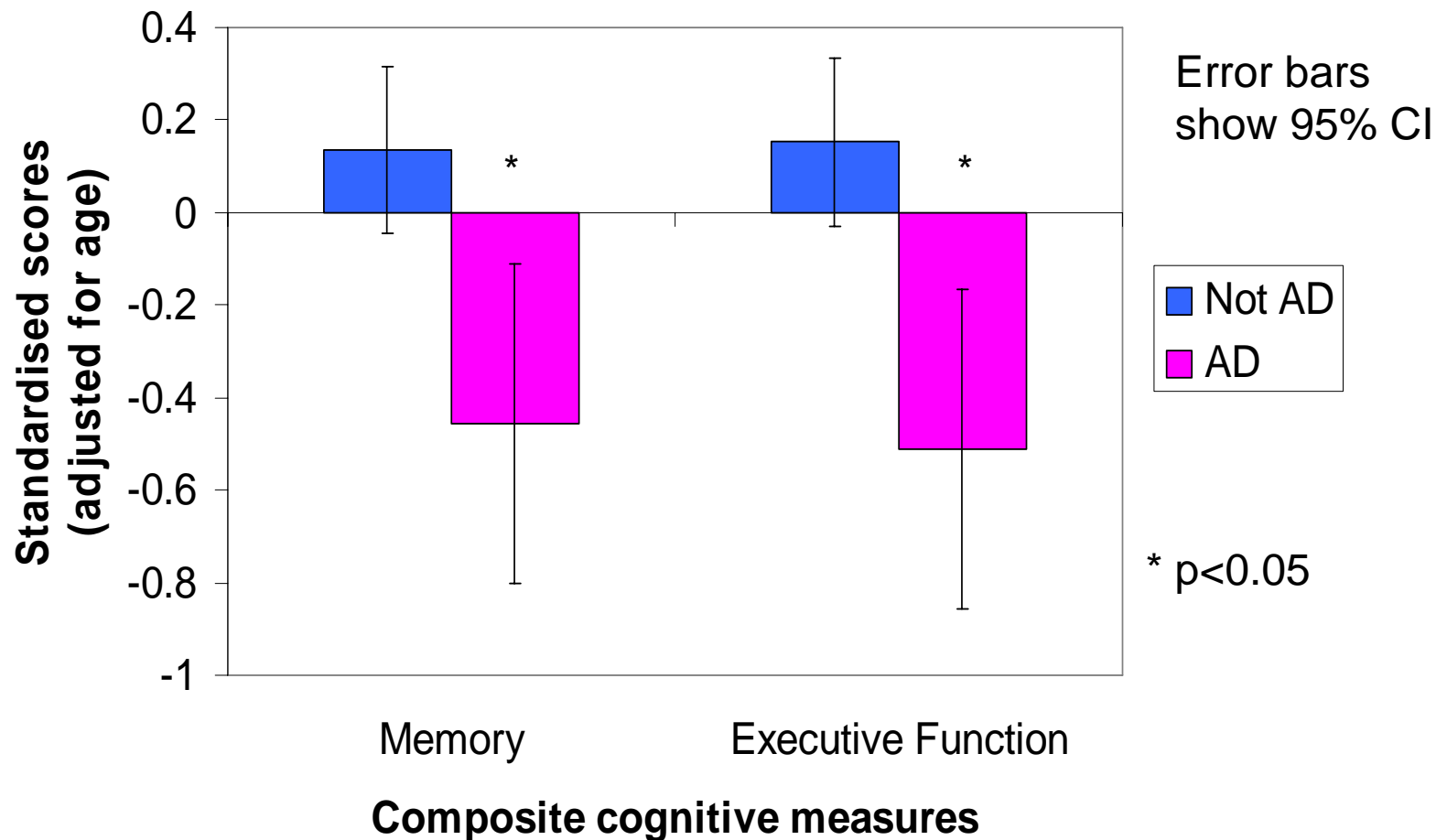
# Cognitive Test Performance: *FTD vs. non FTD - individual EF tasks*



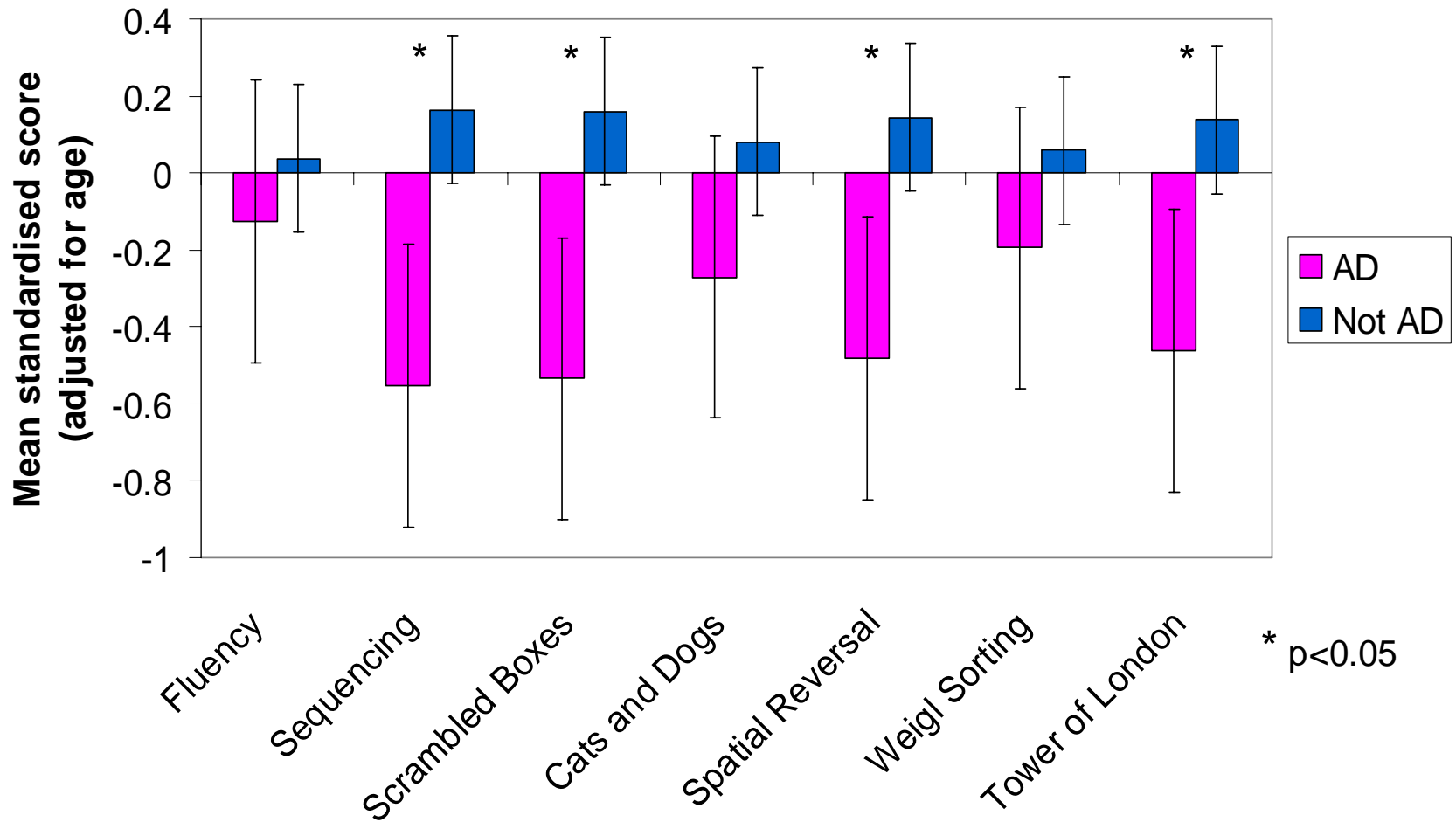
# Cognitive Test Performance: AD vs. non AD - group characteristics

	AD	Not AD	
<b>N</b>	28	94	
<b>Mean age (range)</b>	55 (40-67)	48 (36-72)	* p<0.05
<b>% Male</b>	54	60	non significant
<b>Severity of Learning Disability (ICD 10)</b>			
<b>% Mild</b>	36	35	
<b>% Moderate</b>	54	48	non significant
<b>% Severe</b>	10	17	
<b>Mean BPVS raw score</b>	25	47	* p<0.05

# Cognitive Test Performance: *AD vs. non AD - Results*



# Cognitive Test Performance: *AD vs. non - individual EF tasks*



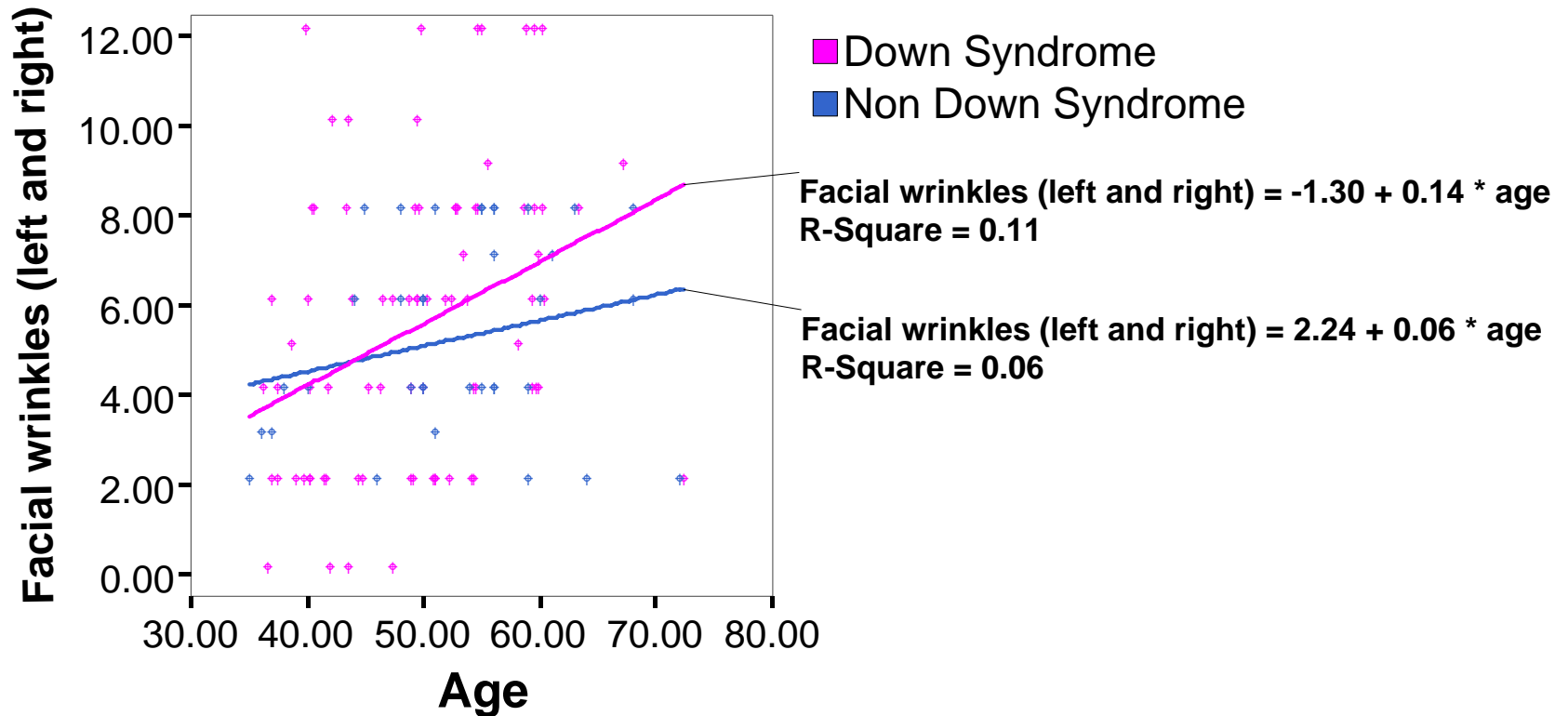
## Conclusions

1. Do personality and behaviour changes mark an early stage in the development of AD in people with DS?
  - ✓ Yes, diagnostic progression from FTD to AD supports this
2. Are these changes associated with impaired performance on neuropsychological tasks measuring frontal lobe functioning (but preserved memory)?
  - ✓ Yes, EF impaired in those diagnosed with FTD relative to those without dementia
  - ✓ Performance on memory tasks only impaired in those with AD

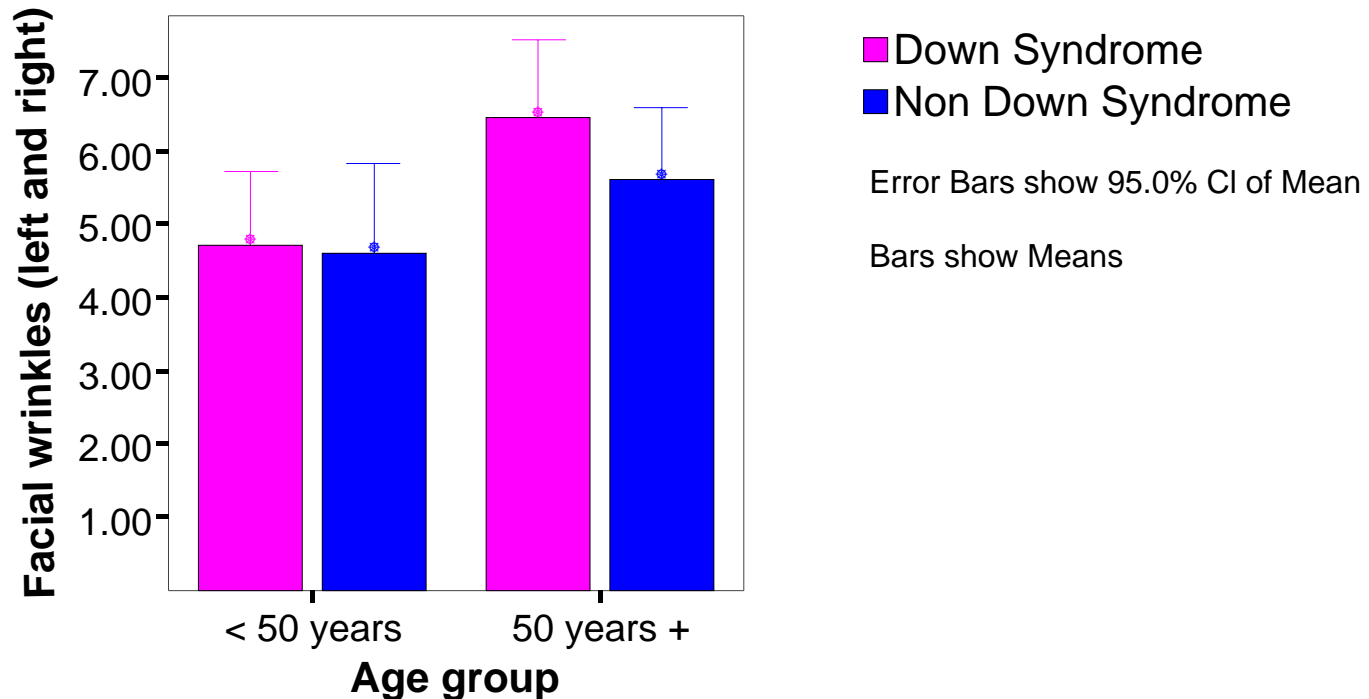
## DS and ageing

- Is AD in people with DS more than just a disorder of the brain?
- How is the reduced life-expectancy explained?
- Is there evidence that people with DS age prematurely?
- If so, what is the relationship between physical markers of ageing and the risk of AD?

# Relationship between age and number of facial wrinkles in participants with and without DS



# Comparison of number facial wrinkles between participants with and without DS (controlling for age)



## ANCOVA

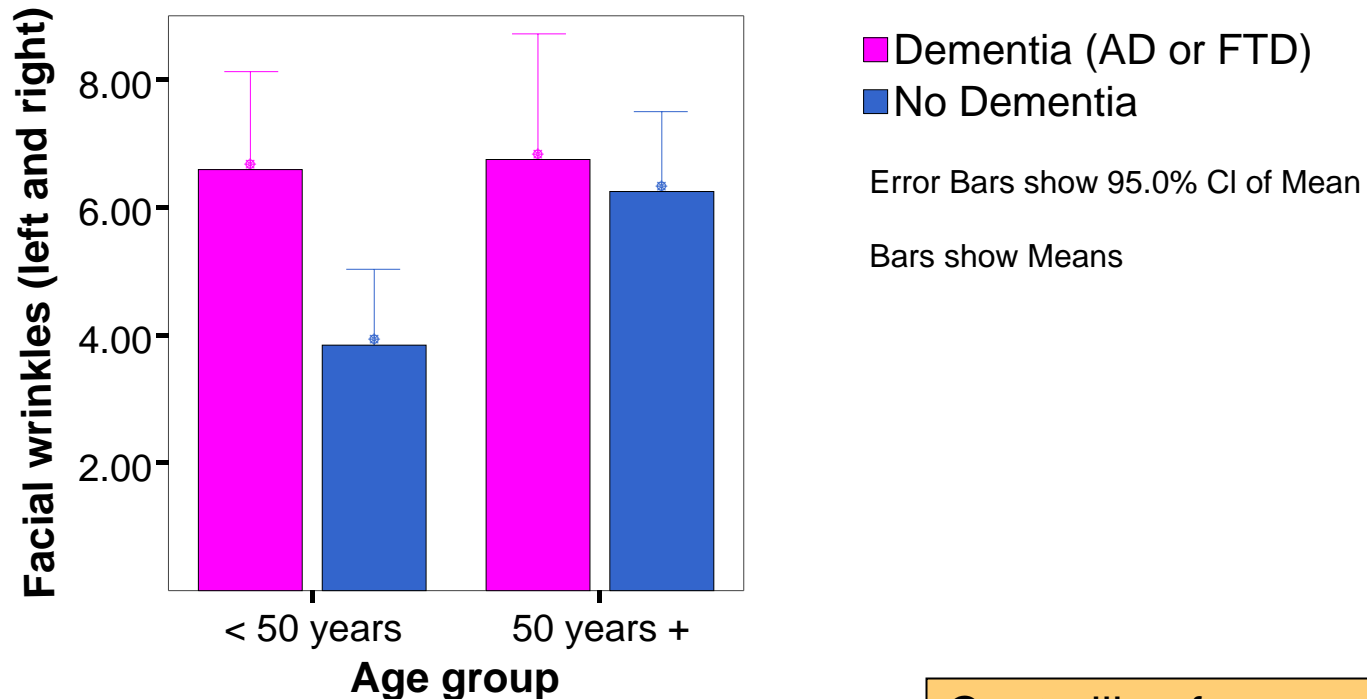
Down syndrome:  $F_{1,111} = 0.729$ ,  $p=0.395$  **NS**

Sex:  $F_{1,111} = 1.067$ ,  $p=0.304$  **NS**

Age (covariate):  $F_{1,111} = 11.015$ ,  $p<0.05$  \*

No significant difference between DS and controls controlling for age

## Comparison of number facial wrinkles between participants with DS with and without dementia (controlling for age)



### ANCOVA

Dementia status:  $F_{1,75} = 5.045$ ,  $p < 0.05$

Sex:  $F_{1,75} = 0.495$ ,  $p = 0.484$

Age (covariate):  $F_{1,75} = 7.149$ ,  $p < 0.05$

Controlling for age, participants with dementia had more facial wrinkles than those without dementia

# Conclusions and implications

- Differential diagnosis
- Present and future treatments
- Services and support
- What mechanisms accounts for the premature ageing?
- Risk and preventative factors

# Acknowledgements

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Learning Disabilities Research Group ([www.LDRG.org.uk](http://www.LDRG.org.uk))