



# An examination of neuromotor and brain 'signatures' in *FMR1* premutation carriers

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Never Stand Still

Medicine

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## Investigators & Collaborators:

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- Dr Anna Hackett
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### **Murdoch Children's Research Institute (MCRI):**

- A/Prof Sylvia Metcalfe

# Fragile X Tremor Ataxia Syndrome (FXTAS)

## **Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X**

**Article abstract**—The authors report five elderly men with the fragile X premutation who had a progressive action tremor associated with executive function deficits and generalized brain atrophy. These individuals had elevated fragile X mental retardation 1 gene (*FMR1*) messenger RNA and normal or borderline levels of *FMR1* protein. The authors propose that elevations of *FMR1* messenger RNA may be causative for a neurodegenerative syndrome in a subgroup of elderly men with the *FMR1* premutation.

NEUROLOGY 2001;57:127–130

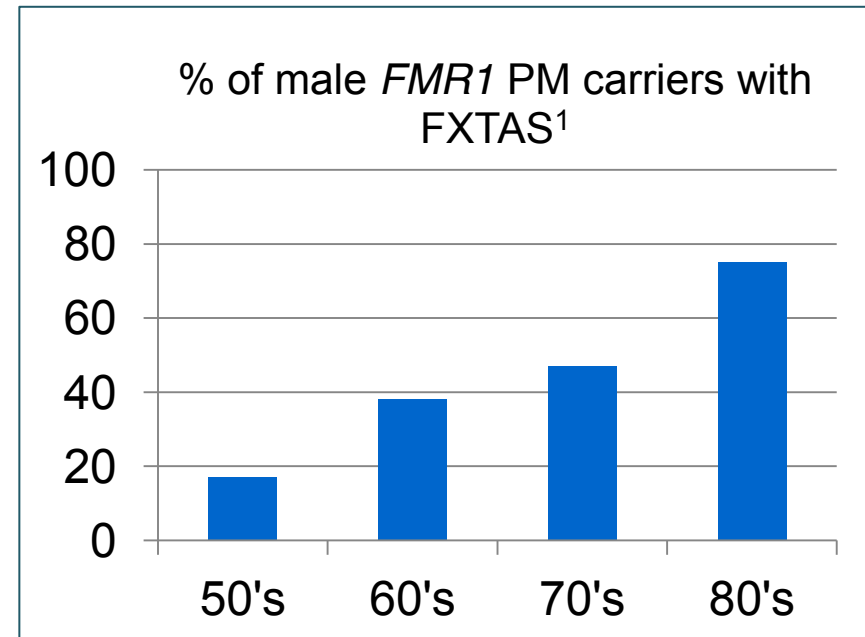
R.J. Hagerman, MD; M. Leehey, MD; W. Heinrichs, MEd; F. Tassone, PhD; R. Wilson, PsyD; J. Hills, PsyD; J. Grigsby, PhD; B. Gage, MD; and P.J. Hagerman, MD, PhD

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# What we know...

- FXTAS is a recently identified neurodegenerative disorder affecting a proportion of premutation (PM) carriers of the *FMR1* gene (59-200 CGG repeats).
- Prevalence:
  - Approximately 40% PM males<sup>1</sup>
  - Approximately 8% PM females<sup>2</sup>
- Penetrance increases with age<sup>1</sup> →



[1] Jacquemont, S., et al. JAMA, 2004. 291(4): p. 460-469. [2] Coffey, S.M., et al. AJHG, Part A, 2008. 146(8): p. 1009-1016.

# Neurological features<sup>1-5</sup>

Clinical presentations vary, but may include the following symptoms:

- Intention tremor
- Gait ataxia
- Parkinsonism
- Peripheral neuropathy
- Autonomic dysfunction

[1] Hagerman, R. J., et al. Neurology, 2001; **57**: p. 127-30. [2] Jacquemont, S., et al. Am J Hum Genet, 2003. **72**(4): p. 869-878.

[3] Berry-Kravis, E., et al. Am J Med Genet A. 2006;143A:19-26. [4] Loesch, D.Z., et al. Clinical Genetics. 2005;**67**:412-417.

[5] Juncos, J. J., et al. Neurogenetics. 2011;**12**:123-35.



# Neuropsychological/Neuropsychiatric profile <sup>1-9</sup>

## Impairments in:

- Global cognitive functioning
- Memory
- Executive functioning
- Working memory
- Information processing

## Elevated rates of :

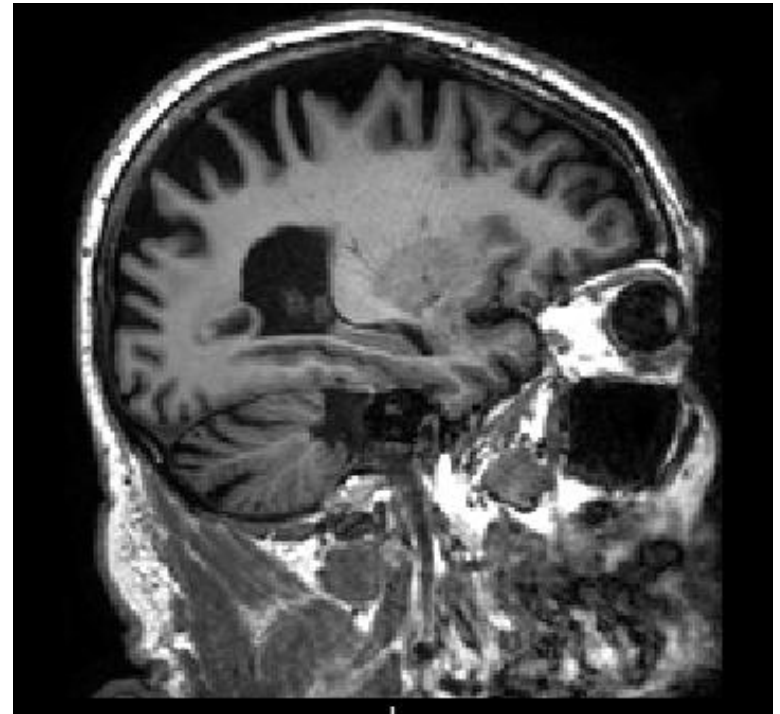
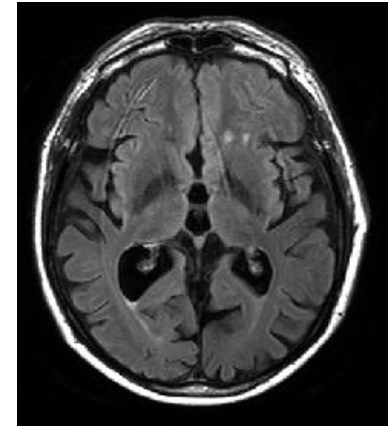
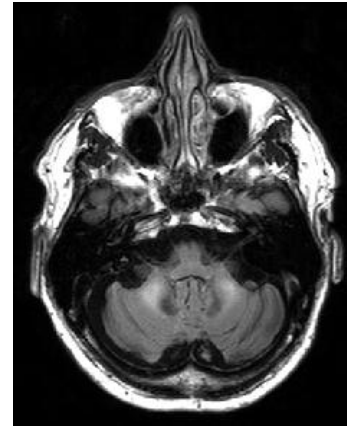
- + Depression
- + Anxiety
- + Irritability
- + Agitation / Aggression
- + Disinhibition
- + Apathy

[1] Bacalman, S., et al. Journal of Clinical Psychiatry, 2006. **67**(1): p. 87-94. [2] Grigsby, J., et al. Neuropsychology, 2008. **22**(1): p. 48-60. [3] Brega, A.G., et al. Journal of Clinical and Experimental Neuropsychology, 2008. **30**(8): p. 853-869. [4] Cornish, K.M., et al. Cortex, 2008. **44**(6): p. 628-636. [5] Cornish, K.M., et al. Brain and Cognition, 2009. **69**(3): p. 551-558. [6] Allen, E.G., et al. Neuropsychology, 2011. **25**(3): p. 404-411. [7] Bacalman, S., et al. Journal of Clinical Psychiatry, 2006. **67**(1): p. 87-94. [8] Hashimoto, R.-i., et al. Brain, 2011. **134**(3): p. 863-878. [9] Adams, P.E., et al. American Journal of Medical Genetics Part B-Neuropsychiatric Genetics, 2009. **153B**(3): p. 775-785.



# Radiological findings <sup>1-5</sup>

- High signal lesions in MCP on T2/FLAIR
- Increased white matter hyperintensities
- Cerebral atrophy
- Decreased white matter integrity as measured by DTI in multiple white matter tracts
- Grey matter loss in multiple brain regions
- Reduced activation in lateral prefrontal cortex during a working memory task



[1] Jacquemont, S., et al. *Am J Hum Genet*, 2003. **72**(4): p. 869-878. [2] Cohen, S., et al. *Neurology*, 2006. **67**(8): p. 1426-1431. [3] Hashimoto, R., et al. *Movement Disord.* **In press**. [4] Hashimoto, R.-i., et al. *J Psychiat Res*, 2011. **45**(1): p. 36-43. [5] Hashimoto, R.-i., et al. *Brain*, 2011. **134**(3): p. 863-878.

# Neuropathological changes & molecular biology

## Neuropathological<sup>1, 2</sup>:

- Cerebral and cerebellar white matter disease
- Loss of axons, myelin and cerebellar Purkinje cells
- Enlarged astrocytes with inclusions in cerebral white matter
- Intranuclear inclusions in neurons and astrocytes throughout the CNS

## Molecular<sup>3-6</sup>:

- Increased production of CGG mRNA in the PM<sup>1-6</sup>
- mRNA “Toxic gain-of-function” mechanism<sup>1-6</sup>

[1] Greco, C.M. Et al. Brain, 2002. **125**; p. 1760-71. [2] Greco, C. M., et al. Brain, 2006. **129**: p. 243-55. [3] Hagerman, R. J., et al . Neurology, 2001; **57**: p. 127-30. [4] Jin, P., et al. Neuron, 2003; **39**: p. 739-47. [5] Hagerman, R. J., et al . Am J Hum Genet, 2004; **74**: p, 1051-56. [6] Garcia-Arocena, D., et al. 2010; **19**, p. R83-89



# Molecular correlates

- Larger CGG repeats associated with:
  - ↑ % of neurons and astrocytes with inclusions in multiple brain regions<sup>1</sup>
  - ↑ FXTAS rating scale scores<sup>2,3</sup>
  - ↑ relative risk for cognitive impairment<sup>4</sup>
  - ↓ age at death<sup>1</sup>
  - ↓ full scale IQ<sup>5</sup> and performance IQ<sup>4</sup>
  - ↓ age of onset of tremor / ataxia<sup>6</sup>
  - ↓ response inhibition<sup>7</sup> and verbal fluency<sup>2</sup> scores
- Increased mRNA associated with:
  - ↑ Psychiatric symptoms<sup>3,4</sup>
  - ↓ Decreased activity in right vIFC during working memory task<sup>8</sup>

[1] Greco, C. M., et al. *Brain*, 2006. **129**:243-55. [2] Grigsby, J. A., et al. *J Neurolog Sci*, 2006; **248**:227-33. [3] Leehey, M. A., et al. *Neurology*. 2008; **70**:1397-1402. [4] Sevin, M. Z., et al. *J Med Genet*, 2009; **46**:818-24. [5] Hessler, D. F., et al. *Am J Med Gen*, 2005; **139B**:115-21. [6] Tassone, F., et al. *Am J Med Gen*, 2007; **144B**:566-69. [7] Cornish, K. M. *Cortex*; 2008; **44**: 628-36. [8] Hashimoto, R.-i., et al. *J Psychiat Res*, 2011. **45**(1): p. 36-43.



# Diagnostic Criteria<sup>1</sup> (inclusion criteria= 55-200 CGG repeats)

Examination	Degree	Observation
Radiological	Major	MRI white matter lesions in MCPs and or brain stem
	Minor	MRI white matter lesions in cerebral white matter
	Minor	Moderate-to-severe generalized atrophy
Clinical	Major	Intention tremor
	Major	Gait ataxia
	Minor	Parkinsonism
	Minor	Moderate-to-severe short-term memory deficiency
	Minor	Executive dysfunction deficit

## Diagnostic categories:

Definite= One major radiological sign + one major clinical symptom

Probable= a) One major radiological sign + one minor clinical symptom, or  
b) Two major clinical symptoms

Possible= One minor radiological sign + one major clinical symptom

[1] Jacquemont, S., et al. Am J Hum Genet. 2003;72:869-78



# Clinical Staging<sup>1</sup>

<b>FXTAS Stage</b>	<b>Description</b>
0	Normal functioning
1	Subtle or questionable signs (i.e., subtle tremor and/or mild balance problems) but no interference with activities of daily living skills (ADLs)
2	Minor, but clear tremor and/or balance problems producing minor interference with ADLs
3	Moderate tremor and/or balance problems and at least occasional falls
4	Severe tremor and/or balance problems requiring the use of cane or walker
5	Uses wheelchair on a daily basis
6	Bedridden

[1] Jacquemont, S., et al. Am J Hum Genet. 2003;72:869-78

# Asymptomatic carriers

Compared to controls with normal *FMR1* alleles, *FMR1* premutation carriers without symptoms of FXTAS have exhibited:

- Deficits in:
  - Memory (LMT score)<sup>1</sup>
  - Executive function (COWAT and BDS composite score)<sup>1</sup>
  - Inhibitory control (in subgroup with >100 CGG repeats)<sup>2</sup>
  - Motor learning (BDS item)<sup>3</sup>
- White matter abnormalities on DTI- significant increases in axial and radial diffusivities in MCP and left cerebral peduncle<sup>4</sup>
- Longitudinal study needed

[1] Grigsby, J. A., et al. *Neuropsychology*. 2008;**22**: 48-60. [2] Cornish, K.M., et al. *Neurology*. 2011;**77**(7):618-622. [3] Brega, A. G., et al. *J Clin Exp Neuropsych*. 2008;**30**:853-69. [4] Hashimoto, R., et al. *Movement Disord*. **In press**.



# Gaps in knowledge

- Some inconsistencies in neuropsychiatric/neuropsychological features (especially among asymptomatic carriers)
- Longitudinal data needed to:
  - Determine clinical trajectories
  - Identify correlates of progression vs non-progression of symptoms
  - Identify pre-clinical markers

Fortunately a number of research groups around the globe are reporting baseline data for cohorts to be followed over time...



# Our overarching aims

1. Establish a cohort of male *FMR1* premutation carriers aged 40+
2. Determine the genetic, cognitive, psychiatric, neuromotor and brain imaging correlates of the *FMR1* premutation and FXTAS



# Participants & Recruitment

## Participants:

- 60 male *FMR1* PM carriers aged 40+
- matched controls with normal *FMR1* alleles

## Recruitment:

- Mail-outs to *FMR1* PM carriers within the GOLD Service database
- Advertisement with the Fragile X Association of Australia
- Mail-outs to Genetic Counselling Services in NSW
- Mail-outs to Neurologists and Movement Disorder specialists
- Advertisement with GP Networks



### Thinking and motor skills in premutation carriers of fragile X

*Recent research has suggested that premutations of the fragile X gene may cause a specific dementia syndrome in mid or late life in some people. The syndrome has been called Fragile X Tremor Ataxia Syndrome (FXTAS) and presents with tremor, balance problems and decline in memory. The syndrome may be found in parents or grandparents of children affected by Fragile X Syndrome and is more common in older men than women. However, not everyone with the premutation will show symptoms. As yet, we do not know why some people who carry the premutation are affected and others are not.*

A group of researchers led by A/Prof Julian Trollor at the University of New South Wales (UNSW) have commenced a study of the effect of the "premutation" of the fragile X gene in older men.

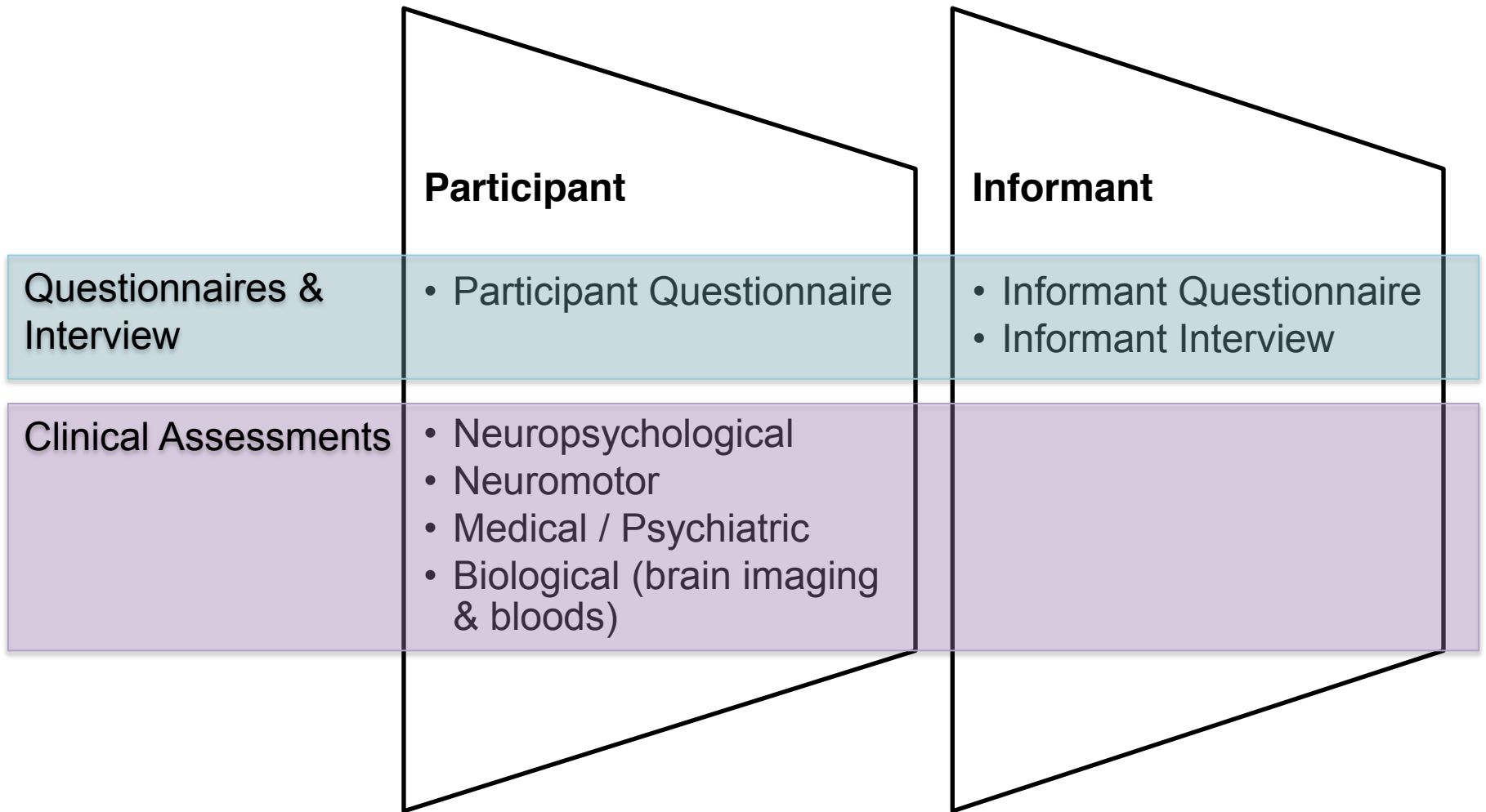
We hope to perform detailed health, balance and memory tests on **men** who are:

- **premutation carriers** of the fragile X gene, and
- over **40 years old**

If you would like to participate in this study, or would like some further information, please call the research team on (02) 9931 9160, or email [fxtas@unsw.edu.au](mailto:fxtas@unsw.edu.au)



# Study Protocol



# Questionnaires and Interview

## Participant:

- Depression, anxiety and stress (DASS)
- Social anxiety (LSAS)
- Autistic traits (AQ)
- Personality (NEO-FFI-3)
- Lifetime experiences (LEQ)
- Successful Ageing (Australian adaptation)

## Informant:

- Cognition and memory (IQCODE, CICAQ, CDR- Informant)
- Neuropsychiatric symptoms (NPI)
- Sleep behaviours
- Activities of daily living (Bayer ADLs)



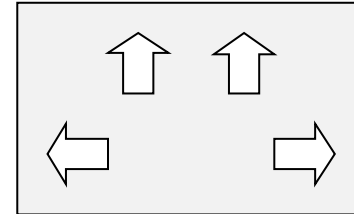
# Neuropsychological Assessment

Domain	Measure
General intelligence	WASI
Premorbid intelligence	NART
Global cognitive functioning	MMSE
Executive function	Hayling Sentence Completion Test Stroop Colour Word Test Behavioral Dyscontrol Scale 2 COWAT Trails B
Working memory	Letter Number Sequencing Digit Span Backwards
Memory	Logical Memory I & II RAVLT Benton Visual Retention Test
Information processing	Digit Symbol Coding Trails A
Attention	Digit Span Forward
Language	Boston Naming Test
Fine motor	Grooved Pegboard

# Neuromotor Assessment

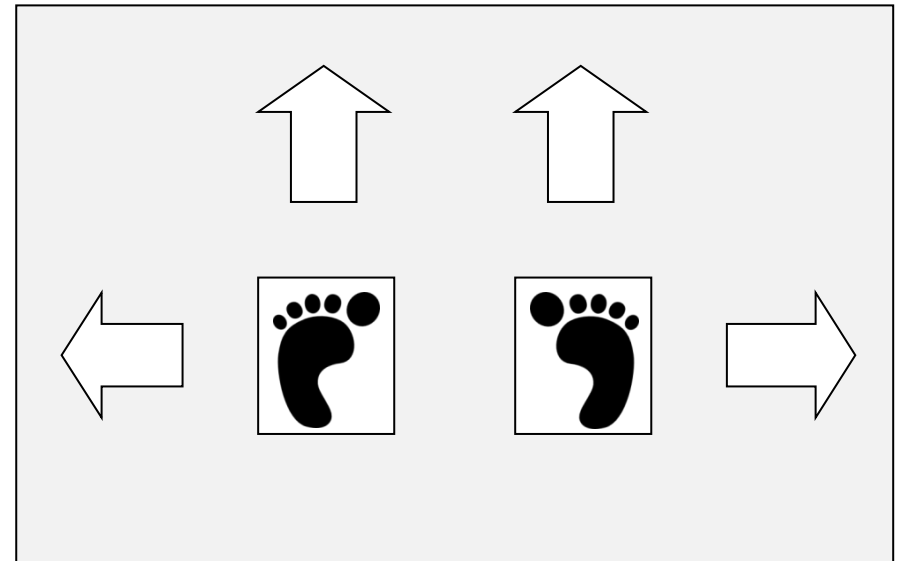
## Gait function:

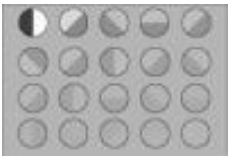
- GAITrite system - computerised walkway assessing gait function from step to step
- Trials: Control and with secondary cognitive task



## Choice Stepping Reaction Time (CSRT):

- Functional test of stepping performance (decision and movement times)
- Trials: Control and with secondary cognitive task





## Falls risk:

- Short-form Physiological Profile Assessment (PPA)<sup>1</sup>:
  - i. Visual contrast sensitivity
  - ii. Proprioception
  - iii. Quadriceps strength
  - iv. Simple reaction time
  - v. Postural sway

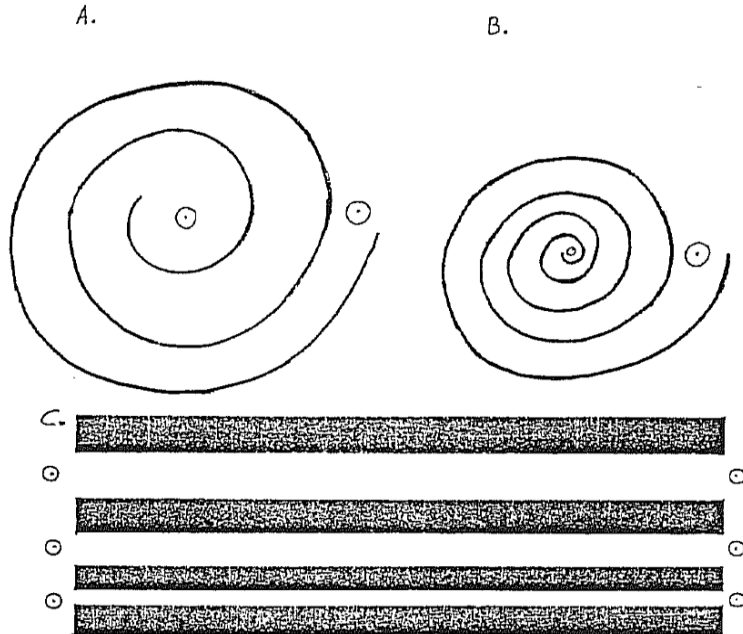
## Leaning balance:

- Maximal balance range and coordinated stability tests<sup>2</sup>

[1] Lord SR et al. Physical Therapy 2003;83:237-252.

[2] Lord SR et al. Archives of Physical Medicine and Rehabilitation 1996;77:232-236.

# Medical / Psychiatric Examination



Neurological symptoms:

- FXTAS Rating Scale<sup>1</sup>

Psychiatric assessment:

- Structured Clinical Interview for DSM-IV Disorders (SCID)

Hearing assessment:

- Pure-tone audiometry

[1] Berry-Kravis, E., et al. *Annals of Neurology*. 2003;**53**:616-623

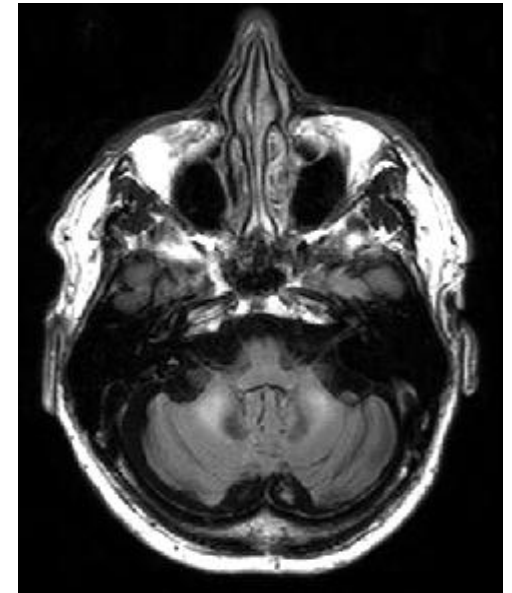
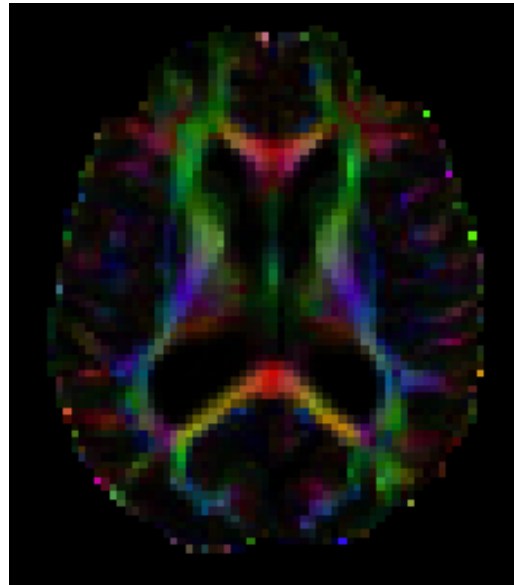
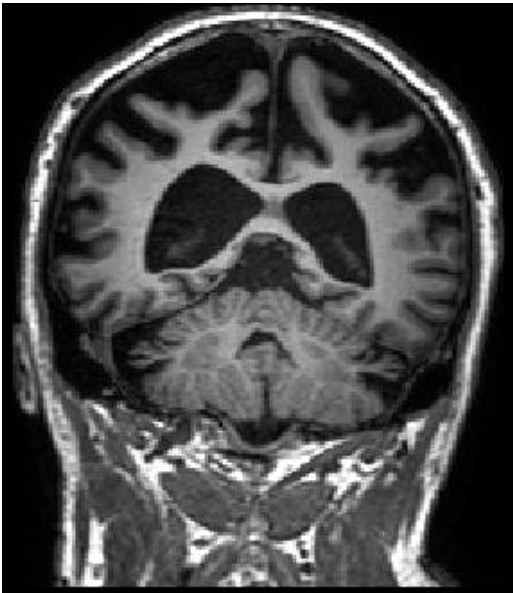
# Biological investigations

## Blood:

- *FMR1* CGG repeats
- *FMR1* mRNA
- FMRP

## Brain imaging:

- T1 & T2-weighted
- DTI
- Resting state fMRI



# Expected outcomes

Baseline data from a cohort of *FMR1* PM carriers:

- Cognitive and neuromotor profiles of *FMR1* PM both with and without FXTAS
- Cross-sectional neural and molecular correlates of psychiatric symptoms and cognitive/neuromotor deficits

With longitudinal follow up...

- Determine predictors and correlates of progression of symptoms
- Determine early or pre-clinical markers to identify those in the earliest phase of the syndrome



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