

# MRI Research in Ataxias

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# Learning Objectives

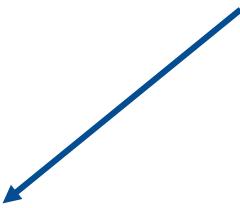
*By the end of this talk you will be able to:*

- \* Define the utility of MRI/MRS in ataxia research (What aspects of pathology can be non-invasively monitored?)
- \* Outline the most commonly used MR modalities to study ataxias

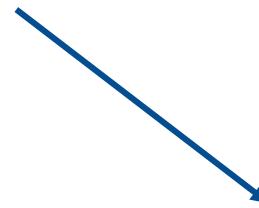
## Do you use quantitative neuroimaging in your research?

- a. Morphometric, e.g. volumetric, MRI
- b. Diffusion MRI
- c. MR Spectroscopy
- d. Perfusion MRI
- e. Functional MRI
- f. Susceptibility weighted MRI
- g. PET/SPECT
- h. Other
- i. I do not use neuroimaging

# MRI in Ataxia Research



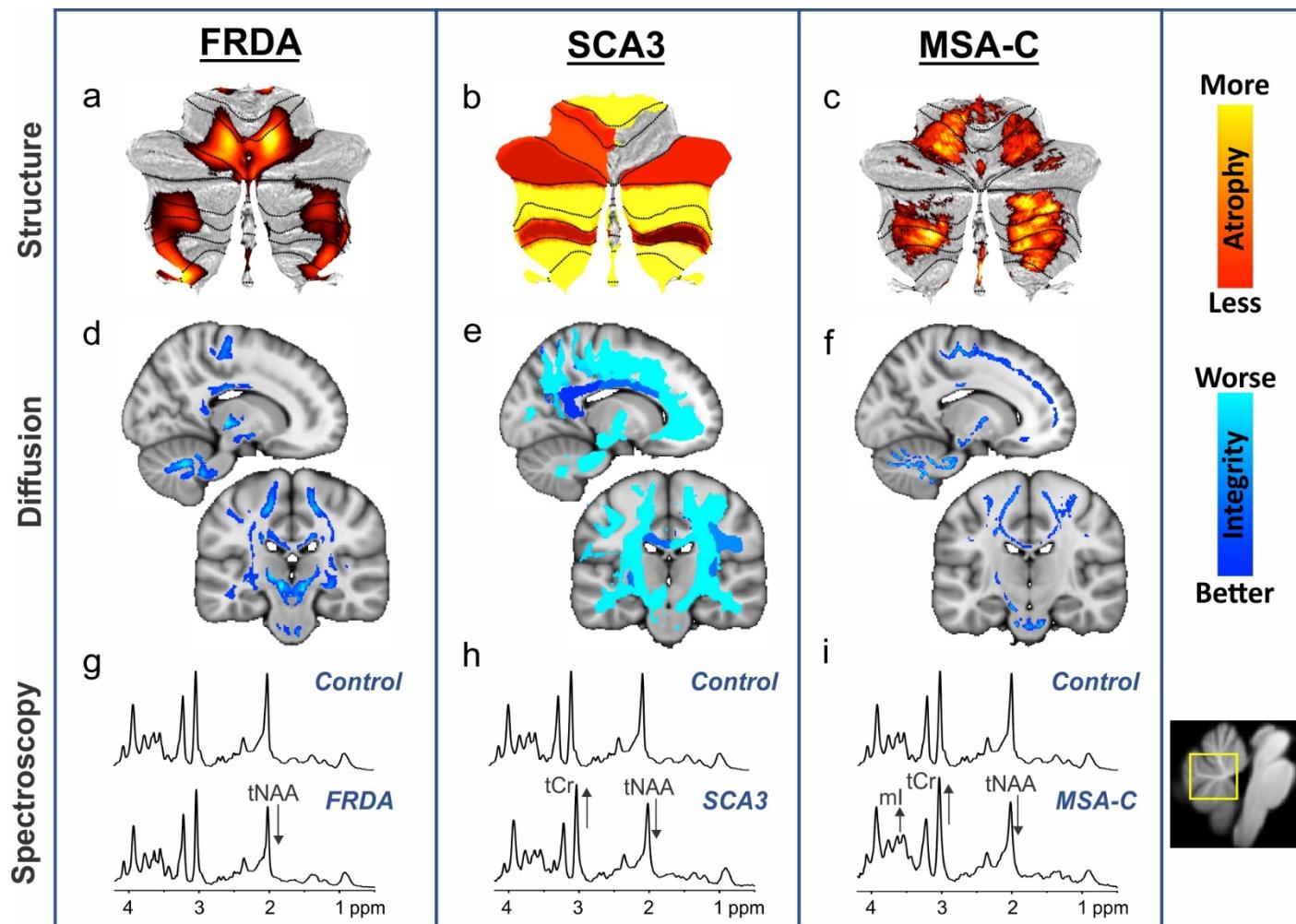
Understanding & monitoring  
pathology



Clinical trial readiness

- ✓ Morphometry
- ✓ Connectivity
- ✓ Function
- ✓ Biochemistry

# Commonly used quantitative imaging modalities in ataxia research

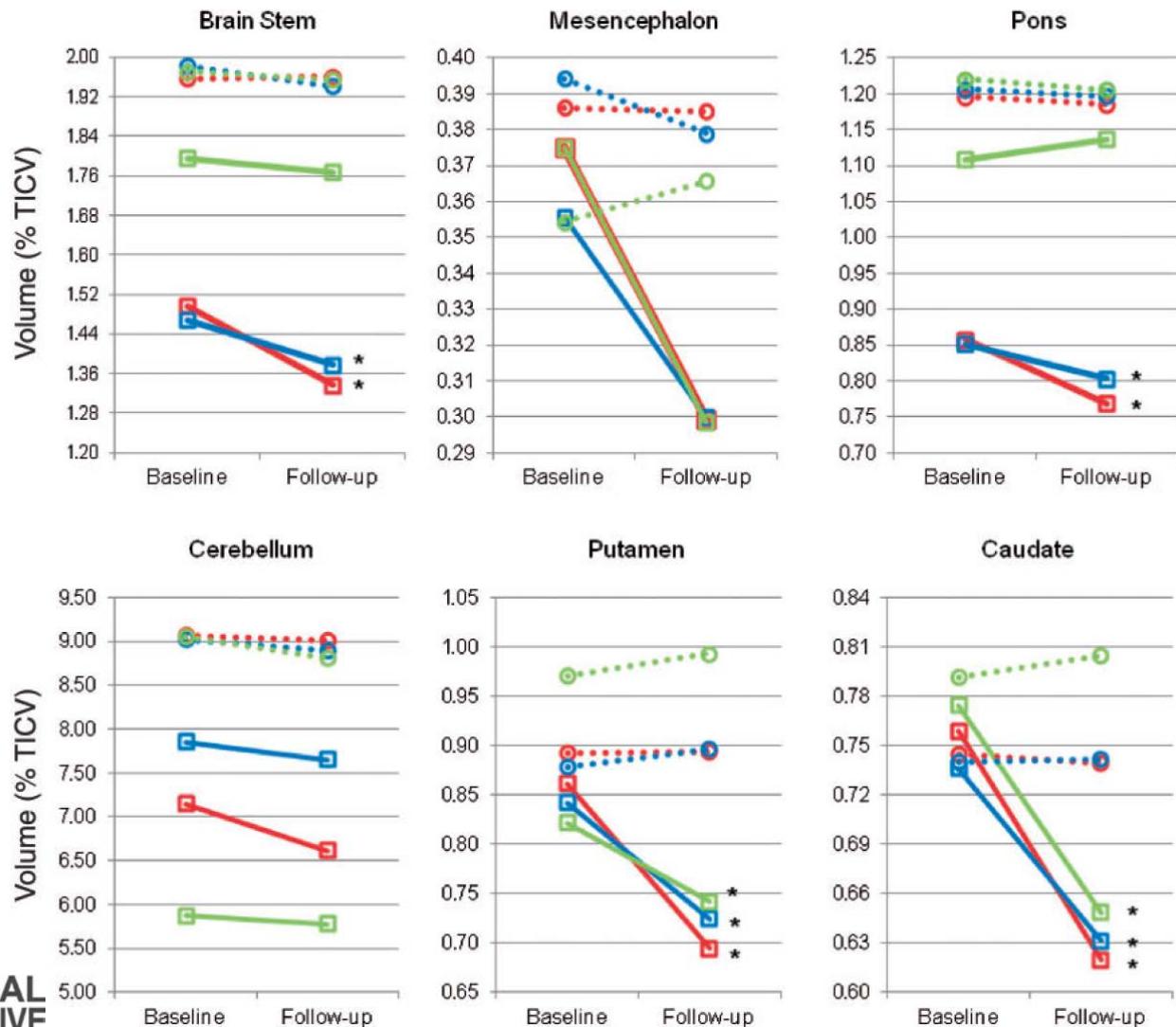


# Genotype-specific atrophy patterns in SCAs



Kathrin Reetz

- Controls SCA1
- Controls SCA3
- Controls SCA6
- SCA1
- SCA3
- SCA6



# MRI more sensitive to change than clinical decline

Effect size = mean annual % change / SD of annual % change

**Table 4** Standardized response means of clinical change for SCA1, SCA3 and SCA6

Clinical score	SCA1	SCA3	SCA6	All genotypes
SARA	1.2	1.4	0.2	0.9
INAS	0.4	0.2	-0.1	0.3
SCAFI	0.2	-0.5	-0.7	0.1
UHDRS-IV	-0.1	-0.6	-1.6	-0.2

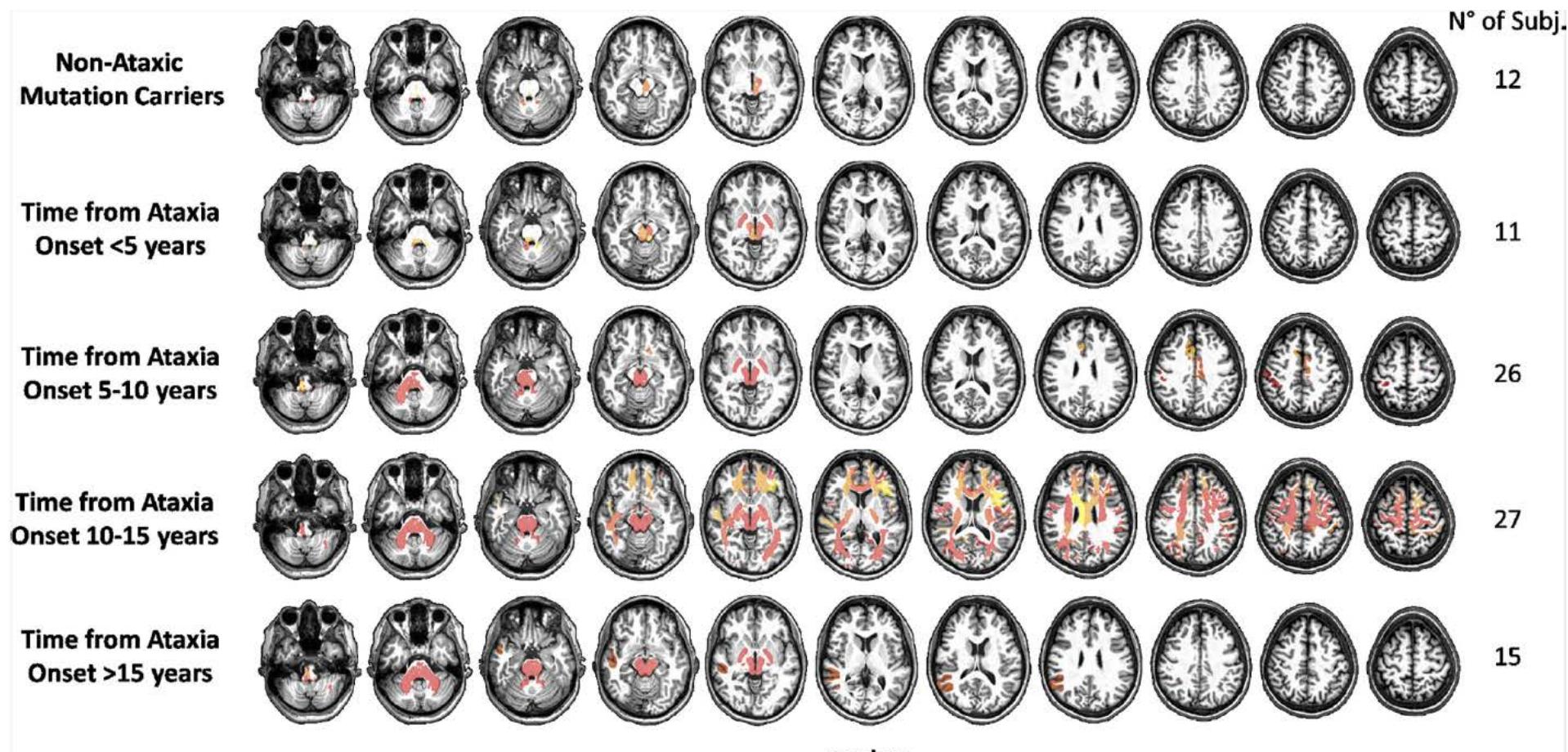
**Table 5** Standardized response means of volume loss rate for SCA1, SCA3 and SCA6

Region	SCA1	SCA3	SCA6	All genotypes
Brainstem	-1.6	-1.1	-0.2	-1.2
Mesencephalon	-0.9	-0.7	-0.8	-0.8
Pons	-1.5	-0.9	0.4	-0.8
Medulla	0.2	0.4	0.4	0.3
Cerebellum	-0.7	-0.5	-0.2	-0.6
Vermis	-0.1	-0.2	-0.1	-0.1
Putamen	-1.3	-1.5	-2.7	-1.2
Caudate	-1.2	-1.6	-3.3	-1.3
Cerebrum	0.0	-0.3	-2.0	-0.2



# Atrophy at premanifest stage in SCA3

Marcondes  
França



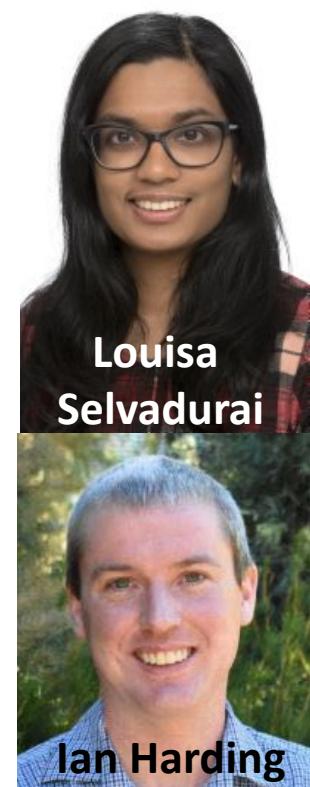
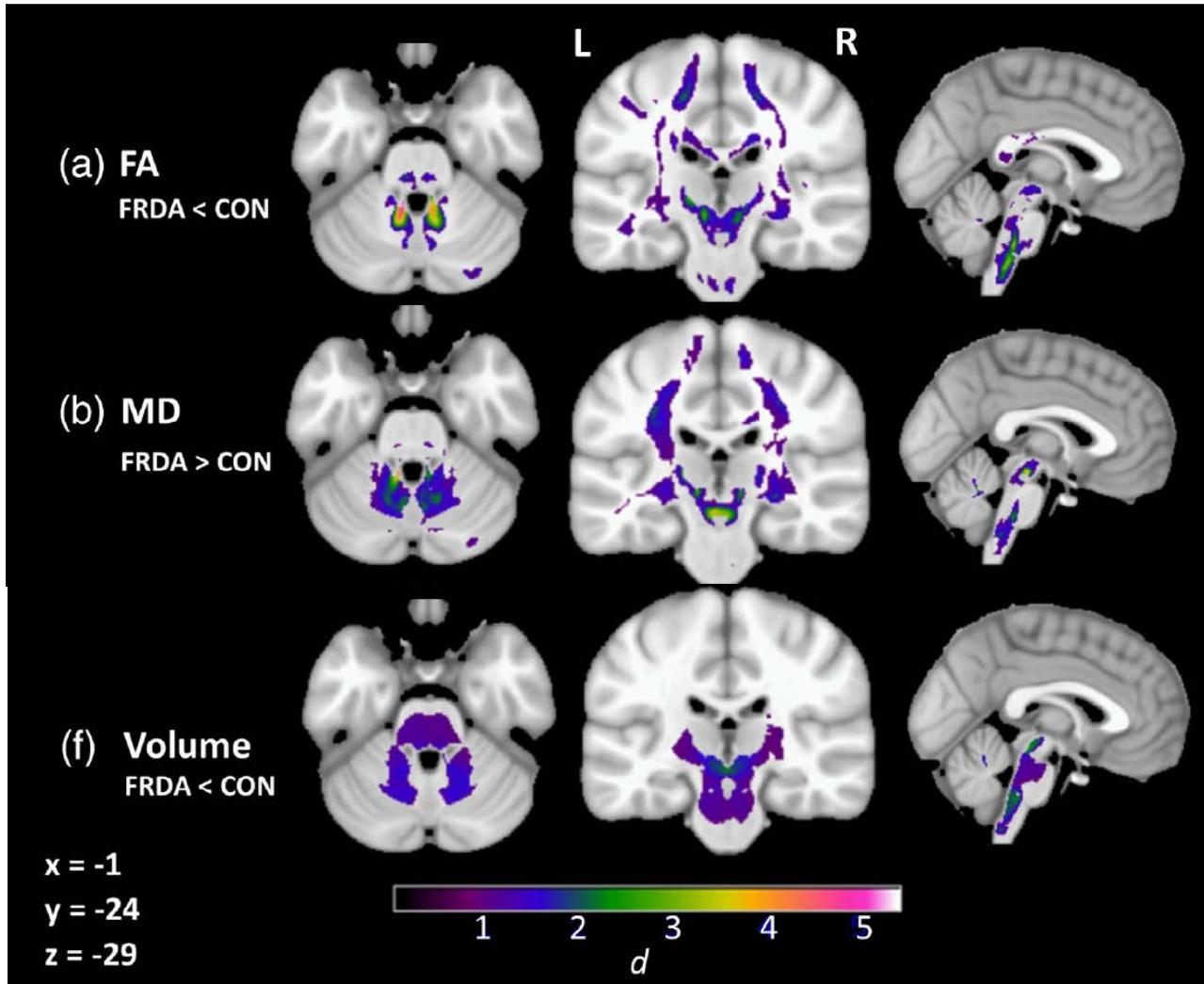
p-values

0.05

<0.0001

Rezende et al,  
Ann Neurol 2018

# Microstructural damage beyond volume loss



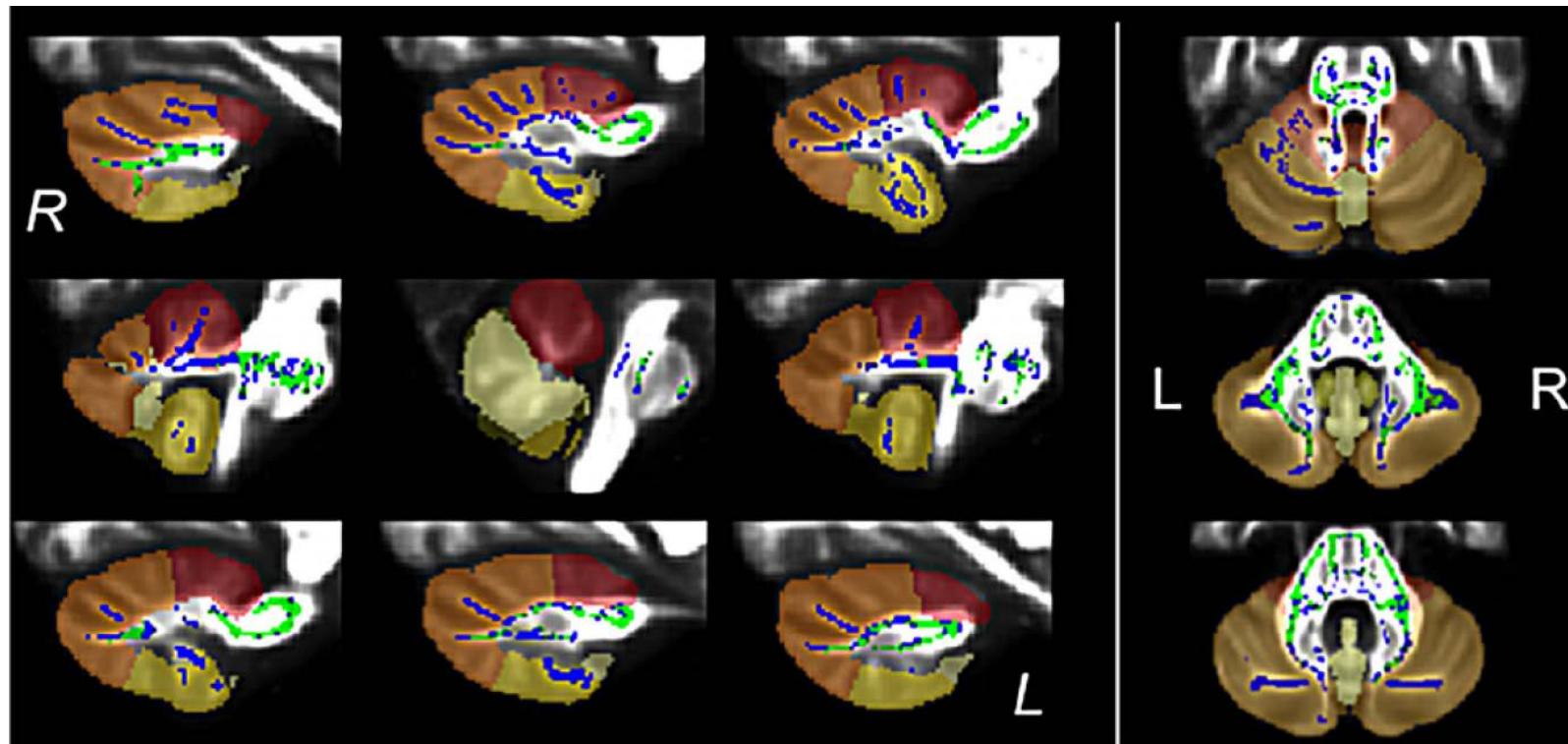
# Microstructural abnormalities distinguish sporadic degenerative ataxias



Jennifer Faber

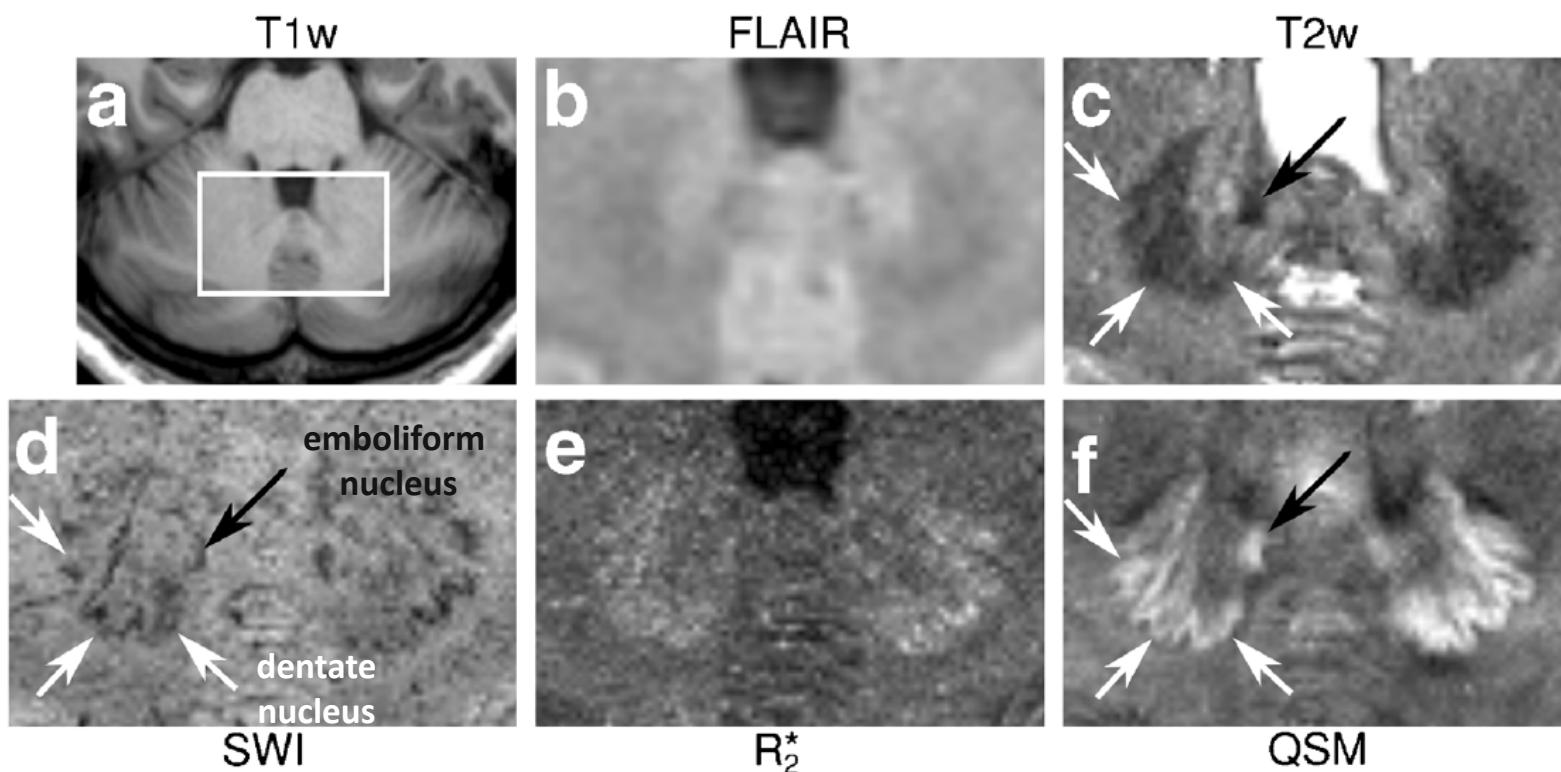


Thomas  
Klockgether

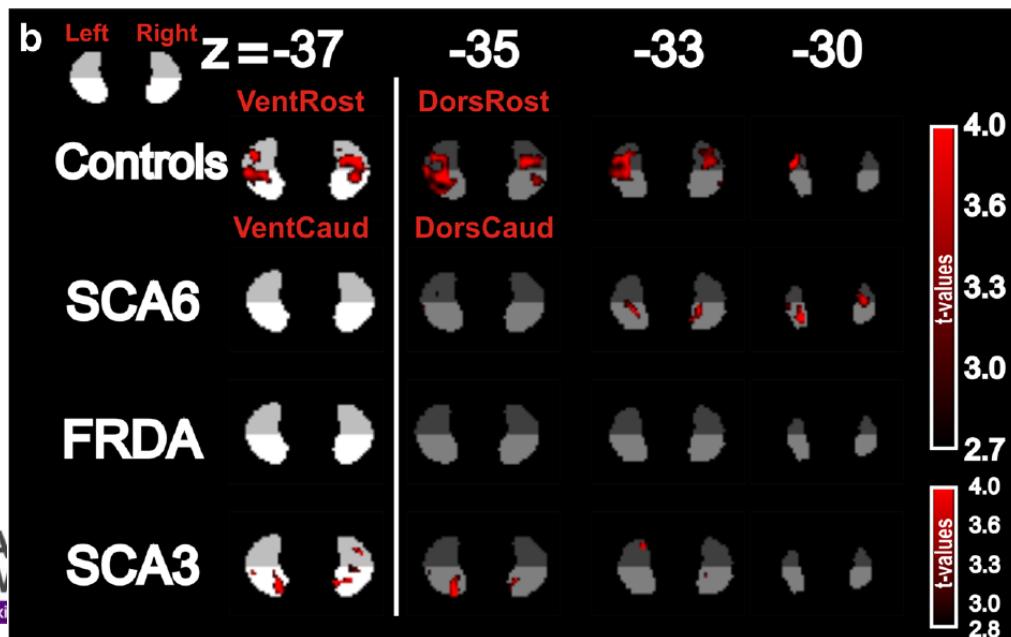
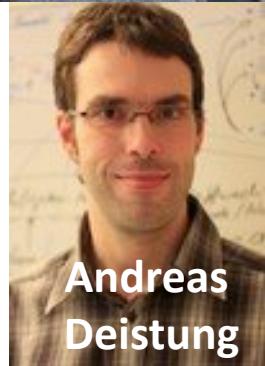
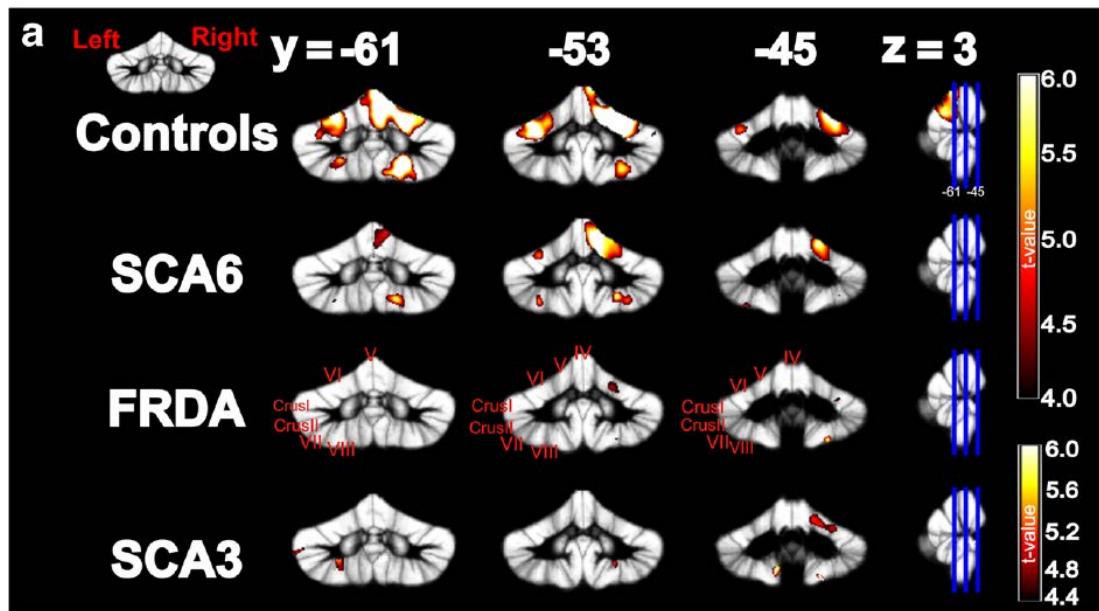


Blue: FA (MSA-C) < FA (Control)  
Green: FA (MSA-C) < FA (SAOA)

# Imaging cerebellar nuclei

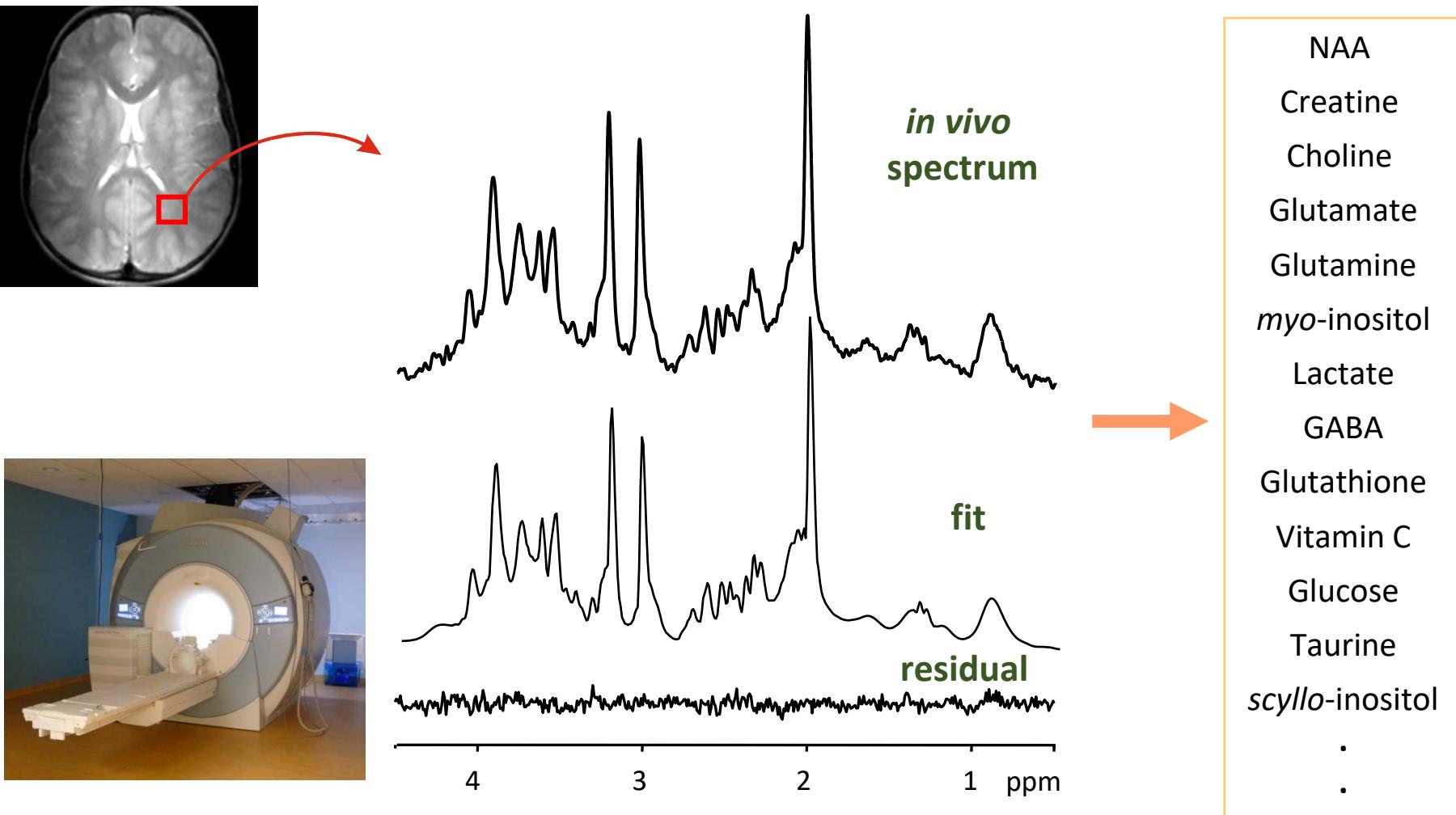


# Imaging functional changes in cerebellum

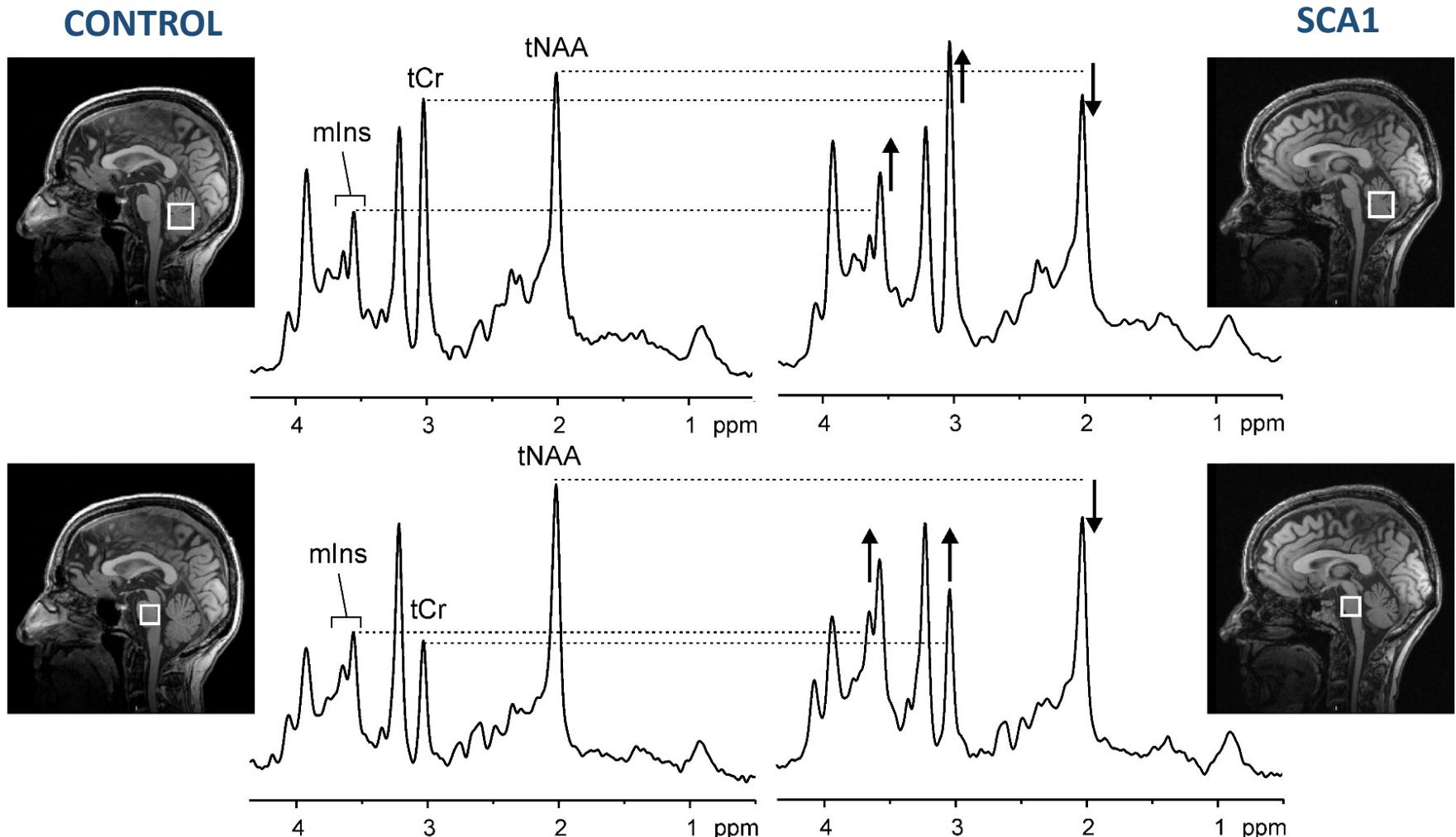


Stefanescu, 2015 Brain  
Deistung, 2016 Cerebellum

# Neurochemistry by MR Spectroscopy

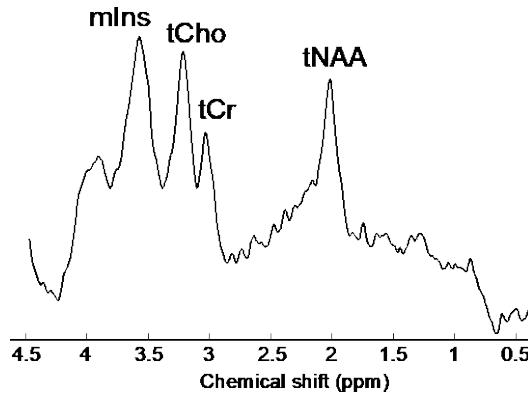


**Neurochemical alterations are detectable in individuals**

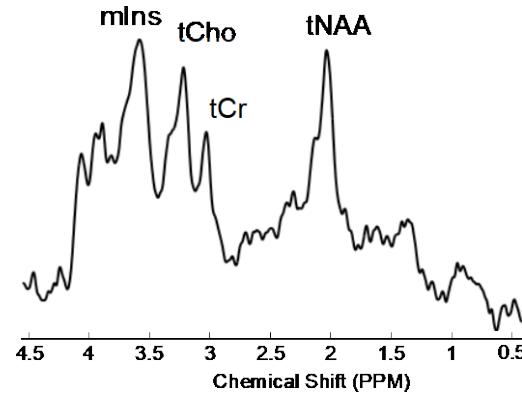


# Which spectra are from participants with FRDA?

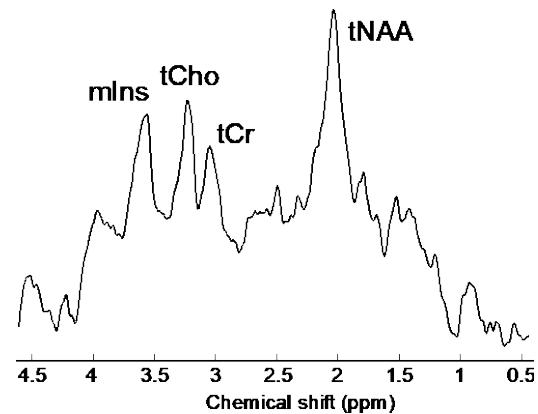
#1



#2

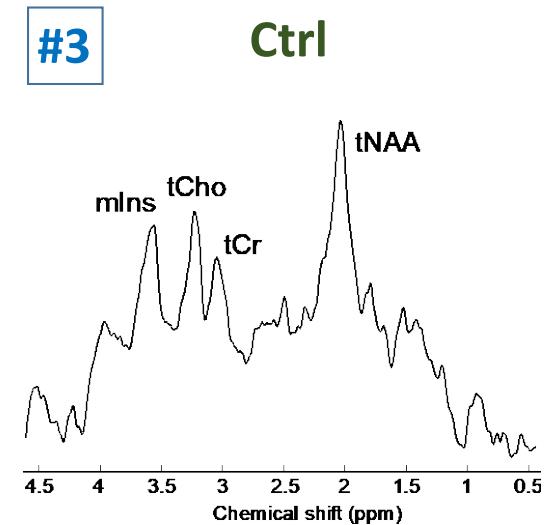
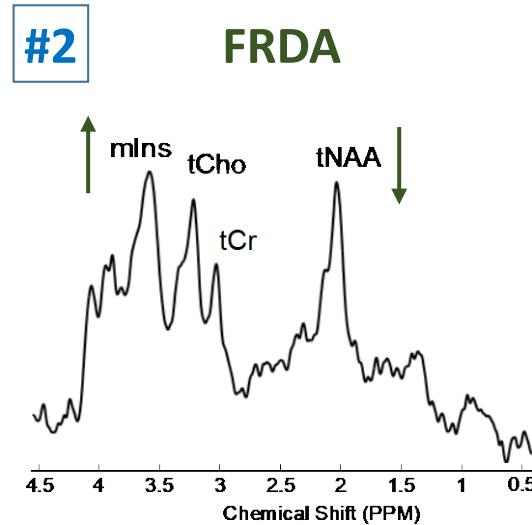
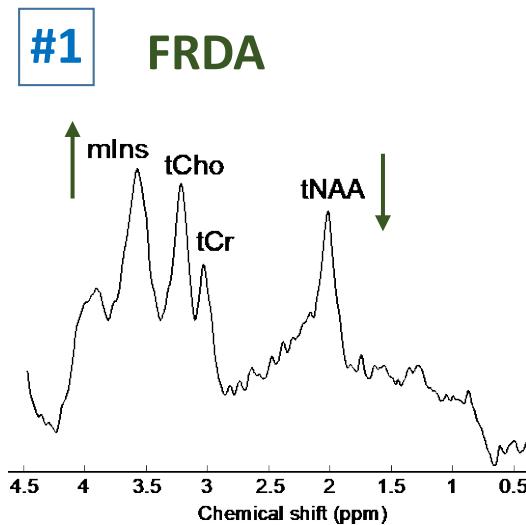


#3



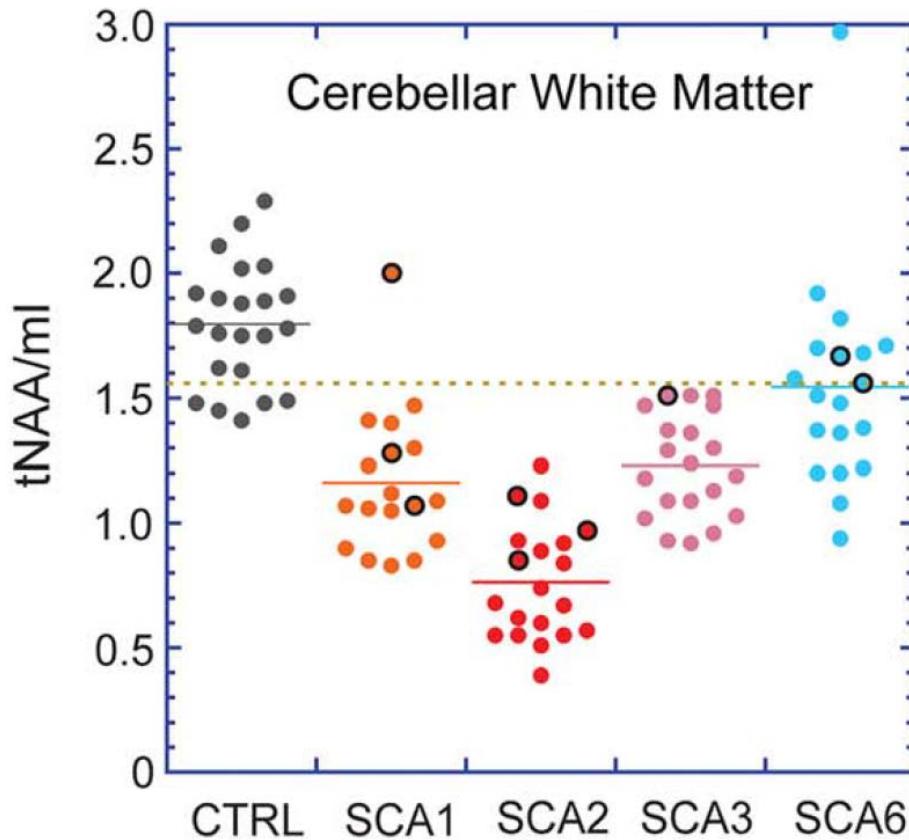
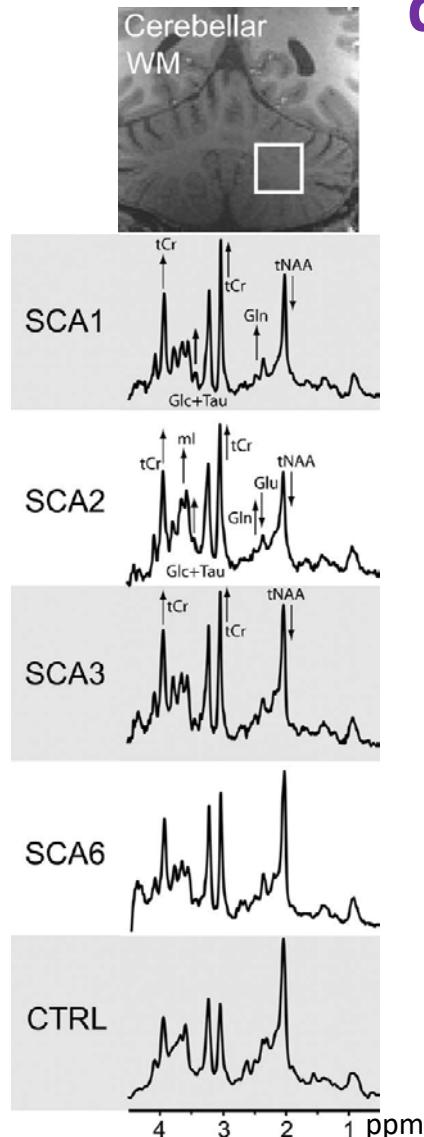
- a. #1 and #2
- b. #2 and #3
- c. #1 and #3

# Which spectra are from participants with FRDA?



a. #1 and #2

# Premanifest neurochemical alterations are detectable in individuals

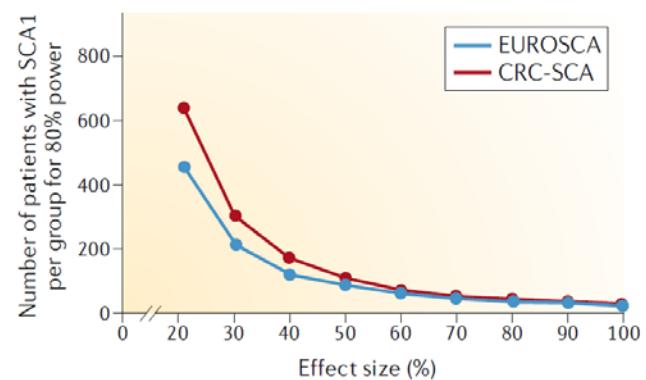
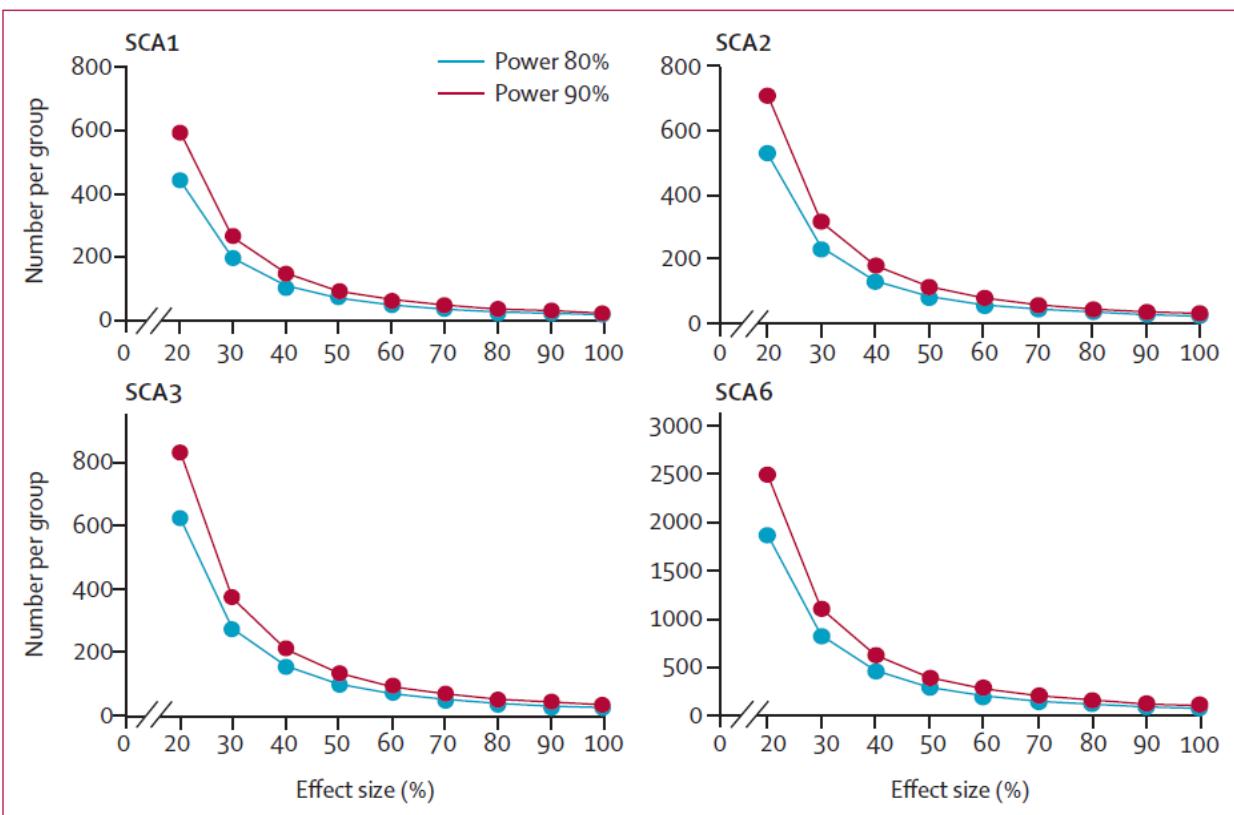




# Need for new outcome measures in SCAs

**Heike Jacobi**  
Neurologist  
Neurology Clinic

**Outcome measure:** Scale for the Assessment and Rating of Ataxia (SARA)  
8 items; evaluates gait, stance, sitting, speech, and limb kinetic functions



**Fig. 4 | Sample size estimation for evaluation of drug efficacy in SCA1.** Figure shows the estimated sample size required for the efficacy of a drug to be tested in a clinical trial of patients with spinocerebellar atrophy 1 (SCA1). Among

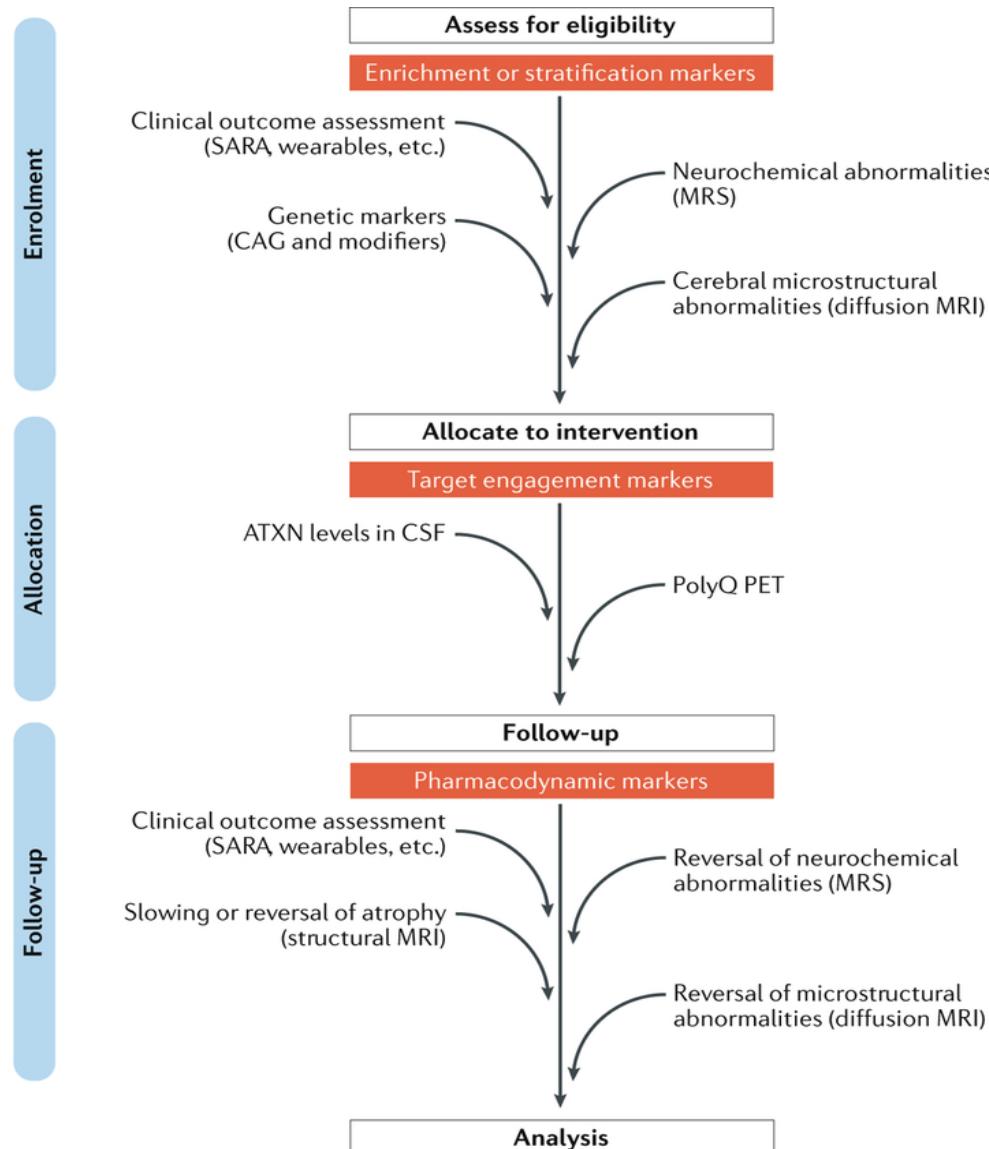
*Ashizawa, Öz, Paulson,  
Nat Rev Neurology 2018*

**Figure 2: Sample size estimates**

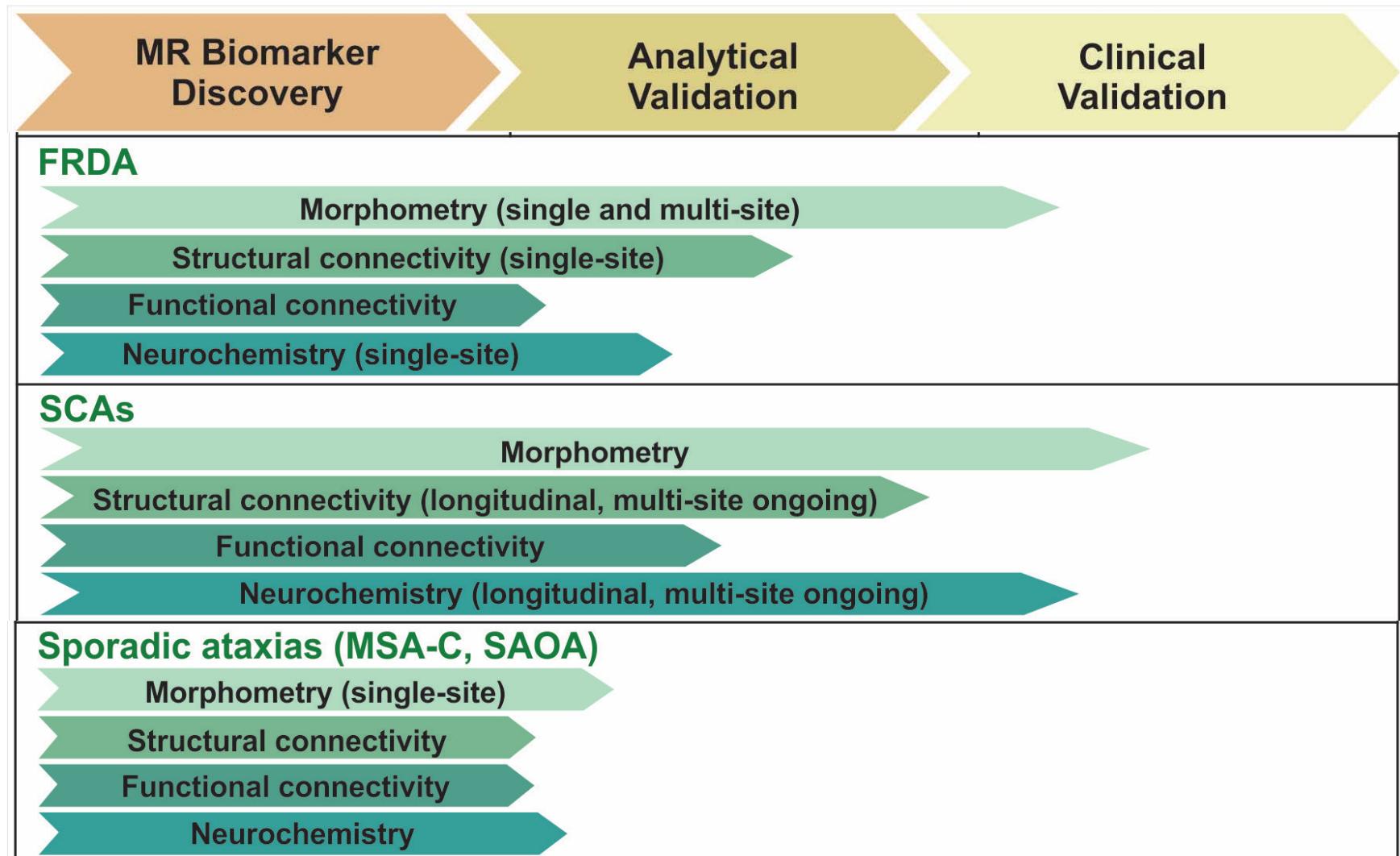
Required sample size per group in two-group interventional trials of 1-year duration for various effect sizes in SCA1, SCA2, SCA3, and SCA6. SCA=spinocerebellar atrophy.

*Jacobi et al, Lancet Neurol 2015*

# Utility of MR Biomarkers in Clinical Trials



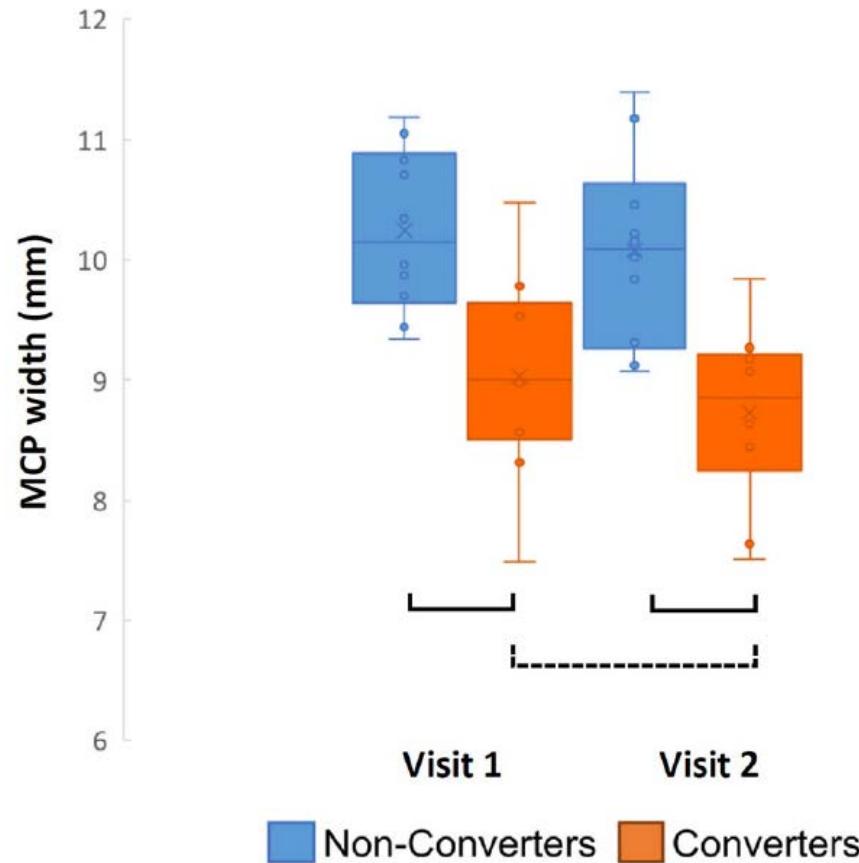
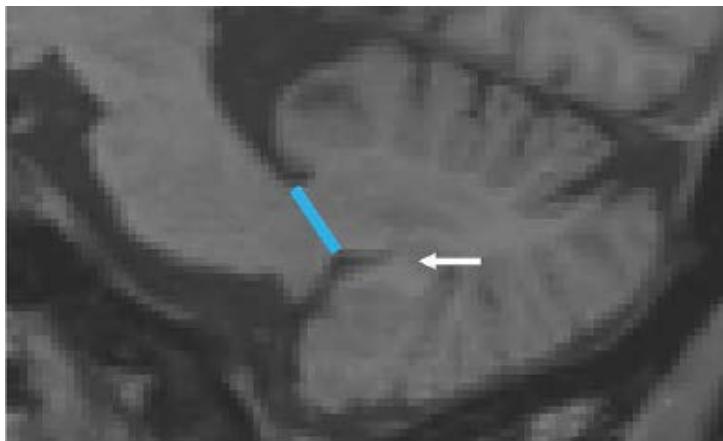
# Status of SCA biomarker validation



# Middle Cerebellar Peduncle Width—A Novel MRI Biomarker for FXTAS?

Annie L. Shelton<sup>1,2,3</sup>, Jun Y. Wang<sup>1,2,4</sup>, Emily Fourie<sup>1,2,3</sup>, Flora Tassone<sup>1,4</sup>, Anna Chen<sup>3</sup>, Lauren Frizzi<sup>3</sup>, Randi J. Hagerman<sup>1,5</sup>, Emilio Ferrer<sup>3</sup>, David Hessl<sup>1,6</sup> and Susan M. Rivera<sup>1,2,3\*</sup>

Fragile X-associated tremor/ataxia syndrome



# ACKNOWLEDGEMENTS



WG3 meeting - March 22, 2021