Advanced multimodal MRI detects premanifest and early-stage alterations in SCA1 and SCA3 with high sensitivity

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READISCA
Clinical Trial Readiness for SCA1 and SCA3

UNIVERSITY OF MINNESOTA

Driven to Discover℠

Background

- **READISCA**: multinational longitudinal clinical trial readiness study for SCA1 and SCA3

- MRI and MRS detect early cerebral and cerebellar changes in SCAs [1,2,3].

AIM

1) Identify morphometric, microstructural and neurochemical MR metrics most sensitive to early abnormalities

2) Investigate associations of MR metrics with early clinical presentation

[1] Reetz et al, Brain 2013, [2] Park et al Front Neurol 2020,
[3] Joers et al Ann Neurol 2018

Table 1: Cohort Characteristics

Variable	Control	SCA1 Preataxic	SCA1 Ataxic	SCA3 Preataxic	SCA3 Ataxic
N	17	11	14	28	37
Gender (female)	7 (41%)	8 (73%)	9 (67%)	19 (68%)	18 (49%)
Age (median)	43	38	46.5	36	50
SARA (median)	*0*	*1*	*8.3*	*1.3*	*7*
CAG repeat length		42	45	70	71.5
Reported age at onset			40 (*N*=11)		45 (*N*=35)

No significant differences in COA btw preataxic SCA vs controls

MR Protocol

Data Analysis

- 6 imaging sites, 3T Siemens

Sequence	Pixel dim. (mm x mm x mm)	TR/TE/TI (ms)
MPRAGE 3D T_1*	0.8 iso	2400/2.22/1000
3D T_2w*	0.8 iso	3200/563/-
DWI*	1.5 iso	3230/89.2/-
MRS**	-	3000/30
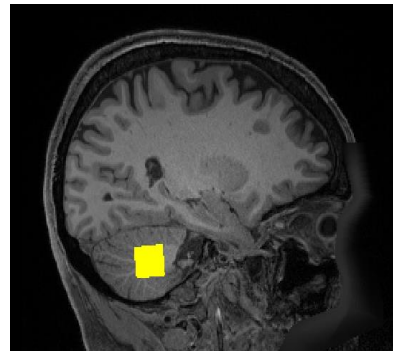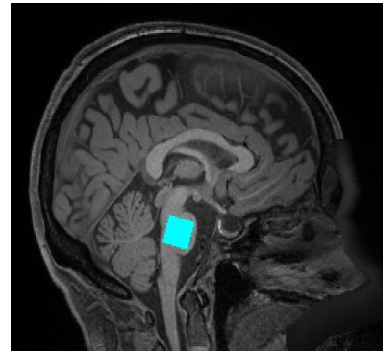
*T1, T2, DWI: HCP lifespan protocol

**Two MRS VOIs used: [1]pons, 16x16x16 mm^3 and [2]cerebellar white matter(CBWM), 17x17x17 mm^3

[4] Fischl 2004 Neuroimage, [5] Romero 2016 NeuroImage, [6] Park et al Front Neurol 2020, [7] Provencher Magn Reson Med 1993

- Blinded to diagnosis

Volumetry

- FreeSurfer 6.0.3[4] for (sub-)cortical and brainstem segmentation.
- CERES tool[5] for cerebellum segmentation.

Diffusion MRI (Microstructure)

- FSL DTIFIT tool for fractional anisotropy (FA), and diffusivities (AD, RD, MD) in white-matter (WM) ROIs [6].

MRS:

- LCModel[7] using water as internal concentration reference.
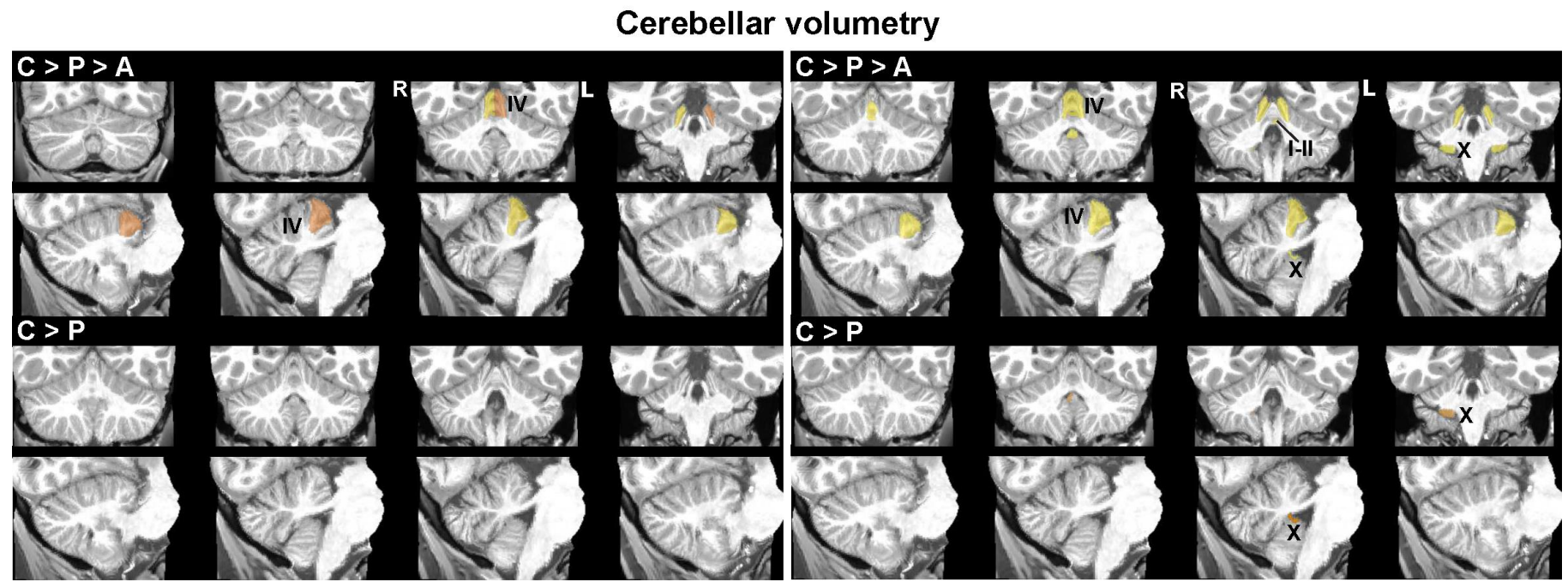
Statistical Analysis

- MR measures compared between preataxic, ataxic SCA and control groups using non-parametric testing accounting for multiple comparisons (Bonferroni-Holm)
- Pairwise comparisons of significant metrics between preataxic and control groups with Dunn adjustment.
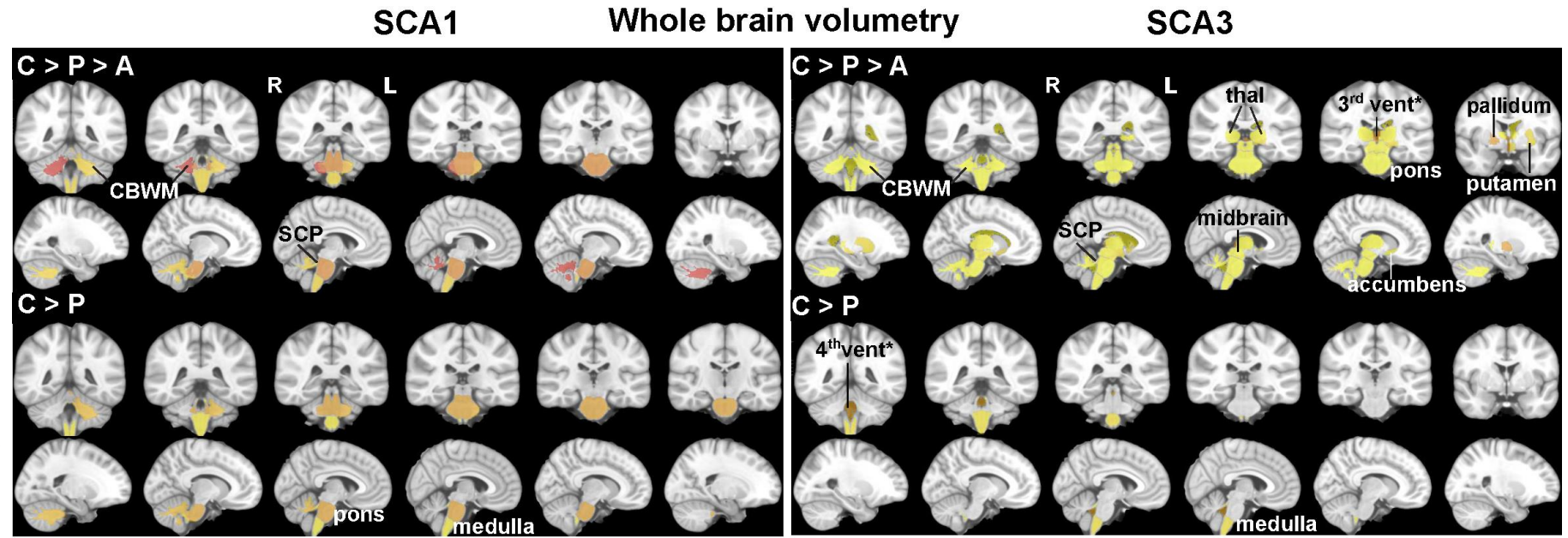
Volumetry RESULTS

Preataxic SCA1- atrophy of pons, medulla and cerebellar white matter

Preataxic SCA3- atrophy of Xth lobule

Whole brain volumetry

SCA1 — C > P > A, C > P

SCA3 — C > P > A, C > P — thal, 3rd vent*, pallidum, CBWM, pons, putamen, SCP, midbrain, accumbens, 4th vent*, medulla

Cerebellar volumetry

C > P > A — IV, I-II, X

C > P — X

p value: 0.05 0.04 0.03 0.02 0.01

Microstructure RESULTS

SCA1 preataxic group: lower FA in pontine crossing tract and inferior cerebellar peduncle.

Widespread increase in mean diffusivity in preataxic SCA3 - cerebellar peduncles, pontine crossing and corona radiata tracts.
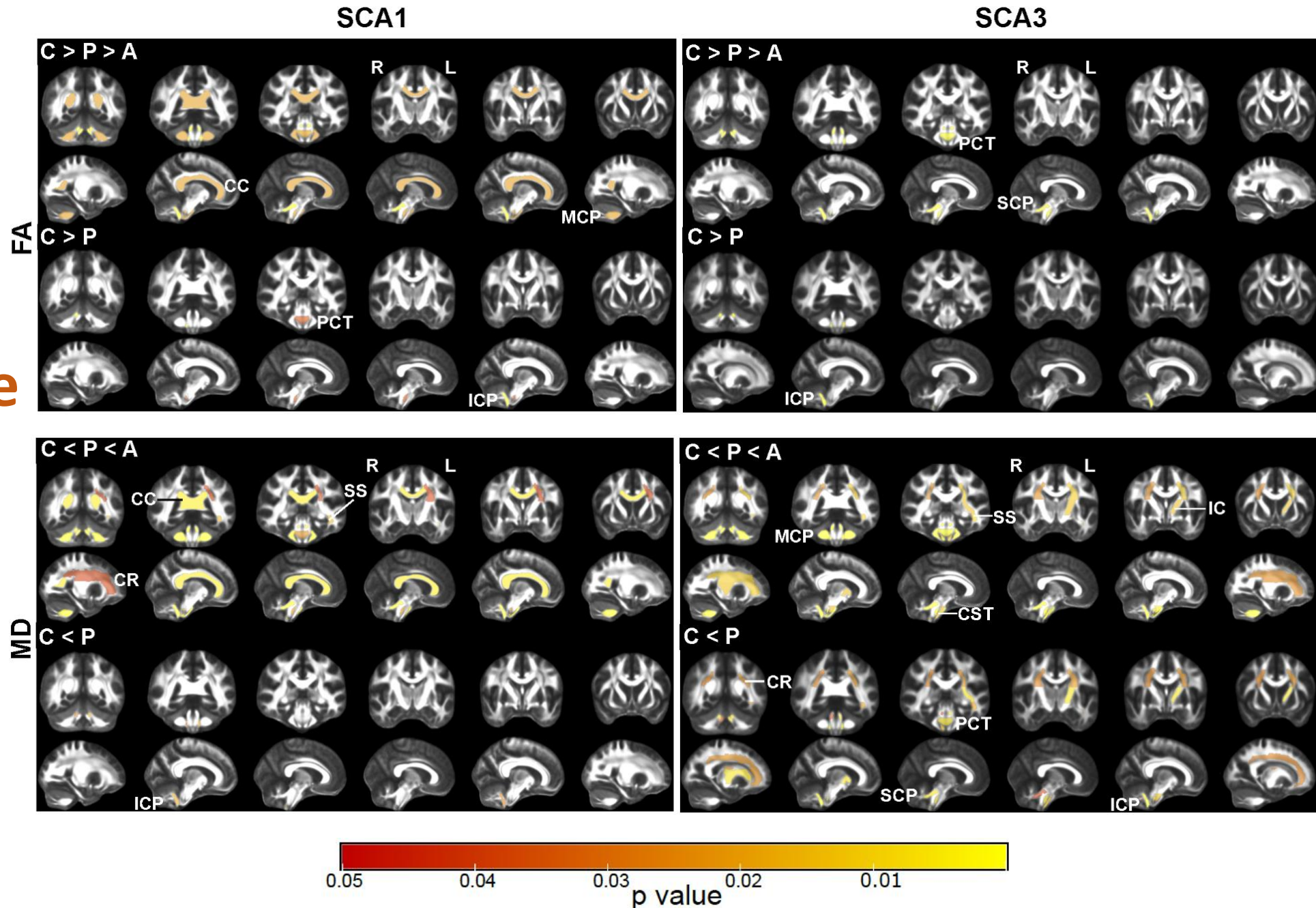
MRS RESULTS
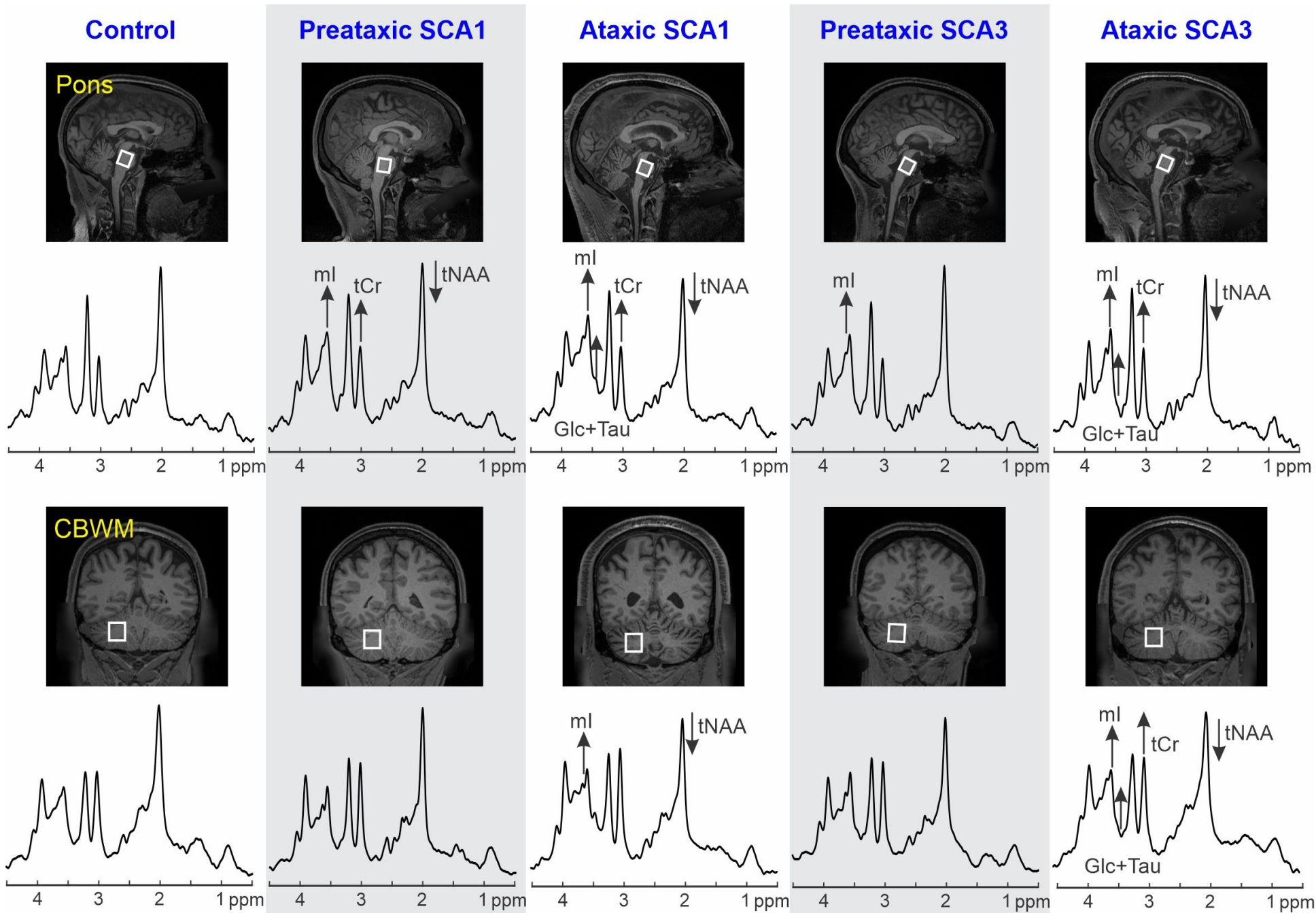
| Metabolite	Biological Significance
total N-Acetyl Aspartate	Neurons, axons (Change in cell number/viability)
myo-Inositol	Glial cell marker, neuroinflammation
total Creatine	Defects in energy metabolism

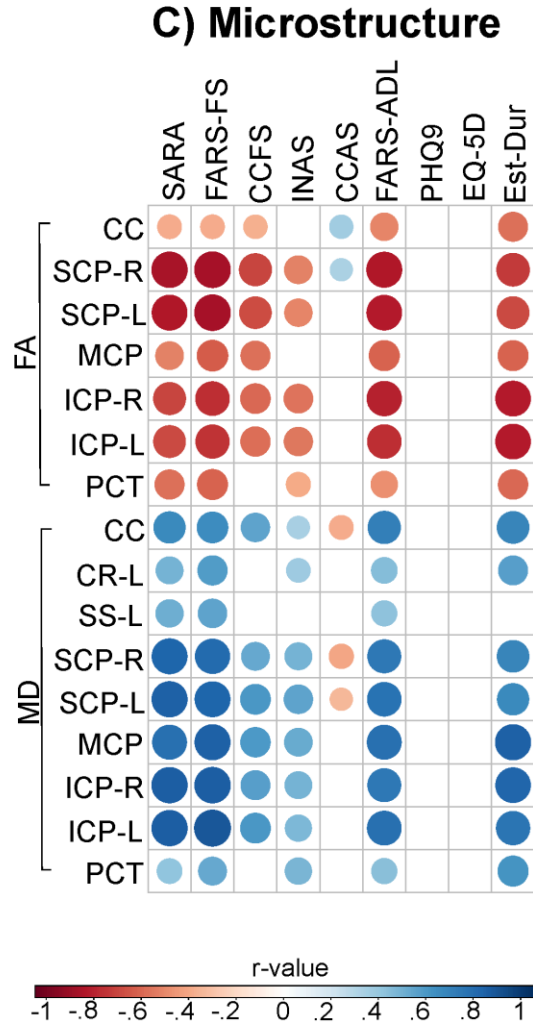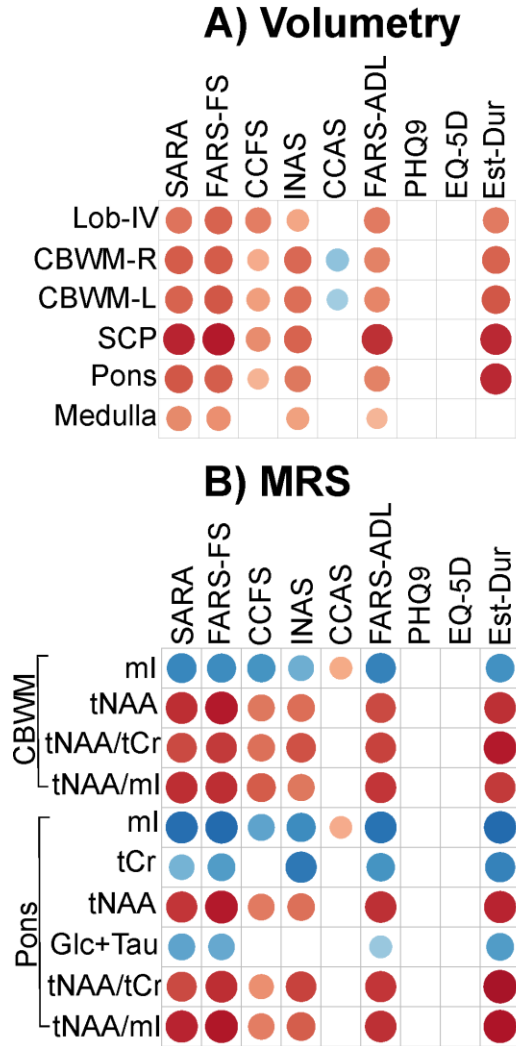# Metrics most sensitive to preataxic abnormalities

SCA1

Metrics most sensitive to preataxic abnormalities
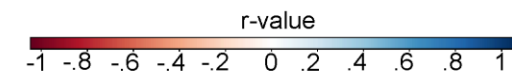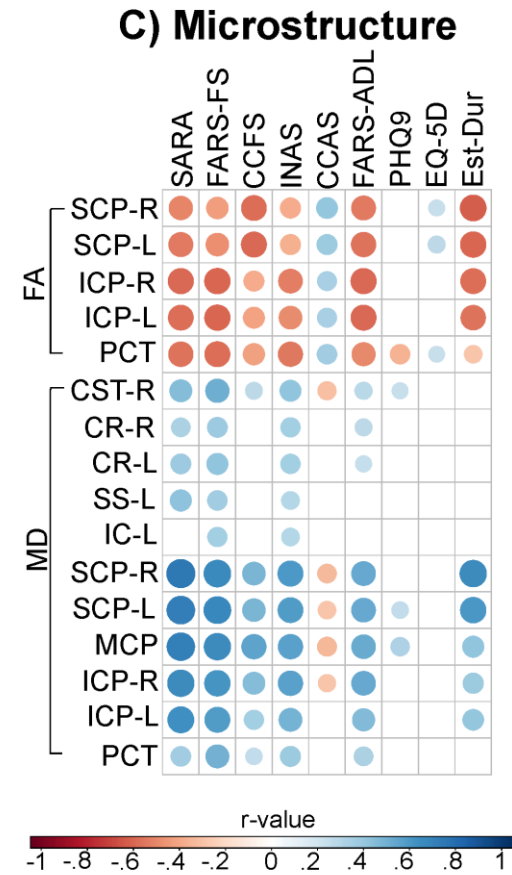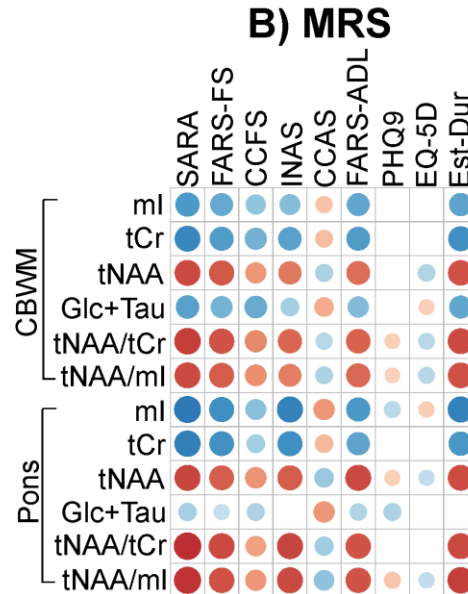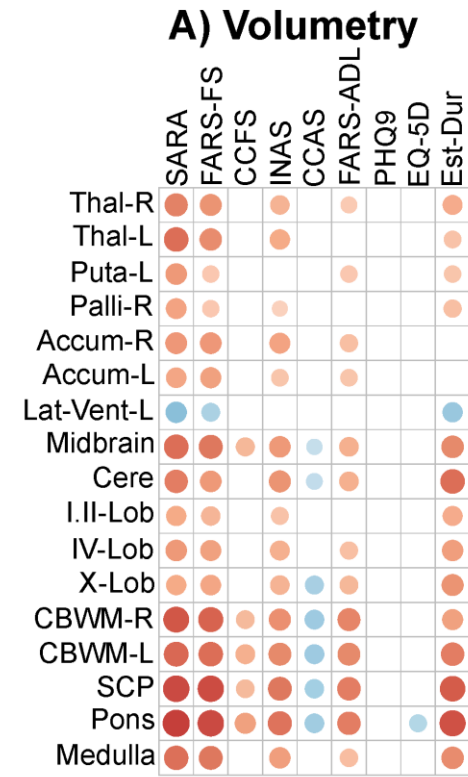
SCA3

Metric: AUC
Vol(SCP): 0.84
Vol(X-R): 0.73
RD(ICP-R): 0.92
ml(Pons): 0.79

** = P < 0.01
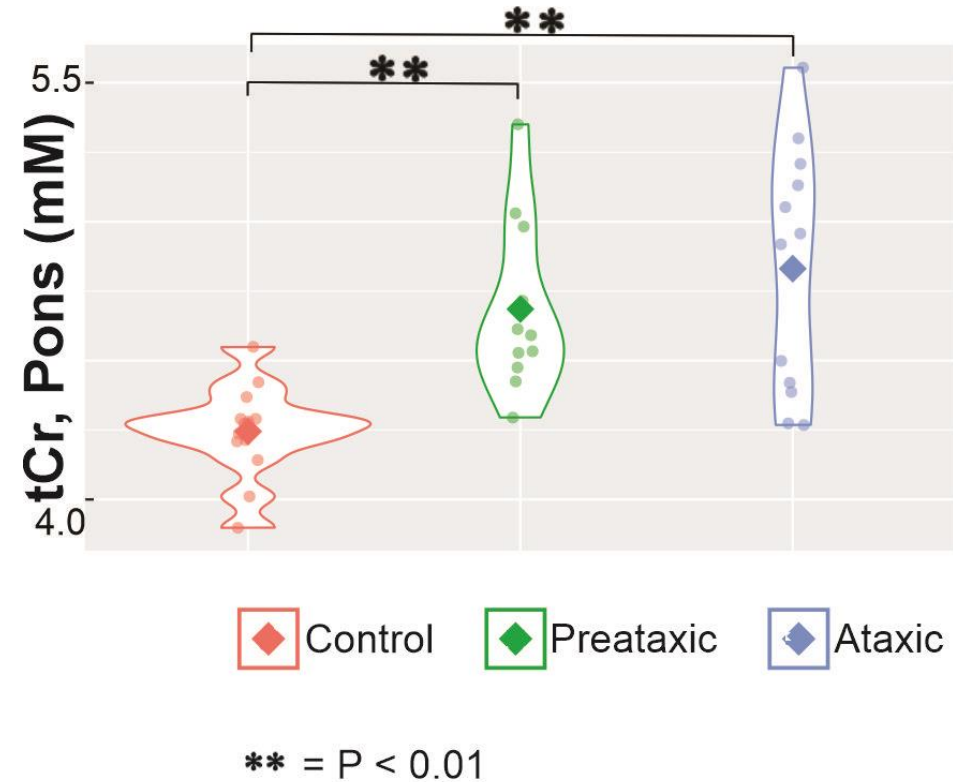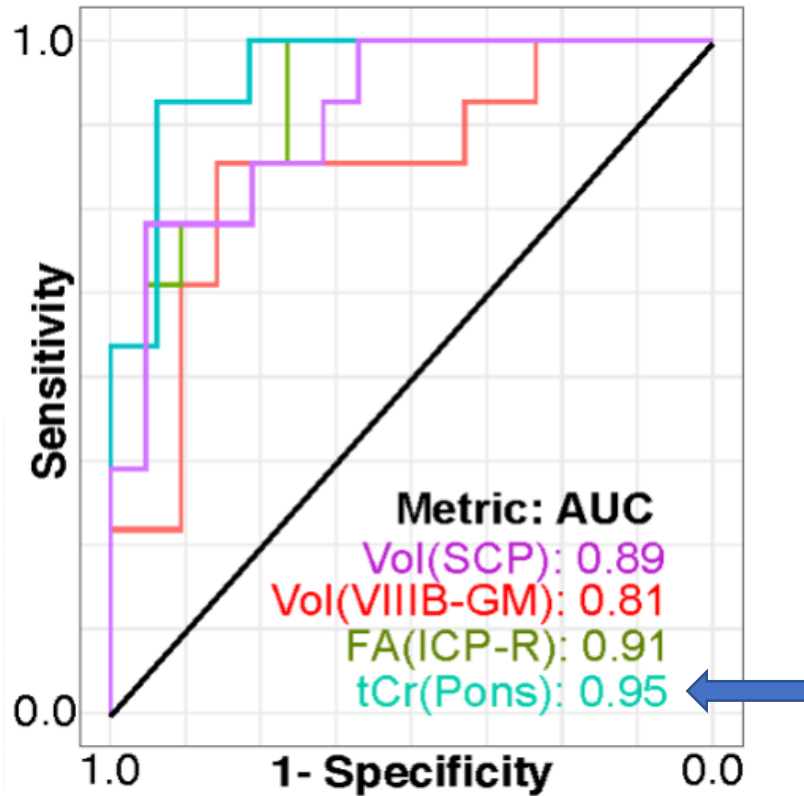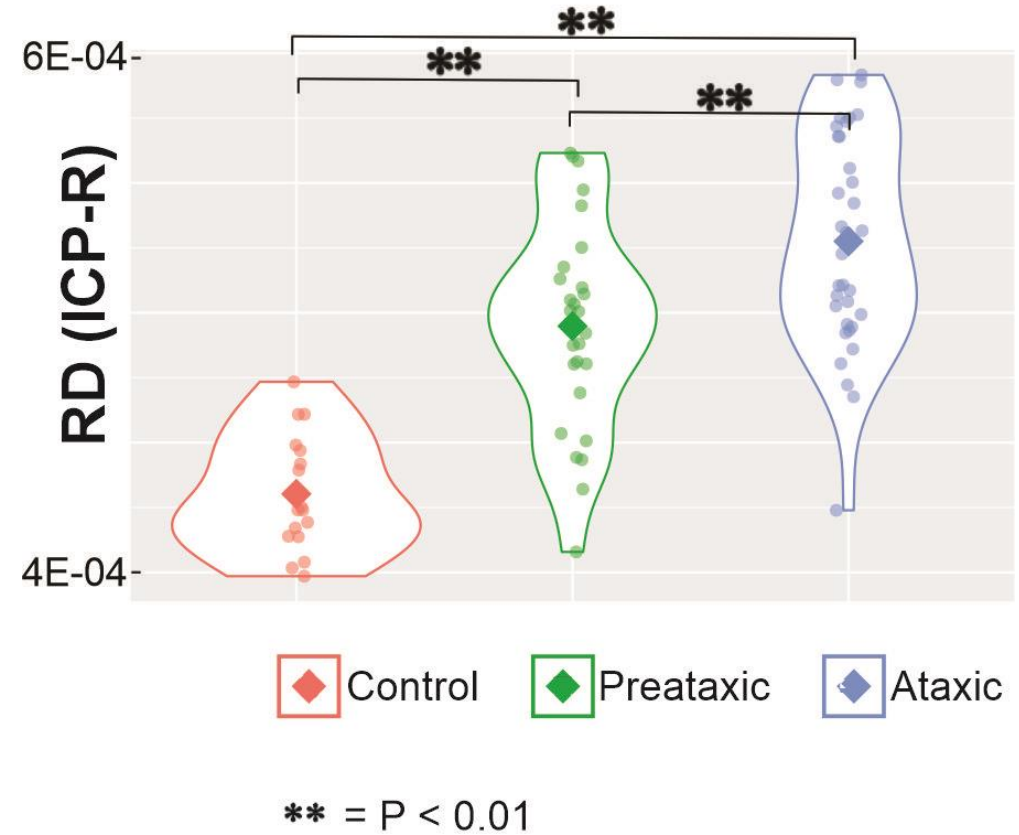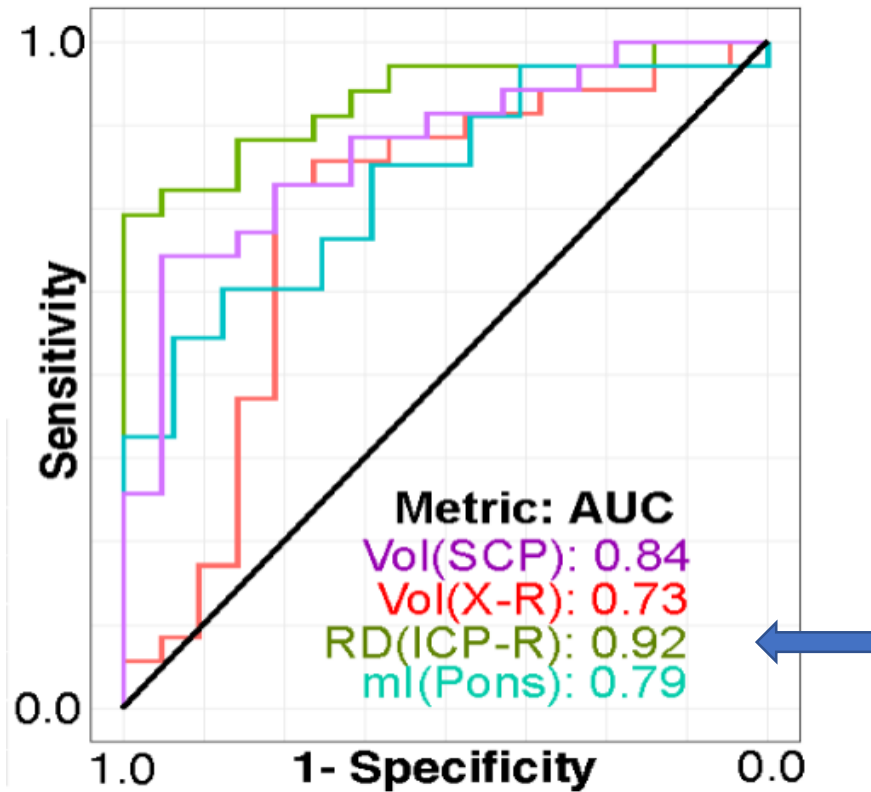
MR – Clinical correlations

SCA1

A) Volumetry

B) MRS

C) Microstructure

SCA3

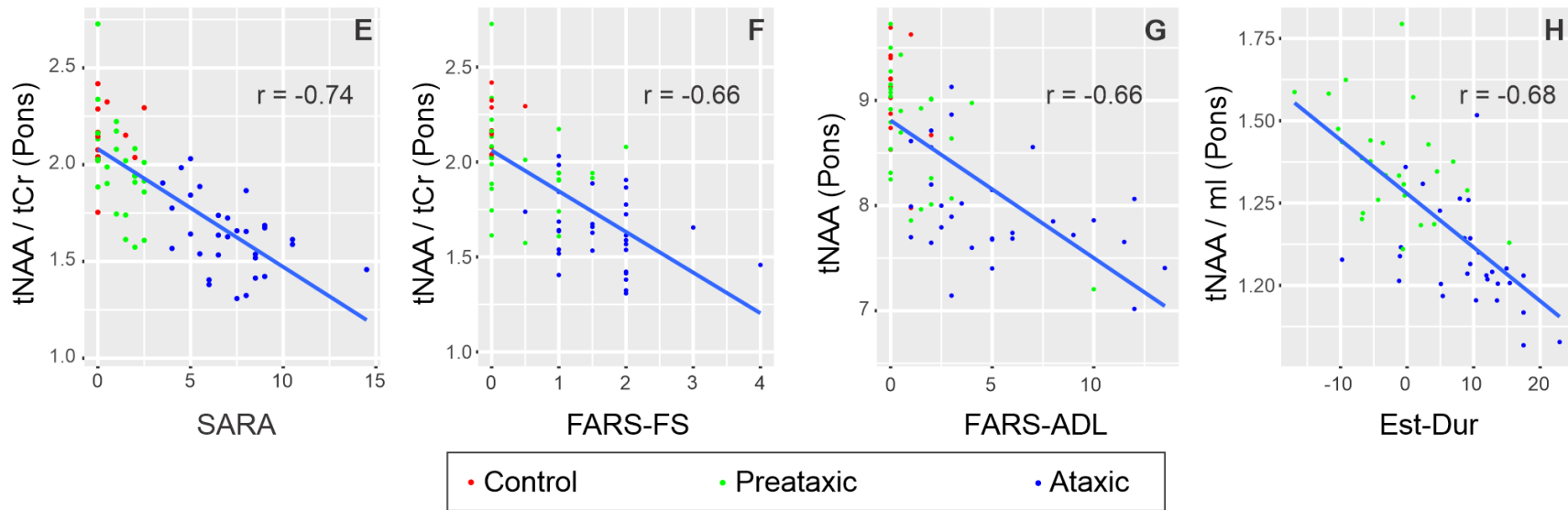**A) Volumetry**

B) MRS

C) Microstructure

MR associations with ataxia symptoms (SARA, FARS-FS), non-ataxia signs (INAS), activities of daily living (FARS-ADL) and estimated ataxia duration (Est-Dur)

Cerebellar afferent and efferent pathways underlie earliest symptoms

MR – Clinical correlations
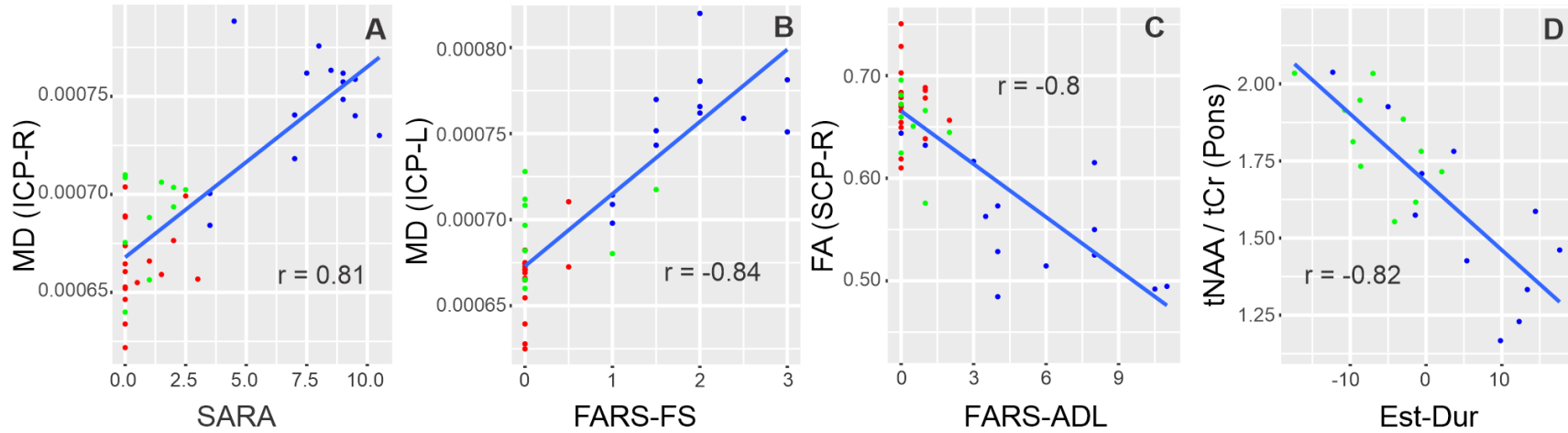
Strongest MR correlates of ataxia, ADL and estimated duration: MRS and diffusion measures

CONCLUSIONS

- ✓ Atrophy and microstructural damage in the brainstem and cerebellar peduncles and neurochemical abnormalities in the pons prominent at preataxic stage

- ✓ A neurochemical measure was the most sensitive metric to preataxic changes in SCA1 and a microstructural metric was the most sensitive metric to preataxic changes in SCA3

- ✓ MR metrics strongly associated with ataxia symptoms, activities of daily living and estimated disease duration

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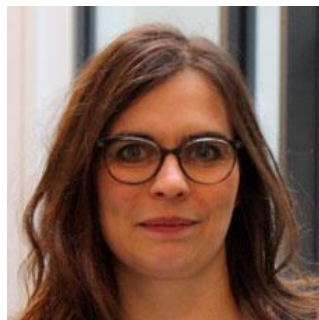
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