

Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

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- 2. What is the current knowledge on the topic? (one to two sentences)**

Disease-modifying therapies including various gene silencing strategies are in the therapeutic pipeline for spinocerebellar ataxias, and their effectiveness is most likely when administered early, prior to substantial neurodegeneration. To facilitate trials at the earliest disease stages, outcome measures are needed to detect changes in the brain at the stage when clinical measures have low sensitivity.

- 3. What question did this study address? (one to two sentences)**

Which MR biomarkers that are collected using standard at 3T MRI equipment are most sensitive to the early changes in the brain before onset of motor symptoms in SCA1 and SCA3? Is it feasible to acquire multi-modal MR data with a harmonized advanced protocol in the multi-site academic trial setting?

- 4. What does this study add to our knowledge? (one to two sentences)**

Neurochemical and microstructural MR metrics distinguish preataxic SCA mutation carriers from matched controls with very high sensitivity (areas under the curve of 0.92-0.95 in ROC analyses) and with higher sensitivity than structural metrics. Multi-modal MR metrics are strongly associated with a comprehensive battery of clinical outcome measures, including patient reported outcomes; and can be collected with a harmonized advanced multi-modal protocol in the multi-site clinical trial setting.

- 5. How might this potentially impact on the practice of neurology? (one to two sentences)**

This work identifies the most sensitive MR markers to early brain pathology in SCA1 and SCA3 and opens the possibility of detecting disease effects in individuals before ataxia onset to facilitate subject stratification in clinical trials.

Draft Tweet:

Advanced MRI detects brain changes in spinocerebellar ataxias before motor symptom onset with high sensitivity in multi-site study.

Abstract

Objective: To identify MR metrics that are most sensitive to early changes in the brain in spinocerebellar ataxia type 1 (SCA1) and type 3 (SCA3) using an advanced multi-modal MRI protocol in the multi-site trial setting.

Methods: SCA1 or SCA3 mutation carriers and controls ($n=107$) underwent MR scanning in the US-European READISCA study to obtain structural, diffusion MRI and MR spectroscopy data using an advanced protocol at 3T. Morphometric, microstructural, and neurochemical metrics were analyzed blinded to diagnosis and compared between preataxic ($n=11$ SCA1, 28 SCA3), ataxic ($n=14$ SCA1, 37 SCA3) SCA and control ($n=17$) groups using non-parametric testing accounting for multiple comparisons. MR metrics that were most sensitive to preataxic abnormalities were identified using receiver operating characteristic (ROC) analyses.

Results: Atrophy and microstructural damage in the brainstem and cerebellar peduncles and neurochemical abnormalities in the pons were prominent in both preataxic groups, when patients did not differ from controls clinically. MR metrics were strongly associated with ataxia symptoms, activities of daily living and estimated ataxia duration. A neurochemical measure was the most sensitive metric to preataxic changes in SCA1 (ROC area under the curve (AUC) =0.95) and a microstructural metric was the most sensitive metric to preataxic changes in SCA3 (AUC =0.92).

Interpretation: Changes in cerebellar afferent and efferent pathways underlie the earliest symptoms of both SCAs. MR metrics collected with a harmonized advanced protocol in the multi-site trial setting allow detecting disease effects in individuals before ataxia onset with potential clinical trial utility for subject stratification.

Abbreviations	Expansion
AD	<u>A</u> xial <u>d</u> iffusivity
CBWM	<u>C</u> erebellar <u>w</u> hite <u>m</u> atter
CC	<u>C</u> orpus <u>c</u> allosum
CCAS	<u>C</u> erebellar <u>c</u> ognitive- <u>a</u> ffective <u>s</u> yndrome
CCFS	<u>C</u> omposite <u>c</u> erebellar <u>f</u> unctional <u>s</u> everity score
COA	<u>C</u> linical <u>o</u> utcome <u>a</u> ssessments
CR	<u>C</u> orona <u>r</u> adiata
CST	<u>C</u> orticospinal <u>t</u> ract
EC	<u>E</u> xternal <u>c</u> apsule
EQ-5D	<u>E</u> uropean <u>q</u> uality of life <u>5</u> <u>d</u> imensions
FA	<u>F</u> ractional <u>a</u> nisotropy
FARS-ADL	<u>F</u> riedreich's <u>a</u> taxia <u>r</u> ating <u>s</u> cale <u>a</u> ctivities of <u>d</u> aily <u>l</u> iving subscale
FARS-FS	<u>F</u> riedreich's <u>a</u> taxia <u>r</u> ating <u>s</u> cale <u>f</u> unctional <u>s</u> taging
FASTESTMAP	<u>F</u> ast, <u>a</u> utomatic <u>s</u> him <u>t</u> echnique using <u>e</u> cho-planar <u>s</u> ignal <u>r</u> eadout for <u>m</u> apping <u>a</u> long <u>p</u> rojections
FOV	<u>F</u> ield of <u>v</u> iew
Glc+Tau	<u>G</u> lucose + <u>t</u> aurine
GRAPPA	<u>G</u> eneralized <u>a</u> utocalibrating <u>p</u> artial <u>p</u> arallel <u>a</u> cquisition
IC	<u>I</u> nternal <u>c</u> apsule
ICP	<u>I</u> nterior <u>c</u> erebellar <u>p</u> eduncle
INAS	<u>I</u> nterinventory of <u>n</u> on- <u>a</u> taxia <u>s</u> igns
MCP	<u>M</u> iddle <u>c</u> erebellar <u>p</u> eduncle
MD	<u>M</u> ean <u>d</u> iffusivity
mI	<u>m</u> yo- <u>I</u> nositol
MPRAGE	<u>M</u> agnetization- <u>p</u> repared <u>r</u> apid <u>g</u> radient- <u>e</u> cho
MRS	<u>M</u> agnetic <u>r</u> esonance <u>s</u> pectroscopy
PCT	<u>P</u> ontine <u>c</u> rossing <u>t</u> ract
PHQ-9	<u>P</u> atient <u>h</u> ealth <u>q</u> uestionnaire- <u>9</u>
RD	<u>R</u> adial <u>d</u> iffusivity
SARA	<u>S</u> cale for the <u>a</u> ssessment and <u>r</u> ating of <u>a</u> taxia

SCP	<u>S</u> uperior <u>c</u> erebellar <u>p</u> eduncle
sLASER	<u>S</u> emi- <u>l</u> ocalization by <u>a</u> diabatic <u>s</u> elective <u>r</u> efocusing
SPACE	<u>S</u> ampling <u>p</u> erfection with <u>a</u> pplication- <u>o</u> ptimized <u>c</u> ontrasts using different flip angle <u>e</u> volution
SS	<u>S</u> agittal <u>s</u> tratum
tCr	<u>T</u> otal <u>c</u> reatine = creatine + phosphocreatine
TE	<u>E</u> cho <u>t</u> ime
tNAA	<u>T</u> otal <u>N</u> - <u>a</u> cetyl <u>a</u> spartate = <i>N</i> -acetylaspartate + <i>N</i> -acetylaspartylglutamate
TR	<u>R</u> epetition <u>t</u> ime
VOI	<u>V</u> olume <u>o</u> f <u>i</u> nterest
WM	<u>W</u> hite <u>m</u> atter

Introduction

Spinocerebellar ataxias (SCAs) are rare autosomal dominant neurodegenerative disorders, the clinical hallmark of which is progressive loss of balance and coordination. SCA1 is the fastest progressing,^{1,2} and SCA3 the most common SCA worldwide.³ Both are polyglutamine diseases caused by translated dynamic CAG repeat expansion mutations and present with degeneration in the cerebellum and brainstem. Disease-modifying therapies including gene silencing strategies are in the SCA therapeutic pipeline.⁴ Effectiveness of such therapies is most likely when they are administered at early disease stages.⁵ However, clinical outcome measures have low sensitivity in early disease necessitating alternative measures to identify trial participants with cerebral and cerebellar changes before onset of ataxia. Non-invasive imaging may allow detection of such early degenerative changes in SCAs, and thereby facilitate trials at early disease stages.

Atrophy of the cerebellum, brainstem and forebrain regions are reliably detected with structural MRI in SCAs,⁶ including in early stage at group level.⁷⁻⁹ In addition, microstructural damage to the white matter (WM) and neurochemical abnormalities that likely precede tissue loss were detectable at subject level in single site studies with few preataxic subjects using diffusion MRI^{10, 11} and magnetic resonance spectroscopy (MRS),^{12, 13} respectively. Hence, studies of larger trial-ready cohorts in the earliest disease stages with a multimodal imaging protocol are warranted.

READISCA¹⁴ is a multinational longitudinal clinical trial readiness study that enrolls preataxic and early ataxic SCA1 and SCA3 mutation carriers¹⁵ and matched healthy controls. READISCA enrolled the largest preataxic SCA cohorts for multimodal imaging thus far. Here we report the baseline structural, diffusion MRI and MRS findings. Our goals were 1) to evaluate the feasibility of collecting multi-modal MR data using a harmonized advanced protocol in the multi-site academic trial setting; 2) to identify the structural, microstructural and neurochemical MR metrics that are most sensitive to early abnormalities in SCA1 and SCA3 mutation carriers; and 3) to investigate the associations of these MR metrics with early clinical presentation in SCA1 and SCA3 as assessed by a comprehensive battery of outcome measures covering motor, non-motor, cognitive function and activities of daily living.

Methods

Study participants and design

The imaging cohort of READISCA included 107 participants who were willing to undergo MRI and clear of MR contraindications (Table 1). They were enrolled at 16 sites¹⁴ in the US and Europe from 2018-2021. The sample size was guided by feasibility to enroll preataxic and very early-stage participants. Participants with a Scale for the Assessment and Rating of Ataxia (SARA)¹⁶ score less than 10 (range 0–40; 0 indicating no ataxia and 40 most severe ataxia) were targeted for enrollment. SCA mutation carriers with $SARA < 3$ were classified as preataxic and those with $SARA \geq 3$ as ataxic.^{15, 17} Control subjects comprised of at-risk individuals (first-degree relatives of patients) who tested negative for SCA1 or SCA3 and healthy volunteers who were unrelated to the patients. Individuals who were diagnosed with a hereditary ataxia other than SCA1 or SCA3, had a concomitant disorder that affected assessment of ataxia, had taken investigational drugs, or had changes in coordinative physical and occupational therapy 2 months prior to participation were excluded.

Participants underwent clinical evaluation at the enrolling sites and were scanned within 9 weeks (87 subjects within 4 weeks) at one of the six imaging sites in the US (University of Minnesota, University of Florida, Johns Hopkins University, Massachusetts General Hospital) and Europe (German Center for Neurodegenerative Diseases, ICM Paris Brain Institute). Site selection was based on MR expertise, prior collaborations that enabled timely initiation of scans in parallel with clinical assessments, and availability of 3T Siemens scanners. All procedures were approved by the Institutional Review Board at each site. Informed consent was obtained from all participants.

Clinical assessments

All subjects underwent the SARA¹⁶ assessment, which is a composite cerebellar ataxia scale, and was used to define the preataxic and ataxic groups as described above. Ataxic participants reported age at ataxia onset (Table 1). In addition, time from ataxia onset was estimated using CAG repeat length for both preataxic and ataxic participants (using long alleles for SCA1¹⁷ and both alleles with a newer improved statistical model for SCA3,¹⁸ which does not display a systematic bias in patients with late-onset ataxia observed with the original Tezenas formula,

Tezenas du Montcel *et al*, Neurology, revision submitted). All participants underwent the clinical outcome assessments (COAs) of READISCA, including the Composite Cerebellar Functional Severity Score (CCFS),¹⁹ Inventory of Non-Ataxia Signs (INAS),²⁰ Cerebellar Cognitive Affective Syndrome (CCAS) scale,²¹ Friedreich's Ataxia Rating Scale Activities of Daily Living (FARS-ADL) and Functional Staging (FARS-FS) subscales,²² Patient Health Questionnaire 9 (PHQ-9)²³ and the EuroQol 5D (EQ-5D) visual analogue scale.²⁴ The COAs that showed significant group differences in the entire READISCA cohort ($n=200$; Tezenas du Montcel *et al*, Neurology, revision submitted) are summarized for the MR cohort in Table 1.

MRI data acquisition

MR data were acquired on 3T Siemens (Erlangen, Germany) scanners (5 Prisma, 1 Skyra) operating under Syngo MR E11 software and using body coil transmission and a 32-channel receive array. Structural and diffusion MRI were acquired with the Human Connectome Project (HCP) Lifespan protocol: **1**) 3D T₁-weighted MPRAGE (0.8mm³ isotropic resolution, repetition time (TR) = 2400ms, echo time (TE) = 2.22ms, inversion time = 1000ms, flip angle = 8°, GRAPPA factor = 2); **2**) 3D T₂-weighted SPACE (0.8mm³ isotropic resolution, TR/TE = 3200/563ms, GRAPPA factor = 2); **3**) multiband diffusion MRI acquired with opposing phase encoding in the anterior-posterior direction and q -space sampling split into two sets of 98, and two sets of 99 volumes, resulting in two sets of 197 volumes including 13 b=0 per PE (184 unique diffusion images). On Prisma scanners, 1.5mm³ isotropic resolution, TR/TE = 3230/89.2ms, multiband acceleration = 4, and b-values = 1500, 3000 s/mm² were used. On the Skyra scanner, 1.7mm³ isotropic resolution, TR/TE = 3390/103.2ms, multiband acceleration = 4 and b-values = 1000, 2000 s/mm² were used. Except b-values, q -space sampling was the same on Prisma and Skyra.

Volumes-of-interest (VOIs) for MRS were pons (16x16x16mm³) and cerebellar WM (CBWM, 17x17x17mm³). VOIs were automatically prescribed with AutoVOI, using predefined voxels on the MNI152 atlas.²⁵ MRS data were collected using sLASER (TR/TE = 3000/30ms, 80 transients),²⁶ which was recommended by expert consensus for high fields.²⁷ Unsuppressed water spectra were obtained as an internal quantification reference and for residual eddy current correction.²⁸ An automated sLASER protocol²⁹ with integrated B₀ and B₁ calibration minimized operator intervention.

MR quality control and preprocessing

DICOM data were de-identified using DicomBrowser³⁰ and T₁ and T₂ datasets were defaced using Face Masking³¹ on site prior to uploading to a Flywheel (<https://flywheel.io/>) instance running on a dedicated server at the University of Minnesota for centralized analysis. To ensure uniform data handling across sites, the data handling pipeline was created within a Docker container at the University of Minnesota and shared with other imaging sites.

All MR data were analyzed blinded to diagnosis. Image sharpness, ringing and contrast-to-noise ratio of T₁ and T₂ data were scored 0-2 in subcortical, grey and white matter regions, as described previously.³² Scores for all image features were averaged. T₁ and T₂ images that passed QC thresholds (Pass 0-0.25, Check 0.5-1, Fail 1.25-2) were preprocessed using the HCP minimal preprocessing pipelines³³ and corrected for gradient non-linearity distortion, bias-field, and readout distortions.³³

Diffusion data were missing for two participants, and another was excluded due to motion artifacts. Diffusion images were corrected for motion artifacts, susceptibility-induced and eddy current distortions³⁴ using the HCP pipelines.³³ Three datasets did not include reversed phase-encoding direction due to operator error, and thus were corrected for susceptibility-induced distortions using Synb0-DISCO³⁵ and for eddy-current and motion artifacts using EDDY from FSL.³⁴

MRS data were missing for two participants. In addition, MRS data were excluded if the VOIs were misplaced when overwriting AutoVOI placement (1 pons spectrum, 3 CBWM spectra) or the linewidth (full-width-at-half-maximum) of the associated water reference was broader than 13Hz (11 pons spectra and 3 CBWM spectra). MRS DICOM files containing channel-combined single-shot sLASER spectra were corrected for frequency, phase and eddy-current errors in an automated pipeline³⁶ using MRspa (<https://www.cmrr.umn.edu/downloads/mrspa/>) before averaging. Single shots with poor water suppression or phase fluctuation indicating subject movement were excluded from averaging.

Volumetry

Cortical, subcortical and brainstem volumes were estimated using FreeSurfer (version 6.0).^{37, 38} Since FreeSurfer only provides white and grey matter segmentations of the cerebellum, CERES (CEREbellum Segmentation, version 1.0), a patch-based multi-atlas segmentation tool,³⁹ was used to estimate cerebellar lobule volumes. CERES was chosen for cerebellar segmentation because it outperformed other tools with respect to repeatability and reproducibility⁴⁰ and cerebellar fissure segmentation in images with cerebellar atrophy.⁴¹ All volumes were normalized by each participant's total intracranial volume.

ROI-based diffusion analysis

To minimize bias from differences in b -values and voxel sizes⁴² between Prisma and Skyra platforms, diffusion volumes with $b=1500\text{s}/\text{mm}^2$ for Prisma and $b=1000\text{s}/\text{mm}^2$ for Skyra were extracted for diffusion tensors calculation. Fractional anisotropy (FA), mean (MD), axial (AD) and radial diffusivity (RD) were subsequently calculated using FSL DTIFIT (FSL version 6.0) in 25 WM ROIs for each subject in their native space as previously described.¹¹ For the list and visualization of the 25 ROI, see Figure 1 in our prior publication.¹¹

A bias was noted in the diffusivity values in the Skyra (up to 20% higher) compared to Prisma data. To address this, diffusion data were acquired with the Prisma and Skyra protocols in the same session on a Prisma scanner from three healthy volunteers. AD, MD, and RD were computed from the same 25 WM ROIs. ROI-specific diffusivity scaling factors (diffusivity obtained with Prisma parameters divided by diffusivity obtained with Skyra parameters) were computed using average data from the three volunteers and ranged from 0.82 to 0.95. Skyra diffusivity values were then multiplied by the corresponding scaling factor. Statistical analysis was completed with both corrected and uncorrected Skyra diffusivities and with and without the Skyra data.

MRS quantification

Preprocessed, averaged spectra were quantified using a simulated basis set²⁸ in LCModel (6.3.0G).⁴³ Metabolite concentrations were corrected for water T_2 relaxation time, tissue water content and CSF contribution in each VOI.¹³ For each VOI, metabolites with mean Cramér-Rao lower bounds (CRLB) $\leq 20\%$ (estimated error of metabolite quantification) for the entire cohort

were included in the statistical analyses. All concentrations except those for which the fitting failed (CRLB=999%) were used when calculating mean CRLBs. For metabolites with strong correlations ($r < -0.7$), only the sum was reported, e.g., total *N*-acetylaspartate (tNAA) = *N*-acetylaspartate + *N*-acetylaspartylglutamate, total creatine (tCr) = creatine + phosphocreatine, total choline = phosphocholine + glycerophosphocholine. Finally, glucose (Glc) + taurine (Tau) was reported if Glc or Tau had mean CRLB >20%.¹²

Statistical analysis

MR and clinical data from control, preataxic and ataxic groups were compared using non-parametric Kruskal-Wallis test. SARA scores were only compared between control and preataxic groups, since SARA was used to classify preataxic and ataxic groups. *P*-values were Holm adjusted for multiple comparisons within each MR analysis (for 55 volumes in FreeSurfer volumetry, 26 volumes in CERES volumetry, 25 regions in each diffusion metric, 19 metabolites in MRS across both VOIs). The metrics that showed statistical significance ($P < 0.05$) in the group comparisons underwent pairwise comparisons between the three groups in the SCA1 and SCA3 cohorts separately using two-tailed *t*-tests with Dunn adjustment for multiple pairwise comparisons. Cohen's *d* were computed for each group comparison as the difference in means divided by the pooled standard deviation, which was calculated as the square root of the mean of each group's variance.

The MR metrics that best distinguished preataxic and control groups were identified using receiver operating characteristic (ROC) analyses. Optimal cut-off for the variables was determined using the Youden's statistic that optimized specificity and sensitivity. The area under the curve (AUC) was calculated for each metric in both SCA1 and SCA3 groups. To assess the potential of multimodal MR metrics in identifying abnormalities at the preataxic stage, bivariate ROC analysis was done for SCA3 only (and not for SCA1 due to small sample size in the preataxic group, $n < 15$).

Pearson correlations between clinical and MR measures that showed significant group differences were computed for SCA1 and SCA3 using all participants' data, as well as without the control group. There were no group effects nor non-linearity that could be visually identified. For diffusivity metrics (AD, RD, MD), we only computed correlations of MD with COAs

because it is representative of both AD and RD and showed the largest number of group differences.

The clinical and imaging data from READISCA are available from the NIMH Data Archive (<https://nda.nih.gov/>, Collection C3155).

Results

Cohort characteristics and matching

Consistent with the reported³ prevalence of SCA3, ~70% of SCA mutation carriers had SCA3 ($n=65$) and ~30% had SCA1 ($n=25$), with 43-44% at the preataxic stage (Table 1). The control group was age- and sex-matched to mutation carriers. As expected, ataxic patients were older than preataxic participants, which was statistically significant for SCA3. Ataxic participants had mild symptoms and minimal disability (median SARA 7-8; functional stage 2). They had ataxia symptoms for 3-6 years. Ataxic groups scored worse than controls on Friedreich's ataxia rating scale functional staging (FARS-FS), inventory of non-ataxia signs (INAS) count and Friedreich's ataxia rating scale activities of daily living (FARS-ADL) subscale. Composite cerebellar functional severity (CCFS) score was significantly different from controls only in the SCA1 ataxic group, and the cerebellar cognitive-affective syndrome (CCAS) scale only in the SCA3 ataxic group. None of the COAs differed significantly between preataxic and control groups.

Early atrophy in SCA1 and SCA3

All structural images passed the QC threshold (score ≤ 1). The regions that showed significant pairwise differences between ataxic groups vs. controls in structural MRI were identical to the regions with significant differences in the 3-group comparisons (shown in the top two rows of each panel in Fig 1), with lower p-values (Supplementary Tables 1, 4). Cerebellar WM, medulla, pons, and superior cerebellar peduncle (SCP) were atrophied in both ataxic groups. In addition, SCA3 ataxic group had atrophy of the thalamus, nucleus accumbens, putamen, pallidum, total and subcortical (striatum, thalamus, pallidum) grey matter. The medulla and SCP were already atrophied at preataxic stage. In addition, the SCA1 preataxic group had atrophy of the pons and left cerebellar WM, and the SCA3 preataxic group displayed enlarged 4th ventricle.

Both ataxic groups had atrophy of cerebellar lobule IV. In addition, the SCA3 ataxic group showed atrophy of lobule X and left lobule I/II, with lobule X atrophied at preataxic stage.

Early microstructural deficits in SCA1 and SCA3

Diffusivity findings were largely identical with and without the Skyra data and with the corrected and uncorrected Skyra values; therefore, we report the statistical findings with the corrected Skyra diffusivities. Similar to volumetric findings, the regions that showed significant pairwise differences between ataxic groups vs. controls in diffusion MRI were identical to the regions with significant differences in the 3-group comparisons (shown in the top two rows of each panel in Fig 2), with lower p-values (Supplementary Tables 2, 5).

Both ataxic groups displayed WM microstructural deficits in the pontine crossing tract (PCT) and cerebellar peduncles (inferior (ICP), superior (SCP), middle (MCP)) as measured by lower FA and higher diffusivities than controls (Fig 2 and Supplementary Tables 2, 5). In addition, corticospinal tract (CST), sagittal stratum (SS) and corona radiata (CR) were affected in both ataxic groups based on higher diffusivities. Corpus callosum (CC) was only affected in ataxic SCA1 (lower FA, higher MD and RD), while external (EC) and internal capsules (IC) were only affected in ataxic SCA3 (higher RD/MD).

PCT and ICP were affected in both preataxic groups. In addition, the SCA3 preataxic group displayed widespread microstructural damage, including all cerebellar peduncles, CR, CST, IC and SS (Fig 2).

Early neurochemical abnormalities in SCA1 and SCA3

MRS data quality was high across groups, with comparable signal-to-noise ratio and linewidths between patients and controls (Supplementary Tables 3, 6).

Group differences for multiple neurochemicals were highly statistically significant for both SCAs, particularly for the pons. For both ataxic groups, levels of tNAA, a marker of neuronal viability, was lower and *myo*-inositol (mI), a putative glial marker, was higher than controls in both VOIs (Fig 3). In addition, tCr and Glc+Tau, which may indicate deficits in energy metabolism, were higher in both VOIs in ataxic SCA3 and in pons in ataxic SCA1 than controls.

Neurochemical differences reached statistical significance only in the pons at preataxic stage. Namely, mI was higher in both preataxic groups than controls. Preataxic SCA1 participants further had lower tNAA and higher tCr than controls. In addition, tNAA/tCr and tNAA/mI ratios, which are widely used measures of neuroglial status, were lower in the pons in both preataxic groups.

MR metrics most sensitive to preataxic disease

ROC analyses were used to identify the metrics most sensitive (highest AUC) to preataxic alterations within each modality (whole brain volumetry, cerebellar volumetry, diffusion MRI and MRS) (Fig 4).

In SCA1, pontine tCr had the highest AUC (0.95) among the top metrics to distinguish preataxic participants from controls. Consistently, violin plots with individual subject data showed little overlap between the pontine tCr levels of the preataxic and control groups and largely equivalent tCr levels in the preataxic and ataxic groups.

In SCA3, RD of ICP had the highest AUC (0.92), and, similar to tCr in SCA1, the ICP RD values for the SCA3 preataxic and ataxic groups largely overlapped. Combinations of two MR metrics distinguished preataxic participants from controls with higher AUC than single metrics (Supplementary Table 7). For example, the combination of ICP FA and cerebral peduncle AD resulted in almost perfect separation of preataxic participants from controls with an AUC of 0.97.

Clinical correlations

In SCA1, ataxia symptoms (SARA, FARS-FS) were significantly associated with volumes and microstructural measures from brainstem (pons, medulla), cerebellum and their connecting pathways, with the strongest associations detected for cerebellar peduncles ($|r|=0.76-0.8$, Fig 5). Strongest neurochemical correlates of ataxia were the neuronal marker tNAA ($|r|\sim 0.71-0.79$), followed by the glial marker mI ($r\sim 0.62-0.76$). MR metrics were also associated with fine motor function (CCFS), non-ataxia signs (INAS), and estimated ataxia duration. Among patient reported outcomes, the FARS-ADL scale showed the same pattern of associations with MR metrics as SARA and FARS-FS, while the European quality of life 5 dimensions (EQ-5D) and

depression/anxiety (PHQ-9) scales lacked these associations. Finally, the cognitive and affective symptoms as measured by the CCAS scale showed moderate associations ($|r| \sim 0.3-0.4$) with CBWM volume, SCP and CC microstructure and the glial marker mI.

Many clinical-MR associations were observed in the larger SCA3 sample (Fig 6). Similar to SCA1, macro- and microstructural metrics in the brainstem, particularly the pons, and cerebellar peduncles were the strongest correlates of ataxic symptoms (SARA, FARS-FS), fine motor skills (CCFS), non-ataxia signs (INAS), FARS-ADL and estimated ataxia duration. Importantly, volumes of several forebrain structures (thalamus, putamen, nucleus accumbens), and diffusivity of major cerebral WM tracts (CR, CST) were associated with ataxia symptoms, non-ataxia signs and FARS-ADL. The larger sample also revealed associations of cerebellar and brainstem macro- and microstructure with cognitive and affective symptoms (CCAS), and of pons and cerebellar peduncle measures with quality of life (EQ-5D) and depression/anxiety (PHQ-9). Neurochemical associations with ataxia symptoms, non-ataxia signs, patient reported outcomes (FARS-ADL, EQ-5D, PHQ-9) and estimated ataxia duration were overall stronger than those of the structural and microstructural metrics.

The pattern of associations was similar without the control data, but associations were weaker. Correlations were not driven by cluster effects, as shown for SARA, FARS-FS, FARS-ADL and estimated duration, the strongest clinical correlates of MR metrics overall (Fig 7). DTI and MRS metrics had the strongest associations with these COA.

Discussion

This study represents the first multi-site clinical trial readiness effort in SCAs to validate morphometric, microstructural, and neurochemical outcome measures using an advanced MR protocol. The data expand our current knowledge on the earliest structural, microstructural and neurochemical abnormalities that are present prior to ataxia onset and demonstrate WM damage that precedes GM damage in both SCAs. Thus, this is the first report of microstructural abnormalities in major WM tracts beyond the cerebellum and brainstem before ataxia onset in SCA3. From the trial readiness perspective, this is the first demonstration that neurochemical (for SCA1) and microstructural (for SCA3) MR metrics detect preataxic abnormalities with exceptionally high sensitivity (AUC >0.9 in ROC analyses) in a multi-site trial setting, that they are more sensitive than structural metrics to earliest changes and that neurochemical and

microstructural metrics are the strongest correlates of ataxia symptoms, activities of daily living and estimated ataxia duration. Most importantly, the data demonstrate the possibility of enriching clinical trial cohorts with those individuals with highest cerebral and cerebellar impairment before ataxia onset (detectable on a single subject level), which is currently not possible based on any clinical or laboratory measurements.

First-in-human testing of gene silencing therapies has begun for SCA3.⁴⁴ Interventions are most likely to slow pathological changes if administered before substantial neurodegeneration⁵ and hereditary SCAs will allow enrollment of mutation carriers in clinical trials before ataxia onset. Functional changes have been documented at the preataxic stage in SCAs using dopamine transporter⁴⁵ and metabolic⁴⁶ imaging. Due to broader availability of MR scanners, we aimed to identify MR endpoints sensitive to early pathology in the trial setting for SCAs, i.e., academic hospitals that house specialized ataxia clinics, which allowed us to implement a state-of-the-art MR protocol at 3T with advanced pulse sequences. The novel combination of morphometric with microstructural and neurochemical markers allowed a broader window into early pathology than prior multi-site MR studies of morphometric changes in SCAs.^{8, 47, 48} We chose ROI-based volumetric and diffusion MRI analyses to identify robust subject-level metrics for use in clinical trials. Future group-level analyses of the same data, e.g., using tractography, will likely identify additional affected areas. The MRS data were limited to two VOIs because SCA-control classifications are driven strongly by metabolite levels in these regions.¹²

We took a conservative statistical approach because the goal was to identify the most robust metrics that may facilitate enrollment of mutation carriers in trials, rather than to provide a detailed account of MR detectable abnormalities. For example, we did not average right and left volumes or combine multiple cerebellar lobules to reduce the number of statistical comparisons. To allow readers access to the full set of findings, we provide adjusted and unadjusted *P*-values (Supplementary Materials). In addition, we primarily utilized univariate statistical analysis because the sample size was still limited for a training and testing set needed to validate a multivariate statistical model, for example to establish an MR score for SCA1 and SCA3.

Atrophy in the brainstem, cerebellum, and SCPs in the ataxic groups was consistent with prior reports^{8, 13, 49, 50} (Fig 1). Notably the WM of the cerebellum was atrophied, while total cerebellar cortex was not, indicative of axonopathy that precedes cell loss. Together with the

microstructural damage in all cerebellar peduncles and brainstem (PCT) these data support WM deficits as the defining features of early-stage pathology in both diseases. Interestingly, RD differences were more prominent than AD in both SCAs, indicating more prevalent myelin loss than axonal injury.^{51,52} While this interpretation is problematic in regions with many crossing fibers,^{52,53} in highly ordered WM tracts, such as those in SCP (FA~0.67), and in the absence of edema, the prominent RD abnormalities are supportive of early oligodendrocyte pathology proposed in SCA3.^{54,55}

Early grey matter damage was limited to select regions of the cerebellar cortex, namely lobules involved in motor processing (IV, I/II) and vestibulocerebellum (lobule X)⁵⁶ and subcortical forebrain structures (thalamus, pallidum, putamen, nucleus accumbens). Importantly, despite large overlap in cerebellar/brainstem regions involved in SCA1 and SCA3, the pattern of tissue damage was genotype-specific, therefore imaging data collected clinical trials should not be pooled across genotypes.

Cerebral involvement was detected with higher sensitivity by diffusion than structural MRI, consistent with microstructural changes preceding tissue loss. Prior work had shown damage to cerebral WM tracts, e.g., CC and CST, in more advanced cohorts with SCA1 and SCA3.^{7,57} The current study revealed the presence of these WM alterations earlier in the disease course.

At preataxic stage, brainstem atrophy was consistent with prior reports.^{7-9,49} In fact, SCP volume was the top volumetric metric that distinguished preataxic participants from controls (Fig 4). Microstructural damage was limited to brainstem (PCT) and cerebellar tracts (ICP) in SCA1, but widespread in SCA3, before ataxia onset. While cerebellar peduncle and midbrain WM damage was reported before ataxia onset in SCA3,⁷ extended cerebral microstructural abnormalities captured in our larger preataxic cohort show that whole brain WM damage is substantial before ataxia onset in SCA3. In addition to larger sample size, the preataxic SCA3 group may have been closer to ataxia onset than the preataxic SCA1 group (Table 1), allowing the detection of more extensive WM damage. However, a systematic bias in the estimated time to ataxia onset is likely for the SCA3 cohort based on the inconsistency between the estimated vs. reported time from onset (9 vs. 3 years) in the ataxic SCA3 group. Ongoing follow-up of the preataxic patients will reveal if the preataxic SCA3 group was indeed closer to onset.

Interestingly, diffusion measures in the ICP were the top DTI metrics that distinguished preataxic

from control groups, with AUC >0.9, for both SCAs, demonstrating impaired spinal input to the cerebellum as a very early event in the disease course. A caudal-rostral progression of SCA3 pathology was proposed previously⁷ and our findings are supportive of this sequence of events for both SCA1 and SCA3, with pathology moving from the medulla to pons, cerebellum and later to cerebrum. In this sequence of events, pontine tissue loss and neurochemical abnormalities were more extensive in preataxic SCA1 than SCA3, possibly predictive of faster disease progression in SCA1 following ataxia onset. Notably, the pontine tCr level distinguished the preataxic SCA1 from controls with the highest AUC among all MR metrics, consistent with our preliminary observation that *individual* mutation carriers can be distinguished from controls based on MRS.¹² This opens the possibility of enriching clinical trial cohorts with those individuals with highest impairment before ataxia onset. Although clinical disease manifestations can be detected before ataxia onset with larger sample sizes,⁹ and preataxic sensory and corticospinal signs were detected in the larger clinical READISCA cohort (N=200) (Tezenas du Montcel *et al*, Neurology, revision submitted), COAs were not significantly different in the preataxic groups than controls with the current sample size, demonstrating the higher sensitivity of the imaging markers to early disease.

It is important for imaging markers to be related to the clinical presentation for their utility as clinically meaningful outcome measures in trials. We detected strong associations ($|r| > 0.7$) of brainstem and cerebellar MR metrics with ataxia despite a limited SARA range. Correlations of macro- and microstructural metrics obtained in the pons, cerebellar peduncles and cerebellar WM and neuroglial markers tNAA and mI in the pons and cerebellar WM particularly stood out, underlining the importance of cerebellar afferent and efferent pathways in early symptomatology in both SCAs. MR-COA correlations were weaker overall for SCA3 than SCA1, potentially due to phenotypic heterogeneity characteristic of SCA3, which may be associated with varying MRI signatures.⁵⁸ Also note that the markers most sensitive to preataxic pathology (e.g. tCr) may not necessarily be the most sensitive to progression (e.g. tNAA, the strongest neurochemical correlate of SARA), consistent with our experience in SCA1 mouse models.^{59, 60}

Patient reported outcome measures are particularly important for FDA approval of new therapeutics. FARS-ADL evaluates the impact of ataxia symptoms on daily activities such as speech, swallowing and motor function (dressing, hygiene, mobility) as reported by patients and

their families, and as such showed a very similar pattern of associations with MR metrics to SARA and FARS-FS. On the other hand, EQ-5D that combines multiple domains including mobility, pain and mental health, and the depression/anxiety scale PHQ-9 were not associated with MR metrics in SCA1 and weakly associated with few structural and neurochemical measures in SCA3. The CCAS scale,²¹ which was designed to detect and quantify the set of impairments identified in patients with cerebellar disorders, showed a higher number of correlations with MR metrics, primarily in the cerebellum and pons.

We further observed moderate-to-strong associations of cerebellar and pons MR metrics with estimated ataxia duration. Existing statistical models to estimate time to ataxia onset in preataxic individuals utilize CAG repeat length and current age.^{17, 18} While they perform well at group level, these estimates carry a large uncertainty in estimating onset age of individual patients. Noninvasive imaging metrics can enrich these parametric models and are expected to reduce the uncertainty of these estimates, which will be critical in subject stratification in trials. The predictive value of MR metrics for ataxia onset will be better understood with longitudinal follow-up data that are currently being collected in the READISCA project.

A limitation of the study was the smaller sample size in the SCA1 group, but the ratio of SCA1 and SCA3 sample sizes was consistent with prior multi-site studies.¹ The smaller sample size in SCA1 coupled with a conservative type I error correction could have limited several MR metrics to reach statistical significance. Future studies need to collect trial readiness data with larger sample sizes in global efforts such as the Ataxia Global Initiative.⁶¹ A technical limitation was the use of scanners from a single vendor. Future trial readiness studies need to incorporate scanners from all major MR vendors. The use of state-of-the-art technologies will likely be limited in multi-site settings that prioritize inclusion of all vendors and scanner models with wide-ranging technical specifications. However, the high resolution utilized here for structural imaging, the basic DTI model for analyzing only the low b-value of the diffusion data, and the neurochemicals of primary interest (tNAA, mI, tCr) will be broadly applicable across vendors and models.

To summarize, morphometric, microstructural, and neurochemical metrics are highly sensitive to pathology before ataxia onset and are associated with patient's daily experiences. Neurochemical and microstructural metrics detected cerebellar and brainstem abnormalities at preataxic stage with higher sensitivity than morphometric measures. Non-invasive access to such

microstructural and biochemical changes before neuronal loss is expected to facilitate clinical trial enrollment of participants at the earliest disease stages, thereby increasing the likelihood of slowing pathological changes by potential therapeutics.

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Author Contributions

STM, TA, CL, GÖ contributed to conception and design of the study; JC, EP, YWP, STM, JMJ, DKD, MP, GB, RV, PE, JF, PC, CUO, PBB, JDS, EMR, SHS, THM, KOB, HP, AD, TK, TA, CL, GÖ contributed to acquisition or analysis of data; JC, EP, CL, GÖ contributed to drafting the

manuscript and preparing the figures. In addition, members of the READISCA Consortium contributed to the collection of clinical data (Supplementary Table 8).

Potential Conflicts of Interest

Dr. Tezenas du Montcel and Lenglet receive research support from Biogen, which develops therapeutics for SCAs. Dr. Schmahmann consults for Biogen and received support from Biohaven, which develop therapeutics for SCAs. Dr. Ashizawa received grants from Biogen and participates in Biohaven clinical trials. Within the last 24 months Dr. Klockgether has received consulting fees from Biogen, UCB and Vico Therapeutics, which are developing therapeutics for SCAs. Dr. Öz consults for IXICO Technologies Limited, which provides neuroimaging services and digital biomarker analytics to biopharmaceutical firms conducting clinical trials for SCAs, and receives research support from Biogen, which develops therapeutics for SCAs.

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Figure captions

Figure 1. Whole brain and cerebellar volumetry. Statistical maps of whole-brain volumetry using FreeSurfer (**A, B**) and cerebellum volumetry using CERES (**C, D**) for SCA1 (**A, C**) and SCA3 (**B, D**). Group comparisons are shown in the top two rows and pairwise comparisons are shown in the bottom two rows in each panel. The *P*-values (Kruskal-Wallis with Holm adjustment for C-P-A group comparisons, pairwise two-tailed t-tests for P vs. C comparisons, $P < 0.05$) are mapped to each of the segmented volumes that are placed on a T1 atlas for whole-brain volumetry. Similarly, *P*-values from cerebellar volumetry are placed on a subject T1 image that was transformed to MNI space. C = control, P = preataxic, A = ataxic, CBWM = cerebellar white matter, SCP = superior cerebellar peduncles, thal = thalamus, vent = ventricle. Ventricles marked with * indicate reversed relationship between groups, i.e. $C < P < A$.

Figure 2. Microstructural MRI metrics from different ROI. Statistical maps of ROI based diffusion MRI analyses show significant differences in fractional anisotropy (**A, B**), axial diffusivity (**C, D**), radial diffusivity (**E, F**) and mean diffusivity (**G, H**) for SCA1 (**A, C, E, G**) and SCA3 (**B, D, F, H**). Group comparisons are shown in the top two rows and pairwise comparisons are shown in the bottom two rows in each panel. The *P*-value maps (Kruskal-Wallis with Holm adjustment for C-P-A group comparisons, pairwise two-tailed t-tests for P vs. C comparisons, $P < 0.05$) are represented on WM ROIs on the FMRIB58 atlas FA map. C = control, P = preataxic, A = ataxic, PCT = pontine crossing tract, MCP = middle cerebellar peduncle, ICP = inferior cerebellar peduncle, SCP = superior cerebellar peduncle, CC = corpus callosum, CST = corticospinal tract, IC = internal capsule, SS = sagittal stratum, CR = corona radiata.

Figure 3. Neurochemical abnormalities from MR spectra. MR spectra from one subject in each cohort. Voxel positions are shown on MPRAGE images. Arrows indicate type I error corrected significant metabolite differences in each SCA group compared to controls. CBWM = cerebellar white matter, mI = *myo*-inositol, tNAA = total *N*-acetylaspartate, tCr = total creatine, Glc+Tau = glucose+taurine.

Figure 4. MR metrics most sensitive to preataxic alterations as identified from ROC analyses. Violin plots (**A, C**) and ROC curves (**B, D**) for the top volumetry (whole brain and cerebellar), diffusion and MRS metrics that best distinguish preataxic SCA1 (**A, B**) and SCA3 (**C, D**) groups from controls. Violin plots are shown for all groups (ataxic, preataxic SCA and control) with two-tailed t-tests of pairwise comparison *P*-values reported, while ROC analyses included control and preataxic groups only. Area under the curve (AUC) for each metric is indicated in the ROC plots. ROC = receiver operating characteristic, Vol = volume, SCP = superior cerebellar peduncle, FA = fractional anisotropy, ICP-R = inferior cerebellar peduncle right, tCr = total creatine, RD = radial diffusivity, mI = *myo*-inositol, VIIIIB = lobule VIIIIB of cerebellum, X = lobule X of cerebellum.

Figure 5. Associations of MR and clinical metrics in SCA1. Statistically significant ($P < 0.05$) Pearson correlations between COAs and volumetric (**A**), neurochemical (**B**) and microstructural (**C**) metrics are shown. Correlation coefficients (*r*) were computed using all participants' data (ataxic SCA1, preataxic SCA1, controls) and are color coded as indicated by the legend bar. The size of the circles also indicates strength of the correlation. SARA = scale for the assessment and rating of ataxia, CCAS = cerebellar cognitive-affective syndrome, CCFS = composite cerebellar functional severity score, INAS = inventory of non-ataxia signs, FARS-FS = Friedreich's ataxia rating scale functional staging, EQ-5D = European quality of life 5 dimensions, PHQ-9 = patient health questionnaire-9, FARS-ADL = Friedreich's ataxia rating scale activities of daily living subscale, Est-Dur = estimated ataxia duration, Lob-IV = lobule IV of cerebellum, CBWM = cerebellar white matter, mI = *myo*-inositol, tNAA = total *N*-acetylaspartate, tCr = total creatine, Glc+Tau = glucose + taurine, CC = corpus callosum, SCP = superior cerebellar peduncle, MCP = middle cerebellar peduncle, ICP = inferior cerebellar peduncle, PCT = pontine crossing tract, CR = corona radiata, SS = sagittal stratum, R = right, L = left.

Figure 6. Associations of MR and clinical metrics in SCA3. Statistically significant ($P < 0.05$) Pearson correlations between COAs and volumetric (**A**), neurochemical (**B**) and microstructural (**C**) metrics are shown. Correlation coefficients (*r*) were computed using all participants' data (ataxic SCA3, preataxic SCA3, controls) and are color coded as indicated by the legend bar. The size of the circles also indicates strength of the correlation. SARA = scale for the assessment and

rating of ataxia, CCAS = cerebellar cognitive-affective syndrome, CCFS = composite cerebellar functional severity score, INAS = inventory of non-ataxia signs, FARS-FS = Friedreich's ataxia rating scale functional staging, EQ5D = European quality of life 5 dimensions, PHQ-9 = patient health questionnaire-9, FARS-ADL = Friedreich's ataxia rating scale activities of daily living subscale, Est-Dur = estimated ataxia duration, I.II-Lob = lobule I & II of cerebellum, IV-Lob = lobule IV of cerebellum, X-Lob = lobule X of cerebellum, Thal = thalamus, Puta = putamen, Palli = pallidum, Accum = nucleus accumbens, Lat-Vent = lateral ventricle, Cere = cerebellum, CBWM = cerebellar white matter, mI = *myo*-inositol, tNAA = total *N*-acetylaspartate, tCr = total creatine, Glc+Tau = glucose + taurine, CC = corpus callosum, SCP = superior cerebellar peduncle, MCP = middle cerebellar peduncle, ICP = inferior cerebellar peduncle, PCT = pontine crossing tract, CR = corona radiata, SS = sagittal stratum, R = right, L = left.

Figure 7. The strongest MR correlates of SARA, functional stage, activities of daily living and estimated disease duration in SCA1 and SCA3. Pearson correlations of MR metrics with the highest correlation coefficient with each of SARA, FARS-FS, FARS-ADL and Estimated Duration are shown for SCA1 (A-D) and SCA3 (E-H). Correlation coefficients (r) were computed using all participants' data (ataxic SCA, preataxic SCA, controls). All correlations had $P < 0.001$.

ICMJE DISCLOSURE FORM

Date: 7/30/2022

Your Name: Tetsuo Ashizawa

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

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		International Parkinson and Movement Disorder Society (MDS)	Vice Chair of the Ataxia Study Group of MDS – no payments
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Date: Click or tap to enter a date.

Your Name: Peter B. Barker

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

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Author Manuscript

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Date: 7/30/2022

Your Name: Khalaf Bushara

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

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6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
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Date: 7/31/2022

Your Name: [Jayashree Chandrasekaran]

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): [Click or tap here to enter text.]

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	<input checked="" type="checkbox"/> None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 7/30/2022

Your Name: Pierrick Coupé

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): [Click or tap here to enter text.](#)

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

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Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 8/1/2022

Your Name: Dinesh K Deelchand

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
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Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 7/31/2022

Your Name: Alexandra DURR

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): [Click or tap here to enter text.]

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. “Related” means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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2	Grants or contracts from any entity (if not indicated in item #1 above).	<input type="checkbox"/> None	
		BIOGEN	Contract to institution
		Triplet Therapeutics	Contract to institution
		National Hospital Clinical Research Program)	Grant to institution
		Roche	Contract to institution
		Wavelife	Contract to institution
		ANR Erare	Grant to institution
3	Royalties or licenses	<input checked="" type="checkbox"/> None	
4	Consulting fees	<input type="checkbox"/> None	
		Wave	Paid to institution
		Askbio	Paid to institution
		UCB	Paid to institution
		Roche	Paid to institution
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
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8	Patents planned, issued or pending	<input type="checkbox"/> None <table border="1"> <tr> <td>B 06291873.5</td> <td></td> </tr> <tr> <td></td> <td></td> </tr> <tr> <td></td> <td></td> </tr> </table>	B 06291873.5						
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10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input type="checkbox"/> None <table border="1"> <tr> <td>Societe francophone de Neurogénétique</td> <td>Présidente</td> </tr> <tr> <td></td> <td></td> </tr> <tr> <td></td> <td></td> </tr> </table>	Societe francophone de Neurogénétique	Présidente					
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ICMJE DISCLOSURE FORM

Date: 8/2/2022

Your Name: Philipp Ehse

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): [Click or tap here to enter text.](#)

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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2	Grants or contracts from any entity (if not indicated in item #1 above).	<input type="checkbox"/> None <table border="1" style="width: 100%; margin-top: 5px;"> <tr> <td style="width: 55%;">EU Horizon 2020, no. 885876 (AROMA)</td> <td style="width: 45%;">Grant to Institution</td> </tr> <tr> <td> </td> <td> </td> </tr> </table>	EU Horizon 2020, no. 885876 (AROMA)	Grant to Institution					
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ICMJE DISCLOSURE FORM

Date: 8/3/2021

Your Name: Jennifer Faber

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: past 36 months									
2	Grants or contracts from any entity (if not indicated in item #1 above).	<input type="checkbox"/> None	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%;">JF is a fellow of the Hertie Network of Excellence in Clinical Neuroscience</td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> </table>	JF is a fellow of the Hertie Network of Excellence in Clinical Neuroscience					
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4	Consulting fees	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td style="width: 50%; height: 15px;"></td><td style="width: 50%;"></td></tr> <tr><td style="height: 15px;"></td><td></td></tr> <tr><td style="height: 15px;"></td><td></td></tr> <tr><td style="height: 15px;"></td><td></td></tr> </table>									
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11	Stock or stock options	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td style="width: 50%; height: 15px;"></td><td style="width: 50%;"></td></tr> <tr><td style="height: 15px;"></td><td></td></tr> <tr><td style="height: 15px;"></td><td></td></tr> </table>							
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td style="width: 50%; height: 15px;"></td><td style="width: 50%;"></td></tr> <tr><td style="height: 15px;"></td><td></td></tr> <tr><td style="height: 15px;"></td><td></td></tr> </table>							
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td style="width: 50%; height: 15px;"></td><td style="width: 50%;"></td></tr> <tr><td style="height: 15px;"></td><td></td></tr> <tr><td style="height: 15px;"></td><td></td></tr> </table>							

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 7/30/2022

Your Name: Guita Banan

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

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12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 8/1/2022

Your Name: [James M. Joers]

Manuscript Title: [Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3]

Manuscript Number (if known): [Click or tap here to enter text.]

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 7/31/2021

Your Name: Thomas Klockgether

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
		SARAhome: A multicenter study in spinocerebellar ataxia type 3 (SCA3)	
3	Royalties or licenses	<input checked="" type="checkbox"/> None	
4	Consulting fees	<input type="checkbox"/> None	
		Biogen	Consulting
		UCB	Consulting
		Roche	Consulting
		Vico Therapeutics	Consulting
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
9	Participation on a Data Safety	<input checked="" type="checkbox"/> None	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	Monitoring Board or Advisory Board	<input type="checkbox"/>	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input type="checkbox"/> None	
		Ataxia Global Initiative	Steering Committee
11	Stock or stock options	<input checked="" type="checkbox"/> None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 8/2/2022

Your Name: Christophe Lenglet

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input type="checkbox"/> None	
		Regents of the University of Minnesota	Patent US 10,641,854 B2 "Systems and Methods for Automatic Voxel Positioning in Magnetic Resonance Spectroscopy" issued to Institution
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	<input checked="" type="checkbox"/> None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 8/1/2021

Your Name: Thomas H. Mareci

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

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Author Manuscript

ICMJE DISCLOSURE FORM

Date: Click or tap to enter a date.

Your Name: Chiadi U. Onyike

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 7/29/2022

Your Name: Gulin Oz

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

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2	Grants or contracts from any entity (if not indicated in item #1 above).	<input type="checkbox"/> None	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%;">National Ataxia Foundation</td> <td>Grant to institution</td> </tr> <tr> <td>Biogen, Inc.</td> <td>Grant to institution</td> </tr> <tr> <td> </td> <td> </td> </tr> </table>	National Ataxia Foundation	Grant to institution	Biogen, Inc.	Grant to institution		
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4	Consulting fees	<input type="checkbox"/> None	
		IXICO Technologies Limited	Received consulting fees
		uniQure biopharma B.V	Received consulting fees
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input type="checkbox"/> None	
		Regents of the University of Minnesota	Patent US 10,641,854 B2 "Systems and Methods for Automatic Voxel Positioning in Magnetic Resonance Spectroscopy" issued to Institution
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input type="checkbox"/> None	
		Scientific Advisory Board, BrainSpec Inc	BrainSpec is developing a software platform designed to make MRS technology accessible to clinicians and researchers. These interests have been reviewed and managed by the University of Minnesota in accordance with its Conflict of Interest policies.
		Medical Research Advisory Board, National Ataxia Foundation	Unpaid participation
10	Leadership or fiduciary role in other board, society,	<input checked="" type="checkbox"/> None	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	committee or advocacy group, paid or unpaid		
11	Stock or stock options	<input checked="" type="checkbox"/> None	
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ICMJE DISCLOSURE FORM

Date: 8/2/2022

Your Name: Young Woo Park

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): [Click or tap here to enter text.](#)

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Author Manuscript

ICMJE DISCLOSURE FORM

Date: 8/2/2022

Your Name: Henry L. Paulson

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): [Click or tap here to enter text.](#)

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	<input type="checkbox"/> None	
		Exicure, Inc.	Last fee received in 2021; no longer an active relationship
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None	

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11	Stock or stock options	<input checked="" type="checkbox"/> None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 3/8/2022

Your Name: Emilien Petit

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

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Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 8/3/2022

Your Name: Michal Považan

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 8/1/2022

Your Name: Eva-Maria Ratai

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): [Click or tap here to enter text.](#)

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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2	Grants or contracts from any entity (if not indicated in item #1 above).	<input type="checkbox"/> None <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%;">5R01CA190901, 5R01NS080816, 5R01HD085813, 5R01HD065762, 5U01NS104326, 5P01AT009965, NSF-1926781, 5R01NS112694, R01 HD099846</td> <td>All to institution</td> </tr> <tr> <td> </td> <td> </td> </tr> </table>	5R01CA190901, 5R01NS080816, 5R01HD085813, 5R01HD065762, 5U01NS104326, 5P01AT009965, NSF-1926781, 5R01NS112694, R01 HD099846	All to institution				
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4	Consulting fees	<input checked="" type="checkbox"/> None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input type="checkbox"/> None	
		Harvard Catalyst	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input type="checkbox"/> None	
		5R01DA047088, 5R01CA190901,	
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None	

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Author Manuscript

ICMJE DISCLOSURE FORM

Date: 8/2/2021

Your Name: Jeremy D. Schmahmann, MD

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): [Click or tap here to enter text.](#)

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Author Manuscript

ICMJE DISCLOSURE FORM

Date: Click or tap to enter a date.

Your Name: S. H. Subramony

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

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Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 8/1/2022

Your Name: Sophie Tezenas du Montcel

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): [Click or tap here to enter text.](#)

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

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I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: C7/30/2022

Your Name: Romain Valabregue

Manuscript Title: Clinically meaningful MR endpoints sensitive to preataxic SCA1 and SCA3

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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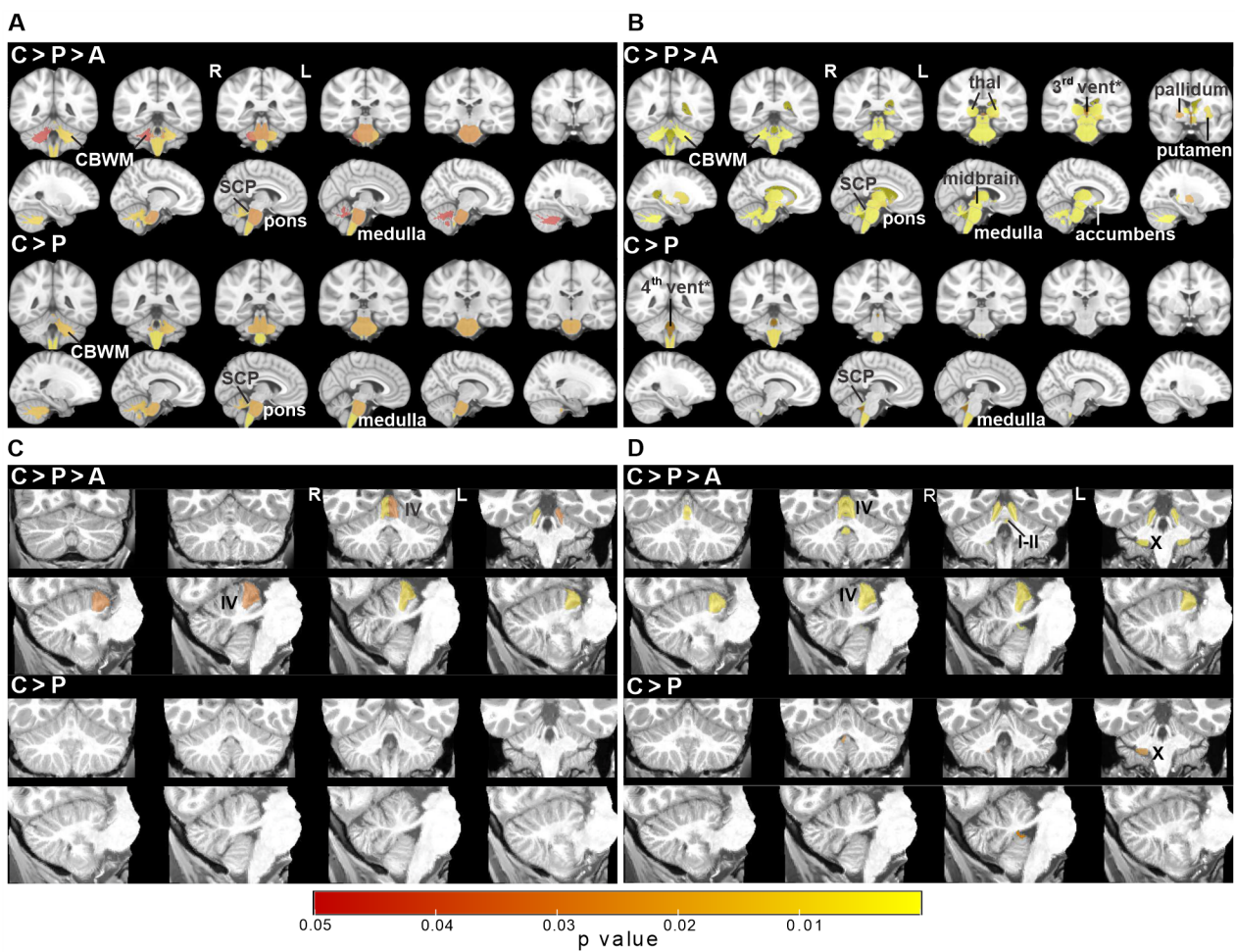
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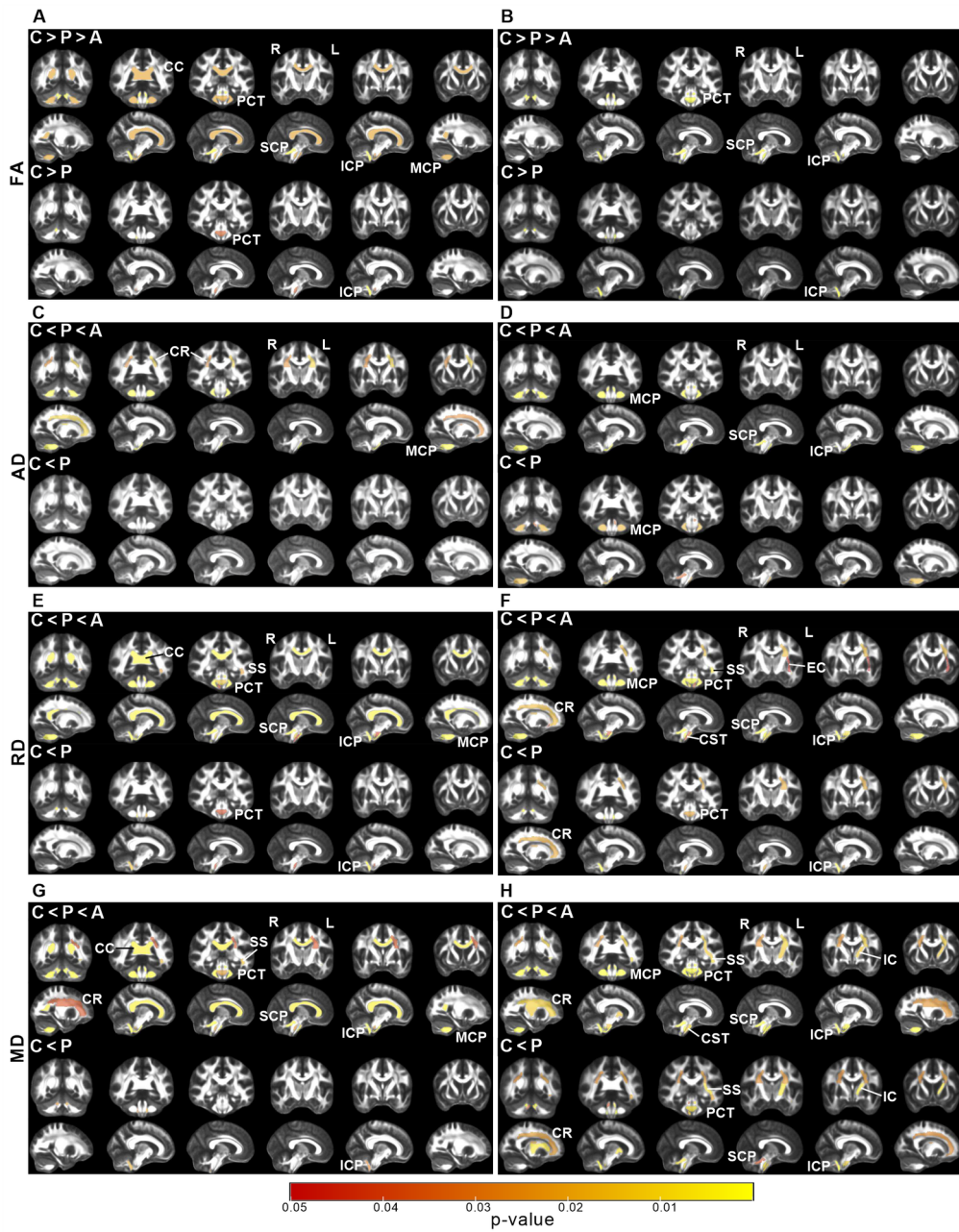
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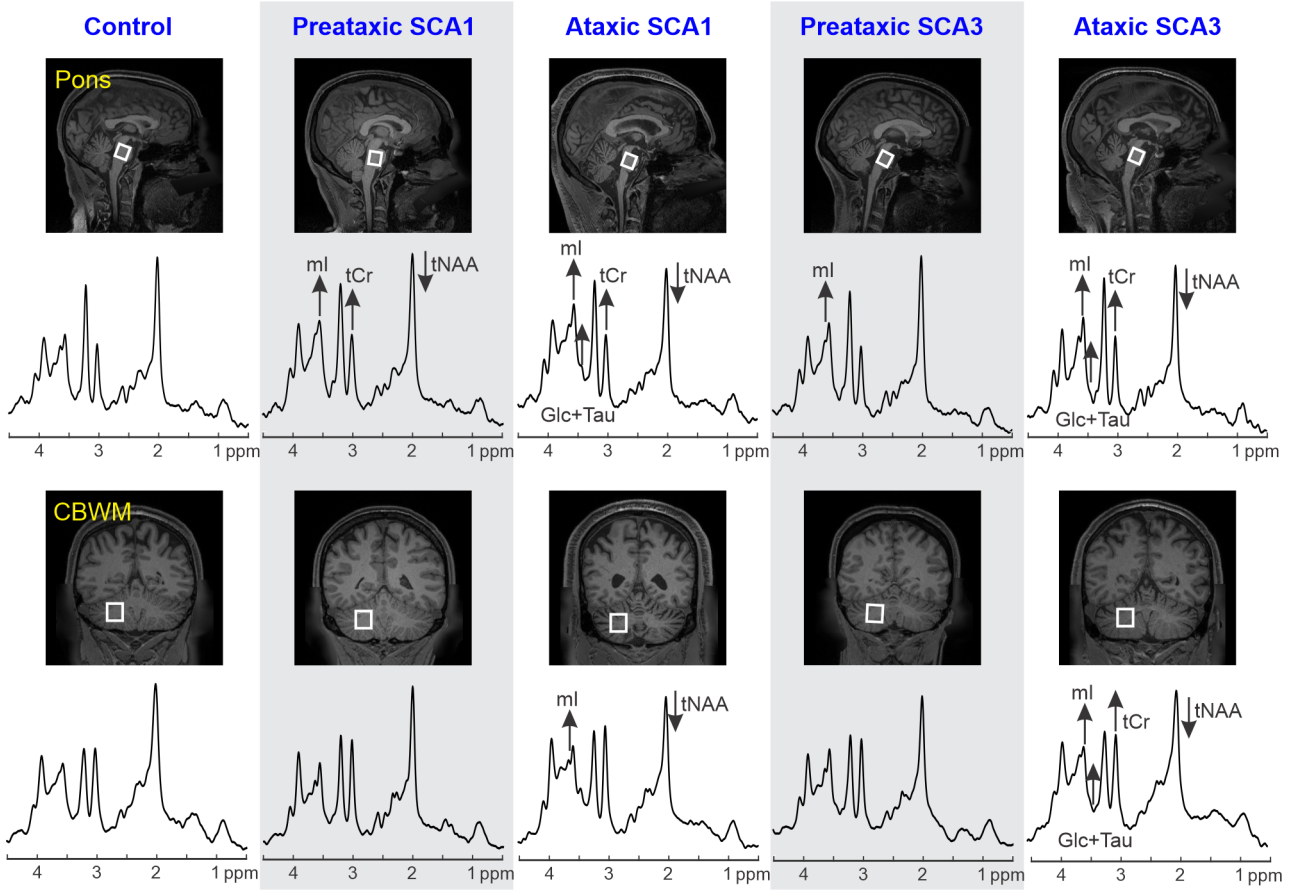




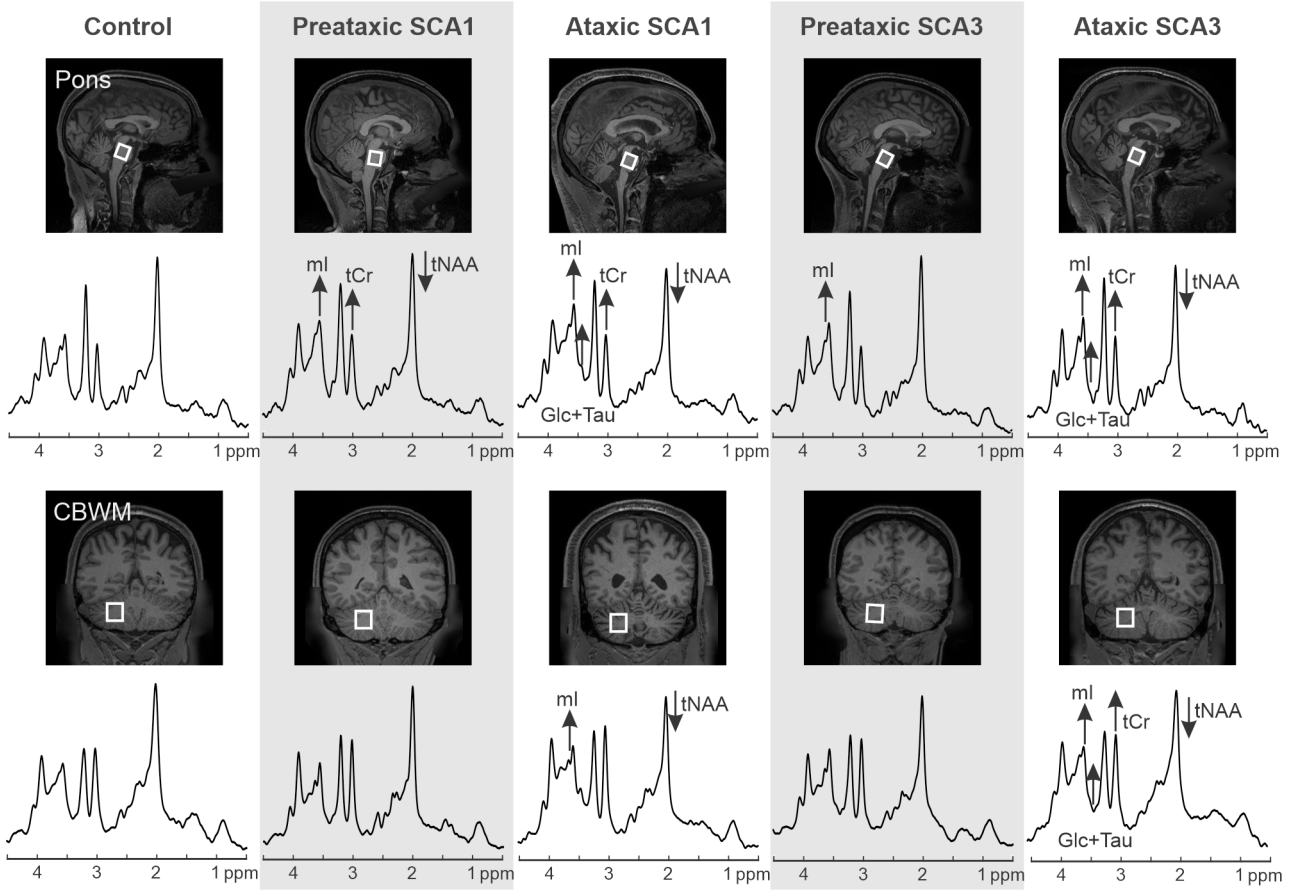
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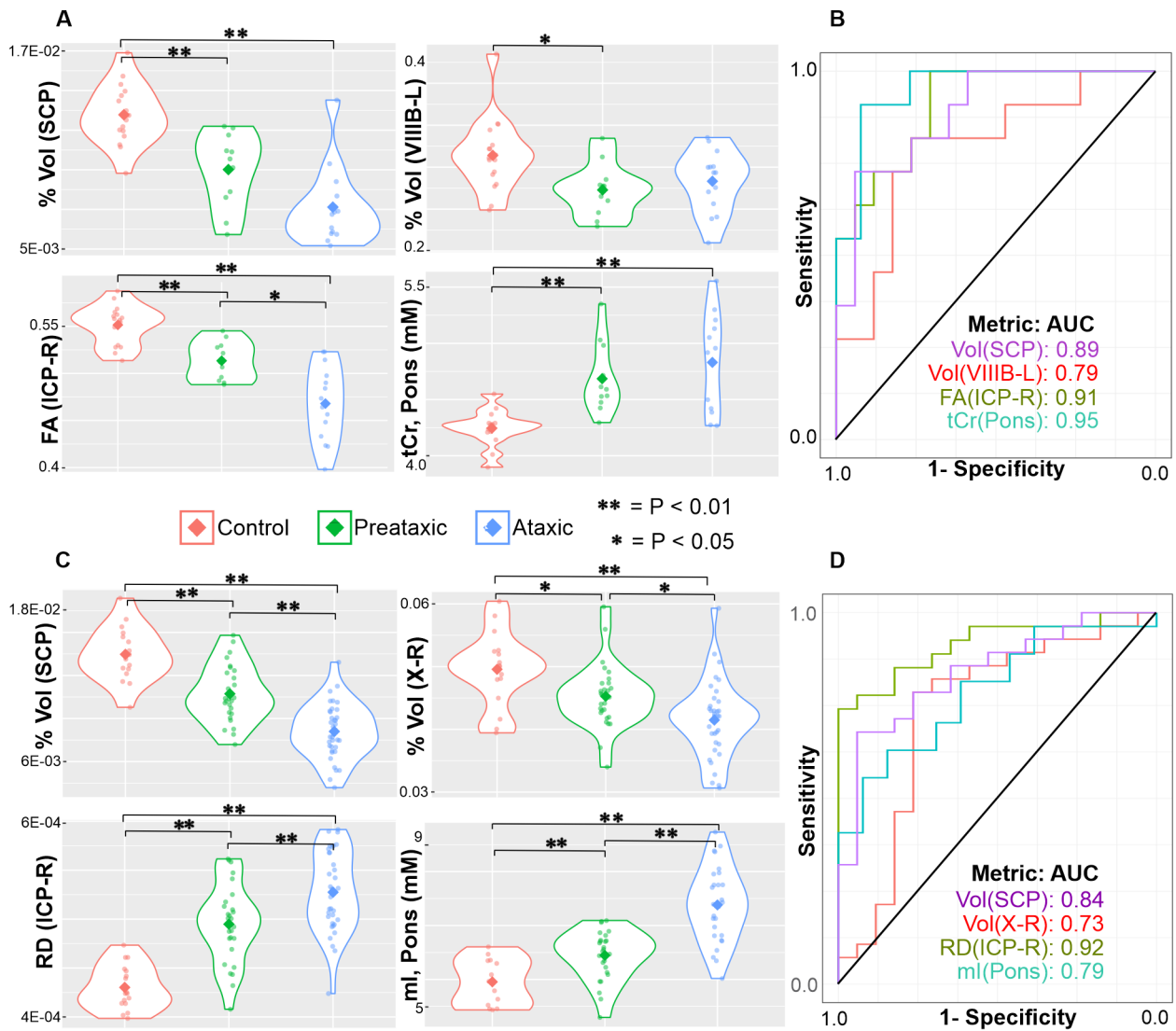
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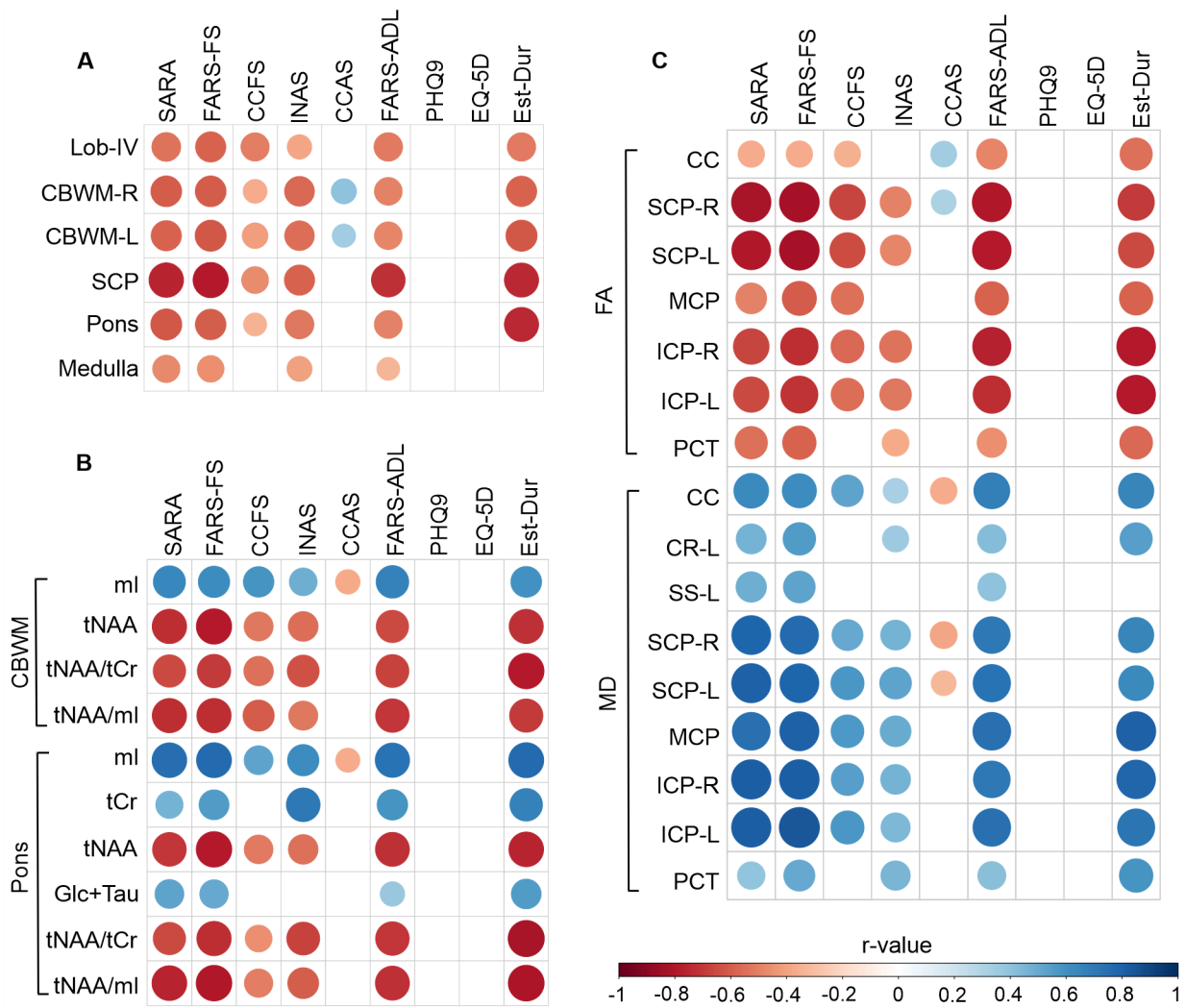
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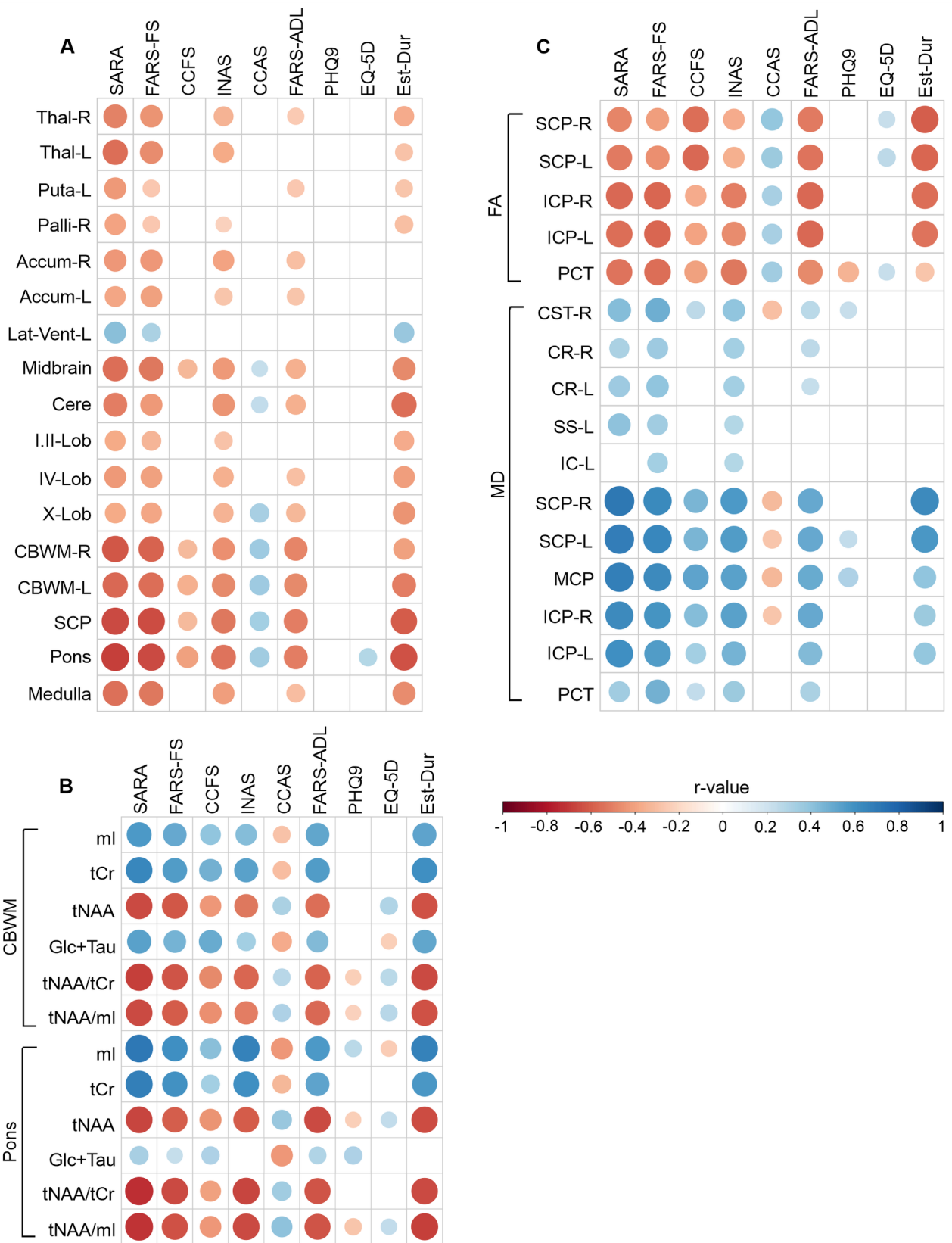
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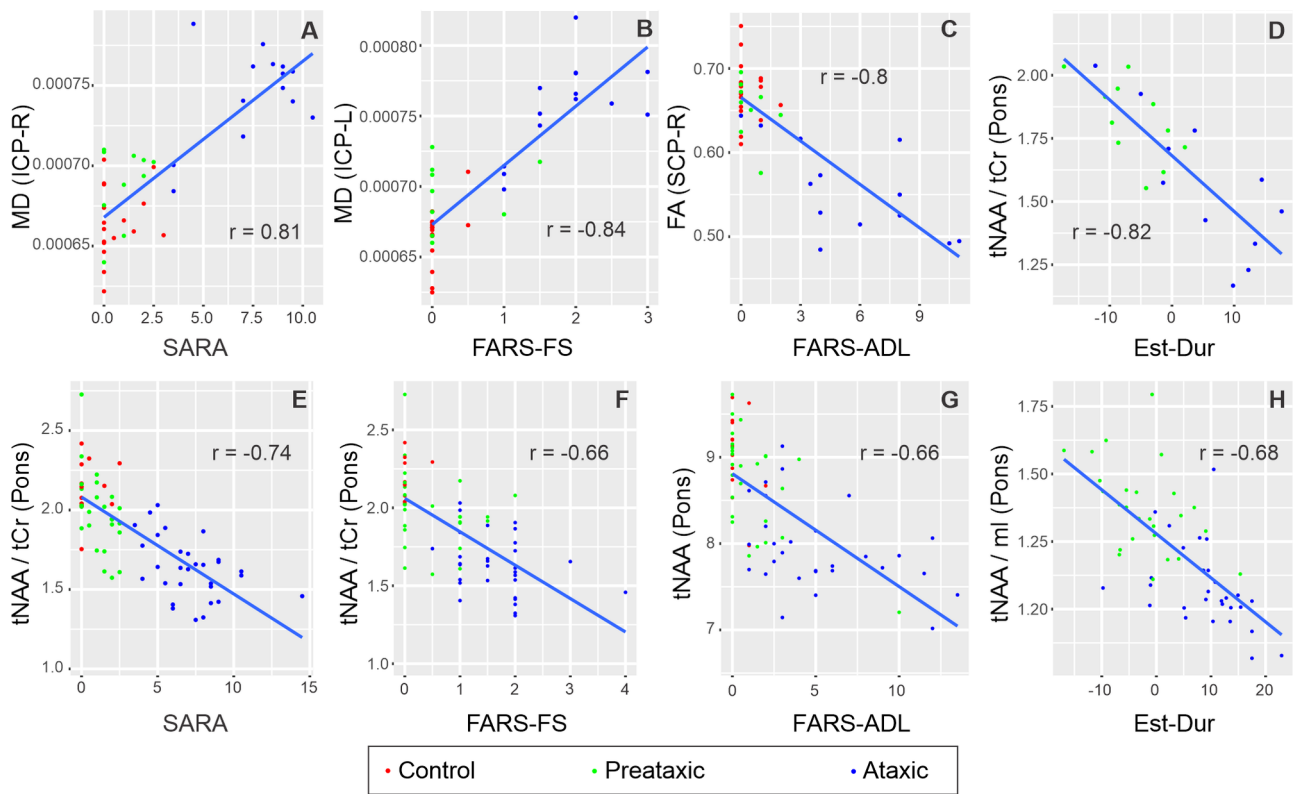
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ANA_26573_READISCA_MR_Fig5.tif



ANA_26573_READISCA_MR_Fig6.tif



ANA_26573_READISCA_MR_Fig7.tif

Table1: Cohort Characteristics

Variable	Control (C)	SCA1 Pretaxic (P)	SCA1 Ataxic (A)	SCA3 Pretaxic (P)	SCA3 Ataxic (A)
N	17	11	14	28	37
Sex (female) ^l	7 (41%)	8 (69%)	9 (67%)	19 (68%)	18 (49%)
Age ^l	43 [34;51]	38 [34.5;45.5]	46.5 [36.5;54]	36 [31.75;41.25] ^b	50 [42;57] ^b
SARA	0 [0;1]	1 [0;1.9] (N=10)	8.3 [7;9]	1.3 [0;2]	7 [5.5;8.5]
CAG repeat length (long allele)		42 [41.5;43.5] ^c	45 [43;46] ^c (N=13)	70 [69;72.25]	71.5 [67;73] (N=36)
CAG repeat length (short allele)		29 [29;30]	29 [29;30] (N=13)	23 [21;27]	23 [20;24] (N=33)
Reported age at onset			40 [35;47.5] (N=11)		45 [37;48] (N=33)
Reported time from ataxia onset			6 [4;12] (N=11)		3 [2;10] (N=33)
Estimated time from ataxia onset ² (years)		-7.01 [-9.18; -2.19] ^b	5.38 [-0.56;12.29] ^b (N=13)	-2.21 [-6.78;2.36] ^b	9.36 [5.04;13.19] ^b (N=36)
CCAS	108 [102;112]	101 [99;104] (N=10)	95 [90;106] (N=13)	101 [94;111] (N=25)	96 [91;102] ^a (N=34)
CCFS	0.878 [0.838;0.930] (N=15)	0.872 [0.845;0.894] ^b (N=8)	0.976 [0.930;1.030] ^{a,b} (N=12)	0.851 [0.835;0.886] ^b (N=25)	0.922 [0.864;0.982] ^b (N=35)
PHQ9	2.0 [0;3.0]	0.5 [0;3.5] (N=10)	5.5 [1.5;8.8]	2.0 [0;4.0]	3.5 [1.0;6.3] (N=36)
FARS-ADL	0 [0;1.0]	0 [0;1.0] ^b (N=10)	4.0 [3.5;8.0] ^{a,b} (N=13)	0.5 [0;1.8] ^b (N=27)	4.0 [2.4;6.3] ^{a,b} (N=36)
FARS-FS	0 [0;0] (N=15)	0 [0;0] ^b (N=9)	2 [1.5;2] ^{a,b}	0 [0;1] ^b	2 [1;2] ^{a,b}
EQ5D	90 [80;90]	90 [81;96] (N=10)	80 [71;89]	90 [80;98] ^b	80 [70;85] ^b (N=36)
INAS	0 [0;1]	1 [0;2] (N=10)	2 [1;2] ^a	1 [0;2] ^b	3 [2;4] ^{a,b}

For qualitative variables, frequencies are provided using percentages and for quantitative variables median and interquartile range [Q1; Q3] are provided. N is provided when values are missing.

^a $P < 0.01$ for pairwise comparison between C and A.

^b $P < 0.01$ for pairwise comparison between P and A within a SCA group.

^c $P < 0.05$ for pairwise comparison between P and A within a SCA group.

¹No significant differences were observed in age and sex between the SCA groups and healthy controls.

²Estimated time from onset (ataxia duration) was calculated for both premanifest and manifest SCA patients using CAG repeat length.

SARA = scale for the assessment and rating of ataxia, CCAS = cerebellar cognitive-affective syndrome, CCFS = composite cerebellar functional severity score, INAS = inventory of non-ataxia signs, FARS-FS = Friedreich's ataxia rating scale functional staging, EQ-5D = European quality of life 5 dimensions, PHQ-9 = patient health questionnaire-9, FARS-ADL = Friedreich's ataxia rating scale activities of daily living