BIGPRO - the SCA3/MJD cohort from South Brazil. An update

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Nothing to disclose

Machado-Joseph disease/spinocerebellar ataxia type 3 (SCA3/MJD) is due to a dominant CAG repeat expansion at *ATXN3.*

The onset of symptoms is around 34-40 yo, though *ATXN3* is expressed since intrauterine life.

We don’t know what is the most advantageous window preclinical time for future disease prevention.

BIGPRO study (ClinicalTrials NCT04229823, https://bigpro.webnode.page) aimed to validate state biomarkers of subclinical progression in the pre-ataxic phase of disease.

BIGPRO STUDY

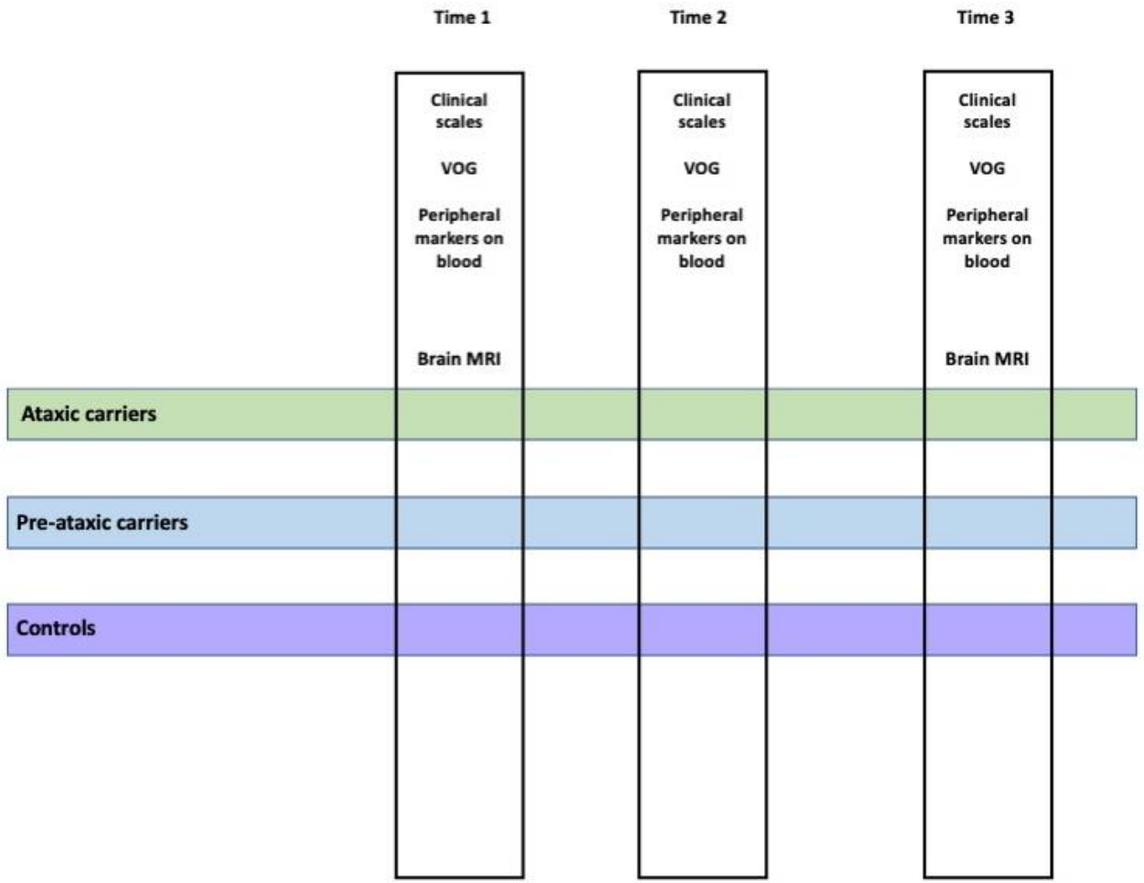
Study plan

ClinicalTrials NCT04229823,and on https://bigpro.webnode.page

Completed

(February 2022)

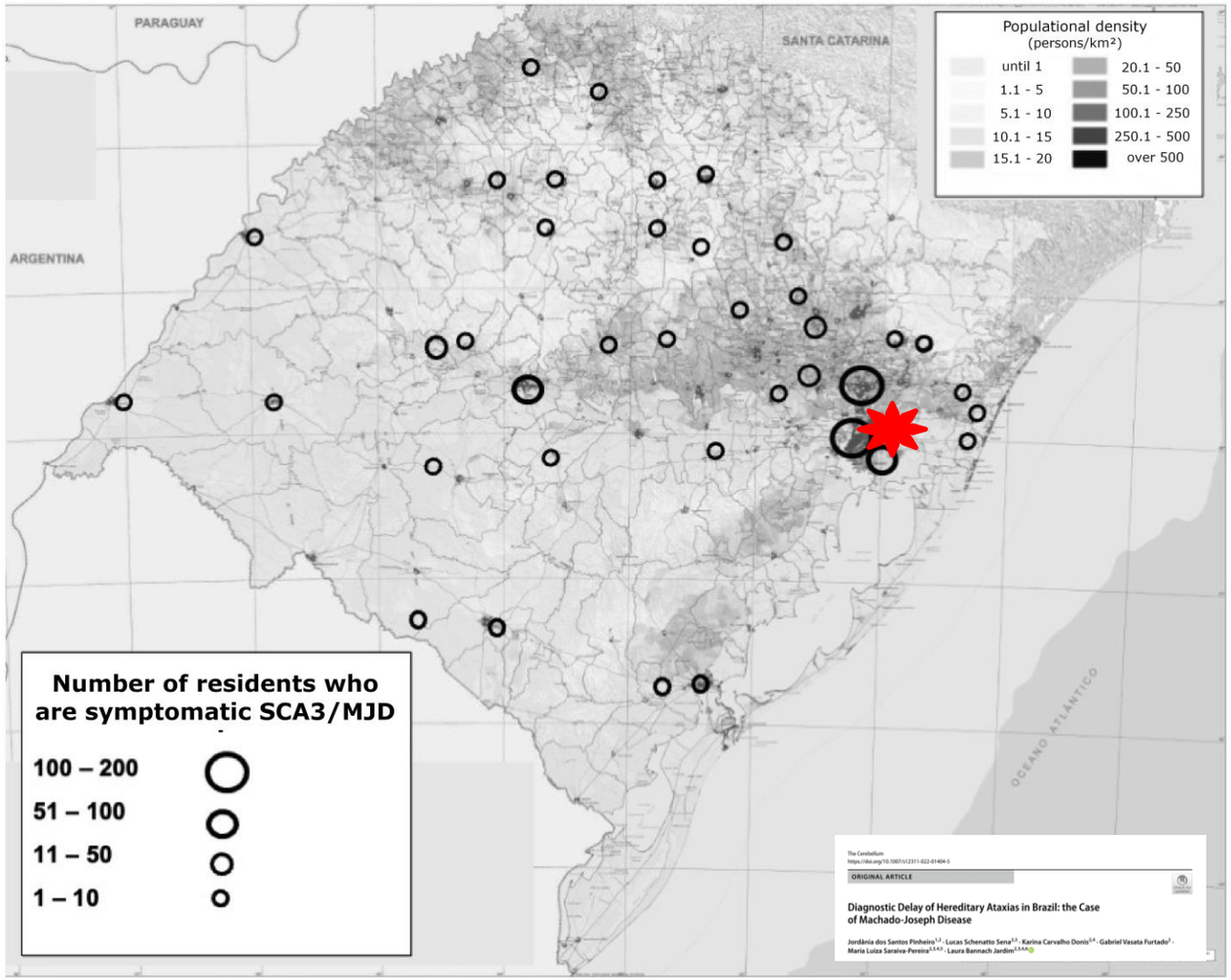
BIOMARKERS AND GENETIC MODIFIERS IN A STUDY OF PRE AND POST-SYMPTOMATIC SCA3/MJD CARRIERS



BIGPRO STUDY

720 symptomatic SCA3/MJD in Rio Grande do Sul State

7:100,000



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BIGPRO STUDY

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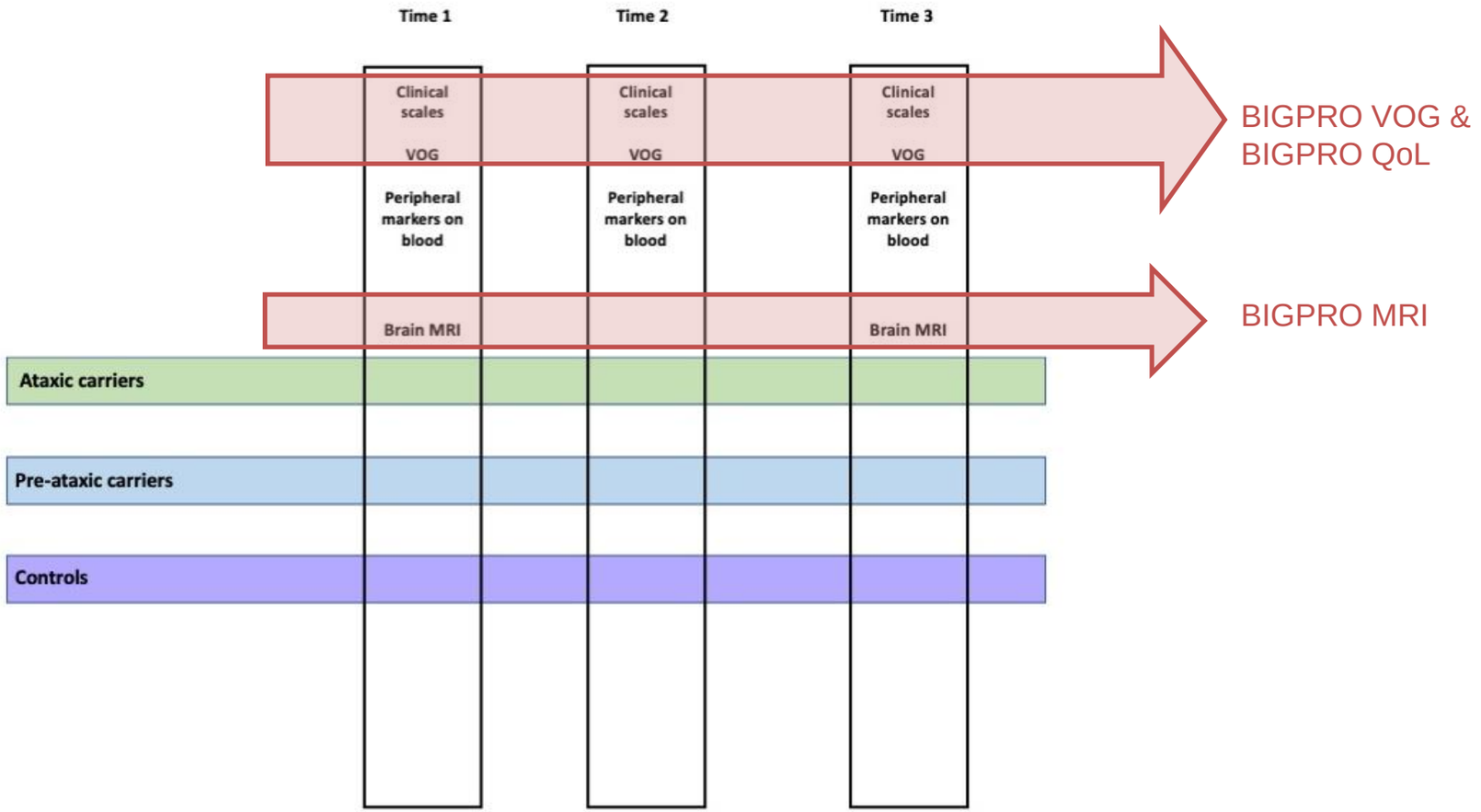

BIGPRO STUDY

CAPES

FAPERGS

PPSUS

Study plan

ClinicalTrials NCT04229823,and on https://bigpro.webnode.page

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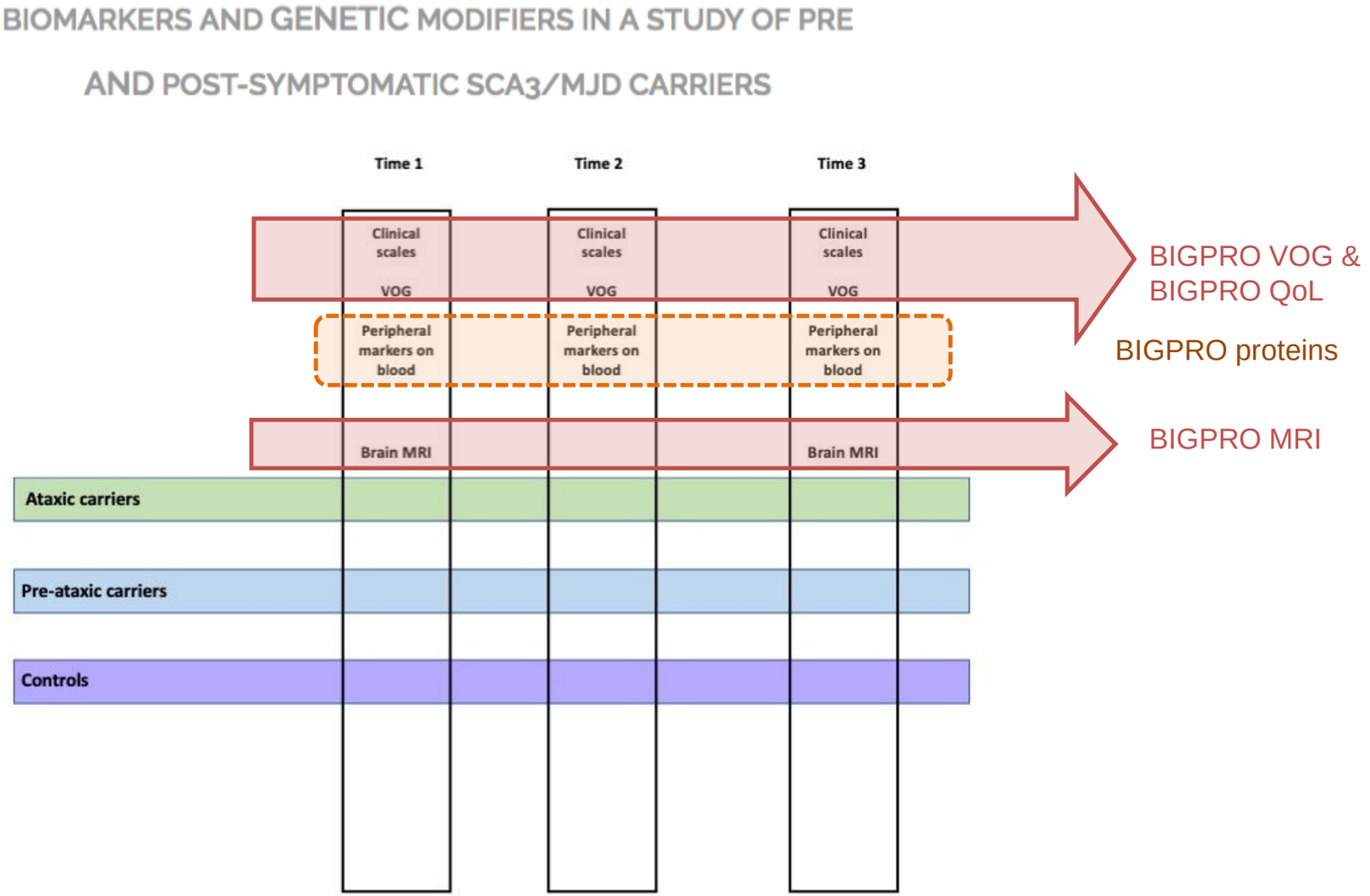

BIGPRO STUDY

Study plan

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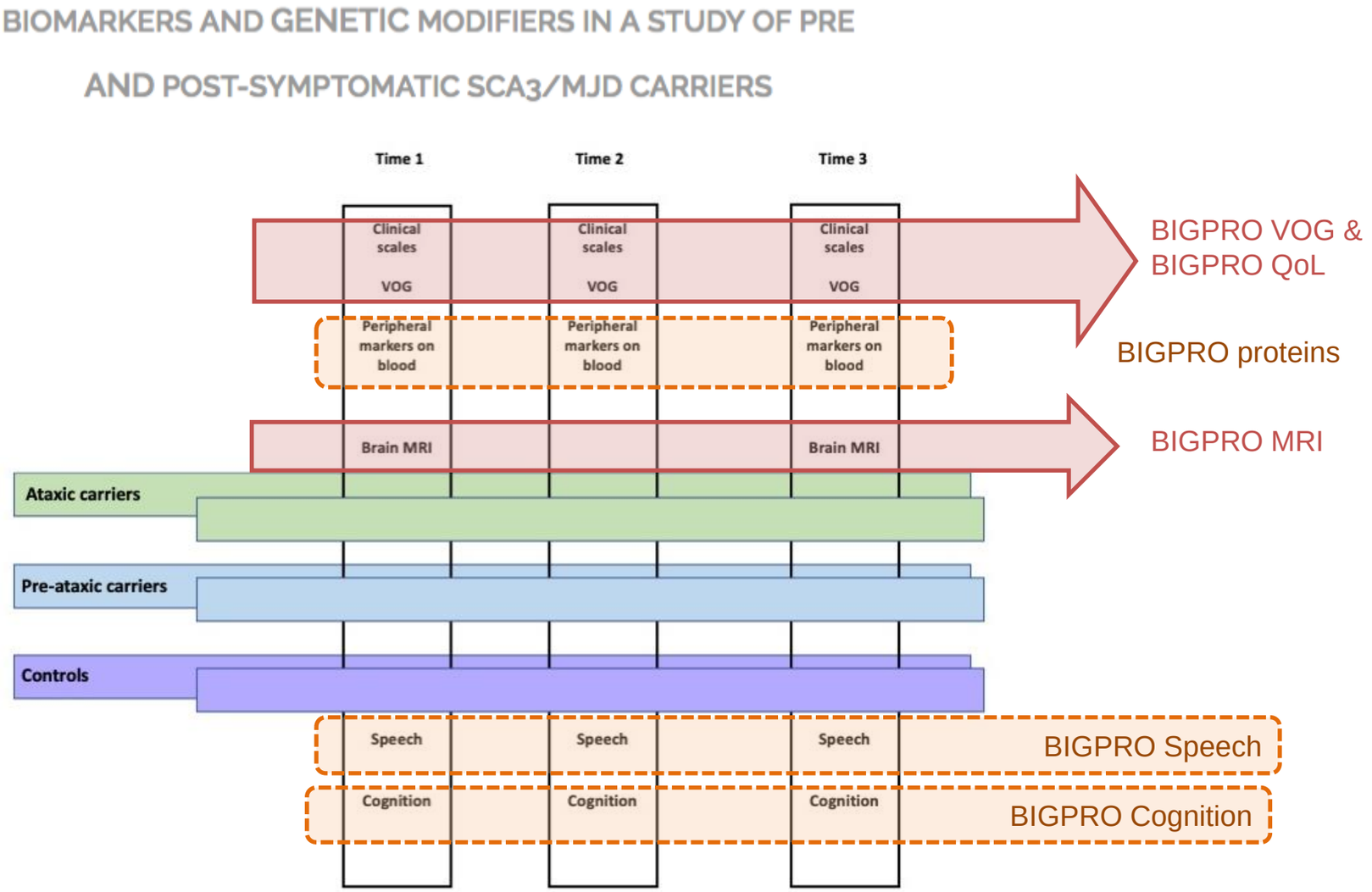

BIGPRO VOG

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Candidates: SARA, NESSCA, ICARS, INAScount, SCAFI, CCFS, and vídeo-oculography

35 ataxics, 38 pre-ataxics, 22 controls

Results already published (de Oliveira et al 2021, Mov Dis, doi: 10.1002/mds.28466 and de Oliveira et al 2022, Mov Dis, doi: 10.1002/mds.29226);

And presented during ICAR 2022. Please check AGI posters.

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BIGPRO VOG
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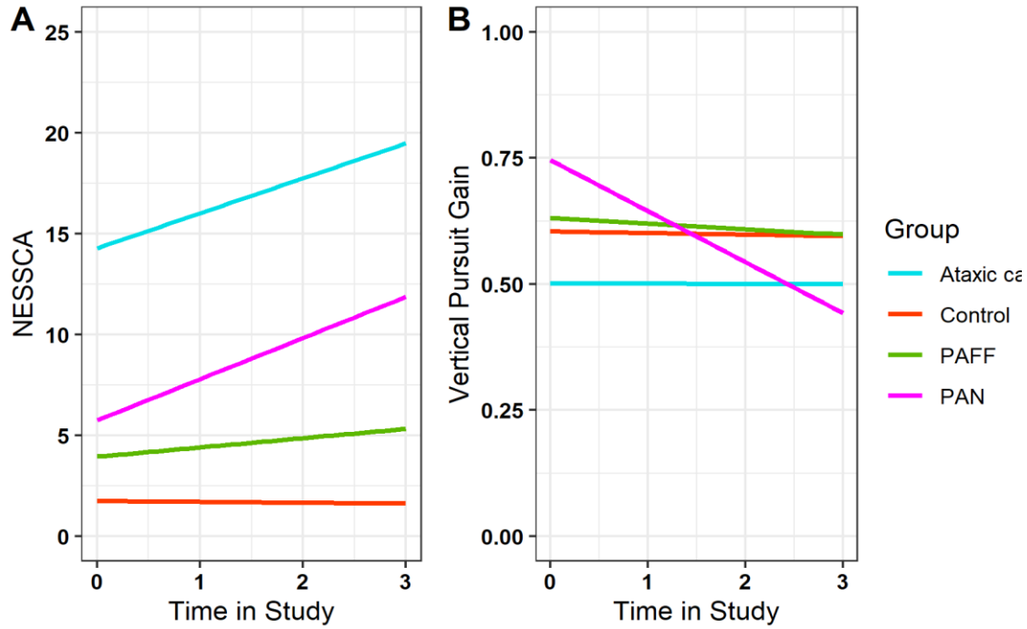
Study time approach revealed that

pre-ataxic carriers at 4 or less years from predicted onset (PAN, in ●) at baseline worsened after 27 months according to:

- NESSCA: 2.04 (0.68) points/year;
  ES of 1.36
- vertical pursuit gain:
  0.101(0.025)/ year;
  ES of 1.17



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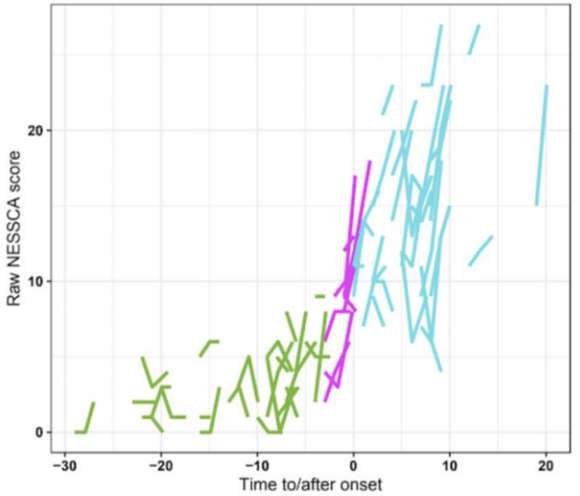
Sample Sizes for pre-ataxic carriers at 4 or less years to the predicted age of onset (PAN), and

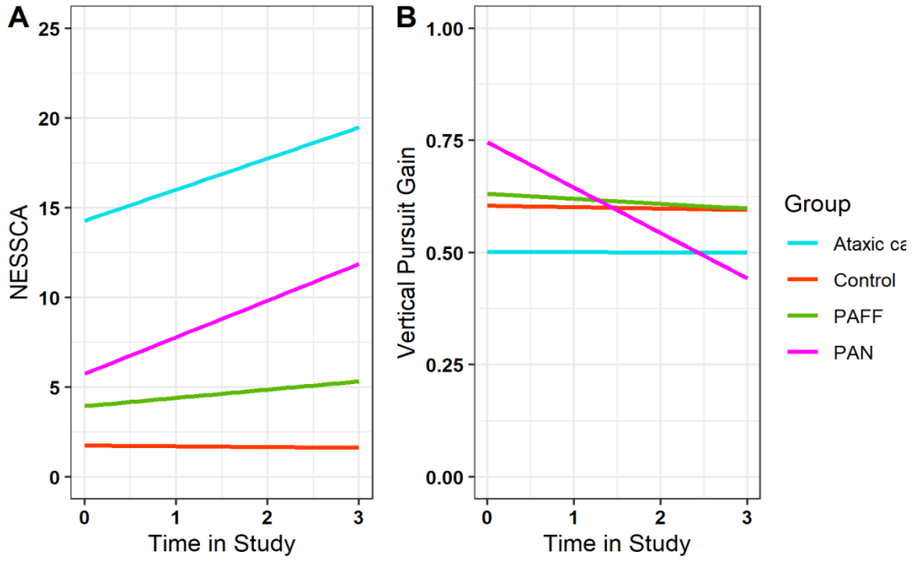
for placebo-controled RCTs with 80% power, 2-year follow-up, p 5%:

- 57 PAN per arm to detect a 50% reduction in the conversion rate.

- 57 PAN per arm to detect a 50% decrease in the progression rate of NESSCA

- 23 PAN per arm to detect a 50% decrease in the progression rate of the vertical pursuit gain





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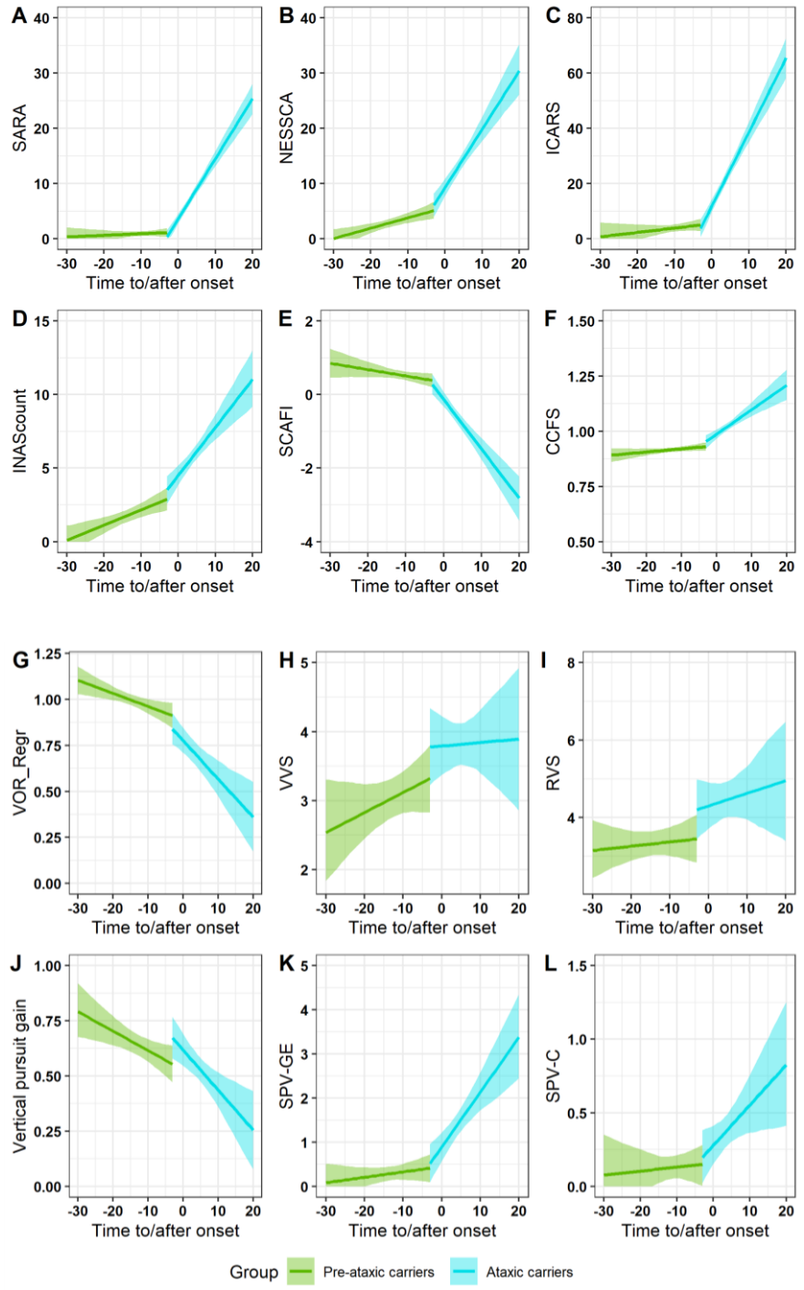
Observing the Time To Onset / Time After Onset dimension:

1) A shift in the slopes of neurological deteriorations occur around 4 years before ataxia onset:

- Mirroring disease process in CNS?
- Floor effects of these instruments?



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BIGPRO QoL

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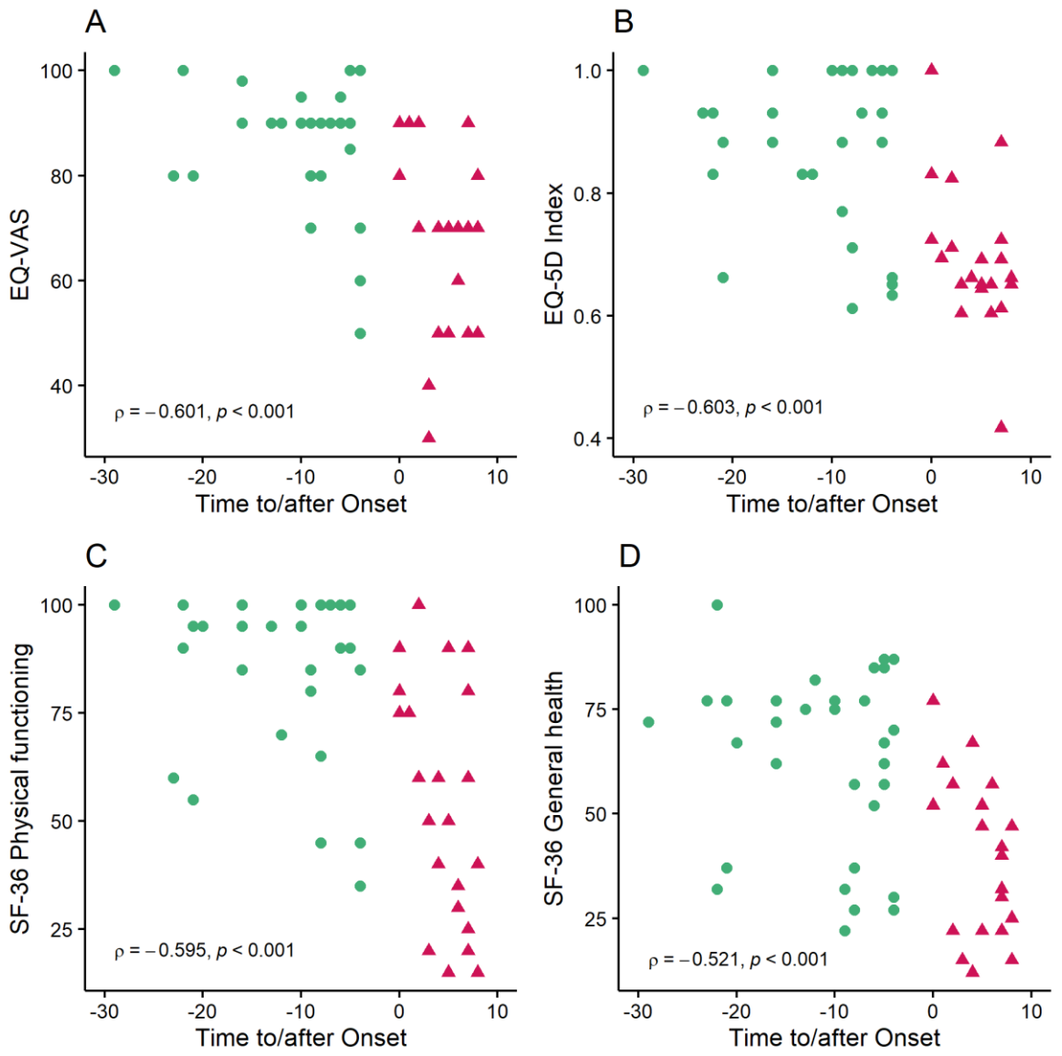
BIGPRO QoL

Twenty-three ataxic carriers,
33 pre-ataxic carriers, and 21 controls.

Baseline results were already published

(Bolzan et al 2022, doi: 10.1007/s12311-021-01299-8)



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BIGPRO MRI

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Baseline: 32 pre-ataxics, 20 controls. Follow-up after 30(7) months: 17 pre-ataxics, 12 controls.

Presented on flash talk presentations at ICAR 2022. Please check AGI posters

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BIGPRO MRI

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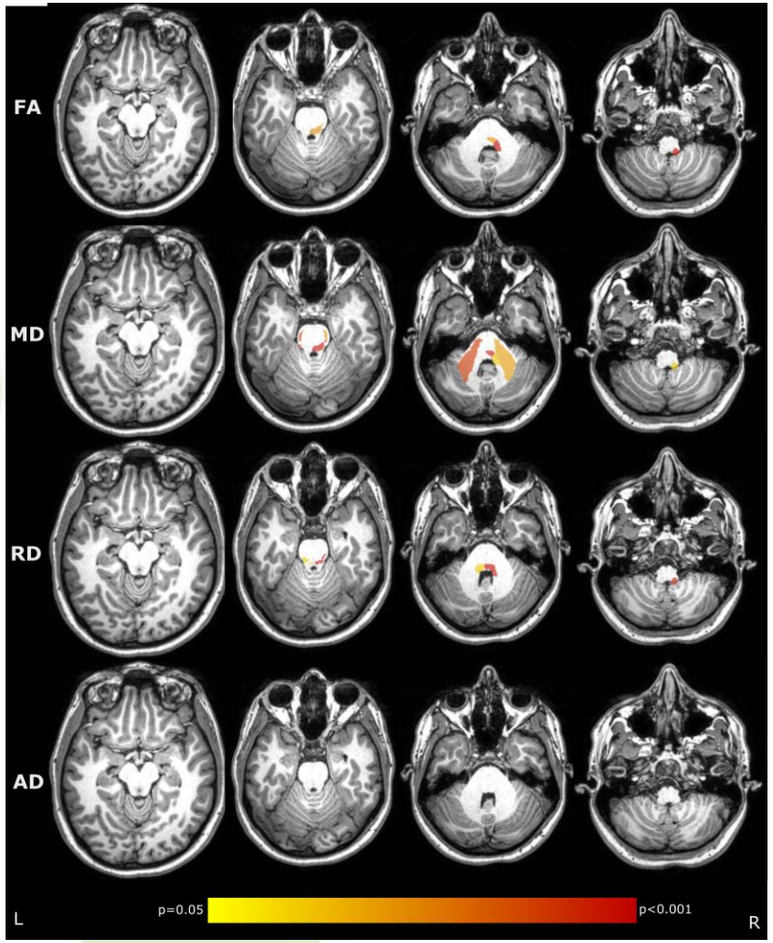
At baseline: DTI variables and cervical C1 área were already altered in pre-ataxic carriers

Markers that distinguished pre-ataxics from controls	
Medial lemniscus	Right, FA Right, MD Right, RD
	Left, RD
Inferior cerebellar peduncle	Right, FA Right, MD Right, RD
Medial cerebellar peduncle	Right, MD
	Left MCP, MD
Cervical área at C1	Spinal cord toolbox



BIGPRO MRI

Completed

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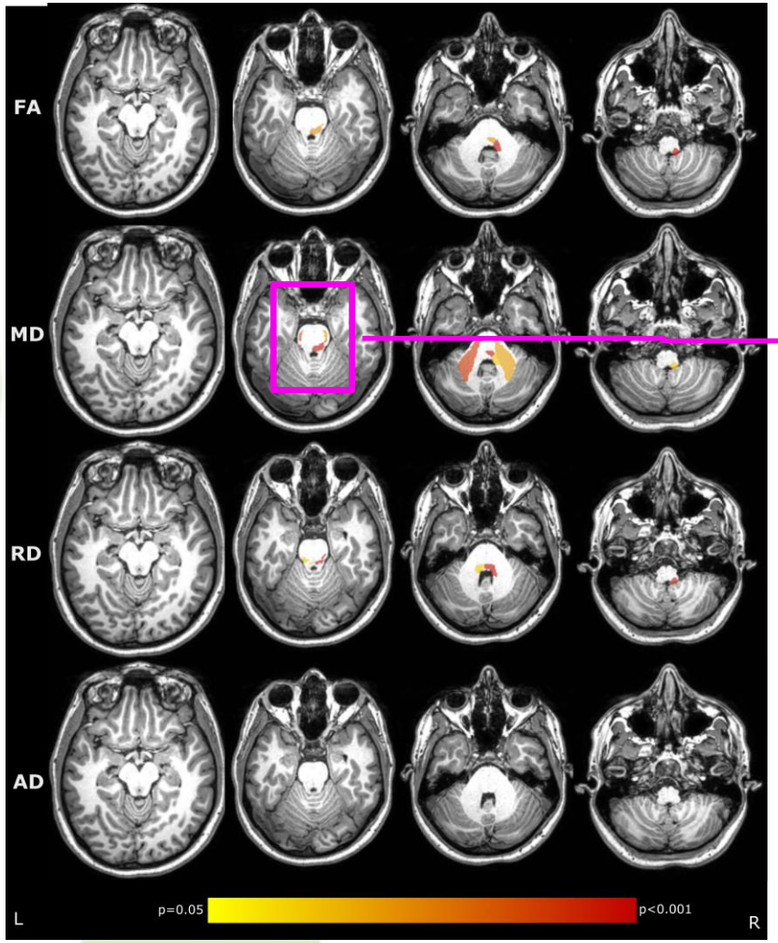

DTI (RD) of the left medial lemniscus correlated with NESSCA

(0.493, p=0.006)

and with the NESSCA item “sensory loss”

(0.462, p=0.009).

BIGPRO MRI

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Longitudinal:

No significant progression was seen in the study time approach.

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Longitudinal:

No significant progression was seen in the study time approach.

Only 17 pre-ataxics were followed-up, and only five of them were PAN

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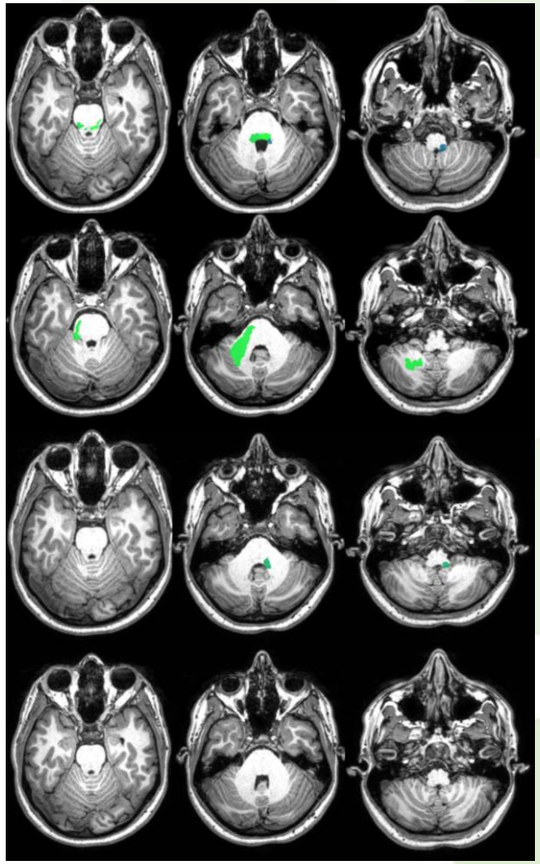
BIGPRO MRI

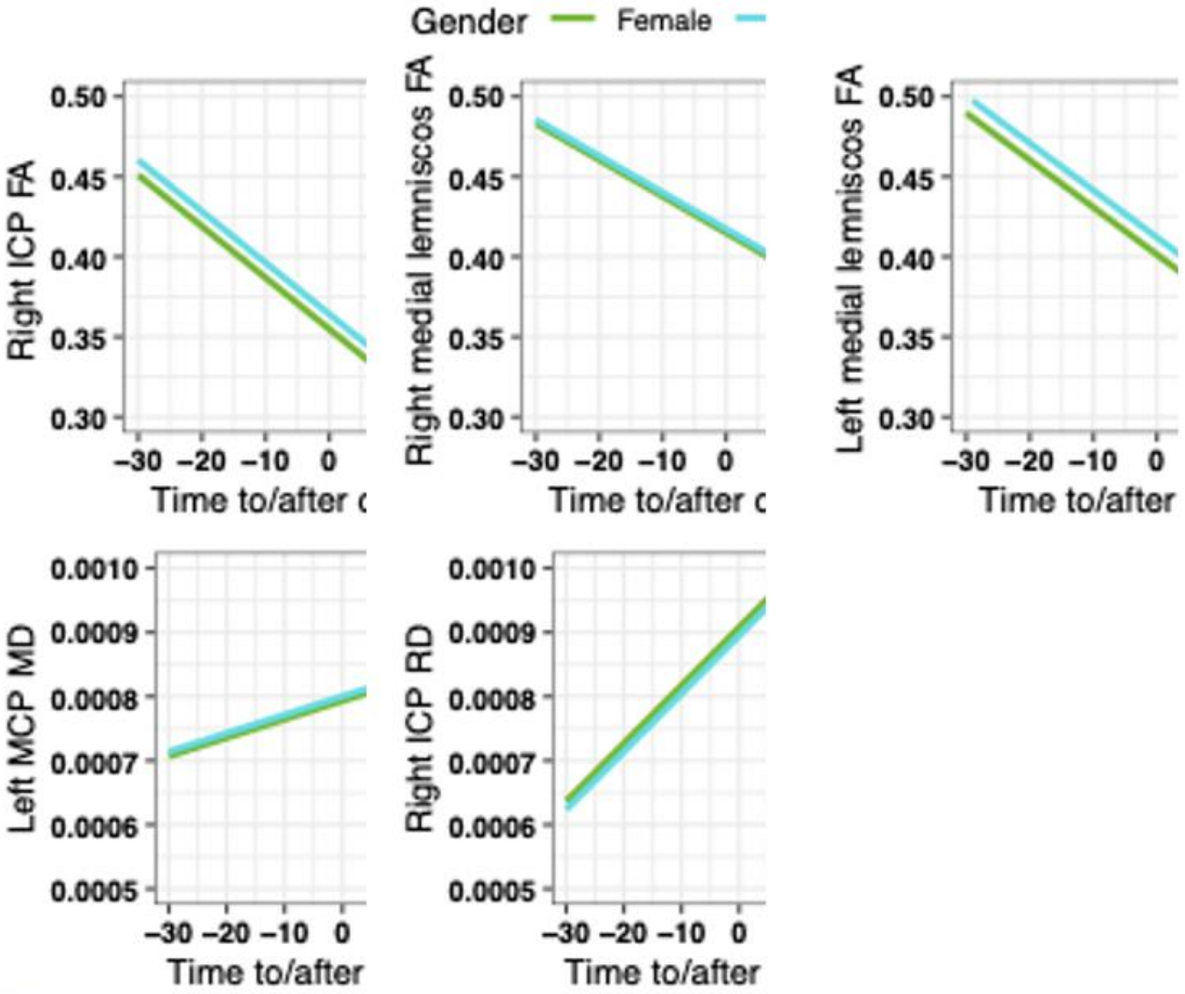
Completed

Longitudinal:

No significant progression was seen in the study time approach.

Relevant progressions in Time Left To Onset approach:





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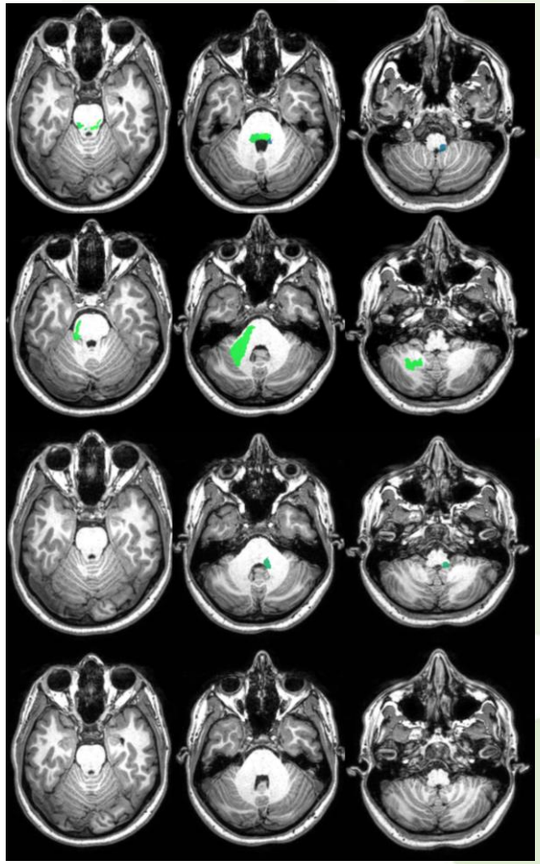

		Annual progression (SE)	p (z-score for MRI)	ES
Medial lemnisci	**Right, FA**	-0.0023 (0.0008)	0.001	**0.20**
	Left, FA	-0.0030 (0.0009)	0.001	**0.18**
	Left, MD	$5.39x10^{-6}$ ($1.59x10^{-6}$)	0.054	**0.15**
	Right, RD	$4.24x10^{-6}$ ($1.21x10^{-6}$)	0.701	0.11
	Left, RD	$6.02x10^{-6}$ ($1.59x10^{-6}$)	0.965	**0.16**
Inferior cerebellar peduncle, right	FA	-0.0032 (0.0011)	0.038	0.11
	MD	$8.58x10^{-6}$ ($2.26x10^{-6}$)	0.164	**0.15**
	RD	$9.05x10^{-6}$ ($2.23x10^{-6}$)	0.001	**0.15**
Medial cerebellar peduncles	**Right, MD**	$2.63x10^{-6}$ ($9.23x10^{-7}$)	0.539	**0.20**
	Left, MD	$2.88x10^{-6}$($9.95x10^{-7}$)	0.001	**0.19**
Cervical area at C1	**Spinal cord toolbox**	-0.53 (0.18)	0.115	**0.17**
Clinical scales	NESSCA	0.17 (0.06)	0.014	0.08
	INAScount	0.10 (0.04)	0.016	0.07
Video-oculography	VORr	-0.009 (0.003)	0.004	-0.14

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BIGPRO proteins

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BIGPRO proteins

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27 ataxic and 36 pre-ataxic carriers, and 19 related controls.

GFAP, eotaxin and **NSE**

Baseline results:

GFAP, eotaxin and NSE did not differ among groups, nor correlated with clinical scales, CAGexp or AOga.

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BIGPRO proteins

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GFAP, eotaxin and **NSE**

Baseline results:

GFAP, eotaxin and NSE did not differ among groups, nor correlated with clinical scales, CAGexp or AOga.

Eotaxin (astrocyte activation?) correlated with RD of the corticospinal tracts (left: rho= -0.330, p= 0.014; right: rho= -0.300, p= 0.026).

NSE (biomarker of neuronal losses) correlated with deep gray matter of the right medulla (rho= 0.276, p=0.041) and with C1 área (rho= 0.365, p=0.0001)

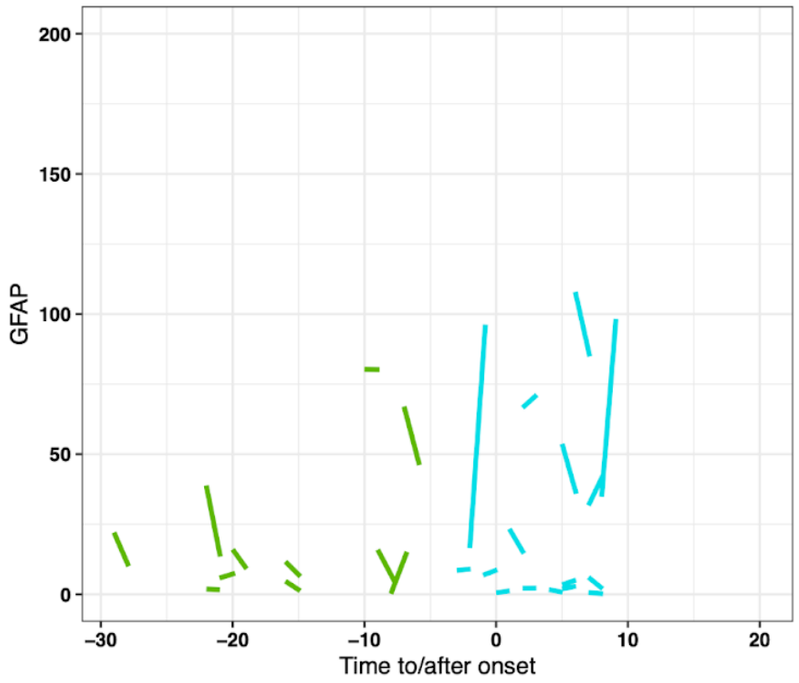
BIGPRO proteins

Completed

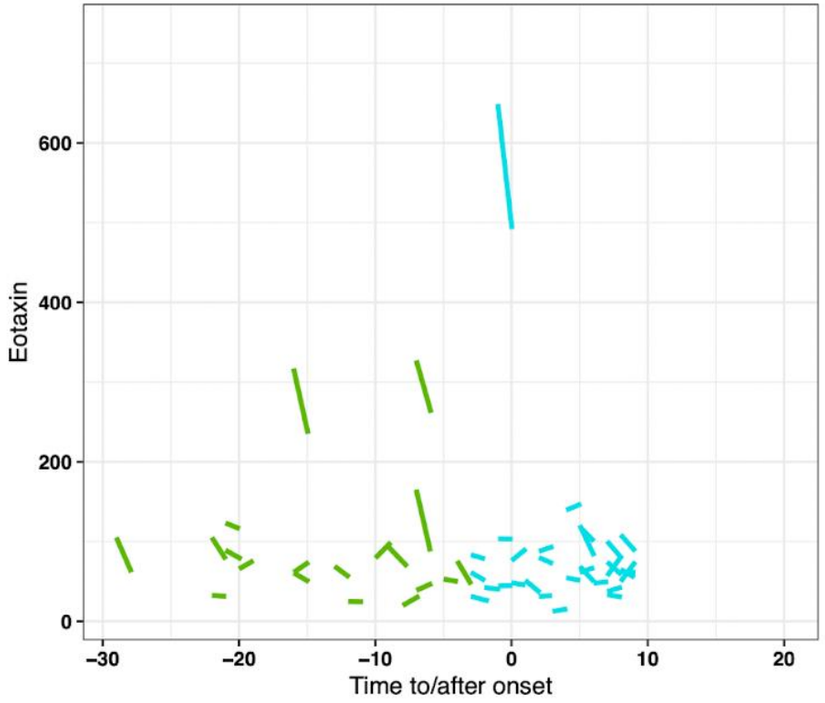
Longitudinal results: after 13 months of baseline, according to TimeToAfter:

Great variability, hard to see any trend of progression.

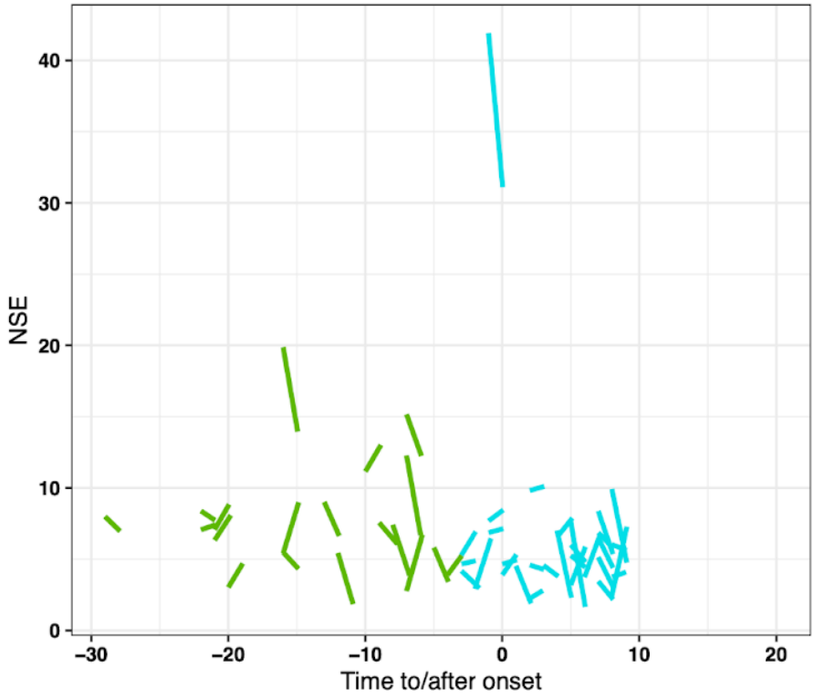
GFAP



Eotaxin



NSE



BIGPRO cognition

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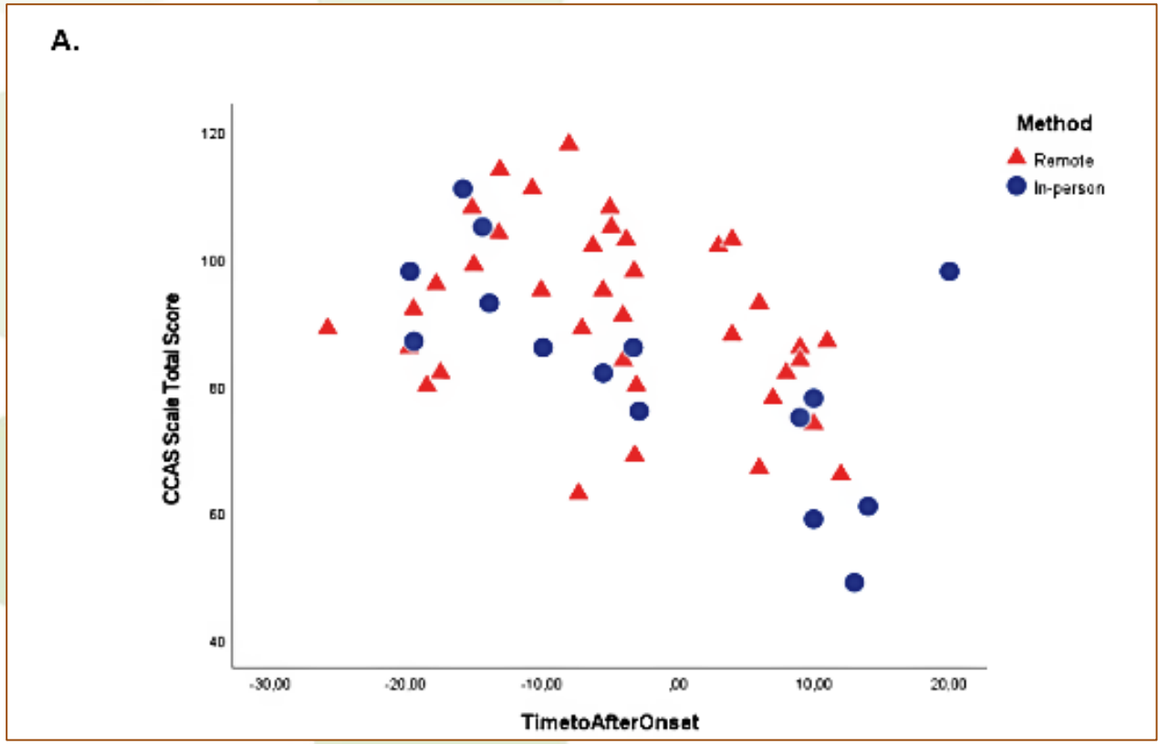
BIGPRO cognition

23 manifest and 35 premanifest carriers, and 58 related and unrelated controls.

Baseline results collected during Covid19 pandemics.

Presented by Gabriela Bolzan in ICAR plenary section and on an AGI poster.



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BIGPRO speech

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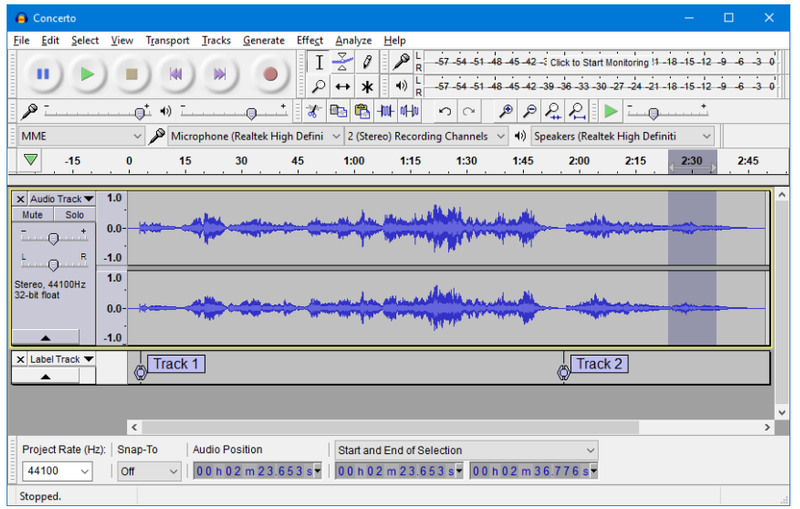
Reliability of the assessments of speech and voice.

37 symptomatic patients. Presented on ICAR poster #470.



Five perceptual and 30 acoustic variables of speech and voice achieved adequate test-retest reliability (Kappa > 0.80 or ICC> 0.70).

Baseline results on 29 ataxic and 29 pre-ataxic carriers, and 22 related controls are underway.

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BIGPRO conclusions, so far

Clinical Trials on pre-ataxic SCA3/MJD carriers should

- Focus on pre-ataxics at four or less years from predicted onset (PAN)
  - How to recruit PAN???
  - How to maintain two-years CT?
  - Frank discussion with families about pre-symptomatic testing.

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BIGPRO conclusions, so far

Clinical Trials on pre-ataxic SCA3/MJD carriers should

- Focus on pre-ataxics at four or less years from predicted onset (PAN)
- Best outcomes in PAN:
  - conversion rate
  - Progression rates of NESSCA and vertical pursuit gain
  - DTI and C1 area are potentially the best candidates – but a new cohort must follow more than 10 PAN for two years, to confirm that and to get sample sizes

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