Internuclear Ophthalmoparesis

5-NOV-2024
18:15-19:00
axel petzold

Disclosures

- NIHR UK
- UCSF (RECOVER trial)
- Stichting MS Research NL
- Zeiss (OCTA, ARI network)
- Heidelberg Academy (speaker)
- Amsterdam UMC (RESTORE trial)
- Novartis (SC OCTiMS, QC PASSOS)
- The Moorfields Biomedical Research Centre
- Fight for Sight Queen Square (Nimodipine trial)

To be covered

- What is the next big “jack pot” in eye-brain care?
- 30 years of research – what did I learn?
- Internuclear ophthalmoparesis
- Supply & Demand
- Clinical trials
- Summary

The next big thing: Brain Repair

- Successfull:
  - Disease Modifying Treatments
  - Thrombolysis
- Failed: neuroprotection
- Novel: Brain Repair
  - Remyelination
  - Plasticity / brain reserve

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Here is what I learned

- 1994-1998 Psychophysics: interesting, time consuming
- 1998-2010 Biomarkers: industrial, group level
- 2010-2017 OCT: big data, individual patient level
- 2017-2024 Eye-movements: elegant, big potential

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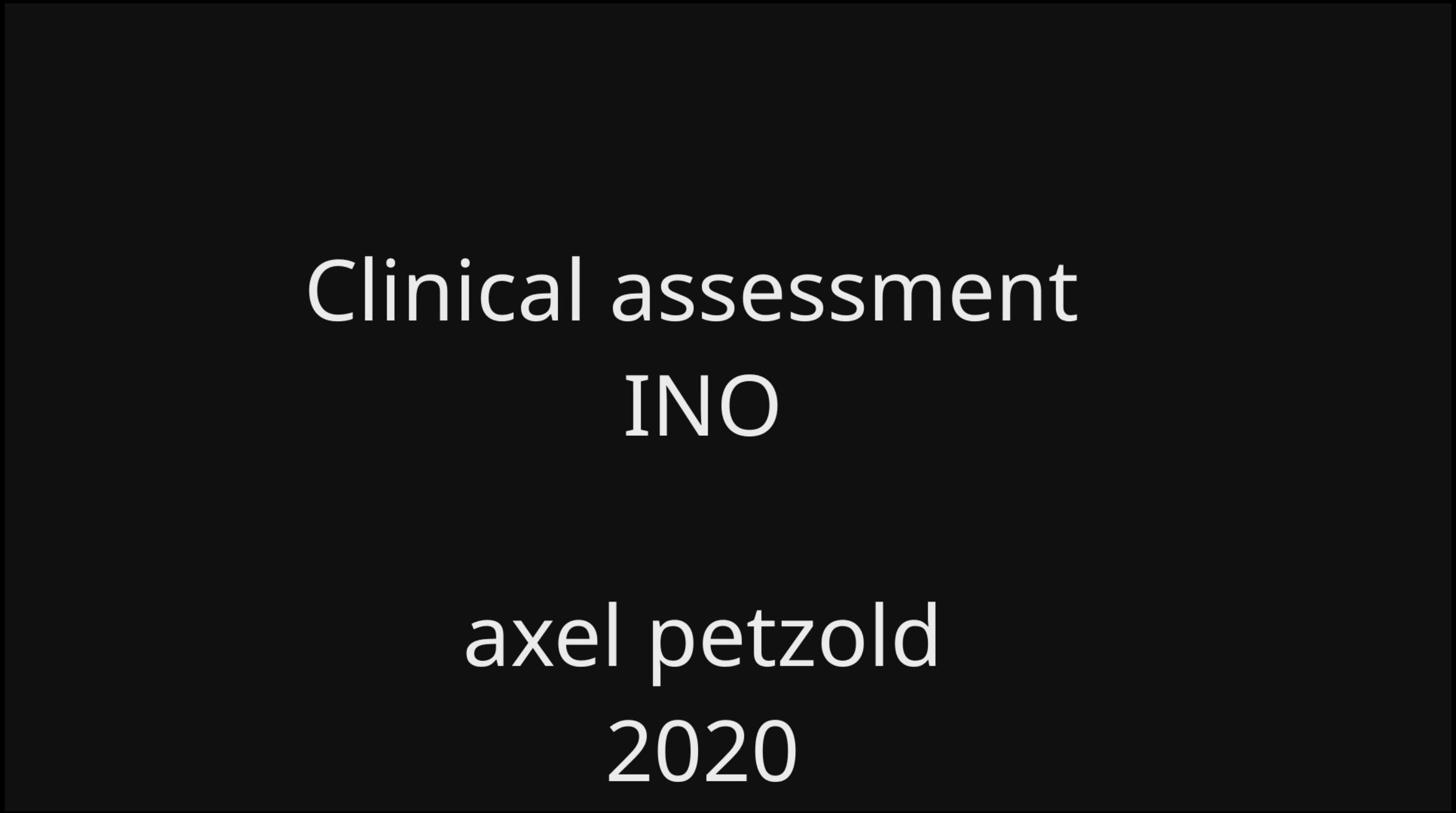
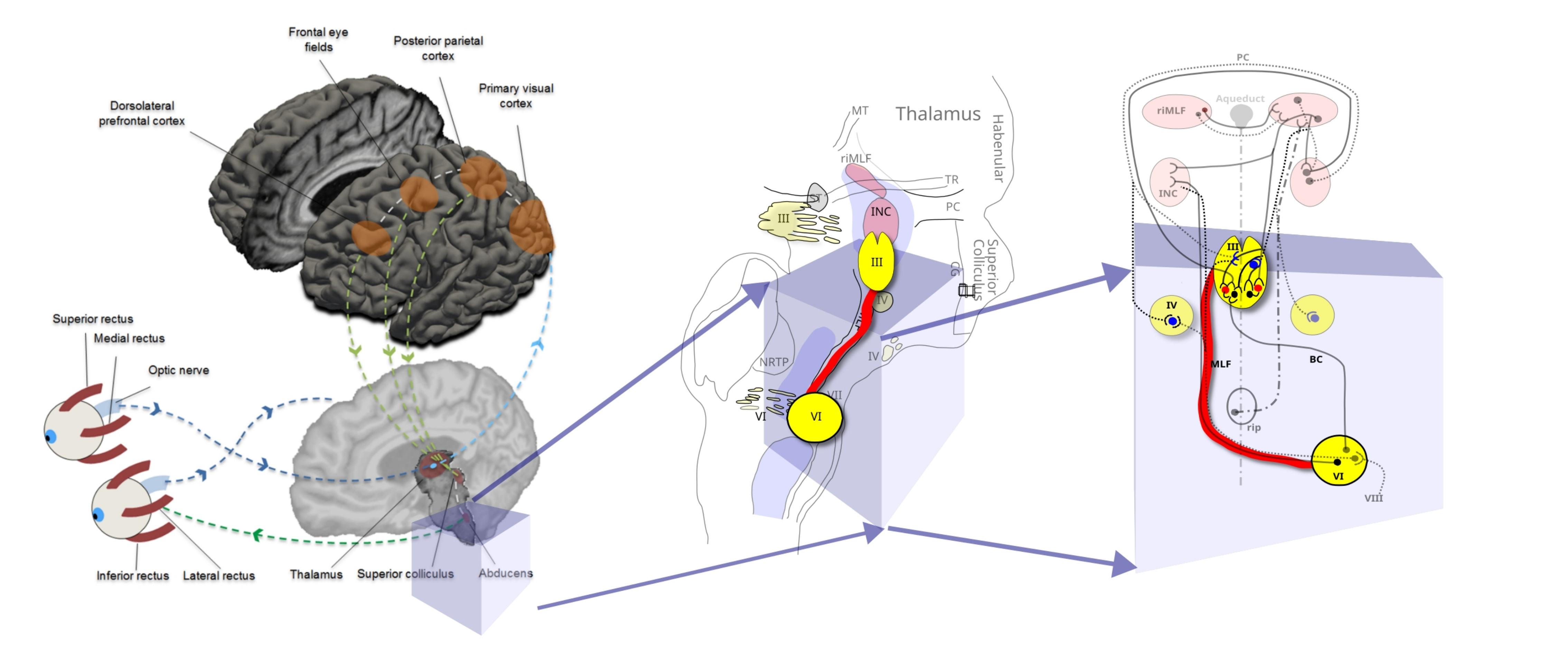
INO: video



/home/petz1/images-ap/eye-movements/ino-clinical.webm

INO: anatomy

Cortical network | **MLF**



Outcome: mistakes

Outcome: v=s:t

Nij Bijvank, J *et al* Brain 2023

INO: a single axon tract

- $v = s / t$

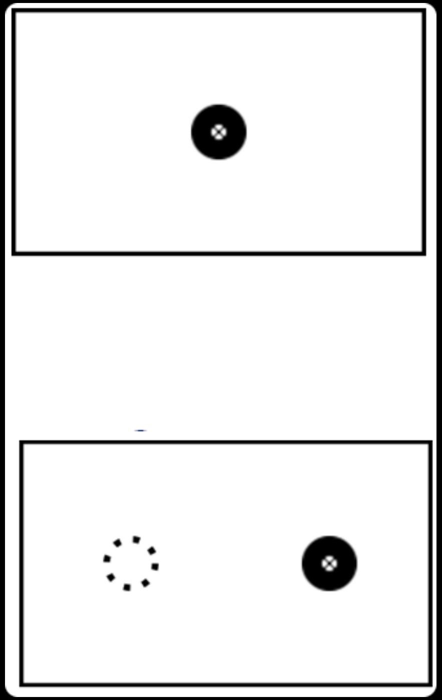
- Let t1 = normal axon, t2 de- and t3 re-myelinated axon, with $t1 < t3 < t2$

- To demonstrate re-myelination one needs to show $v3>v2$

- This is easy in the MFL through quantification of INO

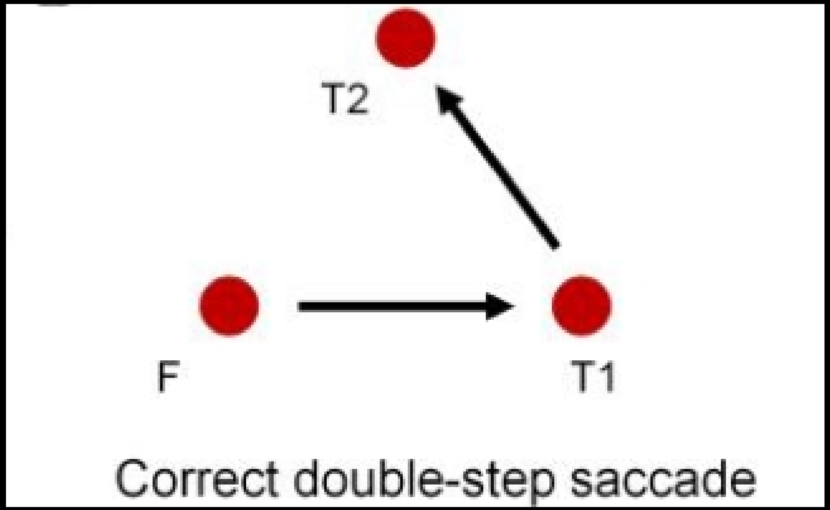
Eye-movements: outcome measures

MLF



Outcome: v=s:t

Cortical network



Outcome: mistakes

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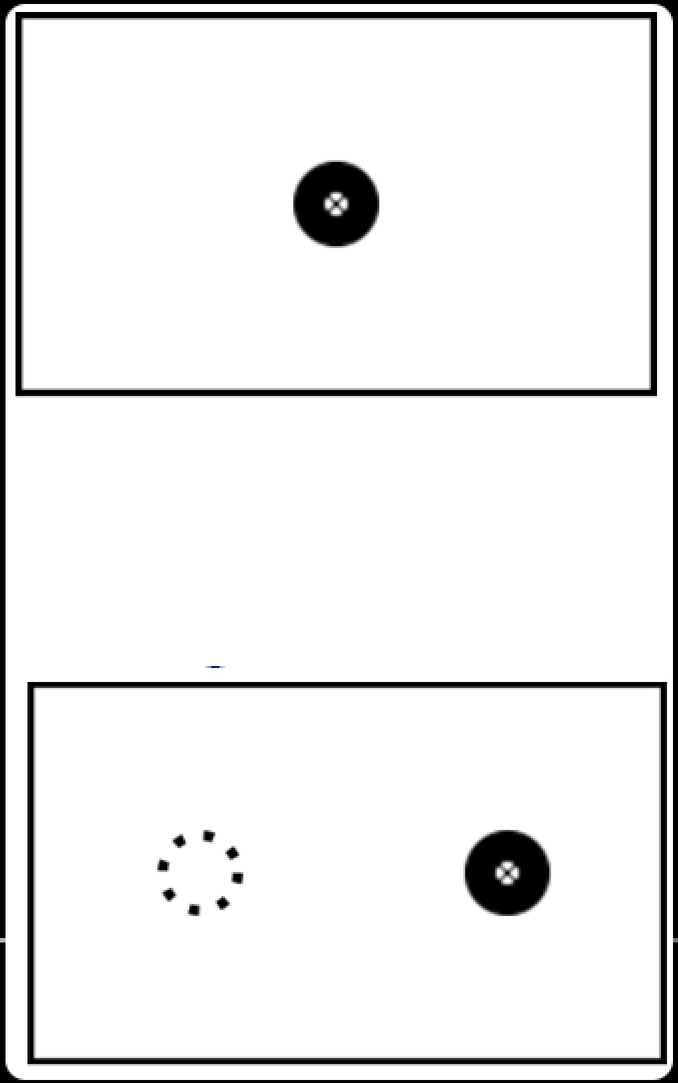
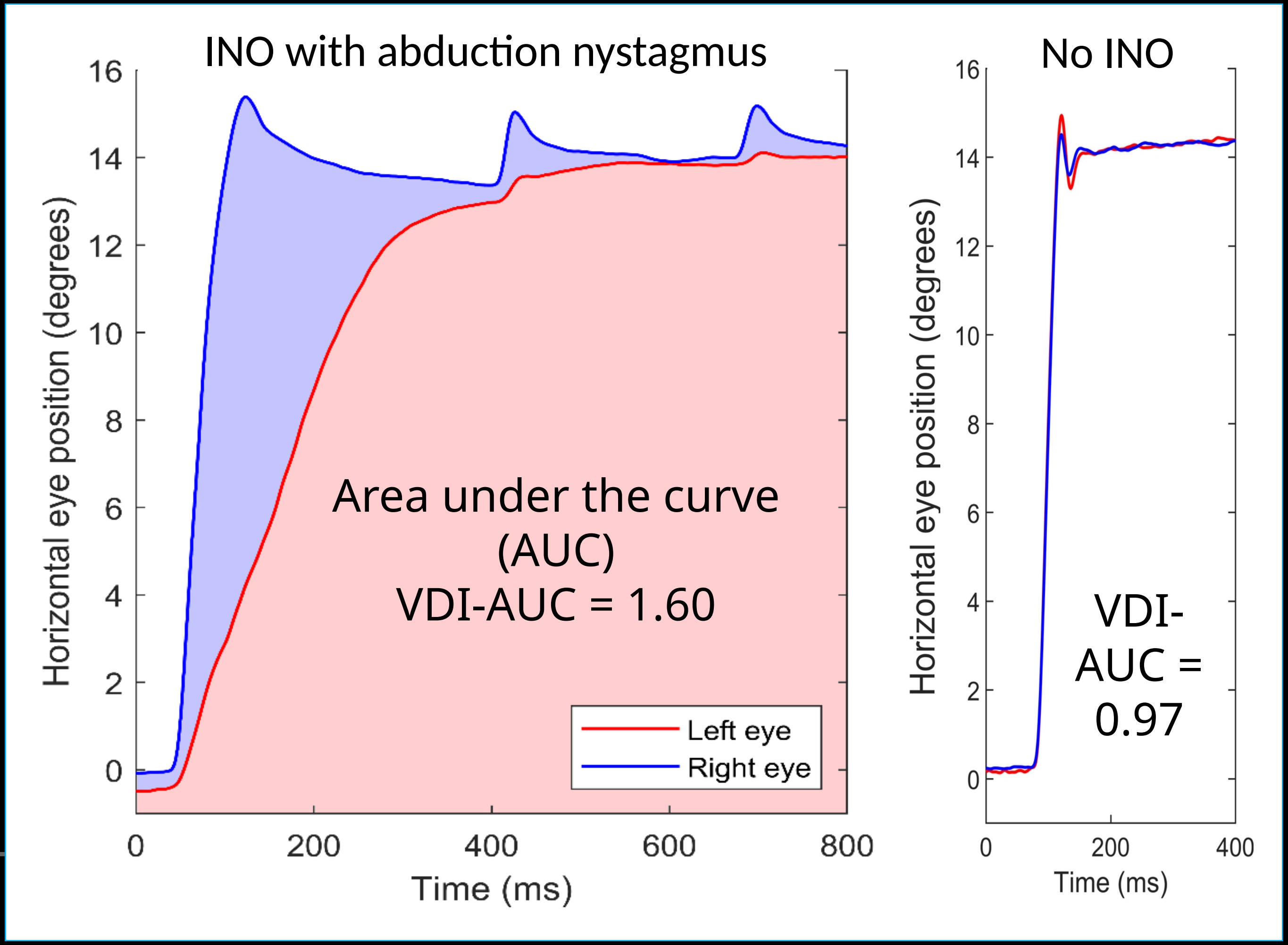
INO: quantification





Sam Hof *et al* ECTRIMS 2023

Relationship to atrophy & cognition

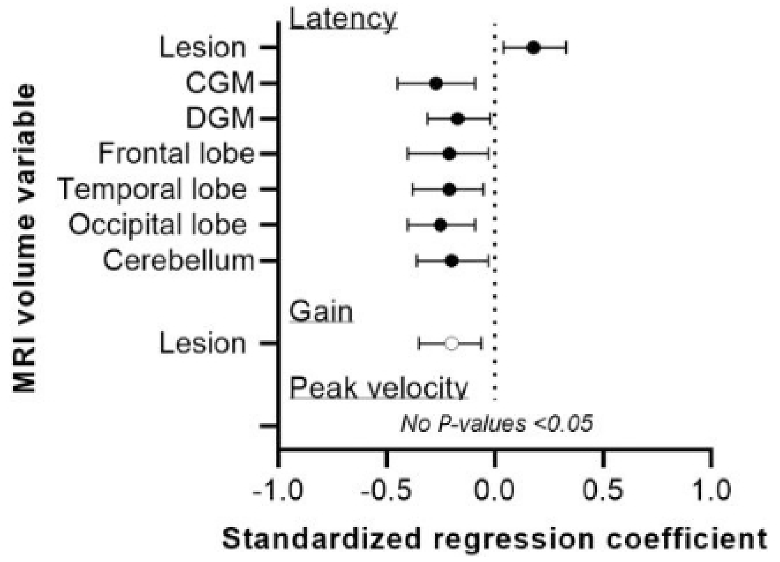


Figure 4 Effect sizes of associations between MRI volume variables and double-step and pro- saccadic parameters. Associations with P-values <0.05 are shown (see Supplementary Tables 3 and 4 for all associations).

Table 3 Adjusted associations between cognitive domain Z-scores and double-step parameters

Double-step parameter (dependent variable)	Cognitive domain (independent variable)	Adjusted model: B	95% CI B	β	P-value
Proportion of correct double-step saccades	Executive functioning	0.040	0.018 to 0.061	0.28	**<0.001**
	Verbal memory	0.044	0.593 to 0.977	0.25	**0.001**
	Information processing	0.093	0.066 to 0.120	0.46	**<0.001**
	Visuospatial memory	0.045	0.021 to 0.069	0.28	**<0.001**
	Working memory	0.036	0.013 to 0.059	0.24	**0.002**
	Attention	0.039	0.012 to 0.066	0.22	**0.006**
Proportion acceptable double-step saccades	Executive functioning	0.041	0.019 to 0.063	0.28	**<0.001**
	Verbal memory	0.041	0.028 to 0.078	0.23	**0.004**
	Information processing	0.093	0.065 to 0.121	0.45	**<0.001**
	Visuospatial memory	0.045	0.021 to 0.070	0.27	**<0.001**
	Working memory	0.039	0.015 to 0.062	0.26	**0.001**
	Attention	0.041	0.013 to 0.069	0.22	**0.004**
Direction difference first saccade	Executive functioning	−1.129	−2.120 to −0.138	−0.18	0.026
	Verbal memory	−1.267	−2.521 to −0.013	−0.17	0.048
	Information processing	−1.799	−1.642 to −0.444	−0.21	0.010
	Visuospatial memory	−1.538	−2.638 to −0.437	−0.22	**0.006**
Absolute error FEP	Executive functioning	−0.265	−0.349 to −0.180	−0.45	**<0.001**
	Information processing	−0.472	−0.575 to −0.368	−0.58	**<0.001**
	Visuospatial memory	−0.117	−0.221 to −0.013	−0.18	0.028
	Working memory	−0.189	−0.285 to −0.092	−0.31	**<0.001**
	Attention	−0.248	−0.359 – −0.137	−0.25	**<0.001**
Horizontal error FEP	Executive functioning	0.099	0.028 to 0.170	0.22	**0.007**
	Information processing	0.186	0.092 to 0.281	0.30	**<0.001**
	Visuospatial memory	0.099	0.021 to 0.178	0.20	0.013
	Working memory	0.089	0.013 to 0.165	0.19	0.021
Vertical error FEP	Executive functioning	0.342	0.230 to 0.455	0.44	**<0.001**
	Verbal memory	0.158	0.008 to 0.309	0.17	0.039
	Information processing	0.591	0.446 to 0.735	0.54	**<0.001**
	Visuospatial memory	0.180	0.043 to 0.316	0.20	0.010
	Working memory	0.268	0.141 to 0.394	0.33	**<0.001**
	Attention	0.305	0.157 to 0.452	0.30	**<0.001**

Nij Bijvank, J *et al* Brain 2023

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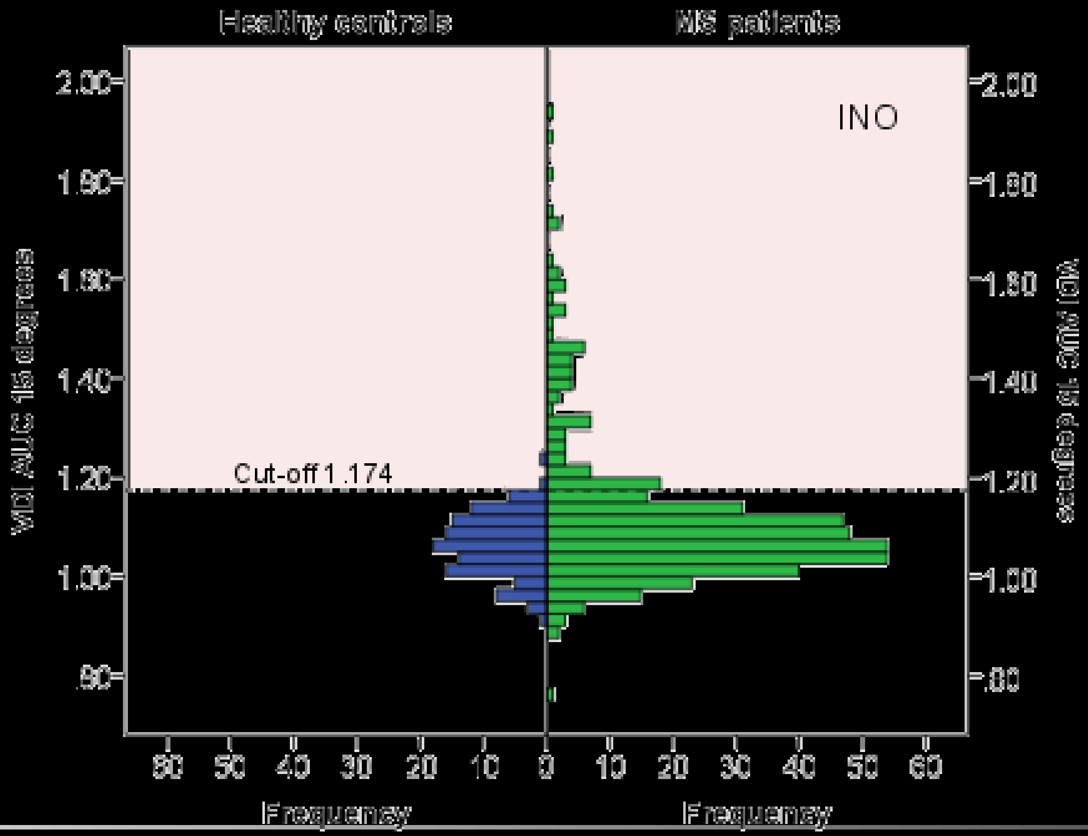
INO prevalence

Cohort study 1: 25%



Cohort study 2: 24%

	PwMS (n=220)			HC
	INO+	**INO-**	**p-value**	**(n=110)**
Female	57%	78%	0.002	73%
EDSS	4.0	3.5	0.044	n/a
SDMT	49	53	0.046	n/a
NHPT	22.20	21.41	0.015	n/a

Nij Bijvank, J *et al* Neurology 2019

Hof, S.N. *et al* MSRD 2022

A Digital Camera-Based Eye Movement Assessment Method for NeuroEye Examination

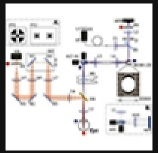
Publisher: IEEE
Cite This
PDF

Mohamed Abul Hassan ; Xuwang Yin ; Yan Zhuang ; Chad M. Aldridge ; Timothy McMurry ; Andrew M. Southerland
All Authors

Abstract
Document Sections

Abstract:
The ability to perform quantitative and automated neurological assessment could enhance diagnosis and treatment in the pre-

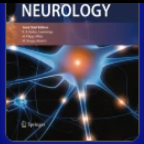
Biomedical Optics Express Vol. 11, Issue 6, pp. 3164-3180 (2020)
• https://doi.org/10.1364/BOE.392849



High-resolution, ultrafast, wide-field retinal eye-tracking for enhanced quantification of fixational and saccadic motion

Maciej M. Bartuzel, Krystian Wróbel, Szymon Tamborski, Michał Meina, Maciej Nowakowski, Krzysztof Dalasiński, Anna Szkulmowska, and Maciej Szkulmowski

Lesion follows function: video-oculography compared with MRI to diagnose internuclear ophthalmoplegia in patients with multiple sclerosis



Journal of Neurology
Aims and scope →
Submit manuscript →

Original Communication | Open access | Published: 31 October 2022
Volume 270, pages 917–924, (2023) Cite this article

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Rawan Omary, Christopher J. Bockisch, Anthony De Vere-Tyndall, Shila Pazahr, Krisztina Baráth & Konrad P. Weber

Abstract

Background

Video-oculography (VOG) is used to quantify functional deficits in internuclear ophthalmoplegia (INO), whereas MRI can detect the corresponding structural lesions in the medial longitudinal fasciculus (MLF). This study investigates the diagnostic agreement of MRI compared to VOG measurements.

NEURO-OPHTHALMOLOGY: EDITED BY HEATHER E. MOSS

Advances in ophthalmic structural and functional measures in multiple sclerosis: do the potential ocular biomarkers meet the unmet needs?

Jiang, Hong[a,b]; Delgado, Silvia[b]; Wang, Jianhua[a,c]
Author Information

Current Opinion in Neurology 34(1):p 97-107, February 2021. | *DOI:* 10.1097/WCO.0000000000000897

BUY
Metrics

Abstract

Purpose of review

Multiple sclerosis is a heterogeneous disorder. Biomarkers to monitor disease activities are highly desirable especially because of the recent shift toward personalized medicine that coincides with the expansion of disease-modifying therapy. The visual system is highly involved in multiple sclerosis, and the rapid advancement of ophthalmic techniques has boosted the development of potential ocular biomarkers for multiple sclerosis management.

Recent findings

Recent studies have found that the rapid thinning of the peripapillary retinal nerve fiber layer and ganglion cell-inner plexiform layer (GCIPL) occurs in the progressive stage. Furthermore, the inter-eye thickness difference of the GCIPL could be used in identifying unilateral optic neuritis to facilitate the early diagnosis of multiple sclerosis. Moreover, the retinal microvascular alterations measured as vessel density were found to be related to the disability and visual function, although a standardized protocol to measure retinal microvascular alterations has not been well established. Additionally, aberrant ocular motility, such as fixation microsaccades, can be used to measure disability objectively.

Summary

The fast expansion of potential ocular biomarkers measured as retinal microstructural, microvascular, and ocular motility changes may facilitate the diagnosis and management of multiple sclerosis.

BASIC AND TRANSLATIONAL RESEARCH

The Study of Remyelinating Therapies in Multiple Sclerosis: Visual Outcomes as a Window Into Repair

Zuroff, Leah R. MD, MSTR; Green, Ari J. MD, MCR

Author Information

Journal of Neuro-Ophthalmology 44(2):p 143-156, June 2024. | *DOI:* 10.1097/WNO.0000000000002149

OPEN

Metrics

Abstract

Introduction:

Amelioration of disability in multiple sclerosis requires the development of complementary therapies that target neurodegeneration and promote repair. Remyelination is a promising neuroprotective strategy that may protect axons from damage and subsequent neurodegeneration.

Article

Augmenting Early Stroke Diagnosis With an Eye-Tracker

Mohamed Abul Hassan, Yan Zhuang, Mohammed E-Rabbi, Chad Aldridge, and 2 more

This is a preprint; it has not been peer reviewed by a journal.

https://doi.org/10.21203/rs.3.rs-4656842/v1

Status: Under Review

npj | digital medicine

Article

September 1985

The Clinical Spectrum of Internuclear Ophthalmoplegia in Multiple Sclerosis

René M. Müri, MD; Otmar Meienberg, MD

Author Affiliations

From the Department of Neurology, University of Bern, Bern, Switzerland. Dr Meienberg is now with the University of Basel, Basel, Switzerland.

Arch Neurol. 1985;42(9):851-855. doi:10.1001/archneur.1985.04060080029011

Abstract

• The eye movements of 100 patients with multiple sclerosis were examined clinically, including a saccade test. Thirty-four cases of internuclear ophthalmoplegia were found, of which 14 were bilateral and 20 were unilateral.

OPEN ACCESS

ARVO Annual Meeting Abstract | July 2019

Frequency of internuclear ophthalmoplegia, nystagmus and other ocular manifestations in multiple sclerosis; a population-based study

Sarah ChaoYing Xu; Eoin Flanagan; Robert Foster; Feng Wang; Muhammad Bhatti; John Chen

Conclusions : While optic neuritis is the most common MS-related ocular condition, many other ocular symptoms can be present. INO being the second most common ocular finding can be subtle and asymptomatic but still play an important role in

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Registered Clinical Trials

NCT05338450 Recruiting

Clemastine Fumarate as Remyelinating Treatment in **Internuclear** Ophthalmoparesis and **Multiple Sclerosis**

Conditions

Internuclear Ophthalmoplegia | Multiple Sclerosis

Locations

Amsterdam, Netherlands

NCT06629155 Not yet recruiting New

Studying Eye Movement Deficits and Cognitive Impairment in Patients with **Multiple Sclerosis** Using Infrared Eye Tracking and Cognitive Tests

Conditions

Internuclear Ophthalmoplegia | Multiple Sclerosis

Locations

Location not provided

NCT05776511 Recruiting

Diagnostic Value of eVOG

Conditions

Multiple Sclerosis | Radiologically Isolated Syndrome | White Matter Lesions

Locations

Nice, France

NCT02391961 Completed WITH RESULTS

Study and Treatment of Visual Dysfunction and Motor Fatigue in **Multiple Sclerosis**

Conditions

Internuclear Ophthalmoplegia | Multiple Sclerosis | Fatigue

Locations

Cleveland, Ohio, United States

NCT04702763 Completed

Eye Movements Recording Using a Smartphone: Comparison to Standard Video-oculography in Patients With **Multiple Sclerosis**

Conditions

Multiple Sclerosis

Locations

Monaco, Monaco

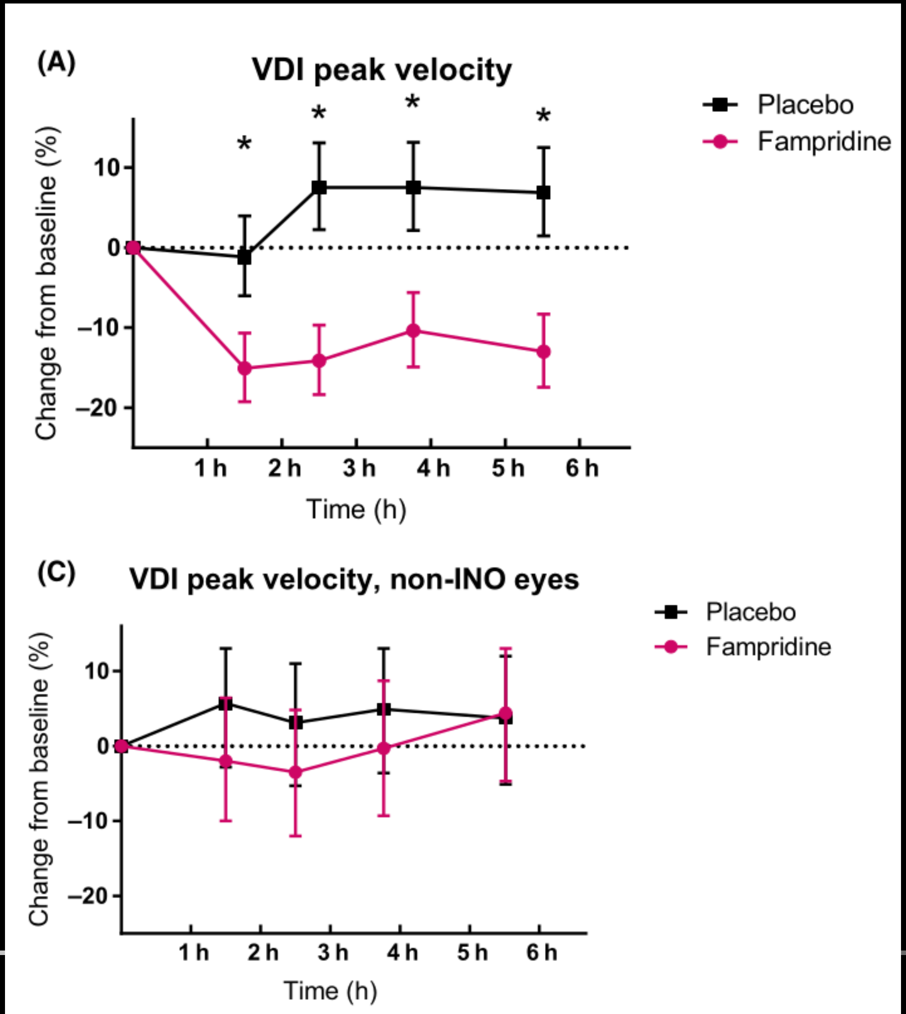
Checked 28-OCT-2024

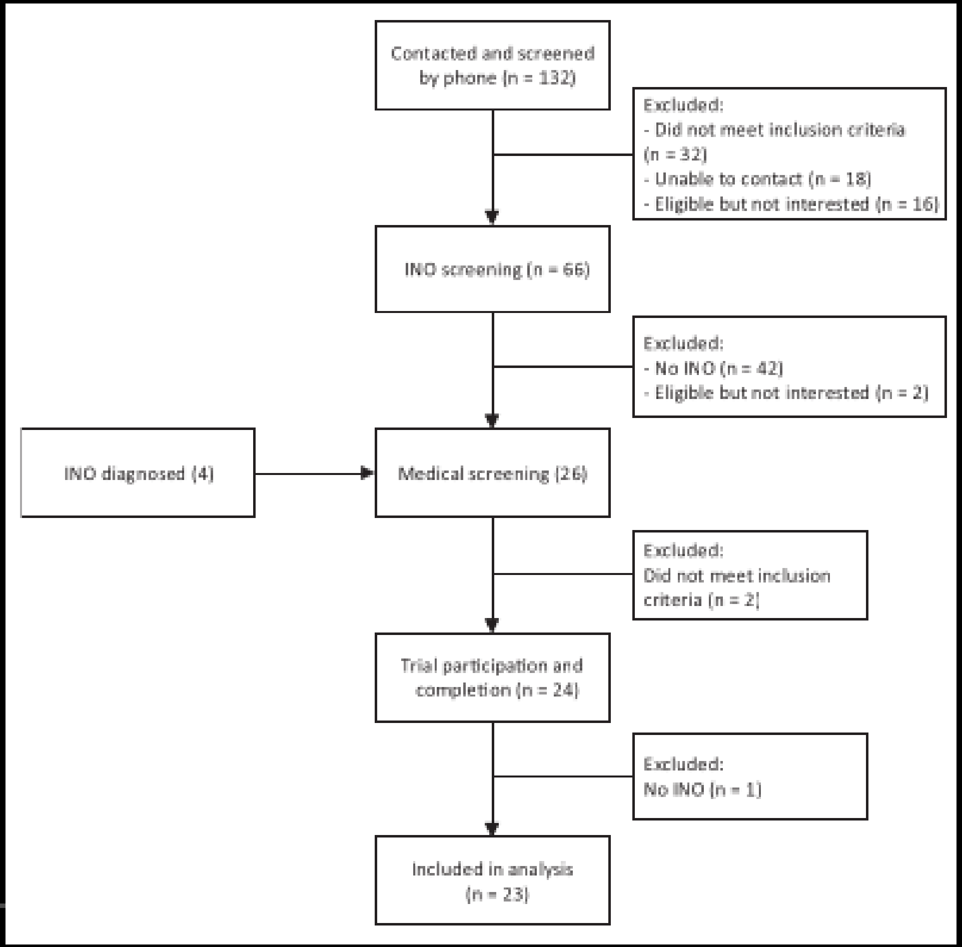
The options

- Optic nerve

- Medial longitudinal fasciculus
- The cortical network governing eye movements

INO: treatment response prediction





Kawita, M.S.K. *et al* CNSNT 2018

RESTORE Trial

EudraCT: 2021-003677-66
ClinicalTrials.gov: NCT05338450

Amsterdam UMC
University Medical Centers

P705

MS Center Amsterdam

A randomised controlled trial for measuring and predicting the effect of remyelinating therapy in multiple sclerosis (RESTORE): Recruitment status

S.N. Hof[1], L.J. van Rijn[2,3], B.M.J. Uitdehaag[1], J.A. Nij Bijvank[1,2], A. Petzold[1,2,4]

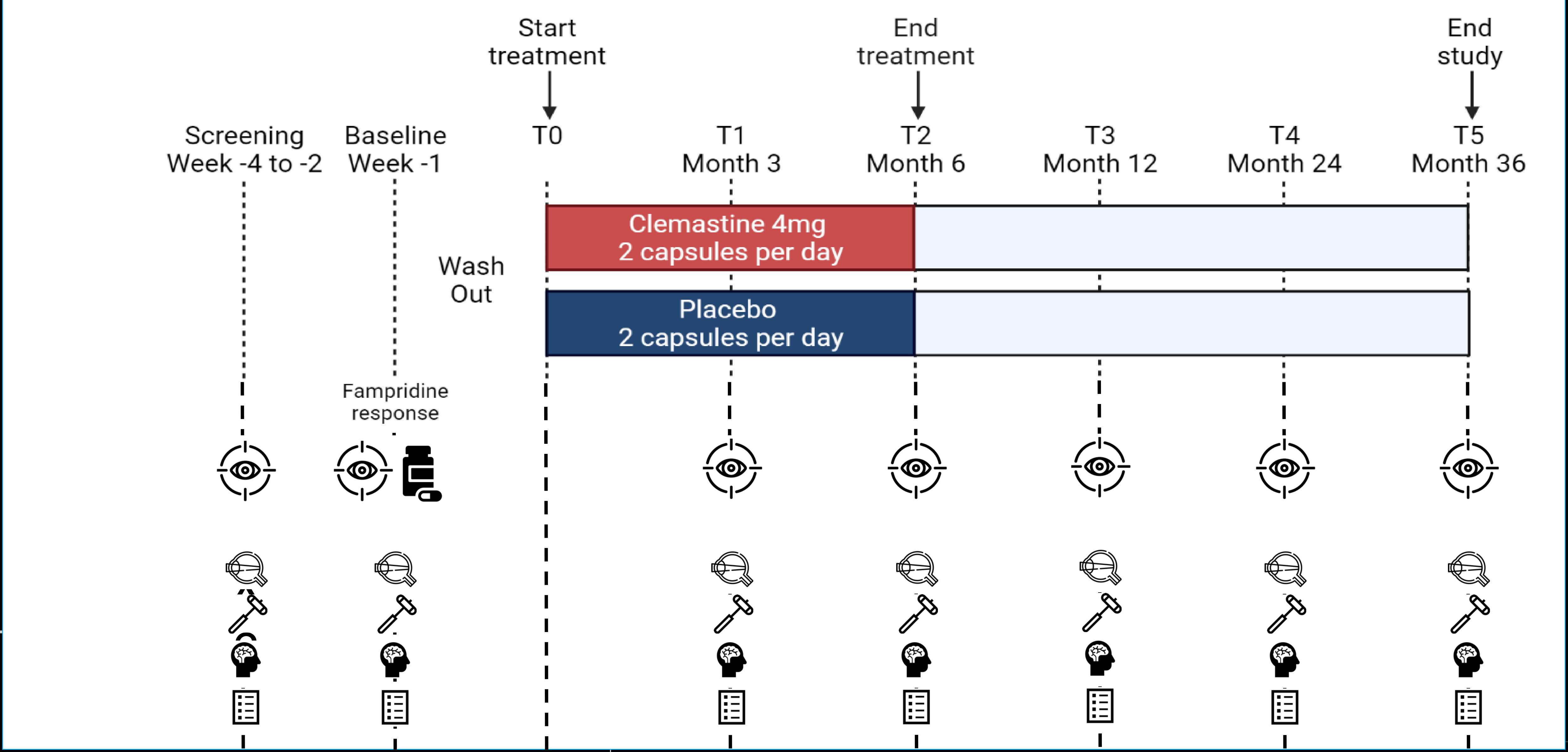
Introduction

- A complementary and generalizable model of remyelination is needed to confirm efficacy of remyelinating therapy.
- Internuclear ophthalmoplegia (INO) provides a model for remyelination of the medial longitudinal fasciculus (MLF) in the brainstem when quantified by infrared oculography.
- This model can be expanded with a test for selecting likely treatment responders by using fampridine.

Conclusions

The RESTORE trial uses a promising model of INO and infrared oculography for measuring remyelination and predicting potential treatment effect.

RESTORE Trial



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RESTORE Trial
(preliminary data)

Baseline characteristics	**Participants (n=23)**
Age (SD)	54 (±11)
% males	54%
% progressive disease	62%
Disease duration, years (SD)	16 (±10)
EDSS (IQR)	4.0 (4.0 – 5.5)
VDI-AUC (SD)	1.584 (±0.313)
Δ VDI-AUC (SD) 3 hours after 10mg fampridine	-0.031 (±0.109)

Sam Hof *et al* ECTRIMS 2023

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Conclusion

- Brain repair is the future
- Lessons learnt: make it simple
  - INO (ideal for video-recording)
  - MFL (single axonal tract)
  - Outcome measure (reproducible, good effect size)
- Clinical trials: sufficient supply (25% in MS)
- Clinical routine: treatment implications