Poster presented at the 9th Joint ECTRIMS-ACTRIMS Meeting, 11–13 October 2023 Milan, Italy.

P1427

A Novel Eye Movement Biomarker Application for Monitoring Multiple Sclerosis Disease Progression

Paul S. Giacomini[1], Natacha Bastien[3], Patrice Voss[1,2], Shamiza Hussein[3], Francis Arseneau[2], François Blanchette[3], Rosemberg Ramos[2], Renaud Robert[3], Étienne de Villers-Sidani[1,2]

[1]Montréal Neurological Institute, McGill University Health Centre, Montréal, QC, Canada; [2]Innodem Neurosciences, Montréal, QC, Canada; [3]Novartis Pharmaceuticals Canada Inc., Montréal, QC, Canada

SUMMARY

We present interim analysis findings from an ongoing longitudinal study following a cohort of persons with MS and healthy controls. Baseline data were collected from the first 60 patients with Multiple Sclerosis (PwMS) with a wide range of disease severity who completed four different visual gaze recording tasks using Innodem Neurosciences' patented Eye-Tracking Neurological Assessment (ETNA™). Comparable technology in the field is solely available with specialized and costly equipment, such as research-grade infrared eye tracking devices.

Eye Movement Metrics (EMMs) were recorded by ETNA™ from PwMS performing four oculomotor tasks. The correlation between EMMs and the following four clinical outcome measures of interest was assessed: Expanded Disability Status Scale (EDSS), Brief International Cognitive Assessment for MS (BICAMS), Multiple Sclerosis Functional Composite (MSFC), and the Symbol Digit Modalities Test (SDMT).[1-5] The preliminary findings demonstrated promising correlations between individual EMMs and validated clinical assessment scale scores, indicating that ETNA™ has the potential to accelerate the identification and monitoring of disease status and progression in MS. Additional information may be found at the public registration of the study on clinicaltrials.gov (ID: NCT05061953).

INTRODUCTION

MS is an inflammatory disease of the central nervous system, characterized by gradual and subtle progression of cognitive and motor impairment along a continuum that is often undetected by standard tests in clinical practice.[6] Although standard clinical assessments have proven invaluable in research and clinical trial settings, their lack of sensitivity to detect subtle cognitive impairment and their lengthy administration time have made their use in routine clinical care a challenge.[7] Increasingly, clinicians require sensitive and precise tools to assist in the evaluation of disease status and progression in PwMS.

In recent years, accumulating evidence supports the link between eye movement anomalies and brain function to inform the presence of neurodegeneration and cognitive impairment.[8] This association was demonstrated using correlations between numerous eye movement parameters and disease or cognitive status measured by standardized MS assessment tools.

OBJECTIVE

The overarching goal of this study is to determine if disease and cognitive status can be estimated with high accuracy based on eye movement parameters alone, using Innodem's patented, mobile, scalable, and accessible eye-tracking technology. This is a report of interim analysis results investigating associations between EMMs measured using ETNA™ and validated clinical assessment scale scores.

RESULTS

Of the 60 participants, 68% were female and the mean age was 51.0. The mean EDSS was 3.5, while mean SDMT was 49.7.

Table 1: Participant demographic data (N=60) and MS-related clinical test scores.

Characteristics and Results		N=60
Age	Mean (SD)	51.0 (10.6)
	Min-Max	26–74
Sex	Female, n (%)	41 (68%)
Expanded Disability Status Scale (EDSS)	Mean (SD)	3.5 (2.0)
	Min-Max	1.0–7.5
Symbol Digit Modalities Test (SDMT)	Mean (SD)	49.7 (13.5)
	Min-Max	22–80
Rey Auditory Verbal Learning Test (RAVLT)	Mean (SD)	54.2 (11.2)
	Min-Max	20–72
Brief Visuospatial Memory Test-Revised (BVMT-R)	Mean (SD)	24.2 (6.9)
	Min-Max	8–36
Timed 25-Foot Walk (T25FW)	Mean (SD)	29.4 (60.2)
	Min-Max	2.8–180.0
9-Hole Pegboard Test (9HPT)	Mean (SD)	31.4 (31.5)
	Min-Max	17.4–165.6
Brief International Cognitive Assessment for MS (BICAMS)	Mean (SD)	0.0 (0.9)
	Min-Max	−2.3 - 1.3
Multiple Sclerosis Functional Composite (MSFC)	Mean (SD)	−0.6 (2.1)
	Min-Max	−6.4 - 1.3

Descriptive statistics are reported as mean, standard deviation (SD); minimum to maximum range for continuous variables; and percentage (%) for categorical variables.

Summary of primary EMMs correlations:

- **Nine** EMMs were significantly correlated with SDMT, with absolute correlation coefficient (acc) ≥ 0.3 (range 0.32-0.55; corrected p<0.05).
- **Five** EMMs were significantly correlated with BICAMS, with acc ≥ 0.3 (range 0.33-0.54; corrected p<0.05).
- **Ten** EMMs were significantly correlated with MSFC, with acc ≥ 0.3 (range 0.30-0.53; corrected p<0.05)
- **Nine** EMMs were significantly correlated with EDSS, with acc correlation coefficient ≥ 0.3 (range 0.31-0.52; corrected p<0.05).

Figure 2 highlights the EMMs that are most strongly correlated with all clinical outcome measures.

Partial Least Squares (PLS) regression analyses show that a small set of EMMs, in combination with age, can explain up to 84% of the variance of the clinical outcome measures. These findings strongly suggest that, with a greater sample size and further development of ML-based tools, we may have the ability to accurately estimate disease severity based on eye movement analysis alone, across the full EDSS range. Figure 3 depicts the relative contribution of each EMM to each partial least squares regression predictor.

CONCLUSIONS

This cross-sectional interim analysis showed promising correlations between individual EMMs and common clinical disease assessment scores, consistent with previously published studies using research-grade eye-trackers. When completed, this study will hopefully demonstrate the reliability of mobile oculomotor assessments for the monitoring of MS progression as a non-invasive, accessible, scalable, and sensitive novel digital biomarker of disease progression – both cognitive and physical MS disability. Future analysis will determine if machine learning models using these EMMs as inputs can serve as reliable and accurate digital EMBs for MS progression.

METHODS

At the time of this interim, cross-sectional analysis, 60 PwMS presenting with varying degrees of disease severity (i.e., with an EDSS ranging from 0 to 7.5) were enrolled. Eligible patients were adults with a confirmed diagnosis of MS who had no signs of progressive increase in physical disability within the preceding 6 months and who had sufficient corrected visual acuity to allow for the accurate reading of the on-screen visual task instructions. The main exclusion criteria were the presence of comorbid neurological or psychiatric conditions to avoid eye movement anomaly confounders, the recent start of medications known to influence ocular motor visual function (e.g., benzodiazepines), and participants who experienced an MS relapse at the time of assessment.

EMMs were recorded in the clinic while participants performed oculomotor tasks (fixation, pro-saccade, anti-saccade, and smooth pursuit) using a 12.9-inch iPad Pro tablet running Innodem Neurosciences' patented eye-tracking software (ETNA™). The completion of these tasks only required the tablet's embedded camera and a short (under 10 min) calibration step, where participants were instructed to follow a slowly moving target (8 degree/second) across the screen.

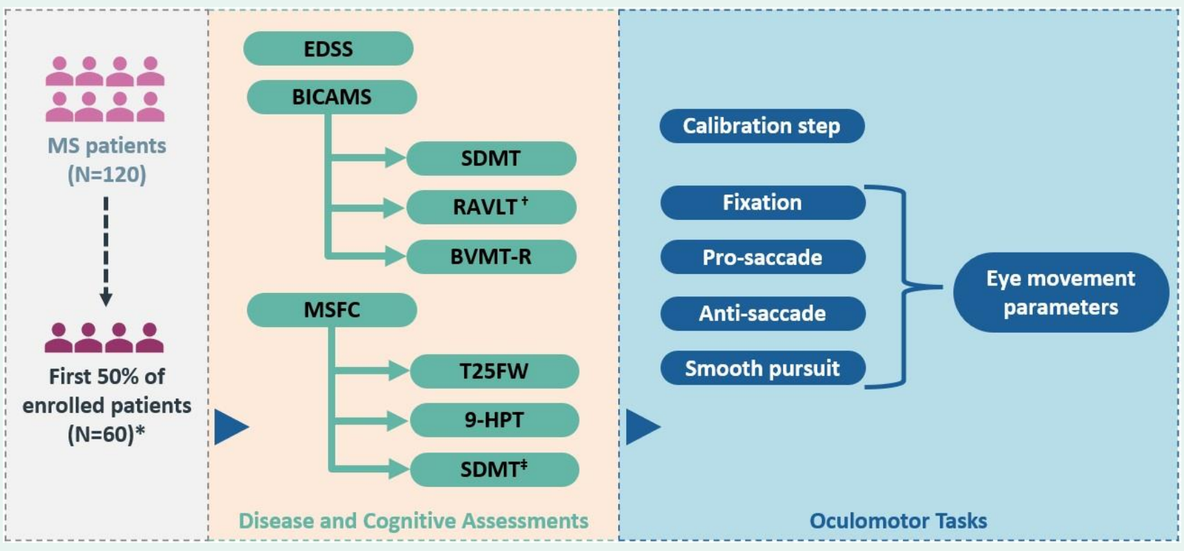

Figure 1: Study design.
EDSS, Expanded Disability Status Scale; BICAMS, Brief International Cognitive Assessment for MS; MS, Multiple Sclerosis; MSFC, Multiple Sclerosis Functional Composite; SDMT, Symbol Digit Modalities Test; RAVLT, Rey Auditory Verbal Learning Test; BVMT-R, Brief Visuospatial Memory Test-Revised; T25FW, timed 25-foot walk; 9HPT, 9-hole pegboard test.
**This interim analysis included 60 out of 120 Multiple Sclerosis patients with EDSS scores ranging from 0 to 7.5*
†RAVLT was selected as a surrogate for the California Verbal Learning Test – Second Edition (CVLT-II) due to its availability in French.
‡SDMT was selected as a surrogate for the Paced Auditory Serial Addition Test (PASAT) to reduce testing time.

Of the 350 EMMs automatically extracted, 20 were selected *a priori* for analysis in this preliminary study. Correlations between EMMs and clinical outcome measures (EDSS, SDMT, BICAMS, and MSFC) were analyzed by calculating the Spearman's ρ correlation coefficient using SAS statistical software suite. Further, to identify which of the EMMs were most relevant to explaining the clinical outcomes, a partial least squares (PLS) analysis was completed. Age was also included as a predictor in PLS analysis.

To continue enrollment of new patients in the study, the protocol requires observation of an absolute correlation of ≥ 0.3 confirmed at the two-sided significance level of 0.05 between at least one EMM (or a combination thereof) and one of the outcome measures (i.e., SDMT, EDSS, modified BICAMS, and modified MSFC) using baseline measurements.

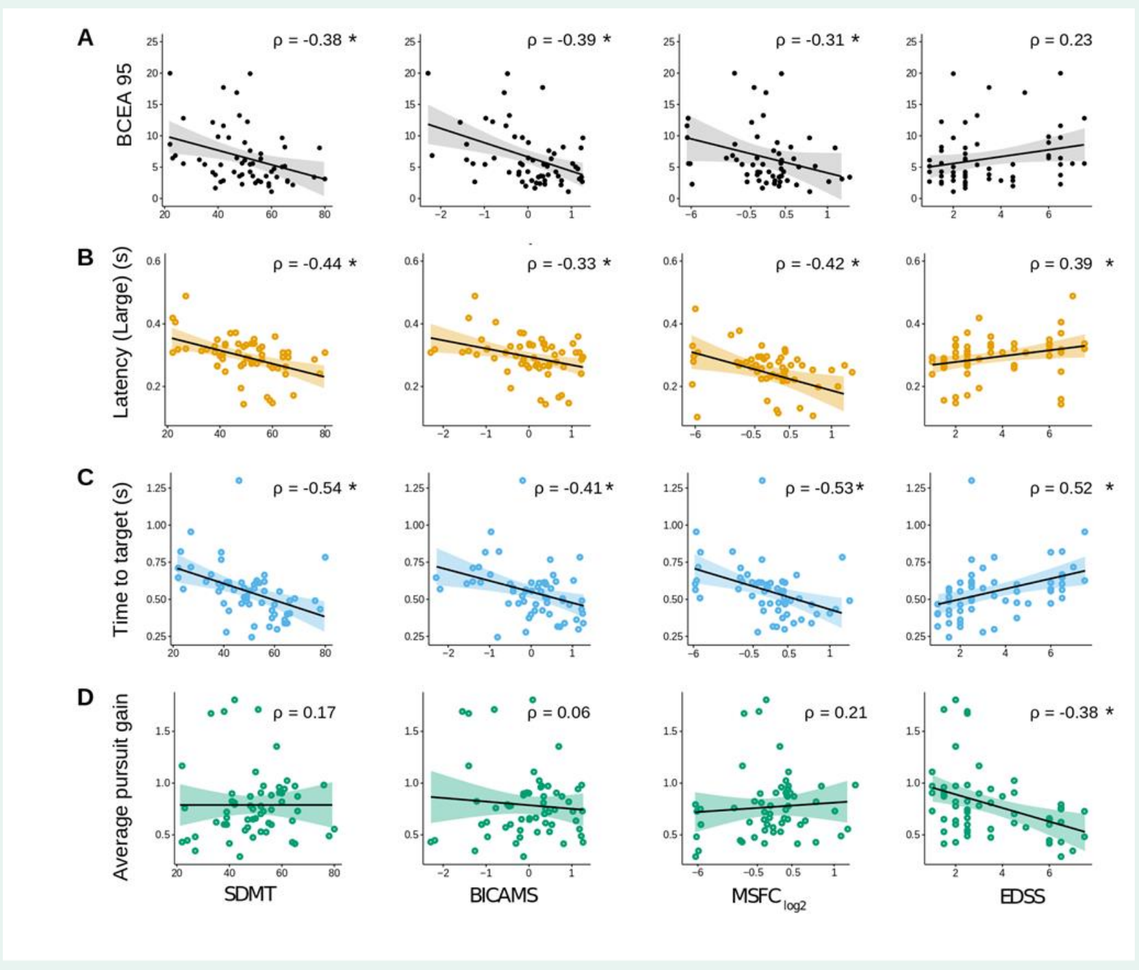

Figure 2: Spearman correlations between select eye-tracking parameters and functional scores. (A) Fixation: BCEA95, (B) Pro-Saccades: large amplitude saccade latency, (C) Anti-Saccades: time to target, and (D) Smooth pursuit: average pursuit gain. All Spearman's ρ correlation values were calculated using the raw data. For visualization purposes only, the MSFC x-axes were rescaled [0.1–0.9] and log2-transformed. *p < 0.05 (corrected for multiple comparisons).

	Predicted R^2	Adjusted R^2
EDSS	0.9405	0.8486
SDMT	0.6752	0.4767
MSFC	0.8706	0.6982
BICAMS	0.8437	0.7334

Figure 3: Heatmap visualization of the relative contribution (normalized absolute value of standardized regression coefficients) of each oculomotor parameter to each PLS regression predictor. Dark squares indicate lesser contributions to the model, whereas lighter/yellow squares indicate greater contributions. Absent squares indicate that the parameter was not used in the final model. S, short amplitude pro-saccade; L, large amplitude pro-saccade.

References

1. Kurtzke, J. F. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983, 33 (11), 1444-1452. DOI: 10.1212/wnl.33.11.1444 From NLM.
2. Benedict, R. H.; Amato, M. P.; Boringa, J.; Brochet, B.; Foley, F.; Fredrikson, S.; Hamalainen, P.; Hartung, H.; Krupp, L.; Penner, I.; et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC Neurol 2012, 12, 55. DOI: 10.1186/1471-2377-12-55 From NLM.
3. Langdon, D. W.; Amato, M. P.; Boringa, J.; Brochet, B.; Foley, F.; Fredrikson, S.; Hämäläinen, P.; Hartung, H. P.; Krupp, L.; Penner, I. K.; et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler 2012, 18 (6), 891-898. DOI: 10.1177/1352458511431076 From NLM.
4. Fischer, J. S.; Rudick, R. A.; Cutter, G. R.; Reingold, S. C. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. Mult Scler 1999, 5 (4), 244-250. DOI: 10.1177/135245859900500409 From NLM.
5. Rudick, R.; Antel, J.; Confavreux, C.; Cutter, G.; Ellison, G.; Fischer, J.; Lublin, F.; Miller, A.; Petkau, J.; Rao, S.; et al. Recommendations from the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force. Ann Neurol 1997, 42 (3), 379-382. DOI: 10.1002/ana.410420318 From NLM.
6. Kuhlmann, T.; Moccia, M.; Coetzee, T.; Cohen, J. A.; Correale, J.; Graves, J.; Marrie, R. A.; Montalban, X.; Yong, V. W.; Thompson, A. J.; et al. Multiple sclerosis progression: time for a new mechanism-driven framework. Lancet Neurol 2023, 22 (1), 78-88. DOI: 10.1016/s1474-4422(22)00289-7 From NLM.
7. Romero, K.; Shammi, P.; Feinstein, A. Neurologists' accuracy in predicting cognitive impairment in multiple sclerosis. Mult Scler Relat Disord 2015, 4 (4), 291-295. DOI: 10.1016/j.msard.2015.05.009 From NLM.
8. Anderson, T. J.; MacAskill, M. R. Eye movements in patients with neurodegenerative disorders. Nature Reviews Neurology 2013, 9 (2), 74-85. DOI: 10.1038/nrneurol.2012.273.

Acknowledgments
This study was funded by Novartis Canada Pharma Inc., Dorval, QC, Canada. Medical writing and design support was provided by Sabitha Rajaruban and Tanya Patrawala at IQVIA Solutions Canada Inc., Mississauga, ON, Canada. The final responsibility for the content lies with the authors.

Disclosures
Paul Giacomini - McGill University Health Centre, Montréal, Québec, Canada.

PG has received research grants from: EMD Serono and F. Hoffmann-La Roche. PG has received honoraria for speaking, advisory board participation or consultation fees from: Alexion, Biogen, Bristol Myers Squibb-Celgene, EMD Serono, Genzyme-Sanofi, Innodem Neurosciences, McKesson, Novartis, Pendopharm, F. Hoffmann-La Roche, and Teva Neuroscience. PG has stock options from Innodem Neurosciences.

Scan this QR code to download a copy of the Poster

Visit the web at:
https://www.medcommshydhosting.com/ectrims2023/index.html