The Canadian Journal of Neurological Sciences (2025), 1–3
doi:10.1017/cjn.2025.10124

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Brief Communication

How Does Time-of-Testing Influence Cognitive Performance in Multiple Sclerosis?

David E. Freedman[1,2], Arun N.E. Sundaram[3,4], Jiwon Oh[4,5] and Anthony Feinstein[1,2]

[1]Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada, [2]Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada, [3]Department of Ophthalmology and Vision Sciences, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada, [4]Division of Neurology, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada and [5]Division of Neurology, Department of Medicine, St. Michael's Hospital, Toronto, Canada

ABSTRACT: People with multiple sclerosis (pwMS) commonly describe cognitive decline later in the day, but few studies have evaluated this perception's validity. In a consecutive sample of 791 pwMS, this study evaluated whether time-of-testing predicted Minimal Assessment of Cognitive Function in MS raw scores, accounting for age, sex, educational years, disease duration, disability and disease-modifying therapy use. The mean age was 43.76 years (SD = 11.30), 76.74% were female and most had mild disability. Later time-of-testing independently predicted reduced Judgment of Line Orientation scores ($p < 0.01$), but not other cognitive variables. In pwMS, there is a diurnal decline in visuospatial cognitive test performance.

RÉSUMÉ : Quelle est l'influence de l'heure des tests sur les performances cognitives dans le cas de la sclérose en plaques ? Les personnes atteintes de sclérose en plaques (SP) décrivent généralement un déclin cognitif survenant plus tard au cours d'une journée, mais peu d'études ont évalué la validité de cette perception. Dans un échantillon consécutif de 791 personnes atteintes de SP, cette étude a évalué si l'heure des tests permettait de prédire les scores bruts au *Minimal Assessment of Cognitive Function in Multiple Sclerosis* (MACFIMS) en tenant compte de l'âge, du sexe, des années d'études, de la durée de la maladie, de l'invalidité et de l'utilisation d'un traitement modificateur de la maladie (TMM). L'âge moyen était de 43,76 ans ($\sigma = 11{,}30$) alors que 76,74 % des personnes étaient des femmes. À noter aussi que la plupart de ces personnes donnaient à voir un handicap léger. L'heure tardive des tests a permis de prédire de manière indépendante une réduction des scores au test dit « *Judgment of Line Orientation* » ($p < 0{,}01$), mais pas d'autres variables cognitives. Chez les personnes atteintes de SP, on observe ainsi un déclin diurne de la performance à des tests cognitifs visuospatiaux.

Keywords: Multiple sclerosis; outcome measurement; cognition; neuropsychology; time of day; time-of-testing

(Received 9 February 2025; final revisions submitted 11 April 2025; date of acceptance 9 May 2025)

Cognitive impairment affects ~40–90% of people with multiple sclerosis (pwMS), contributing to diminished quality of life and functioning.[1] It is thus vital to accurately detect and measure cognition in research studies and clinical care. A common concern of pwMS and investigators is whether the "time-of-testing" affects neurological functioning, including cognitive performance.[2] While this is understandable given diurnal increases in subjective fatigue,[3] regarding objective cognitive measures, the literature is equivocal.[3–5] These studies may be limited by small samples[3–5] and failures to control for confounding variables.[3–5]

In a large clinical sample, this study evaluated whether neuropsychological testing time independently predicts cognitive performance in pwMS. In addition to clarifying conflicting findings, an association between time-of-testing and cognition would have ramifications for occupational functioning and driving in pwMS, patient education, clinical interpretation of cognitive test results and future study design.

Data were obtained from a retrospective chart review of pwMS (diagnosed according to the McDonald criteria[6]) who attended a tertiary neuropsychiatry clinic in Toronto, Canada, between 2020 and 2024 and had a documented time-of-testing. Neuropsychological testing was completed as part of routine care, scheduled to start continuously between 8:00 and 15:00, and was conducted in an office without window exposure. The Sunnybrook Research Ethics Board approved this study.

Testing time was organized in hourly increments. We collected demographic and disease-related data such as age, sex, educational years, employment status, disease duration, neurological disability (measured with the Expanded Disability Status Scale [EDSS]), illness subtype, disease-modifying therapy (DMT) use and Modified Fatigue Impact Scale (MFIS) scores to measure global fatigue.

Corresponding author: David E. Freedman; Email: david.freedman@sunnybrook.ca

Cite this article: Freedman DE, Sundaram ANE, Oh J, and Feinstein A. How Does Time-of-Testing Influence Cognitive Performance in Multiple Sclerosis?. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2025.10124

Table 1. Standardized beta coefficients from linear regression models to predict cognitive raw scores from time-of-testing, adjusted for covariates

	Time-of-testing	Age	Sex	Years of education	Disease duration	EDSS	DMT use
COWAT	0.03	0.09	0.02	0.19**	−0.05	−0.25**	−0.05
JOLO	−0.09**	−0.06	−0.20**	0.09	−0.04	−0.16**	−0.03
CVLT-II-TL	−0.05	−0.09	0.19**	0.27**	−0.08	−0.27**	−0.01
CVLT-II-DR	−0.03	−0.07	0.16**	0.24**	−0.10**	−0.25**	0.01
BVMT-R-TL	−0.07	−0.24**	0.02	0.12**	−0.08	−0.20**	−0.02
BVMT-R-DR	−0.07	−0.21**	0.02	0.12**	−0.08	−0.19**	−0.02
SDMT	−0.06	−0.18**	0.06	0.09**	−0.06	−0.36**	−0.01
PASAT_3sec	−0.02	0.00	−0.14**	0.19**	−0.01	−0.22**	−0.03
PASAT_2sec	−0.05	0.03	−0.13**	0.20**	−0.04	−0.19**	0.02
D-KEFS_corsor	−0.01	−0.12**	−0.08	0.27**	−0.04	−0.23**	−0.02
D-KEFS_desc	−0.01	−0.09	−0.06	0.25**	−0.04	−0.25**	−0.03

Note: EDSS = Expanded Disability Status Scale; DMT use = disease-modifying therapy use; COWAT = Controlled Oral Word Association Test; JOLO = Judgment of Line Orientation; CVLT-II-TL= California Verbal Learning Test (Second Edition) total learning; CVLT-II-DR = California Verbal Learning Test (Second Edition) delayed recall; BVMT-R-TL = Brief Visuospatial Memory Test-Revised total learning; BVMT-R-DR = Brief Visuospatial Memory Test-Revised delayed recall; SDMT = Symbol Digit Modalities Test; PASAT_3 sec = Paced Auditory Serial Addition Test 3-second; PASAT_2 sec = Paced Auditory Serial Addition Test 2-second; D-KEFS_corsor = Delis–Kaplan Executive Function System correct sorts score; D-KEFS_desc = Delis–Kaplan Executive Function System descriptive score.
**if $p < 0.01$.

Cognitive performance was measured using raw scores from the validated Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS).[7] The MACFIMS neuropsychological battery includes indices of verbal fluency and executive function (the Controlled Oral Word Association Test [COWAT]), visuospatial function (Judgment of Line Orientation test [JOLO]), verbal learning and delayed recall (California Verbal Learning Test Second Edition [CVLT-II]), visual learning and delayed recall (Brief Visuospatial Memory Test-Revised [BVMT-R]), processing speed (Symbol Digit Modalities Test [SDMT]), 2- and 3-second versions of the Paced Auditory Serial Addition Test (PASAT) and executive function (Delis–Kaplan Executive Function System [D-KEFS]). The CVLT-II and BVMT-R have scores for total learning (CVLT-II-TL and BVMT-R-TL) and delayed recall (CVLT-II-DR and BVMT-R-DR). The D-KEFS has correct sorts (D-KEFS_corsor) and descriptive scores (D-KEFS_desc). This battery was always administered in the same order.

Preliminary point-biserial or Pearson correlations were computed between time-of-testing and all demographic, disease-related and MACFIMS neuropsychological battery measures. Thereafter, linear regression analyses were conducted to evaluate whether time-of-testing independently predicted cognitive raw scores, adjusting for age, sex, educational years, disease duration, EDSS scores and DMT use. The significance threshold was set at $p < 0.01$ to account for multiple testing.

Of 791 pwMS, the mean age was 43.76 years (SD = 11.30), 76.74% were female, 52.47% were employed and the mean years of education was 15.98 years (SD = 2.94). The mean disease duration was 9.95 years (SD = 8.86), and most participants had mild neurological disability (median = 2.00, IQR = 1.50–3.50) and relapsing illness (84.20%) and received a DMT (76.71%). The mean MFIS score was 50.08 (SD = 16.54). The median time of neuropsychological testing was 11:00 a.m. (IQR = 10:00–13:00). There were no significant associations between time-of-testing and any demographic or disease-related variables.

Later time-of-testing weakly correlated with reduced performance on JOLO ($r = -0.10$, $p < 0.01$), with trends toward significance for BVMT-R-TL ($r = -0.08$, $p = 0.02$), BVMT-R-DR ($r = -0.08$, $p = 0.03$) and SDMT ($r = -0.09$, $p = 0.02$). Supplementary Table 1 details mean cognitive raw scores and correlations with time-of-testing. As noted in Table 1, after adjusting for covariates, later time-of-testing independently predicted reduced performance on JOLO ($\beta = -0.09$, $p < 0.01$) with trends toward significance for reduced BVMT-R-TL ($\beta = -0.07$, $p = 0.03$), BVMT-R-DR ($\beta = -0.07$, $p = 0.05$) and SDMT ($\beta = -0.06$, $p = 0.05$) scores. Time-of-testing was not significantly associated with performance on the COWAT, CVLT-II (both tests), PASAT (both tests) or D-KEFS (both tests).

In pwMS, a later time of neuropsychological testing is associated with reduced visuospatial processing performance, even after accounting for the influences of demographic and disease-related variables. There is no evidence that time-of-testing affects verbal fluency, learning/memory, executive function or processing speed. Contributions of visuospatial processing to BVMT-R and SDMT performance may explain the observed trends of reduced performance on these tests.[8] While cognizant that the cross-sectional retrospective study design prevents determination of causality, these findings are further examined.

Previous research suggests reduced cognitive performance in pwMS at later times of day[3] and after a 4-hour strenuous task;[4] however, these small studies failed to control for confounding variables.[3,4] By addressing these limitations, we clarify that testing time does not influence performance in most cognitive domains, aligning with the null results of a separate small investigation.[5] This may reassure clinicians and pwMS about whether an early or late appointment influences the evaluation of these common areas of cognitive dysfunction.[1] Furthermore, these null results emphasize the specific influence of time-of-testing on JOLO test performance.

To our knowledge, no prior study has examined whether time-of-testing influences visual function or visuospatial cognition in pwMS. Nevertheless, it is known that pwMS experience diurnal increases in fatigue[3] and that fatigue may be associated with reduced oculomotor function (especially saccadic inefficiency)[9] and altered cortico-striato-thalamo-cortical network functional connectivity.[10] What remains unknown is whether there is a diurnal decline in the visuospatial pathway in pwMS. Future

https://doi.org/10.1017/cjn.2025.10124

studies that explore how time-of-testing influences visuospatial cognition should incorporate concomitant measures of eye movements and neuroimaging.

Study limitations include its retrospective cross-sectional exploratory design and no measures of chronotypes, sleep parameters or medications other than DMTs. Additionally, the test administrator and the participant typically determined the testing time in collaboration. While common in clinical testing, work schedules or driving capacity may influence scheduling. Nonetheless, we demonstrated reduced visuospatial cognitive test performance at a later time-of-testing, but it had no influence on other cognitive domains in pwMS. Although clinically relevant, it is unknown whether a diurnal decline in visuospatial cognitive performance translates to occupational or driving performance differences. Our finding supports studies to address these questions.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2025.10124

Data availability statement. The dataset is available from the corresponding author upon reasonable request.

Author contributions. **DEF**: Conceptualization, methodology, formal analysis, data curation, writing – original draft, writing – review and editing; **ANES**: Writing – original draft, writing – review and editing; **JO**: Methodology, writing – review and editing; **AF**: Conceptualization, methodology, writing – review and editing, supervision.

Funding statement. Dr Freedman completed this work during a Multiple Sclerosis Neuropsychiatry Fellowship supported by the Sunnybrook Foundation. Dr Oh received grants to the institution from MS Canada, Brain Canada, Biogen-Idec and Roche.

Competing interests. Dr Oh has received consulting fees from Biogen-Idec, EMD-Serono, Amgen, Novartis, Eli-Lilly, Sanofi and Roche; payment or honoraria from EMD-Serono, Biogen-Idec, Novartis, Roche and Sanofi; and leadership or fiduciary role as Chair of Medical Advisory Committee for MS Society of Canada and Vice President of the Canadian Network of MS Clinics during the conduct of this study. Dr Feinstein has received grants from MS Canada, the MacArthur Foundation and the Knight Foundation; royalties from Johns Hopkins University Press, Cambridge University Press and G Editions; and honoraria from Novartis and Merck Serono during the conduct of this study. All other authors have no relevant financial or nonfinancial interests to disclose.

Ethical statement. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Sunnybrook Health Sciences Centre (no. 5263) on December 30, 2021, with the need for written informed consent waived.

References

1. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *Lancet Neurol*. 2020;19:860–871. DOI: 10.1016/S1474-4422(20)30277-5.
2. Mortensen GL, Theódórsdóttir Á, Sejbæk T, Illes Z. Patient attitudes to routine cognitive testing in multiple sclerosis. *Patient Prefer Adherence*. 2020;14:693–704. DOI: 10.2147/PPA.S245623.
3. Claros-Salinas D, Bratzke D, Greitemann G, Nickisch N, Ochs L, Schröter H. Fatigue-related diurnal variations of cognitive performance in multiple sclerosis and stroke patients. *J Neurol Sci*. 2010;295:75–81. DOI: 10.1016/j.jns.2010.04.018.
4. Krupp LB, Elkins LE. Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology*. 2000;55:934–939. DOI: 10.1212/wnl.55.7.934.
5. Beatty WW, Goretti B, Siracusa G, Zipoli V, Portaccio E, Amato MP. Changes in neuropsychological test performance over the workday in multiple sclerosis. *Clin Neuropsychol*. 2003;17:551–560. DOI: 10.1076/clin.17.4.551.27942.
6. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17:162–173. DOI: 10.1016/S1474-4422(17)30470-2.
7. Benedict RH, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc*. 2006;12:549–58. DOI: 10.1017/s1355617706060723.
8. Patel VP, Walker LAS, Feinstein A. Deconstructing the symbol digit modalities test in multiple sclerosis: the role of memory.*Mult Scler Relat Disord*. 2017;17:184–9. DOI: 10.1016/j.msard.2017.08.006.
9. Zangemeister WH, Heesen C, Röhr D, Gold SM. Oculomotor fatigue and neuropsychological assessments mirror multiple sclerosis fatigue. *J Eye Mov Res*. 2020;13. DOI: 10.16910/jemr.13.4.6.
10. Kampaite A, Gustafsson R, York EN, et al. Brain connectivity changes underlying depression and fatigue in relapsing-remitting multiple sclerosis: a systematic review. *PLoS One*. 2024;19:e0299634. DOI: 10.1371/journal.pone.0299634.