

Comprehensive Clinical Assessment of Vestibular Function in Multiple Sclerosis

Graham D. Cochrane, BA, Jennifer B. Christy, PT, PhD, and Robert W. Motl, PhD

Background and Purpose: Balance disorders and dizziness are common in people with multiple sclerosis (MS), suggesting dysfunction of the vestibular system. Evaluating how people with MS perform on objective clinical vestibular tools will help broaden understanding of vestibular function in MS. This cross-sectional study's goal was to complete a robust battery of vestibular-ocular reflex (VOR), dynamic visual acuity (DVA), subjective visual vertical (SVV), and cervical and ocular vestibular-evoked myogenic potential (c/oVEMP) tests in people with and without MS.

Methods: Forty people with relapsing-remitting MS (Expanded Disability Status Scale [EDSS] ≤ 6.5) and 20 controls completed the vestibular testing battery. Results were compared between groups and correlations with EDSS scores were calculated.

Results: People with MS were less able to visually cancel their VOR and showed a larger variance in response on SVV. EDSS significantly correlated with VOR cancellation, SVV variance, and DVA lines lost; linear regression showed that VOR cancellation and SVV variance significantly predicted EDSS.

Discussion and Conclusion: Vestibular functions requiring central integration of vestibular information, but not reflexive vestibular functions like VEMP, were impaired in people with MS and correlated with EDSS, suggesting that clinical evaluation of functions requiring central integration best evaluates MS-related vestibular dysfunction.

Measures assessing central vestibular integration and not vestibular reflexes may be more sensitive to detecting vestibular deficits in people with mild to moderate MS.

Video Abstract available for more insight from the authors (see Supplemental Digital Content 1, available at: <http://links.lww.com/JNPT/A344>).

Key words: *clinical assessment, multiple sclerosis, vestibular, vestibular rehabilitation,*

(*JNPT* 2021;00: 1–7)

INTRODUCTION

There is a high prevalence of balance disorders (75%) and dizziness (49%-59%) in people with multiple sclerosis (MS), strongly suggesting an underlying dysfunction of the vestibular system.^{1,2} A recent review of vestibular rehabilitation indicates that postural stability and eye-stabilization exercises significantly improve balance and dizziness in MS, further implicating vestibular dysfunction as a cause of balance disorders and dizziness in MS.³ However, as balance requires integration of vestibular, visual, and proprioceptive, impairments in the integration of these 3 sensory systems, rather than a single sensory system, may be primarily responsible for deficits in balance dysfunction in MS.⁴ Moreover, the tool commonly used to quantify dizziness, the Dizziness Handicap Inventory, does not correlate predictably with traditional clinical measures of vestibular function in patients with dizziness.^{5,6} Clinical tools measuring balance dysfunction and dizziness may not be adequate to comprehensively assess vestibular deficits in MS. The identification of specific vestibular functions impaired in MS will help clinicians take better advantage of emerging vestibular-related technology and improve outcome measures for vestibular intervention.⁷

There are several clinical tools to assess functions more specifically governed by vestibular inputs. Video-head impulse testing (vHIT) and rotary chair systems are routinely used to assess the semicircular canal-driven vestibular-ocular reflex (VOR). Studies of VOR in MS have yielded mixed results, with some studies reporting no impairment and others indicating impairment ranging between 5% and 38%.⁸⁻¹⁰ VOR function has been associated with functional gait and fall risk in MS.¹¹ Additionally, dynamic visual acuity (DVA; ie, the ability to read while the head is in motion) is a simple clinical measure to evaluate functional usage of the VOR and can be

Department of Physical Therapy, School of Health Professions, University of Alabama at Birmingham, Birmingham (G.D.C., J.B.C., R.W.M.); and Medical Scientist Training Program, School of Medicine, University of Alabama at Birmingham, Birmingham (G.D.C.).

Funding for this project was obtained through the Foundation of the Consortium of Multiple Sclerosis Centers Workforce of the Future Program. Graham D. Cochrane is funded by the NIH-NIGMS under award T32GM008361. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Portions of the work described here were presented at the American Neurological Association Meeting in October 2020 (Poster Presentation) and will be presented at the Vestibular Oriented Research Meeting in February 2020 (Poster Presentation). No aspect of the work has been previously published.

Graham D. Cochrane developed the smartphone application used in the assessment of SVV here, which is publicly published and for sale on the University of Alabama at Birmingham's Google Play Store; because of this, all authors completed UAB's Conflict of Interest Training modules before data collection began.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jnpt.org).

Correspondence: Graham D. Cochrane, BA, 625 19th Ct S, Birmingham, AL 35205 (gcoch@uab.edu).

Copyright © 2021 Academy of Neurologic Physical Therapy, APTA.

ISSN: 1557-0576/21/00000-0001

DOI: 10.1097/NPT.0000000000000358

assessed through controlled head rotations while the participant reads either a classic Snellen chart or outputs from computer programs. Both methods have demonstrated impaired DVA in MS and studies suggest that people with MS struggle with functional usage of the VOR, regardless of whether VOR gains are intact.^{8,12}

To assess otolith function, vestibular-evoked myogenic potentials (VEMPs) and subjective visual vertical (SVV) tools probe vestibulocochlear nerve/vestibular nuclei reflexes and cortical processing of graviceptive information, respectively. VEMPs have been studied extensively in MS; a review suggests that 71% of people with MS have some type of cervical VEMP (cVEMP, a measure of saccule function) abnormality and that abnormalities occur early.¹³ One study investigating both VEMP methods, cVEMP and ocular VEMP (oVEMP, a measure of utricle function), demonstrated that scores on both measures correlated with Expanded Disability Status Scale (EDSS) scores and may detect brainstem lesions not identifiable by imaging.¹⁴ SVV has been studied in MS, demonstrating that persons with MS have larger deviations from vertical compared with healthy controls and that deviations are associated with fall risk and balance deficits.¹⁵⁻¹⁸

To our knowledge, the aforementioned functions have not been comprehensively evaluated in persons with MS. The comprehensive and concurrent evaluation of these functions in persons with MS would allow for the identification of the functions that differ between persons with MS and controls and are associated with disease severity. Such an evaluation would permit a streamlined and focused vestibular evaluation in the future. The present study administered a battery of clinical vestibular outcomes in persons with MS and controls and examined which functions are significantly affected by MS status and which functions correlate with disease severity. If successful, the results could elucidate specific vestibular endpoints for future studies and clinical use in MS.

METHODS

Participants

This study was approved by the University of Alabama at Birmingham Institutional Review Board and written informed consent was obtained from participants. The sample included 40 persons with MS and 20 controls. The criteria for MS were: age of 21 to 55 years; diagnosis of relapsing-remitting MS; ability to walk with or without aid (EDSS ≤ 6.5); no additional neurological diagnosis unrelated to MS (ie, a diagnosis of optic neuritis was not disqualifying); and no diagnosis of vestibular disease. The controls were sex- and age-matched (27-55 years old) with the MS sample, and had no diagnosed history of neurological or vestibular disease. The sample with MS was recruited in person from an outpatient clinic (n = 28) and through word-of-mouth and flyers (n = 12 of 40 flyers sent). Participants recruited from the clinic were screened by a physician for interest; the number not interested was not recorded. Of those potential participants with MS who indicated interest, 28 of 45 completed the study. Controls were recruited through word-of-mouth (n = 14) and flyers (n = 6).

Procedures

Participants completed a 3-hour battery of clinical vestibular, oculomotor, gait, and balance tests; only vestibular function tests were included in this article. A more in-depth description of these clinical tests and relevant thresholds is presented in Supplement Digital Content 2 (available at: <http://links.lww.com/JNPT/A345>). This battery was split into two 1.5-hour days that were completed within 2 weeks of each other. Day 1 of testing consisted of study explanation, obtaining informed consent, neurological examination, and tests of VOR and SVV/H function. Day 2 consisted of VEMP testing.

Neurological Examination

The participants underwent a neurological examination for EDSS scoring by a Neurostatus-C level examiner.

Clinical Vestibular Tests

Participants completed clinical vestibular tests: rotary chair VOR, SVV, and subjective visual horizontal (SVH) testing; a smartphone-assisted SVV bucket test (BT); a computerized DVA task (cDVA); and a vHIT task (vHIT). Both rotary chair and bucket SVV were completed, as despite measuring the same construct, the BT is more clinically/economically feasible.

Rotary Chair VOR

Participants completed a 15-minute vestibular and oculomotor battery in a Neuroalign (formerly NeuroKinetics, Inc) rotary chair. Participants were immobilized while wearing infrared eye-tracking goggles. VOR testing consisted of oscillations at 0.64 Hz in complete darkness (reflexive VOR), with a visual stimulus surrounding the participant (visual enhancement), and with a single visual target that moved with the participant that the participant was instructed to focus on (VOR cancellation), for 10 seconds each. The outcome variables of interest were the velocity gain of the slow-phase VOR, calculated as the average ratio between eye velocity and chair velocity, and the percentage increase (visual enhancement) and decrease (VOR cancellation) of the velocity gain compared with the 0.64-Hz gain in darkness.

Rotary Chair SVV/SVH

The SVV/H tests examined the participant's perception of vertical/horizontal, respectively. A line stimulus appeared tilted up to 30° clockwise or counterclockwise. The participant pressed buttons to tilt the line to perceived vertical for 6 trials, then to perceived horizontal for 6 trials. The data of interest were the absolute average degrees off true alignment (ie, a participant deviation average of -2° was treated as a deviation of $+2^\circ$) and variance across trials.

Smartphone-Assisted SVV Bucket

The SVV-BT involved placing a bucket over the participant's face with a line on the inner base. A smartphone was mounted onto the outer base, parallel to the inner line, that recorded the angle of the phone and inner line while guiding the examiner, substituting for the traditional BT angle finder.¹⁹ This application has not been approved by the Food and Drug

Administration as a clinical tool and was only used for experimental purposes here. The participant was instructed to close their eyes. The examiner was prompted by the application to turn the line to a preset angle. The participant then was instructed to open their eyes and the bucket was turned by the examiner to true vertical. When the participant believed the line was vertical, they pressed a Bluetooth button that recorded the angle. This was repeated for 12 trials. The data of interest were the absolute average degrees off true alignment and variance across trials.

cDVA

The Bertec Visual Advantage system was used to assess static visual acuity (SVA) and DVA in yaw. The size of the presented optotype changed based on participant response (smaller/larger following a correct/incorrect response, respectively).²⁰ DVA was determined by having the tester move the participant's head in yaw plane sinusoidally between 90° and 120°/s measured by a head-mounted accelerometer. The optotype presented during a leftward or rightward movement to test the participant's ability to identify optotypes during movement toward that side. The variables of interest were the participant's static and dynamic acuity (LogMAR units) and the number of DVA lines lost (a measure of DVA relative to the participant's SVA, averaged between rightward and leftward). Whereas previous studies of DVA in people with MS have used DVA LogMAR, we believe that lines lost is a more specific measure of DVA function as it measures DVA relative to SVA, which is known to be lower in people with MS.²¹

vHIT

The EyeSeeCam (Interacoustics, Middelfart, Denmark) was used to assess the high-frequency gain of the VOR in each of the 6 semicircular canals using a tight-fitting goggle with a camera/accelerometer apparatus fastened over the left eye for all participants. Calibration was completed for both the eye-tracker and accelerometer followed by head thrusts in each canal plane while the participant focused on a visual target at 5 ft until 10 valid trials per canal were recorded. The variables of interest were average gains of the VOR in the lateral, right anterior and left posterior (RALP), and left anterior and right posterior (LARP) canals. Due to the left eye placement of the accelerometer, gains in the LARP canals were approximately 15% larger than the other 2 pairs.²²

cVEMP and oVEMP

Cervical and ocular VEMPS were assessed using methodology and equipment from Intelligent Hearing Systems, Inc (Miami, Florida).^{23,24} A ground electrode was placed on the lower forehead for both measures and a dual-channel inverting electrode was placed on the chest. For cVEMP, cathode electrodes were placed over sternocleidomastoid muscles. The participant turned and raised their head to contract one muscle while tone bursts were delivered via an ipsilateral earphone. For oVEMPs, cathode electrodes were placed below the bottom eyelid of both eyes to measure the inferior recti. Participants held their gaze upward while a clinical skull tapper impacted their forehead. Both inferior recti were recorded from simultaneously until 100 stimuli were recorded. The data

of interest were the latency and baseline electromyographic corrected amplitude for cVEMP and oVEMP waveforms averaged between sides.

Analysis

Statistical analyses were completed using SPSS v27.0. The distribution of scores per variable was visually inspected for normality. All measures besides SVV/H and cDVA measures appeared normally distributed.

Comparison of Vestibular Functions Between Groups

Unequal variance Student's *t* tests (normally distributed variables) and Mann-Whitney *U* tests (SVV/H and cDVA measures) were completed for vestibular variables of interest between MS and controls. A Benjamini-Hochberg (B-H) *P* value correction was used to control for multiple comparisons, and a false discovery rate threshold of 0.10 was used to determine statistical significance due to the exploratory nature of the study.²⁵ Cohen's *d* effect sizes were calculated for all clinical variables.

Intra-MS Statistics

Correlations With EDSS. A Pearson correlation analysis was completed between the EDSS score and a single variable from each clinical test to lower the chance of type I error. VOR cancellation was chosen as the only statistically significant rotary chair VOR measure from the above analysis; rotary chair SVV variance was chosen over SVV absolute deviation due to its statistical significance in the previous analysis and was chosen over SVH variance and BT variance due to it being more common in research and clinical use; DVA lines lost was chosen due to concerns over DVA LogMAR's specificity to vestibular function; lateral canal vHIT gains were chosen due to their more robust area-under-the-curve calculation compared with RALP/LARPs.²⁶ cVEMP and oVEMP waveform latencies were used due to their correlation with the EDSS in previous studies.¹⁴ SVV variance and DVA lines lost were log₁₀ transformed and the transformation resulted in a normal distribution for both measures. Correlation *P* values were rounded to the nearest hundredth and an unrounded α level of 0.05 was used to determine statistical significance.

Linear Regression. Variables statistically significantly associated with the EDSS by Pearson correlation were directly inserted as independent variables into a linear regression model with the EDSS as the dependent variable. An α level of 0.05 was set to determine statistical significance for the model and for individual contributions of independent variables within the model.

RESULTS

Sample Characteristics

The sample demographic and clinical characteristics are reported in Table 1.

Table 1. Sample Demographic and Clinical Characteristics^a

	MS (n = 40)	Controls (n = 20)	P Values
Age, y	42.4 ± 7.7	41.6 ± 8.7	0.72
Sex, n/%	35/88% F, 5/12% M	17/85% F, 3/15% M	0.79
EDSS score, median	2.5 (IQR = 2.25, range 1.0-6.5)
Time since diagnosis, y	9.9 ± 7.2

Abbreviations: EDSS, Expanded Disability Status Scale; F, female; IQR, interquartile range; M, male; MS, multiple sclerosis.

^aP values were calculated by unequal variance *t* tests for age and χ^2 analysis for sex.

Comparison of Vestibular Functions Between Groups

The mean/median scores, standard deviations/interquartile ranges, and Cohen's *d* values for the clinical vestibular function tests are in Table 2.

Rotary Chair VOR

Those with MS had significantly lower VOR cancellation gain with a visual target at 0.64 Hz (B-H *P* = 0.02) despite demonstrating similar VOR gains to controls at 0.64 Hz without the target (B-H *P* = 0.84). There were no other statistically significant differences between groups.

SVV/H

People with MS had significantly larger variances in response on each of the 3 measures of SVV/H: rotary chair SVV (B-H *P* = 0.07), rotary chair SVH (B-H *P* = 0.05), and bucket variance (B-H *P* = 0.07). There were no differences

between groups in absolute deviations from vertical/horizontal on any of the 3 measures.

DVA

The MS sample did not have significant differences in corrected SVA, DVA, or lines lost compared with controls.

vHIT

The sample with MS did not demonstrate significantly higher or lower vHIT gains in the lateral, RALP, nor LARP canals.

Intra-MS Analysis

Pearson Correlations With EDSS Score

The results of the Pearson correlation analyses are presented in Table 3.

There were statistically significant correlations between EDSS and VOR cancellation (Pearson *r* = -0.48, *P* < 0.01), SVV variance (*r* = 0.45, *P* < 0.01), and DVA lines lost

Table 2. Comparison of Vestibular Functions Between People With MS and Controls

	MS (n = 40)	Controls (n = 20)	P Value	B-H Corrected P Value	Cohen's <i>d</i>
Rotary chair VOR					
0.64-Hz VOR gain	0.59 ± 0.22	0.61 ± 0.17	0.69	0.81	-0.09
0.64-Hz enhancement, %	1.77 ± 0.58	1.79 ± 0.44	0.89	0.89	0.00
0.64-Hz cancellation, %	0.61 ± 0.24	0.76 ± 0.08	0.001	<i>0.02^a</i>	-0.81
Rotary chair subjective vertical/horizontal					
Subjective vertical mean	2.09 (2.82)	1.11 (1.87)	0.074	0.31	0.26
Subjective vertical variance	1.50 (2.25)	0.78 (0.81)	0.012	<i>0.06</i>	0.70
Subjective horizontal mean	1.75 (2.01)	1.32 (1.47)	0.17	0.36	0.40
Subjective horizontal variance	1.05 (1.34)	0.40 (0.29)	0.004	<i>0.04</i>	0.85
Bucket subjective vertical					
Bucket mean	1.60 (2.09)	0.96 (1.07)	0.20	0.37	0.32
Bucket variance	1.98 (3.60)	0.91 (0.81)	0.011	<i>0.06</i>	0.71
Dynamic visual acuity					
Static visual acuity (LogMAR)	-0.07 (0.14)	-0.09 (0.12)	0.32	0.52	0.24
Dynamic visual acuity (LogMAR)	0.09 (0.23)	0.04 (0.18)	0.10	0.33	0.34
Lines lost	1.50 (1.40)	1.40 (0.59)	0.21	0.37	0.24
Video-head impulse					
ML gain	1.22 ± 0.28	1.09 ± 0.32	0.13	0.34	0.47
RALP gain	1.13 ± 0.18	1.12 ± 0.22	0.86	0.89	0.06
LARP gain	1.44 ± 0.26	1.48 ± 0.27	0.57	0.75	-0.17
VEMPs					
cVemp P1 latency	13.7 ± 1.3	13.3 ± 0.5	0.15	0.35	0.37
cVemp N1 latency	21.1 ± 2.6	20.6 ± 1.8	0.44	0.66	0.21
cVemp amplitude	12.7 ± 7.6	16.5 ± 7.1	0.11	0.33	-0.50
oVemp N1 latency	8.5 ± 1.7	8.4 ± 1.5	0.79	0.87	0.08
oVemp P1 latency	12.9 ± 2.2	12.3 ± 2.1	0.47	0.66	0.24
oVemp amplitude	5.2 ± 3.5	4.7 ± 2.5	0.64	0.79	0.13

Abbreviations: B-H, Benjamini-Hochberg; cVEMP, cervical-VEMP; LARP, left-anterior, right-posterior canals; ML, medial-lateral vestibular canals; MS, multiple sclerosis; oVEMP, ocular-VEMP; RALP, right-anterior, left-posterior canals; VEMP, vestibular-evoked myogenic potential; VOR, vestibular-ocular reflex.

^aBenjamini-Hochberg corrected *P* values < 0.10 are italicized.

Table 3. Correlations Between Clinical Vestibular Variables With Disability Status in Sample With Multiple Sclerosis (N = 40)

	EDSS Score	
	Pearson <i>r</i>	<i>P</i> Value
VOR cancellation, %	−0.48	≤0.01 ^a
SVV variance (Log)	0.45	≤0.01
DVA lines lost (Log)	0.43	≤0.01
Lateral canal vHIT Gain	0.20	0.22
cVemp P1 latency	−0.06	0.78
oVemp N1 latency	0.22	0.22

Abbreviations: cVEMP, cervical vestibular-evoked myogenic potential; DVA, dynamic visual acuity; EDSS, Expanded Disability Status Scale; oVEMP, ocular vestibular-evoked myogenic potential; SVV, subjective visual vertical; vHIT, video head-impulse test; VOR, vestibular-ocular reflex.

^aSignificant *P* values at $\alpha < 0.05$ are italicized.

($r = 0.43, P < 0.01$). Lateral canal vHIT gains and cVEMP/oVEMP latencies were not significantly correlated with the EDSS. VOR cancellation and SVV variance were significantly correlated with each other ($r = -0.33, P = 0.01$).

Linear Regression

The EDSS was regressed on VOR cancellation, SVV variance, and DVA lines lost. Regression results are presented in Table 4.

The resulting linear model was significant ($F_{(3,33)} = 11.54, P < 0.001$) with an adjusted R^2 of 0.47. VOR cancellation and SVV variance were significant predictors of the EDSS ($P = 0.04, 0.01$, respectively).

DISCUSSION

This study examined whether people with MS differ from controls on clinical tests of vestibular function and how those functions correlate with disease severity.

People with MS demonstrated worse VOR cancellation but no difference in medium-frequency rotary chair VOR without a target and high-frequency VOR on vHIT. Together, these results suggest that the semicircular canals and reflexive VOR brainstem pathways are not significantly impaired in our sample with MS, but that central visual-vestibular integration necessary for the smooth pursuit system to produce an equal and

opposite eye movement to the VOR for VOR cancellation is impaired.

On SVV/H testing, people with MS demonstrated significantly higher variances in response but did not show significantly higher absolute deviations from vertical/horizontal as would be expected from peripheral or vestibular nuclei lesions. Like VOR cancellation deficits and lack of reflexive VOR deficits, this may suggest that central integration of graviceptive input from the otoliths may be more commonly impaired than peripheral/vestibular nuclei pathways. Both the rotary chair and bucket method identified this significant increase in variance.

People with MS did not demonstrate significantly worse corrected SVA or DVA when compared with controls unlike previous studies. We believe this lack of significant difference is due to our participants with MS having mainly mild disease (median EDSS = 2.5) and mild changes in acuity, which can be overcome with corrective lenses. Using our preferred variable, lines lost, instead of DVA LogMAR also did not result in a statistically significant difference between groups. Despite this, lines lost was significantly correlated with the EDSS, although it did not contribute statistically significantly to our regression model of EDSS ($P = 0.13$). This may indicate that DVA does not deteriorate early in disease progression and may not indicate disease status but may decline starting at moderate MS severity. Future studies should investigate DVA lines lost across a larger sample with a larger spread of EDSS severity to evaluate this relationship. Other studies might consider measuring monocular DVA as an additional measure, which we did not do here due to our testing battery's length.

Unlike previous studies, we did not identify/observe common abnormalities on cVEMP/oVEMP. Two persons with MS had a unilateral loss of cVEMP response while a third had a bilateral loss; only one person with MS showed a bilateral loss of oVEMP response. There were no significant differences in latency nor amplitudes of VEMPS and VEMP latencies were not significantly correlated with the EDSS. Whereas a previous study reported significant correlations between latencies and the EDSS, most latencies driving that correlation were found in those with an EDSS ≤ 5.0. As our sample median EDSS was 2.5, it is possible that our sample is less likely to have developed lesions that would impair these reflexes to the extent of the sample in their study despite larger

Table 4. Simple Linear Regression of Vestibular Functions on Expanded Disability Status Scale in a Sample With Multiple Sclerosis

<i>df</i>	Overall Model ANOVA			
	<i>F</i>	<i>P</i> Value	Adjusted r^2	
3,33	11.54	0.00 ^a	0.47	
Coefficients				
	Unstandardized (SE)	Standardized β	t-Statistic	<i>P</i> Value
(Constant)	4.48 (0.82)		5.46	0.00
VOR cancellation	−3.14 (1.16)	−0.38	−2.70	0.01
SVV variance (Log)	0.97 (0.46)	0.31	2.11	0.04
DVA lines lost (Log)	0.85 (0.55)	0.21	1.55	0.13

Abbreviations: ANOVA, analysis of variance; DVA, dynamic visual acuity; SVV, subjective visual vertical; VOR, vestibular-ocular reflex; SE, standard error.

^aSignificant *P* values at $\alpha < 0.05$ are italicized.

reviews suggesting VEMP changes are common early in disease.¹³

Our data suggests that clinical vestibular tests that require central integration of vestibular information are the most likely to be different between people with MS and controls and that these functions decline with increasing levels of disease severity. Importantly, our data indicate that the measures commonly used to assess 2 of these functions (SVV average deviation and VOR gain) may not be strongly associated with MS status or severity. Whereas SVV variance is not typically examined clinically nor in research, it appears to be more sensitive to both MS status and severity than average deviation and should be included in future studies investigating SVV. VOR cancellation requires specialized equipment to ensure head velocity remains at a rate at which the smooth pursuit system can function but may be more worthwhile than reflexive VOR gains.

There are several limitations of our study. Our sample of people with MS had mild-to-moderate disease. Only 10 (25%) had an EDSS score of 4.0 to 6.5. This ensured our sample with MS could complete the entire testing battery, which consisted of walking and balance measures not described here; however, some measures that were not associated with MS status and severity may be associated with outcomes in a sample with more severe disease. In addition, our study only recruited participants with MS who were 55 years or younger to be more confident that any deficits in vestibular function were more likely related to disease than age-related changes; it is possible that older participants with MS may additionally suffer from typical age-related vestibular changes, which may lower our findings' applicability to older samples. Our participants with MS were recruited from a single clinic and by contacting participants of past research; our results may not be generalizable to larger populations of people with MS, as our participants may have different treatment and socioeconomic statuses than the average person with MS due to their active involvement in research. Future studies should attempt to reproduce our study in other samples to better understand whether these deficits in central integration are ubiquitous in people with MS.

CONCLUSIONS

People with MS demonstrated deficits in clinical tests of vestibular function that rely on central integration of vestibular information but not those that probe peripheral vestibular reflexes, and those deficits worsen over the course of MS disease severity. People with MS with mild disease severity may not show deficits on clinical vestibular tests. Future studies should utilize the tools here in samples of people with MS with larger variation in disease severity and elucidate whether these functions improve following vestibular rehabilitation like the traditional outcome measures of balance and dizziness.

Acknowledgments

We thank the Foundation of the Consortium of Multiple Sclerosis Centers MS Workforce of the Future Program for their funding of this project, and the UAB MS Center for aid in recruitment of participants.

REFERENCES

- Marrie RA, Cutter GR, Tyry T. Substantial burden of dizziness in multiple sclerosis. *Mult Scler Relat Disord*. 2013;2(1):21-28.
- Cattaneo D, Jonsdottir J. Sensory impairments in quiet standing in subjects with multiple sclerosis. *Mult Scler*. 2009;15(1):59-67.
- García-Muñoz C, Cortés-Vega MD, Heredia-Rizo AM, Martín-Valero R, García-Bernal MI, Casuso-Holgado MJ. Effectiveness of vestibular training for balance and dizziness rehabilitation in people with multiple sclerosis: a systematic review and meta-analysis. *J Clin Med*. 2020;9(2):590.
- Doty RL, MacGillivray MR, Talab H, et al. Balance in multiple sclerosis: relationship to central brain regions. *Exp Brain Res*. 2018;236(10):2739-2750.
- Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Surg*. 1990;116(4):424-427.
- Yip CW, Strupp M. The Dizziness Handicap Inventory does not correlate with vestibular function tests: a prospective study. *J Neurol*. 2018;265(5):1210-1218.
- Dunlap PM, Holmberg JM, Whitney SL. Vestibular rehabilitation: advances in peripheral and central vestibular disorders. *Curr Opin Neurol*. 2019;32(1):137-144.
- Heravian Shandiz J, Jafarzadeh S, Fathi H, Foroughpour M, Karimpour M. Vestibulo ocular reflex in multiple sclerosis patients without any optic neuritis. *J Optom*. 2020;S1888-4296(20)30077-7.
- Pavlović I, Ruška B, Pavičić T, et al. Video head impulse test can detect brainstem dysfunction in multiple sclerosis. *Mult Scler Relat Disord*. 2017;14:68-71.
- Pavlicic TRB, Pavlovic I, Skoric MK, et al. O97 Video head impulse test in evaluation of brainstem dysfunction in multiple sclerosis. *Clin Neurophysiol*. 2017;128:e210.
- Garg H, Dibble LE, Schubert MC, Sibthorp J, Foreman KB, Gappmaier E. Gaze stability, dynamic balance and participation deficits in people with multiple sclerosis at fall-risk. *Anat Rec (Hoboken)*. 2018;301(11):1852-1860.
- Mañago MM, Schenkman M, Berliner J, Hebert JR. Gaze stabilization and dynamic visual acuity in people with multiple sclerosis. *J Vestib Res*. 2016;26(5/6):469-477.
- Di Stadio A, Dipietro L, Ralli M, Greco A, Ricci G, Bernitsas E. The role of vestibular evoked myogenic potentials in multiple sclerosis-related vertigo. A systematic review of the literature. *Mult Scler Relat Disord*. 2019;28:159-164.
- Gazioglu S, Boz C. Ocular and cervical vestibular evoked myogenic potentials in multiple sclerosis patients. *Clin Neurophysiol*. 2012;123(9):1872-1879.
- da Fonseca BAV, Pereira CB, Jorge F, Simm R, Apostolos-Pereira S, Callegaro D. A disturbed processing of graviceptive pathways may be involved in the pathophysiology of balance disorders in patients with multiple sclerosis. *Arq Neuropsiquiatr*. 2016;74(2):106-111.
- Serra A, Derwenskus J, Downey DL, Leigh RJ. Role of eye movement examination and subjective visual vertical in clinical evaluation of multiple sclerosis. *J Neurol*. 2003;250(5):569-575.
- Ulozienė I, Totilienė M, Balnytė R, et al. Subjective visual vertical and visual dependency in patients with multiple sclerosis. *Mult Scler Relat Disord*. 2020;44:102255.
- Versino M, Colnaghi S, Callieco R, Bergamaschi R, Romani A, Cosi V. Vestibular evoked myogenic potentials in multiple sclerosis patients. *Clin Neurophysiol*. 2002;113(9):1464-1469.
- Zwergal A, Rettinger N, Frenzel C, Dieterich M, Brandt T, Strupp M. A bucket of static vestibular function. *Neurology*. 2009;72(19):1689-1692.
- Hughson WWH. Manual for program outline for rehabilitation of aural casualties both military and civilian. *Trans Am Acad Ophthalmol Otolaryngol*. 1944;48:1-15.
- Sakai RE, Feller DJ, Galetta KM, Galetta SL, Balcer LJ. Vision in multiple sclerosis (MS): the story, structure-function correlations, and models for neuroprotection. *J Neuroophthalmol*. 2011;31(4):362-373.
- Halmagyi GM, Chen L, MacDougall HG, Weber KP, McGarvie LA, Curthoys IS. The Video Head Impulse Test. *Front Neurol*. 2017;8:258.
- Akin FW, Murnane OD. Vestibular evoked myogenic potentials. In: Jacobson GP, Shepard NT, eds. *Balance Function and Management*. San Diego, CA: Plural Publishing, Inc.; 2008.

24. McCaslin DL, Jacobson GP. Vestibular evoked myogenic potentials (VEMPs). In: Jacobson GP, Shepard NT, eds. *Balance Function and Management*. San Diego, CA: Plural Publishing, Inc; 2016.
25. Benjamini YHY. Controlling the false discovery rate: a practical and powerful approach to multiple hypothesis testing. *JR Stat Soc B*. 1995;57:289-300.
26. EyeSeeCam. Instructions for use—EyeSeeCam vHIT—part 1 (Nov 9 apD, 2016) Middelfart (Denmark), Interacoustics A/S. c2020. <https://www.interacoustics.com/balance/software/eyeseecam>.