Multiple Sclerosis and Related Disorders 54 (2021) 103073

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Quantification of smooth pursuit dysfunction in multiple sclerosis

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ARTICLE INFO

Keywords:
Eye tracker
Efferent visual system dysfunction
Saccadic breakdown of smooth pursuit

ABSTRACT

Background: : Smooth pursuit dysfunction is common in MS, but rarely quantified and may be missed on exam.
Methods: : NeuroFitONE™ smooth pursuit performance measures were compared between MS ($n = 20$) and healthy control ($n = 19$) participants.
Results: : Compared to controls, MS patients had lower proportion of smooth pursuit (0.63 vs. 0.73; $p = 0.047$), increased directional (10.1 vs. 8°; $p = 0.014$) and speed noise (4.3 vs. 3.1°/sec; $p = 0.021$) and reduced initiation acceleration (96.83 vs. 115.33°/sec^2; $p = 0.061$). Significant univariate correlations with clinical scores (EDSS, T25-FW) were observed.
Conclusion: : Smooth pursuit dysfunction in MS can be readily quantified and distinguishes MS eyes from healthy controls.

Introduction

With global prevalence estimates of 50–300 per 100,000 individuals, multiple sclerosis (MS) is a common neuro-immunological disease [1]. 30–70% of MS patients experience efferent visual system dysfunction [2,3]. While bedside clinical-neurological examination is limited to the evaluation of grossly-observable oculomotor function, newly developed eye-tracking devices can detect sub-clinical efferent dysfunction [2-4] and could be a promising biomarker of MS disease burden. Deficits in saccades [3,5] have been demonstrated in MS more commonly than smooth pursuit [2,6] using eye tracking devices. The purpose of this study was to quantify smooth pursuit dysfunction in MS patients compared to healthy controls using a novel noninvasive eye tracker (neuroFit ONE™; neuroFit, Inc. Mountain View, CA) for multidimensional assessment of smooth pursuit.

Methods

This is a single center pilot study using the neuroFit ONE™ eye tracker to assess smooth pursuit performance in MS participants compared to healthy controls. We recruited twenty consecutive subjects from the University of California San Diego (UCSD) MS clinic who fulfilled the revised 2017 McDonald MS diagnostic criteria for clinically definite MS, and nineteen healthy controls with no history of neurological disease or strabismus. The study was approved by the UCSD institutional review board (IRB 190497). All subjects provided their written informed consent.

Oculometric performance measures

Using the neuroFit ONE™, subjects completed three 3.75-minute-long eye movement tracking tasks of the left eye composed of 45 trials each (see [4,7] for a detailed description). A chin and forehead rest was used for head stabilization. Each trial consisted of a radial version of Rashbass step-ramp motion [8]. From a central fixation point, the target moved a step in a random direction, then returned through its original location at a constant velocity of 16–24°/second with independently randomized speed, direction, onset timing, and duration of target motion. Ten performance measures were recorded as described previously [4,7]: Pursuit initiation was quantified by initiation latency and pursuit acceleration, steady-state tracking by gain, catch-up saccade amplitude, and the proportion of tracking movement consisting of smooth movement. Direction tuning was quantified by directional anisotropy (oblique effect amplitude), asymmetry (horizontal-vertical bias), and noise (standard deviation of distribution of difference measures), speed tuning by responsiveness to differences in target speed and speed noise (mean standard deviation in eye speed averaged across target speeds).

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https://doi.org/10.1016/j.msard.2021.103073
Received 25 March 2021; Accepted 31 May 2021
Available online 5 June 2021

Table 1
Mean multidimensional oculometric performance measures in MS patients and healthy controls.

		MS patients ($n = 20$)			Healthy controls ($n = 19$)			p	Correlation to clinical scores T25-FW		EDSS	
		median	min	max	**median**	min	max		r_s	p	r_s	p
pursuit initiation	initiation latency (msec)	**186.33**	171.33	215	**184.33**	171.33	198.33	**0.101**	*0.478*	*0.039*	*0.564*	*0.01*
	initiation acceleration (deg/sec^2)	**96.83**	16.67	205	**115.33**	16.67	164	**0.061**	*−0.478*	*0.039*	*−0.519*	*0.019*
steady-state tracking	Gain	**0.78**	0.06	0.91	**0.84**	0.06	0.93	**0.322**	*−0.519*	*0.023*	*−0.484*	*0.031*
	amplitude of catch-up saccades (deg)	**2.33**	1.69	4.26	**2.2**	1.7	3.86	**0.835**	0.248	0.307	0.2777	0.237
	proportion of smooth pursuit	***0.63***	*0.17*	*0.86*	***0.73***	*0.17*	*0.84*	***0.047***	*−0.527*	*0.02*	*−0.673*	*0.001*
direction tuning	directional anisotropy	**0.34**	−0.22	0.79	**0.28**	−0.22	0.56	**0.184**	−0.156	0.523	0.008	0.975
	directional asymmetry	**0.11**	−0.33	0.78	**0.09**	−0.33	0.37	**0.444**	0.392	0.097	0.369	0.11
	directional noise (deg)	***10.1***	*5.47*	*57.3*	***8***	*5.47*	*11.4*	***0.014***	*0.561*	*0.012*	*0.72*	*<0.001*
speed tuning	Responsiveness	**0.46**	−0.38	10.3	**0.3**	−0.38	0.74	**0.749**	−0.14	0.566	−0.175	0.461
	speed noise (deg/sec)	***4.3***	*1.6*	*6.63*	***3.1***	*1.6*	*5.4*	***0.021***	0.12	0.624	0.2	0.398

Statistical analysis

The intraclass correlation coefficient (ICC) was used to assess test-retest reliability between the three tests. As application of the Shapiro-Wilk test of normality showed non-normal distribution of data, differences in mean oculometric performance measures between MS patients and healthy controls were compared using the nonparametric Wilcoxon rank sum test. Spearman's rank-order correlation was used to assess for relationships between oculometric performance measures and age, disease duration, expanded disability status scale (EDSS) and timed 25-foot walk (T25-FW) scores in MS patients (IBM® SPSS Statistics).

Results

Twenty MS participants and nineteen healthy controls were included in the statistical analysis. The groups were similar in age and gender (MS median age 35 years [range 22–74], 55% female and controls 31 years [range 22–64], 58% female).

MS patient characteristics

Median age at diagnosis was 29 years (range 18–60) and the median disease duration at time of testing was 8 years (range 0.25–28). MS subtypes included relapsing remitting ($n = 17$; 85%), primary progressive ($n = 2$; 10%) and secondary progressive MS ($n = 1$; 5%). 16/20 (80%) of patients were on disease-modifying therapy (DMT) at the time of testing. Most recent median EDSS score was 2.25 (range 1–6.5) and median T25-FW (available in 19 patients) was documented as 4.5 (range 3.6–18.4) seconds. Six (30%) patients demonstrated efferent dysfunction in their most recent clinical neurological exam (slowing of saccades $n = 4$, saccadic breakdown of smooth pursuit $n = 2$, nystagmus $n = 2$, internuclear ophthalmoplegia $n = 2$) and five (25%) patients had subjective complaints (diplopia $n = 3$, oscillopsia $n = 2$). Left eye visual acuity (available in 19 patients) was 20/20 ($n = 12$), 20/25 ($n = 4$), 20/30 ($n = 2$) and 20/40 ($n = 1$).

Oculometric performance measures

Table 1 demonstrates an overview of the ten oculometric performance measures assessed. Compared to healthy controls, MS patients had a significantly lower mean proportion of smooth pursuit during steady-state tracking (0.63 [0.17–0.86] vs. 0.73 [0.17–0.84]; $p = 0.047$). Furthermore, MS patients had significantly increased noise both in direction tuning (10.1 [5.47–57.3 vs. 8 [5.47–11.4] degrees; $p = 0.014$) and speed tuning (4.3 [1.6–6.63] vs. 3.1 [1.6–5.4] degrees/*sec;* $p = 0.021$). A relevant point estimate decrease in mean initiation acceleration of eye movements in MS patients did not reach nominal statistical significance (96.83 [16.67–205] vs. 115.33 [16.67–164] degrees/sec^2; $p = 0.061$). There was a significant correlation between EDSS and T25-FW scores and initiation latency, initiation acceleration, gain, proportion of smooth pursuit and direction tuning (Table 1). No correlation was observed between oculometric performance measures and age or disease duration. Good to excellent test-retest reliability was observed for measures of pursuit initiation (initiation latency: ICC=0.882; initiation acceleration: ICC=0.948) and steady-state-tracking (gain: ICC=0.939; catch-up saccade amplitude: ICC=0.793; proportion of smooth pursuit: ICC=0.949) as well as direction noise (ICC=0.927) and speed noise (ICC=0.867).

Discussion

We comprehensively captured and quantified oculomotor dysfunction in MS patients using a novel noninvasive eye tracker (neuroFit ONE™) [4,7]. The technology to measure multidimensional oculometric performance through pursuit initiation, steady-state tracking, direction tuning, and speed tuning opens the opportunity for detailed assessments of different aspects of smooth pursuit dysfunction in MS that have not been well quantified before.

Notably, we quantified saccadic breakdown of smooth pursuit in MS with a significant decrease in the proportion of smooth pursuit in MS patients compared to healthy subjects, consistent with tracking degradation observed using the same methods in other populations with brain pathology [7]. This represents a novel measure to demonstrate deficits in steady-state tracking in MS. Furthermore, we were able to demonstrate significantly increased noise in direction tuning and speed tuning consistent with deficits in the variability of direction and speed. These noise terms measure the magnitude of deviation of ocular tracking from the motion of the stimulus, in parallel with the magnitude of misperception of the speed and direction of the stimulus. Perceptual disturbances such as these may slow the comfortable pace of walking and could contribute to the observed correlation with T25-FW scores.

These oculometric performance measures are objective, quantitative metrics that have not been assessed in MS patients and could be promising future biomarkers to assess the impact of therapies and the risk of sensorimotor mishaps (e.g., falls, car accidents). Furthermore, the observed correlation to EDSS and T25-FW scores underlines the neuroFit ONE's potential as an economical and portable monitoring tool for MS disease progression in clinic environments.

In previous studies, decreases in pursuit gain, latency of pursuit initiation and increases in saccadic amplitudes have been the main measures to identify smooth pursuit dysfunction in MS patients [2,6]. We were unable to reproduce significant differences in these variables, which might be due to the small sample size of this pilot study. This could also be the reason why the observed absolute difference in initiation acceleration did not reach nominal statistical significance, though the point estimate was of potential clinical relevance. It elucidates the importance to reassess our current findings with a larger sample size and to establish validity in a multi-site setting. Furthermore, it will be

essential to assess the longitudinal rate of change of these multidimensional oculometric performance measures to determine their usefulness as a marker of disease progression in MS.

Differences between MS patients and healthy controls were assessed using nonparametric Wilcoxon rank sum test (IBM® SPSS Statistics) and results (p-values) are displayed. Results of Spearman's rank-order correlation between oculometric performance measures and T25-FW and EDSS scores (Spearman correlation coefficients [r_s] and p-values) are displayed in the columns on the right. Significant ($p<0.05$) correlations and differences in performance measures are marked in *italics*. MS = Multiple Sclerosis; T25-FW = timed 25-foot walk; EDSS = expanded disability status scale.

Study funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

Dr. Rempe receives grant funding from the National Multiple Sclerosis Society. N. Dastgheyb, A. Miner and M. Palomino report no disclosures. Dr Kinkel has received honoraria for non-promotional educational activity from Biogen and received speaker fees from Alexion, Biogen, BMS, Genentech and Sanofi-Genzyme. Dr. Liston receives SBIR grant support from the National Institute on Aging. Dr. Graves over the past year has grant/contract research support from the National MS Society, Biogen, and Octave Biosciences. She serves on a steering committee for a trial supported by Novartis. She has received honoraria for a non-promotional, educational activity for Sanofi-Genzyme. She has received speaker fees from Alexion and BMS and served on an advisory board for Genentech.

References

[1] Nicholas, J.A., Electricwala, B., Lee, L.K., Johnson, K.M., 2019. Burden of relapsing-remitting multiple sclerosis on workers in the US: a cross-sectional analysis of survey data. BMC Neurol. 19, 258.
[2] Jozefowicz-Korczynska, M., Pajor, A.M., 2011. Evaluation of the smooth pursuit tests in multiple sclerosis patients. J. Neurol. 258, 1795–1800.
[3] Yousef, A., Devereux, M., Gourraud, P.A., et al., 2019. Subclinical saccadic eye movement dysfunction in pediatric multiple sclerosis. J. Child Neurol. 34, 38–43.
[4] Liston, D.B., Wong, L.R., Stone, L.S., 2017. Oculometric assessment of sensorimotor impairment associated with TBI. Optom. Vis. Sci. 94, 51–59.
[5] Nygaard, G.O., de Rodez Benavent, S.A., Harbo, H.F., et al., 2015. Eye and hand motor interactions with the Symbol Digit Modalities Test in early multiple sclerosis. Mult. Scler. Relat. Disord. 4, 585–589.
[6] Lizak, N., Clough, M., Millist, L., Kalincik, T., White, O.B., Fielding, J., 2016. Impairment of smooth pursuit as a marker of early multiple sclerosis. Front. Neurol. 7, 206.
[7] Liston, D.B., Stone, L.S., 2014. Oculometric assessment of dynamic visual processing. J. Vis. 14, 12.
[8] Rashbass, C., 1961. The relationship between saccadic and smooth tracking eye movements. J. Physiol. 159, 326–338.