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Eye and hand motor interactions with the Symbol Digit Modalities Test in early multiple sclerosis

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ABSTRACT

Purpose: Eye and hand motor dysfunction may be present early in the disease course of relapsing-remitting multiple sclerosis (RRMS), and can affect the results on visual and written cognitive tests. We aimed to test for differences in saccadic initiation time (SI time) between RRMS patients and healthy controls, and whether SI time and hand motor speed interacted with the written version of the Symbol Digit Modalities Test (wSDMT).

Methods: Patients with RRMS ($N=44$, age 35.1 ± 7.3 years), time since diagnosis <3 years and matched controls ($N=41$, age 33.2 ± 6.8 years) were examined with ophthalmological, neurological and neuropsychological tests, as well as structural MRI (white matter lesion load (WMLL) and brainstem lesions), visual evoked potentials (VEP) and eye-tracker examinations of saccades.

Results: SI time was longer in RRMS than controls ($p<0.05$). SI time was not related to the Paced Auditory Serial Addition Test (PASAT), WMLL or to the presence of brainstem lesions. 9 hole peg test (9HP) correlated significantly with WMLL ($r=0.58$, $p<0.01$). Both SI time and 9HP correlated negatively with the results of wSDMT ($r=-0.32$, $p<0.05$, $r=-0.47$, $p<0.01$), but none correlated with the results of PASAT.

Conclusions: RRMS patients have an increased SI time compared to controls. Cognitive tests results, exemplified by the wSDMT, may be confounded by eye and hand motor function.

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease affecting the central nervous system showing both local and more widespread diffuse inflammation and neurodegeneration. Early features of relapsing-remitting multiple sclerosis (RRMS) are varied and may include eye motor disturbances (Reulen et al., 1983; Frohman et al., 2005; Graves and Balcer, 2010), fine motor control of the hand (Cutter et al., 1999) or cognitive dysfunction (Amato and Ponziani, 2001; Amato et al., 2010).

The Symbol Digit Modalities Test (SDMT) (Aron, 1982) is a widely used test of processing speed, recently suggested as sentinel test for cognitive impairment in multiple sclerosis (Van Schependom et al., 2014). It is part of several test batteries used in the assessment of cognitive impairment in MS patients (Benedict et al., 2002; Langdon et al., 2011) and is suggested for use in clinical trials (Benedict et al., 2012). Because of the wide use of the SDMT (Benedict et al., 2004; Drake et al., 2010; Langdon et al., 2011), it is important to identify possible input or output level problems related to the procedure of the test.

Saccadic initiation time (SI time), i.e. the time from a central

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visual cue appears to the onset of an appropriate saccade, may be increased in patients with MS (Reulen et al., 1983) and hence constitute an input problem when performing the SDMT. Complex tests of eye movements, like tests of anti-saccades, have been associated with cognitive dysfunction in MS (Fielding et al., 2009a, 2012), and MS patients appear to spend excessive time on saccadic tasks with distractor stimuli (Fielding et al., 2009b). Recently a test for eye motor speed has been suggested as a bedside assessment tool in MS, as the number of speeded saccades for 30 s was related to both visual and non-visual cognitive tests (Roberg et al., 2014). However, to our knowledge, SI time, relevant for an effective completion of the SDMT, has not been studied in MS patients.

Motor function could affect the response to cognitive tests, like the SDMT. The neuropsychological test batteries for MS patients, like the MACFIMS and BICAMS, where SDMT is included, have recommended the use of the oral version of the SDMT because of possible motor interactions with the written version (Benedict et al., 2002; Langdon et al., 2011). However, oral motor slowing has been found to affect the results of the oral SDMT (oSDMT) (Arnett et al., 2008), indicating that an oral response to the SDMT may not be ideal. The emergence of new disease modifying treatments requires clinicians to carefully monitor their patients' disease progression early in the disease course. In particular the increasing attention on cognitive dysfunction in MS warrants a need for quick and easy assessment of cognitive function in early MS patients. These patients may have a very low disability and minor motor dysfunction. The written version of the SDMT, (wSDMT) is easier to administer for the clinicians and probably would feel more discreet to complete for the patients, and it would therefore be an advantage to both parties if this version of the test could replace the oral version in some instances. It is, however, not known whether hand motor speed is associated with the test results on the wSDMT in such patients.

In this study we aimed at testing whether decrements in eye and hand motor control could confound the test score of the visual SDMT with written response (wSDMT) in early MS patients.

2. Materials and methods

2.1. Patients and controls

Relapsing-remitting MS (RRMS) patients diagnosed within the last three years with no drug abuse and no other neurologic or psychiatric disease, were investigated ($n=48$). Healthy controls ($n=47$) were included for the ophthalmological and eye-tracker analyses, but not tested neurologically. They were recruited from the hospital and university environment and had no medical conditions known to affect the visual pathways. They were matched on age and gender at a group level and, after exclusion (four patients and five controls because of technical problems with the eye tracker, one patient because of febrile acute illness and one control because of possible demyelinating disease), 44 patients and 41 controls were eligible for analyses (Table 1).

All participants gave written informed consent and the project was approved by the regional committee for medical and health research ethics (REK).

2.2. Clinical evaluation

All patients were tested by the same trained neurologist (GON) with the Expanded Disability Status Score (EDSS) and the 9 Hole Peg test (9HP) for hand motor speed. They also underwent a thorough neuropsychological assessment (Nygaard et al., 2014). Results of the auditory 3 s version of the Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977) performed by the patients, and wSDMT (Aron, 1982) performed by all participants, are reported. Ophthalmological examinations were performed by the same trained ophthalmologist (SRB).

All patients underwent detailed MRI within a week of the other examinations. White matter lesion load (WMLL) was estimated from FLAIR and MPRAGE sequences, using the Cascade software, previously applied to an overlapping MS sample (ki.se/en/nvs/cascade) (Damangir et al., 2012; Nygaard et al., 2014). A subset of the patients ($n=32$) were examined by a trained neuroradiologist (PS) and rated according to the presence of white matter lesions (WML) of the brainstem.

Patients' visual evoked potential latency to P100 (VEP P100) were obtained with dimmed light ($\sim$25 lx) and the screen placed 100 cm in front of the eyes with checkerboard patterns (check size 65′, 2 Hz with a 16″ cathode ray tube screen). Three hundred responses were averaged from the mid-occipital lobe (MO, defined to be 5 cm above inion) referenced Fz, (defined by the 10/20 system) with 1–100 Hz band-pass filter. Rejection level was set to $\pm$ 100 μV.

Saccades were acquired using an iView X Hi-Speed eye-tracking (SensoMotoric Instruments, Teltow, Germany). The participants were seated approximately 70 cm from the 18.5″ monitor, measuring a diagonal length of 47 cm, and the constant display resolution was set to 1680 × 1050 pixels. Binocular data were recorded at a sampling rate of 60 Hz. The eye-tracking system is accurate to less than 0.4°.

Participants first fixated on a central cross and made saccadic movements as fast as possible towards a star in the corner of the screen cued by a central appearing arrow instantly replacing the cross (Fig. 1a and b). The test's primary output was SI time, defined as the time from the appearance of the arrow until the onset of an appropriate saccade.

Target areas of interest (tAOI) were defined by circles surrounding the stars in the four corners of the screen (Fig. 1c). Time to tAOI (ttA) was calculated as the time from appearance of the central arrow to the participants' saccade entered the tAOI.

Each participant was given eight trials. The first trial was regarded as a test and discarded. Altogether, 286/308 (93%) of the trials of the patients and 273/287 (95%) of the trials of the controls had good quality and were included in the analyses.

2.3. Statistical analyses

SPSS version 22, Chicago, IL was used for statistical analyses. Independent samples t-test and χ^2-tests were used to test for differences between patients and controls and Pearson bivariate and partial correlations were used to test for associations between the same groups. Linear regression analyses were used to assess the association between motor function and cognitive tests. A significance level of 0.05 was applied for all analyses.

3. Results

3.1. Clinical features

The background and clinical characteristics are listed in Table 1. The groups were comparable concerning age, gender distribution, visual acuity and test results on the wSDMT. The controls' educational level was on average two years higher than that of the patients. VEP p100 was in normal range on group level. Almost half of the patients had undergone known or subclinical optic neuritis (ON) of either or both eyes prior to the examinations.

The patients had a significantly longer SI time than the controls while ttA was comparable (Table 2).

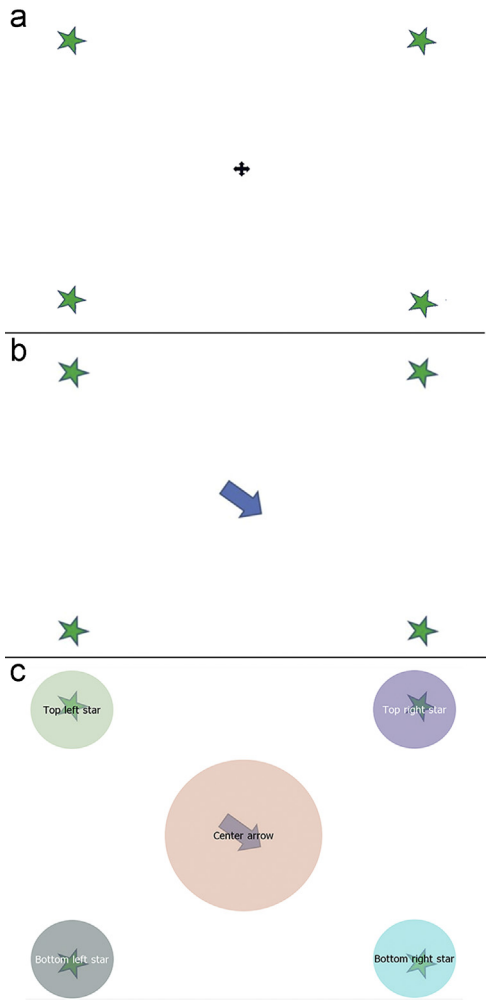

Fig. 1. Screenshots from the eye tracker. (A) fixation slide (corner stars=saccadic targets); (B) task (saccadic cue=pointing arrow); (C) AOIs.

3.2. Association between motor function, disease characteristics and cognitive test results

The patients' SI time was associated with wSDMT, but not with PASAT, as shown in Fig. 2a and b. Furthermore, there were no associations between the patients' SI time and WMLL or VEP P100 (Table 3). ON patients did not present longer SI time than the other patients ($t=1.559$, $p=0.126$), and the patients with and without WML of the brain-stem had similar SI time ($t=0.182$, $p=0.857$). Furthermore, there was no significant association between SI time and age ($r=0.232$, $p=0.129$).

As illustrated in Fig. 2c and d, the patients' hand function (9HP) was associated with the wSDMT, but not with the PASAT. 9HP was also associated with WMLL, but not with VEP P100 latency (Table 3) or WML of the brain-stem ($p=1.000$). Hand function was, however, associated with age ($r=0.481$, $p<0.001$). The association between hand function, wSDMT and WMLL, was still significant after correcting for age (9HP versus wSDMT (partial): $rp=-0.349$, $p=0.025$, 9HP versus WMLL (partial): $rp=0.576$, $p<0.001$).

As expected from previous studies (Brochet et al., 2008; Drake et al., 2010) the results of the wSDMT and PASAT were associated ($r=0.457$, $p=0.002$). When controlling for 9HP ($r=0.511$, $p=0.001$), or SI time ($r=0.455$, $p=0.003$) this association was unchanged.

In the healthy controls, we found no association neither between SI time and wSDMT ($r=-0.189$, $p=0.256$), nor between wSDMT and age ($r=-0.227$, $p=0.176$).

Table 1
Background.

	Patients	Controls	Difference	
	$N=44$	$N=41$	95% CI	p-Value
Female, n (%)	32 (73)	30 (73)		1.000
Age, years ± SD	35.1 ± 7.3	33.2 ± 6.8	−1.2 to 4.9	0.225
Education, years ± SD	15.2 ± 2.1	16.9 ± 3.0	−2.9 to 0.6	0.003
Time since diagnosis, months ± SD	16.3 ± 11.2			
Disease duration, months ± SD	30.7 ± 28.3			
Disease modulatory treatment, n (%)	36 (82)			
EDSS, mean ± SD	1.8 ± 0.8			
EDSS, median (min–max)	1.5 (0–3.5)			
9HP, sec, mean ± SD[a]	20.8 ± 3.8			
T25FWT, sec, mean ± SD[a]	4.0 ± 0.6			
Visual acuity, left eye, LogMar ± SD	−0.04 ± 0.12	−0.08 ± 0.08	−0.01 to 0.08	0.097
Visual acuity, right eye, LogMar ± SD	−0.08 ± 0.09	−0.06 ± 0.11	−0.06 to 0.02	0.381
Previous optic neuritis				
Left eye, n (%)	9 (21)			
Right eye, n (%)	11 (25)			
Both eyes, n (%)	1 (2)			
White matter lesion load, mm^3, mean ± SD[a]	5.4 ± 3.6			
Presence of lesions in brainstem, n (%)	19/32 (59%)			
VEP, delay to p100, left eye, mean ± SD[b]	107.0 ± 9.0			
VEP, delay to p100, right eye, mean ± SD[b]	106.9 ± 7.1			
wSDMT, correct answers, mean ± SD[c]	53.9 ± 8.9	55.8 ± 8.5	−5.8 to 0.3	0.321
PASAT, correct answers, mean ± SD[a]	47.4 ± 9.3			

[a] $n=42$ s.
[b] For two patients VEP delay was not quantifiable on the left or both eyes.
[c] $n=40$ controls.

Table 2
Test results of saccades in patients and controls.

	Patients	Controls	Difference	
	$n=44$	$n=41$	95% CI	p-Value
Saccadic initiation time, ms ± SD	351.7 ± 69.4	326.0 ± 45.0	0.3–51.2	0.047
Time to target AOI, ms ± SD	468.5 ± 84.6	446.0 ± 64.6	−10.2 to 55.1	0.175
Number of valid saccades per participant, total ± SD	6.5 ± 1.1	6.7 ± 0.8	−0.6 to 0.3	0.442

Univariate regression analysis showed 10% of the variance in wSDMT could be explained by the results on SI time, and every extra 10 ms of SI time was associated with a 0.41 point decrease in the wSDMT (Fig. 2a). Regression analysis revealed that 22% of the variance in wSDMT could be explained by the results on the 9HP, and every extra second spent on the 9HP was associated with a 1.1 point decrease in wSDMT (Fig. 2c).

Multivariate linear regression with 9HP and SI time as independent variables and wSDMT as dependent variable revealed that SI time did not add significantly ($p=0.209$) to the model when controlling for 9HP.

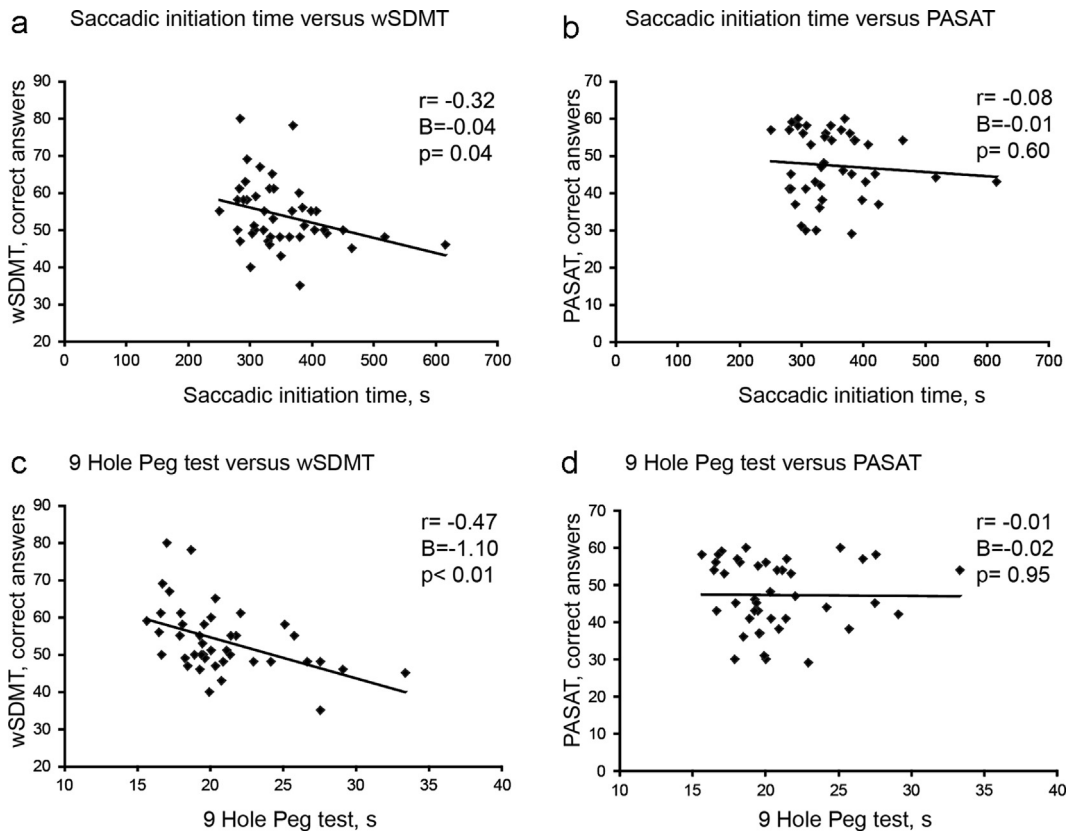

Fig. 2. Association between motor function and cognitive tests in RRMS patients. The scatter plots illustrate the association between (a) SI time and wSDMT, (b) SI time and PASAT, (c) 9HP and SDMT and (d) 9HP and PASAT, respectively. As illustrated, only wSDMT, and not PASAT, is associated with motor function in early RRMS patients.

Table 3
Correlations in RRMS patients.

	WMLL *r* (*p*-value)	VEP P100 *r* (*p*-Value)
SI time	0.038 (0.815)	−0.104 (0.519)
9HP	0.579 (< 0.001)	0.094 (0.560)

In the RRMS patients, SI time was not associated with WMLL or VEP P100, while 9HP was associated with WMLL, but not with VEP P100.

4. Discussion

This study shows that RRMS patients early in the disease course have a longer SI time than healthy controls. SI time was unrelated to other disease characteristics, WMLL and VEP. We also found that both hand function (9HP), and SI time were associated with the test results of the wSDMT, but not with the auditory and oral test of the same functional domains, PASAT.

In contrast to the study by Fielding et al. (2009b) who found prolonged saccadic delay in response to composite, but not to simple cues, we found a prolonged SI time in response to a simple cue. Our sample size is larger than previous ones, and our patients had a shorter disease duration and higher EDSS, possibly accounting for the different findings (Fielding et al., 2009b).

Saccades and cognition are thought to be linked, and recently a test for eye motor speed was suggested as a bedside assessment tool in MS (Roberg et al., 2014). These neuropsychological studies indicate that eye motor disorders may be a sensitive early marker of disseminated disease. Our study showed increased SI time in the absence of cognitive difficulties. We therefore hypothesize that SI time and cognitive decline are caused by separate anatomico-pathological alterations in early RRMS. These domains may not evolve in parallel and identifying the actual impairments may lead to improved care for the patients.

Slowing of hand function has been recognized as a sign in early MS (Cutter et al., 1999), and the patients in our study had a slower hand function than healthy controls in previous studies (Drake et al., 2010). We did not identify any association between 9HP and PASAT. In contrast, studies of the components of the MSFC have identified associations between 9HP and PASAT in large patient samples with long disease duration (Cutter et al., 1999; Drake et al., 2010). The absent association in our study may be explained either by short disease duration, cognitive intactness or by the limited patient sample. The significant association between 9HP and the wSDMT test score indicates that hand function is relevant in solving the wSDMT even in the absence of cognitive dysfunction.

We found associations between hand motor function and WMLL, but no association between SI time and WMLL or brainstem lesions. However, there is considerable evidence that both normal appearing white matter (Kutzelnigg et al., 2005; Bodini et al., 2009) and gray matter (De Stefano et al., 2003; Sailer et al., 2003; Ceccarelli et al., 2008) may be affected in early RRMS patients, and associated with specific symptoms, like cognition and fatigue (Sepulcre et al., 2009; Nygaard et al., 2014). Cerebellar pathology is also related to eye movements disorders, as recently shown in a study of antisaccades and cognition in early MS patients (Kolbe et al., 2014). Thus our study does not exclude associations between SI time and other disease related structural brain changes.

The oSDMT is the most commonly used test in the neuropsychological assessment of MS patients. From our results, showing that SI time affects the wSDMT results, we hypothesize that the results of the oSDMT would be affected by eye motor

decrements. This has, however, not been directly shown in this study, and should be tested separately in future studies. Our study is limited by the fact that the patients were not given both the written and the oral version of the SDMT. This would have contributed to clarify the different and possibly additional motor skills required for performance of the wSDMT. Moreover, the controls did not perform the PASAT, which would have been an additional strength to our analyses.

Low SDMT score is associated with early cognitive dysfunction (Deloire et al., 2006), disease development, imaging (Christodoulou et al., 2003; Benedict et al., 2004; Filippi et al., 2010) and vocational outcomes (Drake et al., 2010) in MS patients. The SDMT may be the best available cognitive test for MS patients (Langdon et al., 2011). The association between wSDMT test score, eye and hand motor function described in this study may in fact contribute to the value of the wSDMT in real life. This study therefore does not oppose the future use of this test, but highlights that impairments other than cognitive difficulties may confound the test results and these should be interpreted with caution in some patient groups.

In conclusion, slowing of eye movements, as well as hand motor function, is associated with the wSDMT test score. Clinicians should be aware that the wSDMT may measure not only cognition, but also eye movements and hand function in early RRMS patients.

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Conflict of interest

None.

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