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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).