REVIEW ARTICLE

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Symbol Digit Modalities Test in progressive multiple sclerosis

Bartosz Gajewski, Iwona Karlińska, Mariusz Stasiołek

Department of Neurology, Medical University of Lodz, Lodz, Poland

ABSTRACT

Introduction. The Symbol Digit Modalities Test (SDMT) is a highly sensitive neuropsychological tool used for the assessment of information processing speed (IPS) in various neurological disorders.

State of the art. In this review, we have focused on the current knowledge regarding the use of SDMT selectively in the evaluation of progressive multiple sclerosis (PMS) patients. A literature review was performed regarding the application of SDMT in PMS, with a focus on the primary progressive and secondary progressive subtypes. Relationships of diverse disease-associated factors with SDMT have been described, including disease course, imaging findings, molecular biomarkers, treatment and others.

Clinical implications. SDMT is a very useful and easily applicable instrument in the diagnostic armamentarium of neurologists and neuropsychologists. It is especially valuable in the evaluation of PMS patients, in whom the prevalence of IPS deficits is higher than in relapsing-remitting multiple sclerosis subjects or in healthy individuals.

Future directions. An emphasis should be laid on larger study groups and differentiating between individual PMS subtypes and their separate analysis in the context of cognitive assessment.

Keywords: Symbol Digit Modalities Test, SDMT, progressive multiple sclerosis, information processing speed, cognitive dysfunction

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disorder of the central nervous system (CNS). Despite numerous studies, the aetiopathogenesis of MS remains not entirely understood. However, the two commonly accepted main pathomechanisms of the disease are inflammatory processes and neurodegeneration [1]. The disease is characterised by a high prevalence in European and North American populations, and is considered to be the main cause of non-trauma-related physical disability in young adults [2]. Due to the potentially detrimental clinical course and the lack of sufficient diagnostic and prognostic tools, as well as fully effective treatments, MS represents a serious challenge for modern medicine and a significant burden for patients, their families and society. The clinical course of MS varies significantly between patients and can change over time. According to the currently accepted criteria, the MS clinical phenotype is divided into relapsing-remitting MS (RRMS) and progressive MS (PMS) [3]. Two main subtypes of PMS can further be distinguished. In the first subtype — primary progressive MS (PPMS), right from the beginning, a gradual accrual of neurological deficits is observed. The other subtype — secondary progressive MS (SPMS), develops after the initial relapsing-remitting course of the disease. Primary progressive MS constitutes c.10% of MS patients, whereas most RRMS patients transition to SPMS over the years [4]. A recent study on this topic indicated the estimated prevalence of SPMS in some Western European

Address for correspondence: Mariusz Stasiołek, Department of Neurology, Medical University of Lodz, Kopcińskiego 22 St., 90–153 Lodz, Poland; e-mail: mariusz.stasiolek@umed.lodz.pl

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and American populations to be 10.9–57.8 per 100,000 [5]. In a longitudinal study on 15,717 RRMS patients, the median time to conversion to SPMS from disease onset was 32.4 years [6]. The percentage of transitions from RRMS to SPMS varies from 18.1–90% of RRMS patients, and the rate of conversion has been shown to be influenced by multiple factors including the disease modifying treatment (DMT) [7, 8].

A crucial aspect of MS is the impact of the disease on the cognitive function of the patient. Cognitive impairment is diagnosed in some MS patients even in the earliest stages of the disease [9]. Initially, the most affected cognitive domains are information processing speed, memory, attention, and executive functions [10, 11]. Importantly, early cognitive decline can be regarded as a negative prognostic factor of the physical disability progression rate [12]. The deterioration of the patients' cognitive function may also worsen their quality of life [13] although some reports do not confirm such an observation [14]. Consequently, the role of neuropsychological examination is emphasised in the proper assessment of the current clinical status of MS patient and as an important element in evaluation of the disease course and response to the therapy [15]. More severe cognitive impairment in SPMS compared to RRMS may be the result of a longer disease duration, higher level of disability, and higher lesion load [10]. Also, people with PMS present more serious cognitive dysfunction than RRMS patients, something which may be attributed to more intense cerebral atrophy in progressive subtypes of the disease [10, 16]. Nonetheless, the increased level of cognitive decline in PPMS cannot be fully explained by the same factors, as this form of MS is not preceded by a remitting-relapsing phase of the disease. It has been suggested that PPMS patients may have a distinguishable cognitive phenotype, with predominant impairment of language and visuospatial skills [17] or verbal learning and memory deficits [18]. However, in some populations of MS patients, no specific set of cognitive features in PPMS has been confirmed [19]. Interestingly, some researchers have suggested that the differences in cognitive profiles between PPMS and RRMS indicate a distinctive pathogenesis of PPMS [20]. However, such reasoning is inconsistent with the results of different studies (as described above) and seems to contradict the developing understanding of the common neurodegenerative processes underlying various clinical forms of MS [21].

In this review, we summarise the current knowledge on the use of the Symbol Digit Modalities Test (SDMT) in PMS. It is the most easily clinically applicable and versatile neuropsychological test used in MS. SDMT, first introduced in 1973, is a brief tool (duration c.5 minutes), widely applicable in various CNS disorders including MS both in adults and children (aged 8+). It is designed to assess information processing speed, which has been identified as one of the most impaired cognitive domains in MS patients [22]. Normal values for this test are grouped by age and educational level, and additionally by sex in children. Patients are asked to substitute a given set of symbols with an assigned number. This can be done either in writing or orally, which is crucial for patients with speech disorders or upper limbs disability such as paresis and ataxia. The high sensitivity of the test in the detection of cognitive dysfunction, proven in many studies, has resulted in its recognition as a basic screening neuropsychological tool for the identification of cognitive impairment in MS patients. Currently, it is widely used in the assessment of disease progression and treatment effectiveness [23]. SDMT can be performed separately or as a part of neuropsychological battery e.g. Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), Minimal Assessment of Cognitive Function in MS (MACFIMS), or Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis (BRB-N) [22–25]. Although no SDMT normalisation study has been carried out in a Polish population, it is of particular interest to mention the Polish validation of the BICAMS battery (by Betscher et al. [26]), of which SDMT is an important part.

Material and methods

The PubMed Medline database was searched using the following search phrases: 'progressive multiple sclerosis' AND 'symbol digit modalities test'. All studies taken into consideration were written in English. 92 full text articles published between 1988 and 2023 were screened, with the date of the last search being 23 January, 2024. The content of all the identified articles was analysed for the data associated with the topic of the review. Reviews and validation studies were excluded from the analysis, with the number of excluded articles being 47. All selected articles had to mention specifically the use of SDMT in progressive subtypes of MS (SPMS, PPMS or both). Those describing RRMS and PMS patients as one group were excluded from analysis. Eventually, 45 articles were incorporated into the review.

Results

A summary of the analysed research papers included in the Results section is set out in Table 1.

SDMT in MS clinical subtypes and healthy controls

As mentioned earlier, many studies have outlined differences in profile and severity of cognitive impairment between PMS and RRMS patients [17, 27], evident in SDMT performance among other means. Several studies have reported a gradation of SDMT score in relation to particular MS subtype [13, 28, 29–36, 37–40]. It is accepted that PMS patients perform more poorly on SDMT than do people with RRMS or healthy individuals. The oldest identified study (from 1988) demonstrated cognitive impairment in 38 PMS

Table 1. Summary of analysed articles

Authors	N (PMS)	N (SPMS)	N (PPMS)	Conclusions regarding SDMT
Beatty et al. [13]	38	–	–	SDMT proven to be most sensitive tool in detection of cognitive impairment among applied neuropsychological tests. Patients on antidepressants or antispasmodics (administered due to bladder dysfunction) had lower scores on SDMT
Podda et al. [28]	474	365	109	Specific phenotype with noticeable and widespread cognitive impairment, more severe clinical course and no mood disorders, characterised by a conspicuous deterioration of information processing speed measured by SDMT
Rodrigues et al. [29]	–	–	16	Different cognitive profile of PPMS patients, including poorer performance on SDMT, compared to RRMS patients and healthy controls
Khan et al. [30]	–	22	–	Lower SDMT scores confirmed in SPMS compared to RRMS patients and/or healthy controls
Prosperini et al. [31]	–	25	–	
Wen et al. [32]	20	10	10	PMS patients performed worse on SDMT than RRMS and healthy controls. PPMS patients had lowest SDMT scores
Huijbregts et al. [33]	126	71	55	Lowest SDMT scores in SPMS patients, in a study including healthy subjects, PPMS and SPMS patients
Charalambous et al. [34]	64	36	28	SPMS patients scored lowest on SDMT among MS subtypes and compared to healthy controls. PPMS patients performed better than SPMS, but had lower scores than RRMS and healthy subjects
Ruet et al. [35]	53	U	41+	PMS subjects more cognitively impaired than RRMS patients, as measured by SDMT. In a group consisting of RRMS and PMS patients, a strong positive correlation between Computerised Speed Cognitive Test (CSCT) and SDMT was established
Lapshin et al. [36]	52	37	15	SPMS patients showed worst performance on SDMT, whereas PPMS and RRMS patients performed worse than patients with clinically isolated syndrome (CIS)
Baumhefner et al. [37]	62	–	–	Correlation between SDMT and area of lesions located in cerebrum, cerebellum and brainstem in MRI
Pérez-Miralles et al. [38]	–	–	43	Correlation between change in grey matter volume of left inferior semilunar lobe and SDMT score after 12-month observation
Colato et al. [39]	–	360	–	Significant correlation of SDMT with one of independent component analysis (ICA) regions (a basal ganglia-fronto-temporal pattern). SDMT decline could be predicted with use of an analysis of six ICA regions
Koch et al. [40] (MRI brain volume loss […]. *Mult. Scler.* 2021)	–	360	–	No significant association between conventional volumetric MRI parameters (whole brain and grey matter volume, contrast enhancing lesions and T2 lesions) and SDMT performance
Cocozza et al. [42]	82	35	47	PPMS patients performed worse than SPMS on SDMT. Volumes of cerebellar regions (Crus I, and to a lesser extent Lobule VI) were suggested as independent predictors of SDMT performance
Tavazzi et al. [45]	42	–	–	Correlation of a novel MRI brain atrophy marker (atrophied T2-lesion volume) and SDMT score at 5-year follow-up in both PMS and RRMS patients. PMS performed worse than RRMS patients
Raji et al. [43]	–	57	–	Worse SDMT performance suggested as typical for patients with thalamic and whole brain parenchymal atrophy
Hänninen et al. [44]	–	36	–	Association between thalamic atrophy and poorer SDMT outcomes
Francis et al. [46]	–	45	–	SDMT showed best correlation with cerebral perfusion among applied neuropsychological tools. Most robust correlation was found between SDMT and quantitative cerebral blood flow (qCBF) and quantitative cerebral blood volume (qCBV)
Testud et al. [47]	–	–	77	Lower perfusion in several brain regions including: left pars triangularis, left lateral orbitofrontal, right medial orbitofrontal, right pars opercularis, right rostral anterior cingulate, right amygdala, and right putamen, correlated with better SDMT score
Eilaghi et al. [48]	–	36	–	Correlation of SDMT score decrease with reduction of normal-appearing white matter (NAWM) relative recirculation (rR) — as a measure of blood-brain barrier integrity
Solanky et al. [49]	–	119	–	No significant relationship between SDMT and metabolic markers in grey matter nor NAWM

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Table 1. cont. Summary of analysed articles

Authors	N (PMS)	N (SPMS)	N (PPMS)	Conclusions regarding SDMT
Van der Walt et al. [52]	–	339	–	No significant correlation between human leukocyte antigen (HLA) genotype and SDMT
Abdelhak et al. [53]	200	–	–	Study currently ongoing. Planned enrollment: 200 PMS patients
Siddiqui et al. [54]	48	–	–	Associations of SDMT with certain cholesterol pathway biomarkers
Jakimovski et al. [55]	53	–	–	OCT parameters demonstrated as significant predictors of cognitive dysfunction assessed with SDMT
Nguyen et al. [57]	22	–	–	No relationship between assessed OCT parameters and SDMT performance
Højsgaard Chow et al. [58]	52	–	–	Positive correlation between Mental Component Summary (synthetic composite of Short Form 36 questionnaire) and SDMT. Weak correlation of 9-Hole Peg Test (9-HPT) for nondominant hand only and SDMT
Koch et al. [59] (Impact of Clinical Outcomes […]. *Mult. Scler.* 2021)	–	889	–	Correlation between decreased SDMT score and worsening on Multiple Sclerosis Impact Scale (MSIS-29)
Andreasen et al. [61]	22	–	–	Correlation between scores in Fatigue Scale for Motor and Cognitive Function (FSMC) and SDMT
Gil-Perotin et al. [62]	33	–	–	No correlation between patient-reported outcomes (including: Multiple Sclerosis Quality of Life [MusiQol], Modified Fatigue Impact Scale [MFIS] and Beck Depression Inventory-II [BDI-II]) and SDMT
Carotenuto et al. [69]	–	22	–	Decreased olfactory performance linked to a reduction in information processing speed measured by SDMT
Sandroff et al. [64]	240	–	–	No correlation between SDMT and cardiorespiratory fitness or moderate-to-vigorous physical activity
Bombardier et al. [65]	U	–	–	Study currently ongoing. Planned and current enrollment: 125 and 117 (PMS and RRMS) patients, respectively
Feinstein et al. [66] (*BMC Neurol.* 2020)	309	–	–	Study currently ongoing. Planned enrollment: 360 PMS patients
Feinstein et al. [67] (*Lancet Neurol.* 2023)	311	227	84	No significant improvement in IPS measured with SDMT over 12-week follow-up
Chow et al. [68]	–	–	60	Association of pack-years and lower SDMT score in patients smoking after disease onset
Renner et al. [60]	75	–	–	PMS patients had decreased SDMT score compared to RRMS, which was associated with employment status and could predict fewer weekly hours spent at work
Mortensen et al. [70]	–	6	–	Poorer outcomes of SPMS patients on SDMT compared to RRMS patients. RRMS patients reported higher impact of cognitive impairment on their quality of life than SPMS patients
Benedict et al. [71]	–	1651	–	Patients treated with siponimod had clinically meaningful (4-point) lower risk of decrease and higher chance of increase in SDMT score
Koch et al. [72] (Is the Symbol Digit Modalities Test […]. *Eur. J. Neurol.* 2021)	–	889	–	Increases in SDMT scores throughout two years of trial, both in natalizumab-treated and placebo group (see text for further inforamtion)
Ziemssen et al. [73]	–	U	–	Study currently ongoing. Planned enrollment: 1,500 SPMS patients
Højsgaard Chow et al. [74]	–	42	–	In a study evaluating effectiveness of dimethyl fumarate treatment, 6% worsening and 16% improvement in SDMT performance was reported throughout observation period. Study points out importance of learning effect
ECTRIMS 2022 [75]	503	253	250	Stable or improved SDMT score after two years of ocrelizumab treatment
Boziki et al. [77]	–	–	22	No significant difference in SDMT scores between ocrelizumab responders and non-responders after 12 months

MRI — magnetic resonance imaging; MS — multiple sclerosis; N (PMS) — number of progressive multiple sclerosis participants in study; N (PPMS) — number of primary progressive multiple sclerosis participants in study; N (SPMS) — number of secondary progressive multiple sclerosis participants in study; OCT — optical coherence tomography; PMS — progressive multiple sclerosis; PPMS — primary progressive multiple sclerosis; RRMS — relapsing-remitting multiple sclerosis; SDMT — Symbol Digit Modalities Test; SPMS — secondary progressive multiple sclerosis; U — unknown number of participants in study; + — unknown additional number of participants in study; - — no such participants in study. In presence of two identical first authorships, shortened title of article and name of journal, or name of journal only, added in order to differentiate papers

patients compared to healthy controls. The authors performed a battery of neuropsychological tests assessing memory, verbal fluency and information processing speed. The difference was most significantly expressed in the results of SDMT, which was also proven to be the most sensitive tool in the detection of cognitive impairment among applied neuropsychological tests, and on which more than 75% of PMS subjects achieved a score below the tenth percentile [13]. In another study, the authors set out to identify distinct and dominating cognitive phenotypes in MS patients, controlling for demographic factors, mood disorders, and clinical course of the disease. Latent class analysis, which is a statistical tool used to qualitatively assess the relations between variables, in order to uncover hidden groupings in data, was employed. A large group of 872 people with MS, including 474 PMS patients, was examined. Apart from SDMT, the authors also used a screening test for cognitive impairment: the Montreal Cognitive Assessment (MoCA). In PMS patients, the most frequent phenotype was the one with marked and widespread cognitive impairment, in which information processing speed impairment, assessed with SDMT, was the predominant deficit. This phenotype was observed in 72.5% of PMS patients, mostly SPMS ones, compared to only 27.5% of RRMS subjects. That study also underlined the higher value of latent *vs.* single variables in neurocognitive assessment [28].

Similarly, a Brazilian case-control study involving 16 PPMS patients indicated the existence of a different cognitive profile in PPMS patients, including poorer performance on SDMT, compared to RRMS patients (n = 50) and healthy controls (n = 66) [29]. In two other cohorts of people with MS (including 22 and 25 SPMS patients respectively), lower SDMT scores were confirmed in SPMS compared to RRMS patients and/or healthy controls [30, 31]. Although most of the studies consistently confirmed worse SDMT performance of PMS patients compared to RRMS ones or healthy controls [29–31], data regarding differences in SDMT performance between PPMS and SPMS patients is equivocal. For instance, a study encompassing relatively large groups of patients (55 PPMS and 71 SPMS) reported lower SDMT scores in SPMS patients [33]. Likewise, a cross-sectional study (PMS n = 64) indicated that SPMS patients reached the lowest scores on SDMT among MS subtypes and compared to healthy controls. PPMS patients performed better than SPMS but still had lower scores than RRMS and healthy subjects [34].

However, in a study analysing regional cortical grey matter damage (assessed with gradient echo MRI), something which has been associated with cognitive decline in MS patients, PMS patients (n = 20) performed more poorly on SDMT than RRMS and healthy controls, and, importantly, PPMS patients (n = 10) had the lowest SDMT scores [32].

Several reports have looked at computerised measures of cognitive assessment in MS. An analysis employing a novel digital tool assessing information processing speed known as the Computerised Speed Cognitive Test (CSCT) along with SDMT, once again revealed that PMS subjects were more cognitively impaired than RRMS patients, as measured by SDMT. In a group consisting of 43 RRMS and PMS patients, a strong positive correlation between CSCT and SDMT was established. The authors suggested CSCT's superiority over SDMT because of its lower practice effect [35]. In another study with the use of a digital variant of SDMT (Computerised Symbol Digit Modalities Test, C-SDMT), SPMS patients (n = 37) showed the worst performance, whereas PPMS (n = 15) and RRMS (n = 44) patients, although better than SPMS, performed worse than patients with clinically isolated syndrome (CIS) [36].

SDMT and MRI

Multiple articles have reported associations between changes on brain MRI and information processing speed measured by SDMT. The parameters analysed in these studies have included number and location of demyelinating lesions, as well as brain atrophy. One of the studies in which a quantitative MRI analysis of brain lesions was applied (PMS n = 62) demonstrated a correlation between the area of lesions located in the cerebrum, cerebellum and brainstem with SDMT performance. A correlation of higher significance was established between SDMT score and lesion load in the cerebrum, rather than in the brainstem or cerebellum. According to the authors, this may be explained by the characteristics of the oral version of SDMT, characterised by considerable involvement of the sense of sight and visuospatial memory [37].

Although the specific pathomechanisms of the development and progression of cognitive impairment in MS are still to be fully elucidated, both white and grey matter injury have been suggested as likely factors of cognitive decline. Particularly, a phenomenon of disconnection of certain neuronal networks caused by axonal damage has been proposed to substantially impact upon cognitive domains such as information processing speed and memory [41].

Several recent studies have focused on brain atrophy parameters and their possible relation to cognitive impairment. A multicentre, prospective cohort study of PPMS patients (Understanding Primary Progressive Multiple Sclerosis [UPPMS]; n = 43) encompassing volumetric MRI analysis of multiple brain regions in association with cognitive performance assessed with SDMT plus other means, indicated a possible ability of specific white and grey matter volume changes to predict cognitive decline. A correlation was found between the change in grey matter volume of the left inferior semilunar lobule of the cerebellum and SDMT score after a 12-month observation [38]. Furthermore, a cross-sectional study (n = 128, PMS n = 82) concentrating on cerebellar atrophy demonstrated that PPMS patients performed worse than SPMS on SDMT, and suggested volumes of Crus I, and to a lesser extent, Lobule VI, to be independent predictors of SDMT performance. The abovementioned articles indicated certain parts of the cerebellum as important brain structures in terms of cognition. These CNS regions are supposedly

connected to attention and executive functions that impact upon information processing speed [42]. Some studies have also underlined the possible role of the thalamus in information processing [43,44]. In a group of 57 people with SPMS, a worse SDMT performance was suggested as typical for patients with thalamic and whole brain parenchymal atrophy [43]. The association of thalamic atrophy with poorer SDMT outcomes was also shown in another cohort of 36 SPMS patients [44].

A few papers have reported the existence of stronger associations between SDMT and non-conventional MRI parameters, compared to conventional measurements. A study based on the data from the ASCEND trial (Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants With Secondary Progressive Multiple Sclerosis) (SPMS n = 360), targeted neuronal networks with the use of a specialised statistical technique i.e. spatial independent component analysis (ICA) of grey matter and its possible relations to cognitive worsening. Compared to conventional morphometrics e.g. whole brain/deep grey matter or lesion volume, ICA components correlated more strongly with clinical parameters including SDMT score. A significant correlation of SDMT was observed with one of the ICA regions (a basal ganglia-fronto-temporal pattern) and SDMT decline could be predicted with the use of an analysis of six ICA regions. The authors concluded that certain ICA components may reflect disease progression measured by SDMT [39].

In line with these observations, in another study based on data from the ASCEND trial, no significant association between conventional volumetric MRI parameters (whole brain and grey matter volume), nor the volume of T2 lesions nor the number or volume of contrast enhancing lesions with SDMT performance, was found [40]. In reference to the previous articles, another study showed an inverse correlation of a novel MRI brain atrophy marker (atrophied T2-lesion volume which represents the volume of lesion replaced by cerebrospinal fluid over time of atrophy progression) and SDMT score at 5-year follow-up in both PMS (n = 42) and RRMS patients. Importantly, this relationship was more pronounced in PMS than RRMS patients [45].

Interesting findings came from research based on perfusion MRI [46, 47]. Assessment of perfusion MRI in 45 SPMS patients revealed that among the applied neuropsychological tools, SDMT showed the best correlation with cerebral perfusion. The most robust correlation was found between SDMT and two perfusion parameters: quantitative cerebral blood flow (qCBF), and quantitative cerebral blood volume (qCBV). It was also demonstrated that hypoperfusion in the superior medial frontal cortex and subcortical grey matter of SPMS subjects correlates the most closely with SDMT among the utilised batteries, although the results were ambiguous [46]. In contrast, a prospective observational cohort study (PPMS n = 77) demonstrated that lower perfusion in several brain regions (including left pars triangularis, left lateral orbitofrontal, right medial orbitofrontal, right pars opercularis, right rostral anterior cingulate, right amygdala, and right putamen) correlated with better SDMT score, which was suggested to be a result of functional maladaptation [47].

Augmented blood-brain barrier (BBB) permeability is an indicator of an active neuroinflammation and may be visualised on MRI as lesions enhancement. A study encompassing 36 SPMS patients highlighted the impact of BBB breakdown on information processing speed, by demonstrating correlation of SDMT score decrease with reduction of normal-appearing white matter (NAWM) relative recirculation (rR) — a quantitative parameter of contrast recirculation anomalies regarded as a substitute measure of BBB integrity [48].

An MR spectroscopy-based, cross-sectional investigation in SPMS patients (n = 119) did not indicate any significant relationship between metabolic markers in grey matter nor NAWM and SDMT. However, several MR-spectroscopy neurometabolites were associated with information processing speed measured by a different test — Paced Auditory Serial Addition Test (3-second) (PASAT3) [49].

SDMT and molecular biomarkers

Recent studies in the field of MS have noted the usefulness of certain molecular biomarkers that would enable earlier diagnosis, better management, and possibly prediction of disease progression. According to the literature, a growing number of potential molecular biomarkers measured in cerebrospinal fluid (CSF) and/or peripheral blood might be useful in the risk assessment of cognitive decline, as well as in explaining the underlying mechanisms of developing cognitive impairment in MS [50]. Several publications on SDMT in association with molecular biomarkers in PMS have been identified as eligible for the purpose of this review. It is believed that human leukocyte antigen (HLA)-DRB1*1501 carriers are more prone to developing MS [51], but the associations between HLA heterogeneity and disease severity is equivocal. In a study investigating the influence of HLA allelic variation on disease clinical course in a population of 339 SPMS patients, no significant correlation between HLA genotype and SDMT was found [52]. A very promising, currently ongoing, longitudinal, prospective multicentre study: Emerging Blood Biomarkers in Progressive Multiple Sclerosis (EmBioProMS; n = 200) is set to demonstrate whether serum biomarkers such as glial fibrillary acidic protein (GFAP; a protein produced mostly by astrocytes for maintaining their shape and mechanical resistance [50]) and neurofilament light chain (NfL; a cytoskeletal protein released after neuronal breakdown, an indicator of neurodegeneration [50]), can differentiate between progressive versus non-progressive MS subtypes and furthermore predict future disease course, with SDMT as a measure of cognitive function [53]. Interestingly, another study reported a number of associations of certain cholesterol pathway biomarkers with SDMT in PMS (n = 48) and RRMS patients. It concluded that higher low-density lipoprotein cholesterol levels were

associated with decreased SDMT score. However, the authors underlined that relations between cholesterol parameters and SDMT still require explanation [54].

SDMT and OCT

Optical coherence tomography (OCT) is a valuable, non-invasive paraclinical tool in MS diagnosis and monitoring, capable of detecting degeneration of retinal neurons, caused by optic neuritis (ON). In addition, thinning of retinal layers indirectly reflects the rate of global CNS atrophy [55]. Alterations of certain OCT parameters e.g. retinal nerve fibre layer (RNFL) enable monitoring of the process of axonopathy and loss of axons, while reduction of another one, ganglion cell layer (GCL), pertains to neuronal degeneration [56]. These changes may correspond to information processing speed impairment in MS patients [55]. Some publications have referred to the relationships between OCT parameters and cognitive functions assessed with SDMT in PMS patients. In a cross-sectional, case-control analysis of the association between visual acuity, OCT parameters and cognition in 53 PMS patients, macular volume (MV) and peripapillary retinal nerve fibre layer (pRFNL) were demonstrated as significant predictors of cognitive dysfunction assessed with SDMT. Moreover, the authors pointed out that while assessing SDMT performance, it is important to account for the visual acuity of the patient and oculomotor deficits such as internuclear ophthalmoplegia, which have been proven to significantly impact upon SDMT score [55]. On the other hand, another study performed on a small group of 22 PMS patients showed no significant relationship between SDMT performance and visual pathway measures such as ganglion cell and inner plexiform thickness, average retinal thickness, and visual or letter acuity [57].

SDMT and quality of life, fatigue, lifestyle and other factors

Several reports have addressed cognitive impairment evaluated with SDMT, describing cognitive functioning as an indicator of the quality of life (QOL) of PMS patients. A retrospective analysis of 52 patients with PMS, assessing the interrelation of cognitive performance (applied tests: SDMT, PASAT and Trail Making Test B (TRAIL-B)), physical ability (assessed on Expanded Disability Status Scale (EDSS), 9-Hole Peg Test (9-HPT), Timed 25-Foot Walking Test (T25FW), and quality of life, showed correlations exclusively between measures of cognitive function and measures of life quality estimated with the use of a Short Form 36 questionnaire (SF-36) and its synthetic composite the Mental Component Summary (MCS). Importantly, the only significant correlation of physical measure and QOL was established between T25FW and Physical Component Summary (PCS) — a subscale of SF-36. Finally, the authors of this article emphasised the importance of the assessment of cognitive impairment in PMS patients, due to its higher association with quality of life as opposed to physical disability [58]. Yet another study using ASCEND data of SPMS patients (n = 889) and measuring the health-related quality of life (HRQOL) reported a correlation between a decreased SDMT score and worsening on the Multiple Sclerosis Impact Scale (MSIS-29). However, in contrast to the previous study, stronger associations were reported for measures of physical disability such as EDSS and T25FW [59].

One another determinant of QOL is professional activity. A study focusing on employment status and its relation to cognitive performance indicated that 75 PMS patients had a decreased SDMT score compared to RRMS, which was associated with employment status and could predict fewer weekly hours spent at work [60]. This aligns with the observation that in MS, the impairment of information processing speed assessed with SDMT is the leading predictor of unemployment among many cognitive tests. Cognitive impairment, including information processing speed, leads to a decline in job performance, which results in reduced productivity, leading to the limitation of working hours or even resignation from work [60].

One vital element of PMS's clinical presentation is fatigue, which can have an impact on neuropsychological functioning. In a small exploratory study in 22 PMS patients, fatigue correlated with information processing speed. A correlation was found between the scores on Fatigue Scale for Motor and Cognitive Function (FSMC) and SDMT performance. Differences need to be acknowledged between fatigue, which is a subjective emotion, and fatigability, which is an objective deterioration of cognitive performance during a single cognitive examination session, although the correlation between fatigue and fatigability still remains unexplained [61]. However, in an observational study of 86 RRMS and 33 PMS patients, assessing how patient-reported outcomes (PROs, including: Multiple Sclerosis Quality of Life [MusiQol], Modified Fatigue Impact Scale [MFIS] and Beck Depression Inventory-II [BDI-II]) can predict MS disability progression, no significant correlation between PROs and SDMT was reported [62].

A few more factors possibly impacting upon information processing speed in PMS patients have been determined, one being physical activity. A positive impact of physical exercise on cognition in RRMS patients has been reported in some studies [63], whereas in PMS the data on this topic is scarce. Two studies assessing the influence of physical activity on cognition in patients with PMS have been carried out recently. A baseline analysis of the first i.e. 'Improving cognition in people with progressive multiple sclerosis' (CogEx study, PMS n = 240), showed no significant correlation between SDMT and cardiorespiratory fitness or moderate-to-vigorous physical activity [64]. The second study — 'Study of Exercise on Impact of Cognitive Functioning in Multiple Sclerosis Patients' (GET Smart), a single-blind, randomised controlled trial currently encompassing 117 RRMS and PMS patients, is designed to verify an improvement of cognitive function (as measured by SDMT among other means) of patients treated with aerobic exercise as compared to a stretching and toning group [65]. The final results of both studies are not yet available.

Lastly, a multisite, randomised, double-blinded, multi-arm, sham-controlled clinical trial (n = 311) assessing the impact of combined cognitive rehabilitation and aerobic exercise on cognitive functions in PMS patients revealed no significant improvement in IPS measured by SDMT, over a 12-week follow-up [66, 67].

Another possible determinant of cognitive impairment in PMS is tobacco use. An exploratory, cross-sectional study of 60 PPMS participants of a placebo-controlled clinical trial of dimethyl fumarate (DMF), included an analysis of the influence of smoking cigarettes on cognition. A significant association between pack-years and lower SDMT score in patients smoking after disease onset was reported [68].

Olfactory dysfunction is one of the deficits observed in neurodegenerative disorders including MS. Olfaction is controlled by the orbitofrontal, visual and cingulate cortex, as well as the cerebellum and insula. MS-induced lesions located in those regions or regional atrophy affecting them can result in impairment of the sense of smell [69]. As discussed above, information processing speed impairment has been correlated with damage to certain CNS locations, including those responsible for olfaction. White matter lesions might cause disruption in neuronal networks, which results in the disconnection of certain areas in the brain that are potentially involved in both olfaction and cognition processes, which further explains the possible correlations between the mentioned domains. Interestingly, a cross-sectional study of olfaction in PMS and its relation to cognition, involving 22 SPMS patients among others, showed a correlation between the University of Pennsylvania Smell Identification Test (UPSIT) and SDMT. Decreased olfactory performance was linked to a reduction in information processing speed [69].

Importantly, a cognitive performance study on a small sample group investigated opinions of patients with MS about cognition testing e.g. with the use of SDMT. That study demonstrated again poorer outcomes of six SPMS patients on SDMT compared to six RRMS patients. Both RRMS and SPMS patients supported the idea of cognitive testing, and perceived SDMT to be a quick and easy test. RRMS patients reported a higher impact of cognitive impairment on their quality of life than did SPMS patients. Interestingly, some patients complained about the shortness of SDMT which in their opinion may have impacted upon the reliability of the test. Some concerns were also raised regarding the influence of testing conditions (see discussion) [70]. It is important to state that such a small study group might be a methodology drawback.

SDMT and disease modifying therapy

Several research papers have described the impact of disease modifying therapy (DMT) on the natural history of PMS including cognitive performance. The Exploring the Efficacy and Safety of Siponimod in Patients With Secondary Progressive Multiple Sclerosis study, (EXPAND), a multicentre, randomised, double-blind, parallel-group, placebo-controlled, event- and exposure-driven phase III trial involving 1,651 patients with SPMS, demonstrated beneficial effects of siponimod treatment in multiple clinical aspects including information processing speed measured by SDMT. Those patients who were treated with siponimod had a clinically meaningful (4-point) lower risk of decrease and a higher chance of increase in their SDMT score. A the same time, the study did not confirm any beneficial effect of siponimod on the scores of other neurocognitive tests such as the Paced Auditory Serial Addition Test (PASAT) or the Brief Visuospatial Memory Test Revised (BVMT-R) [71]. Another study, based on data collected in the ASCEND trial, which assessed natalizumab treatment in 889 SPMS patients, showed an increase in SDMT scores throughout the two years of the trial, both in the natalizumab-treated and the placebo groups. This observation indicated that, under some circumstances, SDMT scores might not illustrate the actual cognitive decline in SPMS patients, and in fact pointed out how practice effect restricts the utility of SDMT in longitudinal studies. There were two possible drawbacks to the study's design. Firstly, SDMT was performed too frequently (every four weeks) which might have amplified the practice effect. Secondly, the worst-performing patients were arbitrarily excluded from the study [72]. An ongoing multicentre, open-label, prospective, non-interventional study called AMASIA ("impAct of Mayzent [siponimod] on secondAry progressive multiple Sclerosis patients in a long-term non-Interventional study in GermAny") is targeted at the evaluation of safety and effectiveness of siponimod in a real-world setting in SPMS patients with an active disease course (planned enrolment: 1,500 subjects, five-year observation). The primary endpoint of AMASIA is a functional composite endpoint comprising EDSS and SDMT, which underlines the meaning of cognitive assessment in the proper analysis of disease progression [73]. An open-label extension trial on 42 SPMS patients (33 of whom completed the 96-week follow-up period), which evaluated the effectiveness of DMF treatment, revealed a 6% worsening and a 16% improvement in SDMT performance (when an 8-point cut-off was applied). These ambiguous outcomes may be explained by the practice effect. This work also raises the issue of the threshold used for the interpretation of significant SDMT score changes [74]. Importantly, a large ongoing open label clinical trial evaluating the effectiveness and safety of ocrelizumab treatment in more than 900 PMS patients (NCT03523858, planned to complete in 2026), includes cognitive impairment assessment with SDMT. An interim analysis on 503 PMS patients (253 SPMS and 250 PPMS) treated with ocrelizumab has been already published. It showed a stable or improved SDMT score after two years of observation in both PMS subgroups [75, 76]. Additionally, a small prospective observational study of 22 active PPMS patients treated with ocrelizumab indicated a trend of higher SDMT scores, at baseline and after 12- or 24-month follow-ups, in ocrelizumab responders *vs.* non-responders. At

the same time, when assessing a clinically significant change in SDMT (≥ 4-point increase or ≥ 4-point decrease), there was no significant difference in the changes of SDMT values between responders and non-responders after 12 months [77].

Discussion

SDMT is a well-known and highly sensitive test for the detection of cognitive impairment in MS. It has been employed as part of numerous batteries of neuropsychological tests designed for people with MS. SDMT addresses information processing speed which is one of the most commonly affected cognitive domains in every MS clinical phenotype, including PMS [78].

Accordingly, it has been demonstrated that SDMT can be used on its own as an effective screening measure of cognitive status in MS [25].

Our overall analysis of the available literature has allowed for the identification of a pattern of SDMT score gradation in different clinical forms of MS. People with MS in general score lower on SDMT than do healthy subjects. Furthermore, PMS patients perform worse on SDMT than do RRMS ones.

However, it is not yet clear which subtype of PMS demonstrates more pronounced deficits in information processing speed as measured by SDMT. This uncertainty is probably due to multiple factors including differences between assessed PMS populations in terms of disease duration, progression rate [79], MS treatment history, comorbidities, education, lifestyle etc. Most probably, SDMT score may be considered as a candidate predictive marker of the quality of life and employment status in PMS [58–60]. In imaging studies, it has been demonstrated that PMS patients' SDMT performance is associated with overall and regional (e.g. cerebellum, thalamus) brain atrophy, lesion load, as well as with cerebral perfusion or abnormalities in NAWM [43, 48]. Additionally, reports concerning correlations between SDMT and blood or CSF biomarkers and OCT in PMS have been published recently [55, 57], although their results need to be confirmed in further groups of patients. The available clinical trial data indicates the practical usefulness of SDMT in monitoring the efficacy of DMT in PMS [71]. However, a correlation of SDMT with the results of non-pharmacological interventions is still to be determined.

SDMT seems to be the most applicable cognition screening test in PMS patients, although some of its constraints should be taken into account. While interpreting the outcomes of SDMT assessment, the following issues should be considered: the impact of DMT, the practice effect, the type of SDMT (oral *vs.* written), SDMT's validation in individual countries, the patient's physical (e.g. speech disorders, visual impairment, oculomotor deficits, paresis or ataxia) and emotional (e.g. depression, anxiety or fatigue) condition during the examination, the conditions in which the test is performed, and the educational level of the participant (this has been proven to impact upon cognitive reserve and performance of SDMT) [80].

Limitations of scientific data included in the review should be also outlined. Firstly, the majority of the studies included relatively small groups of patients. Secondly, the number of studies regarding SDMT assessment in PMS patients is much smaller than in RRMS. Thirdly, a significant proportion of the studies did not differentiate the SDMT results in terms of PMS subtype. Furthermore, in some of the studies only the written form of SDMT was used, which could affect the performance of subjects with more advanced physical disabilities.

It should be noted that the character of our review, which is narrative in nature, imposes obvious limitations. We ask that it be considered an up-to-date guide to the topic, rather than definitive medical evidence.

In our opinion, future research projects should assess SDMT scores in separate SPMS and PPMS patient groups. More research on larger groups of patients is needed.

Finally, it is of great importance to underline that cognitive impairment has been identified by MS patients themselves as one of the foremost deficits, and therefore deserves special attention [66].

Article information

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