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Research Article

The Relation between Cognitive Functioning and Work Outcomes in Patients with Multiple Sclerosis: A Systematic Literature Review

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ABSTRACT

Background: Cognitive dysfunction is increasingly being recognized as an important limiting factor in work participation in patients with multiple sclerosis. This literature review provides a description, synthesis and interpretation of the existing literature and identifies gaps in current knowledge.

Methods: Papers published between 1970 and April 2017 were included. Clinical trials, randomized controlled trials or observational quantitative studies in which data on cognitive factors associated with employment, work functioning or work-related problems were reported. Papers were manually double checked by two blinded reviewers.

Results: A total of 41 papers were included of which 4 described prospective, longitudinal studies. The majority of studies reported positive associations between cognitive functioning and work outcomes (38/41 studies; 93%). Positive associations were found between work outcomes and global cognitive functioning (8/9 studies; 89%), language (8/17 studies; 47%), processing speed/ working memory (23/26 studies; 88%), new learning and memory (12/22 studies; 55%), executive functioning (10/17; 59%), intelligence (1/6; 17%) and self-reported cognitive functioning (14/15; 93%). None of the reviewed studies found a relation between visuospatial processing and work outcomes (0/8; 0%). Models including cognitive measures as well as demographic (age, education), neurological (disability, fine motor coordination, disease course), and psychological variables (depression, personality, fatigue) best predicted work outcomes.

Conclusion: By conducting this review we found ample evidence that objective cognitive functioning (specifically processing speed/ working memory and executive functioning) and self-reported cognitive functioning are important independent associates of work outcomes and these factors should be addressed by healthcare professionals. Future research could benefit from a focus on longitudinal changes in cognition and its relation to work outcomes.

Keywords: Multiple sclerosis, Cognitive dysfunction, Employment, Work functioning, Work participation

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating and neurodegenerative disease affecting the central nervous system [1]. Globally, the median estimated prevalence of MS is 30 per 100.000. MS is mostly diagnosed in relatively young adults -between 20 and 40 years old- who are in the beginning or the midst of their working careers. The disease can have a large impact on education and employment possibilities. MS is characterized by a wide variety of clinical manifestations and symptoms, which makes a person's future labour perspective difficult to predict.

Work participation is important. Besides income, work participation promotes a person's sense of self respect, social contacts and provides a feeling of usefulness and satisfaction. Job loss has been associated with worse self-reported health and increased adverse health behaviours after job loss [2]. A large number of patients with MS (55-58%) are unable to retain employment following diagnosis [3,4]. In those with a paid job, a reduction in hours or work responsibilities, more presenteeism (percentage of work impairment while working due to health problems) and absenteeism (percentage of work time missed due to health problems) is often observed [5,6]. This loss of productivity in MS leads to significant socio-economic costs [7].

Demographic variables like male gender [8-12], female gender [5,13], older age [8,10-16], race [11], lower educational level or less years of education [3,4,9,11,13,14,17-21], lower current financial status [11] and lower occupational prestige ratings [20] have been linked to worse work outcomes. Furthermore, MS features like a progressive disease course [3,14,16,20,22-26], increased symptom severity [18,19], higher disease duration [11,15-17,23,25-27], a higher age at onset [3,9], neurological symptoms like increased disability [5,8,10,13,14,16,17,20,22,25,28,29], fatigue [3,4,12-15,17,20,25,27,30,31], decreased self-reported physical functioning [31], mobility problems [4,12,30,32-34] and arm and hand difficulties [4,12,26,34] have been related to worse work outcomes. In addition, psychological factors like more depression [5,9,10,23,30,34-36], less mood disturbance [20], increased anxiety [10], maladaptive coping [16,37,38], ineffective management of symptoms of MS in the workplace [12] and certain personality traits [5,25,39] have been associated with worse work outcomes. Cognitive dysfunction is increasingly being recognized as an important associate of work participation in patients with MS [40].

Cognitive dysfunction is one of the most common and consequential symptoms of MS and affects an estimated 42-70% of patients with MS [41-43]. Cognitive impairment can emerge early in the disease [44] and can be present at all stages and in all subtypes of the disease [45]. In accordance with the fickle nature of the disease, a wide variety of cognitive deficits can be observed in MS [46]. The 'typical profile' consists of impairment in processing speed/ working memory, new learning and memory, and often executive skills with relative preservation of language functions [42]. These cognitive impairments can seriously disrupt a person's professional and social life and negatively influence quality of life [41,43]. Cognitive skills include paying attention, remembering what we see or hear, expressing ourselves and understanding what people say, being oriented to our surroundings so that we can travel from place to place, but also being able to switch between tasks, and solve problems. Cognitive functioning can 'objectively' be measured using cognitive tests. Besides the objective measure of cognition, self-reported

measures of cognition are frequently used, where people rate their own cognition. Self-reported measures are tended to be a quick, easy and cheap way to retrieve information about a person's functioning [47].

Given the fact that cognitive functioning is increasingly being recognized as an important associate of work participation in patients with MS, a systematic evaluation of the existing literature is needed to further improve our understanding. The current literature review therefore aims to provide a systematic description, synthesis and interpretation of the existing literature about the role of cognitive functioning in work participation in patients with MS. Gaps in the existing literature are identified.

Methods

Search strategy

A literature search was carried out for studies published in PubMed[®], Embase[®] or PsycINFO[®] in the period from 1970- April 2017. MeSh Subject Heading/MeSh terms, words occurring in the title and keywords were used; ('multiple sclerosis') AND ('Employment' OR 'Unemployment' OR 'Work' OR 'Vocational' OR 'Sick Leave' OR 'Job' OR 'occupational health' OR 'absenteeism' OR 'presenteeism' OR 'workplace' OR 'workability' OR 'productivity loss' OR 'job satisfaction' OR 'supported employment' OR 'underemployment') AND ('Cognition' OR 'Cognition disorders' OR 'Cognitive impairment' OR 'Cognitive dysfunction' OR 'Executive function' OR 'Memory' OR 'Memory Disorders' OR 'Attention' OR 'Processing speed and working memory' OR 'Language'). See **Appendix 1** for the specific search terms per database.

Inclusion

Papers were included if they were research articles, i.e. clinical trials, randomized clinical trials (RCT's) or observational quantitative, cross-sectional or longitudinal studies in which data on cognitive factors associated or predictive of work outcomes were reported as primary or secondary outcome measures. Furthermore, papers had to be written in English and the full text needed to be available. Letters to journal's editors, literature reviews, meta-analyses, qualitative papers, commentaries, editorials and case reports were excluded. After the removal of duplicates, abstracts were manually double checked by two blinded reviewers (DvG and KvdH). During checking of abstract a conservative approach was used; even if the information in the abstract was ambiguous, the paper was selected for reading the full article. Studies' reference lists were manually screened to identify additional relevant papers.

Paper selection

The literature search was conducted on April 3, 2017 by the first author and a total of 173 studies were found (Figure 1). After elimination of duplicates, 102 papers were screened. Dissertations, book sections, letters to editors, editorials and papers not in English were eliminated. No full text was available for two papers. Of the remaining 81 papers, abstracts and if applicable, full texts were manually double checked by two blinded reviewers (first and second author). Four additional papers were included after reference list search. A total of 44 articles were excluded. The majority of these studies were excluded because they were not reporting data on cognition and employment (e.g. not taking into account cognition

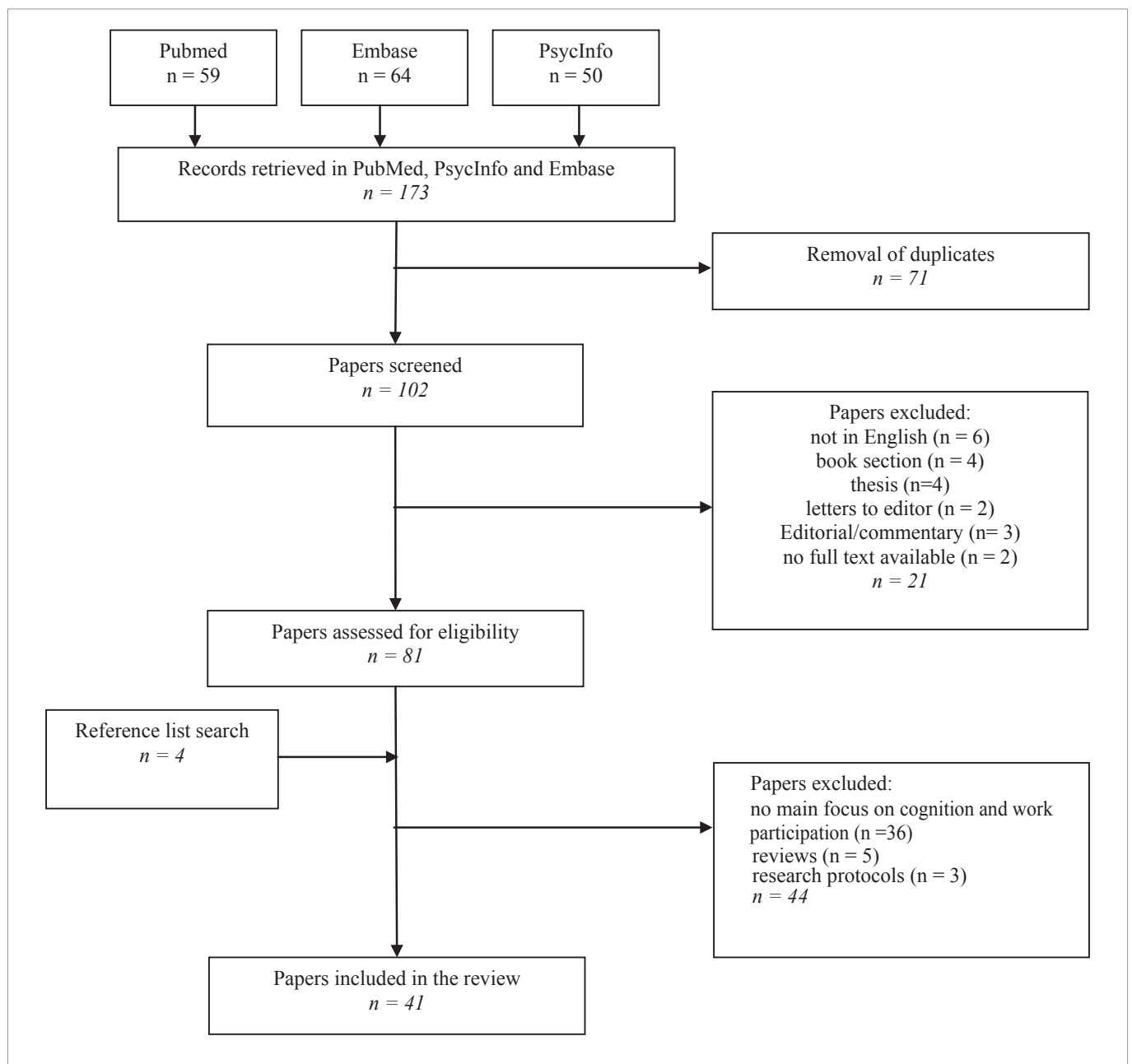


Figure 1: Flow chart of paper selection.

or employment as an outcome measure). Two of the excluded studies were validating assessment tools to assess work-related difficulties in MS [48,49], validated new cognitive tests [50] or compared cognitive tests [51,52]. Two other excluded articles were descriptions of study protocols [53,54]. Five reviews were excluded, the reviews focused on vocational rehabilitation approaches [55,56], work related problems in MS [57] and physical and cognitive function and work status [58]. Four qualitative studies focusing on the role and experiences of work [59,60], work barriers [61] and care needs of patients and family [62], were also excluded. In other studies the associations between cognition and work measures were not clearly reported, i.e. no measures of ability to work among MS patients [63] or mainly focusing on accommodations [64], disclosure at work [65], quality

of life [66,67] or negative work events [68] without a clear link to cognition.

Results

A total of 41 studies were included reporting data of 21.458 patients with MS. Table 1 provides an overview of the sample characteristics of the selected studies.

Measurement of cognitive functioning

Commonly used neuropsychological test batteries in the selected studies were the Minimal Assessment of Cognitive Functioning in MS (MACFIMS) [21,22,40,76,77,81], the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) [5,14,28,29,72,73,75,83] and

Table 1: Sample characteristics of the selected studies.

Reference	MS sample size	Age (mean)	RRMS (%)	MS duration	EDSS (mean/median#)	Employed (%)
Baughman, et al. [69]	44	44.5	-	-	1.3 (AI)	100%
Beatty, et al. [70]	102	44.2	-	9.8	3.4 (AI)	37%
Benedict, et al. [40]	291	45.4	69%	-	3.0	-
Benedict, et al. [71]	52	44.8	92%	8.8	-	100%
Caceres, et al. [72]	110	36.6	100%	<5 years	2.1#	86%
Cadden & Arnett [73]	53	51.7	57%	15.0	4.2	62%
Campbell, et al. [74]	62	49.4	71%	12.0	4.0#	44%
Carrieri, et al. [75]	32	40.0	69%	13.7	3.5	100%
Covey, et al. [76]	47	47.2	81%	14.0	2.5#	49%
Dusankova, et al. [77]	369	34.0	68%	8.0	3.0	50%
Flensner, et al. [13]	257	47.5	73%	-	0-6.5	60%
Fraser, et al. [78]	95	43.5	-	9.6	-	40%
Glad, et al. [9]	188	53.9	56%	22.2	4.7	32%
Glanz, et al. [79]	377	45.4	95%	12.4	1.5#	76%
Goverover, et al. [21]	72	48.5	75%	12.7	-	39%
Honan, et al. [80]	111	44.3/50.9 ^b	67%	8.5/12.6 ^b	-	56%
Honarmand, et al. [5]	106	44.7	62%	9.8	2.5#	39%
Incerti, et al. [81]	60	46.0/42.0 ^a	69/81% ^a	-	3.5/3.3 ^a	52%
Julian, et al. [4]	8867	47.6	-	18.1 ^h	3 [#] (PDDS)	44%
Kordovski, et al. [34]	138	44.7	86%	9.1	-	100%
Krause, et al. [14]	87	45.9/35.0 ^c	66%	10.6/4.5 ^c	4.6/2.3 ^c	55%
Li, et al. [82]	4201	52.0	-	-	-	40%
Moore, et al. [17]	221	46.0	56%	12.3	4.6	57%
Morrow et al [22]	97	43.6	93%	9.2	-	100%
Morse, et al. [15]	30	50.7/44.4 ^d	87%	12.8/10.4 ^d	-	100%
Niino, et al. [28]	184	39.3	91%	-	2.4	49%
Papathanasiou et al [24]	50	41.8	100%	8.8	3.1	70%
Parmenter, et al. [23]	111	44.8	74%	-	2.9	-
Rao, et al. [83]	100	45.5/46.3 ^e	38%	9.0/10.2 ^e	3.9/4.4 ^e	-
Roessler, et al. [18]	139	43.2	49%	-	-	53%
Roessler, et al. [19]	1310	50.0	-	-	-	43%
Roessler, et al. [11]	1839	54.0	-	-	-	41%
Ruet, et al. [29]	65	39.0	83%	31.2 months	2.0#	82%
Sayao, et al. [84]	61	54.9 ^f	98%	27.2 ^f	3.0 ^{#,f}	34.5% ^f
Simmons, et al. [12]	1135	-	-	-	-	40%
Smith & Arnett [20]	50	49.9	56%	10.3	3.5/4.3/5.7 ^g	58%
Strober, et al. [25]	101	47.9/45.1 ^a	62%	12.3/8.8 ^a	4.6/3.2 ^a	53%
Strober, et al. [26]	77	46.5/43.4 ^a	68%	12.4/8.7 ^a	-	52%
Strober & Arnett [16]	68	51.7/46.1 ^a	75%	12.7/8.7 ^a	5.5/4.1 ^a	60%
Van der Hiele, et al. [31]	44	35.6/38.8 ^b	100%	2.0	-	57%
Van der Hiele, et al. [27]	55	44.8/48.5 ^b	100%	9.2/14.0 ^b	3.4/3.7 ^b	36%

Note: EDSS: Expanded Disability Status Scale; PDDS: Patient Determined Disease Steps; AI: Ambulation Index; L: Longitudinal study; a: unemployed versus employed; b: paid employment versus not in paid employment; c: early retired versus employed; d: cut-back versus stable employment; e: cognitively intact versus cognitively impaired; f: at 25-30 years follow-up; g: working versus cut-back versus not-working; h: duration of MS symptoms

the Brief International Cognitive Assessment for multiple sclerosis (BICAMS) [74,77]. These test batteries overlap in the used tests and mainly assess cognitive domains like new learning and memory and processing speed/working memory. Other studies used individual tests or computerized versions of cognitive tests to objectively measure cognitive functioning.

Different measures of self-reported cognitive functioning were used across studies, ranging from a single question about the occurrence of cognitive symptoms (yes/no answer, 4, 5 or 6 point Likert scale) [4,11,17-19], to reasons to stop working [12,20], to validated questionnaires. Questionnaires often used were the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) [34,71,74,77], the Perceived Difficulties Questionnaire (PDQ-20 and the abbreviated form PDQ-5) [13,82], the MSWDQ [80] and the SCL-90-insufficiency in thinking [31]. The BADS-DEX questionnaire [27,31] and the Executive Functioning Index (EFI) [75] were used to examine executive functioning problems. The Disease Impact Profile (DIP) provided self-ratings of memory and attention [31]. Two studies used self-reported cognitive measures as a way to describe their sample, and also reported a relation with vocational outcomes [74,77]. A detailed overview of the cognitive measures used in the selected papers can be found in **Appendix 2**.

Work outcomes

In the included studies different work outcomes were reported. Vocational or employment status was the most common outcome measure. This measure is mostly seen as a dichotomous variable, i.e. being either employed or unemployed. A description of whether a participant is regarded employed or unemployed, or is unemployed due to MS was not always provided [5,18,19,23,24,70,74,83]. Other studies did specify their unemployed group as 'unemployed due to MS' [14,17,73,82]. There is great variability between studies on when a person is regarded part of the employed or unemployed group. For example, some studies in this review included volunteer workers, students, homemakers [27,31] and retired persons [29] to their unemployed group while others included volunteer workers, homemakers and students in the employed group [25,26]. Again other studies excluded these patient groups from analyses [11,72,76,77] or assigned them to a separate analysis group [28]. Among the studies that described their vocational status groups some differentiated between full-time employed, part-time employed or unemployed [9,28,77], but mostly full-time and part-time workers together were regarded as employed [13,21,27,31,84]. Benedict et al. [40] described a conservative and liberal way to classify the employed and unemployed groups in a detailed manner. In the conservative approach working patients were gainfully employed, with pay, full time, without demotion, reported reprimands or loss of pay due to MS related problems. Unemployed patients were required to be receiving formal disability benefits from either public or private source. In the liberal approach working patients were required to be gainfully employed with pay at least 20 hours per week, disabled patients were required to be receiving either formal disability as described above or to be unemployed for reasons reported by them or informants to be disease related.

Instead of looking at the dichotomous employment status, more subtle measures of work functioning have been used in seven studies. Studies have looked into the reduction in working hours or work role (since diagnosis) [15,17,20,80], work productivity including

presenteeism (percentage of work impairment while working due to health problems) and absenteeism (percentage of work time missed due to health problems) [79], on-the-job-barriers [75] and negative work events and accommodations [34,71]. Using these measurements more subtle changes in the workplace can possibly be noticed. Most of the described methods for vocational status are based on self-report. Only one study also used supervisor-reported work performance [69]. In the longitudinal studies work measures are described as changes in employment status or transitions in the work force over a certain time period [4,12,22,29].

Associations between cognitive functioning and work outcomes

The main study outcomes are summarized in Forty-one studies examined whether either objective or self-reported cognitive functioning were associated with work outcomes, and positive univariate or multivariate associations were found in 38 studies (93%), in that better cognitive functioning was related to better work outcomes. In the paragraphs below, outcomes are reported separately for studies including measures of global cognition (3.1.1), language (3.1.2), processing speed/ working memory (3.1.3), new learning and memory (3.1.4), visuospatial processing (3.1.5), executive functioning (3.1.6), intelligence (3.1.7) and self-reported cognitive functioning (3.1.8). The method by which cognitive tests were assigned to these domains can be found in **Appendix 3**. Cognitive tests were categorized based on the categorization of cognitive domains used for the MACFIMS battery [40].

Global cognition: Measures of global cognitive functioning were mostly based on the number of cognitive tests impaired or consisted of composite test scores. In eight of the total of nine studies (89%) that included a measure of global cognition, a relation was found with work outcomes. In four of these studies, positive associations were found between measures of global cognition and work outcomes, in that lower global cognitive functioning or cognitive impairment was linked to unemployment [70,74,83], and with worse work performance rated by supervisors of patients with MS [69]. In four studies worse global cognitive functioning or deterioration was seen as an independent predictor of work outcomes (i.e. unemployment [73,77], worse vocational status after 7 years and a deterioration in vocational status in 7 years [29], or experiencing more work barriers [75]) based on regression analyses. One study did not find an association between global cognition in terms of the percentage of patients with MS classified as cognitively impaired and employment status [5]. The latter study did however find associations between employment status and subtests of language and processing speed/ working memory.

Language: Verbal ability or language was most often measured with the Controlled Oral Word Associations Test (COWAT) or Word List Generation (WLG). In eight of the total of 17 studies (47%) that included a language measure, a relation was found with employment outcomes. In five of these studies, positive associations were found between language and work outcomes, in that worse scores on language tasks were seen in unemployed patients with MS compared to employed patients with MS [5,24,28,40,77]. Three studies reported language measures to be (one of the) predictors of work outcomes based on regression analyses, in that worse scores on language tasks were predictive for unemployment [70,72] and less

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Table 2: Main results of the studies examining associations between cognitive functioning and work outcomes in patients with Multiple Sclerosis (pwMS).

Reference	Cognitive domain	Main results regarding cognition and employment
Baughman, et al. [69]	Global cognition (based on tests of new learning and memory, processing speed/ working memory, and executive functioning)	-Work performance of cognitively impaired individuals was rated more poorly by supervisors, even in the absence of physical disability. In contrast, work performance was rated higher by cognitively impaired than cognitively unimpaired participants.
Beatty, et al. [70]	Global cognition Language Processing speed/ working memory New learning and memory Visuospatial processing Executive functioning Intelligence (Abstraction)	-Employed pwMS performed significantly better on nearly all neuropsychological variables examined (except for visuospatial processing) and showed impairment in less cognitive domains than unemployed pwMS. -Multiple regression analysis indicated that decreased walking ability, higher age, and worse performance on tests of memory (SRT and STM) and language (letter fluency) were predictive of unemployment.
Benedict, et al. [40]	Language Processing speed/ working memory New learning and memory Visuospatial processing Executive functioning	-Employed pwMS (using a liberal definition) performed better on most neuropsychological tests than disabled pwMS, except for the visuospatial processing test. -Logistic regression analysis revealed that a progressive disease course (SPMS vs RRMS) and worse performance on tests of verbal memory (CVLT-II) and processing speed/ working memory (PASAT) were most predictive of a decreased vocational status (using a conservative definition). - Logistic regression analysis revealed that depression (depressed vs not depressed), progressive disease course (SPMS vs RRMS) and worse performance on tests of verbal memory (CVLT-II) and executive functioning (DKEFS-Sorting) were most predictive of decreased vocational status (using a liberal definition).
Benedict, et al. [71]	New learning and memory Processing speed/ working memory Self-reported cognitive and neuropsychiatric functioning	-PwMS reporting negative work events performed worse on measures of ambulation and processing speed/ working memory (PASAT) and showed higher depression scores and more self-reported cognitive and neuropsychiatric problems (MSNQ). PwMS reporting accommodations performed worse on measures of ambulation and processing speed/ working memory (PASAT). -A logistic regression revealed that worse ambulation, worse processing speed/ working memory (PASAT) and higher depression scores were found predictive of work challenged status (presence of self-reported negative work events and accommodations).
Caceres, et al. [72]	Language Processing speed/ working memory New learning and memory	-Logistic regression analysis showed that better performance on measures of language (WLG) and processing speed/ working memory (PASAT) were significant predictors of preserved employment status.
Cadden & Arnett [73]	Global cognition (based on measures of language, processing speed/ working memory, new learning and memory and executive functioning)	-In (separate) logistic regression analyses decreased composite scores for motor function and cognition and increased fatigue were significantly associated with unemployment. -In a logistic regression analysis using only cognitive sub composites, decreased processing speed remained significantly associated (SDMT and Digit Symbol-Coding) with unemployment, even after controlling for performance on tests of memory and executive function.
Campbell, et al. [74]	Global cognition (number of tests impaired) New learning and memory Processing speed/ working memory	-Greater rates of unemployment were associated with an increased number of tests failed. -The unemployed group scored worse on tests of new learning and memory (CVLT-II and BVM-T-R) and processing speed/ working memory speed (SDMT) than the employed group.
Carrieri, et al. [75]	Global cognition (based on new learning and memory and processing speed/ working memory) Executive functioning Self-reported executive functioning	-Regression analyses showed that worse objective cognitive performance (a combination of the SDMT, SRT and SPART) predicted barriers ascribed to company policy, that a worse planning score predicted barriers ascribed to accessibility, and that worse self-reported executive functioning predicted increased difficulties in cognitive and task related abilities.
Covey, et al. [76]	Executive functioning (also including tests of processing speed/ working memory) Non-executive functioning (including tests of language, new learning and memory and visuospatial processing)	-Logistic regression analysis revealed that better scores on a composite measure of processing speed/ working memory and executive functioning (PASAT, SDMT, DKEFS-Sorting) was predictive of better vocational outcomes in pwMS (a group of patients with Systemic Lupus Erythematosus was also included, but disease status did not modify the observed relationship).

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Dusankova, et al. [77]	Global cognition Language Processing speed/ working memory New learning and memory Visuospatial processing Executive functioning	-Significant negative associations were found between preserved employment status and all neuropsychological tests except for visuospatial processing (JLO). -In a logistic regression model adjusted for age, sex, education, EDSS, depression and anxiety, better verbal memory performance (CVLT-II) was independently associated with preserved employment.
Flensner, et al. [13]	Self-reported problems with memory, attention and concentration	-PwMS with no capacity to work reported more cognitive problems than pwMS with capacity to work. -In a multiple logistic regression for capacity to work (including self-reported cognitive problems), low physical disability (EDSS), low fatigue, higher level of education, male sex and lower age were significant predictors of higher work capacity.
Fraser, et al. [78]	Language New learning and memory Processing speed/ working memory Executive functioning Intelligence	-Univariate logistic regression analyses revealed that better performance on measures of language (COWAT) and processing speed/ working memory (SDMT) were associated with vocational stability. -Multivariate logistic regression analysis revealed better language performance (COWAT) as a significant predictor of vocational stability over the past 6-24 months.
Glad, et al. [9]	Processing speed/ working memory	-No relations were found between employment status and processing speed/ working memory (PASAT).
Glanz, et al. [79]	Processing speed/ working memory	-Significant negative associations were found between processing speed/working memory (SDMT) and absenteeism and overall work impairment, but not with presenteeism. -Multivariate regression analyses revealed that absenteeism was not significantly associated with processing speed/working memory (SDMT), disability level, disease duration, depression, fatigue and anxiety. -Multivariate regression analyses revealed that presenteeism was significantly associated with increased fatigue, disability level and depression, but not with processing speed/ working memory (SDMT). -Multivariate regression analyses revealed that overall work impairment was significantly associated with increased fatigue and disability level, but not with processing speed/ working memory (SDMT).
Goverover, et al. [21]	Language Processing speed/ working memory New learning and memory Visuospatial processing Executive functioning	-Using point biserial correlations, it was found that more years of education, less fatigue and better performance on measures of visual memory (BVMT-R) and processing speed (SDMT) were associated with being employed.
Honan, et al. [80]	New learning and memory Attention Processing speed/ working memory Executive functioning Self-reported work difficulties (general cognitive and prospective memory difficulties) Intelligence (Abstraction)	-PwMS in paid employment scored higher on all the cognitive tests relative to those who were unemployed, with the exception of the SILS Abstraction scale. -Perceived general cognitive and prospective memory difficulties in the workplace and performance on the respective cognitive tests (SDMT, 10 Word list and Cambridge Prospective Memory Test) were found to predict unemployment and reduced work hours due to MS since MS diagnosis.
Honarmand, et al. [5]	Global cognition Language Processing speed/ working memory New learning and memory	-Unemployed pwMS scored significantly lower on tests of processing speed/ working memory (SDMT, PASAT) and language (WLG) than employed pwMS. -In a logistic regression model, the personality trait 'agreeableness', less depression, and better scores on the MSFC (9-Hole Pegboard, 25 Foot Timed Walk Test and PASAT, a measure of processing speed/ working memory) were associated with being employed.
Incerti, et al. [81]	Language Processing speed/ working memory New learning and memory Visuospatial processing Executive functioning	-Processing speed/ working memory performance (SDMT) was better in employed than unemployed pwMS.
Julian, et al. [4]	Self-reported cognitive functioning	-Among other factors (i.e. lower educational level, reported worsening of symptoms over 6 months and problems with mobility, hand function and fatigue), perceived cognitive impairment predicted work loss 1.5 years later, while re-entry was associated with fewer perceived cognitive problems.

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Kordovski, et al. [34]	New learning and memory Processing speed/ working memory Self-reported cognitive and neuropsychiatric functioning	-Work-challenged pwMS (those who reported 1 or more negative work events) had more pronounced deficits in motor ability and lower scores on tests of visual memory and processing speed/ working memory (BVMT-R and PASAT) and had more self-reported cognitive and neuropsychiatric problems (MSNQ) and depression than their relatively stable counterparts (reporting 0 or 1 negative work events).
Krause, et al. 14]	Language New learning and memory Processing speed/ working memory	-Early retired compared with employed pwMS scored significantly higher in neurological disability, depressive symptoms and fatigue and significantly lower in processing speed/ working memory (SDMT and PASAT) and health related quality of life. -In a logistic regression analysis, higher neurological disability, higher age and more fatigue were identified as significant predictors of early retirement in MS.
Li, et al. [82]	Self-reported cognitive functioning	-A logistic regression analysis showed that, together with self-reported psychological (higher depressive symptoms) and physical components (fatigue, mobility problems, diminished physical strength and stamina), decreased self-reported cognitive functioning contributed to the prediction of unemployment.
Moore, et al. [17]	Self-reported problems with memory	-Patients who changed their employment role or working hours since diagnosis were older and reported more fatigue, pain and memory problems than patients who were still employed but without any changes. -In multinomial regression analyses, increased disability level, less years of education, longer disease duration and higher levels of fatigue were most predictive of decreases in employment status (change/ no change or left employment).
Morrow, et al. [22]	Language Processing speed/ working memory New learning and memory Visuospatial processing Executive functioning	-Using logistic regression analyses, both baseline and a decline in processing speed/ working memory (SDMT) and verbal memory (CVLT-II) performance predicted a deterioration in vocational status 3 years later.
Morse, et al. [15]	Executive functioning Other measures (language, processing speed/working memory and intelligence) not included in regression.	-Individuals in the cutback employment group demonstrated significantly worse overall performance on multitasking ability than the stable employment group. -Logistic regression revealed that increased fatigue and lower performance on a test of executive functioning (i.e. SET, a test for multitasking ability) were significant predictors of cutback employment status.
Niino, et al. [28]	Language Processing speed/ working memory New learning and memory	-Patients categorized as 'unemployed because of MS' had lower scores than other social activity groups (students, employed and homemakers) in all cognitive domains, except for spatial memory-immediate recall (SPART). -Logistic regression analysis indicated that lower processing speed/ working memory (SDMT) and increased physical disability (EDSS) were predictive of unemployment.
Papathanasiou, et al. [24]	Language Processing speed/ working memory New learning and memory Executive functioning	-Unemployed patients with RRMS scores significantly lower than employed patients on all neuropsychological measures, except for a test of complex attention. -Logistic regression analysis revealed that better memory performance (verbal and visual memory) and executive functioning (TMT B) were the best predictors of being employed.
Parmenter, et al. [23]	Executive functioning	-Logistic regression showed that better performance on tests of executive functioning (i.e. conceptual reasoning; DKEFS description score and WCST categories) was most predictive of being employed.
Rao, et al. [83]	Global cognition (based on tests of language, processing speed/ working memory and new learning and memory)	-Cognitively impaired patients were less likely to be working and reported a greater impact on their work-related activities than the cognitively intact patients.
Roessler, et al. [18]	Self-reported cognitive problems	-A logistic regression analysis showed that increased severity and persistence of symptoms, lower educational attainment, and the presence of cognitive problems (self-reported) impairment were associated with unemployment.
Roessler, et al. [19]	Self-reported cognitive impairment	-A logistic regression analysis showed that lower educational attainment, increased severity and persistence of symptoms, and the presence of self-reported cognitive impairment were associated with unemployment.
Roessler, et al. [11]	Self-reported cognitive impairment	-A logistic regression analysis revealed that unemployment (versus part-time employment) was significantly associated with increased age, male gender, lower educational attainment, lower current financial status, and more disability. -A logistic regression analysis revealed that unemployment (versus full-time employment) was significantly associated with increased age, race, lower educational attainment, lower current financial status, increased duration of illness, moderate or severe cognitive symptoms, and more disability.

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Ruet, et al. [29]	Processing speed/ working memory New learning and memory Global cognition (based on the measures above) Language	-Logistic regression analysis revealed that worse vocational status at follow up (7 years later) was significantly associated with lower baseline processing speed/ working memory (SDMT and PASAT), higher EDSS scores and higher age. Vocational status deterioration over 7 years was significantly associated with worse baseline processing speed/ working memory (SDMT and PASAT). -Logistic regression analysis revealed that vocational status at follow up, and its deterioration over 7 years was significantly associated with global cognitive deterioration.
Sayao, et al. [84]	Language New learning and memory Processing speed/ working memory	-There were no differences between those employed (full or part time) compared with those not employed on any of the cognitive tests
Simmons, et al. [12]	Self-reported reasons for employment loss	-The most frequently listed symptoms relating to employment loss 4 years later, and perceived risk of losing current employment, were fatigue, mobility-related symptoms, arm and hand difficulties, and cognitive deficits.
Smith & Arnett [20]	Language Processing speed/ working memory New learning and memory Executive functioning Intelligence Self-reported cognitive problems as reason for work status change	-The not working group had significantly greater physical disability than the cut-back and working groups and significantly more fatigue than the working group. The cut-back group had significantly more years of education and higher occupational prestige ratings than the not working group. The working group reported significantly greater mood disturbance compared with the not working group. -Employment status was unrelated to age, gender, full scale IQ estimate, disease duration, diagnosis duration or cognitive functioning. -Ninety per cent of the cut-back group reported that fatigue was a primary symptom responsible for their work status change, whereas 86% of the not working group reported that broad physical/neurological symptoms were responsible for their change in work status. Only 10% of the cut-back group and 29% of the not working group reported that cognitive symptoms were responsible for their work status changes.
Strober, et al. [25]	Language Processing speed/ working memory New learning and memory Visuospatial processing Executive functioning	-Unemployed pwMS had a longer disease duration, a higher proportion with a progressive disease course, more neurological impairment, more fatigue, lower performance on tests of processing speed/ working memory (SDMT) and learning and memory (SRT) and a lower level of the personality characteristic 'persistence' than employed pwMS. -Based on a forward logistic regression analysis, increased physical disability (EDSS), decreased processing speed/ working memory (SDMT) and a lower level of persistence were the strongest predictors of unemployment.
Strober, et al. [26]	Language Processing speed/ working memory New learning and memory Visuospatial processing Executive functioning Premorbid intelligence	-Unemployed individuals performed worse on measures of memory, processing speed/ working memory speed, and executive functioning than employed pwMS. -In a logistic regression analysis, lower processing speed/ working memory speed (SDMT) was found to be the sole predictor of unemployment in a model including disease-related variables, MSFC and cognitive variables.
Strober & Arnett [16]	Processing speed/ working memory	-Those who left the workforce were older, had longer disease duration, were more likely to have a progressive course, reported greater disability, were more likely to endorse utilization of maladaptive coping behaviours and performed worse on a processing speed/ working memory test (SDMT).
Van der Hiele, et al. [31]	Self-reported cognitive functioning (general cognitive functioning, new learning and memory, concentration and executive functioning)	-Employed pwMS reported better physical functioning, better memory functioning and a lower physical impact of fatigue than unemployed patients. -In employed pwMS better self-reported memory functioning and less social fatigue were associated with more working hours. -In a logistic regression model better physical functioning was retained as the sole predictor of employment.
Van der Hiele, et al. [27]	Executive functioning Visuospatial processing Self-reported executive functioning Premorbid intelligence	-Unemployed pwMS had a longer disease duration, reported more organizing and planning problems, higher distractibility, more cognitive fatigue and completed slightly less categories on the WCST than employed pwMS.
<p>Note: pwMS: patients with MS; EDSS: Expanded Disability Status Scale; MSFC: Multiple Sclerosis Functional Composite; SRT: Selective Reminding Test; STM: Brown Peterson Short Term Memory Test; CVLT-II: California Verbal Learning Test-II; MSNQ: Multiple Sclerosis Neuropsychological Screening Questionnaire; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; SPART: 10/36 Spatial Recall Test; COWAT: Controlled Oral Word Association Test; BVMT-R: Brief Visuospatial Memory Test- Revised; JLO: Judgment of Line Orientation Test; DKEFS-Sorting: Delis-Kaplan Executive Function System Sorting Test; WLG: Word List Generation; SET: Modified Six Elements Test; WCST: Wisconsin Card Sorting Test; TMT: Trail Making Test; L: prospective longitudinal study</p>		

vocational stability in a period of 6-26 months [78]. Nine studies did not find an association between language and employment [14,20-22,25,26,29,81,84]. A critical analysis of differences between studies that did and did not find associations between language measures and work outcomes revealed that two non-significant studies used composite scores of language [14,29], while studies that did report an associations used individual language tests in their analyses. Some of the non-significant studies had a relatively small sample size (using multivariate testing) [20,84], focused on benign MS [84], or excluded severely cognitive impaired patients [81].

Processing speed and working memory: Processing speed and working memory were most often measured with the Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT). Of the total of 26 studies that included a measure of processing speed and working memory, 23 studies (88%) found such a measure to be related to employment outcomes. In 12 studies processing speed and working memory measures were positively associated with work outcomes, in that worse scores on processing speed and working memory tasks were observed in unemployed or work challenged (experiencing 1 or more negative work events) patients with MS compared to employed or non-work challenged patients with MS [5,14,16,21,24,34,70,74,77,81]. In two studies, worse scores on processing speed and working memory were linked to worse vocational stability and more absenteeism [78,79]. In another 11 studies, measures of processing speed and working memory speed were found to be (one of the) predictors of work outcomes based on regression analyses, in that worse scores on processing speed and work memory tasks were predictive for unemployment [25,26,28,40,72,73,76,80], deterioration in vocational status after 3 and 7 years [22,29], being work challenged (experiencing 1 or more negative work events) [71] and reduced work hours due to MS [80]. Three studies did not find an association between work outcomes and measures of processing speed and working memory [9,20,84]. A critical analysis of differences between studies that did and did not find associations between processing speed and working memory and work outcomes revealed that two of the non-significant studies mainly focused on benign MS [9,84]. Another study was characterized by a relatively small sample size [20].

New learning and memory: The studies in this review mostly focused on verbal and visual memory as measured with the Selective Reminding Test (SRT), California Verbal Learning Task-II (CVLT-II), Brief Visuospatial Memory Test-Revised (BVRT-R) or 10/36 Spatial Recall Test (SPART). Of the total of 22 studies that including a measure of new learning and memory, 12 studies (55%) found positive associations between visual and/or verbal memory performance and work outcomes. In six of the 12 studies new learning and memory measures were positively associated with work outcomes, in that worse scores on new learning and memory tasks were observed in unemployed or work challenged (experiencing 1 or more negative work events) patients with MS compared to employed or non-work challenged patients with MS [21,25,26,28,34,74]. In six studies, measures of new learning and memory, verbal memory in particular, were found to be (one of the) predictors of work outcomes based on regression analyses, in that worse scores on new learning and memory tasks were predictive for unemployment [24,40,70,77,80], a deterioration in vocational status after 3 years [22], and reduced work hours due to MS [80]. Ten studies did not find an association between

new learning and memory and work outcomes [5,14,20,29,71-73,78,81,84]. A critical analysis of differences between studies that did and did not find associations between new learning and memory and work outcomes revealed that three of the non-significant studies used composite scores to indicate the presence or absence of new learning and memory impairment [14,29,73], which was not the case in studies where an association was found. In one of the non-significant studies, the composite score of memory functioning was only included in a multivariate analysis [73], in which the composite score of processing speed explained most variance. Two of the non-significant studies used more subtle work outcomes (e.g. negative work events) [71,78], while most significant studies used employment status as an outcome measure. Some of the non-significant studies were characterized by a relatively small sample size [20,84], focused on benign MS [72,84] or excluded severely cognitive impaired patients [81].

Visuospatial processing: Visuospatial perception or processing was mostly measured with the Judgment of Line Orientation test (JLO). The measure was taken into account in eight studies [21,22,25,26,40,70,77,81]. In none of the studies a relationship was found between visuospatial processing and work outcomes.

Executive functioning: Executive functioning was mostly measured with the Delis-Kaplan Executive Function System (DKEFS) Card Sorting Test, Wisconsin Card Sorting Test (WCST) and Trail Making Test (TMT). A total of 16 studies included measures of executive functioning. In 10 of these 17 studies (59%) a relation was found between executive functioning and employment outcomes. Four studies found positive associations between executive functioning and work outcomes, in that worse scores on executive functioning tasks were observed in unemployed patients with MS compared to employed patients with MS [26,27,70,77]. Six studies found executive functioning to be (one of the) predictors of work outcomes based on regression analyses, in that worse scores on executive functioning tasks were predictive for unemployment [23,24,40,76], having cutback working hours due to MS [15] and experiencing more barriers at work [75]. Another seven studies did not find an association between executive functioning and work outcomes [20-22,25,73,78,81]. A critical analysis of differences between studies that did and did not find associations between executive functioning and work outcomes revealed that one of the non-significant studies was characterized by a relatively small sample size [20] or excluded severely cognitive impaired patients [81]. Several non-significant studies used only one test of executive functioning (D-KEFS-Sorting) [21,22,25,81], while many significant studies used a test battery with a more pronounced focus on executive functioning [15,23,27,75,76]. In one of the non-significant studies, the composite score of executive functioning was only included in a multivariate analysis [73], in which the composite score of processing speed explained most variance.

Intelligence: Different measures were used to determine whether (pre-morbid) intelligence was associated with work outcomes, using either (subtests of) the Wechsler Adult Intelligence Scale, (subtests of) the Shipley Institute of Living Scale, the National Adult Reading Test or Wide Range Achievement Test. A total of six studies reported a measure of (pre-morbid) intelligence in relation to work outcomes [20,26,27,70,78,80]. Only one study (17%) found a positive association between a subtest on an intelligence test (verbal abstracting) and work outcomes [70]. In that study, lower verbal abstracting scores were observed in unemployed patients with MS compared to the employed patients with MS.

Self-reported cognitive functioning: Measures of self-reported cognitive functioning ranged from single yes/no questions to validated questionnaires such as the MSNQ. Fifteen studies used measures of self-reported cognitive functioning [4,11-13,17-20,27,31,34,71,75,80,82]. All but one [20] of these 15 studies (93%) described a relation between self-reported cognitive functioning and employment outcomes. Seven studies reported negative associations between the presence or extent of self-reported cognitive problems (including general cognitive impairment, new learning and memory problems, difficulties with organizing and planning, and thinking problems) and work outcomes, in that unemployed and work challenged (experiencing 1 or more negative work events) patients with MS reported more self-reported cognitive problems compared to employed and non-work challenged patients with MS [31,34,71]. In other studies more self-reported cognitive problems were linked to reduced capacity to work [13], reduced work hours [27], or decreased employment (role or work hours) since diagnosis [17]. In one study, self-reported cognitive problems were reported as a reason of employment loss or risk of losing current employment [12].

In another seven studies [4,11,18,19,75,80,82], self-reported cognitive functioning was found to be (one of the) predictors of work outcomes based on regression analyses, in that more self-reported cognitive problems or the presence of self-reported problems were predictive for unemployment [11,18,19,80,82] and reduced work hours [80], and experiencing more barriers at work [75]. More self-reported cognitive problems were predictive of work loss after 1.5 years, while workforce re-entry was predicted by experiencing less cognitive problems [4]. The one non-significant study was characterized by a relatively small sample size [20].

Discussion

This review was performed to systematically evaluate the existing literature about the association between cognitive functioning and work outcomes in patients with MS, and to identify knowledge gaps. Our literature search revealed 41 studies on this topic. The majority of these studies suggest that better objective cognitive functioning (in 91% of the studies, 29/32) and self-reported cognitive functioning (in 93% of the studies, 14/15) are associated with better work outcomes. The only two prospective, longitudinal studies that used a cognitive test battery found that changes in employment status after 3 and 7 years were predicted by both baseline cognitive performance and cognitive deterioration during those years [22, 29]. These data underline the importance of understanding and treating cognitive dysfunctioning and/or adjusting of work content/conditions in patients with MS when striving towards optimal work participation.

Objective cognitive functioning

The included studies used a wide diversity of cognitive measures. The majority of studies reported positive associations between work outcomes and global cognitive functioning (8/9 studies; 89%), processing speed and working memory (23/26 studies; 88%), executive functioning (10/17; 59%) and new learning and memory (12/22 studies; 55%). Less often, positive associations were reported between work outcomes and measures of language (8/17 studies; 47%) and pre-morbid intelligence (1/6; 17%). No associations were found between visuospatial processing (0/8; 0%) and work outcomes.

In summary, measures of processing speed and working memory, executive functioning and new learning and memory were mostly

found to be predictive or related to employment status and other work outcomes. Deficits in these domains are in accordance with the 'typical cognitive profile' seen in MS patients [42]. Not surprisingly, information processing and working memory performance as measured with the SDMT and/or PASAT was most often retained as a predictor of work outcomes, and even as a predictor of future employment status [22,29].

In total, only three studies did not find any association between work outcomes and measures of cognitive functioning (e.g. self-reported or objective cognitive functioning). Two of these studies mainly included patients with benign MS, Clinically Isolated Syndrome or Relapsing-Remitting MS, in which the degree of cognitive impairment was not enough to impact work outcomes [9,84]. The other study only used multivariate testing and compared three groups (e.g. working, cut back hours and not working) in which the sample size of one of the groups was relatively small (n=10), possibly resulting in a lack of power to detect cognitive differences [20]. A critical analysis of differences between studies that did and did not find associations between work outcomes and cognitive measures provided us with interesting insights about the context in which cognitive measures are less sensitive associates of work outcomes, for example in case of a cognitively 'healthy' sample, in case of a lack of sensitive measures of cognitive functioning, when lumping together different cognitive measures in a composite score, when other (cognitive) measures explain more variance or in (some) cases where more subtle work outcomes are used.

Deficits in processing speed and working memory are considered most prevalent in MS and a key deficit underlying other cognitive dysfunction in MS [85,86]. However, other 'cognitive profiles' not necessarily including processing speed have also been reported. A recent study reported evidence for seven cognitive profiles in MS, i.e. attention and basic executive function (including processing speed), planning and high-level executive function, verbal memory and language, executive and visuospatial performance time, fatigue-depression, visuospatial function, and basic attention and verbal/visual working memory [87]. Processing speed and working memory performance may be the most commonly found predictor of work outcomes, but executive functioning, new learning and memory, and language are also important predictors, possibly depending on the profile of cognitive impairment in the studied sample. When solely taking into account studies examining multiple cognitive predictors of work outcomes, many report models of work outcomes that combine measures of processing speed and working memory with measures of new learning and memory [40,80], executive functioning [40], or language [72]. Others report models combining measures of learning and memory with measures of language [70], measures of executive functioning [24] and measures of objective and self-reported cognitive functioning [27,80].

In future studies on the relationship between cognitive performance and work participation it seems important to keep focusing on multiple cognitive domains.

Self-reported cognitive functioning

Self-reported cognitive functioning was positively associated with work outcomes in almost all of the studies (93%) including such as measure. Measures of self-reported cognitive functioning ranged from single yes/no questions to validated questionnaires. Self-report

measures may be sensitive to subtle changes in cognition that are not yet visible using objective cognitive measurements. On the other hand, self-reports of cognitive performance are prone to under- and over estimation, and related to factors like depression, anxiety, coping and psychological stress [88-91]. Interestingly, one of the reviewed studies found that depression could not explain the relationship between self-reported cognitive difficulties and work outcomes, but that depression did influence perceptions of cognitive difficulties [80].

One of the reviewed studies found that performance on motor and cognitive tests as well as self-reported depression and neuropsychological functioning predicted the presence of negative work events [71]. The authors suggested that the importance of self-reported depression and neuropsychological functioning may be greater when the more subtle aspects of work functioning are measured. In conclusion, self-reports of cognitive functioning may not be directly related to objective cognitive functioning, but they are clinically relevant with respect to subtle aspects of work functioning, and may impact important life decisions related to work participation.

Further research should more thoroughly investigate the separate roles of self-reported and objective cognitive functioning in relation to work outcomes including mediating psychological variables, such as depression, personality and coping.

Work participation as a multifactorial problem

While the current review focuses specifically on cognitive functioning as a factor in work participation, it is well-known that decreased work participation in MS is a multifactorial problem. Based on the reviewed studies, it seems that measures of cognitive functioning in combination with other demographic, neurological and psychological variables such as age [11,29,70], current financial status [11], education [4,11,18,19], race [11], walking ability [4,5,12,70,71], disability [11, 25, 29], fine motor coordination [4,5,12], self-reported disease severity [18,19], disease course [18,19,40], disease duration [11], self-reported worsening of MS symptoms [4], fatigue [4,12,15,28], depression [5,40,71] and personality [5,25] provided the best prediction of work participation in MS.

Gaps and future directions

This review identified 41 studies concerning the association between cognitive functioning and work outcomes in patients with MS. The studies varied greatly with respect to sample size (ranging from 32 to 8867), patient's average age (ranging from 34 to 54 years), educational level and clinical features, such as MS subtype, average EDSS score (ranging from 1.5-4.7) and disease duration (ranging from 2 – 18.9 years). In reviewing the available literature we should be aware of a possible outcome reporting bias, where some outcomes are reported but not others, depending on the nature and direction of the results [92]. Several studies did not adequately report confounding patient characteristics, such as MS subtype, level of disability, time since diagnosis and employment rate. Job type was mostly not included, while certain professions may better tolerate a decline in cognitive performance. Furthermore, only four prospective longitudinal studies were identified and two of them solely included measures of self-reported cognitive functioning. These studies showed that both baseline and a deterioration in processing speed and working memory speed and/or new learning and memory predicted a deterioration in vocational status at follow-up [22,29] and that baseline self-reported cognitive deficits predicted future employment

loss [4,12], while fewer perceived cognitive problems predicted re-entry [4]. These findings provide support for a causal relation between cognitive impairment and employment loss, and provide insight into clinically meaningful changes. More prospective longitudinal studies, with large samples, and better characterization of the study sample are needed to better understand the relation between changes in cognitive functioning and work participation over time.

The variety of ways in which employment status was defined and the fact that work outcomes were mostly included as a secondary outcome measure, made it difficult to generalize findings. Employment status was not always clearly operationalized. In studies that did provide a definition, great variability occurred, for example in specifying whether unemployment was due to MS, or whether or not the employed group included homeworkers, volunteers or part-time workers. Only few studies used more subtle work-related changes that may occur prior to leaving the work force, including changes in the number of working hours or responsibilities, absenteeism, presenteeism, work ability, work capacity, work-barriers, negative work events, the need for accommodations and work-related difficulties. In future research it is important to define employment status in a reproducible manner and to ascertain whether employment leave is due to MS characteristics and not because of other confounding factors. Future studies could benefit from taking into account more subtle work outcomes and by also taking into account re-entry into the workforce.

For this literature review we should keep in mind that the inclusion of papers in the period between 1991 and 2017 could have influenced the relation between cognitive functioning and work outcomes as work modality, work culture and environment may have changed over time.

Various cognitive measures were used and the same cognitive task was seen as reflecting different cognitive domains in different studies. For example, the WLG task was used as a test of language, information processing speed and executive functioning. To be able to compare the studies included in this review, we categorized the cognitive tests based on the categorization used for the MACFIMS battery [40] (Appendix 3).

Although we should always keep in mind that cognitive tests are almost never reflective of a single cognitive domain, future studies might categorize cognitive tests according to the neurocognitive domains as described in the DSM 5 [93]. A consensus in neurocognitive domains would increase the generalizability within brain disease, provide a better link between science and healthcare, and would lead to a better harmonisation of concepts and assessment tools. Furthermore, validated questionnaires, such as the MSNQ [94] or MSWDQ [49], should be used to measure self-reported cognitive and neuropsychiatric functioning in daily life or specifically at work. A final gap, in our opinion, is that a handful of studies used composite scores to indicate the presence or absence of cognitive impairment. Such a measure of global cognitive functioning was almost always found to be associated with work outcomes, but lacks specificity and therefore clinical relevance.

As decreased work participation is clearly a multifactorial problem, future studies should combine cognitive variables with demographic, neurological, psychological and work-related variables, in order to provide the best prediction of future work participation in MS.

Conclusion

We can conclude that self-reported and objective cognitive functioning, specifically in terms of processing speed and working memory, executive functioning, new learning and memory, has a well-established and possibly causal relationship with work participation in MS. The current body of evidence could benefit from well-designed studies addressing the methodological problems and gaps in the literature identified by this review. Specifically, prospective longitudinal studies are needed, to establish whether cognitive dysfunction precedes and predicts work outcomes, and to better understand clinically meaningful changes in cognitive functioning. Future studies would benefit from a better characterization of the study sample, including more information about the type of job, and more subtle work outcomes such as changes in the number of working hours and responsibilities, absenteeism, presenteeism, work ability, work capacity, work-barriers, negative work events, the need for accommodations, work-related difficulties and re-entry into the workforce. As cognitive problems can be treated through neuropsychological and vocational rehabilitation interventions [95,96] the clinical implication is to start monitoring both objective and self-reported cognitive functioning as soon as possible after MS is diagnosed.

Declaration of Interest

Dennis van Gorp reports honoraria for presentations from Genzyme, outside the submitted work. Karin van der Hiele received honoraria for consultancies, presentations and advisory boards from Genzyme and Merck Serono, outside the submitted work. Huub Middelkoop reports no disclosures. Leo Visser reports honoraria for lectures, grants for research and honoraria for advisory boards from Genzyme, Merck Serono, Novartis and TEVA Netherlands.

Author Contribution

Dennis van Gorp, MSc: study conception and execution, wrote manuscript. Dr. Karin van der Hiele: study conception and execution, wrote manuscript. Prof. Dr. Huub Middelkoop: study conception, manuscript review and critique. Prof. Dr. Leo Visser: study conception, manuscript review and critique. All authors have read, commented on the manuscript and approved the final manuscript.

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Appendix 1 Search terms

Pubmed:

((((((((((((((((((("Cognition"[Mesh] OR "Cognition Disorders"[Mesh]) OR "Executive Function"[Mesh]) OR "Attention"[Mesh]) OR "Memory"[Mesh]) OR "Cognitive Dysfunction"[Mesh] OR ("Orientation"[Mesh] OR "Memory Disorders"[Mesh] OR "Neurocognitive Disorders"[Mesh] OR "Aphasia"[Mesh] OR "Apraxias"[Mesh])) OR "Mental Processes"[Mesh]) OR "Speech Disorders"[Mesh])) OR Cognition[Title] OR Cognition Disorders[Title] OR Neurocognitive disorder[Title] OR cognitive dysfunction[Title] OR executive function[Title] OR attention[Title] OR memory[Title] OR memory disorder[Title] OR speech disorder[Title] OR mental processes[Title])) AND (((((((((((((((((((((((((((((((((((((((employment [Title] OR employment[MeSH Terms] OR unemployment[Title] OR unemployment[MeSH Terms] OR work[MeSH Terms] OR work[Title] OR vocational[MeSH Terms] OR vocational[Title] OR sick leave[MeSH Terms] OR sick leave[Title] OR absenteeism[MeSH Terms] OR absenteeism[Title] OR job[MeSH Terms] OR job[Title] OR occupational health[MeSH Terms] OR occupational health[Title] OR vocational rehabilitation[MeSH Terms] OR vocational rehabilitation[Title] OR presenteeism[MeSH Terms] OR presenteeism[Title] OR workplace[MeSH Terms] OR workplace[Title] OR workability[MeSH Terms] OR workability[Title] OR productivity loss[MeSH Terms] OR productivity loss[Title] OR job satisfaction[MeSH Terms] OR job satisfaction[Title] OR employer[MeSH Terms] OR employer[Title] OR underemployment[MeSH Terms] OR underemployment[Title] OR supported employment[MeSH Terms] OR supported employment[Title])) AND ((multiple sclerosis[MeSH Terms] OR multiple sclerosis[Title]))

Embase:

(Multiple sclerosis kw.Sh.Ti.) AND (employment.kw,sh,ti. OR unemployment.kw,sh,ti. OR work.kw,sh,ti. OR Vocational kw,sh,ti OR sick leave.kw,sh,ti. OR job.kw,sh,ti. OR occupational health. kw,sh,ti. OR absenteeism.kw,sh,ti. OR presenteeism.kw,sh,ti. OR workplace.kw,sh,ti. OR workability.kw,sh,ti. OR productivity loss. kw,sh,ti. OR job satisfaction.kw,sh,ti OR supported employment. kw,sh,ti. OR underemployment.kw,sh,ti.) AND (Cognition Disorders kw, sh, ti. OR cognition kw,sh,ti. OR Cognitive impairment kw, sh, ti. OR Cognitive dysfunction kw, sh, ti. OR Executive function kw, sh, ti. OR Attention kw,sh,ti. OR Memory kw,sh,ti. OR Memory Disorders kw,sh,ti OR Information Processing kw,sh,ti. OR verbal fluency kw,sh,ti.)

Psycinfo:

(ZU "employment") or TI employment OR (ZU "employment status") or TI employment status OR (ZU "employment, supported") or TI supported employment OR (ZU "unemployment") or TI unemployment OR (ZU "work") or TI work OR (ZU "vocational rehabilitation") or TI vocational rehabilitation OR (ZU "sick leave") or TI sick leave OR (ZU "occupational health") or TI occupational health OR (ZU "absenteeism") or TI absenteeism OR (ZU "presenteeism") or TI presenteeism OR (ZU "workplace") or TI workplace OR (ZU "productivity") or TI Productivity OR (ZU "job satisfaction") or TI Job Satisfaction) AND ((ZU "cognition") or TI cognition OR (ZU "cognition disorders") or TI cognition disorders OR (ZU "cognitive ability") or TI cognitive ability OR (ZU "cognitive impairment") or TI cognitive impairment OR (ZU "executive function") or TI executive function OR (ZU "attention") or TI attention OR (ZU "memory") or TI memory OR (ZU "memory disorders") or TI memory disorders OR (ZU "verbal fluency") or TI Verbal Fluency) AND) OR TI Multiple sclerosis).



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Appendix 2: Measurement of cognitive functioning in the selected papers	
Study	Cognitive measures
Baughman et al. (2015)	CVLT-II, SDMT, TMT A-B, Digit span test, WCST
Beatty et al. (1995)	Vocabulary; Digit span; Letter fluency; Category fluency; SDMT; Boston Naming Test; Benton Line Orientation Test; Brown Peterson Short Term Memory Test; New Map Test; SRT; WCST; Shipley Institute of Living Scale-Abstraction Test
Benedict et al. (2006)	COWAT, JLO, CVLT-II, BVMT-R, SDMT, PASAT, DKEFS-Sorting (MACFIMS)
Benedict et al. (2014)	MSNQ; CVLT-II, BVMT-R, SDMT, PASAT
Caceres et al. (2014)	SRT, SPART, SDMT, PASAT, WLG (BRB-N)
Cadden & Arnett (2015)	Digit Symbol-Coding; SDMT; PASAT; CVLT-II; 10/36 Spatial Recall Test; BVMT-R; COWAT; Animal naming; D-KEFS-Sorting
Campbell et al. (2017)	SDMT, CLVT-learning, BVMT-R-learning (BICAMS)
Carrieri et al. (2014)	SDMT; SRT; SPART; Naturalistic spatial planning task; EFI
Covey et al. (2012)	COWAT, JLO, CVLT-II, BVMT-R, SDMT, PASAT, DKEFS-Sorting (MACFIMS)
Dusankova et al. (2012)	COWAT, JLO, CVLT-II, BVMT-R, SDMT, PASAT, DKEFS-Sorting (MACFIMS)
Flensner et al. (2013)	PDQ
Fraser et al. (2009)	WAIS-III (Vocabulary, Similarities, Digit Span, Information, and Letter/Number Sequencing); COWAT; WMS-III; RCFT; Category Test; TMT A-B; SDMT
Glad et al. (2011)	PASAT
Glanz et al. (2012)	SDMT
Goverover et al. (2015)	COWAT, JLO, CVLT-II, BVMT-R, SDMT, PASAT, DKEFS-Sorting (MACFIMS)
Honan et al. (2015)	Cambridge Prospective Memory Test; 10-word list, SDMT, Abstraction scale of the Shipley Institute of Living Scale; Auditory Consonant Trigrams Test; Zoo Map Test; MSWDQ
Honarmand et al. (2011)	SRT, SPART, SDMT, PASAT, WLG (BRB-N)
Incerti et al. (2017)	COWAT, JLO, CVLT-II, BVMT-R, SDMT, PASAT, DKEFS-Sorting (MACFIMS)
Julian et al. (2008)	Self-reported cognitive performance
Kordovski et al. (2015)	SDMT, PASAT, CVLT-II, BVMT-R; MSNQ
Krause et al. (2013)	SRT, SPART, SDMT, PASAT, WLG (BRB-N)
Li et al. (2015)	PDQ-5
Moore et al. (2013)	Self-reported memory problems
Morrow et al. (2010)	COWAT, JLO, CVLT-II, BVMT-R, SDMT, PASAT, DKEFS-Sorting (MACFIMS)
Morse et al. (2013)	SET; COWAT; PASAT; SDMT; TMT; Zoo Map Test; Vocabulary
Niino et al. (2014)	SRT, SPART, SDMT, PASAT, WLG (BRB-N)
Papathanasiou et al (2015)	TMT A-B, Semantic and phonological verbal fluency task; Central Nervous System Vital Signs (a computerized cognitive screening battery; in this study the verbal and visual memory, symbol digit coding, stroop, shifting attention and continuous performance test were used)
Parmenter et al. (2007)	WCST; DKEFS-Sorting
Rao et al. (1991)	SRT, SPART, SDMT, PASAT, WLG (BRB-N)
Roessler et al. (2001)	Self-reported cognitive impairment (symptom present vs symptom not present)
Roessler et al. (2004)	Self-reported cognitive impairment
Roessler et al. (2015)	Self-reported cognitive impairment
Ruet et al. (2013)	SRT, SPART, SDMT, PASAT, WLG (BRB-N); WAIS-R (testing conceptualization)
Sayao et al. (2011)	PASAT; SRT; COWAT; 7/24 Spatial Recall
Simmons et al. (2010)	Self-reported reasons for employment loss
Smith & Arnett. (2005)	COWAT; 7/24 Spatial Recall; SRT; PASAT; computerized Tower of Hanoi; SDMT; Shipley Institute of Living Scale-Abstraction Test; Shipley Institute of Living Scale-Vocabulary Test; WAIS-R (total IQ)
Strober et al. (2012)	COWAT; JLO; PASAT; SDMT; SRT; 10/36 Spatial Recall Test; DKEFS-Sorting
Strober et al. (2014)	Wide Range Achievement Test; COWAT; JLO; Digit span; SDMT; Logical Memory; WCST; SCWT; MSFC

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Strober & Arnett (2016)	SDMT
van der Hiele et al. (2014)	SCL-90-R scale 'insufficiency of thinking and acting'; BADS-DEX; DIP
Van der Hiele et al. (2015)	BADS-DEX; NART; TMT; SCWT; WCST; RCFT-Copy; BADS

Minimal Assessment of cognitive function in multiple sclerosis (MACFIMS):

- Controlled Oral Word Association Test (COWAT)
- Judgment of Line Orientation Test (JLO)
- California Verbal Learning Test-II (CVLT-II)
- Brief Visuospatial Memory Test –Revised (BVRT-R)
- Symbol Digit Modalities Test (SDMT)
- Paced Auditory Serial Addition Test (PASAT)
- Delis-Kaplan Executive Function System Sorting Test (DKEFS-Sorting)

Brief Repeatable Battery of Neuropsychological Tests (BRB-N):

- Selective Reminding Test (SRT)
- 10/36 Spatial Recall Test (SPART)
- Symbol Digit Modalities Test (SDMT)
- Paced Auditory Serial Addition Test (PASAT)
- Word List Generation Test (WLG)

Brief International Cognitive Assessment for MS (BICAMS)

- Symbol Digit Modalities Test (SDMT)
- California Verbal Learning Test – learning (CVLT-learning)
- Brief Visuospatial Memory Test –Revised-learning (BVRT-R-learning)

Others:

- Trailmakingtest (TMT)
- Wisconsin Card Sorting Test (WCST)
- Wechsler Memory Scale III (WMS-III)
- Wechsler Adult Intelligence Scale III (WAIS III)
- National Adult Reading Test (NART)
- Rey Complex Figure Test (RCFT)
- Modified Six Elements Test (SET)
- Behavioural Assessment of the Dysexecutive Syndrome (BADS)- Dysexecutive Questionnaire (BADS- DEX)
- Disability and Impact Profile (DIP)
- Symptom Checklist-90-R (SCL-90-R)
- Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ)
- Perceived Deficit Questionnaire 5 (PDQ 5)
- Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ)
- Questionnaire Executive Function Index (EFI)

Appendix 3: Cognitive domains.

Cognitive domains	Tests
Language	Controlled Oral Word Association Test (COWAT) Letter fluency Phonological verbal fluency Word List Generation Test (WLG) Category fluency Animal Naming Boston Naming Test
Processing speed and working memory	Symbol Digit Modalities Test (SDMT) Paced Auditory Serial Addition Test (PASAT) Digit Span (WAIS-III) Digit Symbol-Coding (WAIS-III) Auditory Consonant Trigrams Test
New learning and memory	California Verbal Learning Test-II (CVLT-II) Brief Visuospatial Memory Test –Revised (BVRT-R) Selective Reminding Test (SRT) 10/36 Spatial Recall Test (SPART) 7/24 Spatial Recall Verbal Memory Test (WAIS-III) Wechsler Memory Scale III (WMS-III) Brown Peterson Short Term Memory Test New Map Test Rey Complex Figure Test- immediate and delayed recall (RCFT) Cambridge Prospective Memory Test 10-Word list Logical memory (WMS-III)

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Visuospatial processing	Judgment of Line Orientation Test (JLO) Benton Line Orientation Test Rey Complex Figure Test- copy (RCFT)
Executive functioning	Delis-Kaplan Executive Function System Sorting Test (DKEFS-Sorting) Stroop Test (Color-Word Naming) Stroop Color Word Test (SCWT) Trail Making Test A and B (TMT A; TMT B) Wisconsin Card Sorting Test (WCST) Modified Six Elements Test (SET) Letter-Number Sequencing (WAIS-III) Naturalistic spatial planning task Category Test Zoo Map Test (Behavioural Assessment of the Dysexecutive Syndrome (BADS)) Continuous performance test Tower of Hanoi
(Pre-morbid) intelligence	Verbal comprehension (Wechsler Adult Intelligence Scale III; WAIS III) Vocabulary (WAIS-III) Similarities (WAIS-III) Information (WAIS-III) Conceptualisation (Wechsler Adult Intelligence Scale-Revised; WAIS-R) IQ (WAIS-R) Shipley Institute of Living Scale-Abstraction Test Shipley Institute of Living Scale-Vocabulary Test Wide Range Achievement Test National Adult Reading Test (NART)
Self-reported cognitive functioning	Disability and Impact Profile (DIP) scales 'memory' and 'concentration' Symptom Checklist-90-R (SCL-90-R) scale 'insufficiency of thinking and acting' Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) Perceived Deficit Questionnaire 5 (PDQ 5)- memory, attention and concentration Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ) Behavioural Assessment of the Dysexecutive Syndrome- Dysexecutive Questionnaire (BADS-DEX) Questionnaire Executive Function Index (EFI) Self-reported general cognitive performance Self-reported cognitive impairment Self-report rating of memory Self-reported reasons for employment loss