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Comparing diagnostic criteria for the diagnosis of neurocognitive disorders in multiple sclerosis

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ABSTRACT

Background: People with multiple sclerosis (MS) commonly experience cognitive impairment associated with the disease, but there is currently no agreed-upon operational definition for identifying the presence of that impairment, in either research or clinic contexts. The International MS Cognition Society (IMSCOGS) established a task force to begin to examine this issue and this paper represents the results of an initial pilot investigation. The aim of this paper was to compare two criterion sets to determine how to identify cognitive impairment among people with MS: the general Diagnostic and Statistical Manual (DSM-5) Criteria for neurocognitive disorders and criteria derived from existing MS research (scores in two domains fall 1.5 standard deviations below normative controls).

Methods: Two hundred and ten people with MS presented for a brief cognitive evaluation in an MS Multidisciplinary Clinic at a midwestern academic medical center in the United States. Participants were generally middle aged (average 51.5 years), female (73.8%), and white (93.3%). McNemar's test was computed to compare the number of individuals whose cognitive test score performance was deemed cognitively normal, mildly impaired, or more significantly impaired.

Results: DSM-5 criteria classified 87.2% of the sample as cognitively impaired, where 66.7% were more mildly impaired and 20.5% more significantly impaired. By contrast, research-based criteria classified 63.3% of the sample as cognitively impaired, with 49.5% as mildly impaired and 13.8% as more significantly impaired.

Conclusions: These findings indicate that compared to research criteria, the DSM-5 criteria classified far more people with MS as having cognitive impairment secondary to the disease. The paper discusses the potential benefits and drawbacks of the two diagnostic methods, highlighting that more work will be needed in order to establish a standardized and validated method for characterizing these impairments.

1. Introduction

Cognitive impairment (CI) is common among people with multiple sclerosis (PwMS), occurring in up to 65% of people living with the disease (Ruano et al., 2017, McKay et al., 2019). Impairments can occur in any cognitive skill but are most common in processing speed, complex attention, episodic memory, and executive functions (Benedict et al., 2020). Although these commonalities exist, the specific pattern of CI among PwMS can be highly heterogeneous, even within the same disease course/subtype, and response to intervention/treatment can be

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minimal (Nelson et al., 2011, Sandroff et al., 2019, Preziosa et al., 2021). Ramifications of CI can be far-reaching and include job performance difficulties, job loss, relationship difficulties, increased need for caregiving, financial mismanagement, loss of driver's license, loss of independence, and other factors affecting quality of life (Coleman et al., 2013). As such, CI in MS has a large impact on patient lives, thus early diagnosis is important but remains challenging in daily clinical practice due to time limitations and varying opinions on which approach to use.

In clinical care, identification of CI is important for several reasons, including provision of community-based services (such as disability benefits), communication and understanding for patients and between providers, and identification of needs. In research, many groups have therefore investigated different approaches to the correct diagnostic labeling of cognitive deficits in this population, which has resulted in highly variable approaches with no single clear evidenced-based criteria for diagnosing CI in PwMS (Fischer et al., 2014). Existing research dichotomizes CI (impaired versus preserved) with no further characterization of depth or breadth. One of the typical approaches is to identify CI when a score falls at least 1.5 SD below the mean based on normative comparison, but some studies have further required impaired performance on a certain proportion of the tests administered (Benedict et al., 2020). Other studies have utilized similar criteria, such as requiring that at least two scores fall at least 1.5 SD below the normative mean, or a more stringent 2 SD below the normative mean on at least two different tests (Feuillet et al., 2007, Migliore et al., 2017). Researchers in Italy attempted to tackle this issue by developing an Italian consensus for cognitive assessment in MS, which recommended a cutoff of 1.5 standard deviations (SD) below the normative mean combined with a failure on at least 20-30% of the tests administered, in at least 2 different cognitive domains (Amato et al., 2018). With the exception of the Symbol Digit Modalities Test (SDMT), different studies also utilize diverse cognitive batteries, some of which may have varying sensitivity to detecting CI in MS. Clearly, these different approaches will result in a different proportion of subjects being identified as CI, and could mask some differences in the cognitive profile of MS. Within the last several years, there have been efforts to identify cognitive phenotypes among PwMS, which so far suggests that there may be several, significantly different phenotypes, but more research in this area is needed (Leavitt et al., 2018, Podda et al., 2021, De Meo et al., 2021). The lack of a universally accepted best method for diagnosing and identifying CI in PwMS contributes to the variability across studies addressing the presence and number of impaired, as well as the depth and breadth of specific deficits. In turn, this creates difficulty in the clinic when attempting to identify what, if any, intervention might be best or most appropriate for individual patients.

Toward this effort, a useful comparison might be what has been adopted by researchers and clinicians studying other neurodegenerative diseases. Perhaps the most comprehensive approach has been in Alzheimer's disease (AD). This began with the introduction of the concept of Mild Cognitive Impairment (MCI) and operational criteria for its diagnosis (Petersen et al., 1999), and recently updated cognitive-based criteria for the identification of MCI, which has been well received (Bondi et al., 2014, Jak et al., 2009, Artero et al., 2006, Albert et al., 2011). These criteria significantly improved detection of CI due to AD and led to more stable diagnoses and the delineation of distinct preclinical cognitive phenotypes (Jak et al., 2009). Other neurodegenerative disease groups have similarly established diagnostic guidelines that include cognitive deficits, such as primary progressive aphasia, frontotemporal dementia, Parkinson's disease, and Lewy body disease (Litvan et al., 2012, Rascovsky et al., 2011, Gomperts, 2016, Marshall et al., 2018). Researchers and clinicians studying the cognitive effects of HIV and epilepsy have also followed suit (Antinori et al., 2007, Norman et al., 2021). Universal characterization of the cognitive effects of specific diseases has without doubt advanced research in these areas. Identification of standardized criteria for CI in PwMS would help advance the study of CI and possible interventions targeted toward the cognitive effects of MS.

Although research efforts help inform clinical practice, resources for clinicians working in many clinics (especially in America) are limited to criteria set forth by the American Psychiatric Association in their most recent edition of Diagnostic and Statistical Manual (DSM-5) or the most recent edition of the International Classification of Diseases (ICD) (World Health O 1993, American Psychiatric Association A 2013). The current paper will focus on DSM-5; see Tables 1-2 for the diagnostic criteria for Mild Neurocognitive Disorder (Mild NCD) and Major Neurocognitive Disorder (Major NCD). In general, the DSM-5 requires evidence of modest cognitive decline from baseline but no effect on functional ability (Mild NCD), or significant cognitive decline from baseline coupled with functional impairment due to cognitive issues (Major NCD). These diagnoses are nonspecific with respect to underlying etiology. The CI of other common etiologies (AD, vascular disease, HIV, and Parkinson's disease) have been more specifically characterized in the DSM-5, while a description of CI in MS is missing, underscoring the lack of guidance for clinicians in this area. Although the DSM-5 has been lauded by some for the increased clarity and objectivity in diagnostic criteria, there has also been some opposition (Watts, 2012, Blazer, 2013). The neurocognitive disorder task force for the DSM-5 chose to move away from the term dementia in part due to the tendency of that term to be used synonymously with AD, and the reluctance to use the term to characterize the deficits of younger people (Sachdev et al., 2015). These changes are particularly salient to clinicians working with PwMS, where the CI of MS should not be conflated with that of AD, CI may develop in younger people, and the severity may vary significantly. The criteria for neurocognitive disorders were intended to focus on early detection, but this was largely driven by AD etiology (Blazer, 2013). The task force was not concerned with overpathologizing neurocognitive disorders, but the DSM-5 has broadly been criticized for doing so (Watts, 2012, Sachdev et al., 2014). Although early identification is important, given that Mild NCD is not to be considered 'pre--dementia' and does not necessarily progress to Major NCD, the reduced

Table 1
DSM-5 criteria for Mild Neurocognitive Disorder. Note: Taken directly from the DSM-5[27]. The DSM-5 further requires specification regarding etiology and whether the disorder occurs with behavioral disturbance.

A Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:	1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).	
C The cognitive deficits do not occur exclusively in the context of a delirium.	
D The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).	

Table 2
DSM-5 criteria for Major Neurocognitive Disorder (Dementia). Note: Taken directly from the DSM-5[27]. The DSM-5 further requires specification regarding etiology, whether the disorder occurs with behavioral disturbance, and severity (mild, moderate, severe).

A Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:	1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).	
C The cognitive deficits do not occur exclusively in the context of a delirium.	
D The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).	

threshold for diagnosing this condition may lead to overpathologization (Sachdev et al., 2015).

The aim of this paper is to compare two criterion sets to determine how they characterize cognitive impairment among PwMS: the general DSM-5 Criteria for neurocognitive disorders and Investigational Research Criteria (derived from existing MS research; more information on these can be found below in the methods section) (American Psychiatric Association A 2013). The hypothesis is that the DSM-5 Criteria will identify a greater proportion of the sample as cognitively impaired.

2. Material and methods

2.1. Participants

The present study is a retrospective chart review of patients seen in the MS Multidisciplinary Clinic of the University of Wisconsin Hospital and Clinics. Individuals were referred for a clinically indicated neuropsychological exam combined with appointments with other MS-specialist providers. Inclusion criterion was a confirmed diagnosis of MS according to the McDonald Criteria (Thompson et al., 2018). For some, their visit to this clinic was their first exposure to a neuropsychological examination, while others had been evaluated previously (though none were evaluated <12 months prior). Exclusion criteria were: 1) evidence of suboptimal engagement with cognitive tests, 2) presence of a significant/potentially confounding psychiatric disorder such as schizophrenia or substance use disorder, and 3) presence of a potentially confounding comorbid neurological disease such as epilepsy or stroke. All participants completed neuropsychological examination and were assigned a diagnosis at the conclusion of the evaluation. This study was approved by the University of Wisconsin School of Medicine and Public Health Institutional Review Board (2016-1017).

2.2. Neuropsychological assessment

A neuropsychological test battery was designed for this clinic to be both brief in duration and comprehensive in terms of skills measured. Tests selected measured skills often impaired in people with MS (such as processing speed and learning/memory), but also other domains to allow for full differential diagnosis in the clinic setting. Most subtests of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were used, as well as other tests outlined below (Randolph, 2012). The RBANS was developed as a brief tool to characterize cognitive issues among both younger and older adults; it measures skills including basic auditory attention, visual confrontation naming, visuoconstruction, angle estimation, rote verbal learning and memory, structured verbal learning and memory, and incidental memory of visual information (Randolph et al., 1998) Also utilized were the Trail Making Test (Parts A and B, measuring visuomotor speed and cognitive set-shifting), SDMT (both written and oral measurements of processing speed), Controlled Oral Word Association Test (COWAT; letter fluency), Category Fluency, and the Stroop Test (processing speed and response inhibition) (Reitan and Wolfson, 1985, Smith, 1982, Strauss et al., 2006, Golden and Freshwater, 1978). Both forms of the SDMT were always administered in the order of written first, then oral. Premorbid IQ was estimated using the Wide Range Achievement Test Fourth Edition (WRAT-4), Word Reading subtest (Wilkinson and Robertson, 2006). The battery includes some aspects of Rao's Brief Repeatable Battery (BRB; SDMT, Stroop Test, COWAT) as well as some tests which are similar to those in the BRB (list learning/memory, story learning/memory, visual memory) (Peyser et al., 1990). In clinic, normative comparison was computed using published test-specific norms (RBANS, SDMT, Stroop, WRAT-4) or population-based norms (Trail Making Test, COWAT, Category Fluency) (Heaton et al., 1991).

2.3. Self-report measures

Participants also completed self-report measures of fatigue, depression, and anxiety (the Fatigue Assessment Inventory, Beck Depression Inventory-Fast Screen, and the State-Trait Anxiety Inventory) to fully assess for symptoms which may have influenced cognition in the clinic setting (Schwartz et al., 1993, Beck et al., 2000, Spielberger, 1983).

2.4. Diagnostic conclusions

Based on clinical interview, medical record review, neuropsychological test data, and self-report measures, neuropsychologist LMH assigned a clinical diagnosis using both sets of diagnostic criteria (DSM-5 Criteria and the Investigational Research Criteria). Diagnoses assigned were Mild NCD, Major NCD, or Cognitively Normal.

The DSM-5 Criteria can be found in Tables 1-2 (American Psychiatric Association A 2013). As outlined in these tables, the DSM-5 does not quantify the degree of cognitive decline necessary for diagnosis. For a diagnosis of Mild NCD, an individual must possess "modest" cognitive decline but the deficits do not interfere with independent daily functioning. For a diagnosis of Major NCD, an individual must possess "significant" cognitive decline and the deficits interference with independent daily functioning. Exclusionary criteria include delirium and mental disorders such as Major Depressive Disorder. To make a direct comparison to these criteria, research criteria commonly found in MS literature were combined with the DSM-5 structure, henceforth termed "Investigational Research Criteria," and outlined in Tables 3-4. These criteria state that the individual must possess cognitive impairment that falls at least 1.5 SD below the mean on tests spanning at least two cognitive domains, which is the most commonly used approach in current MS research (Benedict et al., 2020). Mild NCD due to MS would be assigned if the cognitive deficits were not interfering with independent daily functioning, while Major NCD due to MS would be assigned if the cognitive deficits were interfering with independent daily functioning.

Table 3
Investigational research criteria for Mild Neurocognitive Disorder (Due to MS).

A Cognitive decline from a previous level of performance (at least 1.5 standard deviations below the normative mean) in two or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition):	1. Evidence of at least modest cognitive decline based on: a Preference for documentation by standardized neuropsychological testing; OR, b If standardized neuropsychological testing is not available or possible, another quantified clinical assessment; and 2. Evidence of adequate engagement or effort in the clinical assessment of cognitive skills
B The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).	
C The cognitive deficits do not occur exclusively in the context of a delirium.	
D The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).	

Table 4
Investigational research criteria for Major Neurocognitive Disorder (Due to MS).

A Cognitive decline from a previous level of performance (at least 1.5 standard deviations below the normative mean) in two or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:	1. Evidence of substantial cognitive impairment based on: a Preference for documentation by standardized neuropsychological testing; OR, b If standardized neuropsychological testing is not available or possible, another quantified clinical assessment; and 2. Evidence of adequate engagement or effort in the clinical assessment of cognitive skills
B The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).	
C The cognitive deficits do not occur exclusively in the context of a delirium.	
D The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).	

2.5. Statistical analysis

All statistical tests were performed using SPSS version 28 (IBM, Armonk, NY, United States). Descriptive statistics were computed. McNemar's test (Fagerland et al., 2013) was deployed to determine whether there were differences in the way the two sets of criteria categorized the participants in this sample.

3. Results

3.1. Demographic and clinical characteristics

Two hundred and ten PwMS completed an evaluation in the MS Multidisciplinary Clinic and met inclusion/exclusion criteria. On average, participants were middle-aged (51.5 years ± 11.4 years), with 23.8% of the sample aged 60 or older at the time of evaluation. Largely consistent with existing MS literature and the clinic's location in the northern part of the midwestern United States, most participants were white women (93.3% white, 73.8% women). Most had a clinical course characterized as relapsing-remitting (59.5%), 12.9% were classified as secondary-progressive, 13.3% as primary progressive, and 11% progressive-relapsing. Most were well educated (14.33 ± 2.47 years) and of average estimated intelligence (Standard Score 99.83 ± 13.79). Age at MS onset was in the 30s (35.60 ± 10.51 years) and disease duration was more than 1.5 decades (15.73 ± 10.90 years).

3.2. Comparing Diagnostic Criteria

When using DSM-5 Criteria, 87.2% of the sample was classified as having some form of CI. Specifically, 66.7% of the sample was classified as having Mild NCD and 20.5% of the sample as having Major NCD. By comparison, when using the Investigational Research Criteria, 63.3% of the sample was identified as impaired. Specifically, 49.5% of the sample was classified as having Mild NCD and 13.8% was classified as Major NCD. See Fig. 1 for a visual depiction of these data. McNemar's test was statistically significant ($p < .001$), indicating that the DSM-5 Criteria classified significantly more individuals in this sample as having a neurocognitive disorder, compared to the Investigational Research Criteria. Table 5 depicts the classification of individuals according to each criteria set.

Focusing on the Investigational Research Criteria, individuals diagnosed with Mild NCD exhibited only a few test scores which fell in the impaired range on average based on gender, age, and education comparison. See supplemental Table 6 for raw score comparisons and visual depiction of impaired scores. Specifically, these included some aspects of processing speed (Stroop word reading z-score -1.98 and color naming z-score -1.84). By contrast, when focusing on individuals diagnosed with Major NCD, they exhibited abnormalities on Trails A and B (z-score -1.68 and -1.95 respectively), both written and oral SDMT (z score -2.35 and -2.37 respectively), other aspects of processing speed (Stroop word reading and color naming z-score -2.47 and -2.62, respectively), COWAT and semantic fluency (z-score -1.92 and -1.57 respectively), figure copy (z-score -1.91), list learning (z-score -1.67), story learning and recall (z-score -1.67 and -1.72, respectively), and figure recall (z-score -1.69).

Supplemental Table 6 also illustrates these same raw score comparisons using the DSM-5 Criteria. Individuals who met criteria for Mild NCD exhibited only one impaired test score for age and education: one measure of processing speed (Stroop word reading z-score -1.66). By contrast, when focusing on individuals who met criteria for Major NCD, they exhibited numerous test score abnormalities compared to others of their same age and education, including Trails A and B (z-score -1.75 and -1.96 respectively), both written and oral SDMT (z-score -2.26 and -2.20 respectively), other measures of processing speed (Stroop word reading and color naming –z-score -2.40 and -2.35 respectively), COWAT letter fluency (z-score -1.68), figure copy and recall (z-score -1.71 and -1.50, respectively), and story recall (z-score -1.50).

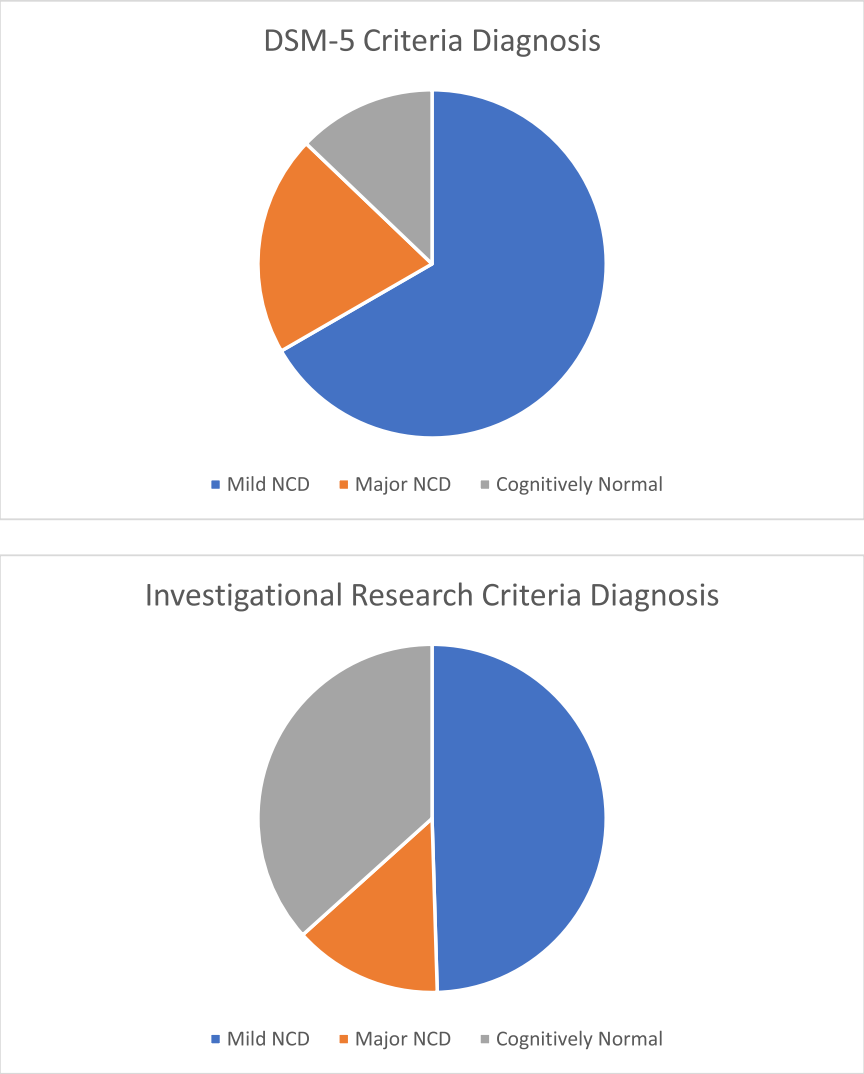

Fig. 1. Visual comparison of the cognitive diagnosis for PwMS by diagnostic criterion set.

Table 5
Grid depicting the classification of diagnosis based on differing criteria.

		Investigational Criteria		
		Normal	Mild NCD	Major NCD
DSM-5 Criteria	Normal	28	–	–
	Mild NCD	50	89	–
	Major NCD	–	14	29

4. Discussion

This study aimed to determine whether the clinical DSM-5 Criteria would differently classify neurocognitive disorders in PwMS compared to commonly used research criteria. Results of this study revealed that the DSM-5 Criteria classified far more PwMS as having a neurocognitive disorder. This study indicates that using the DSM-5 Criteria in MS may identify significantly more PwMS as impaired compared to current research practices, which could be problematic. For instance, a significantly larger proportion of PwMS identified as having CI could be construed as overpathologizing the cognitive issues PwMS face. This approach may introduce more error in this measurement and could yield diagnoses which are less reliable or stable over time. In clinic, there can be a psychological impact of receiving a neurocognitive diagnosis, particularly if the deficits are significant enough to warrant a diagnosis of Major NCD (i.e., dementia); coping with a diagnostic label presents additional challenges (Goretti et al., 2010). In fact, a frequent question posed by PwMS in clinic is whether they will develop dementia, and there is confusion regarding whether the term dementia is synonymous with AD. Previous research has shown that CI in MS does considerably impact patient lives, but the development of impairment so severe it could be labeled dementia is unclear given that research typically only dichotomizes CI in MS. Relatedly, there is also a reluctance among some healthcare professionals to label neurocognitive disorders or dementia in PwMS, who are typically younger on average than individuals with other neurodegenerative diseases (Westervelt, 2015). Anecdotally, there is also a sense among some clinicians that the DSM-5 Criteria are somewhat subjective and less precise than other approaches, especially for causes the DSM-5 has not outlined in detail.

However, one advantage of the DSM-5 approach could be earlier identification of CI so that intervention can occur sooner (Kim et al., 2017, Kalb et al., 2018, Parmenter et al., 2007, Chen et al., 2021). The general consensus is that cognitive rehabilitation in MS is effective and should be frequently used to help ameliorate the day-to-day effects of cognitive deficits (DeLuca et al., 2020). Although this type of intervention can be both a rehabilitation and prophylactic strategy, research has suggested that certain interventions are more beneficial depending on baseline cognitive skills, with the implication that early intervention allows for greater skill development (Chiaravalloti and DeLuca, 2015).

Very early detection of deficits would therefore be a necessary component to determine the most helpful rehabilitation strategies. In addition, provision of clinical care in the United States usually requires a qualifying diagnosis (including home healthcare assistance, visits with rehabilitation specialists, or government-based financial benefits). Although there is concern regarding possible psychological harm of a false-positive neurocognitive diagnosis or nocebo effects, it is important to balance these with potential benefits to the patient (such as access to resources, validation of their subjective complaints/concerns). There is also concern that avoidance of terms that characterize serious CI (such as dementia) is harmful to PwMS who need to make informed decisions about their healthcare, such as selection of appropriate disease-modifying therapy (Giovannoni, 2017). This may argue for a greater emphasis on early identification through routine screening, and perhaps more comprehensive screening than the SDMT alone.

4.1. Limitations

This study was based on a sample of convenience; individuals who were scheduled in a MS Multidisciplinary Clinic at a single institution, based on subjective complaints of CI or suspicion of CI by the MS neurologist. As a result, this sample may be comprised of more impaired individuals than the general MS population. Due to time, material, and space limitations, a longer neuropsychological battery was not possible, and as such a recommended battery for measurement of CI in MS was not used (such as the Minimal Assessment of Cognitive Function in MS - MACFIMS, (Benedict et al., 2006, Benedict et al., 2002). the Brief International Cognitive Assessment for MS - BICAMS (Langdon et al., 2012), or BRB (Rao et al., 1991, Rao, 1990)). As a result, the tests used may not have had sufficient sensitivity and reliability to detect the CI of MS. Some individuals in this sample were naïve to neuropsychological testing while others were not, which may have impacted performance on some tests. This sample is overwhelmingly comprised of white, North American women and there is a lack of racial diversity (even for a sample of PwMS), which may be a function of the clinic's geographic location. Therefore, these results may not be generalizable to other geographic locations or the population of MS as a whole.

4.2. Future directions

In the quest for a standardized and validated method to characterize the CI of MS, one important point for future discussion should be how the presence of neuropsychiatric symptoms should be addressed. In both of the currently examined diagnostic criteria sets, psychiatric symptoms/disorders are considered exclusions for diagnosis. This should therefore be investigated for MS as well, as MS can affect specific aspects of psychiatric functioning such as emotional and inhibitory control, as well as fatigue, depression and anxiety, all of which may impact cognition (Boeschoten et al., 2017, Feinstein, 2004). In addition, continued characterization and understanding of the functional challenges PwMS face is important to more accurately determine the ways in which cognitive limitations impact daily life skills (van Dam et al., 2021). Results of this study indicate that a measurable percentage of the clinic sample may present with CI significant enough to cause functional impairment (20.5% or 13.8% depending on criteria used); this is generally consistent with a previous study that identified 22% of its clinic sample as having dementia (Benedict and Bobholz, 2007). Adding healthy control and longitudinal data could help to assess specificity and prognostic value. Such studies could also add other measures of clinical impairment (such as the Expanded Disability Status Scale – EDSS) and neuroimaging. Once consensus has been achieved with respect to how CI should be operationally defined and diagnosed for PwMS, the next priority should be to continue to characterize the distinct cognitive phenotypes of MS, which represents a new approach in the neuropsychology of MS. Universally adopted diagnostic criteria that can be used internationally will not only advance future research but also elevate this work in MS and facilitate comparisons across other CNS disorders. Replication of these results in PwMS living in other parts of the world and attending other clinics would be helpful in working toward this consensus. The prospective goal is to fully characterize an improved nosology for identification and diagnosis of cognitive impairment in MS, which will hopefully lead to improved services and interventions for people living with MS.

5. Conclusions

Comparison of DSM-based and research-based criteria for characterizing the CI of MS illustrates that these different criterion sets yield very different rates of cognitively impaired PwMS. Based on these findings, future work examining other methods for diagnostic labeling should be undertaken so that the best method can be identified. Ideally, this work will help inform both research and clinical practice, where a correct diagnostic label has the potential to offer PwMS more comprehensive services that they may need.

Declaration of Competing Interest

Dr. Hancock has received honoraria from Can Do MS, the MS Association of America, and the National MS Society of America. She has also received grant funding from BMS, NIH, and Clinical & Translational Science Institute and Advancing a Healthier Wisconsin Research and Education Program.Dr. Hermann serves on a Medtronics DSMB and receives support from the NIH.Dr. Schoonheim serves on the editorial board of Frontiers of Neurology and has received research support, compensation for consulting services or speaker honoraria from the Dutch MS Research Foundation, ARSEP, Eurostars-EUREKA, ZonMW, ExceMed, Amsterdam Neuroscience, Atara, Biogen, Celgene/BMS, Merck, MedDay and Sanofi-Genzyme.Mr. Hetzel has no declarations of interest.Dr. Brochet has received honoraria or consulting fees from Novartis, BMS, Sanofi, Janssen, Roche, Biogen, and Merck. Dr. DeLuca has received honoraria or consulting fees from Novartis, BMS, Sanofi-Genzyme, Roche, Biogen, MedRhythms and Merck. He has also received grant funding from Biogen, EMD Serono, Roche, CMSC, NIH, NMSS and MS Society of Canada.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103479.

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