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The integration of clinical data in the assessment of Multiple Sclerosis - a review / Ostellino, S., Benso, A., Politano, G.M.M.. - In: COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE. - ISSN 0169-2607. - ELETTRONICO. - 221:(2022), p. 106900. [10.1016/j.cmpb.2022.106900]

Availability:
This version is available at: 11583/2964320 since: 2022-06-04T19:22:42Z

Publisher:
ELSEVIER

Published
DOI:10.1016/j.cmpb.2022.106900

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http://dx.doi.org/10.1016/j.cmpb.2022.106900

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18 November 2026

The integration of clinical data in the assessment of Multiple Sclerosis - a review

Sofia Ostellino[a], Alfredo Benso[a], Gianfranco Politano[a,*]

[a]*Department of Control and Computer Engineering, Politecnico di Torino, Italy*

Abstract

Background and Objectives: Multiple Sclerosis (MS) is a neurological disease associated with various and heterogeneous clinical characteristics. Given its complex nature and its unpredictable evolution over time, there isn't an established and exhaustive clinical protocol (or tool) for its diagnosis nor for monitoring its progression. Instead, different clinical exams and physical/psychological evaluations need to be taken into account. The Expanded Disability Status Scale (EDSS) is the most used clinical scale, but it suffers from several limitations. Developing computational solutions for the identification of bio-markers of disease progression that overcome the downsides of currently used scales is crucial and is gaining interest in current literature and research. **Methods:** This Review focuses on the importance of approaching MS diagnosis and monitoring by investigating correlations between cognitive impairment and clinical data that refer to different MS domains. We review papers that integrate heterogeneous data and analyse them with statistical methods to understand their applicability into more advanced computational tools. Particular attention is paid to the impact that computational approaches can have on personalized-medicine. **Results:** Personalized medicine for neuro-degenerative diseases is an unmet clinical need which can be addressed using computational approaches able to efficiently integrate heterogeneous clinical data extracted from both pri-

*Corresponding author

Email addresses: sofia.ostellino@polito.it (Sofia Ostellino), alfredo.benso@polito.it (Alfredo Benso), gianfranco.politano@polito.it (Gianfranco Politano)

vate and publicly available electronic health databases. **Conclusions:** Reliable and explainable Artificial Intelligence are computational approaches required to understand the complex and demonstrated interactions between MS manifestations as well as to provide reliable predictions on the disease evolution, representing a promising research field.

Highlights

- Multiple Sclerosis (MS) progression needs to be monitored through heterogeneous clinical measures.
- Cognitive assessment via neuropsychological tests (NP) is fundamental and informative in MS monitoring.
- Computerized NPs allow good quality and efficient cognitive examinations.
- Computational integration of data related to different neurodegenerative disease domains is a promising research field.
- Artificial Intelligence is, at the moment, the most promising computational approach to extract new knowledge from large sets of available clinical data.

Keywords: Multiple Sclerosis, Clinical data, Computational integration, Neuropsychological tests, Cognitive assessment, Personalized medicine, Bio-markers

1. Introduction

Multiple sclerosis (MS) is a chronic disease characterized by intra-patient and inter-patient variability in terms of disease course, progression, and efficacy of treatments. MS, like other neurodegenerative conditions, is a wide spectrum disease which multisymptomatic characteristics require a comprehensive health evaluation at both diagnosis and follow-up. Disease monitoring is crucial and

challenging as MS involves multiple physiological domains: there isn't a single and widely accepted bio-marker informative enough to be used for planning a personalized treatment. For this reason, a lot of research is currently focused on the identification of bio-markers [1] for personalized predictions.

1.1. Disease characteristics

MS is a complex chronic autoimmune disease that affects the central nervous system (CNS): myelinated axons are attacked by the immune system, a process leading to a wide spectrum of symptoms depending on the localization of the resulting lesion. Main symptoms, as summarized in Figure 1, include optic neuritis, partial myelopathy, dizziness, motor dysfunctions, fatigue, loss of balance, paraesthesia, depression, and cognitive impairment [2].

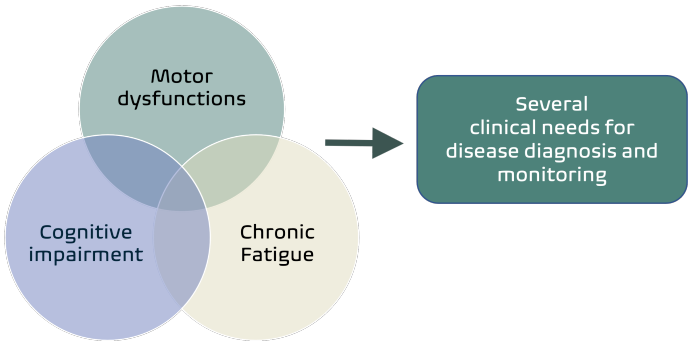


Figure 1: MS diversified symptomatology.

MS is typically diagnosed in young adults (twice as many women are involved as men) between 20 and 40 years of age and is usually characterized by an accumulation of disability in time, having a massive impact on everyday life. Three MS clinical phenotypes are well-defined according to the time interval between relapses, the recovery capacity, and the accumulation of disability [3]: *Relapsing-remitting MS (RRMS)* and *Primary-progressive MS (PPMS)* are the two main clinical sub-types that characterize the onset in the 85% and 10-15% of the cases, respectively; over 2/3 of RRMS cases will convert to *Secondary-progressive MS (SPMS)* within 10/15 years,

Both genetic and environmental aspects have a significant role in MS onset and, although a cure is not known yet, several disease modifying therapies (DMTs) are available. DMTs aim at delaying the progression of the disease and the consequent accumulation of disability, primarily avoiding the formation of new lesions [4]. Nowadays[5], 2.8 million people are living with MS around the globe (1 in 3,000 people). In Italy, 127,317 (1 every 500 people) people are living with MS, and 3.400 new people are diagnosed with MS every year(approximately 283 diagnoses every month). Since it is a chronic disease, MS represents a lifetime cost for the patient, caregivers, and the whole healthcare system. MS costs can be divided in direct (i.e. medical visits, MRI) and indirect costs (i.e. lack of productivity at work), which are more difficult to estimate properly, but are significantly higher than direct costs by a factor of three [6]. In Italy, MS direct costs for each patient range between 20,000 and 39,000 euros per year [7]. Since DMTs (Disesase Modifying Therapies) represent the largest direct medical cost for both patients and the health-care system, it is crucial to choose the most suitable treatment for each patient, as well as to change it when it loses efficacy, minimizing the risk of administering the wrong combination of therapies, and losing precious time and economical resources. In current medical practice, therapies are often selected and modified by trial-and-error[8, 9].

1.2. Challenges of personalized medicine for MS

MS is commonly differentially diagnosed following a suspect clinical manifestation, a condition identified as a clinically isolated syndrome (CIS). McDonald criteria are used and accepted by clinicians to confirm and guide the differential diagnosis of MS, and to minimize the risk of misdiagnosis, as the spectrum of MS symptoms is wide and may overlap with other diseases [10]. Since there is not a single diagnostic tool or a single symptom suggestive of MS, its diagnosis requires combining different clinical evaluations that include [2]:

- MRI data (lesion load and brain atrophy that assess lesion dissemination in time and space, and neurodegeneration),

- visual, motor, and sensory evoked potentials,
- cerebrospinal fluid (CSF) examination,
- general neurological examination.

Although, the Extended Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) are two accepted clinical measures (COMs) of the disease severity and progression[11], they cannot be considered complete, reliable, and exhaustive tools. EDSS is more used than MSFC but has some limitations, as EDSS scores can vary a lot due to the complex scoring rules and the subjectivity of the examiner. EDSS lacks linearity between score difference and clinical severity and it relies heavily on the evaluation of motor function and the ability to walk. Neither EDSS nor MSFC use MRIs evaluation in their scores. The main features on which COMs rely are their validity, their reliability, and their sensitivity to change. In recent years, EDSS limitations have pushed for the development of new, more comprehensive, and reliable COMs. Unfortunately, the inclusion of the evaluation of cognitive functions, fatigue, depression, and many other relevant features, is difficult because it is not clear how these hidden symptoms interact, and how to reliably evaluate and consistently quantify them [12].

Among these above mentioned hidden symptoms, the prevalence of cognitive impairment (CI) in MS is very high, ranging between 40% and 65%[13], and it is present in all MS subtypes (in terms of performances and affected domains)[14]. The cognitive domains impaired in MS are information processing speed, learning, and working memory, visual-spatial processing, executive functions and verbal fluency. Cognitive functions can be evaluated via different neuropsychological (NP) test batteries that estimate the degree of impairment through a variety of tasks that target different domains [14, 15]. Despite the profound effect of CI on the quality of life, and its presence since the very beginning of the disease, it is often neglected and not routinely assessed [16].

It is therefore clear that personalized medicine for neurodegenerative diseases like MS is an unmet clinical need, and that the currently used clinical and

imaging bio-markers are not able to follow disease progression at an individual level. In this context is thus crucial to adopt and implement tools that rely on multidimensional and composite prognostic bio-markers, taking into consideration the widest possible set of symptoms [16, 14].

2. Materials and Methods

This Review focuses on how, given the presence of correlations between different clinical data, computational methods belonging to the Machine Learning field can mitigate the limitations of current evaluation scales. To understand the complex interplay between MS manifestations and to provide reliable predictions on the disease evolution, requires both a systematic collection of heterogeneous clinical assessments, and reliable and explainable computational approach. In this context, Artificial Intelligence is becoming more and more reliable in identifying (bio)markers by integrating and analyzing large sets of data, and in discovering hidden knowledge and patterns[17]. However, such methods need to be trained on a huge amount of data, in order to be robust. Several databases that collect MS data do exist, for example the MSBase[1] dataset, or the Italian Multiple Sclerosis Registry[2]. Since the integration of data from different domains is a key step in analyzing SM progression, we analyze the most significant papers where NP test data for CI assessment is coupled with the investigation of different clinical features and measures, such as the analysis of brain magnetic resonance images (MRI), motor and gait functions, EDSS, and others. MS impact on the brain is usually investigated through MRI imaging. Automatic image analysis is an open field in literature, and while some of the presented papers adopted automatic measures, some others relied on manual annotation or visual estimation of image characteristics. The focus on CI is justified by its subtle and informative nature that can be assessed with non-invasive methods. Computerized NP tests enable a reliable and "normal-

[1] https://www.msbase.org/

[2] https://registroitalianosm.it/en/index.php

ized" data collection, which is the first step towards the quantification of the test performance, and the standardization of its administration.[1]. We explore how such contributions could pave the way to personalized medicine for the identification of bio-markers at an individual level, demonstrating the presence of correlation between different clinical measures which can in turn represent a knowledge base for the development of computational methods. We included both papers that adopted traditional paper-and-pencil or oral NP tests, as well as those which used computerized NP tests.

2.1. Selection criteria

We looked at papers published between 2000 and 2021 that evaluate the cognitive impairment of at least one cognitive domain via a NP test (administered either via a traditional paper-and-pencil approach or a computerized approach), and that look for correlations between cognitive measures and other clinical evidences. We selected 36 papers that explore the relationship between CI and MR images characteristics, and 32 papers that explore the CI in connection with motor functioning, fatigue and depression, as shown in Figure 2.



Figure 2: Works selection.

Since our focus is the integration of multi-domain data, we filtered out those works that do not investigate the relationships between cognitive impairment and at least two other disease domains. 24 papers were finally taken into consideration, 16 of which implement a computerized NP test by re-adapting a single traditional standardized test (oral or paper-and-pencil), or a complete NP test battery. The analysis carried out in the papers relies mostly on standard (and sometimes automated) statistical methods; the central point of our review is not

to discuss the methods, but instead to focus on the type of data they process and on their performances in order to understand their applicability into more advanced computational methods.

Although different single tests or test batteries are used, each paper evaluates more than one cognitive domain, and information processing speed is always taken into consideration. Self-administration plays a key role: some of the computerized tests were implemented to be smartphone-applications, with the aim of facilitating self-administration, while others are intended to be self-administered in clinics without any need for trained personnel. Cognitive assessment has different duration, spanning from a few minutes to hours, and different disease aspects are examined. Computerized tests permit data manipulation, facilitating multi-centre studies, standardization, and test administration during a single visit, thus saving precious time and resources [15]. Moreover, computerized applications make it easier to accurately measure reaction times that are crucial for the evaluation of the impairment of information processing speed that is the majorly involved cognitive domain; moreover, they can be integrated in self-monitoring smartphone applications that the patients can periodically use outside the clinic.

A rapid insight on the papers is given in Table 1 (computerized NP tests), and Table 2 (not computerized NP tests). For each paper we report the type of NP testing that was carried out, the duration of such testing (if given, in minutes), the type of MRI analysis and MRI metrics (if present), and other clinical data such as EDSS or motor function scales taken into consideration for patient assessment.

Table 1: Papers where NP tests are computerized

Author	*NPtest*	*Duration (min)*	*Score*	*MRI metrics*	*MRI analysis*	*Other Data*
Golan et. al [18]	CAB	60	Global cognitive score (GCS)	GM volume, WM volume	Automatic - icobrainms	EDSS, Patient determined disease steps (PDSS)
Razavi et. al [19]	ICA	5	ICS score	-	-	Serum neurofilaments NfL
Pham et. al [20]	MS Suite Test	15	Tests scores	Brain parenchymal fraction, T2 lesion load	Automatic	EDSS
Cohen et. al [21]	MSST	A few	MSST score	GM and WM volume, lesion load	SIENAX segmentation	-
Dongen et. al [22]	Multiple Screener	15	Tests scores	-	-	EDSS, disease severity, depression
Cotter et. al [23]	CANTAB	15	Test scores	-	-	Depression (GDS scale), EDSS, disease duration
Rudick et. al [24]	MSPT	30	Test scores	-	-	EDSS, disease duration, patient report
Rao et. al [25]	PST, 9PHT	A few	Test scores	T2 lesion load	Manual	EDSS
Edgar et. al [26]	CDR	20	Test scores	-	-	9PHT, EDSS, MSFC
Sonneville et. al [27]	Amsterdam NP test	70	Test scores	-	-	EDSS, disease duration
Lapshin et. al [28]	SDMT, PASAT	20	Test scores	-	-	-

Pellicano et. al [29]	ANAM	30	Test scoes	-	-	EDSS
Achiron et. al [30]	MCCB	50	GCS	T2 lesions volume, cortical thickness	Automatic	-
Boukalova et. al [31]	SDMT, PASAT	15	Tests scores	-	-	Level test
Arnett et. al [32]	SDMT, PASAT	15	Tests scores	-	-	Depression, coping
Papathan. et. al [33]	CNS-VS	30	Test scores	-	-	EDSS, depression
Macaron et. al [34]	PST	-	Test scores	Semi-automatic	Cord atrophy and deep GM volumes	Depression, multiple PROMs, employment
Baldassarri et. al [35]	NPTs	-	Test scores	Fully-automatic	T2LV, WBF, TV, CA	Multiple PROMs

Table 2: Papers where NP tests are not computerized

Author	*NPtest*	*Duration (min)*	*Score*	*MRI metrics*	*MRI analysis*	*Other Data*
Kuhle et. al [36]	BVMTR, CVLTII, and JLO	90	Test scores	-	-	NfL, EDSS, 9PHT, T25FWT
Kiiski et. al [37]	Adapted MACFIMS	35	Test scores	-	-	Evoked potentials ERPs
Patti et. al [38]	SDMT, PASAT, MCST and SRWL	90	Test scores	GM, WM volume	Automatic	EDSS
D'Orio et. al [39]	CVLT-II, BCMT-R, COWAT, WCST, PASAT	-	Test scores	-	-	Self-reported fall frequency, T25FWT

Lund et. al [40]	32 tests battery	-	Global score	T2 lesion load and volumes, normal appearing brain tissue	Semi-automatic thresholding	EDSS, MSIS
Sandi et. al [41]	BICAMS	15	BICAMS score	-	-	Fatigue, EDSS
Batista et. al [42]	-	Test score	Thalamus and neocortical atrophy	Semi-automatic	-	EDSS

3. Results

From the analysis of selected papers and the results they present, we infer some considerations about the existance of correlation between clinical data like MRI imaging and the types of NP tests mostly used for CI.

Golan et al.[18] explored the associations between brain volumes and cognitive scores derived from the Cognitive Assessment Battery (CAB). They focused on the most common MS phenotype, relapsing-remitting MS supporting the power of multi-domain assessment. They show a strong correlations between the global cognitive performance and brain volumes, both in grey matter and white matter, and highlight the possibility of investigating brain pathology through cognitive assessment, as thalamic and lateral ventricles volumes correlated with cognitive performance better than lesions and cortical volumes.

While the CAB battery requires 60 minutes to be completed, the test developed by Pham et al.[20] emulates the Symbol Digit Modalities Test (SDMT) [43] with a 15-minute smartphone-based application that is part of the MS Suite Test, a self-administered comprehensive battery. Test score positively correlated with brain parenchymal fraction and T2 lesion load. The cognitive domain targeted by such test is the information processing speed: traditional orally administered paper-and-pencil SDMT evaluates the performance by counting the

number of correct responses, loosing information about reaction times and insights on test execution. These information are instead not lost and easy to compute with a computerized approach.

The Processing Speed Test (PST), an iPad version for the SDMT, was developed by Rao et al. [25]: PST correlated with T2 white matter lesion load more strongly than SDMT, making the PST a more valid indicator of brain damage involvement in MS symptomatology. CI can manifest early and silently in disease course, when its signs are not detectable with traditional paper tests, and it would be useful to rely on tools that permit the identification of those patients for which the risk of conversion from the radiologically isolated syndrome (RIS) to the clinically defined MS (CDMS) is high and who benefit of a therapeutic intervention strategy before conversion, as the 51% of RIS patients convert to MS in 5 years from onset.

The extensive work of Macaron et al. [34] point out the value of the PST test: they demonstrate that the PST score is less susceptible to mood effects, and that it is associated with MRI metrics such as the measures of diffuse and focal white and gray matter injury. They suggest that the PST can be a valid marker of neurodegeneration. Baldassarri et al. [35] evaluated the associations between neuroperformance tests (NPTs), patient reported outcome measures (PROMs) and MRI metric, on one of the largest patient cohorts: among the NPTs they included the PST, the contrast sensitivity test (CST), the manual dexterity (MDT), and the walking speed test (WST). A fully-automated MRI analysis was performed, calculating the T2-lesion (T2LV) and thalamic (TV) volumes, the whole brain fraction (WBF), and the cervical spinal cord cross-sectional area (CA): this study is an example of a comprehensive and multi-domain assessment that enables to detect disease worsening.

The MS Screen Test (MSST) smartphone-based application battery was administered to a population of RIS patients by Cohen et al.[21], who managed to distinguish between healthy control and RIS patients, identifying correlations between MSST performances and gray/white matter volumes, and lesion load.

The involvement of cortical pathology and the interplays of gray and white

matter damage was also reported by Pellicano et al.[29] and Achiron et al.[30]. They did not rely on self-assessment tools, but instead implemented time demanding computerized batteries; they demonstrated the relevance of the relationship between CI and the damage of normal appearing grey matter and white matter volume loss in specific brain regions, that is not detectable with traditional MRI analysis.

Pellicano et al.[29] explored the role of normal-appearing white matter, cortical and normal-appearing gray matter volumes. They found correlations between test performances and brain volumes acquired with high-field MRI.

Achiron et al. [30] applied high-resolution imaging and observed that cortical thickness was present in specific brain regions and correlated with test scores. Although they did not consider several MS phenotypes, their results put in evidence that cortical pathology is related to cognitive impairment and that it involves specific brain areas.

Subclinical MS manifestations are lost with usual clinical assessment methods and need to be monitored with constancy. As already said, self-assessment permits the adaptation of tools for home testing and, if used in clinics, does not require the presence of a clinician, saving time and economical resources. This concept was exemplified by Dongen et al.[22], that adapted the Brief International Cognitive Assessment for MS (BICAMS) battery in the computerized Multiple Screener Battery, demonstrating its reliability, stressing the necessity of providing clinicians with digital tools for a rapid screening of MS patients, in order to collect baseline data and follow-up data.

As mentioned before, one of the needs in the monitoring of people with MS is the identification of the conversion between phenotypes: Lapshin et al.[28] did not specifically looked for correlations between clinical data but did demonstrate that via computerized tests it is possible to find differences between MS phenotypes, including the clinically isolated syndrome. The identification of disease phenotypes is crucial and challenging; Papathanasiou et al.[33] focused on RRMS and SPMS using the CNS-VS computerized batteries, pointing out the inadequacy of traditional tests, their dependence upon neuropsychologists,

and the amount of time required for carrying out the test and interpreting the results. However, they did not find specific cognitive patterns characteristic of each sub-type; this is suggestive of a highly variable neuropsychological conditions within the same disease type that is worth further exploring, relying on the assumption that a single clinical evidence cannot be sensitive to MS variability, neither NP tests, nor MRI measures.

Other MS characteristics need to be taken into consideration to complete the picture, such as disease course, its severity, duration, the degree of disability, and other factors. The Integrated Cognitive Assessment (ICA) battery developed by Razavi et al.[19] is feasible for a high-frequency administration, and strongly correlated with the level of serum neurofilament (NfL), a promising fluid biomarker that reflects neuronal damage for brain disorders. The correlation with the ICA scores is relevant as fluid biomarkers evaluation have higher costs and invasivity, lower accessibility and cannot be remotely tested.

The EDSS is the most used clinical outcome measure and brings with it several limitations: Rudick et al.[24] developed the MSPT to efficiently examine cognition, manual dexterity, visual function, balance, and walking speed via an iPad-based application, adapting the traditional 9PHT and SDMT in a new computerized version. Their findings correlated with EDSS estimated by clinicians without being prone to the reader and allowing repeatable results. The MSPT is therefore proposed as a valid alternative to EDSS.

Cotter et al. [23], used the Cambridge Neuropsychological Test Automated Battery (CANTAB) and took into consideration both the EDSS and depression, that was evaluated via a touchscreen version of the Geriatric Depression Scale (GDS).

Subtle but typical symptoms of MS are depression and fatigue, both difficult to objectively quantify. Arnett et al.[32] showed how depression and coping strategies are related to traditional SDMT and Paced Auditory Serial Addition Test (PASAT) scores, presenting the complex interactions between cognition and psychological conditions, where coping mechanisms vary between subjects, influencing depression and quality of life.

Studies included in this review evaluate fatigue via self-assessment or questionnaires, but it can also be estimated with gait-analysis, as it has several manifestations (Daly et al.[44]), even if it has a high variability, and it is prone to subjective perception.

The papers presented so far implement computerized tests or batteries for smartphone applications, which take a few minutes to complete, or more extended ones that are thought to be used in clinical setup. Advantages of computerized batteries are evident when comparing them to applications that follow the traditional approach of paper-and-pencil tests or oral tests. The Montreal Cognitive Assessment (MoCA) test, for instance, was orally administered by Abou et al.[45]. They found a correlation between MoCA paper performances, MRI measures, and physical disability, considering differences in sustained attention between disease phenotypes. Unfortunately, the oral administration of the test is prone to errors and have all the previous listed drawbacks; it is nevertheless relevant to notice, once again, that disease phenotypes are distinguishable using cognitive assessment.

Paper-and-pencil batteries are, in general, time consuming: the batteries proposed by Patti et al.[38] and Kule et al.[36] are 90 minutes long. Interestingly, Kule et al.[36] attempted to correlate brain volume, lesion load measures, EDSS, Nine-Hole Peg Test (9PHT), and Timed 25 Foot Walk (25FW) with serum NfL. They did not find significant correlation since NfL levels depend on immunomodulatory treatments that are not taken into consideration in this paper. This highlights the huge number of interplays that occur in MS.

Event related potentials (motor, visual or auditory) (ERPs) are another clinical exam often used in clinics to assess disease status and that reflect MS manifestations: Kiiski et al.[37] found that ERPs during a visual odd ball task could predict information processing speed deterioration, correlating ERPs findings with cognitive scores derived from an adaptation of the traditional Minimal Assessment of Cognitive Function in MS (MACFIMS) battery; given their results, they propose the ERPs as a valid alternative to long and not sensitive batteries to obtain objective and reproducible results.

4. Discussion

Through the analysis performed in this Review, it is possible to conclude that strong correlations between clinical data do exists. Moreover, the evidence of correlations between MRI metrics and several CI symptoms, strongly suggests that computerized NP assessment should be always paired with traditional imaging analysis, being informative and reliable against conventional MRI drawbacks, such as its difficulties in detecting cortical lesions.

Furthermore, fluid bio-markers are also object of discussion in several papers, and the evidence of their correlations with cognitive functions highlights the necessity of investigating how expensive or invasive physiological exams and NP tests are, related to each other. To understand that, means to understand how and when such examination can be used in combination, or when cognitive assessment can partially substitute time consuming exams that are not always administered to large patient cohorts.

The comparison between works that use computerized adaptation of neuropsychological tests and those that perform traditional NP tests, allowed us to summarise the advantages of computerized NP assessment:

- they are not subject to reader's errors when reporting scores,
- they are scalable, accessible,
- they permit a frequent administration and a continuous monitoring of MS patients, collecting reliable data while reducing the risk of missing important and subtle changes in the clinical status (generally, MS patients undergo a neurological visit per year).
- they do not necessarily depend on the presence of a clinician, being often categorized as a self-assessment tools,
- they are not invasive,
- they permit the measure of precise reaction times during the test,

- fast NP assessment can be used for detecting those patients who need a full cognitive examination, while allowing a precise and complete screening of every patient,

- they can be integrated with external tools for gait-assessment, ERPs, or eye-tracking technologies, allowing to collect multiple clinical data synchronously, in the exact same conditions.

The evidence of correlations between such clinical metrics and NP tests support the idea of providing neurologists with efficient and clinically meaningful tools for monitoring patients over time, easily including baseline evaluations and progression, and having the possibility of practically manipulating data and comparing it with standardised data-sets.

Different clinical exams can be computerized: several software applications have been developed for image analysis, fatigue assessment, gait-analysis, and, as we have highlighted in this review, the same thing can be done with cognition. The use of scales or tools that are more precise and valid, is a promising direction along with the practical adoption of such tools in the everyday clinical practice: the majority of papers selected for this review that followed this approach were published between 2019 and 2020, being a clear sign of the attention that these topics are gaining.

Finally, given the limitations of clinical scales such as EDSS, Artificial Intelligence (AI) approaches, as machine learning or deep learning algorithms, are promising tools to attempt identifying new bio-markers of disease status and progression. AI methods allow the manipulation of big data, extracting useful information that can deepen the knowledge in disease mechanisms, and resolve the unsatisfied need of digital bio-markers [46]. AI is also extremely useful in highlighting subtle but important differences between subjects, and is therefore a promising approach towards personalized medicine by consolidating the therapeutic choices for every single patient, defining a risk profile, providing supplementary information, and minimizing therapeutic costs.

5. Conclusions

Personalized medicine for neuro-degenerative diseases like Multiple Sclerosis is a still unmet clinical need which can be addressed via efficient data integration and extraction from private or publicly available electronic health databases. The implementation of computerized cognitive assessment in the routine clinical practice is a promising direction that can have practical and positive effects on MS monitoring, enabling an easy collection and manipulation of clinical data. It also allows frequent self-monitoring, which minimizes the risk of loosing informative but rare disease manifestations, and allows the acquisition of measures that can not be detected during traditional examinations, such as reactions to stimuli. This field needs further exploration, but its relevance is clear.

The complexity of neurological diseases can be tackled with Artificial Intelligence approaches. Such methods, to be reliable and explainable, require a huge amount of data for training and testing: computerized approaches allow the incorporation of clinical data with public available data-set, and this can certainly help in the definition of a prognostic bio-marker capable of adequately integrate information about disease domains.

This Review presented MS as a heterogeneous disease on which it is necessary to deepen the knowledge taking advantage of the amount of data that can be acquired following a computerized approach. It is possible to integrate measurements that correspond to different disease domains and the combination of such evidences can compensate the downsides that, nowadays, hinder an efficient implementation of MS patients monitoring, such as costs in terms of time and resources.

References

[1] Denissen, Stijn, et al. , Towards multimodal machine learning prediction of individual cognitive evolution in multiple sclerosis, Journal of Personalized Medicine 11 (12) (2021) 1349. doi:https://doi.org/10.3390/jpm11121349.

[2] Goldenberg, M. Marvin, Multiple Sclerosis Review, Pharmacy and Therapeutics 37 (3) (2010) 175.

[3] I. Grossman, A. Miller., Multiple Sclerosis pharmacogenetics: Personalized Approach towards Tailored Therapeutics, EPMA 1 (1) (2010) 317–27. doi:10.1007/s13167-010-0020-7.

[4] Calabresi, A. Peter, Diagnosis and Management of Multiple Sclerosis, American Family Physician 70 (10) (2004) 1935–44.

[5] 2020 data from the atlas of ms, https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms.

[6] Maria Pia Amato et al., The Costs of Multiple Sclerosis: A Cross-Sectional, Multicenter Cost-of-Illness Study in Italy, Journal of Neurology 249 (2) (2002) 152–63. doi:10.1007/PL00007858.

[7] M. Ponzio et al., Economic Impact of Multiple Sclerosis in Italy: Focus on Rehabilitation Costs, Neurological Sciences 36 (2) (2015) 227–34. doi:10.1007/s10072-014-1925-z.

[8] G. Kobelt et al., New Insights into the Burden and Costs of Multiple Sclerosis in Europe, Multiple Sclerosis 23 (8) (2017) 1123–36. doi:10.1177/1352458517694432.

[9] G. Furneri et al., Cost-effectiveness analysis of escalating to natalizumab or switching among immunomodulators in relapsing-remitting Multiple Sclerosis in Italy, BMC Health Services Research 19 (1) (2019) 436. doi:10.1186/s12913-019-4264-1.

[10] Thompson, J. Alan, Diagnosis of Multiple Sclerosis: 2017 Revisions of the McDonald Criteria, The Lancet. Neurology 17 (2) (2018) 162–73. doi:10.1016/S1474-4422(17)30470-2.

[11] Meyer-Moock, Sandra, et al., Systematic literature review and validity evaluation of the expanded disability status scale (edss) and the multi-

ple sclerosis functional composite (msfc) in patients with multiple sclerosis, BMC Neurology 14 (2014) 58. doi:https://doi.org/10.1186/1471-2377-14-58.

[12] H.Inojosa et al., Clinical Outcome Measures in Multiple Sclerosis: A Review, Autoimmunity Reviews 19 (5). doi:10.1016/j.autrev.2020.102512.

[13] Maria Pia Amato et al., Cognitive Assessment in Multiple Sclerosis - an italian consensus, Neurological Sciences 39 (8) (2018) 1317–24. doi:10.1007/s10072-018-3427-x.

[14] Huijbregts et al., Cognitive Impairment and Decline in Different MS Subtypes, Journal of the Neurological Sciences 245 (1-2) (2006) 187–94. doi:10.1016/j.jns.2005.07.018.

[15] R. Kalb et al., Recommendations for cognitive screening and management in Multiple Sclerosis care, Multiple Sclerosis 24 (13) (2018) 1665–80. doi:10.1177/1352458518803785.

[16] I. K. Penner, Evaluation of cognition and fatigue in Multiple Sclerosis: Daily practice and future directions, Acta Neurologica Scandinavica 134 (S200) (2016) 19–23. doi:10.1111/ane.12651.

[17] Manglani, Heena R., et al., Demand with low supply: A pipeline for personalized integrative medicine in multiple sclerosis, Multiple Sclerosis and Related Disorders 58 (12) (2022) 103493.

[18] E. D'Amico et al., The association between mri brain volumes and computerized cognitive scores of people with Multiple Sclerosis, Brain and Cognition 145 (10). doi:10.3390/ijms17101725.

[19] Khaligh-Razavi, Seyed-Mahdi et al., A self-administered, artificial intelligence (AI) platform for cognitive assessment in Multiple Sclerosis (ms), Brain and Cognition 20 (1) (2020) 193. doi:10.3390/ijms17101725.

[20] L.Pham et al., Smartphone-based Symbol-Digit Modalities Test reliably measures cognitive function in Multiple Sclerosis patients, MedRxivdoi:10.1101/2020.03.09.20033316.

[21] M. Cohen et al., Digital biomarkers can highlight subtle clinical differences in radiologically isolated syndrome compared to healthy controls, Journal of Neurologydoi:10.1007/s00415-020-10276-w.

[22] Dongen et al., Introducing multiple screener: An unsupervised digital screening tool for cognitive deficits in MS, Multiple Sclerosis and Related Disorders 38. doi:10.1016/j.msard.2019.101479.

[23] Cotter et al., Investigating domain-specific cognitive impairment among patients with Multiple Sclerosis using touchscreen cognitive testing in routine clinical care, Frontiers in Neurology 9 (5). doi:10.3389/fneur.2018.00331.

[24] R.Rudick et al., The Multiple Sclerosis performance test (MSPT): An ipad-based disability assessment tool, Journal of Visualized Experiments : JoVE (88). doi:10.3791/51318.

[25] S.M. Rao et al., Processing speed test: Validation of a self-administered, IPad®-based tool for screening cognitive dysfunction in a clinic setting, Multiple Sclerosis 23 (14) (2017) 1929–37. doi:10.1177/1352458516688955.

[26] C.Edgar et al., Cognitive performance in relapsing remitting Multiple Sclerosis: A longitudinal study in daily practice using a brief computerized cognitive battery, BMC Neurology 11 (2011) 68. doi:10.1186/1471-2377-11-68.

[27] L.M. J. De Sonneville et al., Information processing characteristics in subtypes of Multiple Sclerosis, Neuropsychologia 40 (11) (2002) 1751–65. doi:10.1016/S0028-3932(02)00041-6.

[28] H. Lapshin et al., Detecting cognitive dysfunction in a busy Multiple Sclerosis clinical setting: A computer generated approach, European Journal of Neurology 21 (2) (2014) 281–86. doi:https://doi.org/10.1111/ene.12292.

[29] C. Pellicano et al., Cognitive impairment and its relation to imaging measures in Multiple Sclerosis: A study using a computerized battery, Journal of Neuroimaging: Official Journal of the American Society of Neuroimaging 23 (3) (2013) 445–52. doi:10.1111/j.1552-6569.2011.00687.x.

[30] A. Achiron et al., Superior temporal gyrus thickness correlates with cognitive performance in Multiple Sclerosis, Brain Structure and Function 218 (4) (2013) 943–50. doi:10.1007/s00429-012-0440-3.

[31] A. K. Boukhvalova et al., Smartphone level test measures disability in several neurological domains for patients with Multiple Sclerosis, Frontiers in Neurology 10 (2019) 943–50. doi:10.3389/fneur.2019.00358.

[32] P.A. Arnett et al., Relationship between coping, cognitive dysfunction and depression in Multiple Sclerosis, The Clinical Neuropsychologist 16 (3) (2002) 341–55. doi:10.1076/clin.16.3.341.13852.

[33] A. Papathanasiouet al., Cognitive impairment in relapsing remitting and secondary progressive Multiple Sclerosis patients: Efficacy of a computerized cognitive screening battery, ISRN Neurology 2014. doi:10.1155/2014/151379.

[34] Macaron, G., et al., Cognitive processing speed in multiple sclerosis clinical practice: Association with patient-reported outcomes, employment and magnetic resonance imaging metrics, European Journal of Neurology 27 (2020) 1238–49. doi:https://doi.org/10.1111/ene.14239.

[35] Baldassari, Laura E., et al., Technology-enabled comprehensive characterization of multiple sclerosis in clinical practice, Multiple Sclerosis and

Related Disorders 38 (2020) 101525. doi:https://doi.org/10.1016/j.msard.2019.101525.

[36] J. Kuhle al., Serum neurofilament is associated with progression of brain atrophy and disability in early ms, Neurology 88 (9) (2017) 826–31. doi:10.1212/WNL.0000000000003653.

[37] H. Kiiski al., Machine learning EEG to predict cognitive functioning and processing speed over a 2-year period in Multiple Sclerosis patients and controls, Brain Topography 31 (3) (2018) 346–63. doi:10.1007/s10548-018-0620-4.

[38] F. Patti et al., Lesion load may predict long-term cognitive dysfunction in Multiple Sclerosis patients, PLoS ONE 10 (3). doi:10.1371/journal.pone.0120754.

[39] V. D'Orio et al., Cognitive and motor functioning in patients with Multiple Sclerosis: Neuropsychological predictors of walking speed and falls, Journal of the Neurological Sciences 125 (5) (2012) 338–44. doi:10.1111/j.1600-0404.2011.01574.x.

[40] H. Lund et al., Cognitive deficits in Multiple Sclerosis: Correlations with T2 changes in normal appearing brain tissue, Acta Neurologica Scandinavica 125 (5) (2012) 338–44. doi:10.1111/j.1600-0404.2011.01574.x.

[41] D.Sandi et al., The hungarian validation of the brief international cognitive assessment for Multiple Sclerosis (BICAMS) battery and the correlation of cognitive impairment with fatigue and quality of life, Multiple Sclerosis and Related Disorders 4 (6) (2015) 499–504. doi:10.1016/j.msard.2015.07.006.

[42] S. Batista et al., Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in Multiple Sclerosis, Journal of Neurology 259 (1) (2012) 139–46. doi:10.1007/s00415-011-6147-1.

[43] S. Batista et al., Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for Multiple Sclerosis, Multiple Sclerosis 23 (5) (2017) 721–33. doi:10.1177/1352458517690821.

[44] Daly et al., Neuropsychological function in patients with chronic fatigue syndrome, Multiple Sclerosis, and depression, Applied Neuropsychology 8 (12-22). doi:10.1207/S15324826AN0801_3.

[45] A. Abouelmaaty al., Correlation between brain magnetic resonance imaging, cognitive dysfunction and physical disability in Multiple Sclerosis, Journal of the Neurological Sciences 405 (2019) 332. doi:10.1016/j.jns.2019.10.1452.

[46] S. J. Goodwin, Multiple Sclerosis: integration of modeling with biology, clinical and imaging measures to provide better monitoring of disease progression and prediction of outcome, Neural Regeneration Research 11 (12) (2016) 1900–03. doi:10.4103/1673-5374.195274.