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ORIGINAL ARTICLE

The Italian Neuroimaging Network Initiative (INNI): enabling the use of advanced MRI techniques in patients with MS

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Abstract Magnetic resonance imaging (MRI) is an important paraclinical tool to diagnose and monitor multiple sclerosis (MS). Conventional MRI measures lack of pathological specificity and are weakly correlated with MS clinical manifestations. Advanced MRI techniques are improving the understanding of the mechanisms underlying tissue injury, repair, and functional adaptation in MS; however, they require careful standardization. The definition of standardized methods for the collection and analysis of advanced MRI techniques is central not only to improve the understanding of disease pathophysiology and evolution, but also to generate research hypotheses, monitor treatment, increase cost-effectiveness and power of clinical trials. We promoted the Italian Neuroimaging Network Initiative (INNI), involving centers and investigators with an International recognized expertise, with the major goal to determine and validate novel MRI biomarkers to be utilized as predictors and/or outcomes in future MS studies. The INNI initiative supported the creation of a centralized repository, where advanced structural and functional MRI scans available at the participating sites, with the related clinical and neuropsychological data, are collected. These data will be used to perform research studies to identify clinical, neuropsychological and imaging biomarkers characteristics of the entire spectrum of MS. INNI will be instrumental to help to define standardized MRI and clinical protocols towards an increasing uptake of personalized interventions for people with MS at a national and international level. Upon approval of the INNI Steering Committee, the data collected in the online database will be shared with any research center detailing specific research proposals on disease pathophysiology or treatment effects.

Keywords Multiple sclerosis · Magnetic resonance imaging · Advanced MRI techniques · Network · Data sharing

Members of INNI Network is listed in the acknowledgements.

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Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease affecting the central nervous system (CNS) of young adults in Western countries leading, in most cases, to severe and irreversible clinical disability. Magnetic resonance imaging (MRI) has an high sensitivity in detecting macroscopic tissue abnormalities in patients with MS. Conventional MR sequences

(dual-echo, fluid-attenuated inversion recovery and T1-weighted imaging) provide important pieces of information for diagnosing MS [1–3], understanding its natural history, and assessing treatment efficacy [4, 5]. Unfortunately and despite this, standardization of MR procedures outside the setting of clinical trials (with regard to scanning protocol and frequency, sequence parameters, and outcome measures) is still lacking. Furthermore, in patients with established MS, the strength of the associations between conventional MRI findings and the clinical manifestations of the disease remains modest, at best. This is likely due to the low specificity of conventional MRI in the evaluation of the heterogeneous pathological substrates of the disease, its inability to provide an estimate of such a damage outside focal lesions, and the fact that it does not give information on the mechanisms through which the CNS recovers after tissue injury has occurred.

The identification of clinical, neuropsychological and imaging biomarkers characteristic of the entire spectrum of MS, and the definition of standardized methods for their collection and analysis are central not only to improve the understanding of disease pathophysiology and evolution, but also to generate research hypotheses, monitor treatment, and increase cost-effectiveness and power of clinical trials. The application of modern structural and functional MRI techniques to the study of MS patients is improving the understanding of the mechanisms responsible for the accumulation of irreversible clinical deficits in this disease. While structural MR techniques have allowed to quantify in vivo the extent and severity of disease-related damage in the different CNS compartments [6–10], the use of functional imaging techniques has highlighted that the presence and efficiency of brain plasticity might have a role in limiting the clinical consequences of MS-related tissue damage, at least at some stages of the disease [11, 12].

Despite having provided important pieces of information, the studies conducted so far in MS have several drawbacks, including the small samples of patients enrolled (which are representative of a limited range of clinical phenotypes), and the recruitment of selected groups of patients (for instance, without overt clinical impairment of the investigated systems). As a consequence, it remains to be established whether their results are robust enough to be considered representative of what really occurs in MS as a whole. Furthermore, advanced MRI techniques still require careful standardization, monitoring of scanner stability over time, and normative values as a reference. Therefore, despite the extensive use of these techniques in the research setting of highly specialized centers, their application in the assessment of MS patients in routine clinical practice has yet to be realized. In addition, a standardization of advanced MRI across different centers remains challenging. Should this be achieved, it would be possible to collect large MRI data sets of MS patients, who would enable generating and testing specific hypotheses.

Against this background, we promoted the Italian Neuroimaging Network Initiative (INNI), which involves centers and investigators with an International recognized expertise, with the major goal to determine and validate novel MRI biomarkers to be utilized as predictors and/or outcomes in future MS studies. In addition, INNI aims also to guide the application of MRI in MS at a national level.

The first two goals of this initiative were: (1) the creation of a web-based system with available clinical, neuropsychological and MRI data at the participating centers, to allow data sharing; (2) the use of such data to perform large-scale studies to define the role of clinical, neuropsychological and advanced imaging biomarkers in understanding MS pathophysiology. Subsequently, the INNI initiative will help to define standardized MRI and clinical protocols for the evaluation of patients with MS at a national level in Italy, allowing to integrate a large amount of data obtained from different centers. Responsible data sharing is in the public interest, however, it raises complex challenges. To help addressing these challenges and to answer people with MS 'call to action', the Italian MS Society Foundation, in line with its the Research Strategy Map [13], has promoted a data sharing research initiative. Within this framework, INNI will be instrumental towards an increasing uptake of personalized interventions for people with MS.

Here, we present the project, the centers involved, the structure and rules governing the initiative and the web-based system of clinical, neuropsychological and MRI data that has been implemented to allow data sharing.

Methods

The INNI project has been promoted by the Neuroimaging Study Group of the Italian Society of Neurology and is financially supported by a research Grant from the Fondazione Italiana Sclerosi Multipla (FISM 2013/S/1). FISM is the owner of the database, according to the Italian law on copyright. INNI currently involves four MS centers in Italy (Milan, Neuroimaging Research Unit, San Raffaele Scientific Institute; Rome, Department of Neurology and Psychiatry, Sapienza University; Naples, Department of Neurological Sciences, Second University of Naples/Neurological Institute for Diagnosis and Care ''Hermitage Capodimonte''; Siena, Department of Medicine, Surgery and Neuroscience, University of Siena).

The first phase of the project was dedicated to legal issues and to obtaining approval from local Ethical committees at the founding sites. A Steering Committee (SC) was appointed, including representatives of the four

promoting centers and of FISM. The SC ensures that the INNI project adheres to the study design and methodology laid out in the Grant submission. In the first project phase, the SC took care of: (1) defining inclusion/exclusion criteria and creating standard forms for the collection of clinical, neuropsychological and MRI data; (2) supporting the creation of the online database where such data have to be uploaded; and (3) defining guidelines to regulate the access levels to the online database.

INNI database

Main inclusion/exclusion criteria

To be included in the database, subjects have to be healthy controls (i.e., subjects with no previous history of neurological, psychiatric, or medical disorders, and a normal neurological exam), or patients with clinically definite MS, a clinically isolated syndrome (CIS) suggestive of MS, or a radiologically isolated syndrome (RIS). For patients, a neurological evaluation within 6 months from the MRI scan is also required. Only adult subjects (i.e., age $\geq$18 years) are included in the database.

Neurological evaluation

The variables chosen for inclusion in the INNI neurological evaluation form are reported in Table 1. Such form includes a section with the main information about disease history (e.g., disease onset date, type of onset, date of evolution to progressive phenotypes, information about previous relapses, etc.) and one section with global and specific clinical disability scales. Disease-modifying and symptomatic treatments (with treatment start and end dates) can also be recorded into the system.

Neuropsychological assessment

The variables chosen for inclusion in the INNI neuropsychological evaluation form are reported in Table 2. In this form, it is possible to collect scores from the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) [14], Brief International Cognitive Assessment of Multiple Sclerosis (BICAMS) [15], Wisconsin card sorting test (WCST) [16], Stroop test [17], MS quality of life-54 items (MSQoL-54) questionnaire [18], as well as information about fatigue [19, 20] and depression [21–23].

The INNI online platform includes optional forms, where results of blood, evoked potentials and cerebrospinal fluid examinations can be entered.

Table 1 Neurological information collected in the INNI database

Category	Collected variable
Date	Visit date
Disease history	Phenotype*
	Multiple choice: ☐ HC; ☐ RIS; ☐ CIS; ☐ RRMS; ☐ SPMS; ☐ PPMS; ☐ BMS; ☐ Other
	Type of onset*
	Multiple choice: ☐ Monofocal; ☐ Multifocal; ☐ NA
	Symptoms
	Multiple choice: ☐ ON; ☐ Hemispheric; ☐ Brainstem-Cerebellum; ☐ Spinal cord; ☐ Other
	Disease onset date
	Date of conversion to CDMS
	Date of evolution to SPMS
	Date of evolution to BMS
	Date of reaching EDSS = 4
	Date of reaching EDSS = 6
	Disease duration
	Last relapse date
	Last steroid treatment date
	Total number of previous relapses
	Relapses involving the right upper limb
Clinical scales	EDSS*
	Pyramidal FS
	Cerebellar FS
	Brainstem FS
	Sensory FS
	Bowel and bladder FS
	Visual FS
	Mental FS
	MSFC
	Ambulation index
	Right and left maximum FT (30 s)
	Right and left 9HPT
	T25FW

Fields marked with (*) are mandatory

HC healthy control, *RIS* radiologically isolated syndrome, *CIS* clinically isolated syndrome, *MS* multiple sclerosis, *RR* relapsing-remitting, *SP* secondary progressive, *PP* primary progressive, *BMS* benign multiple sclerosis, *CD* clinically definite, *ON* optic neuritis, *NA* not applicable, *EDSS* expanded disability status scale, *FS* functional score, *FT* finger tapping, *9HPT* nine hole peg test, *T25FW* timed 25-foot walk test

MRI examination

Since advanced MR techniques [in particular, diffusion tensor (DT) MRI and resting state (RS) fMRI] particularly benefit from the use of high-field magnets, it was decided to include in the online database only MRI scans acquired at 3.0 T (at least in the initial phase of the project).

Table 2 Neuropsychological information collected in the INNI database

Category	Collected variable
Date	Visit date
BRB-N battery	SRT
	SPART
	SDMT
	PASAT 2″/3″
	WLG
BICAMS	CVLT-II
	BVMT-R
WCST	Number of administered tests
	Total number of errors
	Percentage of errors
	Perseverative responses
	Percentage of perseverative responses
	Perseverative errors
	Percentage of perseverative errors
	Not perseverative errors
	Percentage of not perseverative errors
	Conceptual level responses
	Percentage of conceptual level responses
	Number of categories completed
Stroop (short version or 100 items)	Interference time (raw, corrected or equivalent score)
	Interference errors (raw, corrected or equivalent score)
MSQoL-54	Physical score
	Mental score
Fatigue	FSS
	MFIS (total, physical, cognitive and psychosocial scores)
Depression	MADRS
	CMDI
	BDI
	STAI-Y1/Y2

BRB-N brief repeatable battery of neuropsychological tests, *SRT* selective reminding test, *SPART* spatial recall test, *SDMT* symbol digit modalities test, *PASAT* paced auditory serial addition test, *WLG* word list generation, *WCST* Wisconsin card sorting test, *BICAMS* Brief International Cognitive Assessment of Multiple Sclerosis, *CVLT* California verbal learning test, *BVMT-R* brief visuospatial memory test—revised, *MSQoL-54* MS quality of life—54 items, *FSS* fatigue severity scale, *MFIS* modified fatigue impact scale, *MADRS* Montgomery–Asberg depression scale, *CMDI* Chicago multiscale depression inventory, *BDI* Beck depression inventory, *STAI* state-trait anxiety inventory

Based on surveys collected at the participating sites and of the cumulative experience of the SC members, it was decided that the MRI protocol had to include (minimum requirements): (1) sequences for lesion quantification [dual echo (DE) or T2-weighted/fluid-attenuated inversion recovery (FLAIR) scans] acquired with axial orientation and a slice thickness of no more than 3 mm; (2) sequences for atrophy quantification acquired using high-resolution 3D T1-weighted scans [24]; (3) DT MRI sequences acquired with $\sim$30 diffusion-weighted direction and a nearly isotropic spatial resolution [25]; (4) RS fMRI sequences covering all brain, with at least 140 scans and an acquisition session at least 5 min long [26].

Additional advanced MRI sequences (such as double inversion recovery, magnetization transfer MRI, susceptibility weighted imaging, etc.) can be uploaded, whenever available.

Creation of the INNI online database

The INNI online database was developed in collaboration with the consortium GARR, the Italian network for research and education (http://www.garr.it). The INNI platform allows the central collection of subjects' clinical, neuropsychological and MRI data by means of user-friendly interfaces. When uploaded into the system,

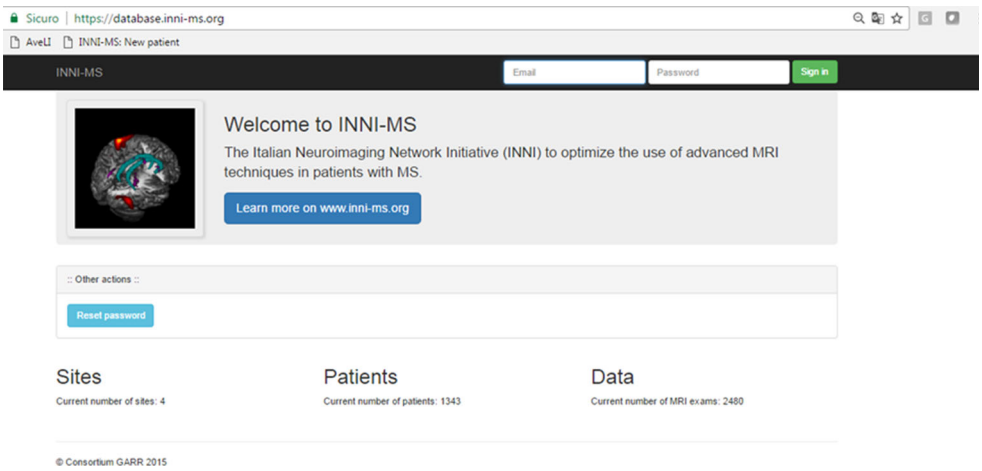

Fig. 1 Home page of the INNI online platform. Database functions are available only upon signing in with appropriate login and password

DICOM files are automatically split into the different sequences composing the examination, and a semi-automatic assignment of each sequence to the appropriate label (e.g., DE, FLAIR, 3D T1, DT MRI, RS fMRI, etc.) is performed. No identifying patients' information is stored in the INNI platform: patient data are assigned to a unique identification code (ID). To ensure subjects' privacy, any personal information is also deleted from the DICOM files.

The online INNI database is available at: https://database.inni-ms.org. It was developed by the GARR consortium in 2015 and formally tested in November 2016. The database content is available for authorized users only, who received appropriate login and password. For each participating center, two profiles can access the INNI database: (1) the Site Administrator (site responsible and main contact person), and (2) the Data Manager, who is in charge for data upload.

Guidelines for the access to the INNI online data

The SC defined different profiles for centers who are willing to join the INNI initiative. According to their category (research or profit institutions) and according to the number of patients shared in the online platform, the center will be defined as "Research User", "Research Contributor", "Profit User" or "Profit Contributor", with different restrictions on visibility of database content and access to the data. More details about these profiles can be found on the website http://www.inni-ms.org (Fig. 1).

Data analysis

On 13th January 2017, a query was run on database content, and an Excel sheet including all uploaded MRI scans was produced. To be included in this search, MRI data had to be coupled with a valid demographic/neurological assessment. We performed some descriptive analyses on this population using SPSS software version 23.0. The main subjects' characteristics were reported as means ± standard deviations (SD) or frequencies for continuous and categorical variables, respectively.

Results

Neurological evaluation

Data from 1310 subjects with a baseline neurological evaluation have been uploaded in the INNI database. There are 908 patients with MS (304/604 males/females, mean age = 39.8 years, SD = 11.4 years) and 402 healthy controls (183/219 males/females, mean age = 40 years, SD = 15.3 years). The main demographic and clinical characteristics of these subjects are shown in Table 3. In details, there are 590 patients (65%) with relapsing-remitting (RR) MS, 139 (15%) secondary progressive (SP) MS, 58 (6%) benign MS (defined as a disease duration ≥15 years and an EDSS ≤3.0), 62 (7%) primary progressive (PP) MS, 53 (6%) CIS and 6 (1%) RIS patients. Figure 2 shows the frequency of compilation of the main neurological variables included in the online form. Of the 908 MS patients included in the database, 90 (10%) have only a baseline neurological evaluation, while 817 (90%) have at least one follow-up neurological evaluation (total number of follow-up examinations = 838, median follow-up time = 1.04 years, range = 14 days–7.5 years).

Neuropsychological assessment

Two-hundred and two healthy controls (50.2%) and 865 MS patients (95.2%) underwent at least one neuropsychological evaluation. The frequency of compilation of the main neuropsychological variables in the online form is

Table 3 Main demographic and clinical information of healthy subjects and patients with multiple sclerosis (MS) collected in the INNI database

	Healthy subjects $N = 402$	All MS patients $N = 907$	CIS patients $N = 53$	RRMS patients $N = 590$	BMS patients $N = 58$	SPMS patients $N = 139$	PPMS patients $N = 62$
M/F	183/219	303/604	25/28	185/405	22/36	45/94	29/33
Mean age [years] (range)	40.0 (18–77)	39.8 (18–77)	29.9 (18–50)	36.9 (18–63)	43.8 (28–66)	48.9 (26–68)	52.4 (30–77)
RH/LH/A	382/12/8	847/31/29	51/2/0	553/18/19	51/3/4	126/6/5	60/1/1
Mean education [years] (range)	15.4 (5–20)	13.3 (3–20)	13.5 (8–20)	13.6 (4–20)	14.0 (8–20)	12.3 (5–20)	11.7 (3–18)
Mean disease duration [years] (range)	–	11.4 (0.04–45)	0.9 (0.09–13)	8.9 (0.04–39)	20.5 (15–36)	20.2 (1–44)	14.5 (2–45)
Median EDSS (range)	–	2.0 (0.0–9.0)	1.0 (0.0–2.0)	1.5 (0.0–7.0)	2.0 (1.0–3.0)	6.0 (1.0–9.0)	6.0 (2.5–8.5)

M male, *F* female, *RH* right handers, *LH* left handers, *A* ambidextrous, *CIS* clinically isolated syndrome, *RR* relapsing-remitting, *BMS* benign multiple sclerosis, *SP* secondary progressive, *PP* primary progressive, *EDSS* Expanded Disability Status Scale

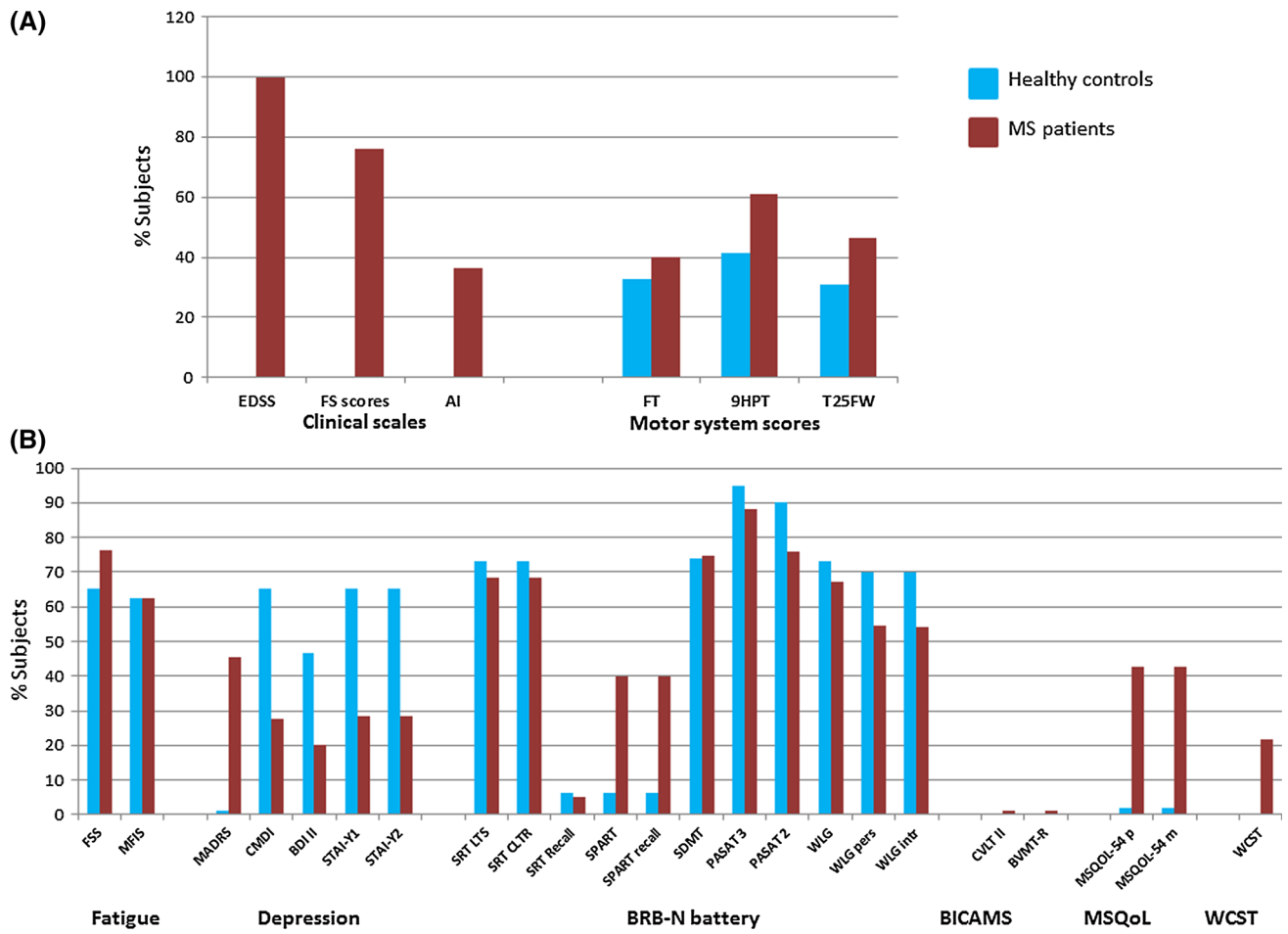

Fig. 2 Frequency of compilation of the main neurological (**a**) and neuropsychological (**b**) scores of the INNI database in patients with multiple sclerosis (MS) and healthy controls. *EDSS* Expanded Disability Status Scale score, *FS* functional systems, *AI* ambulation index, *FT* finger tapping, *9HPT* nine hole peg test, *T25FW* timed 25-foot walk, *FSS* fatigue severity scale, *MFIS* modified fatigue impact scale, *MADRS* Montgomery–Asberg depression scale, *CMDI* Chicago multiscale depression inventory, *BDI* Beck depression inventory; *STAI* state-trait anxiety inventory, *SRT* selective reminding test, *LTS* long term storage, *CLTR* consistent long term retrieval, *SPART* spatial recall test, *SDMT* symbol digit modalities test, *PASAT* paced auditory serial addition test, *WLG* word list generation, *MSQoL* MS Quality of life—54 items (p = physical; m = mental), *CVLT* California verbal learning test, *BVMT-R* brief visuospatial memory test—revised, *WCST* Wisconsin card sorting test

Table 4 Parameters used for the acquisition of the main MRI sequences included in the INNI database

Sequence	Milan	Naples	Rome	Siena
Coil	8-channel head coil	8-channel head coil	12-channel head coil	32-channel head coil
Dual echo	TR = range 2599–2910 ms	TR = 3080 ms	TR = range 3320-5310 ms	TR = 4000 ms
	TE = 16/80 ms	TE = 24/127.5 ms	TE = 10/103 ms	TE = 15/100 ms
	FA = 90°	FA = 90°	FA = 150°	FA = 90°
	Matrix = 256 × 256	Matrix = 256 × 384	Matrix = 384 × 384	Matrix = 240 × 240 (recon 352 × 352)
	FOV = 240 × 240 mm	FOV = 240 × 240 mm	FOV = 220 × 220 mm	FOV = 240 × 240 mm
	Thickness = 3 mm	Thickness = 3 mm	Thickness = range 3 mm	Thickness = 3 mm
	No. of slices = range 44–50	No. of slices = 44	No. of slices = range 45	No. of slices = 44
	Orientation = axial	Orientation = axial	Orientation = axial	Orientation = axial
3D T1-weighted	TR = 25 ms	TR = 6.988 ms	TR = 1900 ms	TR = 10 ms
	TE = 4.6 ms	TE = 2.85 ms	TE = 2.9 ms	TE = 3.9 ms
	FA = 30°	TI = 650 ms	TI = 900 ms	TI = 900 ms
	Matrix = 256 × 256	FA = 8°	FA = 9°	FA = 8°
	FOV = 230 × 230 × 176 mm	Matrix = 256 × 256	matrix = 256 × 256	Matrix = 256 × 256
	Thickness = 0.8 mm	FOV = 256 × 256 × 199.2 mm	FOV = 256 × 256 × 176 mm	FOV = 256 × 256 × 192 mm
	No. of slices = 220	Thickness = 1.2 mm	Thickness = 1 mm	Thickness = 1 mm
	Orientation = axial	No. of slices = 166	No. of slices = 176	No. of slices = 192
	TR = 7.0 ms	Orientation = sagittal	Orientation = sagittal	Orientation = axial
	TE = 3.2 ms			
	TI = 900 ms			
	FA = 8°			
	Matrix = 256 × 240			
	FOV = 256 × 240 × 192 mm			
	Thickness = 1 mm			
	No. of slices = 192			
	Orientation = sagittal			
DT MRI	TR = 8775 ms	TR = 10,000 ms	TR = 12,200 ms	TR = 7036 ms
	TE = 58 ms	TE = 83 ms	TE = 94 ms	TE = 95 ms
	FA = 90°	FA = 90°	FA = 90°	FA = 90°
	Matrix = 112 × 88	Matrix = 128 × 128	Matrix = 96 × 96	Matrix = 128 × 96
	FOV = 240 × 230 mm	FOV = 320 × 320 mm	FOV = 192 × 192	FOV = 320 × 240 mm
	Thickness = 2.3 mm	Thickness = 2.5 mm	Thickness = 2 mm	Thickness = 2.5 mm
	No. of slices = 55	No. of slices = 38	No. of slices = 72	No. of slices = 50
	Orientation = axial	Orientation = axial	Orientation = axial	Orientation = axial
	b values = 0/900 s/mm^2	*b* values = 0/1000 s/mm^2	*b* values = 0/1000 s/mm^2	*b* values = 0/900 s/mm^2
	Diffusion directions = 35	Diffusion directions = 32	Diffusion directions = 30	Diffusion directions = 33

Table 4 continued

Sequence	Milan	Naples	Rome	Siena
RS fMRI	TR = 3000 ms	TR = 1508 ms	TR = 3000 ms	TR = 3000 ms
	TE = 35 ms	TE = 32 ms	TE = 30 ms	TE = 35 ms
	FA = 90°	FA = 90°	FA = 89°	FA = 90°
	Matrix = 128 × 128	Matrix = 64 × 64	Matrix = 64 × 64	Matrix = 128 × 128
	FOV = 240 × 240 mm	FOV = 256 × 256 mm	FOV = 192z192 mm	FOV = 240 × 240 mm
	Thickness = 4 mm	Thickness = 4 mm	Thickness = 3 mm	Thickness = 4 mm
	No. of slices = 30	No. of slices = 29	No. of slices = 50	No. of slices = 30
	Orientation = axial	Orientation = axial	Orientation = axial	Orientation = axial
	No. of scans = 200	No. of scans = 240	No. of scans = range 140–200	No. of scans = 200

DT MRI diffusion tensor magnetic resonance imaging, *RS fMRI* resting state functional magnetic resonance imaging, *TR* repetition time, *TE* echo time, *TI* inversion time, *FA* flip angle, *FOV* field of view

reported in Fig. 2. Most frequently collected tests were the paced auditory serial addition test (PASAT) and symbol digit modalities test (SDMT) scores of the BRB-N battery, and information about fatigue. Depression scores were collected in the majority of MS patients, using different depression scales across sites. Ninety-five healthy controls (47%) and 810 MS patients (93%) have at least one follow-up neuropsychological evaluation (total number of follow-up examinations = 652, median follow-up time = 1.18 - years, range = 4 days–7.5 years).

MRI examination

MRI scans were all acquired using 3.0 T scanners (Milan and Siena: Intera and Achieva, respectively, Philips Medical Systems, Best, The Netherlands; Rome: Magnetom Verio, Siemens, Erlangen, Germany; Naples: Signa HDxt, GE Healthcare, Milwaukee, USA). The parameters of the main MRI sequences used at each site are summarized in Table 4.

Of the 1310 subjects with a baseline MRI scan, 116 healthy controls (29%) and 467 MS patients (51%) have at least one follow-up examination (total number of follow-up scans = 1087, median follow-up time = 1 year, range = 2 days–7.5 years). All main MRI sequences were acquired in the large majority of subjects, as shown in Fig. 3.

Discussion

In this paper, we present the INNI initiative, a network created by four centres leading the neuroimaging research of MS in Italy, with the major goal to define standardized methods of collection and analysis of advanced MR imaging techniques, and to identify clinical, neuropsychological and imaging biomarkers characteristic of the entire spectrum of MS. The online platform for the central collection of data is now ready, and includes a rather large population of control subjects and MS patients. These subjects have a homogeneous neurological and neuropsychological evaluation, and the MRI acquisition was performed with a similar strategy across sites. Major scanner upgrades have been codified into the database, to perform proper adjustments of the MRI analysis produced by using INNI data. Therefore, future analysis run on subjects from the INNI database are likely to be powerful, accurate and representative of the general MS population. The large number of subjects included in the database will also allow to select samples with homogeneous and particular characteristics (to address specific research questions) or to perform studies on rare disease phenotypes (which are usually underrepresented in single center studies).

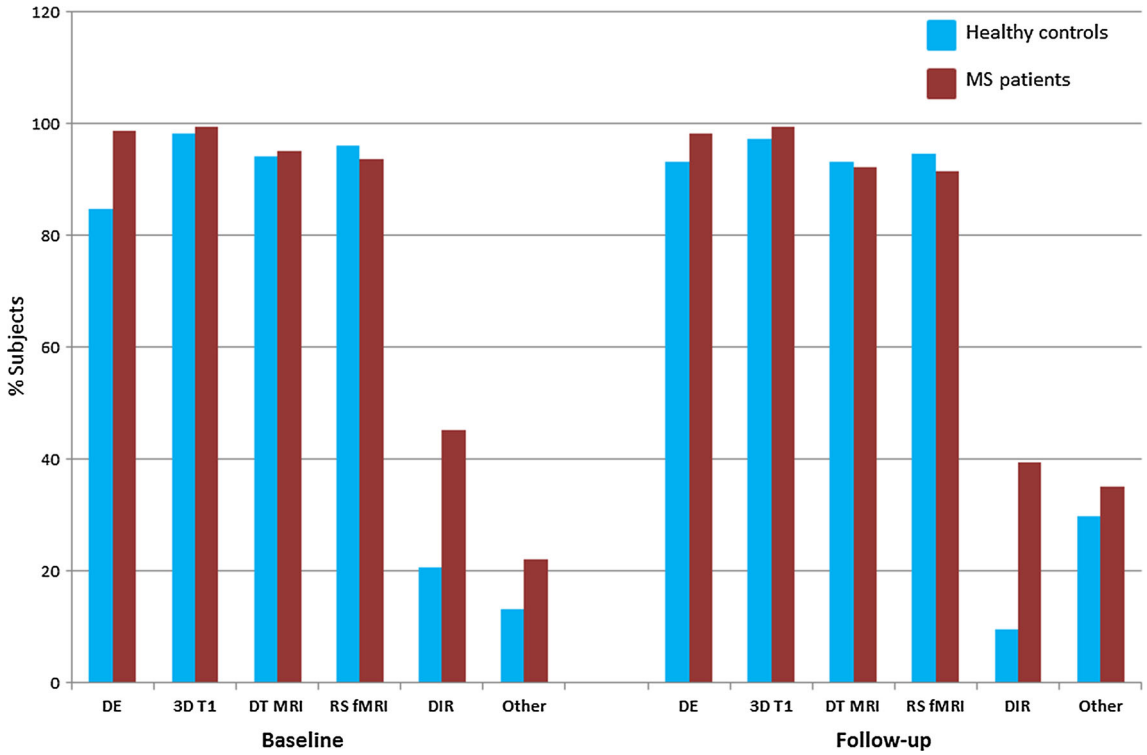

Fig. 3 Frequency of acquisition of the main MRI sequences of the INNI database in patients with multiple sclerosis (MS) and healthy controls, at baseline and follow-up examinations. *DE* dual echo, *DT MRI* diffusion tensor MRI, *RS fMRI* resting state functional MRI, *DIR* double inversion recovery

The next step of the INNI initiative will be to use the data available in the database for specific research projects. Planned, short-term research projects include: (1) investigation of functional abnormalities within RS networks related to cognition and correlation with structural damage within cognitive-related tracts and cognitive performance; (2) exploration of abnormalities of the sensorimotor RS network and their association with clinical and MRI variables; (3) assessment of RS functional connectivity alterations in the main brain functional networks according to T2 lesion volume (high vs low) and physical/cognitive disability scores (high vs low) to explore the functional substrates of the extremes of the clinical-MRI paradox observed in MS; (4) quantification of global and regional distribution of white matter and gray matter lesions, with the creation of lesion probability maps of white matter and cortical lesions, and correlation between lesion location in the different white matter/gray matter structures and dysfunction of selected brain networks at rest.

In addition to performing specific research studies, future aims of the INNI network will be the creation of a standardized protocol of acquisition of advanced structural and functional MR techniques, to be applied for the study of patients with MS. This will allow to homogenize the approach to MS patients at a national level. This will require the circulation of a questionnaire to all the centers which have an interest to the project to collect information concerning scanners and coils, as well MRI parameters currently employed for the study of patients with MS. Then, after considering the sequences that are at present used at each center, a common acquisition protocol will be defined. In a first phase, only sequences for the quantification of T2 lesions and atrophy (DE, FLAIR, 3D T1-weighted MRI) will be standardized. Advanced MRI sequences (DT MRI, RS fMRI, DIR and MT MRI) might be applied initially only at sites predisposed to or currently using these techniques, and also for these sequences a common protocol will be designed. The common standardized protocol will include some suggestions for periodical quality assessment (QA) of MRI images, to monitor MRI scanners performances and avoid image quality deterioration with time. If required, peripheral centers will be helped in the set-up of the protocol, through a dummy run procedure. The data acquired with the standardized protocol will be made available in the INNI online database for future projects. These dataset will represent an invaluable source for future studies of predictors of the disease.

Another long-term goal of the INNI initiative will be instructing neurologists involved in the cure of MS patients in the use, evaluation and interpretation of information derived from advanced MRI techniques. This will imply to

design standardized and centralized procedures for daily-life implementation of advanced MRI measures. Providing harmonization of procedures and allowing selection for evidence-based therapeutic strategies, will play a key role for a better management of the disease.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest M Filippi is Editor-in-Chief of the *Journal of Neurology*; serves on a scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Merk-Serono, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer's Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA). G. Tedeschi has received compensation for consulting services and/or speaking activities from Bayer Schering Pharma, Biogen Idec, Merck Serono, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck Serono, and Fondazione Italiana Sclerosi Multipla. Antonio Gallo received honoraria for speaking and travel Grants from Biogen, Sanofi-Aventis, Merck Serono, Genzyme, Teva, Bayer-Schering and Novartis. P. Pantano has received funding for travel from Novartis, Genzyme and Bracco and speaker honoraria from Biogen. N. De Stefano has received honoraria from Schering, Biogen Idec, Teva Pharmaceutical Industries Ltd, Novartis, Genzyme Corporation, Roche, and Merck for consulting services, speaking, and travel support. He serves on advisory boards for Biogen Idec, Merck, Novartis, Genzyme Corporation, and Roche. He has received research Grant support from the Italian MS Society. P. Zaratin works for Fondazione Italiana Sclerosi Multipla. M.A. Rocca received speakers honoraria from Biogen Idec, Novartis, Genzyme, Sanofi-Aventis, Teva and Merk Serono and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla.

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