

# The Italian Alzheimer's Disease Neuroimaging Initiative (I-ADNI): Validation of Structural MR Imaging

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database (<http://adni.loni.usc.edu/>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf).

**Abstract.**

**Background:** The North American Alzheimer's Disease Neuroimaging Initiative (NA-ADNI) was the first program to develop standardized procedures for Alzheimer's disease (AD) imaging biomarker collection.

**Objective:** We describe the validation of acquisition and processing of structural magnetic resonance imaging (MRI) in different Italian academic AD clinics following NA-ADNI procedures.

**Methods:** 373 patients with subjective memory impairment ( $n = 12$ ), mild cognitive impairment ( $n = 92$ ), Alzheimer's dementia ( $n = 253$ ), and frontotemporal dementia ( $n = 16$ ) were enrolled in 9 Italian centers. 22 cognitively healthy elderly controls were also included. MRI site qualification and MP-RAGE quality assessment was applied following the NA-ADNI procedures. Indices of validity were: (i) NA-ADNI phantom's signal-to-noise and contrast-to-noise ratio, (ii) proportion of images passing quality control, (iii) comparability of automated intracranial volume (ICV) estimates across scanners, and (iv) known-group validity of manual hippocampal volumetry.

**Results:** Results on Phantom and Volunteers scans showed that I-ADNI acquisition parameters were comparable with those one of the ranked-A ADNI scans. Eighty-seven percent of I-ADNI MPRAGE images were ranked of high quality in comparison of 69% of NA-ADNI. ICV showed homogeneous variances across scanners except for Siemens scanners at 3.0 Tesla ( $p = 0.039$ ). A significant difference in hippocampal volume was found between AD and controls on 1.5 Tesla scans ( $p < 0.001$ ), confirming known group validity test.

**Conclusion:** This study has provided standardization of MRI acquisition and imaging marker collection across different Italian clinical units and equipment. This is a mandatory step to the implementation of imaging biomarkers in clinical routine for early and differential diagnosis.

**Keywords:** Alzheimer's disease, hippocampus, intracranial volume, magnetic resonance imaging, mild cognitive impairment, standardized operating procedures

## INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disorder. Over the last few years, there has been strong interest in identifying individuals at earlier stages of AD, before AD dementia criteria are met [1]. Several biomarkers, both biological and imaging, have been introduced in the new diagnostic NIA-AA criteria for AD [2, 3]. These are indicators of specific changes characterizing the in vivo neuropathological cascade that occurs during different clinical stages of AD [4, 5].

Although sophisticated quantitative methods to analyze neuroimaging markers do exist, it should be underlined that standardization of these imaging markers is currently limited, and results often vary from laboratory to laboratory [2]. Heterogeneity of biomarker collection and measurement is a barrier to their translation into daily clinical practice. For these reasons, several worldwide initiatives are developing standard operating procedures to minimize the variability of biomarkers collection. The North American Alzheimer's Disease Neuroimaging Initiative (NA-ADNI) [6, 7] represents the flagship program that established a platform for biomarker collection and measurement with standardized procedures. The major goals of the NA-ADNI are: (i) to develop improved methods that will lead to uniform standards for acquiring longitudinal multisite magnetic resonance imaging

(MRI) and positron emission tomography (PET) data on patients with AD, patients with mild cognitive impairment (MCI), and elderly controls, and (ii) to build an accessible data repository that describes the biomarkers longitudinal changes [8]. After the development of the NA-ADNI, other ADNI initiatives were established. In Europe, the pilot European-ADNI (E-ADNI) and AddNeuroMed were the first initiatives to implement the MRI protocol of acquisition compatible to the NA-ADNI [9–11]. ADNI initiative have also been launched in South America (Argentina-ADNI) and Asia (Japan, Korea, Taiwan, and China) [12, 13]. The Australian ADNI, also known as the Australian Imaging Biomarkers and Lifestyle Flagship Study of Aging (AIBL), was launched in 2006 with the intention of recruiting 1,000 individuals (over the aged 60) who underwent neuroimaging biomarkers in order to assess their utility as AD indicators [14]. All of these worldwide initiatives have been set up to develop AD biomarkers using the same ADNI standardized MRI and clinical protocols.

This paper illustrates the design and early results of Italian ADNI (I-ADNI). The NA-ADNI platform for structural MRI was implemented in nine Italian academic outpatient memory clinics covering the national territory with the main aim to promote the use of structural MRI ADNI sequences. I-ADNI applied the NA-ADNI imaging protocol on a naturalistic series of patients with cognitive disorders. The validity

of acquisition and processing was estimated detecting: signal-to-noise ratio and contrast-to-noise ratios; quality control pass; comparability of craniometric features (intracranial volume) across scanners; and known-group validity of brain structural features (hippocampal volume).

## MATERIALS AND METHODS

Nine Italian academic Memory Clinics have been involved in the study. The Coordinating Center was IRCCS Centro San Giovanni di Dio, Brescia (OU1, PI: G.B. Frisoni). The academic Memory clinics involved in the project were: IRCCS Santa Lucia Foundation, Rome (OU2, PI: U. Sabatini); SDN Foundation Naples, Naples (OU3, PI: A. Soricelli); Campus Bio\_Medico University, Rome (OU4, PI: F. Vernieri); University of Foggia (OU5, PI: C. Babiloni); Fond. IRCCS Istituto Neurologico Besta, Milan (OU6, PI: M.G. Bruzzone); IRCCS Mondino National Institute of Neurology Foundation, Pavia (OU7, PI: E Sinforiani); Second University of Naples, Naples (OU8, PI: G. Tedeschi); and Centro Neurolesi “Bonino-Pulejo”, Messina (OU9, PI: P. Bramanti).

The Coordinating Center was responsible for clinical and MRI data including: case report form development, implementation of clinical and neuropsychological database, implementation of ADNI platform for structural MRI, MR sequences storage, MRI quality control. In addition, the overall data analysis was carried out by IRCCS Centro San Giovanni di Dio Fatebenefratelli. The project management was taken by Giovanni B. Frisoni. The study protocol was approved by the local ethics committee and all participants signed informed participation consents.

### Patients

The nine Italian academic Memory Clinics enrolled 395 outpatients between 1 January 2009 and 31

October 2011. Twelve of them were subjective memory impairment (SMI) individuals, 92 MCI patients, 253 AD patients, and 16 frontotemporal dementia (FTD) patients. In addition, a group of 22 cognitive intact persons (CTRL) participated voluntarily in the study. The exclusion criteria were: stroke, psychiatric diseases, neurological diseases other than cognitive impairment. Clinical criteria for each diagnosis were: NINCDS-ADRDA criteria for probable AD [15] and Nears Criteria for FTD [16]; MCI was defined as the presence of objective impairment in memory or other cognitive domains (performance lower than the fifth percentile on neuropsychological tests as detailed below) in the absence of functional impairment. SMI individuals were persons worried about their memory performances without any objective cognitive deficit. All participants underwent a clinical and neuropsychological assessment.

### Clinical and neuropsychological assessment

We assessed global cognition with the Mini-Mental State Examination (MMSE) [17] and depressive symptoms using the pertinent subscales of the Brief Symptom Inventory (BSI) [18]. BSI subscores range from 0 to 4, higher scores indicating more severe symptoms. The Clinical Dementia Rating scale was used to quantify the severity of symptoms of dementia. We administered a set of neuropsychological tests to assess long term memory (Story Recall Test, Rey–Osterrieth complex figure, recall), attention and executive functions (Trail Making Test A and B), language abilities (Letter and Category Fluency Test), and visuo-spatial skills (Rey–Osterrieth complex figure, Copy). We corrected the results for age and education, according to the Italian normative populations. Moreover, hypertension, heart disease, diabetes mellitus, and hypercholesterolemia were investigated based on clinical history. Finally, the Instrumental Activities of Daily Living were collected to assess the functional status of subjects [19].

Table 1  
Demographic features of the Italian ADNI sample

Diagnosis		Controls	p	SMI	p	MCI	p	AD	p	FTD
	n 1.5 T/3 T	18/4		6/6		69/23		152/101		13/3
	n total	22		12		92		253		16
General features	Age, y	70 ± 7	–	68 ± 12	–	70 ± 7	–	71 ± 27	–	69 ± 9
	Education, y	9 ± 5	–	10 ± 5	–	8 ± 4	–	8 ± 5	*	12 ± 6
	Women	16 (73%)	–	8 (66%)	–	50 (54%)	–	160 (63%)	*	4 (25%)
Clinical features	MMSE	29 ± 1	–	29 ± 1	–	27 ± 2	*	20 ± 5	–	20 ± 6

\**p* values <0.05 between adjacent groups on ANOVA, Chi-square, or Fisher tests. n 1.5 T/3 T, number of subjects scanned at 1.5 or 3.0 Tesla; SMI, subjective memory impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease; FTD, frontotemporal dementia; MMSE, Mini-Mental State Examination. Values denote mean ± standard deviation or number (%).

Table 2  
 Technical features of ADNI-qualified scanners and number of MPRAGE scans acquired during the study

Center (OU)/Scanner location	Manufacturer/model	Field strength	Coil	MP-RAGE (n)
IRCCS Centro S. Giovanni di Dio (OU1), Brescia	GE Signa Excite	1.5 T	8 channels head	23
IRCCS Fondazione S. Lucia (OU2), Rome	Siemens Allegra	3 T	8 channels head	27
Fond. SDN Naples (OU3), Naples	Philips Achieva	3 T	8 channels head	63
University Campus Bio_Medico (OU4), Rome	Siemens, Avanto	1.5 T	8 channel head	63
University of Foggia/"La Sapienza" University (OU5), Rome	Siemens Sonata	1.5 T	Body	27
Fond. IRCCS Istituto Neurologico Besta (OU6), Milan	Siemens Avanto	1.5 T	12 channels head	25
Fond. IRCCS Mondino (OU7), Pavia	Philips Intera	1.5 T	8 channel head	48
University of Naples (OU8), Naples	GE Signa HDx 14.0_M5A	3 T	8 channel head	43
Centro Neurolesi "Bonino-Pulejo" (OU9), Messina	Siemens Sonata	1.5 T	8 channel head	24

### MR imaging

#### Data acquisition

Three hundred and forty-three MR scans from routine patients were acquired, of which 210 at 1.5 and 133 at 3.0 Tesla respectively. MRI acquisition activities were divided into: i) a preparatory phase, ii) site qualification, iii) experimental subjects scanning, and iv) MP-RAGE quality ranking of overall images acquired.

The preparatory phase involved the collection of the I-ADNI MRI scanner features in terms of manufacturer, coils adopted, and magnetic strength (see Table 2). The description of the practical procedures concerning the image transmission of the data collected in this study on a centralized repository at the FBF has been detailed to every partner of the I-ADNI consortium.

The site qualification phase entailed the successful installation of the ADNI sequences. This step consisted in setting up and checking the correct configuration of the official ADNI protocol parameters (<http://adni.loni.usc.edu/methods/documents/mri-protocols/>) on every scanner of the project according to the features collected. The scan protocol included: 1) Localizer Scan (20 s); 2) Straight Sagittal 3D Magnetization-Prepared Rapid Acquisition Gradient-echo (MPRAGE) (8–10 min); 3) Straight Sagittal 3D MPRAGE – REPEAT – (8–10 min); 4) B1 Calibration Scan Phase Array Coil (if applicable) (30 s); 5) B1 Calibration Scan Body Coil (if applicable) (30 s); and 6) Axial Dual Echo T2 Fast Spin Echo (FSE) (5 min). Furthermore, OU2-OU3 and OU8 acquired diffusion tensor imaging and resting state functional MRI sequences (not reported here).

To test if MRI passed the qualification phase, each I-ADNI center acquired the whole scan protocol on a local volunteer subject to verify the adherence to the official ADNI protocol and the absence of artifacts

(e.g., movement, ringing, wrap around, metal artifacts). The MPRAGE images were corrected following the image correction steps (i.e., N3, B1, and GradWarp) provided by ADNI (<http://adni.loni.usc.edu/methods/mri-analysis/mri-pre-processing/>) and specific indexes of MRI signal quality (i.e., signal to noise ratio (SNR) and peak signal to noise ratio (PSNR)) were derived considering the whole brain slices of the 3D stack. Then, the above parameters have been compared with ranked-A ADNI reference scans in order to define the goodness of the I-ADNI site acquisition. The main software adopted during the site qualification phase were ImageJ, MIPAV, MRIcro, MNI tools, and the Gradient Non-linearity Unwarping Tool.

Starting from year 2 onward, the NA-ADNI MagPhan<sup>®</sup> phantom was circulated among all I-ADNI sites to measure *post-hoc* inter-scanner signal repeatability. The ADNI phantom consists of spherical inclusions inside a 20 cm diameter water-filled clear urethane shell. Inclusions are copper sulfate filled polycarbonate spherical shells: four 3.0 cm spheres with copper sulfate concentrations of 0.9, 1.2, 1.7, and 2.4 mM are used for SNR and contrast noise ratio (CNR) information measurements.

During the whole lifetime of the project, each MPRAGE sequence was graded for artifacts in a qualitative manner by an experienced individual at the Coordinating Centre. In line with NA-ADNI procedures (<http://www.adni-info.org/Scientists/Pdfs/adni-procedures-manual12.pdf>), a scan with a 1 ranking was considered a high quality scan, a 2 ranking was considered a medium quality scan, and a 3 ranking was considered a low quality scan. From the NA-ADNI database, we extracted MPRAGE ranking of 791 scans acquired by ADNI protocol and compared the proportion of MPRAGE assessed of high quality between the I-ADNI and the NA-ADNI. All the I-ADNI MPRAGE images used in the present article are those with a high-quality evaluation.

#### *Automated intracranial volume*

The intracranial volumes (ICV) of the I-ADNI cohort were segmented with the Freesurfer (5.1 version) image analysis package (<http://surfer.nmr.mgh.harvard.edu/>). The automated procedure for image segmentation and volume measurement includes the following steps [20]: intensity normalization [21], removal of non-brain tissue [22], and transformation to Talairach space. This technique has been widely validated against manual tracings in healthy individuals and patients with neurologic diseases [20, 23]. Moreover, from the NA-ADNI database (<https://ida.loni.usc.edu/login.jsp>), we selected the ICVs measured by Freesurfer of 745 subjects matched by age, gender, strength field, protocol of MPRAGE acquisition (ADNI1), and scanner models to our I-ADNI subjects. Subsequently, we compared the homogeneity variances of ICV among scanners of the two different cohorts stratified by strength field.

#### *Information on the ADNI*

Data used in the preparation of this article were obtained from the ADNI database (<http://adni.loni.usc.edu/>). The NA-ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a \$60 million, 5-year public private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date, these three protocols have recruited over 1,500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for

ADNI-1, ADNI-2, and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see <http://www.adni-info.org/>.

#### *Manual hippocampal segmentation*

##### *Hippocampal boundary*

All the hippocampi were manually segmented according to a prototype of the Harmonized Protocol for the Hippocampal Volumetry [24]. The most rostral slice was considered where the hippocampus was separated from the amygdala by the alveus. The boundaries of the hippocampal head were considered the most medial gray matter (GM), i.e., the visible morphological boundary of the structure, adjacent to liquor of the ambient cistern. The ventral boundary of the hippocampus was defined by the white matter (WM) of the parahippocampal gyrus. The medial boundary was the boundary with the WM of the parahippocampal gyrus and/or the liquor of the ambient and the perimesencephalic cistern. In the most caudal slices, the medial boundaries consisted of the GM belonging to the isthmus, or to the vestigial hippocampal tissue that has been excluded from the tracing. The software used for the manual segmentation was the Multitracer V1.0 software.

##### *Learning phase*

Ten NA-ADNI MPRAGE images with different medial temporal lobe atrophy at Medial Temporal Atrophy Scale [25] acquired twice (both 1.5 and 3 Tesla) on the same subjects were selected. An expert tracer from the coordinating center segmented the hippocampi of these images according to the protocol described above. These segmentations were considered the reference standard. A tracer, from each operative unit, segmented the 10 NA-ADNI MPRAGE images twice according to the strength field of each MRI scan. The learning phase was considered concluded once each tracer achieved an intra-class coefficient of correlation (ICC) greater than 0.80. Reliability results on manual hippocampal segmentation showed an ICC between 0.85 and 0.99 (Supplementary Table 1, test-retest reliability). The inter-rater reliability versus the reference standard tracing ranged from 0.86 to 0.99 at 3T, and from 0.82 to 0.97 at 1.5T scanners (Supplementary Table 1, inter-rater reliability versus reference). Considering only OUs at 3T, we found an ICC of 0.93 (CI 95%  $0.81 \pm 0.95$ ) for the right hippocampus, and of 0.92 (CI 95%  $0.78 \pm 0.98$ ) for the left one, while 1.5 Tesla scanners showed an ICC of

0.87 (CI 95%  $0.66 \pm 0.98$ ) for the right and 0.93 (CI 95%  $0.76 \pm 0.99$ ) for the left hippocampus.

After the learning phase, all the MPRAGE images were manually oriented along the anterior-posterior commissural line by the MRIcro software and the hippocampi of the entire sample were manually traced from each OU.

#### Statistical analysis

After the assessment of the homoscedasticity with the Bartlett test, MPRAGE phantom acquisition scans were compared among different I-ADNI sites using the analysis of the variance (ANOVA).

Sociodemographic and clinical features, neuropsychological performances, and ICVs were compared among clinical groups with the ANOVA for continuous variables (*post-hoc* analysis were done using Bonferroni correction), and with the  $\chi^2$  test for dichotomous variables. The Levene's test was applied to verify the homogeneity of variances of ICVs acquired using the same scanner model between I-ADNI and NA-ADNI cohort. For each center, the intra-class correlation coefficient (absolute model) of hippocampal tracings was computed to assess the intra- and inter-reliability. A test of linear trend was executed to test whether the right/left hippocampal volumes, manually traced, were linearly related to the disease progression (from CTRL to AD), across different field strengths. Moreover, known group validity by the Mann-Whitney U-test was executed comparing the hippocampal volume of controls and AD patients. All statistical analyses were performed using SPSS software version 12.0.

## RESULTS

Sociodemographic features revealed no significant difference among groups except for the educational level, where MCI and AD were less educated than FTD patients ( $p=0.028$  and  $p=0.007$ , respectively). Moreover, FTD were mainly men than AD patients ( $p=0.003$ , Table 1). The activities of daily living were more compromised in AD than MCI patients ( $p<0.001$ , Supplementary Table 2). Neuropsychological performances showed a significant global cognitive deterioration in AD than MCI ( $p<0.001$ ). Moreover, MCI performed worse than SMI ( $p<0.001$ ) and, as expected, AD patients were more impaired than MCI ( $p<0.001$ ) in long term memory performances. Furthermore, AD patients showed significantly lower language and psychomotor speed abilities than MCI

patients ( $p<0.001$  and  $p=0.019$  respectively, Supplementary Table 2). As expected, the main clinical features of SMI were memory complaints in absence of objective cognitive deficits and functional impairment. Instead, MCI patients were characterized by the presence of cognitive decline in one or more domain without functional impairment. AD patients showed a severe cognitive impairment with a greater functional deterioration (Supplementary Table 3).

#### ADNI phantom's SNR and CNR results

Table 2 reports the technical features of each scanner and the number of MPRAGE sequences acquired in each OU. Details of the protocols adopted by the different I-ADNI sites are represented in Supplementary Table 4a. Test-retest scanning sessions were acquired from a group of 9 volunteers (56% male and 44% female, mean age  $42 \pm 18$  years). From each volunteer, two T13D (scan-rescan) and one axial-PD/T2-FSE volumes (8 sites, 1 subject per site, 16 T13D acquisitions, 8 Dual Echo FSE acquisitions) were obtained. The nine scanners showed good adherence to the original NA-ADNI protocol with negligible changes in terms of both spatial and temporal resolution. During the site qualification phase, every I-ADNI MPRAGE scan was rated by SNR and PSNR. These metrics were equal and even better than those of the ranked-A scans acquired in the original NA-ADNI study, indicating good acquisition quality. All the I-ADNI sites successfully performed the site qualification phase (Supplementary Table 4b). The inter scanner signal repeatability results from post-hoc analysis on the MagPhan<sup>®</sup> phantom are summarized in Fig. 1. The SNR analyses consist of extracting from the image data the spherical regions of the four copper sulfate shells. SNR intensity values were taken as the mean intensity of the voxels in that area. The mean intensity of a subsection of  $35 \times 35$  voxels band immediately outside the phantom shell was taken as estimation of the background signal. CNR intensity values were then computed as signal differences among all pairs of spherical shells. Seven out of nine I-ADNI sites exhibited similar SNR and CNR patterns to each other ( $p>0.05$ ). Only one center (OU8) displayed slight warping effect distortion. The remaining two I-ADNI centers (OU2 and OU4) acquired the phantom but the data were not analyzed due to technical issues (i.e., phantom rotated; not fitted into the coil; not positioned properly; not identical location with respect to the isocenter).

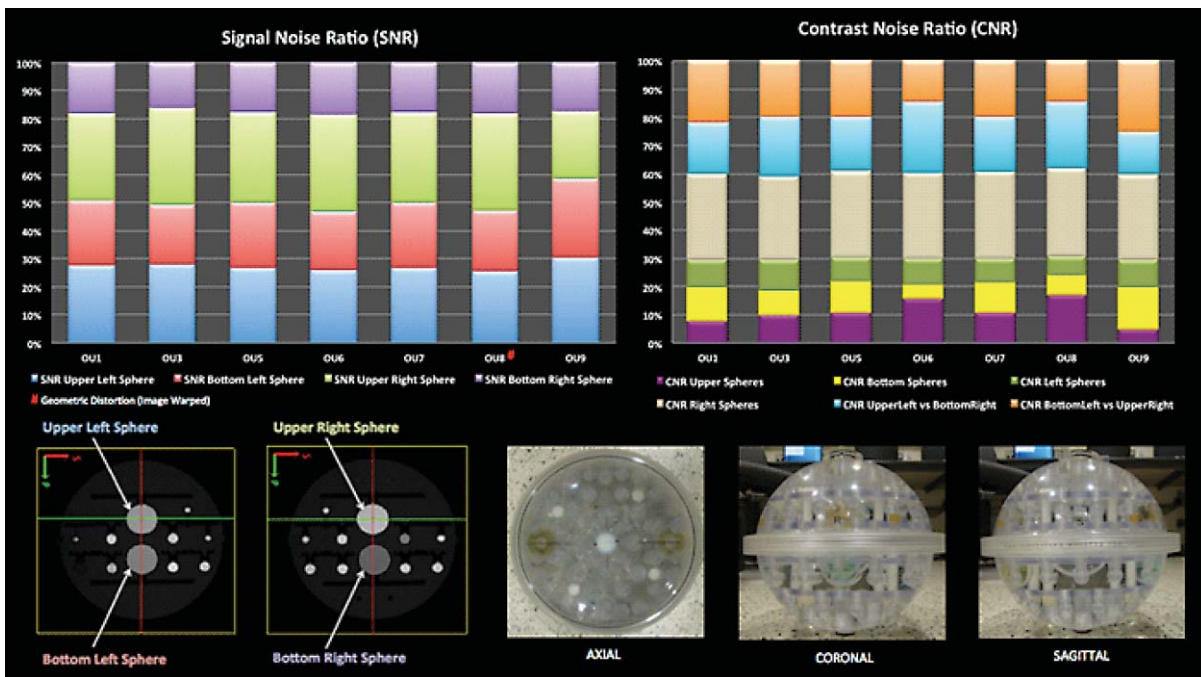


Fig. 1. Post-hoc inter-scanner signal repeatability. Relative stacked column graphs show comparable SNR and CNR values in I-ADNI qualified centers. OU8 showed geometric distortion. OU2 and OU4 phantom data are not available. Photographs of the MagPhan<sup>®</sup> phantom and typical acquisition slices are also shown in the bottom. Each phantom's sphere is filled with a copper sulfate solution that generates different levels of signal intensity. OU1, IRCCS Centro S. Giovanni di Dio, Brescia; OU2, IRCCS Fondazione S. Lucia, Rome; OU3, Fond. SDN Naples, Naples; OU4, University Campus Bio\_Medico, Rome; OU5, University of Foggia/"La Sapienza" University, Rome; OU6, Fond. IRCCS Istituto Neurologico Besta, Milan; OU7, Fond. IRCCS Mondino, Pavia; OU8, University of Naples, Naples; OU9, Centro Neurolesi "Bonino-Pulejo", Messina.

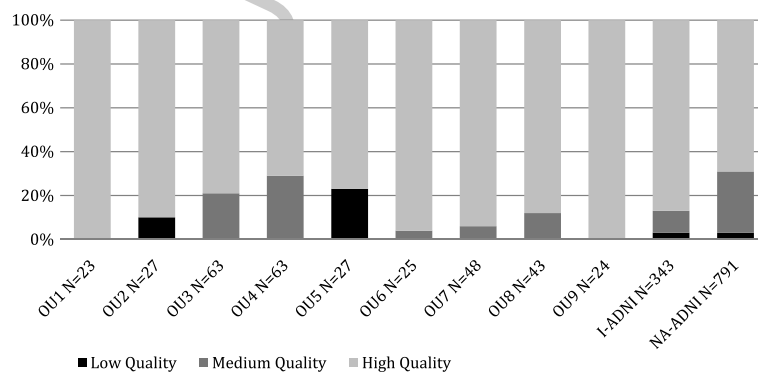


Fig. 2. Proportion of MP-RAGE scans assessed with low, medium, and high quality across I-ADNI operative units (OU) and in the I-ADNI and NA-ADNI total sample.

**MPRAGE quality controls results**

Considering each I-ADNI OU, 70% or higher of MPRAGE acquired were assessed of high quality. This percentage reached 87% considering the total sample of MPRAGE acquired during the study. This propor-

tion is higher than NA-ADNI MPRAGE images that showed high quality scans of 69%. Moreover, I-ADNI cohort showed a lower proportion of medium quality MPRAGE scans in comparison to NA-ADNI (10% and 28%, respectively), while the percentage of low quality MPRAGE scans were the same between cohorts (Fig. 2).

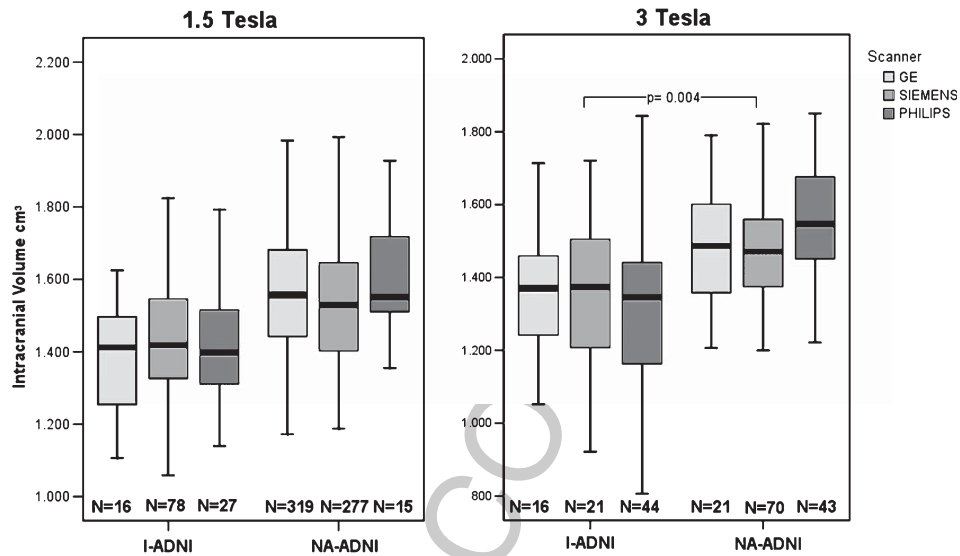


Fig. 3. Stability of automated ICV measurements across different scanners.  $p$  denotes significant value at Levene's test. The only statistical difference is between Siemens scanner at 3T.

#### Automated intracranial volume estimates across scanners

We found homogeneous variances in the automated ICV between NA-ADNI and I-ADNI scanners ( $p > 0.05$ ). When we compared the ICV between scanner models we found homogeneous variances in the ICV of GE and Philips scanners ( $p > 0.05$ ). Siemens scanners showed homogeneous variances in ICV at 1.5T but not at 3T ( $p > 0.05$  and  $p = 0.039$  respectively, Fig. 3). Furthermore, considering exclusively I-ADNI scanners, *post-hoc* comparisons revealed a significant higher ICV for the UO6 ( $p < 0.05$  with Bonferroni correction) compared to that obtained from all other I-ADNI units, with the 1.5T. No ICV differences were found among 3T scanners (Supplementary Figure 1).

#### Known group validity of manual hippocampal volumetry

Box plots in Fig. 4 show the hippocampal volume and the interquartile variability according to diagnosis and field strength. There is a proportional increase of hippocampal atrophy according to the disease progression confirmed by the linear trend analysis at 1.5T ( $p < 0.001$ ). Hippocampal volumes resulted significantly different between controls and AD patients ( $p < 0.001$ ); the former showed an hippocampal atrophy of 26% at 1.5 Tesla. Known group validity was not performed in the 3.0 Tesla groups due to the lack of enough control subjects.

## DISCUSSION

In this manuscript, we described the validation of procedures of acquisition and processing of structural MRI in different Italian academic AD clinics following NA-ADNI procedures. This is the first Italian study applying standardized procedures for the collection and analysis of MR imaging for AD. I-ADNI has built a platform, capitalizing on academic Italian National Health Service Centers, for the use of harmonized parameters for structural MRI acquisition and processing. The sample of patients enrolled in the I-ADNI can be considered representative of those attending memory clinics [26, 27].

The analysis of volunteer scans showed no quality difference among sites. Indeed, the mean SNR found in each site was higher than the mean SNR obtained from NA-ADNI MPRAGE images at 1.5 and 3 Tesla. The phantom analysis provided precise estimates of intensity and linear geometrical scale factors distortion. Based on field experience to date, the greatest practical value of incorporating the MagPhan phantom measurements was identify scanner errors through central monitoring and harmonize scanner acquisition differences. Results obtained from MRI phantom, circulated among I-ADNI centers, showed that the overall SNR and CNR metrics were equal among centers ensuring high reliability. Finally, it is reassuring to note that 86% of I-ADNI MPRAGE images were assessed of high quality; this percentage was higher of those obtained from NA-ADNI ranking.



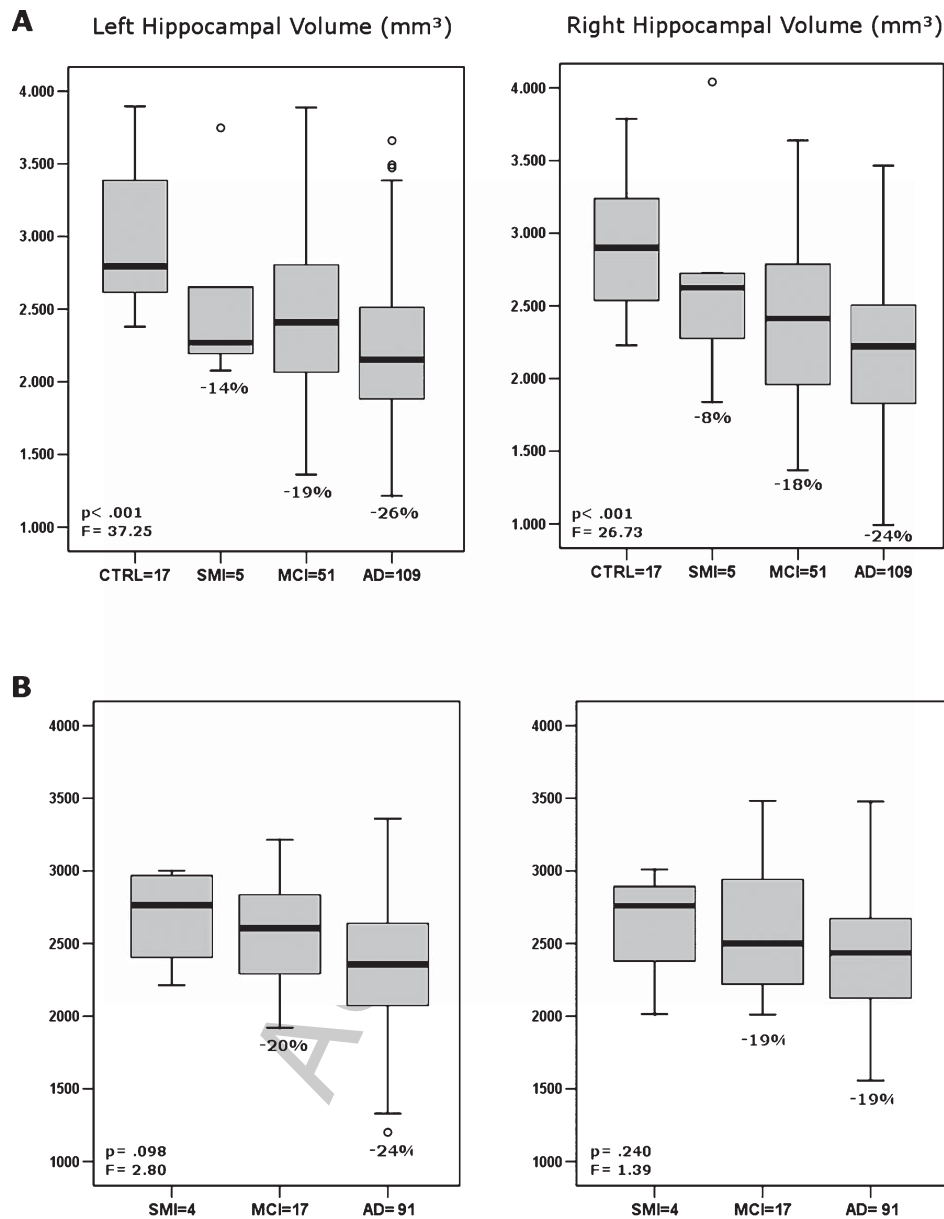


Fig. 4. Known-group validity of manual hippocampal segmentation on 182 magnetic resonance images at 1.5T (A) and on 112 at 3T (B). Volumes are normalized to total intracranial volume. Percentages indicate the proportion of hippocampal atrophy in each group versus controls or SMI subjects.  $p$  and  $F$  values denote the significance of the linear test for trend. AD, Alzheimer's disease; CTRL, controls; MCI, mild cognitive impairment; SMI, subjective memory impairment.

Findings on ICV confirmed the stability of MRI quantification related to the implementation of the same MRI acquisition protocol. Indeed, although there was an intrinsic variance due to different population characteristics, when we compared ICVs computed from scans acquired with the same scanner model from different subjects we found homogeneous variances between the two cohorts (I-ADNI and NA-ADNI). Moreover, exclusively considering the I-ADNI sample,

*post-hoc* analysis of variance revealed no differences between memory clinics except for one operative unit. These results indicated a reduced ICVs variability between centers and the possibility to compare the MRI data between different Italian academic clinical centers.

The goodness of our hippocampal results have been also highlighted by the known group validity method that showed significant hippocampal atrophy in AD

patients compared to their controls. Moreover, MCI hippocampal volume resulted between the volume of individuals with subjective memory impairment and that of the patients with AD. AD patients showed the greatest level of atrophy when compared to the other groups of subjects enrolled in the study.

### Limitations

Ideally, in order to minimize error variance, an ADNI like multi-site reproducibility using a large sample of volunteers scanned repeatedly at all sites and within a short period of time, should be used. Such a study is extremely challenging for the associated huge cost and need of great coordination. On this prospective, our study has some limitations relative to this ideal scenario: a) in the site qualification phase, useful to fine tuning all the acquisition parameters according to the NA-ADNI standard, each MRI site scanned a different set of subjects preventing direct comparison of the scanners; and b) only one phantom acquisition has been completed in all the I-ADNI centers, mainly due to the lack of time, preventing the acquisition repeatability and stability of the scanners in the longitudinal period.

In addition, more efforts should be done in the future to collect standardized biological AD markers (amyloid- $\beta$  and tau levels in cerebrospinal fluid, measure of glucose hypometabolism, and *in vivo* brain amyloid burden) as done from other ADNI initiatives.

One more limitation was the harmonization of MPRAGE images only. Other studies such as Pharmacog (<http://www.alzheimer-europe.org/Research/PharmaCog>) included harmonization of diffusion tensor imaging and resting state functional MRI sequences [28].

### CONCLUSIONS

This study reports the harmonization of the ADNI sequences of structural MR in nine academic Memory Clinics in Italy. The aim of the I-ADNI was to demonstrate the feasibility of implementing the NA-ADNI methods enrolling and assessing a naturalistic population. It will now be possible to compare the brain structural features of patients studied in these Memory Clinics with those of patients studied in other worldwide ADNI initiatives.

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### SUPPLEMENTARY MATERIAL

Supplementary tables and figure are available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-132666>.

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