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Alzheimer's & Dementia 4 (2008) 255–264

Alzheimer's & Dementia

Featured Articles

The pilot European Alzheimer's Disease Neuroimaging Initiative of the European Alzheimer's Disease Consortium

Giovanni B. Frisoni[a,*], Wouter J. P. Henneman[b], Michael W. Weiner[c], Philip Scheltens[d], Bruno Vellas[e], Emma Reynish[e,f], Jaroslava Hudecova[a], Harald Hampel[g,h], Katharina Burger[h], Kaj Blennow[i], Gunhild Waldemar[j], Peter Johannsen[j], Lars-Olof Wahlund[k], Giancarlo Zito[l], Paolo M. Rossini[l], Bengt Winblad[k], Frederik Barkhof[b], and the Alzheimer's Disease Neuroimaging Initiative

[a]*IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy*
[b]*Department of Radiology, VU University Medical Centre, Amsterdam, The Netherlands*
[c]*Center for Imaging of Neurodegenerative Diseases, Veterans Administration Medical Center and Departments of Radiology, Medicine, Psychiatry, and Neurology, University of California, San Francisco, San Francisco, CA, USA*
[d]*Department of Neurology and Alzheimer Center, VU University Medical Centre, Amsterdam, The Netherlands*
[e]*INSERM U. 558, Gerontopole, Pole Geriatrie, Centre Hospitalier Universitaire, Toulouse, France*
[f]*Geriatric Medicine, Department of Clinical and Surgical Sciences, University of Edinburgh, Edinburgh, UK*
[g]*Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Trinity Centre for Health Sciences, The Adelaide and Meath Hospital Incorporating The National Children's Hospital, Dublin, Ireland*
[h]*Department of Psychiatry, Alzheimer Memorial Center, Ludwig-Maximilian University, Munich, Germany*
[i]*Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden*
[j]*Department of Neurology, Rigshospitalet, Section 2082, Copenhagen University Hospital, Copenhagen, Denmark*
[k]*Alzheimer Research Center and Division of Clinical Geriatrics, Department of Neurobiology Caring Sciences and Society, Karolinska Institutet, Stockholm, Sweden*
[l]*Ospedale S Giovanni Calibita Fatebenefratelli e AFaR – Associazione Fatebenefratelli per la Ricerca, Roma, Italy*

Abstract

Background: In North America, the Alzheimer's Disease Neuroimaging Initiative (ADNI) has established a platform to track the brain changes of Alzheimer's disease. A pilot study has been carried out in Europe to test the feasibility of the adoption of the ADNI platform (pilot E-ADNI).
Methods: Seven academic sites of the European Alzheimer's Disease Consortium (EADC) enrolled 19 patients with mild cognitive impairment (MCI), 22 with AD, and 18 older healthy persons by using the ADNI clinical and neuropsychological battery. ADNI compliant magnetic resonance imaging (MRI) scans, cerebrospinal fluid, and blood samples were shipped to central repositories. Medial temporal atrophy (MTA) and white matter hyperintensities (WMH) were assessed by a single rater by using visual rating scales.
Results: Recruitment rate was 3.5 subjects per month per site. The cognitive, behavioral, and neuropsychological features of the European subjects were very similar to their U.S. counterparts. Three-dimensional T1-weighted MRI sequences were successfully performed on all subjects, and cerebrospinal fluid samples were obtained from 77%, 68%, and 83% of AD patients, MCI patients, and controls, respectively. Mean MTA score showed a significant increase from controls (left, right: 0.4, 0.3) to MCI patients (0.9, 0.8) to AD patients (2.3, 2.0), whereas mean WMH score did not differ among the three diagnostic groups (between 0.7 and 0.9). The distribution of both MRI markers was comparable to matched US-ADNI subjects.

*Corresponding author. Tel.: +39-030-3501-361; Fax: +39-030-3501313. E-mail address: gfrisoni@fatebenefratelli.it

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doi:10.1016/j.jalz.2008.04.009

Conclusions: Academic EADC centers can adopt the ADNI platform to enroll MCI and AD patients and older controls with global cognitive and structural imaging features remarkably similar to those of the US-ADNI.
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Keywords: Alzheimer's disease; Mild cognitive impairment; Imaging; CSF; ADNI; EADC

1. Introduction

In the U.S., the Alzheimer's Disease Cooperative Study is a network of about 60 academic centers that during the last 20 years have developed common clinical standards and procedures for multicenter clinical studies and trials (https://adcs.ucsd.edu). This network has allowed the deployment of the hitherto largest single project on Alzheimer's disease (AD), the Alzheimer's Disease Neuroimaging Initiative (ADNI) [1], a multicenter study that has enrolled and is following about 200 AD patients, 400 mild cognitive impairment (MCI) patients, and 200 normal older persons with clinical (neuropsychological tests), imaging (high-resolution structural magnetic resonance imaging (MRI), fluorodeoxyglucose and amyloid positron emission tomography [PET]), and biologic markers of AD (blood, cerebrospinal fluid [CSF], and urinary analytes). Clinical data, images, and biologic samples are collected by using standardized protocols. The data will facilitate development and validation of disease markers for early diagnosis and for surrogate outcomes in clinical trials of disease-modifying drugs in AD.

A group of 50 clinical and research centers (the European Alzheimer's Disease Consortium [EADC], http://eadc.alzheimer-europe.org) has during the past 10 years carried out clinical trials and multicenter studies and provides the infrastructure necessary to adopt the ADNI platform in Europe. Currently (October 2007), EADC sites are running Europe-wide prospective clinical studies, namely EU FP5 ICTUS, Impact of Cholinergic Treatment Use, http://eadc.alzheimer-europe.org/ictus.html; EU FP6 DESCRIPA, Development of screening guidelines and criteria for predementia Alzheimer's disease, http://www.descripa.eu; EU FP6 EDAR, Beta amyloid oligomers in the early diagnosis of AD and as marker for treatment response, http://www.edarstudy.eu; and EU FP7 neuGRID, http://www.neuGRID.eu, in addition to clinical trials with anti-amyloid compounds (tramiprosate and tarenflurbil) in which clinical data, images, and biologic samples are collected in a standardized fashion.

This article illustrates the design and reports findings of the pilot European ADNI study. The aim of the pilot E-ADNI is to demonstrate the feasibility of implementing the ADNI methods in seven selected sites of the EADC, enrolling and assessing a restricted number of subjects (aim: three MCI, three AD, and three controls per site). Some specific features of this study should be underlined. First, PET imaging markers have not been collected in this pilot phase, because previous studies have already shown the feasibility of large multicenter fluorodeoxyglucose PET studies in Europe [2]. Second, at variance with the US-ADNI, special emphasis has been placed on imaging markers of cerebral small vessel disease, which is frequently associated with AD, by including T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) MR sequences. Last, the project has a cross-sectional design, and no follow-up is envisioned.

The specific aims of this report were descriptive and consisted of the following: (1) presenting the clinical and neuropsychological features of the experimental groups; (2) describing the structural imaging markers of neurodegeneration and cerebral small vessel disease (medial temporal atrophy [MTA] and white mater hyperintensities [WMHs]); and (3) comparing the clinical, neuropsychological, and imaging features of the pilot E-ADNI with matched US-ADNI subjects. Other conventional biologic markers (CSF tau and amyloid beta) as well as nonconventional imaging and biologic markers that have been assessed in the pilot E-ADNI (resting state functional MRI, diffusion tensor imaging, and plasma amyloid) will be reported elsewhere.

2. Methods

2.1. Sites and organigram

Subjects were enrolled at the following seven EADC sites: VU Medical Centre, Amsterdam, The Netherlands (principal investigator [PI] Philip Scheltens); IRCCS Centro San Giovanni Di Dio Fatebenefratelli, Brescia, Italy (PI Giovanni B. Frisoni); MDRU, Rigshospitalet, Copenhagen, Denmark (PI Gunhild Waldemar); Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany (PI Harald Hampel); Ospedale S Giovanni Calibita, Isola Tiberina, Roma (PI Paolo Maria Rossini); Huddinge Hospital, Huddinge, Sweden (PI Lars-Olof Wahlund); Centre Hospitalier Université de Toulouse, France (PI Bruno Vellas).

Responsibility for clinical data, including adaptation of the US-ADNI case report form and collection of the clinical variables, was taken by Bruno Vellas (Toulouse); for MRI data, including installation of ADNI sequences, scanner qualification, image quality control, image collection, and analysis, Fred Barkhof (Amsterdam); for CSF issues including adaptation of the US-ADNI CSF collection protocol, centralized collection of samples, and assaying, Harald Hampel (Munich); plasma issues including adaptation of the US-ADNI plasma collection protocol, centralized collection of samples, and assaying, Kaj Blennow (Gothenburg). Giovanni B. Frisoni (Brescia) was responsible for the overall

project management; training of personnel in enrollment sites; monitoring of data, image, and sample collection; and reporting.

2.2. Patients

Between January 1 and March 31, 2007, each center was asked to enroll three consecutive new patients with AD, three with MCI, and three cognitively intact older controls. Each subject underwent MRI scan and lumbar puncture under routine clinical conditions, standardized image, and biosample collection procedures. Controls were older patients undergoing prostate or hip surgery with spinal anaesthesia (Brescia and Rome), true volunteers, usually patients' spouses (Amsterdam, Stockholm, Toulouse, and Copenhagen), and persons with memory complaints that were believed after appropriate clinical and instrumental exams to be due to psychological factors (Munich).

Criteria for enrollment of MCI patients were age between 55 and 90 years, complaints of memory loss by the patient and confirmed by a family relative, Mini-Mental State Examination [MMSE] score of 24 and higher, overall Clinical Dementia Rating score of 0.5 and at least 0.5 on memory, and score on the logical memory test lower than 1.5 standard deviations from the age-adjusted mean [3]. Exclusion criteria were Geriatric Depression Scale score of 6 or higher, modified Hachinski ischemia score greater than 5, significant neurologic or psychiatric illness, use of antidepressant drugs with anticholinergic side effects, high dose of neuroleptics or chronic sedatives or hypnotics, antiparkinsonian medication, and use of narcotic analgesics. Criteria for AD were similar, with the exception that the MMSE score had to be between 20 and 26, the overall Clinical Dementia Rating score had to be 0.5 or 1, and they had to satisfy National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD.

Written informed consent was obtained from all patients and controls. The study was reviewed and approved first by the Ethics Committee of the coordinating site (Comitato Etico delle Istituzioni Ospedaliere Cattoliche [CEIOC]) and then by Ethics Committees of all other sites. None of the subjects fulfilled the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for probable vascular dementia [4].

2.3. Clinical/neuropsychological data

A Case Report Form (CRF) was developed on the basis of that used in the US-ADNI study (English version is online at http://www.centroAlzheimer.it/E-ADNI_project.htm). Administrative issues, patient demographics, informant demographics, family history, cognitive course, rating scales, medications, medical history, physical exam, and neurologic exam were assessed in the pilot E-ADNI CRF in the same way as the US-ADNI CRF. The English version of the CRF was used in Copenhagen, Stockholm, Munich, and Amsterdam, whereas translated versions with local idioms were used in Italy and France. Validated local versions of the neuropsychological tests were used in all sites.

The Rey Auditory Verbal Learning Test was not included in the pilot E-ADNI battery to avoid interference with word list recall test of the Alzheimer's Disease Assessment Scale, cognitive portion (ADAS-Cog) because all cognitive tests were done in a single assessment. The Digit Span Forward and Backward were not included for time constraints. The North American Reading Test was not used because corresponding versions in local idioms were lacking. Validated test versions included in the battery of the pilot E-ADNI are available in different languages.

2.4. MRI

2.4.1. Data acquisition

MRI acquisition activities were divided into a preparatory phase, site qualification, scanning of travelling volunteers, and experimental subject scanning. All MRI scans were performed on 1.5 Tesla machines. The following scanners were used in the study: Amsterdam, Siemens Sonata, Siemens, New York, NY; Brescia, GE Excite; GE Healthcare, UK; Copenhagen, Siemens Vision; Munich, Siemens Vision; Roma, Philips Achieva; Philips Healthcare, Best, The Netherlands; Stockholm, Siemens Avanto; and Toulouse, Siemens Vision.

The preparatory phase consisted of the agreement on the MR protocol by all involved sites and the description of practical procedures concerning scan acquisition, image transmission, and quality control. The scan protocol included a single three-dimensional T1-weighted gradient echo sequence, two B1-calibration scans (performed with head and body coil as receivers, respectively), a PD/T2-weighted dual echo sequence, a diffusion tensor imaging (DTI), and a resting state functional MRI (fMRI) sequence. This protocol deviated from the US-ADNI in the following ways: (1) the omission of a routinely performed second three-dimensional T1-weighted sequence (in case of improper scan quality, for example as a result of motion, MRI technicians were instructed to rescan a patient), and (2) the addition of DTI and resting state fMRI sequences (results of which will be presented in a separate report) followed by a phantom replacement scan. A scan manual was developed by the Amsterdam site (online at http://www.centroAlzheimer.it/E-ADNI_project.htm) describing practical procedures, as well as giving a detailed description of the scan protocol and instructions for MRI technicians concerning scan performance and image labelling and transmission. All sites successfully performed a test scan, after which the scan protocol was saved in the scanner directory. ADNI phantoms

(http://www.phantomlab.com/magphan_adni.html) were distributed to all sites in the preparatory phase.

During the travelling volunteer phase, three volunteers from Amsterdam visited the seven participating sites and underwent MR scanning between December 2006 and February 2007. The volunteers were scanned twice at each site with the full scan protocol, and an ADNI phantom scan was acquired after each volunteer was scanned. Volunteer scans will allow comparison of geometric distortion, as well as signal- and contrast-to-noise variation across, within, and between scanners. More details of volunteer scanning and the pertinent results will be provided elsewhere.

During the experimental subject scanning phase, AD patients, MCI patients, and elderly controls were scanned at each MRI site between January and March 2007. Quality control consisted of visual inspection and assessment of consistency of scan parameters with those used for the travelling volunteers. All scans were uploaded in Digital Imaging and Communication in Medicine (DICOM) format and successfully passed the quality control procedure at the Image Analysis Center (IAC) in Amsterdam (www.iac-amsterdam.nl), with special emphasis on the quality of the three-dimensional T1-weighted sequence (GM-WM contrast, signal-to-noise ratio, complete brain coverage, no infolding). Good image quality was defined as no ringing effect, no movement artifacts, no wrap-up effects, no visually appreciable signal inhomogeneities, and good grey matter/white matter contrast on visual inspection.

2.4.2. MRI markers

These consisted of visual rating scales for MTA and WMH. MTA was rated on reconstructed coronal, T1-weighted images by using the five-point rating scale (range, 0 to 4) described by Scheltens et al [5]. Higher scores represent more severe atrophy. Scores were given for left and right medial temporal lobe separately. WMH was assessed by using the four-point rating scale described by Fazekas et al [6]. One score is given per scan, ranging from zero (no WMH) to three (severe WMH), by using FLAIR and T2-weighted images. All ratings were performed by a single observer trained according to standard operating procedures at the IAC, blinded to group allocation.

2.5. Biologic samples: CSF and blood

CSF, blood collection, and shipment protocols were developed by and agreed between Munich and Gothenburg (online at http://www.centroAlzheimer.it/E-ADNI_project.htm), aiming to achieve optimal assaying procedures for total tau, ph-tau, and Aβ42 in the CSF and Aβ40 and Aβ42 in plasma. CSF and blood were pre-processed at each site and divided into two batches. One batch of fresh CSF and fresh plasma was sent immediately after collection to the storage sites (Munich for CSF and Gothenburg for plasma).

The other was frozen and sent with all other site samples at the end of the study. *APOE* was genotyped at the local enrolling sites in all but one subject with blood obtained independently from that of the pilot E-ADNI. More details of biologic sample collection will be provided elsewhere.

2.6. US-ADNI subjects

Clinical data of all the US-ADNI subjects (186 AD, 394 MCI, and 229 controls) available as of August 20, 2007 were downloaded from http://www.loni.ucla.edu/ADNI/Data. The 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 biologic markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

The PI 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 more than 50 sites across the U.S. and Canada. For up-to-date information see www.adni-info.org.

MR images were downloaded of 22 AD, 19 MCI, and 18 controls matched 1:1 by age, gender, and MMSE score to the E-ADNI sample and were assessed by using the same visual rating scales for MTA and WMH by the same rater. Sociodemographic and cognitive features of this subgroup can be accessed at http://www.centroalzheimer.it/public/USADNI_forratingscales.pps.

2.7. Statistical analysis

Differences of continuous variables between European and U.S. sites and among AD, MCI, and controls were tested with two-way analysis of variance (ANOVA) where factors were site (two levels) and diagnosis (three levels). The full factorial model was first tested including the site and diagnosis main effects as well as their site $\times$ diagnosis interaction. If the interaction proved significant, significance of the main effects was disregarded, and post hoc comparisons with Student *t* test were carried out between diagnostic groups and confirmed with the nonparametric Mann-Whitney *U* test. When the interaction did not prove significant, an ANOVA model was tested including only main effects; in this case no post hoc comparisons are needed. Significance of the diagnosis main effect will not be reported because this would reflect the overwhelming significance of the much larger U.S. groups.

Differences of dichotomous variables were tested by site (all diagnoses together) and in each individual site $\times$ diagnosis group pairs with the χ^2 test. Differences of ordinal variables (MTA and WMH scores) were tested with Mann-Whitney *U* test.

Table 1
Subject enrollment and data collection of the pilot E-ADNI study

	AD		MCI		Controls		Total	
	N (%)	Cases per site	N (%)	Cases per site	N (%)	Cases per site	N (%)	Cases per site
CRF*	22 (reference)	2 to 6	19 (reference)	0 to 4	18 (reference)	1 to 4	59 (reference)	3 to 10
MR scan†	22 (100)	2 to 6	19 (100)	0 to 4	18 (100)	1 to 4	58 (100)	3 to 10
Lumbar puncture‡	17 (77)	0 to 6	13 (68)	0 to 4	15 (83)	0 to 3	45 (76)	0 to 10
Blood§	19 (86)	1 to 6	17 (89)	0 to 4	17 (94)	1 to 4	53 (90)	3 to 10

NOTE. The denominator of percentages is N of the first row, representing 100% (reference).
* Including full neuropsychological battery.
† At least valid 3D acquisition.
‡ With viable CSF reaching the collection center in Munich safely.
§ With viable blood reaching the collection center in Gothenburg safely.

For the sake of conservativeness, the threshold for statistical significance was set at $P < .05$ uncorrected. Given the relatively small group size of the pilot E-ADNI, power analyses were carried out to assess the minimum difference that would result statistically significant, given the available group sizes (alpha = .05, power 80%).

3. Results

3.1. Enrollment

Table 1 shows that all subjects who had a completely filled CRF also underwent a successful MR scan consisting of at least one good quality structural T1-weighted 3D image. CSF was collected and successfully sent to the storage site in Munich in about three of four subjects overall, and blood reached Gothenburg in nine of 10. Enrollment rate was 3.5 subjects per site per month, ranging between 2.0 and 8.0 subjects per month in the different sites (2 in Copenhagen, 2.5 in Stockholm, 3 in Munich, Brescia, Rome, and Amsterdam, and 8 in Toulouse.

3.2. Sociodemographics, clinical, and genetic features

Table 2 shows that the subjects enrolled in the pilot E-ADNI were generally younger than their U.S. counterparts, and in controls female subjects were relatively fewer. Not surprisingly, education was 4 to 6 years higher in the U.S. than the European subjects. As expected, cognitive variables were indicative of increasingly better performance from AD to MCI to controls, and cognitive tests denoting general cognition (MMSE, ADAS-Cog, and Clinical Dementia Rating-Sum of Boxes (CDR-SOB) were remarkably similar, compared with subjects from the US-ADNI; the MMSE differed by 0.3 and ADAS-Cog by 2.0 points at most. The logical memory–delayed recall test tended to be higher in MCI patients from the pilot E-ADNI than the US-ADNI, and the opposite was true in controls. Data on individual ADAS-Cog subscales can be found at http://www.centroalzheimer.it/public/ADAS_Cog_subscales.pps.

Behavioral and disability variables indicated increasingly better status from AD to MCI to controls. Subjects from the pilot E-ADNI tended to report marginally more depressive symptoms (difference of less than 1 symptom on average on the Geriatric Depression Scale) than US-ADNI subjects. Disability, assessed with the Functional Assessment Questionnaire, was comparable to US-ADNI subjects, with the largest discrepancy being just over 2 points within the group of MCI patients, and behavioral disturbances on the NeuroPsychiatric Inventory were strikingly similar between European and U.S. sites (data on individual behavioral disturbances can be found at http://www.centroalzheimer.it/public/NPI_Q_subscales.pps).

Comorbidities were evenly distributed in the three pilot E-ADNI diagnostic groups ($P > .09$), and this was true also in US-ADNI groups. However, disease prevalence was always, as previously reported [7], markedly higher in the U.S. than European subjects ($P < .05$ for all diseases); the extreme instance was the 13-fold difference of musculoskeletal diseases of MCI patients, where prevalence was 5% and 65%, respectively ($P < .001$).

There was a mild and nonsignificant trend toward decreasing frequency of the ε4 allele of *APOE* from AD through MCI to controls that could be appreciated (33%, 26%, and 22%, respectively; P of χ^2 test for trend, 0.27), but this was much more marked in the US-ADNI groups (42%, 33%, and 14%, respectively; $P < .001$), whereas a clear trend toward increasing frequency of the ε2 allele was also evident (2%, 4%, and 8%, respectively; $P < .001$).

3.3. Neuropsychological tests

Table 3 shows that most neuropsychological test scores were in line with the expected increasingly better performance from AD to MCI to controls and were generally similar between pilot E-ADNI and US-ADNI subjects. Some tests were performed marginally better by US-ADNI subjects: clock drawing between 0.1 and 0.8 higher score, trial making A between 13 and 19 seconds faster, digit-symbol substitution test between 6.1 and 9.3 higher score, and Boston naming without cue between 0.5 and 2.2. Category 2 of the category fluency test showed an opposite pattern in MCI and controls; MCI of the pilot E-ADNI

Table 2
Comparison of sociodemographic, clinical, and genetic features between pilot E-ADNI and US-ADNI

	AD		MCI		Controls		Significance on	
	Pilot E-ADNI	US-ADNI	Pilot E-ADNI	US-ADNI	Pilot E-ADNI	US-ADNI	ANOVA or χ^2	
Number	22	186	19	394	18	229	Site	Interaction
Sociodemographics								
Age, y	74.6 ± 9.2	75.2 ± 7.6	68.9 ± 11.3	74.7 ± 7.5	71.2 ± 9.2	75.9 ± 5.0	<.0005	NS
Sex, F	11 (50%)	88 (47%)	9 (47%)	141 (36%)	4 (22%)	110 (48%)	NS	—
Education, y	10.5 ± 4.3	14.7 ± 3.14	11.1 ± 4.4	15.7 ± 3.1	10.8 ± 3.0	16.0 ± 2.9	<.0005	NS
Cognition								
MMSE	23.2 ± 3.2	23.3 ± 2.0	27.3 ± 2.1	27.0 ± 1.8	29.1 ± 0.7	29.1 ± 1.0	NS	NS
CDR-SOB	4.8 ± 2.1	4.4 ± 1.6	1.3 ± 1.0	1.6 ± 0.9	0.06 ± 0.17	0.03 ± 0.12	NS	NS
ADAS-Cog	19.8 ± 8.2	18.6 ± 6.3	11.4 ± 5.9	11.6 ± 4.4	8.2 ± 3.1	6.2 ± 2.9	NS	NS
Logical memory–delayed recall	1.7 ± 3.2	1.2 ± 1.8	5.8 ± 4.0**	3.8 ± 2.7	11.6 ± 3.4	13.0 ± 3.6	—	.005
Behavior & disability								
Geriatric Depression Scale	2.4 ± 1.8	1.7 ± 1.4	2.5 ± 1.9	1.6 ± 1.4	1.2 ± 1.0	0.8 ± 1.1	<.0005	NS
Functional Assessment Quest.	12.8 ± 7.0	13.1 ± 6.8	1.6 ± 1.8	3.8 ± 4.5	0	0.1 ± 0.6	NS	NS
NeuroPsychiatric Inventory	3.1 ± 3.8	3.6 ± 3.4	1.6 ± 1.6	1.8 ± 2.6	0.2 ± 0.4	0.4 ± 0.9	NS	NS
Physical comorbidity								
Cardiovascular diseases	9 (44%)**	133 (70%)	7 (37%)***	279 (72%)	6 (33%)**	153 (67%)	<.0005	—
Respiratory diseases	2 (11%)	34 (18%)	3 (16%)	86 (22%)	1 (5%)	50 (22%)	.05	—
Musculoskeletal diseases	5 (48%)***	115 (61%)	1 (5%)	252 (65%)	6 (33%)	159 (69%)	<.0005	—
Endocrine-metabolic diseases	4 (19%)*	80 (42%)	2 (11%)	137 (35%)	0 (0%)	89 (39%)	<.0005	—
Gastrointestinal diseases	4 (19%)	70 (37%)	3 (16%)	159 (41%)	2 (11%)	105 (46%)	<.0005	—
Renal and genitourinary diseases	6 (29%)	77 (41%)	5 (26%)	172 (44%)	5 (28%)	111 (49%)	.01	—
APOE genotyping								
ε2 allele	2 (5%)	8 (2%)	2 (5%)	29 (4%)	2 (6%)	38 (8%)	NS	—
ε3 allele	26 (62%)	213 (56%)	26 (68%)	488 (63%)	26 (72%)	354 (77%)	NS	—
ε4 allele	14 (33%)	157 (42%)	10 (26%)	257 (33%)	8 (22%)	66 (14%)	NS	—

NOTE. Figures denote number (%) or mean ± standard deviation. The number of subjects with apoE genotypes of AD, MCI, and controls in the pilot E-ADNI is 21, 19, and 18, respectively, and in the US-ADNI 189, 387, and 229, respectively. ANOVA and χ^2 test significance of the site main effect (European vs U.S.) and the interaction of site × diagnosis. In the case of significant main effects, asterisks denote significance of post hoc comparisons within diagnostic groups between pilot E-ADNI and US-ADNI at

* $P < .05$

** $P < .01$, and

*** $P < .001$.

Table 3
Neuropsychological battery scores of the pilot E-ADNI versus US-ADNI subjects

	AD		MCI		Controls		Significance on ANOVA	
	Pilot E-ADNI	US-ADNI	Pilot E-ADNI	US-ADNI	Pilot E-ADNI	US-ADNI	Site	Interaction
Clock								
Drawing	2.6 ± 1.5	3.4 ± 1.3	3.9 ± 1.0	4.2 ± 1.0	4.6 ± 0.9	4.7 ± 0.7	.004	NS
Copying	4.4 ± 0.9	4.3 ± 1.0	4.7 ± 0.5	4.7 ± 0.7	4.8 ± 0.8	4.9 ± 0.4	NS	
Category fluency								
Category 1	11.4 ± 5.8	12.3 ± 4.9	18.4 ± 7.6*	15.9 ± 4.9	20.8 ± 6.1	19.9 ± 5.6	NS	NS
Category 2	8.0 ± 3.6	7.9 ± 3.4	12.8 ± 3.8*	10.8 ± 3.5	13.5 ± 4.8	14.7 ± 3.9	—	.03
Trial making								
Trial A	81 ± 38	68 ± 37	64 ± 34	45 ± 23	43 ± 29	36 ± 13	.001	NS
Trial B	198 ± 84	199 ± 87	162 ± 98	130 ± 73	103 ± 39	89 ± 44	NS	NS
Trial B–A	126 ± 64	133 ± 76	98 ± 73	86 ± 63	60 ± 34	53 ± 39	NS	NS
Digit symbol								
Total score	17.4 ± 11.0	26.7 ± 13.1	28.1 ± 14.4	36.9 ± 11.2	39.6 ± 10.9	45.7 ± 10.2	<.0005	NS
Boston naming								
Without cue	19.6 ± 7.5	21.8 ± 6.5	23.7 ± 5.6	25.0 ± 4.5	26.9 ± 3.4	27.4 ± 2.7	.043	NS
With cue	20.7 ± 7.7	22.3 ± 6.3	24.7 ± 4.9	25.5 ± 4.1	27.1 ± 3.4	27.8 ± 2.3	NS	NS

NOTE. Group size is shown in brackets. ANOVA tests significance of the site main effect (European vs US) and the interaction of site × diagnosis. In case of significant main effects, asterisks denote significance of post hoc comparisons within diagnostic groups between pilot E-ADNI and US-ADNI on Student t test at * $P < .05$.

scored 2 points higher than MCI of the US-ADNI, and controls of the US-ADNI scored 1.2 points higher than pilot E-ADNI subjects. Post hoc t tests were checked with the nonparametric Mann-Whitney U test and confirmed in all cases.

3.4. MRI assessment

MTA scores increased from elderly control subjects to MCI to AD patients on both the left and right side (Fig. 1). The difference between controls and MCI patients did not reach statistical significance (left, $P = .11$; right, $P = .07$ on Mann-Whitney U test). In AD patients, MTA on both sides showed significant difference compared with controls and MCI patients. MTA scores in U.S. subjects tended to be slightly higher than in the European in almost all diagnostic groups, but this trend never reached significance ($P \geq .087$). WMH scores were remarkably low and did not differ among pilot E-ADNI diagnostic groups and were of similar magnitude between European and U.S. subjects.

3.5. Power analysis

Power analyses for all the variables shown in Tables 2 and 3 and Figure 1 showed that the minimum difference that would result statistically significant given the available MCI group size was 1.2 points on the MMSE, 2.6 n the ADAS-Cog, and 1.6 on the logical memory–delayed recall test. Minimum differences tended to be greater in AD and lower in healthy controls for the larger variance in the former and lower in the latter groups. The minimum difference of MTA score was between 0.5 and 0.7 in the three diagnostic groups. Such minimum differences were much smaller than the difference among diagnostic groups for the MMSE, ADAS-Cog, logical memory–delayed recall test, and at least between MCI and AD, for MTA score, indicating that the design of our study was appropriate to demonstrate the cognitive and structural similarity between the pilot E-ADNI and the US-ADNI groups. Power analyses of the neuropsychological tests confirmed this view. The full power analyses can be found online at http://www.centroalzheimer.it/public/Power_analyses.doc.

4. Discussion

In this article, we report the design as well as the clinical, neuropsychological, and imaging characteristics of the experimental groups from the pilot E-ADNI study. We show the feasibility of the collection of clinical data, biologic samples, and MRI data within a European multicenter setting. Characteristics of the diagnostic groups are similar to the US-ADNI.

An important finding of this study is that the clinical features of the subjects recruited in the pilot E-ADNI were clinically comparable to those recruited in the US-ADNI. Despite the fact that subjects were approximately 5 years younger in the former group and notwithstanding some statistically significant differences, global cognitive function as assessed by the MMSE and CDR-SOB were only fractions of points different in the two studies, logical memory was also similar, and ADAS-cog total scores were never more than 2 points apart. To a certain extent, the observed similarity also applies to the results of the neuropsychological test battery, where some tests (clock drawing, trial making A, digit symbol, and Boston naming without cue) indicated systematically poorer performance in the U.S.

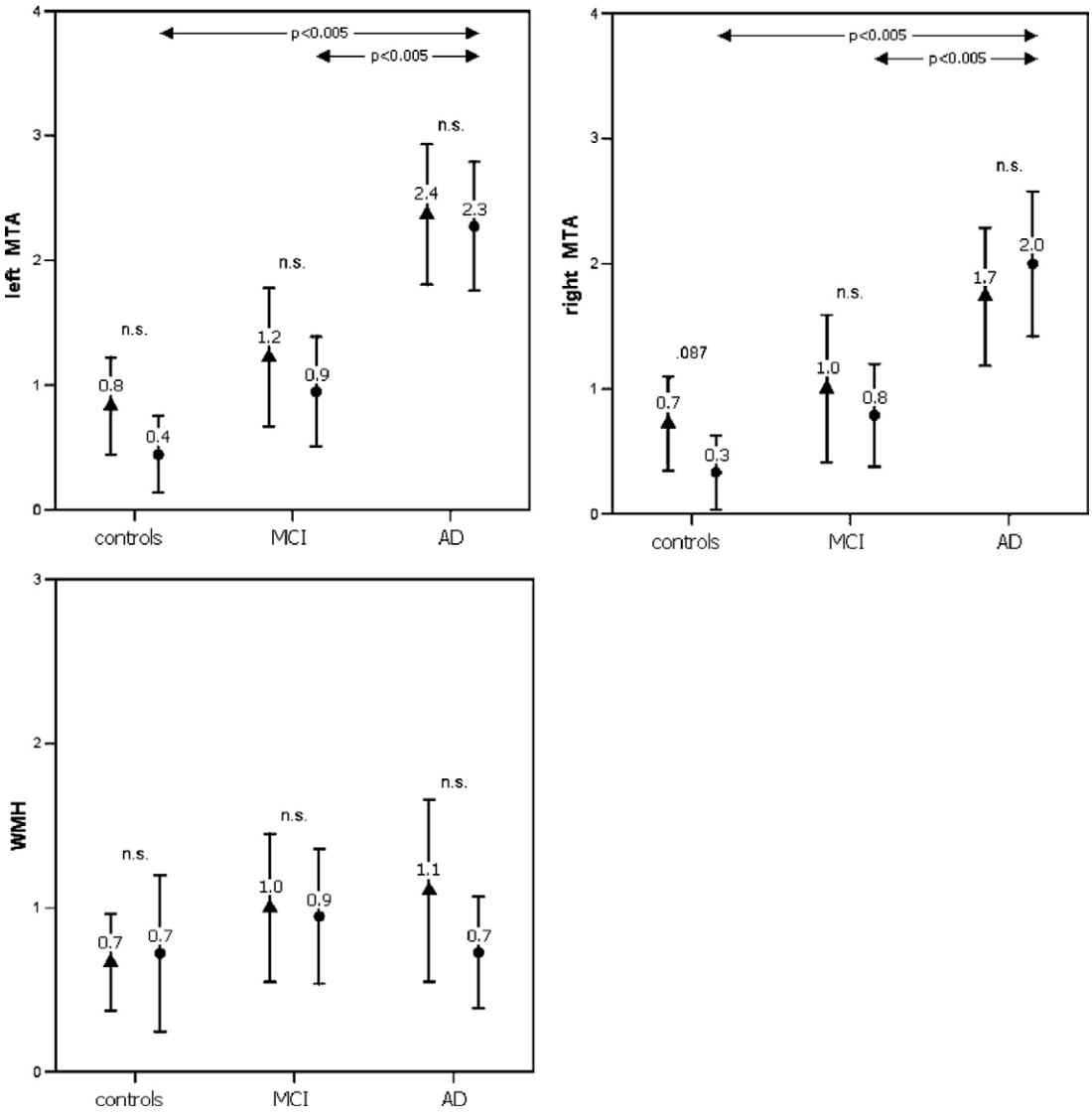

Fig. 1. Mean scores of MTA and WMH per diagnostic group (Controls, n = 18; MCI, n = 19; and AD, n = 22). Means are given for subjects from pilot E-ADNI study (●) and subjects from the US-ADNI (▲) matched 1:1 for age, gender, and MMSE. Whiskers denote 95% confidence interval. Arrows denote group differences between pilot E-ADNI groups. Significance figures are on Mann Whitney *U* test.

subjects, and the category fluency 2 tests indicated poorer performance of only U.S. MCI patients. Although a consistent neuropsychological pattern cannot be identified, future ADNI efforts will need to specifically address the homogeneity of neuropsychological test administration and scoring with the US-ADNI. These observations indicate that despite the classification uncertainties surrounding the concept of MCI [8], patients classified as MCI, in terms of global severity and to a certain extent of neuropsychological profile, are similar in European and U.S. studies. The tendency to a difference in years of education between the U.S. and Europe might at least in part be due to the different health coverage in the European Union and U.S.

It is reassuring to note that a good quality 3D T1-weighted MRI scan was acquired for all 59 recruited subjects, supporting our choice to omit a routine repeat 3D T1-weighted sequence. However, the quality assessment consisted only of visual inspection, detailed analysis of variations in signal-to-noise and contrast-to-noise ratios, and geometric distortion by using phantom data, and data from travelling volunteers will follow. Because the sites of our study might be among those with higher familiarity with high-resolution sequences among those of the European Alzheimer's Disease Consortium, and quality performance might decrease in a larger E-ADNI study. Omission of the routine repeat scan allowed an addition to the MRI protocol, consisting of DTI and rs-fMRI sequences. Analysis of this data is ongoing and will be reported elsewhere.

Structural MR features have been assessed with visual rating scales to explore disease effects. Although quick and

easy, the scales we have used to rate MTA and subcortical cerebrovascular disease have been shown to yield good reliability and correlate well with hippocampal and WMH volume [9–12]. The distribution of scores in the pilot E-ADNI groups was as expected, with MTA increasing from controls to MCI patients to AD patients. WMH scores were similarly low among groups. Importantly, structural measures of MTA and WMH were not significantly different between the European and U.S. groups; the measure closest to significance was right MTA score in controls ($P = .087$). Although the criteria for the recruitment of our MCI patients were slacker than those of the US-ADNI because we have been unable to carry out a strict centralized assessment of the diagnosis made by enrolling sites, it is good to see that cerebrovascular comorbidity of the European diagnostic groups is equally low, consistent with the expectation of enrollment of primarily degenerative cases.

It is interesting to note that the European subjects seemed to have much lower comorbidity than their U.S. counterparts, and this was true for all the assessed diseases (cardiovascular, respiratory, musculoskeletal, endocrine-metabolic, gastrointestinal, renal, and genitourinary), although with different degrees of statistical significance. The differences can hardly be explained by the marginally older age of U.S. subjects and contrast with their higher educational attainment. The difficulty of achieving a satisfactory concordance of physical health assessment in multicenter clinical studies is a well-known issue in the epidemiologic literature [13,14] that will need to be more thoroughly addressed in future ADNI efforts.

A few remarks on enrollment are warranted. The enrollment rate of the pilot E-ADNI sites was 2.8 subjects per month per site, implying that to recruit 800 subjects, as in the US-ADNI, it would take 20 sites for 14.3 months or 40 sites for 7.1 months. Although this compares favorably with the US-ADNI in which enrollment has needed 60 sites for 12 months, it should be acknowledged that the pilot E-ADNI sites might be among the most performing, motivated, and with more sophisticated technology among those of the European Alzheimer's Disease Consortium centers. Thus, the mean performance of a larger group of 20 or 40 sites might be lower than estimated on the basis of the performance of the present study. On the other hand, it is fair to acknowledge that as a result of budgetary restrictions, among pilot E-ADNI sites a large media campaign to favor patient and control enrollment such as that of the US-ADNI has not been carried out.

The high proportion of patients as well as controls who successfully underwent lumbar puncture should be emphasized. The proportion of subjects accepting lumbar puncture ranged from 68% to 83% in the European and 58% to 63% in the U.S. groups, with the greatest difference in the controls (83% vs 58%). Although it is true that the subjects in this study have been recruited aiming to 100% CSF collection rate and we fell short of reaching that goal, whereas the US-ADNI aimed at 20% and reached about 60%, it should also be recognized that subjects were enrolled in a reasonably short period of time, indicating that a larger European ADNI might achieve both a fast recruitment rate and a reasonably high rate of lumbar punctures. On the other hand, our study did not include fluorodeoxyglucose PET, and if this had been part of our protocol, the resulting burden of assessment to subjects might have led to a decrease of the rate of the proportion of lumbar punctures.

We conclude that by using the ADNI platform for clinical/neuropsychological and volumetric MR data collection, academic European Alzheimer's Disease Consortium centers can enroll patients and controls similar to those of the US-ADNI and can collect CSF from a high proportion of subjects.

Acknowledgments

Some of the data used in the preparation of this article were obtained from the U.S. Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). As such, the investigators within the US-ADNI contributed to the design and implementation of US-ADNI and/or provided data but did not participate in analysis or writing of this report.

The pilot European ADNI study was funded thanks to an unrestricted grant by the Alzheimer's Association. Principal Investigator is Giovanni B. Frisoni (Italy), PIs of the Clinical program Bruno Vellas (France), of the MR Imaging program Frederik Barkof (The Netherlands), and of the Biological Marker program Harald Hampel (Ireland/Germany) and Kaj Blennow (Sweden). Support for clinical assessment was provided by: Samantha Galluzzi in Brescia and Pierre-Jean Ousset in Toulouse. Support to acquire MR scans was provided by: Alberto Orlandini, Ivan Villa, and Jorge Jovicich in Brescia; Alberto Bellelli and Nicola Lupoi in Rome; Pierre Payoux in Toulouse; and Egill Rostrup in Copenhagen. Support to process blood and CSF was provided by: Giuliano Binetti, Luisa Benussi, and Roberta Ghidoni in Brescia; Rosanna Squitti in Rome; Christian Vincent in Toulouse; and Oda Jakobsen in Copenhagen.

We thank Roberto Molinari and Valeria Clementi (General Electric) for help with the installation of the ADNI sequences on the GE scanner in Brescia. Petra Pouwels, Hugo Vrenken and Joost Kuijer (VU University Medical Center, Amsterdam) are greatly acknowledged for their aid in defining the MRI scan protocol, the data collection and quality control of MRI scans. Anna Caroli and Marco Lorenzi (IRCCS Fatebenefratelli, Brescia) helped with the statistical analysis.

The US ADNI (Principal Investigator: Michael Weiner; NIH grant U01 AG024904) is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and through generous contributions from the following: Pfizer Inc, Wyeth Re-

search, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Merck & Co Inc., AstraZeneca AB, Novartis Pharmaceuticals Corporation, Alzheimer's Association, Eisai Global Clinical Development, Elan Corporation plc, Forest Laboratories, and the Institute for the Study of Aging, with participation from the U.S. Food and Drug Administration. Industry partnerships are coordinated through the Foundation for the National Institutes of Health. The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory of Neuro Imaging at the University of California, Los Angeles.

Supplementary Online Data

Note: Supplementary materials accompanying this article include the English version of the case report form used in the pilot E-ADNI, the MR scan manual, the image transmittal forms, the biological sample collection and shipment protocol, the scores on the ADAS-Cog and NeuroPsychiatric Inventory subscales, the sociodemographic and clinical features of the subgroup of US ADNI used to score MTA and WMH, and power analysis. The pertinent files can be accessed by visiting the online version of *Alzheimer's & Dementia* at www.alzheimersanddementia.org, and at doi: 10.1016/j.jalz.2008.04.009.

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