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The pilot European Alzheimer's Disease Neuroimaging Initiative (E-ADNI) of the European Alzheimer's Disease Consortium

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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 MCI, 22 with AD, and 18 older healthy persons using the ADNI clinical and neuropsychological battery. ADNI compliant MR scans, CSF and blood samples were shipped to central repositories. Medial temporal atrophy (MTA) and white matter hyperintensities (WMH) were assessed by a single rater using visual rating scales.

*Some of the data used in the preparation of this article were obtained from the US 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.

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Results—Recruitment rate was 3.5 subjects per month per site. The cognitive, behavioural and neuropsychological features of the European subjects were very similar to their US counterparts. 3D T1-weighted MRI sequences were successfully performed on all subjects and CSF samples obtained from 77%, 68%, and 83% of AD, MCI, and controls. Mean MTA score showed a significant increase from controls (left, right: 0.4, 0.3) to MCI (0.9, 0.8) to AD (2.3, 2.0), while 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.

Conclusions—Academic EADC centres can adopt the ADNI platform to enrol MCI and AD patients and older controls with global cognitive and structural imaging features remarkably similar to those of the US ADNI.

Keywords

Alzheimer's disease; mild cognitive impairment; imaging; CSF; ADNI; EADC

INTRODUCTION

In the US, the Alzheimer's Disease Cooperative Study is a network of about 60 academic centres that in the last 20 years have developed common clinical standards and procedures for multicentre 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 (1), a multicentre study that has enrolled and is following up about 200 AD patients, 400 MCI patients, and 200 normal older persons with clinical (neuropsychological tests), imaging (high resolution structural MR, fluorodeoxyglucose and amyloid PET), and biological markers of Alzheimer's disease (blood, CSF, and urinary analytes). Clinical data, images, and biological samples are collected 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 centres (the European Alzheimer's Disease Consortium — EADC <http://eadc.alzheimer-europe.org>) has in the past 10 years carried out clinical trials and multicentre 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 pre-dementia 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) where clinical data, images, and biological samples are collected in a standardized fashion.

This paper 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 7 selected sites of the EADC enrolling and assessing a restricted number of subjects (aim: 3 MCI, 3 AD, and 3 controls per site). Some specific features of this study should be underlined. First, PET imaging markers have not been collected in this pilot phase, since previous studies have already shown the feasibility of large multicentre 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 FLAIR MR sequences. Lastly, the project has a cross-sectional design, and no follow-up is envisioned.

The specific aims of this report are descriptive and consist of: (i) presenting the clinical and neuropsychological features of the experimental groups, (ii) describing the structural imaging markers of neurodegeneration and cerebral small vessel disease (medial temporal atrophy, MTA, and white matter hyperintensities, WMHs); and (iii) comparing the clinical, neuropsychological, and imaging features of the pilot E-ADNI with matched US ADNI subjects. Other conventional biological markers (CSF tau and Abeta) as well as non-conventional imaging and biological markers that have been assessed in the pilot E-ADNI (resting state functional MRI, diffusion tensor imaging, and plasma Abeta) will be reported elsewhere.

METHODS

Sites and organigram

Subjects were enrolled at the following 7 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), Dept 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 enrolment sites; monitoring of data, image, and sample collection; and reporting.

Patients

Between January 1st and March 31st 2007, each centre was asked to enrol 3 consecutive new patients with AD, 3 with MCI, and 3 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 believed after appropriate clinical and instrumental exams to be due to psychological factors (Munich).

Criteria for enrolment of MCI patients were: age between 55 and 90 years, complaints of memory loss by the patient and confirmed by a family relative, MMSE 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 neurological 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 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 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 (CEIOC-Comitato Etico delle Istituzioni Ospedaliere Cattoliche), then by Ethics Committees of all other sites. None of the subjects fulfilled the NINDS-AIREN criteria for probable vascular dementia (4).

Clinical/neuropsychological data

A Case Report Form (CRF) was developed based on 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 Neurological 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, while translated versions using 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 in order to avoid interference with word list recall test of the ADAS-Cog as 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.

MR imaging

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; Brescia, GE Excite; Copenhagen, Siemens Vision; Munich, Siemens Vision; Roma, Philips Achieva; 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 3D T1-weighted gradient echo sequence, two B1-calibration scans (performed using head and body coil as receivers, respectively), a PD/T2-weighted dual echo sequence, a diffusion tensor imaging (DTI) and a resting state fMRI sequence. This protocol deviated from the US ADNI in: (i) the omission of a routinely performed second 3D T1-weighted sequence (in case of improper scan quality, for example due to motion, MRI technicians were instructed to rescan a patient), and (ii) 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 7 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.

In 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 DICOM format and successfully passed the QC procedure at the Image Analysis Center (IAC) in Amsterdam (www.iac-amsterdam.nl), with special emphasis on the quality of the 3D 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 artefacts, no wrap up effects, no visually appreciable signal inhomogeneities, and good grey matter/white matter contrast on visual inspection.

MRI markers

These consisted of visual rating scales for MTA and WMH. MTA was rated on reconstructed coronal, T1-weighted images, using the five point rating scale (range 0-4), 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 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), 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.

Biological 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 A β 42 in the CSF, and A β 40 and A β 42 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 1 subject with blood obtained independently from that of the pilot E-ADNI. More details of biological sample collection will be provided elsewhere.

US ADNI subjects

Clinical data of all the US ADNI subjects (186 AD, 394 MCI, and 229 controls) available as of August 20th 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 magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

The Principle Investigator of this initiative is Michael W. Weiner, M.D., VA Medical Centre 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. For up-to-date information see www.adniinfo.org.

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

Statistical analysis

Differences of continuous variables between European and US sites and among AD, MCI, and controls were tested with 2-way analysis of variance (ANOVA) where factors were *site* (2 levels) and *diagnosis* (3 levels). The full factorial model was first tested including the *site* and *diagnosis* main effects as well as their *site x diagnosis* interaction. If the interaction proved significant, significance of the main effects was disregarded and post-hoc comparisons with Student's t-test were carried out between diagnostic groups and confirmed with the non parametric 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 as this would reflect the overwhelming significance of the much larger US groups.

Differences of dichotomous variables were tested by site (all diagnoses together) and in each individual *site x diagnosis* group pairs with the chi-square test. Differences of ordinal variables (MTA and WMH scores) were tested with Mann-Whitney U-test.

For the sake of conservativeness, the threshold for statistical significance was set at $p < 0.05$ 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 ($\alpha = 0.05$, power 80%).

RESULTS

Enrolment

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 3 out of 4 subjects overall, and blood reached Gothenburg in 9 out of 10. Enrolment 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).

Sociodemographics, clinical, and genetic features

Table 2 shows that the subjects enrolled in the pilot E-ADNI were generally younger than their US counterparts and in controls females were relatively fewer. Not surprisingly, education was 4 to 6 years higher in the US 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 CDR-SOB) were remarkably similar, compared to subjects from the US-ADNI, the MMSE differing 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.

Behavioural 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 behavioural disturbances on the NeuroPsychiatric Inventory were strikingly similar between European and US sites (data on individual behavioural disturbances can be found at http://www.centroalzheimer.it/public/NPI_Q_subscale.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 US than European subjects ($p < .05$ for all diseases), the extreme instance being the 13-fold difference of musculoskeletal diseases of MCI patients, where prevalence was 5 and 65% respectively ($p < .001$).

There was a mild and non significant trend towards decreasing frequency of the $\epsilon 4$ allele of apoE from AD through MCI to controls could be appreciated (33, 26, and 22%; p of chi-square test for trend 0.27), but this was much more marked in the US ADNI groups (42, 33 and 14%; $p < .001$), where a clear trend towards increasing frequency of the $\epsilon 2$ allele was also evident (2, 4, and 8%; $p < .001$).

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

MRI assessment

MTA scores increased from elderly control subjects to MCI to AD patients on both the left and right side (figure). The difference between controls and MCI patients did not reach statistical significance (left $p = 0.11$; right $p = 0.07$ on Mann-Whitney U-test). In AD patients, MTA on both sides showed significant difference compared with controls and MCI patients. MTA scores in US subjects tended to be slightly higher than in the European in almost all diagnostic groups, but this trend never reached significance ($p > 0.087$). WMH scores were remarkably low and did not differ among pilot E-ADNI diagnostic groups and were of similar magnitude between Europeans and US subjects.

Power analysis

Power analyses for all the variables shown in tables 2 and 3 and the figure 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 on 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.

DISCUSSION

In this manuscript, 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, biological 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 the US ADNI. Despite 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 US subjects and the category fluency 2 tests indicated poorer performance of only US MCI patients. While 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 US studies. The tendency to a difference in years of education between the US and Europe might at least in part be due to the different health coverage in the EU and US.

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, and detailed analysis of variations in signal-to-noise and contrast-to-noise ratios, and geometric distortion, using phantom data and data from travelling volunteers will follow. Because the sites of our study may be among those with the higher familiarity with high resolution sequences among those of the European Alzheimer’s Disease Consortium, and quality performance may 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 white matter hyperintensity 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 US groups, the measure closest to significance being right MTA score in controls ($p=0.087$). Although the criteria for the recruitment of our MCI patients were slacker than those of the US ADNI as 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, consistently with the expectation of enrolment of primarily degenerative cases.

It is interesting to note that the EU subjects seemed to have much lower comorbidity than their US 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 US subjects and contrast with their higher educational attainment. The difficulty of achieving a satisfactory concordance of physical health assessment in multicentre clinical studies is a well known issue in the epidemiological literature (13,14) that will need to be more thoroughly addressed in future ADNI efforts.

A few remarks on enrolment are warranted. The enrolment rate of the pilot E-ADNI sites was 2.8 subjects per month per site, implying that in order 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 favourably with the US ADNI where enrolment has needed 60 sites for 12 months, it should be acknowledged that the pilot E-ADNI sites may be among the most performing, motivated and with more sophisticated technology among those of the EADC centres. Thus, the mean performance of a larger group of 20 or 40 sites might be lower than estimated based on performance of the present study. On the other hand, it is fair to acknowledge that due to budgetary restrictions nowhere among pilot E-ADNI sites has a large media campaign to favour patient and control enrolment such as that of the US ADNI 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 LP ranged from 68 to 83% in the European and 58 to 63% in the US groups, with the greatest difference in the controls (83 vs. 58%). While 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, while 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 FDG PET, and had this 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 centres can enrol patients and controls similar to those of the US ADNI, and can collect CSF from a high proportion of subjects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure.

Mean scores of medial temporal atrophy (MTA) and white matter hyperintensities (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.

Table 1
Subject enrolment and data collection of the pilot E-ADNI study. The denominator of percentages is N of the first row, representing 100% (reference).

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

¹ including full neuropsychological battery

² at least valid 3D acquisition

³ with viable CSF reaching safely the collection centre in Munich

⁴ with viable blood reaching safely the collection centre in Gothenburg

Table 2

Comparison of sociodemographic, clinical, and genetic features between pilot E-ADNI and US ADNI. Figures denote number (%) or mean $\pm$ SD. The number of subjects with apoE genotypes of AD, MCI, and controls in the pilot E-ADNI is 21, 19, and 18, and in the US-ADNI 189, 387, and 229. ANOVA and χ^2 test significance of the “site” main effect (EU vs. US) and the interaction of site x diagnosis.

		AD		MCI		Controls		Significance on	
		pE-ADNI	US-ADNI	pE-ADNI	US-ADNI	pE-ADNI	US-ADNI	ANOVA or χ^2	Interaction
Number		22	186	19	394	18	229		
Sociodemogr.	Age, yrs	74.6 $\pm$ 9.2	75.2 $\pm$ 7.6	68.9 $\pm$ 11.3	74.7 $\pm$ 7.5	71.2 $\pm$ 9.2	75.9 $\pm$ 5.0	<.0005	n.s.
	Sex, F	11 (50%)	88 (47%)	9 (47%)	141 (36%)	4 (22%)*	110 (48%)	n.s.	---
	Education, yrs	10.5 $\pm$ 4.3	14.7 $\pm$ 3.14	11.1 $\pm$ 4.4	15.7 $\pm$ 3.1	10.8 $\pm$ 3.0	16.0 $\pm$ 2.9	<.0005	n.s.
Cognition	Mini Mental State Exam	23.2 $\pm$ 3.2	23.3 $\pm$ 2.0	27.3 $\pm$ 2.1	27.0 $\pm$ 1.8	29.1 $\pm$ 0.7	29.1 $\pm$ 1.0	n.s.	n.s.
	Clinical Dementia Rating SOB	4.8 $\pm$ 2.1	4.4 $\pm$ 1.6	1.3 $\pm$ 1.0	1.6 $\pm$ 0.9	0.06 $\pm$ 0.17	0.03 $\pm$ 0.12	n.s.	n.s.
	ADAS-Cog	19.8 $\pm$ 8.2	18.6 $\pm$ 6.3	11.4 $\pm$ 5.9	11.6 $\pm$ 4.4	8.2 $\pm$ 3.1	6.2 $\pm$ 2.9	n.s.	n.s.
	Logical Mem - Delayed Recall	1.7 $\pm$ 3.2	1.2 $\pm$ 1.8	5.8 $\pm$ 4.0**	3.8 $\pm$ 2.7	11.6 $\pm$ 3.4	13.0 $\pm$ 3.6	---	.005
Behaviour	Geriatric Depression Scale	2.4 $\pm$ 1.8	1.7 $\pm$ 1.4	2.5 $\pm$ 1.9	1.6 $\pm$ 1.4	1.2 $\pm$ 1.0	.8 $\pm$ 1.1	<.0005	n.s.
& disability	Functional Assessment Quest.	12.8 $\pm$ 7.0	13.1 $\pm$ 6.8	1.6 $\pm$ 1.8	3.8 $\pm$ 4.5	0	.1 $\pm$ 0.6	n.s.	n.s.
	NeuroPsychiatric Inventory	3.1 $\pm$ 3.8	3.6 $\pm$ 3.4	1.6 $\pm$ 1.6	1.8 $\pm$ 2.6	.2 $\pm$ 0.4	.4 $\pm$ 0.9	n.s.	n.s.
Physical	Cardiovascular diseases	9 (44%)*	133 (70%)	7 (37%)*	279 (72%)	6 (33%)*	153 (67%)	<.0005	---
comorbidity	Respiratory diseases	2 (11%)	34 (18%)	3 (16%)	86 (22%)	1 (5%)	50 (22%)	0.05	---
	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 dis.	6 (29%)	77 (41%)	5 (26%)	172 (44%)	5 (28%)	111 (49%)	0.01	---
ApoE	ϵ 2 allele	2 (5%)	8 (2%)	2 (5%)	29 (4%)	2 (6%)	38 (8%)	n.s.	---
genotyping	ϵ 3 allele	26 (62%)	213 (56%)	26 (68%)	488 (63%)	26 (72%)	354 (77%)	n.s.	---
	ϵ 4 allele	14 (33%)	157 (42%)	10 (26%)	257 (33%)	8 (22%)	66 (14%)	n.s.	---

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

For further information on statistical analysis see text.

* p<.05

** p<.01

*** p<.001.

Neuropsychological battery scores of the pilot E-ADNI versus US-ADNI subjects. Group size is shown in brackets. ANOVA tests significance of the "site" main effect (EU vs. US) and the interaction of site x diagnosis.

Table 3

	AD		MCI		Controls		Significance on ANOVA	
	pE-ADNI	US-ADNI	pE-ADNI	US-ADNI	pE-ADNI	US-ADNI	Site	Interaction
<i>Clock</i>								
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	n.s.
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	n.s.	n.s.
<i>Category Fluency</i>								
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	n.s.	n.s.
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
<i>Trial Making</i>								
Trial A	81±38	68±37	64±34	45±23	43±29	36±13	.001	n.s.
Trial B	198±84	199±87	162±98	130±73	103±39	89±44	n.s.	n.s.
Trial B—A	126±64	133±76	98±73	86±63	60±34	53±39	n.s.	n.s.
<i>Digit Symbol</i>								
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	n.s.
<i>Boston Naming</i>								
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	n.s.
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	n.s.	n.s.

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's t-test at

For further information on statistical analysis please see text

* p<.05

** p<.01

*** p<.001