

Alzheimer's Disease Neuroimaging Initiative in Europe

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Abstract

The North American Alzheimer's Disease Neuroimaging Initiative (ADNI) was originally conceived as a study to develop markers of disease progression, but has also become a strong technological platform for the multi-centric collection of clinical data and imaging and biological markers. Because the ADNI platform was first imported in Europe, thanks to the pilot European ADNI, several ADNI-related initiatives have flourished, funded by the European Commission's 7th Framework Programme, national governments, and the Alzheimer's Association aimed at: (i) collecting fresh data ADNI style (FP7 AddNeuroMed, Innovative Medicine Initiative Pharma-Cog/European ADNI, Swedish ADNI, and Italian ADNI); (ii) developing standard operational procedures for the collection of markers (International Harmonization of CSF Abeta42 and tau, and European Alzheimer's Disease Consortium–ADNI Harmonization of Hippocampal Volumetry); and (iii) developing infrastructures for the treatment of ADNI data (FP7 neuGRID and outGRID, and the French Centre pour l'Acquisition et le Traitement de l'Image). Although this fragmented scenario is not surprising given the structure of scientific funding in Europe, opportunities are being developed for high order networking and harmonization at the continental level (Joint Programming for Neurodegenerative Diseases).

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ADNI; Alzheimer's disease; International cooperation; Joint Programming

1. Introduction

The North American ADNI [1] was originally conceived as a study to develop markers of disease progression. A prospective design was devised with collection of serial information on cognitive performance, brain structural and metabolic changes, and biochemical changes in the cerebrospinal fluid indicative of brain amyloidosis and neurodegeneration in 800 persons, with cognitive deterioration ranging from absent to dementia. The main outcome of ADNI was supposed to be the development of markers to be used as surrogate outcomes in clinical trials of disease modifying drugs to facilitate phase II-III studies.

However, the unprecedented size of the effort (60 academic centers in the United States and Canada) made harmonization of data collection procedures a preliminary and high priority need. Harmonization was driven by the most challenging modality, that is structural magnetic resonance imaging (MRI), where the lack of standards for image

acquisition of scanner vendors made sophisticated analysis of pooled data impossible. The ADNI MR Core group developed ad hoc 3D T1-weighted sequences—some of which are nonproprietary—that gave comparable grey-white matter contrast irrespective of scanner, effectively reducing the error variance of the ADNI multicentric study to that of a unicentric study [2]. Harmonized procedures for metabolic—and later amyloid—positron emission tomography (PET) image collection were developed by the PET Core group [1] and for the collection and processing of biological fluids (CSF, blood, and urine) were developed by the Biological Core group [3]. Together with an extensive and detailed protocol for the collection of clinical and neuropsychological test variables by the Clinical Core [4], these procedures represent a formidable data collection methodological platform for prospective multicentric studies of patients with Alzheimer's and other neurodegenerative conditions. By adopting the ADNI platform, other studies should be able to reduce inter-center variance and compare the baseline and prospective clinical and instrumental features of their study population to that of the ADNI.

The ADNI platform for data collection was first imported in Europe, thanks to the pilot European ADNI, and several

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ADNI-related initiatives have since flourished with different aims, from the development of standard operational procedures for the collection of markers to the development of infrastructures for the treatment of ADNI data, and the collection of fresh ADNI compatible data (Table 1). We will here review the most significant ADNI-related initiatives that have been or are being carried out in Europe or led by European scientists.

2. Data collection projects based on the ADNI platform

2.1. Pilot European ADNI

The aim of the pilot E-ADNI (Tables 1, 2) was to test the feasibility of the adoption of the ADNI platform in Europe [5]. Seven academic centers of the European Alzheimer's Disease Consortium (EADC) based in Amsterdam (P.I. P. Scheltens), Copenhagen (P.I. G Waldemar), Munich (P.I. H Hampel), Rome (P.I. PM Rossini), Stockholm (P.I. L.-O. Wahlund), Toulouse (P.I. B Vellas), and Brescia assessed 19 patients with mild cognitive impairment (MCI), 22 with Alzheimer's disease (AD), and 18 older healthy persons with the ADNI clinical and neuropsychological battery, adapted for the multilingual setting, and collected ADNI compliant high resolution 3D structural MR scans under the guidance of a core image lab (Amsterdam, P.I. F. Barkhof). CSF and blood samples were also collected after the ADNI biological sample collection procedures, and shipped to central repositories (in Munich and Gotheborg, P.I. K Blennow) in duplicate (fresh and frozen) [6]. Three young travelling volunteers were also scanned in all centers to assess across scanner variability, and DTI and resting state functional MRI sequences were acquired for experimental subjects and travelling volunteers. 18F-fluorodeoxyglucose (FDG) PET was not included.

Although age of the European MCI patients and controls was about 5 years younger than their US counterparts, cognitive features were very similar, cognitive performance differing by 0.3 points of Mini Mental State Exam and 2.0 of Alzheimer's Disease Assessment Scale, cognitive subscale at most. CSF samples were collected from 77%, 68%, and 83% of AD, MCI, and controls, respectively. The neuropsychological features of the sample were extremely similar to those of the US ADNI counterparts. Medial temporal atrophy, assessed with the Scheltens's scale, was increasing from controls (around 0.5) to MCI (around 1.0), to AD (around 2.0), whereas Fazekas's white matter hyperintensities scale score was low and similar in the three groups (between 0.6 and 0.8) [5]. Storage and shipment effects (not frozen with regular mail versus immediately frozen) were significant for CSF t-tau and p-tau181, but effect size was below 10% as were plasma concentrations of Abeta42 and Abeta40. CSF Abeta42 was increasing and total tau concentrations decreasing from AD to MCI and controls. Plasma Abeta42 and Abeta40 were both increasing from AD to MCI and controls [6].

The pilot E-ADNI has shown that academic European Alzheimer's centers can collect CSF from a remarkably high proportion of subjects and that the adoption of the ADNI platform results in the selection of a clinical population strikingly similar to that of the US ADNI.

2.2. AddNeuroMed

This has been funded as a forerunner for the IMI, Innovative Medicines Initiative, a new funding scheme that the European Commission has launched to foster the development of new therapeutically active drugs through a public–private partnership between academic institutions and the European Federation for Pharmaceutical Industries and Associations [7] (Tables 1, 2). The feasibility study of IMI was the Innomed project, where Innomed-PredTox was the a preclinical biomarkers for toxicology project (<http://www.innomed-predtox.com>) and Innomed-AddNeuroMed the clinical biomarkers for Alzheimer's disease branch (<http://www.innomed-addneuromed.com>). AddNeuroMed was aimed at improving experimental models of Alzheimer's for biomarker discovery and identify biomarkers for Alzheimer's disease suitable for early diagnosis, prediction of the development of dementia in patients with MCI, and monitoring disease progression for use in clinical trials and practice.

AddNeuroMed in itself has preclinical and clinical components in addition to platform technologies. The platform technologies that are applied to both preclinical and clinical workstreams include: proteomics, genomics, lipidomics, neuroimaging, information technologies. The clinical component is responsible for the identification and assessment of a cohort of people with dementia, with MCI, and older people without memory problems. Over 700 people across Europe (about 250 cases, 250 controls, 250 MCI) were recruited to the study and have been assessed at regular intervals (baseline and 3, 6, 9, 12 months and beyond). Assessments include tests of memory, function, behaviour, as well as blood tests and brain scans. Some subjects have had spinal fluid taps.

The imaging work package is intended to provide data from a longitudinal MRI study on a pan-European cohort of subjects with probable AD, normal elderly controls, and those at risk of AD [8]. In addition, MRI and spectroscopy investigations in transgenic animal models of AD complement these data. AddNeuroMed has used the ADNI sequences for structural MRI on 1.5T scanners, all other data and biosample collection procedures being proprietary. AddNeuroMed continues to follow-up participants and to analyze the data collected. Funding for this is from local, country-specific sources, but in particular the National Institute for Health Research in the United Kingdom.

2.3. Pharma-Cog (E-ADNI)

On January 1, 2010, the IMI (<http://www.imi.europa.eu>) has launched the Pharma-Cog project (prediction of cognitive properties of new drug candidates for neurodegenerative

Table 1
ADNI-related initiatives in Europe or led by EU scientists

	Funding agency	Budget	Duration	Timelines	Principal investigators	Countries
Data collection						
Pilot E-ADNI	Alzheimer Association	\$250k	1.5 yr	Closed May 2007	Frisoni	IT, FR, GE, NL, SW, DE
AddNeuroMed	EC	€8.6 M	40 mo	Assessment ongoing	Lovestone	FI, PL, UK, IT, GR, FR
Pharma-Cog Workpackage 5 (E-ADNI)	EC IMI	€4.5 M	5 yr	Started Dec 2009, ongoing	Irving-Blin-Frisoni	SP, IT, GE, FR
Swedish ADNI	Alzheimer Association	€30k	2 yr	Closed 2009	Winblad-Wahlund	SW
Italian ADNI	NHS	€600k	2 yr	Closing Jun 2011	Frisoni-Tagliavini	IT
Development of standard operational procedures						
International harmonization of CSF Aβ ₄₂ , total tau, and p-tau	Alzheimer Association	\$800k	4 yr	Started 2009, ongoing	Blennow	40 Labs (EU, US, Japan, Australia, Brazil)
EADC-ADNI harmonization of hippocampal volumetry	Lilly–Wyeth	€70k	2 yr	Closing 2012	Frisoni-Jack	24 centres in EU, US, Canada, and Australia
Infrastructure development						
neuGRID	FP7	€2.7 M	3 yr	Closing Jan 2011	Frisoni	IT, FR, SP, CH, UK, SW
outGRID	FP7	€440 K	2 yr	Closing Dec 2011	Frisoni-Toga-Evans	IT, FR, UK, US, CD
Centre pour l'Acquisition et le Traitement de l'Image	French National Foundation on AD and RD	€3 M+	3 yr	Starting 2010	Mangin-Lehericy	FR

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; EC, European Commission; IMI, Innovative Medicines Initiatives; NHS, National Health System; EADC, European Alzheimer's Disease Consortium; FP7, 7th Framework Programme; AD and RD, Alzheimer's disease and related diseases.

diseases in early clinical development), the so far only IMI project on neurodegenerative diseases (Tables 1, 2). Pharma-Cog aims to develop tools to streamline AD drug discovery, therefore accelerating the delivery of effective medication to patients.

A multidimensional “MATRIX” approach will be implemented throughout this €22 M project by conducting parallel pharmacodynamic studies in animals, healthy volunteers, and selected patient cohort (*x* axis), using the same fully translational pharmacodynamic end points (*y* axis), the same provocation challenges and therapeutic interventions (*z* axis) using single dose and medium-term treatment. This approach is based on: (i) multi-modal data collection from harmonized animal and human models, (ii) extraction of selected features from this data collection (biomarkers/animals, healthy volunteer models, physiological, and pharmacological challenges), and (iii) advanced quantitative pharmacological assessment of the data generated across modalities and studies.

A large section of the project (Workpackage 5 “Identification of Biomarkers Sensitive to Disease Progression: Clinical Studies”) is funded on the ADNI protocols for clinical, neuropsychological, structural imaging, CSF, and blood data and sample collection that was pioneered in the pilot E-ADNI. Novel imaging and peripheral markers will also be added to this battery in the context of a serial 3-year clinical study of patients with early cognitive impairment. Pharma-Cog WP5 is so far the only project in Europe with the largest overlap with the North American ADNI. A separate section (Workpackage 6 “Characterisation of Transgenics and Development of Imaging, Electrophysiological, and Biological Markers for Disease Modifying Drugs: Animal studies”) will study single, double, and triple transgenic mice overex-

pressing human mutated forms of amyloid precursor protein, PS1 and tau that will be characterised using a marker MATRIX homologous to that used in Workpackage 5.

2.4. Swedish ADNI

The Swedish ADNI was a study where two sites (Malmö and Stockholm) recruited and assessed three AD and three MCI patients, and three healthy controls (Tables 1, 2). Study subjects underwent baseline MRI with the ADNI sequences, and only in one site, neuropsychological assessment, CSF, and blood sampling following the ADNI protocols was carried out. Clinical follow-up was carried out 1 year after baseline. The Swedish ADNI will continue in the mainstream of a larger country-wide initiative, the Swedish BrainPower (<http://www.swedishbrainpower.se/eng/index.htm>), a multi-disciplinary project addressing social, clinical, and basic science issues related to AD and other dementias. The Swedish BrainPower is made of 10 core projects, has started in 2010, and will continue for 5 years. It is funded with 100M SEK (€10 M) by the Wallenbergs Foundation.

2.5. Italian ADNI

In 2008, the Italian Ministry of Health has funded a “Strategic Programme” aimed to develop and validate a multimodal protocol for the diagnosis and tracking of AD in the prodromal phase (Malattia di Alzheimer: sviluppo e validazione di un protocollo multifattoriale per la diagnosi e il monitoraggio della fase prodromica e incipiente). The imaging core (Diagnosis of incipient Alzheimer disease: development of ADNI-based imaging markers for use by the National Health System) aims to promote the use of structural ADNI sequences and

Table 2
European projects aimed at collecting fresh data based on the ADNI data and sample collection platform

	Pilot E-ADNI	AddNeuroMed	Pharma-Cog Workpackage 5	Italian ADNI	Swedish ADNI
Design					
Diagnostic categories	AD MCI CTR	AD MCI CTR	MCI CSF Ab42+ MCI CSF Ab42-	Naturalistic population	AD MCI CTR
No. patients	59	247+242+208	75+75	480	18
Assessments	Only baseline	0, 3, 12 mo; annually thereafter	Biannual for 3 yr	Only baseline	Clinical 1 yr follow-up
No. centres	7	7	8	10	2
ADNI methods for data collection					
Clinical variables	Yes	No	Yes	No	Yes
Npsy tests	Yes	No	Yes	No	Yes
Structural MR 1.5T	Yes	Yes	No	Yes	Yes
Structural MR 3.0T	No	No	Yes	Yes	N.A.
FDG PET	N.A.	No	N.A.	No	N.A.
Amyloid PET	N.A.	N.A.	No	No	N.A.
Blood collection	Yes	Yes	Yes	N.A.	Yes
CSF collection	Yes	Partial	Yes	N.A.	Yes

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; AD, Alzheimer's disease; MCI, mild cognitive impairment; CTR, healthy elderly controls; CSF, cerebrospinal fluid; MR, magnetic resonance; FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography; N.A., not available.

standardized hippocampal volumetry as routine diagnostic procedures in leading academic clinical centers of the National Health Service (Tables 1, 2) (<http://www.centroalzheimer.org/sito/progettazioni.php>). After scanner qualification, 480 patients come to observation for memory and other cognitive complaints in 10 Italian memory clinics and will undergo 1.5T and 3.0 T volumetric structural MRI with the ADNI sequences. Appropriately trained tracers will segment the hippocampus and compare the volume to the distribution of local and US-ADNI healthy controls. A subgroup of patients will also undergo 18F-FDG PET following the ADNI image acquisition protocol and electroencephalography.

The project is tightly linked to the European Alzheimer's Disease Consortium (EADC)-ADNI Harmonization of Hippocampal Volumetry (see further on) such that at the end of the project National Health Service clinical centers will be familiar with the whole pipeline from MR image acquisition to hippocampal marker collection and interpretation.

3. Projects for the development of standard operational procedures for ADNI data

3.1. International harmonization of CSF Abeta42 and tau

The objective of this Alzheimer's Association's-funded effort is to standardize CSF biomarker measurements between laboratories (Table 1). The program consists of two parts. The first is a standardized protocol for lumbar puncture (LP) and CSF sample processing (The Alzheimer's Association flow chart for LP and CSF processing), and participating clinical laboratories should adhere to national quality guidelines and have received a national (or international) accreditation for medical laboratories. The second is an external quality control program that will allow a comparison of CSF biomarker levels between laboratories (and thus also

publications), and evaluation of the longitudinal stability of CSF biomarker levels within laboratories. The aim is to standardize biomarkers between laboratories, and not to identify the "true" biomarker level. Forty laboratories worldwide are taking part to this initiative.

3.2. EADC-ADNI harmonization of hippocampal volumetry

In Alzheimer's disease (AD), estimating hippocampal atrophy has potential uses in early diagnosis and as a surrogate outcome in clinical trials of disease modifying drugs. The most reliable and widely used procedure is volumetry of the hippocampus through manual outlining by an expert rater on high-resolution MR images. However, different anatomical landmarks and measurement environments result in wide different estimates across laboratories worldwide, thus preventing the comparison of different studies and trials and limiting transfer of the marker to clinical practice. Aim of the project (http://www.centroalzheimer.org/sito/ip_sops_e.php) is to harmonize protocols for manual tracing of the hippocampus at 1.5T and 3T MRI and develop hippocampal masks that can serve as references for rater qualification and validation of automated algorithms (Table 1).

Twenty-four centers in Europe, United States, Canada, and Australia are taking part; all the centers have first-hand experience on hippocampal volumetry in AD. The project consists of three main phases. (i) Nine different protocols for hippocampal volumetry have been identified in the scientific literature, and a survey of discrepancies has been carried out (<http://www.centroalzheimer.it/public/SOPs/online>). Sample hippocampi have been segmented following each of the protocols and the appropriateness of segmentation checked with the protocols' authors (<http://www.centroalzheimer.it/public/SOPs/online>). A Delphi technique will be used to reach

consensus on anatomical landmarks and measurement environment, thereby identifying a harmonized protocol. (ii) The harmonized protocol will be used by expert and nonexpert raters to segment ADNI images and a small image dataset for which pathological data are available, and (iii) probabilistic masks will be developed based on expert tracings. Part of phase (i) has been completed in 2009, and the project is ongoing.

The use of the harmonized protocol will allow to produce consistent estimates of hippocampal volumes across laboratories worldwide. This will foster wider adoption of hippocampal volumetry as a marker for early diagnosis in AD, comparability of natural history studies, and comparison of effect sizes of different therapies on disease progression.

4. Development of infrastructures for the management of ADNI data

4.1. *neuGRID* and *outGRID*

neuGRID (www.neuGRID.eu) was thought of and designed as the repository of the European ADNI, but has come to be much more than that. It is a user-friendly Grid-based research e-Infrastructure, where the collection/archiving of large amounts of imaging data is paired with computationally intensive data analyses (Table 1) <http://www.centroalzheimer.it/public/SOPs/online> [9]. When completed early in 2011, neuroscientists will be able to run computationally intensive image analysis pipelines on large datasets (in the range of thousands) such as ADNI, thanks to distributed grid services. In a representative “use case,” a researcher interacts with *neuGRID* to process the ADNI dataset using a pipeline such as (but not limited to) cortical thickness extraction. After processing on the grid is complete, provenance data is used to verify the output and the results are exported into the user’s tools for statistical analysis and advanced visualization. In a context where a large image dataset such as ADNI is public, *neuGRID* aims to bring algorithms and computational resources in a user-friendly environment to the desktop of each individual researcher, who will thus be able to run analyses that would normally require mainframe or cluster computing.

Two infrastructures with similar aims are operational or under construction in North America. In Canada, the Montreal Neurological Institute aims to develop the pan-Canadian platform CBRAIN (Canadian Brain Imaging Research Network, <http://cbrain.mcgill.ca>) for exchange and distributed processing of 3D/4D brain imaging data. In the United States, the LONI—Laboratory of Neuro Imaging at UCLA (the University of California, Los Angeles—<http://www.LONI.ucla.edu>)—already provides several algorithm pipelines to perform a wide range of brain image analyses that come with an intelligent and interactive distributed visual programming environment. The *outGRID* project (www.outGRID.eu) aims at promoting interoperability among these three infrastructures. Through Fact Finding activities, technical information about the three infrastructures will be col-

lected and shared, with the ultimate aim of identifying and formalizing technical specifications to achieve full interoperability. By disseminating *outGRID*’s information in scientific communities, worldwide synergies with the *neuGRID*-CBRAIN-LONI triad will be encouraged. *outGRID* will be a first step toward full interoperability among *neuGRID*, CBRAIN, and LONI, and the development of a global research infrastructure that might radically change the way science is done in the field of computational neuroscience in much the same manner that the world wide web has changed the way to communicate and exchange documents.

4.2. *Centre pour l’Acquisition et le Traitement de l’Image* and other national networks

The French Presidential plan for Alzheimer’s disease will, among other things, fund a network to organize the collection of standardised high quality image datasets, promote research on aging and dementias, and improve both routine practice and research studies (Table 1). The *Centre pour l’Acquisition et le Traitement de l’Image* (CATI) will benefit both research and clinical practice. For research studies, the CATI will provide assistance to design and build studies, access to the image providing network, a portfolio of image processing algorithm pipelines, the databasing of raw and processed data, the opportunity to contribute to a national database, a portfolio of statistical meta-analysis tools, and assistance from the experts of the CATI at any stage of the procedure. In clinical practice, the CATI will work on transferring scientific knowledge to routine clinical applications of imaging for AD, such as early and differential diagnosis and monitoring of disease progression. The tools and procedures of the CATI will be developed to stick as much as possible to the ADNI standards.

In Germany, the German Dementia Competence Network (DCN) is a research platform of university departments that teamed up to perform long-term studies on dementia, including cross-sectional and prospective longitudinal cohort studies and clinical trials. The DCN has established procedures for standardized multicenter acquisition of clinical, biological and imaging data, for centralized data management, and for the evaluation of new treatments. The recruitment started in 2003, before the ADNI protocols for data collection were developed, and some of the results of the DCN have been used to design and develop the North American ADNI [10].

5. Conclusions

In Europe, ADNI has attracted great attention from its very start and has fostered the development of several initiatives aimed at collecting fresh data following the ADNI collection protocols, developing standard operational procedures for marker collection, and developing infrastructures for the treatment of ADNI data. However, current efforts are fragmented, and harmonization and coordination are urgently needed. Indeed, opportunities are being developed for high-order

networking and harmonization of these as well as all other initiatives on AD at the continental level (Joint Programming for Neurodegenerative Diseases) (http://www.consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/intm/111721.pdf). The Joint Programming initiative aims to coordinate the largest share of AD research in Europe, coming from national grants, thus minimizing duplications and enhancing efficiency. The ADNI platform is a natural tool for transnational co-operations on clinical populations. Some European scientists and policy makers have realized its merits and potential and are going to adopt it, despite being developed outside Europe.

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Did you know?

The screenshot shows the website for Alzheimer's & Dementia, the journal of the Alzheimer's Association. The main content area displays the 'Current Issue' for November 2008 (Vol. 6, No. 6). A 'Now Included on MEDLINE' badge is prominently featured. Below this, there are sections for 'Featured Articles' and 'Journal Access'. The 'Journal Access' section includes a link for 'Full-text articles' and a 'Journal Access' button. A red arrow points to the 'Journal Access' button. The 'Journal Access' section also includes links for 'Activate Online Access', 'Buy a Subscription Now', and 'Access Neurology of Aging'.

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