

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 Aβ42 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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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

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