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Alzheimer's Disease Neuroimaging Initiative special issue

This special issue of *Neurobiology of Aging* is the first editorial initiative centered solely around research papers arising from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Studies are authored by research groups spanning three continents. This unusual event is due to the uniqueness of the ADNI in the field of Alzheimer's disease (AD) and clinical neuroscience in general.

The North American ADNI

ADNI was originally conceived in North America as a study to develop markers of AD progression to be used as surrogate outcomes in clinical trials of disease modifying agents to facilitate phase II-III studies and foster the development of innovative drugs (Mueller et al., 2005). A prospective design was devised with collection of serial information every 6 months on cognitive performance, brain structural and metabolic changes with MR and FDG PET, and biochemical changes in the CSF, blood, and urine indicative of brain amyloidosis and neurodegeneration in 800 persons with cognitive deterioration ranging from absent to mild cognitive impairment (MCI) to dementia. The North American ADNI was funded for 5 years by NIH-NIA and Pharma industry with US$60mn (€46mn). As a precompetitive public-private partnership, all collected data were supposed to be made public soon after collection to foster exploitation by researchers worldwide. As data collection gained momentum and the first results started to appear, a genome-wide association study and a substudy on amyloid imaging were added. Approaching the end of the funding period (October 2009), a bridge grant was won (ADNI-GO), aiming to expand the MCI severity window with 200 patients falling in the mildest end of the MCI spectrum, and recently a grant for ADNI2, stretching assessment of ADNI1 and ADNI-GO subjects by five more years, enrolling 550 new subjects, and expanding markers to 18 F amyloid imaging and MR-based diffusion, perfusion, and resting functional, with an overall funding of about US$150mn (€115mn). A thoughtful and instructive insider view on the problems that had to be solved before launching ADNI and how they were addressed can be found in Zaven Kachaturian's Editorial opening a special issue on ADNI of the journal *Alzheimer's and Dementia* where reviews by ADNI core leaders and Worldwide ADNI initiatives can be found that usefully complements the present special issue of NBoA (Khachaturian, 2010).

The ADNI platform for data and sample collection

Soon after inception, ADNI raised great interest in the neuroscientific community, which immediately perceived its innovative nature. As the first results came in, it became clear that it would reach far beyond the intended aim. The unprecedented size of the effort (60 academic centers in the USA and Canada) made harmonization of data and sample collection and image acquisition a mandatory preliminary requirement. Procedures for the harmonized collection of clinical and neuropsychological data, structural MR, FDG PET, amyloid PET, and CSF, blood, and urine collection were developed by leading world experts. This set of procedures represented a formidable methodological platform to collect disease markers in prospective multicentric studies of patients with AD and other neurodegenerative conditions.

Worldwide ADNI

Alzheimer's researchers worldwide soon adopted one or more of the disease markers collected "ADNI style" as the foundations for where to develop their multicenter programs. Efforts were initiated in Europe (Frisoni, 2010), Australia (Ellis et al., 2009), and Japan (Arai, 2009) where variable combinations of the ADNI markers were collected following the ADNI protocols. On top of this, the individual projects would add the collection of project-specific innovative markers. Some of the articles in the present issues come from the European (Liu et al., 2010) and Australian efforts (Rowe et al., 2010).

Public ADNI-based e-infrastructures

One of the most innovative features of the North American ADNI is that all information that can be stored in digital format is published soon after quality check in a public repository (www.loni.ucla.edu/ADNI). The availability of image datasets of unprecedented size (the North American ADNI might reach almost 10,000 structural 1.5 T MR scans and 2,500 FDG PET scans) paired with the increasing availability of sophisticated but computationally intensive algorithm pipelines that can extract meaningful disease markers (cortical thickness, voxel-based gray matter

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density, cortical structural connectivity, etc.) has led to the development of *ad hoc* electronic infrastructures (Redolfi et al., 2009) aiming to offer imaging laboratory capabilities to researchers working in environments devoid of pre- and post-processing imaging facilities. Their usefulness will increase with the increasing availability of compatible image datasets that might be pooled with the North American ADNI. Images from the Australian ADNI can already be found in the same public repository as the North American ADNI (www.loni.ucla.edu/ADNI). Fostered by the notion that harmonization of neuroimages acquired from multiple vendor scanners is feasible, initiatives are being developed in Europe aiming to offer Alzheimer's centers at the national level the centralized harmonization and quality control of images acquired following the ADNI protocol (Khachaturian, 2010).

Dynamic biomarkers and the pathophysiology of AD

The power of the multimodal longitudinal design of ADNI studies has allowed us to expand previous observations on the pathophysiology of AD and outline a hypothetical but comprehensive scenario where brain amyloid deposition starts decades before the appearance of the first, albeit mildest, clinical symptoms, is followed first by synaptic failure (indexed by progressive impairment of glucose metabolism), then subclinical neurodegeneration (indexed by gray matter atrophy), and finally clinical symptoms (Frisoni et al., 2010; Jack et al., 2010). This scenario is still largely hypothetical, but an increasing number of observations are contributing (Caroli et al., 2010; Greene and Killiany, 2010) – and will continue to contribute – to confirm it. The dynamics of amyloid deposition is of particular relevance for its possible role as the starting event of the cascade leading to neurodegeneration (Apostolova et al., 2010; Rowe et al., 2010). This conceptual framework will need to be further refined by including the effect of factors that might modify the slopes of marker change such as genetic background (Lakatos et al., 2010; Tosun et al., 2010), and general and cerebral metabolism (Ho et al., 2010). The dynamics of atrophic changes, reflecting neurodegeneration, across different brain structures (Madsen et al., 2010), will be elucidated through serial studies.

Predicting cognitive deterioration at the MCI asymptomatic stages

The hypothesis outlined above leads to at least two corollaries. The first is that diagnosis of AD at the stage of MCI, and probably even earlier, is feasible with a battery of diagnostic disease markers. The composition of the battery, however, may differ across the different severity stages of the disease. At the MCI stage, the most credited diagnostic battery is one made of medial temporal atrophy, temporoparietal glucose metabolism, CSF markers (Abeta42 and tau), and amyloid imaging. Structural imaging markers, in particular when obtained through accurate postprocessing techniques, have particularly high feasibility and good accuracy (Chou et al., 2010; Desikan et al., 2010; Liu et al., 2010). Atrophy rates might be more sensitive to conversion than single shot measurements (Risacher et al., 2010), although for diagnostic purposes might be less practical. Research on markers that might accurately predict cognitive deterioration in healthy persons with no cognitive deficits is in its infancy, but meaningful results are starting to appear (Nettiksimmons et al., 2010).

Optimizing the design of the clinical trials of the future

The second corollary is that markers of disease progression may or may not be the same as diagnostic markers, and that which tracking marker is more sensitive to change will depend on the stage of the disease (Cummings, 2010). Developing valid markers sensitive to AD progression is a highly active research area and will require a deep understanding of factors that might possibly delay or accelerate progression such as age, gender, and genetic background (Hua et al., 2010). Clinical trials of patients with AD at the MCI stage will benefit from screening in only those MCI patients who do have AD pathology (Kohannim et al., 2010) and screening out those patients who show an MCI phenotype but do not harbor AD, thus decreasing error variance and maximizing the chance to detect a positive signal if the drug is effective. However, the cost and benefit of also screening out true positive should be critically weighed (Lorenzi et al., 2010). A novel method to boost the power of future clinical trials is to reduce the between-subject variability at trial entry by statistical adjustment of outcomes for baseline covariates (Schott et al., 2010).

Development of SOPs for disease markers

For early diagnosis with disease markers to be applicable in routine settings, however, standard operational procedures need to be in place to allow consistent and repeatable measures of the marker throughout all diagnostic centers worldwide. An international initiative is currently being carried out with the sponsorship of the Alzheimer's Association aimed to develop standard operational procedures to consistently assay Abeta42 and tau in the CSF. A similar effort is presently under way, under the patronage of the Alzheimer's Association aimed to develop a harmonized protocol for the manual segmentation of the hippocampus and measurement of hippocampal volume (www.hippocampal-protocol.net). In addition to serve as a diagnostic marker, the harmonized protocol will allow to validate automated algorithms for hippocampal segmentation versus a single, agreed, and valid gold standard.

Conclusions

The ADNI is one of the top blockbusters of Alzheimer's research of recent years. More than 100 scientific papers have been published with ADNI data so far, and its unprec-

edented potential to study neurodegenerative disorders and contribution to foster drug development has affected also non-Alzheimer's areas. Despite being alive, healthy, and thrust into the future, ADNI has already left a legacy to neuroscientists. The debate is lively on how to develop large multicenter, multimodal, and prospective studies in asymptomatic persons at risk of developing AD (www.PAD2020.org), and a study with a design similar to ADNI is being launched in patients with Parkinson's disease (Parkinson's Progression Markers Initiative) funded by the Michael J. Fox Foundation for Parkinson's Research. The knowledge accumulated by the ADNI and ADNI-related initiatives will be instrumental to the development of effective therapeutic drugs for patients with neurodegenerative disorders that might finally bring tangible benefits to the quality of life of patients and their caregivers.

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Speaking on behalf of all the investigators involved with the ADNI project, we are extremely grateful to Giovanni Frisoni, Paul Coleman, and *Neurobiology of Aging* for devoting a special issue to scientific studies using ADNI data. From the very beginning, ADNI was conceived as a team effort involving support from the National Institutes of Aging (many thanks to Richard Hodes and Neil Buckholz) from the pharmaceutical industry, and which would represent the combined efforts of many investigators in the field of AD. We believe that our decision to release all raw and processed data through a website (http://www.loni.ucla.edu/ADNI) without any embargo was the correct thing to do.

To date investigators around the world have published more than 100 papers using ADNI data. In April 2010 we learned that our competitive renewal, called "ADNI2" is likely to be funded by the National Institutes of Aging, and we are hoping for continued industry support. This means that the ADNI project will continue until 2015, at least.

Finally, I and all the ADNI Core leaders and other investigators are open to suggestions and criticisms. We want this project to serve the AD community and we need to hear more feedback on how to perform a better job. Most importantly, we encourage all scientists around the world to use our data in imaginative ways for hypothesis testing and data exploration and our only request is that those individuals who use the data, follow the simple rules in the "Data Use Agreement."

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