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Clinical core of the Alzheimer's Disease Neuroimaging Initiative: progress and plans

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Abstract

The Clinical Core of the Alzheimer's Disease Neuroimaging Initiative (ADNI) has provided clinical, operational and data management support to ADNI since its inception. This paper reviews the activities and accomplishments of the core in support of ADNI aims. These include the enrollment and follow-up of over 800 subjects in the three original cohorts: healthy controls, amnesic MCI (now referred to as late MCI, or LMCI) and mild Alzheimer's disease (AD) in the first phase of ADNI (ADNI 1), with baseline longitudinal clinical and cognitive assessments. These data, when combined with genetic, neuroimaging and cerebrospinal fluid measures, have provided important insights into the neurobiology of the AD spectrum. Further, these data have facilitated the development of novel clinical trial designs. ADNI has recently been extended with funding from an NIH Grand Opportunities (GO) award, and the new ADNI GO phase has been launched; this includes the enrollment of a new cohort, called early MCI (EMCI), with milder episodic memory impairment than the LMCI group. An application for a further 5 years of ADNI funding (ADNI 2) was recently submitted. This funding would support ongoing follow-up of the original ADNI 1 and ADNI GO cohorts, as well as additional recruitment into all categories. The resulting data would provide valuable data on the earliest stages of AD, and support the development of interventions in these critically important populations.

Keywords

Alzheimer's disease; ADNI; clinical trials

1. Introduction

The goals of the Alzheimer's Disease Neuroimaging Initiative (ADNI) are accomplished through the enrollment and longitudinal follow-up of cohorts of individuals with mild cognitive impairment (MCI) and mild Alzheimer's disease (AD), as well as cognitively normal older individuals. These ADNI subjects were selected on the basis of specific criteria and enrolled at the 57 ADNI performance sites in North America. They are followed with medical evaluations, clinical, cognitive, functional and behavioral assessments. In addition, they undergo biochemical biomarker, structural and functional neuroimaging, and genetic

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assessments under the guidance of the ADNI biomarker, MRI, PET and genetics cores, respectively.

The ADNI Clinical Core is responsible for operational and data management aspects of study, including subject recruitment, retention and assessment activities at all sites. Core activities also include development of the protocol and procedures manuals, regulatory oversight, maintenance of the ADNI network of performance sites, monitoring of site staffing, recruitment, compliance and data entry, financial subcontracting, study supply management, and development and maintenance of the ADNI data system in accordance with the aims of the program and the ADNI Executive Committee. The Clinical Core also manages the process of adjudicating conversion of subjects from one diagnostic category to another.

The first funding cycle of ADNI (referred to as ADNI 1) supported the recruitment of 400 individuals with amnesic MCI according to the Petersen criteria as operationalized by the Alzheimer's Disease Cooperative Study (ADCS), along with 200 cognitively normal older individuals and 200 with mild AD (Petersen, Aisen et al. 2010). Toward the end of 2009, ADNI was awarded additional support, in the form of a Grand Opportunities grant, from the National Institute on Aging for a two year period to allow further longitudinal follow-up, imaging and data analysis for the ADNI 1 cohorts, as well as the recruitment of a fourth cohort of less impaired individuals with MCI. The phase of study funded by this award is referred to as ADNI GO. At about the same time, an application was submitted to NIH by the ADNI investigators requesting a 5 year extension of ADNI, referred to as ADNI 2.

This report, adapted from the ADNI 2 grant application, summarizes progress of the ADNI Clinical Core, including the proposed activities for ADNI 2.

2. Background and overview of ADNI Clinical Core

Currently, no therapies are available for AD that alter the underlying nature of the disease process. Fortunately, there are more than 100 compounds under investigation by various pharmaceutical companies and university medical centers around the world. Most of these therapies are designed to have an impact on the underlying disease process itself. The earlier the intervention takes place, presumably, the greater the protection against further neuronal damage will be appreciated.

ADNI has established pre-competitive collaboration and real-time data sharing among academia and industry investigators to clarify the relationships among demographic, genetic, clinical, cognitive, neuroimaging and biochemical measures throughout the course of AD neurobiology, in order to facilitate the development of effective therapeutics. The project has provided insights into disease mechanisms, and has provided guidance, based primarily on the use of standardized biomarkers, to drug development programs. ADNI has increased the rate of drug development; disease-modifying therapies will arrive in the clinic sooner. A number of the leading disease-modifying drug development programs are now employing ADNI methodology toward more efficient trial design, particularly in the critically important early (pre-dementia) AD population.

AD can be diagnosed with reasonable accuracy at the dementia stage. In fact, a recent evidence-based medicine review of the literature by the American Academy of Neurology documented that clinicians were quite accurate when the clinical diagnoses were subsequently compared to neuropathological findings (Knopman, DeKosky et al. 2001). However, as one identifies the disease process at an earlier point in the clinical continuum, the precision of the diagnosis is reduced. An important challenge is to try to identify the process at the pre-dementia stage and enhance the specificity of the clinical diagnosis through the use of imaging and other biomarkers. This approach assumes an underlying cascade of pathological events that lend

themselves to intervention (Jack, Knopman et al. 2010; Petersen 2010). Biochemical and neuroimaging biomarkers can provide a window on the underlying neurobiology, facilitating early identification and intervention. Figure 1 presents a hypothetical model of the trajectories of biomarkers that have been studied in ADNI 1 and will continue to be followed longitudinally during the continuation of ADNI (Jack, Knopman et al. 2010). To test this model, it is essential to acquire very long-term longitudinal follow-up; the ADNI 2 proposal covers up to a decade of follow-up of the original ADNI 1 subjects. As is indicated in Figure 1, there is evidence that the accumulation of A β ₄₂ (presumed by some investigators to be the molecular trigger in AD neurodegeneration) occurs early in the process. This can be detected by molecular imaging techniques such as PET scanning using an amyloid-specific ligand or through measurement of cerebrospinal fluid (CSF) A β ₄₂. The next event involves neuronal injury and dysfunction which may be detected by FDG-PET measures of regional metabolic activity, elevated levels of CSF tau indicating neuronal damage, phospho-tau indicating accumulating tangle pathology, and MRI volumetric changes. When a threshold of neuronal dysfunction is reached, cognitive and then functional manifestations of AD accelerate. However, as mentioned above, by this point in the continuum, it is likely that considerable damage has occurred in the central nervous system, and some of this may be irreversible. Consequently, most investigators believe that early intervention is preferable to waiting to treat individuals when the full dementia syndrome is present.

As shown in Figure 1, amyloid biomarker abnormalities are present during the asymptomatic stage. Ideally, one would like to intervene at this point to have the greatest impact on subsequent neuronal damage. However, there is a tremendous challenge to identifying subjects at risk with sufficient sensitivity and specificity in the asymptomatic stage to allow intervention at this point. ADNI 2 will address the role of neuroimaging and other biomarkers at the stage of early clinical symptom presentation (early MCI, or EMCI). Ultimately, it may be feasible to move diagnosis and intervention into the asymptomatic stage.

ADNI 1 has focused on subjects with amnesic mild cognitive impairment (aMCI). The construct of MCI has been extensively evaluated around the world and thousands of studies have been completed in the past decade (Petersen, Roberts et al. 2009). While all these studies are not entirely consistent, the wealth of the data coalesce to indicate that aMCI is an identifiable entity with a predictable progression to clinical dementia (Gauthier, Reisberg et al. 2006). However, data to be reviewed below from ADNI 1 indicate that significant structural and functional imaging changes as well as chemical biomarker profiles are evident at the MCI stage as defined in ADNI 1 (Petersen, Aisen et al. 2010).

In ADNI GO and ADNI 2, we will study a group of subjects with less severe memory impairment than found in the MCI cohort enrolled in ADNI 1. It is important to emphasize that these subjects will still meet criteria for aMCI, but they will be at an earlier point in the clinical spectrum. With funding from the National Institute on Aging through the GO grant, we will be recruiting 200 early MCI (EMCI) from 2009 to 2011. In ADNI 2, we propose to continue to follow these EMCI subjects along with 202 subjects who are cognitively normal and 274 subjects who have late MCI (LMCI) (as defined in ADNI 1) going forward. In addition, we will recruit new cohorts of 150 cognitively normal subjects, 100 additional EMCI subjects, 150 LMCI subjects, and 150 subjects with mild AD. ADNI 2 thus combines these newly recruited subjects with those recruited in ADNI 1 and ADNI GO.

ADNI 1 clearly established the utility of ¹¹C PIB amyloid imaging; ADNI GO and ADNI II (if funded), will examine the more widely feasible ¹⁸F amyloid imaging (AV-45). ADNI 2 will confirm and extend the striking findings linking regional brain volumes (e.g., hippocampal volume, regional cortical thickness) to AD progression, providing a potential selection criterion, covariate or outcome measure for trials, as well as the utility of functional brain

measures by FDG-PET. The striking correspondence between CSF A β ₄₂ and amyloid imaging will be confirmed and extended to the EMCI population. The utility of measures appropriate to primary care settings for the screening and selection of mildly impaired subjects will be assessed.

The primary purpose of this ongoing work is to continue to elucidate disease mechanisms, improve the efficiency of trial designs, and characterize a very early stage of disease, EMCI, that may be optimal for disease-modification interventions.

The ADNI Clinical Core facilitated the accomplishment of the ADNI aims, including the recruitment and retention of over 800 subjects (229 normals, 380 LMCI, 210 AD), retention of subjects with an annual attrition rate of only 6%, electronic data capture, quality control and reporting, and coordination of FDG-PET, ¹¹C11 PIB PET, 1.5T MRI, 3T MRI and CSF biomarkers. It has also initiated the ADNI GO project, which will include the recruitment and follow-up of an additional 200 subjects with EMCI. The ADNI Clinical Core Infrastructure utilizes the ADCS Administrative, Clinical Operations, Medical and Data Cores, all located at UCSD.

A novel feature of ADNI is public data access. Immediately following completion of processing and quality control procedures, ADNI data are placed on a public website that is available to any qualified investigator worldwide. Thus far the data have been accessed by thousands of investigators and dozens of pharmaceutical firms.

3. Clinical core progress: ADNI 1 subjects

ADNI 1 began enrollment in late 2005 and completed enrollment of 819 subjects in 2007. Fifty-seven sites in the U.S. and Canada participated in the enrollment. Details of the inclusion criteria, recruitment and baseline characterization of the ADNI 1 cohorts has been recently reported (Petersen, Aisen et al. 2010). Key characteristics are shown in Table 1. The annual change scores on key cognitive and clinical assessments of subjects in the three clinical groups over the course of 12 months are shown in Table 2. Of particular note, 16% of the MCI subjects in ADNI 1 converted to AD in the first 12 months, and an additional 24% converted in the second year.

4. Clinical trial design progress

The real-time, public sharing of ADNI demographic, clinical, cognitive and biomarker data has facilitated clinical trial design in academic and industry programs world-wide.

The great majority of AD drug development programs focus on symptomatic and disease-slowing effects in subjects with AD dementia (Rafii and Aisen 2009). The most widely-used co-primary outcome measures for such trials are the ADAS-cog for cognition and the CDR-SB for clinical status. The Neuropsychiatric Inventory (NPI) is the standard measure of behavioral symptoms. Each of these measures is part of the assessment battery of ADNI. Therefore, trialists can and do use the shared ADNI data to explore the relationships among demographic parameters and performance on these measures, can explore analytical methods and covariance structures, and can estimate the power of various trial designs. The value of genetic, biochemical and neuroimaging biomarkers for subject selection, reduction of explained variance and supportive outcome measures can likewise be explored.

There is a growing consensus that the optimal population for disease-modification programs is not AD dementia, but rather pre-dementia individuals on the spectrum of AD neurobiology (Rafii and Aisen 2009). It is reasonable to assume that interventions targeting the pathophysiological mechanisms underlying AD will have the greatest effect before the

pathology is at the advanced stage that corresponds to dementia. Many efforts are under way by academic, industry, foundation and government groups to facilitate this direction; these efforts include proposed revisions to diagnostic criteria, and various meetings and task forces to explore trial design issues.

ADNI data have provided the basis for much of this work. ADNI has focused on amnesic MCI, and has included the leading candidate outcome measures and biomarkers, allowing assessment of proposed trial designs. Importantly, ADNI data have revealed that appropriate use of standard outcome measures and biomarkers can yield powerful and feasible trial designs for the pre-dementia (MCI) population.

Specifically, ADNI 1 data (Aisen 2009) indicate:

- a. The CDR-SB is a powerful outcome measure in mild AD and MCI.
- b. In MCI, the ADAS-cog13 (which includes delayed word recall and number cancellation tasks) is superior to the ADAS-cog11 in a 24 month trial.
- c. Covariates reduce samples sizes by 10-15 % in LMCI and mild AD
- d. Selection of LMCI subjects using CSF A β ₄₂ reduces sample sizes

Rate of change designs in comparison to survival to dementia designs, and the impact of biomarker selection and covariates

We have used ADNI data to propose study designs (Table 3) for disease-modifying interventions in the pre-dementia population (Aisen 2009). For such a trial, it is rational to select subjects with evidence of amyloid accumulation in brain; ADNI data suggest that amyloid PET imaging and low CSF A β ₄₂ are equivalent indicators of amyloid accumulation. Subjects meeting the ADNI criteria for amnesic MCI and selected based on an abnormal amyloid biomarker would meet the proposed research criteria for AD [9], and consensus meetings suggest that standard AD-type cognitive and clinical co-primary outcome measures will be appropriate for pivotal trials, and a single clinical measure may be appropriate for a Phase II proof of concept trial. Using ADNI data, we have shown that a two-year treatment period in this population, with appropriate covariates, has reasonable power to demonstrate effects on primary measures (Donohue et al, submitted). A design similar to this has recently been launched as a Phase II proof of concept trial of a secretase inhibitor (ClinicalTrials.gov identifier NCT00890890).

5. The potential value of neuroimaging measures as surrogate outcomes

ADNI data have confirmed that the annual change and variance for neuroimaging measures provides much better power to detect disease-slowng effects than do standard cognitive and clinical measures.

For example, Table 4 provides group sizes for a study aiming to demonstrate a 25% slowing of disease progression as indicated by one year change in various outcome measures (analyzed by linear mixed effects models), with 80% power and an alpha of 0.05. In general, we observe that hippocampal volumetric change has excellent power in AD and MCI. This suggests that for an intervention expected to slow clinical progression and brain atrophy, a Phase II a one year proof of concept trial in AD might be conducted with reasonable sizes. The sample sizes in the table above can be substantially reduced by the incorporation of biomarker selection criteria and covariates.

To extend this idea further, we have found that 6 month change in volumetric MRI measures provides good power to demonstrate slowing of progression in MCI. For example, for a 6

month trial to demonstrate 25% slowing in AD and MCI would require 1055 and 13074 subjects using the ADAScog, 1084 and 3388 using the CDR-SB, but only 216 and 528 for hippocampal volume. If we optimize biomarker selection and covariates, a 6 month proof of concept study is feasible. We note that the 6 month change in hippocampal volume is highly correlated with later interval changes, and is correlated to later decline in cognitive and clinical measures.

6. ADNI GO and EMCI

The continuation of ADNI has been greatly facilitated by the award of funds through the NIH Grand Opportunity program. It provides support to ADNI activities over a two year period, overlapping with and supplementing the first year of this proposed ADNI 2 project. Specifically, the GO award is supporting the following Clinical Core activities:

1. Two years of longitudinal follow-up for the original ADNI late MCI (LMCI) and cognitively normal (CN) cohorts.
2. The recruitment of a new cohort of early MCI (EMCI) subjects with milder episodic memory impairment than classical LMCI subjects enrolled in ADNI I.
3. The addition of new cognitive and clinical measures.
4. Additional biomarker and imaging data collection (as described in the corresponding sections of this application).

The EMCI group is a newly characterized set of subjects to be recruited in the GO grant funding period. To assess the clinical characteristics of the EMCI and LMCI subject groups, we interrogated the database from the NIA-sponsored Alzheimer's Disease Center Program through the National Alzheimer's Coordinating Center (NACC) under the direction of Dr. Walter Kukull. We used the NACC database since it represents subjects who were classified as MCI using essentially the same criteria proposed in ADNI. However, since there was no sub-categorization of EMCI or LMCI in the NACC database, we imposed the proposed criteria and instruments for ADNI GO and ADNI 2 on previously collected aMCI subjects. The summary of the cognitive characteristics of LMCI subjects from ADNI 1 has been described above, but the features of EMCI subjects have not been characterized, and consequently, a comparison of these two clinical groups at baseline and with respect to rates of progression from the NACC database is shown in Table 5. As can be seen, the EMCI subjects represent individuals with milder degrees of cognitive and functional impairment than the LMCI subjects and their rate of progression is slower. We anticipate the subjects recruited in ADNI 2 will conform to these general clinical characteristics.

7. Primary care physician instruments

Since MCI is a sufficiently mild condition, it is most likely that individuals with this degree of cognitive complaint will present initially to primary care physicians (PCP). As such, there is a need to develop instruments that can be administered efficiently and inexpensively in the PCP setting to allow the clinicians to determine which patients might be candidates for further evaluation and possibly therapies. Toward this end, we have selected a brief cognitive instrument to allow detection of the cognitive aspects of MCI and a functional instrument to determine the degree of functional impairment.

The primary screening tools for ADNI to determine if a person is eligible for the trial involve delayed recall of one paragraph from the Logical Memory subtest of the Wechsler Memory Scale-Revised to provide a metric of memory function to corroborate the individual's cognitive complaint, and the CDR to be certain that the degree of memory function represents a change from the previous level of performance. The combination of these instruments is designed to determine that a person is cognitively and functionally impaired but not to the extent that they

would constitute criteria for dementia. However, using the Logical Memory paragraph and the CDR would be too time consuming in the PCP setting, and consequently, brief instruments need to be evaluated to see if they may be appropriate for the PCP.

The brief cognitive instrument that has been selected is the Montreal Cognitive Assessment test (MoCA) which is designed to detect subjects at the MCI stage of cognitive dysfunction (Nasreddine, Phillips et al. 2005). This instrument has been shown to have adequate sensitivity and specificity in clinical settings to detect suspected MCI. The MoCA is believed to be more sensitive than general screening instruments such as the MMSE or the Short Test of Mental Status. The MoCA can be administered in approximately ten minutes.

For a functional assessment, we have selected the Measurement of Everyday Cognition (ECog) (Farias, Mungas et al. 2008). This instrument has been developed to assess functional impairment of a very mild nature as can be seen in MCI. The ECog is an informant-rated questionnaire comprised of multiple subscales and takes approximately ten minutes to administer. Previous research on this instrument indicates that ECog correlates well with established measures of functional status and global cognition but only weakly with age and education. ECog was able to differentiate among cognitively normal, MCI and AD subjects. Results of ECog suggest that it is a useful tool for the measurement of general and domain-specific everyday functions in the elderly.

The MoCA and ECog will be administered to all participants in ADNI GO but will not be used for any screening or diagnostic decisions themselves. Rather, the traditional screening measures involving the single paragraph from the Logical Memory subtest and the CDR will be used to determine the appropriate level of function for subjects in ADNI GO just as it was in ADNI 1. However, the performances of the MoCA and ECog will be followed to determine their ability to differentiate among the four groups.

8. Plans for ADNI 2

ADNI 2, if funded, will continue and build on the aims of ADNI 1 and ADNI GO. All HC, EMCI and LMCI subjects will be followed into the new grant period, providing up to 10 years of longitudinal data on these normal and mildly impaired subjects. This will be essential to inform the model proposed in Figure 1, and link early cognitive, clinical and biomarker changes to later clinically important decline. Cross-sectional and longitudinal characterization will continue, including documentation of conversions across diagnostic categories. In particular, the long-term characterization of HC and EMCI subjects, including LPs, amyloid imaging, FDG-PET and volumetric MRI, will facilitate trial design in these critically important populations. Important subgroups within these cohorts will be defined by amyloid biomarkers and APOE genotype.

In ADNI 2, we will extend this still further, by adding 3 month volumetric MRI scans for all newly enrolled subjects, to explore the feasibility of this measure for brief proof of concept trials, and for interim analysis/adaptive designs for longer trials.

The goal of ADNI 2 is to obtain as close to 100% participation in lumbar puncture as is feasible. ADNI 1 aimed for 25% participation and achieved more than 50% participation. For ADNI GO and ADNI 2, we aim to limit recruitment to those that consent to LP. Exceptions will be made to meet other goals such as minority recruitment.

9. ADNI 2 clinical trial design aims: extending the results from ADNI 1

As described above, ADNI 1 data suggest the feasibility of longitudinal change designs in selected LMCI subjects selected for amyloid accumulation using CSF A β ₄₂. In ADNI 2 we

will enroll 150 additional LMCI subjects, and all (or nearly all) will have both CSF A β ₄₂ and ¹⁸F AV-45 amyloid imaging. We will thus have an independent sample of similar size to that used for the ADNI 1 power estimates. We will confirm the utility of CSF A β ₄₂ selection, the equivalent value of AV-45 amyloid imaging, the utility of genotype and MRI volumetric (and other disease stage) covariates, and confirm the group size estimates.

We hypothesize that it will be feasible to extend these ideas to the milder EMCI population. That is, we propose that selection of EMCI subjects by amyloid markers, and utilizing disease stage and APOE covariates, with CDR-SB alone or with ADAScog as continuous outcomes, we will have reasonable power to demonstrate disease modifying effects. We expect that clinical effects of modifying disease mechanisms will be greater at the earlier EMCI stage, offsetting the slower rates of decline. Thus we may have similar group sizes to power EMCI studies to demonstrate a 40% effect as we do to power LMCI studies to see a 30% effect.

We also hypothesize that longitudinal change designs will be advantageous compared to survival to AD in the EMCI population, as it is in LMCI.

10. ADNI 2: extending clinical trial design evaluation to the EMCI population

The evaluation of the EMCI cohort will include analysis of longitudinal trajectories of cognitive and clinical assessments, MRI volumetric measures, FDG-PET as well as amyloid imaging and CSF markers. The impact of APOE genotype (and potentially other genetic markers) on these trajectories will be assessed. Subgroups selected by amyloid biomarkers, as well as cutoff values of hippocampal volume, FDG-PET activity and cognitive and clinical assessments will likewise be examined. The value of biomarker covariates in reducing unexplained variance of longitudinal change will be analyzed.

A major purpose of examining this new cohort in this manner will be to inform trial design. We hypothesize that we will be able to extend similar design features that have yielded exciting findings in the LMCI cohort to this more mildly impaired population. We aim to provide feasible trial designs for studies enrolling EMCI subjects.

Our specific hypothesis is that we can select subjects using amyloid biomarkers (AV-45 imaging or CSF A β ₄₂), perhaps also using APOE genotype selection, to define an EMCI subpopulation with longitudinal decline on standard or supplemented measures that will allow proof of concept and pivotal testing of disease-modifying agents. While amyloid biomarkers represent primary selection candidates, we will also evaluate other biomarkers including CSF tau and P-tau (noting that the latter may be particularly appropriate for neuroprotection and kinase inhibitor studies, respectively).

11. ADNI 2: extending trial designs to the asymptomatic population

As indicated in Table 2 above, we expect that cognitive and clinical measures will not be feasible outcomes in symptomatic individuals, even those selected using biomarkers. While we expect to see some decline in standard measures, at this stage the efficiency of such measures is unlikely to yield feasible trial sizes. In this population, we hypothesize, however, that potential surrogate measure will allow proof of concept trial design. That is, as we increase our recruitment and long-term follow-up of asymptomatic subjects during ADNI 2, we will explore the trajectories on imaging measures (such as entorhinal cortex atrophy, regional cortical thickness measures, and FDG-PET measures) in subjects selected on the basis of genotype and/or markers of amyloid or tau pathology.

An essential aim of ADNI 2 is also to examine the relationship between longitudinal change and later conversion to dementia in asymptomatic, EMCI and LMCI subjects. In addition to

the comparison of longitudinal change and survival to diagnosis trial designs, this will strengthen the link between (ie, establish the predictive value of) early change in cognitive, clinical and biomarker measures to later clinical progression. While the experience of interventional studies will be essential, the ADNI 2 analyses can support the validation of potential surrogates by establishing predictive value.

12. Summary

The ADNI experience has been illuminating for the field in demonstrating that clinical, imaging and chemical biomarker data can be reliably collected in a multicenter study. The standardization of procedures has been accomplished and well-characterized cohorts of clinical subjects have been recruited and followed. The continued participation rate has been excellent, and the longitudinal data have informed numerous studies on AD neurobiology and have provided important guidance to clinical trial design. The true value of these data reside in the long-term follow-up of the subjects to carefully map the cognitive, clinical, biochemical and neuroimaging changes across the full spectrum of Alzheimer's pathology, guiding the development of effective interventions.

Acknowledgments

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AD Progression

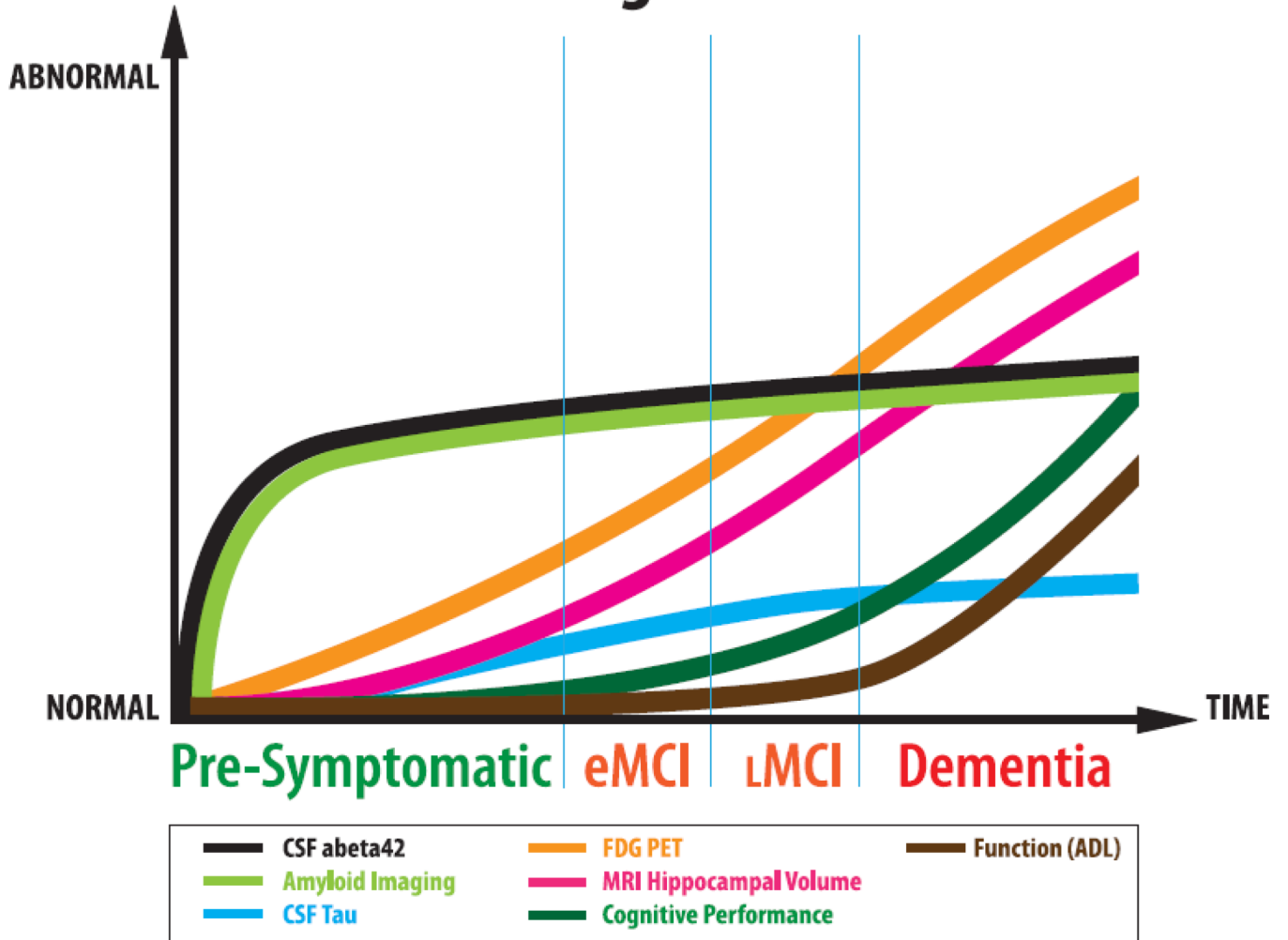


Figure 1. Trajectories of biomarkers during the progression of AD. This hypothetical graph is designed to capture the following points: 1. CSF A β ₄₂ and amyloid PET, reflecting amyloid accumulation in brain, move in tandem. 2. Amyloid accumulation precedes cognitive and functional decline by years, and changes only gradually once symptoms develop. 3. Compared to CSF A β ₄₂ and amyloid PET, CSF tau, MRI volumes and FDG-PET are more dynamic biomarkers of disease progression across the spectrum of AD neurobiology. 4. Cognitive decline becomes evident at the onset of EMCI, and accelerates as the disease progresses. 5. Functional decline becomes evident at the onset of dementia, and accelerates as the disease progresses. 6. All of these points are conjectural to varying degrees; they require confirmation with long-term longitudinal follow-up in ADNI 2 and beyond. [Reprinted from *Lancet Neurology*, 2010, with modifications.]

Table 1

Baseline characterization of ADNI 1 cohorts.

| Characteristic | Controls (n = 229) | MCI (n = 398) | Mild AD (n = 192) |
|---|--------------------|------------------|-------------------|
| Age, mean \pm SD, y | 75.8 \pm 5.0 | 74.7 \pm 7.4 | 75.3 \pm 7.5 |
| Education, mean \pm SD, y | 16.0 \pm 2.9 | 15.7 \pm 3.0 | 14.7 \pm 3.1 |
| Sex (% Female) | 48.0 | 35.4 | 47.4 |
| Apolipoprotein E ϵ 4, % carriers | 26.6 | 53.3 | 66.1 |
| MMSE Score | 29.1 \pm 1.0 | 27.0 \pm 1.8 | 23.3 \pm 2.1 |
| CDR Global Score | 0.0 \pm 0.0 | 0.5 \pm 0.0 | 0.7 \pm 0.3 |
| CDR Sum of Boxes | 0.0 \pm 0.1 | 1.6 \pm 0.9 | 4.3 \pm 1.6 |
| GDS Score | 0.8 \pm 1.1 | 1.6 \pm 1.4 | 1.7 \pm 1.4 |
| ADCS MCI-ADL (FAQ) Score | 0.1 \pm 0.6 | 3.9 \pm 4.5 | 13.0 \pm 6.9 |
| ADAS-Cog total | 6.2 \pm 2.9 | 11.5 \pm 4.4 | 18.6 \pm 6.3 |
| ADAS word list delayed recall | 2.9 \pm 1.7 | 6.2 \pm 2.3 | 8.6 \pm 1.6 |
| AVLT Trials 1-5 | 43.3 \pm 9.1 | 30.7 \pm 9.0 | 23.2 \pm 7.7 |
| AVLT delayed recall | 7.4 \pm 3.7 | 2.8 \pm 3.3 | 0.7 \pm 1.6 |
| AVLT DR/Trial 5 % | 65.8 \pm 27.6 | 32.1 \pm 31.3 | 11.2 \pm 22.0 |
| Trails A (seconds) | 36.5 \pm 13.2 | 44.9 \pm 22.8 | 68.0 \pm 36.9 |
| Trails B (seconds) | 89.2 \pm 44.3 | 130.7 \pm 73.5 | 198.9 \pm 87.2 |
| Category fluency (animal) | 19.9 \pm 5.6 | 15.9 \pm 4.9 | 12.4 \pm 4.9 |
| Category fluency (vegetable) | 14.7 \pm 3.9 | 10.7 \pm 3.5 | 7.8 \pm 3.3 |
| Number cancellation* | 0.4 \pm 0.7 | 1.0 \pm 0.9 | 1.8 \pm 1.3 |
| Boston naming test | 27.9 \pm 2.3 | 25.5 \pm 4.1 | 22.4 \pm 6.2 |
| Digits backwards | 7.2 \pm 2.2 | 6.2 \pm 2.0 | 5.0 \pm 1.8 |
| Clock drawing | 4.7 \pm 0.7 | 4.2 \pm 1.0 | 3.4 \pm 1.3 |

Table 2

Annual change in cognitive and clinical assessment scores for ADNI 1 cohorts.

| Assessment | Controls | MCI | Mild AD |
|------------------------------|-----------------|-----------------|-----------------|
| | Mean±SD (N) | Mean±SD (N) | Mean±SD (N) |
| MMSE Score | 0.0±1.4 (211) | -0.7±2.5 (358) | -2.4±4.1 (162) |
| CDR Global Score | 0.0±0.1 (207) | 0.0±0.2 (358) | 0.3±0.5 (160) |
| CDR Sum of Boxes | 0.1±0.3 (207) | 0.6±1.2 (358) | 1.6±2.2 (160) |
| GDS Score | 0.2±1.2 (211) | 0.4±1.8 (358) | 0.3±1.8 (159) |
| ADCS MCI-ADL (FAQ) Score | 0.1±1.0 (210) | 1.9±4.0 (354) | 4.6±5.6 (161) |
| ADAS-Cog total | -0.5±3.0 (210) | 1.1±4.4 (357) | 4.3±6.6 (161) |
| AVLT Trials 1-5 | 0.2±7.8 (209) | -1.3±6.3 (357) | -3.6±5.7 (156) |
| AVLT delayed recall | 0.4±3.4 (210) | -0.4±2.4 (358) | -0.5±1.6 (155) |
| AVLT DR/Trial 5 % | 4.9±43.7 (209) | -5.0±28.3 (353) | -7.1±21.0 (147) |
| Trails A (seconds) | -2.3±11.2 (211) | 1.2±16.1 (358) | 3.9±21.7 (157) |
| Trails B (seconds) | -6.6±38.0 (210) | 9.0±56.1 (352) | 20.0±85.6 (133) |
| Category fluency (animal) | 0.5±4.6 (211) | -0.7±4.4 (358) | -1.5±4.0 (160) |
| Category fluency (vegetable) | -0.1±3.5 (211) | -0.6±3.1 (358) | -1.0±2.8 (160) |
| Number cancellation* | 0.0±0.7 (209) | -0.1±0.9 (354) | 0.3±1.4 (155) |
| Boston naming test | 0.5±1.7 (210) | -0.2±2.9 (356) | -1.5±3.7 (159) |
| Digits backwards | 0.1±1.9 (211) | -0.3±1.7 (356) | -0.2±1.7 (152) |
| Clock drawing | 0.0±0.8 (211) | -0.1±1.0 (357) | -0.4±1.3 (162) |

Table 3

Clinical trial design scenarios utilizing change in continuous outcomes being explored in ADNI. [Reproduced from Alzheimer's Research & Therapy, 2009]

| | Mild AD Trial | Early AD Trial | Very Early AD Trial |
|---|--|--|--|
| Cognitive Status | Mild dementia | Mild cognitive impairment | Cognitively normal |
| Clinical Dementia Rating global score | 0.5-1 | 0.5 | 0 |
| MMSE range | 16-26 | 25-30 | 28-30 |
| Biomarker for subject selection | None | Amyloid imaging and/or CSF A β ₄₂ | Amyloid imaging and/or CSF A β ₄₂ |
| Biomarker for subject stratification | None or APOE genotype | APOE genotype | APOE genotype |
| Primary cognitive outcome measure | ADAScog11 | ADAScog12 (includes delayed recall) | Sensitive memory and/or exec. fxn test |
| Primary global/functional outcome measure | CDR-SB | CDR-SB | none |
| Analysis covariates | Baseline cognition and regional brain volume | Baseline cognition and regional brain volume | Regional brain volume |
| Biomarker outcome | Regional brain atrophy | Regional brain atrophy | Regional brain atrophy (as surrogate endpoint) |
| Duration of treatment | 18 months | 24 months | 24-36 months |
| Primary analysis | Change score or slope of co-primaries: ADAScog11, CDR SB | Change score or slope of co-primaries: ADAScog12, CDR-SB | Regional brain atrophy rate and cognitive decline |

Table 4

Comparison of imaging and cognitive/clinical outcome measures to power trials.

| | Hipp.vol.(avg, L&R, Dale)* | FDG-PET (Jagust)** | ADAS-cog 11 | MMSE | CDR-SB |
|-----|----------------------------|--------------------|-------------|------|--------|
| MCI | 208 | 3360 | 4099 | 4162 | 954 |
| AD | 99 | 255 | 407 | 632 | 465 |

* Average of left and right hippocampal volumes, as calculated by Anders Dale's lab at UCSD.

** Posterior cingulated activity on FDG-PET scanning, as calculated by William Jagust's lab at UC Berkeley.

Table 5

MCI data from NACC; annual rates of progression and instrument means.

| | EMCI (N = 181) | LMCI (N = 369) |
|---|-----------------------|-----------------------|
| Progression to Dementia (Year 1) | 12% | 27% |
| Progression to CDR 1 (Year 1) | 7% | 15% |
| MMSE | | |
| Baseline | 28.0 (1.6) | 27.3 (1.8) |
| Year 1 | 27.6 (2.1) | 26.2 (2.8) |
| CDR – SB | | |
| Baseline | 1.2 (0.9) | 1.5 (1.0) |
| Year 1 | 1.6 (1.3) | 2.1 (1.6) |
| FAQ | | |
| Baseline | 3.7 (5.3) | 4.7 (5.6) |
| Year 1 | 5.5 (6.9) | 6.5 (6.4) |

Table 6

Characteristics of four ADNI cohorts and Logical Memory delayed recall cutoff scores (see text).

| | CN | EMCI | LMCI | AD |
|-----------------|----------|-------|----------|----------|
| CDR | 0 | 0.5 | 0.5 | 0.5-1 |
| MMSE | 24-30 | 24-30 | 24-30 | 20-26 |
| LM-DR (cutoffs) | | | | |
| Education: 0-7 | ≥ 3 | 3-6 | ≤ 2 | ≤ 2 |
| 8-15 | ≥ 5 | 5-9 | ≤ 4 | ≤ 4 |
| ≥ 16 | ≥ 9 | 9-11 | ≤ 8 | ≤ 8 |
| Dementia | No | No | No | Yes |

Table 7

Number of subjects followed in ADNI 2, including those recruited in ADNI 1 and ADNI GO.

| | ADNI 1 | ADNI GO | ADNI 2 | Cumulative |
|------|--------|---------|--------|------------|
| | 202 | | 150 | 352 |
| EMCI | | 200 | 100 | 350 |
| LMCI | 274 | | 150 | 424 |
| AD | | | 150 | 150 |