World Wide Alzheimer's Disease Neuroimaging Initiative
Teleconference Minutes
December 5 / 6, 2016
10:00 am Eastern/ 9:00 am Central / 7:00 am Pacific, December 5
12:00 pm Japan, December 6

Attendees:

Steve Arneric	Ron Petersen
Laurel Beckett	Naren Rao
Patricio Chrem	Andy Saykin
Paige Cramer	Kira Sheinerman
Jim Hendrix	Holly Soares
John Hsiao	Gary Tong
Takeshi Iwatsubo	Arthur Toga
Dorothy Jones-Davis	John Trojanowski
Rima Kaddurah-Daouk	Mike Weiner
Richard Margolin	

I. **Roll Call and Welcome** Jim Hendrix welcomed the group to the meeting and reviewed the agenda.

II. Progress Updates

a) **NA-ADNI** - Michael Weiner

ADNI-3
ADNI-3 is in the start-up phase. One site, U. of Rochester, is enrolling subjects and 4-5 other sites are on the verge of getting approval for enrolling subjects. More than half of all the sites have submitted their IRB documents. Mike had hoped that the start-up would move more quickly than with previous ADNI grants but it doesn't appear to be the case due to regulatory requirements. Sites are reporting that it looks like most of the ADNI-2 subjects will roll over into ADNI-2. There is general optimism about enrollment but it will really ramp-up in 2017.

Tau PET
NA-ADNI now has data from over 100 Tau PET scans. Bill Jagust's analysis of the data shows that people who are amyloid positive have more Tau than people who are amyloid negative. In addition, people who are more advanced clinically have more Tau. Bill is a little surprised that people who have advanced to AD dementia have not advanced to the Braak 4-5 stage as expected. The Tau in people that are amyloid negative is limited to the MTL areas and is at very low levels. The pattern of Tau accumulation in ADNI appears to be of the Braak type.

CSF Biomarkers
Les Shaw's team is processing all the ANDI samples in the Roche Cobas platform. The data is expected to be released in late March or early April of 2017.

DoD ADNI
This study is funded by the US Department of Defense and is studying Vietnam War veterans who are in their 60's, 70's and 80's with a history of TBI and/or PTSD. Recently results show that people with a history of a loss of consciousness concussion for at least 3 minutes (a moderate TBI) are cognitively normal and show no AD biomarker related changes. In contrast, the PTSD subjects have more cognitive problems, they have a high clinical dementia rating and have a higher rate of diagnosed MCI yet their MRI's appear normal. In addition, the amyloid PET scans on the PTSD subjects are showing low amyloid levels. The PET amyloid positives in the PTSD subjects are about 5% compared with 20-25% amyloid PET positive in the control group. Kewei Chen of the Banner Institute hypothesized that this may be due to the use of SSRI's in subjects with PTSD. Kewei did sub-group analysis of the PTSD population looking at their use of SSRI's and found low amyloid is associated with SSRI use. This finding supports previous work published by Yvette Sheline showing reduction in amyloid with the use of SSRI's in mice. There is a third study showing low amyloid levels in people with a history of major depression and SSRI use.

Genetics
Andy Saykin reported on two new studies from the Genetics Core. They have started working on the first methylation study in blood as well as a telomere study. Data on both studies is expected in the first quarter of 2017.

Metabolomics
Rima Kaddurah-Daouk is leading a large international team that is doing analyses of various classes of metabolites from blood. The initial profiling was done in ADNI-1 and work on ADNI-2 baseline is just beginning with plans for longitudinal analysis. This work is also connected to the AMP-AD project lead by NIA and the sister project M^2OVE-AD that is focused on vascular pathways. Rima reported that they have recently un-blinded 3 large data sets. They identified early biochemical changes that are correlated with changes in Aβ and Tau imaging and with cognitive decline. It appears that changes in membrane structure and function and with lipid metabolism correlate very well with changes in Aβ and Tau. The second major finding is looking at cholesterol metabolism and the production of bile acids that occur in the liver and in the gut. It is known that the gut microbiome and the bacteria play a central role in the clearance of cholesterol via bile acids. They have identified a metabolic profile in AD patients and the changes in the bile acids correlate with changes in imaging including cortical thickness as well as cognitive and executive function.

b) Japanese ADNI - Takeshi Iwatsubo
J-ADNI has studied 537 cases including 234 with late amnestic MCI, 149 mild AD, and 154 cognitively normal subjects from 2008-2014. The NBDS database funded by the Japanese government is now complete and for open access worldwide since last February. It includes more than 3000 case reports, 2500 MRI images, 1400 FDG PET, 600 PiB PET images, and data from 340 CSF samples. This data is accessible to international researchers. The only requirement for access is approval from the

researcher's local ethics committee and then approval application to the central committee for the NBDS database for final approval. They are currently writing a paper on the basic features of the J-ADNI population including the clinical progression changes and the relation to amyloid pathology. They are also starting collaboration with NA-ADNI to compare data from the two studies.

J-ANDI-2 was renamed in 2015 the AMED pre-clinical AD Study with Hiroshi Mori of Osaka City U. as the PI. Delays have occurred due to the interruption in 2014 and low funding. However, recently an add-on study in five sites to include Tau PET has been partially funded for launch in 2017. They are using AV1451 and THK-5351 as tracers.

Recently the first patient was brought in at the Osaka City site. This patient is cognitively normal and is amyloid positive by PiB PET but was excluded due to sever white matter change, numerous microbleeds and cortical impact. So now they are awaiting the opening of additional sites including the Tokyo site.

c) **Argentina ADNI** - Patricio Chrem

Patricio provided an update on Arg-ADNI. He reported that 45 of the 56 subjects with baseline data (CSF Aβ-tau, FDG and PiB PET) have been followed for 30 months. They have already evaluated 43 of the 45 subjects at 30 months. There has been an unexpectedly high drop-out rate in the early AD group while the dementia group is still active in the study. After 30 months, 40 subjects have completed CSF Ab analysis, 53 have completed a FDG PET and 50 have completed a PiB PET scan. They are now planning a 60 month follow-up that will include a neuropsychiatric assessment, MRI scan, social and economic questionnaire of dementia. The team will also perform PiB and Tau PET scans. They are currently discussing which Tau tracer to use. They are trying to choose between AV1451 and THK--5351. Mike offered to connect Patricio via e-mail with Bill Jagust and Chris Rowe to discuss the Tau tracers.The group is also part of DIAN with 6 participants enrolled so far. They have also received a 3-year grant to study the genetics and biomarkers

III. Post Meeting Adendum

a) **Europe ADNI** - Giovanni Frisoni

Giovanni was unable to attend the meeting but provides the update below on resent activities in Europe.

The European Joint Program of Neurodegenerative Diseases (link below) has recently awarded 10 projects that will work on various aspects related to the harmonization and alignment of brain imaging methods. Projects started in September 1st, 2016 and should be completed within 9 months.

One of the projects, led by Giovanni Frisoni and Jorge Jovicich, is focusing on the identification of critical factors that are current challenges to the harmonization of pathology biomarkers extracted from large scale multi-centric neuroimaging (MRI,

PET/SPECT, EEG) data in neurodegenerative studies. We are currently developing a survey that will help us define such harmonization barriers. In its preliminary form the survey covers three main areas: i) barriers for effectively participating in large multi-centric neuroimaging studies, ii) barriers for prioritizing biomarkers derived from neuroimaging data, iii) specific barriers for the harmonization of biomarkers derived from multi-centric MRI/PET/SPECT/EEG data. The results from the survey will be used to develop a proposal of funded actions that should be prioritized to address the most pressing harmonization challenges.

JPND link: http://www.neurodegenerationresearch.eu/initiatives/annual-calls-for-proposals/closed-calls/brain-imaging-working-groups-2016/brain-imaging-working-groups/

EPAD

EPAD (European Prevention of Alzheimer's Dementia) is a multi-center research initiative that aims for insights to promote secondary prevention of Alzheimer's Disease. In a virtual registry, subjects' information of multiple existing cohorts is assembled, from which individuals at risk are chosen and included in a longitudinal cohort study, assessing cognitive and biomarker data. Out of those, participants for the third phase will be selected and enter into proof-of-concept trials with drug candidates or drug combinations.
While several European centers have already started assessment for the longitudinal study, in Geneva we are in the process of providing data of one clinical cohort to the EPAD registry and are preparing to start, so that the first participant may be included into the longitudinal study with the beginning of 2017. A second, population-based, cohort has signed an agreement for scientific collaboration and will enter now the process of practical preparations in the weeks to come.

AMYPAD

The central purpose of the AMYPAD consortium is to study the value of β-amyloid imaging as a diagnostic and therapeutic marker for AD. The AMYPAD program proposes to study the onset, dynamics and clinical relevance of brain β-amyloid in the spectrum from normal ageing, through subjective cognitive impairment (SCI) towards mild cognitive impairment (MCI) due to AD. β-amyloid-PET will be used in a very large number of subjects recruited from population studies, as well as memory clinics cohorts. In close collaboration with EPAD, the cohorts will be followed with careful longitudinal monitoring and MRI to determine (surrogate) outcomes of cognitive decline and neurodegeneration.
AMYPAD program started on October 2016. Currently, after having received input from EMA on the design and outcomes of the diagnostic study the protocol is going to be defined. For the prognostic study, in discussion there are the logistic (resources and governance) activities and the connections between AMYPAD and EPAD.

IV. Next Meeting – The next meeting will be scheduled in the spring and will be held during normal business hours in Asia and Australia.


WW-ADNI
alzheimer's association