EMIF Deliverable 2.2: Validated criteria for presymptomatic AD and prodromal AD

Executive summary

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The objectives of this task were to apply algorithms developed for the diagnosis of Alzheimer's Disease to several observational cohorts that have contributed data to EMIF-AD.

The algorithms are based on 2 sets of diagnostic criteria, proposed by the International Working Group (IWG2; Dubois et al, 2014) and the National Institute of Aging / Alzheimer's Association (NIA-AA; McKhann et al, 2011, Albert et al 2014, and Sperling et al, 2011), respectively. An additional objective is to identify and characterize those subjects in whom the IWG2 and NIA-AA criteria produce different diagnostic results.

Since data is still accruing from several EMIF-D cohorts, this represents a progress report, based on 5 cohorts obtained to date: DESCRIPA, Sant Pau, IDIBAPS, EDAR, and Antwerp.

As in the initial application of the algorithm to the North American ADNI dataset summarized in last year's report, choices needed to be made for amyloid and neuronal injury biomarkers and their cut-off values, and for measures defining cognitive dysfunction, for which no universal consensus exists as yet. Differences in the NIA-AA and IWG-2 diagnostic approaches include requirement for both amyloid and tau abnormalities when CSF was used as a biomarker in IWG2, the incorporation of neuronal injury biomarkers to define likelihood of AD in NIA-AA, and the concept of preclinical AD as a continuum of pathology defined by biomarkers and subtle evidence of cognitive impairment in NIA-AA, vs an at-risk state in IWG2.

Subjects were included in this analysis only if biomarkers relevant to AD were available.

Since amyloid PET was not available in any of these cohorts, CSF was required for application of the IWG2 criteria. In addition, hippocampal volume permitted application of the NIA-AA criteria in nearly half of the DESCRIPA cohort. Among cognitively normal subjects, all classified NIA-AA stage 0 (no biomarker evidence of Alzheimer pathology) were also considered IWG2-normal, but the latter also included subjects classified NIA-AA preclinical AD stages 1-2 by virtue of abnormal CSF amyloid with or without abnormal NI biomarkers, or classified as SNAP (suspected non-AD pathophysiology) by virtue of abnormal NI biomarker(s) with normal amyloid. Similarly, some subjects considered by IWG2 criteria as MCI not due to AD, or unclassifiable, met NIA-AA criteria for high or intermediate likelihood of MCI due to AD, or SNAP. In the previous year's analysis, based on ADNI, formal inclusion of NI biomarkers in NIA-AA allowed for more accurate estimation of progression free survival, even in subjects deemed not to have Alzheimer pathology. In this progress report, summary statistics of the diagnostic cross-tabulation, and summary statistics of several baseline characteristics of the subjects by cohort and diagnostic group, were produced.

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Additional statistical analyses comparing the diagnostic groups in the pooled cohorts will be undertaken when the cohorts are complete.

Four additional cohorts will be added within the first half of 2016. These will be integrated with the 5 cohorts summarized in this progress report, to generate the final year 3 report.

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