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

Executive summary

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The objectives of this analysis are to operationalize 2 diagnostic frameworks for AD, e.g. the modified IWG-2 framework (Dubois et al, 2014, modified by Dubois 2016) and the newly revised NIA-AA framework (Jack 2018), and to assess their concordance, using 2 independent observational datasets, the European Medical Information Framework for AD (EMIF-AD, hereafter abbreviated simply as EMIF) and the Alzheimer's Disease Neuroimaging Initiative. The EMIF-AD dataset included 10 observational cohorts that have data on amyloid, tau, and neuronal injury biomarkers available in EMIF-AD: Amsterdam, Antwerp, CITA, DESCRIPA, EDAR, Gothenberg, IDIBAPS, Lausanne, Pharmacog, and Sant Pau. Inclusion of a comparison dataset of approximately the same size from North America, ADNI, will allow for assessment of the demographic translatability of the frameworks, To facilitate direct comparison of EMIF and ADNI, the classification will be made using a set of amyloid, tau, and neuronal injury biomarkers common to both datasets, i.e., CSF Aβ42, phospho-tau, and total tau, respectively. An additional objective is to compare baseline characteristics of nondemented subjects from these 2 datasets by diagnostic classification according to the IWG2 or NIA-AA frameworks.

In spite of significant differences in demographic and baseline disease characteristics, application of the AD diagnostic frameworks to the ADNI and EMIF-AD datasets yielded very similar subgroup patterns within each framework. Subgroups differed in consistent ways for a number of variables related to AD, including age, ApoE4 genotype, global clinical and key neuropsychological measure, and brain volumetrics. The subgroups also had less variance in these measures, compared to the undifferentiated population.

Comparing the virtues of each framework, similarities in the mapping algorithm for subjects with normal cognition yielded a very similar pattern of subgroup characteristics. In subjects with MCI, subjects classified as prodromal AD were highly similar in both frameworks, but the NIA-AA framework had the advantage of differentiating subjects with normal AD biomarkers, from those with only amyloid or tau biomarkers, who had intermediate features with respect to prodromal AD. It should be noted, however, that the high concordance of p-tau and t-tau, evident in the relatively small number of subjects meeting criteria for concomitant Alzheimer's and suspect non-Alzheimer's pathological change, seems to provide little basis to consider them as independent biomarkers of tau and neuronal injury, respectively.

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