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Appendix E1

Study Participants

Cognitively normal was defined as a Mini-Mental-State-Examination (MMSE) score between 25 and 30 (inclusive), Clinical Dementia Rating (CDR) global score of 0, no evidence of depression and no memory complaints. Mild cognitive impairment (MCI) was defined as an MMSE score between 24 and 30 (inclusive), CDR global score of 0.5, report of memory complaints and no significant functional impairment. Finally, subjects with Alzheimer's disease (AD) dementia met the relevant criteria of the National Institute on Aging and Alzheimer's Association (NIA-AA) and the National Institute of Neurologic and Communicative Disorders and Stroke-AD and Related Disorders Association (NINCDS–ADRDA) for AD dementia and probable AD, respectively. APOE genotypes were not considered as the data are available only for 59.30% (*n* = 211) of the study cohort. Validated summary metrics for the memory (ADNI_mem; derived from: Rey Auditory Verbal Learning test, AD Assessment Scale-cognitive subscale, MMSE and Wechsler Memory Test-logical memory I) and executive cognitive domains (ADNI_ef; derived from the Wechsler Adult Intelligence Scale-Revised, Digit Symbol Substitution and Digit Span backward, Trail Making Test parts A and B, animal and vegetable Category Fluency and Clock Drawing Test) were also included. Summary cognitive scores were chosen over individual cognitive tests to use more comprehensive and robust measures of domain-specific cognitive performance.

MRI Acquisition and Analysis

The ADNI imaging protocol includes 3T MRI examinations at 54 different sites including GE (GE 750, 750 W, GE Healthcare), Siemens (Magnetom Prisma, PrismaFit, Skyra, Verio Trio/TIM, Siemens Healthcare, Erlangen, Germany), and Philips (Achieva, Ingenia 3T CX, Philips Medical System) MRI Systems. We included T2*-GRE sequences (repetition time (TR) 650 ms, echo time (TE) 20 ms, flip angle (FA) 20 degrees) and T1-MPRAGE (TR 2300 ms, TE 2.95 ms, FA 9 degrees) sequences in our study. On T2* imaging, microhemorrhage-derived hemosiderin deposits yield a hypointense signal, enabling in vivo detection. A more detailed description of MH detection and atlas assignment methods is available in the ADNI Methods document "Micro-haemorrhage Assessment on ADNI-GO/2 T2*-Weighted Images" by Clifford R. Jack, Jr., M.D, Mayo Clinic, Rochester MN available on http://adni.loni.usc.edu/. Briefly, experienced raters counted MH in T2* native space images. The raters assessments were captured in a longitudinal framework at the Aging and Dementia Imaging Research Laboratory at the Mayo Clinic in Rochester, MN. Each MH was spatially assigned using a T1-MPRAGE image based on a 35-region atlas included in the Mayo Clinic Adult Lifespan Template (MCALT) available on NITRC (https://www.nitrc.org/projects/mcalt). The T1-MPRAGE image was affine registered to the T2*-GRE image for automatic atlas region assignments of the potential MH findings. The localization and status of each finding, an estimate of tissue probability (gray matter versus white matter versus CSF) and the assigned atlas locations were recorded.

The ratings were performed by 5 Medical Imaging Analysts (MIA) at the Department of Radiology, Mayo Clinic, Rochester, United States. MIAs were specially trained to assess microhemorrhages and other medical findings. All findings were then presented to a board certified neuroradiologist to confirm or deny each finding identified by the MIA. Disagreements are handled in periodic meetings to discuss questionable MH and achieve a consensus among multiple neuroradiologists. The MIAs and the neuroradiologists all have been through a laboratory qualification process and routinely requalify to make sure everyone is meeting the standards. The neuroradiologists all had over 20 years of clinical experience, except for one with approximately 10 years of experience. All MH investigators received the images anonymized and were blinded for the clinical diagnosis. Reading sessions were ongoing and were performed directly after an individual scan has passed protocol and visual quality control checks.

PET Acquisition and Analysis

Cerebral tau depositions were assessed using 18F-AV1451 tau PET imaging. A T1-MPRAGE scan acquired at the same visit was segmented and parcellated in the participant's native space using FreeSurfer (v 5.3.0, Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Boston, USA, http://surfer.nmr.mgh.harvard.edu/). Each 18F-AV1451 scan was coregistered to the corresponding MPRAGE image. The mean standardized uptake value within each FreeSurfer-derived region was calculated. FreeSurfer regions were consecutively used to calculate composite standardized uptake value ratios (SUVR) in a defined composite region comprising the left and right entorhinal, fusiform, inferior temporal, mid temporal and parahippocampal cortex and the amygdala as reported previously [24, 26]. Additionally, lobar tau SUVRs for the frontal, parietal, temporal and occipital lobe were calculated. Whole cerebellum was used as a reference region.

Fibrillar Aβ accumulation was assessed using two different Aβ imaging tracer compounds, 18F-florbetaben (FBB) (n = 75) or 18F-AV45 (n = 281); both tracers yield comparable Aβ binding patterns [27]. The closest Aβ scan in time from the MH MRI was used for each participant (mean time difference in days for Aβ PET: 65.10, SD 131.00; for tau PET: 87.30, SD 145.60). A global SUVR composite score comprising frontal, lateral parietal and lateral temporal and anterior/posterior cingulate cortex was calculated based on FreeSurfer regions [27]. Additionally, lobar SUVRs for the frontal, parietal, temporal and occipital lobe were generated. Again, whole cerebellum was used as a reference region.

CSF Biomarker Analysis

CSF biomarkers concentrations for Aβ1–42, *p*-tau181 and *t*-tau were available at timepoint T-1 for n = 198 participants and at timepoint T0 for n = 66 participants. Aliquoted samples were analyzed using the electrochemiluminescence immunoassay (ECLIA) Elecsys on a fully automated Elecsys cobas e 601instrument (Roche Diagnostics GmbH, Penzberg, Germany) using a single lot of each reagents for each of the 3 measured biomarkers. The analysis was performed using an analysis protocol described in detail elsewhere [29]. The detailed methods description: "ADNI3: Batch analysis of Aβ1-42, *t*-tau and *p*-tau181 in ADNI1 and ADNIGO/2 CSF using the fully automated Roche Elecsys and cobas e immunoassay analyzer system" is available for download on http://adni.loni.usc.edu/.