Florbetapir PET

We obtained the mean florbetapir standardized uptake value ratio (SUVR) for each participant. A detailed description of florbetapir PET acquisition and processing can be found on ADNI website (http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/) or in previously published reports.[28] Briefly, the subject's first florbetapir image was co-registered to their magnetic resonance image and segmented into Freesurfer (version 4.5.0, Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital, Massachusetts, MA, USA; https://surfer.nmr.mgh.harvard.edu/)-defined cortical regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal). Next, the mean florbetapir uptake from these gray matter regions was extracted relative to the uptake in the whole cerebellum. Participants were classified as aMCI with low Aβ burden (aMCI Aβ-) or aMCI with high Aβ burden (aMCI Aβ+) according to SUVR cut-off of 1.11 for amyloid positivity.[28]

FDG-PET preprocessing

We collected the most preprocessed form of FDG-PET data from ADNI to investigate the relationship between ADNI-EF and rCMglc. ADNI-PET protocol was strictly followed in each site. ADNI preprocessing steps of FDG-PET data were previously described.[25] Briefly, a quality control process was applied to all scans, which included assessment of image resolution and uniformity, checks for statistical noise, motion assessment across temporal frames, and visual checks for common artifacts. Then, using the original raw PET images, the different temporal frames were co-registered. All image sets, including dynamic image and single-frame averaged image sets, were reoriented to a common spatial orientation and interpolated onto a uniform image grid. To reduce inter-scanner differences (17 different scanner models from three vendors), the images were smoothed with a scanner-specific filter derived from each site's Hoffman phantom, and then provided a common isotropic resolution of 8-mm full-width at half-maximum resolution.[25] We further preprocessed for group-level analysis. These scans were adjusted for their origin, and spatially normalized to the Montreal Neurological Institute (MNI, McGill University, Montreal, Canada) space using Statistical Parametric Mapping 12 (SPM12) (Institute of Neurology, University College of London, London, UK) implemented in MATLAB (MathWorks; Massachusetts, MA, USA). They were then smoothed with a Gaussian kernel of 8-mm full-width at half-maximum. Finally, global normalization using proportional scaling was performed, as it has a higher signal to noise compared to that of cerebellar count normalization.[29]

A region of interest (ROI)-based approach was also applied to investigate the association between rCMglc and clinical progression. The automatic anatomic labeling (AAL) algorithm and a region-combining method were applied to set ROIs to measure regional brain metabolism in the bilateral ACC (AAL template No. 31–32), bilateral PCC (AAL template No. 35–36), and bilateral PreCu (AAL template No. 67–68).[30]

Statistical analysis

The correlations between ADNI-EF and rCMglc were analyzed separately for aMCI Aβ- and aMCI Aβ+ groups using a multiple regression model with age, sex, education, and APOE genotype as covariates. Statistical threshold was set at $p<0.001$, uncorrected for multiple comparisons, with an extent threshold of greater than 50 contiguous voxels. CDR-SOB was further added as a covariate to the multiple regression model to control for clinical severity. These analyses were performed using SPM12 (Institute of Neurology, University College of London).

Demographic and clinical data were compared between groups by separate one-way analysis of variance (ANOVA) and χ^2 tests for continuous and categorical variables, respectively. Multiple linear regression analysis was conducted to investigate the associations between rCMglc and clinical progression as measured by CDR-SOB at 1 year later. Age, sex, education, and APOE ε4 genotype were included in the first step using the "Enter" method to control for their effects on CDR-SOB; then, ACC, PCC, and PreCu metabolism were included using the "Stepwise" method. Additional multiple linear regression analysis was also conducted to investigate the associations between rCMglc and further clinical progression (CDR-SOB) 5 years later. These analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA), and p values <0.05 were considered statistically significant.

Ethics statement

Institutional Review Boards approved the study procedures across institutions participating in ADNI. Written informed consent to share data for scientific research purposes was obtained from each participant. A request for access to data was approved by the ADNI Data and Publication Committee (https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_DSP_Policy.pdf). The institutional review board of Chosun University also approved the present study (IRB no. 2-1041055-AB-N-01-2017-28).

RESULTS

Participant characteristics at baseline and follow-up

Based on mean SUVR, aMCI group was divided into aMCI Aβ- (n=230) and aMCI Aβ+ (n=268). The demographic and clinical characteristics of the 498 subjects are presented in Table 1. No group differences in sex or education were found; however, aMCI Aβ- group was younger than aMCI Aβ+ group. APOE ε4 carriers were more frequent among aMCI Aβ+ subjects. CDR-SOB, FAQ, MMSE, and ADNI_EF scores were significantly worse in aMCI Aβ+ group compared to those in aMCI Aβ- group. Among them, 409 (82.1%) subjects completed evalua-