10.1148/radiol.2018180092

Appendix E1

According to the inclusion criteria of the ADNI study, the EMCI participants had to have (i) a subjective memory concern; (ii) an abnormal memory function score on the Logical Memory II subscale (9–11 for 16 or more years of education; 5–9 for 8–15 years of education; 3–6 for 0–7 years of education); (iii) a Mini-Mental State Examination (MMSE) score between 24 and 30 (inclusive); (iv) a Clinical Dementia Rating (CDR) ≥ 0.5 with memory box score must be at least 0.5; (v) General cognition and functional performance sufficiently preserved such that a diagnosis of AD cannot be made by the site physician at the time of the screening visit; (vi) Stability of Permitted Medications (stable doses of antidepressants lacking significant anticholinergic side effects; estrogen replacement therapy; gingko biloba; washout from psychoactive medication for at least 4 weeks prior to screening; ChEI and memantine were allowed if stable for 12 weeks prior to screen). The inclusion criteria for late MCI participants were the same as those for early MCI participants apart from a lower threshold of memory function score on the Logical Memory II subscale (< = 8 for 16 or more years of education; < =4 for 8–15 years of education; < =2 for 0–7 years of education). To have a diagnosis of AD, all AD participants must have: (i) a subject memory concern; (ii) abnormal memory function score on the Logical Memory II subscale (< = 8 for 16 or more years of education; < =4 for 8–15 years of education; < =2 for 0–7 years of education); (iii) MMSE scores between 20 and 26 (inclusive); (iv) CDR = 0.5 or 1.0; (v) NINCDS/ADRDA criteria for probable AD; (vi) Stability of Permitted Medications for 4 weeks.

Information on dosing schedules for ChEI and memantine was manually extracted. Moreover, medications with potential anticholinergic effect were screened and classified as low, medium or high anticholinergic effects according to the Anticholinergic Cognitive Burden (ACB) scale (low effect = 1, medium effect = 2, high effect = 3) (37) and an AC+ participant (participants taking anticholinergic medications) was defined as taking medication with medium or high anticholinergic effect at the baseline visit for at least one month (38,39).

Appendix E2

Preprocessing of resting-state fMRI datasets included motion correction, slice timing correction, brain extraction, spatial smoothing (FWHM: 5 mm) and high-pass temporal filtering. To seed FC in the NBM, a mask (16 voxels, 581 mm^3) was manually created on fMRI datasets using coronal plane for each subject based on landmarks and the published stereotactic probabilistic maps of NBM (13) to derive NBM averaged time series as input regressors for individual and group mean NBM FC maps. Nuisance regressors were defined as signal averaged from manually-created masks of the central deep white matter (162 voxels, 5888 mm^3), signal averaged over the manually-created masks of ventricles (81 voxels, 2944 mm^3) and six parameters obtained by rigid body head motion correction, and then were used in the general linear model. We did not use the mean global signal as a regressor to avoid introducing spurious anticorrelations (24). Z statistical images of each individual were based on Z > 2.3 and a corrected cluster significance threshold of $P < .05$. Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) with automatic outlier de-weighting (20) in FSL 5.0.10. Age and

mean relative displacement which is the net amount of motion between consecutive functional volumes (21) were treated as further between-subject covariates of no interest in all higher-level analyses. *Z* statistical images of high-level analyses were estimated based on $Z>1.96$, and a family-wise error (FWE)-corrected cluster significance threshold of $P < .05$. All results were masked by gray matter masks obtained from the MNI152 template.

Given that the NBM seed regions were manually drawn, an in-house Matlab code was developed to test the robustness of the manual drawing method. To test the robustness of manual seed region selection, an in-house Matlab code was developed to test the robustness of the manual drawing method. Specifically, a function was used to detect the edge voxels for the seed region mask. Then one voxel was added to or removed from the four directions of the manual seed region each time, ie, top, right, bottom, and left was added or removed. Thus, four FC maps of each subject were calculated based on the computer modified region and the correlation coefficient between the original (manually drawn mask) and modified seed region FC maps were calculated at each voxel. The correlation coefficients were then averaged for each subject.

The averaged voxel-wise correlation between NBM FC strength obtained using manually drawn masks and that obtained using the in-house Matlab code was strong (mean ± SD: r = 0.95 ± 0.06). There was no significant difference in the averaged correlation coefficient between subgroups (healthy [mean ± SD]: 0.95 ± 0.06; EMCI [mean ± SD]: 0.95 ± 0.05; LMCI [mean ± SD]: 0.95 ± 0.05; AD [mean ± SD]: 0.95 ± 0.08; $P = .97$).

Figure E1: NBM FC difference among HC, MCI and AD using F-test (Red-Yellow). Significant level was at corrected $P < .05$. All results were masked by gray matter masks obtained from MNI 152 template.

Figure E2: NBM FC mapping in subjects not on AC. (A) NBM FC difference among HC, MCI and AD using F-test (Red-Yellow). Significant level was at corrected $P < .05$. (B): Difference NBM FC map MCI and HC (Blue-Light blue = reductions in MCI, pair-wise *t* test, corrected $P < .025$) and (C): Difference NBM FC between AD and HC (Red-Yellow: increased FC in AD, using pairwise *t* test, corrected $P < .025$). All results were masked by gray matter masks obtained from MNI 152 template. All *t* test analyses were controlled for age and mean relative displacement.

Figure E3: NBM FC and cognition. Negative correlation map between baseline ADAS-Cog and NBM FC located in significant clusters (blue-light blue) in a group of participants including healthy, EMCI and LMCI participants who were not on ChEI treatment or AC ($n = 111$). All results were masked by gray matter masks obtained from MNI 152 template. Scatterplot of negative correlation between baseline ADAS-Cog and NBM FC in significant clusters (Blue-Light blue). All analyses were controlled for age and mean relative displacement. Significant level was at corrected $P < .05$.