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Medial temporal lobe (MTL) – default-mode network (DMN) functional connectivity disruption in the early stages of the progression of Alzheimer's disease in a multimodal ADNI3 MP-RAGE and EPI-BOLD Basic cohort

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Abstract

Background: A cross-sectional same-session multi-modal analysis (T1, rsfMRI) was applied to identify potential biomarkers of the progression from cognitively normal (CN) to significant memory concern (SMC) and early and late mild cognitive impairment (EMCI, LMCI) in Alzheimer's disease.

Methods: An ADNI3 EPI-BOLD Basic sub-population (N = 133) with baseline diagnosis CN (N = 45), SMC (N = 46), EMCI (N = 22), and LMCI (N = 20), matched for age (p = 0.61), education (p = 0.26), gender (p = 0.26), morphometric (FreeSurfer 7), and fMRI (AFNI) measurements, was processed with a hybrid a priori data-driven method that identified anchor-target ROI pairs in rsfMRI [1]. ROI pairwise correlations were False Detection Rate (FDR) corrected in a parallel group-level one-way four-factor (CN, SMC, EMCI, LMCI) ANOVA and post hoc pairwise t tests were performed for significant tests only.

Results: A 3-mm grid of ROI (r = 6mm) seeds in left MTL yielded 488 ROI "anchors". 3D (Fisher Z-transformed) correlation maps were computed for each subject for each anchor ROI and input to a group-level one-way four-factor 3D ANOVA. Cluster analysis (N_{vox} = 20; p = 0.02; P = 3.45) of the 3D F statistic maps yielded 1,774 target ROIs. An r = 6mm ROI was placed at the center of mass of each target cluster. ROI anchor-target pair correlations were input to a group-level one-way four-factor ANOVA FDR corrected (q = 0.005; p^* = 0.0035, permutation, N = 1000) which identified 1,179 significant tests. Post hoc pairwise t tests only on the significant ANOVA tests were FDR-corrected (q = 0.005) and yielded 163 significant SMC-CN tests ($p^* = 6.8\times10^{-4}$); 158 EMCI-CN tests ($p^* = 6.6\times10^{-4}$); and 120 LMCI-CN tests ($p^* = 5.1\times10^{-4}$). The significant target ROI masks were summed which identified 35-44 clusters. The same hybrid a priori data-driven method was then applied in independent runs using as anchor regions the left amygdala, thalamus, substantia nigra, and accumbens area. The resultant spatial distribution of significant target ROI masks predominantly, but not

uniformly coincided with DMN-associated regions. An independent analysis of right hemisphere yielded similar results.

Conclusions: A hybrid a priori data-driven approach applied to anchor ROIs in MTL and multiple subcortical regions identified target ROIs that were predominantly, but not uniformly associated with DMN.

[1] Grajski, K. A., Bressler, S., and ADNI. (2019). Neuroimage Clin. 2019;23:101860.