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 Advanced cohort

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Background:

A cross-sectional same-session multi-modal analysis of T1 structural MRI and resting-state functional connectivity (rsfMRI) was performed to assess potential biomarkers of the progression from cognitively normal (CN) to significant memory concern (SMC) and early and late mild cognitive impairment (EMCI, LMCI).

Methods:

An ADNI-3 EPI-BOLD Advanced protocol sub-population (N=49) with baseline diagnosis CN (N=14), SMC (N=15), EMCI (N=11) and LMCI (N=9), matched for age (p=0.37), education (p=0.65), gender (p=0.29), and morphometric (FreeSurfer 7) and fMRI (AFNI) measurements, was processed with a hybrid *a priori* data-driven method for identifying anchor-target ROI pairs in rsfMRI [1]. Anchor-target 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:

MRI. FreeSurfer subcortical segmentation, but not cortical thickness, yielded significant tests in a parallel group-level one-way four-factor ANOVA test (q=0.05, $p^*=2.8\text{x}10^{-3}$) for left hippocampus. rsfMRI. A 3-mm grid of ROI (r=6mm) seeds in left MTL yielded 1,012 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 3,954 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^*=0.0067, estimated by permutation, N=1000) which identified 1,454 significant tests (ROI pairs). *Post hoc* pairwise t tests only on the significant ANOVA tests were FDR-corrected (q=0.005) and yielded 34 significant SMC-CN tests ($p^*=1.1\text{x}10^{-4}$); 329 EMCI-CN tests ($p^*=1.1\text{x}10^{-3}$); and 78 LMCI-CN tests ($p^*=2.6\text{x}10^{-4}$). For each pairwise contrast, the significant target ROI masks were summed which resulted in 20-50 clusters which were bilaterally distributed in MTL and 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.