Graph theoretical analysis of resting-state functional MRI reveals widespread disconnection in amnestic mild cognitive impairment

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TARGET AUDIENCE: Neuroscientists and clinicians with an interest in Alzheimer’s disease

PURPOSE

Early Alzheimer’s disease, and to a lesser extent mild cognitive impairment due to prodromal Alzheimer’s disease, are associated with disconnection across the nodes of the default mode network. Existing studies using independent component and seed based analyses have demonstrated significant effects at the level of group comparisons and correlation with clinical scores, yet the effect sizes are inadequate to attain a clinically relevant separation [1,2]. In part, this limitation stems from issues in the data analytical approach: segregation of individual components on the basis of signal priors is of limited biological plausibility. Recently, graph theoretical approaches have been applied, which capture the connectivity of all brain regions together without attempting to separate discrete components [3,4]. Such approaches may have fundamental biological relevance because amyloid pathology accumulates preferentially in highly-connected nodes and tau pathology may migrate trans-synaptically [5]. In this recently published study [6], we conducted an explicit comparison of independent component analysis and graph-based analysis of resting state functional connectivity in a group of patients with amnestic mild cognitive impairment, and hypothesized that the latter approach would increase sensitivity to disease related changes.

MATERIAL AND METHODS

Participants 49 patients with amnestic mild cognitive impairment were recruited from the Specialist Dementia Clinic of Catholic University of Rome and imaged at the IRCCS Santa Lucia Foundation, Rome. Approval from the ethics committee of the Santa Lucia Foundation was obtained and all subjects gave written informed consent. Patient characteristics were as follows: age 70.2±8.7 years, 25 female, MMSE score 26.4±1.8. Clinical Dementia Rating 0.5, Rey auditory verbal learning test corrected scores 31±6 immediate, 4.6±2.4 delayed; 26 patients had single-domain and 23 multiple-domain amnesic mild cognitive impairment; at one year follow-up 13 out of 34 retested patients had converted to Alzheimer’s disease. Control characteristics were as follows: 32 cognitively normal participants, 14 female, age 65.9±8.0 years.

Data acquisition

Resting state functional MRI was performed on a single-channel 3.0 T Siemens Allegra scanner using a gradient-echo echo-planar sequence having TR=2080 ms, TE=30 ms, matrix 64x64, voxel size 3x3 mm2, 2.5 mm slice thickness, no gap, flip angle 70°, 32 axial slices, 216 volumes.

Data analysis

After standard slice timing correction, realignment, normalization and smoothing with a 8 mm Gaussian kernel, group-level spatial independent component analysis was performed using the Group ICA Toolbox v. 2.0 (University of New Mexico, USA) and setting 12 components as determined through the minimum description length criterion. Graph-based analysis was performed as described in detail elsewhere [7]; in brief, regional time-series were extracted for each of 742 regions, determined by iterative parcellation of individual grey matter. Polynomial detrending and low-pass filtering were performed, followed by regression of movement parameters, white matter and cerebrospinal fluid signal, temporally filtered with the same settings. The matrix of Pearson correlation coefficients was then calculated and thresholded at r>0.15, 0.2...0.75 to yield node degree values. Full details and source code in the journal article associated to this abstract [6].

Statistics

Comparisons of patients and controls were conducted using two-tailed t-tests with correction for age and root-mean-square volume-to-volume head displacement. For default-mode network maps, inclusive masking was applied, with p<0.005 voxel-level thresholding and p<0.05 FWE cluster-level thresholding. For node degree measurements, smoothing between adjacent regions was performed and FDR-correction applied over all regions. See [6] for details.

RESULTS

Default-mode network connectivity was reduced in the precuneus/posterior cingulate region, particularly on the right (peak [8,-44,26] mm, kE 447 voxels, cluster-level pFWE=0.01), with an additional more anterior cluster in the medial parietal region. Node degree loss was much more widespread and gradually ensued for r>0.25, peaking at r=0.60. At this threshold, reduced node degree was most pronounced in cuneus, pre-cuneus, posterior cingulate, supramarginal and angular gyri, inferior and superior parietal lobules, pre- and post-central gyri (Figure 1). Additionally, patients were characterized by reduced network completeness, average clustering and global efficiency for r>0.35.

DISCUSSION

While node degree changes were widespread and strongly significant across the majority of the medial and lateral parietal cortex, with extension to cingulate, temporal and occipital areas but also frontal lobe and insula, default mode network strength was significantly reduced only in a relatively small cluster in posterior cingulate. Notably, graph-based analysis revealed that connectivity is disrupted not only between default mode network hubs, but also with other regions, likely as a downstream effect. Graph-based analysis appears to have vastly superior sensitivity to functional disconnection than independent component analysis in amnestic mild cognitive impairment [6].

REFERENCES