A graph-theory approach to study the effect of cognitive load on resting state networks

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Introduction Functional connectivity analyses of magnetic resonance imaging (fc-MRI) data aim to elucidate relationships between signals originating in spatially distinct brain regions. A number of recent studies have shown that functional imaging data sets from individuals or groups of subjects can be resolved into several distinct 'sub-networks', each of which comprises a set of distributed brain regions in which signal changes are correlated [1-3]. These correlations are interpreted as reflecting a functional connectivity between the brain regions involved. The emphasis on interaction between different brain structures in the study of functional connectivity is a good conceptual match for considering the data as a graph, or complex network [4], of nodes and links. In this representation, image voxels or parcellated brain regions represent the nodes and a measure of similarity in their responses defines the links between them [5-7]. In this abstract we focused on a particular type of graph based method that identifies nodes that play central roles within the network structure. Specifically we calculated Eigenvector Centrality (EC) maps [8] of the brain in two different conditions: at rest and during a 2-back verbal working memory task.

Methods Nine healthy right-handed subjects participated in this study after giving informed consent. All the participants underwent two steady-state fMRI experiments: one at rest (no task, eyes open) and one performing a 2-back verbal working memory task throughout the run. Each run lasted for 8 min 24 sec. Functional data were collected by using a 2D gradient-echo echo-planar sequence at 3T (Siemens Allegra system), sensitive to BOLD contrast (TR/TE=2100/30ms, flip angle= 70°, voxel size 3x3x2.5-mm^3, matrix 64x64, 32 slices (1.25-mm skip)). A T1 weighted whole-brain structural scan was also acquired (1.33x1.33x1 mm^3). *PREPROCESSING:* EPI time series underwent several preprocessing steps before centrality analysis. Pre-processing was carried out using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and home made scripts working in Matlab (The Mathworks, Inc.). The functional images from each subject were corrected for motion using rigid-body volume registration. Slice-timing correction compensated for the order of slice acquisition. Anatomical scans were registered to fMRI and segmented in order to extract grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) probability maps. Sources of spurious variance were removed from the data through linear regression, including: (i) six rigid body realignment parameters, (iii) average signal from white matter, (iv) average signal from cerebrospinal fluid and (v) a linear trend. The regressors needed in the steps (iii) and (iv) were obtained averaging the intensity of the EPI time-series inside the WM and CSF masks obtained after the segmentation step, respectively. In order to avoid the inclusion of unwanted GM information inside each mask, CSF and WM maps were eroded slice-wise with a square kernel of three voxels along the boundaries. Afterwards data were band-pass filtered in the time domain (0.009 Hz < f < 0.08 Hz). A common grey matter mask (CGM) was created considering the intersection in the standard (Montreal Neurological Institute, MNI) space of the grey matter probability maps (obtained by the segmentation procedure) thresholded at 0.9. *CENTRALITY ANALYSIS:* A functional link between two time series x_i (t) and x_j (t) was defined by means of the linear cross-correlation coefficient r_{ij}. In the construction of the networks, a functional connection between two brain sites was assumed as an undirected and weighted edge (being the weight $w_{ij}=r_{ij}$). For each subject a correlation matrix was calculated including connections among the voxels belonging to the CGM back-projected in the subject space. A further threshold was applied to the correlation matrix, above which individual voxels were said to be connected. The threshold was defined such that the relationship S~log(N)/log(D) was the same across subjects, where N was the number of nodes and D the average of the number of connections between nodes (the average degree of the network). The correlation matrix was then converted in a distance matrix by the transformation $d_{ij}=((1-r_{ij})/2)^{1/2}$. As last step the distance matrix underwent a stochastic normalization (each column was divided by the sum of its elements). EC and DC maps were calculated for each subject and for each experimental condition, and then transformed [9] in order to ensure that they obey a Gaussian normal distribution. Before statistical analysis, centrality maps were normalised to MNI and smoothed (8x8x8 fwhm). Afterwards they were analysed by means of a permutation method able to output cluster-based two samples t-tests (http://www.fmrib.ox.ac.uk/fsl/randomise/).

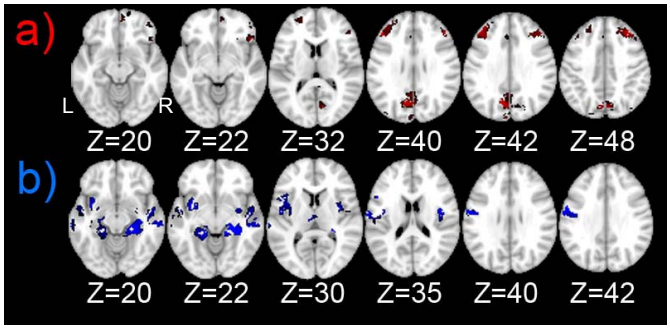

Figure 1. The P-value maps of a) the R>2B t-test (p<0.001, uncorr.) and b) the R<2B t-test (p<0.001, uncorr.) are reported. The statistics was reached by running 10000 Monte Carlo permutations.

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Results EC maps were calculated on networks thresholded at S=2 and composed of ~25,000 voxels. A two samples t-test was calculated both for the condition R>2B and for R<2B. Figure 1a shows the output of the R>2B two samples t-test (p<0.001, uncorr.). The statistical analysis elicited five regions that show a decrease of centrality, passing from the resting condition to the demanding cognitive task: the Posterior Cingulate Cortex/Precuneous and the Medial Prefrontal Cortex (the main regions of the default mode network), the Middle Frontal Gyrus (bilaterally) and the right Frontal Orbital Cortex. Figure 1b shows the output of the R<2B two samples t-test (p<0.001, uncorr.). Nine regions showed an increase of centrality passing from the resting fixation to the working memory task: Hippocampal formations (bilaterally), Insular Cortex (bilaterally), Thalamus (bilaterally), left Primary Somatosensory Cortex (BA3b) and Secondary Somatosensory Cortex/ Parietal Operculum (bilaterally).

Discussion and Conclusions Centrality in graph theory refers to a measure of the node's importance within a network. By definition, EC favours nodes connected to other nodes that are themselves highly central within the network. We showed (consistently with functional connectivity literature) that areas belonging to the Deafult Mode Network tend to reduce their central role in the functional architecture of the brain passing from the resting condition to cognitive activity. Moreover, our results show that, when the brain is engaged in a demanding working memory task, the centrality of the brain nodes is re-organized, in order to enhance the efficiency of communication between regions known to be fundamental for the good performance of the task (i.e. hippocampal and thalamic formations for the storage and synchronization of information). These results may suggest that resting state networks represent spatiotemporal basis function that are dynamically assembled and modulated during different behavioural states.