Acknowledgments:

Memory has a key role in driving resting-state processes, that DMN regions are ‘recruited’ to solve task-specific goals. Interestingly, when extrapolated to potential linearity which is not strictly true with the BOLD signal and pre-definition of interacting regions. Overall these findings give supporting evidence to the notion that clinical applications, these results suggest that Granger causality correlations between the DMN sub-regions might be a stronger biomarker than spatial DMN map relative to the resting state condition, the parahippocampal area no longer having a key role. This is consistent with the expected activation of this task which involves ‘switch’ to show significant causal relations to DMN subregions, particularly medial prefrontal cortex, which changes the internal causal relations within the DMN.

Methods

Tasks and MRI acquisition: Eight subjects (3 females mean age 24±0.5 years) participated in this study. A 4.0 T Bruker Medspec scanner equipped with an eight-channel multi receive system was used. Structural images (3D MPRAGE, 1x1x1 mm³, GRAPPA IPAT = 2, [9]) and BOLD EPI data, corrected for distortion with the PSF method [10]. (TR/TE = 2000/33ms, flip angle=73°, 3x3x3 mm³) were acquired. Subjects were imaged for 10 minutes whilst resting (eyes closed) followed by visual attention task blocks in which they were instructed to respond as quickly as possible to a lateralized visual target with an ipsilateral or a contralateral button press, according to the instruction (respectively coded by a square and a diamond) that they saw at the beginning of each trial. A masked instruction (smaller square or diamond) or neutral shape (star) preceded subliminally each visible instruction. fMRI analysis: The overall analysis for each task consisted of two main steps: i) determine the spatial map of DMN regions by finding clusters that are temporally correlated or anticorrelated with PCC, ii) take the time courses in these regions and evaluate Granger causality for all pair-wise combinations. fMRI analysis was performed in AFNI (Cox, 1996). Pre-processing consisted of motion correction, temporal band-pass filtering (0.01 Hz<f<0.08Hz), spatial normalization to standard Talairach space and spatial smoothing (Gaussian, FWHM 6mm). Several sources of nuisance covariates (six head motion parameters, whole brain signal, signal from the white matter and the CSF) were eliminated using linear regression. To define key areas of the DMN a seed-based cross-correlation analysis was calculated by extracting the BOLD time course from posterior cingular cortex (PCC), then computing the correlation coefficient between that time course and the time course from all other brain regions. Temporal correlation coefficients relative to PCC were converted to z-scores by using Fisher's r-to-z transformation. For group analysis, we computed fixed-effects. Finally, population-based z-score maps were corrected for multiple comparisons at a significance level of P < 0.05. For Granger causality analysis [6], we computed the mean time series of all voxels within PCC, medial prefrontal cortex (MPFC), left and right angular gyrus (LANG and RANG), left parahippocampal formation (LHF), left inferior parietal lobule (LIPL) and left posterior fusiform gyrus (LPFG) was calculated. These last two regions were respectively found in a separate study [11] to be the main areas involved during the execution of the same visual attention task, and interpreted as respectively involved in motor attention and shape encoding.

Results

The activation maps (left) in Fig. 1 and Fig. 2 show group t-maps of regions functionally correlated with a PCC seed during resting state and the cognitive task state, respectively. Regions positively correlated with the seed PCC included MPFC, LANG, RANG, and parahippocampal gyrus (red). LIPL and LPFG regions were anticorrelated with PCC (blue). The spatial distribution of the functional connectivity maps within DMN changed little during the resting state and task state. The LIPL and LPFG show most of the activation during the task, as expected [11]. The right panels of Fig.1 and Fig.2 show the Granger causality analysis of region (MPFC, LANG, RANG and LHF) positively correlated with the seed PCC and the regions (LIPL and LPFG) which were anticorrelated with PCC during resting state and task state. Violet lines indicate significant (p < 0.05 corrected) uni-directional causality, and arrows indicate the direction of causality.

Discussion and Conclusions

During the resting state we found two key functional patterns: i) the left parahippocampal formation has a key role in causally driving the sub regions of the DMN correlated with PCC, supporting a strong role of memory to drive the DMN, and ii) there are non-DMN areas that are anticorrelated with PCC, having causal correlations with themselves but no causal correlations with the DMN. During the visual attention task we found that key non-DMN areas expected to work in the visual attention task ‘switch’ to show significant causal relations to DMN subregions, particularly medial prefrontal cortex, which changes the internal causal relations within the DMN relative to the resting state condition, the parahippocampal area no longer having a key role. This is consistent with the expected activation of this task which involves considerable task switching processes. These findings need to be further validated due to the known limitations of the Granger causality method, including assumed linearity which is not strictly true with the BOLD signal and pre-definition of interacting regions. Overall these findings give supporting evidence to the notion that memory has a key role in driving resting-state processes, that DMN regions are ‘recruited’ to solve task-specific goals. Interestingly, when extrapolated to potential clinical applications, these results suggest that Granger causality correlations between the DMN sub regions might be a stronger biomarker than spatial DMN map differences.

Acknowledgments: Support for this research was provided by the government of the Provincia Autonoma di Trento, Italy, Project PAT Post-doc 2006.