

Resting state fMRI during continuous cognitive processing reveals dynamical changes of brain networks involving cerebral cortex and cerebellum

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While task-dependent responses of specific brain areas during cognitive tasks are well established, much less is known about the changes occurring in Resting State Networks (RSN) during continuous cognitive processing (1, 2). In this work we implemented a multi-session protocol to assess functional connectivity (FC) changes in RSNs before, during and after a naturalistic fMRI stimulation involving a narrated story. A clustering analysis was performed to have a global view of these FC changes. The underlying hypothesis is that the engagement of the brain in activity caused by the listening to a narrated story generates dynamical changes in the RSNs and that these changes reflect distinct patterns depending to the involvement of the networks in elaborating sensory or cognitive contents. Interestingly, specific cerebellar nodes were involved beyond pure sensory signal elaboration suggesting a close association of cerebellar activity to continuous cognitive processing.

8 healthy subjects (age 39.62 ± 5.85) underwent MRI examination using a 3T Philips Achieva scanner. Individual rs-fMRI scans were acquired using a FFE-EPI sequence (TR/TE=4000/25ms, voxel size=3x3x3.5mm³, FOV=230mm, gap=0.5mm, 43 slices, 120 volumes). A HR 3DT1-weighted scan was also collected using a FFE sequence (TR/TE/TI=6.9/3.1/824ms, flip angle 5°; 180 slices; voxel-size=1x1x1mm³, FOV=256mm) for anatomical reference.

The acquisition protocol consisted in four repetitions of the fMRI scan (labelled pre, story, post1 and post2). The experiment was designed to study RSN dynamical changes in response to an evolving complex cognitive stimulation, performed during the second fMRI acquisition (story). The cognitive stimulation was achieved through delivering a narrated story designed to stimulate a specific mental engagement.

For each subject, rs-fMRI images were pre-processed and then treated with the Independent Component Analysis (ICA) to characterise RSNs. ICA analyses were carried out using MELODIC (FSL, www.fmrib.ox.ac.uk/fsl). A non-parametric permutation test (dual regression) was then applied to create and compare group-specific maps for each independent spatial map, using age and gender as additional covariates in the model (3, 4).

For each RSN we calculated two parameters: relative change in FC (rcFC) and relative change in spatial extent (rcSpE). For each scan, values of FC magnitude and spatial extent for each RSN

were normalised respectively to the values of FC magnitude and spatial extent measured in pre, as well as at their peak values. For each RSN, values of rcFC and rcSpE were tested across fMRI scans with ANOVA using SPSS to detect significant ($p < 0.05$) changes in RSNs behaviours across the 4 fMRI scans. Finally, we calculated a composite relative total change parameter, rcT, defined as $[rcT(j) = rcFC(j) \cdot rcSE(j)]_{RSN}$, with $j = \text{pre, story, post1, post2}$. The index rcT allowed us to have an overall view of the dynamical changes for each RSN between scans over time. To assess the RSNs dynamical behaviour, we run a k-means clustering (5) analysis in Orange (<http://orange.biolab.si>) using as input argument rcT values for each RSN and each scan of interest. k-means was run limiting the partition to three clusters ($k=3$), according to the hypothesis that RSNs may behave differently when been a sensory, cognitive or mixed sensory-cognitive network (6).

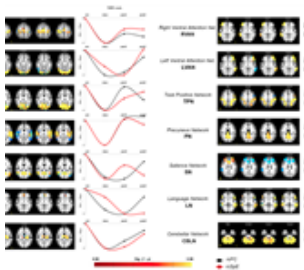
14 RSNs were identified from ICA analysis based on their frequency spectra (see Fig.1). All the RSNs showed significant ($p < 0.01$) desynchronization during the story, signified by decrease in rcFC and rcSpE when comparing values of the story with pre. The comparison of story with post1 and post2 gave an indication of the dynamical process of FC changes for each RSN (Fig.1). The repeated measures ANOVA revealed that RSNs varied in rcFC ($F_{2,25} = 40.14$, $p < 0.001$) and rcSpE ($F_{2,25} = 26.51$, $p < 0.001$) across the four scans of the study. For all RSNs, significant differences were observed when comparing rcSpE and rcFC between pre and story, post1 and post2, suggesting that listening to the story perturbed the state of each network with respect to both the initial and the final time point of the experiment (i.e. pre and post2). No significant differences were observed when comparing rcSpE between story and post1, suggesting that the story affected the RSNs also after the listening phase.

The kinetics of recovery, when looking at both rcSpE and rcFC, varied across networks with two main patterns being visually recognised that we called: short-lasting (transient), e.g. shown by the sensory network AN, and long-lasting (persistent), e.g. shown by the cognitive network FCN. Most RSNs, showed complex patterns of changes with intermediate short- and long-lasting kinetics of recovery, depending on rcSpE and rcFC.

Clustering analysis confirmed that different RSNs had a range of kinetic behaviours. k-means sorted the RSNs into three clusters (C1, C2, C3) as shown in Fig.2. By averaging the rcT values across scans in each cluster, we were able to determine the kinetics of recovery typical of these three clusters (Fig.3). In C1, the changes peaked in post1 and then did not fully recover even in post2. In C2, the changes peaked in story and recovered rapidly already during post1. Therefore, C1 was a long-lasting cluster and C2 a short-lasting cluster. C3, which included the cerebellar network (CBLN, see Fig.2), was associated to a more complex kinetics, being “intermediate” between the short- and long-lasting behaviours of C1 and C2.

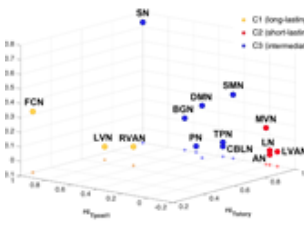
By analysing the dynamical changes of RSNs it has been possible to identify consistent FC changes in networks involved in processing the sensory information influx and its cognitive content. We interpreted these changes within the RSNs as an indication that the cognitive context of the story was able to engage the subjects and continued to do so even after the conclusion of the story, possibly reflecting internal rehearsal and continued mental elaboration. In particular, sensory networks, such as AN and MVN, showed changes mostly limited to the narration period, while cognitive networks (including FCN) showed protracted changes lasting beyond the end of narration. Other networks, including the CBLN, showed intermediate changes, suggesting their circuitries (or part of them) have a role in supporting the sensorial reception of the story as well as in the cognitive processing of its content. The complex behaviour of CBLN emerged also from clustering analysis, giving a further indication that the cerebellum may be engaged not only in sensory-motor control but also in cognitive processing.

Figure 1



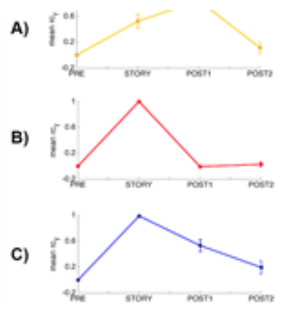
changes observed in the 14 RBMs of this study. For each RBM, images on the left are displaying the network, to the four nodes of the network. Each one of these four pictures shows the resting state image of the RBM on a pre, early, post1 and post2, numbered into the nodes on each of the RBM half (from L to R). For each RBM, images are sorted on each of the RBM half during the experiment.

Figure 2



3D scatter plot showing the results of a means clustering (3 clusters: C1, C2, C3) across RBMs for C1 (in yellow) contains LBNs showing long-lasting changes, while C2 (in red) contains LBNs that show short-lasting changes. C3 (in blue) contains seven LBNs with an intermediate behavior. The 3D plot represents the three dimensions of the 3-means input data, i.e. H_T , H_V and H_S . To give a better view of the position of the LBNs in the 3D space, the projection of each point i of H on the H_T plane is shown.

Figure 3



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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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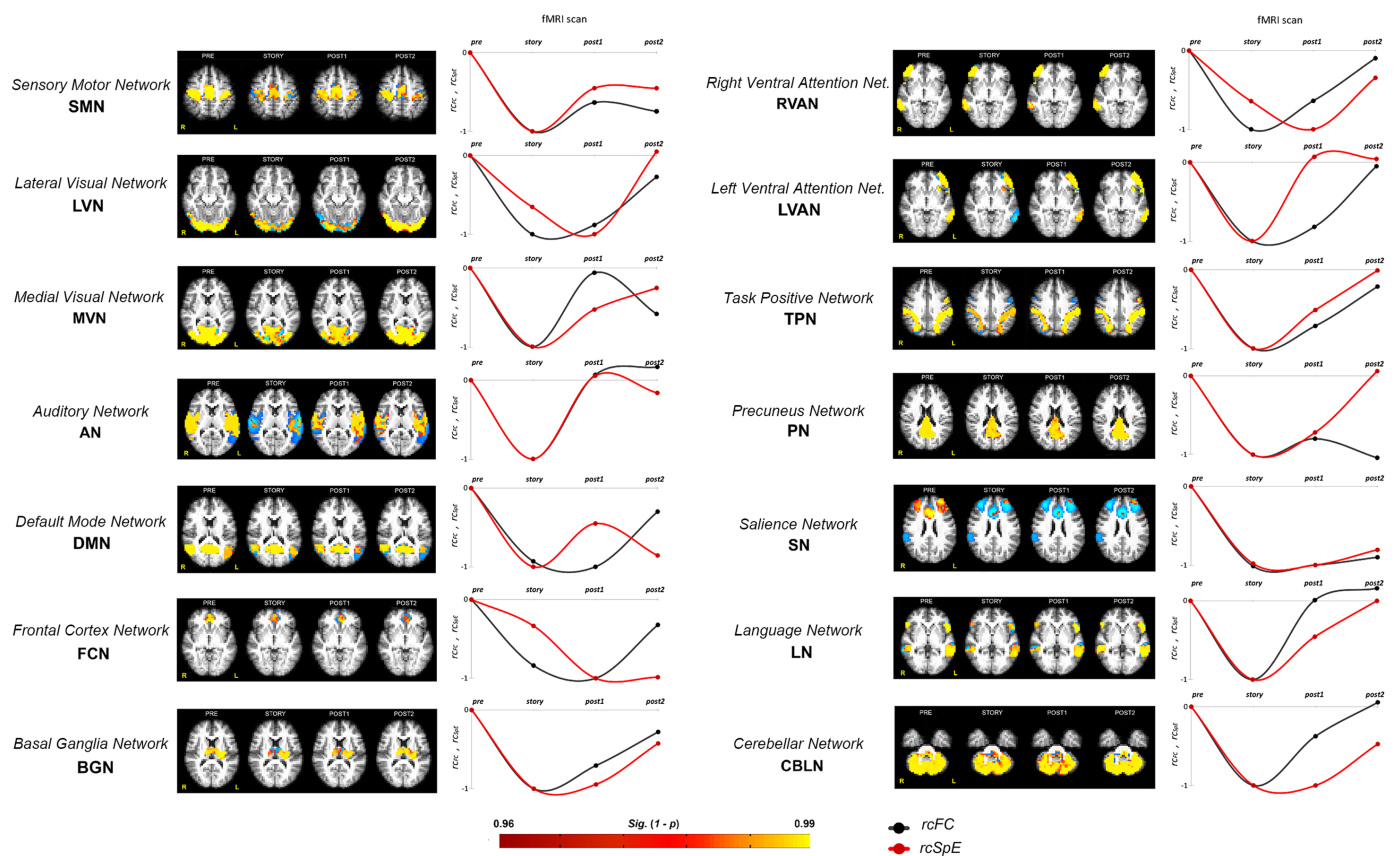


Fig. 1 - Patterns of FC changes observed in the 14 RSNs of this study. For each RSN, images on the left are displaying the network, at the same slice position, as it appears during the four scans of the protocol. Each one of these four pictures shows the resting state shape of the RSN (voxels in yellow-red) during the ongoing scan (pre, story, post1 and post2), overlaid onto the mask (in blue) of the RSN itself (from ICA analysis). For each RSN, we report on the right the dynamics of rcFC (in black) and rcSpE (in red) during the experiment.

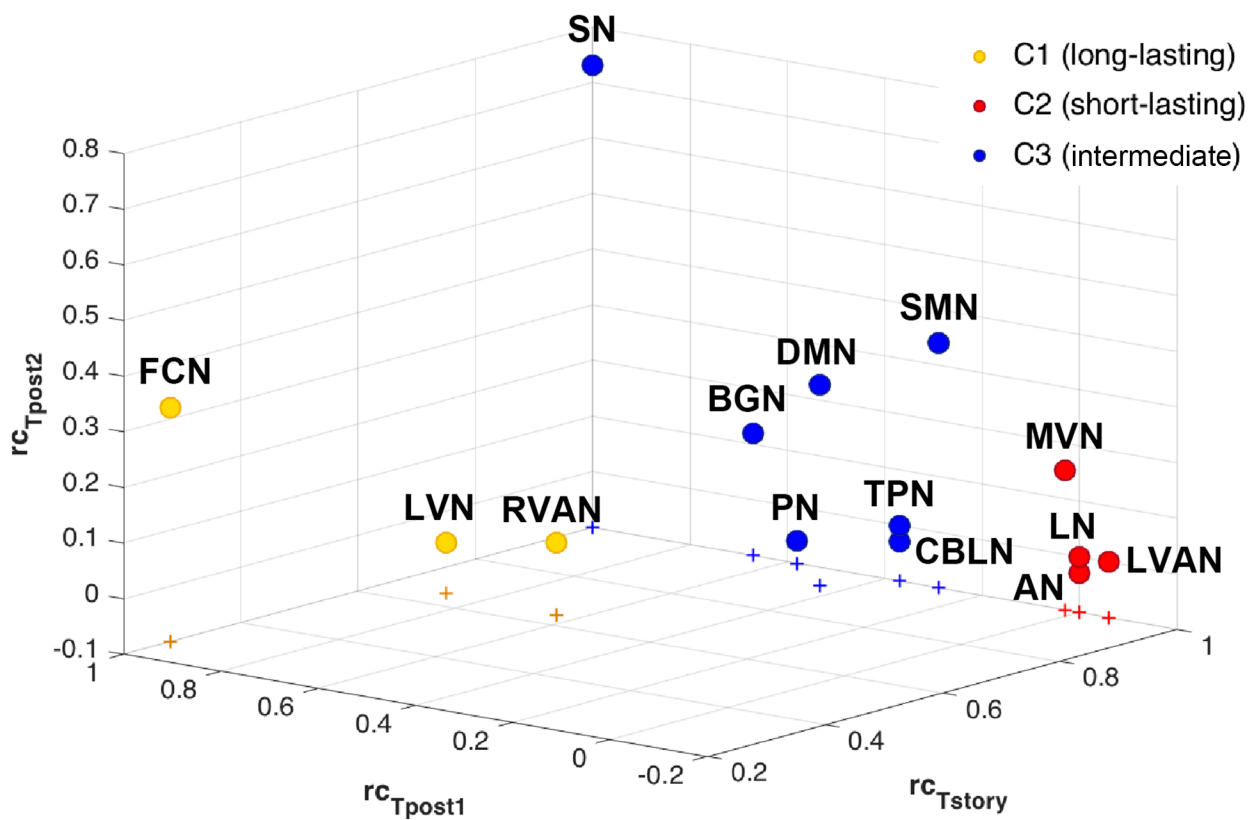


Fig.2 - 3D scatter plot showing the results of k-means clustering (3 clusters: C1, C2, C3) across RSN behaviours. C1 (in yellow) contains LSNs showing long-lasting changes, while C2 (in red) contains LSNs (including AN and MVN) showing short-lasting changes. C3 (in blue) contains seven LSNs with an intermediate behaviour. The axes of the 3D plot represent the three dimensions of the k-means input data, i.e. rc_{Tstory} , rc_{Tpost1} , rc_{Tpost2} . To give a better view of the position of the LSNs in the 3D space, the projection of each point onto the $rc_{Tpost1} / rc_{Tpost2}$ plane is shown.

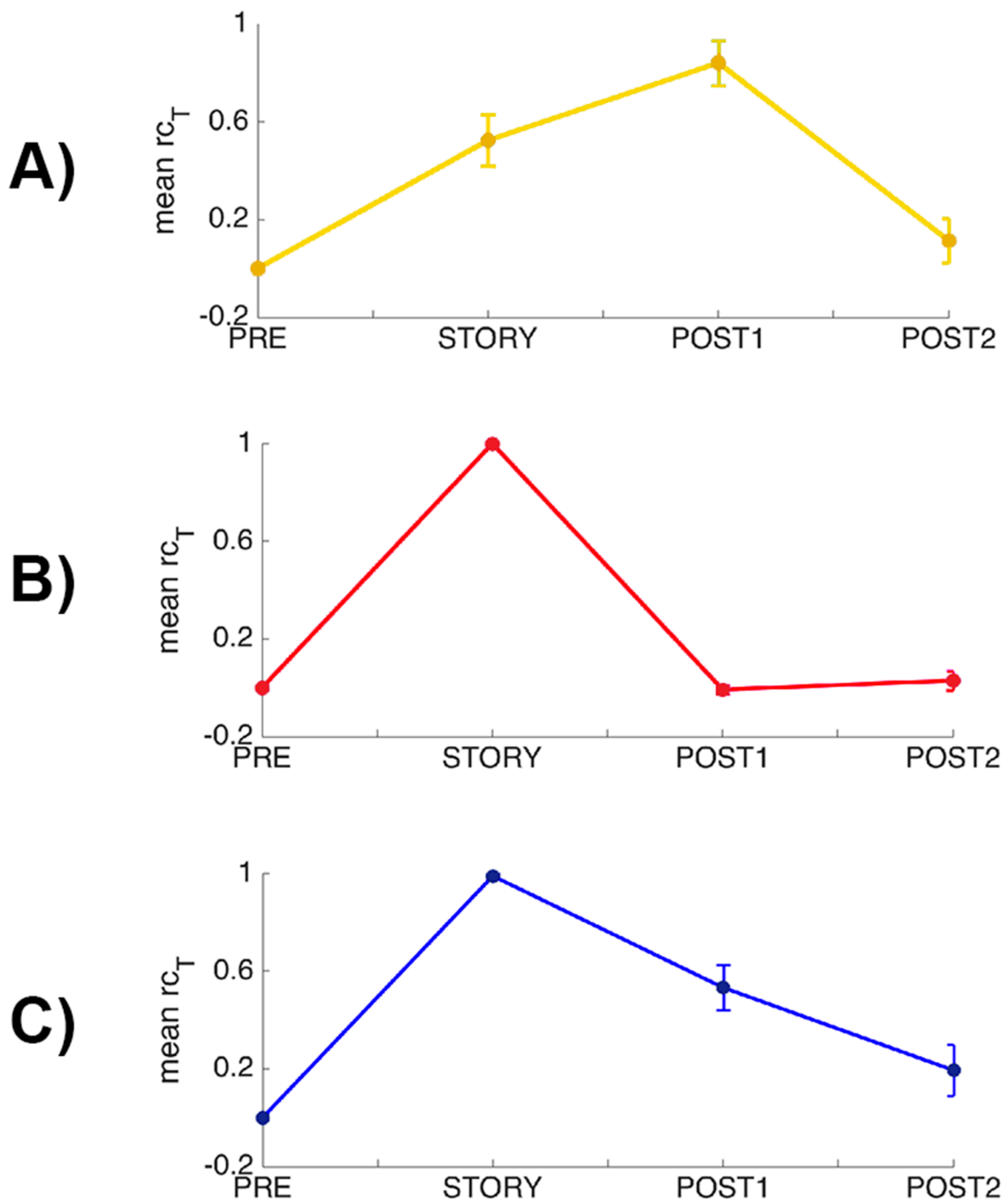


Fig. 3 - Mean rc_T values of each cluster: (A) C1 or short-lasting cluster (in yellow), (B) C2 or long-lasting cluster (in red), (C) C3 or intermediate cluster (in blue).