Dynamic changes of Resting State Networks depict short-term plasticity of the brain

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Target Audience: Researchers and clinicians who are interested in the analysis of short-term dynamic organization of the resting state networks.

Purpose: Resting state functional MRI (rs-fMRI) allows detecting the *resting state networks* (RSNs), which represent a pool of functionally connected areas that display functional connectivity (FC) at "rest". Despite the large number of studies describing RSNs in healthy controls, only few reports attempt to suggest how some of these RSNs intrinsically change over space and time when stimulated by external inputs.[1-3] In particular, during the execution of complex "continuous" cognitive tasks, such as listening to a story or watching a movie, the brain elaborates information over multiple domains and time scales, integrating it across space and over time. In this work we used the rs-fMRI framework to investigate the dynamic changes in brain activity occurring in subjects listening to a narrated story, designed with specific characteristics in order to stimulate specific cognitive domains. This work therefore investigates whether during specific cognitive tasks some RSNs respond to the stimulus featuring short-term pattern evolutions. **Methods:** MRI acquisitions: 8 healthy subjects (mean age 70.35±5.56) underwent MRI examination using a 3T MR Philips Achieva (Philips Healthcare, Best, The Netherlands) with a 32-channel head coil. All subjects were of Italian mother tongue with normal audition, and all provided written informed consent. For each subject rs-fMRI images were acquired using a fast field echo planar imaging (FFE-EPI) sequence with TR/TE=4000/25ms, voxel size=3x3x3.5mm^3, FOV=230mm, gap=0.5 mm, 43 slices, for a total of 120 volumes and a total acquisition time (AT)=8.04min. A high resolution 3D T1-weighted scan was also collected using a FFE sequence (TR/TE=6.9/3.1ms; flip angle 5°; 180 sagittal slices; voxel size=1x1x1mm^3, FOV=256mm) for anatomical reference. Experimental design: a specific acquisition protocol including 4 consecutives rs-fMRI scans (labelled respectively: PRE, STORY, POST1 and POST2) was designed to study RSNs dynamic changes in response to the execution of a continuous complex cognitive stimulation, performed during the entire duration of the second rs-fMRI acquisition (STORY). The cognitive task for the experiment consisted of a 7 min. story in Italian language, written to contain specific cognitive elements, including visual-spatial imagery, error detection and error/novelty, to stimulate specific cognitive processes and brain areas, including attention and working memory[4] (the plot of the story is inspired to the famous "Harry Potter" tales). fMRI analysis: for each subject rs-fMRI images were analysed using the Independent Component Analysis (ICA) computational method in order to characterise RSNs. ICA analyses were carried out using MELODIC (FSL[5], version 4.1.9). A non-parametric permutation test (dual regression)[5] was then applied to create and compare group-specific maps for each independent spatial component, using 5000 permutations with age and gender as additional covariates in the contrasts design. This step allowed to detect statistically significant differences in RSNs between the 4 consecutive runs of the fMRI protocol. Statistical maps were family-wise error (FWE) corrected with a threshold of $p \leq 0.05$ for statistic significance.

Results and Discussion: Group ICA analysis resulted in 33 independent components, 15 of which were recognized as part of 13 RSNs. Two are the major findings of this study: **1**) Overall, our results reveal that all the RSNs, show significant changes (p=0.001, FWE-corrected) in terms of both mean FC and spatial extent of the resting-state network in response to the listening of the story. In particular, significant differences were found when comparing RSNs mean FC and RSNs number of active voxels before and during the task (Fig.1, PRE and STORY). No significant differences were observed when comparing RSNs mean FC and spatial extent before the story (PRE) and during the last rs-fMRI acquisition after the task (POST2), suggesting an almost complete recovery of the "rest" condition for all the RSNs after the listening of the story within 20 minutes from the story. **2**) Each RSN changes in the synchronization of the network FC within-network during the experiment following a specific pattern of alteration in response to the stimulus. Nine of the 13 RSNs, including the task positive network (TPN), the default mode network (DMN), the dorsal attention network (DAN) and the auditory network (AN), responded to the listening of the story showing a quick significant decrease of FC, reaching a minimum FC during the "STORY" and immediately starting to recover the "rest" state in "POST1" (Fig.1a). Moreover, three RSNs, the lateral visual network (LVN), the right ventral attention network (R-VAN), the salience network (SN) and in particular the cerebellum network (CBLN) showed a delayed (in time) response to the stimulus, reaching a minimum FC in POST1 and partially recovering the "rest" state at the end of POST2 (Fig.1b). Only the medial prefrontal cortex network (mPFCN) showed a delayed (in time) response to the stimulus resulted in a long-time response to the stimulus without recovering the "rest" condition at all within the end of the experiment.

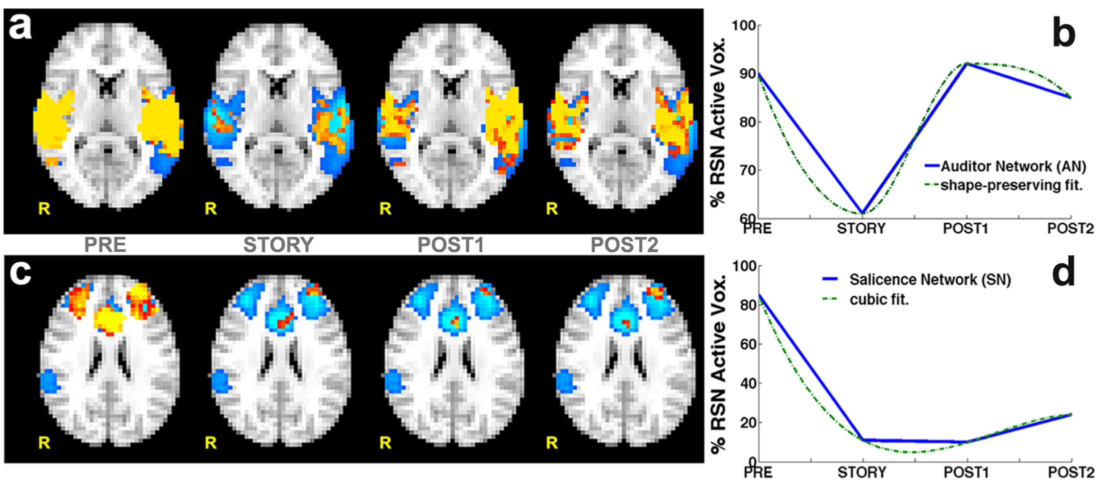

Fig.1: Distinct dynamics of alteration during the 4 consecutive rs-fMRI acquisitions (PRE, STORY, POST1 and POST2) obtained for the Auditory Network (**a**,**b**) and the Salience Network (**c**,**d**). In (**a**) and (**c**) the *blue* clusters represents the mask of the RSN, while the *red-yellow* clusters represents the voxels active within the network during the ongoing rs-fMRI acquisition (PRE, STORY, POST1 and POST2).

Conclusions: Our results confirm that during the execution of a complex cognitive task, such as listening to a story, most of the RSNs change in terms of both spatial extension and FC values; the changes are following specific temporal patterns suggesting a dynamic reorganization of their functional interaction in order to perform the listening task. Moreover, the different dynamics of alteration we observed in response to the stimulus suggest the hypothesis of a spatiotemporal hierarchy of changes in the RSNs, the levels of which depend on the typology of the activity (sensorial or cognitive) each RSN is involved in. Under this hypothesis, the RSNs such as the AN, which are related to the sensory (low) level of activity, responded to short-time-scale changes in the auditory input, while other networks such as the mPFCN and the CBLN, which are involved in cognitive (high) levels of activity, had the longest temporal receptive window, likely integrating information needed for comprehension of the full narrative. **Acknowledgements:** The MS Society in UK, NIHR UCL-UCLH BRC, MSIF (Du Pré grant), the Institute C.Mondino (Pavia, Italy) and the University of Pavia for grant funding. **References:** [1]Lerner Y et al.(2011) J Neurosci 31(8):2906-2915. [2]Berns GS et al.(2013) Brain Connect. [3]Kauppi JP et al.(2010) Front Neuroinform4:5. [4]Schlegel A et al.(2013) PNAS 110(40):16277-16282. [5]FSL, http://www.fmrib.ox.ac.uk/fsl.