

Mapping resting-state dynamics on spatio-temporal graphs: a combined functional and diffusion MRI approach

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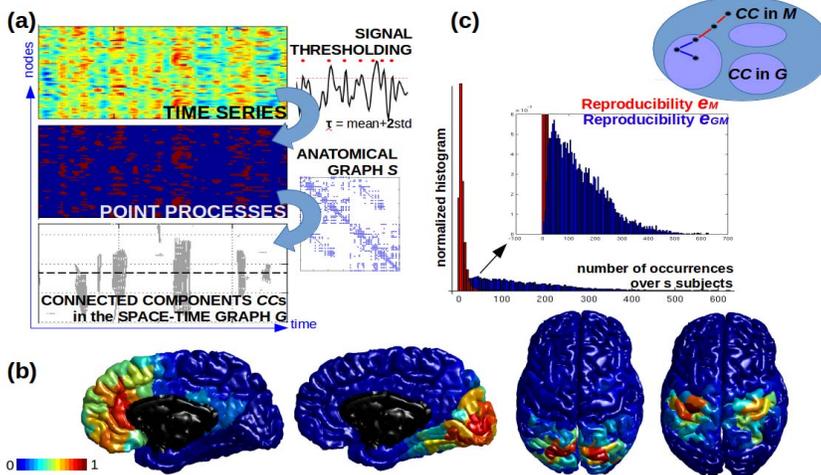
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Target audience: Researchers interested in dynamic aspects of brain resting state activity and structure-function relationship.

Purpose: Magnetic resonance imaging allows inferring overall brain structural (SC) and functional (FC) networks. These connectivity measures are plausibly inter-related¹. A growing body of recent literature suggests that a static description of functional connectivity (e.g. with simple correlation measures) might be over simplistic, and reproducible dynamic brain states have been shown with sliding window or single-volume co-activation approaches². It is nonetheless unclear which dynamic FC formalism is more appropriate and how the anatomical substrate might be considered. In the present methodology, we aim at going further in the mapping of *spatio-temporal resting state functional sub-networks* through considering nodes that are simultaneously close in space (the space of the anatomical connectivity substrate (SC)) and time (temporally co-active). Our detection of functional units relies on the representation of the structural and functional data as a *spatio-temporal graph*. First, (i) we describe the construction of such spatio-temporal graph and functional sub-networks extraction. We then (ii) identify representative spatio-temporal patterns by k-means clustering detected functional sub-networks in a suitable feature space, and (iii) compare representative patterns with intrinsic connectivity networks (ICNs) extracted from a task-based functional database³. Importantly, we (iv) investigate the impact of the anatomical information on the resulting dynamic functional sub-network by comparing the anatomically informed spatio-temporal graph with a simpler functional co-activation mapping.

Methods: $s=75$ healthy subjects (46M/29F, 29+/-9yo) underwent an MRI session composed by MPRAGE, diffusion spectrum imaging (DSI) and resting state functional MRI (rs-fMRI; TA 9min, TR 1920ms) sequences. MPRAGE volumes were segmented into $n=488$ cortical regions (nodes)⁴. Subject-wise binary structural connectivity matrices were generated combining cortical segmentation, DSI reconstruction and streamline tractography. A group-wise representative structural connectivity graph S was estimated by considering anatomical edges present in at least 50% of the subjects. Thorough rs-fMRI pre-processing included motion correction, regression of motion signals and average WM and CSF signals, linear detrending, spatial TV-denoising, temporal filtering (0.01-0.1 Hz), z-transformation. Average node-wise rs-fMRI time series were temporally concatenated across subjects (for a total of $t=20'700$ time points) and reduced to binary point processes by signal thresholding ($\tau=2\text{std}$; different τ were tested)⁵. (i) For dynamic spatio-temporal networks mapping and multi-modal integration, we propose to build a spatio-temporal graph G . The graph is composed of t temporal layers, each one composed of n nodes representing the brain functional configuration at each time point. We define two nodes to be connected in G if (1) both nodes are active (i.e. bear a supra-threshold point process value) at the same or one-step following time steps (i.e. are causal neighbors), and (2) are anatomically connected according to S (fig.a). Each connected component CC of the spatio-temporal graph defines a spatio-temporal sub-network of dynamic functional activity. (ii) Representative patterns of spatio-temporal activity were investigated by clustering the detected CC s in a suitable feature space. Each CC was reduced to a feature vector v of length n , where each element of v represents the normalized number of occurrences of the corresponding brain nodes in the CC . The feature vectors were classified into $k=12$ clusters using the k-means algorithm (different k were tested). (iii) The centroids ('median sub-networks') of the 12 clusters depict representative patterns of spatio-temporal activation, and were spatially compared with ICNs extracted from the BrainMap task-based neuroimaging database³. (iv) In order to investigate the role of the SC graph on the spatio-temporal networks structure, we compared G with a simpler co-activation mapping graph M . As G, M is composed of t layers, each one composed of n nodes. The nodes are connected if they are active at the same or one-step following time points (no anatomical information is taken into account). Reproducibility of edges e_{GM} in M common to G (i.e. with anatomical substrate), and of edges e_M in M with no anatomical substrate were evaluated by counting their relative number of occurrence across subjects (histograms in fig.c).

Results: The spatio-temporal graph G generated from the 75 subjects rs-fMRI recordings and group structural graph S included 2768 connected components, i.e. 37 CC s per subject on average, with mean duration 11 s, and 29 active brain regions on average. Figure b shows a sub-set of 4 out of 12 cluster centroids from CC s k-means. The colormap represents the normalized temporal persistence of individual nodes within individual CC s. Each one of the 12 centroids could be associated with a known functional circuit as fronto-medial, sensorimotor, fronto-parietal, visual, auditory or temporal areas, and spatially overlapped a restricted subset of the 20 ICNs of the BrainMap database³ (average best overlap between CC and single ICN $70\% \pm 9\%$) (fig.b: fronto-medial, ventral visual stream, dorsal visual stream and sensorimotor). The 12 clusters were represented in each one of the 75 subjects, suggesting CC s reproducibility across subjects. We then considered the role of the structural connectivity graph S within our framework. By construction, the edges e_{GM} in G are a subset of the edges e_M in M ; CC s of G (violet in fig.c) are a sub-set of the CC s in M (light blue in fig.c), and each CC in M contains one or more CC s identified in G (schematic representation in fig.c). e_{GM} were consistently reproducible across subjects (mean 144 ± 102), compared to poorly reproducible e_M (mean 8 ± 7) (fig.c).



Discussion: In this work we isolated in time and space reproducible spatio-temporal sub-networks of resting state activity. Differently from other approaches², our method does not require any windowing of the signals. The 12 centroids of CC s clusters are anatomically well delineated and consistently overlap known functional circuits. The edges e_{GM} of the spatio-temporal graph are reproducible across subjects and draw links between nodes that are topologically close structurally and temporally. The integration of the structural information is fundamental to separate functional co-activation sub-network which are not anatomically linked and can potentially represent different functional phenomena. Moreover, the integration of SC allows the denoising of patterns detection by excluding the poorly reproducible edges e_M (fig.c).

Conclusion: The spatio-temporal graph layout, connected components detection and clustering constitute a mathematically sound and flexible methodology for the extraction of spatio-temporal networks of dynamic functional activity. This original framework can be exploited to investigate functional patterns dynamics (CC s recurrence), patterns of signals propagation along the cortex (within-cluster dynamics), nodal dynamics, and structure-function interplay. The investigation of these dimensions is potentially useful for the uncovering of dynamic functional connectivity mechanisms, in health and diseases.

References: 1.Hermundstad AM et al., *PNAS* (2013), 110(15):6169-6174. 2.Hutchison MR et al. *Neuroimage* (2013), 80:360-378. 3.Laird AR et al. *J Cognitive Neurosci* (2011), 23(12):4022-4037. 4.Cammoun L et al. *J Neurosci Meth* (2012), 203(2):386-397. 5.Tagliazucchi E et al., *Front Physiol* (2012), 3(15).