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

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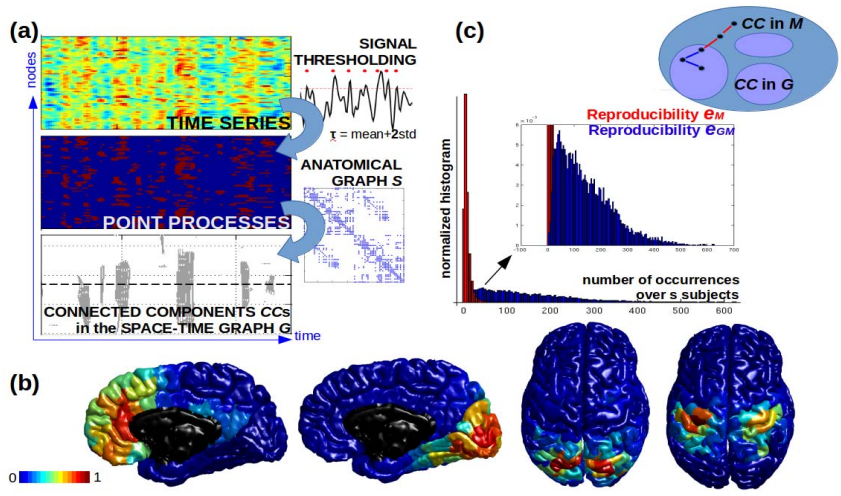
Target audience: Researchers interested in dynamic aspects of brain resting state activity and structure-function relationship.

Purpose: Magnetic resonance imaging allows inferring overall brain structural (SC) and functional (FC) networks. These connectivity measures are plausibly inter-related[1]. A growing body of recent literature suggests that a static description of functional connectivity (e.g. with simple correlation measures) might by over simplistic, and reproducible dynamic brain states have been shown with sliding window or single-volume co-activation approaches[2]. 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 database[3]. 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 (τ=2std; 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 CCs 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 database[3]. **(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 CCs 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 CCs k-means. The colormap represents the normalized temporal persistence of individual nodes within individual CCs. 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 database[3] (average best overlap between CC and single ICN 70%+/-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 CCs 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; CCs of G (violet in fig.c) are a sub-set of the CCs in M (light blue in fig.c), and each CC in M contains one or more CCs 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 approaches[2], our method does not require any windowing of the signals. The 12 centroids of CCs 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 (CCs 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.

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