NeuroImage 155 (2017) 490–502

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Transient networks of spatio-temporal connectivity map communication pathways in brain functional systems

Alessandra Griffa[a,b,*], Benjamin Ricaud[c], Kirell Benzi[c], Xavier Bresson[c], Alessandro Daducci[b], Pierre Vandergheynst[c], Jean-Philippe Thiran[a,b], Patric Hagmann[a,b]

[a] Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne (UNIL), Lausanne 1011, Switzerland
[b] Signal Processing Laboratory 5 (LTS5), École Polytechnique Fédérale de Lausanne (EPFL), Lausanne 1015, Switzerland
[c] Signal Processing Laboratory 2 (LTS2), École Polytechnique Fédérale de Lausanne (EPFL), Lausanne 1015, Switzerland

A R T I C L E I N F O

Keywords:
Resting-state fMRI
Diffusion MRI
Brain connectivity
Multilayer network
Temporal network
Brain dynamics
Point-process
Communication-through-coherence
Spatio-temporal connectome

A B S T R A C T

The study of brain dynamics enables us to characterize the time-varying functional connectivity among distinct neural groups. However, current methods suffer from the absence of structural connectivity information. We propose to integrate infra-slow neural oscillations and anatomical-connectivity maps, as derived from functional and diffusion MRI, in a multilayer-graph framework that captures transient networks of spatio-temporal connectivity. These networks group anatomically wired and temporary synchronized brain regions and encode the propagation of functional activity on the structural connectome. In a group of 71 healthy subjects, we find that these transient networks demonstrate power-law spatial and temporal size, globally organize into well-known functional systems and describe wave-like trajectories of activation across anatomically connected regions. Within the transient networks, activity propagates through polysynaptic paths that include selective ensembles of structural connections and differ from the structural shortest paths. In the light of the communication-through-coherence principle, the identified spatio-temporal networks could encode communication channels' selection and neural assemblies, which deserves further attention. This work contributes to the understanding of brain structure-function relationships by considering the time-varying nature of resting-state interactions on the axonal scaffold, and it offers a convenient framework to study large-scale communication mechanisms and functional dynamics.

Introduction

In the human brain, a functional system refers to a set of interconnected brain regions involved in the treatment of a specific task, that can be perceptual, motoric, cognitive or emotional (Laird et al., 2009). Functional systems show a large variety of brain activation patterns (Park and Friston, 2013), adapt to different conditions (Bassett et al., 2013; Braun et al., 2015; Spadone et al., 2015), interact dynamically (Cocchi et al., 2013) and demonstrate coherent (Smith et al., 2009) but non-stationary (Hutchison et al., 2013) behavior at rest. Indeed, a key aspect of the brain is its ability to adapt to multiple conditions through context-dependent interactions among neuronal units. The functional response to external and internal demands requires a flexible coupling of different brain units that are structurally connected through a complex but fixed axonal network (Bullmore and Sporns, 2012; De Pasquale et al., 2015; Deco et al., 2015). This process necessarily involves an efficient and context-dependent selection of structural communication channels among multiple possible structural paths. It has been advocated that the specific architecture of the whole-brain structural network (or connectome) is optimized for, and supports efficient communication and flexible switching among discrete functional states (Senden et al., 2014; Ponce-Alvarez et al., 2015; Hellyer et al., 2015; Goñi et al., 2013; Honey et al., 2010). However how functional interactions unfold through the structural connectome has been only partially investigated, and our understanding of large-scale brain communication processes remain limited. In this work we introduce a new methodological framework based on multilayer-graph formalism to follow the propagation of time-dependent functional patterns through viable structural pathways for communication. The multilayer graph combines structural connectivity information estimated from diffusion magnetic resonance imaging (dMRI) and functional dynamics derived from resting-state functional MRI (rs-fMRI).

The brain functional connectivity, i.e. the statistical dependency between the oscillations of brain units, has been widely investigated by

* Correspondence to: Service de Radiodiagnostic et Radiologie Interventionnelle - BH Bugnon 46, CH-1011 Lausanne, Switzerland.
E-mail address: alessandra.griffa@epfl.ch (A. Griffa).

http://dx.doi.org/10.1016/j.neuroimage.2017.04.015
Received 13 February 2017; Accepted 6 April 2017
Available online 12 April 2017

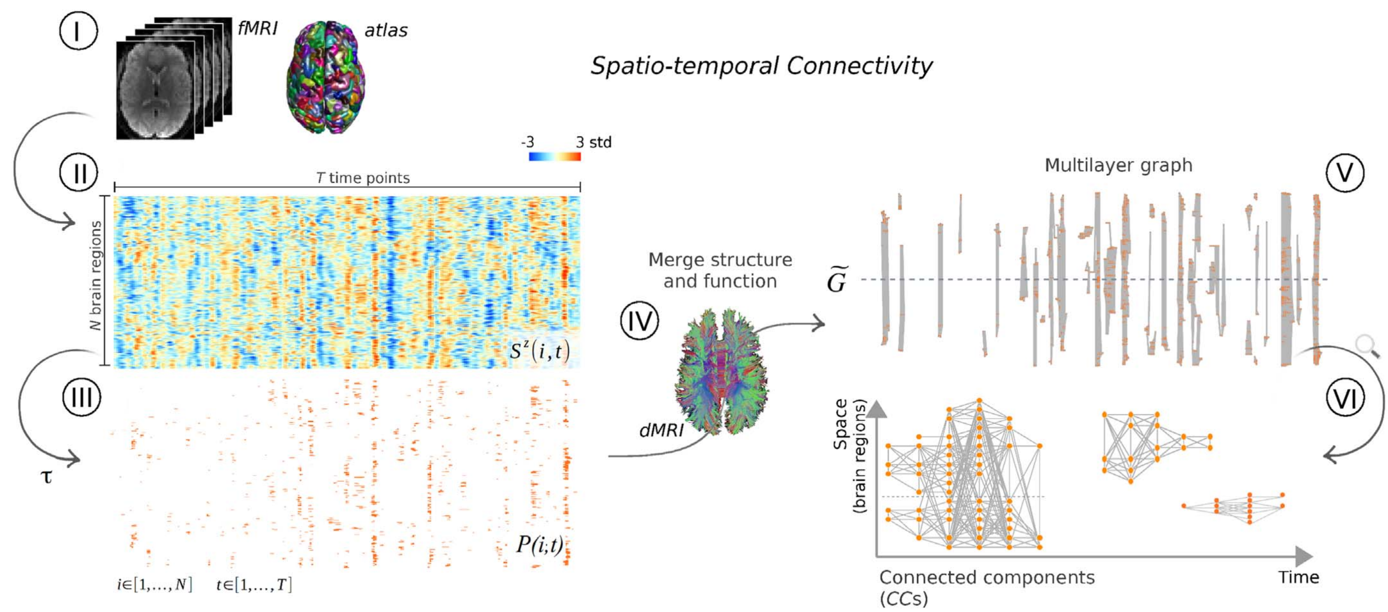

Fig. 1. Construction of a spatio-temporal connectome. (I) The cortical brain volume is segmented into N regions of interest according to a given atlas. Each brain region is associated with an average functional time series of length T time points derived from fMRI data. (II) Regional fMRI time series are z-scored and represented in the figure as a matrix $S^z(i,\ t)$ of size NxT ($\in[1,\ldots,N]$, $t\in[1,\ldots,T]$). (III) The z-scored fMRI time series are reduced to binary point-processes by applying a threshold τ. The elements of the resulting matrix *P(i,t)* represent the active or quiescent status of the brain region i at time point t. A multilayer graph $\widetilde{G}$ is then constructed by merging the point-processes and the anatomical connectivity information derived from dMRI tractography (IV). (V) Each node of $\widetilde{G}$ represents a specific brain region at a given time point; two nodes are connected in $\widetilde{G}$ if (i) they are co-active at the same or neighboring time points AND (ii) they are linked by a white matter tract. In panel (V) the nodes of $\widetilde{G}$ are pictured in orange and the edges in grey; disconnected nodes and edge directionality are not shown. The weakly connected components (*CCs*) of the multilayer graph extend spatially (across different brain regions) and temporally (over multiple time points) and represent transient networks of spatio-temporal connectivity. Panel (VI) show a zoom of some representative *CCs* of $\widetilde{G}$.

means of rs-fMRI studies that highlight the modular structure of the brain architecture and decompose it into a set of reproducible resting state networks (RSNs) (Damoiseaux et al., 2006; Fox et al., 2005; Yeo et al., 2011). Although traditional approaches implicitly assume that the resting-state activity is stationary over an fMRI recording, an increasing effort has been devoted to the characterization of resting-state dynamics (Hutchison et al., 2013; Calhoun et al., 2014). In this regards two main methodological directions can be identified: temporal sliding window approaches, or time-resolved investigation of short functional events through point-process analysis (i.e., thresholding of fMRI signals) or regularized deconvolution methods (Hutchison et al., 2013; Preti et al., 2017). While sliding-window approaches are a natural extension of more traditional functional connectivity analyses, they posit methodological challenges in terms of balance between window selection and temporal resolution of observed dynamics (Leonardi and Van De Ville, 2015; Zalesky and Breakspear, 2015; Telesford et al., 2016). On the other side, methods detecting short functional events require a certain degree of parameter tuning and relies on the conceptualization of resting-state dynamics as sparse sequence of key functional activations (Petridou et al., 2013; Tagliazucchi et al., 2016). Both approaches have delivered qualitatively comparable findings (Preti et al., 2017), showing that at short temporal scales functional patterns can significantly diverge from classical RSNs (Allan et al., 2015; Hutchison et al., 2013). During a resting-state period, the brain might explores a space of states (functional configurations persisting for a transient but sufficiently long periods of time (Kitzbichler et al., 2009; Calhoun et al., 2014)) with cortical areas engaging and disengaging in variable functional subnetworks (Liu and Duyn, 2013; Zalesky et al., 2014; Betzel et al., 2016). These dynamics give rise to complex (and possibly temporally and spatially overlapping) patterns of interaction (Karahanoğlu and Van De Ville, 2015), which have been related to behavioral variables (Chang et al., 2016) and cognitive processes (Bassett et al., 2011; Chen et al., 2015).

Conceptually, the transient functional couplings observed in resting-state dynamics can be associated with time-dependent communication processes. At the mesoscopic scale it has been proposed that transient patterns of temporal coherence, among the electrical oscillations of structurally wired neural groups, provide temporal windows for effective communication and implement mechanisms of selective information processing (Fries, 2005). This communication-through-coherence (CTC) mechanism pertains to neural coupling in the gamma and beta frequency bands (Fries, 2005, 2015), but might be reflected at the coarser spatial and temporal scales accessible with magnetic resonance imaging (MRI) (Deco and Kringelbach, 2016). Crucially, the CTC hypothesis explicitly relates the transient functional coupling between wired nervous regions with their inter-communication and efficient information flow.

In the present study we develop a framework that captures resting-state interactions among anatomically connected brain regions in the form of transient network of spatio-temporal connectivity. Specifically, we define a spatio-temporal connectome as a multilayer graph (Kivelä et al., 2014) that specifies node proximity both in the temporal and in the spatial domains. On one hand, proximity in time is expressed by time-resolved co-activation of brain regions at neighboring time points, as detected through a point-process analysis of rs-fMRI time series. On the other hand, anatomical proximity is expressed by brain regions' adjacency in the structural connectome, as estimated from dMRI tractography. The weakly connected components of the resulting multilayer graph conveniently represent time-dependent events of synchronous activation among anatomically wired regions, a possible expression of brain communication processes. After the methodological description of the spatio-temporal connectome framework, we explore its feasibility through synthetic data and we introduce different measures for the characterization of the connected components of the multilayer graph. These connected components reveal time-varying pathways of activity propagation and, by being clustered, identify reproducible patterns of spatio-temporal connectivity across fMRI recordings and across multiple subjects. We report on the organization of these patterns, and we investigate their internal dynamics. We discuss the relevance of considering functional dynamics in combination with the underlying structural wiring to study large-scale brain communication mechanisms and activity propagation routing.