NeuroImage 160 (2017) 84–96

Contents lists available at ScienceDirect

NeuroImage

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

Functional connectivity dynamically evolves on multiple time-scales over a static structural connectome: Models and mechanisms

Joana Cabral[a,b,*], Morten L. Kringelbach[a,b], Gustavo Deco[c,d]

[a] Department of Psychiatry, University of Oxford, UK
[b] Center for Music in the Brain, Aarhus University, Denmark
[c] Center of Brain and Cognition, Universitat Pompeu Fabra, Barcelona, Spain
[d] ICREA, Institució Catalana de Recerca i Estudis Avancats (ICREA), Spain

ARTICLE INFO

Keywords:
Resting-state
Network model
Dynamic FC
Envelope FC

ABSTRACT

Over the last decade, we have observed a revolution in brain structural and functional *Connectomics*. On one hand, we have an ever-more detailed characterization of the brain's white matter structural connectome. On the other, we have a repertoire of consistent functional networks that form and dissipate over time during rest. Despite the evident spatial similarities between structural and functional connectivity, understanding how different time-evolving functional networks spontaneously emerge from a single structural network requires analyzing the problem from the perspective of complex network dynamics and dynamical system's theory. In that direction, bottom-up computational models are useful tools to test theoretical scenarios and depict the mechanisms at the genesis of resting-state activity.

Here, we provide an overview of the different mechanistic scenarios proposed over the last decade via computational models. Importantly, we highlight the need of incorporating additional model constraints considering the properties observed at finer temporal scales with MEG and the dynamical properties of FC in order to refresh the list of candidate scenarios.

Introduction

Within the rapidly growing field of brain *Connectomics*, two main modes of connectivity emerge: Structural and Functional (Biswal et al., 1995; Sporns et al., 2005; Hagmann et al., 2008; Sporns, 2011). While the first refers to the anatomical white-matter fibers connecting brain areas, which remain relatively constant over short time scales, the latter refers to any measure of co-variation between brain signals at different locations and depends strongly on the paradigm and the time-window considered (Fig. 1).

When computed over sufficiently long sessions at rest, the whole-brain map of functional connections, generally termed *Functional Connectome*, reveals some similarities with the *Structural Connectome* (Greicius et al., 2009; van den Heuvel et al., 2009; Biswal et al., 2010; Hermundstad et al., 2013). However, this relationship is not trivial and has been the subject of investigation of several theoretical and computational research groups over the last decade (Honey et al., 2007; Ghosh et al., 2008b; Izhikevich and Edelman, 2008; Deco et al., 2009; Honey et al., 2009; Cabral et al., 2011; Deco and Jirsa, 2012; Deco et al., 2013; Cabral et al., 2014a; Messe et al., 2015; Ponce-Alvarez et al., 2015; Atasoy et al., 2016; Robinson et al., 2016; Spiegler et al., 2016). Following different reduction lines and alternative mechanistic approaches (which we will review below), these works have demonstrated via whole-brain network models how the neuroanatomical network structure can shape spontaneous brain activity on very slow time-scales, giving rise to consistent patterns of Functional Connectivity (FC).

Given the wide variety of candidate scenarios to explain the source of resting-state FC patterns, it becomes necessary to establish further model constraints in order to refresh the list of candidate scenarios and foster our understanding of the network mechanisms underlying resting-state activity. Novel insights into resting-state FC have been revealed by MEG studies (de Pasquale et al., 2010; Brookes et al., 2011b; Hipp et al., 2012; Hipp and Siegel, 2015) and by investigations on the temporal dynamics of FC (Chang and Glover, 2010; Handwerker et al., 2012; Smith et al., 2012; Hutchison et al., 2013a; Allen et al., 2014; Zalesky et al., 2014).

In the present work, we provide an overview of the latest findings in the literature of resting-state FC, focusing on the properties observed at finer temporal scales with MEG and the dynamical properties of FC. We review existing whole-brain generative models of resting-state activity, with a special focus on their mechanistic scenarios. Finally,

* Corresponding author at: Department of Psychiatry, University of Oxford, UK.

http://dx.doi.org/10.1016/j.neuroimage.2017.03.045
Accepted 20 March 2017
Available online 23 March 2017

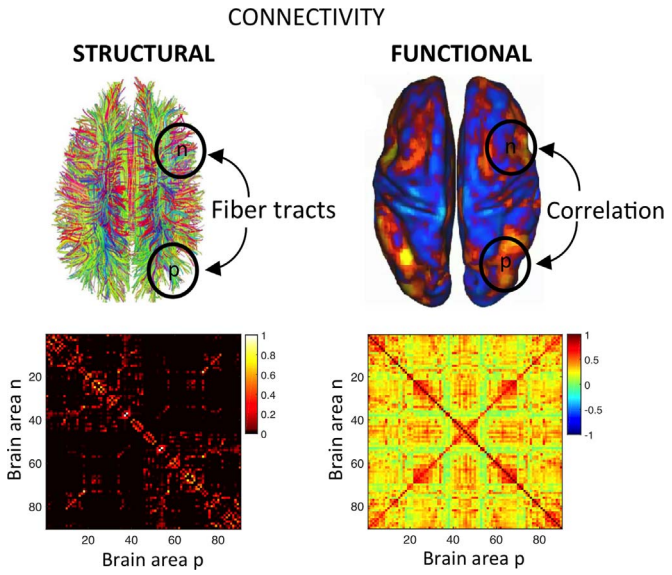

Fig. 1. Structural vs functional connectivity. (Left) Advanced tractography algorithms allow reconstructing the white matter fiber tracts from Diffusion-MRI. The structural connectivity matrix SC (n,p) is estimated in proportion to the number of fiber tracts detected between any two brain areas n and p. (Right) On the other hand, the functional connectivity matrix FC (n,p) is computed as the correlation between the brain activity (e.g. BOLD signal) estimated in areas n and p over the whole recording time. Here, the areas refer to 90 non-cerebellar brain areas from the AAL template.

we compare the different candidate models and comment on their capacity to survive the constraints imposed by novel empirical evidence.

Static structural connectivity

The development of advanced tractography algorithms applied to Diffusion-MRI has allowed detecting – non-invasively and at the whole-brain level – the white matter fiber tracts connecting brain areas (Sporns et al., 2005; Hagmann et al., 2008). This permits the construction of large-scale networks where nodes represent brain areas and links reflect the anatomical connectivity between them. Considering macro-scale brain parcellations in the order of 100 regions, the Structural Connectome of healthy adults remains relatively stable across sessions when compared with the rapid changes occurring at the dynamical level (Sporns, 2011). Any srtuctural alterations occurring at this macro-scale are typically very slow, either when associated to the brain's natural development and aging, or to disease (Bartzokis et al., 2003; Hagmann et al., 2010; Takeuchi et al., 2010). Note however, that the entire map of neural connections ambitioned by the Human Connectome Project (www.humanconnectomeproject.org) may reveal higher individual variability and changes on shorter time-scales. Yet, it remains acceptable to consider that the Structural Connectivity (SC) is static when compared to the fast changes observed in FC.

Functional connectivity

Functional Connectivity is defined as the temporal dependence of neuronal activity patterns of anatomically separated brain regions typically measured as the co-variation between brain signals originating at different locations (Aertsen et al., 1989; Friston et al., 1993; van den Heuvel and Hulshoff Pol, 2010). The term *Functional Connectome* is generally used to refer to the whole map of functional connections across the whole brain (Biswal et al., 2010). Since meaningful large-scale functional networks have been detected from correlations between slow (< 0.1 Hz) BOLD signal fluctuations at rest (Biswal et al., 1995; Lowe et al., 1998; Damoiseaux et al., 2006), resting-state fMRI has been the leading technique to measure brain-wide FC (Biswal et al., 2010; van den Heuvel and Hulshoff Pol, 2010). Assuming a stationary perspective, correlations are commonly measured over the whole recording time, resulting in a single, temporally invariant Functional Connectome, which can be expressed in mathematical terms as a grand-average FC matrix, where each entry *FC(n,p)* refers to the correlation between the signals averaged over all voxels in brain areas *n* and *p*. This approach allows for a direct comparison with the Structural Connectome defined over the same parcellation scheme (van den Heuvel et al., 2009) and has been particularly useful for the optimization and validation of resting-state models through the comparison with the simulated FC matrix (Honey et al., 2009; Cabral et al., 2011; Deco and Jirsa, 2012; Deco et al., 2013; Messe et al., 2015; Ponce-Alvarez et al., 2015).

Frequency-specific Envelope FC

Although BOLD signal correlations have proved meaningful in the study of resting-state FC (Biswal et al., 2010; van den Heuvel and Hulshoff Pol, 2010), an important shortcoming of fMRI approaches is that fluctuations occurring on the faster timescales of neurophysiological processes (~2–100 Hz) are not captured (Engel et al., 2013). For this reason, the fast local dynamics has been left largely unconstrained in models of resting-state activity (Ghosh et al., 2008b; Honey et al., 2009; Deco et al., 2011, 2013; Cabral et al., 2014a). Exploring the neurophysiological counterpart of BOLD signal activations, experimental studies have shown a relationship with local increases in the power of neural activity, not only in the gamma-frequency band (Logothetis et al., 2001, 2003; Nir et al., 2007), but also at lower frequencies (He et al., 2008; Scholvinck et al., 2010; Magri et al., 2012; Tagliazucchi et al., 2012b; Keller et al., 2013). However, for accurately measuring resting-state FC non-invasively and at the whole-brain level using MEG, the correlation patterns resulting from volume conduction need to be suppressed before analyzing functional connectivity. Such methods have only recently become available bringing insightful information for the investigation of resting-state FC occurring at faster time-scales (Brookes et al., 2011a, 2011b; Hipp et al., 2012; Engel et al., 2013; Marzetti et al., 2013; Hipp and Siegel, 2015). These studies point in the direction that the BOLD signal fluctuations observed in the brain at rest are associated to aperiodic fluctuations in the power of neural oscillations occurring in a particular frequency range (see Fig. 2). Since the information is assumed to be *carried* in the power (or squared amplitude) of the oscillations in a given frequency band, these oscillations are commonly termed *carrier* oscillations.

According to Brookes et al. (2011b) and Hipp et al. (2012), the best agreement between MEG-based and fMRI-based FC is obtained for carrier oscillations in the alpha and beta frequency ranges (8–32 Hz). However, a wider range of frequencies between 2 and 128 Hz has been found to play a role in shaping the large-scale dynamical interactions yielding functional networks (Hipp and Siegel, 2015). Notably, different fMRI-based functional connections were found to be associated to different carrier frequencies, showing that BOLD correlation reflects different types of neuronal interactions across the brain (Hipp and Siegel, 2015).

In order to consider the FC occurring at different carrier frequencies, one approach is to filter the data into a range of frequency bands and obtain the corresponding amplitude envelopes using the Hilbert transform. The Hilbert transform represents a narrowband signal, $s(t)$, in the time domain as a rotating vector with an instantaneous phase, $\varphi(t)$, and an instantaneous amplitude, $A(t)$ such that $s(t) = A(t)\cos(\varphi(t))$. Given that the bands are sufficiently narrow to allow for a correct estimation of the Hilbert transform, the envelope FC can be easily computed as the correlation matrix of amplitude signals for each frequency band (Fig. 3). This results in a series of frequency-specific Envelope FC matrices that can be used as a heuristic measure to fit resting-state models (Cabral et al., 2014b; Deco et al., 2017).

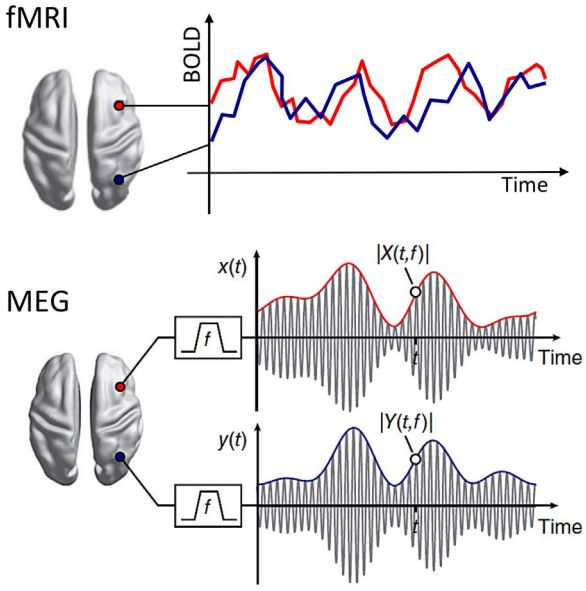

Fig. 2. Functional Connectivity assessed with fMRI or MEG. (Top) fMRI-based functional connectivity is assessed as the correlation between the BOLD signals recorded at different locations. (Bottom) Resting-state functional connectivity in MEG is assessed by first band-pass filtering the MEG signal (before or after the source estimation), extracting the amplitude envelope (red and blue lines) of the underlying carrier oscillation (black) and subsequently computing the correlation between envelopes. This strategy results in a set of frequency-specific FC. Bottom figure adapted from Hipp et al. (2012).

FC dynamics

In recent years, several works have shown that the Functional Connectome is not stationary, but instead evolves over time (Chang and Glover, 2010; Handwerker et al., 2012; Jones et al., 2012; Hutchison et al., 2013a, 2013b; Allen et al., 2014; Calhoun et al., 2014; Leonardi et al., 2014; Zalesky et al., 2014; Hansen et al., 2015). This has brought a new perspective to study resting-state activity by considering the temporal dimension of FC. In that direction, Calhoun et al. (2014) proposed the term *Chronnectome* to describe the time-varying properties of the Functional Connectome. Interestingly, the expanding idea is that the FC evolves as a multi-stable process passing through multiple and reoccurring discrete FC states, rather than varying in a more continuous sense (Hutchison et al., 2013a; Allen et al., 2014; Hansen et al., 2015; Preti et al., 2016). While different methodological approaches have been proposed to analyze the FC in the temporal domain (see Preti et al. (2016) for a comprehensive review) and to test for its statistical significance (Hutchison et al., 2013b; Hindriks et al., 2015a; Leonardi and Van De Ville, 2015; Zalesky and Breakspear, 2015), the best methodology to explore dynamic changes in FC is still to be decided. In the following, we briefly describe some of the methods to assess dynamic FC, which we find useful to apply in the analysis of whole-brain resting-state models.

Assessing dynamic FC. The most common and straightforward approach to investigate the temporal evolution of FC is the *Sliding-Window Correlation* (SWC) (Sakoglu et al., 2010; Handwerker et al., 2012; Jones et al., 2012; Hutchison et al., 2013b; Allen et al., 2014; Hansen et al., 2015). This is achieved by calculating the correlation matrix, FC(t), within a given time-window (t-x:t+x), and successively shifting this window in time resulting in a time-varying FC_{NxNxT} matrix (where N is the number of brain areas and T the number of time windows considered) (see Fig. 4 for an illustration). However, the fundamental nature of the SWC technique implies the choice of a fixed window length, which limits the analysis to the frequency range below the window period, so the ideal window length to use remains under debate (Sakoglu et al., 2010; Hutchison et al., 2013a; Leonardi and Van De Ville, 2015; Zalesky and Breakspear, 2015; Laumann et al., 2016; Preti et al., 2016).

Following the limitations of sliding-window analysis, a number of methods have been proposed to estimate the FC(t) at the instantaneous level. For instance, *Coherence Connectivity* (CC) consists in computing the phase coherence between time series at each recording frame (Glerean et al., 2012; Ponce-Alvarez et al., 2015; Deco and Kringelbach, 2016). In brief, the instantaneous BOLD phase of area n at time t, $\theta_n(t)$, is estimated using the Hilbert transform. Given the phase, the angle between two BOLD signals is given by their absolute phase difference: $\Theta_{np}(t)=|\theta_n(t) - \theta_p(t)|$. Then, the $CC(t)$ between a pair of brain areas n and p is calculated as:

$$CC_{np}(t) = \cos(\Theta_{np}(t)), \quad n, p \in N=1, \ldots, 90,$$

where values range between −1 (areas in anti-phase) and 1 (in-phase).

Another simple and quasi-instantaneous measure of coupling is the *Multiplication of Temporal Derivatives* (MTD) (Shine et al., 2015). The MTD measure consists in first calculating the temporal derivative (TD_n) of each time series (s_n) of length t by performing a first-order differencing $TD_n=ds_n/dt$ (i.e. subtracting the value of $s(t-1)$ from the value of $s(t)$). For each pair of areas n and p, the MTD at time t is given by:

$$MTD_{np}(t)=\frac{TD_n(t)\times TD_p(t)}{SD_n \times SD_p}$$

where SD_n is the standard deviation of TD_n. Positive MTD scores

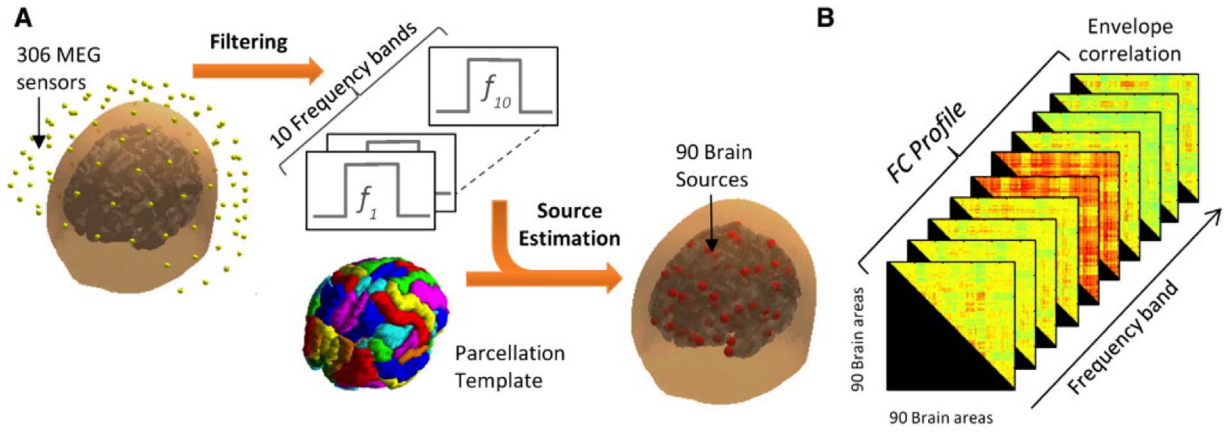

Fig. 3. Frequency-specific envelope FC from MEG data. (A) The MEG signals are filtered into different frequency bands and projected into a number of source locations using a beamformer technique. (B) For each frequency band, the amplitude envelopes are estimated for each brain area and the correlation matrix between envelopes is computed, resulting in a set of frequency-specific envelope FC matrices (or FC profile). Adapted from Cabral et al. (2014b).

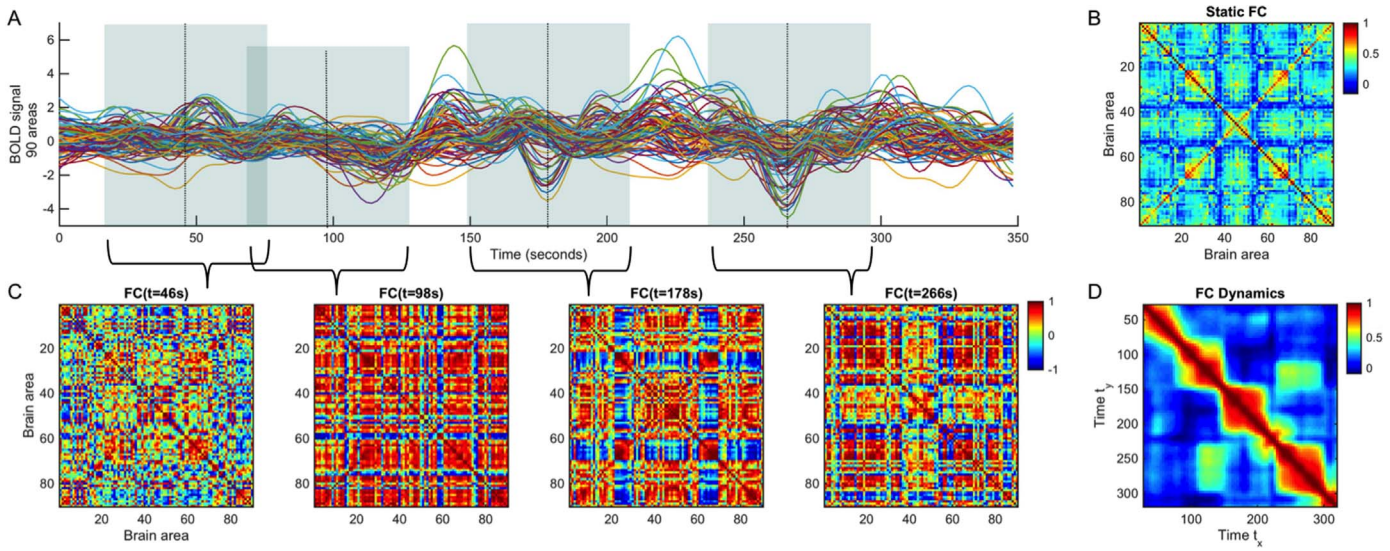

Fig. 4. FC dynamics based on sliding-window correlation. (A) BOLD signal at 90 locations from one healthy adult at rest (350 seconds, TR=2 s). (B) The static FC is computed as the correlation matrix (90×90) of BOLD time courses over the whole recording time. (C) Example of correlation matrices FC(t) obtained for sliding-windows of 60 seconds centered at different time points *t*. (D) The time-versus-time matrix of FC Dynamics, FCD(t_x,t_y) is obtained by correlating any FC(t_x) centered at time t_x with any FC(t_y) centered at time t_y.

reflect 'coupling' in the same direction of signal change across nodes, whereas negative scores reflect 'anti-coupling' (that is, signal in one node increasing while the other is decreasing).

Although instantaneous measures are more susceptible to high-frequency noise fluctuations, they can be smoothed (using e.g. a simple moving-average) without the methodological constraints imposed by the correlation measure.

Beyond the methods described above, other approaches worth noting include time-frequency analysis (Chang and Glover, 2010; Yaesoubi et al., 2015), phase-dependent eigen connectivities (Preti et al., 2016) or point process analysis (Tagliazucchi et al., 2012a; Liu and Duyn, 2013).

FCD matrix. To analyze the time-evolving FC(t) matrices – defined either using SWC, CC, MTD or other – it is useful to compute a time-versus-time matrix representing the functional connectivity dynamics (*FCD*), where each entry *FCD(t_1, t_2)* is defined by a measure of resemblance between FC(t_1) and FC(t_2) (see Fig. 4D). Since the FC(t) matrices are symmetric across the diagonal, resemblance is typically estimated between vectors containing all values above the diagonal (or below) of each FC(t) matrix. This resemblance can be quantified using Pearson's correlation or cosine similarity (i.e. normalized inner product) between the FC(t) vectors at times t_1 and t_2. Epochs of stable FC patterns are reflected as square blocks around the FCD diagonal and reoccurrences of the same pattern appear as square blocks distant from the diagonal. Hence, the typical FCD matrix during the resting-state has a checkerboard appearance (Hutchison et al., 2013a; Hansen et al., 2015).

FC states. Although the FCD matrix contains rich information about the time-dependencies of the FC(t), in order to define a discrete number of FC states that reoccur over time and across subjects, it is necessary to the apply a clustering algorithm. The different FC states may then be characterized in different aspects, namely their spatial configuration, duration (or dwell time/lifetime), probability of occurrence (or fractional occupancy) or switching trajectories. Following the work of Allen et al. (2014) and Hansen et al. (2015) applied unsupervised k-means clustering to all FC(t) across all subjects to characterize the switching dynamics of FC, which revealed a number of FC patterns that temporarily emerge -and often reoccur- within the same session. Using another approach, Baker et al. (2014) applied Hidden Markov Models (HMM) to the amplitude envelopes of MEG signals and identified fast transient FC states in spontaneous human brain activity with spatial topographies similar to those of well-known resting state networks. Notably, the FC states were found to last very shortly (100-200ms), suggesting that the resting brain is constantly changing between different patterns of activity much more rapidly than previously thought (Vidaurre et al., 2016).

Models of resting-state activity

Given the evident network dynamics emerging spontaneously at rest and its spatial similarity with the underlying structural connectivity, whole-brain network models are a useful tool to investigate the biophysical mechanisms underlying resting-state activity. By considering the dynamics emerging spontaneously from the interplay between brain areas when these are embedded in the neuroanatomical network, one can analyze the observed phenomena in the light of empirical data and formulate scenarios for the physiological origin of resting-state activity. This is achieved by considering a whole-brain network model where nodes refer to brain areas and links refer to the connections between them (Fig. 5). The activity of each brain area is represented by one or more mathematical expressions representing the spontaneous behavior of isolated brain areas with an additive term representing the input received by anatomically connected areas (the main equations of the models discussed herein are reported in the *Supplementary Information*).

Generative mechanistic scenarios

Following different lines of thought, a variety of scenarios have been proposed for the genesis of resting-state activity, including multi-stability, supercritical bifurcations, chimera synchronization, self-organizing patterns, connectome-specific harmonics or simply correlated noise-induced deviations from the equilibrium (studies proposing these scenarios are reviewed in the following and summarized in Table 1). To test and validate these scenarios, theoreticians make use of computational models where similar behaviors can be obtained from very reduced network models. Depending on the reduction line, the node dynamics can be represented with different degree of biophysical realism and complexity, ranging from detailed models of coupled spiking neurons with specific neurotransmitters, to neural-field or neural-mass models or even to phenomenological mesoscopic models.

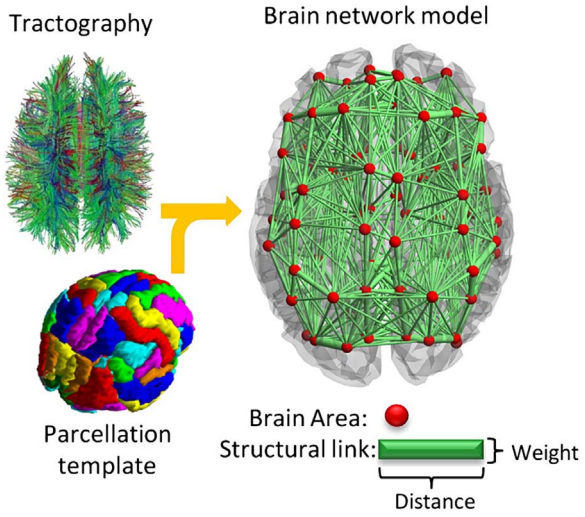

Fig. 5. In whole-brain network models, nodes refer to brain areas defined according to a given parcellation scheme, and links refer to the connections between them, typically obtained from DTI/DSI –based tractography. Adapted from Cabral et al. (2014b).

Importantly, different generative models may be used to test the same mechanistic scenario and vice-versa. As such, beyond their mathematical definitions (which can be found in the *Supplementary Information*), we focus here on the mechanistic scenarios proposed by the different studies for the genesis of resting-state activity. In Table 1, we made an attempt to summarize and compare the different models focusing on their biophysical and dynamical properties. However, it is important to note that other relevant models (including variations of the ones considered herein) have been used to explain different phenomenological aspects of resting-state activity not considered in the current review (Petkoski and Jirsa; Freyer et al., 2011; Deco et al., 2012; Senden et al., 2012; Nakagawa et al., 2014; Hindriks et al., 2015b; Vasa et al., 2015; Vuksanovic and Hovel, 2015; Robinson et al., 2016).

At the brink of multi-stability. Starting with the most detailed generative model, Deco and Jirsa (2012) opted to represent each brain area by a network of interconnected excitatory and inhibitory spiking neurons (Brunel and Wang, 2001; Izhikevich and Edelman, 2008). When uncoupled, the neural pools are characterized by a stable pattern of low firing activity in all cortical areas. As the coupling between areas increases, the collective behavior of spiking neurons can settle into new patterns of high firing activity (the so-called *ghost attractors*), while the state of low firing activity is still stable. In this critical range of coupling, the system is at the brink of multi-stability (where different stable states co-exist) and small noise perturbations can induce transitions between states, leading to slow fluctuations that modulate the hemodynamic signal, reproducing the empirical FC obtained from fMRI.

With a similar bifurcation diagram, the *Dynamic Mean Field Model* (DMF) (Deco and Jirsa, 2012; Deco et al., 2013; Hansen et al., 2015) reduces the complexity of the spiking neurons model to a small set of differential equations representing the ensemble dynamics in each cortical area, leading to similar results. In Hansen et al. (2015), the dynamic mean-field model was modified to adopt enhanced non-linearity in order to obtain a better fit with the FCD matrix.

In brief, these works propose a common scenario in which the brain is a multi-stable dynamical system and the phenomena observed at rest are the result of noise-driven explorations of its dynamical repertoire.

Table 1
Comparison between different models of whole-bran resting-state activity.

		Biophysical properties	Dynamical regime			Model Validation			Literature
			Uncoupled units	Coupled units	Origin of slow fluctuations	Spatial	Temporal	Spectral	
						Static FC	FC Dynamics	Envelope FC	
Neural models	Spiking Neurons	Integrate-and-fire excitatory and Inhibitory neurons (AMPA, NMDA, GABA receptors)	Fixed point	Multi-stability between Fixed Points	At the brink of Multi-stability	Yes	Yes	?	(Izhikevich and Edelman, 2008, Deco and Jirsa, 2012)
	Conductance-based	Membrane potential of E and I pools controlled by ionic conductance and NMDA receptors	Chaotic with oscillations	Chaotic (range of frequencies)	Intermittent self-organization from chaos	Yes	Yes	Yes	(Honey et al., 2007, Honey et al., 2009, Gollo and Breakspear, 2014, Zalesky et al., 2014, Gollo et al., 2015)
Neural-mass reductions	Neural Field	Coupled excitatory and Inhibitory pools of neurons	Limit-Cycle	Limit-Cycle	Connectome-specific Harmonics	Yes	?	?	(Atasoy et al., 2016)
	FitzHugh-Nagumo	Membrane potential of neuronal pool with recovery time-constants	Fixed Point	Fixed point or Limit-cycle (10Hz)	Vicinity of a Supercritical Bifurcation	Yes	?	Yes	(Ghosh et al., 2008a, b, Stefanescu and Jirsa, 2008, Messe et al., 2014)
	Wilson-Cowan	Coupled excitatory and Inhibitory pools of neurons	Limit-Cycle (40Hz)	Limit-Cycle (40Hz)	Meta-stable Chimera Synchronization	Yes	?	?	(Deco et al., 2009, Messe et al., 2015)
	Kuramoto γ Oscillators	Oscillator representing synchronous neuronal firing	Limit-Cycle (40, 60Hz)	Intrinsic Limit-cycle (γ) or Collective Limit-cycle (α,β)	Meta-stable Chimera Synchronization	Yes	Yes	Yes	(Cabral et al., 2011, Wildie and Shanahan, 2012, Cabral et al., 2014)
	Hopf Model With Neural Oscillations	Bifurcation representing Synchronous vs Asynchronous neuronal firing	Fixed point	Fixed point or Limit-Cycle (2-30Hz)	Vicinity of Supercritical bifurcation & Meta-stable Synchronization	Yes	Yes	Yes	(Deco et al., 2017)
	Dynamic Mean Field	Synaptic input currents and firing rates	Fixed point	Multi-stability between Fixed Points	At the brink of Multi-stability	Yes	Yes	No	(Deco and Jirsa, 2012, Deco et al., 2013, Hansen et al., 2015)
	Kuramoto Ultra-slow Oscillators	Oscillator representing BOLD fluctuations	Limit-Cycle (0.1Hz)	Limit-Cycle (0.05Hz)	Meta-stable Chimera Synchronization	Yes	Yes	No	(Ponce-Alvarez et al., 2015)
	Hopf Model With Ultra-Slow Oscillations	Slow-oscillations representing BOLD fluctuations	Fixed point	Fixed point or Limit Cycle (0.04-0.07Hz)	Vicinity of a supercritical Bifurcation	Yes	Yes	No	(Deco et al., 2016)
Mesoscopic Models	Linear Stochastic Model	Noise representing firing rate deviations	Fixed Point	Fixed Point	Noise deviations around equilibrium	Yes	No	No	(Fernandez Galan, 2008, Cabral et al., 2012, Goni et al., 2014, Hansen et al., 2015)
	Spatial Autoregression	Structured Noise	-	-	-	Yes	No	No	(Messe et al., 2014, Messe et al., 2015)

So far, the faster timescales of neurophysiological rhythms have not been carefully explored in this scenario.

Intermittent self-organization from chaos. Considering the biophysical properties of the neuronal membrane, the *conductance-based model* defines the membrane potential of excitatory and inhibitory populations of neurons as a function of ionic conductance through voltage-gated and ligand-gated ion channels as well as passive conductance of leaky ions (Hodgkin and Huxley, 1952; Breakspear et al., 2003; Honey et al., 2007; Honey et al., 2009). Simulated activity was described as chaotic displaying spontaneous self-organizing patterns (Honey et al., 2007, 2009). Intermittent synchronization and desynchronization between brain regions was reported at 10 Hz, with locked epochs ranging between 50 and 300 m s. When computing inter-area correlations between the simulated hemodynamic responses (< 0.1 Hz), significant agreement with fMRI-based FC was found (cc=0.7).

Investigating the temporal dynamics of FC, Zalesky et al. (2014) used the conductance-based model on macaque connectivity and showed the emergence of coordinated fluctuations in FC akin to those seen in human data from the Human Connectome Project. Addressing the faster timescales of neurophysiological rhythms, Gollo and Breakspear (2014) and Gollo et al. (2014) found that, for intermediate coupling strengths where resonance and frustration coexist, different meta-stable synchronization patterns arise depending on the time delay between brain areas and the network size.

Taken together, these studies make proof of the powerful dynamical complexity of the conductance-based model, which remains a likely scenario to explain resting-state activity.

In the vicinity of a supercritical bifurcation. Adopting a perspective from dynamical systems' theory Ghosh et al. (2008b) proposed a reduced model where each brain area, when uncoupled, is a dynamical system operating in an equilibrium state (fixed point). On receiving sufficient input, the neural population is perturbed from its equilibrium state and starts oscillating (engaging in a limit-cycle). This type of behavior can be represented mathematically by a supercritical bifurcation, which represents the transition between a fixed point and a limit-cycle. The system returns to the equilibrium in a characteristic transient manner that depends on the dynamic repertoire of the system, which is shaped by the spatial and temporal properties of the SC (links and transmission delays). Given the frequency of oscillations observed with EEG (most power at 10 Hz during rest) and the large-scale structure of resting-state networks (up to 20 cm), the authors emphasize the importance of considering the time delays between brain areas induced by a finite propagation speed (Ghosh et al., 2008a). The authors test this scenario with different neural-mass models with a supercritical bifurcation, namely Hopf oscillators, Wilson-Cowan systems, and *FitzHugh-Nagumo* systems, all providing similar results. In brief, in this approach each population is characterized by a degree of excitability, in which the increase of excitation parameterizes the onset of oscillations emerging from a quiescent state. When the populations are embedded in a network and operating near the critical boundary, oscillations emerge and dissipate, leading to slow envelope fluctuations shaped by the space-time structure of the couplings.

This dynamical scenario where brain areas operate near the critical border of a supercritical bifurcation was recently re-considered in the works by Deco et al. (2016), Deco et al. (2017) and Spiegler et al. (2016).

Focusing solely on the slow mesoscopic behavior observed in fMRI, Deco et al. (2016b) considered a fundamental frequency in the range of meaningful resting-state BOLD fluctuations, i.e. around 0.05 Hz. Notably, simulations with this *Ultra-slow Hopf model* not only show an excellent fit with the empirical FC (cc=0.75) but also display a rich FC dynamics, with time-dependencies that fit the empirical observations. Yet, this model disregards the relationship with the fast neurophysiological rhythms observed during rest.

More recently, Deco et al. (2017) proposed a *Hopf Model with fast oscillations* considering that brain areas can resonate at one (or multiple) fundamental frequencies, ranging between 2 and 30 Hz in agreement with the spectral profile of resting-state activity revealed by MEG. In this model, the meta-stable synchronization of oscillations is accompanied by an increase in the power of the corresponding oscillations, leading to slow and aperiodic envelope fluctuations of narrow-band carrier oscillations.

Exploring the network dynamics beyond the resting-state, Spiegler et al. (2016) investigated the result of focal stimulation on a whole-brain network model with long-range heterogeneous SC together with short-range homogeneous SC. At rest, the operating point of each network node is at the same distance to a supercritical Andronov-Hopf bifurcation. An excitatory stimulation pushes the system closer to criticality by selectively moving the operating point of particular network nodes closer to an Andronov-Hopf bifurcation. Because the stimulation propagates via the heterogeneous SC, some stimulation sites result in widespread and long-lasting patterns that shape dynamically responsive brain networks, some of which corresponding to known resting-state networks (Spiegler et al., 2016).

In sum, this scenario where brain areas operate in the vicinity of a supercritical bifurcation provides a mechanistic explanation for the different spatial, temporal and spectral phenomena observed in the brain, not only at rest but also following stimulation, so it is likely to become a strong candidate in the new generation of whole-brain network models.

Meta-stable chimera synchronization. From a different mechanistic perspective, Deco et al. (2009) considered the behavior of coupled *Wilson-Cowan* units with self-sustained oscillations in the gamma-frequency band in agreement with experimental (Buhl et al., 1998; Fisahn et al., 1998) and theoretical neurophysiological studies (Brunel and Wang, 2003). When coupled in a neuroanatomical network structure and for sufficiently weak coupling, different sub-networks can temporarily synchronize while the whole network never fully synchronizes (in a so-called *Chimera* regime) (Shanahan, 2010). With a sufficient degree of noise and for sufficiently large delays, the system switches between different partially synchronized network states (defined by the SC), which leads to correlated BOLD signal within sub-networks.

In order to further explore the mechanisms of Chimera synchronization, Cabral et al. (2011) used coupled *Kuramoto Gamma-band Oscillators* to show that, even in the absence of noise, the space-time structure of the human brain network supports a robust meta-stable dynamics where different sub-networks temporally synchronize and desynchronize over time, on a time-scale much slower (< 0.1 Hz) than the local fast gamma-band oscillations. This meta-stable regime (where partially synchronized states are only stable for a limited period in time) induces spontaneous fluctuations in the synchrony degree of sub-networks leading to correlated slow BOLD-signal fluctuations (Shanahan, 2010; Cabral et al., 2011; Wildie and Shanahan, 2012).

In the light of MEG observations, meta-stable Chimera synchronization was further found to generate slow envelope fluctuations at different carrier frequencies fairly reproducing frequency-specific envelope FC (Cabral et al., 2014b). This occurs in the model because brain areas alternate between a) their intrinsic limit-cycle at 40 Hz and b) the collective limit-cycles of synchronized sub-networks (which occur at reduced frequencies due to the time delays between brain areas (Niebur et al., 1991)). In this scenario, resting-state brain rhythms

are divided into: i) gamma-band oscillations as the intrinsic frequency of a brain area, ii) a broad spectrum of collective network frequencies (or carrier frequencies) including alpha- and beta-rhythms, and iii) ultra-slow aperiodic envelope fluctuations modulated by slow fluctuations in the synchrony degree.

Also worth mentioning, Ponce-Alvarez et al. (2015) considered *Ultra-slow Kuramoto Oscillators* with a fundamental frequency at 0.05 Hz, revealing the transient formation and dissolution of multiple communities of synchronized brain regions on very slow time-scales. Although this approach explicitly neglected the contribution of faster neurophysiological rhythms, it found consistent approximation of the temporal and spatial FC patterns of empirical fMRI data.

In sum, these studies show that resting-state activity can be interpreted from the perspective of meta-stable partial synchronization in complex networks.

Connectome-specific harmonic waves. Recently, Atasoy et al. (2016) demonstrated that the collective dynamics of human cortical activity at the macroscopic scale can be predicted by the eigendecomposition of the Laplace operator of the Structural Connectome. This mathematical framework lies at the heart of most self-organizing patterns in nature, including theories of heat, light, sound, electricity, magnetism, gravitation and fluid mechanics (Stewart, 1999). Remarkably, different resting-state networks are matched by the spatial patterns (Laplacian eigenfunctions) corresponding to certain natural frequencies (Laplacian eigenvalues) of the Structural Connectome (obtained at high-resolution, with more than 20,484 nodes)(Atasoy et al., 2016). This work presents evidence that the eigenvectors of the connectome Laplacian, or connectome harmonics, yield frequency-specific spatial patterns, providing a simple yet almost universal description for patterns of synchrony throughout the cortex. In order to demonstrate the emergence of these patterns from the cortico-cortical and thalamo-cortical interactions, the global network behaviour was modelled with a neural field model of coupled excitatory and inhibitory neural populations (see the *Supplementary Information* for further model details).

Noise deviations around the equilibrium. A different approach to explain resting-state activity was proposed in Cabral et al. (2012) where noise-induced perturbations at rest are assumed to be so small that they only induce firing rate deviations around the stable asynchronous state (fixed point), with a characteristic exponentially decaying damping time-scale back to the fixed point. The firing rate deviations around the fixed point are described by a *Linear Stochastic Model* (see *Supplementary Information*), which can be reduced from a Wilson-Cowan system by removing the inhibitory populations and saturation function (Fernandez Galan, 2008; Goni et al., 2014). Since brain areas within a sub-network receive correlated noisy input from the structural connectivity, for a critical degree of coupling they display correlated fluctuations in firing rate, leading to a fair approximation of the empirical grand-average FC (Cabral et al., 2012; Messe et al., 2014). However, the *Linear Stochastic Model* fails to reproduce the typical FCD patterns (Hansen et al., 2015) and faster neurophysiological rhythms are neglected.

Spatial autoregression. Without any implicit dynamics, the simultaneous autoregressive (SAR) model expresses the BOLD signal as a purely linear combination of noise fluctuations in all regions (Messe et al., 2014, 2015). Notably, this 'model' performs as good or even better than other models in predicting the empirical FC from the SC (Messe et al., 2015). This happens because the ability of different models to predict the static FC from SC can be reduced to a simple stationary linear process associated to the SC matrix that is implicit to all models (Messe et al., 2015). Although this study is important to depict the core similarity between all models, the investigation of the genesis of resting-state activity cannot be assessed in phenomenological terms with this model, since it disregards any dynamical aspect.

Validation of resting-state models

With the availability of human Structural Connectivity and the corresponding fMRI-based Functional Connectivity, a number of whole-brain computational models have focused in predicting the FC from the underlying SC and thus, led to the idea that model performance consists in optimizing the correlation between the simulated and empirical FC patterns (Honey et al., 2009; Cabral et al., 2011; Deco et al., 2013; Messe et al., 2015; Ponce-Alvarez et al., 2015). This has misled some to believe that models serve (only) as a tool to predict function from structure, disregarding the powerful capacity of bottom-up computational models to investigate physiological mechanisms occurring in nature. For instance, Messe et al. (2015) have shown that even a linear stochastic model can successfully predict the grand-average FC. Although this simple model can be useful to make specific predictions of SC effects on FC, it does not generate any type of dynamics so it is useless in phenomenological terms.

Before the availability of whole-brain human SC-FC, models searched to replicate other aspects of resting-state dynamics, namely in terms of complexity, number of dynamical components, cluster synchronization and frequency of slow fluctuations (Honey et al., 2007; Ghosh et al., 2008a, 2008b; Deco et al., 2009). Notably, all these models were later found to successfully predict the FC from SC, reinforcing their phenomenological potential (Messe et al., 2015).

Given the growing experimental evidence reviewed in Section 2 and the wide range of candidate scenarios described above, we consider that resting-state models must go through a common set of validation steps in order to refresh the list of accepted candidates. We propose that this validation contemplates 3 dimensions: Spatial, Spectral and Temporal (in Table 1 we report whether any of these 3 validation steps has been successfully addressed):

Spatial validation. At a global level, the static FC matrix contains important information regarding the spatial organization of the Functional Connectome. Since the simulated FC matrix is calculated from the SC, the level of fitting between simulated and empirical FC patterns is strongly dependent on the quality of the SC and the resolution of the parcellation considered, so any quantitative comparison between models must rely on the same empirical data (Messe et al., 2015). In other words, in purely bottom-up models, the lack of important inter-hemispheric links in the SC will impose a limit up to which models can reach in fitting the FC. The same occurs if important networks features are not captured with sufficient detail in the parcellation scheme. Nevertheless, if caution is taken in its interpretation, the prediction of FC patterns in spatial terms should remain an important step towards the heuristic validation of computational models.

Beyond fitting the FC matrix, the detection of meaningful functional networks associated to pre-established resting-state networks (RSNs) also serves as a measure of validation of simulated FC in spatial terms. For instance, Atasoy et al. (2016) measured similarity between the Connectome harmonics and 7 reference RSNs using mutual information in order to assess the predictive power of Connectome harmonics for RSNs.

In addition, since ICA-based methods have proved useful in detecting consistent RSNs in fMRI (Beckmann et al., 2005; Damoiseaux et al., 2006) and MEG studies (Brookes et al., 2011b), the application of ICA-based approaches to simulated data is likely to

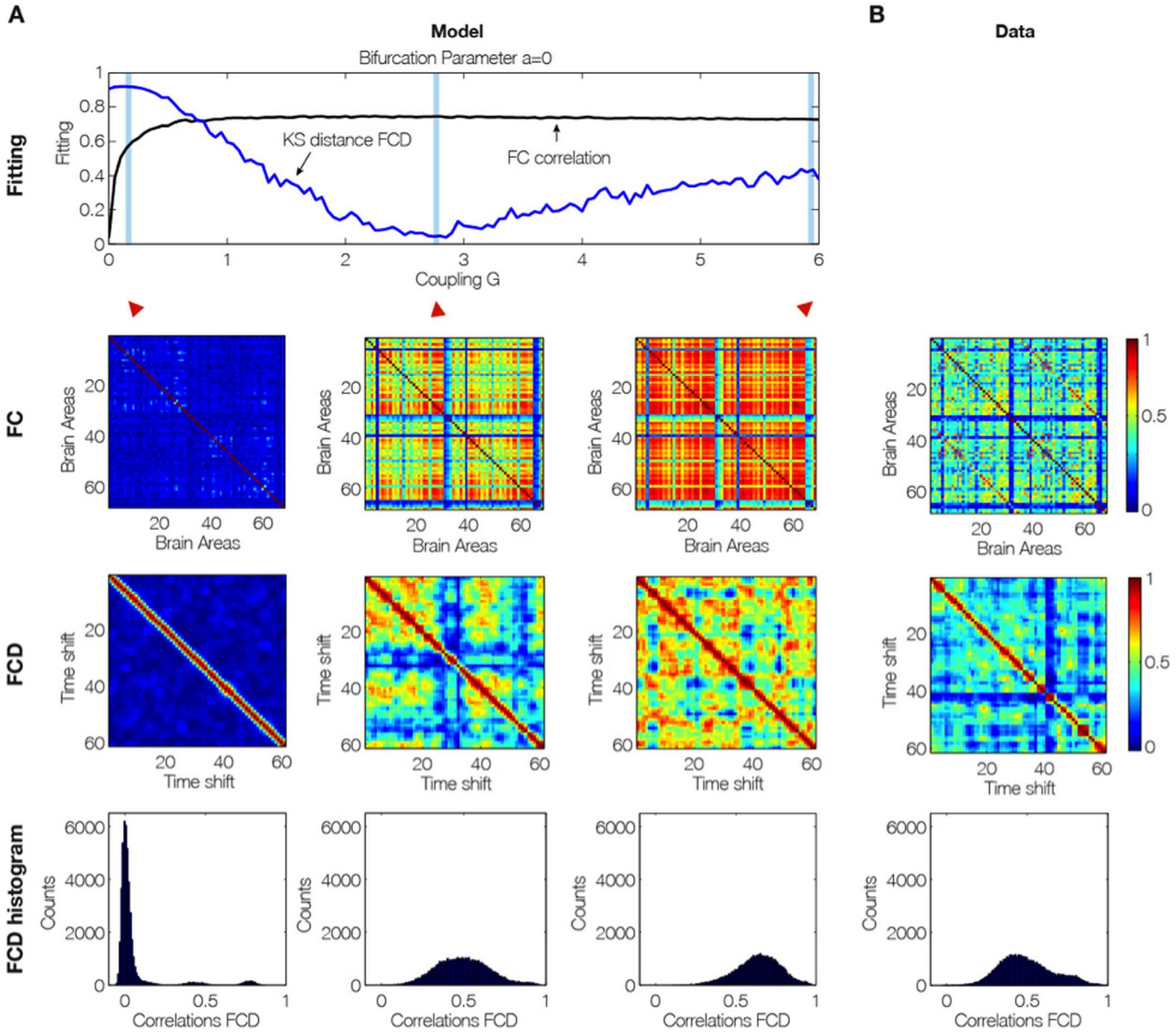

Fig. 6. Fitting the model to the histogram of FCD values. (A) The figure shows the fitting of the *Hopf Model* (Deco et al., 2016) to empirical fMRI data as a function of the global coupling parameter, G. The fitting is evaluated either as the correlation with the empirical FC matrix (black line) or as the KS-distance between histograms of FCD values (blue line). Below, the grand-average FC matrix, FCD matrix and FCD histogram are shown for 3 working points (weak, optimal and strong G). (B) Empirical FC and FCD matrices together with the FCD histogram obtained from a single healthy subject. Figure reproduced from Deco et al. (2016).

reveal spatial FC patterns similar to the ones obtained experimentally.

Temporal validation. As discussed in *Section FC Dynamics*, resting-state FC is known to evolve over time, so it is important to verify which models replicate the checkerboard pattern of FCD matrices. Since the FCD matrices are computed on a time-versus-time basis, comparison between simulated and empirical FCD matrices cannot be performed using similarity or correlation measures. As such, the current approach is to compare the histograms of FCD values (Hansen et al., 2015; Deco et al., 2017; Deco and Kringelbach, 2016; Deco et al., 2016). Indeed, the difference between FCD histograms has shown to be a sensitive measure to fit the models as it considers the time-dependencies of the FC (Fig. 6). If the patterns of FC(t) are constant over time (i.e. no FC dynamics), the histogram of FCD values appears shifted to 1. On the other hand, if FC(t) patterns are unrelated over time, the FCD distributions are shifted to zero. Instead, the histogram of FCD values obtained from real subjects (shown in Fig. 6B) displays a peak at intermediate values together with a long tail towards high FCD values, indicating the existence of periods of weak temporal similarities alternated with periods of high similarity between FC(t) patterns. Computing the Kolmogorov-Smirnov distance (KS-distance) between empirical and simulated FCD histograms (Fig. 6A, blue line) allows searching for the range of parameters where the models generate time-evolving FC(t) patterns with similar temporal similarities (Hansen et al., 2015; Deco et al., 2017; Deco and Kringelbach, 2016; Deco et al., 2016).

Although the FCD histogram provides valuable information regarding the temporal dependencies of FC in general terms, it misses specific aspects such as the lifetime of FC patterns or their switching frequency. Applying a k-means clustering (Allen et al., 2014; Hansen et al., 2015) or HMM (Baker et al., 2014) to both empirical and simulated FC(t) to compare the properties of re-occurring FC patterns would provide an additional validation of the FC dynamics generated by resting-state

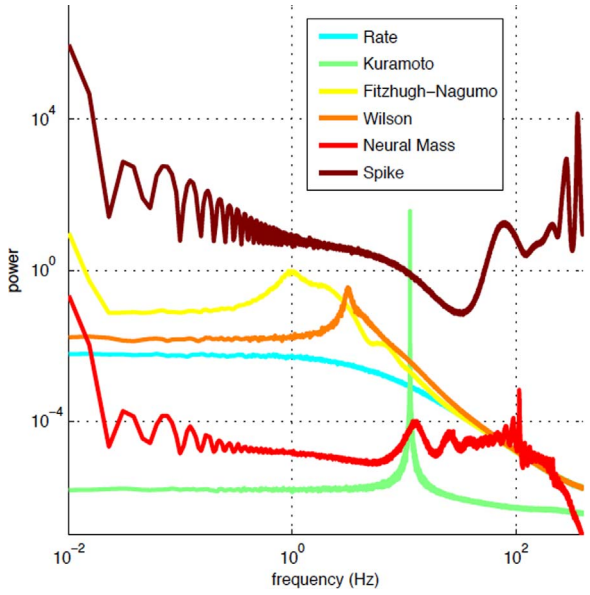

Fig. 7. Power spectra of simulated activity obtained with different computational models (Messe et al., 2015). Spectra were obtained at the point of optimal fit with the grand-average FC matrix and averaged across all regions. Note however that the local dynamics is very sensitive to model parameters. Figure reproduced from Messe et al. (2015).

models.

Spectral validation. We understand by spectral validation any measure that considers the frequency spectrum of resting-state rhythms, ranging from the fast oscillations observed with electrophysiology, EEG and MEG (mainly in the alpha, beta and gamma ranges) to the slow aperiodic fluctuations of BOLD signals and narrow-band envelopes (typically below 0.1 Hz) (Engel et al., 2013). Although most models have proposed mechanisms for the origin of slow aperiodic BOLD signal fluctuations, the faster neural rhythms have not always been carefully addressed. Messe et al. (2015) made an attempt to compare the power spectra of simulated data obtained with different computational models showing a variety of oscillatory behaviors (Fig. 7). While the aim of resting-state models is not necessarily to quantitatively replicate the power spectrum of brain activity during rest, it is important to consider it at least qualitatively, in order to investigate the link between slow envelope fluctuations and the underlying oscillatory activity observed in resting-state MEG studies.

One approach to perform a validation in the frequency domain is to obtain the frequency-specific envelope FC matrices (see *Section Frequency-specific Envelope FC*) and compare with the ones obtained empirically from MEG (Cabral et al., 2014b; Deco et al., 2016a). Importantly, rather than aiming at an optimal quantitative fit (which largely depends on the bands and the number of brain areas considered), this measure should be used to search for the range of parameters where the models better explain the data in phenomenological terms.

A new generation of resting-state models

By refreshing the list of candidate models of resting-state activity through the incorporation of the spatial, temporal and spectral constraints proposed herein, a better insight about the mechanisms occurring in the complexity of the resting brain may be assessed. As can be seen in Table 1, different models have shown to generate simulated brain activity with a) a grand-average FC matrix of BOLD signals fitting the empirical one, b) slow aperiodic power fluctuations of faster oscillatory signals, and/or c) time-evolving patterns of FC. Since all models achieve a fairly good prediction of the static FC, the selective process of candidate models occurs at the level of FC Dynamics and Envelope FC.

In general terms, FC Dynamics is obtained when the system supports at least two possible FC states and the system switches between them on a slow time-scale. This is achieved when models operate in a critical regime, such that transitions at the critical border induce a reconfiguration of FC. Notably, most of the proposed mechanistic scenarios operate at the edge of criticality, so apart from the *Linear Stochastic Model* (Cabral et al., 2012) and the *Spatial Autoregressive Model* (Messe et al., 2014) (which has clearly no implicit dynamics), all the other models -even the ones not specifically tested for Dynamic FC- are likely to display time-dependencies in the FCD matrix. Note however, that when the model parameters have been optimized to fit the static FC (which occurs for a much broader range of parameters), it is likely that they need to be further adjusted in order to match the histogram of empirical FCD values (see Fig. 6). For instance, in Hansen et al. (2015), the parameters of the dynamical mean-field model were slightly modified to enhance non-linearities and obtain a better fit of the empirical FC Dynamics.

Regarding the spectral validation, Envelope FC can only be meaningfully obtained if a) the models generate oscillations in the range of neurophysiological rhythms and b) the power of these oscillations is modulated over space and time by the SC. Even if arising from different generative mechanisms, several models display oscillations at the node level, namely the conductance-based model (Honey et al., 2007), the FitzHugh-Nagumo model (Ghosh et al., 2008b), the Hopf model (Deco et al., 2017; Spiegler et al., 2016), the Wilson-Cowan model (Deco et al., 2009) and the Kuramoto oscillators (Cabral et al., 2014b). In addition, while in more mesoscopic models the fast oscillations were explicitly neglected (Cabral et al., 2012; Ponce-Alvarez et al., 2015; Deco et al., 2016), they have been simply disregarded in the network of spiking neurons (Deco and Jirsa, 2012) or not specifically adjusted to neural frequencies in the model by Atasoy et al. (2016), so these models may be adapted and/or extended to include neurophysiological rhythms. Moreover, fluctuations in the power of such oscillations can originate from different scenarios, namely: damped oscillations –i.e. the oscillations emerge and dissipate from a quiescent equilibrium state – (Honey et al., 2007; Ghosh et al., 2008b) or metastable synchronization –i.e. a temporary increase in phase synchrony is accompanied by an increase in amplitude (Cabral et al., 2014b; Deco et al., 2017).

In conclusion, while we are not able in the current review to predict which mechanism is more likely to be at the genesis of resting-state activity, we can predict which ones will most likely fail and hence restrict the list of candidate scenarios. Indeed, models that explicitly neglected the faster neurophysiological rhythms focusing solely on fMRI observations, namely the *Spatial Autoregressive Model*, the *Linear Stochastic Model*, the *Dynamic Mean Field Model* and the *Hopf* or *Kuramoto Models* with only *Ultra-Slow* (< 0.1 Hz) *oscillations* (in Table 1, the first 5 from the bottom) are likely to be left out, since they do not address all the time-scales implicated in resting-state activity.

Finally, rather than competing against each other, all these modeling works are part of a large collaborative effort undertaken over the last decade to investigate the complex mechanisms underlying resting-state activity. Looking at the problem from different perspectives, each model has brought insightful information at different levels, irrespective of its individual flaws. In the complexity of the brain, it is likely that different mechanisms coexist and interplay at different levels. For instance, the connectome-specific harmonics studied by Atasoy et al. (2016) are likely to explain the spatial structure of the self-organizing patterns observed by Honey et al. (2007), which in turn may be associated to meta-stable synchronization (Cabral et al., 2011) in a system with multiple ghost attractors (Deco and Jirsa, 2012) with noise-induced transitions (Ghosh et al., 2008b). Moreover, the time-

delays between brain areas (Ghosh et al., 2008a; Deco et al., 2009) may not only serve as a mechanism to frustrate zero-lag synchronization and promote meta-stability (Gollo and Breakspear, 2014), but also to induce resonance at slower network-specific frequencies (Cabral et al., 2014b), which in turn may serve to convey multiplexed information via different frequency channels (Deco et al., 2017). While this reasoning is purely hypothetical, it illustrates how the knowledge gained from the different models may be combined to obtain a unified theoretical model of resting-state activity.

Discussion

Over the last decade, resting-state activity has been investigated by theoretical works for its intriguing network dynamics and for its implications in understanding the brain's functional organization. Several mechanistic scenarios have been proposed for the genesis of resting-state activity using bottom-up computational models. Despite their fundamental differences, all models agree on a common essential ingredient: the Structural Connectome. Indeed, the structural network is found to nicely shape long-range FC computed over extended recording sessions. However, beyond the static correlation between BOLD signals, other intriguing features of resting-state activity must be taken into account in order to come up with a unifying theoretical model encompassing all the experimental observations.

In this work, we have reviewed different models of resting-state activity and commented on their phenomenological potential to explain the experimental observations of resting-state FC in spatial, temporal and spectral terms.

A single SC for multiple FCs

The existence of multiple configurations of FC unfolding from the same SC leads us to view the live brain from the perspective of dynamical systems' theory as a multi-stable system: the same neuroanatomical structure supports a large repertoire of stable dynamical states (Deco et al., 2011). When we engage in a specific task, a network of functionally-relevant brain areas is activated (i.e. visual network, motor network, attention network, etc.) inducing a quick re-configuration of whole-brain FC while the SC remains practically unchanged (Buckner et al., 1996). From the perspective of dynamical systems, this is suggestive of a phase transition where the system switches from one state to another in response to a given trigger. Notably at rest, when no specific task is being executed, the brain displays the activation of different functionally-meaningful networks (Damoiseaux et al., 2006). This resting state is particularly interesting from the perspective of dynamical systems because it appears to reflect an exploration of the dynamical repertoire of macro-scale brain states arising from the same neuroanatomical structure (Tognoli and Kelso, 2014; Deco and Kringelbach, 2016).

Whole-brain network models

Following the intriguing network dynamics observed in resting-state activity, a number of theoretical works have used reduced whole-brain network models to investigate the activity emerging from the interplay of brain areas in the neuroanatomical network. However, even with high degrees of abstraction and with low-resolution SC, the solutions for the network dynamics are complex and hardly assessed analytically, so theoretical works resource to computational models in order to simulate the network activity and compare it with different features observed in resting-state recordings. One of these features is the emergence of slow (< 0.1 Hz) spatio-temporally organized fluctuations yielding a FC matrix that replicates the fMRI-based FC.

With the recent but imperative inclusion of the temporal dimension in the analysis of resting-state FC, together with the insights coming from MEG studies, models of resting-state activity need to be re-evaluated. Importantly, even when these constraints were not initially imposed, and even if some adaptations must be undertaken, their mechanistic scenarios may remain valid in phenomenological terms. For instance, before the availability of whole-brain human SC and FC, the conductance-based model (Honey et al., 2007), the FitzHugh-Nagumo model (Ghosh et al., 2008b) and the Wilson-Cowan model (Deco et al., 2009) were purely focused in explaining the origin of ultra-slow resting fluctuations (using macaque connectivity). Later, the same models were found to achieve a fairly good fit of the empirical FC when run with the human SC (Honey et al., 2009, Messe et al., 2015). Similarly, Zalesky et al. (2014) later found that the network simulations with the conductance-based model exhibit a rich FC dynamics, in agreement with experimental data. In another example, Cabral et al. (2011) first showed how the synchrony degree of coupled Kuramoto oscillators modulated the BOLD signal. Only later, the synchrony degree was found to modulate the power of network oscillations, making the link between fMRI and MEG findings (Cabral et al., 2014b).

As discussed in *Section A new generation of resting-state models* we do not aim in this review to evaluate the performance of the different models but rather to present the list of proposed mechanisms and discuss their phenomenological value in the light of different features of resting-state activity.

We find that the models that explicitly neglected the faster neurophysiological rhythms focusing solely on fMRI observations, namely the *Spatial Autoregressive Model,* the *Linear Stochastic Model, the Dynamic Mean Field Model*, the *Hopf Model with Ultra-Slow oscillations* or the *Kuramoto Model with Ultra Slow Oscillations* have the lowest phenomenological value, since they do not address all the time-scales implicated in resting-state activity.

Mechanisms of resting-state activity

Even with a refreshed list of resting-state models, we find that different mechanistic scenarios remain acceptable for the genesis of resting-state activity. On a common basis, resting-state activity appears to be the product of a peculiar type of network dynamics where the system lies in a critical regime. Systems operating at criticality are highly responsive to perturbations (Bak and Paczuski, 1995; Beggs, 2008; Chialvo, 2010), so we can hypothesize that being in this regime at rest allows the brain to rapidly switch to a function-specific state in response to an internal or external trigger. Moreover, complex network topologies (typically, but not necessarily, scale-free) have been shown to enhance self-organized criticality (Rubinov et al., 2011; Beggs and Timme, 2012) so the neuroanatomical connectivity structure certainly plays a role in shaping the macro-scale critical behavior of the resting brain. In this general framework, a phase transition in one brain area (e.g. from a fixed point to a limit-cycle, or from incoherence to synchrony with its neighbors) spreads through the network structure inducing slow and brain-wide fluctuations that modulate the power of local neuronal oscillations as well the local metabolic demand (captured by the BOLD signal).

Despite this common picture, we identify a number of fundamental properties that still distinguish the different scenarios and deserve further investigation, namely the role of noise, the role of time-delays between brain areas and the range of natural frequencies emerging from an isolated neural mass.

While noise plays a key role in driving spontaneous phase transitions in the FiztHugh Nagumo model (Ghosh et al., 2008b), the Wilson-Cowan model (Deco et al., 2009) and the Hopf model (Deco et al., 2017), it can be neglected in the Kuramoto model with time delays (Cabral et al., 2014b) and in the conductance-based model (Honey et al., 2007) because meta-stability is intrinsically induced by frustration mechanisms (Gollo and Breakspear, 2014).

In terms of time-delays, since all the 'surviving' models consider the time-scales of neurophysiological rhythms -with periods in the same order of magnitude of time delays between brain areas (~10–100 ms) –

it is important to consider the effects of time-delays in the global network dynamics. Indeed, the presence of delays in dynamical networks not only frustrates zero-lag synchronization and promotes meta-stability (Yeung and Strogatz, 1999; Gollo et al., 2014) but also facilitates resonance at other delay-dependent frequencies (Niebur et al., 1991; Cabral et al., 2014b). As such, we believe the role of time-delays in the brain's network dynamics deserves further exploration.

In addition, there appears to be a disagreement regarding the intrinsic frequency of individual brain areas. On one side, oscillations were set in the gamma range in the Wilson-Cowan model (Deco et al., 2009) and the Kuramoto model (Cabral et al., 2014b), in agreement with direct electrophysiological experiments (Nir et al., 2007; Miller et al., 2009; Scholvinck et al., 2010) and theoretical models of neural networks (Abbott and van Vreeswijk; 1993, Ermentrout et al., 2001; Brunel and Wang, 2003). On the other hand, the FiztHugh-Nagumo model (Ghosh et al., 2008b) directly considered the most powerful frequency peak (10 Hz) observed in EEG and MEG recordings at rest (Lopes da Silva et al., 1997; Buzsaki, 2006). In Deco et al. (2016a), a range of natural frequencies between 2 and 30 Hz was tested with the Hopf model, finding the best agreement with MEG-based envelope FC matrices for an intrinsic frequency at 12 Hz. These approaches are phenomenologically different because the relationship between locally generated gamma rhythms and large-scale alpha and beta rhythms remains unclear. In Gollo et al. (2015), the parameters of the conductance-based model were set such that neural masses oscillate with two timescales: a fast fluctuation of approximately 110 Hz (emerging mainly at weak coupling between brain areas) superimposed on a slow oscillation of approximately 8 Hz. Notably, synchronization at this slower timescale occurs in clusters, shaping different functional networks. Similarly, Cabral et al. (2014b) coupled 40 Hz oscillators with heterogeneous time-delays between brain areas and showed that cluster synchronization occurred at reduced frequencies falling between 10–20 Hz. As such, whether alpha and beta rhythms are generated locally within a neural mass or originate at the network level from time-delayed interactions remains one of the main questions to understand the mechanisms of resting-state activity.

Future perspectives

Modeling the network dynamics in the resting state should be seen only as a starting point (yet crucial) to understand whole-brain network dynamics. Indeed, the resting brain can rapidly switch to a task by activating a functionally-relevant network in response to a specific trigger. As such, beyond further validation procedures in the resting-state, some theoretical works have started to perturb the models to investigate their response to stimulation, namely with the activation/stabilization of meaningful functional networks (Cocchi et al., 2015; Gollo et al., 2016; Spiegler et al., 2016). It is likely that such approach will bring a paradigm shift in whole-brain network models, which, rather than being termed Resting-State Models, will become a new generation of Whole-Brain Functional Models.

Such models have the potential of becoming increasingly helpful in the preparation of clinical interventions, including brain stimulation techniques such as transcranial magnetic/electrical stimulation or deep brain stimulation. However, in order to achieve such goal, we believe it is important to first obtain an accurate picture of the complex network dynamics occurring in the brain at rest.

Acknowledgements

JC and MLK were supported by the ERC Consolidator Grant CAREGIVING (n. 615539) and the TrygFonden Charitable Foundation. GD was supported by the ERC Advanced Grant: DYSTRUCTURE (n. 295129) and by the Spanish Research Project PSI2016-75688-P and by the European Union's Horizon 2020 research and innovation program under grant agreement n. 720270 (HBP SGA1).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuroimage.2017.03.045.

References

Abbott, L.F., van Vreeswijk, C., 1993. Asynchronous states in networks of pulse-coupled oscillators. Phys. Rev. E, State Phys., Plasmas, Fluids, Relat. Interdiscip. Top. 48, 1483–1490.
Aertsen, A.M., Gerstein, G.L., Habib, M.K., Palm, G., 1989. Dynamics of neuronal firing correlation: modulation of "effective connectivity". J. Neurophysiol. 61, 900–917.
Allen, E.A., Damaraju, E., Plis, S.M., Erhardt, E.B., Eichele, T., Calhoun, V.D., 2014. Tracking whole-brain connectivity dynamics in the resting state. Cereb. Cortex 24, 663–676.
Atasoy, S., Donnelly, I., Pearson, J., 2016. Human brain networks function in connectome-specific harmonic waves. Nat. Commun. 7, 10340.
Bak P., Paczuski M., 1995. Complexity, contingency, and criticality. In: Proceedings of the National Academy of Sciences of the United States of America. 92, pp. 6689–6696.
Baker, A.P., Brookes, M.J., Rezek, I.A., Smith, S.M., Behrens, T., Probert Smith, P.J., Woolrich, M., 2014. Fast transient networks in spontaneous human brain activity. eLife 3, e01867.
Bartzokis, G., Cummings, J.L., Sultzer, D., Henderson, V.W., Nuechterlein, K.H., Mintz, J., 2003. White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study. Arch. Neurol. 60, 393–398.
Beckmann, C.F., DeLuca, M., Devlin, J.T., Smith, S.M., 2005. Investigations into resting-state connectivity using independent component analysis. Philos. Trans. R. Soc. Lond. Ser. B, Biol. Sci. 360, 1001–1013.
Beggs, J.M., 2008. The criticality hypothesis: how local cortical networks might optimize information processing. Philos. Trans. Ser. A, Math., Phys., Eng. Sci. 366, 329–343.
Beggs, J.M., Timme, N., 2012. Being critical of criticality in the brain. Front. Physiol. 3, 163.
Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34, 537–541.
Biswal B., Mennes M., Zuo X., Gohel S., Kelly C., Smith S., Beckmann C., Adelstein J., Buckner R., Colcombe S., Dogonowski A., Ernst M., Fair D., Hampson M., Hoptman M., Hyde J., Kiviniemi V., Kotter R., Li S., Lin C., Lowe M., Mackay C., Madden D., Madsen K., Margulies D., Mayberg H., McMahon K., Monk C., Mostofsky S., Nagel B., Pekar J., Peltier S., Petersen S., Riedl V., Rombouts S., Rypma B., Schlaggar B., Schmidt S., Seidler R., Siegle G., Sorg C., Teng G., Veijola J., Villringer A., Walter M., Wang L., Weng X., Whitfield-Gabrieli S., Williamson P., Windischberger C., Zang Y., Zhang H., Castellanos F., Milham M., 2010. Toward discovery science of human brain function. In: Proceedings of the National Academy of Sciences of the United States of America. 107, pp. 4734–4739.
Breakspear, M., Terry, J.R., Friston, K.J., 2003. Modulation of excitatory synaptic coupling facilitates synchronization and complex dynamics in a biophysical model of neuronal dynamics. Network 14, 703–732.
Brookes, M.J., Hale, J.R., Zumer, J.M., Stevenson, C.M., Francis, S.T., Barnes, G.R., Owen, J.P., Morris, P.G., Nagarajan, S.S., 2011a. Measuring functional connectivity using MEG: methodology and comparison with fcMRI. NeuroImage 56, 1082–1104.
Brookes M., Woolrich M., Luckhoo H., Price D., Hale J., Stephenson M., Barnes G., Smith S., Morris P.,2011b. Investigating the electrophysiological basis of resting state networks using magnetoencephalography. In: Proceedings of the National Academy of Sciences of the United States of America. 108, pp. 16783–16788.
Brunel, N., Wang, X.J., 2001. Effects of neuromodulation in a cortical network model of object working memory dominated by recurrent inhibition. J. Comput. Neurosci. 11, 63–85.
Brunel, N., Wang, X.J., 2003. What determines the frequency of fast network oscillations with irregular neural discharges? I. Synaptic dynamics and excitation-inhibition balance. J. Neurophysiol. 90, 415–430.
Buckner R., Bandettini P., O'Craven K., Savoy R., Petersen S., Raichle M., Rosen B., 1996. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. In: Proceedings of the National Academy of Sciences of the United States of America. 93, pp. 14878–14883.
Buhl, E.H., Tamas, G., Fisahn, A., 1998. Cholinergic activation and tonic excitation induce persistent gamma oscillations in mouse somatosensory cortex in vitro. J. Physiol. 513 (Pt 1), 117–126.
Buzsaki, G., 2006. Rhythms of the Brain. Oxford University Press, Oxford.
Cabral, J., Hugues, E., Kringelbach, M.L., Deco, G., 2012. Modeling the outcome of structural disconnection on resting-state functional connectivity. NeuroImage 62, 1342–1353.
Cabral, J., Hugues, E., Sporns, O., Deco, G., 2011. Role of local network oscillations in resting-state functional connectivity. NeuroImage 57, 130–139.
Cabral, J., Kringelbach, M.L., Deco, G., 2014a. Exploring the network dynamics underlying brain activity during rest. Progress. Neurobiol. 114, 102–131.
Cabral, J., Luckhoo, H., Woolrich, M., Joensson, M., Mohseni, H., Baker, A., Kringelbach, M.L., Deco, G., 2014b. Exploring mechanisms of spontaneous functional connectivity in MEG: how delayed network interactions lead to structured amplitude

envelopes of band-pass filtered oscillations. NeuroImage 90, 423–435.
Calhoun, V.D., Miller, R., Pearlson, G., Adali, T., 2014. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron 84, 262–274.
Chang, C., Glover, G.H., 2010. Time-frequency dynamics of resting-state brain connectivity measured with fMRI. NeuroImage 50, 81–98.
Chialvo, D.R., 2010. Emergent complex neural dynamics. Nat. Phys. 6, 744–750.
Cocchi, L., Sale, M.V., Lord, A., Zalesky, A., Breakspear, M., Mattingley, J.B., 2015. Dissociable effects of local inhibitory and excitatory theta-burst stimulation on large-scale brain dynamics. J. Neurophysiol. 113, 3375–3385.
Damoiseaux J., Rombouts S., Barkhof F., Scheltens P., Stam C., Smith S., Beckmann C., 2006. Consistent resting-state networks across healthy subjects. In: Proceedings of the National Academy of Sciences of the United States of America. 103, pp. 13848-13853.
de Pasquale F., Della Penna S., Snyder A., Lewis C., Mantini D., Marzetti L., Belardinelli P., Ciancetta L., Pizzella V., Romani G., Corbetta M., 2010. Temporal dynamics of spontaneous MEG activity in brain networks. In: Proceedings of the National Academy of Sciences of the United States of America. 107, pp. 6040–6045.
Deco, G., Cabral, J., Woolrich, M., Stevner, A., Van Hartevelt, T.J., Kringelbach, M.L., 2017. Single or multiple frequency generators in on-going brain activity: a mechanistic whole-brain model following empirical MEG evidences. Neuroimage. http://dx.doi.org/10.1016/j.neuroimage.2017.03.023.
Deco G., Jirsa V., McIntosh A., Sporns O., Kotter R., 2009. Key role of coupling, delay, and noise in resting brain fluctuations. In: Proceedings of the National Academy of Sciences of the United States of America. 106, pp. 10302–10307.
Deco, G., Jirsa, V.K., 2012. Ongoing cortical activity at rest: criticality, multistability, and ghost attractors. J. Neurosci.: Off. J. Soc. Neurosci. 32, 3366–3375.
Deco, G., Jirsa, V.K., McIntosh, A.R., 2011. Emerging concepts for the dynamical organization of resting-state activity in the brain. Nat. Rev. Neurosci. 12, 43–56.
Deco, G., Kringelbach, M., 2016. Metastability and coherence: extending the communication through coherence hypothesis using a whole-brain computational perspective. Trends Neurosci. 39, 432.
Deco, G., Kringelbach, M.L., Jirsa, V., Ritter, P., 2016. The dynamics of resting fluctuations in the brain: metastability and its dynamical cortical core. Biorxiv..
Deco, G., Ponce-Alvarez, A., Mantini, D., Romani, G.L., Hagmann, P., Corbetta, M., 2013. Resting-state functional connectivity emerges from structurally and dynamically shaped slow linear fluctuations. J. Neurosci.: Off. J. Soc. Neurosci. 33, 11239–11252.
Deco, G., Senden, M., Jirsa, V., 2012. How anatomy shapes dynamics: a semi-analytical study of the brain at rest by a simple spin model. Front. Comput. Neurosci. 6, 68.
Engel, A.K., Gerloff, C., Hilgetag, C.C., Nolte, G., 2013. Intrinsic coupling modes: multiscale interactions in ongoing brain activity. Neuron 80, 867–886.
Ermentrout, B., Pascal, M., Gutkin, B., 2001. The effects of spike frequency adaptation and negative feedback on the synchronization of neural oscillators. Neural Comput. 13, 1285–1310.
Fernandez Galan, R., 2008. On how network architecture determines the dominant patterns of spontaneous neural activity. PloS one 3, e2148.
Fisahn, A., Pike, F.G., Buhl, E.H., Paulsen, O., 1998. Cholinergic induction of network oscillations at 40 Hz in the hippocampus in vitro. Nature 394, 186–189.
Freyer, F., Roberts, J.A., Becker, R., Robinson, P.A., Ritter, P., Breakspear, M., 2011. Biophysical mechanisms of multistability in resting-state cortical rhythms. J. Neurosci.: Off. J. Soc. Neurosci. 31, 6353–6361.
Friston, K.J., Frith, C.D., Liddle, P.F., Frackowiak, R.S., 1993. Functional connectivity: the principal-component analysis of large (PET) data sets. J. Cereb. 13, 5–14.
Ghosh, A., Rho, Y., McIntosh, A.R., Kotter, R., Jirsa, V.K., 2008a. Cortical network dynamics with time delays reveals functional connectivity in the resting brain. Cogn. Neurodyn. 2, 115–120.
Ghosh, A., Rho, Y., McIntosh, A.R., Kotter, R., Jirsa, V.K., 2008b. Noise during rest enables the exploration of the brain's dynamic repertoire. PLoS Comput. Biol. 4, e1000196.
Glerean, E., Salmi, J., Lahnakoski, J.M., Jaaskelainen, I.P., Sams, M., 2012. Functional magnetic resonance imaging phase synchronization as a measure of dynamic functional connectivity. Brain Connect. 2, 91–101.
Gollo, L.L., Breakspear, M., 2014. The frustrated brain: from dynamics on motifs to communities and networks. Philos. Trans. R. Soc. Lond. Ser. B, Biol. Sci., 369.
Gollo, L.L., Mirasso, C., Sporns, O., Breakspear, M., 2014. Mechanisms of zero-lag synchronization in cortical motifs. PLoS Comput. Biol. 10, e1003548.
Gollo LL, Roberts J, Cocchi L., 2016. Mapping how local perturbations influence systems-level brain dynamics. Arxiv eprint arXiv. 1609, 00491.
Gollo, L.L., Zalesky, A., Hutchison, R.M., van den Heuvel, M., Breakspear, M., 2015. Dwelling quietly in the rich club: brain network determinants of slow cortical fluctuations. Philos. Trans. R. Soc. Lond. Ser. B, Biol. Sci., 370.
Goni J., van den Heuvel M., Avena-Koenigsberger A., Velez de Mendizabal N., Betzel R., Griffa A., Hagmann P., Corominas-Murtra B., Thiran J., Sporns O., 2014. Resting-brain functional connectivity predicted by analytic measures of network communication. In: Proceedings of the National Academy of Sciences of the United States of America. 111, pp. 833–838.
Greicius, M.D., Supekar, K., Menon, V., Dougherty, R.F., 2009. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb. Cortex 19, 72–78.
Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. PLoS Biol. 6, e159.
Hagmann P., Sporns O., Madan N., Cammoun L., Pienaar R., Wedeen V., Meuli R., Thiran J., Grant P., 2010. White matter maturation reshapes structural connectivity in the late developing human brain. In: Proceedings of the National Academy of Sciences of the United States of America. 107, pp. 19067–19072.
Handwerker, D.A., Roopchansingh, V., Gonzalez-Castillo, J., Bandettini, P.A., 2012. Periodic changes in fMRI connectivity. NeuroImage 63, 1712–1719.
Hansen, E.C., Battaglia, D., Spiegler, A., Deco, G., Jirsa, V.K., 2015. Functional connectivity dynamics: modeling the switching behavior of the resting state. NeuroImage 105, 525–535.
He B., Snyder A., Zempel J., Smyth M., Raichle M., 2008. Electrophysiological correlates of the brain's intrinsic large-scale functional architecture. In: Proceedings of the National Academy of Sciences of the United States of America. 105, pp. 16039–16044.
Hermundstad A., Bassett D., Brown K., Aminoff E., Clewett D., Freeman S., Frithsen A., Johnson A., Tipper C., Miller M., Grafton S., Carlson J., 2013. Structural foundations of resting-state and task-based functional connectivity in the human brain. In: Proceedings of the National Academy of Sciences of the United States of America. 110, pp. 6169–6174.
Hindriks, R., Adhikari, M.H., Murayama, Y., Ganzetti, M., Mantini, D., Logothetis, N.K., Deco, G., 2015a. Can sliding-window correlations reveal dynamic functional connectivity in resting-state fMRI? NeuroImage 127, 242–256.
Hindriks, R., Woolrich, M., Luckhoo, H., Joensson, M., Mohseni, H., Kringelbach, M.L., Deco, G., 2015b. Role of white-matter pathways in coordinating alpha oscillations in resting visual cortex. NeuroImage 106, 328–339.
Hipp, J.F., Hawellek, D.J., Corbetta, M., Siegel, M., Engel, A.K., 2012. Large-scale cortical correlation structure of spontaneous oscillatory activity. Nat. Neurosci. 15, 884–890.
Hipp, J.F., Siegel, M., 2015. BOLD fMRI correlation reflects frequency-specific neuronal correlation. Curr. Biol. 25, 1368–1374.
Hodgkin, A.L., Huxley, A.F., 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. 117, 500–544.
Honey C., Kotter R., Breakspear M., Sporns O., 2007. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. In: Proceedings of the National Academy of Sciences of the United States of America. 104, pp. 10240–10245.
Honey C., Sporns O., Cammoun L., Gigandet X., Thiran J., Meuli R., Hagmann P., 2009. Predicting human resting-state functional connectivity from structural connectivity. In: Proceedings of the National Academy of Sciences of the United States of America. 106, pp. 2035–2040.
Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., Della Penna, S., Duyn, J.H., Glover, G.H., Gonzalez-Castillo, J., Handwerker, D.A., Keilholz, S., Kiviniemi, V., Leopold, D.A., de Pasquale, F., Sporns, O., Walter, M., Chang, C., 2013a. Dynamic functional connectivity: promise, issues, and interpretations. NeuroImage 80, 360–378.
Hutchison, R.M., Womelsdorf, T., Gati, J.S., Everling, S., Menon, R.S., 2013b. Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques. Hum. Brain Mapp. 34, 2154–2177.
Izhikevich E., Edelman G., 2008. Large-scale model of mammalian thalamocortical systems. In: Proceedings of the National Academy of Sciences of the United States of America. 105, pp. 3593–3598.
Jones, D.T., Vemuri, P., Murphy, M.C., Gunter, J.L., Senjem, M.L., Machulda, M.M., Przybelski, S.A., Gregg, B.E., Kantarci, K., Knopman, D.S., Boeve, B.F., Petersen, R.C., Jack, C.R., Jr., 2012. Non-stationarity in the "resting brain's" modular architecture. PloS one 7, e39731.
Keller, C.J., Bickel, S., Honey, C.J., Groppe, D.M., Entz, L., Craddock, R.C., Lado, F.A., Kelly, C., Milham, M., Mehta, A.D., 2013. Neurophysiological investigation of spontaneous correlated and anticorrelated fluctuations of the BOLD signal. J. Neurosci.: Off. J. Soc. Neurosci. 33, 6333–6342.
Laumann, T.O., Snyder, A.Z., Mitra, A., Gordon, E.M., Gratton, C., Adeyemo, B., Gilmore, A.W., Nelson, S.M., Berg, J.J., Greene, D.J., McCarthy, J.E., Tagliazucchi, E., Laufs, H., Schlaggar, B.L., Dosenbach, N.U., Petersen, S.E., 2016. On the Stability of BOLD fMRI Correlations. Cereb. Cortex..
Leonardi, N., Shirer, W.R., Greicius, M.D., Van De Ville, D., 2014. Disentangling dynamic networks: separated and joint expressions of functional connectivity patterns in time. Hum. Brain Mapp. 35, 5984–5995.
Leonardi, N., Van De Ville, D., 2015. On spurious and real fluctuations of dynamic functional connectivity during rest. NeuroImage 104, 430–436.
Leopold, D.A., Murayama, Y., Logothetis, N.K., 2003. Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. Cereb. Cortex 13, 422–433.
Liu X., Duyn J., 2013. Time-varying functional network information extracted from brief instances of spontaneous brain activity. In: Proceedings of the National Academy of Sciences of the United States of America. 110, pp. 4392–4397.
Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. Nature 412, 150–157.
Lopes da Silva, F.H., Pijn, J.P., Velis, D., Nijssen, P.C., 1997. Alpha rhythms: noise, dynamics and models. Int. J. Psychophysiol.: Off. J. Int. Organ. Psychophysiol. 26, 237–249.
Lowe, M.J., Mock, B.J., Sorenson, J.A., 1998. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. NeuroImage 7, 119–132.
Magri, C., Schridde, U., Murayama, Y., Panzeri, S., Logothetis, N.K., 2012. The amplitude and timing of the BOLD signal reflects the relationship between local field potential power at different frequencies. J. Neurosci.: Off. J. Soc. Neurosci. 32, 1395–1407.
Marzetti, L., Della Penna, S., Snyder, A.Z., Pizzella, V., Nolte, G., de Pasquale, F., Romani, G.L., Corbetta, M., 2013. Frequency specific interactions of MEG resting state activity within and across brain networks as revealed by the multivariate interaction measure. NeuroImage 79, 172–183.
Messe, A., Rudrauf, D., Benali, H., Marrelec, G., 2014. Relating structure and function in

the human brain: relative contributions of anatomy, stationary dynamics, and non-stationarities. PLoS Comput. Biol. 10, e1003530.
Messe, A., Rudrauf, D., Giron, A., Marrelec, G., 2015. Predicting functional connectivity from structural connectivity via computational models using MRI: an extensive comparison study. NeuroImage 111, 65–75.
Miller K., Weaver K., Ojemann J., 2009. Direct electrophysiological measurement of human default network areas. In: Proceedings of the National Academy of Sciences of the United States of America. 106, pp. 12174–12177.
Nakagawa, T.T., Woolrich, M., Luckhoo, H., Joensson, M., Mohseni, H., Kringelbach, M.L., Jirsa, V., Deco, G., 2014. How delays matter in an oscillatory whole-brain spiking-neuron network model for MEG alpha-rhythms at rest. NeuroImage 87, 383–394.
Niebur, E., Schuster, H.G., Kammen, D.M., 1991. Collective frequencies and metastability in networks of limit-cycle oscillators with time delay. Phys. Rev. Lett. 67, 2753–2756.
Nir, Y., Fisch, L., Mukamel, R., Gelbard-Sagiv, H., Arieli, A., Fried, I., Malach, R., 2007. Coupling between neuronal firing rate, gamma LFP, and BOLD fMRI is related to interneuronal correlations. Curr. Biol. 17, 1275–1285.
Petkoski S., Jirsa V. Effects of time-delays for the non-stationary dynamic of the resting state. Clinical Neurophysiology. 127, e48.
Ponce-Alvarez, A., Deco, G., Hagmann, P., Romani, G.L., Mantini, D., Corbetta, M., 2015. Resting-state temporal synchronization networks emerge from connectivity topology and heterogeneity. PLoS Comput. Biol. 11, e1004100.
Preti, M.G., Bolton, T.A., Ville, D.V., 2016. The dynamic functional connectome: state-of-the-art and perspectives. NeuroImage.
Robinson, P.A., Zhao, X., Aquino, K.M., Griffiths, J.D., Sarkar, S., Mehta-Pandejee, G., 2016. Eigenmodes of brain activity: neural field theory predictions and comparison with experiment. NeuroImage 142, 79–98.
Rubinov, M., Sporns, O., Thivierge, J.P., Breakspear, M., 2011. Neurobiologically realistic determinants of self-organized criticality in networks of spiking neurons. PLoS Comput. Biol. 7, e1002038.
Sakoglu, U., Pearlson, G.D., Kiehl, K.A., Wang, Y.M., Michael, A.M., Calhoun, V.D., 2010. A method for evaluating dynamic functional network connectivity and task-modulation: application to schizophrenia. Magma 23, 351–366.
Scholvinck M., Maier A., Ye F., Duyn J., Leopold D., 2010. Neural basis of global resting-state fMRI activity. Proceedings of the National Academy of Sciences of the United States of America 107:10238-10243.
Senden, M., Goebel, R., Deco, G., 2012. Structural connectivity allows for multi-threading during rest: the structure of the cortex leads to efficient alternation between resting state exploratory behavior and default mode processing. NeuroImage 60, 2274–2284.
Shanahan, M., 2010. Metastable chimera states in community-structured oscillator networks. Chaos 20, 013108.
Shine, J.M., Koyejo, O., Bell, P.T., Gorgolewski, K.J., Gilat, M., Poldrack, R.A., 2015. Estimation of dynamic functional connectivity using multiplication of temporal derivatives. NeuroImage 122, 399–407.
Smith S., Miller K., Moeller S., Xu J., Auerbach E., Woolrich M., Beckmann C., Jenkinson M., Andersson J., Glasser M., Van Essen D., Feinberg D., Yacoub E., Ugurbil K., 2012. Temporally-independent functional modes of spontaneous brain activity. In: Proceedings of the National Academy of Sciences of the United States of America. 109, pp. 3131–3136.
Spiegler, A., Hansen, E.C., Bernard, C., McIntosh, A.R., Jirsa, V.K., 2016. Selective activation of resting-state networks following focal stimulation in a connectome-based network model of the human brain. eNeuro, 3.
Sporns, O., 2011. Networks of the Brain. Cambridge, Mass, MIT Press, London.
Sporns, O., Tononi, G., Kotter, R., 2005. The human connectome: a structural description of the human brain. PLoS Comput. Biol. 1, e42.
Stewart, I., 1999. Mathematics: holes and hot spots. Nature 401, 863–865.
Tagliazucchi, E., Balenzuela, P., Fraiman, D., Chialvo, D.R., 2012a. Criticality in large-scale brain FMRI dynamics unveiled by a novel point process analysis. Front. Physiol. 3, 15.
Tagliazucchi, E., von Wegner, F., Morzelewski, A., Brodbeck, V., Laufs, H., 2012b. Dynamic BOLD functional connectivity in humans and its electrophysiological correlates. Front. Human. Neurosci. 6, 339.
Takeuchi, H., Sekiguchi, A., Taki, Y., Yokoyama, S., Yomogida, Y., Komuro, N., Yamanouchi, T., Suzuki, S., Kawashima, R., 2010. Training of working memory impacts structural connectivity. J. Neurosci.: Off. J. Soc. Neurosci. 30, 3297–3303.
Tognoli, E., Kelso, J.A., 2014. The metastable brain. Neuron 81, 35–48.
van den Heuvel, M.P., Hulshoff Pol, H.E., 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 20, 519–534.
van den Heuvel, M.P., Mandl, R.C., Kahn, R.S., Hulshoff Pol, H.E., 2009. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Hum. Brain Mapp. 30, 3127–3141.
Vasa, F., Shanahan, M., Hellyer, P.J., Scott, G., Cabral, J., Leech, R., 2015. Effects of lesions on synchrony and metastability in cortical networks. NeuroImage 118, 456–467.
Vidaurre, D., Quinn, A.J., Baker, A.P., Dupret, D., Tejero-Cantero, A., Woolrich, M.W., 2016. Spectrally resolved fast transient brain states in electrophysiological data. NeuroImage 126, 81–95.
Vuksanovic, V., Hovel, P., 2015. Dynamic changes in network synchrony reveal resting-state functional networks. Chaos 25, 023116.
Wildie, M., Shanahan, M., 2012. Metastability and chimera states in modular delay and pulse-coupled oscillator networks. Chaos 22, 043131.
Yaesoubi, M., Allen, E.A., Miller, R.L., Calhoun, V.D., 2015. Dynamic coherence analysis of resting fMRI data to jointly capture state-based phase, frequency, and time-domain information. NeuroImage 120, 133–142.
Yeung, M.K.S., Strogatz, S.H., 1999. Time delay in the Kuramoto model of coupled oscillators. Phys. Rev. Lett. 82, 648–651.
Zalesky, A., Breakspear, M., 2015. Towards a statistical test for functional connectivity dynamics. NeuroImage 114, 466–470.
Zalesky A., Fornito A., Cocchi L., Gollo L., Breakspear M., 2014. Time-resolved resting-state brain networks. In: Proceedings of the National Academy of Sciences of the United States of America. 111, pp. 10341–10346.