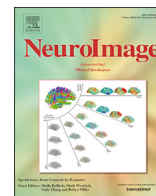


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Cortical cores in network dynamics



F. de Pasquale^{a,*}, M. Corbetta^{b,c}, V. Betti^{d,e}, S. Della Penna^f

^a Faculty of Veterinary Medicine, University of Teramo, Teramo, Italy

^b Department of Neuroscience, University of Padua, Padua 35128, Italy

^c Departments of Neurology, Radiology, Neuroscience, and Biomedical Engineering, Washington University, St. Louis, MO 63101 USA

^d Department of Psychology, University of Rome La Sapienza, 00185, Rome, Italy

^e Fondazione Santa Lucia, Istituto Di Ricovero e Cura a Carattere Scientifico, 00142, Rome, Italy

^f Institute for Advanced Biomedical Technologies and Department of Neuroscience, Imaging and Clinical Sciences, “G. D’Annunzio” University, Chieti, Italy

ABSTRACT

Spontaneous brain activity at rest is spatially and temporally organized in networks of cortical and subcortical regions specialized for different functional domains. Even though brain networks were first studied individually through functional Magnetic Resonance Imaging, more recent studies focused on their dynamic ‘integration’. Integration depends on two fundamental properties: the structural topology of brain networks and the dynamics of functional connectivity. In this scenario, cortical hub regions, that are central regions highly connected with other areas of the brain, play a fundamental role in serving as way stations for network traffic. In this review, we focus on the functional organization of a set of hub areas that we define as the ‘dynamic core’. In the resting state, these regions dynamically interact with other regions of the brain linking multiple networks. First, we introduce and compare the statistical measures used for detecting hubs. Second, we discuss their identification based on different methods (functional Magnetic Resonance Imaging, Diffusion Weighted Imaging, Electro/Magneto Encephalography). Third, we show that the degree of interaction between these core regions and the rest of the brain varies over time, indicating that their centrality is not stationary. Moreover, alternating periods of strong and weak centrality of the core relate to periods of strong and weak global efficiency in the brain. These results indicate that information processing in the brain is not stable, but fluctuates and its temporal and spectral properties are discussed. In particular, the hypothesis of ‘pulsed’ information processing, discovered in the slow temporal scale, is explored for signals at higher temporal resolution.

Introduction

Two complementary principles underlie cognition in the brain: functional specialization and dynamic integration (Fox and Friston, 2012; Tononi et al., 1994). Over the past two decades it has been shown that spontaneous brain activity (i.e. at rest in the absence of any task) is organized in functionally specialized large-scale networks (or resting state networks – RSNs) (Attwell and Laughlin, 2001; Biswal et al., 1995; Fox et al., 1988; Snyder and Raichle, 2012). Several RSNs have been observed: attentional, visual, somato-motor, auditory, language, executive control, and default systems that roughly correspond to different functional domains (Doucet et al., 2011; Glasser et al., 2016; Hacker et al., 2013; Yeo et al., 2011). These networks were originally studied assuming temporal stationarity, but recent methodological developments indicate that these networks are dynamic (i.e. they evolve over time). For recent reviews, see (Hutchison et al., 2013; Preti et al., 2016), although see the critique on the influence on the fMRI dynamics of head motion, sampling variability and fluctuating sleep state reported in (Laumann et al., 2016). We posit that efficient processing of information necessarily must involve dynamic (i.e. time varying) integration among spatially

separate networks as behavior unfolds. A possible mechanism easing this dynamic integration is the presence of structural and functional ‘hub’ regions. By hub it is meant a node showing either many connections or connections that place it in a central position for facilitating the communication within a network (Power et al., 2013). The centrality can be assessed by several metrics, as discussed in the next section, and the connections can be both structural or functional. A fundamental question is whether ‘structural’ and ‘functional’ hubs correspond (Cole et al., 2014; Shirer et al., 2012; van den Heuvel and Sporns, 2013b).

However, most of what we know about brain dynamic integration comes either from structural studies (e.g. diffusion weighted imaging -DWI- imaging) that infer aspects of temporal organization based on the structural properties of brain networks, or from functional studies, mainly functional magnetic resonance imaging (fMRI), that examines this integration at low temporal resolution. This review focuses on the issue of dynamic integration as examined with electrophysiological methods that allow for high temporal resolution, specifically magnetoencephalography (MEG), electroencephalography (EEG), and electrocorticography (EcoG). First, we briefly discuss different measures that have been adopted to identify structural or functional hubs in the brain

* Corresponding author.

E-mail address: fdepasquale@unite.it (F. de Pasquale).

(Bassett and Sporns, 2017; van den Heuvel and Sporns, 2013b). This is important since differences among these measures, and the different metrics to estimate the spatiotemporal structure of connectivity typically lead to discrepancies in the literature on the precise localization of central regions, (Buckner et al., 2009; Bullmore and Sporns, 2012; Cole et al., 2010; de Pasquale et al., 2012; de Pasquale et al., 2013; Hagmann et al., 2008; Power et al., 2013; Tomasi and Volkow, 2011; van den Heuvel and Sporns, 2013b). Next, we introduce the concept of *dynamic core*, defined as a set of brain regions showing the most consistent dynamic centrality with the rest of the brain (de Pasquale et al., 2016; de Pasquale et al., 2013). These areas appear to be overlapping with structural and functional hubs as identified with fMRI and DWI. We characterize the temporal and frequency properties of these regions, and the dynamics of their centrality. We propose that this dynamic core plays a fundamental role for an efficient and flexible communication across different functional domains. Specifically, such communication is not stable, but slowly varies over time allowing for different temporal modes of network interaction. These can be altered during active behavior and disease, and may relate to faster modes of network synchronization.

Cortical hubs in the brain

Identification of cortical hubs: measures of centrality

Several local and global measures can be applied from graph theory to characterize the topology of networks and to identify central (hub) regions (Bassett and Sporns, 2017; Bullmore and Sporns, 2009; Sporns, 2013). In this framework, a graph is an ordered set of nodes and edges represented by brain voxels (or parcels) and some measure of their coupling, respectively. The coupling is typically represented by structural (anatomical links), functional (statistical and symmetric dependence), or effective (causal interactions) connectivity information (Friston, 1994). The graph can be binarized (i.e. all connections are either 0 or 1) or weighted and directed or undirected. A directed graph consists of a set N of nodes and a set E of edges which are ordered pairs of elements of N . The edges have a direction associated with them. On the contrary, in an undirected graph the edges are bidirectional and thus correspond to unordered pairs of nodes. Directed edges can be obtained from effective connectivity or tract tracing studies. Since the concept of centrality involves different aspects such as the number of edges, their strength and quality (intra vs inter-modular connections), the definition of a cortical hub depends on the metrics adopted. In what follows, we provide an overview, far from exhaustive, of some typical measures of centrality, more details can be found in (Rubinov and Sporns, 2010).

The degree K (for a complete list of abbreviations used in the text, see Table 1) is defined as the number of edges connecting a node in a binary graph, see eq. (1) in SI. In weighted graphs it is defined as the sum of edge weights connecting to a node. This measure is widely adopted, for example it has been reported that high K nodes, obtained from structural connectomes, tend to be more connected to each other forming a “Rich Club” (van den Heuvel and Sporns, 2011). However, as noted in (Power et al., 2013), a drawback of K is its dependence on the community size. This implies that assessing the centrality through K might inflate the importance of nodes that belong to large networks. In fact a node with high K may be either a connector (connecting nodes of different modules) or a provincial (connecting nodes within the same module) hub.

An alternative measure, less sensitive to the eventual inflation induced by the community size, is the betweenness centrality (BC), see eq. (2) in SI, defined as the number of times a node participates in a shortest path (i.e. the node acts as a bridge between the strongest connections of any two nodes). BC is more sensitive to detecting connector hubs than provincial ones, and it often co-varies with other measures of nodal centrality (Zuo et al., 2012).

Another measure of hubness, less influenced by the community size, is the participation index (PI), see eq. (3) in SI, that measures how ‘well-distributed’ the links of a node are among different modules. The PI of a

Table 1
List of abbreviations adopted in the text and figures.

Abbreviation	Full Name	Abbreviation	Full Name
α band	[8, 13] Hz	L/R mt	Left/Right Middle Temporal
ACC	Anterior Cingulate Cortex	L/R pips	Left/Right Posterior Intraparietal Sulcus
AD	Alzheimer Disease	L/R put	Left/Right Putamen
AIC	Anterior Insula Cortex	L/R SII	Secondary somatosensory region Language Network
aTL	Anterior Temporal Lobe	LAN	
AUD	Auditory Network	LFP	Local Field Potential
β band	[14, 25] Hz	LPC	Lateral Prefrontal Cortex
BC	Betweenness Centrality	MOG	Middle Occipital Gyrus
BLP	Band Limited Power	mPFC	Medial Prefrontal Cortex
CCN	Cognitive Control Network	MTG	
D L/R PFC	Dorso (Left/Right) Prefrontal Cortex	PCC	Posterior Cingulate Cortex
D/V AN	Dorsal/Ventral Attention Network	PFC	Prefrontal Cortex
DC	Degree Centrality	PI	Participation Index
DMN	Default Mode Network	PMC	Pre-Motor Cortex
DPFC	Dorso Prefrontal Cortex	PPC	Posterior Parietal Cortex
EVC	Eigenvector Centrality	θ band	[3.5, 7] Hz
FEF	Frontal Eye Field	RSN	Resting State Networks
FPN	Fronto Parietal Network	SFC	Superior Frontal Cortex
γ band	[27, 70] Hz	SMA	Supplementary Motor Area
GE	Global Efficiency	SMN	Sensory Motor Network
HMM	Hidden Markov Model	STG	Superior Temporal Gyrus
IFG*	Inferior Frontal Gyrus	TMPFC	Temporal Cortex
Insula*			
L/R AG/IPL	Left/Right Angular Gyrus	V1,2,3,7	Visual Areas 1,2,3,7
L/R CS	Left/Right Central Sulcus	VIS	Visual Network

node is close to 1 if its links are uniformly distributed among all modules, and 0 if all its links are within its own module (Guimera and Nunes Amaral, 2005). Thus, this measure classifies hubs as nodes participating to a large number of communities (i.e. showing a large number of edges linking them to different modules). Nodes with a high PI behave as connector hubs while nodes with a low PI as provincial ones. Thus, it may happen that a node with a high degree scores a low PI, as in the case of a provincial hub, while K and PI agree in connector hubs. For this reason, the role of a node can be determined, to a great extent, by its within-module degree and its participation index, which define how the node is positioned in its own module and with respect to other modules, see (Guimera and Nunes Amaral, 2005; Sporns et al., 2007). Notably, PI depends on the outcome of the decomposition of the network into modules, and thus on the modularity measure adopted.

The measures K , BC, PI are local metrics. A global measure of centrality, although less used than the previous ones, is the recursive Eigenvector Centrality (EVC). In eq. (4) in SI we provide the mathematical definition, see (Lohmann et al., 2010; Zuo et al., 2012). The EVC classifies a node as central only if it is connected to other central nodes and thus it measures the influence of a node in a network. It assigns relative scores to all nodes in the network based on the concept that connections to high-scoring nodes contribute more to the score of the node in question than equal connections to low-scoring nodes. For this reason, EVC provides complementary information compared to K , since the EVC of a node connected through few but important links might be large despite a low K and vice versa. An important aspect in the analysis of binary graphs and related estimation of centrality is the choice of the threshold. This is discussed in the Supplementary Information.

Functional hubs in fMRI and MEG

By measuring K , fMRI hubs (van den Heuvel and Sporns, 2013b) were mainly found in the Default Mode Network (DMN, in regions/nodes such as Posterior Cingulate Cortex (PCC), Medial Prefrontal Cortex (mPFC), Angular Gyrus (AG)), see Fig. 1A and Table 1 (Buckner et al., 2009; Cole et al., 2010; de Pasquale et al., 2013; Tomasi and Volkow, 2010; Zuo et al., 2012). Additional functional cores have reported in the Somato Motor Network (SMN, in the Supplementary Motor Area (SMA) and Central Sulcus (CS)), in the Visual network (VIS) (Tomasi and Volkow, 2011) and frontoparietal (FPN) networks (regions marked by * in Table 1) (Zuo et al., 2012). When using PI as a measure of centrality, Power et al. found a poor agreement with findings in the DMN (Power et al., 2013). In fact, the authors emphasize a different set of associative regions more closely related to the FPN, DAN, and CCN (see Fig. 1B, Table 1). However, given the uncertain spatial localization, some hub regions labeled as DMN, for example AG, could easily fall within the FPN (Cole et al., 2014; Vincent et al., 2008), and some regions in (de Pasquale et al., 2013) fall within the DAN and SMN.

Compared to fMRI, the spectral richness of electrophysiological techniques (MEG, EEG, and EcoG) allows the analysis of both slow (band limited power, BLP) and fast (signal) temporal scales. These aspects are particularly important when studying the temporal dynamics, see (Larson-Prior et al., 2013) for a review. At the slow timescale, comparable to that measured with fMRI (~ 0.01 – 0.1 Hz), the highest centrality was consistently found in the β -band using different metrics and connectivity estimates (see Fig. 1C–F) (de Pasquale et al., 2012; de Pasquale et al., 2016; Hipp et al., 2012). In particular, in (Hipp et al., 2012) (Fig. 1C) normalized BC peaks at about 16 Hz (range 8–32 Hz) with maximal centrality in parietal, temporal, lateral and medial prefrontal cortex (Fig. 1D). Accordingly, in (de Pasquale et al., 2012), where time-varying correlation of β -BLP and weighted K were computed, central nodes were localized mainly in the DMN (PCC, bilateral AG and mPFC), DAN (left PIPS) and SMN (left CS). When using BC on the same data set (de Pasquale et al., 2016), the most central nodes were again PCC, bilateral PIPS, and SMA (see Fig. 1E–F). This latter set of regions partially overlaps with those found by means of BC computed on orthogonalized power times series (Hipp et al., 2012). By using graphs obtained from leakage-corrected β -BLP time series, K hubs were confirmed in PCC and bilateral AG (Maldjian et al., 2014). Notably, there is evidence that central regions in MEG are identified in the β -band, independently of the connectivity estimator and metrics of centrality. In particular, PCC was still a hub when analyzing connectivity at the fast time scale, although in different bands (α or γ) (Jin et al., 2014). Interestingly, by combining K and EVC to detect central nodes, bilateral precuneus, inferior parietal, precentral and supramarginal regions were identified as hubs in MEG (β - and γ -BLP), fMRI, and DWI (Garces et al., 2016). At fast timescale, using the Phase Locking Index to estimate connectivity, frequency specific sets of K based hubs were identified in the α , β and γ -band (Hillebrand et al., 2012). Other relevant papers include (de Haan et al., 2012; Jin et al., 2014; Schmidt et al., 2014).

In summary what did we learn? First, not surprisingly, the identification of central areas strongly depends on the method (e.g. fMRI, MEG), the metric (e.g. K , BC or PI) and the threshold used to derive the graphs, see SI and (Zuo et al., 2012). However, several MEG and fMRI studies using different metrics point to the DMN, specifically PCC and AG in parietal cortex as hubs. Certainly other networks including FPN, DAN, and SMN also contain central regions. For a recent work on the anatomical scaffold of these central regions, see (de Pasquale et al., 2017).

Core networks, the architecture of interaction among cortical hubs

It has been suggested that the presence of cortical hubs, especially connectors, is important for integrating information across functionally

specialized networks, see for example (de Pasquale et al., 2016). Furthermore, the modulation of hub dynamics occurring under different cognitive states or disease is of considerable interest, especially because it might provide important insights on the neurophysiological processes underlying behavior and cognition. These aspects are reported in SI. However, since behavior requires a flexible reconfiguration of task networks, the integration must occur across domains, notwithstanding the high energetic cost of neural architectures connecting spatially distant local modules.

Computational studies suggested that a balance between segregation and integration may be achieved through networks emphasizing the local efficiency through highly connected local modules, expert at processing one kind of information, and the integration through sparse inter-module connections involving a small number of hubs. This architecture is denoted ‘Small World’ (Bassett and Bullmore, 2006, 2016) and it has been observed across a wide range of imaging modalities including MEG (Stam, 2004; Valencia et al., 2008), fMRI, DWI (Achard et al., 2006; Salvador et al., 2005; Vaessen et al., 2010; van den Heuvel et al., 2008), EEG (Smit et al., 2008) and tract-tracing (Hilgetag and Kaiser, 2004; Sporns et al., 2004). The original idea behind small-worldness paved the way for many successive works on the communication among these few central regions. In a very influential paper, Van de Heuvel and colleagues (van den Heuvel and Sporns, 2011) presented a refinement of the hubs/small world idea by showing that the brain not only contains hubs, but these are preferentially connected in a ‘Rich Club’ (see Fig. 2). Using deterministic tractography and a high-resolution parcellation of the brain, they mapped sub-cortical and neocortical hubs and examined their structural links. High K nodes tend to form denser connections among themselves than with lower K nodes. These regions include bilateral superior fronto-parietal regions, including PCC, as well as subcortical regions such as hippocampus, thalamus, and putamen. Connections linking non Rich-Club to Rich Club nodes are called feeder (see Fig. 2A), while edges connecting non-Rich Club regions are labeled ‘local’ (Fig. 2B) and connections among rich-club members are called ‘rich-club’ (Fig. 2C). A model for these results suggests that hubs communicate as a strongly interlinked ensemble able to flexibly link to different peripheral networks in the course of different tasks. This idea was explored later on in fMRI showing that a common set of hub regions tend to co-activate across a large number of different cognitive tasks (Cole et al., 2013, 2014). This organization is a plausible solution to the issue of flexible control since the rich club contains nodes participating in other networks (Gollo et al., 2015; van den Heuvel and Sporns, 2013a; van den Heuvel and Sporns, 2013b). In fact, it has been shown that rich-club nodes distribute across different RSNs with a certain degree of overlap (see Fig. 2D). However, it must be noted that in (van den Heuvel and Sporns, 2013a) it was also reported that inter-modular connections are disproportionately represented by hub-connections and these regions play a critical role in network communication also in terms of longer fiber-lengths and higher network traffic (Collin et al., 2014; van den Heuvel et al., 2012). Finally, this architecture, might also be a convenient way to protect global communication in the brain in the course of damage or diseases (Kaiser et al., 2007). In the case of one malfunctioning hub, distant effects may be felt in the system (Tuovinen et al., 2016), but the effect on global communication may be alleviated by strong connections among other hubs. In summary, the challenge of flexible behavioral control leads to the possibility that the brain exploits a small world architecture in which a few highly inter-connected regions function as bridges dynamically linking to peripheral nodes involved in local processing.

Cortical cores as a tool of dynamic network integration

Temporal and spectral dynamics of brain networks

It is well established that the electrophysiological signals recorded from surface/deep electrodes show fractal features (e.g. scale-free

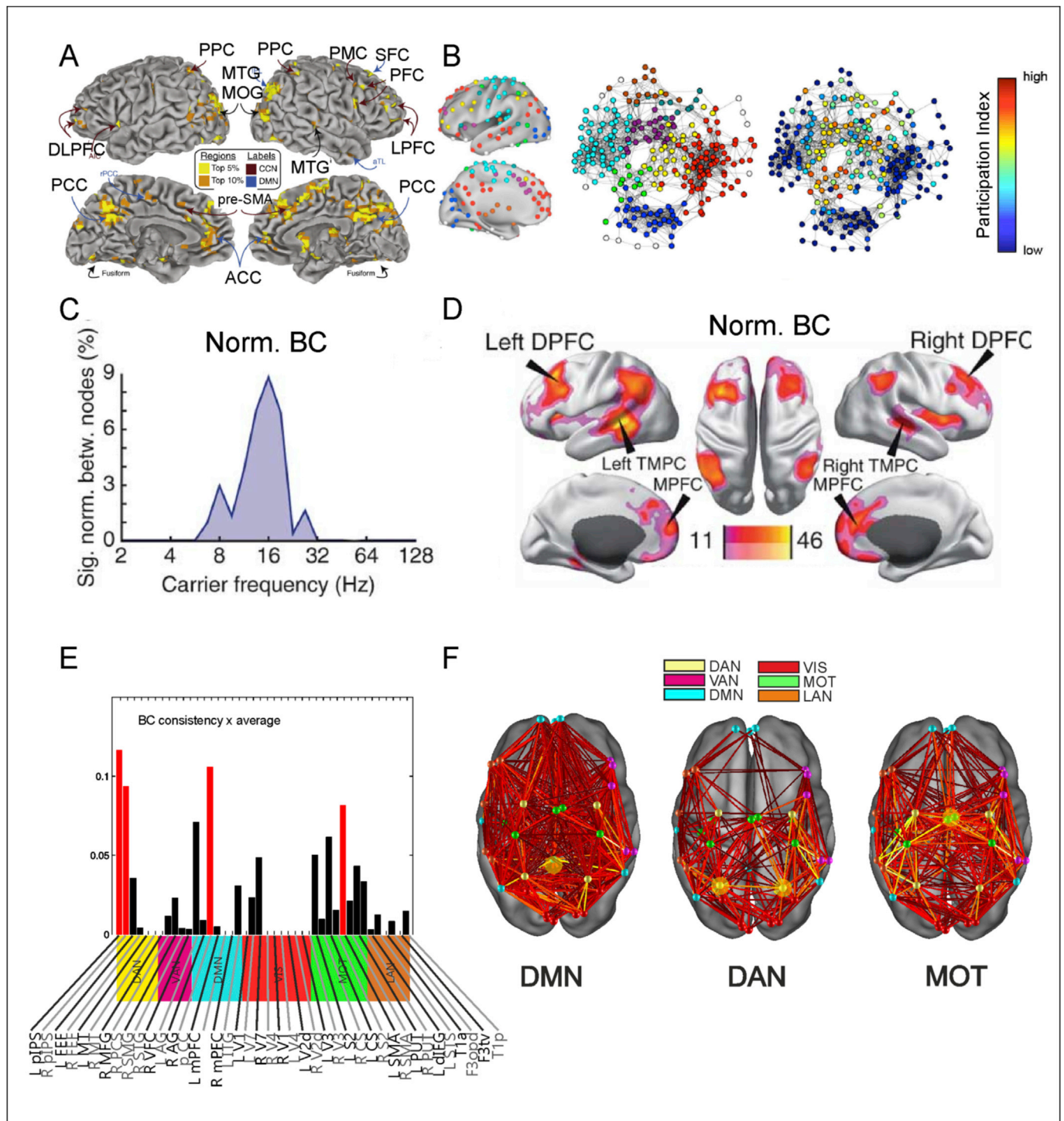


Fig. 1. Functional hubs in the human brain.

(The adopted labels are reported in Table 1)

A) Top 5% and 10% fMRI hubs found through weighted degree obtained from functional connectomes. The majority of top 5% hubs are comprised in the Default Mode Network (blue labels) and the entire set of cognitive control network (CCN) (red labels) contains all top 10% hubs (Adapted with permission from (Cole et al., 2010)). B) To identify nodes that routinely participate in multiple communities, the Participation Index can be adopted. Here, this was computed on communities evaluated on the binary graph thresholded at 5% connection density. Communities are shown on the surface (left) and through a spring-embedded plot. (Adapted with permission from (Power et al., 2013)). C) The percentage of central nodes evaluated by means of the Betweenness Centrality (BC). The reported nodes show significantly increased centrality compared to the average value in the brain ($p < 0.05$). These results were obtained from MEG Band Limited Power connectivity matrices following signal orthogonalization. The larger, statistically significant percentage of hubs is found at the carrier frequencies in the β band, extending also to the α band (adapted with permission from (Hipp et al., 2012)). D) From the same graph as in C), regions showing the highest centrality at 16 Hz were found in bilateral medial/dorso-prefrontal and Temporal Cortex (see Table 1 for the definition of labels). The centrality evaluated by means of Betweenness Centrality is statistically masked at two levels of significance, one corrected for the number of nodes ($p < 0.05$, saturated color scale) and the other uncorrected ($p < 0.05$) (Adapted with permission from (Hipp et al., 2012)). E) Hubs estimated from β Band Limited Power dynamic connectivity. It is reported the product of the mean Betweenness Centrality (BC) across epochs of high internal connectivity for the Default, Dorsal/Ventral Attention, Motor, Visual and Language Networks and the consistency of BC in the same epochs. The hubs characterized by a strong and consistent centrality in all epochs (red bars) are the Posterior Cingulate, left/right posterior interparietal sulcus and supplementary motor area, see Table 1 for the definition of labels (Adapted with permission from (de Pasquale et al., 2016)). F) Topography of connections of the above hubs (yellow) shows a large number of external connections driving the high value of centrality. These topographies are obtained in epochs of high internal connectivity for the above mentioned networks (Adapted with permission from (de Pasquale et al., 2016)).

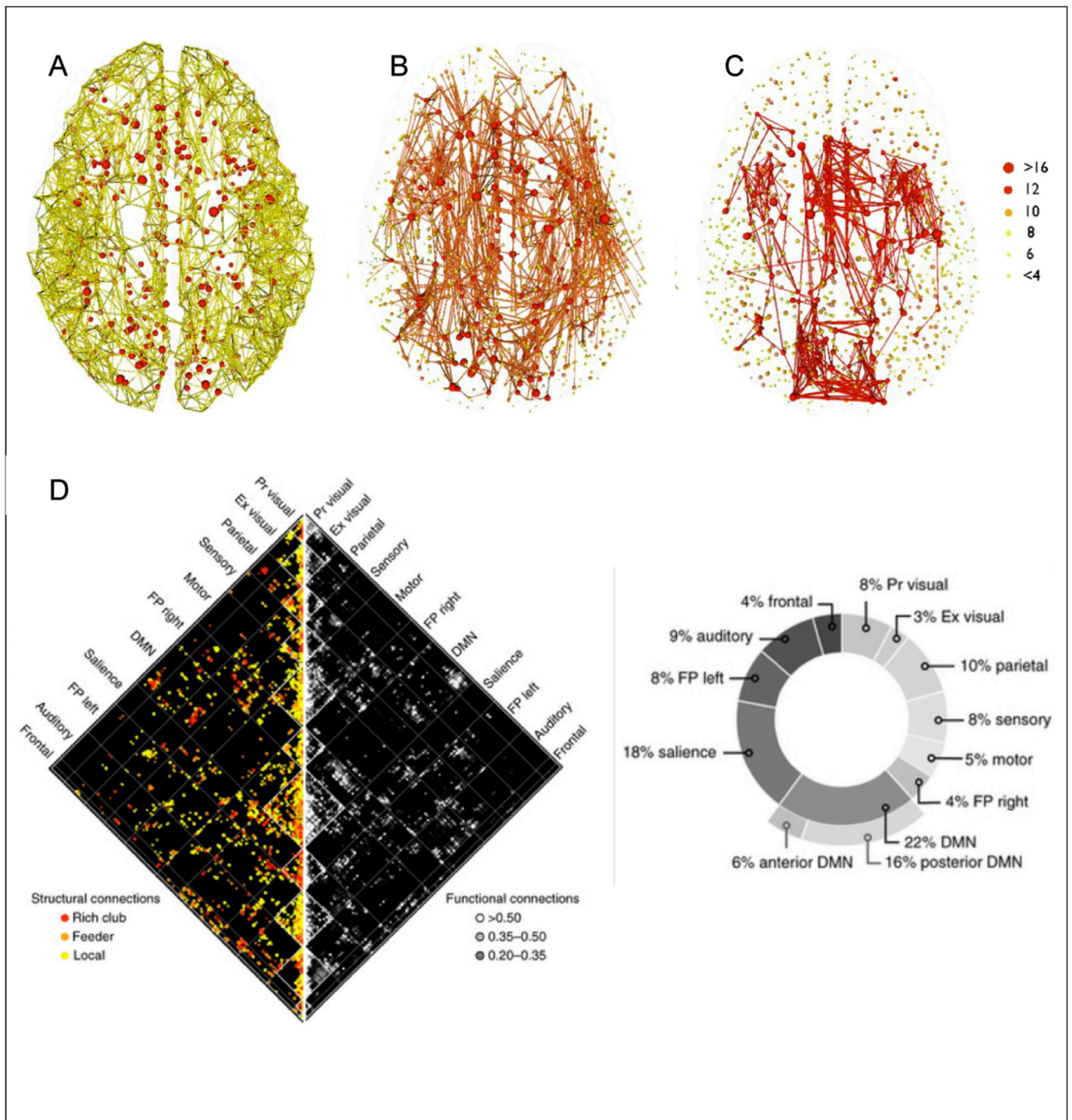


Fig. 2. The Rich Club model.

Structural brain hubs exhibit a strong tendency to be mutually and densely interconnected, forming a structural core or “Rich Club”. This central high-cost, high-capacity backbone for global brain communication comprises a set of spatially widely distributed brain regions including portions of the precuneus, anterior and PCC, superior frontal cortex, superior parietal cortex and the insula, all in both hemispheres. Edges connecting Rich Club to non-Rich Club regions are labeled as ‘feeder’ (A), while edges connecting non-rich club regions are labeled as ‘local’ (B) and connections among rich-club members are called ‘rich-club’ (C). Nodal degree K is reported on the right. Rich club nodes are selected based on $k > 10$ (red circles) (Adapted with permission from (Sporns, 2014)). (D) (left Panel) structural Diffusion Tensor Imaging (left triangle) vs fMRI (right triangle) connections averaged across a group of 75 healthy volunteers. Functional modules are based on independent component analysis: Pr visual, primary visual; Ex visual, extrastriate visual; FP, frontoparietal; (right Panel) Distribution of Rich Club nodes in relation to resting state networks, expressed as proportions across networks (Adapted with permission from (van den Heuvel and Sporns, 2013a).

properties) and are incredibly rich in the frequency domain ranging from [0.001, >500] Hz (Buzsaki and Draguhn, 2004). This spectral richness leads to three fundamental observations for our discussion.

First, brain networks observed with fMRI correspond to interactions

involving both fast and slow electrophysiological signals. At slow frequencies (<4 Hz), the coupling based on the slow cortical potential represents one electrophysiological correlate of these networks, while at higher frequencies such correspondence is lost (Hacker et al., 2017; He

et al., 2008, 2010; Nir et al., 2008). The other correlate is the BLP coupling at different frequencies. In ECoG studies, interactions occurring at γ , α and β bands have been associated to fMRI RSNs (Hacker et al., 2017; He et al., 2008; Keller et al., 2013; Leopold et al., 2003; Nir et al., 2008). MEG studies have mainly reported similarities between fMRI and MEG RSNs in α - and β -BLP (Brookes et al., 2011b; de Pasquale et al., 2010; de Pasquale et al., 2012; de Pasquale et al., 2016; Hipp et al., 2012).

Second, there appears to be frequency specific interactions both within/across networks. Mantini et al. originally showed that EEG signals at different frequencies differently contributed to fMRI signals recorded in various RSNs (Mantini et al., 2007). A predominance of α power was recorded in parietal and visual regions, while a predominance of β power in SMN regions. MEG studies found stronger interactions among VIS regions in the α -BLP, DAN in the α - and β -BLP, SMN in the β -BLP, and DMN also in α - and β -BLP, and at a lesser extent in the θ -BLP (Brookes et al., 2011a, 2012; de Pasquale et al., 2010; de Pasquale et al., 2012; Hipp et al., 2012). In addition, across-network interactions were also found spectrally selective. In the signal domain, DAN-VIS interactions (estimated from imaginary coherence) occur in the α -band while DAN-SMN interactions occur in the β -band (Marzetti et al., 2013). It must be noted that at a larger spatial scale, when analyzing the correspondence between fMRI and MEG functional connections across the entire cortex, the correction of signal-to-noise ratio (SNR) across frequencies suggested the involvement of a wider range of frequencies, namely [2, 128] Hz (Hipp and Siegel, 2015); (see (Palva and Palva, 2012) for methodological discussions). Very recently, Hacker et al. found in ECoG recordings that regions involved in internal cognition (DMN, FPN) were more strongly correlated in the θ band, whereas regions more involved in sensory-attention-motor processing (DAN, SMN) were more strongly coupled in the α band (Hacker et al., 2017).

Third, and more importantly, these connectivity patterns are not static but slowly (in the order of seconds) vary over time. de Pasquale and colleagues observed that the coupling between regions of a RSN slowly changed over time alternating periods of strong and weak coupling (de Pasquale et al., 2010). In a subsequent work, they showed that the alternation of strong/weak network coupling (at least for some central networks like DMN or regions like PCC) predicted varying degree of across-network interactions (see next paragraph). Notably, in this work, RSN connectivity and its temporal dynamics were studied in source space by means of the combination of a Minimum Norm Estimator, Independent Component Analysis and the Pearson correlation coefficient as a measure of coupling over sliding windows (Betti et al., 2013; de Pasquale et al., 2010; de Pasquale et al., 2012; de Pasquale et al., 2016; Mantini et al., 2011). However, in other MEG studies such as (Brookes et al., 2014) a beamforming technique supported by a leakage correction (that could also be applied to Minimum Norm solutions, see for example (Wens, 2015)) and canonical correlation were used to retrieve time-varying functional interactions (O'Neill et al., 2015). Interestingly, even though MEG signals are acquired at very high temporal resolution (~ 1000 KHz), and different groups adopted different approaches to measure time-varying interactions, there is consensus that these fluctuations of coupling occur at slow temporal scales (few seconds). This is comparable to what found in fMRI. Of note, while in fMRI the temporal scale is limited by the temporal resolution induced by the neurovascular coupling, in MEG the duration of the sliding window is longer than the available MEG temporal resolution (around 1 ms), but it represents a good compromise between the robustness of the connectivity estimator and the temporal resolution of the investigated fluctuations. It is possible that these slow time scales reflect the adopted measure (BLP), and that faster frequencies would be observed in the signal domain. This is the case for the so called MEG brain states, see (Baker et al., 2014), as discussed in Section 5.

The time-varying nature of connectivity has also been investigated with fMRI, but is controversial if the observed dynamics truly reflects non-stationarity (Hutchison et al., 2013; Preti et al., 2016) or rather just a

poor estimate (influenced by motion artifacts and sampling variability) of a static coupling (Laumann et al., 2016). Early findings showed significant fluctuations of inter-regional correlation (Chang and Glover, 2010), mainly involving across-module interactions (Zalesky et al., 2014). However, estimates of correlation in time are limited by several factors including the number of available samples (Zalesky and Breakspear, 2015), residual subject's motion, see (Power et al., 2015), and a severe trade-off between robustness and temporal resolution. Alternative approaches have been proposed including dynamic spectral analyses (Yaesoubi et al., 2015), data-driven temporal ICA (Smith et al., 2012) and connectivity states extraction (Allen et al., 2014), see next section. Another important aspect is the connection between brain structure and dynamics which is related to network motifs. These are the building blocks of the network (Milo et al., 2002; Sporns and Kotter, 2004) and provide a testbed for many hypotheses on empirical data as well as in computational models. In this context, apex nodes can be considered the core nodes of network motifs. They appear more often in hub regions and play an important role in brain structure (Harriger et al., 2012) and dynamics (Alstott et al., 2009; Gollo et al., 2014; Senden et al., 2012, 2014; Vasa et al., 2015; Wei et al., 2017). Moreover, frustrated network motifs can be considered a structural basis for dynamic connectivity since they facilitate dynamic functional connectivity via metastable transitions (Gollo and Breakspear, 2014).

Finally, the slow and fast temporal scales of network interaction, the frequency specificity by network and the time varying interactions have important implications on how cortical cores may interact at rest and during task processing. This is considered in the next section.

Dynamic core network as the substrate for an efficient global communication in the brain.

The time-frequency properties of the functional architecture are fundamental to unravel mechanisms of dynamic integration in the brain (Bassett and Sporns, 2017). There are several important questions to be addressed: do hub regions show fluctuations in their centrality similarly to other networks? What are the implications of these fluctuations for other regions that are connected to the hubs? Do these fluctuations have a functional implication in healthy processing, aging, or disease? fMRI studies tend to show that these central regions are topologically stable during a task as compared to rest (Cole et al., 2013, 2014; Chiang et al., 2016; Liao et al., 2015), but these results are just beginning to come in, and other studies show a significant reorganization of network interaction during task performance (see for example, Spadone et al., 2015). Moreover, it must be considered that the limited temporal resolution of fMRI may miss fast transient variations in topology. MEG results instead provide a very interesting insight on cortical dynamics of RSNs and hubs. In one set of observations, de Pasquale and colleagues (de Pasquale et al., 2012) showed that in the β -BLP, the DMN represented a functional core of integration in the brain. This was observed during epochs of high internal coupling of this RSN. Specifically, in these epochs, PCC, bilateral AG, and mPFC were strong K hubs. Similar observations were made for other networks/hubs including DAN/left PIPS and SMN/left CS. Interestingly, these nodes spent only a small part of time (20–30%) in epochs of high centrality, and these epochs did not overlap indicating that different hubs significantly alternated their central role, see Fig. 3A (de Pasquale et al., 2016). These results were then the first hint that there may be a link between dynamic connectivity and integration. In other words, the amount of integration among different networks seems to increase when some networks (DMN, DAN, SMN) are more strongly coupled. More recently, in (de Pasquale et al., 2016) this work was extended by focusing on BC as a measures of centrality. This measure, as previously described, emphasizes 'connector hubs' and thus accounts more explicitly for interactions among different networks. The temporal evolution of BC was estimated and, on average, high BC nodes included again PCC (DMN), bilateral PIPS (DAN), and SMA (SMN, see Fig. 3B). In agreement with the prior MEG study, but in contrast to fMRI studies indicating stable hubs over time, peaks of high BC occurred about 40% of time. Again, these hubs asynchronously alternated epochs of high and

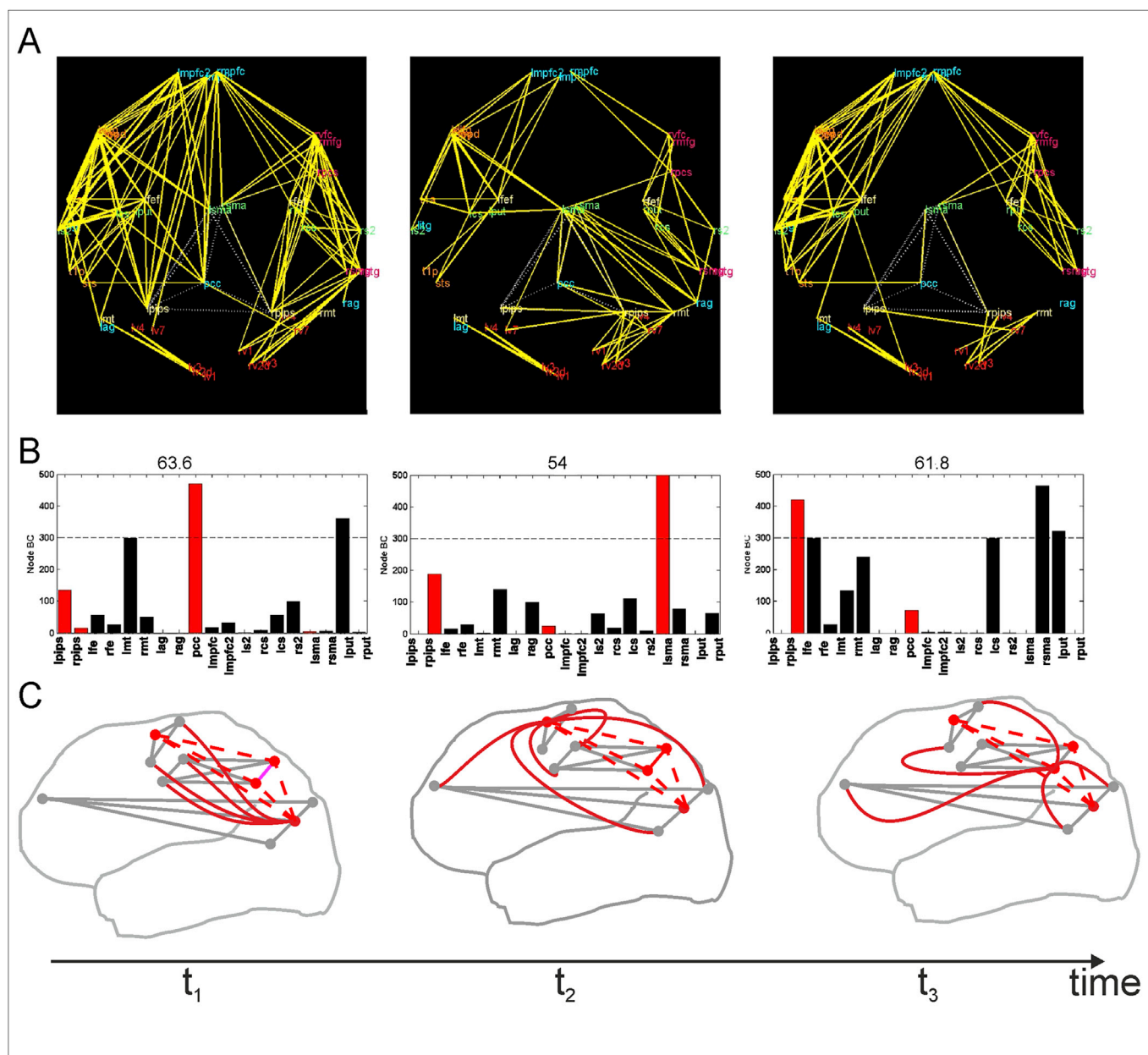


Fig. 3. The dynamic core network.

A set of functional hubs alternate their centrality forming a dynamic core of integration.

A) Dynamic binary graphs obtained from the β Band Limited Power connectivity matrices at three representative time samples. B) Centrality as estimated through the Betweenness Centrality at the three epochs as in A), together with the random graph significance threshold (dotted line). Hubs forming the core network are transiently central: Posterior Cingulate Cortex (left), Supplementary Motor Area (middle) and right Posterior Intraparietal Sulcus (right). C) Schematic model of the dynamic mechanism underlying the core network: central nodes alternate their central role to ensure an efficient communication in the whole brain dynamically. (Adapted from (de Pasquale et al., 2016)).

low centrality, forming what can be defined as a ‘dynamic core network’ (Fig. 3C). Notably, the regions comprising this dynamic core network largely overlap with the previously discussed “Rich Club” (van den Heuvel and Sporns, 2013a). Perhaps the most intriguing result of this study was that epochs of high BC correspond to periods of high global efficiency in the whole brain. The Global Efficiency (GE) is defined as the average of the reciprocal shortest path length over all the network nodes (Rubinov and Sporns, 2010). For RSNs including hubs of the core network, epochs of high internal connectivity (i.e. epochs in which the RSN shows a higher internal connectivity as compared to the rest of the brain) predicted epochs of maximal GE (see for example a representative timecourse of DMN in Fig. 4A). Interestingly, these epochs correspond to peaks of centrality of PCC, see Fig. 4B (left panel - red bar). This property seems to be lost outside these temporal windows and the centrality of the

DMN is mainly realized by external to DMN connections (Fig. 4C, black bar). To study if the GE peaks could be predicted by epochs of high internal coupling of these networks, de Pasquale and colleagues classified through Receiver-Operator-Curves these time intervals (Fig. 4D): epochs of high internal connectivity within DMN, DAN and SMN predicted more than 70% of GE peaks (see Fig. 4E). These epochs of high internal connectivity were also epochs of high centrality for hubs included in the dynamic core network. Of note, this mechanism linking the dynamic core network, fluctuations of BC, and GE occurred specifically in the β -BLP.

In summary, these findings link in a novel mechanistic framework three results. First, RSNs dynamically fluctuate and these fluctuations involve changes in within/across network interactions. These occur specifically between hub regions of specific RSNs and other nodes in periods of strong coupling for the central networks. Second, these hubs

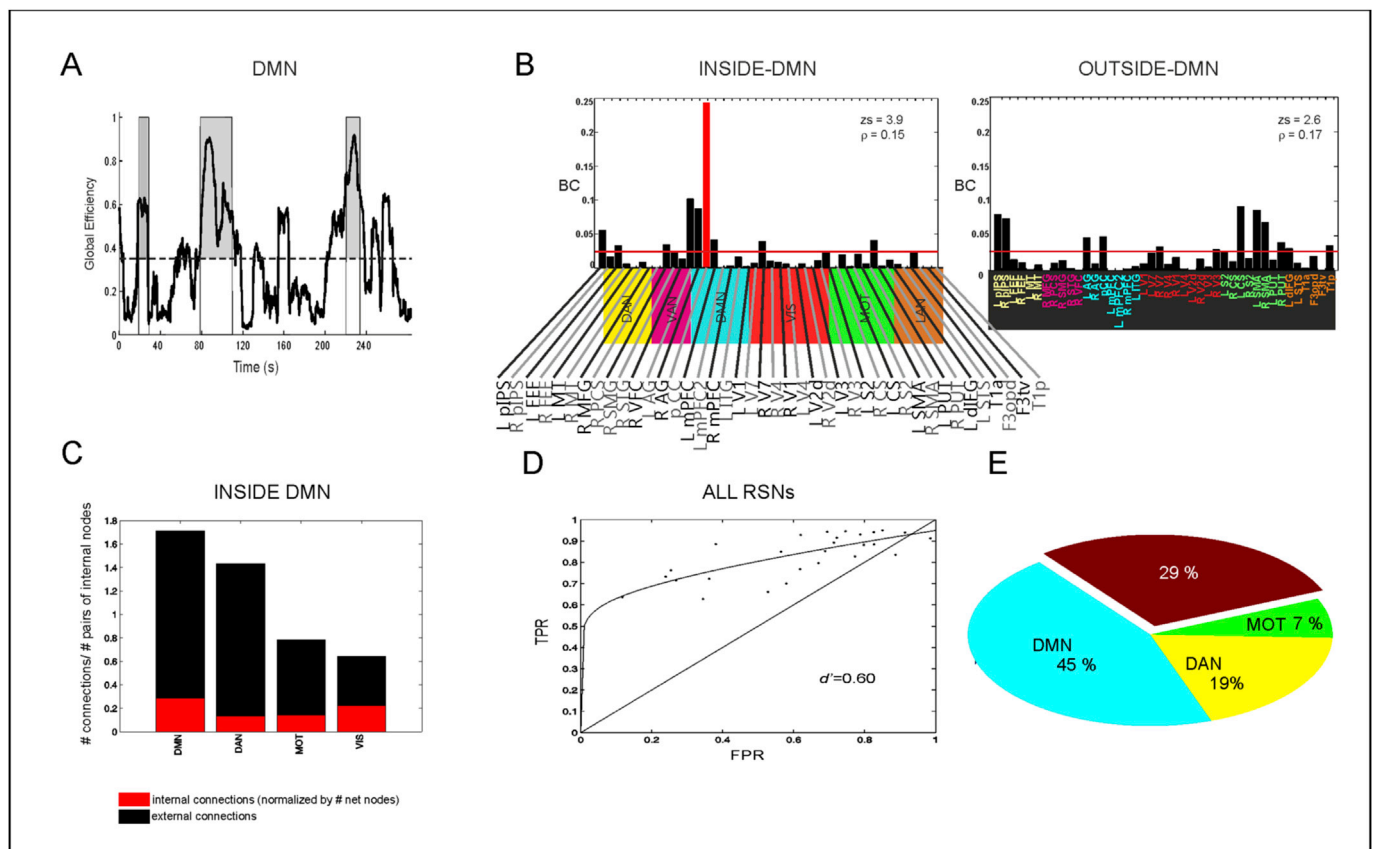


Fig. 4. The Global Efficiency of integration.

The dynamic core network corresponds to an optimal strategy of the brain in maximizing the efficiency of communication as measured through the global efficiency.

A) Transient global efficiency for a representative run. Epochs of high internal coupling for the Default Mode Network, shown as shaded areas, overlap with epochs of high Global Efficiency. B) Notably, these epochs correspond to high centrality for the Posterior Cingulate Cortex (red bar), a hub in the dynamic core network (left panel). Outside these epochs the centrality of this node is lower (right panel). C) Percentage of connections contributing to the centrality of the Default Mode Network. The centrality of this network is realized by a consistent proportion of external connections (black) compared to internal ones (red). D) The Receiver Operator Curve analysis shows that epochs of high internal coupling for the involved networks classify peaks of global efficiency. E) Incremental percentage of classification of GE peaks computed for the networks involved in the dynamic core. DMN classifies 45%, DAN increments this value by 19% and MN by 7%. Overall, 71% of the GE peaks are covered by these three RSNs internal coupling, see Table 1 for the definition of labels. (Adapted from (de Pasquale et al., 2016)).

are consistent over time, but they are engaged at different times. Third, epochs of high RSN coupling and centrality correlate and predict periods of high efficiency in the brain. As a whole, these findings suggest the novel idea that transfer of information, as captured by GE, occurs with a ‘pulsatile’ regime controlled by the dynamics of network integration, at least in the resting state. However, additional MEG studies are required to fully characterized such pulses (e.g. in terms of time-intervals etc ...).

This framework fits a number of recent studies. Zalesky and colleagues linked the dynamics of fMRI connectivity to a measure of efficiency (Regional Efficiency, a measure of nodal not global efficiency like GE) (Zalesky et al., 2014). They reported that the most dynamic connections link elements from topologically distinct subsystems. These connections involve known DMN and FPN hubs that spontaneously increase, for brief intervals, their efficiency producing temporarily globally integrated network states. Since the integration through long connections might involve higher metabolic costs, their results suggest that brain dynamics reflects a balance between integration of information and metabolic expenditure (Zalesky et al., 2014). They also support the idea that this transfer of information, occurring in specific epochs controlled by the dynamics of network interaction, enables otherwise segregated network elements to access a cognitive global workspace. The transient exploration of this workspace may allow the brain to efficiently balance segregated and integrated dynamics. A related study explored the origin of slowly fluctuating patterns of cortical synchronization and found that these patterns match well the activity within the Rich Club regions (Gollo et al., 2015). Furthermore, it has been shown that fluctuations of global

efficiency alter patterns of activity in local neuronal populations elicited by changes in incoming sensory stimuli (Cocchi et al., 2017). Accordingly, it was reported the presence of multiple cortical timescales involving the emergence and dissolution of interactions of cortical regions within the human visual system (e.g. with frontal eye fields) when the neural activity is perturbed (e.g. by means of Trans Magnetic Stimulation) was reported in (Cocchi et al., 2016).

To summarize, dynamic interactions among hubs occur at multiple time scales, but also involve epochs of variable integration hence probably information processing. Thus, the brain seems to exploit a temporal ‘multi-scale pulsed’ mode for network communication where slower time scales provide information about the state of the system, while faster time scales reflect the temporal details of behavior (this is elaborated more the next section). This new perspective opens up a number of interesting new issues for the field. In particular, it would be fundamental to understand why the temporal dynamics in interacting brain networks occur on a slow temporal scale, what is its origin (biophysical, neuronal), functional significance and the role played by fast synchronizations during task/cognitive processes.

Cortical cores and slow vs. fast dynamic brain states

The results reviewed thus far indicate that brain networks are not segregated but dynamically integrated, and this property varies over multiple temporal scales: slow, in the order of seconds, and fast in the order of hundreds of milliseconds. Here, we elaborate on the functional

roles of hub/cortical dynamics at rest and during task processing. We will first consider the slow temporal scale.

The slow time-varying nature of BLP interactions at rest suggest that these must reflect processes that are not changing rapidly as a function of environmental or behavioral conditions. The mechanism linking the dynamic core network and GE occurs in the β -BLP, which has been proposed to reflect the band signaling the “status quo” of a current behavioral state (Engel and Fries, 2010). Therefore, one possibility is that these slow β -BLP fluctuations reflect endogenous states occurring at a slow temporal scale. Gollo and colleagues (Gollo et al., 2015) proposed that the time-frequency of hub-regions match the slow time-scales of autonomic regulation which are hence closely synced to affective experiences, for a review of this emerging field see (Seth and Friston, 2016). In contrast, the topology of the surrounding ‘feeder’ regions (see previous definition and Fig. 2A) shows rapidly fluctuating dynamics likely to be crucial for fast perceptual processes. It was suggested that the ‘Rich Club’ nodes promote a stable, dynamical core of spontaneous activity related to internal processes, and highly unstable dynamical transitions in the periphery (Gollo et al., 2017). A similar notion that peripheral areas of the brain’s network change as a function of task demands, while a central core remains relatively stable, is also part of the interpretation of recent fMRI studies on the role of hubs in cognition (Cole et al., 2014). Another interesting idea is that the dynamics in core regions reflects anticipatory processes, both spatial and temporal. Spadone et al. compared fMRI functional connectivity both at rest and during a demanding visuospatial attention task (Spadone et al., 2015). Despite an overall preservation of network structure they showed a significant increase in across network interactions between DAN regions involved in control and VIS regions involved in stimulus analysis. More importantly, they found that, during attention, directional interactions between DAN and VIS became more strongly top-down. On the contrary, functional interactions (as measured via temporal correlation) within the DAN, a central network, did not change from rest to task, and thus were set up in ways to anticipate task states. This relates to the idea of spontaneous activity as a prior proposed to explain the similarity between RSN and task states in fMRI (see also (Raichle, 2011)). Accordingly, Betti et al. recently showed that slow temporal scale dynamic fluctuations in the core predict the dynamics during a natural visual stimulation. The idea that dynamics in core regions synchronize multiple brain states is also suggested by Smith et al. that used temporal ICA to decompose different temporal components in spontaneous activity (Smith et al., 2012). In fact, at the slow time scale of the fMRI functional connectivity, Multiple Temporal Functional Modes (TFM) were identified, and the centrality of a node was measured by the overlap among them. Interestingly, DMN regions were found to be involved in many of these modes concerning semantic and language systems. When multiple temporal functional modes were averaged, a complete DMN topography was recovered with the strongest overlap in PCC. Now, if TFMs represent how modes of connectivity evolve over time, in this evolution, the observation that PCC at distinct temporal epochs is involved with many different RSNs seems to suggest that its dynamics allows it to coordinate interactions among separate functional systems. Therefore, the centrality of this node does not reflect a single state, rather the combination in time of multiple ones.

Which is the relationship between slow and fast temporal scale dynamics? Overall more research is needed on this point. There has been important work on the notion of EEG microstates, reported for the first time in (Lehmann et al., 1987). They showed that the electric topography of the scalp does not change randomly and continuously over time, but remains stable for ~80–120 ms; these periods of quasi-stability were termed “EEG microstates”. Surprisingly, only few (between four and six) distinct microstates are still consistently observed at rest. Recently, it has been shown that these rapidly changing microstates correlate significantly, albeit not strongly, with activity in fMRI RSNs after convolution with the hemodynamic response function (Van de Ville et al., 2010). While there is some uncertainty in linking microstates to fMRI networks, EEG microstates nicely link to ongoing investigations of brain dynamics

in whole brain recordings. Microstates have time scales that are in the range of cognitive processes, and show a scale-free dynamics. This might be the basis for the rapid reorganization and adaptation of the functional networks in the brain (Van de Ville et al., 2010). However, caution must be taken when comparing states across EEG and fMRI or MEG. In fact, these EEG states are extracted in time epochs corresponding to peaks of Global Field Power while fMRI and MEG connectomes are based on some measure of synchronicity. However, since those peaks correspond to moments of overall high activity and thus likely to high synchronicity, some cross-modal agreement is not unexpected. Notably, recent work shows an interesting link between microstates and cortical hubs. In fact, Pascual-Marqui and colleagues observed that all microstates have common generators in PCC, while three microstates additionally include activity in the left occipital/parietal, right occipital/parietal, and anterior cingulate (Pascual-Marqui et al., 2014). Thus, these generators appear to be a fragmented version of DMN supporting the notion that these regions activate sequentially at high temporal resolution, and that this RSN might correspond to a very low-pass time filtered version of this faster dynamics. Moreover, they show that PCC acts an important hub in connections mediating the microstate transitions, sending alpha and beta oscillatory information to all other microstate generator regions.

Brain states have also been identified with MEG. Baker and colleagues (Baker et al., 2014), using Hidden Markov Models, revealed transient (100–200 ms) brain states whose spatial topographies somehow resembled those of well-known RSNs. In this temporal dynamics of state transitions, functional hubs would seem essential. Yet PCC was notably absent possibly due to its interaction with multiple states, which would make it not detected with this strategy of analysis. A more speculative avenue of investigation is the relationship between ongoing microstates, and a general synchronization in the slow/fast temporal scale. Task synchronization, especially in the high frequency range (high γ) has been shown to index selective cortical communication during visuomotor and attentional processing, as well as a number of other cognitive processes (working memory, language, navigation, etc.) (Engel et al., 2001; Melloni et al., 2007). An interesting recent development in the conceptualization of task dependent synchronization is that this mechanism does not only provide a way for spatially linking task relevant neuronal populations, but also as a mechanism for temporally sampling the environment (Vanrullen and Dubois, 2011). In this respect, the alternation between cycles of excitation and inhibition provides temporal windows for perception and motor behavior, as well as cortical synchronization between distant neural populations. This notion might be linked to the temporal prior idea on the possible interaction between slow and fast temporal scales. This has been shown to occur through a number of cortical mechanisms, such as amplitude-amplitude/phase-amplitude/phase-phase interactions (Jensen and Colgin, 2007).

Theoretical aspects of hub dynamics and brain states

The observation that functional cores and their dynamics play a fundamental role in a ‘pulsed’ (i.e. non stationary) synchronization of distinct functional modules, seems to be supported also by theoretical and modeling studies, see (Breakspear, 2017; Cabral et al., 2017) for a review on computational models. The notion of distinct functional connectivity states recurring at different points in time is compatible with models of neuronal connectivity (Deco and Corbetta, 2011; Deco et al., 2011). Accordingly, a ‘dynamic repertoire’ of states is expected to be continuously explored to more quickly adopt the optimal network configuration for a given impending input (Deco et al., 2011). Such dynamic exploration, where brain states never set in a fixed point (Cabral et al., 2014), can provide the flexibility required to adapt to the rapidly changing computational demands of cognitive processing (Bressler and Tognoli, 2006). Hansen and colleagues showed that the resting state regime has a rich structure, characterized by rapid transitions switching between a few discrete connectivity states, see Fig. 5A and B (Hansen

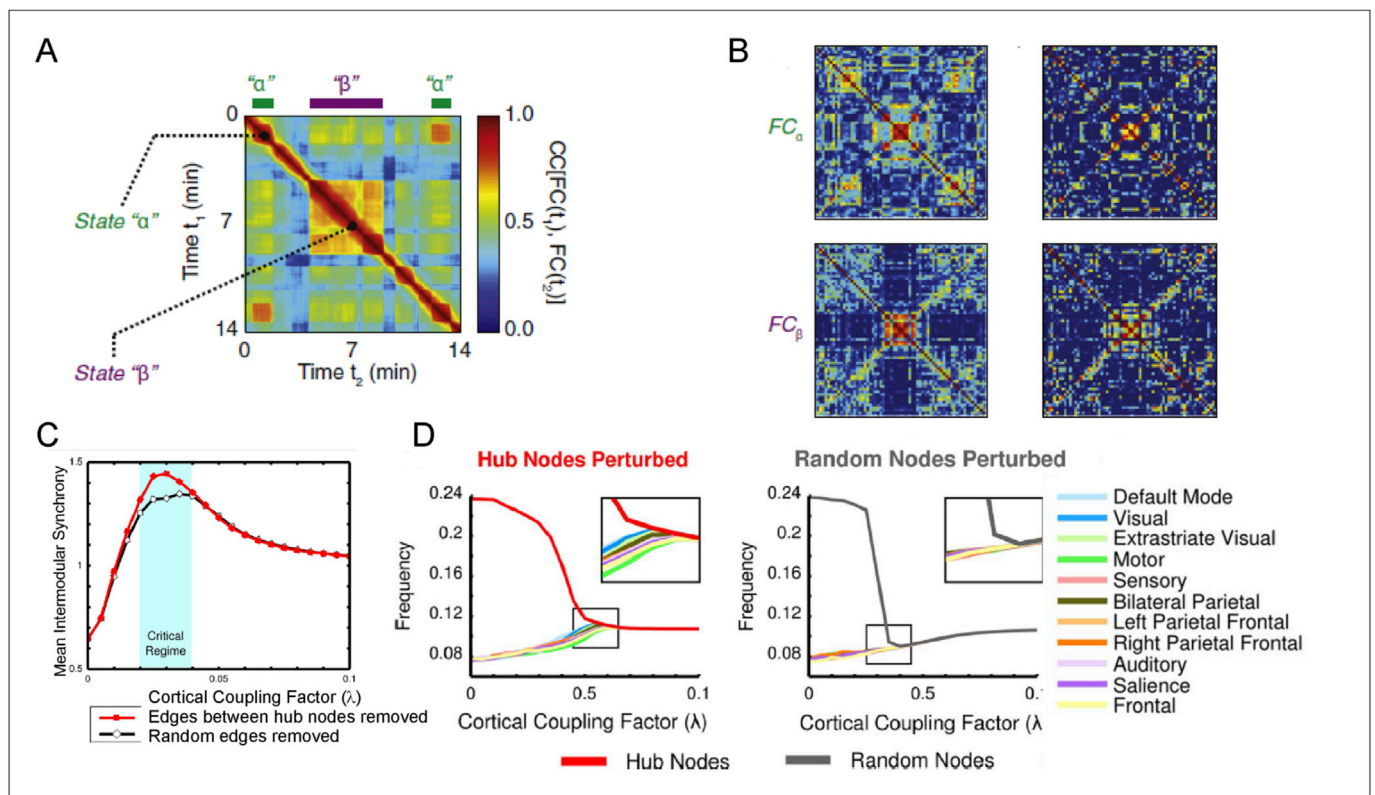


Fig. 5. Models of dynamic integration through cortical cores.

Models of non-stationarity reveal a rich structure characterized by rapid transitions between a few discrete connectivity states reminiscent of some of the most frequently observed Resting State Networks.

A) An appropriate choice of the parameters adopted in the enhanced non-linearity mean-field model leads to an out-of-equilibrium dynamics associated with a self-organized switching between functional connectivity (FC) states (α and β) as revealed by the block structure of the matrix modeling the dynamics of Functional Connectivity. Epochs of stability in the α and β states are reported in green and violet, respectively. B) Note the correspondence between representative functional connectivity matrices (left) obtained from time windows within "α" state epochs (FC_α , top) or within "β" state epochs (FC_β , bottom) and the empirical connectivity matrices extracted from BOLD data (right). (Adapted with permission from (Hansen et al., 2015)). C) The connectivity among hubs plays a fundamental role in linking distinct modules in the brain. When hubs are disconnected, the modularity increases. The ratio between the mean intra-modular synchrony and the whole brain synchrony is reported as a function of the cortical coupling factor when either edges between hub nodes (red) or random edges (black) have been removed. In the critical regime the intra-modular synchrony increases when hub connectivity is suppressed. D) The effect of perturbation of internal modular frequencies on the whole brain synchrony. When the internal frequencies of "Rich Club" nodes are altered, the rest of the modules are unable to synchronize. The synchronization is recovered when the hub nodes' frequency comes down to the range of frequencies of the functional modules (left panel). When a random set of nodes, equal in number to the previous set, is perturbed the functional modules are able to synchronize before these nodes join at a whole brain shared frequency. (Adapted from (Schmidt et al., 2015)).

et al., 2015). This nicely links to the small dimensionality of both EEG and MEG states. In particular, a slight enhancement of the non-linearity in the model is sufficient to broaden the repertoire of possible network behaviors, leading to modes of fluctuations that are reminiscent of the observed RSNs. These can span multiple functional connectivity states and a given state can generate fluctuation patterns related to multiple RSNs similarly to what observed in Temporal Functional Modes observed with fMRI, and transitions among MEG states (Baker et al., 2014; Smith et al., 2012).

How does the brain move among these cognitive states? Again, cortical hubs seem to play a fundamental role in such transitions. In fact, Schmidt et al. (2015), by employing a Kuramoto model combined with structural (DTI) connectivity reported that cortical hubs facilitate the intermodular communication and global integration. They showed that hub nodes lead to synchronization of functional modules (see Fig. 5C). Notably, the suppression of connectivity among hubs resulted in an elevated modular state, indicating that hub-to-hub connections are critical in intermodular synchronization. These results are consistent with the empirical observations reported in (de Pasquale et al., 2016). In addition, the model suggests that the perturbation of connectivity among hubs prevents the synchronization of functional modules (Fig. 5D). In other words, the hub dynamics seems to have a causal influence on the functional module synchronization.

Future directions

At this stage of development, it is relatively well established that the brain contains central areas that are structurally and functionally well connected with more peripheral regions. There is also growing evidence that these regions may be important for linking functionally specialized modules of the brain across different tasks. However, more studies are needed on the spatio-temporal and spectral modifications occurring in the core regions at rest and during active behavior.

An important advance highlighted here is that core regions show variable strength of integration with more peripheral regions, and that this fluctuating centrality is related to global efficiency and putatively information processing. We hypothesize that this dynamic integration reflects a *pulsed* mode of information processing that is dependent on the temporal scales of connectivity across the brain, slow in the order of seconds or fast in the order of hundred of milliseconds. A fundamental question then, is the relationship between connectivity at slow vs. fast-time scales and related dynamics. Do network interactions observed at different time-scales and frequencies reflect separate processes (e.g. endogenous homeostatic vs. sensory-attention-motor states) or similar neural processes that unfolds at different temporal scales? Is the dynamics of hubs the same for slow or fast activity fluctuations? (He, 2014; Linkenkaer-Hansen et al., 2001; Van de Ville et al., 2010). The functional

significance of these multi-scale properties is of considerable interest. To this aim, some effort has already been done in characterizing multilayer networks. This modeling, where nodes are connected by different types of edges in different layers, allows to encode in the same network information gathered from different imaging modalities, time, and frequency scales (Brookes et al., 2016). The characterization of multidimensional hubs and their architecture of interaction is certainly an exciting future development, see for example the first characterization of hubs in multi-frequency networks (De Domenico et al., 2016). Furthermore, by extending these approaches, multidimensional brain states might be estimated. In this framework, the characterization of cortical cores would be crucial in understanding transitions across states, as supported by the preliminary evidence of the involvement of PCC and DMN as sources of EEG microstates (Pascual-Marqui et al., 2014).

Another key question is the functional role of the internal dynamics. It is well established that most of the metabolic budget of the brain is spent in intrinsic activity, and that task activity costs relatively little (Attwell and Laughlin, 2001; Raichle and Mintun, 2006). It has also been proposed that connections between hubs are in general longer and more expensive metabolically to maintain (Bullmore and Sporns, 2012). Then, there must be a significant functional advantage in maintaining such a high ongoing cost, partly due to hub organization and dynamics. Thus, an intriguing question is whether functional hubs and their dynamics encode at rest models of behavior and environment that are helpful during actual behavior (i.e. an internal model). We believe that this question will lead to significant insight on the role of spontaneous activity in the brain.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.neuroimage.2017.09.063>.

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