

# Accepted Manuscript

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PII: S1053-8119(17)30809-1

DOI: [10.1016/j.neuroimage.2017.09.063](https://doi.org/10.1016/j.neuroimage.2017.09.063)

Reference: YNIMG 14376

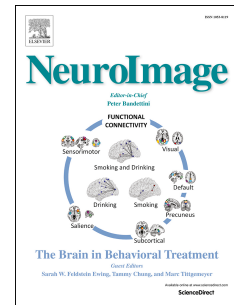
To appear in: *NeuroImage*

Received Date: 7 May 2017

Accepted Date: 28 September 2017

Please cite this article as: de Pasquale, F., Corbetta, M., Betti, V., Della Penna, S., Cortical cores in network dynamics, *NeuroImage* (2017), doi: [10.1016/j.neuroimage.2017.09.063](https://doi.org/10.1016/j.neuroimage.2017.09.063).

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# Cortical cores in network dynamics

F. de Pasquale<sup>1</sup>, M. Corbetta<sup>2</sup>, V. Betti<sup>3,4</sup>, S. Della Penna<sup>5</sup>

<sup>1</sup> Faculty of Veterinary Medicine, University of Teramo, Teramo, Italy;

<sup>2</sup> Department of Neuroscience, University of Padua, Padua 35128, Italy; Departments of Neurology, Radiology, Neuroscience, and Biomedical Engineering, Washington University, St. Louis, MO 63101 USA;

<sup>3</sup> Department of Psychology, University of Rome La Sapienza, 00185, Rome, Italy;

<sup>4</sup> Fondazione Santa Lucia, Istituto Di Ricovero e Cura a Carattere Scientifico, 00142, Rome, Italy,

<sup>5</sup> 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.

## 1. 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

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

8 However, most of what we know about brain dynamic integration comes either from structural studies  
9 (e.g. diffusion weighted imaging -DWI- imaging) that infer aspects of temporal organization based on the  
10 structural properties of brain networks, or from functional studies, mainly functional magnetic resonance  
11 imaging (fMRI), that examines this integration at low temporal resolution. This review focuses on the issue  
12 of dynamic integration as examined with electrophysiological methods that allow for high temporal  
13 resolution, specifically magneto-encephalography (MEG), electroencephalography (EEG), and  
14 electrocorticography (EcoG). First, we briefly discuss different measures that have been adopted to identify  
15 structural or functional hubs in the brain (Bassett and Sporns, 2017; van den Heuvel and Sporns, 2013b).  
16 This is important since differences among these measures, and the different metrics to estimate the  
17 spatiotemporal structure of connectivity typically lead to discrepancies in the literature on the precise  
18 localization of central regions, (Buckner et al., 2009; Bullmore and Sporns, 2012; Cole et al., 2010; de  
19 Pasquale et al., 2012; de Pasquale et al., 2013; Hagmann et al., 2008; Power et al., 2013; Tomasi and  
20 Volkow, 2011; van den Heuvel and Sporns, 2013b). Next, we introduce the concept of *dynamic core*,  
21 defined as a set of brain regions showing the most consistent dynamic centrality with the rest of the brain  
22 (de Pasquale et al., 2016; de Pasquale et al., 2013). These areas appear to be overlapping with structural  
23 and functional hubs as identified with fMRI and DWI. We characterize the temporal and frequency  
24 properties of these regions, and the dynamics of their centrality. We propose that this dynamic core plays a  
25 fundamental role for an efficient and flexible communication across different functional domains.  
26 Specifically, such communication is not stable, but slowly varies over time allowing for different temporal  
27 modes of network interaction. These can be altered during active behavior and disease, and may relate to  
28 faster modes of network synchronization.

29

## 30 2. Cortical hubs in the brain

31

### 32 *Identification of cortical hubs: measures of centrality*

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

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

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

15 Another measure of hubness, less influenced by the community size, is the participation index (PI), see eq.  
16 (3) in SI, that measures how ‘well-distributed’ the links of a node are among different modules. The PI of a  
17 node is close to 1 if its links are uniformly distributed among all modules, and 0 if all its links are within its  
18 own module (Guimera and Nunes Amaral, 2005). Thus, this measure classifies hubs as nodes participating  
19 to a large number of communities (i.e. showing a large number of edges linking them to different modules).  
20 Nodes with a high PI behave as connector hubs while nodes with a low PI as provincial ones. Thus, it may  
21 happen that a node with a high degree scores a low PI, as in the case of a provincial hub, while  $K$  and PI  
22 agree in connector hubs. For this reason, the role of a node can be determined, to a great extent, by its  
23 within-module degree and its participation index, which define how the node is positioned in its own  
24 module and with respect to other modules, see (Guimera and Nunes Amaral, 2005; Sporns et al., 2007).  
25 Notably, PI depends on the outcome of the decomposition of the network into modules, and thus on the  
26 modularity measure adopted.

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

### 37 *Functional hubs in fMRI and MEG*

38 By measuring  $K$ , fMRI hubs (van den Heuvel and Sporns, 2013b) were mainly found in the Default Mode  
39 Network (DMN, in regions/nodes such as Posterior Cingulate Cortex (PCC), Medial Prefrontal Cortex  
40 (mPFC), Angular Gyrus (AG)), see **Fig. 1A** and **Table 1** (Buckner et al., 2009; Cole et al., 2010; de Pasquale et  
41 al., 2013; Tomasi and Volkow, 2010; Zuo et al., 2012). Additional functional cores have reported in the  
42 Somato Motor Network (SMN, in the Supplementary Motor Area (SMA) and Central Sulcus (CS)), in the  
43 Visual network (VIS) (Tomasi and Volkow, 2011) and frontoparietal (FPN) networks (regions marked by \* in  
44 **Table 1**) (Zuo et al., 2012). When using PI as a measure of centrality, Power et al. found a poor agreement  
45 with findings in the DMN (Power et al., 2013). In fact, the authors emphasize a different set of associative  
46

1 regions more closely related to the FPN, DAN, and CCN (see **Fig. 1B, Table 1**). However, given the uncertain  
2 spatial localization, some hub regions labeled as DMN, for example AG, could easily fall within the FPN  
3 (Cole et al., 2014; Vincent et al., 2008), and some regions in (de Pasquale et al., 2013) fall within the DAN  
4 and SMN.

5 Compared to fMRI, the spectral richness of electrophysiological techniques (MEG, EEG, and EcoG) allows  
6 the analysis of both slow (band limited power, BLP) and fast (signal) temporal scales. These aspects are  
7 particularly important when studying the temporal dynamics, see (Larson-Prior et al., 2013) for a review. At  
8 the slow timescale, comparable to that measured with fMRI ( $\sim 0.01-0.1$  Hz), the highest centrality was  
9 consistently found in the  $\beta$ -band using different metrics and connectivity estimates (see **Fig. 1C-F**) (de  
10 Pasquale et al., 2012; de Pasquale et al., 2016; Hipp et al., 2012). In particular, in (Hipp et al., 2012) (**Fig. 1C**)  
11 normalized BC peaks at about 16Hz (range 8-32 Hz) with maximal centrality in parietal, temporal, lateral  
12 and medial prefrontal cortex (**Fig. 1D**). Accordingly, in (de Pasquale et al., 2012), where time-varying  
13 correlation of  $\beta$ -BLP and weighted K were computed, central nodes were localized mainly in the DMN (PCC,  
14 bilateral AG and mPFC), DAN (left PIPS) and SMN (left CS). When using BC on the same data set (de  
15 Pasquale et al., 2016), the most central nodes were again PCC, bilateral PIPS, and SMA (see **Fig. 1E-F**). This  
16 latter set of regions partially overlaps with those found by means of BC computed on orthogonalized power  
17 times series (Hipp et al., 2012). By using graphs obtained from leakage-corrected  $\beta$ -BLP time series, K hubs  
18 were confirmed in PCC and bilateral AG (Maldjian et al., 2014). Notably, there is evidence that central  
19 regions in MEG are identified in the  $\beta$ -band, independently of the connectivity estimator and metrics of  
20 centrality. In particular, PCC was still a hub when analyzing connectivity at the fast time scale, although in  
21 different bands ( $\alpha$  or  $\gamma$ ) (Jin et al., 2014). Interestingly, by combining K and EVC to detect central nodes,  
22 bilateral precuneus, inferior parietal, precentral and supramarginal regions were identified as hubs in MEG  
23 ( $\beta$ - and  $\gamma$ -BLP), fMRI, and DWI (Garces et al., 2016). At fast timescale, using the Phase Locking Index to  
24 estimate connectivity, frequency specific sets of K based hubs were identified in the  $\alpha$ ,  $\beta$  and  $\gamma$ -band  
25 (Hillebrand et al., 2012). Other relevant papers include (de Haan et al., 2012; Jin et al., 2014; Schmidt et al.,  
26 2014).

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

### 33 34 **3. Core networks, the architecture of interaction among cortical hubs**

35  
36 It has been suggested that the presence of cortical hubs, especially connectors, is important for  
37 integrating information across functionally specialized networks, see for example (de Pasquale et al., 2016).  
38 **Furthermore, the modulation of hub dynamics occurring under different cognitive states or disease is of**  
39 **considerable interest, especially because it might provide important insights on the neurophysiological**  
40 **processes underlying behavior and cognition. These aspects are reported in SI.** However, since behavior  
41 requires a flexible reconfiguration of task networks, the integration must occur across domains,  
42 notwithstanding the high energetic cost of neural architectures connecting spatially distant local modules.

43 Computational studies suggested that a balance between segregation and integration may be achieved  
44 through networks emphasizing the local efficiency through highly connected local modules, expert at  
45 processing one kind of information, and the integration through sparse inter-module connections involving

1 a small number of hubs. This architecture is denoted ‘Small World’ (Bassett and Bullmore, 2006; Bassett  
2 and Bullmore, 2016) and it has been observed across a wide range of imaging modalities including MEG  
3 (Stam, 2004; Valencia et al., 2008), fMRI, DWI (Achard et al., 2006; Salvador et al., 2005; Vaessen et al.,  
4 2010; van den Heuvel et al., 2008), EEG (Smit et al., 2008) and tract-tracing (Hilgetag and Kaiser 2004;  
5 Sporns and Zwi 2004). The original idea behind small-worldness paved the way for many successive works  
6 on the communication among these few central regions. In a very influential paper, Van de Heuvel and  
7 colleagues (van den Heuvel and Sporns, 2011) presented a refinement of the hubs/small world idea by  
8 showing that the brain not only contains hubs, but these are preferentially connected in a “Rich Club” (see  
9 **Fig.2**). Using deterministic tractography and a high-resolution parcellation of the brain, they mapped sub-  
10 cortical and neocortical hubs and examined their structural links. High K nodes tend to form denser  
11 connections among themselves than with lower K nodes. These regions include bilateral superior fronto-  
12 parietal regions, including PCC, as well as subcortical regions such as hippocampus, thalamus, and  
13 putamen. Connections linking non Rich-Club to Rich Club nodes are called feeder (see **Fig.2A**), while edges  
14 connecting non-Rich Club regions are labeled ‘local’ (**Fig.2B**) and connections among rich-club members are  
15 called ‘rich-club’ (**Fig.2C**). A model for these results suggests that hubs communicate as a strongly  
16 interlinked ensemble able to flexibly link to different peripheral networks in the course of different tasks.  
17 This idea was explored later on in fMRI showing that a common set of hub regions tend to co-activate  
18 across a large number of different cognitive tasks (Cole et al., 2014; Cole et al., 2013). This organization is a  
19 plausible solution to the issue of flexible control since the rich club contains nodes participating in other  
20 networks (Gollo et al., 2015; van den Heuvel and Sporns, 2013a; van den Heuvel and Sporns, 2013b). In  
21 fact, it has been shown that rich-club nodes distribute across different RSNs with a certain degree of  
22 overlap (see **Fig.2D**). However, it must be noted that in (van den Heuvel and Sporns, 2013a) it was also  
23 reported that inter-modular connections are disproportionately represented by hub-connections and these  
24 regions play a critical role in network communication also in terms of longer fiber-lengths and higher  
25 network traffic (Collin et al., 2014; van den Heuvel et al., 2012). Finally, this architecture, might also be a  
26 convenient way to protect global communication in the brain in the course of damage or diseases (Kaiser et  
27 al., 2007). In the case of one malfunctioning hub, distant effects may be felt in the system (Tuovinen et al.,  
28 2016), but the effect on global communication may be alleviated by strong connections among other hubs.  
29 In summary, the challenge of flexible behavioral control leads to the possibility that the brain exploits a  
30 small world architecture in which a few highly inter-connected regions function as bridges dynamically  
31 linking to peripheral nodes involved in local processing.

#### 32 33 **4. Cortical cores as a tool of dynamic network integration**

##### 34 35 *Temporal and spectral dynamics of brain networks*

36 It is well established that the electrophysiological signals recorded from surface/deep electrodes show  
37 fractal features (e.g. scale-free properties) and are incredibly rich in the frequency domain ranging from  
38 [0.001, >500] Hz (Buzsaki and Draguhn, 2004). This spectral richness leads to three fundamental  
39 observations for our discussion.

40 First, brain networks observed with fMRI correspond to interactions involving both fast and slow  
41 electrophysiological signals. At slow frequencies (<4 Hz), the coupling based on the slow cortical potential  
42 represents one electrophysiological correlate of these networks, while at higher frequencies such  
43 correspondence is lost (Hacker et al., 2017; He et al., 2008; He et al., 2010; Nir et al., 2008). The other  
44 correlate is the BLP coupling at different frequencies. In ECoG studies, interactions occurring at  $\gamma$ ,  $\alpha$  and  
45  $\beta$  bands have been associated to fMRI RSNs (Hacker et al., 2017; He et al., 2008; Keller et al., 2013; Leopold

1 et al., 2003; Nir et al., 2008). MEG studies have mainly reported similarities between fMRI and MEG RSNs in  
2  $\alpha$ - and  $\beta$ -BLP (Brookes et al., 2011b; de Pasquale et al., 2010; de Pasquale et al., 2012; de Pasquale et al.,  
3 2016; Hipp et al., 2012).

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

20 Third, and more importantly, these connectivity patterns are not static but slowly (in the order of  
21 seconds) vary over time. de Pasquale and colleagues observed that the coupling between regions of a RSN  
22 slowly changed over time alternating periods of strong and weak coupling (de Pasquale et al., 2010). In a  
23 subsequent work, they showed that the alternation of strong/weak network coupling (at least for some  
24 central networks like DMN or regions like PCC) predicted varying degree of across-network interactions  
25 (see next paragraph). Notably, in this work, RSN connectivity and its temporal dynamics were studied in  
26 source space by means of the combination of a Minimum Norm Estimator, Independent Component  
27 Analysis and the Pearson correlation coefficient as a measure of coupling over sliding windows (Betti et al.,  
28 2013; de Pasquale et al., 2010; de Pasquale et al., 2012; de Pasquale et al., 2016; Mantini et al., 2011).  
29 However, in other MEG studies such as (Brookes et al., 2014) a beamforming technique supported by a  
30 leakage correction (that could also be applied to Minimum Norm solutions, see for example (Wens, 2015))  
31 and canonical correlation were used to retrieve time-varying functional interactions (O'Neill et al., 2015).  
32 Interestingly, even though MEG signals are acquired at very high temporal resolution ( $\sim 1000$  KHz), and  
33 different groups adopted different approaches to measure time-varying interactions, there is consensus  
34 that these fluctuations of coupling occur at slow temporal scales (few seconds). This is comparable to what  
35 found in fMRI. Of note, while in fMRI the temporal scale is limited by the temporal resolution induced by  
36 the neurovascular coupling, in MEG the duration of the sliding window is longer than the available MEG  
37 temporal resolution (around 1ms), but it represents a good compromise between the robustness of the  
38 connectivity estimator and the temporal resolution of the investigated fluctuations. It is possible that these  
39 slow time scales reflect the adopted measure (BLP), and that faster frequencies would be observed in the  
40 signal domain. This is the case for the so called MEG brain states, see (Baker et al., 2014), as discussed in  
41 Section 5.

42 The time-varying nature of connectivity has also been investigated with fMRI, but is controversial if the  
43 observed dynamics truly reflects non-stationarity (Hutchison et al., 2013; Preti et al., 2016) or rather just a  
44 poor estimate (influenced by motion artifacts and sampling variability) of a static coupling (Laumann et al.,  
45 2016). Early findings showed significant fluctuations of inter-regional correlation (Chang and Glover, 2010),

1 mainly involving cross-module interactions (Zalesky et al., 2014). However, estimates of correlation in  
2 time are limited by several factors including the number of available samples (Zalesky and Breakspear,  
3 2015), residual subject's motion, see (Power et al., 2015), and a severe trade-off between robustness and  
4 temporal resolution. Alternative approaches have been proposed including dynamic spectral analyses  
5 (Yaesoubi et al., 2015), data-driven temporal ICA (Smith et al., 2012) and connectivity states extraction  
6 (Allen et al., 2014), see next section. Another important aspect is the connection between brain structure  
7 and dynamics which is related to network motifs. These are the building blocks of the network (Milo et al.,  
8 2002; Sporns and Kotter, 2004) and provide a testbed for many hypotheses on empirical data as well as in  
9 computational models. In this context, apex nodes can be considered the core nodes of network motifs.  
10 They appear more often in hub regions and play an important role in brain structure (Harriger et al., 2012)  
11 and dynamics (Alstott et al., 2009; Gollo et al., 2014; Senden et al., 2014; Senden et al., 2012; Vasa et al.,  
12 2015; Wei et al., 2017). Moreover, frustrated network motifs can be considered a structural basis for  
13 dynamic connectivity since they facilitate dynamic functional connectivity via metastable transitions (Gollo  
14 and Breakspear, 2014).

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

18

#### 19 *Dynamic core network as the substrate for an efficient global communication in the brain*

20 The time-frequency properties of the functional architecture are fundamental to unravel mechanisms of  
21 dynamic integration in the brain (Bassett and Sporns, 2017). There are several important questions to be  
22 addressed: do hub regions show fluctuations in their centrality similarly to other networks? What are the  
23 implications of these fluctuations for other regions that are connected to the hubs? Do these fluctuations  
24 have a functional implication in healthy processing, aging, or disease? fMRI studies tend to show that these  
25 central regions are topologically stable during a task as compared to rest (Cole et al. 2013; 2014; (Chiang et  
26 al., 2016; Liao et al., 2015), but these results are just beginning to come in, and other studies show a  
27 significant reorganization of network interaction during task performance (see for example, Spadone et al  
28 2015). Moreover, it must be considered that the limited temporal resolution of fMRI may miss fast  
29 transient variations in topology. MEG results instead provide a very interesting insight on cortical dynamics  
30 of RSNs and hubs. In one set of observations, de Pasquale and colleagues (de Pasquale et al., 2012) showed  
31 that in the  $\beta$ -BLP, the DMN represented a functional core of integration in the brain. This was observed  
32 during epochs of high internal coupling of this RSN. Specifically, in these epochs, PCC, bilateral AG, and  
33 mPFC were strong K hubs. Similar observations were made for other networks/hubs including DAN/left  
34 PIPS and SMN/left CS. Interestingly, these nodes spent only a small part of time (20-30%) in epochs of high  
35 centrality, and these epochs did not overlap indicating that different hubs significantly alternated their  
36 central role, see **Fig. 3A** (de Pasquale et al., 2016). These results were then the first hint that there may be  
37 a link between dynamic connectivity and integration. In other words, the amount of integration among  
38 different networks seems to increase when some networks (DMN, DAN, SMN) are more strongly coupled.  
39 More recently, in (de Pasquale et al., 2016) this work was extended by focusing on BC as a measures of  
40 centrality. This measure, as previously described, emphasizes 'connector hubs' and thus accounts more  
41 explicitly for interactions among different networks. The temporal evolution of BC was estimated and, on  
42 average, high BC nodes included again PCC (DMN), bilateral PIPS (DAN), and SMA (SMN, see **Fig.3B**). In  
43 agreement with the prior MEG study, but in contrast to fMRI studies indicating stable hubs over time,  
44 peaks of high BC occurred about 40% of time. Again, these hubs asynchronously alternated epochs of high  
45 and low centrality, forming what can be defined as a 'dynamic core network' (**Fig.3C**). Notably, the regions  
46 comprising this dynamic core network largely overlap with the previously discussed "Rich Club" (van den



1 Heuvel and Sporns, 2013a). Perhaps the most intriguing result of this study was that epochs of high BC  
2 correspond to periods of high global efficiency in the whole brain. The Global Efficiency (GE) is defined as  
3 the average of the reciprocal shortest path length over all the network nodes (Rubinov and Sporns, 2010).  
4 For RSNs including hubs of the core network, epochs of high internal connectivity (i.e. epochs in which the  
5 RSN shows a higher internal connectivity as compared to the rest of the brain) predicted epochs of maximal  
6 GE (see for example a representative timecourse of DMN in **Fig.4A**). Interestingly, these epochs correspond  
7 to peaks of centrality of PCC, see **Fig.4B** (left panel - red bar). This property seems to be lost outside these  
8 temporal windows and the centrality of the DMN is mainly realized by external to DMN connections  
9 (**Fig.4C**, black bar). To study if the GE peaks could be predicted by epochs of high internal coupling of these  
10 networks, de Pasquale and colleagues classified through Receiver-Operator-Curves these time intervals  
11 (**Fig.4D**): epochs of high internal connectivity within DMN, DAN and SMN predicted more than 70% of GE  
12 peaks (see **Fig.4E**). These epochs of high internal connectivity were also epochs of high centrality for hubs  
13 included in the dynamic core network. Of note, this mechanism linking the dynamic core network,  
14 fluctuations of BC, and GE occurred specifically in the  $\beta$ -BLP.

15 In summary, these findings link in a novel mechanistic framework three results. First, RSNs dynamically  
16 fluctuate and these fluctuations involve changes in within/across network interactions. These occur  
17 specifically between hub regions of specific RSNs and other nodes in periods of strong coupling for the  
18 central networks. Second, these hubs are consistent over time, but they are engaged at different times.  
19 Third, epochs of high RSN coupling and centrality correlate and predict periods of high efficiency in the  
20 brain. As a whole, these findings suggest the novel idea that transfer of information, as captured by GE,  
21 occurs with a 'pulsatile' regime controlled by the dynamics of network integration, at least in the resting  
22 state. However, additional MEG studies are required to fully characterized such pulses (e.g in terms of  
23 time-intervals etc...).

24 This framework fits a number of recent studies. Zalesky and colleagues linked the dynamics of fMRI  
25 connectivity to a measure of efficiency (Regional Efficiency, a measure of nodal not global efficiency like  
26 GE) (Zalesky et al., 2014). They reported that the most dynamic connections link elements from  
27 topologically distinct subsystems. These connections involve known DMN and FPN hubs that spontaneously  
28 increase, for brief intervals, their efficiency producing temporarily globally integrated network states. Since  
29 the integration through long connections might involve higher metabolic costs, their results suggest that  
30 brain dynamics reflects a balance between integration of information and metabolic expenditure (Zalesky  
31 et al., 2014). They also support the idea that this transfer of information, occurring in specific epochs  
32 controlled by the dynamics of network interaction, enables otherwise segregated network elements to  
33 access a cognitive global workspace. The transient exploration of this workspace may allow the brain to  
34 efficiently balance segregated and integrated dynamics. A related study explored the origin of slowly  
35 fluctuating patterns of cortical synchronization and found that these patterns match well the activity within  
36 the Rich Club regions (Gollo et al., 2015). Furthermore, it has been shown that fluctuations of global  
37 efficiency alter patterns of activity in local neuronal populations elicited by changes in incoming sensory  
38 stimuli (Cocchi et al., 2017). Accordingly, it was reported the presence of multiple cortical timescales  
39 involving the emergence and dissolution of interactions of cortical regions within the human visual system  
40 (e.g. with frontal eye fields) when the neural activity is perturbed (e.g. by means of Trans Magnetic  
41 Stimulation) was reported in (Cocchi et al., 2016).

42 To summarize, dynamic interactions among hubs occur at multiple time scales, but also involve epochs  
43 of variable integration hence probably information processing. Thus, the brain seems to exploit a temporal  
44 'multi-scale pulsed' mode for network communication where slower time scales provide information about  
45 the state of the system, while faster time scales reflect the temporal details of behavior (this is elaborated  
46 more the next section). This new perspective opens up a number of interesting new issues for the field. In

1 particular, it would be fundamental to understand why the temporal dynamics in interacting brain  
2 networks occur on a slow temporal scale, what is its origin (biophysical, neuronal), functional significance  
3 and the role played by fast synchronizations during task/cognitive processes.  
4

## 5 **5. Cortical cores and slow vs. fast dynamic brain states**

6

7 The results reviewed thus far indicate that brain networks are not segregated but dynamically  
8 integrated, and this property varies over multiple temporal scales: slow, in the order of seconds, and fast in  
9 the order of hundreds of milliseconds. Here, we elaborate on the functional roles of hub/cortical dynamics  
10 at rest and during task processing. We will first consider the slow temporal scale.

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

1 Which is the relationship between slow and fast temporal scale dynamics? Overall more research is  
2 needed on this point. There has been important work on the notion of EEG microstates, reported for the  
3 first time in (Lehmann et al., 1987). They showed that the electric topography of the scalp does not change  
4 randomly and continuously over time, but remains stable for ~80–120 ms; these periods of quasi-stability  
5 were termed “EEG microstates”. Surprisingly, only few (between four and six) distinct microstates are still  
6 consistently observed at rest. Recently, it has been shown that these rapidly changing microstates correlate  
7 significantly, albeit not strongly, with activity in fMRI RSNs after convolution with the hemodynamic  
8 response function (Van de Ville et al., 2010). While there is some uncertainty in linking microstates to fMRI  
9 networks, EEG microstates nicely link to ongoing investigations of brain dynamics in whole brain  
10 recordings. Microstates have time scales that are in the range of cognitive processes, and show a scale-free  
11 dynamics. This might be the basis for the rapid reorganization and adaptation of the functional networks in  
12 the brain (Van de Ville et al., 2010). However, caution must be taken when comparing states across EEG  
13 and fMRI or MEG. In fact, these EEG states are extracted in time epochs corresponding to peaks of Global  
14 Field Power while fMRI and MEG connectomes are based on some measure of synchronicity. However,  
15 since those peaks correspond to moments of overall high activity and thus likely to high synchronicity,  
16 some cross-modal agreement is not unexpected. Notably, recent work shows an interesting link between  
17 microstates and cortical hubs. In fact, Pascual-Marqui and colleagues observed that all microstates have  
18 common generators in PCC, while three microstates additionally include activity in the left  
19 occipital/parietal, right occipital/parietal, and anterior cingulate (Pascual-Marqui et al., 2014). Thus, these  
20 generators appear to be a fragmented version of DMN supporting the notion that these regions activate  
21 sequentially at high temporal resolution, and that this RSN might correspond to a very low-pass time  
22 filtered version of this faster dynamics. Moreover, they show that PCC acts an important hub in  
23 connections mediating the microstate transitions, sending alpha and beta oscillatory information to all  
24 other microstate generator regions.

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

## 42 43 **6. Theoretical aspects of hub dynamics and brain states**

44

45 The observation that functional cores and their dynamics play a fundamental role in a ‘pulsed’ (i.e. non  
46 stationary) synchronization of distinct functional modules, seems to be supported also by theoretical and

1 modeling studies, see (Breakspear, 2017; Cabral et al., 2017) for a review on computational models. The  
2 notion of distinct functional connectivity states recurring at different points in time is compatible with  
3 models of neuronal connectivity (Deco and Corbetta, 2011; Deco et al., 2011). Accordingly, a ‘dynamic  
4 repertoire’ of states is expected to be continuously explored to more quickly adopt the optimal network  
5 configuration for a given impending input (Deco et al., 2011). Such dynamic exploration, where brain states  
6 never set in a fixed point (Cabral et al., 2014), can provide the flexibility required to adapt to the rapidly  
7 changing computational demands of cognitive processing (Bressler and Tognoli, 2006). Hansen and  
8 colleagues showed that the resting state regime has a rich structure, characterized by rapid transitions  
9 switching between a few discrete connectivity states, see **Fig. 5A,B** (Hansen et al., 2015). This nicely links to  
10 the small dimensionality of both EEG and MEG states. In particular, a slight enhancement of the non-  
11 linearity in the model is sufficient to broaden the repertoire of possible network behaviors, leading to  
12 modes of fluctuations that are reminiscent of the observed RSNs. These can span multiple functional  
13 connectivity states and a given state can generate fluctuation patterns related to multiple RSNs similarly to  
14 what observed in Temporal Functional Modes observed with fMRI, and transitions among MEG states  
15 (Baker et al., 2014; Smith et al., 2012).

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

26

## 27 **7. Future directions**

28

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

34 An important advance highlighted here is that core regions show variable strength of integration with  
35 more peripheral regions, and that this fluctuating centrality is related to global efficiency and putatively  
36 information processing. We hypothesize that this dynamic integration reflects a *pulsed* mode of  
37 information processing that is dependent on the temporal scales of connectivity across the brain, slow in  
38 the order of seconds or fast in the order of hundred of milliseconds. A fundamental question then, is the  
39 relationship between connectivity at slow vs. fast-time scales and related dynamics. Do network  
40 interactions observed at different time-scales and frequencies reflect separate processes (e.g.  
41 endogenous homeostatic vs. sensory-attention-motor states) or similar neural processes that unfolds at  
42 different temporal scales? Is the dynamics of hubs the same for slow or fast activity fluctuations? (He,  
43 2014; Linkenkaer-Hansen et al., 2001; Van de Ville et al., 2010). The functional significance of these multi-  
44 scale properties is of considerable interest. To this aim, some effort has already been done in characterizing  
45 multilayer networks. This modeling, where nodes are connected by different types of edges in different  
46 layers, allows to encode in the same network information gathered from different imaging modalities,

1 time, and frequency scales (Brookes et al., 2016). The characterization of multidimensional hubs and their  
 2 architecture of interaction is certainly an exciting future development, see for example the first  
 3 characterization of hubs in multi-frequency networks (De Domenico et al., 2016). Furthermore, by  
 4 extending these approaches, multidimensional brain states might be estimated. In this framework, the  
 5 characterization of cortical cores would be crucial in understanding transitions across states, as supported  
 6 by the preliminary evidence of the involvement of PCC and DMN as sources of EEG microstates (Pascual-  
 7 Marqui et al., 2014).

8 Another key question is the functional role of the internal dynamics. It is well established that most of  
 9 the metabolic budget of the brain is spent in intrinsic activity, and that task activity costs relatively little  
 10 (Attwell and Laughlin, 2001; Raichle and Mintun, 2006). It has also been proposed that connections  
 11 between hubs are in general longer and more expensive metabolically to maintain (Bullmore and Sporns,  
 12 2012). Then, there must be a significant functional advantage in maintaining such a high ongoing cost,  
 13 partly due to hub organization and dynamics. Thus, an intriguing question is whether functional hubs and  
 14 their dynamics encode at rest models of behavior and environment that are helpful during actual behavior  
 15 (i.e. an internal model). We believe that this question will lead to significant insight on the role of  
 16 spontaneous activity in the brain.

## 17 **Figure legends**

### 18 **Figure 1. Functional hubs in the human brain.**

19 (The adopted labels are reported in **Table 1**)

20 A) Top 5% and 10% fMRI hubs found through weighted degree obtained from functional connectomes.  
 21 The majority of top 5% hubs are comprised in the Default Mode Network (blue labels) and the entire set of  
 22 cognitive control network (CCN) (red labels) contains all top 10% hubs (Adapted with permission from (Cole  
 23 et al., 2010)).

24 B) To identify nodes that routinely participate in multiple communities, the Participation Index can be  
 25 adopted. Here, this was computed on communities evaluated on the binary graph thresholded at 5%  
 26 connection density. Communities are shown on the surface (left) and through a spring-embedded plot.  
 27 (Adapted with permission from (Power et al., 2013)).

28 C) The percentage of central nodes evaluated by means of the Betweenness Centrality (BC). The  
 29 reported nodes show significantly increased centrality compared to the average value in the brain ( $p <$   
 30  $0.05$ ). These results were obtained from MEG Band Limited Power connectivity matrices following signal  
 31 orthogonalization. The larger, statistically significant percentage of hubs is found at the carrier frequencies  
 32 in the  $\beta$  band, extending also to the  $\alpha$  band (adapted with permission from (Hipp et al., 2012)).

33 D) From the same graph as in C), regions showing the highest centrality at 16 Hz were found in bilateral  
 34 medial/dorso-prefrontal and Temporal Cortex (see **Table 1** for the definition of labels). The centrality  
 35 evaluated by means of Betweenness Centrality is statistically masked at two levels of significance, one  
 36 corrected for the number of nodes ( $p < 0.05$ , saturated color scale) and the other uncorrected ( $p < 0.05$ )  
 37 (Adapted with permission from (Hipp et al., 2012)).

38 E) Hubs estimated from  $\beta$  Band Limited Power dynamic connectivity. It is reported the product of the  
 39 mean Betweenness Centrality (BC) across epochs of high internal connectivity for the Default,  
 40 Dorsal/Ventral Attention, Motor, Visual and Language Networks and the consistency of BC in the same  
 41 epochs. The hubs characterized by a strong and consistent centrality in all epochs (red bars) are the  
 42 Posterior Cingulate, left/right posterior interparietal sulcus and supplementary motor area, see **Table 1**  
 43 for the definition of labels (Adapted with permission from (de Pasquale et al., 2016)).

1 F) Topography of connections of the above hubs (yellow) shows a large number of external connections  
 2 driving the high value of centrality. These topographies are obtained in epochs of high internal connectivity  
 3 for the above mentioned networks (Adapted with permission from (de Pasquale et al., 2016)).  
 4

#### 5 **Figure 2. The Rich Club model.**

6 Structural brain hubs exhibit a strong tendency to be mutually and densely interconnected, forming a  
 7 structural core or “Rich Club”. This central high-cost, high-capacity backbone for global brain  
 8 communication comprises a set of spatially widely distributed brain regions including portions of the  
 9 precuneus, anterior and PCC, superior frontal cortex, superior parietal cortex and the insula, all in both  
 10 hemispheres. Edges connecting Rich Club to non-Rich Club regions are labeled as ‘fedeeer’ (A), while edges  
 11 connecting non-rich club regions are labeled as ‘local’ (B) and connections among rich-club members are  
 12 called ‘rich-club’ (C). Nodal degree  $K$  is reported on the right. Rich club nodes are selected based on  $k > 10$   
 13 (red circles) (Adapted with permission from (Sporns, 2014)).

14 D) (left Panel) structural Diffusion Tensor Imaging (left triangle) vs fMRI (right triangle) connections  
 15 averaged across a group of 75 healthy volunteers. Functional modules are based on independent  
 16 component analysis: Pr visual, primary visual; Ex visual, extrastriate visual; FP, frontoparietal; (right Panel)  
 17 Distribution of Rich Club nodes in relation to resting state networks, expressed as proportions across  
 18 networks (Adapted with permission from (van den Heuvel and Sporns, 2013a)).  
 19

#### 20 **Figure 3. The dynamic core network.**

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

22 A) Dynamic binary graphs obtained from the  $\beta$  Band Limited Power connectivity matrices at three  
 23 representative time samples. B) Centrality as estimated through the Betweenness Centrality at the three  
 24 epochs as in A), together with the random graph significance threshold (dotted line). Hubs forming the core  
 25 network are transiently central: Posterior Cingulate Cortex (left), Supplementary Motor Area (middle) and  
 26 right Posterior Intraparietal Sulcus (right). C) Schematic model of the dynamic mechanism underlying the  
 27 core network: central nodes alternate their central role to ensure an efficient communication in the whole  
 28 brain dynamically. (Adapted from (de Pasquale et al., 2016)).  
 29

#### 30 **Figure 4. The Global Efficiency of integration.**

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

33 A) Transient global efficiency for a representative run. Epochs of high internal coupling for the Default  
 34 Mode Network, shown as shaded areas, overlap with epochs of high Global Efficiency.

35 B) Notably, these epochs correspond to high centrality for the Posterior Cingulate Cortex (red bar), a  
 36 hub in the dynamic core network (left panel). Outside these epochs the centrality of this node is lower  
 37 (right panel).

38 C) Percentage of connections contributing to the centrality of the Default Mode Network. The centrality  
 39 of this network is realized by a consistent proportion of external connections (black) compared to internal  
 40 ones (red).

41 D) The Receiver Operator Curve analysis shows that epochs of high internal coupling for the involved  
 42 networks classify peaks of global efficiency.

43 E) Incremental percentage of classification of GE peaks computed for the networks involved in the  
 44 dynamic core. DMN classifies 45%, DAN increments this value by 19% and MN by 7%. Overall, 71% of the  
 45 GE peaks are covered by these three RSNs internal coupling, see **Table 1** for the definition of labels.  
 46 (Adapted from (de Pasquale et al., 2016)).

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## Figure 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 ( $\alpha$  and  $\beta$ ) as revealed by the block structure of the matrix modeling the dynamics of Functional Connectivity. Epochs of stability in the  $\alpha$  and  $\beta$  states are reported in green and violet, respectively.

B) Note the correspondence between representative functional connectivity matrices (left) obtained from time windows within “ $\alpha$ ” state epochs ( $FC\alpha$ , top) or within “ $\beta$ ” state epochs ( $FC\beta$ , 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)).

### Table 1

List of abbreviations adopted in the text and figures.

### Supplementary Figures

#### Figure S1. Core flexibility and reconfigurations.

A) Flexible hub theory. Histograms summarize the spread of the functional connectivity estimates across 64 tasks. The mean of the network variable connectivity (GVC) for the Fronto Parietal Network is statistically higher than for the other networks. Adapted with permission from (Cole et al., 2013).

B) Core-periphery organization. (Top) Example of a network with a modular organization where high-degree nodes (brown) bridge distinct modules composed mostly by low-degree nodes (blue). (Bottom) Nodes in the core (purple) are more densely connected with one another than nodes in the periphery (green).

C) The anatomical distribution of regions in the core, bulk, and periphery appears to be spatially contiguous. The core primarily contains sensorimotor and visual processing areas, the periphery primarily contains multimodal association areas, and the bulk contains the remainder of the brain. Adapted with permission from (Bassett et al., 2013).

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<b>Abbreviation</b>	<b>Full Name</b>	<b>Abbreviation</b>	<b>Full Name</b>
$\alpha$ 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
aTL	Anterior Temporal Lobe	LAN	Language Network
AUD	Auditory Network	LFP	Local Field Potential
$\beta$ 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	$\theta$ band	[3.5, 7] Hz
FEF	Frontal Eye Field	RSN	Resting State Networks
FPN	Fronto Parietal Network	SFC	Superior Frontal Cortex
$\gamma$ band	[27, 70] Hz	SMA	Supplementary Motor Area
GE	Global Efficiency	SMN	Sensory Motor Network
HMM	Hidden Markov Model	STG	Superior Temporal Gyrus
IFG* Insula*	Inferior Frontal Gyrus	TMPFC	Temporal Cortex
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

