Opinion

Rethinking segregation and integration: contributions of whole-brain modelling

Gustavo Deco, Giulio Tononi, Melanie Boly and Morten L. Kringelbach

Abstract | The brain regulates information flow by balancing the segregation and integration of incoming stimuli to facilitate flexible cognition and behaviour. The topological features of brain networks, in particular network communities and hubs, support this segregation and integration but do not provide information regarding how external inputs are processed dynamically (that is, over time). Experiments in which the consequences of selective inputs on brain activity are controlled and traced with great precision could provide such information. However, such strategies have thus far had limited success. By contrast, recent whole-brain computational modelling approaches have enabled us to start assessing the effect of input perturbations on brain dynamics *in silico*.

Evolution has developed many different strategies for the survival of species. The relative evolutionary success of mammals has been made possible by sophisticated brains that can combine information from current stimuli with past memories to predict the future and to adapt behaviour accordingly. The healthy human brain segregates and integrates information from sensory modalities, the body and memory. Take the example of a tennis player who effortlessly integrates past memories with the colour, movement and shape of a tennis ball and segregates it from the changing background of the tennis court and crowd, to allow her to predict the ball's trajectory and planning how best to position her body and tennis racket to return the ball beyond her opponent's reach. The integrated information can be formally defined as the information possessed by a system that is above and beyond the information that is available from the sum of its parts[1, 2]. Such information integration has been linked to consciousness but it can also proceed without awareness[3]. However, we are still lacking a full understanding of the principles that underlie this fundamental process.

The most direct way to discover the brain mechanisms that underlie segregation and integration would be to use neuroimaging methods to map whole-brain structure and function. Much important progress has been made in this regard using sophisticated meta-analyses that have pooled data from thousands of task-related neuroimaging studies probing and testing the brain in many different ways[4]. Such meta-analyses, however, present many important potential confounds, including their cross-sectional nature. Instead, neuroimaging methods should ideally be used in the same individual to map the structural and functional pathways from each of the very large number of possible unimodal and multimodal inputs to the integration this information in a final common pathway, and to map the underlying spatiotemporal dynamics. However, it is nearly impossible for human participants to sit through experiments that could both explore a vast repertoire of diverse inputs and control the full dynamics of the human brain. Using direct causal brain interference methods such as transcranial magnetic stimulation (TMS) also provides a promising approach to causally interfere with brain networks. However, there are significant ethical problems associated with causally interfering with the human brain [5, 6].

The difficulty of controlling the full range of inputs to an individual brain is an additional reason why neuroimaging-based investigations of segregation and integration of information have so far

focused on topological aspects of brain organization and/or resting-state activity, which is based on processing and coordinating internal rather than external input [7]. However, the relatively poor spatiotemporal resolution (typically on the timescale of seconds) and the indirect nature of whole-brain neuroimaging measures (such as functional MRI (fMRI)) have thus far limited the utility of these methods for examining the dynamics of segregation and integration in the brain.

In this Opinion article, we argue that whole-brain computational modelling based on and constrained by neuroimaging data can help to gain new insights into segregation and integration. We first describe the currently available topological measures that are obtained using graph theory from neuroimaging studies of connectomics, and that support the notion of segregation and integration of input information. We propose that whole-brain computational modelling can improve these measures and we provide a brief description of the fundamental principles of whole-brain models. Such models can be used to improve our understanding of the dynamics of input processing, namely by systematically perturbing model networks, thereby providing new useful measures of segregation and integration. These models can also provide new information about how the processes of segregation and integration change over time. In particular, we propose new dynamic measures for the integrative 'binding' of information over time, which are different from existing 'rich clubs' of structural connectivity hubs, which are, by their very nature, more static. Importantly, we show how the new perturbational segregation and integration measures can be applied to distinguish between states of consciousness and between health and disease. Finally, we discuss how generative whole-brain computational models may increase our understanding of the fundamental principles of human brain function in health, as well as their breakdown in neuropsychiatric disorders.

Topological brain measures

Neuroimaging methods that are capable of mapping the structural and functional connectivity of the human brain have started to map the architecture of the structural and functional networks in the human brain [8] (FIG. 1). An important goal of these studies is to establish the human connectome — "the complete description of the structural connectivity (the physical wiring) of an organism's nervous system" [7]. Here, we argue that this purely structural description could usefully be extended to include the *functional* connectivity of the connectome, which combined can enable the complex integration and segregation of relevant information over time.

Collecting topological and functional data. Neuroimaging methods can study brain activity on several timescales and with varying degrees of spatial precision. In humans, the most popular methods for mapping structure and connectivity *in vivo* on the scale of millimetres include MRI and diffusion imaging (diffusion weighted imaging (DWI) or diffusion tensor imaging (DTI)), which uses methods sensitive to the influence of the major fibre tracts on the diffusion of water [9, 10] (FIG. 1a). These major tracts can then be reconstructed by combining models of water diffusion with deterministic or probabilistic tract-tracing methods [11, 12]. There are, however, significant limitations to these methods, such as the lack of information on the directionality of the connections and the indirect nature of the connectivity measures [13].

The activity of the brain is typically measured both with indirect methods (fMRI) and positron emission tomography (PET)) and direct methods (high-density electroencephalography (EEG) and magnetoencephalography (MEG)). Functional connectivity between brain regions is defined as the statistical dependence between neurophysiological signals in different brain areas, and is typically determined by calculating the relationship between regional time-series using correlations, mutual

information or coherence [14, 15]. Traditional functional neuroimaging studies measured task-related activity but, in the past decade, many studies have measured cerebral spontaneous resting-state activity over several minutes[16]. These resting state MRI (rs-MRI) studies have reported highly reproducible and organized patterns of brain activity [17, 18], which overlap with task-related activity patterns [19]. Combining rs-MRI with DTI has helped build the first drafts of the human connectome [20-22]. Importantly, rs-MRI studies offer complementary information to task-based fMRI studies, especially in exploring the basic principles of self-organising brain dynamics. For clinical studies, rs-MRI also has the advantage in eschewing the need to teach participants to engage in tasks that are often boring and repetitive. Both rs-MRI and task-based fMRI studies provide multi-purpose datasets that can be used to study multiple, interacting networks [23, 24].

The primary advantages of rs-MRI over task-based fMRI approaches are the ease of acquisition and analysis, which facilitates large-scale cross-sectional and longitudinal human studies. As mentioned above, approaches based on rs-MRI are also well suited to many different populations, including individuals who may not be able to perform tasks. Nevertheless, rs-MRI can also include important potential confounds (such as unstable wakefulness [25]) and the data can be compromised by physiological signals (such as cardiac or respiratory signals and head motion)[26]. Progress has, however, been made in addressing these issues; for example, building automated methods for the assessment of sleep stages [27] and minimizing the effects of head motion and physiological signals on rs-MRI data [28, 29].

Building connectomes and measuring integration. Neuroimaging data can be further processed using tools from, for example, graph theory to build the human connectome (FIGs 1b–1d). Specifically, graph theory tools have proven to be useful for characterizing the topology of brain systems as well as that of other complex systems such as social networks and the internet [30, 31]. Graph theory can be used to analyze nodes (neurons and brain regions) and edges (connections and pathways) from DTI and rs-MRI data. So far, however, much of this research has been largely descriptive [32]. The starting point of a graph-theoretical analysis of structural data is to create a brain network comprising a number of nodes, which is achieved by parcellating the human brain into tens to hundreds of small regions [20]. Connectivity measurements are then calculated as the strength of the edges between the nodes of the system [33].

The advances in mapping the human connectome have identified some of the features of brain architecture that, as a plausible working hypothesis, may turn out to be necessary and sufficient for integration and segregation in the brain (FIG. 1e). They have revealed that the human brain can be described as a small-world network [34, 35] that is structured around a large number of spatially distributed network communities with clustered connectivity, in which the local computations are likely to be highly segregated [32, 36] (but see Markov and colleagues [37]). In this small-world network, the integration of the segregated information is aided by network hubs, which link network communities and ensure efficient communication and information integration. Some of these hubs have high and diverse patterns of dense interconnectivity [31]. This central core or 'rich club' of important hubs has been suggested to play an important role in global (that is, across the whole brain) information integration [38] (FIG. 1e).

Taken together, the results of graph theoretical analysis of structural brain data suggest that segregation and integration of information in the brain are reflected in the network topology as segregated, spatially distributed network communities and the integrative network hubs connecting them, respectively. However, this is only a description of the network architecture supporting segregation and integration; it does not describe the causal mechanisms underlying functional

separation and integration. In particular, a graph theoretical approach using structural MRI data does not describe the dynamics of functional activity associated with information integration in healthy individuals, or differentiate between, for example, conscious versus non-conscious states (for which TMS-induced perturbations have shown some promise). Such graph-theory-based approaches to investigating 'structural' (that is, anatomical) segregation and integration have been complemented by studies assessing 'functional' segregation and integration (that is, brain activity correlations) on the basis of the mutual information (that is, a measure of mutual dependence between random variables) that is derived from functional connectivity data between brain regions. In addition to these correlational measures, it is possible to perturb the brain using, for example, TMS and measure the resulting functional brain activity changes to assess the brain's 'effective' connectivity. These approaches have led to another topological definition of integration (using functional data), namely the overall deviation from statistical independence across a set of nodes. In turn, this has led to a definition of functional clustering as the ratio between the integration within a set of nodes and the mutual information between that set of nodes and the rest of the system [39]. Other possible measures of functional clustering include neural complexity [40] (defined as the coexistence of functional segregation and integration within the same network) and integrated information (defined as the mutual information across the weakest partition of a system) [41-43].

Combining these approaches has led to the development of the perturbational complexity index[44] as a way to quantify the amount of information contained in EEG responses to changes in cortical activity following a brief perturbation with TMS. Information can be measured as the compressibility of a signal, with information-dense responses having poorer compressibility than responses with less information. The perturbational complexity index can be defined as an empirical index of segregation (that is, the differentiation of responses) and integration. This index of TMS-induced perturbations of cortical activity has proven useful for characterizing the changes between consciousness states (wake, sleep and anesthesia) as well as the consequences of various brain lesions [44]. However, it is important to note that TMS induces only a very brief perturbation to brain activity and can only be used to perturb the cortex and not subcortical areas. It is also difficult to map the full consequences of such a brief perturbation in terms of changes in spatiotemporal activity.

Here, we further complement these functional approaches by proposing that significant progress can be made by using whole-brain models to further elucidate the candidate brain mechanisms of segregation and integration using existing spatiotemporal connectomic data combined with systematic perturbations to accurately simulate and predict brain activity.

Whole-brain computational models

Accurately modelling brain function using computational models is difficult, given the very large number of neurons and the underspecified connectivity at the neural level. Significant progress has been made developing whole-brain computational models that can reproduce some of complexity and important features of the real brain *in vivo*. These whole-brain models endeavour to strike the right balance between complexity and manageability by taking their lead from statistical physics, where it has been shown that macroscopic physical systems obey laws independently of their mesoscopic constituents [45]. Indeed, the emergent collective macroscopic behaviour of brain models has been shown to be only weakly dependent on the details of individual neuron behaviour [46]. The models therefore typically use various mesoscopic top-down approximations of brain complexity with dynamical networks of local brain area attractor networks [47]. The simplest models use basic neural mass or mean-field models to capture the changes in mean firing rate [48], similar to how the

temperature of a gas captures the mean local particle velocity, whereas the most advanced models have used a dynamic mean-field model derived from a proper reduction of a detailed spiking neuron model [49].

The dynamics of whole-brain models rely on reducing the complexity of connectivity by using a given brain parcellation. Historically, this has been carried out based on careful studies of the properties of the underlying brain tissue [50], which has been supplemented with modern neuroimaging parcellations that typically range from tens to several hundreds of regions [20]. The optimal parcellation of brain regions is not currently clear but could require fine-grained parcellations with hundreds of regions [51], but current popular choices include fewer regions such as the Desikan-Killiany/Hagmann parcellation with 66 cortical regions [52, 53] , and the automated anatomical labeling (AAL) parcellation with 116 regions (cortical, subcortical and cerebellum) [54].

Combining a parcellation with structural connectivity data (obtained from tractography from DWI or DTI) provides a structural connectivity matrix that can be used in the whole-brain computational model. The parameters are systematically varied to simulate and compare the dynamics and fixed points of the global network system of attractors with the neuroimaging data (obtained, for example, from rs-MRI) (FIG. 2a). In other words, the dynamical entrainment and correlations between different local brain region dynamics are essentially shaped by the underlying structural connectivity[55-60]. As such, whole-brain computational models can provide a mechanistic explanation of the origin of resting-state networks, as has been shown for resting-state networks derived from rs-MRI data [61, 62] and for resting-state networks derived from MEG data [63]. An important finding from this research is that the model that provides the best fit to empirical resting-state functional connectivity matrices is obtained when the model brain network is subcritical [49, 58, 64] (BOX 1).

Elucidating mechanisms

Combining whole-brain computational models with neuroimaging data offers great potential for obtaining a better understanding of the computational and biophysical mechanisms underlying the functioning of the healthy human brain, which is superior to the understanding that can be extracted from topological and correlational measures [8]. In particular, the ability of whole-brain computational models to model spontaneous resting-state and task-related activity, combined with the possibility to perturb the model in specific ways by changing the input and connectivity locally, can yield important new information.

Measuring perturbational segregation. A measure of perturbational segregation can be obtained if any node of the brain network is perturbed and the functional consequences are measured in a whole-brain computational model in which local nodal levels of excitation and inhibition are rebalanced to maintain negligible levels of short-range correlations [58]. Once the dynamical working point of the model has been adjusted using empirical measures of resting functional connectivity [57], the model can be perturbed by a random set of Gaussian inputs (that is, the same variance of Gaussian noise is maintained but a subset of random regions is stimulated; FIG. 2b). The overall statistical dependence among all the nodes can easily be estimated from the mutual information between nodes for each of the random set of inputs (assuming Gaussanity; this is easily calculated as minus logarithm of the determinant of correlation matrix). More formally, the perturbational segregation is calculated through the entropy of the set of evoked patterns assuming a Gaussian distribution and is defined as [65]:

$$H = 0.5(\mathrm{n}(1+\log(2\pi)) + \sum_{i=1}^{n} \log(\lambda_i)) \quad (1)$$

Where n is the number of evoked patterns (typically n=1000) and λ_i are the eigenvalues of the covariance matrix of the evoked activity of the excitatory connections. To avoid numerical problems in the estimation of the segregation, obfuscating noise of variance $\sigma^2_{noise} = 0.001$ can be introduced [66] so that the perturbational segration (ie information capability I_C) is finally given by:

$$I_C = 0.5\sum_{i=1}^{n}(1+\log(\frac{\lambda_i}{\sigma^2_{noise}})) \quad (2)$$

The novel measure of perturbational segregation can then be defined by normalising this measure by the maximal possible value of the mutual information given by random inputs. In other words, this is a measure of the capability of the brain to process information.

Measuring perturbational integration. Similarly, integration can be defined using perturbations applied to whole-brain models to measure the effects of systematic stimulation on how the brain integrates information. This novel measure of perturbational integration can be defined by using the length of the largest connected component — that is, the largest connected graph of nodes (described below) — in the binarized functional connectivity matrix obtained from such a model (after thresholding).

More specifically, for a given absolute threshold θ between 0 and 1, the functional connectivity matrix FC can be binarized (using the criteria $|FC_{ij}| < \theta$; which determines if it will be given a value of 0 and 1) and the largest component extracted as a measure of integration. The largest component is the length (number of nodes) of the connected sub-graph of the undirected graph defined by the binarized matrix (which itself is considered as an adjacency matrix). This is the largest sub-graph in which any two vertices are connected to each other by paths, and which connects to no additional vertices in the super-graph (FIG. 2b**)**. Finally, to get a measure that is independent of the threshold, this curve can be integrated in the range of the threshold between 0 and 1. This integration measure is normalized by the maximal number of connected brain areas (that is, all N areas) for each integration step and by the number of integration steps such that the maximal integration is normalized to one. For each possible external stimulation, this integration measure is calculated. We define perturbational integration as the average of the integration over a large amount of instantiations of external stimulations (typically at least 1000). FIG. 2c**,** shows how perturbational integration evolves as a function of changing the global coupling parameter in a realistic whole-brain model.

Furthermore, BOX 2 shows how perturbational segregation and integration change in networks with very different topological characteristics, namely different degrees of small-worldness — from a fully ordered lattice structure to a completely random graph.

Binding information over time

The measures of information segregation and integration using the methods of perturbational segregation and integration rely on using grand-averaged connectivity measures over time to calculate the functional activity. However, the evolution of activity over time also clearly influences information segregation and integration. It is a major goal of neuroscience to describe the temporal

changes in segregation and integration. Such a description would increase our understanding of fundamental brain function and of concepts such as awareness and consciousness.

The generalization from static grand-averages to dynamic temporal measures of perturbational segregation and integration described above is fairly straight-forward: instead of taking the grand average of the FC collapsed over time, the FC can be split into in smaller windows of time[67], so that the perturbational integration can be calculated for each sliding window. Here, we use between 30 and 120 seconds since smaller time-windows on the scale of, say, four seconds can yield spurious fluctuations [68] (see bottom right panel of FIG. 2a). Specifically, for each brain region, the largest component that includes this region can be calculated and integrated over all thresholds used to binarize the FC in a similar way as before, but now separately for each sliding window. This yields the amount of perturbational integration involving a given brain region as a function of time. Integrating perturbational integration over all time windows yields a measure of perturbational spatiotemporal integration; that is, temporal binding (which is related to the binding problem [69] — how distributed information is bound and made available to consciousness[70]). FIG. 2c shows that the amount of temporal binding increases as the model is approaching the optimal dynamical working point.

Evaluating temporal binding reveals which nodes within the network are more integrative, or binding, across both space and time. These nodes can be said to comprise the brain's 'binding club', by analogy with the 'rich club' of regions that were identified on the basis of measures of topological integration [32] (FIG. 3a). Note, however, that there could be many possible definitions of binding and future research will need to determine the most appropriate. For example, one alternative is to define binding as the variability of correlations between pairs of regions (in terms of connectivity at the edge level). FIG. 3b shows this alternative temporal binding for each edge and for each node (summed over the edges) at the model's dynamic working point, using data from participants going from wakefulness to sleep.

Future areas of research will be to establish whether there is substantial overlap between nodes participating in the 'temporal binding club' and in the rich club. This is important as the nodes belonging to the rich club are thought to be important for information integration among distributed brain regions [32], where recent graph-based analyses of windowed 'dynamic' resting state fMRI data have found an overlap between the rich club and regions showing maximum dynamic functional connectivity. We hypothesize that nodes belonging to the temporal binding club could be important for mediating the concatenation of different brain states during cognitive sequences, and as such may be important for facilitating awareness.

Brain states in health and disease

The measures of perturbational segregation, integration and temporal binding introduced above reveal important features of brain organization. Their utility has to be assessed, however, in their ability to distinguish between different state changes, such as sleep and wakefulness, and for distinguishing between the human brain in health and disease.

As a proof of principle of this ability, our proposed measures were able to track changes in functional connectivity over time as healthy participants were either awake or asleep, and showed marked differences in binding and functional connectivity between these two behavioural states [71] (FIG. 3b). Interestingly, when comparing sleep with wake, the binding measure decreased to capture the functional disconnection over time while there was an increase in mean functional connectivity. This is consistent with the observation that binding of external information is clearly decreased during sleep, as well as existing evidence showing that the sleeping brain is more

functionally connected due to synchronization of the slow sleep waves [72]. Furthermore, the results suggest that there are specific brain regions that are important for temporal binding within the cortex.

The new measures of segregation and integration have also been applied to rare structural neuroimaging data obtained from a patient with Parkinson disease to examine changes in functional connectivity that may be triggered by structural reorganization following deep brain stimulation (DBS) [73]. We modelled the structural changes using a whole-brain computational model [74], and observed that the clinical improvement following six months of DBS of the subthalamic nucleus was mirrored by the long-term structural changes which when used with the model were closer to results from of normal participants than the before the operation (FIGs 4a,b). As shown in FIG 4c, the perturbational measures of segregation and integration were also sensitive to the improvements (that is, alleviation of symptoms) following DBS. This finding could potentially shed light on the underlying mechanisms for DBS in rebalancing functional brain networks [75].

Conclusions

In this Opinion article, we have shown that whole-brain computational modelling can be used to improve our understanding of segregation and integration of information in the human brain. One of the key possibilities that is offered by whole-brain computational models is the ability to systematically perturb the inputs and measure the functional consequences of this perturbation. This provides novel insights into the fundamental principles of brain function. In particular, a better understanding of segregation and integration of information can lead to novel ways to distinguish between different states of consciousness and between the brain in health and disease.

However, despite the current exciting progress, many challenges and limitations to whole-brain computational modelling remain. Broadly speaking, more research is needed, first, to make the models more realistic (for example, by taking into account the unfolding of activity across many temporal timescales) and, second, to further refine the models such that they can be reliably used in individual participants based on the empirical data obtained from that individual — rather than working on a group level. Before being able to deliver individual biomarkers, however, the models will have to able to identify biomarkers that stratify a broad-illness phenotype into a finite number of treatment-relevant subgroups.

The temporal description and prediction of functional activity with whole-brain computational models is becoming ever more important [67]. As shown in this Perspective, it is important to move beyond grand-average functional connectivity matrices and to start measuring the temporal binding of information. The study of the temporal evolution of functional correlations across time reveals aspects of brain dynamics that can never be expressed in a grand-average based description of functional connectivity over time. The concept of meta-stability has also been introduced to accurately describe the dynamical regime of models inferred from empirical data and therefore can be used for describing how self-assembling processes of the brain are engaging and disengaging over time [76]. Further research is needed to identify the relationship between meta-stability and multi-stability as described in this Perspective (BOX 1). A practical application of investigating the temporal dynamics could be the identification of novel types of biomarkers, such as an information theoretic (entropic) measure of the time dynamics of correlation pairs of brain regions. This temporal measure of variability could be a complementary biomarker segregating disease progression and the response to treatment.

The overall goal of computational neuroscience is to create models of the brain that are sufficiently powerful and precise to infer a large range of detailed underlying processes from

neuroimaging data in individuals in both health and disease. This mechanistic information could potentially be useful for understanding the breakdown of information processing in neuropsychiatric disorders [8, 77] and as such it could identify biologically homogenous subtypes that cut across phenotypic diagnosis [78] and thereby aid in the development of a stratified neuropsychiatry[79].

Most importantly, further insights into the principles of information segregation and integration in the human brain may offer fundamental insights into the very nature of awareness and consciousness. It has been proposed that integration can happen without awareness and that consciousness may only be needed for the integration of novel information [3]. The underlying mechanisms for information segregation and integration are not fully understood, but it is likely that causal whole-brain computational models may help elucidate the fundamental principles.

Gustavo Deco is at the Center for Brain and Cognition, Computational Neuroscience Group, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Roc Boronat 138, Barcelona, 08018, Spain, and the Institució Catalana de la Recerca i Estudis Avançats (ICREA), Universitat Pompeu Fabra, Passeig Lluís Companys 23, Barcelona, 08010, Spain.

Giulio Tononi and Melanie Boly are at the Department of Psychiatry, University of Wisconsin-Madison, WI 53719, USA.

Melanie Boly is also at the Department of Neurology, University of Wisconsin-Madison, WI 53702, USA.

Morten L. Kringelbach is at the Department of Psychiatry, University of Oxford, OX3 7JX Oxford, UK, and the Center of Functionally Integrative Neuroscience (CFIN), Aarhus University, 8000 Aarhus C, Denmark.

Correspondence to G. D.
e-mail: gustavo.deco@upf.edu

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Competing interests statement
The authors declare no competing interests.

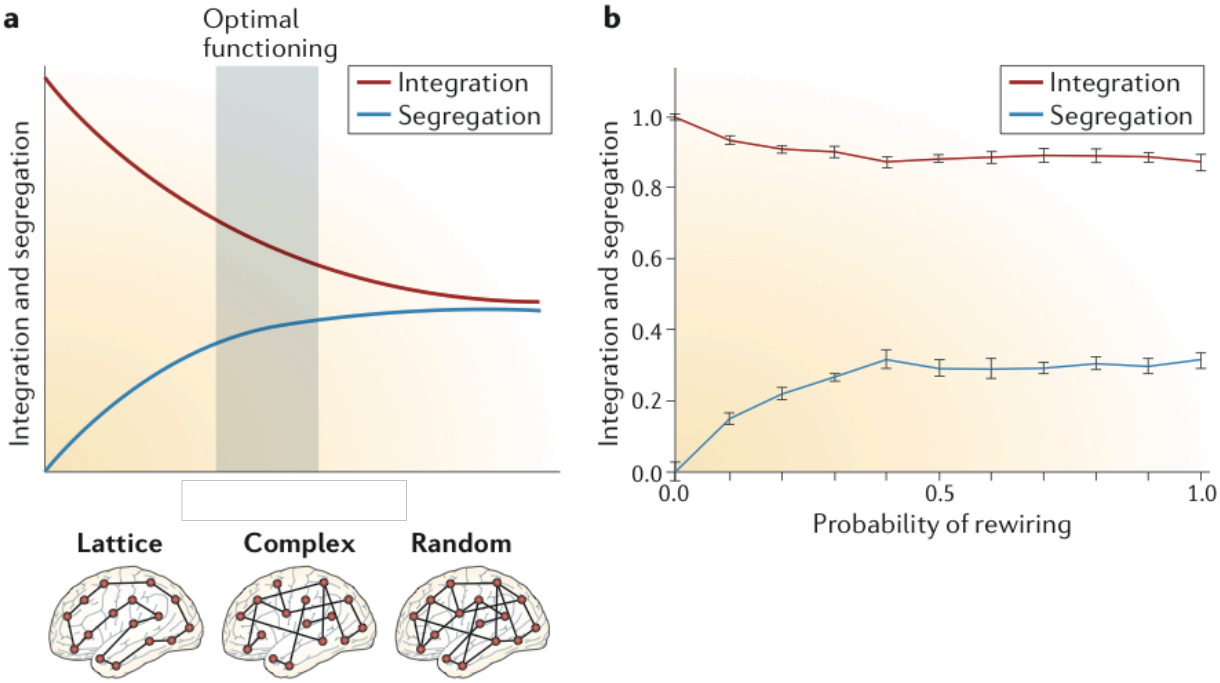
Box 1 | **Multi-stability and sub-criticality**

The dynamic interaction of functionally specialized but widely distributed brain regions in humans can be analyzed by combining structural neuroanatomical data and brain activity data. To this end, whole-brain activity can be modelled in terms of a network of local-area attractor networks. The connections between brain areas are given by the structural connectivity matrix based on DTI or DWI tractography [54, 80]. Specifically, we assume that the number of white matter tracts that connect brain areas corresponds to the strength of the reciprocal synaptic projections between these areas. In addition, this structural connectivity is scaled by a global factor, which is a critical control parameter and can be varied systematically to study the dynamics and fixed points of the whole-brain model. Brain activity data from neuroimaging experiments (involving fMRI, MEG and/or EEG) reveals highly structured spatiotemporal activity patterns, even in the resting brain. This structure is revealed in the functional connectivity matrix, which comprises all pair-wise correlations between areal activities. Specifically, the so-called resting-state networks emerge as segregated sub-matrices within the functional connectivity matrix.

By incorporating both brain structure (anatomical connectivity) and activity dynamics (functional connectivity), a whole-brain neurodynamical model can explain the emergence of resting-state networks mechanistically. Some neurodynamical models have used simple oscillatory dynamics [56, 63, 81, 82], whereas others have used a more realistic spontaneous state dynamics [62]; even more detailed and realistic local models (at the node level) have considered excitatory and inhibitory populations of spiking neurons coupled through NMDA, AMPA and GABA synapses [61]. By means of dynamic mean-field modelling [49], the activity of detailed spiking models can be reduced to a more tractable model of the activity of local neuronal ensembles that allow an analytical treatment of the equations and consequently the derived integration and segregation [58].

As it turns out, a simulated functional connectivity best matches the empirical functional connectivity when the whole-brain network is subcritical — more specifically, when both a spontaneous state (that is, low activity in all areas) and several excited states (that is, high activity in selected areas) are stable attractors states of the model. In other words, multistability around a spontaneous state defines an operating point such that system activity stochastically explores the dynamic repertoire inherent to the structural connectivity [49, 61]. Similarly, the concept of metastability is a measure of how variable brain states are as a function of time; for example, how the synchronization between the different brain regions fluctuates across time. The concepts of multi- and metastability are possible scenarios for the resting state and it is an active area of research to determine which is a more accurate description [76].

Readers can explore these concepts by using ‘The Virtual Brain’, which is a freely available neuroinformatics platform with a user-friendly interface that allows users to perform simulate, analyze and compare models with neuroimaging data[83].



Box 2 | **Integration and segregation in small-world architectures**

It is informative to consider how varying degrees of small-worldness in the structural connectivity affect a network's ability to segregate and integrate. To answer this question, a realistic whole-brain model can be outfitted with different artificial connectivities, ranging from a structured lattice to completely random connectivity (see the figure, part **a**). In this model, all artificial connectivities use the same parcellation (116 regions in the automated anatomical labelling parcellation) and the same number of edges, and the degree of small-worldness is manipulated with the procedure of Watts and Strogatz [84]. In a nutshell, this procedure yields networks with defined structural features such as the clustering coefficient or the average shortest path length. The well-known Watts and Strogatz connectivity combines a large clustering coefficient with a small average shortest path length. The key idea is to depart from a regular lattice and to redefine the links between two nodes according to the probability of rewiring (see the x-axis of figure, part **b**); that is, if two nodes are linked, that link will be maintained or reallocated to another node according to such probability.

Simulations of such networks demonstrate that as the connectivity changes gradually from an ordered lattice to complete randomness, perturbational integration decreases, whereas perturbational segregation increases (see the figure, part **a**). Intuitively, integration decreases because randomness destroys the level of clustering and therefore the length of the largest component, whereas the segregation increases because randomness increases the capability to distinguish two different external inputs. This increase in segregation is a consequence of how the increase in disconnection generates different patterns and therefore increases the entropy. Optimal function (that is, achieving a balance between segregation and integration) is obtained at an intermediate level of connectivity, between order and randomness. Note that in the figure, the perturbational integration (red line in part b) is normalized to a maximum of 1 and the segregation (black line in part b) is normalized to a minimum of zero. The error bar in part b corresponds to 100 different instantiations of possible rewirings.

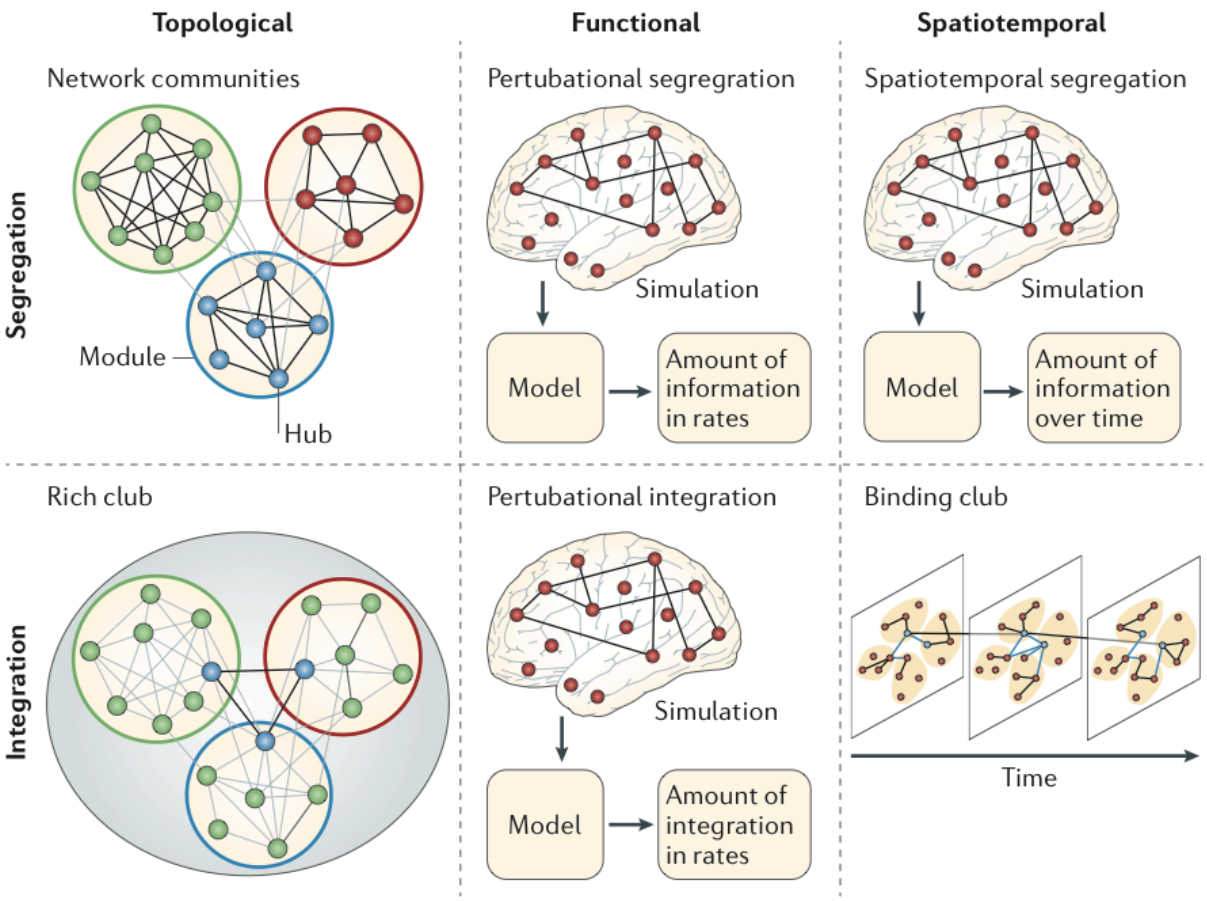


Figure 1 | **Segregation and integration measures can be improved using whole-brain modelling. a |** Measures of segregation (top row) and integration (bottom row) come from the topological, functional and spatiotemporal domains (columns). Segregation is supported by densely connected network communities whereas integration is promoted by network hubs that are rich in connections between the communities, the so-called 'rich club', whose members have high graph measures of node degree and betweenness. We argue that functional measures of segregation and integration can improve on previous topological measures by using whole-brain computational models that can be systematically perturbed by introducing random inputs and where the functional consequences of this perturbation can be measured. The pertubational segregation is a measure of the capacity of the brain to convey the amount of information provided by arbitrary external inputs during systematic perturbation. The arbitrary external inputs are measured in rates; that is, averaged over time. Similarly, perturbational integration is a measure of how effective, during systematic perturbation, the brain is in integrating (rather than conveying) information from arbitrary external inputs distributed across different brain regions. Combining spatiotemporal information can yield even more precise and sensitive measures of the variability of information processing in the brain over time. Spatiotemporal perturbational segregation can measure the ability of the brain to encode the information over time varying inputs. Spatiotemporal perturbational integration, or simply 'binding', can be used to characterize the effectiveness of integration of distributed information across the whole brain over time.

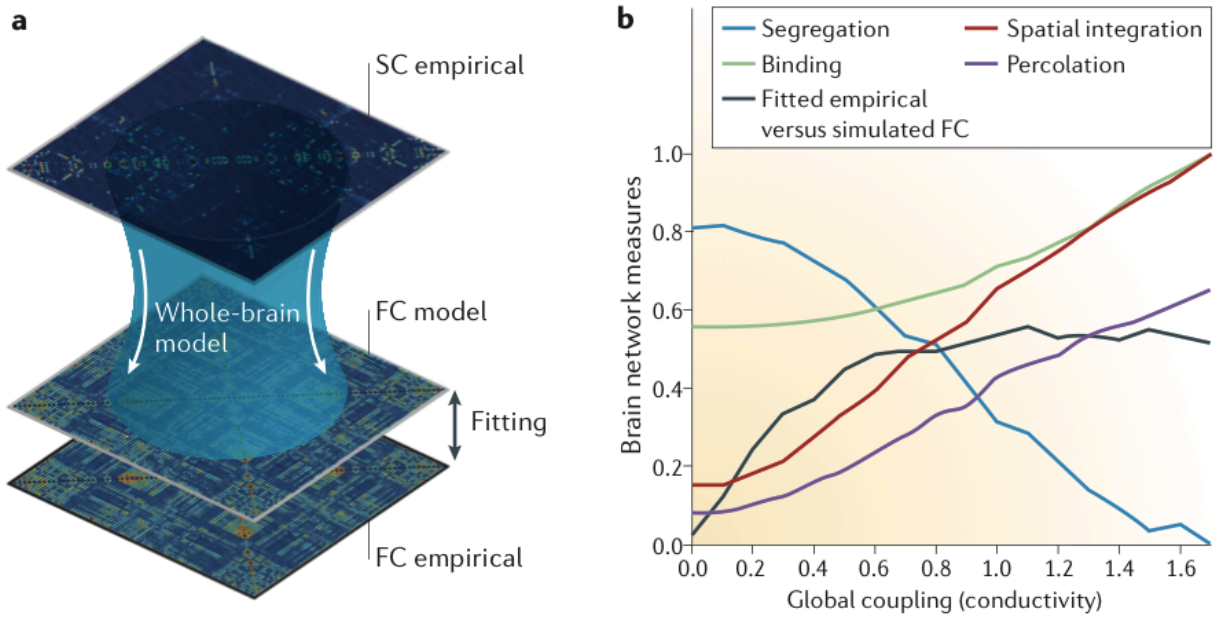


Figure 2 | **Using whole-brain computational modelling. a** | Whole-brain computational modelling of empirical neuroimaging data use structural connectivity data (SC empirical) obtained using DTI and tractography between a parcellation of the human brain, and functional connectivity data (FC empirical) obtained, for example, from BOLD fMRI data. A whole-brain model can be constructed using a set of stochastic differential equations coupled according to the connectivity matrix (global and individual coupling). **b** | An example of how measures of perturbational segregation and integration can be obtained from whole-brain computational modelling. The coupling parameter linearly scales the empirically obtained structural connectivity (from DTI tractography), corresponding to the assumption that each fibre has the same biophysical conductivity; that is, similar postsynaptic currents. The simulations show that perturbational segregation and integration are complementary measures: segregation decreases and integration decreases as global coupling (or conductivity) increases. When global coupling is weak, there is high segregation (blue line) and low integration (red line), because perturbed nodes are disconnected and behave independently. By contrast, when global coupling is strong, integration is high and segregation is low, because perturbed nodes are coupled. The black line indicates the correspondence (Pearson correlation) between the simulated functional connectivity and the empirical functional connectivity matrix (based on spatiotemporal blood-oxygen-level dependent (BOLD) activity). Intriguingly, the point when integration and segregation have similar normalized values is when the simulated and empirical functional connectivity match each other (at global coupling of around 0.8), suggesting that the optimal working point of a brain network occurs when segregation and integration are balanced.

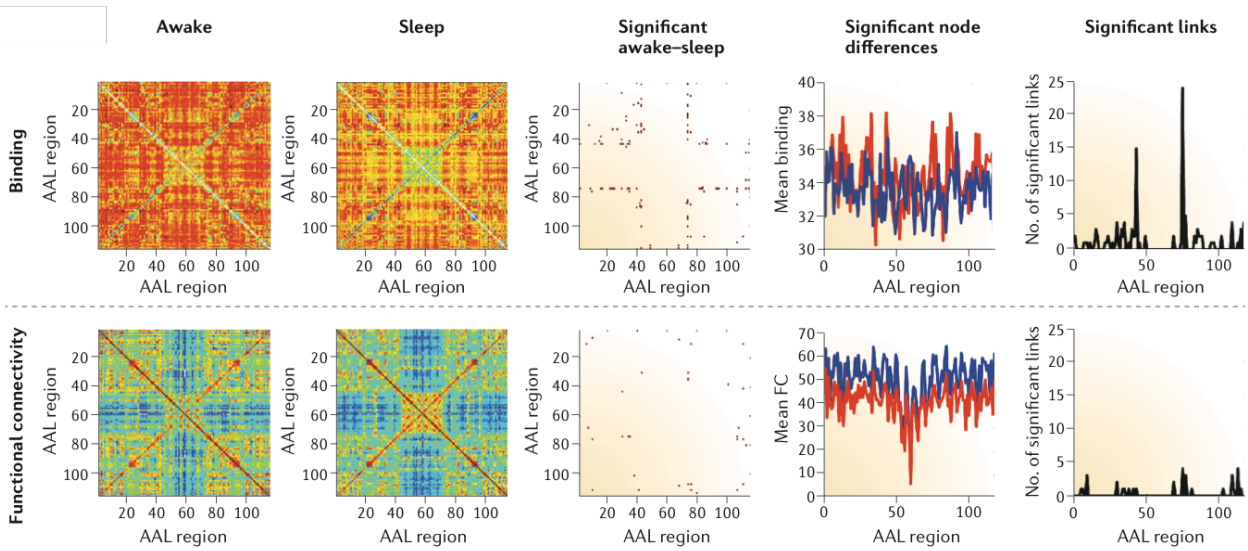


Figure 3 | **Using the binding to extend our understanding of integration in the human brain. a |** IWe used a binding measure on previously published neuroimaging data obtained when subjects were either awake or asleep [71, 85, 86] and show that the new measure is both sensitive and accurate in mapping this important and common change in consciousness. The figure plots the analysis of changes between AAL regions in functional connectivity (FC, bottom row) and binding measurements (top row). For each row, the first column shows the matrices for the awake condition (averaged over participants), whereas the second column shows the matrices for the sleep condition. The colours indicate binding and FC from low (blue) over medium (yellow) to high (dark red). The third column plots the significantly different pair connections in both conditions (dots in the matrices); that is, the pairs that passed significance testing corrected for multiple comparisons ($p<0.05$). The fourth column plots the mean value for each area (for FC and binding) with the blue line corresponding to the sleep condition and the red line to the awake condition. As can be seen by comparing columns 1,2 and 4, the binding decreases in sleep whereas the mean FC increases. This result fits well with existing evidence that the sleeping brain is more globally connected functionally because it is more synchronized due to the slow sleep waves [72], whereas the binding measure instead captures the functional disconnection over time. The fifth column shows significant differences between the sum for each area of the number of connections with the rest of the nodes. Note that the new binding measure shows significance levels that are much more sensitive thano those for the FC.

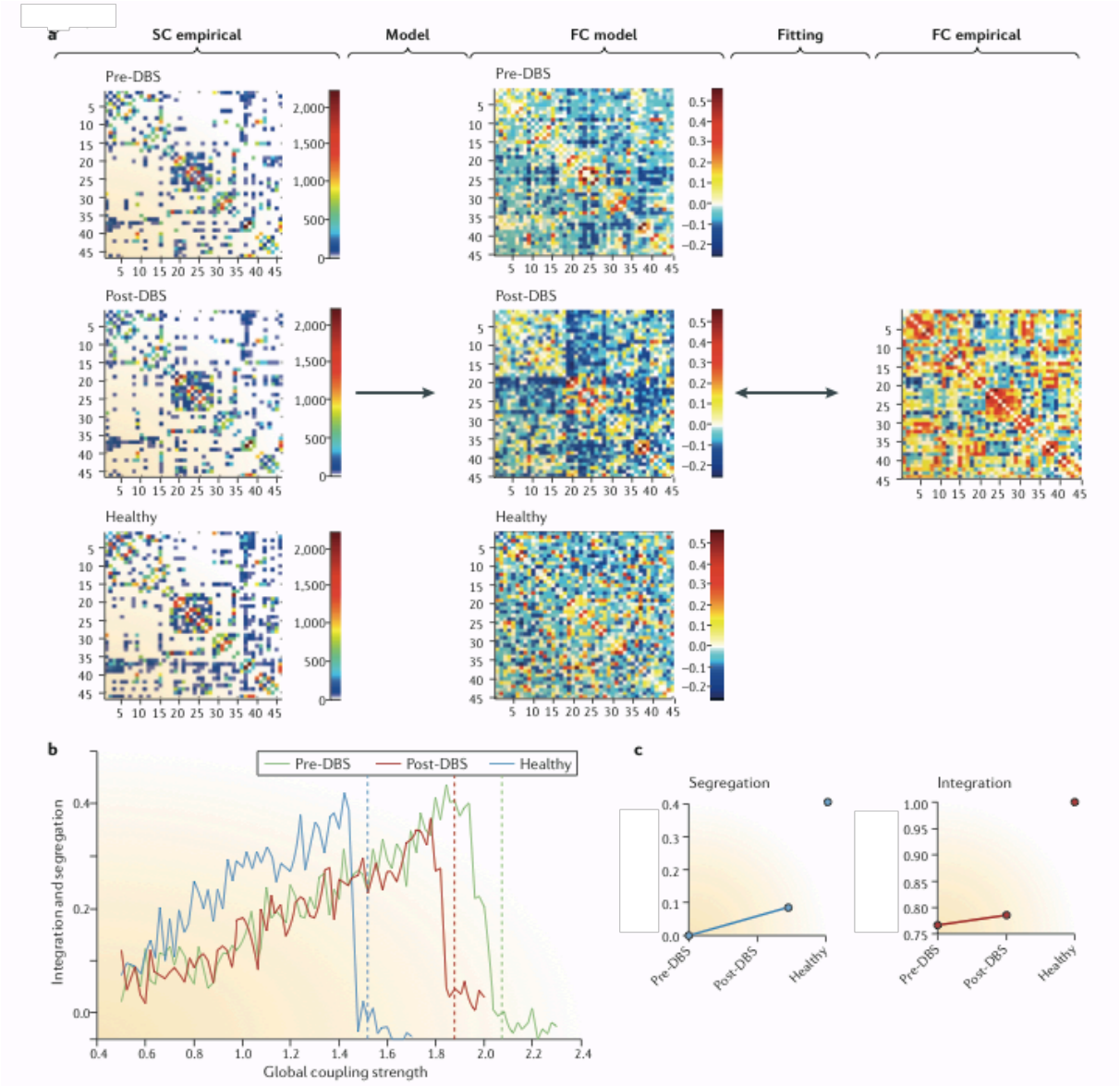


Figure 4. Using perturbational segregation and integration measures to characterize health and disease. a | Changes in structural connectivity following six months of deep-brain stimulation (DBS) of the subthalamic nucleus to alleviate the symptoms of Parkinson disease (PD) [74]. The figure shows the structural connectivity matrices between 45 brain regions (x and y-axes) in a unique case of DBS patient with pre- and post-DBS DTI scans compared with those of healthy individuals (left column). The colours in the matrices indicate the connectivity strength from low (blue) over medium (yellow) to high (dark red). The middle column shows the corresponding functional connectivity matrices produced by the model (blue arrow) from the structural connectivity, which is then fitted (blue two-way arrow) to the empirically obtained functional connectivity matrix from these individuals (right column). **b** | The fit quality is plotted as a function of coupling strength, for pre- and post-operative DBS patient and healthy individuals [74]. The optimal operating point for the whole-brain computational model is defined as the point where modeled and empirical functional connectivity match; this is reflected in the region of the graph just before the bifurcation point (sudden dip), which is very different between healthy (blue) and pre-DBS (black). DBS shifts the operating regime of the model (shown in red) closer to that of healthy individuals, evidencing the plasticity of recovery of cortical function by DBS. It was shown that this functional recovery in PD affected cortical connectivity, even though the source of the disease and the area of DBS stimulation is sub-cortical [74]. **c** | Measures of perturbational segregation (in blue) and integration (in red) are also sensitive to the functional improvements following DBS surgery, as shown by the increase in both measures between pre, post and healthy.

Biographies

Gustavo Deco is ICREA Research Professor and Full Professor at the UPF, where he heads the Computational Neuroscience Group and directs the Center for Brain and Cognition. Recognised as a world leader in computational neuroscience, he has led pioneering work in dynamical modelling of human brain activity. He is an ERC Advanced grantee and member of the Human Brain Project. He has published 4 books, more than 210 papers in International Journals and 30 book chapters.
Gustavo Deco's homepage: http://www.cns.upf.edu

Guilio Tononi is a neuroscientist and psychiatrist who holds the David P. White Chair in Sleep Medicine, as well as a Distinguished Chair in Consciousness Science, at the University of Wisconsin. His main focus is on focus on two neurobiological problems: the mechanisms and functions of sleep, and the neural substrates of consciousness.
Guilio Tononi's homepage: http://tononi.psychiatry.wisc.edu

Melanie Boly is a neurologist and neuroscientist. She has worked for more than fourteen years in the field of altered states of consciousness such as vegetative state, sleep and anesthesia, under the mentorship of Steven Laureys, Pierre Maquet, Adrian Owen and Karl Friston. Her research aims at combining neuroimaging techniques such as PET, functional MRI, TMS-EEG, and high density EEG to a theoretical framework, the Integrated Information Theory of Consciousness, hoping to uncover the neural mechanisms of the level and contents of consciousness in healthy subjects and neurological patients.
Melanie Boly's homepage: http://www.melanieboly.org/

Professor **Morten L Kringelbach** is the director of *Hedonia: TrygFonden Research Group*, a transnational research group based at the universities of Oxford, UK and Aarhus, Denmark. His research uses behavioural, neuroimaging, neurosurgical and computational methods for understanding pleasure and its underlying brain networks in health and disease.
Morten L Kringelbach's homepage: http://www.kringelbach.org

Glossary

Connectome
The complete description of the structural connections between elements of a nervous system.

Graph theory
A branch of mathematics that deals with the formal description and analysis of graphs. A graph is defined simply as a set of nodes (vertices) linked by connections (edges), and may be directed or undirected. When describing a real-world system, a graph provides an abstract representation of the system's elements and their interactions.

Bifurcation
One of the basic tools of analysis of dynamical systems, which is defined by qualitative changes of the asymptotic behavior of the system ("attractors") under parameter variation.

Criticality
At the brink of a bifurcation, the system displays certain characteristic dynamic features, of which most are related to enhanced fluctuations.

Diffusion tensor imaging (DTI)
An MRI technique that takes advantage of the restricted diffusion of water through myelinated nerve fibres in the brain to infer the anatomical connectivity between brain regions.

Functional connectivity
Statistical association — for example, significant correlations — between neurophysiological measurements recorded from anatomically distinct neurons or regions at several time points.

Mean-Field model
The mean-field approximation consists of replacing the temporally averaged discharge rate of a cell with an equivalent momentary activity of a neural population (ensemble average) that corresponds to the assumption of ergodicity. According to this approximation, we characterize each cell assembly by means of its activity population rate.

Edges
In a brain graph, an edge between nodes (regions or neurons) indicates that the nodes are anatomically or functionally connected.

Small-world architecture
A term used to describe complex networks that have a combination of both random and regular topological properties; that is, high efficiency (short path-length) and high clustering, respectively.

Metastability
In dynamical systems refers to a state which falls outside the natural equilibrium state of the system but persists for an extended period of time.

Magnetoencephalography
(MEG). A method of measuring brain activity by detecting minute perturbations in the extracranial magnetic field that are generated by the electrical activity of neuronal populations.