OPINION

Rethinking segregation and integration: contributions of whole-brain modelling

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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 about 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 led to the development of 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 memories to predict the future and to adapt behaviour accordingly. The healthy human brain segregates and integrates information from sensory modalities, the body and memories. Take the example of a tennis player, who effortlessly integrates their memories with the colour, movement and shape of a tennis ball and segregates this information from the changing background of the tennis court and the crowd. These processes enable the player to predict the trajectory of the ball and to plan how best to position their body and tennis racket to return the ball beyond the reach of their opponent. The integrated information can be formally defined as the information a system has besides the information that is available from the sum of its parts[1,2]. Such integration of information has been linked to consciousness, but it can also proceed without awareness[3]. However, we still lack 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 that probed and tested the brain in many different ways[4]. However, such meta-analyses present many important potential confounds, including their cross-sectional nature. Instead, neuroimaging methods would 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 integrate 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 range of diverse inputs and control the full dynamics of the human brain. The use of direct causal brain interference methods such as transcranial magnetic stimulation (TMS) also provides a promising approach to study brain networks. However, there are notable ethical problems associated with causally interfering with the human brain[5,6].

The difficulty in controlling the full range of inputs to an individual brain is another reason why neuroimaging-based investigations of information segregation and integration have so far focused on the 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 (which is 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 use 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 be used to gain new insights into segregation and integration. We describe the currently available topological measures that are obtained from neuroimaging studies of connectomics using graph theory 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. By systematically perturbing model networks, such models can be used to improve our understanding of the dynamics of input processing and thereby provide 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 (FIG. 1). These measures 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 measures of segregation and integration 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 can map 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]. An important goal of these studies is to establish the human connectome, which is defined as "the complete description of the structural connectivity (the physical wiring) of an organism's nervous system" (REF. 7). Here, we argue that this purely structural description could be amended to include the functional connectivity of the connectome, and such combined knowledge may enable us to understand the complex segregation and integration of relevant information over time.

Collecting topological and functional data. Neuroimaging methods can be used to study brain activity on several timescales and with varying degrees of spatial precision. In humans, the most popular

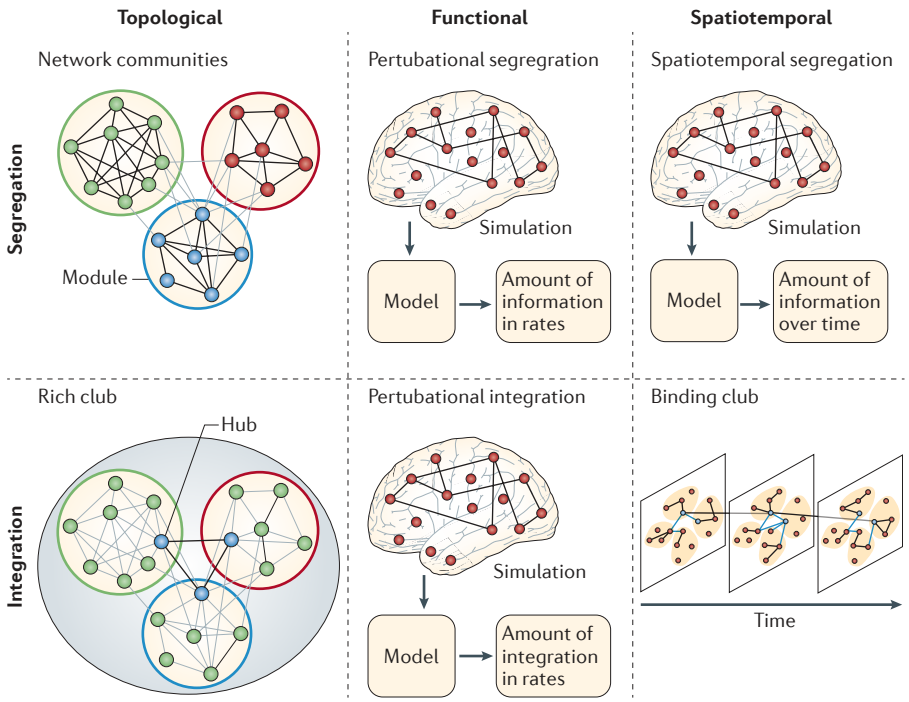


Figure 1 | **Segregation and integration measures can be improved using whole-brain modelling.** Measures of segregation (top row) and integration (bottom row) come from the topological, functional and spatiotemporal domains (columns). Segregation is supported by densely connected network communities, whereas integration is promoted by network hubs that are rich in connections between the communities, the so-called rich club, members of which have high graphical 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 in which the functional consequences of this perturbation can be measured. The perturbational 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 at 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 information over time with 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.

methods for mapping structure and connectivity *in vivo* on the scale of millimetres include MRI and diffusion imaging (such as diffusion-weighted imaging (DWI) or diffusion tensor imaging (DTI)), which uses methods that are sensitive to the influence of the major fibre tracts on the diffusion of water[9,10]. These major tracts can then be reconstructed by combining models of water diffusion with deterministic or probabilistic tract-tracing methods[11,12]. However, there are notable 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].

Brain activity is typically measured using both indirect methods (such as fMRI and positron emission tomography) and direct methods (such as 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 spontaneous resting-state activity in the regions of the brain 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 to 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-organizing brain dynamics. For clinical studies, an advantage of rs-MRI is that there is no need for participants to engage in tasks that are often boring and repetitive. Both rs-MRI studies and task-based fMRI studies provide multipurpose data sets that can be used to study multiple, interacting networks[23,24].

The primary advantages of the rs-MRI approach over the task-based fMRI approach are the ease of data acquisition and of data analysis, which facilitate large-scale cross-sectional and longitudinal human studies. As mentioned above, approaches that are 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]. However, progress has been made in addressing these issues: for example, by building automated methods for the assessment of sleep stages[27] and by 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. Specifically, tools from graph theory have proved 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 analyse nodes (that is, neurons and brain regions) and edges (that is, 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 several nodes, which is achieved by parcellating the human brain into tens to hundreds of small regions[20]. Measurements of connectivity are then calculated as the strength of the edges between the nodes of the system[33].

The advances in mapping the human connectome have led to the identification of some of the features of brain architecture that, as a plausible working hypothesis, may be necessary and sufficient for segregation and integration in the brain. These advances 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 REF. 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 interconnectivity and diverse patterns of dense interconnectivity[31]. This central core or rich club of important hubs has been suggested to have a key role in global (that is, across the whole brain) integration of information[38].

Taken together, the results of graph theoretical analysis of structural brain data indicate 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 that connect them, respectively. However, this is only a description of the network architecture that supports segregation and integration; it does not describe the causal mechanisms that underlie functional segregation and integration. In particular, a graph theoretical approach using structural MRI data does not describe the dynamics of functional activity associated with the integration of information 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 for investigating 'structural' (that is, anatomical) segregation and integration have been complemented by studies that assess '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 changes in functional brain activity 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 (which is defined as the coexistence of functional segregation and integration within the same network)[40] and integrated information (which is 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 that is 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 proved to be useful for characterizing the changes between consciousness states (such as wakefulness, sleep and anaesthesia) 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 substantial progress could be made by using whole-brain models to further elucidate the candidate brain mechanisms of segregation and integration. These models use 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. Substantial progress has been made in the development of whole-brain computational models that can reproduce some of the complexity and important features of the brain *in vivo*. These whole-brain models strive to find the right balance between complexity and manageability by taking their lead from statistical physics, in which 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 dynamic 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] — similarly to how the temperature of a gas captures the mean local particle velocity — whereas the most advanced models use a dynamic mean-field model derived from a proper reduction of a detailed spiking neuron model[49].

Glossary

Bifurcation
One of the basic tools to analyse dynamic systems. It is defined by qualitative changes in the asymptotic behaviour of the system ('attractors') under parameter variation.

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

Edges
In a brain graph, edges denote anatomical or functional connections between nodes, which may indicate brain regions or neurons.

Graph theory
A branch of mathematics that deals with the formal description and analysis of graphs. A graph is simply defined as a set of nodes (vertices) that are linked by connections (edges) and can be directed or undirected.

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

Mean-field models
Mean-field approximations consist of replacing the temporally averaged discharge rate of a cell with an equivalent momentary activity of a neural population (the ensemble average) that corresponds to the assumption of ergodicity. According to these approximations, each cell assembly is characterized by its activity population rate.

Metastability
In dynamic systems, metastability refers to a state that falls outside the natural equilibrium state of the system but persists for an extended period of time.

Small-world architecture
This term is used to describe complex networks that have a combination of random and regular topological properties.

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 on the basis of 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], although current popular choices include fewer regions, such as the Desikan–Killiany parcellation[52] or Hagmann parcellation[53] with 66 cortical regions, and the automated anatomical labelling parcellation with 116 regions (including cortical and subcortical regions, and the 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. 1). In other words, the dynamic entrainment and correlations between different local brain region dynamics are essentially shaped by the underlying structural connectivity[55–60]. Therefore, whole-brain computational models can provide a mechanistic explanation for the origin of resting-state networks, as has been shown for resting-state networks derived from rs-MRI data[61,62] and 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 that underlie the functioning of the healthy human brain, which is superior to the understanding that can be acquired 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, could yield important new information.

Box 1 | Multistability and subcriticality

The dynamic interaction of functionally specialized but widely distributed brain regions in humans can be analysed 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 diffusion tensor imaging or diffusion-weighted imaging 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 crucial 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 functional MRI, magnetoencephalography and/or electroencephalography) reveal highly structured spatiotemporal activity patterns, even in the resting brain. This structure is revealed in the functional connectivity matrix, which comprises all pairwise correlations between areal activities. Specifically, the so-called resting-state networks emerge as segregated submatrices within the functional connectivity matrix.

By incorporating both brain structure (anatomical connectivity) and activity dynamics (functional connectivity), a whole-brain neurodynamic model can explain the emergence of resting-state networks mechanistically. Some neurodynamic models have used simple oscillatory dynamics[56,63,81,82], whereas others have used 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 allows analytical treatment of the equations and consequently the derived segregation and integration[58].

As it turns out, 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 attractor 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 multistability 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 using The Virtual Brain, which is a freely available neuroinformatics platform with a user-friendly interface that enables users to perform, simulate, analyse and compare models with neuroimaging data[83].

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 dynamic 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; see FIG. 2a). The overall statistical dependence among all of 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]:

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

where n is the number of evoked patterns (typically $n = 1{,}000$) 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 segregation (that is, information capability (I_C)) is finally given by:

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

The novel measure of perturbational segregation can then be defined by normalizing this measure by the maximal possible value of the mutual information given by random

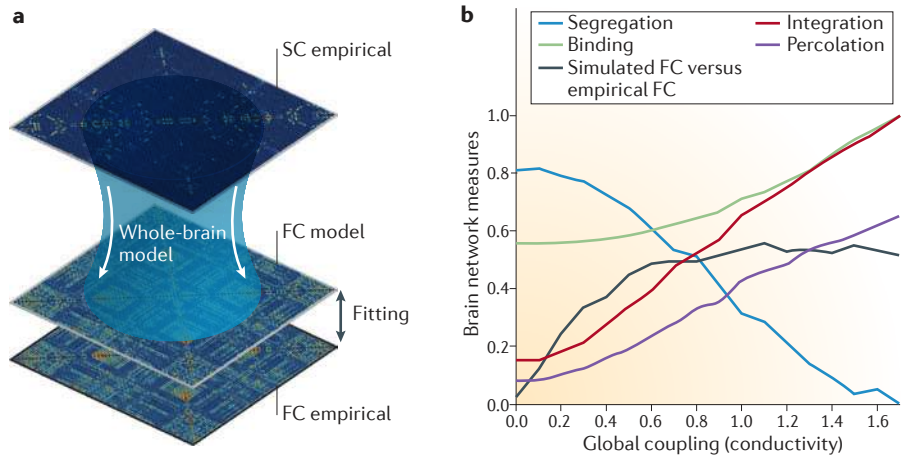


Figure 2 | **Using whole-brain computational modelling.** **a** | Whole-brain computational modelling of empirical neuroimaging data uses structural connectivity (SC) data obtained from diffusion tensor imaging (DTI) tractography between a parcellation of the human brain, and functional connectivity (FC) data obtained, for example, from blood oxygenation level-dependent (BOLD) functional MRI. 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 SC (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 increases as global coupling (or conductivity) increases. When global coupling is weak, there is high segregation and low integration, 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 FC and the empirical FC matrix (based on spatiotemporal BOLD activity). Intriguingly, the point at which segregation and integration have similar normalized values is when the simulated and empirical FC 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.

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 that are 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 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 (designated FC in the criteria below) can be binarized (using the criterion $|FC_{ij}| < \theta$; which determines whether it will be given a value of 0 or 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 that connects to no additional vertices in the super-graph (FIG. 2a). 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 1. This integration measure is calculated for each possible external stimulation. We define perturbational integration as the average integration over a large amount of instantiations of external stimulations (typically at least 1,000). FIGURE 2b 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 key goal of neuroscience to describe the temporal changes that occur in segregation and integration. Such a description would increase our understanding of fundamental brain function and of concepts such as awareness and consciousness.

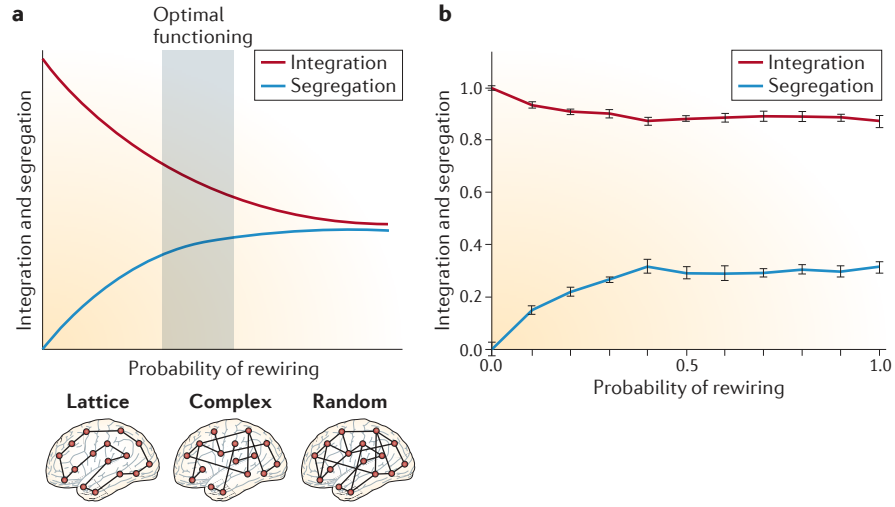
The generalization from static grand averages to dynamic temporal measures of perturbational segregation and integration described above is fairly straightforward: instead of taking the grand average of the functional connectivity collapsed over time, the functional connectivity can be split into smaller windows of time[67], so that the perturbational integration can be calculated for each sliding window. Here, we use between 30 seconds and 120 seconds, as smaller time windows on the scale of, for example, 4 seconds can yield spurious fluctuations[68] (see the bottom right panel of FIG. 1). Specifically, for each brain region, the largest component that includes this region can be calculated and integrated over all thresholds used to binarize the functional connectivity 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. Assimilating perturbational integration over all time windows yields a measure of perturbational spatiotemporal integration: that is, temporal binding. (Temporal binding is related to the binding problem[69]: that is, how distributed information is bound and made available to consciousness[70].) FIGURE 2b shows that the amount of temporal binding increases as the model is approaching the optimal dynamic working point.

The evaluation of 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 'binding club' of the brain, by analogy with the 'rich-club' regions that were identified on the basis of measures of topological integration[32]. Note, however,

Box 2 | **Segregation and integration in small-world architectures**

It is informative to consider how varying degrees of small-world architecture in the structural connectivity affect the ability of a network to segregate and integrate information. 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 using the procedure designed by Watts and Strogatz[84]. In brief, 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; 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 gradually changes 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 segregation increases because randomness increases the capability to distinguish between 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. The optimal function (that is, achieving a balance between segregation and integration) is obtained at an intermediate level of connectivity, between order and randomness. Part **b** of the figure shows the results of measuring integration and segregation as a function of the probability of rewiring in whole-brain computational modelling. Note that the perturbational integration is normalized to a maximum of 1 and that the segregation is normalized to a minimum of 0. The error bars in part **b** represent the s.e.m. across 100 instantiations of possible rewirings. Part **a** of the figure is adapted with permission from REF. 8, Elsevier.



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). FIGURE 3 shows this alternative temporal binding for each edge and for each node (summed over the edges) at the dynamic working point of the model, using data from participants going from wakefulness to sleep.

Future areas of research will include establishing whether there is substantial overlap between nodes that participate 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 in 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 regions and regions that show 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. However, their use has to be assessed in terms of their ability to distinguish between changes in different states, such as sleep and wakefulness, and to distinguish between the human brain in health and in 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. 3). Interestingly, when comparing sleep with wake, the binding measure decreased to capture the functional disconnection over time, whereas mean functional connectivity increased. 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 owing 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 showed that the effect of DBS-induced structural alterations on functional brain changes (following 6 months of DBS of the subthalamic nucleus) was to shift the neural dynamics back towards a healthy regime (FIG. 4a,b). As shown in FIG. 4c, the perturbational measures of segregation and integration were also sensitive to the improvements (that is, an 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 the 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

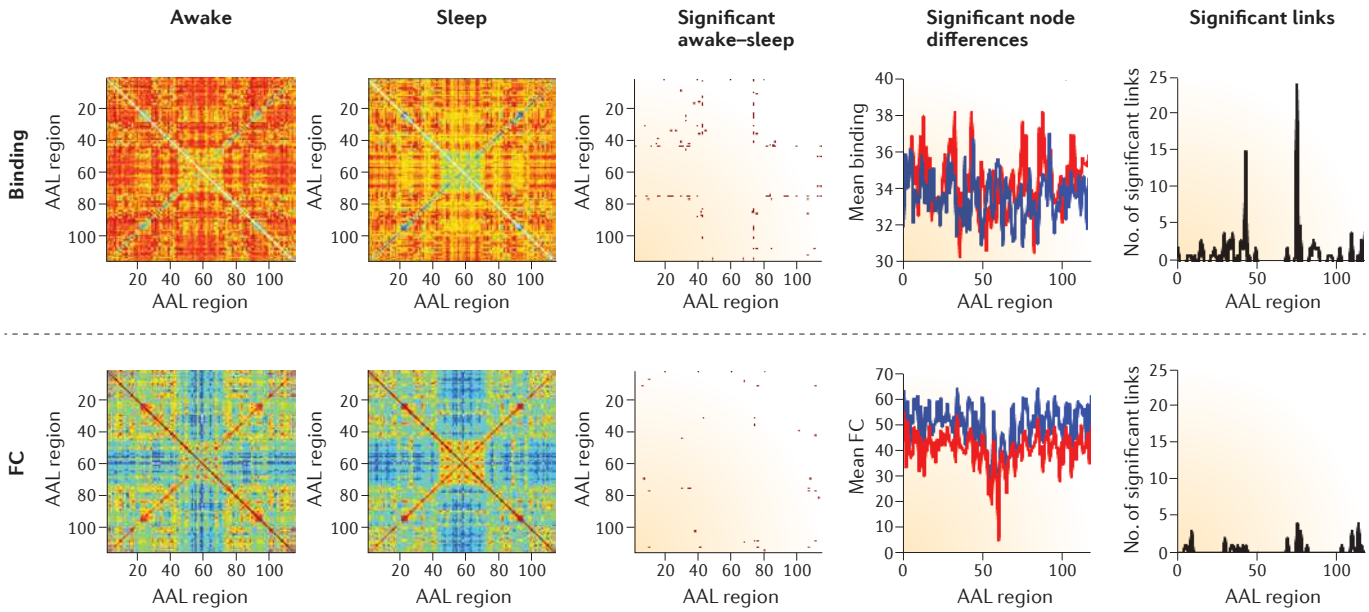


Figure 3 | **Using the binding to extend our understanding of integration in the human brain.** We used a binding measure on previously published neuroimaging data obtained from subjects who were either awake or asleep[71,85,86] and show that the new measure is both sensitive and accurate in mapping this important and common change in consciousness. The figure plots the analysis of changes between automated anatomical labelling (AAL) regions in binding measurements (top row) and functional connectivity (FC; bottom 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) to high (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 corresponding to the awake condition. As can be seen by comparing column 1, column 2 and column 4, the binding decreases in sleep, whereas the mean FC increases. This result complements existing evidence that the sleeping brain is more globally connected functionally because it is more synchronized owing 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 than those for the FC.

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 in 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 so that they can be reliably used in individual participants based on the empirical data obtained from that individual (rather than working at a group level). However, before being able to deliver individual biomarkers, 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 derived from whole-brain computational models are becoming even more important[67]. As shown in this Opinion article, 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 metastability has also been introduced to accurately describe the dynamic regime of models inferred from empirical data and can therefore be used to describe how self-assembling processes of the brain are engaging and disengaging over time[76]. Further research is needed to identify the relationship between metastability and multistability, as described in this Opinion article (BOX 1). A practical application of investigating the temporal dynamics could be the identification of novel types of biomarkers, such as an information theoretical (that is, entropic) measure of the time dynamics of correlation pairs of brain regions. This temporal measure of variability could be a complementary biomarker that segregates 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 cover more than one phenotypic diagnosis[78] and thereby aid in the development of stratified neuropsychiatry[79].

Most importantly, further research 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

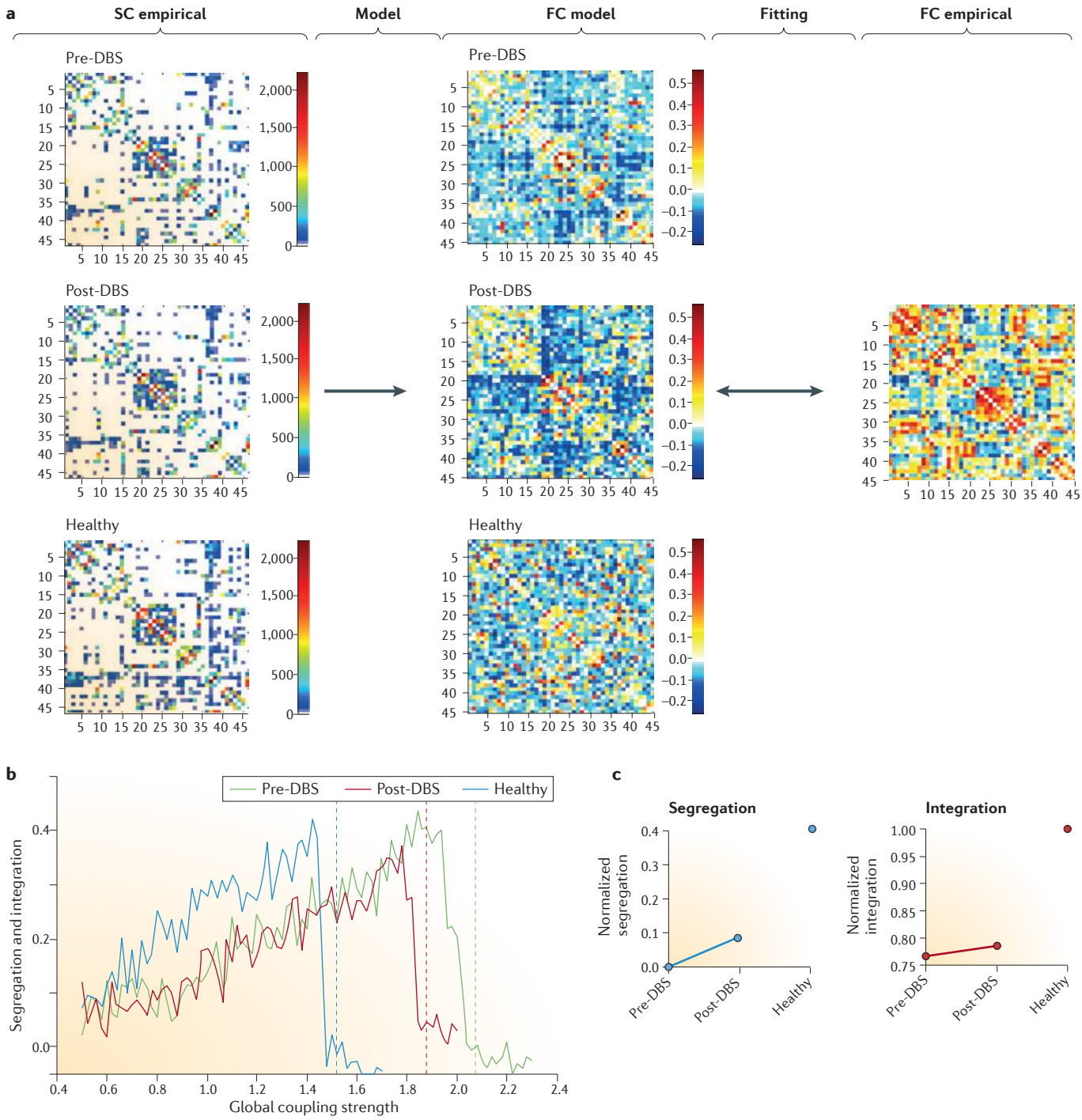


Figure 4 | **Using perturbational segregation and integration measures to characterize health and disease.** **a** | Changes in structural connectivity (SC) following 6 months of deep brain stimulation (DBS) of the subthalamic nucleus to alleviate the symptoms of Parkinson disease[74]. The column on the left shows the SC matrices — derived from diffusion tensor imaging scans — between 45 brain regions (*x* and *y* axes) for an individual with Parkinson disease pre-DBS and post-DBS versus those from healthy individuals. The colours in the matrices indicate the connectivity strength from low (blue) to high (dark red). The middle column shows the corresponding functional connectivity (FC) matrices produced by the model from the SC, which is then fitted (two-way arrow) to the empirically obtained FC matrix from these individuals (right column). **b** | The fit quality is plotted as a function of coupling strength, for the preoperative and postoperative DBS patient and healthy individuals[74]. The optimal operating point for the whole-brain computational model is defined as the point at which modelled and empirical FC match; this is reflected in the region of the graph just before the bifurcation point (sudden dip), which is very different between healthy individuals and pre-DBS individuals. DBS shifts the operating regime of the model closer to that of healthy individuals, providing evidence that DBS induces plasticity and allows recovery of cortical function. It was shown that this functional recovery in Parkinson disease affected cortical connectivity, even though the source of the disease and the area of DBS is subcortical[74]. **c** | Measures of perturbational segregation and integration are also sensitive to functional improvements following DBS surgery, as shown by the increase in both measures between pre-DBS and post-DBS individuals. Adapted from REF. 74.

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 to elucidate the fundamental principles.

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Competing interests statement
The authors declare no competing interests.

FURTHER INFORMATION
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