Rethinking segregation and integration in the human brain: contributions of whole-brain computational 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. 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 (i.e. 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*.

Introduction

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 current stimuli with past memories to predict the future and to adapt behaviour accordingly. The healthy human brain is very good at segregating and integrating information from different sensory modalities, which is combined with memory traces and with information about the current state of the brain and body to guide predictions and decision-making processes needed for adaptive behaviour. Take the example of a tennis player who effortlessly can integrate the colour, movement and shape of a tennis ball whilst segregating this object from the changing background of the tennis court and crowd, while she is predicting its trajectory and planning how best to position her 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 which 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 awareness³. 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 underlying segregation and integration would be to use neuroimaging methods to map whole-brain structure and function. Much important progress has been made in sophisticated meta-analyses pooling data from thousands of task-related neuroimaging studies probing and testing the brain in many different ways⁴. Such meta-analyses however present many significant potential confounds, including their cross-sectional nature. Instead, ideally neuroimaging methods should be used in the same individual to map the structural pathways from each of the very large number of possible unimodal and multimodal inputs to their integration leading to a final common pathway, as well as to map the underlying spatiotemporal dynamics. Yet, 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 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}. Here, we argue that whole-brain computational modelling based on and constrained by neuroimaging data can help to gain new insights into segregation and integration.

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 input⁷. However, the relatively poor spatiotemporal resolution (typically on the timescale of seconds) and the indirect nature of whole-brain neuroimaging measures (such as fMRI) have thus far limited the utility of these methods for examining the dynamics of segregation and integration in the brain. Here we propose to complement these studies by taking advantage of recent advances in whole-brain computational modeling. This approach can expand the topological and functional information derived from neuroimaging studies to inform and enlighten us about both the fundamental computational principles that underlie input processing *and* the temporal dynamics within a particular brain architecture that support the seamless segregation and integration of input information.

In this Perspective, we first describe currently available topological measures obtained using graph theory from neuroimaging studies of connectomics, which 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 by their very nature are 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 as well as their breakdown in neuropsychiatric disorders.

Topological measures of brain function

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 brain⁸ (**Figure 1**). An important goal of these studies is to establish the human connectome⁷ — “the complete description of the structural connectivity (the physical wiring) of an organism's nervous system”. Yet, here we argue that this purely structural description could usefully be extended to include the functional connectivity of the connectome which can enable the complex integration and segregation of relevant information over time.

Collecting topological and functional neuroimaging 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 magnetic resonance imaging (MRI) and diffusion weighted/tensor imaging (DWI/DTI), which uses sequences sensitive to the influence of the major fibre tracts on the diffusion of water^{9, 10} (**Figure 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 of directionality of the connections and the indirect nature of the connectivity measures¹³.

The activity of the brain is typically measured both with indirect methods (functional MRI, fMRI) and positron tomography (PET)) and direct methods (high-density electroencephalography, EEG) and magnetoencephalography (MEG). Functional connectivity between brain regions is defined as the statistical dependence between these neurophysiological signals in different brain areas — typically 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 measured over several minutes¹⁶. These resting state (rs-MRI) studies have found highly reproducible and organized patterns of brain activity^{17, 18}, which overlap with task-related activity patterns¹⁹. Combining rs-MRI with DTI has helped build the first drafts of the human connectome²⁰⁻²². 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 provides multi-purpose datasets that can be used to study multiple, interacting networks^{23, 24}.

Compared to task-based fMRI approaches, the primary advantages of rs-MRI are the ease of acquisition and analysis, which facilitates large-scale cross-sectional and longitudinal human studies. As mentioned, approaches based on rs-MRI are also well suited to many different populations, including those who may not be able to perform tasks. Rs-MRI can also include important potential confounds (such as unstable wakefulness²⁵) and the data can be compromised by physiological signals (such as cardiac/respiratory signals and head motion²⁶). Progress has however been made in addressing these issues, e.g. building automated methods for assessment of sleep stages²⁷ and minimizing the effects of head motion and physiological signals on rs-MRI data^{28, 29}.

Building the connectome and measuring segregation and integration

Neuroimaging data can be further processed using tools from e.g. graph theory in order to build the human connectome (**Figure 1B-D**). 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, brain regions) and edges (connections, pathways) from DWI/DTI and rs-MRI data. So far, however, much this research has been largely descriptive³². 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 regions²⁰. Connectivity measurements are then calculated as the strength of the edges between the nodes of the system³³.

The advances in mapping the human connectome have identified some of 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 (**Figure 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 colleagues³⁷). 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 interconnectivity³¹. 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 integration³⁸ (see **Figure 1E**).

Taken together, the results of graph theoretical analysis of cerebral structural 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. Yet, 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, nor does it differentiate between e.g. conscious versus non-conscious states (for which TMS-induced perturbations have shown some promise). Such graph-theory based approaches to investigating “structural” (i.e. anatomical) segregation and integration have been complemented by studies assessing “functional” segregation and integration (i.e. brain activity correlations) on the basis of the mutual information (i.e. a measure of mutual dependence between random variables) derived from functional connectivity data between brain regions. In addition to these correlational measures, it is possible to perturb the brain using, for example, transcranial magnetic stimulation (TMS) and to 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 system³⁹. 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)

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 (i.e. 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, anesthesia) as well as the consequences of various brain lesions⁴⁴. 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 in terms of changes in spatiotemporal activity based on such a brief perturbation.

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 using whole-brain computational models that can reflect and reproduce the complexity and some of the 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 constituents⁴⁵. Indeed, the emergent collective macroscopic behaviour of brain models has been shown to be only weakly dependent on the details of individual neuron behaviour⁴⁶. The models therefore typically use various mesoscopic top-down approximations of brain complexity with dynamical networks of local brain area attractor networks⁴⁷. The simplest models use basic neural mass or mean-field models to capture the changes in mean firing rate⁴⁸, 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 model⁴⁹.

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 tissue⁵⁰, which has been supplemented with modern neuroimaging parcellations that typically range from tens to several hundreds of regions²⁰. The optimal parcellation of brain regions is not currently clear but could require fine-grained parcellations with hundreds of regions⁵¹, yet current popular choices include fewer regions such as the Desikan-Kalianny/Hagmann parcellation with 66 cortical regions⁵², and the automated anatomical labeling (AAL) parcellation with 116 regions (cortical, subcortical and cerebellum)⁵³.

Combining a parcellation with structural connectivity data (obtained from tractography from DWI/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 (e.g. obtained from rs-MRI) (**Figure 2A**). In other words, the dynamical entrainment and correlations between different local brain region dynamics are essentially shaped by the underlying

structural connectivity⁵⁴⁻⁵⁹. 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^{60, 61} and for resting-state networks derived from MEG data⁶². 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, 57, 63} (see **Box 1**).

Using whole-brain models to elucidate mechanisms of segregation and integration

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 measures⁸. 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 very specific ways by changing input and connectivity locally, can yield important new information.

Using whole-models to measure perturbational segregation

A measure of *perturbational segregation* is 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 correlations⁵⁷. Once the dynamical working point of the model has been adjusted using empirical measures of resting functional connectivity⁵⁶, the model can be perturbed by a random set of Gaussian inputs (i.e same variance of Gaussian noise but stimulating a subset of random regions, see **Figure 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 as⁶⁴:

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

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. In order to avoid numerical problems in the estimation of the *segregation*, obfuscating noise of variance $\sigma_{noise}^2 = 0.001$ can be introduced⁶⁵ so that the segregation is finally given by:

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

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 *information capability* of the brain, i.e. the capability of the brain to process information. **Figure 2C** shows how this measure evolves in a realistic model which simulates resting state neuroimaging data. 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, i.e. 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 (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 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.

Measuring perturbational integration

Similarly, integration can be defined using perturbations applied to whole-brain models in order to measure the effects of systematic stimulation on how the brain integrates information. The resulting measure of *perturbational integration* can be defined by using the length of the largest connected component, i.e. 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 (using the criteria $|FC_{ij}| < \theta$, ie a value of 0 and 1 otherwise) can be binarized 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 (**Figure 2B**). Finally, in order 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 (i.e. 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 we then calculated this *integration* measure. We define *perturbational integration* as the average of the *integration* over a large amount of instantiations of external stimulations (typically at least 1000). In **Figure 2C** it is shown 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 in the human brain

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 smaller windows of time⁶⁶, so that the perturbational integration can be calculated for each sliding window. We here use between 30-120 seconds since smaller time-windows on the scale of, say, four seconds can yield spurious fluctuations⁶⁷ (see bottom right panel of **Figure 2A**). Specifically, for each brain region the largest component that includes this region can be calculated, 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, i.e. *temporal binding* (related to the *binding problem*⁶⁸ - how distributed information is bound and made available to consciousness⁶⁹). **Figure 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 identified based on measures of topological integration³² (**Figure 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 (edge level). **Figure 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 regions³², 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.

Characterizing different states of the brain 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 significant differences between these two behavioral states⁷⁰ (**Figures 3B**). Interestingly, in sleep the binding measure is able to capture the functional disconnection over time in contrast to the increase in mean functional connectivity. The latter is consistent with existing evidence showing that the sleeping brain is more functionally connected due to synchronization of the slow sleep waves⁷¹. 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 neuroimaging data obtained from patients with Parkinson's disease to examine changes in functional connectivity that may be triggered by structural reorganization produced by deep brain stimulation (DBS)⁷². We first

modelled structural changes in these patients using whole-brain computational models ⁷³, and observed an improvement in the performance of the model compared to that of normal participants following six months of DBS of the subthalamic nucleus (**Figure 4A and 4B**). As shown in **Figure 4C**, the perturbational measures of segregation and integration were 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 ⁷⁴.

Conclusions

In this perspective 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 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.

Yet, 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, e.g. 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 the individual – rather than working on a group level.

The temporal description and prediction of functional activity with whole-brain computational models is becoming ever more important ⁶⁶. 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 ⁷⁵. 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/or 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, 76} and as such it could identify biologically homogenous subtypes that cut across phenotypic diagnosis ⁷⁷ and thereby aid in the development of a stratified neuropsychiatry ⁷⁸.

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.

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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, we model whole-brain activity 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/DWI tractography^{53, 79}. 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 (fMRI, MEG, 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^{55, 62, 80, 81}, whereas others have used a more realistic spontaneous state dynamics⁶¹; 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 synapses⁶⁰. By means of dynamic mean-field modelling⁴⁹, the activity of detailed spiking models can be reduced to a more tractable model of the activity of local neuronal ensembles that allow an analytic treatment of the equations and consequently the derived integration and segregation⁵⁷.

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, 60}. Similarly, the concept of metastability is a measure of how variable are the brain states 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 description⁷⁵.

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 data⁸².

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, panel a, bottom). In this model, all artificial connectivities use the same parcellation (116 regions in the AAL parcellation) and the same number of edges, and the degree of small-worldness is manipulated with the procedure of Watts-Strogatz⁸³. 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-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 a probability of rewiring (x-axis of the plot in panel B), i.e. if two nodes are linked, that link will be maintained or reallocated to another node according to that probability of rewiring.

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, panel 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 because, due to the disconnection, they will generate different patterns and therefore increase 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 (see the figure, panel a, blue bar). Note that in the figure, the perturbational integration (red line in panel B of the figure) is normalized to 1 in its maximum and the segregation (black line in panel B of the figure) to zero in its minimum, i.e. 0 at probability of rewiring zero. The error bar in panel B corresponds to 100 different instantiations of possible rewirings.

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Figure legends

A

B

C

Figure 1. Segregation and integration measures can be found using connectomics and graph theory. A)

First, a connectome can be extracted from neuroimaging data. Typically, topological measures of structural connectivity (SC) require MRI and DTI, as well as a parcellation scheme (here is used automatic anatomical labeling, AAL) and apply tractography measures between the regions. Similarly, functional connectivity (FC) can be obtained functional neuroimaging measures of brain activity, e.g. EPI images sampling the BOLD time course (tc) in each voxel. Combining this with a parcellation scheme can recreate the regional time courses for each of the regions in the parcellation. The mean FC matrix is typically created from correlating the regional time courses. **B)** Second, the connectomics of the topological and functional networks can be characterized using graphs where the nodes are the regions, and the edges are the connections between regions. The column shows three matrices: the top matrix shows the connection strengths (in shades of gray) between 20 brain regions, the middle matrix shows binarization at a given threshold (here 50% is used) and the bottom matrix shows the binary connectivity reordered to an optimal modularity partition, which in this example has three modules (colored in orange, blue, and red); also shown in a spring-embedded 2D network diagram with the three modules circled. In the example, regions A, Q and T are clearly hubs with a high degree (number of connections), betweenness centrality (placed on many of the short paths in the network), and participation co-efficient (distributed connections across network modules). In contrast, region A has low clustering given that most of the topological neighbours are mutually unconnected. In contrast, region O has high clustering, and region H has low betweenness, while region G has low participation coefficient, and region N has low degree. **C)** Applying these topological measures on human neuroimaging data shows five distinct network communities (default mode, cingulo-opercular, fronto-parietal, somatomotor and visual modules)⁸⁴. Equally, high levels of node degree are found in network hubs in specific parts of the human brain, typically in medial parietal, cingulate, superior frontal, prefrontal and temporal cortices⁸⁵.

A

B

C

Figure 2. Segregation and integration measures can be improved using whole-brain modeling. 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. In the review 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 *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, i.e. 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. **B)** 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 e.g. 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). **C)** An example of how measures of perturbational segregation and integration can be obtained from whole-brain computational modelling (see main text).

Figure 3. Extending our understanding of integration in the human brain - from the ‘rich club’ to the ‘binding club’. **A)** The ‘rich-club’ concept has been a very influential concept in thinking about integration and conferring robustness to the structural core of the human brain⁸⁶ (left panel). The ‘rich club’ is a set of hubs with high degree and betweenness that are also highly connected among one another. Yet, the rich club is solely defined in topological networks and does not take into account the dynamics. We propose to extend our understanding of integration over time by using the whole-brain computational modeling framework where integration can be investigated during systematic perturbation of inputs. This perturbational spatiotemporal integration over the time domain can be useful in finding regions that bind spatiotemporal brain activity. The right panel demonstrates graphically the concept of a binding club where the members are those nodes (in blue) which show more variability in the correlations over time (see text for precise definition). **B)** We used a binding measure on neuroimaging data obtained when subjects were either awake or asleep⁷⁰ and showed 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 the 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), while the second column shows the matrices for the sleep condition. The third column plots the significantly different pair connections in both conditions (dots in the matrices), i.e. the pairs that passed significance testing corrected for multiple comparisons. 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 waves⁷¹, 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 compared to 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's disease (PD) ⁷³. The figure shows the structural connectivity matrices pre- and post-DBS compared with healthy (left column). 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 of 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 ⁷³. 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 Parkinson's disease affected cortical connectivity, even though the source of the disease and the area of DBS stimulation is sub-cortical ⁷³. **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 between pre, post and healthy.