Understanding Principles of Integration and Segregation using Whole-Brain Computational Connectomics: Implications for Neuropsychiatric Disorders

Louis-David Lord [1], Angus B. Stevner [1,2], Gustavo Deco [3,4], Morten L. Kringelbach [1,2]

[1] *Department of Psychiatry, University of Oxford, Oxford, United Kingdom*

[2] *Center for Music in the Brain, Aarhus University, Aarhus, Denmark*

[3] *Center for Brain and Cognition, Universitat Pompeu Fabra, Barcelona, Spain*

[4] *Instituci Catalana de la Recerca i Estudis Avanats (ICREA), Universitat Pompeu Fabra, Barcelona, Spain*

Corresponding Author:

Professor Morten L.Kringelbach, Department of Psychiatry, University of Oxford, Oxford, UK. morten.kringelbach@psych.ox.ac.uk, tel: 0044-1865613118

Abstract

To survive in an ever-changing environment, the brain must seamlessly integrate a rich stream of incoming information into coherent internal representations that can then be used to efficiently plan for action. The brain must, however, balance its ability to *integrate* information from various sources with a complementary capacity to *segregate* information into modules which perform specialized computations in local circuits. Importantly, evidence suggests that imbalances in the brain's ability to bind together and/or segregate information over both space and time is a common feature of several neuropsychiatric disorders. Most studies have however until recently strictly attempted to characterize the principles of integration and segregation in static (i.e. time-invariant) representations of human brain networks, hence disregarding the complex spatiotemporal nature of these processes. In the present Review, we describe how the emerging discipline of *whole-brain computational connectomics* may be used to study the causal mechanisms of the integration and segregation of information on behaviorally-relevant timescales. We emphasize how novel methods from network science and whole-brain computational modelling can expand beyond traditional neuroimaging paradigms and help to uncover the neurobiological determinants of the abnormal integration & segregation of information in neuropsychiatric disorders.

Keywords: brain connectivity, network analysis, integration & segregation, neuropsychiatric disorders, computational modelling

TABLE OF CONTENTS

Contents

Small-World Brain Networks: A Blueprint for Integration & Segregation

In order to promote survival, the brain must be capable of integrating a wide range of incoming stimuli from its environment and seamlessly "bind" this complex stream of information into meaningful internal representations that are then used to plan for the next action. For example, a tennis player attempting to return his opponent's serve must quickly integrate visual and auditory stimuli from the tennis court (e.g. the positioning of the opponent, the racket and the incoming ball), together with proprioceptive information from the body in order to initiate the appropriate motor responses to hit a successful return. Whilst a capacity for functional integration is undeniably important, the brain must also be able to segregate information into distinct modules, which perform specialized local computations (e.g. for individual sensory modalities). An extreme yet relevant example of excessive integration would be an epileptic seizure, where an abnormally large number of brain areas begin to fire in synchrony and the brain as a system no longer capable of processing information in a meaningful way.

There has recently been much interest in understanding which organizational features and brain mechanisms enable the efficient integration and segregation of information, and the emerging evidence suggests that a complex synergy between both structural and functional determinants is likely involved. Whilst fundamentally interesting, the importance of understanding the dynamics and mechanisms of integration and segregation in the human brain also has important clinical implications, as several lines of evidence now suggest the ability to efficiently bind and/or segregate information may be altered in neuropsychiatric disorders.

In recent years, novel measures of the brain's functional organization have emphasized the importance of temporal coding and coordinated neuronal oscillations in distributed networks. This has represented an important paradigm shift from the study of individual brain regions in isolation. Whilst structural brain networks summarize the pattern of anatomical connections between regions pairs making up the network nodes, functional brain networks are derived from estimates of statistical dependencies between interregional activity signals over time, typically averaged over long recording intervals (i.e. minutes) **(Figure 1A)**. Investigations of large-scale structural and functional networks derived from neuroimaging data have revealed valuable insights about the topological organization of the human brain in health and disease (1-3) **(Figure 1B)**. It has notably been established that both structural and functional networks in the human brain exhibit "small-world" character (2, 4, 5). Small-worldness is a concept borrowed from a branch of mathematics called graph theory, which studies the mathematical structures used to model pairwise relations

between large sets of interacting objects, also known as “graphs”. As such, small-world networks are found not only in the brain, but in a vast range of complex systems of across the biological, physical and social sciences (4).

At the mesoscopic level, a key feature of small-world networks is the existence of ’modules” (also known as communities): sub-networks of densely interconnected nodes only sparsely connected to the rest of the network. Whilst communities in structural networks tend to be spatially compact it should be noted that, in the case of functional brain networks, the belonging of a set of nodes to the same community does not necessarily imply anatomical proximity between them (6). Another defining feature of small-world networks is the presence of long-range, cross-modular connections, which enable the efficient routing of information between modules by minimizing both connection distances and wiring costs (7, 8). Other notable advantages of a small-world architecture include conferring resilience to the system by buffering the effects of randomly introduced perturbations, as well as enabling richer patterns of distribution of information than non-modular systems of equivalent size (6, 9, 10).

In addition to *small-worldness* another important property of complex networks is scale-free behavior. In scale-free networks, the node degree distribution often follows a gradual (‘heavy-tail’) power law decay which implies that the network lacks a characteristic scale (11). In the human brain, functional networks studied at very high spatial resolution (i.e. voxel-level) using fMRI have indeed provided evidence for a scale-free degree distribution (12, 13). However exponentially truncated power-law degree distributions have instead been reported in anatomical brain networks recorded from diffusion-weighted MRI (14), which implies that the probability of a highly connected node or hub is greater than in an equivalent random network but less than would be expected in a purely scale-free network.

At the local level, graph theory also enables the characterization of individual nodes and of their contributions to the network’s organization. For example, a special class of nodes commonly referred to as ”connector hubs” play a particularly important role towards integrating information across the system by accessing different modules and coordinating their activity in both resting and task states (6, 15, 16). Such nodes are typically characterized by a combination of standard local graph metrics including: high *degree-centrality* (i.e. total number of connections) as well elevated scores on the *betweenness-centrality* and *participation coefficients* measures. These standard local graph metrics respectively reflect the tendency of a node to be involved in a high proportion of the shortest topological paths between other node pairs in the network, and of a given node’s tendency

to form connections to network communities other than its own. Connector nodes have indeed been postulated to enable the modules to maintain their functional autonomy in the presence of increased processing demands on the whole system (15). Conversely, "provincial" hubs may also have high *degree-centrality*, but will link together nodes within the same specialized module and thus have low *betweenness-centrality* and *participation coefficients*. Other nodes will play a more peripheral role in the network topology and have relatively low scores on each of these local measures **(Figure 1B)**.

The initial characterization of the brain's modular organization and small-world attributes provided a promising new framework, or "blueprint", to understand how the brain may balance the conflicting demands for the individual specialization of local sub-networks, and the long-range integration of specialized network modules, within the spatial and metabolic boundaries of the system. There are nevertheless significant limitations associated with these findings. First, some authors have argued that studies of whole-brain neuroanatomical connectivity may have underestimated the proportion of inter-areal projections and consequently the cortical network density (17). These new anatomical links may have been missed notably because they link widely separated areas and tend to be sparse, therefore requiring high imaging resolution for their detection (17, 18). Moreover, the study of static network representations of the brain, whilst undeniably informative, does not explain the spatiotemporal integration and segregation of information in the human brain at behaviorally-relevant timescales. In addition, cross-sectional neuroimaging studies of functional connectivity are, by design, generally not suited to provide causal mechanistic insights into the brain's global network dynamics.

Segregation & Integration in Neuropsychiatric Disorders

Structural and Time-Averaged Functional Networks

Changes in functional and structural connectivity have been reported in several neuropsychiatric disorders (1, 2, 19) **(Figure 2)**. Evidence suggests that these network changes may notably lead to a loss of small-world organization, and disruptions in the balance between the integration and segregation of information. For example, in Alzheimer's disease, long-range functional connections between spatially-remote brain modules are impaired which results in longer topological distances between specialized sub-networks, but the clustering of individual local communities is relatively unaffected by this pathology (20, 21). On the other hand, functional brain networks in schizophrenia have been associated with both decreases in clustering and increased path length, the combined effect of which can be summarized as a "subtle randomization" of global brain connectivity, and consequent loss of small-world character (22, 23). It should be noted that, despite the significant

differences in small-worldness identified in patient cohorts relative to matched controls, the brain nevertheless preserves basic small-world properties in the patients, in comparison to randomly generated graphs of equivalent size.

Clinical studies of patients with focal brain lesions following stroke and/or head trauma also provide a useful explanatory framework for how disruptions in small-world network connectivity may underlie the symptoms of neuropsychiatric disease (24). It has long been observed that focal lesions could be accompanied by unexpected cognitive and behavioral deficits that would not be predicted from the local functional properties of the affected area (25). Evidence from empirical and computational studies has supported the idea that damage to "connector hub" regions supporting integration across the whole brain may have different effects on network function than lesions localized to the provincial hubs defined earlier (2, 26, 27). For example, damage to brain regions important for communication between sub-networks (but not to those brain regions important for communication within sub-networks) leads to global changes in the modular organization of the brain, and a loss of small-world character (28). Lesions to provincial hubs would therefore be expected to yield specific clinical deficits, whilst damage to connector hubs may result in pervasive cognitive and/or behavioral impairments extending across several cognitive domains (2, 27, 29).

Dynamical Integration & Segregation

Recent functional neuroimaging studies have demonstrated that the functional connectivity between brain areas is not stable over time (30). This can be empirically observed by considering the temporal variability of FC estimated at individual connections (31), or alternatively the transition dynamics between a small repertoire of FC patterns stable for short periods of time, known as "FC states", which are reproducible across time and individual subjects (32, 33).

In order to flexibly integrate communication between specialized sub-networks, it has been proposed that the human brain strikes a metastable balance between the local segregation of function and the global integration of information (34-36). Recent neuroimaging studies have notably considered the time-evolution of the modular organization of brain functional networks. Dynamical connectivity analyses of resting-state fMRI suggested that whole-brain functional networks alternate between periods of high and low modularity, hypothesized to represent states where segregated information processing and global integration across community boundaries respectively dominate the system (37, 38). Intermittent episodes of global synchronization interspersed between otherwise segregated network states might allow network elements access to a cognitive workplace needed for cognitive functioning in a metabolically-efficient manner (31).

Preliminary evidence suggests that functional connectivity dynamics may be sensitive to disease processes in the human brain. Schizophrenia patients exhibit reduced dynamism of time-varying network connectivity (39). This is notably expressed by more limited transitions between specific FC states relative to controls (40); an observation consistent with cognitive and behavioural inflexibility reported in this disorder (41). Another dynamic connectivity analysis of SZ patients reported that, on average, schizophrenia patients spend less time than healthy controls in network activity states typified by the strong, large-scale connectivity postulated to support global integration (42). This supports the prevailing notion of SZ as a disorder of integration. Furthermore, although less pronounced than in SZ, a similar lack of flexibility in the transient exploration of FC-states have also been reported in patients with bipolar disorder (40).

In light of the above, a mechanistic understanding of how the brain dynamically integrates and segregates information over time may provide critical new insights into the aetiology of neuropsychiatric disorders. This could notably lead to the development of potential new biomarkers based on the brain's transient network dynamics beyond the time-averaged functional connectivity.

Investigating Disease Mechanisms with Whole-Brain Computational Modelling

Overview of Whole-Brain Computational Models

The main premise of whole-brain computational models comes from statistical physics where it has been shown that macroscopic physical systems obey laws that are independent of their microscopic constituents. The firing dynamics of local neuronal populations may accordingly be approximated by stochastic differential equations without detailed knowledge of the behavior and structure of individual neurons. Reduced dynamic mean field models or even simpler approximations of neural signals such as the Kuramoto oscillator ignore the interactions between single neurons within a brain region and instead consider their ensemble dynamics (43, 44). Whole-brain computational models may then constrain and couple the local dynamics between brain areas according to the underlying structural connectivity of the brain measured empirically with diffusion tensor imaging (DTI) **(Figure 3)**.

By constraining the modelled activity according to the structural properties of the brain, the system operates within a biologically-plausible space-time structure for coupling, conduction delays and noise (43, 44). The dynamics generated by such models consist of neural time series that can be represented in space and time as functional networks and analyzed using the same tools and approaches applied to empirical neuroimaging data. Recently developed whole-brain models have

indeed shown promise towards replicating many features of the empirical functional connectivity of both healthy subjects and patients (43-46). Thus, whole-brain computational models have the potential to clarify the relationship between brain structure and function on multiple timescales, and help identify mechanisms underlying functional imbalances in neuropsychiatric disorders. For a detailed review of whole-brain computational models, the reader is invited to consult: (43, 44).

Of immediate relevance to the present Review, whole-brain computational models can be used to test mechanistic hypotheses about the neural mechanisms balancing the integration and segregation of information in simulated brain networks by employing perturbational approaches (**Figure 3)**. Integration and segregation can be thought of as complementary processes in the human brain; a global increase in integration will jointly lead to globally decreased segregation and vice-versa (**Figures 4,5D**). Although global integration and segregation values mirror each other, they are nevertheless estimated in whole-brain models by using different mathematical approaches. *Perturbational integration* is defined by considering the length of the largest connected component of the binarized network as an estimate of the amount of integration in the system after each perturbation, and *perturbational segregation* is calculated through the entropy of the set of evoked patterns assuming a Gaussian distribution of stimulations (**Figure 3B**).

Neuroanatomical Connectivity

Global changes in the structural connectivity of the brain represent a pathological hallmark of several neuropsychiatric disorders, including some neurodevelopmental disorders such as schizophrenia and autism. In addition to the neuroimaging studies that have noninvasively mapped the topology of white-matter networks to reveal significant abnormalities in these clinical groups (47-50), several disease-associated polymorphisms for neuropsychiatric disorders such as SZ and ASD are indeed implicated in the development and maturation of the brain's structural connectome. Disease-associated genes and their downstream effectors regulate molecular biological processes including (but not limited to): axonal guidance (51) synapse formation (52-54) and myelination (55, 56). Despite strong integrative evidence linking white-matter abnormalities to neuropsychiatric disease, the relationship between pathological changes in the structural connectome and brain dynamics remains unclear. This is partly due to the complex, symbiotic relationship between brain structure and function at the systemic scale, which cross-sectional neuroimaging studies of clinical groups are generally not capable to explore (48).

Whole-brain computational models have begun to provide insights into causal mechanisms via which the anatomical connectome shapes and constrains the brain's global dynamical repertoire in both health and disease (44, 46, 57). In broad agreement with the recent empirical findings from dynamical functional connectivity analyses discussed above, the network organization of white matter fiber tracts shapes the repertoire of transient networks states explored by the simulated neural dynamics, without being its sole determinant (46, 58). The relationship between brain structural connectivity and dynamics is therefore analogous to the way in which the geological bedding of a river basin influences its flows of water; the physical structure strongly constrains the flow of water, but other factors such as atmospheric conditions and rainfalls also influence the behavior of the system in non-trivial ways.

A natural use for whole-brain models is to thus investigate how changes in the structure of the brain may influence global brain dynamics *in silico*, especially as it pertains to the integration and segregation of information. The effects of structural brain changes on the organizational properties of emergent functional networks in schizophrenia have notably been investigated (45) . The effects of a pathological disconnection were simulated by randomly pruning anatomical connections in the network in a stepwise manner, thereby reducing the small- world character of the original anatomical connectome. These structural disconnections resulted in simulated functional networks with topological attributes replicating those empirically observed in the time-averaged FC networks of SZ patients (22). The changes included an increase in global efficiency, decrease in clustering, randomization of the degree distribution, the combined effect of which led to deviations from a small-world topological organization. This virtual experiment demonstrated that structural changes in white matter connectivity, analogous to those driven by pathological processes, can cause imbalances between integration and segregation on a functional level by altering the spatial patterns explored by the neural activity.

A recent computational study employed a complementary approach and outfitted an otherwise realistic whole-brain model with a range of artificial structural connectivities: from a structured lattice to a completely random connectome (4, 36). Simulation of whole-brain dynamics on the different structural networks demonstrated that, as the structural connectivity gradually changes from an ordered lattice to a disordered graph, *perturbational integration* decreases because randomness shortens the length of the largest component in the network at a given threshold. *Perturbational segregation*, on the other hand, follows an opposite trend and increases as the structure approaches a random topology. Importantly, the optimal balance between functional

integration and segregation is obtained at an intermediate structural connectivity between order and randomness (36) **(Figure 4)**.

Taken together, the findings from whole-brain computational modelling studies highlight the importance of the neuroanatomical connectome towards shaping global brain dynamics in a manner that enables both locally specialized computations, and global communication. Significant deviations from this optimal structural organization as a result of pathological processes are likely to impair the brain's global functional organization and the dynamical exploration of network states.

Excitatory-to-Inhibitory Balance

A small-world structural connectome is necessary but not sufficient to enable the balanced integration and segregation of information processes in the human brain. To sustain complex mental functions, the neuroanatomical connectivity must act synergistically with another key ingredient to generate the requisite dynamical repertoire: a balanced ratio of excitation to inhibition (E/I). The E/I ratio is a form of homeostatic plasticity that maintains neuronal activity within a narrow range needed for healthy functioning; it refers to the relative levels of excitatory and inhibitory drive in a neural circuit (59, 60). Recent experimental evidence suggests that the E/I ratio remains relatively stable in pyramidal neurons over both space and time **(Figure 5A)**. This is notably achieved by continually adapting the synaptic strengths of parvalbumin-expressing inhibitory interneurons onto principal cells proportionally to their respective excitatory drive (61). Examples of the distinct types of reciprocal interactions between principal cells and inhibitory interneurons which generate high-frequency local oscillations are schematically represented in **Figure 5B**.

Disruptions in E/I homeostasis have been implicated in neuropsychiatric disorders. Pathological elevations in the cellular balance of excitation and inhibition (E/I) in neural microcircuitry may notably underlie behavioral abnormalities in schizophrenia and autism (62, 63). Aberrant E/I balance could indeed represent the converging point of several genetic polymorphisms, molecular pathways and pathophysiological characteristics associated with these disorders, including gain of function phenotypes in ion channels and synaptic proteins (64), and enhanced high-frequency cortical oscillations (65, 66).

Evidence has been coalescing around the idea that E/I balance may be a neurobiological determinant for maintaining the brain’s dynamical regime near criticality (67, 68). Criticality is a state characterized by the spontaneous emergence of self-similar dynamics over the spatial and temporal domains in complex physical systems poised between order and randomness (69).

Experimental evidence suggest that brain dynamics exhibit a large degree of concordance with those expected for a system near criticality (70, 71). In the critical state, the dynamics of the system are dominated by small bursts of local (i.e. segregated) activity, yet large avalanches of globally synchronized (i.e. integrated) activity, referred to as ''neuronal avalanches", occasionally arise which cover nearly the entire system (72, 73). Operating near criticality may be ecologically advantageous for the brain by notably enabling the flexible integration (i.e. coactivation of a few large clusters) and segregation (i.e. coactivation of many small clusters) of information, thereby maximizing the system's information processing capabilities (69, 73). Importantly, a balanced E/I ratio is thought to be needed to sustain a critical dynamical regime, and thereby balance the processes of integration and segregation of information over the entire system (67, 73, 74) **(Figure 5C)**.

Whole-brain computational models have recently been used to investigate the mechanistic relationships between the E/I ratio, critical dynamics, neural plasticity and systemic integration & segregation balance at the scale of macroscopic brain networks. In whole-brain models the E/I ratio would dictate the dynamical regime of local neural masses, and help shape network activity across the entire system via symbiotic interactions with the underlying structural connectivity (43, 44). In light of the aforementioned evidence linking E/I homeostasis to the activity of inhibitory interneurons in local populations, Hellyer and colleagues used a mean field model adapted with a simple local learning rule that adjusted the inhibitory weight within each node such that the summed excitation of the node equaled a target E/I value, thereby introducing homeostatic inhibitory plasticity into the whole-brain computational model (75). The introduction of this parameter is physiologically relevant since, as mentioned above, parvalbumin-expressing inhibitory interneurons continually modulate the strength of their inputs to principal cells as a function of the excitatory activity *in vivo*, and inhibitory synapses can rapidly adapt to changes in the local network activity to scale the activity in cortical circuits (76).

In this model, the introduction of homeostatic inhibitory plasticity helped maximize the dynamical repertoire of the brain by enabling dynamics consistent with criticality, and improved the correspondence between the modelled and empirical resting-state connectivity. The brain may therefore use local inhibitory plasticity to remain in a safe activity regime whilst optimizing the richness of the global dynamics by bringing the functional network states close to criticality. This would in turn optimize the system's ability to both integrate and segregate information in response to environmental demands (75, 77).

Alternative approaches to incorporating inhibitory plasticity in whole-brain models have also been employed, including a feedback inhibition control (FIC) algorithm used to adjust the strength of inhibitory weights recursively and adapt to a target excitatory firing rate of 3–4 Hz (78, 79). Consistent with (75), the introduction of FIC also significantly enhanced the model's prediction of the fMRI human resting functional connectivity (78). While other forms of plasticity such as Hebbian learning and spike-timing dependent plasticity (STDP) also play a role in shaping large-scale network dynamics, these have not yet been directly incorporated in whole-brain models of human functional neuroimaging data. STDP models have been proposed but studies so far have been restricted to small or homogeneous networks (80, 81), and are indeed unstable without the complementary presence of homeostasic mechanisms without which "winner takes all dynamics" will dominate the system (82). We however note that a whole-brain computational model has been shown efficient at testing a hypothesis regarding Hebbian-like plasticity following DBS treatment for Parkinson's disease (83, 84). In more detail, it possible to simulate *in silico* the effects of a strengthened white-matter connectivity between the stimulation site in the subthalamic nucleus (STN) and the thalamus, and show that this specific connection was predictive of the spontaneous dynamics associated with symptom alleviation.

Another whole-brain modelling study has shown that, for a fixed structural connectome, manipulating the global conductance of the model can have a profound impact on the functional network dynamics (36). In biological terms, an increase in the model's global conductance parameter would be equivalent to scaling up the excitatory couplings between brain areas. This may be consistent, for example, with mutations in the genes coding for receptor proteins controlling excitatory glutamate signaling, which have been implicated in SZ and ASD (85, 86). The enhancement of global excitatory coupling would be expected to increase long-range correlations in the network. A decrease in global coupling should have the opposite effect, and effectively simulate a shift in the E/I balance favoring inhibition. Whole-brain computational models have demonstrated that the best fit between the simulated and empirical functional connectivity matrices is obtained when the system operates in a metastable synchronization state where excitation and inhibition are balanced (43, 44, 87). Importantly, the measures of perturbational integration and segregation also become optimally balanced at these intermediate global conductance values (36). As expected from theoretical predictions of criticality, exceeding this optimal global coupling value leads to enhanced systemic integration at the expense of segregation, and reducing it results in lower perturbational integration scores and increased segregation **(Figure 5D)**.

Virtually all whole-brain computational models available to date do not incorporate neurobiological information about E/I neurochemistry. This would involve locally measuring the activity of GABA-ergic and glutamatergic transmission in vivo, as these neurotransmitter systems respectively act as the main determinants of the brain's inhibitory and excitatory drives. Measuring acute changes in these neurotransmitters using neurochemical imaging has however proven methodologically challenging. Acute increases in synaptic GABA have recently been successfully measured using positron emission tomography (PET) (88), but there remains no suitable NMDA or AMPA PET tracers available. Despite this methodological limitation, the results from recent whole-brain computational studies nevertheless provide convincing evidence that imbalances in the brain's excitatory drive and/or inhibitory plasticity, consistent with those implicated in some neuropsychiatric disorders, may significantly alter the brain's dynamical repertoire and impact the system's ability to efficiently integrate and segregate information.

Finally, it should be emphasized that whilst the E/I ratio and small-world anatomical connectome represent distinct neurobiological determinants of global brain dynamics, they nevertheless act synergistically to promote a critical dynamical regime. Computational studies have notably shown that different avalanche behaviors are observed as a function of the density of long-range connections in a simulated brain network, and that power-law behavior of avalanche size, long-range temporal correlations and 1/f noise typical of a system poised at criticality arise when a set of interacting idealized neurons are connected in a small-world configuration (89). Conversely, spike-timing dependent-plasticity can, in the presence of a balanced E/I ratio, reorganize a globally connected simulated neural network spontaneously into a functional network that has both small-world and scale-free topology (90). Moreover, whole-brain modelling studies have recently demonstrated that the communication-through-coherence mechanisms observed in neurophysiological studies (91-93) (i.e. stating that two groups of neurons communicate most effectively when their excitability fluctuations are coordinated in time (94)) can be achieved within whole-brain computational models consistent with the small-world anatomy of the human brain provided that the brain operates at a critical working point where the system shows maximal metastability (95).

Modelling Integration & Segregation over Time

Limitations of Dynamic Mean Field and Oscillatory Whole-Brain Models

Initial attempts at modelling whole-brain network activity successfully replicated the empirical FC when averaged over long recording intervals (i.e. several minutes), but did not accurately reproduce

the spontaneous state transitions between FC-states observed in the empirical data (58, 96). To leverage on the full potential of whole-brain computational modelling, it is important for *in silico* neural dynamics to capture not only the time-averaged representations of FC (which are strongly constrained by the SC), but the temporal evolution of the brain's functional network organization, as recently evidenced by dynamical functional connectivity analyses of empirical neuroimaging data. We further believe that the ability to model the spatiotemporal dynamics underlying integration and segregation could reveal causal mechanistic insights into neuropsychiatric disorders.

Time-Dependent Clinical Phenotypes

Time is of the essence when studying the clinical manifestations of neuropsychiatric disorders. While neuropsychiatric syndromes are most often characterized on the basis of stable brain differences, this contrasts with the reality that a patient's symptoms can vary substantially over time. To design better treatments, it is therefore important to characterize not only the stable brain differences in clinical populations, but also the more rapid neural mechanisms that may underlie acute changes in mental status and behavior. For example, the neural processes that mediate rapid transitions from a relatively stable behavioural state to a full-blown psychotic episode in SZ patients; or a sudden panic attack in a previously asymptomatic individual with PTSD or panic disorder.

There are obvious methodological and ethical limitations that prevent continuous brain monitoring of such patients in their everyday life, and hence the characterization of acute symptomatic episodes. State-of-the-art whole-brain computational models accurately matching the dynamical features of patients' network activity could help bypass this methodological bottleneck and help understand the neurobiological bases of abnormal spatiotemporal integration and segregation of information in neuropsychiatric disorders.

Towards Time-Sensitive Whole-Brain Computational Models

Hansen and colleagues made an important first step towards this goal by developing an "enriched" mean-field model of macroscopic brain activity that accounted for the non- stationarity of resting state activity (58). This was done by introducing bistability at the level of single brain regions *in silico*, which effectively enhanced the nonlinearity of the modelled dynamics. In this new configuration, the dynamics explored a richer repertoire of configurations that was less constrained by the structural connectivity, and instantiated FC-state switching qualitatively consistent with prior empirical observations.

Another promising modelling approach to capture the richness of the temporal network dynamics is the use of a neural mass model based on the normal form of a Hopf bifurcation, which combines aspects of both asynchronous and oscillatory behavior (97) **(Figure 6)**. Until recently, there have been two main categories of whole-brain computational models: oscillatory and asynchronous models. Oscillatory models have demonstrated that the best-fit with the time-averaged, empirical FC is observed at the dynamic working point where metastability (i.e. the amount of variability between brain states as a function of time) is maximized (43, 87, 98). On the other hand, asynchronous models have demonstrated that the simulated functional connectivity best matches the empirically observed FC when multistability around a spontaneous state defines the operating point of the system (44, 46, 99). This means that the stable attractor states of the system respectively are a spontaneous state characterized by low activity in all regions, and several excited states characterized by high energy between selected regions. Importantly, the Hopf bifurcation model may capture the best of both models and demonstrate that the temporal dynamics of resting state fluctuations emerge at the edge of the transition between asynchronous to oscillatory behaviour.

The predictive validity of whole-brain dynamical models will ultimately depend on their ability to capture the rich repertoire of FC states observed in empirical data. In addition, it will be important for the models to accurately reflect the relevant state-to-state transition probabilities and "dwell times" (58, 96, 100). This will in the first instance require further empirical neuroimaging studies to gather the necessary information about FC states features and statistics (in both health and disease) to provide a strong empirical foundation on which to optimize the models. Time-sensitive whole-brain models would ultimately make it possible to investigate the consequences of targeted brain changes on the statistics of network activity explorations, which are indeed disrupted in neuropsychiatric disorders (39, 40, 42, 100).

Measures of Spatiotemporal Integration & Segregation

The extent to which useful information about the integration/segregation balance will be gained from state-of-the-art whole-brain computational models will notably depend upon the parallel development of novel measures to characterize the time-evolution of the integration and segregation of information. Since the dynamics generated by whole-brain models consist of neural time series that can be analyzed using the same tools and approaches applied to empirical neuroimaging data, it will be natural to investigate the modelled activity by exploiting some of the same methods used to track the dynamics of integration/segregation of information in empirical data such as time-evolving modularity and dynamic cartographic analysis.

Dynamic cartographic analysis characterizes the dynamical contributions of individual nodes towards balancing integration & segregation (**Figure 7A**). This analytical approach has revealed that individual brain regions show significant changes in their relative within- and between-module connectivity over time (38). Some fronto-parietal, striatal and hippocampal regions notably spent a greater proportion of the time acting as "connector hubs" promoting global integration, as estimated by high cross-modular connectivity. However it is actually another class of regions, termed "peripheral nodes", which dominates the dynamical cartographic landscape: peripheral nodes were characterized by low-to-medium within-module connectivity and low between-module connectivity. This indicates that that the majority of brain regions are in fact topologically isolated over time, and it is thus a minority of connector hub regions that provided a functional bridge between otherwise functionally segregated communities to enable windows of global integration over time (38).

Whole-brain models confer the additional capacity to extend beyond the empirical data and freely inject the system with simulated inputs at different time points and quantify the effect of systematic perturbations on the functional network organization. This enables a different set of dynamical integration/segregation measures that could not be studied empirically in human subjects due to obvious ethical and safety constraints. Notably, the measures of perturbational integration & segregation presented in **Figure 3B** and discussed in detail in (36) can easily be extended to the time-domain. For example, spatiotemporal perturbational integration, or simply ''spatiotemporal binding" can be used to characterize the effectiveness of the integration of distributed information across the brain over time (36), as outlined in **Figure 7B**. This measure may reflect which nodes within the network contribute the most to 'binding" (i.e. integrating) information over both space and time.

Furthermore, whole-brain computational models have already provided novel insights into structure-to-function relationships in human brain networks. Structural network hubs identified from diffusion tensor imaging data have been suggested to be vital for integration and segregation of information, and especially those regions belonging to the so-called "rich-club" which show dense interconnectivity amongst each other (101). Until recently this had however not been examined in terms of the brain's functional temporal dynamics. For example, while the hippocampus is well known to receive multimodal input and play a critical role in memory formation and global integration, graph theoretical studies of the structural connectome had

surprisingly failed to demonstrate the topological centrality of this region. Thus, by using a whole-brain computational model constrained by the empirical SC of the macaque brain and in which information flow was modelled as a discrete-event queueing network, it was shown that the hippocampus in fact receives a disproportionately high level of information flow and acts a convergence zone for the network (102). Similarly, another whole-brain modelling study recently examined the effects of *in silico* lesions to the highest-ranking "binding nodes" identified using the methodology introduced above on measures of systemic integration and encoding of information capability. It was found that removal of the binding-nodes had a more profound effect on the aforementioned measures than removal of the "rich-club" regions whose topological importance is solely defined by the anatomical connectome (103).

Conclusion

The integration/segregation balance is intrinsically linked to some of the most complex phenomena of modern neuroscience; from the spontaneous emergence of resting-state networks to higher cognition, and perhaps even consciousness. Beyond basic research, an accumulating body of evidence suggests that imbalances between integration & segregation of information may be directly implicated in neuropsychiatric disorders. A deeper understanding of the neurobiological determinants of global integration/segregation may thus have promising clinical implications, including the identification of potential new biomarkers and therapeutic targets.

Static (i.e. time-invariant) representations of the brain's structural and functional network connectivity have provided a useful blueprint for how the brain may balance local/modular specialization and global communication. However, static network representations involve significant methodological and conceptual limitations, notably since the typical FC matrix calculation ignores the importance of time; and correlational neuroimaging analysis is generally not suited to provide causal mechanistic insights into the underlying neurobiology of disease. We believe these limitations have made it challenging for traditional neuroimaging approaches to identify network-based biomarkers for neuropsychiatric disorders of adequate sensitivity and specificity for clinical use.

In this Review, we have outlined how the emerging field of whole-brain computational connectomics can help address these limitations. We first summarized the findings from state-of-the-art analyses of empirical neuroimaging data which reflect the dynamical features of brain functional connectivity; a growing body of work which has begun to provide a comprehensive perspective on the non-trivial evolution of integration/segregation over time. We have further

demonstrated how generative whole-brain models could be used to investigate neurobiologically-realistic mechanisms of disease. We have notably proposed that two key ingredients must act synergistically to efficiently balance functional integration and segregation in the healthy brain: 1) a small-world structural connectome, and 2) balanced ratio of excitation- to-inhibition in local neuronal populations. These pillars for healthy brain network organization are known to be disrupted in several disease states, including schizophrenia and autism.

An important next step for the emerging field of computational connectomics will be to implement new models capable of accurately replicating not only time-averaged FC, but the dynamical features of the brain's functional network organization. Such advances could make it possible to move beyond correlational neuroimaging analysis to reveal the underlying mechanisms of disease at the systems-level, particularly as it pertains to imbalances in the integration/segregation of information.

In conclusion, we propose that brain computational models of disease have the potential to accurately reflect the convergence of diverse cellular and molecular abnormalities at the level of cortical circuits and their statistical interactions on many timescales. Upon further refinement, whole-brain models may eventually contribute to the emergence of a stratified neuropsychiatry, and personalized therapeutics in psychiatric care.

Competing Interests:

The authors declare they have no competing interests.

Author Contributions:

LDL, MLK and GD wrote the paper. LDL, ABS, MLK made the Figures. MLK, ABS and GD edited the paper.

Funding:

LDL is supported by the Canadian Institutes of Health Research CIHR), the Canadian Centennial Scholarship Fund, and the Mann Senior Scholarship from Hertford College (University of Oxford). MLK is supported by European Research Council (ERC) Consolidator Grant: CAREGIVING (615539). GD is supported by ERC Advanced Grant: DYSTRUCTURE (295129) and by the Spanish Research Project PSI2013-42091-P.

References:

1. Bassett DS, Bullmore ET. Human brain networks in health and disease. Current opinion in neurology. 2009;22(4):340.
2. Fornito A, Zalesky A, Breakspear M. The connectomics of brain disorders. Nature Reviews Neuroscience. 2015;16(3):159-72.
3. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nature Reviews Neuroscience. 2009;10(3):186-98.
4. Watts DJ, Strogatz SH. Collective dynamics of 'small-world'networks. nature. 1998;393(6684):440-2.
5. Bassett DS, Bullmore E. Small-world brain networks. The neuroscientist. 2006;12(6):512-23.
6. Sporns O, Betzel RF. Modular brain networks. Annual review of psychology. 2015;67(1).
7. Bullmore E, Sporns O. The economy of brain network organization. Nature Reviews Neuroscience. 2012;13(5):336-49.
8. Clune J, Mouret J-B, Lipson H. The evolutionary origins of modularity. Proceedings of the Royal Society of London B: Biological Sciences. 2013;280(1755):20122863.
9. Yamaguti Y, Tsuda I. Mathematical modeling for evolution of heterogeneous modules in the brain. Neural Networks. 2015;62:3-10.
10. Newman ME. Models of the small world. Journal of Statistical Physics. 2000;101(3-4):819-41.
11. Barabási A-L, Albert R. Emergence of scaling in random networks. science. 1999;286(5439):509-12.
12. Eguiluz VM, Chialvo DR, Cecchi GA, Baliki M, Apkarian AV. Scale-free brain functional networks. Physical review letters. 2005;94(1):018102.
13. van den Heuvel MP, Stam CJ, Boersma M, Pol HH. Small-world and scale-free organization of voxel-based resting-state functional connectivity in the human brain. Neuroimage. 2008;43(3):528-39.
14. Iturria-Medina Y, Sotero RC, Canales-Rodríguez EJ, Alemán-Gómez Y, Melie-García L. Studying the human brain anatomical network via diffusion-weighted MRI and Graph Theory. Neuroimage. 2008;40(3):1064-76.
15. Bertolero MA, Yeo BTT, D'Esposito M. The modular and integrative functional architecture of the human brain. 2015.
16. Sporns O. Network attributes for segregation and integration in the human brain. Current opinion in neurobiology. 2013;23(2):162-71.
17. Markov NT, Ercsey-Ravasz M, Van Essen DC, Knoblauch K, Toroczkai Z, Kennedy H. Cortical high-density counterstream architectures. Science. 2013;342(6158):1238406.
18. Vezoli J, Falchier A, Jouve B, Knoblauch K, Young M, Kennedy H. Quantitative analysis of connectivity in the visual cortex: extracting function from structure. The Neuroscientist. 2004;10(5):476-82.
19. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends in cognitive sciences. 2011;15(10):483-506.
20. Stam C, Jones B, Nolte G, Breakspear M, Scheltens P. Small-world networks and functional connectivity in Alzheimer's disease. Cerebral cortex. 2007;17(1):92-9.
21. Sanz-Arigita EJ, Schoonheim MM, Damoiseaux JS, Rombouts S, Maris E, Barkhof F, et al. Loss of 'small-world'networks in Alzheimer's disease: graph analysis of FMRI resting-state functional connectivity. PloS one. 2010;5(11):e13788.
22. Lynall M-E, Bassett DS, Kerwin R, McKenna PJ, Kitzbichler M, Muller U, et al. Functional connectivity and brain networks in schizophrenia. The Journal of Neuroscience. 2010;30(28):9477-87.
23. Alexander-Bloch AF, Gogtay N, Meunier D, Birn R, Clasen L, Lalonde F, et al. Disrupted modularity and local connectivity of brain functional networks in childhood-onset schizophrenia. Frontiers in systems neuroscience. 2010;4.
24. Pandit AS, Expert P, Lambiotte R, Bonnelle V, Leech R, Turkheimer FE, et al. Traumatic brain injury impairs small-world topology. Neurology. 2013;80(20):1826-33.
25. Devinsky O, D'Esposito M. Neurology of Cognitive and Behavioral Disorders: AAN Enterprises; 2004.
26. Honey CJ, Sporns O. Dynamical consequences of lesions in cortical networks. Human brain mapping. 2008;29(7):802-9.
27. Warren DE, Power JD, Bruss J, Denburg NL, Waldron EJ, Sun H, et al. Network measures predict neuropsychological outcome after brain injury. Proceedings of the National Academy of Sciences. 2014;111(39):14247-52.
28. Gratton C, Nomura EM, Pérez F, D'Esposito M. Focal brain lesions to critical locations cause widespread disruption of the modular organization of the brain. Journal of cognitive neuroscience. 2012;24(6):1275-85.
29. Aerts H, Fias W, Caeyenberghs K, Marinazzo D. Brain networks under attack: robustness properties and the impact of lesions. Brain. 2016:aww194.
30. Calhoun VD, Miller R, Pearlson G, Adal\i T. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron. 2014;84(2):262-74.
31. Zalesky A, Fornito A, Cocchi L, Gollo LL, Breakspear M. Time-resolved resting-state brain networks. Proceedings of the National Academy of Sciences. 2014:201400181.

32. Allen EA, Damaraju E, Plis SM, Erhardt EB, Eichele T, Calhoun VD. Tracking Whole-Brain Connectivity Dynamics in the Resting State. Cerebral Cortex. 2014;24(3):663-76.
33. Baker AP, Brookes MJ, Rezek IA, Smith SM, Behrens T, Smith PJP, et al. Fast transient networks in spontaneous human brain activity. eLife. 2014;3.
34. Varela F, Lachaux J-P, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. Nature reviews neuroscience. 2001;2(4):229-39.
35. Kelso JS. Multistability and metastability: understanding dynamic coordination in the brain. Philosophical Transactions of the Royal Society B: Biological Sciences. 2012;367(1591):906-18.
36. Deco G, Tononi G, Boly M, Kringelbach ML. Rethinking segregation and integration: contributions of whole-brain modelling. Nature Reviews Neuroscience. 2015;16(7):430-9.
37. Betzel RF, Fukushima M, He Y, Zuo X-N, Sporns O. Dynamic fluctuations coincide with periods of high and low modularity in resting-state functional brain networks. arXiv preprint arXiv:151106352. 2015.
38. Shine JM, Bell PT, Koyejo O, Gorgolewski KJ, Moodie CA, Poldrack RA. Dynamic fluctuations in integration and segregation within the human functional connectome. arXiv preprint arXiv:151102976. 2015.
39. Miller RL, Yaesoubi M, Calhoun VD. Higher dimensional analysis shows reduced dynamism of time-varying network connectivity in schizophrenia patients. Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE2014. p. 3837-40.
40. Rashid B, Damaraju E, Pearlson GD, Calhoun VD. Dynamic connectivity states estimated from resting fMRI Identify differences among Schizophrenia, bipolar disorder, and healthy control subjects. Frontiers in human neuroscience. 2014;8.
41. Sitnikova T, Rosen BR, Lord L-D, West WC. Understanding human original actions directed at real-world goals: The role of the lateral prefrontal cortex. NeuroImage. 2014;103:91-105.
42. Damaraju E, Allen E, Belger A, Ford J, McEwen S, Mathalon D, et al. Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. NeuroImage: Clinical. 2014;5:298-308.
43. Cabral J, Kringelbach ML, Deco G. Exploring the network dynamics underlying brain activity during rest. Prog Neurobiol. 2014;114:102-31.
44. Deco G, Kringelbach ML. Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. Neuron. 2014;84(5):892-905.
45. Cabral J, Hugues E, Kringelbach ML, Deco G. Modeling the outcome of structural disconnection on resting-state functional connectivity. Neuroimage. 2012;62(3):1342-53.
46. Deco G, Jirsa VK, McIntosh AR. Resting brains never rest: computational insights into potential cognitive architectures. Trends in neurosciences. 2013;36(5):268-74.
47. Maximo JO, Cadena EJ, Kana RK. The implications of brain connectivity in the neuropsychology of autism. Neuropsychology review. 2014;24(1):16-31.
48. Fornito A, Bullmore ET. Reconciling abnormalities of brain network structure and function in schizophrenia. Current opinion in neurobiology. 2015;30:44-50.
49. Fornito A, Zalesky A, Pantelis C, Bullmore ET. Schizophrenia, neuroimaging and connectomics. Neuroimage. 2012;62(4):2296-314.
50. Valk SL, Di Martino A, Milham MP, Bernhardt BC. Multicenter mapping of structural network alterations in autism. Human brain mapping. 2015;36(6):2364-73.
51. Chen Q-Y, Chen Q, Feng G-Y, Lindpaintner K, Wang L-J, Chen Z-X, et al. Case-control association study of Disrupted-in-Schizophrenia-1 (DISC1) gene and schizophrenia in the Chinese population. Journal of psychiatric research. 2007;41(5):428-34.
52. Stefansson H, Petursson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, et al. Neuregulin 1 and susceptibility to schizophrenia. The American Journal of Human Genetics. 2002;71(4):877-92.
53. Mei L, Xiong W-C. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. Nature Reviews Neuroscience. 2008;9(6):437-52.
54. Fatemi SH, Snow AV, Stary JM, Araghi-Niknam M, Reutiman TJ, Lee S, et al. Reelin signaling is impaired in autism. Biological psychiatry. 2005;57(7):777-87.
55. Roussos P, Haroutunian V. Schizophrenia: susceptibility genes and oligodendroglial and myelin related abnormalities. Frontiers in cellular neuroscience. 2014;8.
56. Mighdoll MI, Tao R, Kleinman JE, Hyde TM. Myelin, myelin-related disorders, and psychosis. Schizophrenia research. 2015;161(1):85-93.
57. Honey C, Sporns O, Cammoun L, Gigandet X, Thiran J-P, Meuli R, et al. Predicting human resting-state functional connectivity from structural connectivity. Proceedings of the National Academy of Sciences. 2009;106(6):2035-40.
58. Hansen EC, Battaglia D, Spiegler A, Deco G, Jirsa VK. Functional connectivity dynamics: modeling the switching behavior of the resting state. Neuroimage. 2015;105:525-35.
59. Haider B, Duque A, Hasenstaub AR, McCormick DA. Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. The Journal of neuroscience. 2006;26(17):4535-45.
60. Okun M, Lampl I. Instantaneous correlation of excitation and inhibition during ongoing and sensory-evoked activities. Nature neuroscience. 2008;11(5):535-7.

61. Xue M, Atallah BV, Scanziani M. Equalizing excitation-inhibition ratios across visual cortical neurons. Nature. 2014;511(7511):596-600.
62. Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature. 2011;477(7363):171-8.
63. Jardri R, Denève S. Circular inferences in schizophrenia. Brain. 2013;136(11):3227-41.
64. Bourgeron T. A synaptic trek to autism. Current opinion in neurobiology. 2009;19(2):231-4.
65. Orekhova EV, Stroganova TA, Nygren G, Tsetlin MM, Posikera IN, Gillberg C, et al. Excess of high frequency electroencephalogram oscillations in boys with autism. Biological psychiatry. 2007;62(9):1022-9.
66. Gomot M, Belmonte MK, Bullmore ET, Bernard FA, Baron-Cohen S. Brain hyper-reactivity to auditory novel targets in children with high-functioning autism. Brain. 2008;131(9):2479-88.
67. Shew WL, Yang H, Yu S, Roy R, Plenz D. Information capacity and transmission are maximized in balanced cortical networks with neuronal avalanches. The Journal of neuroscience. 2011;31(1):55-63.
68. Turkheimer FE, Leech R, Expert P, Lord L-D, Vernon AC. The brain's code and its canonical computational motifs. From sensory cortex to the default mode network: A multi-scale model of brain function in health and disease. Neuroscience & Biobehavioral Reviews. 2015;55:211-22.
69. Bak P. How nature works: the science of self-organized criticality: Springer Science & Business Media; 2013.
70. Chialvo DR. Emergent complex neural dynamics. Nature physics. 2010;6(10):744-50.
71. Expert P, Lambiotte R, Chialvo DR, Christensen K, Jensen HJ, Sharp DJ, et al. Self-similar correlation function in brain resting-state functional magnetic resonance imaging. Journal of The Royal Society Interface. 2011;8(57):472-9.
72. Beggs JM, Plenz D. Neuronal avalanches in neocortical circuits. The Journal of neuroscience. 2003;23(35):11167-77.
73. Beggs JM. The criticality hypothesis: how local cortical networks might optimize information processing. Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences. 2008;366(1864):329-43.
74. Tagliazucchi E, Chialvo DR. Brain complexity born out of criticality. arXiv preprint arXiv:12110309. 2012.
75. Hellyer PJ, Jachs B, Clopath C, Leech R. Local inhibitory plasticity tunes macroscopic brain dynamics and allows the emergence of functional brain networks. NeuroImage. 2016;124:85-95.
76. Hartmann K, Bruehl C, Golovko T, Draguhn A. Fast homeostatic plasticity of inhibition via activity-dependent vesicular filling. PloS one. 2008;3(8):e2979.
77. Tognoli E, Kelso JS. The metastable brain. Neuron. 2014;81(1):35-48.
78. Deco G, Ponce-Alvarez A, Hagmann P, Romani GL, Mantini D, Corbetta M. How local excitation–inhibition ratio impacts the whole brain dynamics. The Journal of Neuroscience. 2014;34(23):7886-98.
79. Deco G, McIntosh AR, Shen K, Hutchison RM, Menon RS, Everling S, et al. Identification of optimal structural connectivity using functional connectivity and neural modeling. The Journal of Neuroscience. 2014;34(23):7910-6.
80. Pfister J-P, Gerstner W. Triplets of spikes in a model of spike timing-dependent plasticity. The Journal of neuroscience. 2006;26(38):9673-82.
81. Clopath C, Büsing L, Vasilaki E, Gerstner W. Connectivity reflects coding: a model of voltage-based STDP with homeostasis. Nature neuroscience. 2010;13(3):344-52.
82. Litwin-Kumar A, Doiron B. Formation and maintenance of neuronal assemblies through synaptic plasticity. Nature communications. 2014;5.
83. van Hartevelt TJ, Cabral J, Møller A, FitzGerald JJ, Green AL, Aziz TZ, et al. Evidence from a rare case study for Hebbian-like changes in structural connectivity induced by long-term deep brain stimulation. Frontiers in behavioral neuroscience. 2015;9.
84. Van Hartevelt TJ, Cabral J, Deco G, Møller A, Green AL, Aziz TZ, et al. Neural plasticity in human brain connectivity: the effects of long term deep brain stimulation of the subthalamic nucleus in Parkinson's disease. PloS one. 2014;9(1):e86496.
85. Barnby G, Abbott A, Sykes N, Morris A, Weeks DE, Mott R, et al. Candidate-gene screening and association analysis at the autism-susceptibility locus on chromosome 16p: evidence of association at GRIN2A and ABAT. The American Journal of Human Genetics. 2005;76(6):950-66.
86. Itokawa M, Yamada K, Yoshitsugu K, Toyota T, Suga T, Ohba H, et al. A microsatellite repeat in the promoter of the N-methyl-D-aspartate receptor 2A subunit (GRIN2A) gene suppresses transcriptional activity and correlates with chronic outcome in schizophrenia. Pharmacogenetics and Genomics. 2003;13(5):271-8.
87. Cabral J, Hugues E, Sporns O, Deco G. Role of local network oscillations in resting-state functional connectivity. Neuroimage. 2011;57(1):130-9.
88. Stokes PR, Myers JF, Kalk NJ, Watson BJ, Erritzoe D, Wilson SJ, et al. Acute increases in synaptic GABA detectable in the living human brain: a [11 C] Ro15-4513 PET study. Neuroimage. 2014;99:158-65.
89. Lin M, Chen T. Self-organized criticality in a simple model of neurons based on small-world networks. Physical Review E. 2005;71(1):016133.
90. Shin C-W, Kim S. Self-organized criticality and scale-free properties in emergent functional neural networks. Physical Review E. 2006;74(4):045101.

91. Bosman CA, Schoffelen J-M, Brunet N, Oostenveld R, Bastos AM, Womelsdorf T, et al. Attentional stimulus selection through selective synchronization between monkey visual areas. Neuron. 2012;75(5):875-88.
92. Schoffelen J-M, Oostenveld R, Fries P. Neuronal coherence as a mechanism of effective corticospinal interaction. Science. 2005;308(5718):111-3.
93. Fries P. Rhythms for cognition: communication through coherence. Neuron. 2015;88(1):220-35.
94. Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends in cognitive sciences. 2005;9(10):474-80.
95. Deco G, Kringelbach ML. Metastability and coherence: extending the communication through coherence hypothesis using a whole-brain computational perspective. Trends in neurosciences. 2016;39(3):125-35.
96. Kringelbach ML, McIntosh AR, Ritter P, Jirsa VK, Deco G. The Rediscovery of Slowness: Exploring the Timing of Cognition. Trends in cognitive sciences. 2015;19(10):616-28.
97. Deco G, Kringelbach ML, Jirsa V, Ritter P. The dynamics of resting fluctuations in the brain: metastability and its dynamical cortical core. bioRxiv. 2016:065284.
98. Ghosh A, Rho Y, McIntosh AR, Kötter R, Jirsa VK. Noise during rest enables the exploration of the brain's dynamic repertoire. PLoS Comput Biol. 2008;4(10):e1000196-e.
99. Honey CJ, Kötter R, Breakspear M, Sporns O. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proceedings of the National Academy of Sciences. 2007;104(24):10240-5.
100. Jones D, Vemuri P, Murphy M, Gunter J, Senjem M, Machulda M, et al. Nonstationarity in the 'resting brain's' modular architecture. Alzheimer's and Dementia. 2012;8(4):P689.
101. Van Den Heuvel MP, Sporns O. Rich-club organization of the human connectome. The Journal of neuroscience. 2011;31(44):15775-86.
102. Mišić B, Goñi J, Betzel RF, Sporns O, McIntosh AR. A network convergence zone in the hippocampus. PLoS Comput Biol. 2014;10(12):e1003982.
103. Deco G, Van Hartevelt T, Fernandes H, Stevner A, Kringelbach M. The most relevant human brain regions for functional connectivity: Evidence for a dynamical workspace of binding nodes from whole-brain computational modelling. NeuroImage. 2016;In Press.
104. Collins FS, Varmus H. A new initiative on precision medicine. New England Journal of Medicine. 2015;372(9):793-5.
105. Di Martino A, Yan C-G, Li Q, Denio E, Castellanos FX, Alaerts K, et al. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. Molecular psychiatry. 2014;19(6):659-67.
106. Szewczyk-Krolikowski K, Menke RA, Rolinski M, Duff E, Salimi-Khorshidi G, Filippini N, et al. Functional connectivity in the basal ganglia network differentiates PD patients from controls. Neurology. 2014;83(3):208-14.
107. Denève S, Machens CK. Efficient codes and balanced networks. Nature neuroscience. 2016;19(3):375-82.

Figures

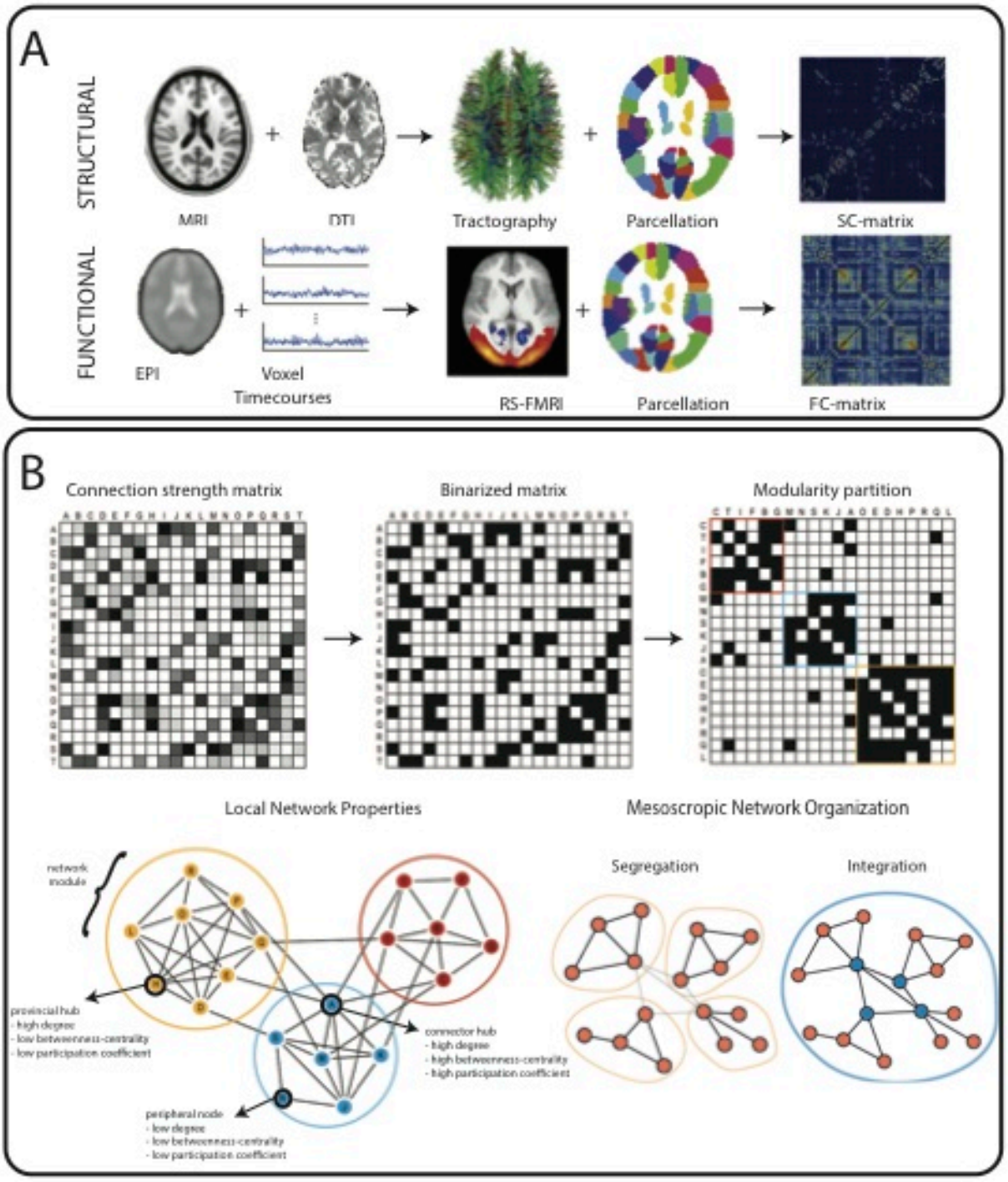

Figure 1. Investigating Human Brain Connectivity with Neuroimaging and Graph Theory. A) *To create a structural connectivity (SC) network, MRI and DTI data are required on which tractography analysis is then performed to uncover the presence (or absence) of structural links between region pairs in the chosen parcellation scheme. These interactions are ultimately summarized in the SC matrix. To create a functional connectivity (FC) matrix brain activity is measured; in this case using resting-state fMRI to record BOLD time courses in each voxel in the*

brain. This is then combined with a parcellation scheme to recreate the regional time courses for each of the regions in the parcellation. The FC matrix is then typically created from correlating interregional timecourses. ***B)*** *The connection strength matrices introduced in (A) may then be thresholded to derive a binarized representation of the connections in the system. This binarized network representation can in turn be used to study either the organization of brain networks at the mesoscopic level (i.e. community structure) or at the local level (i.e. topological properties of individual network nodes), both of which can reveal useful insights into the network organization.*

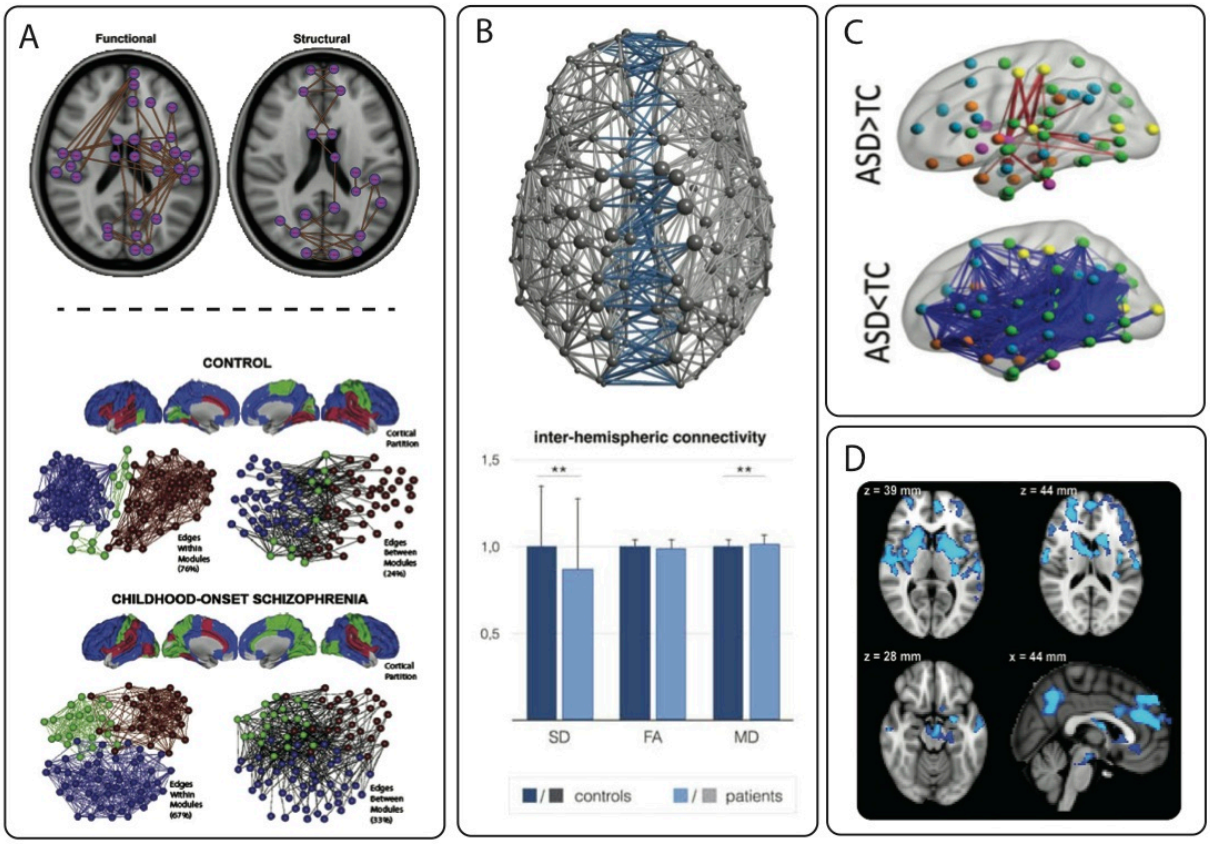

Figure 2. Brain Structural and Functional Connectivity Changes in Neuropsychiatric Disorders. ***A)*** *Top: In schizophrenia, reduced resting state functional and structural connectivity have been reported in subnetworks of interconnected regions (49). Bottom: Significant between-group differences in the modularity architecture of the brain have been found in resting-state fMRI data of childhood-onset schizophrenia patients relative to healthy controls (23).* ***B)*** *In bipolar I disorder, interhemispheric anatomical connections show marked reductions in patients relative to controls, while intrahemispheric structural connectivity is comparatively unchanged (104).* ***C)*** *Whole-brain resting-state functional connectivity analysis of subjects with Autism Spectrum Disorders (ASD) reveals both increases (top panel) and decreases (bottom panel) in FC relative to healthy controls (105).* ***D)*** *Resting-state fMRI connectivity data shows that Parkinson's disease patients show reduced functional connectivity within the basal ganglia network in a wide range of regions. This same study showed that the functional connectivity deficits can be improved with medication (106). Panel (C) adapted from Di Martino et al. (105).*

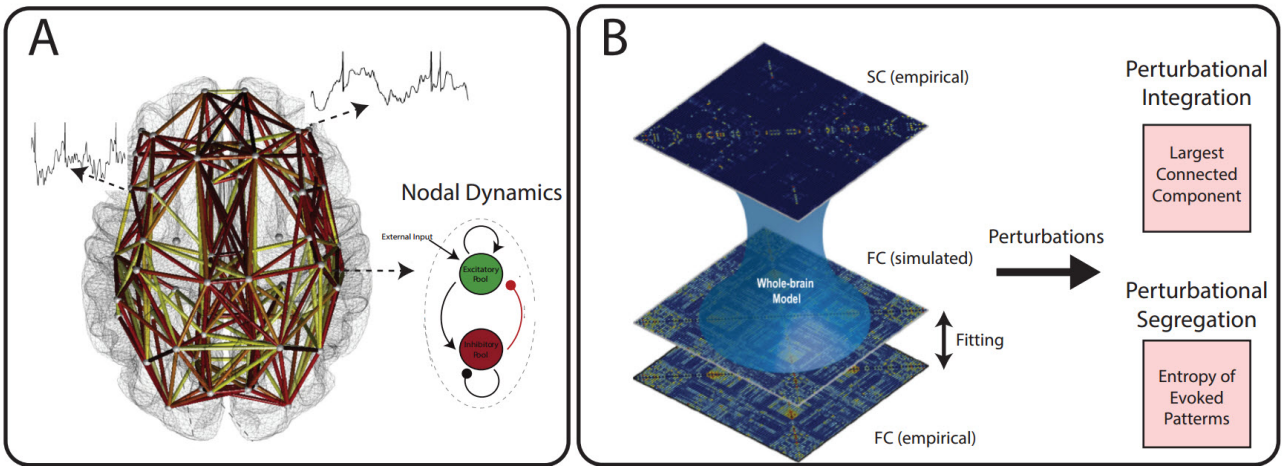

Figure 3. Overview of Whole-Brain Computational Modelling. **A)** *Whole-brain computational modelling of functional neuroimaging data uses empirical structural connectivity (SC) data obtained from diffusion tensor imaging (DTI) tractography, and functional connectivity (FC) data on the corresponding anatomical parcellation. A whole-brain model can be constructed by coupling the simulated local node dynamics (in this exemplar case, a simple mean-field model) according to the SC. The modelled activity is thus constrained by both the strength of each anatomical coupling and the physical distance between brain regions, and further scaled according to a global conductance parameter. (43, 44).* ***B)*** *A whole-brain computational model previously tuned to match the empirical data may be subjected to extrinsic perturbations, in silico. This is done by injecting the modelled dynamics with a random set of Gaussian inputs. The amount of integration in the system can be calculated after each perturbation: perturbational integration is defined by considering the length of the largest connected component of the binarized network as an estimate of the amount of integration in the system after each perturbation. Similarly, perturbational segregation is calculated through the entropy of the set of evoked patterns assuming a Gaussian distribution of stimulations (36). Panel A adapted from Hellyer et al. (75).*

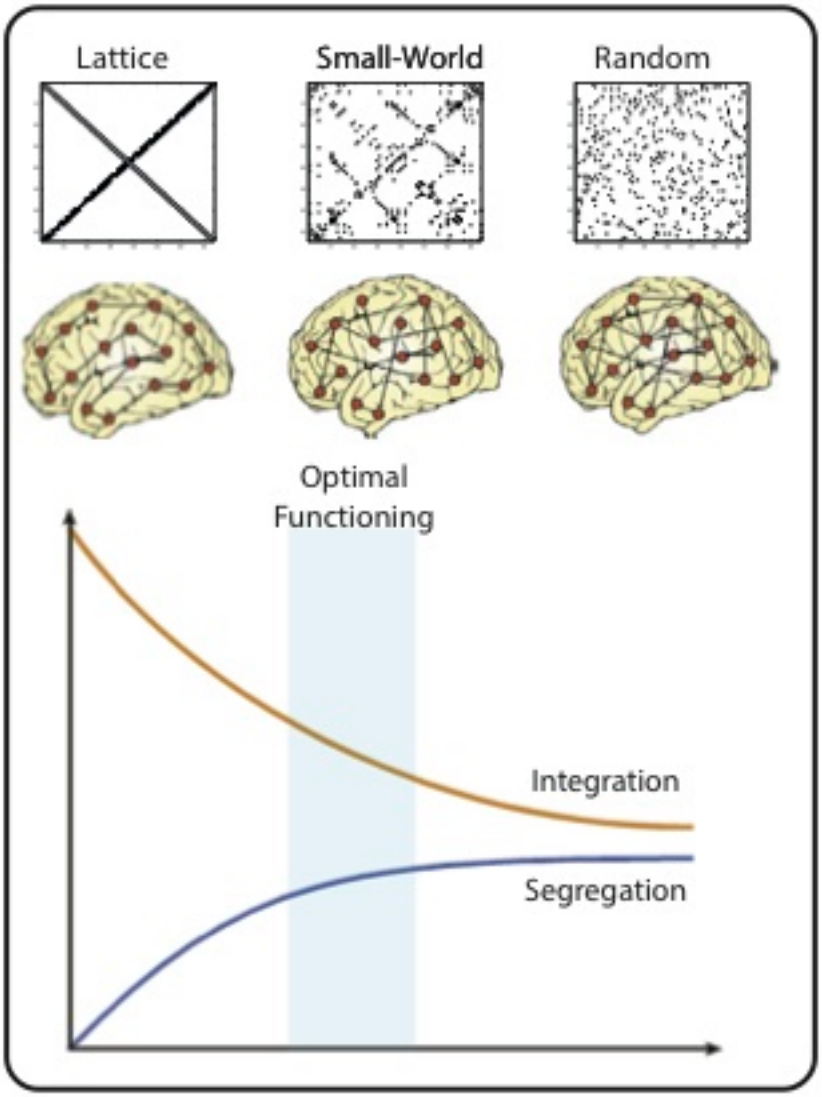

Figure 4. Influences of Brain Structural Connectivity on Integration & Segregation. *To investigate the effect of different degrees of small-world architecture of the structural connectome on the integration & segregation of neural activity in silico, an otherwise realistic whole-brain model can be outfitted with different artificial structural connectomes. Simulations whole-brain dynamics on the different structural networks demonstrated that, as the structural connectivity gradually changes from an ordered lattice to a disordered graph, perturbational integration decreases because randomness shortens the length of the largest component in the network, whilst perturbational segregation follows the opposite trend because randomness increases the capability to distinguish between two different external inputs. The optimal balance between functional integration and segregation is obtained at an intermediate (i.e. small-world) structural connectivity between order and randomness (36).*

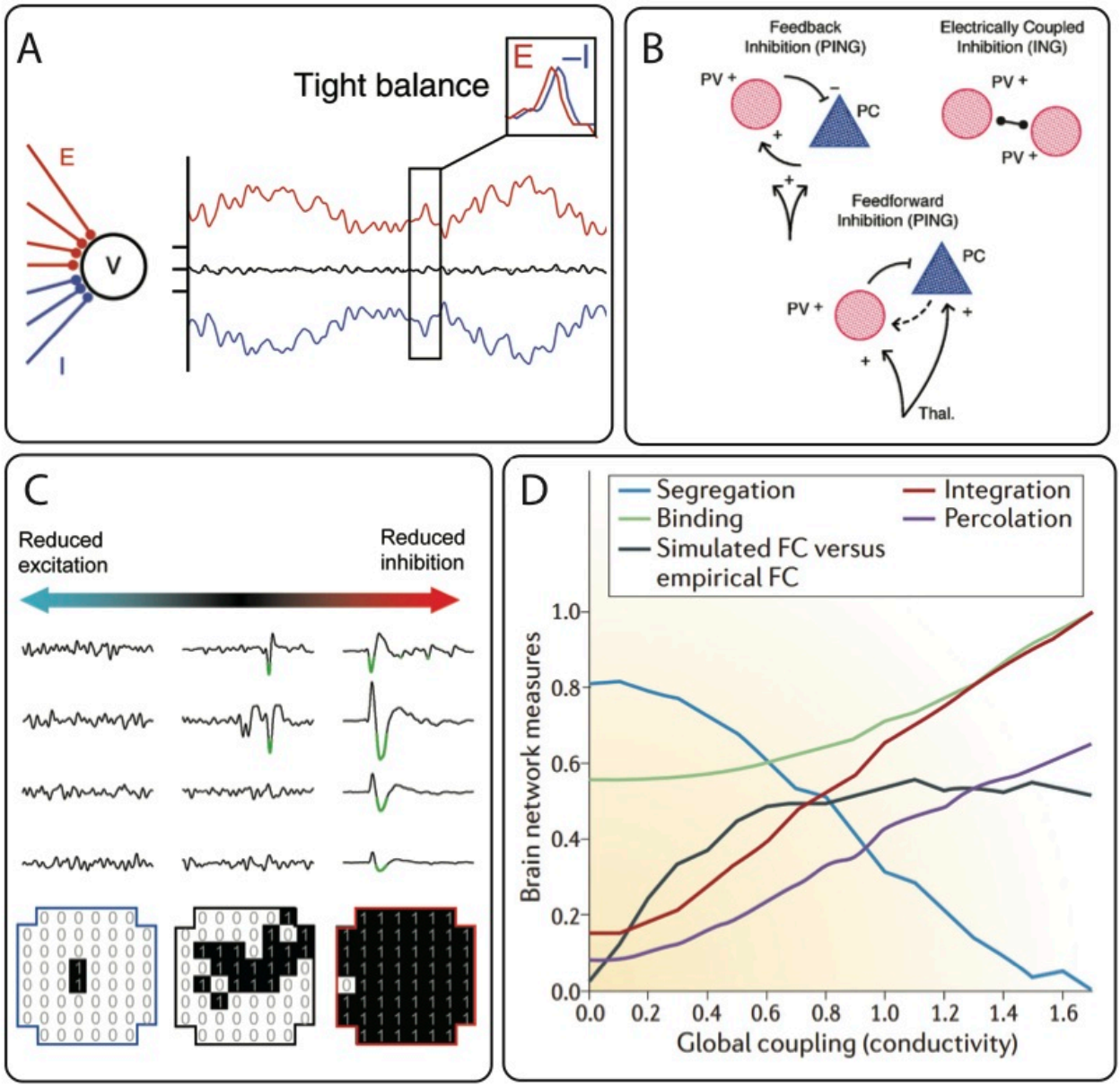

Figure 5. Influences of the E/I Balance on Integration & Segregation. A) *To allow for healthy brain function, excitation (red) and inhibition (blue) must be tightly balanced over both space and time.* ***B)*** *Reciprocal interactions between excitatory pyramidal cells and inhibitory interneurons at the level of cortical microcircuits maintain the E/I ratio within a narrow range capable of generating high-frequency neural oscillations (68).* ***C)*** *Local field potential (LFP) recordings experimentally recorded under conditions of suppressed excitation (left), suppressed inhibition (right) or unperturbed E/I (middle). Population LFP events represented as binary patterns: 1=active site; 0=inactive. Suppressed excitation leads to a loss of integration as only the activation of isolated small network clusters is possible (bottom left). Suppressed inhibition leads to a loss of segregation and co-activation of large clusters covering nearly the entire system (bottom right), reflecting excessive integration. Balanced E/I (bottom middle) enables the co-activation of clusters of all sizes (67).* ***D)*** *Scaling up the global conductance parameter in a whole-brain computational*

model has a profound impact on the functional network dynamics. Whole-brain computational models have shown that the best fit between the simulated and empirical functional connectivity matrices is obtained when the system operates in a metastable synchronization state where excitation and inhibition are balanced. The measures of perturbational integration and segregation also become optimally balanced at these intermediate global conductance values (36). Graphics for: (A) adapted from Deneve et al. (107); (C) adapted from Shew et al. (67).

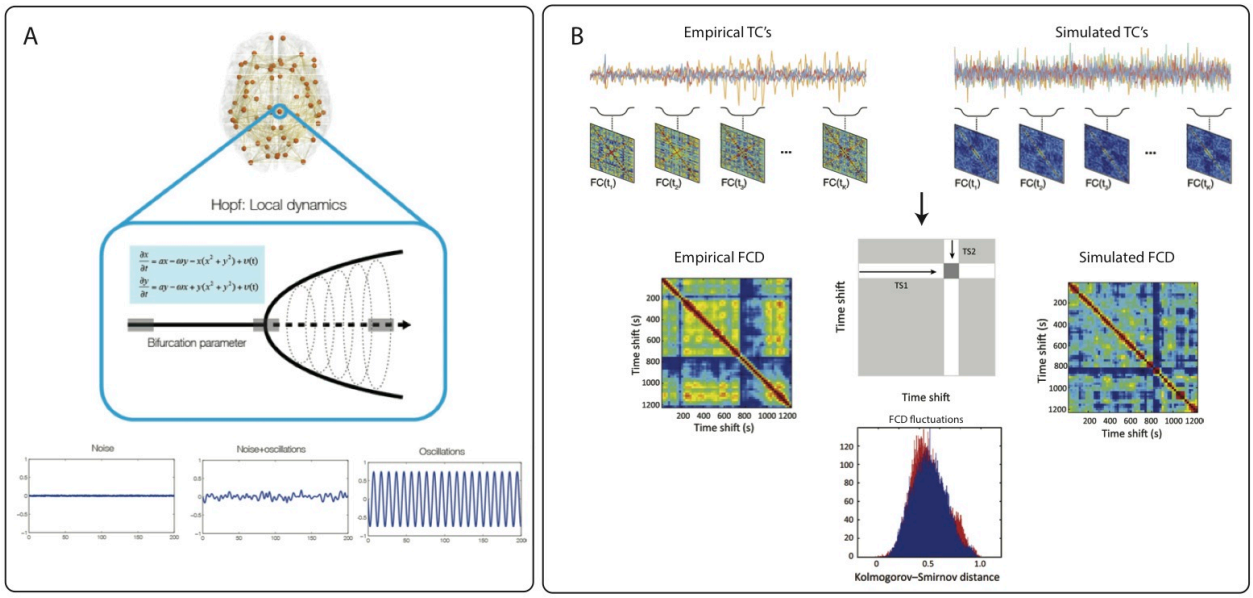

Figure 6. A Dynamic Hopf Computational Model of Brain Function. A) *The recently developed Hopf whole-brain computational model is a neural mass model based on the normal form of a Hopf bifurcation that combines features of both asynchronous and oscillatory behavior. As with earlier whole-brain models, the Hopf model is based on the empirical structural connectivity (SC) to constrain the dynamics in a biologically-plausible space-time architecture. At the level of local neural masses, depending on the bifurcation parameter, the local model generates a noisy signal (left), a mixed noisy and oscillatory signal (middle) or an oscillatory signal (right). It is at the border between noisy and oscillatory behaviour (middle) that the simulated signal achieves the best fit with the empirical data (97).* ***B)*** *Simulated neural dynamics from the Hopf model are fitted to the dynamical functional connectivity (FCD) matrix of the empirical data, which allows the model to reflect the brain's dynamical repertoire of network states, rather than merely capturing the time-averaged FC. For comparing the FCD statistics between the empirical and simulated data, the distributions of the upper triangular elements of the FCD matrices of individual subjects are compared by means of the Kolmogorov-Smirnov distance between them. The Kolmogorov–Smirnov distance quantifies the maximal difference between the cumulative distribution functions of the two samples. Graphics in panel (B) adapted from Hansen et al. (58) and Deco et al. (97)*

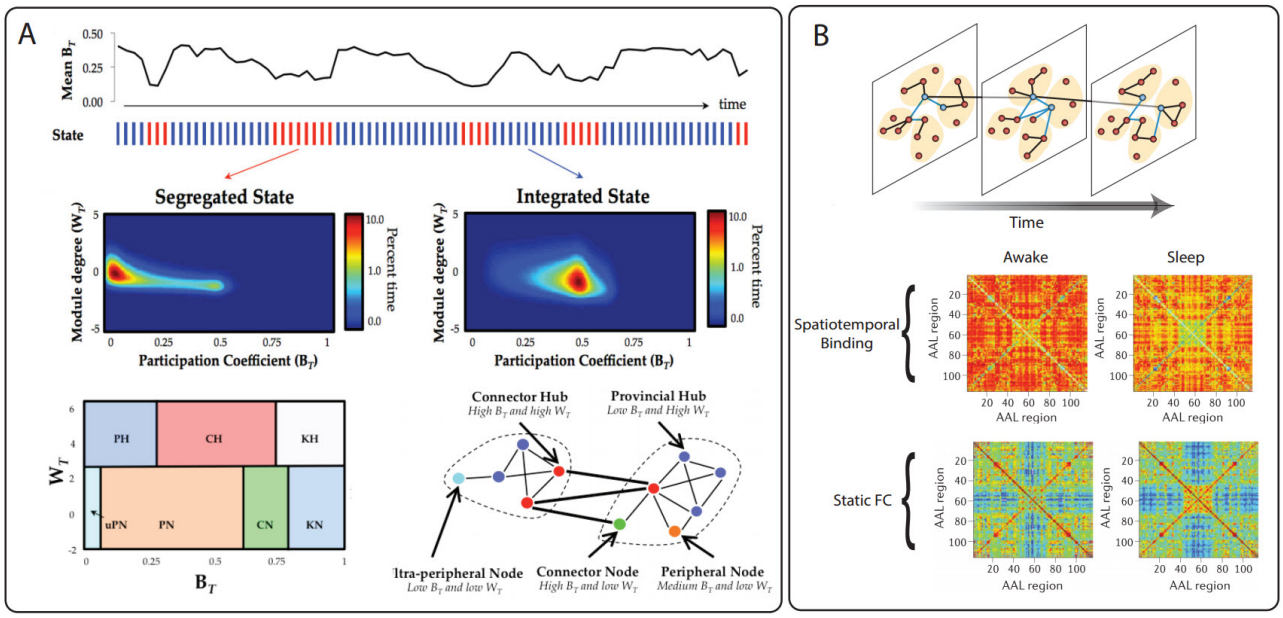

Figure 7. Measures of Spatiotemporal Integration & Segregation. A) *Dynamic Cartographic Analysis performed on empirical functional connectivity data. Each time window (top) is broadly partitioned into either an "integrated" topological state or "segregated" topological state using k-means clustering. The heatmaps show the mean cartographic profile of the segregated topological state (left) in which most nodes spend a high-proportion of time serving as peripheral nodes in the network topology. Conversely the mean cartographic profile of the integrated topological state comprises a significant proportion of nodes serving as hubs between different modules over the recording interval (38).* ***B)*** *The measures of perturbational integration and segregation introduced earlier may also be extended to the time domain. For example, spatiotemporal perturbational* integration, *or simply ''spatiotemporal binding" can be used to characterize the effectiveness of the integration of distributed information across the brain over time. For each brain region, the largest component that includes a given node is calculated. This is repeated separately for each sliding window, and assimilating this information over all time windows then yields the spatiotemporal "binding score" for a particular brain region. Experimental results indicate that this spatiotemporal binding measure is capable of capturing the functional disconnection over time during sleep, as reflected by lower regional binding scores. By contrast, the time-averaged functional connectivity matrix for the same data shows that the sleeping brain is more globally connected functionally (bottom) (97). Panel (A) adapted from Shine et al. (38).*