Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders

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Abstract

The study of human brain networks with *in vivo* neuroimaging has given rise to the field of connectomics, furthered by advances in network science and graph theory informing our understanding of the topology and function of the healthy brain. Here, our focus is on the disruption in neuropsychiatric disorders (pathoconnectomics) and how whole-brain computational models can help generate and predict the dynamical interactions and consequences of brain networks over many timescales. We review methods and emerging results that exhibit remarkable accuracy in mapping and predicting both spontaneous and task-based healthy network dynamics. This raises great expectations that whole-brain modelling and computational connectomics may provide an entry point for understanding brain disorders at a causal mechanistic level and that computational neuropsychiatry can ultimately be leveraged to provide novel, more effective therapeutic interventions e.g. through drug discovery and new targets for deep brain stimulation.

Introduction

The ability of modern neuroimaging to map the structural and functional connectivity of the normal human brain *in vivo* has given rise to the *connectome* (Sporns et al., 2005) as the complete map of the brain's neural elements and their structural interactions that allow complex integration and segregation of relevant information (Sporns, 2013). Network science has used the mathematical theory of graphs to characterize brain systems and their relation to other complex systems (Bullmore and Sporns, 2009; van den Heuvel and Sporns, 2013). Much of this research has been mostly descriptive but whole-brain computational models have started to make inroads in understanding the link between structural and functional brain connectivity and their potential breakdown in disease (Cabral et al., 2014a; Deco and Corbetta, 2011; Deco et al., 2011a; Honey and Sporns, 2008).

The study of disruptions to the normal human connectome has started to generate exciting new insights into the disrupted networks in neurological and psychiatric disorders (Van Den Heuvel et al., 2010). These network findings make it clear that neurological and psychiatric disorders often share underlying brain network pathology (such as in patients with Parkinson's disease who show both depressive and motor symptoms), which makes traditional diagnostic boundaries less meaningful (Buckholtz and Meyer-Lindenberg, 2012; Uhlhaas and Singer, 2012). In this review, we make the argument for computational modeling of connectomics as a rational way to generate new insights into general principles of brain function in health and disease.

Neuropsychiatric disorders are devastating not only to individuals but a growing and serious health burden for society. Take, for example, major depressive disorder which, with a 17% lifetime prevalence, is the leading cause of years lost to disability worldwide and which is predicted to be the largest contributor to the worldwide burden of disease by 2030 (WHO, 2008). While there has been some progress, the paucity of reliable animal models and the inadequacy of current treatments such as antidepressants would indicate that new research strategies are needed (Holtzheimer and Mayberg, 2011). Early interventions are key to halting and controlling disease and have been shown to be far more cost-effective than later interventions (Heckman, 2006).

There are many reasons for the disappointing progress in the nosology and diagnostics of neuropsychiatric disorders but fundamentally the problem can be tracked to a lack of causal understanding of the underlying biological mechanisms. This understanding has been further confused by a large number of statistically significant, but minimally differentiating findings (Kapur et al., 2012). What is clearly needed is a better understanding of the fundamental principles of brain function and the way that the brain can become unbalanced in neuropsychiatric disorders (Kringelbach et al., 2011). This may in time lead to novel ways of identifying biologically homogenous subtypes that cut across phenotypic diagnosis (Cuthbert and Insel, 2013). Such biomarker-defined subtypes can only come from measuring clinically meaningful differences between relevant clinical populations to facilitate a deeper understanding of the underlying brain mechanisms. This would open up the possibility for identifying biomarkers that stratify a broad-illness phenotype into a finite number of treatment-relevant subgroups (Trusheim et al., 2007).

In recent years, the advances in neuroimaging, genomics and computational modelling have raised great expectations for such a stratified psychiatry (Maia and Frank, 2011; Montague et al., 2012; Stephan et al., 2006). Here we expand on the previous computational psychiatry approaches by incorporating whole-brain computational modelling informed by connectomics, and not just applied to psychiatric disorders but also to neurological disorders, hence the new focus on computational neuropsychiatry and connectomics. Importantly, the current literature differs on what is thought to constitute a *computational* (as opposed to *mathematical*) modelling approach. Some authors have restricted the term "computational" to models of information processing (e.g. Montague et al., 2012) while others stress the inference aspect of the term and use this to refer to generative models (e.g. Stephan and Mathys, 2014). Please note that these generative models take their lead from statistics representing the joint probability of parameters and data, including both priors on the parameters and a likelihood function. The generative whole-brain models considered in this review contain a likelihood function but no priors.

Computational connectomics aims to model not only the spontaneous dynamics of brain connectivity networks during rest but also task-related dynamics in health and disease. Computational neuropsychiatry, as discussed here, aims to describe the whole or partial breakdown of these task-related network dynamics in mechanistic terms in order to be able to provide computer models that can rebalance these dynamics *in silico*. A direct outcome of such models would be to generate rational ways for effective brain interventions to rebalance the networks e.g. for drug discovery and new targets for deep brain stimulation.

In this review we first discuss the relevance of connectomics to neuropsychiatry. We review the methods and findings of using network science to map the structural and functional brain networks in health and disease. We discuss the potential using these topological measures for discovering potential biomarkers for neuropsychiatric disorders. We point out, however, that these types of networks features are limited in their ability to establish genuine links between structure and function. As such they are limited in disentangling the underlying mechanism for computation in the healthy brain, as well the breakdown in disease. We propose that this gap might be bridged using whole-brain modelling. Furthermore, we provide an overview of the current state-of-the-art of whole-brain computational modelling and the application for understanding disease.

Relevance of connectomics to neuropsychiatry

The connectome is defined as a comprehensive map of neural connections in the brain on many spatial scales (Sporns et al., 2005). In humans, this description is typically supported by the use of diffusion weighted/tensor imaging (DWI/DTI), which measures the constraining of white-matter fiber tracts by the diffusion of water molecules, typically on a scale of millimetres (Basser and Pierpaoli, 1996; Beaulieu, 2002). The connectivity between brain regions can then be reconstructed in multiple ways (Hagmann et al., 2010; Johansen-Berg and Rushworth, 2009), using diffusion imaging measures of fractional anisotropy, local level of mean diffusivity, radial diffusivity and axial diffusivity. This tractography can be combined with other imaging sequences such as magnetic transfer imaging to get more direct measures of physiological parameters such as axon diameter and myelin content. The primary advantages of these diffusion imaging

techniques are the ease of acquisition and analysis which facilitate large-scale cross-sectional and longitudinal human studies. Yet, there are also significant limitations to these methods including the indirect nature of connectivity measures and the lack of information of directionality (Jones and Cercignani, 2010).

In a similar way, the functional connectivity between brain regions refers to the statistical dependence of neurophysiological neural signals as recorded with indirect measures such as functional MRI and PET, or with direct measures of neural activity such as MEG and EEG. Typically, functional connectivity is measured by analyzing the relationship between regional time-series with e.g. correlations, coherence or mutual information (Bassett et al., 2011; Stam et al., 2009) (see Figure 1).

Functional connectivity measures on spontaneous activity recorded during rest over several minutes have shown highly reproducible and organized patterns of activity (Damoiseaux et al., 2006; Greicius et al., 2003) which overlap with task-related activity (Fox and Raichle, 2007). This functional connectivity has been shown to be constrained by structural connectivity (Honey and Sporns, 2008; Honey et al., 2009) but functional and structural connectivity are not identical, especially not over shorter time-scales of minutes and seconds (Allen et al., 2014; Baker et al., 2014). Indeed, characterizing and understanding the relationship between functional and structural connectivity across many temporal time-scales from milliseconds over minutes and hours to days and months remain one of the most exciting challenges of the field.

The analysis of the topology and overall organization of brain networks has typically used constructs from graph theory to represent regions as nodes and connections as edges. The brain can be parcellated into a number of distinct regions, which has historically been carried out based on careful studies of the properties of the underlying brain tissue (Zilles and Amunts, 2010). Modern neuroimaging parcellations typically range from tens to several hundreds of regions (Craddock et al., 2013). The optimal parcellation of brain regions is not currently clear but some of the most popular choices include the Hagmann parcellation with 66 cortical regions (Hagmann, 2005) and the automated anatomical labeling (AAL) parcellation with 116 cortical, subcortical and cerebellar regions (Tzourio-Mazoyer et al., 2002).

The graph theoretical approach has allowed for the characterization of key features of brain networks (see Figure 2). The research has shown that brain architecture comes from optimizing the economic trade-off between the cost (i.e. minimizing connection density) and the efficiency of network function (i.e. minimizing the characteristic path length) (Bullmore and Sporns, 2012). The human brain is thus a small-world network (Watts and Strogatz, 1998) with many locally connected clusters of modules (Newman, 2006). These anatomical modules form the potential basis for functional segregation of information (Sporns, 2013). Furthermore, the graph theoretical degree and centrality measures provide important topological information on the role of each region (node) in the integration of information. Central brain regions with high measures of degree and centrality are referred to as hubs (Bullmore and Sporns, 2009). Some of these hubs have high and diverse 'rich' patterns of dense interconnectivity (van den Heuvel and Sporns, 2013). This central 'rich club' has been suggested to play an important role for global brain integration (Van Boven and Loewenstein, 2003).

These graph theoretical measures have been successful in characterizing defining topological features of the normal human brain (Bullmore and Sporns, 2009; Sporns et al., 2007), and, as we will show below,

significant efforts have concentrated on measuring how these change in neuropsychiatric disease (Greicius, 2008). Some have labeled this effort *pathoconnectomics*, as the mapping of abnormal brain networks (Rubinov and Bullmore, 2013). It is important to remember, however, that such topological measures are not the only measures of brain function and that the temporal segregation and integration of information is equally if not more important. This is especially true of neuropsychiatric disorders such as bipolar disorder where temporal integration and segregation of information are clearly compromised (Whybrow, 1998).

One of the advantages of using functional and structural connectivity measures such as DWI/DTI and resting state MRI/MEG in neuropsychiatry is that these measures require very little effort on the part of the patient. In order, however, to make sure that these measures can be used in a clinical setting, it is important to carry out quality control to ascertain that they are valid, reliable, sensitive and specific – and that potential biomarkers have predictive value (Castellanos et al., 2013). E.g. to test validity of existing measures, promising but not conclusive comparisons have been made between DWI/DTI with definitive tract-tracing methods in the non-human primate (Kelly et al., 2010; Margulies et al., 2009). Overall, the quality control of the research is going on in parallel while these measures are being implemented in clinical settings. This has progressed given the moderate-to-high test–retest reliability across scans (Castellanos et al., 2013), but studies are ongoing examining the consistency of findings within a given scan (Chang and Glover, 2010), as well as across magnets and sites (Biswal et al., 2010; Tomasi and Volkow, 2010).

The hope is that pathoconnectomics could to lead to potential biomarkers for neuropsychiatric disorders. These biomarkers can potentially help on multiple levels, i.e. the determination of the presence or absence of a disease (i.e., diagnosis); staging of a disease; determination of risk prognosis; and prediction and monitoring of clinical response to an intervention (Castellanos et al., 2013). E.g. there is already cautious optimism of how disease state prediction could potentially be made from resting state functional connectivity (Craddock et al., 2009), how changes in insula activity could be used as a metabolism-based treatment-specific biomarker (McGrath et al., 2013) and how there is reduced functional connectivity with the basal ganglia network in PD patients, which improve with medication (Szewczyk-Krolikowski et al., 2014) (see Figure 3).

In the following, we review some of the findings of this emerging field of disordered topological brain networks. These findings are mostly correlational and the development of potential biomarkers will have to move beyond these measures to use causal methods such as whole-brain computational models.

Clinical topological brain connectivity findings leading to potential biomarkers

The rate of growth of neuroimaging studies using functional connectivity has increased compared to traditional task-based studies (Snyder and Raichle, 2012). Typically such studies use resting state functional MRI (rs-MRI) and are increasingly used to address clinical questions (Kelly et al., 2012). There are many advantages to rs-MRI including better signal-to-noise compared to task-based studies; more applicable for patients who may not be able to perform tasks; potential circumvention of task-related confounds and the multi-purpose nature of datasets which can be used to study multiple, interacting networks (Fox and Greicius, 2010).

Yet, the proliferation and widespread availability of rs-MRI across multiple centers and populations mean that care has to be taken to ensure the validity, reliability, sensitivity and specificity of the data (Castellanos et al., 2013). Current results all too often rely on "significance chasing with under-powered studies" as well as "approximate replications" (Kapur et al., 2012). Large-scale datasets are required for obtaining scientifically valid biomarkers and the neuroimaging community will have to start to make data available online at a faster rate that currently (Milham, 2012; Weiner et al., 2013).

The uncontrolled nature of rs-MRI remains a potential confound (Buckner et al., 2013), especially when used to study changes in functional connectivity between clinical groups. There are potentially deleterious effects of aliasing of cardiac/respiratory signals and particularly head motion (Power et al., 2012), which are starting to be addressed with automated methods (Patel et al., 2014; Power et al., 2014). A pertinent example is how participants exhibit unstable wakefulness during scanning which could introduce confounding effects. This is especially important given that studies using simultaneous EEG-fMRI have shown that different stages of sleep are associated with different functional connectivity patterns compared to the awake state (Picchioni et al., 2013), e.g. the breakdown of long-range temporal dependence in default mode and attention networks during deep sleep (Tagliazucchi et al., 2013). If rs-MRI is to be used routinely in patient populations with potentially very different patterns of sleep to those of controls, it will be important to implement appropriate monitoring and modelling of vigilance. Progress has been made in developing methods of automatic sleep staging using machine learning algorithms (Tagliazucchi et al., 2012), which has subsequently been used to on large rs-MRI datasets of over 1000 participants, showing a third of the participants fall asleep within 3 minutes (Tagliazucchi and Laufs, 2014).

Not withstanding these potential confounds with functional connectivity, a growing number of studies have found differences in structural and functional connectivity between normal and neuropsychiatric populations (Greicius, 2008). Examples include Alzheimer's disease (Binnewijzend et al., 2011; Damoiseaux et al., 2012; Greicius et al., 2004; Supekar et al., 2008), post-traumatic stress disorder (Karl et al., 2006), dementia (Buckner et al., 2000; Rombouts et al., 2009), autism (Kennedy et al., 2006; Weng et al., 2010), multiple sclerosis (Bonavita et al., 2011), bipolar disorder (Lim et al., 2013) and major depression (Greicius et al., 2007; Veer et al., 2010; Wang et al., 2012) (see Figure 3).

Schizophrenia is the paradigmatic example of such topological differences in neuropsychiatry and has long been hypothesized to be the result of abnormal brain connectivity (Bleuler, 1911; Kraepelin, 1919; Wernicke, 1874). This hypothesis has become possible to test with the emergence of neuroimaging methods (Friston and Frith, 1995). Many neuroimaging studies have reported altered structural and functional connectivity in schizophrenia (van den Heuvel and Fornito, 2014).

In terms of structural changes, studies have shown changes in clustering and modularity structure (van den Heuvel et al., 2013) pointing to a segregated pattern of network organisation. There is also longer average path length and reductions in global communication efficiency (Zalesky et al., 2011). Taken together this is suggestive of reduced communication between local segregated networks. Functional changes have also been found a subtle randomization of functional networks, with decreased small-world properties, lower clustering coefficients and fewer high-degree hubs (Bassett et al., 2012; Liu et al., 2008; Lynall et al., 2010).

Such changes in structural and functional connectivity could potentially lead to novel biomarkers for neuropsychiatric disorders (Castellanos et al., 2013) but, as mentioned above, there are many obstacles to progress. In addition to the technical problems mentioned, it is also important to link these to clinical variables such as prognosis, expected treatment response and risk. But perhaps most importantly it will be important to move beyond correlations to predictive, causal methods such as whole-brain computational modelling.

The role of whole-brain models in modelling brain function

Topological network models are useful as descriptive tools for characterizing brain organization in health and disease. But in order for this description to have clinical importance, it needs computational models that can simulate and predict observed functional brain activity. Mapping the human connectome is only the first step to establishing the links between function and structure needed to understand how integration and segregation are implemented in the human brain.

The main premise of these models comes from statistical physics where it has been shown that macroscopic physical systems obey laws that are independent of their mesoscopic constituents (Haken, 1975). One of the main difficulties of computational brain modelling is to strike the best balance between complexity and realism. Given the astronomical number of neurons in the human brain and the lack of accurate information of specific connectivity at the neural level, it is neither feasible nor desirable to create intricate models of, say, each individual neuron and its connections. Instead, whole-brain computational models have typically used various mesoscopic top-down approximations of the underlying complexity with dynamical networks of local brain area attractor networks having proved most successful (Cabral et al., 2014a) (see Figure 4).

Among the common assumptions for successful computational modelling is that explicit structural features (e.g. dendritic spines) or temporal details of neural networks (e.g. the spiking dynamics of single neurons) are irrelevant for generating complex mesoscopic dynamics. Instead, the emergent collective behaviour of such dynamics is only weakly sensitive to the details of individual neuron behaviour (Breakspear and Jirsa, 2007). Basic neural mass or mean-field models capture the changes in the mean firing rate (Brunel and Wang, 2003), while more advanced models use parameter dispersion in the neurons and therefore have a richer dynamical repertoire (Stefanescu and Jirsa, 2008). Further refinements include a dynamic mean field model derived from a proper reduction of the detailed spiking model (Deco et al., 2013c). This reduced dynamic mean field model ignores the interaction between single neurons within a cortical area and instead considers the ensemble dynamics.

The dynamics of a whole-brain computational model uses the structural connectivity between brain regions in a given parcellation as a description of the synaptic connections between neurons in those areas. These inter-regional connections are weighted by the strength specified in the structural connectivity matrix and by a global control parameter of the global conductivity of the fibres which is assumed to be equal across the brain. These parameters can then be varied systematically to simulate and compare the dynamics and fixed points of the global network system of attractors with functional connectivity data from

neuroimaging experiments. This functional connectivity data contains highly structured spatiotemporal activity patterns that emerge across the brain at rest when measured with different neuroimaging methods, e.g. rs-MRI or rs-MEG. The dynamical entrainment and correlations between different local brain region dynamics are shaped by the underlying structural connectivity (Deco et al., 2011b, 2013b; Deco et al., 2014a; Deco et al., 2014b; Ghosh et al., 2008; Honey et al., 2009). Whole-brain computational models can thus give a mechanistic explanation of the origin of normal resting state networks. Several studies have successfully done so for both rs-MRI (Deco and Jirsa, 2012; Honey et al., 2007) and rs-MEG (Cabral et al., 2014b), and has even been used to model important features of sleep (Deco et al., 2013a) (see Figure 5).

The research shown that the best fit of empirical resting functional connectivity matrices is obtained when the brain network is subcritical, i.e. in a region where the spontaneous state is stable (as measured by low firing activity across all brain regions) (Deco et al., 2009). There are, however, other attractor states corresponding to excited states with high firing activity which are also stable. In other words, the multi-stability around a stable spontaneous state defines an operating working point of the system such that the noise explores a meaningful dynamic repertoire that is inherent in the neuroanatomical connectivity (Deco and Jirsa, 2012; Deco et al., 2013c). It is also an important research area to develop models that take into account the non-stationarity of signals which has been shown in rs-MRI (Allen et al., 2014; Hutchison et al., 2013) and rs-MEG (Baker et al., 2014).

These complex models may seem difficult to get a handle on for neuroscientists but recently this has become a lot easier with the exciting development of The Virtual Brain (www.thevirtualbrain.org). This is a neuroinformatics platform that aims to provide a user-friendly interface, allowing users to perform customized simulations, analyze the results and compare them with neuroimaging results (Ritter et al., 2013).

Whole-brain models and disease

Whole-brain computational models aim to provide a full understanding of the segregation and integration of spatiotemporal information across networks, and can provide insight into how dysfunction in network activity may underlie mental health disorders. It has been argued that individuals and species rely on pleasure as the essential source of motivation to seek rewards and avoid punishments (Kringelbach, 2005). Careful neuroscientific studies have mapped the neural systems necessary and sufficient for the predictions and decisions underlying approach and avoidance behavior associated with positive and negative affect (Berridge and Kringelbach, 2013). The networks underlying anhedonia, the lack of pleasure, are compromised in the diseased brain (Treadway and Zald, 2011) and, specifically, disruptions have been demonstrated to the predictive coding underlying reinforcement learning (Stephan et al., 2006).

Overall, whole-brain computational models have demonstrated that the spontaneous activity in the brain at rest as well as task-related activity depend strongly on the properties of the underlying structural connectivity and the dynamical working point (Deco and Corbetta, 2011). Damage to the structural connectome can therefore have potentially very severe impact on the resulting functional connectivity. Changes in structural brain connectivity can arise in many ways with severe examples such as stroke, traumatic brain injury, neurosurgical lesions and neuropsychiatric disorders – and much less severe examples

such as mild traumatic brain injury, aging and learning. Importantly, the functional consequences of the damage are not limited to the lesion site but can also be observed at the macroscopic scale using functional connectivity measures such as rs-MRI and rs-MEG. On the other hand, changes in the dynamical working point also cause alterations of the whole brain dynamics which has been associated with e.g. schizophrenia (as described in the next section) (Cabral et al., 2012a; Cabral et al., 2012b).

The success of whole-brain computational models in modelling normal spontaneous brain function opens up the possibility of using them as unique predictive tools for investigating the impact of structural connectivity damage, e.g. permanent and reversible lesions in humans (Alstott et al., 2009; Van Hartevelt et al., 2014) and other animals (Honey and Sporns, 2008), as well as in disease states with altered structural connectivity (Cabral et al., 2013; Cabral et al., 2012b). The results show that even very precise lesions in one hemisphere can generate altered functional connectivity between distant brain regions, often across both hemispheres (Alstott et al., 2009). Not surprisingly, the altered patterns of functional connectivity depend significantly on the location and size of lesion relative to its role in the whole-brain networks. In the following, we will discuss examples of the functional consequences of both local and more global alterations of structural connectivity.

Whole-brain computational modelling of neuropsychiatric disorders

In terms of neuropsychiatric disorders, schizophrenia has been used as an important test case for the efficacy of whole-brain models, as demonstrated by Cabral and colleagues who investigated the functional consequences of structural disconnection using two different computational models (using nodes with stable asynchronous state (Cabral et al., 2012a) and with self-sustained oscillations (Cabral et al., 2012b)). Both models explored the impact of a brain-wide decrease of the coupling strength, i.e. the dynamical working point, in the properties of simulated resting-state functional networks. The coupling strength in both models essentially scales the excitatory-to-excitatory coupling between brain regions, which is controlled by mechanisms involved in long-range signal transmission. Examples of such mechanisms include axonal connectivity, which is dependent on the number, density and coherence of axon fibres, as well as synaptic mechanisms which include neurotransmission and plasticity (see Figure 6).

The performance of the model was tested by comparing the graph theoretical measures applied on the simulated functional connectivity matrices with experimental data obtained from healthy controls and patients with schizophrenia (Lynall et al., 2010). The results showed that the simulated healthy functional networks were found to have graph properties in the range of the ones reported experimentally. Decreasing the structural connectivity, either globally or locally, resulted in network reorganization in the simulated functional connectivity networks which were characterized by increases in hierarchy, efficiency and robustness, a decrease in small-worldness and clustering as well as a narrower degree distribution. This is in correspondence to measures reported in schizophrenia patients (Lynall et al., 2010). Theoretical results indicate that changes in both global and local levels of pathoconnectomics can induce the same qualitative changes in functional brain connectivity.

Neurosurgery and computational models

Precise neurosurgical lesions have traditionally been used to alleviate the symptoms of otherwise treatment-resistant disorders such as the tremor in Parkinson's disease and essential tremor. Unfortunately, the permanency and side-effects of these radical neurosurgical procedures are often severe. Over the last twenty years, the advent of the reversible, neurosurgical procedure of deep brain stimulation (DBS) has shown remarkable results in helping to alleviate the symptoms of otherwise treatment-resistant movement disorders such as Parkinson's disease (PD), essential tremor and dystonia (Kringelbach et al., 2011) with over 100.000 patients having been implanted to date, mainly for PD (Lozano and Lipsman, 2013). The success of DBS targets for movement disorders has been the product of carefully utilizing animal models (such as MPTP for PD) but has also been the result of serendipity during human lesional neurosurgery. DBS could potentially be used for other indications such as neuropsychiatric disorders (Lozano, 2012) but there is a lack of good animal models to test potential DBS brain targets. This is where whole-brain computational methods might be rather useful in helping to predict the clinical outcomes pre-surgically.

The underlying mechanisms of DBS are still debated but the efficacy of DBS must related to at least three main biophysical factors: A) DBS stimulation parameters such as frequency, voltage, and amplitude; B) physiological properties of the DBS target region; C) interactions between DBS electrode and the surrounding brain tissue and structural connectivity (Kringelbach et al., 2007). Overall, the evidence suggests that the individual structural connectivity of the DBS target combine with these biophysical properties to help rebalance widespread dynamic brain networks (Kringelbach et al., 2011; McIntyre and Hahn, 2010).

Whole-brain computational modelling has only started to be used to inform functional neurosurgery. In a unique case of a DBS PD patient with structural connectivity DTI measures pre-DBS and six-months post-DBS, Van Hartevelt and colleagues were able to use network science and computational modelling to determine the structural changes and predict the functional consequences (Van Hartevelt et al., 2014). Graph theoretical measures found significant localised structural changes as a result of long-term DBS in sensory-motor, prefrontal/limbic, and olfactory brain regions which are known to be affected in PD. Excitingly, whole-brain computational modelling showed the impact of DBS-induced structural alterations on functional brain changes to shift the neural dynamics back towards a healthy regime. This is the first demonstration that DBS can lead to a topological reorganisation towards healthy bifurcation of the functional networks measured in controls, which is suggestive of potential neural mechanisms for the alleviation of symptoms.

Whole-brain computational modelling combined with individual structural connectivity could thus play a significant role not only in helping improve pre-surgical targeting by predicting the outcome but also more generally in the discovery of new, potential DBS targets for existing disorders. Overall, it will soon be possible to use whole-brain computational models to predict the outcome of both invasive (e.g. DBS) and non-invasive (e.g. neurotransmitter changes) changes to structural connectivity and their potential to rebalance the disordered brain networks (Kringelbach et al., 2011).

The success of such a research program will depend significantly on the incorporation of reward circuitry, which has shown to be compromised in neuropsychiatric disorders. A large body of research in humans and other animals has shown a network of strongly connected regions that would appear to encode the pleasure of fundamental rewards (such as food, sex and social stimuli) as well as more abstract rewards (such as music and money) (Kringelbach and Berridge, 2009). Causal evidence from other animals points to regions that act as pleasure generators or 'hedonic hotspots' which can help animals want, like and learn about the stimuli that help ensure survival (Peciña and Berridge, 2005). A problem with parts or all of this circuitry can lead to anhedonia, which is a common problem for many neuropsychiatric disorders (Treadway et al., 2009). While some computational models make much of local changes in such local circuits, the main importance lies in the global changes in activity. Whole-brain computational models could help understand how the local regions interact over time with other regions to change global activity which in turn can to help allocate brain resources. Understanding this interaction in a normal population is likely to lead to novel interventions targeted at rebalancing these networks in neuropsychiatric disorders.

Conclusion

In summary, we have tried to show some of the progress which leads to great expectations for how whole-brain computational modelling and connectomics may be levered to alleviate human suffering by facilitating a better understanding of fundamental brain function and leading to the discovery of new, more effective interventions. We have also discussed some of the potential obstacles to this nascent field but none of the obstacles are in principle insurmountable (Linden, 2012).

The explicit linkage of human neuroimaging data with whole-brain computational modelling has shown great potential not only for a deeper understanding of the computational and biophysical mechanisms underlying healthy resting state and task/stimuli evoked activity, but also for the discovery of the causes of the breakdown in neuropsychiatric disorders. This mechanistic information would then be useful as potential biomarkers for individual patients. In addition, this information can be used to monitor the progress for existing therapies, helping to predict the outcome at an early stage which opens the possibility of tailoring specific treatments to specific patient groups in a stratified neuropsychiatry. Importantly, this will also help our understanding the origin and mechanistic causes of disease and open up for novel interventions and treatments.

In this review we have presented some promising examples of existing approaches for computational modeling of neuropsychiatric disorders. Yet, there are clearly many limitations and much more research is needed. In this context, we envisage three main avenues of research for improving computational models of brain activity: 1) Better characterization and understanding of functional activity on many temporal timescales; 2) the use of these new temporal measurements for making the whole-brain models more realistic and thus more informative, and 3) the prediction and characterization of brain activity in individual patients based on resting-state brain activity.

First, the use of temporal description of functional activity has become an increasingly important topic (Allen et al., 2014). It has been shown that the resting state dynamical correlations evidenced and broadly

used in a grand average functional connectivity matrix (shown in this review) does not emerge from stationary dynamics. On the contrary, the temporal structure of these correlations changes over time which must be associated with the capacity of the brain to integrate not only spatial but also temporal information, i.e. how the brain perform *binding of information*. For example, the study the temporal evolution of functional correlations across time reveals the differential aspects of the underlying dynamics that can never be expressed through a grand average description of functional connectivity over time. This in turn opens up for novel types of biomarkers (e.g. an entropic description of the time dynamics of such correlation pairs of brain regions).

Second, the temporal measurements mentioned above could help us to further constraint the models in a number of important ways. E.g most current models use a global conductivity coupling parameter, but this constraint could be relaxed and each fiber could have its own conductivity, i.e. the strength of this particular connection. This, in turn, would open up for the possibility for considering the influence of neurotransmitters on the structure and dynamics. Such whole-brain models could start to help predict the effect of pharmacological manipulations on brain activity and therefore could be rather useful for drug discovery.

The inclusion of more structural-dynamics in whole brain models as well as more constraining temporal measures would add new promising aspect to connectomics, namely the *effective connectivity matrix*, which thanks to computational modelling with richer temporal information will complement the existing structural and functional connectivity matrices.

Furthermore, not only could the synaptic connections be better adapted to predict the empirical data but this is also possibilities for improving the characteristics of the local dynamics in each brain region. At the moment the regional local dynamics are considered homogeneous as a matter of simplification but could be extended to deal with different *heterogeneous* local dynamical nodes derived from the temporal information in functional data.

Third, whole-brain models combined with resting state activity offer a way to characterize and predict the activity of individual brains not only during rest but also during tasks. As mentioned earlier, this is particular useful in patients, since the acquisition of resting state activity is much easier than task-based activity, especially in unresponsive and difficult patient populations. Furthermore, even with healthy subject it is not feasible to characterize brain activity during many tasks because of time limitations. Based on the current evidence showing that resting state activity is strongly linked to task-evoked activity, it would be possible to construct an individualized brain model for a specific patient just by fitting the resting state activity with the structural connectome. Then, *off-line*, the particular brain model can be studied computationally and dynamically by applying a large number of external stimulations/tasks and characterize quantitatively the functional consequences. For example, integrative spatio-temporal measurements and entropic measurements can be used to describe how well a particular brain encodes all external stimuli/tasks which in turn can be defined and used for diagnostic, supervision and prediction.

In many ways, the holy grail of computational connectomics and neuropsychiatry is to create whole-brain models which can infer a large range of detailed pathophysiological processes from measured neuroimaging data. At the same time, their complexity and size will introduce some major numerical and inferential

challenges, e.g. problems of model identifiability (i.e., uniquely defined parameter values) and overfitting (i.e., seeing meaningful patterns in noise) when applying the model to empirical data. As large-scale models will increasingly strive to incorporate biological complexity and allow for connection-specific coupling values, one may expect to see some convergence with other modelling approaches for inferring parameter values of dynamic system models from measured neuroimaging data. In particular, the statistical methodology of dynamic causal models (DCMs), which are usually restricted to much smaller networks with up to approximately ten nodes, could prove useful (Friston et al., 2003).

Already, the whole-brain models discussed in this review share many conceptual similarities with DCMs, including the emphasis of a neural mass or mean-field model perspective and the use of identical forward models for fMRI. In the future, DCMs may usefully contribute to further development of whole-brain models by virtue of their Bayesian foundation which is crucial for dealing with problems of identifiability and overfitting; furthermore, this grounding in probability theory allows for formal comparison of competing model formulations in terms of evidence (Bayesian model selection, BMS) (Friston and Penny, 2011). One may anticipate that the statistical advances established by DCM in recent years will find their way into future whole-brain models, particularly when aiming for estimates of effective connectivity (Friston et al., 2013). Furthermore, the ability to detect signs of overfitting through BMS is likely to prove crucial when enhancing the biological realism of whole-brain models.

In addition, the whole-brain computational models will obviously also depend on the quality of neuroimaging data in order to help generate potential biomarkers. In particular, it will be crucial to obtain more accurate information about timing of neural events in the whole network. While individual neuroimaging modalities such as MEG have shown great promise in providing direct measures of neural activity, it is likely that progress will come from the combination of multi-modal neuroimaging data.

The exciting future possibilities for computational neuropsychiatry might also be further refined by genomic information. Studies have started to combine whole-genome analyses with whole-brain data to discover genetic variants that reliably affect the brain (Medland et al., 2014) and large-scale genomics have started to unveil the genetic architecture of psychiatric disorders (Gratten et al., 2014). Still, neuropsychiatric disorders come about through genetic predisposition and environmental stress originating in the first two decades of life (Kessler et al., 2005), and so it is also important to create developmental models which can help understand and develop early interventions to halt and control disease, likely to be far more cost-effective than later interventions (Heckman, 2006).

Overall, as shown in this review, on the present evidence the great expectations for applying computational and connectomic approaches to neuropsychiatry are well founded. Further developing and refining whole-brain computational models and bringing them to bear on understanding neuropsychiatric disorders offers exciting prospects for interdisciplinary neuroscience and the potential to help alleviate the suffering associated with mental health disorders.

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Figures

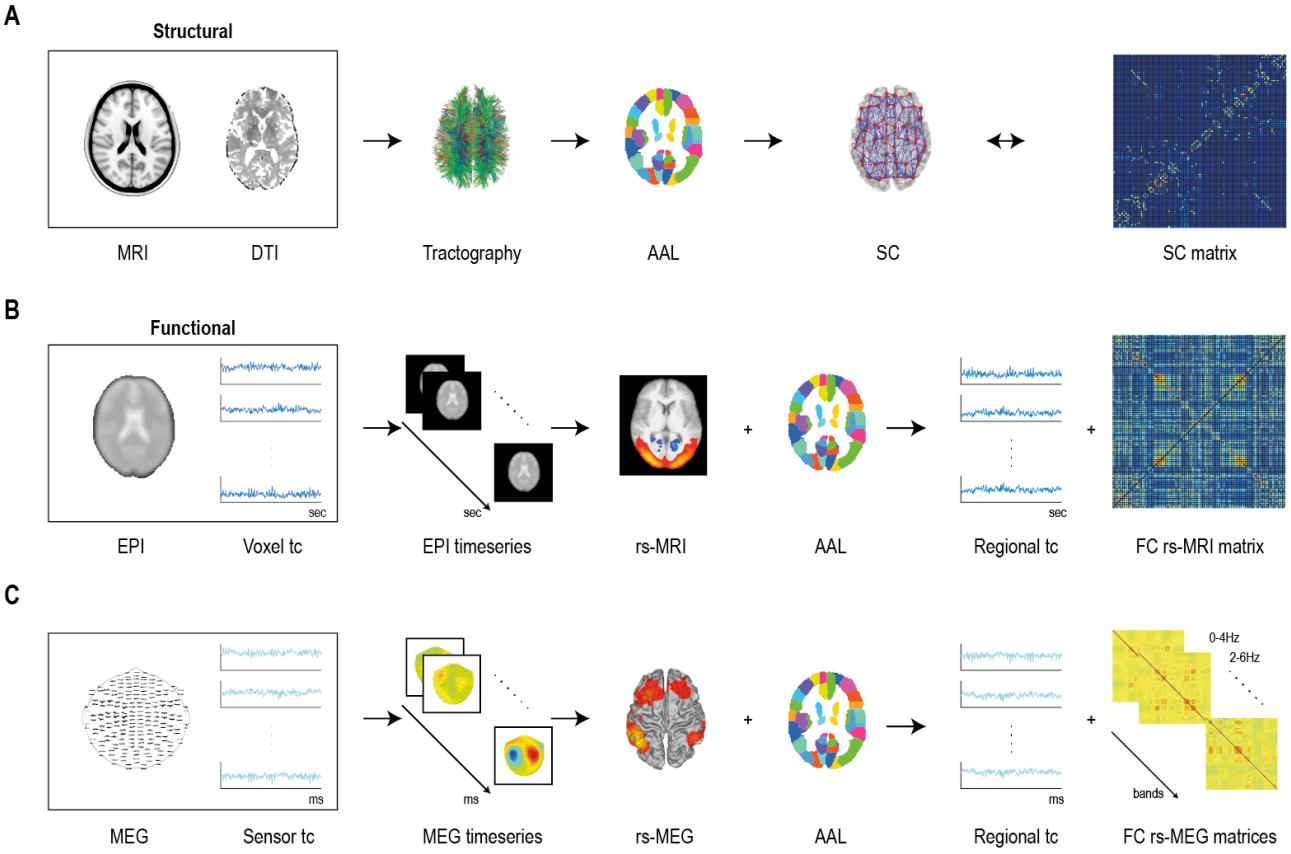

Figure 1. Connectomics using human neuroimaging techniques. *A) Creating the individual structural connectivity (SC) requires MRI and DTI, as well as a parcellation, e.g. such as AAL. B) Creating the individual functional connectivity has traditionally required measuring the resting state MRI (rs-MRI), typically using EPI images sampling the BOLD timecourse in each voxel in the brain. This is then combined with a parcellation scheme to recreate the regional timecourses for each of the regions in the parcellation. The FC matrix is then typically created from correlating these timecourses between regions. C) A more detailed FC matrix can be created from recording resting state MEG (rs-MEG). The sensor data can be transformed to the source space of the brain using the individual's MRI and a source reconstruction method such as beamforming. Combining this with a parcellation scheme allows for the extraction of regional timecourses, typically ordered across different frequency bands, which can be correlated into resulting FC rs-MEG matrices.*

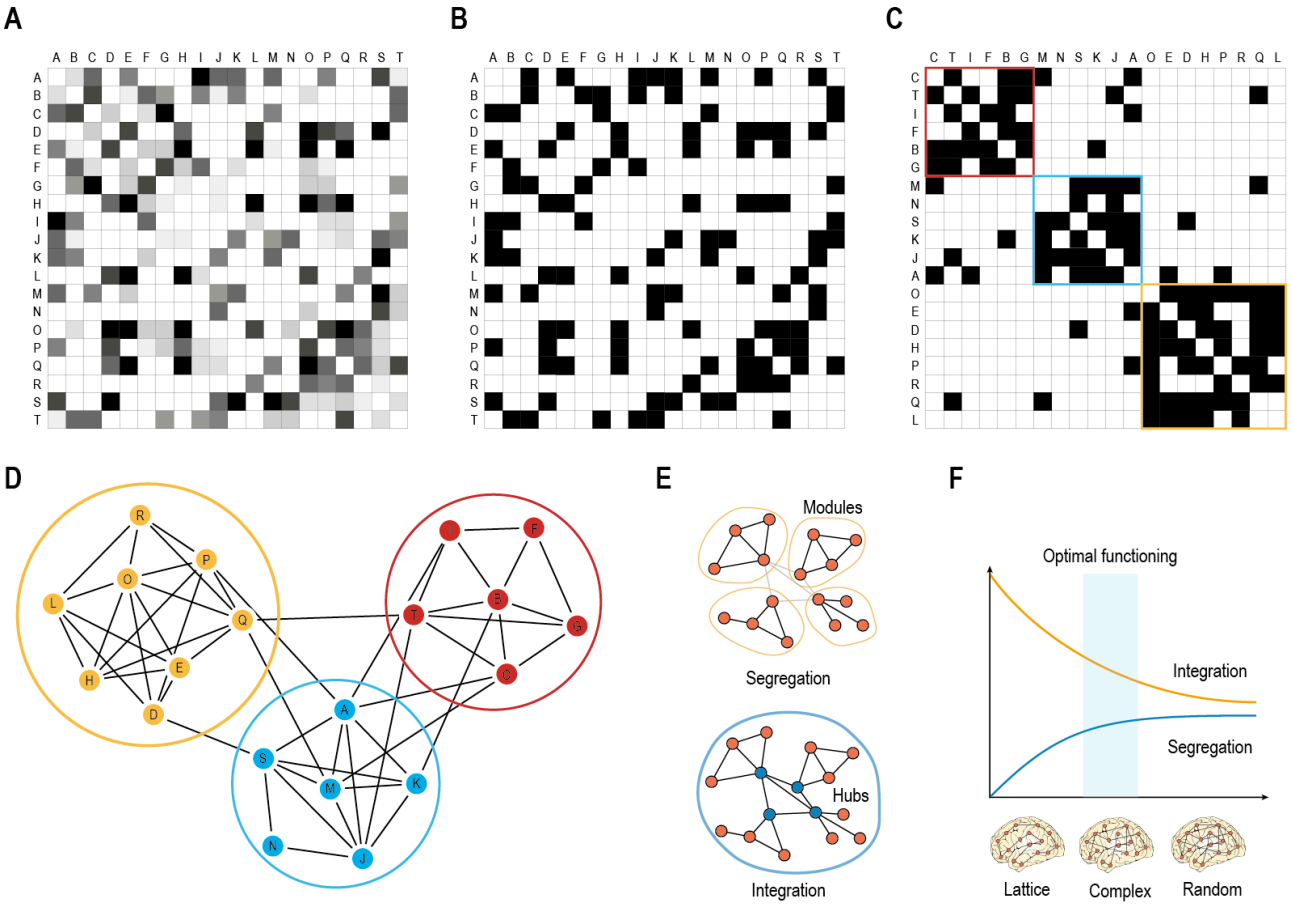

Figure 2. Network science. *Connectomics is concerned with characterizing the way that different regions connect to each other. A brain network can be characterized using graphs where the nodes are the regions and the edges are the connections between regions. Here, we introduce some of the key concepts in network models. A) The example shows a matrix with the connection strengths (in shades of grey) between twenty brain regions. B) This connectivity can be binarized at a given threshold of connectivity strength (here, we have used 50%). C) This binary connectivity can then be reordered to an optimal modularity partition, with this example having three modules (coloured in orange, blue and red). D) Another way to visualize this network is to use a spring-embedded two-dimensional network diagram, with the three modules circled. E) The topology of networks can be separated into segregated modules and integrative hubs. F) The key issue for optimal functioning for any brain is to balance the amount of spatial segregation and integration. In the example with 20 brain regions, region A is clearly a hub with a high degree (number of connections), betweenness centrality (placed on many of the short paths in the network) and participation coefficient (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. Figures B-D adapted from (Sporns, 2014).*

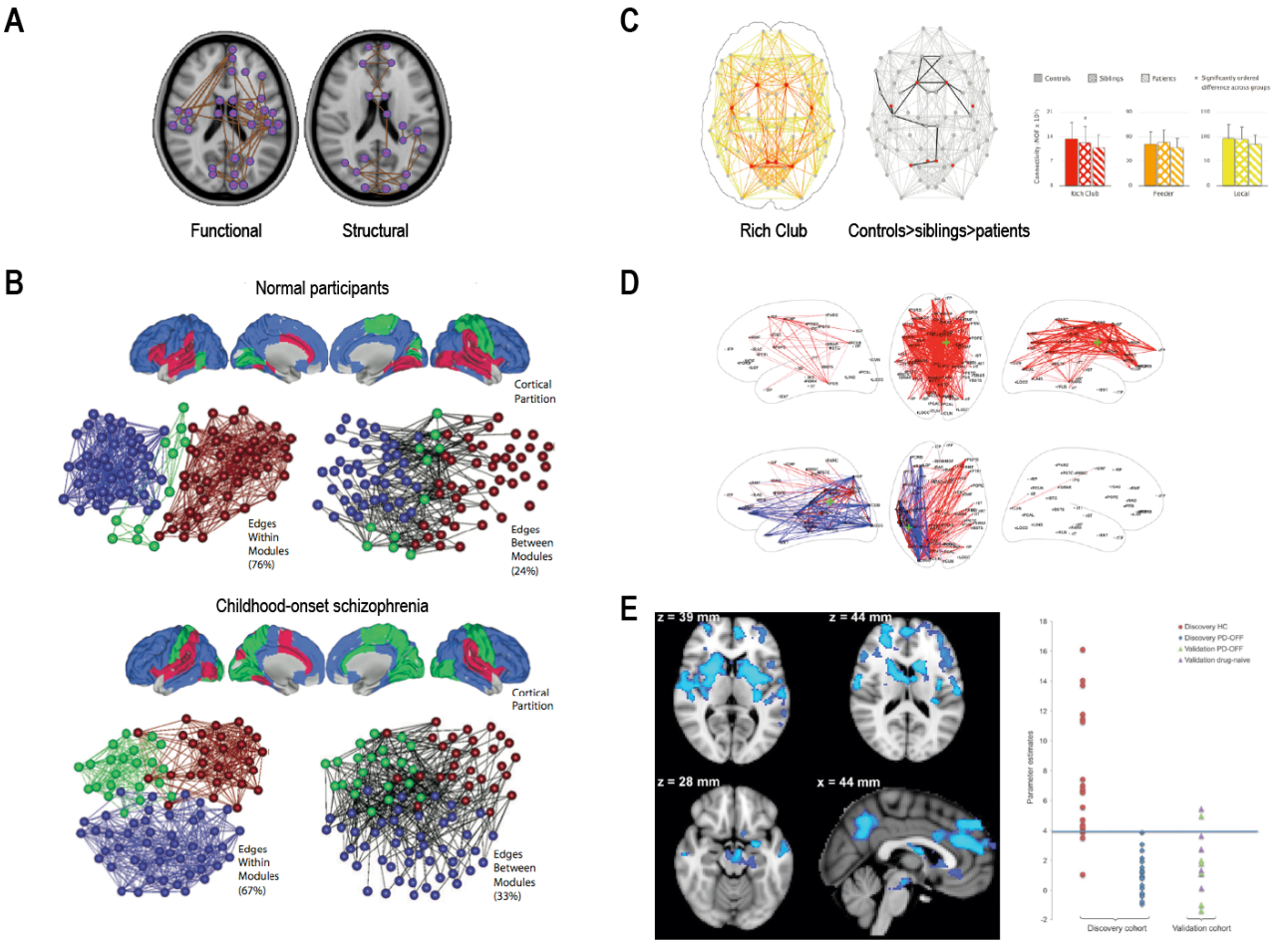

Figure 3. Examples of structural and functional changes in neuropsychiatric disorders. *A) Reduced resting-state functional and structural connectivity in sub-networks of interconnected edges were found in two independent studies of patients with schizophrenia (Fornito et al., 2012). B) Significant changes in modularity were found between patients with childhood-onset schizophrenia and a control population. (Alexander-Bloch et al., 2010). C) Schizophrenia patients showed reduced connectivity, predominantly in the rich club connections, with intermediate levels found in non-affected siblings (Collin et al., 2014). D) Significant impact of lesions to whole-brain connectivity was shown resulting from a mid-line lesion (top) and parietal lesion (bottom) (Alstott et al., 2009). E) An example of a potential biomarker for PD was found using rs-MRI, where PD patients showed reduced functional connectivity with the basal ganglia network (BGN) in a wide range of regions, which improved with medication. The average functional connectivity with BGN differentiated PD patients from controls with 100% sensitivity and 89.5% specificity. Subsequent validation showed 85% accuracy (Szewczyk-Krolikowski et al., 2014).*

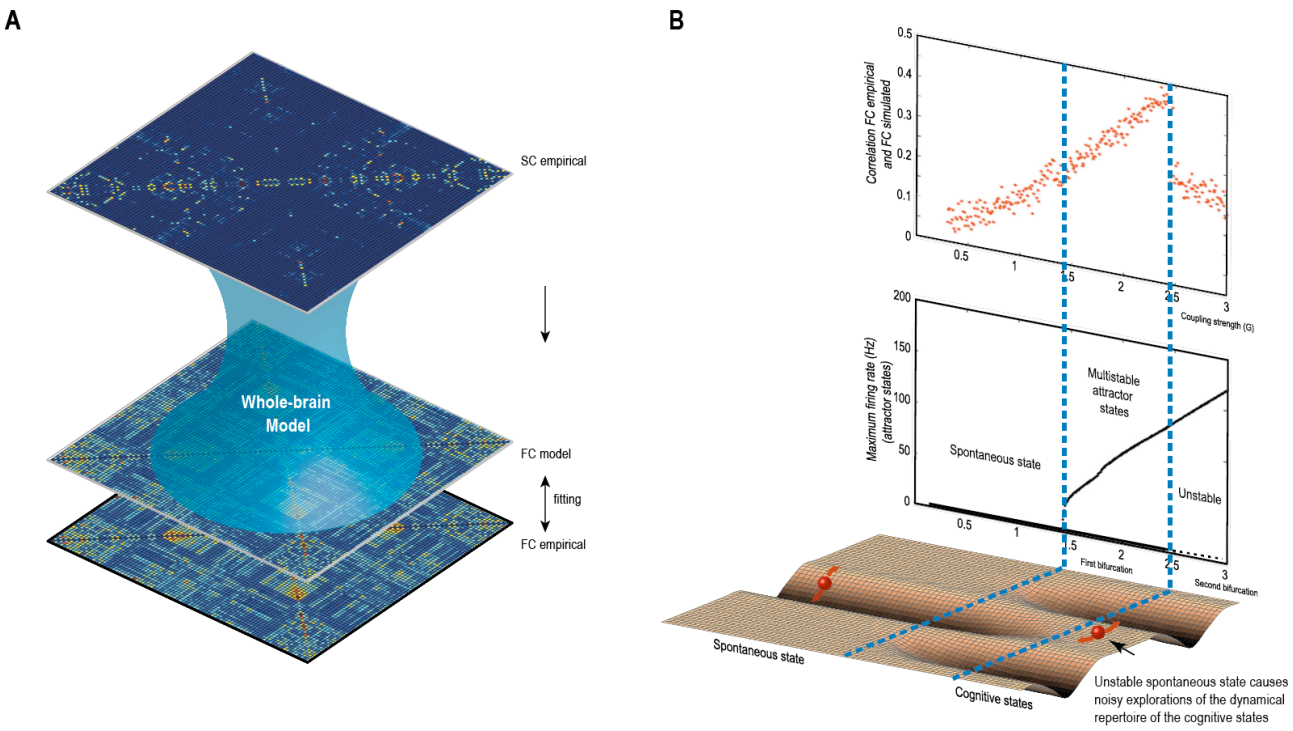

Figure 4. Overview of whole-brain computational models. *A) Linking between the structural and functional dynamics can be explored using whole-brain computational modelling of empirical neuroimaging data. Structural connectivity data can be obtained using DTI and tractography between a parcellation of the human brain that can provide a structural connectivity matrix. A whole-brain model can be constructed using a set of stochastic differential equations coupled according to the connectivity matrix, where the model can be validated by comparing model and empirical spatiotemporal neuroimaging data. B) The whole-brain model is able to best fit the empirical resting functional magnetic resonance imaging data when the brain network is critical (i.e., at the border of a dynamical bifurcation point), so that, at that operating point, the system defines a meaningful dynamic repertoire that is inherent to the neuroanatomical connectivity (Deco et al., 2013b).*

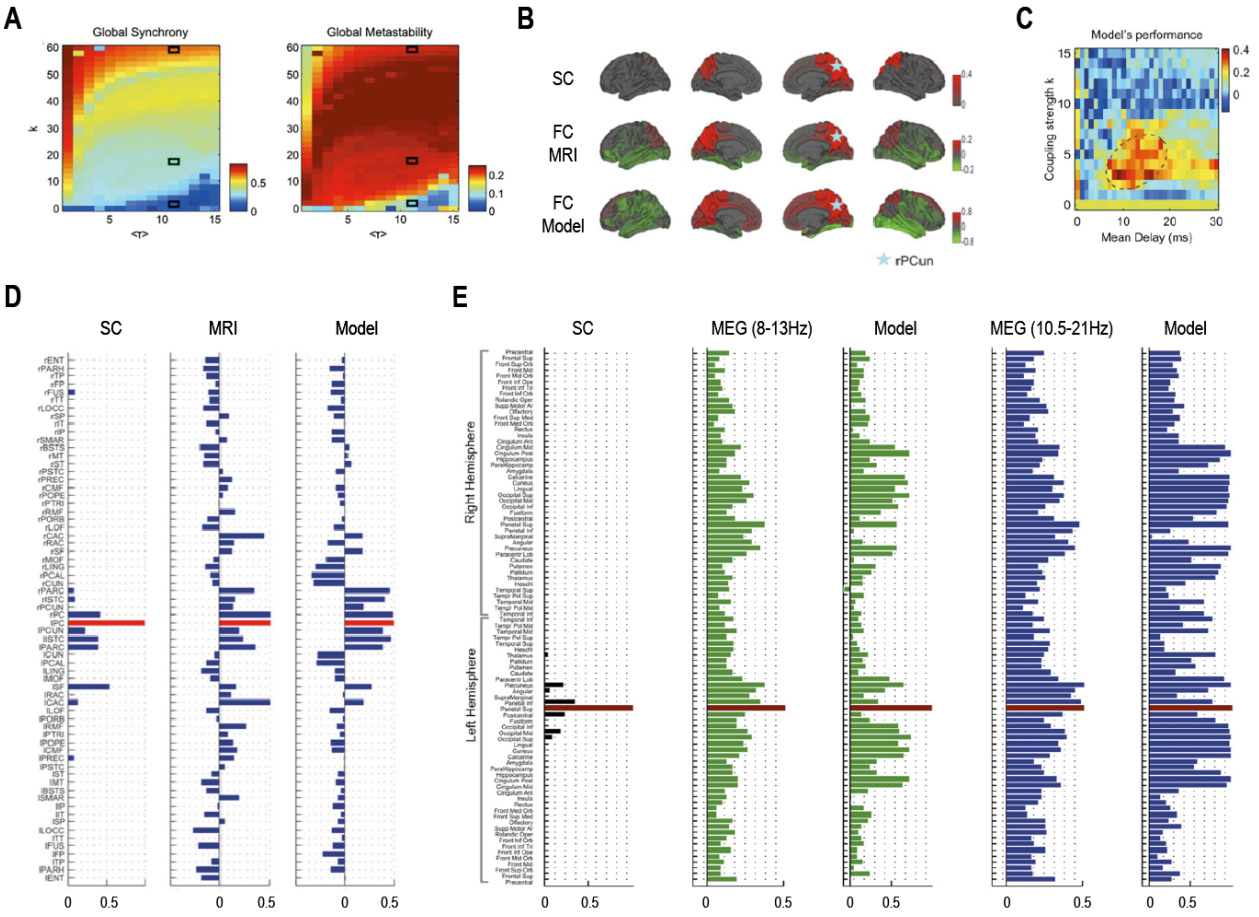

Figure 5. Modelling and predicting normal dynamics of neuroimaging (rs-MRI and rs-MEG). *Whole-brain computational models have managed to simulate and predict empirical neuroimaging data from rs-MRI and rs-MEG in normal participants (Cabral et al., 2011; Cabral et al., 2014b). A) Creating a whole-brain model using the normal structural connectivity can be tested against empirical rs-MRI data, where the best fit requires a realistic dynamical working point in terms of parameters determining global synchrony and metastability. B) At the highlighted working point, the whole-brain model reproduces many spatial features of the empirical functional connectivity shown here from a seed in right cuneus. C) Similarly, the same whole-brain model but now used for rs-MEG shows the best performance at similar realistic values of coupling strength and mean of delay distribution. D) The full connectivity profiles of simulated and model rs-MRI show very good correspondence e.g. using a seed in right cuneus. E) Equally, there is a strong correspondence between the simulated and empirical connectivity profiles for e.g. a region of superior parietal cortex and the activity measured with rs-MEG in different bands.*

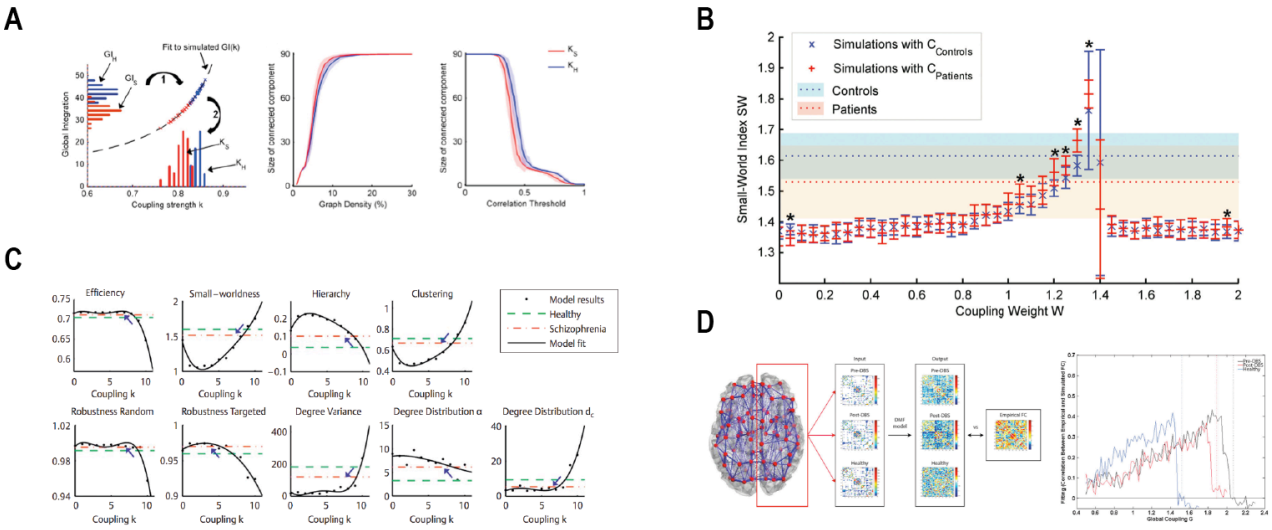

Figure 6. Examples of whole-brain computational modelling of schizophrenia and Parkinson's Disease. *A) Whole-brain computational modelling was used to simulate functional networks in schizophrenia and health using global integration values reported experimentally. This showed significant fragmentation in the simulated functional networks between the two groups as shown by the number of connected components as a function of graph density and correlation threshold (Cabral et al., 2012a). B) Significant changes small-world index between schizophrenia patients and control patients were found using a whole-brain computational model and varying the global coupling weight (Cabral et al., 2013). C) Similarly, simulations showed that the model predicted well the experimentally observed measures of graph theoretical measures as a function of the coupling strength (Cabral et al., 2012b). D) Whole-brain computer models have also been useful for other neuropsychiatric disorders such as PD and combined with a causal intervention. A computational model using the changes in pre- and six-months post-DBS showed significant recovery of structural network connectivity as a result of using DBS to alleviate the symptoms of PD (Van Hartevelt et al., 2014).*

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