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Towards the virtual brain: network modeling of the intact and the damaged brain

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ABSTRACT

Neurocomputational models of large-scale brain dynamics utilizing realistic connectivity matrices have advanced our understanding of the operational network principles in the brain. In particular, spontaneous or resting state activity has been studied on various scales of spatial and temporal organization including those that relate to physiological, encephalographic and hemodynamic data. In this article we focus on the brain from the perspective of a dynamic network and discuss the role of its network constituents in shaping brain dynamics. These constituents include the brain's structural connectivity, the population dynamics of its network nodes and the time delays involved in signal transmission. In addition, no discussion of brain dynamics would be complete without considering noise and stochastic effects. In fact, there is mounting evidence that the interaction between noise and dynamics plays an important functional role in shaping key brain processes. In particular, we discuss a unifying theoretical framework that explains how structured spatio-temporal resting state patterns emerge from noise driven explorations of unstable or stable oscillatory states. Embracing this perspective, we explore the consequences of network manipulations to understand some of the brain's dysfunctions, as well as network effects that offer new insights into routes towards therapy, recovery and brain repair. These collective insights will be at the core of a new computational environment, the Virtual Brain, which will allow flexible incorporation of empirical data constraining the brain models to integrate, unify and predict network responses to incipient pathological processes.

Key words

Virtual brain • Connectivity • Dynamics • Space-time structure • Network modeling • Brain damage

Introduction

An increasing body of research indicates that "network dysfunction" in the cortex – a disturbance in key, distributed forms of information processing – is the final common pathway mediating between a myriad of underlying incipient molecular and neuronal pathologies and their varied clinical expression. At the same time, compensatory network dynamics should underlie clinical recovery, either through the natural history of a remitting disorder or through specific clinical interventions. Numerous lines of clinical evidence support the network basis of brain function, dysfunction, and repair. Classic studies have documented that the perturbation of a single brain region or node can affect the network as a whole (Hughlings Jackson, 1884; von Monakow, 1911). Whether the manipulation of certain network parameters enables the restoration of brain function remains to be demonstrated. Our primary goal in this

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article is to provide a firm theoretical basis for the idea that manipulation of network parameters may be useful for the recovery of brain function. Any successes in this domain stand to have an enormous impact to the field of neuroscience. The work discussed here summarizes our scientific objective and the network approach that we take as a group.

Large-scale brain network models refer to mathematical and computational models that have spatiotemporal characteristics typically not encountered in the more traditional neural network literature. The network nodes represent brain regions, which incorporate a realistic computational model of their internal dynamics. The network links between brain regions represent interregional pathways that convey neuronal signals, not instantaneously but with a finite transmission speed. The resultant time delay may often be negligible in intraregional networks, but not on larger scales involving multiple brain regions. Large-scale brain networks are well suited to describe the generation of spatiotemporal activity patterns observable in scalp topographies such as EEG and MEG, as well as the BOLD signal. With only a few notable exceptions discussed below, most extant brain network models do not explicitly use a biologically realistic connectivity matrix derived from empirical measurements of anatomical pathways, but make generic simplifying assumptions about the topology, density and range of the underlying large scale connectivity (Jirsa and Haken, 1996; Robinson et al., 1997; Breakspear et al., 2004). Model-driven multimodal integration has not been often attempted either, though some recent examples link neuronal activity (local field potential and firing rate of neural masses) to EEG/MEG (see for instance Jirsa et al., 2002; Valdes-Sosa et al., 2009).

As a first step, a series of large-scale models has explored the spatiotemporal dynamics that arise on an anatomically based cortical model. The emphasis has been on intrinsic dynamics rather than those resulting from stimulus-evoked processing. A large body of empirical work has shown that spontaneous brain activity during wakeful rest is not purely random but rather displays detailed spatiotemporal structure, which includes the slow fluctuating spatiotemporal patterns observed in the fMRI BOLD signal (Biswal et al., 1995) and the rapid fluctuations in electrical activity observable in EEG and MEG (e.g. Lehmann, 1971; Breakspear et al., 2004). Understanding how this activity emerges in the absence of an externally imposed task is not a trivial problem. In complex dynamical systems like the brain, the collective result of system-wide dynamics is difficult to predict even with near-perfect knowledge of all major contributing factors (e.g., cortical-cortical connectivity, local cortical dynamics, and intracortical connectivity). Across time scales usually considered in fMRI, the patterning of resting state networks appears largely dependent on anatomical connectivity, although it is less constrained on the faster time scales of EEG. Both modeling and empirical work illustrate that anatomical connections enable functional connections to emerge, but that there are a number of possible functional connectivity patterns that can be expressed around the same anatomical skeleton. Beyond connectivity, the dynamics of this global pattern are also shaped by other factors including the local dynamics of the brain regions, signal transmission delays, and noise. In the following, we review recent progress in each of these fields.

Quantitative analysis of structural and functional brain networks

Recent methodological advances, especially in the application of whole-brain noninvasive neuroimaging approaches, have revealed the architecture of structural and functional brain networks in unprecedented detail. Diffusion imaging and tractography allow the comprehensive mapping of inter-regional pathways (Johansen-Berg and Behrens, 2009) and resting-state fMRI has demonstrated that spontaneous neural activity exhibits characteristic spatiotemporal patterns (Fox and Raichle, 2007). A key issue for systems and cognitive neuroscience concerns the relation between structural and functional networks – how does the anatomy of the brain shape and constrain dynamic interactions, and how do these interactions in turn mold the efficacy and strength of structural links? Moreover, what are the implications of these relationships for fluctuating cognitive processes, including sensory integration, attention and consciousness?

An important set of tools for the analysis of brain networks is provided by graph theory, the quantita-

tive study of complex networks, composed of sets of nodes and edges (Bullmore and Sporns, 2009). Numerous graph metrics are available, roughly classifiable into measures that assess the degree of local ordering, global communication, and regional participation, which we refer to as measures of segregation, integration and influence, respectively (Rubinov and Sporns, 2010). Measures of *segregation* capture the degree to which the network's nodes are clustered together, forming densely connected communities (modules) that are more weakly interconnected amongst each other. Community detection is of special relevance because structural and functional modules are often found to coincide with sets of brain regions and pathways that are functionally related – they often form known sensory or motor systems or jointly participate in a particular task domain (e.g. Dosenbach et al., 2007). Measures of global *integration* assess the capacity of the network to exchange information. Integration is facilitated by a preponderance of short paths between pairs of nodes, which defines the global "communication distance" across the network. Integration can be measured by computing the average length of the shortest paths, or by deriving a closely related (essentially inverse) measure of global *efficiency*. Measures of *influence* quantify the centrality of individual nodes (or edges), for example with respect to the overall exchange of information across the network. Graph metrics have been shown to be robust and reliable across multiple imaging runs (Deuker et al., 2009), although their numerical values are greatly dependent on the partitioning scheme used to define nodes and edges (Zalesky et al., 2009). Additional advantages are that they can be applied to networks derived from anatomical as well as physiological data, and can be compared across imaging modalities, individual subjects or clinical conditions. The application of graph-theoretical methods to human brain data sets has already demonstrated that structural and functional networks have characteristic, nonrandom attributes. Large-scale structural networks derived from DTI or DSI measurements exhibit a high propensity for clustering of nodes into structural modules, coupled with a high capacity for global information flow, the hallmarks of a small-world organization (Hagmann et al., 2007, 2008; Iturria-Medina et al., 2008; Gong et al., 2009). Modules are coupled via hub nodes, representing highly connected and highly central regions of the brain. These regions are located primarily within the parietal and frontal lobes of the cerebral cortex, and aggregated to form a prominent posteromedial core (Hagmann et al., 2008). Large-scale functional networks exhibit a similar organization, with several studies documenting functional clusters or modules (He et al., 2009), highly connected hub nodes (Buckner et al., 2009), and high efficiency (Bassett et al., 2009). Both structural and functional networks appear to be organized on several hierarchically nested scales (e.g. Meunier et al., 2009, Basset et al., 2010), with modules that are composed of smaller modules, a type of organization that may have deep implications for the complexity of neural dynamics. While graph theoretical tools have now been widely employed in the human brain, it should be noted that the interpretation of graph metrics in the context of neuroscience sensitively depends on the choice of nodes and edges (Rubinov and Sporns, 2010). In general, graph metrics are more easily interpreted in structural networks, where potential causal paths of information exchange can be unambiguously identified, while path-based metrics may yield spurious results in functional networks, particularly those based on pair-wise cross-correlation (e.g. Muskulus et al., 2009).

An exciting prospect, and one that is directly relevant to the main topic of this article, is the use of graph-based approaches to investigate the relationship of structural to functional networks. This can be carried out within a neurocomputational model (Honey et al., 2007; Ghosh et al., 2008; Deco et al., 2009), where the structural coupling matrix is known and functional networks are derived from spontaneous or evoked dynamics, or by comparing imaging data that records structural and functional connectivity from the same set of human subjects (Honey et al., 2009). The availability of empirical data on both structural and functional connectivity allows an investigation of how much of the dynamic pattern of functional connectivity can be predicted from the underlying anatomy (Honey et al., 2010). Computational models of functional connectivity can reconstitute patterns of empirically derived functional couplings between brain regions to a significant extent (Fig. 1). While these results argue for a major role of the anatomy in shaping functional interactions, they should be viewed as indicative of

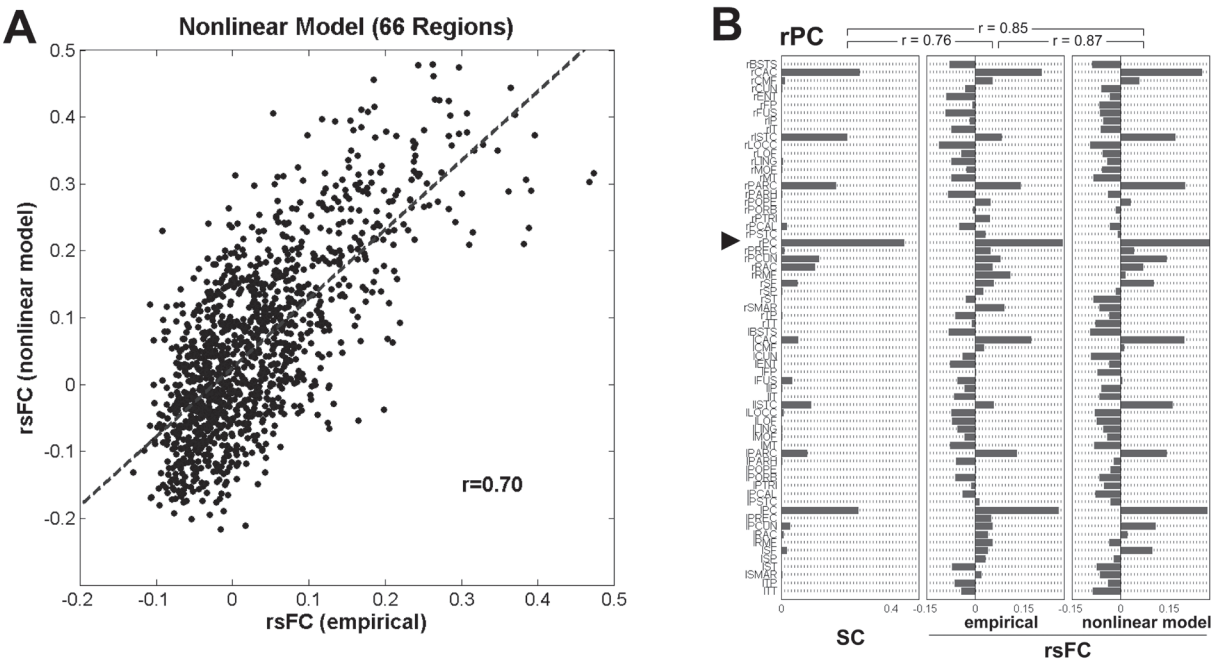

Fig. 1. - (A) Scatter plot of functional connectivity between 66 cortical regions covering both cerebral hemispheres derived from a set of empirical observations of resting-state fMRI ("rsFC empirical") and from a computational neural mass model ("rsFC nonlinear model"). The correlation between empirical and modeled functional connectivity is strong and highly significant ($r = 0.70$, $p < 0.001$). (B) Connection profiles for structural connectivity ("SC") as well as empirical and modeled functional connectivity ("rsFC") for a single region, the posterior cingulate cortex in the right hemisphere. Note the high correlation between all three profiles. Data replotted from Honey et al. (2009).

a dynamic, not a static, relationship. Modeling studies, reviewed in more detail below, clearly demonstrate that functional connectivity is constrained but not rigidly determined by the topology of anatomical linkages, and that functional connections form a rich repertoire of actual or potential couplings that greatly expands upon the relatively limited set of direct anatomical connections. The richness and diversity of functional connectivity is a major challenge for our understanding of structure-function relationships in the human brain.

Principles of multiscale modeling in brain networks

Empirical research motivates a computational approach that is mindful of the presence of repeating patterns of structural (Nunez, 1997) and topological (Meunier et al., 2009; Basset, 2010) principles of organization across a recursive hierarchy of spatial and temporal scales. In this regards, computational neuroscience may have much to benefit from the physical sciences, where multiscale dynamics have been identified and studied in a variety of complex systems – particularly in the field of "critical phenomena" (Amit and Martin-Mayor, 1984).

One can identify three potential approaches to this challenge. The first approach parallels that taken in the physical sciences, by explicitly employing a unifying multiscale framework (Breakspear and Stam, 2005; Fusi et al., 2005; Kiebel et al., 2008). That is, a recursive set of scale-specific governing equations are specified, with a single underlying rule that links each scale iteratively with the next. In physical settings, such as fluid turbulence and magnetization, this has been seamlessly achieved within an elegant mathematical framework called the "renormalization approach" whereby a single scaling operation, the *renormalization group*, can be identified and written down (Wegner and Houghton, 1973). Critical phenomena, such as phase transitions and spatiotemporal chaos, occur when this scaling factor is close to unity – implying self-affinity amongst the tiers of the hierarchy. A phase transition towards macroscopic phenomena and large-scale correlations occurs rela-

tively rapidly (as in the onset of magnetization) if, under the action of a tuning parameter, the scaling factor passes from below to above unity quickly. Conversely near-criticality may robustly occur if the scaling factor is close to unity in a broad region of parameter space. This may be of special significance in neural systems, where evidence for criticality has been observed in *in vitro* tissue culture (Beggs and Plenz, 2003), as well as *in vivo* in primate cortical activity (Petermann et al., 2009). Furthermore, evidence of strong large-scale correlations has been reported in human resting state brain rhythms (Freyer et al., 2009). Similarities to the formal renormalization approach appear in multiscale neuronal models in both the spatial (Breakspear and Stam, 2005) and temporal (Fusi et al., 2005; Kiebel et al., 2008) domains although they differ in the degree to which they have been explicitly mapped onto neuronal substrates. For example, Fusi et al. (2005) appeal to synaptic processes occurring over different time scales, whereas Kiebel et al. (2008) propose a mapping between time scales and bottom-up anatomical substrates of the human cortex.

In complex physical systems (such as turbulence) spatiotemporal structures emerge dynamically from a substrate (such as water) that has no macroscopic structure in the absence of an energy flux. In contrast, different scales of the cortical hierarchy arguably do have scale-specific rules of organization which exist, to varying degree, alongside the dynamics which they support. This challenges the notion of a single multiscale framework for brain dynamics. A more pragmatic approach to the preceding one might be termed the "multiscale minded" approach and is embodied in many large-scale models of the human brain (Deco et al., 2008; Breakspear et al., 2010). By this, we mean modelling approaches that engage brain dynamics predominantly at one particular scale, but are nonetheless cognizant of processes at adjacent finer and/or coarser scales. An overarching principle is the technique of scaling up from small to large-scales not by brute force, but rather by dimension reduction techniques – such as the mean field approximation – that allows details at one scale to be embodied in fewer degrees of complexity at the next (for review, see Deco et al. 2008; Breakspear and Knock, 2008). In this way, processes at small scales – such as the time scales of dendritic filtering – can nonetheless enter as parameters at coarse scales (e.g. Robinson et al., 2004). Similarly, we advance the notion of "digging down" from coarse to finer scales by adding specific details – such as synaptic plasticity – in order to test specific hypotheses – such as their contribution to dynamic neuronal assemblies in cortical-like ensembles (Rubinov et al., 2010). In this way, no particular scale is afforded a privileged status but rather multiple scales are seen to operate in a mutually interdependent manner. Moreover, depending on the exact requirements, computational loads for model implementation are relatively light, ranging from what could be deployed on a laptop computer, to something that may require several days on a modest server, allowing a rapid exchange between theory, experiment and hypothesis.

What are the implications if the multiscale nature of brain dynamics is not considered? The answer to this question may be found in the outcome of the various large projects that are premised in a third approach towards models of large-scale neuronal systems that may be termed the "brute force" approach – that is of building very large computational ensembles of spiking neurons. For example, the "Blue Brain" project aims to incorporate the detailed three-dimensional morphology of individual neurons, their ion channel composition, the distributions and electrical properties of different neuronal classes and their relative proportions into detailed models of neuronal microcircuitry (Markram, 2006). These detailed microcircuits are then considered the elementary building blocks of increasingly larger – but *not* coarser – scale models, as computational resources permit. The lack of an explicit multiscale architecture entails several drawbacks. These models are extraordinarily difficult to implement, requiring advanced supercomputing, and their output can be difficult to interpret as the complexity of the model approaches the complexity of the brain itself.

These three approaches are outlined in Fig. 2. At this stage, we propose that the principles exemplified in the second approach represent the optimal trade-off between complexity and tractability. Crucially, their very abstraction – which some may regard as a compromise – provides the key mechanism for testing scale-specific hypotheses concerning neurobiological mechanisms. That is, the presence or absence of a particular detail in two otherwise identical models allows one to infer, using appropriate model comparison techniques (Friston et al., 2007) precisely whether

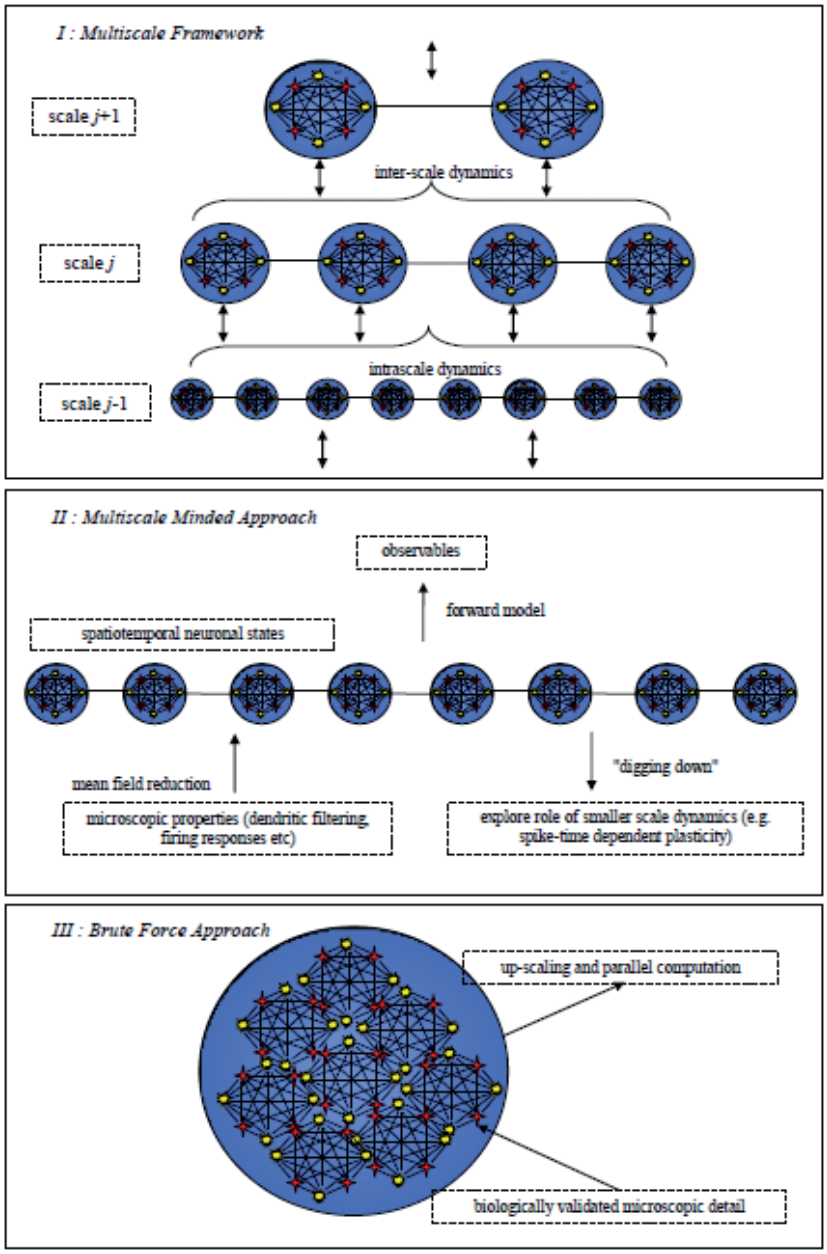

Fig. 2. - Schema of three approaches to dealing with the brain's multiscale complexity: Approach I (multiscale framework) incorporates intra- and inter-scale principles of organization over a hierarchical tier (j = 1, 2,…, N) of dynamics. Approach II (multiscale-minded) takes a pragmatic approach to the dynamics of a particular scale, whilst also incorporating smaller scale processes (left) and also remaining aware of processes at smaller scales that may be lost during the mean field reduction (right). Forward models allow specific such models to be tested with model inversion schemes. Approach III (brute force) incorporates biologically validated information at the microscopic scale of the cell compartment and has the objective of large-scale simulation through massive parallel computation.

that mechanism is required for the observed phenomena of interest. By employing such an approach, together with dimension reduction approaches, one can construct increasingly sophisticated – but not necessarily more complicated – generative and hypothesis-driven models for different data sets.

Spatiotemporal dynamics arising in brain networks

Brain networks are nonlinear spatiotemporal dynamic systems that are characterized by the fact that they are comprised of cortical and subcortical networks.

Due to their spatial separation and finite transmission speeds, communication between brain regions includes time delays, which is in sharp contrast to communication in local networks where these delays are negligible. The coupling between any two regions in a brain network is a function of the connection strength, their symmetry (or direction) and the time delay. These properties are referred to as the *space-time structure* of a given coupling where space refers to the coupling strengths and time to the associated delays. From previous work (Honey et al., 2007; Ghosh et al., 2008a, 2008b; Deco et al., 2009, Cabral et al., unpublished) it appears that the space-time structure of interregional couplings is the crucial component of brain network dynamics, at least as far as resting state dynamics is concerned. When the intrinsic dynamics of a network node is manipulated, the resulting brain network dynamics remains invariant under these changes, whereas manipulations of the space-time structure of the couplings result in profound functional reorganization. For these reasons it is worthwhile to take a closer look at the effects of such manipulations, and to illustrate them with the help of some intuitive examples.

The simplest case of coupling with time delay involves a recurrent connection within a linearly stable neuronal population at rest. Mathematically this is expressed as

$$\dot{x} = -x - \mu x(t - \tau)$$

where x(t) is the time-dependent neural population activity, μ the coupling strength and τ the time delay. When calculating the stability of the rest state of this population, stable and unstable regions are obtained as functions of μ and τ as illustrated in Fig. 3. The stable region of the equilibrium is limited by two curves (the so-called critical lines), to the right by the vertical line at μ = 1 which identifies the onset of a non-oscillatory instability, and to the left by the curved line, which identifies the onset of unstable oscillatory activity. The area in between these lines (traced out by three parallel lines) is the stable rest state of population activity, whereas dynamics outside the rest state are unstable. For this trivial example the space-time structure is just a point in the plane spanned by the coupling strength μ and the time delay τ. Manipulation of the coupling's space-time structure translates to navigation within this plane. If the time delay is negligible (τ = 0), then only variations along the horizontal line are possible

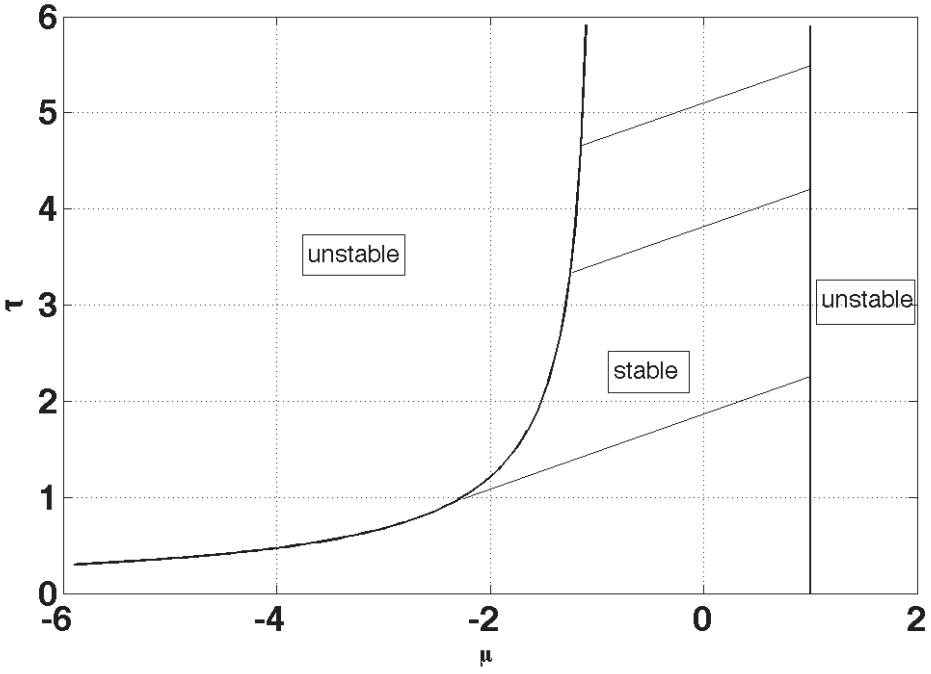

Fig. 3. - Stability diagram of a single neuronal population with delayed self-coupling.

and oscillatory behavior is completely non-existent. The rest state can be left only through a non-oscillatory instability by increasing the coupling strength towards positive (excitatory) values.

The introduction of a time delay enriches the dynamic repertoire and allows for oscillations in the neighborhood of the left critical line for non-zero time delay, that is $\tau = \tau_c$. The frequency ω of the oscillation is given by the coupling strength

$$\omega = \sqrt{\mu^2 - 1}$$

and reflects a network property, specifically the coupling's space-time structure, rather than a property of the neuronal population.

The simplistic scenario of one neural population with a self-coupling may appear artificial. However, it is instructive since the same insights gained here are recovered in the case of two coupled neural populations. Consider two neural populations described by their activities x_1 and x_2, respectively,

$$\dot{x}_1 = -x_1 - \mu_{12} x_2(t - \tau)$$
$$\dot{x}_2 = -x_2 - \mu_{21} x_1(t - \tau)$$

where the coupling strengths are denoted by μ_{12} and μ_{21}. The regions of stability and instability of the resting state are indicated in Fig. 4 as functions of the coupling strengths and the time delay τ. As in the previous situation of one population and self-coupling, we find critical zones defining the borders between stable and unstable régimes. For $\tau = 0$ the critical zone is a line indicating a non-oscillatory instability. When traversing this line from the stable to the unstable region by changing the coupling strengths, the neural population activity begins to grow exponentially, but does not oscillate. When the time delay is introduced, there are critical surfaces, indicated by *SU* in Fig. 4a, showing the critical values of the time delay $\tau = \tau_c$, at which the neural population activity begins to increase in an oscillatory fashion. The oscillation frequency is entirely determined by the network connectivity,

$$\omega = \sqrt{\mu_{12}^2 + \mu_{21}^2 - 1}$$

The critical surfaces in Fig. 4a are two topologically disconnected surfaces. A simpler and more compact representation of this situation is obtained when we calculate the eigenvalue of the connectivity matrix, $\lambda = a + ib$, and display the stability zones as a function of the real and imaginary part of the eigenvalue (see Fig. 4b). Here the more complicated situation with multiple critical surfaces in Fig. 4a translates into one critical surface that converges towards a central cylinder as the time delay τ increases. This manipula-

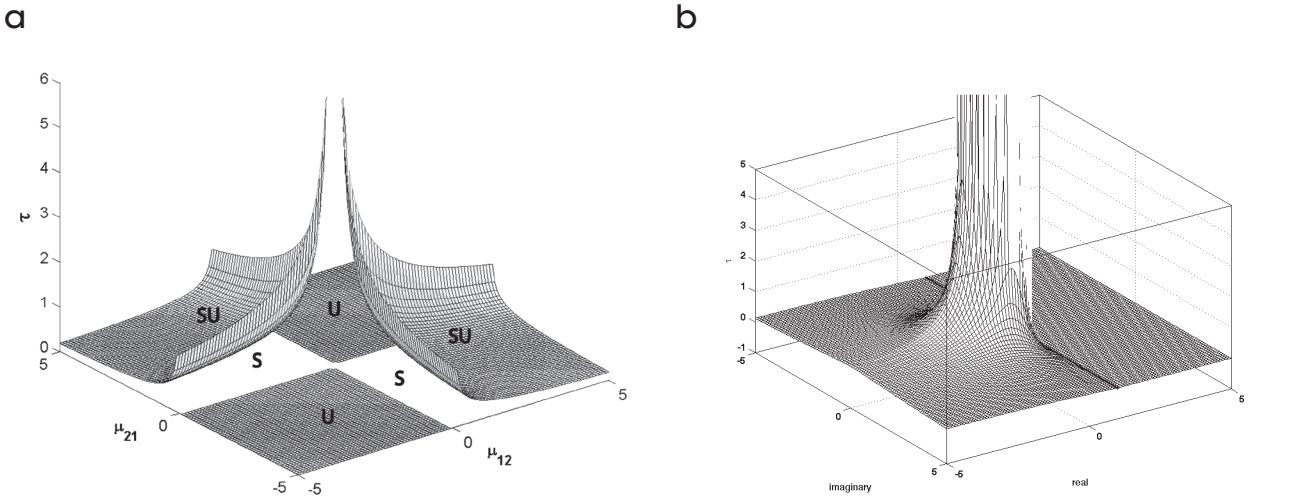

Fig. 4. - Stability diagram of two delay-coupled neural populations. (a) The critical zones are plotted as functions of the coupling weights μ12 and μ21, and the time delay τ. (b) The critical zone is plotted as a function of the real and imaginary part of the eigenvalue of the connectivity matrix, as well as the time delay (see Jirsa and Ding, 2004).

tion illustrates how a well-chosen transformation of the coupling's space-time structure may simplify the system's representation of stability zones.

In the previous paragraphs we have illustrated two of the crucial effects when dealing with the space-time structure of couplings: First, the introduction of time delays into a network enriches the network dynamics and creates behaviors that are absent otherwise; second, when performing appropriate manipulations of the space-time structure, we can generate simplified representations of the network behavior. This latter insight is relevant in the context of restoration of brain function. It suggests that an appropriate metric of the space-time structure of the coupling will allow us to perform informed manipulations thereof with the objective to navigate the brain network dynamics into desirable (that is healthy) parameter régimes.

A concern that arises in this context is the availability of structural connectivity data. The anatomical database Cocomac, developed by Rolf Kötter (Stephan et al., 2001; Kötter, 2004) is unique in the sense that it contains directed connectivity data, whereas due to the nature of the measurements DTI/DSI provides us only with non-directed estimates of anatomical connections. Does the absence of directed connectivity in these latter matrices pose a problem for the investigations of the space-time structure of coupling? To put it differently, what constraints does the artificial symmetry in the connectivity matrix as introduced by DTI/DSI impose? Knock et al. (2009) discussed the symmetry breaking effects of connectivity by means of a direct comparison of the functional organization between Cocomac and DSI-based connectivity data. In the following, we summarize the insights pertaining to the use of symmetric and asymmetric connectivity matrices. Reconsider the two neural populations with the coupling strengths μ_{12} and μ_{21} as we discussed above, but now write $\mu_{12} = \mu$ and $\mu_{12} = \mu + \varepsilon$. If $\varepsilon = 0$, then the connectivity matrix is symmetric, else it is asymmetric. The stability of the rest state of the network of two populations with no time delay is actually determined by the condition

$$-1 \pm \sqrt{\mu(\mu + \epsilon)} < 0$$

When the degree of asymmetry is sufficiently small, $\varepsilon \ll \mu$, then this condition can be approximated by

$$-1 \pm (\mu + \epsilon/2) < 0$$

which essentially expresses the fact that the critical surfaces defining the borders of the stability régimes remain intact but may be deformed by minor changes on the scale of ε. This result generalizes to the situation in networks when one common time delay is considered (Jirsa and Ding, 2004). In other words, we can infer that the connectivity information provided by DTI/DSI will be sufficient to reconstruct the real brain network dynamics faithfully, if the degree of asymmetry expressed by ε is small. This situation will radically change though, if ε is large. The eigenvalues of the connectivity matrix read

$$\lambda = \pm\sqrt{\mu(\mu + \epsilon)}$$

which become imaginary for sufficiently large and negative ε and thus may introduce novel oscillatory phenomena that are entirely absent for symmetric connectivity. In particular the oscillation frequency will scale linearly with the square root of the degree of asymmetry,

$$\omega = \sqrt{\epsilon}.$$

In real world situations, the space-time structure of the couplings has a significantly higher degree of complexity (see Fig. 5), but the functional consequences introduced by the presence of time delays and symmetry breaking are all present.

To more fully understand the rich spatiotemporal patterns of brain network dynamics, novel metrics operating directly on the space-time structure of the couplings are needed. The decomposition of the connectivity matrix into its eigenvectors and eigenvalues is just one means of manipulating these structures. Others, taking into account the complexity of the connectivity, still need to be developed. The creation of such metrics and representations will allow us to better navigate the complex dynamic landscapes which contain the critical curves and surfaces separating stable and unstable types of behaviors. The active manipulation of these dynamic ingredients will be a key component to enable the development of novel routes of brain regeneration and repair.

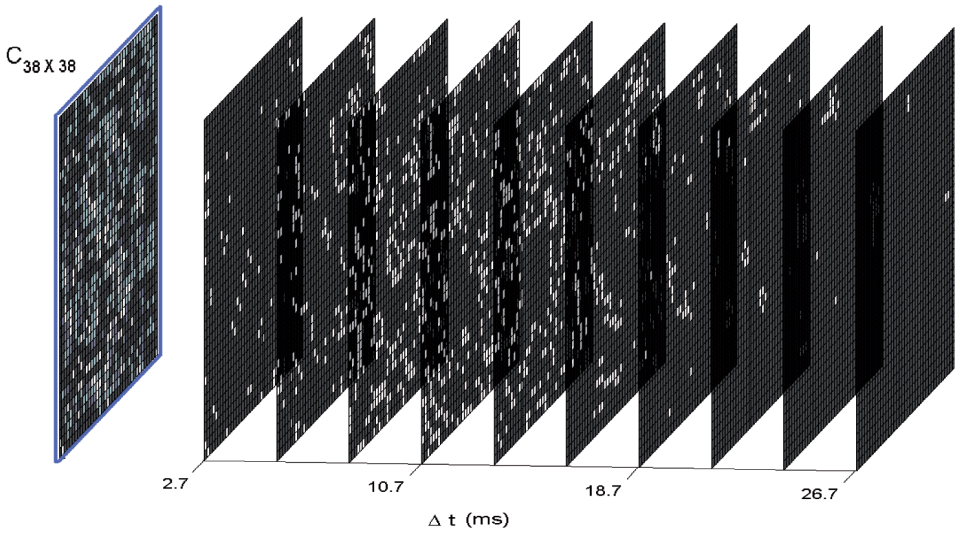

Fig. 5. - Space-time structure of the couplings of a 38-node network obtained from the Cocomac database (replotted from Ghosh et al., 2008). We illustrate the distribution of connection weights in the space spanned by the two areas connected and the time delay involved. This space-time structure of couplings has been used by Ghosh et al. (2008) and Deco et al. (2009). The grey scale code indicates the strength of connections ranging from weakest (white) to strongest (black) connection. For a velocity of 1 m/s the mean time delay is around 70 ms, which represents a lower estimate, because the distances used to compute the delay between two nodes are taken to be the Euclidean distances in physical space. The projection of the elements in the space-time structure to the plane with time delay equal to zero is shown to the left. Figure adapted from Ghosh et al., 2008.

Noise in brain networks

Brain activity exhibits a high degree of variability in the course of resting and task-evoked activity, and both within and between individual behavioral trials. The challenging question is: are these fluctuations just an inevitable side-effect of the neuronal substrate without playing any computational role or do they have functional relevance? Historically, brain functions were thought of as primarily involving feedforward information processing that generates behavior from the ground up by transformations of sensory, cognitive, and motor representations (Hubel and Wiesel, 1968; Barlow, 1990). In this framework, intrinsic spontaneous activity can only reflect noise. Alternatively, one can conceive the brain as not just a passive sensorimotor analyzer driven by sensory information, but as a system that actively generates and maintains predictions about forthcoming sensory stimuli, cognitive states and actions (Llinas et al., 1998; Varela et al., 2001; Engel et al., 2001; Friston, 2002). This class of models emphasizes the role of spontaneous ongoing activity in maintaining active representations that are modulated rather than determined by sensory information. Accordingly, in this case, spontaneous ongoing activity does not reflect trivial noisy fluctuations, but on the contrary, the spontaneous ongoing activity is shaped and organized by the noise into structured spatiotemporal profiles that reflect the functional architecture of the brain, possibly encode traces of previous behavior, or even predict future decisions.

Furthermore, experimental and theoretical evidence reveal that the spontaneous ongoing activity of local cortical circuits result from a global balance between excitatory and inhibitory synaptic currents. Experimental observations *in vitro* (Shu et al., 2003) as well as *in vivo* (Haider et al., 2006) demonstrate an ongoing temporal evolution between excitation and inhibition, which exhibits remarkable proportionality within and across neurons in active local networks. Theoretical studies (Amit and Brunel, 1997; Brunel and Wang, 2001) indicate that this global balance between excitation and inhibition is in fact beneficial for sustaining a stable spontaneous state and even more it may allow for rapid transitions between relatively stable network states, permitting the modulation of neuronal responsiveness

in a behaviorally relevant manner. One classical example is attention: a balanced network is particular suitable for biased competition (Rolls and Deco, 2002; Deco and Rolls, 2005), i.e. it is particularly sensitive for amplifying the rate modulation of weak external bottom-up or top-down attentional biases.

At the level of global cortical circuits, it would be relevant for behavior if the global network of cortical and subcortical areas would show a similar dynamical balance, which would also allow a particular sensitivity for permitting rapid transitions between stable global network states associated with cognitive functions. During the last decade, a large number of experimental investigations have been focused on the characterization and study of the global spontaneous brain activity during rest (i.e. intrinsic, and not stimuli- or task-evoked) (Biswal et al., 1995; Arieli et al., 1996; Shulman et al., 1997; Gusnard and Raichle, 2001; Raichle and Mintun, 2006). These results suggest that the brain is indeed organized into a finite number of distinct oscillating resting state networks that then become coordinated during task conditions.

Under resting state conditions, the brain shows global dynamics that can emerge due to its intrinsic characteristics, uncontaminated by the immediate influence of tasks and stimuli. These intrinsic characteristics are given by the underlying neuroanatomical connectivity matrix, by the temporal delays in the communications between different brain areas, and also by the general level of fluctuations present in each area. Importantly, the balanced dynamical state can produce patterns of anti-correlation in the global dynamics without the use of long range inhibition. The key idea is to associate the patterns of anticorrelation as reported in the fMRI literature with the level of synchronization between different brain regions. In fact, recent theoretical models (Honey et al., 2007; Ghosh et al., 2008; Deco et al., 2009) have shown the relevance of the characteristic "small-world" structure of the underlying connectivity matrix between different brain area, using realistic neuroanatomical information on the macaque cortex (CoCoMac, see Kötter, 2004), as well as between regions of human cortex (Honey et al., 2009). In all these models, the common underlying mechanism is the following: ongoing fluctuations destabilize the groundstate, producing excursions in the dynamical repertoire of the global brain network, and resulting in oscillations (damped or non-damped) similar in structure to those that are experimentally observed in resting state subnetworks (see also McIntosh et al., 2010). In other words, the space-time structure of coupling and time delays in the presence of noise defines a dynamic framework for the emergence of resting brain fluctuations.

These models (Honey et al., 2007; Ghosh et al., 2008; Deco et al., 2009) have also shown how the level of synchronization is directly associated with the BOLD-signal. They demonstrate how fast local dynamics generate the slow 0.1 Hz fluctuations at the global level, thus establishing a specific link between local neuronal communication and global cortical dynamics. Furthermore, patterns of anti-correlation emerge as the result of noise-driven transitions between different multi-stable cluster synchronization states. This multi-stable state emerges in coupled oscillator systems because of the delay transmission times stressing the relevance of the space-time structure of couplings in networks, where the anatomical connectivity captures the spatial component and the transmission time delays the temporal component thereof. For example, in the model of Deco et al. (2009) two clusters of oscillators are shown to exhibit slow fluctuations of their synchrony level and of their BOLD signal (Fig. 6), which are anticorrelated for a range of noise levels (Fig. 7), in line with experimental observations (Fox et al., 2005). Additionally, for an optimal noise level the anticorrelation is maximal, indicating the presence of stochastic resonance, which allows network dynamics to respond with high sensitivity.

We believe that the particular dynamics of the intrinsic properties of the brain are useful for keeping the system in a high-competition state between the different subnetworks that may be used during different tasks. In this way a relatively weak external stimulation is able to stabilize one or the other subnetwork giving rise to evoked activity and stimulus-dependent processing. The anticorrelated fluctuating structure of the subnetwork patterns in the resting state is particularly convenient in this regard. Metaphorically speaking, the resting state is like a tennis player waiting for the service of his opponent. The player is not statically at rest, but rather actively moving making small jumps to the left and to the right, just because in this way, when the fast ball is coming the player can rapidly react.

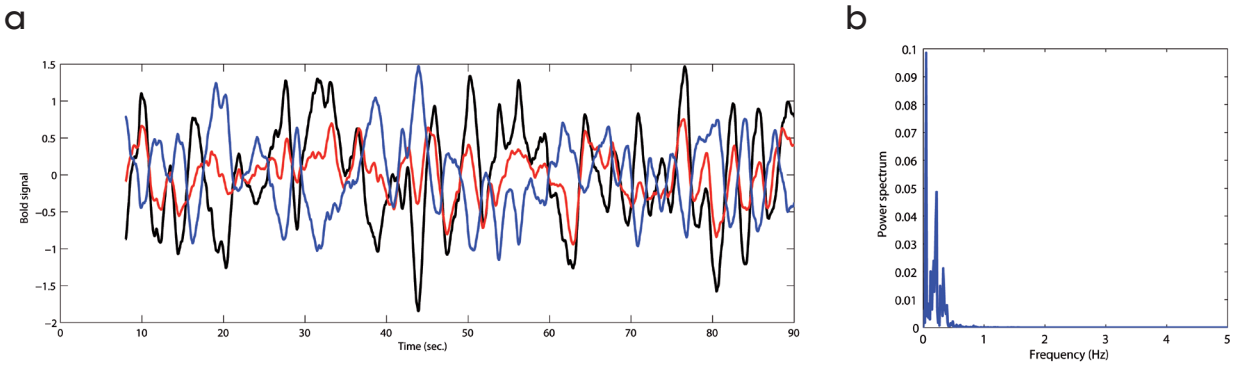

Fig. 6. - BOLD signal analysis. (A) BOLD fluctuations for each community (1: black; 2: red) and for the difference (blue). (B) Power spectrum of the difference in BOLD signal between the two communities. Figure adapted from Deco et al., 2009.

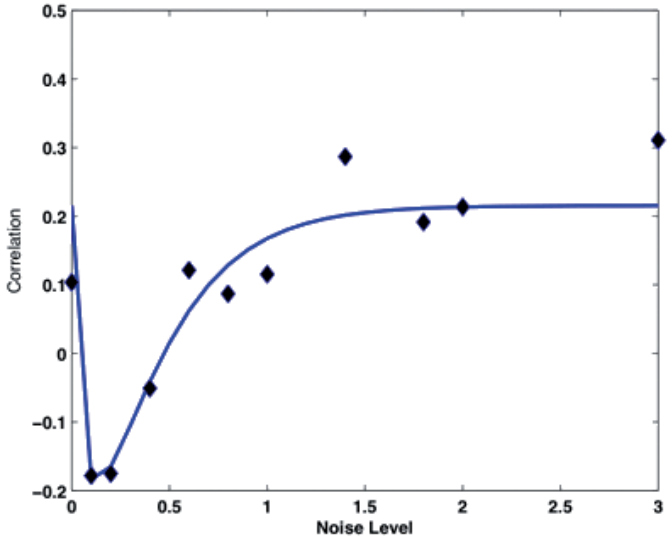

Fig. 7. - Correlation between the level of synchronization of the two network communities versus the level of noise: simulations (points) and nonlinear least-squared fitting using an a-function (curve). Note the stochastic resonance effect: there is an optimal fluctuation level for which both communities are maximally anticorrelated. Figure adapted from Deco et al., 2009.

Thus the active resting state (fluctuating between multistable states) can be sensitive to external signals that will provoke the activation of one of the available multistable states.

Future directions: modeling brain damage and repair

Does the manipulation of the space-time structure of the couplings suggest routes towards brain recovery? One means to answer this question will be through combining lesion studies and a modeling approach. A computational model of the structure and dynamics of the macaque cortex attempted to establish relationships between structural centrality of a lesion site and the functional impact resulting from the lesion (Honey and Sporns, 2008). The structural network consisted of 47 regions of macaque visual and somatomotor cortex and their interconnections, and neural dynamics were simulated with a neural mass model (Breakspear et al., 2003). Lesions of highly connected and highly central hub nodes consistently produced lesion effects that extended far beyond the actual lesion site. The extent of these non-local lesion effects was largely determined by the modularity or

community structure of the underlying structural network. Lesions of highly connected and highly central hub regions had the largest effects on functional connectivity and information flow, while lesions of peripheral nodes had little effect on information flow elsewhere in the network. This model was subsequently extended to the human cortex (Alstott et al., 2009). The structural connectivity matrix (derived from the study of Hagmann et al., 2008) was lesioned in two ways. The first method involved sequential deletion of single nodes, which were selected randomly, or on the basis of high degree or centrality. The structural effect of the lesion on the remaining network was assessed using procedures analogous to other network vulnerability studies (e.g. Barabási and Albert, 1999; Achard et al., 2006). The second method involved the placement of localized lesions around selected central locations defined by a standard brain coordinate. Around this central point, a fixed number of nodes (ROIs) and their attached edges were removed from the structural matrix, and the spontaneous dynamics of the remaining brain were recorded and compared to the dynamic pattern of the intact brain. The functional impact of localized lesions was then quantified by determining the difference between the spontaneous functional connectivity of the intact and lesioned brain. Sequential node deletion revealed that the human brain structural network was resilient to random node deletions and deletion of high-degree nodes, but much less resilient to deletion of high centrality nodes. Localized lesion analysis showed that the centrality of the removed

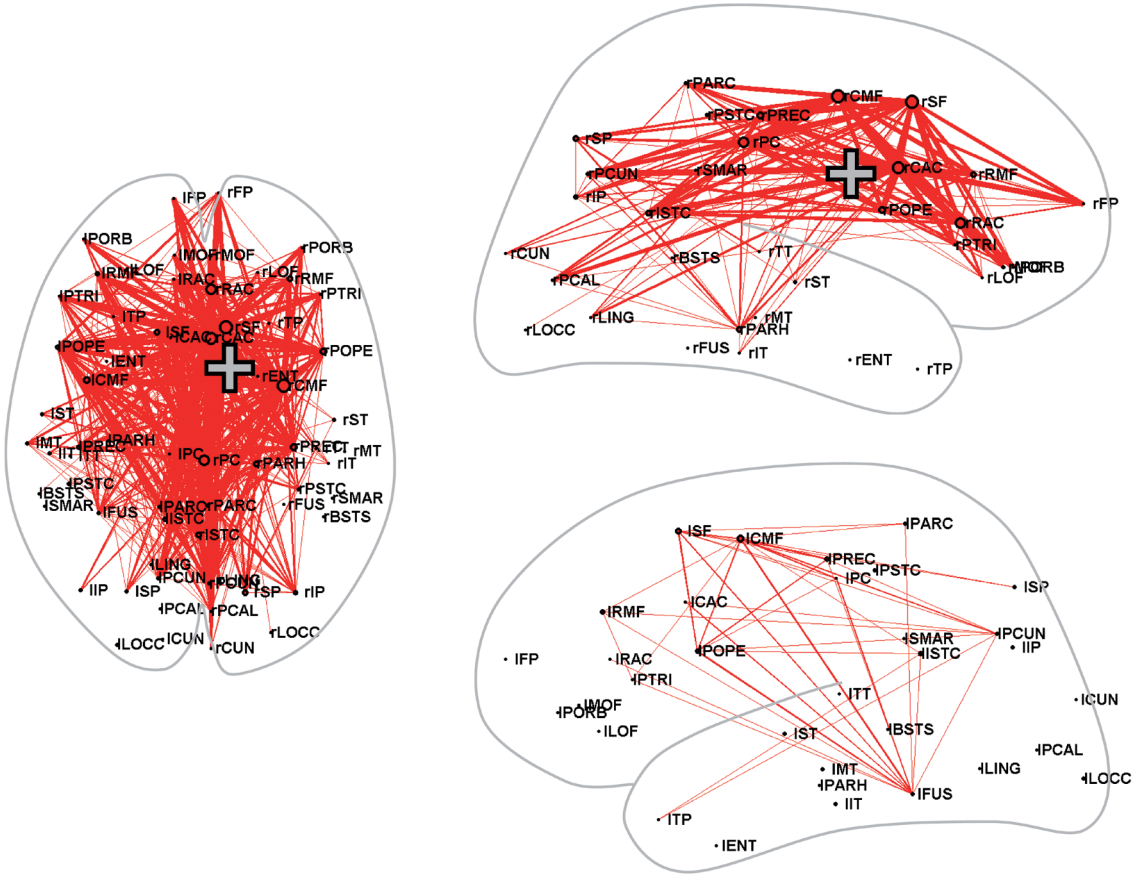

Fig. 8. - Dynamic consequences of lesions in a computational model of the human brain. Lesions were centered approximately at the location of the cross and covered about 5% of the cortical surface around the right hemisphere anterior cingulate cortex. Functional connections across the brain that were significantly changed (increased or decreased) are shown in a dorsal view of the brain (plot on the left) as well as within the left and right hemispheres. Note that the lesion, while limited to only one hemisphere, results in disruptions of functional connectivity in both ipsilateral and contralateral hemispheres, and also results in non-local disruptions of functional connectivity between remote region pairs. Modified from Alstott et al., 2009.

nodes was highly predictive of the functional impact of the lesion. Among the most disruptive were lesions of structures along the cortical midline, including the anterior cingulate cortex (Fig. 8), the posterior cingulate cortex, as well as those in the vicinity of the temporoparietal junction. Lesions of areas in primary sensory and motor cortex had relatively little impact on patterns of functional connectivity.

These initial studies clearly illustrate the differential effects of disrupting the manipulation of the spatial aspects of couplings on the functional organization of brain network dynamics. In light of the prior discussions in this article, other relevant approaches towards the manipulation or control of the brain's functional organization are parameters that enable the communication across dynamic scales (such as time constants on a given scale of organization), time delays and noise characteristics. The latter mechanism is discussed in detail by McIntosh et al (this issue). To what degree can we use the insights gained from these studies to reconstruct or recover a desirable functional organization? A first step towards this goal is certainly the identification of the structural and dynamic components of functional networks that enable high cognitive and behavioral performance. Second, we suggest the hypothesis that a reconstitution of a given specific functional organization, such as the resting state, will represent an important step towards the improvement of the general functional organization, eventually with beneficial behavioral effects. To test this hypothesis, a multilayered research program is needed that allows integrating the components that provided the basis for the brain network models discussed in this article. The models we presented here each have somewhat different structural bases (e.g., CoCoMac vs. DSI connectivity) and generators for the neural dynamics (e.g., chaotic vs. Wilson-Cowan oscillators). By merging these ingredients in a single computational platform, we will be able to assess the impact of parametric manipulations across a range of models. An important development that comes from such a platform is the capacity to incorporate different empirical data into the model. Since the model itself can generate EEG, MEG and fMRI BOLD data, these same data acquired from empirical sources can act as hard constraints for the types of signals the model must generate. In addition, the model would be able to incorporate structural information obtained from classical anatomy or noninvasive neuroimaging, as well as the implementation of multiple experimental paradigms besides the resting state. Providing such a link between empirical data and the computational platforms opens a completely new avenue of research.

In essence, what we are moving towards is a Virtual Brain that embodies the critical principles that we propose as enabling large-scale neocortical dynamics and acts as a means to merge structural and functional data. The informatics challenge is formidable, but not unattainable. There are numerous efforts that have amassed large imaging data sets, and made use of these data for population level studies of brain structure (http://www.brain-child.org/). Similar efforts exist for functional data (e.g. http://nbirn.net/research/function/index.shtm, http://www.nitrc.org/projects/fcon_1000/), and correlated structural, functional and behavioral data will soon become available in the course of the Human Connectome Project. The critical innovation for us is that the Virtual Brain becomes the mechanism to take these data and integrate them into a single synthetic brain. From a population average, the Virtual Brain can generate functional data that can be analyzed with exactly the same tools that are typically used for experimental data. Moreover, the Virtual Brain will be able to incorporate data sets recorded from individual human subjects, allowing insights into how unique features of an individual's brain affect its large-scale neural dynamics. This has profound implications for clinical use, where a single patient's brain can be modeled as an instantiation of the Virtual Brain, enabling a detailed assessment of which parameters most contribute to that person's dysfunction. Finally, the Virtual Brain may be endowed with the capacity to reorganize in the face of experience or in the event of damage or disease. The Virtual Brain thus becomes a laboratory to assess the most effective means by which reorganization and functional recovery can take place through modeling factors that re-establish stable spatiotemporal dynamics. We suggest that, from the perspective of therapeutic intervention and rehabilitation, the potential impact of the Virtual Brain is profound.

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