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The Brain Connectivity Workshops: Moving the frontiers of computational systems neuroscience

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Abstract

Understanding the link between neurobiology and cognition requires that neuroscience moves beyond mere structure-function correlations. An explicit systems perspective is needed in which putative mechanisms of how brain function is constrained by brain structure are mathematically formalized and made accessible for experimental investigation. Such a systems approach critically rests on a better understanding of brain connectivity in its various forms. Since 2002, frontier topics of connectivity and neural system analysis have been discussed in a multidisciplinary annual meeting, the Brain Connectivity Workshop (BCW), bringing together experimentalists and theorists from various fields. This article summarizes some of the main discussions at the two most recent workshops, 2006 at Sendai, Japan, and 2007 at Barcelona, Spain: (i) investigation of cortical micro- & macrocircuits, (ii) models of neural dynamics at multiple scales, (iii) analysis of "resting state" networks, and (iv) linking anatomical to functional connectivity. Finally, we outline some central challenges and research trajectories in computational systems neuroscience for the next years.

Keywords

neural systems analysis; effective connectivity; nonlinear dynamics; fMRI; EEG; MEG; DCM; model comparison; resting state; microcircuits

Introduction

Since the 19th century, many neuroscientific attempts towards understanding the relation between structure and function in the human brain have been focused on assigning particular cognitive functions to distinct brain regions (see Marshall & Fink 2003 for a review). These attempts, grounded epistemologically in analysis[1], have been mostly based on post mortem lesion studies and, more recently, functional neuroimaging and transcranial magnetic

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[1]Here, we refer to *analysis* as the process of splitting a complex phenomenon or system into small parts, each of which is studied in isolation, ignoring interactions or interdependencies among the parts. In contrast, *synthesis* explicitly considers the interactions amongst parts and the resulting collective behaviour, striving for a more complete view of the system.

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stimulation in vivo, creating a large database of isolated structure-function correlations over the years. In contrast, approaches based on principles of synthesis, aiming for formal, mechanistic descriptions of how the behaviour of neuronal systems results from the interactions of their elements, have long played a relatively minor role. This was partially due to lack of suitable methodology, partially due to insufficient crosstalk between experimental and theoretical neuroscientists. Over the last decade, however, explicitly system-based approaches have become a very important research agenda in neuroscience. It is now a widely held notion that understanding structure-function relations requires biologically informed models of neural system dynamics (Friston 1994, 2002; Horwitz et al. 1999; McIntosh 2000; Stephan 2004). It is interesting to note that a very similar change of perspective, away from functional attributions to individual elements and towards mechanistic models of their interactions, has occurred in molecular biology and genetics (Kitano 2002). “Systems biology” is the current buzz word, a trend that revitalises old insights, dating back to the 1940s (see von Bertalanffy 1969), how mechanistic insights into complex biological processes can be obtained, i.e. through formal system modeling (Chong & Ray 2002).

Models of neural system dynamics are very tightly linked to brain connectivity in its various forms (Friston 1994; Horwitz et al. 1999; Stephan 2004). *Structural connectivity*, i.e. the anatomical layout of axons and synaptic connections, determines which neural units can directly interact with each other and thus constrains the system's functional and effective connectivity (Zeki & Shipp 1998). *Functional connectivity* subsumes non-mechanistic descriptions of statistical dependencies between individual system elements, e.g. correlations between time series from different brain regions. In contrast, *effective connectivity* refers to causal effects, i.e. the direct influences that system elements exert on another. Since 2002, frontier topics of connectivity and neural system analysis have been discussed in an annual meeting, the Brain Connectivity Workshop (BCW). To date, workshops have been held in Düsseldorf 2002 (organisers: Rolf Kötter and Karl Friston[2]), Cambridge 2003 (Ed Bullmore, Lee Harrison, Lucy Lee, Andrea Mechelli and Karl Friston), Havana 2004 (Pedro Valdés-Sosa and Rolf Kötter), Boca Raton 2005 (Viktor Jirsa and Anthony Randal McIntosh), Sendai 2006 (Jorge Riera and Karl Friston) and Barcelona 2007 (Gustavo Deco, Viktor Jirsa and Barry Horwitz). Covering a wide spectrum of experimental and computational methods and following a strongly discussion-oriented format, the BCW has established itself as an important forum for multidisciplinary approaches to neural system analysis. It has successfully stimulated international collaborations amongst various laboratories from theoretical and experimental disciplines. The results of this interdisciplinary crosstalk are becoming increasingly visible in a number of high-profile publications on joint work by workshop attendants from different laboratories and countries (e.g. Breakspear et al. 2006a; Honey et al. 2007; Lee et al. 2006; Sporns & Kötter 2004)[3].

This article reviews key discussions at the two most recent workshops in Sendai 2006 and Barcelona 2007. It focuses on four topics of which the first two were discussed at Sendai and the latter two were discussed at Barcelona: (i) investigation of cortical micro- & macrocircuits, (ii) models of neural dynamics at multiple scales, (iii) analysis of “resting state” networks, and (iv) linking anatomical to functional connectivity. Please note that due to the large number of different workshop sessions, this choice is necessarily subjective and cannot cover the entire breadth of topics discussed at the two workshops. Furthermore, given space constraints, we cannot provide an exhaustive review of all presentations but are

[2]For reports on the inaugural meeting see Lee et al. 2003; Ramnani et al. 2002; Stone & Kötter 2002.
[3]Additional important publications have resulted from these workshops: a special issue in the journal Neuroinformatics (Bullmore et al. 2004), a theme issue in the Philosophical Transations of the Royal Society (Valdes-Sosa et al. 2005), and a handbook on brain connectivity (Jirsa & McIntosh 2007).

required to focus on a few representative examples. Finally, we outline some challenges and central research trajectories in computational systems neuroscience for the future. For further details, the reader is referred to a series of forthcoming review papers about the micro-architecture of the cerebral cortex and its impact on functional neuroimaging (Riera et al. 2008), and on dynamic systems theory and its applications to neuroscience (Deco et al. 2008).

Cortical micro- and macrocircuits

Understanding the statistics of cortical connections at different spatial scales (e.g. long-range axonal connections and local micro-circuits with their complicated laminar and columnar organization) is a prerequisite for building realistic system models of neuronal network dynamics. Following the pioneering study by Felleman and Van Essen (1991), a series of database projects and large-scale analyses have significantly enhanced our knowledge of the principles underlying anatomical connectivity patterns. The challenge is not simply a lack of data: for example, several large-scale databases exist for connections in several species (e.g. human, monkey, rodent) and at two different physical scales (i.e. microscopic and long-distance connections) (e.g. Bota et al. 2005; Burns et al. 2006; Scannell et al., 1999; Stephan et al., 2001; Muhammad and Markram, 2005). Instead, the major problem is to understand the organizational principles underlying the enormous complexity of structural connectivity patterns, both at the level of microcircuitry, i.e. connections linking different neuronal populations within a brain region, and at the level of long-distance inter-regional connections. How do we best analyze the available data, fill critical gaps in our present knowledge by means of new experimental techniques, relate intra-areal microcircuits to inter-areal connections and derive functional implications from the connectional architecture of the brain? These questions were addressed by several presenters at the Sendai workshop.

Gilad Silberberg (Karolinska Institute, Sweden) presented combined anatomical and electrophysiological analyses of cortical layer V, elucidating one particular link between local microcircuitry and long-distance inputs: Pyramidal cells activate neighboring inhibitory Martinotti cells which, in return, target and reduce the excitability of the distal parts of the pyramidal dendrites, which receive a large proportion of glutamatergic long-distance inputs from other cortical regions. Critically, this feedback inhibition is frequency-dependent due to strong synaptic facilitation of the pyramidal-to-Martinotti connections. This mechanism ensures tight control over local excitatory-inhibitory balance and regulates to what degree local columnar processing is influenced by long-distance inputs (Silberberg & Markram 2007).

Another mechanism for controlling the balance between excitation and inhibition and for modulating oscillations in larger networks might be based on electrical synapses via gap-junctions; these could play an important role in promoting synchronous activity between GABAergic interneurons (Gibson et al., 2005). This mechanism was addressed by Roger Traub (State University of New York, USA) who discussed the impact that gap junctions, which have been found between axons and dendrites of different neuronal cell types in the hippocampus (Hamzei-Sichani et al. 2007), have on oscillatory network behaviour in the hippocampus, particularly with regard to gamma frequency (30-80Hz) oscillations and “ultrafast” (>80Hz) oscillations (Traub et al. 2004). He emphasized that our understanding of how gap junctions influence network dynamics is still in its infancy and that further work will be needed, both concerning experimental identification of gap junctions in the cortex, and system models for understanding their functional role. The experimental characterization of gap junctions will require a combination of neuroanatomical methods (e.g. electron microscopy) and physiological techniques.

The necessity of multi-methods approaches for understanding neuronal circuits was also stressed by Kathleen Rockland (RIKEN Brain Science Institute, Japan) who presented anatomical data from single axon analyses in visual cortex based on tracing techniques and light microscopy. She highlighted the complexity of long-range axons and pointed out that we currently have very little data on the geometry of axonal configurations and their postsynaptic targets. Progress in these areas is urgently needed and requires application of sophisticated anatomical tracing techniques combined with physiological methods for neuron-specific manipulations, for example genetically targeted optical control of neuron-specific activity (Boyden et al. 2005).

David Van Essen (Washington University, St Louis, USA) shifted the focus to the level of inter-areal connections. He presented several neuroinformatics developments, e.g. the PALS-B12 human cortical atlas (Van Essen & Dierker 2007), which enable a wide range of analyses of anatomical and functional connectivity data. As an example, he showed neuroinformatics-based analyses that imply a relation between sulcal abnormalities in Williams' syndrome and abnormal inter-areal connectivity (Van Essen et al. 2006). This finding is in accordance with the hypothesis that cortical folding is shaped by the tension induced by axonal long-range connections during neurodevelopment (Van Essen 1997; Hilgetag & Barbas 2006).

Three other speakers pursued the theme of inter-areal connectivity, focusing on the relation between structural connectivity patterns and functional principles. Randy McIntosh (Rotman Institute, Toronto, Canada) used PET data from a sensory learning paradigm (Mcintosh et al. 2003) to define functional networks in subjects who were aware or unaware of the learning process, respectively. These networks were then evaluated with regard to specific computational properties. For this purpose, he used anatomical macaque connectivity data from the CoCoMac database (Stephan et al. 2001), mapped these data to putatively corresponding regions in the human brain (Kötter & Wanke 2005) and then, for each network element, computed network participation indices (NPIs). NPIs are graph-theoretical indices describing how network structure constrains the capacity of each network node for information processing (Kötter & Stephan 2003). His analyses resulted in hypotheses about which inter-areal interactions are critical in this paradigm for becoming aware of the learning process. These hypotheses can be tested experimentally, e.g. using a combination of neuroimaging and transcranial magnetic stimulation (TMS).

Rolf Kötter (University of Nijmegen, The Netherlands) presented another integrated structural-functional analysis. He applied a linear network model to local field potentials (LFPs) that had been recorded from 15 different cortical areas of the macaque monkey during a visual go/no-go task (Bressler et al. 1993). Using stochastic parameter estimation techniques (simulated annealing), he estimated the weights and delays of inter-areal connections in this network and compared the results against anatomical data from the CoCoMac database. Again, this approach resulted in a number of directly testable hypotheses, e.g. which of the currently non-investigated anatomical connections are likely to exist and which of the connections in the network are critical for late components in the LFPs that differentiate “go” and “no-go” conditions.

Olaf Sporns (Indiana University, USA) extended this theme of how to link structural connectivity patterns to specific neurophysiological or cognitive processes one step further. He showed how evolutionary optimization techniques can be used to find structural connectivity patterns that would optimize a range of information-theoretical and computational properties of neurobiological networks (Sporns et al. 2002). An exciting practical application of these techniques is that they can be used to optimize the behavior of robots that interact with their environment (Lungarella & Sporns 2006). Mitsuo Kawato

(ATR Computational Neuroscience Laboratories, Japan) presented a complimentary approach to this issue, showing how one might achieve real time control of robots by online decoding of measurements of human brain activity. This approach is based on hierarchical Bayesian models for decoding information contained in neuroimaging data of different modalities (e.g. fMRI and MEG).

Functional investigation of cortical circuits in the living human brain can only be performed through non-invasive neuroimaging techniques; currently, functional MRI, PET, EEG, MEG and some optical imaging techniques are most widely used. Importantly, these techniques measure neuronal responses only indirectly. For example, fMRI provides hemodynamic signals that represent an indirect index of synaptic activity in neuronal populations but are also influenced by various non-neuronal factors. We must therefore consider more than just the activity of interconnected neurons when trying to infer the function of cortical circuits from neuroimaging measurements. Other cell types (e.g. glia cells, endothelial cells, smooth muscle cells) contribute to the generation of hemodynamic neuroimaging data. Understanding their role is therefore important when formulating generative models[4] of neuroimaging data that can be inverted to infer the neuronal processes that underlie hemodynamic measurements. David Attwell (University College London, UK) discussed experimental evidence that hemodynamic responses do not simply reflect the local metabolic demands of activated neuronal tissue in a “feedback” fashion (Attwell & Iadecola 2002). Instead, they may be better understood as resulting from a “feedforward” system in which glutamate-evoked calcium influx in postsynaptic neurons activates the production and release of vasodilatory agents, including nitric oxide, adenosine and arachidonic acid metabolites (Lauritzen 2005). Together with results from theoretical models indicating that most brain energy is used to power glutamate-induced postsynaptic currents rather than presynaptic or glial activity (Attwell and Laughlin, 2001), he suggested that the BOLD signal most likely reflects the neuronal processing occurring within a brain area (including subthreshold postsynaptic events), rather than the output from or input to that area.

A major challenge for the future is to construct models which combine insights into physiological mechanisms of hemodynamic signal generation with mechanisms linking cortical micro- and macrocircuits to activity patterns. One important development in this direction was introduced by Jorge Riera (Tohoku University, Japan). He presented a stochastic dynamic model for describing the time course of neuronal and vascular mesoscopic variables, as well as their interactions, within a basic cortical unit (Riera et al., 2006). The model was formulated using a state space formalism, enabling the use of classical strategies for state-filtering and parameter estimation from measured data; the feasibility of this approach was demonstrated using concurrent fMRI and EEG recordings (Riera et al., 2007). Overall, this model incorporates data about both the microcircuitry in primary visual cortex and about the physiological mechanisms that underlie vascular responses to changes in neural activity (as discussed above). It thus provides an important convergence of analyses of structural connectivity and physiological mechanisms.

Neural dynamics at multiple scales

Given the overwhelming complexity of the brain, it is mandatory for any neural system model to find a sufficiently parsimonious, and yet neurobiologically plausible, conceptual framework for investigating neuronal dynamics. How can we optimally investigate the

[4]A generative model is a model which describes explicitly how observed data are assumed to have been generated. In a Bayesian framework, for example, a generative model supplies the mathematical form of the likelihood function (including the probability densities of error terms) and the prior densities of the parameters. This enables one to create artificial data by randomly sampling from these densities.

functional coupling between neuronal populations, derive the mechanisms underlying synchronization of oscillatory activity and understand interactions across multiple spatial and temporal scales? These questions, which were elegantly summarized in the opening speeches by the honorary presidents of the Sendai workshop, Ryuta Kawashima and Shun-ichi Amari, are at the heart of systems neuroscience. They can be addressed by three complementary approaches that currently constitute a very active area of research. The first approach focuses on the temporal relationships of oscillatory activity in different brain regions as expressed, for example, in terms of coherence or synchronization. The motivation for this approach is that the connectivity between different neuronal populations may critically rely on coherence: Oscillations of average membrane potential do not only affect the output of the population, but also its sensitivity to input, and therefore only coherently oscillating neuronal groups may be able to interact effectively (Fries 2005). Despite its intuitive appeal, this mechanistic idea is still quite general and is usually tested by applying time-frequency analyses directly to measured signals, e.g. from individual EEG/MEG sensors. In order to test specific instantiations of this idea, one may want to use a parameterized model that represents distinct neurophysiological processes from lower scales that are not directly measured. This is possible with a second approach, neural mass models (NMMs; Freeman 1972), which operate at a mesoscopic spatial scale roughly corresponding to cortical macrocolumns. NMMs represent neuronal populations by the modes of statistical distributions of their relevant neurophysiological properties, e.g. average membrane potential and average firing rate. This approach offers a parsimonious way of parameterizing and scrutinizing the neurophysiology of interacting populations, for example, in terms of the roles of neuronal cell types (pyramidal cells, inhibitory interneurons, etc.) and the properties of their connections (e.g. conduction delays, synaptic weights). Critically, if NMMs are combined with an appropriate forward model of how neural activity is expressed at the level of scalp electrodes, these parameters can even be estimated from empirical data and assessed statistically, using Bayesian inversion (Kiebel et al. 2006) or filtering techniques (Riera et al. 2007). However, other important questions are not easily addressed directly by NMMs. For example, it is not trivial (albeit feasible in an indirect way, see below) to model the effects of neuromodulatory transmitters since the necessary anatomical infrastructure (e.g. transmitter-specific receptors) is below the spatial scale which is represented in NMMs. Questions like these are usually the domain of a third approach that uses large sets of individually modeled neurons which interact. Usually, these are compartmental models of neurons (e.g. integrate-and-fire neurons) which allow one to model quite detailed aspects of neuronal dynamics, e.g. the effect that transmitter-specific ion channels or connections with different synaptic sites in the dendritic tree have on the population dynamics. However, due to the very large number of parameters involved and the strong dependencies between them, it is usually not possible to invert these models (i.e. fit them to empirical data and get meaningful parameter estimates). Instead, they can be used for simulations to generate predictions about the system's behavior in different domains of the parameter space (see, for example, Husain et al. 2004 and Deco et al. 2004).

In practice, the fact that the approaches briefly summarized above operate on different spatial scales of neuronal dynamics[5] means that the choice amongst them depends on the specific scientific question asked. The most interesting challenge perhaps is to find ways of conceptually linking these approaches and bridging the scales, a challenge which was addressed by several presentations at both the Sendai and Barcelona workshop and which we will discuss further in the final section of this paper. For example, at Sendai, Olivier Bertrand (INSERM U280, Lyon, France) reported results from studies which compared the

[5]Note that this classification is not meant to be a rigid one. For example, analyses of oscillatory activity and coherence can also be performed at the microscopic scale, e.g. when applied to local field potentials from single- or multi-unit recordings.

dynamics of oscillatory networks in humans that were measured at different spatial scales, i.e. by means of intracranial EEG and scalp EEG, respectively (Bertrand & Tallon-Baudry 2000). In intracranial recordings of brain responses to visual and auditory stimuli, he found clear evidence for separate oscillatory processes in the beta and gamma bands. Specifically, in his experiments, beta oscillations tended to show desynchronization when evoked responses and gamma oscillations were emerging, sometimes followed by a rebound of activity after gamma oscillations had returned to baseline. In contrast to the intracranial data, detection of these oscillations was much more difficult in scalp recordings with EEG and MEG. This could have been due to the existence of multiple oscillatory generators in the beta and gamma ranges: it may be that only during those periods when the generators are phase-synchronized, a measurable oscillatory signal is found at the scalp level.

Karl Friston (Wellcome Trust Centre for Neuroimaging, London) presented recent developments in Dynamic Causal Modeling (DCM), a general framework for making inferences about processes at the neural level given measured imaging data (see Friston et al. 2003 for the first paper on DCM and Stephan et al. 2007a for a recent review). For EEG/MEG data, for example, DCM is based on a nonlinear NMM of interacting cortical columns consisting of pyramidal cells, inhibitory interneurons and spiny stellate cells (David et al. 2006). This model can be used for investigating a wide range of questions at different spatial and temporal scales. For example, one can probe the role of different neuron types and their connections for oscillatory activity and coherence (David & Friston 2003), the impact of time constants or inter-regional conduction delays on steady-state frequency spectra (Moran et al. 2007b) or the magnitude of synaptic strengths and spike-frequency adaptation during pathophysiological processes (Moran et al. 2007a). By enabling statistical inference about (unobserved) neural processes at small spatial scales, DCM can thus provide mechanistic accounts of spatially large-scale phenomena, measured at the sensor level.

Regardless of the spatio-temporal scale of interest, a central aspect of all models of effective connectivity is the question how causal relationships amongst neuronal populations are best inferred mathematically. For example, DCM uses deterministic delay differential equations whose parameters are estimated from measured data using variational Bayesian inversion (Friston et al. 2007). Two other speakers presented alternative approaches for characterizing effective connectivity. Tohru Ozaki (Institute of Statistical Mathematics, Japan) proposed to use innovation methods to explore causal relations based on a voxel-wise searching strategy. He presented this method in the general context of heteroscedastic state space modelling and filtering techniques. Pedro Valdes-Sosa (Cuban Neuroscience Center, Havana) presented a methodology that involved the use of Granger causality on spatial manifolds. He proposed a multivariate autoregressive model for EEG/fMRI data and based its parameter estimation on a maximization-minorization (MM) algorithm (Valdes-Sosa et al. 2005), using a combination of different penalty functions to ensure a balance between sparseness and smoothness of cortical connectivity.

Michael Breakspear (University of New South Wales, Sydney, Australia) presented a neural field model[6] for multiscale spatio-temporal analyses of human epilepsy data. In the spatial domain, he explored the influence of global (between-population) coupling on local (within-population) dynamics. In the temporal domain, he compared modeling results to EEG data from patients with primary generalized seizures and demonstrated, using bifurcation analysis of the model, how cortical activity at different temporal scales was coupled in a nonlinear and dynamic fashion, leading to potential instabilities and seizures (Breakspear et al. 2006b).

[6]Neural field models are a specific type of NMMs in which the brain is not treated as consisting of discrete units but as a spatial continuum (c.f. Robinson et al. 1997).

Gustavo Deco (University of Barcelona, Spain) presented a model of interacting cortical areas each of which consisted of multiple populations of biophysically realistic integrate-and-fire neurons. Using two complementary analytical approaches, he investigated the neurophysiological mechanisms underlying biased competition during attention (Deco & Rolls 2005) and decision-making (Deco et al. 2007). In an analysis of stationary dynamics, he used a mean-field reduction, effectively treating the model as a NMM, to investigate how different operational regimes of the network depended on the values of various model parameters. Additionally, he investigated the nonstationary dynamic behavior of the neuronal spiking rates, using the full integrate-and-fire model (i.e. numerical integration without any mean-field reduction). Together, these two approaches enabled him to draw some rather fine-grained conclusions. For example, with regard to attention, the model explained why backward connections between cortical areas should be about 2.5 times weaker in strength than the corresponding forward connections. Furthermore, this analysis showed that top-down attentional effects can be explained in terms of shifting the neurons' nonlinear activation function (i.e. firing rate as a function of input current). Thus, the model offered new insights into possible mechanisms of attention, going beyond the classical "biased competition" hypothesis, and showed that attention can be seen as a dynamical process that emerges implicitly from a neuronal multi-attractor network.

This work by Deco and colleagues demonstrates that there are important points of contact between NMMs operating on a mesoscopic scale and biophysically more detailed and fine-grained models, like ensembles of Hodgkin-Huxley or integrate-and-fire neurons. First, as in the example above, NMMs can be derived from a mean field reduction of ensemble activity on a microscopic scale (c.f. Deco et al. 2005; Loh et al. 2007). Second, given a careful parameterization of the model and suitable experimental manipulation, NMMs can be capable of indirectly assessing certain aspects of neuronal dynamics whose structural support is located at a microscopic scale. As an example, Liljenstrom & Hasselmo (1995) and Moran et al. (2007a) have shown how NMMs can be used to indirectly investigate processes at a microscopic level, e.g. how specific changes in neurotransmission alters spike frequency adaptation of neurons. Third, models consisting of large ensembles of biophysically realistic neurons can be used to establish the construct validity of NMMs. For example, Lee et al. (2006) used the detailed biophysical model of Tagamets & Horwitz (1998) to generate synthetic fMRI data; subsequently, they verified that a simple NMM (i.e. DCM) was able to recover the mechanisms by which the data were generated. And finally, as pointed out in the presentation by Karl Friston mentioned above, one of the goals of the ongoing development of DCM is to construct models that bridge mesoscopic and microscopic scales. For example, such models could be based on a simplified variant of the biophysically grounded parameterization of Hodgkin-Huxley or integrate-and-fire models. One of the main challenges will be to find a suitable set of prior densities that eschew problems with parameter interdependencies and model inversion.

Analysis of "resting state" networks

A particular type of network analysis that has become quite fashionable in recent years is to study so-called "resting state" networks by means of fMRI: subjects are instructed to close their eyes and " think of nothing " while whole brain BOLD images are acquired over an extended period. The resulting time series are then low-pass filtered (typically using a threshold of 0.1 Hz) and subjected to various kinds of functional connectivity analyses (e.g. Greicius et al. 2003), ranging from simple seed voxel correlation analyses to eigenimage analysis (using principal component analysis, singular value decomposition or partial least squares) and independent component analysis (ICA). One of the sessions at the Barcelona 2007 workshop was dedicated to resting state fMRI and contrasted this approach with

models of effective connectivity that infer causal relationships within a priori defined networks that are perturbed experimentally.

In an introductory talk to the topic, the pioneer of resting state fMRI, Bharat Biswal (Dept of Radiology, University of New Jersey, USA), provided an overview of what insights into the structure and function, respectively, of brain networks may be gained by resting state fMRI. His initial fMRI study on resting state functional connectivity (Biswal et al. 1995) renewed a previous line of research from PET that investigated inter-regional correlations during rest (Horwitz et al. 1984). Following Biswal's study, numerous resting state fMRI studies have been conducted in both healthy volunteers and patients and resulted in two main findings. First, in many cases, the spatial pattern of correlations in low-frequency BOLD signal fluctuations between two cortical regions appears to be similar to the structural connectivity pattern as known from tract tracing work in primates (e.g. Biswal et al. 1995; Vincent et al. 2007). Second, networks defined by application of eigenimage analysis or ICA to resting state data often resemble networks that one typically observes during specific cognitive, sensory or motor tasks (e.g. Damoiseaux et al. 2006). In other words, they look as if they "recapitulate the functional architecture of responses evoked by experimentally administered tasks" (Vincent et al. 2007). These two topics, the possible relevance of resting state fMRI data for inferring structural and function principles of brain organization, were addressed by two further speakers in this session. With regard to structural insights, Ed Bullmore (Cambridge University, UK) focused on topological features of cortical networks defined by resting state fMRI data (Achard et al. 2006). Applying a discrete wavelet transform to resting state fMRI data and using the results for graph-theoretical analyses, he showed that resting state networks possess a "small world" topology at different temporal scales, expressed most saliently in the low-frequency interval 0.03-0.06 Hz. Following the definition by Watts & Strogatz (1998), networks are said to have "small world" properties if they combine a high clustering index (i.e. high proportion of locally connected clusters) with a short characteristic path length (i.e. the average distance between any two network nodes is low). Such network types support efficient parallel information processing at relatively low connection cost. Since this type of network architecture has previously been demonstrated using anatomical connectivity data in various species (e.g. Hilgetag et al. 2000; Sakata et al. 2005; Sporns & Zwi 2004), Bullmore concluded that the correlated, low-frequency oscillations in human fMRI may reflect the underlying anatomical connectivity of the cortex.

Challenging the view that resting state fMRI signals may be simply a by-product of the system's anatomical connectivity structure, Michelle Hampson (Yale University) examined the strength of functional connections across a range of different conditions (e.g. during different cognitive tasks and during rest) and then correlated, across subjects, the ensuing measures of functional connectivity with behavioural measures. For example, during both a working memory task and at rest, she investigated the functional connectivity between the posterior cingulate cortex and the medial frontal gyrus and ventral anterior cingulate cortex, respectively. She found that working memory performance and functional connectivity, both during the task and at rest, were strongly correlated across subjects (Hampson et al. 2006a). Similarly, she found that the functional connectivity between the angular gyrus and the left inferior frontal gyrus measured during reading and at rest, respectively, was correlated to behavioral measures of reading ability (Hampson et al. 2006b). These findings suggest that individual differences in functional coupling between brain regions at rest might predict differences in cognitive abilities for which these brain regions are important.

In the general discussion on resting state fMRI, a number of workshop participants expressed their concerns about the role of physiological artifacts and problems of interpreting resting state data. One issue raised was that, due to the lack of controlled

experimental manipulations, the interpretation of resting state fMRI results is fairly unconstrained: while one typically obtains complex patterns that can be associated with various functional interpretations, there are few, if any criteria, for deciding between these interpretations. Another concern is that there are a number of physiological rhythms which have been shown to influence resting state fMRI signals but tend to be ignored by a large majority of ongoing studies. These potential confounds are either in the low frequency domain of interest (e.g. cyclic vasomotion) or have been shown to be aliased into low-frequency bands (e.g. cardiac and breathing rhythms; Lowe et al. 1998; Shmueli et al. 2007), particularly for the moderate to slow sampling rates required by multi-slice acquisitions. Characterizing and controlling for these potential confounds is an important challenge for forthcoming resting state fMRI studies.

Linking anatomical to functional connectivity

Another session at the Barcelona workshop focused on new approaches for linking anatomical to functional connectivity. Viktor Jirsa (Theoretical Neuroscience Group, CNRS, Marseille) used methods from non-linear dynamics systems theory to challenge the common view that cognitive processes can be considered as a sequence of discrete states, with each state possessing a discrete representation in terms of neuronal population activity. As an alternative, he suggested mathematical descriptions of cognitive processes as a structured flow on a low-dimensional manifold. He emphasized that within this framework the connectivity amongst neuronal populations makes it possible that a given cognitive process could have multiple representations in terms of functional coupling patterns.

Steven Bressler (Center for Complex Systems and Brain Sciences, Florida Atlantic University) reviewed results of large-scale analyses of functional and effective connectivity (Bressler & Tognoli 2006). These connectivity measures were obtained from local field potential data of recordings from primate cortex, using a large number of electrodes covering multiple cortical regions. His analyses demonstrated that the functional strength of a given anatomical pathway can switch rapidly, at the millisecond scale, depending on the requirements of the cognitive processes. In line with other proposals (McIntosh 2000), he suggested that this transient coupling of distributed neuronal ensembles and the ensuing formation of large-scale neuronal configurations (or “neuronal context”) represents a fundamental principle of how the static infrastructure provided by anatomical brain connectivity patterns can flexibly support a wide range of functions.

One widespread physiological mechanism for achieving this transient and context-dependent change in coupling strength amongst neuronal populations is gain control (Salinas & Sejnowski 2001). This mechanism relies on non-linear interactions amongst synaptic inputs to the same neuron, e.g. by means of voltage-sensitive ion channels, and represents a critical mechanism for various neurobiological processes, including top-down (attentional) modulation, learning and effects by modulatory transmitters. Klaas Enno Stephan (Wellcome Trust Centre for Neuroimaging, London) presented a non-linear extension of dynamic causal modeling (DCM) which can be applied to measured fMRI data. This model allows one to make statistical inference about whether the data reflect gain control processes, i.e. how the connection between two neural populations is enabled or gated by activity in other neural populations. Simulations and empirical results demonstrated the face validity and practical usefulness of this model. This nonlinear extension of DCM enhances the biological plausibility of DCM and enables more sophisticated inferences about dynamic changes of neuronal connectivity that underlie measured fMRI data.

Some central research questions for the future

There is a broad consensus in the neurosciences that mathematical system models are extremely helpful, if not indispensable, for a mechanistic understanding of neural systems. As outlined in this article, major progress is currently being made in mathematical modeling of neurophysiological and cognitive processes. A central question, however, concerns the validity of such models. This question has many different aspects, only some of which will be briefly touched on here. A first aspect concerns model comparison and model selection: given several alternative hypotheses, and thus multiple competing models, about the mechanisms underlying a given system, how can we decide which of these models is best? The critical point is that competing models cannot be compared on the basis of relative fit alone; instead, their relative complexity must be considered as well (Pitt & Myung 2002). From a Bayesian perspective, the ideal approach to model comparison, assuming that all models have equal a priori probability, is the so-called model evidence: the probability of observing the data given a specific model (Bishop 2006; MacKay 2003). In this framework, two models can be compared by computing their evidence ratio or Bayes factor (Kass & Raftery 1995)[7]. Importantly, the model evidence provides a principled way to assess the balance between model fit and model complexity as well as the generalizability of the model, eschewing the need for computationally expensive methods like cross-validation. Despite these advantages, suitable approximations to this measure are so far rarely used in evaluating dynamic models of neural systems, with the notable exception of DCM (c.f. Penny et al. 2004; Stephan et al. 2007b). Model development and validation would benefit from a more widespread use of Bayesian model comparison or corresponding techniques. Having said this, it is usually impossible to explore the space of all plausible models for a given data set, and there is no guarantee that the model identified as optimal by a Bayesian (or any other) selection procedure is a “good” model and not just somewhat better than other “bad” models. Model selection should therefore not be viewed as an automatic procedure for uncovering the “true” model but should be used in conjunction with other validation methods.

A second aspect of model validity concerns the relation between specific model parameters and specific neurophysiological processes or properties. In other words, does fitting of the model to data yield parameter estimates which are veridical representations of the neurophysiological processes which we want to infer from the measured data? For example, the interpretability of parameter estimates may be impaired due to problems with system identifiability (e.g. dependencies amongst parameters that prevent unique estimates). This is a very important problem for biological system models in general (c.f. Gutenkunst et al. 2007), which is only starting to be addressed in the context of neural system models applied to neurophysiological measurements (e.g. Deneux & Faugeras 2006; Stephan et al. 2007b). Alternatively, even in the absence of identifiability problems, model parameter estimates might be difficult to interpret because they reflect some mixture of effects. Generally, empirical studies are urgently needed which use well-controlled manipulations of neural systems to generate sharp predictions about the expected behavior of specific model parameters. For this kind of validation, close collaboration between theorists and experimentalists will be critical.

One aspect of neural system models that is likely to receive an increasing amount of attention in the future is the role of “noise”. Many models that are currently used for understanding neurophysiological data are deterministic and do not account for stochastic

[7]It should be noted that many tests derived from frequentist statistics, like t-tests or ANOVA, evaluate the likelihood ratio of two nested models. Therefore, they represent a specific class of model selection which, in contrast to Bayes factors, does not take into account uncertainty about the parameters and their interdependencies.

events at the neuronal level (but see Harrison et al. 2005). However, there is considerable evidence for probabilistic components in neuronal dynamics (e.g. Gluckman et al. 1998; Moss et al. 2004) and a major challenge is to clarify whether this “noise” is just some epiphenomenon of certain aspects of neuronal processing, or whether it plays an important role for brain functions. Some neuronal computations may be facilitated by stochastic dynamical effects, for example, noise may enable probabilistic jumps across barriers in the energy landscape describing the flow of dynamics in attractor networks. Such probabilistic effects might be crucial for decision-making processes and prevent deadlocks in symmetric situations where the available choices are equally valuable (Deco et al. 2007).

Finally, we would like to point out that the ultimate test of how well system models help us to understand brain mechanisms is their application to clinical questions. The hope is that, given a neurophysiologically plausible and validated model, parameter estimates can be used for objective and precise diagnostic classification of individual patients (c.f. Stephan et al. 2006). Additionally, if their parameters are interpretable in neurophysiological terms, such models could provide predictions about optimized therapeutic approaches for individual patients. For example, a model in which specific parameters represent the functional status of specific neuromodulatory transmitter systems might be useful in predicting which particular combination of drugs should be used for an individual patient. This predictive power distinguishes model-based approaches from blind classification techniques; although the latter may be useful for clinical decision-making (e.g. Azari et al. 1993), they are mechanistically uninformative and neither provide insight into the pathophysiology nor generate predictions about new treatment strategies. Other fields, e.g. cardiovascular research, are currently making promising progress towards mechanistic models that are clinically useful for individual patient assessment and treatment (Zenker et al. 2007). The breadth and depth of research presented at the Brain Connectivity Workshops at Sendai 2006 and Barcelona 2007 justify an optimistic view that computational systems neuroscience may be making similar contributions to clinical problem-solving in the not too distant future.

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References

Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J. Neurosci. 2006; 26:63–72. [PubMed: 16399673]

Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. J. Cereb. Blood Flow Metab. 2001; 21:1133–1145. [PubMed: 11598490]

Attwell D, Iadecola C. The neural basis of functional brain imaging signals. Trends Neurosci. 2002; 25:621–625. [PubMed: 12446129]

Azari NP, Pietrini P, Horwitz B, Pettigrew KD, Leonard HL, Rapoport JL, Schapiro MB, Swedo SE. Individual differences in cerebral metabolic patterns during pharmcotherapy in Obsessive-Compulsive disorder: A Multiple regression/discriminant analysis of positron emission tomographic data. Biol. Psychiat. 1993; 34:798–809. [PubMed: 8292684]

Bertrand O, Tallon-Baudry C. Oscillatory gamma activity in humans: a possible role for object representation. Int. J. Psychophysiol. 2000; 38:211–223. [PubMed: 11102663]

Bishop, C. Pattern recognition for machine learning. Berlin: Springer; 2006.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 1995; 34:537–541. [PubMed: 8524021]

Bota M, Dong HW, Swanson LW. Brain architecture management system. Neuroinformatics. 2005; 3:15–48. [PubMed: 15897615]

Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. Millisecond-timescale, genetically targeted optical control of neural activity. Nat. Neurosci. 2005; 8:1263–1268. [PubMed: 16116447]

Breakspear M, Bullmore ET, Aquino K, Das P, Williams LM. The multiscale character of evoked cortical activity. NeuroImage. 2006a; 30:1230–1242. [PubMed: 16403656]

Breakspear M, Roberts JA, Terry JR, Rodrigues S, Mahant N, Robinson PA. A unifying explanation of primary generalized seizures through nonlinear brain modeling and bifurcation analysis. Cereb Cortex. 2006b; 16:1296–1313. [PubMed: 16280462]

Bressler SL, Coppola R, Nakamura R. Episodic multiregional cortical coherence at multiple frequencies during visual task performance. Nature. 1993; 366:153–156. [PubMed: 8232553]

Bressler SL, Tognoli E. Operational principles of neurocognitive networks. Int. J. Psychophysiol. 2006; 60:139–148. [PubMed: 16490271]

Bullmore E, Harrison L, Lee L, Mechelli A, Friston K. Brain Connectivity Workshop, Cambridge UK, May 2003. Neuroinformatics. 2004; 2:123–125.

Burns GA, Cheng WC, Thompson RH, Swanson LW. The NeuARt II system: a viewing tool for neuroanatomical data based on published neuroanatomical atlases. BMC Bioinformatics. 2006; 7:531. [PubMed: 17166289]

Chong L, Ray LB. Whole-istic biology. Science. 2002; 295:1661.

Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF. Consistent resting-state networks across healthy subjects. Proc. Natl. Acad. Sci. USA. 2006; 103:13848–13853. [PubMed: 16945915]

David O, Friston KJ. A neural mass model for MEG/EEG: coupling and neuronal dynamics. NeuroImage. 2003; 20:1743–1755. [PubMed: 14642484]

David O, Kiebel SJ, Harrison LM, Mattout J, Kilner JM, Friston KJ. Dynamic causal modeling of evoked responses in EEG and MEG. NeuroImage. 2006; 30:1255–1272. [PubMed: 16473023]

Deco G, Rolls ET, Horwitz B. 'What' and 'where' in visual working memory: A computational neurodynamical perspective for integrating fMRI and single-cell data. J. Cogn. Neurosci. 2004; 16:683–701. [PubMed: 15165356]

Deco G, Rolls ET. Neurodynamics of biased competition and cooperation for attention: a model with spiking neurons. J. Neurophysiol. 2005; 94:295–313. [PubMed: 15703227]

Deco G, Scarano L, Soto-Faraco S. Weber's law in decision making: integrating behavioral data in humans with a neurophysiological model. J. Neurosci. 2007; 27:11192–11200. [PubMed: 17942714]

Deco G, Jirsa VK, Robinson PA, Breakspear M, Friston KJ. The dynamic brain: From spiking neurons to neural masses and cortical fields. PLoS Comput. Biol. 2008 in press.

Deneux T, Faugeras O. Using nonlinear models in fMRI data analysis: model selection and activation detection. NeuroImage. 2006; 32:1669–1689. [PubMed: 16844388]

Felleman DJ, Van Essen DC. Distributed hierarchical processing in the primate cerebral cortex. Cereb. Cortex. 1991; 1:1–47. [PubMed: 1822724]

Freeman WJ. Linear analysis of the dynamics of neural masses. Ann. Rev. Biophys. Bioeng. 1972; 1:225–256. [PubMed: 4346305]

Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci. 2005; 9:474–480. [PubMed: 16150631]

Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Hum. Brain Mapp. 1994; 2:56–78.

Friston KJ. Beyond phrenology: What can neuroimaging tell us abut distributed circuitry? Ann. Rev. Neurosci. 2002; 25:221–250. [PubMed: 12052909]

Friston KJ, Harrison L, Penny W. Dynamic causal modelling. NeuroImage. 2003; 19:1273–1302. [PubMed: 12948688]

Friston K, Mattout J, Trujillo-Barreto N, Ashburner J, Penny W. Variational free energy and the Laplace approximation. NeuroImage. 2007; 34:220–234. [PubMed: 17055746]

Gluckman BJ, So P, Netoff TI, Spano ML, Schiff SJ. Stochastic resonance in mammalian neuronal networks. Chaos. 1998; 8:588–598. [PubMed: 12779762]

Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. USA. 2003; 100:253–258. [PubMed: 12506194]

Gutenkunst RN, Waterfall JJ, Casey FP, Brown KS, Myers CR, Sethna JP. Universally sloppy parameter sensitivities in systems biology models. PLoS Comput Biol. 2007; 3:e189.

Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT. Brain connectivity related to working memory performance. J. Neurosci. 2006a; 26:13338–13343. [PubMed: 17182784]

Hampson M, Tokoglu F, Sun Z, Schafer RJ, Skudlarski P, Gore JC, Constable RT. Connectivity-behavior analysis reveals that functional connectivity between left BA39 and Broca's area varies with reading ability. NeuroImage. 2006b; 31:513–519. [PubMed: 16497520]

Hamzei-Sichani F, Kamasawa N, Janssen WG, Yasumura T, Davidson KG, Hof PR, Wearne SL, Stewart MG, Young SR, Whittington MA, Rash JE, Traub RD. Gap junctions on hippocampal mossy fiber axons demonstrated by thin-section electron microscopy and freeze fracture replica immunogold labeling. Proc. Natl. Acad. Sci. USA. 2007; 104:12548–12553. [PubMed: 17640909]

Harrison LM, David O, Friston KJ. Stochastic models of neuronal dynamics. Phil. Trans. R. Soc. Lond. B. Biol. Sci. 2005; 360:1075–1091. [PubMed: 16087449]

Hilgetag CC, Barbas H. Role of Mechanical Factors in the Morphology of the Primate Cerebral Cortex. PLoS Comput. Biol. 2006; 2:e22. [PubMed: 16557292]

Hilgetag CC, Burns GA, O'Neill MA, Scannell JW, Young MP. Anatomical connectivity defines the organization of clusters of cortical areas in the macaque monkey and the cat. Phil. Trans. R. Soc. Lond. B Biol. Sci. 2000; 355:91–110. [PubMed: 10703046]

Honey CJ, Kötter R, Breakspear M, Sporns O. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proc Natl Acad Sci USA. 2007; 104:10240–10245. [PubMed: 17548818]

Horwitz B, Duara R, Rapoport SI. Intercorrelations of glucose metabolic rates between brain regions: application to healthy males in a state of reduced sensory input. J. Cereb. Blood Flow Metab. 1984; 4:484–499. [PubMed: 6501442]

Horwitz B, Tagamets BA, McIntosh AR. Neural modelling, functional brain imaging, and cognition. Trends Cogn. Sci. 1999; 3:91–98. [PubMed: 10322460]

Husain FT, Tagamets MA, Fromm SJ, Braun AR, Horwitz B. Relating neuronal dynamics for auditory object processing to neuroimaging activity: a computational model and an fMRI study. NeuroImage. 2004; 21:1701–1720. [PubMed: 15050592]

Jirsa, V.; McIntosh, AR. Handbook of Brain Connectivity. Berlin: Springer; 2007.

Kiebel SJ, David O, Friston KJ. Dynamic causal modelling of evoked responses in EEG/MEG with lead field parameterization. NeuroImage. 2006; 30:1273–1284. [PubMed: 16490364]

Kitano H. Systems biology: a brief overview. Science. 2002; 295:1662–1664. [PubMed: 11872829]

Kötter R, Stephan KE. Network participation indices: characterizing component roles for information processing in neural networks. Neural Netw. 2003; 16:1261–1275. [PubMed: 14622883]

Kötter R, Wanke E. Mapping brains without coordinates. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2005; 360:751–766. [PubMed: 15971361]

Lauritzen M. Reading vascular changes in brain imaging: is dendritic calcium the key? Nat. Rev. Neurosci. 2005; 6:77–85. [PubMed: 15611729]

Lee L, Harrison LM, Mechelli A. A report of the functional connectivity workshop, Dusseldorf 2002. NeuroImage. 2003; 19:457–65. [PubMed: 12814594]

Lee L, Friston K, Horwitz B. Large-scale neural models and dynamic causal modelling. NeuroImage. 2006; 30:1243–1254. [PubMed: 16387513]

Liljenström H, Hasselmo ME. Cholinergic modulation of cortical oscillatory dynamics. J. Neurophysiol. 1995; 74:288–297. [PubMed: 7472331]

Loh M, Rolls ET, Deco G. A dynamical systems hypothesis of schizophrenia. PLoS Comput. Biol. 2007; 3:e228. [PubMed: 17997599]

Lowe MJ, Mock BJ, Sorenson JA. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. NeuroImage. 1998; 7:119–132. [PubMed: 9558644]

Lungarella M, Sporns O. Mapping information flow in sensorimotor networks. PLoS Comput. Biol. 2006; 2:e144. [PubMed: 17069456]

Marshall JC, Fink GR. Cerebral localization, then and now. NeuroImage. 2003; 20(Suppl 1):S2–7. [PubMed: 14597291]

McIntosh AR. Towards a network theory of cognition. Neural Netw. 2000; 13:861–870. [PubMed: 11156197]

McIntosh AR, Rajah MN, Lobaugh NJ. Functional connectivity of the medial temporal lobe relates to learning and awareness. J. Neurosci. 2003; 23:6520–6528. [PubMed: 12878693]

MacKay, DJC. Information theory, inference, and learning algorithms. Cambridge: Cambridge University Press; 2003.

Moran RJ, Stephan KE, Kiebel SJ, Rombach N, O'Connor WT, Murphy KJ, Reilly RB, Friston KJ. Bayesian estimation of synaptic physiology from the spectral responses of neural masses. NeuroImage. 2007a in press.

Moran RJ, Kiebel SJ, Stephan KE, Reilly RB, Daunizeau J, Friston KJ. A neural mass model of spectral responses in electrophysiology. NeuroImage. 2007b; 37:706–720. [PubMed: 17632015]

Moss F, Ward LM, Sannita WG. Stochastic resonance and sensory information processing: a tutorial and review of application. Clin. Neurophysiol. 2004; 115:267–281. [PubMed: 14744566]

Muhammad AJ, Markram H. NEOBASE: databasing the neocortical microcircuit. Stud. Health. Technol. Inform. 2005; 112:167–177. [PubMed: 15923726]

Penny WD, Stephan KE, Mechelli A, Friston KJ. Comparing dynamic causal models. NeuroImage. 2004; 22:1157–1172. [PubMed: 15219588]

Pitt MA, Myung IJ. When a good fit can be bad. Trends Cogn. Neurosci. 2002; 6:421–425.

Ramnani N, Lee L, Mechelli A, Phillips C, Roebroeck A, Formisano E. Exploring brain connectivity: a new frontier in systems neuroscience. Functional Brain Connectivity, 4-6 April 2002, Dusseldorf, Germany. Trends Neurosci. 2002; 25:496–497. [PubMed: 12220872]

Riera JJ, Watanabe J, Kazuki I, Naoki M, Aubert E, Ozaki T, Kawashima R. A state-space model of the hemodynamic approach: nonlinear filtering of BOLD signals. NeuroImage. 2004; 21:547–567. [PubMed: 14980557]

Riera JJ, Wan X, Jimenez JC, Kawashima R. Nonlinear local electrovascular coupling. I: A theoretical model. Hum. Brain Mapp. 2006; 27:896–914. [PubMed: 16729288]

Riera JJ, Jimenez JC, Wan X, Kawashima R, Ozaki T. Nonlinear local electrovascular coupling. II: From data to neuronal masses. Hum. Brain Mapp. 2007; 28:335–354. [PubMed: 16933303]

Riera JJ, Schousboe A, Waagepetersen HS, Howarth C, Hyder F. The micro-architecture of the cerebral cortex: functional neuroimaging models and metabolism. NeuroImage. 2008 in press.

Sakata S, Komatsu Y, Yamamori T. Local design principles of mammalian cortical networks. Neurosci. Res. 2005; 51:309–315. [PubMed: 15710495]

Salinas E, Sejnowski TJ. Gain modulation in the central nervous system: where behavior, neurophysiology, and computation meet. Neuroscientist. 2001; 7:430–440. [PubMed: 11597102]

Scannell JW, Burns GA, Hilgetag CC, O'Neil MA, Young MP. The connectional organization of the cortico-thalamic system of the cat. Cereb. Cortex. 1999; 9:277–299. [PubMed: 10355908]

Shmueli K, van Gelderen P, de Zwart JA, Horovitz SG, Fukunaga M, Jansma JM, Duyn JH. Low-frequency fluctuations in the cardiac rate as a source of variance in the resting-state fMRI BOLD signal. NeuroImage. 2007; 38:306–320. [PubMed: 17869543]

Silberberg G, Markram H. Disynaptic inhibition between neocortical pyramidal cells mediated by Martinotti cells. Neuron. 2007; 53:735–746. [PubMed: 17329212]

Sporns O, Tononi G, Edelman GM. Theoretical neuroanatomy and the connectivity of the cerebral cortex. Behav. Brain Res. 2002; 135:69–74. [PubMed: 12356436]

Sporns O, Kötter R. Motifs in brain networks. PLoS Biol. 2004; 2:e369. [PubMed: 15510229]

Sporns O, Zwi JD. The small world of the cerebral cortex. Neuroinformatics. 2004; 2:145–162. [PubMed: 15319512]

Stephan KE, Kamper L, Bozkurt A, Burns GAPC, Young MP, Kötter R. Advanced database methodology for the Collation of Connectivity data on the Macaque brain (CoCoMac). Phil. Trans. R. Soc. Lond. B Biol. Sci. 2001; 356:1159–1186. [PubMed: 11545697]

Stephan KE. On the role of general system theory for functional neuroimaging. J. Anat. 2004; 205:443–470. [PubMed: 15610393]

Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. Biol. Psychiatry. 2006; 59:929–939. [PubMed: 16427028]

Stephan KE, Harrison LM, Kiebel SJ, David O, Penny WD, Friston KJ. Dynamic causal models of neural system dynamics: current state and future extensions. J. Biosci. 2007a; 32:129–144. [PubMed: 17426386]

Stephan KE, Weiskopf N, Drysdale PM, Robinson PA, Friston KJ. Comparing hemodynamic models with DCM. NeuroImage. 2007b; 38:387–401. [PubMed: 17884583]

Stone JV, Kötter R. Making connections about brain connectivity. Trends Cogn Sci. 2002; 6:327–328. [PubMed: 12140078]

Tagamets MA, Horwitz B. Integrating electrophysiological and anatomical experimental data to create a large-scale model that simulates a delayed match-to-sample human brain imaging study. Cereb. Cortex. 1998; 8:310–320. [PubMed: 9651128]

Traub RD, Bibbig A, LeBeau FE, Buhl EH, Whittington MA. Cellular mechanisms of neuronal population oscillations in the hippocampus in vitro. Annu. Rev. Neurosci. 2004; 27:247–278. [PubMed: 15217333]

Valdés-Sosa PA, Kötter R, Friston KJ. Introduction: multimodal neuroimaging of brain connectivity. Philos Trans R Soc Lond B Biol Sci. 2005; 360:865–867. [PubMed: 16087431]

Valdés-Sosa PA, Sánchez-Bornot JM, Lage-Castellanos A, Vega-Hernández M, Bosch-Bayard J, Melie-García L, Canales-Rodríguez E. Estimating brain functional connectivity with sparse multivariate autoregression. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2005; 360:969–981. [PubMed: 16087441]

Van Essen DC. A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature. 1997; 385:313–318. [PubMed: 9002514]

Van Essen DC, Dierker D, Snyder AZ, Raichle ME, Reiss AL, Korenberg J. Symmetry of cortical folding abnormalities in Williams syndrome revealed by surface-based analyses. J. Neurosci. 2006; 26:5470–5483. [PubMed: 16707799]

Van Essen DC, Dierker DL. Surface-based and probabilistic atlases of primate cerebral cortex. Neuron. 2007; 56:209–225. [PubMed: 17964241]

Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, Zempel JM, Snyder LH, Corbetta M, Raichle ME. Intrinsic functional architecture in the anaesthetized monkey brain. Nature. 2007; 447:83–86. [PubMed: 17476267]

Von Bertalanffy, L. General System Theory. New York: George Braziller; 1969.

Watts DJ, Strogatz SH. Collective dynamics of ‘small-world’ networks. Nature. 1998; 393:440–442. [PubMed: 9623998]

Zeki S, Shipp S. The functional logic of cortical connections. Nature. 1988; 335:311–317. [PubMed: 3047584]

Zenker S, Rubin J, Clermont G. From Inverse Problems in Mathematical Physiology to Quantitative Differential Diagnoses. PLoS Comput Biol. 2007; 3:e204. [PubMed: 17997590]