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WORKSHOP REPORT

The functional brain connectivity workshop: report and commentary

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Abstract

This report summarizes the presentations and discussions at a recent workshop entitled 'Functional Brain Connectivity', held in Düsseldorf, Germany. The aims of the workshop were to bring together researchers using different approaches to study connectivity in the brain, to enable them to share conceptual, mathematical and experimental ideas and to develop strategies for future work on functional integration. The main themes that emerged included: (1) the importance of anatomical knowledge in understanding functional interactions the brain; (2) the need to establish common definitions for terms used across disciplines; (3) the need to develop a satisfactory framework for inferring causality from functional imaging and electroencephalographic/magneto-encephalographic data; (4) the importance of analytic tools that capture the dynamics of neural interactions; and (5) the role of experimental paradigms that exploit the functional imaging of perturbations to cortical interactions.

1. Introduction

This is the report of a workshop held in Düsseldorf, Germany, on 4–6 April 2002 entitled 'Functional Brain Connectivity' organized by Rolf Kötter (Heinrich Heine University, Dusseldorf) and Karl Friston (University College London). The workshop was supported by contributions from the Boehringer Ingelheim Foundation, EU Thematic Network 'Computational Neuroscience and Neuroinformatics', Heinrich Heine University Düsseldorf and Universitätsklinikum Düsseldorf.

This event represented an opportunity to bring together prominent researchers using different approaches to study connectivity and to allow them to exchange conceptual, mathematical and experimental ideas. It was hoped that, by inviting researchers with diverse

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areas of interest, new insights would be gained into the study of functional integration within the human brain. It is evident from the list of speakers and topics that follows, that the diverse nature of this field was well represented:

- Ed Bullmore (University of Cambridge, UK): Significance of connectivity differences between groups of fMRI data.
- Peter Buzas (Ruhr-Universitat Bochum, Germany): Fine structure of cortical connections—fine structure of cortical maps.
- Karl Friston (University College London, UK): Dynamic causal modelling.
- Rainer Goebel (University of Maastricht, Netherlands): Combining fMRI and DTI—constraints for functional connectivity analysis.
- Barry Horwitz (National Institutes of Health, USA): Using simulation modelling to determine the neural correlates of functional connectivity.
- Mark Hubener (Max-Planck-Institute, Germany): Studying connectivity with optical imaging.
- Martin A Koch (University of Hamburg, Germany): An investigation of functional and anatomical connectivity using MRI.
- Randy McIntosh (University of Toronto, Canada): Linking cognitive function and brain through neural context.
- Tomas Paus (McGill University, Montreal, Canada): Imaging and stimulating the human brain.
- Nicholas Schiff (Cornell University, New York, USA): Quantitative approaches to system identification in human epilepsies.
- Dirk Schubert and Rolf Kotter (Heinrich Heine University, Dusseldorf, Germany): Mapping functional connectivity through optical stimulation.
- Olaf Sporns (Indiana University, USA): From neuroanatomy to functional brain connectivity—and back?
- Jim V Stone (Sheffield University, UK): Independent component analysis—principles and applications.
- Wim Vanduffel (Leuven Medical School, Belgium): Ground truth for functional connectivity measures.
- Karl Zilles (Institute of Medicine, Research Centre Jülich, Jülich, Germany): Contribution of post-mortem studies to functional and diffusion tensor imaging.

One specific aim of the workshop was to '*explore the possibility that one level of enquiry can inform or be constrained by others*', for example, using anatomical data to constrain models of interaction between brain regions. It is hoped that this report provides a fair representation of the views expressed by the participants.

On the web-site advertising the workshop 'functional connectivity' was defined as '*the statistical interdependence of functional phenomena whose causal relationships need to be scrutinized with the aid of further information, particularly about the structural organization of the system*'. It became apparent that this definition, as well as others that are commonly used in this field, needed further specification to facilitate communication among the participants and for use in the future. The process of defining concepts and terms and the conclusions reached by the participants form part of this report. The report is divided into three sections: (1) connectivity: definitions, causality and inference (2) experimental techniques and developments and (3) analytic techniques and modelling.

2. Connectivity: definitions, causality and inference

Three different types of connectivity were discussed during the workshop: anatomical, functional and effective connectivity. This section focuses on the definitions and limitations of these concepts and their relevance to the study of how the brain works, particularly with respect to the current shift in emphasis from studies of functional segregation to functional integration. In the context of this report, anatomical connectivity is a description of the physical structures connecting two cells or brain regions. Functional and effective connectivity are descriptions of the relationships between patterns of neural activity therefore they involve measurements of neural function. Precise definitions of functional and effective connectivity are discussed in more detail in section 2.3.

2.1. Anatomical connectivity

Although the definition anatomical connectivity was not directly addressed, there were a number of discussions about anatomy that encompassed two main themes: firstly, the role of anatomical data in neuroimaging and computational simulations, and secondly the boundary between anatomical description and functional characterization of connections. The first of these two issues was addressed directly by the provocative question: Why do you need to know any anatomy? Would it be acceptable to simply infer the presence of an anatomical connection from the functional characteristics of a system? The consensus reached was that knowledge of anatomy is important to determine the presence or absence of connections between cortical areas. This provides plausible biological constraints for theories and inferences about neural interactions when analysing functional neuroimaging data and developing computer simulations. Having agreed that some knowledge of anatomy is important for all levels of inquiry, the question became: What measurements of anatomical connectivity are the most useful to the study how the brain works? Knowing if there are direct connections between two neurones or cortical areas is clearly important, but a complete description of the connections includes information such as the receptor subtypes at synapses (e.g. AMPA versus NMDA), the ratio of inhibitory to excitatory interneurones, the number of connections and their physiological impact (modulatory top–down versus driving bottom–up inputs). At this point the boundary between anatomy and function becomes blurred, and this applies equally to descriptions of connections and regions. Peter Buzas suggested that the cells he investigates in primary visual cortex might be better classified if they were divided according to their responses to physiological stimuli rather than their morphology; i.e. functional instead of anatomical criteria (see section 3.3). Karl Zilles pointed out that the labelling of macaque cortical areas, e.g. V2-5 (areas processing different aspects of visual stimuli), is based on functional characteristics and it is almost impossible to distinguish between these areas using anatomical criteria alone.

2.2. Functional segregation versus functional integration

Characterizing brain activity in terms of the functional specialization of sensorimotor and higher cognitive brain areas is the primary approach to functional neuroimaging data. However, characterizing brain activity in terms of functional specialization does not reveal anything about how different brain regions communicate with each other, despite the fact that communication is an implicit assumption of this specialization. For instance, the neural correlates of semantic processing can be identified using written words by virtue of the assumption that visual regions interact with semantic regions. Thus, analyses of neural activity based solely on

functional specialization provide only a limited account of the neuronal substrate of the processes investigated. Alternative approaches have therefore been developed, in the context of functional neuroimaging, to investigate the integration of functionally specialized areas.

2.3. Functional and effective connectivity

The approaches mentioned in section 2.2 use a number of concepts and definitions derived from multiunit microelectrode recording of separable spike trains (Aertsen and Preissl 1991, Gerstein and Perkel 1969). In this context, *functional connectivity* is defined as the 'temporal correlations between spatially remote neurophysiological events' (Friston *et al* 1993a), whereas *effective connectivity* is defined as 'the influence that one neural system exerts over another either directly or indirectly' (Friston *et al* 1993b). At the level of multiunit microelectrode recordings, functional connectivity can result from stimulus-locked transients, evoked by a common afferent input, or may reflect stimulus-induced phasic coupling of neuronal assemblies, mediated by synaptic connections among brain areas. Ed Bullmore pointed out that there are practical differences in the characterization of functional and effective connectivity in multiunit electrode recording and functional neuroimaging techniques, specifically issues of spatial and temporal resolution, and that this may have implications for the relevance of these definitions across disciplines.

During the initial discussions Karl Friston expanded on the motivation behind these definitions of functional and effective connectivity within the context of functional neuroimaging: namely, to emphasize the difference between *descriptions of patterns* of neural activity and possible *explanations of their origins*. Functional connectivity reduces to testing the null hypothesis that activity in two regions share no mutual information, mutual information is a statistical description of the degree to which two regions demonstrate similar behaviour or statistical interdependence (Cover and Thomas 1991). In other words, the characterization of brain activity in terms of functional connectivity is 'model free'. In contrast, characterizing brain activity in terms of effective connectivity requires a causal or acausal model, in which regions and connections of interest are specified by the researcher, often constrained by a combination of neuroanatomical, neuropsychological and functional neuroimaging data. This is a crucial point when considering the distinction between functional and effective connectivity because it emphasizes the shift from a description of what the brain does to a theory of how it does it.

2.4. Problems associated with inferring causality from functional neuroimaging data

It is difficult to distinguish unambiguously between functional and effective connectivity simply by looking at the data because temporal correlations between neurophysiological events in separate neural systems (functional connectivity) may or may not be due to the influence that one neural system exerts over another (effective connectivity). Ed Bullmore discussed two possible ways of inferring effective connectivity and highlighted the problems associated with each of them as follows.

2.4.1. Temporal precedence. One method of inferring causality involves the principle of 'temporal precedence': if activity in area A occurs prior to activity in area B, then activity in A might cause activity in B through connections between the two areas. However, in the context of functional magnetic resonance imaging (fMRI), temporal precedence at the neuronal level may be masked at the haemodynamic level, because of the temporal smoothing inherent in the coupling between synaptic activity and perfusion changes. In extreme cases,

one region may cause activity in another but, because of different latencies in the coupling between synaptic activity and perfusion changes, the haemodynamic response in the 'target' region may actually occur *before* the haemodynamic response in the 'source' region. Even the use of electroencephalographic (EEG) and magneto-encephalographic (MEG) studies, which provide a temporal resolution in the order of milliseconds, may not provide a satisfactory solution since temporal precedence is not unambiguously linked to causality.

2.4.2. Perturbing the system. A second way of inferring causality might involve perturbing the system. The majority of functional neuroimaging experiments involve experimental manipulations of neural activation in the form of stimuli, be they visual, auditory, psychological etc. There are two important advantages of using perturbation studies over traditional experimental techniques. Firstly, the manipulation is under explicit experimental control and can therefore be precisely located in time and is independent of the subject's ability to perform a task. Secondly, it is possible to selectively alter the neural activity in specific cortical areas and to assess the effect that this has on the ability to perform a task and on the activity and interactions between the non-perturbed areas. A variety of perturbation studies where direct electrical stimulation of exposed cortex, cortical cooling and transcranial magnetic stimulation (TMS) are combined with different functional imaging techniques are described in section 3.4. Tomas Paus described experiments that combined TMS with functional imaging (positron emission tomography—PET) to examine the local and distant effects of TMS on haemodynamic responses in human subjects. However, it is worth remembering that the way in which TMS affects neuronal function is still not well understood and it may be difficult to define precisely the spatial extent of TMS effects, locally and in connected areas (Walsh and Rushworth 1999).

2.5. Conclusions and future research

Although functional imaging experiments are generally based on the principle of functional specialization, this type of analysis does not provide information about how different brain regions communicate with each other. In contrast, the analysis of functional and effective connectivity addresses neuronal interactions. Although functional connectivity and effective connectivity can be invoked at a conceptual level in both electrophysiology and neuroimaging, the nature and the scale of the neurophysiological measures provided by these techniques differ considerably. The combination of simultaneously acquired microscopic measures (obtained using multiunit electrode recording) and macroscopic measures (obtained through PET and fMRI scanning) is desirable for a better understanding of functional integration in the brain. However, there was general agreement that this has not yet been achieved and remains an important area for further research.

3. Experimental techniques and developments

The informal atmosphere of this workshop provided an opportunity for researchers to outline new areas of research and present preliminary results. In many cases it was not possible to provide a detailed account of the techniques used, and so in this section many of the technical developments are introduced with a superficial level of description, and more emphasis is placed on their potential contribution to the study of functional integration. The section is divided according to the four main themes that emerged during the discussions, many of which were common across the wide range of methods, from characterization of microscopic cortico–cortical connections to perturbation studies in human subjects.

3.1. Bridging the gap between different species

One of the themes discussed on several occasions was the 'information gap' that exists between the wealth of anatomical and single unit recording data in monkeys and the paucity of reliable information about the micro- and macroscopic connections within the human central nervous system. Two presentations in particular highlighted different approaches to this problem. The approach taken by Wim Vanduffel has been to perform fMRI studies at 1.5 T in awake, behaving monkeys (Vanduffel *et al* 2001). In this way, data from nearly identical experimental paradigms (visual motion processing for example) can be compared between monkeys and humans, as well as enabling fMRI data to be compared to single unit work within the same species.

Karl Zilles, on the other hand, presented a number of experimental techniques that he and his group have developed to study anatomical connectivity of post-mortem human brains. One technique involves differential myelin staining of white matter tracts, for example the optic radiation (Burgel *et al* 1997). A non-linear warping algorithm (Schormann and Zilles 1998) is then used to produce 'population maps' from the histological data represented on a normalized reference brain, reconstructed from MR images (Burgel *et al* 1999). Other techniques included autoradiographic imaging of receptor subtypes within the cortex and basal ganglia, demonstrating that different cortical areas have unique receptor profiles or 'fingerprints', with marked differences between primary sensory areas, such as auditory (Morosan *et al* 2001, Rademacher *et al* 2001) and somatosensory (Geyer *et al* 2001) cortex, and association areas. An important point raised during this presentation involved the relationship between cortical cytoarchitecture and gross surface anatomy: studies of post-mortem human brains reveal large intersubject variability (up to 2 cm) in the position of cytoarchitectural borders with respect to sulcal and gyral anatomy (Amunts *et al* 2000). This calls into questions the validity of using these landmarks to define the functional anatomy of the brain. Non-linear warping is also being used to compile the anatomical data from the human brain into a multi-modal 3D representation with a single spatial reference system, from microscopic, cellular detail to the surface anatomy and white matter tracts (Mazziotta *et al* 2001, Roland *et al* 2001). Using the same spatial reference system, data from functional imaging studies can be interpreted with respect to probabilistic population anatomy (Binkofski *et al* 2002, Bodegard *et al* 2001).

3.2. Diffusion tensor imaging

Diffusion tensor imaging (DTI) was the subject of several presentations and discussions. DTI (Basser *et al* 1994) is an imaging technique predicated on the random movement of water molecules within biological tissue. At a microscopic level, the diffusion of water molecules is rendered non-random by the presence of sub-cellular structures such as the cytoskeleton and axonal membranes. When the structures obstructing the movement of water are arranged on a larger scale, for example in bundles of parallel axonal fibres, then the diffusion within a voxel is non-random or anisotropic and can be characterized using MRI. In order to achieve this, diffusion weighted images are acquired using a diffusion-sensitized MRI sequence along several gradient directions (Le Bihan 1995). From these data, the degree of anisotropy within a voxel and the direction and speed of diffusion can be calculated. As diffusion within nerve fibres bundles is fastest in the direction parallel to the fibres, it is possible to use information about the speed and direction of diffusion to determine the pathways of white matter tracts within the brain (Douek *et al* 1991). For a recent review of the theory and potential uses of DTI see Le Bihan *et al* (2001).

Questions about DTI centred on several main issues: What is the likely limit on the spatial resolution of this technique? What type of information will it provide us with? How can the current fibre tracking algorithms be validated? What role will DTI have in the analysis of effective connectivity? The consensus reached was that DTI is an exciting and potentially valuable technique, even if it is unlikely to reach the resolution of single neurones or synaptic connections and therefore will not replace the anatomical methods such as fibre tracing. Indeed, Ed Bullmore suggested that the population maps of human white matter tract distributions described by Karl Zilles might be useful as a method of providing biological constraints to guide DTI tracking algorithms.

Several presentations discussed validation of DTI results: the awake monkey fMRI set-up of Wim Vanduffel enables DTI results in monkeys to be compared to current anatomical knowledge of the macaque. In a similar vein, Rainer Goebel showed DTI data from anaesthetized cats, which has been used to compare the performance of a variety of different tracking algorithms, the results of which will be compared to post-mortem tract tracing experiments in the same animals (Kim *et al* 2001). Goebel's work uses fMRI to locate cortical areas activated during visual stimulation that are then used as the starting points for tracking. In this approach the functional data is used to constrain the estimation of anatomical connections. Martin Koch presented a similar experiment using DTI and a Monte Carlo simulation to estimate the probability of two functionally correlated voxels, within a single slice of human cortex, being anatomically connected (Koch *et al* 2002).

The utility of DTI as a research tool will depend on how reliable and reproducible these various tracking methods prove to be. The potential applications for information from DTI are currently unexplored. Firstly, DTI may be clinically useful for assessing subtle changes in white matter anatomy, for example during recovery from brain lesions. Secondly, in analyses of effective connectivity DTI data may be useful as a constraint on possible anatomical connectivity, but there are several pitfalls and it is unlikely to provide information about the direction or functional classification of connections. It should be borne in mind that DTI does not measure 'connections' but simply large tracts of similarly orientated myelinated axonal processes. This scepticism about DTI reflected a deeper question: 'Does macroscopic anatomy add anything to a complete characterization of effective connectivity in terms of physiology and function?'

3.3. Using functional characteristics to infer anatomical connections

Using functional data to infer the presence of anatomical connections is not confined to human brain mapping. Dirk Schubert and Rolf Kotter presented a series of experiments exploring the relationship between the functional characteristics of cells in rat barrel cortex and the synaptic connections between different cell types within cortical layers of the same barrel and between neighbouring barrels. These experiments, an extension of previously published work (Schubert *et al* 2001), record post-synaptic changes in the membrane potential of a single cell, in response to photolytic release of caged glutamate to generate maps of effective connectivity. These are compared to detailed anatomical data from a three-dimensional reconstruction of the recorded cell, using biocytin staining. One limitation of the technique it that only one cell can be reconstructed, therefore the location of cells providing the synaptic connections can only be inferred: using the fact that the approximate location of the soma is known, and that there is a monosynaptic connection to some part of the dendritic tree of the target cell. There were many suggestions regarding future applications for this technique, including the use of glutamate agonists and antagonists to look at neurotransmitter specificity.

Mark Hubener presented preliminary results from another experimental technique, where functional data were used to infer the presence of anatomical connections. In these experiments electrical stimulation was used to establish anatomical connections which were then compared to functional data acquired using optical imaging. Brief pulses of electrical stimulation to the cat primary visual cortex generated small areas of increased neuronal activity at the site of stimulation and at additional nearby sites. It was postulated that these patterns were generated by the propagation of action potentials via horizontal connections. The patterns of increased activity were compared to the increased activity generated in response to visual stimuli (gratings) with different spatial orientations. The similarities in size and location of the activated areas were striking, suggesting that the functional maps generated in response to physiological stimuli depend in part upon the same anatomical connections that are responsible for the patterns seen after direct electrical stimulation. Tomas Paus suggested during the discussion that severing the horizontal connections surrounding the stimulating electrode would be a useful method of assessing their role.

Peter Buzas also presented work that addressed the integration of functional characteristics and lateral cortical connections within the primary visual cortex. These experiments combine anatomical data from three-dimensional reconstruction of different cortical cells (pyramidal, spiny stellate and basket cells) with cortical maps of orientation, direction and ocular dominance preference, obtained by optical imaging (Buzas *et al* 1998, 2001). This approach highlights differences in the functional characteristics of short-and long-range axonal projections from the same cell. Short-range, local axonal projections tend to have similar orientation, direction and ocular dominance preferences to those of the soma, whereas long-range connections project to sites with a range of different preferences. Peter Buzas pointed out that even in cells with similar morphology and anatomical connectivity, the functional characteristics of these connections are very different, raising the issue of how best to classify these different cell types: according to their anatomical or functional features.

3.4. Perturbation studies

Experimental techniques that involve destruction of anatomical connections or experimental manipulation of the excitability of cortical areas formed another important theme. The ability to experimentally activate or deactivate an area of the brain during a task, and during functional imaging, is a powerful method for exploring effective connectivity and causality. Such techniques are available for animal models and the development of awake monkey fMRI raises the possibility of combining reversible lesion studies such as cortical cooling (Chafee and Goldman-Rakic 2000) with functional imaging. Tomas Paus discussed TMS as a technique for altering neural activity in humans under explicit experimental control. TMS is non-invasive and safe when used within published guidelines (Wassermann 1998). An externally generated, rapidly changing magnetic field (applied by a coil placed over the subject's head) induces electric currents which can be used in different ways: as single or paired pulses to measure cortical excitability (Rothwell 1999), as single pulses and short trains to interrupt or enhance behaviour such as attention, motion awareness or reaction time (Jahanshahi and Rothwell 2000) and as longer trains of repetitive stimulation to induce changes in cortical excitability that outlast the duration of the stimulation both at the site stimulated and in connected areas (Munchau *et al* 2002).

Tomas Paus has developed a method of combining TMS with PET that has enabled him to carry out a series of experiments that are very similar in concept to those described by Mark Hubener, comparing changes in neural activity secondary to artificial stimulation with patterns evoked by physiological stimuli. For example, the effect of stimulating the frontal eye fields,

compared to performing saccades (Paus *et al* 1997, 1998). The advantages of combining TMS with functional imaging were highlighted: firstly, as TMS is independent of behaviour, observed changes in neural activity are not confounded by the subjects' ability to perform a task or by the strategy used. Secondly and perhaps of more interest, the combination of TMS with PET can be used to alter the activity of one brain area and observe the effects on activity in other areas, either in response to further TMS or during behavioural paradigms. This experimental strategy lends itself very readily to an analysis of effective connectivity (see section 2.4).

4. Analytic techniques and modelling

The brain's connectivity, both anatomical and functional, is highly plastic, given the changing environment to which it adapts, for example during development and learning or in response to disease. It is an objective of the neuroscientific community to develop robust metrics and convincing explanations of the dynamic nature of neural connectivity associated with sensorimotor and cognitive processes in health and disease.

4.1. Time-series analysis

A recurrent theme throughout the presentations was the use of time-series analysis tools to describe and model the brain as a dynamic system. Given a generic system of interacting units from which it is only possible to observe a sub-population of physiological parameters, (e.g. haemodynamic, electrical or magnetic recordings) a characterization of the system as a whole (including unobserved variables) is still possible from the time series because information of the unobserved states is embedded within the time series of the observed states. This is the notion of temporal embedding. Time series analysis techniques are therefore a possible way of extracting dynamic characterizations of the underlying state variables responsible for our observations. These methods are used to analyse EEG/MEG and local field potential (LFP) recordings (Bressler *et al* 1999) and are becoming increasingly popular in fMRI and PET data analysis.

A problem faced by experimentalists measuring signals produced from different sources within the brain is that data collected at a distance, e.g., at a scalp electrode with EEG, are mixtures of signals from different sources. A challenge is then to try and separate the individual sources given only the mixed data. An analogy is the familiar cocktail party scenario where one can imagine isolating a single voice in contrast to the others, given a mixture of all voices heard from your location within the room. Jim Stone described an algorithm designed for this purpose called independent-component analysis (ICA) (Stone 2002. Demonstrations and Matlab code at www.shef.ac.uk/ ∼pc1jvs).

Nicholas Schiff described a time series analysis procedure called hierarchical decomposition (Repucci *et al* 2001. See also www-users.med.cornell.edu/ ∼jdvicto/nlardf.html #introduction) to characterize a 'fingerprint' of the underlying non-linear dynamics that may generate scalp EEG signals during temporal lobe epilepsy (TLE) and absence seizures. Crucially, this approach aims to bridge the gap between observations of measured brain activity at the scalp surface and possible explanations of the hierarchical structure of electrical generators deep within the brain. See endnote 1

Schiff demonstrated the procedure on multichannel EEG recordings during a TLE seizure. Such data is said to have a high dimension in that there are many measurements from many electrodes. High-dimensional data can be difficult to analyse due both to the amount of computation involved and the possibility that the interesting signals maybe dispersed over

many of the dimensions. The dimensionality of any data set can however be reduced using an algorithm called principal component analysis (PCA) (Chatfield and Collins 1980). PCA can be used to find a small set of coordinates that capture the majority of variance within the data. As these coordinates are linear functions of the original data space they are referred to as a subspace. This procedure reduces the number of parameters needed to model the data. After PCA the time series are parametrized using a multivariate linear autoregressive model, before rotating the series into a hierarchical structure. A linear autoregressive (AR) model (model order 20) is used to over fit each time series and what is left is modelled as a non-linear AR process (an AR process being one whose current state is dependent on previous states in its recent history). The bilinear term estimated from this procedure is then tested for goodness of fit that is plotted on a two-dimensional graph, with each axis representing a different time lag, up to 20 lags. The result is what Schiff describes as a 'fingerprint' of a non-linear parameter that survives the linear overfitting at earlier stages of the procedure. Despite gross differences in the raw EEG data from TLE and absence seizures they share similar 'fingerprints', raising the question of whether they are generated by similar dynamics deep within the brain. If the method has succeeded in capturing a characteristic feature of underlying non-linear coupling between oscillatory generators responsible for the globally synchronous activity during seizures, then could such characterizations exist for particular cognitive task?

See endnote 2

4.2. Models of effective connectivity

Randy McIntosh discussed the central issue of plasticity within large-scale neural networks. Data from early PET experiments were modelled using structural equation modelling (SEM) (McIntosh and Gonzalez-Lima 1994) to demonstrate stimulus-dependent changes of inter-regional connectivity. SEM is a technique that attempts to estimate influence among latent variables assumed to be responsible for generating the neuroimaging data. The technique was originally used in econometrics and was popular in sociological studies (Maruyama 1997). An example of a latent variable underlying data within this context is intelligence quota (IQ). IQ is only ever measured vicariously through observable measures such as language and numerical tests. Given latent variables and their hidden nature, models are necessary to estimate their properties, in particular interactions among themselves. Returning to neuroimaging data the latent variables are disparate brain regions participating within a large-scale network. The degree of inter-dependence among them then becomes a measure of interest that SEM provides a method of estimating using instantaneous correlations within the data.

These experiments were crucial in establishing large-scale networks of cortical activity as a possible substrate of cognitive or sensori-motor tasks, along with providing a simple measure of stimulus dependent short-term plasticity using functional neuroimaging techniques. The notion of coordinated cortical networks subserving behaviour provides a source of diversity for neural representations, which has led to the notion of neural context (McIntosh 1999). Cortical regions activated similarly within different tasks, for example Area 46 activated during visual object and spatial recognition, are distinguished by differences in activities of connected regions, in other words the context of connected cortical activity matters. A functionally specialized region then becomes dependent on its network of cortical influences and no longer has a functionally static response. SEM initiated efforts to model such stimulus-dependent neural dynamics with the development of increasingly sophisticated models being the topic of further discussions during the workshop.

Karl Friston outlined a synthesis of models developed over the past decade and demonstrated how they were special cases of a more generic dynamic description of brain function. He made the distinction between the use of statistics to describe correlations

among neural activations and modelling causal structures that could explain these observations. Treating the brain as a dynamic system from which we are able to observe certain variables (changes in BOLD signal, electrical or magnetic signals) over time given particular inputs (experimentally designed perturbations of the system) we can attempt to estimate parametric descriptions of the underlying states upon which these observations are dependent. Starting from the general state and observation equations describing the temporal evolution of a system, expressions of effective connectivity were derived and demonstrated equivalence between alternative measures including SEM (Buechel and Friston 1997) and the Volterra approach (Friston 2001).

The talk ended with a brief description of dynamic causal modelling (DCM), describing coupling between interacting states within the general framework of multiple input, multiple output (MIMO) systems. In its current form the state equations are expanded according to a bilinear approximation, with the linear terms describing 'latent' couplings among the states without input and the bilinear term estimating the modulation of these couplings given inputs to the system. The procedure reduces the highly non-linear dynamics of the brain to a tractable linear problem of estimating couplings given experimental causes (inputs) and measured responses. Bayesian methods are used to estimate coupling parameters contained within the state equations. During the discussion of this work, clarifications were made regarding the scope of these analyses: firstly, that they are useful for designed experiments where the investigator is only interested in outputs that vary with the experimental manipulations and secondly, that these methods are not applicable to systems with non-controllable dynamic elements; i.e. factors with their own intrinsic activity, such as epileptic foci.

4.3. Investigating the links between anatomy and function using computational simulations

Olaf Sporns presented his work on the relationship between structure and function of complex systems using computational simulations to explore the principles underlying their dependence (Sporns *et al* 2000). The objective is to investigate the dialogue between structure and function through synthetic models of functionally realistic networks, looking for emergent structural 'motifs' and similarities with real neural structures. Considering a system composed of individual units, interacting among themselves to varying degrees, clusters of activity emerge. Such clusters can be considered as functionally specialized aggregates of activity reminiscent of neuroanatomical findings, with regional specialization to specific sensorimotor or cognitive functions e.g. vision (Zeki 1978). However, a balance exists between the amount of specialization and the degree to which these regions functionally integrate. Sporns described a mathematical property called 'complexity' which is a metric based on the mutual information among hierarchical bipartitions of a system. The metric is dependent on the balance between functional specialization and integration, being zero at the extremes and maximal in between. Artificially generated 'complex' systems reveal structural motifs that share salient features with real neural systems, in that functional clustering is a consistent feature of optimally complex systems. Such measures of real networks (using 'wiring diagrams' of cat and monkey brains) demonstrate that these neural systems exist at a near maximal level of complexity and that this can be reduced through pathology.

4.4. The use of simulation modelling to study effective connectivity

The contribution from Barry Horwitz raised a fundamental issue about the biological plausibility of the models used for effective connectivity. Horwitz reviewed a series of realistic and carefully constructed forward models, based on neurophysiological principles

that could be used to generate simulated imaging data. Furthermore, such models were able to accommodate experimental perturbations of the sort discussed by Thomas Paus, namely TMS, as well as standard cognitive and sensori-motor challenges. The critical utility of this approach is that it explicitly models the underlying neuronal substrate of measured responses and, vicarious measures of effective connectivity. More generally, the approach described by Horwitz afforded us tenable forward models of observed imaging data that explicitly embodied realistic neuronal dynamics and inter-regional integration. A good example of this approach can be found in Husain *et al* (2002).

4.5. Possible future approaches to the study of functional integration

As mentioned in section 2.4, the issue of what we are willing to accept as a causal explanation of our observations was a persistent theme throughout discussions and the topic of Ed Bullmore's presentation. Scientific methodology traditionally explores mechanistic explanations of causal structure. Phenomena are understood through a process of reducing the whole to its constituent parts and building up a mechanistic understanding of each step. However given highly complex organizations of matter such as brains this approach is insensitive to principles of collective order. Such systems are not explained by reduction to their individual parts, as its very nature is an expression of the whole. Such a holistic perspective produces fundamentally different accounts of causal structure. Synergetics (Haken 1983) was given as an example of such an approach.

Synergetics is a theory of self-organization, a ubiquitous phenomena throughout nature. The dynamics of systems consisting of many components (such as atoms, neurons or neural populations) is often governed by a few variables called order parameters. The equations describing the dynamics of the order parameters can capture salient features of the collective behaviour of phase transitions without modelling the microscopic properties explicitly, thereby dramatically reducing the complexity of the model.

Synergetic principles have been applied to EEG/MEG data analysis, describing long-range spatiotemporal patterns of cognitive and sensorimotor tasks (Kelso and Haken 1997). In line with such a holistic approach, mean field approaches (Treves 1993) to modelling macroscopic neural behaviours share a similar character. In the same way that statistical thermodynamic theory characterizes the macroscopic property of temperature in terms of statistical distributions of an ensemble of microscopic units (atoms) within a system, such approaches hope to describe spatiotemporal neural patterns in terms of statistical distributions of microscopic states such as neuronal firing properties.

5. Conclusions

This workshop recognized the significant progress made in recent years, in understanding the anatomical structure and functional architecture of the central nervous system and provided insights into recently developed experimental and analytical methods for characterizing functional integration. By bringing together researchers from diverse backgrounds it was possible to gain new insights into the strengths and weaknesses of their different approaches and to identify important directions for future research. The functional brain connectivity workshop was a stimulating and enjoyable experience because of the informal nature of the presentations, the lively discussions and the wide range of expertise assembled.

The important issues arising from the workshop are summarized in what follows:

(1) Anatomical detail has an important role in the study of functional integration within the brain, and this includes information about characteristics of these connections such as

the types of receptors and neurotransmitters and if they provide inhibitory or excitatory inputs.

(2) The distinction between functional and effective connectivity, as implied by the definitions framed by Karl Friston, is an important conceptual tool to select the appropriate methods for characterizing functional integration.

(3) There is a need to define a satisfactory framework for inferring causality at the temporal and spatial resolution of EEG, MEG and fMRI data. This may be helped by the development of experimental paradigms to explicitly address the issue of effective connectivity and to reduce the divide between electrophysiology and functional imaging. These include further work on combined single unit recording and fMRI and perturbation studies such as combined electrical stimulation with optical imaging, reversible deactivation in monkey fMRI studies and the combination of TMS with EEG, PET and, potentially, fMRI in human subjects.

(4) Statistical and modelling frameworks such as hierarchical decomposition and DCM that enable the non-linear dynamics of neural interactions to enter analyses of brain activity are important developments and may play a role in the study of functional integration and in addressing issues of causality.

(5) Many participants expressed the view that they would welcome such an event becoming an annual occurrence as a forum for shaping the future of functional integration research.

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