Making connections about brain connectivity

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The Functional Brain Connectivity workshop was organized by Rolf Kötter and Karl Friston, and held in Düsseldorf, Germany, on 4–6 April, 2002.

This three-day workshop on brain connectivity comprised 15 presentations by speakers using a wide variety different research techniques, including functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), optical imaging (OI) and computational modelling. Each speaker used only two transparencies, resulting in a very interactive and informal workshop. As might be expected, the resultant animated discussions between researchers from different scientific disciplines generated much heat, but also a few beams of much needed light.

Functional, effective and structural connectivity

The very first presentation by Wim Vanduffel (Leuven Medical School, Belgium) led to a defining theme of the workshop: the distinction between functional, effective and structural connectivity. Essentially, structural connectivity refers to the direct anatomical connections between brain regions, whereas functional connectivity refers to a statistical dependency between the activities of different regions without regard to any underlying anatomical connection.

These terms were coined during the pioneering attempts by Gerstein, Aertsen and colleagues to infer the nature of neuronal interactions from multi-electrode recordings, as recalled by Günther Palm (University of Ulm, Germany). Building on these early discussions, the distinction between functional and effective connectivity was first formally identified by Karl Friston (Wellcome Department of Cognitive Neurology, London, UK) in 1994. With Friston on hand to resolve disagreements over these definitions, it emerged that his original motivation for making such a distinction was to force researchers to be explicit about the nature of putative relationships among brain regions. Specifically, Friston argued that establishing effective connectivity between brain regions demands a precise mathematical specification of the nature of the proposed functional relationship in a way that functional connectivity does not. In other words, effective connectivity implies a precise mathematical model, whereas functional connectivity does not. The ensuing discussion soon showed that this seemingly clear distinction leads on to the question of what characterizes a model.

Analyzing connectivity

Presentations of methods for analysing connectivity between brain regions were divided into two groups: those investigating structural connectivity using *in vivo* DTI (Rainer Goebel, University of Maastricht, The Netherlands; Martin A. Koch, University Clinics Hamburg-Eppendorf, Germany) and those using post-mortem human anatomical techniques (Karl Zilles, Research Centre Jülich, Germany). Owing to its technical limitations, DTI is presently no rival to *in vivo* tracer or post-mortem myeloarchitectonic methods. Indeed, Zilles emphasized that anatomical techniques imply that the Talairach atlas, which is the *de facto* standard for imaging coordinates, is essentially inaccurate. Zille cogently made this point by presenting actual brain slices (which neatly subverted the conference limit of two transparencies). Despite the limitations of DTI, Goebel demonstrated the potential for this method to identify the anatomical pathways associated with activations observed using fMRI in the same subject.

Methods for inferring connectivity included independent component analysis (James Stone, Sheffield University, UK), dynamic causal modelling (K Friston, Wellcome Functional Imaging Laboratory, London, UK), and structural equation modelling (A. Randy McIntosh, University of Toronto, Canada). A free-ranging and provocative discussion on the role of causality in connectivity was also led by Ed Bullmore (University of Cambridge, UK).

Presentations of methods for inferring the local functional topography of single cortical regions included optical imaging (Peter Buzás, Ruhr-Universität Bochum, Germany; Mark Hübener, Max-Planck-Institut fur Neurobiologie, Martinsried, Germany) and light-induced release of 'caged' neurotransmitters (Schubert and Rolf Kötter, Heinrich Heine Universität Düsseldorf, Germany).

Buzás obtained a multi-dimensional fingerprint of a single pyramidal cell in primary visual cortex by defining the response profile of each pre-synaptic bouton in terms of preference of the target cell for ocularity, orientation and direction. The preferences of the target cells for each of these parameters were inferred from spatial maps obtained by optical imaging of intrinsic signals. The response profile of each bouton from a single pyramidal cell was then plotted as a single point in a 3D graph, in which the axes represented ocularity, orientation and direction preference. The resultant distribution of points gives a functional fingerprint for a single pyramidal cell and provides a functional decomposition of the neuron. However, despite the visually compelling nature of such distributions, it is difficult to compare different pyramidal cell fingerprints in the form of raw 3D distributions of points.

One example of 'cross-fertilization' to emerge from this interdisciplinary meeting was in the discussion of how several of the analytical techniques mentioned previously could be used to extract relevant features to provide a parametric description of each fingerprint. By contrast, Hübener

used optical imaging to estimate how high- and low-spatial frequencies are coded by different sets of neurons in primary visual cortex. He presented the surprising finding that, whereas other 1D quantities, such as orientation, are represented over many small contiguous ranges by spatially adjacent neurons, spatial frequency appears to be represented by two disjointed sets of neurons. Schubert and Kötter presented cutting-edge technology for mapping functional inputs of defined neurons in brain slices using multi-site optically induced neurotransmitter release from an inactivating UV-sensitive 'caging' group. Focal release of glutamate, for example, is used to identify the spatial distribution of presynaptic neuronal cell bodies without the confounding factor of electrically activated fibres of passage. Although both the anatomical and functional connectivities are much better defined at this microcircuit level than at the macroscopic level of large-scale brain systems, the general problem of disentangling effective interacting pathways appears as difficult to solve at this more detailed level as it is at the macroscopic level. The novel methods currently being developed for macroscopic analysis of connectivity might also be applicable for data obtained at the microcircuit level.

Computational models of connectivity

Presentations on computational models included the intriguing result from Olaf Sporns (Indiana University,IN, USA) that evolving model networks in which selective fitness is a measure of architectural complexity produce networks that contain clusters of neurons with sparse inter-cluster interconnections. A surprising, but crucial, side-effect of this is that total inter-neuronal 'wire-length' is minimized – a constraint thought to be important in the evolution of the human brain. Other systematic insights into the principles of large-scale wiring in brains might soon become apparent from the first comprehensive database of tracing-derived connectivity information on the macaque brain (Kötter and colleagues; http://www.cocomac.org).

On a personal note, our overall impression from this wide-ranging workshop is that the days of neo-phrenology are over. Very soon, it will be insufficient to establish that a given brain region or neuron 'lights up' during a single experimental task. In the brave new world of effective connectivity, it is the underlying inter-region and inter-neuronal contingencies and temporal dynamics that will form the foundation upon which rigorous descriptions of brain function will be built.

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