

domain. Public access to the data will await peer-reviewed publication, anticipated in early 2003.

In addition to the possibility of identifying clinical candidates, one outcome of the program is certain to be the discovery of new biological activities of known drugs. This will inform new attempts to dissect pathogenic mechanisms and identify sub-cellular and molecular players. Further, even if none of the 1040 compounds is immediately useful for humans, the information about their unexpected actions should provide valuable leads to the development of related drugs.

Cautions

Most of the tested drugs are currently available to doctors and, thus, to patients. All consortium participants were

concerned about the premature release of potentially misleading preliminary data. Both the participants and the sponsors of the consortium are naturally eager to move potential treatments quickly from bench to bedside. With this goal in mind, all agreed to expedite careful statistical analysis and to publish as quickly as possible. All also agreed on the desirability of extending the experiment further, to the rapid testing of candidate compounds in animal models of neurodegeneration.

Conclusions

Although the scientific impact of this unusual collaboration is still unknown, the results of the cooperative experience are clearly positive. Investigators from 26 independent academic laboratories exchanged unpublished data, formulated shared goals and devised a plan to achieve

them. Whether or not a new treatment immediately emerges from this effort, this consortium has already defined a new method for joining forces to speed drug discovery in academia.

Jill Heemskerk*

Technology Development Program, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA.

*e-mail: heemskj@ninds.nih.gov

Allan J. Tobin

Brain Research Institute, University of California, Los Angeles, CA 90095, USA.
e-mail: atobin@mednet.ucla.edu

Lisa J. Bain

206 Lake Road, Fleetwood, PA 19522, USA.
e-mail: lbain@nasw.org

Exploring brain connectivity: a new frontier in systems neuroscience

Narender Ramnani, Lucy Lee, Andrea Mechelli, Christophe Phillips, Alard Roebroek and Elia Formisano

Functional Brain Connectivity, held on 4–6 April 2002, Dusseldorf, Germany.

The organization of the primate brain is based upon two complementary principles. The first is that of 'modularity' – specialization of function within different regions of the brain, with local assemblies of neurons in each area performing their own unique operations on their inputs. The second is that functions are emergent properties of interacting brain areas within networks. This dichotomy lends itself to two corresponding approaches to explaining function. One is 'functional segregation', in which the aim is to localize functions to specific brain areas – this has been the dominant approach. The other is 'functional integration', in which function is explained in terms of the flow of information between brain areas. Until recently, there has been little focus on the distributed nature of information processing in the brain. However, lessons from traditional neuroanatomy and neurophysiology tell us that the application of functional segregation on its own will not explain brain function:

the brain is a massively parallel structure. It is composed of numerous networks of interconnected areas, and information is transferred and transformed within these. The challenge now is to understand brain function in terms of the dynamic flow of information in neuronal networks across the brain. Recently there has been a rapid expansion of interest in this issue in several different disciplines. Each has made significant contributions and has generated its own perspective on the issue, but this level of diversity makes integration between disciplines difficult. To redress this, Rolf Kötter (C & O Vogt Brain Research Institute, Dusseldorf, Germany) and Karl Friston (Wellcome Dept of Imaging Neuroscience, London, UK) organized a multi-disciplinary workshop on Functional Brain Connectivity. The conference brought together researchers from several disciplines whose common interest was to develop a better understanding of how the principle of functional integration is implemented in the brain. It is beyond the scope of this report to cover the events in the workshop

comprehensively. Rather, we have focused on four themes that emerged as key areas of interest and controversy.

Conceptual and theoretical frameworks for studying connectivity

One of the emergent themes at the workshop was the realization that the widely used terms 'functional' and 'effective' connectivity have had different meanings depending on the scientific background of the researcher. General discussion resulted in a degree of convergence. Studies of functional connectivity look for temporal correlations between neurophysiological events, regardless of the anatomical routes through which such influences are exerted. However, studies of effective connectivity look for the influence that one neural system exerts over another in the context of a particular anatomical model that specifies such routes a priori. The characterization of brain activity in terms of functional connectivity is therefore 'model-free', whereas the characterization of brain activity in terms of effective connectivity requires a 'causal

model', in which regions and connections of interest are specified by the researcher. There was also some emphasis on the fact that conceptual notions of connectivity can be invoked in both electrophysiology and neuroimaging, and that the nature and the scales of these methods differ considerably. It was generally agreed that distinguishing unambiguously between functional and effective connectivity might not be possible simply by looking at the data. These difficulties are the reason why, in practice, the characterization of imaging data in terms of either functional or effective connectivity often depends on the hypotheses that motivate the study.

Functional and structural connectivity in the human brain

A major source of controversy was the issue of whether or not *in vivo* magnetic resonance imaging (MRI)-based tract-tracing methods are useful for characterizing anatomical connectivity in the human brain. Recent studies have suggested that patterns of white matter fibres can be mapped non-invasively *in vivo* using diffusion tensor imaging (DTI). One application of this approach is to use data from such studies to guide functional imaging studies of functional and effective connectivity. There was a clear polarization of views: Rainer Goebel (University of Maastricht, The Netherlands) presented results in which anatomical connectivity (as measured by DTI) and functional activity [using high-field functional MRI (fMRI)] were investigated in anaesthetized cats. Martin Koch (University of Hamburg, Germany) illustrated a comparison of anatomical connectivity (as measured with DTI) with functional connectivity (as measured with fMRI in a resting state) in human subjects. Despite emphasizing the importance of validation, both Goebel and Koch defended the usefulness of such approaches. However, Karl Zilles (Institut für Medizin, Jülich, Germany) asserted that DTI is not useful for mapping anatomical connectivity, because DTI estimates fibre trajectories only indirectly and is inherently incapable of revealing anatomical connectivity at the synaptic level. He presented an alternative probabilistic analysis of fibre-tracts in a standard reference space that might be used to complement structural and functional data in the same reference space.

Statistical methods for measuring connectivity

A core theme in the workshop was the development and use of statistical methods to characterize connectivity in the brain. Friston introduced the principles of 'dynamical causal modelling'. In this framework, brain circuits can be represented as dynamic systems, and the effective connectivity between brain areas then characterized. This depends on a description of the system in terms of differential equations, the parameters of which reflect the coupling between brain regions and the relationship between neuronal activity (the hidden state variable), the measured haemodynamic fMRI response (output) and the stimuli presented to the patient (input). Jim Stone (University of Sheffield, UK) presented the general idea behind independent component analysis, the goal of which is to recover independent sources given only sensor observations that are unknown linear mixtures of the unobserved independent source signals. Nicholas Schiff's (Weill Medical College, Cornell University, NY, USA) talk introduced the use of auto-regressive (AR) models on electrophysiological time series. The basic idea of AR models is that one can predict the signal at a specific time as a combination of the signal at previous time instants and a noise component). The AR model can be linear (with the signal expressed as a linear combination of the previous values) or non-linear (with the combination involving interactions between the previous values).

Connectivity examined with physiological methods and models

Physiological methods of studying connectivity can be based on both observation (i.e. simultaneously observing the responses of neuronal populations in different parts of a network) and intervention (i.e. observing the effects of disrupting neuronal activity in sites remote to the disruption). Mark Hubener (Max Planck Institute of Neurobiology, Martinsried, Germany) presented results from an experiment in which anatomical connections revealed by direct electrical stimulation were compared with functional data from optical imaging of visual cortex. Similarities in size and location of activated areas suggested that functional

responses to physiological stimuli depend, in part, on anatomical connections revealed by electrical stimulation. The ability to manipulate the excitability of a brain area during functional imaging is a powerful tool. Tomas Paus (Montreal Neurological Institute, Canada) discussed transcranial magnetic stimulation (TMS) as a technique for altering neural activity in humans. He presented a method of combining TMS with positron emission tomography (PET), and a series of experiments comparing changes in neural activity secondary to TMS with patterns evoked by physiological stimuli. Because TMS is independent of behaviour, changes in neural activity are not confounded by the ability of a subject to perform a task, or by strategy. Secondly, the combination of TMS with PET can be used to alter activity of one brain area and observe the effects on activity elsewhere – an experimental strategy lending itself readily to analyses of effective connectivity.

In summary, this worthwhile workshop provided a forum in which there was a great deal of thoughtful and constructive debate that was often lively and controversial. The diverse backgrounds of those attending ensured there was ample scope for most to make a contribution and to learn from those outside their own immediate fields. It succeeded in its purpose, which was to assist inter-disciplinary integration by identifying common strands of interest and thinking across many areas of functional brain research.

Narender Ramnani*

Centre for fMRI of the Brain, University of Oxford, UK.

*e-mail: nramnani@fmrib.ox.ac.uk

Lucy Lee

Andrea Mechelli

Wellcome Dept of Imaging Neuroscience, University College London, University of London, UK.

Christophe Phillips

Cyclotron Research Centre, University of Liege, Belgium.

Alard Roebroeck

Elia Formisano

Dept of Neurocognition, University of Maastricht, The Netherlands.