Non-invasive imaging of brain structure and function in neural connectivity analysis

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The organisation of the brain amounts to ordered topography, wherein sets of neural connections preserve the relative organisation of cells between regions. This topography often characterises projections from peripheral sense organs to the brain, but it also seems to contribute to the anatomical and functional organisation of higher brain centres, for reasons that are poorly understood.
Various authors suggest that greater understanding of brain topographic maps could prove pivotal in fostering strong links between genetics, neurophysiology and cognition.
To unravel the trillions of neural connections in the human brain and promote a fundamental understanding of brain function and dysfunction, new approaches are needed. These approaches should be based on principles of synthesis, aiming to arrive at formal, mechanistic descriptions of how the behaviour of neuronal systems results from the interactions of their elements.

Until a decade ago, brain connectivity and neural system analysis were low down on the scientist's agenda. This was partly due to the absence of suitable methodologies and partly due to a lack of exchanges between experimental and theoretical neuroscientists. To gain a better understanding of brain connectivity in its various forms an explicit systems perspective is needed in which putative mechanisms of how brain function is constrained by brain structure are mathematically formalised and made accessible for experimental investigation.
Until now, researchers and theorists from various fields have responded to the neural system analysis challenge by investigating and analysing cortical micro- and macrocircuits, models of neural dynamics at multiple scales and "resting state" networks, and linking anatomical and functional connectivity.
Models of neural system dynamics are very closely linked to brain connectivity in its various forms. *Structural connectivity*, i.e. the anatomical layout of axons and synaptic connections, determines which neural units can interact with each other directly and thus constrains the system's functional and effective connectivity. *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 one another.

A novel application of MRI is emerging as a critical tool in brain connectivity and neural system analysis. We refer to diffusion spectrum imaging (DSI), which has been used successfully to document neural fibres running through the human cortex, paving the way for the neuroscientist to investigate brain structure and function.
Neuroimaging has indeed proved to be extremely useful in neuroscience research and of great benefit in studying the human brain in healthy and diseased states. Non-invasive brain imaging offers a unique opportunity to peer into the inner workings of the brain to monitor normal and abnormal changes in structure and function, to diagnose human brain disorders and to monitor response to therapy. Today, brain imaging can encompass multiple levels of analysis, e.g. from molecules to cell activity to neural connections, using multi-modality approaches.
Diffusion spectrum imaging (DSI) could serve as the means for developing a fundamental understanding of the brain. As Sporns has pointed out, "If we know how the brain is connected, we can predict what the brain will do".
For some time now, researchers have also been using other forms of diffusion imaging to create gradient maps that indicate the diffusion of water molecules through brain tissue. Diffusion tensor imaging (DTI), another type of mapping, may be used with functional magnetic resonance imaging (fMRI), or in place of it, to show the paths taken by brain fibres, thereby allowing critical tracts to be avoided during neurosurgery. DTI may also be used to identify areas of the brain associated with thought processes and to explore whether and how brain connectivity changes with advancing age or during the course of disease and dysfunction.
Used to measure acute alterations in the segregation of neuronal functions and connectivity within the brain, fMRI is being applied largely experimentally to assess brain function associated with focal brain lesions, the process of reconnecting parallel neural processing networks during recovery, and the reorganisation of motor and language networks following rehabilitation.

Functional brain imaging is an area of neuroscience research that is rich in complex data – complex in both the temporal and the spatial domain – that allow investigation of the neural basis of human sensory, motor, emotional and cognitive function. This very richness precludes easy understanding and creates the need for an equally elaborate computational approach to data analysis and, equally important, data interpretation. Computational modelling of functional brain imaging data can occur at multiple levels (microscopic and macroscopic), and bridging models will be necessary to blend all these approaches into coherent and consistent accounts of brain function. Computational modelling and functional brain imaging data are extremely helpful, if not indispensable, for a mechanistic understanding of neural systems.

There is, indeed, broad consensus in the neurosciences that mathematical system models are probably indispensable for such an understanding and considerable progress is currently being made in the mathematical modelling of neurophysiological and cognitive processes.

These new computational models are more clearly defined and more detailed than their qualitative counterparts. They can be set up to be consistent with both single-neuron and whole-system levels of operation, allowing physiological results to be meshed with behavioural data – thus closing the gap between neurophysiology and human behaviour.

There is considerable diversity between mathematical models with respect to the model designing methodology, the degree to which neurophysiological processes are taken into account and the way in which data (behavioural, electrophysiological, neuroimaging, etc.) constrain a model. Moreover, given the brain's overwhelming complexity, it is mandatory for any neural system model to find a sufficiently energy-efficient, yet neurobiologically plausible, conceptual framework for investigating the neuronal dynamics, neural functional integration and changes in connectivity that are critical for development, learning, perception and adaptive response to neural injury and brain damage.

A central question, however, concerns the validity of such models. This question has many different aspects.

One aspect is that of model comparison and model selection: in the presence of several alternative hypotheses about the mechanisms underlying a given system, and thus multiple competing models, how can we decide which of these models is best?

A second aspect, relating to model validity, concerns the relationship between specific model parameters and specific neurophysiological processes or properties.

Quantitative analysis of the properties of neural networks provides a level of clarity and detail that is essential to answering these questions, as shown by the growing interest, among scientists, in the mathematical approach to neural connectivity.

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