Archives Italiennes de Biologie, 148: XX-XX, 2010.

Overview: integrating computational, cognitive and clinical expertise to understand brain network recovery

A.R. MCINTOSH[1], F. GHILARDI[2], O. SPORNS[3]

[1] Rotman Research Institute of Baycrest Centre, University of Toronto, Toronto, Ontario, Canada; [2] SMILab, Department of Physiology and Pharmacology, City University of New York School of Medicine, New York, USA; [3] Department of Psychological and Brain Sciences Programs in Neuroscience and Cognitive Science, Indiana University, Bloomington, Indiana, USA

Network theories of cognition suggest that units in the brain process information in some coordinated spatial and temporal order to support cognition and behavior. In bridging between the neural dynamics and cognitive function, most theories have made use of traditional neuropsychological studies with patient populations, wherein cognitive functions are ascribed to the area(s) that are damaged in the patients. When complemented with neuroimaging, such information provides clues about "where" in the brain certain cognitive operations are likely to take place, but provide virtually no information on "how" this operation occurs.

Perhaps one problem with making the translation to "how" is that we know so little about how the damaged brain operates. It is well-known that damage to specific brain regions results in widespread changes that compromise normal network functions. Disruption of a network – via damage to nodes or the connections among nodes – can result in cognitive and behavioral dysfunction. What is unclear is how much to attribute the dysfunction to the loss of the region per se, versus the operations of dysfunctional network. It is clear that there would be main gains from a concerted exploration of the network dynamics of the damaged nervous system, both in terms of the initial responses and the factors that govern the course of recovery.

A better appreciation of the network dynamics in the damaged nervous system can impact on two levels. First, in terms of neuroscience theory, if we find that many of the dysfunctions come about because of network reorganization, then this will change how we consider the translation of brain function to behavior. Second, examining the operations of the damaged brain from the perspective of interacting neural systems will provide new insights into the reorganization that takes place after damage. An increasingly prevalent idea in the field of cognitive rehabilitation is to design interventions exploiting "neural plasticity" to help individuals with brain damage develop "new strategies" for accomplishing tasks in everyday life – but it is not quite clear what rehabilitation professionals mean when they use such terms. Focusing directly on the operations of the damaged brain, we may be able to define better the conditions that determine how networks will reorganize (e.g., locations, severity, and extent of the neurological damage). Coupled with detailed neuropsychological and psychosocial information on the patient, new principles that govern brain network reorganization could better inform rehabilitation strategies.

The articles collected in this Special Issue reflect the concerted effort of a group of researchers whose interests intersect in the areas of clinical, cognitive and computational neuroscience, with a thematic focus on network mechanisms of brain recovery (the Brain Network Recovery Group or Brain NRG: www.brainnrg.org). These papers capture our achievements over our first 5 years. The articles roughly align along two domains: one focused on

Corresponding Author: Anthony Randal McIntosh, Rotman Research Institute, Baycrest, 3560 Bathurst Street, Toronto, Ontario, M6A 2E1, Canada – Tel.: 416 785 2500 ext 3522 - Fax: 416 785 2862 - Email: rmcintosh@rotman-baycrest.on.ca

theoretical and methodological developments and second is the application to studies of brain network recovery.

In their paper, *Jirsa et al*. propose a new computational platform, the Virtual Brain, which can be used to predict a brain network's responses to pathological processes, in terms of dysfunctions, recovery and repair. In their theoretical framework, they explain the emergence, during the resting state, of structured spatio-temporal patterns from noise-driven explorations of network functional states. Structural connectivity, population dynamics of network nodes, time delays in signal transmission, and noise are presented as the main players that shape the dynamics of the brain's networks.

The construction and analyses of large, heterogeneous neuroimaging and related data of patient population and normal control groups is indeed of crucial importance to understand the complex neural circuitry and the processes that support brain function and recovery from injuries. *Gee and colleagues* present a detailed overview of three systems that have been recently implemented to predict cognitive and behavioral recovery after stroke or other types brain injury and disease.

Price and colleagues used one of these three systems, PLORAS, to predict which stroke patients without object recognition and hand movements deficits would have chronic difficulties in how to use an object. They found five of such patients in a database of 157. By comparing the lesions sites of these five patients and searching the entire database for ~~patients with for~~ patients who had damage to any part of regions, they identified which regions in temporal and parietal lobes impair the ability to gesture object use and which parts need to be intact to support it after damage. This method provides an impressive framework to predict the consequences of brain damage.

Solodkin et al. proposes the "virtual brain transplantation", a detailed and quantifiable anatomical description of the regions affected directly by the stroke. This is a semi-automated method that is based on preprocessing high resolution T1-weighted images by "filling in" the lesion with "transplanted virtual tissue" from the nonstroke hemisphere. This provides "normal" anatomical landmarks for standard alignment and inflation algorithms developed for normal subjects. This approach can potentially facilitate group-level fMRI analyses in patients with large cortical strokes.

In an exhaustive review, *McIntosh et al.* provide us with compelling evidence that, indeed, a noisy brain is a healthy brain. Maturation and development correspond to an increasing number of possible functional network configurations for a given situation that can be captured in the variability of endogenous and evoked responses or "brain noise". In infants and children, such an increase in brain noise is paralleled by stable behavior and performance accuracy. In normal old adults, brain noise continues to change, but not as globally as in early development. The relation between high brain noise and stable behavior is maintained, but the relationships differ by region, suggesting changes in local dynamics that then impact on potential network configurations. These data, when considered in concert with the extant modeling work presented in *Jirsa et al*, suggest that maturational changes in brain noise represent the enhancement of functional network potential – the brain's dynamic repertoire.

Such investigations can be extended to brain dysfunction in patients with neurological problems, as demonstrated in two different patient populations. In an elegant study, *Protzner et al*. measured the "brain noise" in patients with temporal lobe epilepsy who had intracranial hippocampal electrodes. They recorded and analyzed brain signal complexity during a memory task of encoding and recognition and found that the epileptogenic hippocampus showed less complexity – or noise – than the healthy hippocampus, mostly during the encoding phase. In a longitudinal study, *Yourganov et al.* explored the functional connectivity with fMRI in stroke patients recovering from unilateral stroke affecting the motor area. They used and compared different measure of brain noise and complexity to predict the changes of performance in a series of behavioral task.

The understanding of the neural substrates of cognitive functions and their pathological changes is extremely important in order to increase the odds of their potential recovery. High Density EEG in conjunction with behavioral tasks can be helpful in defining the neural bases of cognitive and other symptoms and in measuring the plasticity changes occurring during sleep. The work by *Perfetti and colleagues* show that in patients with Parkinson's disease, the pattern of the EEG correlates of attentional processes of movement planning predict sequence learning and working memory abilities. It further suggests that motor and non-motor signs might share common bases and, thus, have similar responses to the same therapy. This approach and these results can help in designing and testing the efficacy of novel rehabilitative approaches in Parkinson's disease and other neurological disorders. In compelling study, *Sarasso et al.* present preliminary data on the use of topographical analysis of sleep slow-wave activity in the investigation of plastic changes underpinning functional recovery in aphasic stroke patients. This technique can be used in several neurological populations, as it allows for a non-invasive and repeatable assessment of local brain changes.

Finally, the review paper by Tononi reminds us that it is both specialization and functional integration in brain networks that are responsible both for the brain's cognitive proficiency and robustness, as well as for generating consciousness. In the first theoretical part of his work, he revisits and extends concepts related to the idea that consciousness is a function of a system's capacity for information integration. Both the quantity and the quality of experience can be accounted for in terms of the information structures – or *qualia* – generated by a complex of mechanisms. He discusses how information integration can vary with the spatial and temporal grain size of the interactions within a system, introducing the definition of 'emergence'. He then considers how a system's capacity for information integration reflects its ability to 'match' the causal structure of the world. In the second part of his article, Tononi provides strong arguments to the fact that understanding information integration is important for analyzing cognitive functions, their pathological changes, and for efficiently promoting their potential recovery.

Final words

Over the years, our work has evolved in numerous new directions. New collaborations and partnerships have formed, new ground has been broken in understanding how the brain responds and adapts to injury and disease. Sadly, one of us was not to see this Special Issue become a reality. Rolf Kötter, a central member of our group from the very beginning, passed away in June 2010. Rolf's many scientific and intellectual contributions were absolutely essential for the success of the group as a whole, spanning from neuroanatomy to recovery of function in patient groups. One of his seminal contributions, not only to our group but to the broader scientific community, was the creation of the CoCoMac database (www.cocomac.org). This database was an important innovation for the neuroscience community, providing an integrated on-line source for information on anatomical connections in the brains of non-human primates. Without question, CoCoMac was a key factor in enabling the explosive development of graph theory applications to neuroanatomy, and for the development of large-scale computational models (e.g., *Jirsa et al.*). Our feelings of sympathy are with his wife and children. We hope that the memory of Rolf will give his family the strength to deal with this tragic loss. We will miss Rolf, and we will always remember him as a tremendous scientist and as a wonderful person.