Connecting the dots

Drs Alard Roebroeck and Michael Capalbo, of the Computational Brain Connectivity lab, outline their research into human brain connectivity that aims to reveal the mechanics behind behaviour and visual perception – insights that are helping unravel the mysteries of the human condition.

Could you begin by giving a brief overview of the key research aims of the Computational Brain Connectivity (CBC) lab?

The CBC lab aims at measuring brain connectivity and understanding how it supports computation in the human brain. We measure brain connectivity mainly using advanced magnetic resonance imaging (MRI) systems and microscopes. Then, by constructing and testing computer models of how structural connections shape neuronal activity, we understand more about the function of all the connections. If we can measure the connections and understand how they support computation and inference, we learn more of how our brain embodies who we are: what we remember, how we react and what we believe.

Do you face any challenges in devising connectivity models of the brain? How do you overcome these difficulties?

Understanding the brain requires unravelling and understanding the complex connected networks of neurons within it, which is a gigantic challenge. Just one cubic millimetre of cerebral cortex contains 50-100,000 neurons that use 4 km of axonal wiring to make at least 300 million local connections. Many thousands of such local microcircuits in turn make remote connections to other cortical and subcortical brain areas.

Mapping and understanding this system requires overcoming several technical challenges in using some of the world’s biggest human MRI machines combined with advanced light microscope techniques. The large amount of high-resolution MRI and microscope data is analysed with large highly parallelised computers to deliver higher resolution atlases of connectivity in the human brain.

How did you derive your connectivity model of the visual system? To what extent does this model improve on previous attempts?

The ultimate connectivity of the human visual system is still unknown, but this does not stop us from trying to propose a large-scale computational structure of the visual system. One of the limitations of the computational models proposed to date is that the time it takes for the neural signal to reach a certain area often seems inconsistent with the place of that area in the overall structure of the system. For example, the signal might arrive relatively quickly at an area located ‘higher’ in the visual system – i.e. an area in the front of the brain responsible for higher order functions – and slowly at an area located in the ‘lower’ part – i.e. the subcortical regions of the brain.

In our computational work, we have combined data about the known connectivity in the monkey brain with microelectrode timing data to find a network structure that is consistent with both. The results show that timing data can be explained when the network contains direct routes from the lower areas to higher areas. We show that our model has fewer limitations than previous models and might explain unresolved issues in the study of connectivity in the human brain.

How do you gather information on cognition? What have you discovered as a result?

One might say that modern imaging methods are better at relating the brain to behaviour but only provide indirect evidence, whereas ex vivo methods provide more direct and detailed proof that is harder to relate to behaviour. We aim to bring together all these methods on different scales as ‘converging evidence’. For example, in one study we combined function from in vivo microelectrode recording with structure from tracing techniques to arrive at a large-scale map of the visual system. Another example would be the work in which we tried to set a ‘gold standard’ for diffusion MRI (dMRI). In this work, we combined ex vivo optical microscopy of stained tissue with detailed ex vivo dMRI to see exactly what in vivo dMRI tells us about structural connectivity.

Do you have plans for further research? If so, what do you expect to achieve in the coming year?

We would like to combine a search for structural connectivity between brain areas involved in perception with measurements of functional interactions between these areas. To do so, we need methods that can assess this at both the micro and macro scale. We would like to relate results from light microscopes, utilising new techniques such as two-photon microscopy and light sheet microscopy, to results from diffusion imaging acquired with the high-end systems we have available. In turn, we would like to relate these findings to the function of the brain through functional MRI. We believe the integrative approach is the only way to truly understand the mechanisms behind perception, and also behaviour in general.
Neuroscience researchers at Maastricht University in The Netherlands are integrating a number of methods in order to map connectivity in the human brain and aid the treatment of neurological disorders.

THE HUMAN BRAIN is a unique and extraordinary organ, and one of the most complex biological systems known to exist. Although many other organs contain the same number of cells as the brain, it is the intricate connectivity between brain cells that sets it apart. Each of its 85 billion neurons makes on average 10,000 connections with other neurons, enabling the brain to complete incredible cognitive tasks. Although scientists are now aware of the structure and role of each area of the brain, it remains an enigmatic and puzzling system. Understanding a system that is so dependent on connections requires describing and mapping connectivity, and research in this field promises to finally unlock the secrets of the human mind.

Making connections

In recent years, neuroscientists have become increasingly fascinated by the connectome – a structural and functional atlas of the brain. Compiling these data is a task of immense proportions, requiring every connection between every cell to be described (on the micro scale), as well as all the connections between each different area of the brain (on the macro scale). It is complicated further by the fact that there are so many connections that they cannot be coded in genes.

The Human Genome Project was a similarly vast undertaking that is now widely considered a success. It is perhaps partly this story that inspires such fervour in neuroscientists – a project that seemed unfathomable but was aided by advances in technology and ultimately finished ahead of schedule. Connectomics may have the same effect on neuroscience that genomics had on genetics, but with the potential to provide an even greater understanding of the brain’s influence on human behaviour.

Merging techniques

When confronting the immensity of the brain’s connectome, it can be helpful to divide the concept of connectivity into two parts: structural and functional connectivity. Structural connectivity involves the structural links between physical cells, whereas functional connectivity is the correlation between the activities of different brain structures. In order to build up a complete map of all connections in the brain on both a macro and micro scale, both of these approaches must be considered.

This is the foundation of the research at Maastricht University’s Faculty of Psychology and Neuroscience (FPN) in The Netherlands. Led by Drs Alard Roebroeck and Michael Capalbo within the larger Neuroimaging and Neuromodeling Methods lab of Professor Rainer Goebel, the Computational Brain Connectivity (CBC) lab aims to overcome the limitations of current models used to assess connectivity. Roebroeck and Capalbo argue that models often provide incompatible results, even when describing the same system. The team is integrating multiple approaches, combining data obtained from advanced optical microscopy with neuroimaging results, in order to develop more comprehensive and robust models.

Many methods

Light microscopy techniques may be the most basic and obvious way to study connectivity by investigating how neurons or groups of neurons are physically connected. The benefit of these methods is that they provide direct proof of activity or connections, and can measure at the micro scale. An explosion of new methods, such as two-photon microscopy and optogenetics, has enabled new ways of probing activity and functional connectivity. However, they can only be used in animals as they require either introducing genetic modifications or invasive recordings and subsequent post-mortem analysis in prepared brain slices. In addition, due to the invasive and time-consuming nature of such techniques, results are gathered incrementally and scattered across hundreds of separate research publications. In contrast, magnetic resonance imaging (MRI) techniques can take images of the brain and its activity in living human subjects while they are awake and behaving, but require significant interpretation and most offer information on connectivity only on the macro scale. A promising avenue pursued by the CBC lab is to apply both MRI and light microscopy techniques to human brain tissue post-mortem. This multi-modal approach benefits from the combined strengths of the techniques for structural connectivity.

Towards efficiency

In early work published in 2008, Capalbo and colleagues utilised a database of information from studies of the macaque monkey brain –
INTELLIGENCE

COMPLICATED CONNECTIONS: THE NEED FOR AN INTEGRATIVE APPROACH

OBJECTIVES
The CBC lab aims to measure brain connectivity and understand how it supports computation in the human brain, by constructing computer models of how structural connections shape neuronal activity.

TEAM MEMBERS

Group leader: Dr Alard Roebroeck

Team: Dr Michael Capalbo, Dr Martin Havlicek, Matteo Bastiani, MSc, Arne Seehaus, MSc, Shubharthi Sengupta, MSc, Robbert Harms, MSc

CONTACT

Dr Alard Roebroeck
Department of Cognitive Neuroscience
Maastricht Brain Imaging Centre (MBIC)
Faculty of Psychology & Neuroscience
Maastricht University
Universiteitssingel 40
Maastricht, 6229 ER
The Netherlands
E a.roebroeck@maastrichtuniversity.nl

Dr Michael Capalbo
Faculty of Psychology & Neuroscience
Maastricht University
Universiteitssingel 40
Maastricht, 6229 ER
The Netherlands
T +31 43 388 4037
E m.capalbo@maastrichtuniversity.nl

www.cbclab.org
www.maastrichtuniversity.nl/web/Profile/m.capalbo.htm

DR ALARD ROEBROECK obtained his PhD from Maastricht University in 2006 on diffusion tensor imaging and functional connectivity using functional magnetic resonance imaging (fMRI). He is currently Assistant Professor at the Faculty of Psychology and Neuroscience, Maastricht University and co-Director of the Brains Unlimited ultra-high field MRI scanner lab.

DR MICHAEL CAPALBO is currently the Director of Undergraduate Studies at the Faculty of Psychology & Neuroscience. His current research is on the connectivity of the visual system studied with fMRI, diffusion MRI and computer models.

CoCoMac – to create a model of the large-scale structural connectivity of the visual system. These data were then combined with single-unit recording data in order to find networks with a connectivity pattern that fitted both datasets. The resultant, more constrained model not only eliminated observed inconsistencies, but also provided insight into possible connections that had not been investigated at the time, or had been excluded. It also offered solutions to previously unresolved issues in the human visual system. Importantly, Capalbo’s revised model was shown to be capable of being extended to include newer, and other kinds of data.

A year later, Roebroeck and collaborators published a detailed investigation into the best way to study how different brain areas interact. This knowledge is important for all research into connectivity. The results showed that no single model is best: “The brain is an immensely complex system that is neither linear, nor deterministic, and therefore unlikely to be accommodated by one single ‘master’ model,” argues Roebroeck. Hence, instead of striving for this master model, Roebroeck set out a clear path for the development of connectivity models in cognitive neuroimaging, requiring transparency in model assumptions and arguments for the relative merits of different models before conducting a study.

A related investigation by Roebroeck, Matteo Bastiani and colleagues later set out to assess diffusion MRI (dMRI) methods used to study the human macro-scale connectome, in which all individual measurements have to be put together to reconstruct complete brain fibres. This study provided a complete overview and quality assurance technique for every method proposed. Roebroeck, Arne Seehaus and collaborators recently combined MRI and light microscopy to define a ‘gold standard’ for connectome construction using dMRI.

FACILITATING RESEARCH

dMRI measures the directional gradient of water diffusion in the brain with an MRI scanner to visualise fibre bundles. By computationally analysing raw dMRI data, large fibre bundles can be traced between areas, allowing connectivity of large coherent bundles of axons to be inferred.

Now taking advantage of the new Scannexus facility in their university, which houses three MRI scanners with large magnet strengths – the strongest scanner being one of only four 9.4 Tesla scanners in the world – the CBC group can see the brain in far more detail than before, as well as refine the dMRI technique. Whereas the standard resolution for scanners is around a few millimetres, the state-of-the-art Scannexus facilities can view at resolutions under a millimetre. Such level of detail is a crucial improvement, as the layers of neurons in the cortex of the brain have a thickness often measured in hundreds of micrometres.

CLINICAL APPLICATIONS

The CBC group contributes expertise in advanced dMRI and mapping protocols acquired in their research to enhance diagnostic capability and understanding of the effects of neurodegenerative and neuroinflammatory diseases. For instance, their work with MRI and dMRI has led to active ongoing collaborations in diagnostics and treatment improvements for multiple sclerosis.

The team also collaborates with several specialists from inside and outside their institute who are experts on deep brain stimulation, a treatment for several neurological diseases, most prominently Parkinson’s disease. State-of-the-art MRI devices could improve localisation of the brain areas that need to be stimulated and thereby improve treatment efficacy and reduce the strain on the patient during surgery.

As Capalbo observes: “Neuroscience, cognitive neuroscience and computational neuroscience are all partly defined by the methods they employ”. By striving to improve methods, the CBC team is expanding the reach of these disciplines in the hope of realising the dream of one day completely mapping human brain connectivity.