The human connectome: just another 'ome?

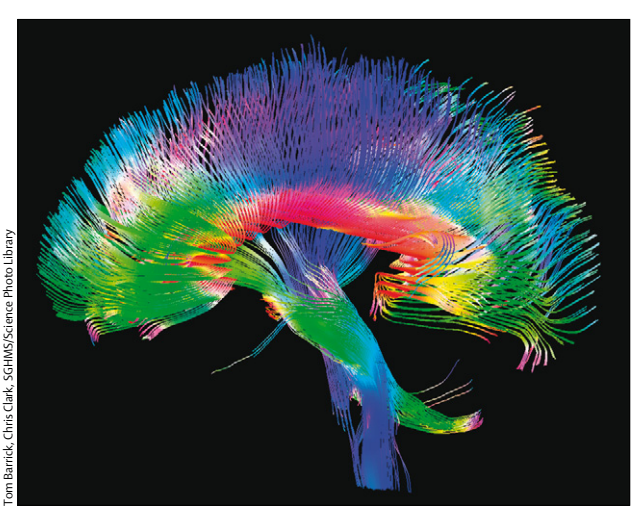
After the Human Genome Project there came proteomes, transcriptomes, and epigenomes. There was even a Human Microbiome Project launched last year by the US National Institutes of Health. Are neuroscientists just jumping on the 'ome bandwagon, or is there truly a benefit to deciphering and detailing the human connectome? Ruth Williams reports.

We are still a long way from understanding how the human brain is wired, yet this might change with recent advances in imaging technology. Diffusion-based MRI approaches have reached unprecedented levels of resolution, and promise to zoom in even further. Boosted by this promise, in July last year the National Institutes of Health (NIH) Blueprint for Neuroscience Research launched the US$30 million, 5-year Human Connectome Project. Its primary aim is to compile imaging data from hundreds of participants into a circuitry map of the human brain. As Nora Volkow, director of the National Institute on Drug Abuse (NIH, Bethesda, MD, USA), puts it, it will be a map of the brain's information highways.

For more on the **Blueprint for Neuroscience Research** see neuroscienceblueprint.nih.gov

For more on the **Human Connectome Project** see www.humanconnectomeproject.org

News of this neurological roadmap has generated much excitement and enthusiasm. One researcher raved that it was a "great project", and that "NIH should be congratulated". Another described it as the greatest conceptual leap forward in neuroscience since the discoveries in the 19th century of the effects of focal brain damage.



Tom Barrick, Chris Clark, SGHMS/Science Photo Library

However, not everyone is feeling so enthusiastic about the initiative. It has been suggested that the project is simply a means for the USA to systemise and control the data, and to appoint itself as leader of the connectivity field. It has also been suggested that the initiative is a way for a small group of insiders to give themselves large sums of money. So do the pessimists have a point, or is funding the Human Connectome Project money well spent?

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Clifford Jack, a radiologist at the Mayo Clinic (Rochester, MN, USA), says that while he thinks the scientific questions posed by the connectome initiative are interesting, he fears that the project will result in "huge NIH expenditure relative to the scientific productivity". He suggests that "science would be much better served by funding more individual investigator-initiated grants".

Richard Frackowiak, neurologist at the Centre Hospitalier Universitaire Vaudois (Lausanne, Switzerland) agrees: "They keep inventing these mega initiatives instead of just getting down in the lab to do it!" He points out that there are already many individual groups of investigators around the globe producing connectivity data. His own group is among them.

One of Frackowiak's concerns is that systematising the data might make it harder for some groups to publish findings on the topic. "They want to create a great big bunch of rules so that we won't be able to publish anything, unless we do it their way", he says, comparing it to the situation with the image repository for functional MRI whereby certain journals demand that researchers deposit their data in a repository before considering those data for publication.

Arthur Toga, neurologist at the University of California Los Angeles School of Medicine (CA, USA), insists there is a genuine benefit to systematising data in this way. With one-off studies, he says, there may or may not be associated genotype data, electrophysiological data, or functional data. If there was a mandate on the collection of these data, he says, you could begin to understand the relation between how the brain is wired, how this wiring varies in the population, and how it relates to functional activity. "By dictating both the scope and the magnitude of the project in a single effort, it gives us a unique opportunity to put this all together", he says.

"What you really need are methods that are standardised", argues Frackowiak, "because the data themselves are very specific to the particularities of the experiment."

Were Toga's suggested strategy to be realised, the Connectome Project would go far beyond being a mere neurological highway map. Indeed, says Volkow: "If you map the highways of the United States you will get an idea of the importance of cities and states and geographical locations, but you need to have the dynamic of traffic—how frequently

and when and in which directions these highways are used—to get the real picture of how these communications work."

Whether or not collecting multimodal data, as Toga suggests, is feasible, Frackowiak does agree that the project would be a worthwhile pursuit if the connectome provided structural and functional data together.

Perhaps some of the objections have arisen because researchers are simply not clear on what the Human Connectome Project will entail. Indeed, even those directly involved are not sure. Story Landis, director of the National Institute of Neurological Disorders and Stroke and a member of the Blueprint for Neuroscience Research team, says: "We don't know what actually the final project is going to look like. What we're going to do is put out a request for applications and investigators will come in with what they think is the best way to come up with the connectome."

One thing that does seem likely is that initial funding will favour efforts to improve imaging technology. It is the recent advances in diffusion-based imaging approaches—such as diffusion tensor imaging and high angular resolution diffusion imaging—that have allowed the Human Connectome Project to even be considered possible. Currently, these techniques provide resolution to the fibre tract level, but greater spatial resolution is possible, believe Volkow and Landis. Maybe even down to just a few millimetres. "We realise that we're not going to see individual synapses but we'll see major pathways and probably minor pathways", Landis says. Pumping funds to the technologists now is thus a good move, says Volkow. Landis concurs: "When they started the Human Genome Project the technology simply wasn't there, but by investing and pushing the technology, now you can get billions of sequence bits for almost pennies." The same will be true for live brain imaging technology, she says.

Further down the road, funding will no doubt favour efforts aimed at assimilating all the data. If the Human Connectome Project turns out to be the multimodal database that Toga envisages, it is possible that the data would be primarily available in a visual way, for example as a 3D reconstruction, but that researchers would be able to focus on connections of interest and retrieve associated data distributions. For example, you might ask to see the connections within the frontal lobes of 35–45-year-old, right-handed women, says Toga. The output would then not only give you the 3D anatomical data for this demographic but also all the functional and genetic data.

"This approach is going to shape our understanding of brain diseases in a fundamental way for many years to come."

Of course, the search criteria might not be right-handed women, but patients with Parkinson's disease, Huntington's disease gene carriers, or patients with dystonia. These disorders, along with others including Alzheimer's disease, schizophrenia, and drug addiction, have been shown to have associated connectivity changes. Having a large, accessible database of connections from both healthy individuals and patients would provide insight into how such connectivity changes relate to disease symptoms. This, in turn, will be of benefit for predicting prognosis as well as for treating disease.

However, there are certain disorders and conditions for which mapping changes and predicting prognosis might not be possible, says Volkow. Diffusion MRI approaches rely on detecting the movement of water. Thus, in situations where water content is altered, such as stroke, oedema, and alcoholism, data may not be reliable.

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The Human Connectome Project must come up with a solution to this watery problem for its full potential to be realised. In the meantime, however, there are a substantial number of neurological disorders for which the project will serve as an invaluable resource. As Giovanni Frisoni, neurologist at the National Center for Research and Care of Alzheimer's Disease (Brescia, Italy) says: "This approach is going to shape our understanding of brain diseases in a fundamental way for many years to come."

There might be some technological issues to resolve, there might be some insider research groups that receive an unfair chunk of the funds, and there might even be some frustrating rules to abide by when submitting data. However, when weighed up against the potential of the Human Connectome Project, these concerns disappear from the minds of most researchers. One concern that does remain, however, is how exactly to build the thing.

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