"The Human Connectome Project: Progress and Prospects" with David Van Essen and Matthew Glasser

Transcript of Cerebrum Podcast

Guest: David C. Van Essen, Ph.D., is the Alumni Endowed Professor in the Department of Neuroscience at Washington University in St. Louis. He has served as editor-in-chief of the *Journal of Neuroscience*, founding chair of the Organization for Human Brain Mapping, and president of the Society for Neuroscience. He is a fellow of the AAAS and received the Peter Raven Lifetime Achievement Award from the St. Louis Academy of Science and the Krieg Cortical Discoverer Award from the Cajal Club. Van Essen is internationally known for his research on the structure, function, connectivity, and development of cerebral cortex in humans and nonhuman primates. He led the Human Connectome Project (HCP) and co-leads two Lifespan HCP projects that will acquire and share data on brain circuitry in childhood and in aging.

Guest: Matthew F. Glasser, Ph.D., a medical student at Washington University in St. Louis, completed his Ph.D. training with David Van Essen. Glasser has over a decade of experience in brain imaging research with a focus on brain anatomy and brain imaging methods development, and has authored or coauthored 41 peer-reviewed articles. He is best known for his work on reconstructing the arcuate fasciculus, the main connection between the brain's language areas; for developing novel or improved methods for mapping cortical areas, such as mapping the amount of neuronal insulation, called myelin, of the cortical grey matter based on clinical T1-weighted / T2-weighted MRI images; and for producing a new multi-modal map of the human cerebral cortex. Glasser is pursuing clinical training in neuroradiology to be a physician-scientist neuroradiologist.

Host: Bill Glovin serves as editor of *Cerebrum* and the *Cerebrum Anthology: Emerging Issues in Brain Science*. He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: On today's *Cerebrum* podcast, you're in for a real treat. The topic is the Human Connectome Project, one of the most ambitious projects in the history of neuroscience. With us are two of the key contributors, Drs. David Van Essen and Matthew Glasser, co-authors of our most recent *Cerebrum* article, "The Human Connectome Project: Progress and Prospects."

Those in neuroscience know Dr. Van Essen as a major player, a professor in the Department of Neuroscience at Washington University. He has served as editor-in-chief of the *Journal of Neuroscience*, is founding chair of the Organization for Human Brain Mapping, and a past president of the Society for Neuroscience,

but he also happens to be one of the pioneers of the Human Connectome Project, and in fact, a leader of the entire initiative.

His younger colleague, Dr. Glasser, completed his Ph.D. training with Dr. Van Essen. Dr. Glasser has over a decade of experience in brain imaging research and has authored or co-authored 41 peer-reviewed articles.

Before we begin, just a little about the project. The project used 1,200 volunteers, collaborators from several institutions, and MRI technology to create a spectacular new map of the brain. The map details nearly 100 previously unknown regions, an unprecedented glimpse into the machinery of the human mind.

That's enough from me. Welcome, gentlemen. Let's begin with: Were there unexpected surprises, both positive and negative?

David Van Essen: Well, I guess you could say the project went with some challenges but relatively smoothly. I was pleasantly surprised that we actually acquired our target number of data from 1,200 subjects, and high-quality imaging data from 1,100 of these subjects, so that was the good news, as we had hoped, but wasn't a certainty. In terms of going down to a very different level, and say, what was perhaps most surprising about the project for me personally, I'm fascinated by aspects of cortical parcellation that we've talked about at length in the article, and the two things that were surprising and scientifically most interesting to me were that the left and right hemispheres are as symmetric as we found them to be. They're not perfectly so, but all 180 areas are present in both left and right sides and the asymmetries between one side and the other are more modest than one might have guessed. Also, the fact that individuals differ in the arrangement or topology of their cortical areas is something that was definitely a surprise to me and something that Matt has explored in significant and interesting detail. Maybe he wants to say more on one or both of those fronts.

Matthew Glasser: Yeah, so I agree that the hemispheres are very symmetric. Interestingly, even if cortical areas are present in both hemispheres, they might be doing somewhat different things, so there's a particular network of cortical areas that seem to be more involved in language tasks in the left hemisphere across the average of many people, but in the right hemisphere maybe involved more in some kinds of visual tasks. There's certainly 180 areas in each hemisphere, but they may be doing different things in those hemispheres. On the question of individual variability, I was also very surprised to see that we were able to find these cortical areas and map them in multiple modalities and show that it's not like noise or something that's causing this individual variability, differences in the relationship between particular cortical area and its neighbors. We could see that across multiple modalities, and that really gave us confidence that these are real findings.

Bill Glovin: Advances in imaging are happening all the time, and since this was a project that took place in two phases from 2010 to this past summer, did the methodology shift over time?

Matthew Glasser: No. I think we were very fortunate for the NIH to have given us this development period at the beginning of the project. We were able to spend the first two years on basically improving the MRI acquisition, improving the MRI analysis methods so that we would be able to have a stable, but still cutting-edge data acquisition and analysis approach throughout the rest of the project and, in fact, in large parts we're actually continuing that approach into the follow-up projects. We have a lifespan project, an aging connectome project, and then a number of connectomes in disease projects that perhaps David can tell us a little bit more about.

Bill Glovin: Yeah. I think I'm going to get to them a little later. Have there been any groundbreaking studies published as a result of the project, and what did they reveal?

David Van Essen: Well, perhaps it's a bit immodest, but we think the cortical parcellation story that was published in *Nature* this summer is what is most exciting to us and has certainly had all signs of showing a strong impact in the field because it's essentially a new and better map of the arrangement of areas in the cerebral cortex that people have been longing for, for more than a century. It's not the final story, but it is a significant enough advance that we anticipate that many investigators, not only those using human connectome project data, but using the maps for their own studies, will be able to benefit from this. There have been other studies that and more than 140 publications emerging from the use of The Human Connectome Project.

A handful of those are, I think, are notably intriguing. One of them, for example, showing that using functional connectivity, a resting-state functional connectivity as one measure of brain circuitry, there is an arrangement of functional connectivity that correlates with a set of anotypic or behavioral and demographic characteristics that are more positive on one end of the spectrum and more negative on the other end of the spectrum, and that collection is correlated with brain connectivity. This is just an opening salvo and challenge and an exciting opportunity to relate brain circuits to brain behavior, but it's turning out to be a very daunting matter to do this incisively and in a robust way.

Bill Glovin: As your article points out, the project was a collaboration between 11 institutions and 36 investigators and mapped the genomes of 1,200 participants. Will the next phase of the project include more collaborators and more participants?

David Van Essen: Yes. The lifespan development and lifespan aging projects that Matt just touched upon briefly are both larger efforts. They involve four institutions that

are involved in data collection and one Oxford University that's continuing to contribute to data analysis. Each of them will target a larger number of subjects, basically 1,500 subjects in each of the age bands, children and aging. It's a scaling-up of the numbers of subjects and number of investigators needed to make it happen. It's a scaling-down in terms of the amount of data that we acquire from each subject, given practical constraints, so that puts an imperative on trying for even additional refinements. Going back to the issue of making improvements in the methodology, there are some that we're capitalizing on and a few more that are fingers-crossed in the offing that will benefit these lifespan projects and also the projects related to different diseases that can hopefully gain excellent-quality data from scans, even though they're not quite the same duration as they were for the young adult project that we have been talking about.

Bill Glovin: Are there issues when so many collaborators are involved, and how is a multi-collaborative project such as this one best managed?

David Van Essen: By good team work and commitment to listening to all voices, and seeking consensus whenever possible in reaching a timely decision once all voices and opinions have been heard and discussed, but it's an interesting and fascinating social endeavor as well as a scientific endeavor, indeed.

Bill Glovin: A phase I've come across in just about every article we've published is whether it's about tau proteins or new approaches for epilepsy, lithium as a mood stabilizer, is the more we learn, the more there is to learn. I couldn't help but note the use of that phase in your article's opening paragraph. I know this might be difficult, but can you sum up briefly what you hope to learn in the next phase of the project?

Matthew Glasser: Well, I think it's an important question. How can we translate some of these advances to help patient care? In terms of our new map of the brain, that's actually one that has a relatively straightforward way that we can translate it, at least in some circumstances. In addition to making that new map, we actually were able to train a machine learning tool, which we call an aerial classifier, to find the brain areas in new subjects that weren't a part of the original data set. What that means is that if we have patients to come into the hospital who need to have a neurosurgical procedure done, and the neurosurgeons want to know where these brain areas are so that they can try to avoid them while doing an operation, all we need to do is to get the right MRI scanning sequences on those patients and then we would be able to actually find those areas in individual subjects and use them for surgical planning. That would be a very straightforward kind of translation of some of this work.

More broadly, though, having a map like this is going to be really valuable to the field so that we're able to... If one investigator does a neuroimaging study and finds a set of results and their colleague does a different study, these investigators would be able to know if there are results in the same brain area

or are they in neighboring brain areas or brain areas that are further away? It will help us put together the results from different studies and try and get a better sense of what's going on. I think those are the two biggest advances and ways that the new map can help drive our understanding of diseases and actually even contribute to patient care.

David Van Essen: Speaking to the other half of the question, the more we learn, the more we realize how much there is to learn. I would, at a kind of higher-level characterization of it, emphasize how truly daunting it is to really understand how the human brain works, how it computes, how it conveys messages like what's going on in this conversation, having the ability to probe and interrogate the living human brain with a functional and structural MRI, as we've been talking about, is really an exciting advance, but it's still not letting us listen in to individual neurons. We're listening into hundreds of thousands of neurons at each brain location we can tap into, so the ability to use a combination of methodologies, some of which are yet to be invented, still leaves open the question, can the human brain ever truly understand the human brain in the level of detail that we want for answering our curiosity, but also addressing the full spectrum of challenges related to human disease? These are exciting times, but I tend to balance optimism with a sense of caution that the problems are really large and truly daunting.

Bill Glovin: We recently published an article by Karel Svoboda on two-photon microscopy, which goes beyond MRI capability in that it uses lasers and fluorescents to generate detailed images of neuro networks in animal models. Does two photon have any potential use in the next phase of the project, or is it relevant?

Matthew Glasser: Well, I think we have to be careful about which types of techniques are really appropriate to use in human beings, so like we were discussing earlier with neurosurgical cases, there are certain times in which it's appropriate to do a more invasive study. For example, people have done things like implanting electrical grids when trying to map epilepsy in particular individuals for later neurosurgical removal of an epileptic focus. If you have that grid in there already, you can record from it and maybe try and learn a little bit about how the brain is working, but two-photon microscopy is probably not something you could use on a living person ethically, but certainly it would be very helpful in animal models that you were mentioning to try and understand how some of these very small structures are behaving.

David Van Essen: Also, in the context of tissue that has been taken from human surgical samples in epilepsy surgeries, the Allen Institute of Brain Science is capitalizing on two-photon imaging and a variety of very sophisticated methods to probe brain surface at a microscopic level in human tissue that's been brought into the lab and can be studied for days at a time. This is another example of essentially a bridging technology that will provide exciting information, but, as Matt said, cannot be done inside the skull of a living individual.

Bill Glovin: How about other emerging technologies such as advances in genetics and The Human Genome Project? Do you see any tie to findings in that area to the next phase of the project or even down the line further?

David Van Essen: Well, we are at the late stages of completing the genotyping of all 1,200 subjects, or nearly all of them, in the HCP Project that's now wrapping up, and that information will be deposited in the resource repository on the DB Gap and will be available to investigators around the world. Hopefully, they will be able to probe that data in connection with what we have learned about brain circuits and how they vary across individuals to tie in with the genetic information, but how much to expect from that, given that most or at least many genotyping studies require much larger numbers of individuals to pick out the meaningful signals from a population with the kind of variability found in the human genome, that remains to be seen. These are very interesting opportunities, but it's hard to predict what and when will make major discoveries relating genetics to brain circuits.

Bill Glovin: You talked a little bit about the next phase of the project relating to lifespan. Is the funding in place for it, and what will be your roles in the next phases?

David Van Essen: There are a number of projects that are funded, and I have involvement in several of them. The Lifespan Connectome Projects, three of them are funded. One of them is babies from zero to five years. I'm not directly involved in that. The other two, children from 5 to 21, and aging from 36 to 100 plus. I'm one of nine co-principal investigators involved in both of those projects. I'm also on the connectome coordination facility informatics endeavor along with Dan Marcus to handle the data sharing and data management aspects of these lifespan projects, and also a set of more than a dozen connectomes related to human disease, smaller individually, but an aggregate of a large number of major projects related to disease connectomes. Matt has continued to be involved and he may speak to it, but he's at a scientific and technical contribution level, continues to provide invaluable advice on various fronts relating to these projects.

Matthew Glasser: Right. If things work out as I'd like them too, I will remain at Washington University for my medical residency and continue to be involved in these projects as I'm able to during my clinical training.

Bill Glovin: Just yesterday Mark Zuckerberg and his wife Priscilla Chen announced the pledge of $3 billion to fight disease, and even though NIH spends 10 times that amount a year to fight disease, does that kind of commitment filter down to neuroscience and this project?

David Van Essen: I expect it will certainly filter down to neuroscience in a very big way. It remains to be seen in detail how it will play out, but the fact that Cori Bargmann, a very distinguished neuroscientist, is going to be leading that effort is, I would say, good for basic research as well as the translational issues that motivate the

funding of this effort. I would draw attention to the Allen Institute for Brain Science, which has entailed an investment approaching $1 billion already that has achieved dramatic successes in basic science and its relevance to clinical disorders in ways that I touched upon earlier, but has a very broad and highly successful portfolio. The partnership between public and private funding that has had such a huge impact over the decades grows even brighter with the commitment of individuals like Paul Allen and Bill and Linda Gates and now the Zuckerberg team on bringing major additional resources to bear is excellent news for the progress we can anticipate.

Bill Glovin: Last question. Dr. Van Essen. When you first started out could you have ever predicted that neuroscience would have made the kinds of advances that are associated with this project?

David Van Essen: No is the short answer. I remember back to my graduate student and post-doctoral days working as a post-doc in the laboratory of Hubel and Wiesel, the Nobel Laureates for their studies of visual cortex and I remember thinking, gee, I wonder if they skimmed the cream of the crop and are left on the curds and whey for the rest of us to mop up. Little did I realize just how much more exciting advances could occur. And it goes back to the point, the more we learn, the more we realize how much there is to learn, but we can be excited by the continuing emergence of new technologies and bright young talent to capitalize on that. It's a very fascinating time to be associated with brain research.

Bill Glovin: And that concludes our conversation with Dr. Van Essen and Dr. Glasser. For more information or to read the article log on to dana.org. See you next time.