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Human connectomics — What will the future demand?

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ABSTRACT

Significant resources are now being devoted to large-scale international studies attempting to map the connectome — the brain's wiring diagram. This review will focus on the use of human neuroimaging approaches to map the connectome at a macroscopic level. This emerging field of human connectomics brings both opportunities and challenges. Opportunities arise from the ability to apply a powerful toolkit of mathematical and computational approaches to interrogate these rich datasets, many of which are being freely shared with the scientific community. Challenges arise in methodology, interpretability and biological or clinical validity. This review discusses these challenges and opportunities and highlights potential future directions.

This special issue on The Connectome is timely. There has been a recent explosion of large-scale international projects aiming to elucidate the structural and functional connections of the human brain. These typically use diffusion tractography measures of structural connectivity (Jbabdi and Johansen-Berg, 2011; Sotiropoulos et al., 2013), or resting functional magnetic resonance imaging (fMRI) measures of functional connectivity (Biswal et al., 2010; Smith et al., 2013), though other types of data can also be considered (Evans, 2013; Larson-Prior et al., 2013; Scholvinck et al., 2013). Many of the established projects are discussed at length in this issue, including the Human Connectome Project (Setsompop et al., 2013; van Essen et al., 2013) and 1000 Functional Connectomes from the US, the Brainnetome Project from China (Jiang, 2013), and the CONNECT project in Europe (Assaf et al., 2013). More recent developments, including the Brain Initiative in the US (www.nih.gov/science/brain), and the Human Brain Project in Europe (www.humanbrainproject.eu), promise yet more petabytes of connectome data being made available to the community in the years to come.

So what are we going to do with all this data, and what does it all mean? In this review I will discuss the challenges and opportunities raised by human connectomics, and speculate on potential future directions of this rapidly evolving field.

Although there are enormous current efforts at defining the connectome, one provocative question is whether or not this is the right time to devote resources to this problem. Parallels have been drawn between large-scale projects to define the human connectome, and the Human Genome Project, as they share a common aim to chart aspects of human biology. However, one important distinction between the fields of genomics and connectomics concerns methodology. At the time that the Human Genome Project was conceived, methodology was already able to definitively and accurately identify genes from human DNA, albeit rather slowly. The technology has advanced since then and entire genomes can now be sequenced much more rapidly and efficiently, as evidenced by the recent publication of over 1000 fully sequenced human genomes (Abecasis et al., 2012). However, if the individual genome that was originally sequenced for the Human Genome Project was sequenced again today the same sequence would be derived. Human genomics technology is therefore at a stage where data collected today will remain a valuable resource to be analysed in future to address new questions.

The situation is somewhat different for human connectomics. We know that our methods for interrogating the human connectome are not perfect. Therefore the maps that we build are not definitive, but rather they are our best current estimates. These will evolve over time as methods for acquisition and analysis improve, but will always remain estimates. One argument is that the immaturity of the available methodology means that efforts to map the human connectome are premature. I suggest that there can still be significant value and information content in our current best guesses at the human connectome, and that large scale international efforts to map the connectome will kick start the technological advances that will move us to being able to define more accurate brain map estimates in future.

Some of those technological advances are nicely showcased in the current special issue. For example, the outstanding diffusion data achievable on the unique scanner engineered specifically for the MGH-UCLA HCP and equipped with 300 mT/m gradients and a

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64-channel coil, are highlighted (McNab et al., 2013; Setsompop et al., 2013). The WU-Minn HCP, whose aim is to acquire and make freely-available multimodal data on a large number of participants, is using a 3T scanner equipped with 100 mT/m gradients, as well as a 7 T scanner, to produce excellent quality data (Sotiropoulos et al., 2013; Ugurbil et al., 2013). For those of us with more off-the-shelf hardware, there are still prospects for significant improvements in image acquisition, through use of cutting-edge pulse sequences that could be implemented on many clinical systems (Ugurbil et al., 2013). Importantly, improving data quality offers more than just incremental advances in accuracy or resolution. If data quality improves substantially then this opens up new possibilities for qualitatively different types of analyses or interpretation that simply cannot be supported by current typical acquisition schemes. For example, very rapid acquisition of resting fMRI data allows for dynamic network analysis (Smith et al., 2012), increased diffusion contrast offers the possibility of fitting more complex biophysical models (Assaf et al., 2013; Sotiropoulos et al., 2013).

Much of this special issue is devoted to advances in analysis methodology for interrogating connectomes. At the preprocessing end, there has been significant recent progress in data clean-up and artefact correction for both diffusion (Glasser et al., 2013; Sotiropoulos et al., 2013) and functional MRI (Glasser et al., 2013; Liu, 2013; Murphy et al., 2013; Smith et al., 2013; Yan et al., 2013). Once we have our cleaned-up data, significant challenges arise in building brain connectomes. Many of the articles in this special issue address challenges such as defining nodes and edges. Fornito et al. nicely set out the ideal characteristics for nodes and edges and summarise current progress in meeting these goals (Fornito et al., 2013). Many early connectome studies used atlas regions of interest to define network nodes, and this approach has the advantage of simplicity. However, it has since become clear that choice of network nodes really matters (de Reus and van den Heuvel, 2013; Zalesky et al., 2010), and multiple different schemes have been proposed, ranging from anatomically informed schemes (Caspers et al., 2013) to data-driven parcellations (Varoquaux and Craddock, 2013; Woolrich and Stephan, 2013).

One curious feature of many connectome studies is that they focus only on regions of the cerebral cortex, ignoring subcortical or cerebellar structures. This appears to be an accident of how approaches to defining nodes have evolved, rather than a deliberate strategy. It goes without saying that cortico-subcortical connectivity and cortico-cerebellar connectivity (as well as connections between subcortical nuclei or within the cerebellum) play fundamental roles in human cognition and disease and cannot be overlooked if our representations of the connectome are to be useful. More recently, efforts have been made to incorporate these structures into our representations of the connectome, and advances such as the creation of the CIFTI image format, which flexibly allows for storage of surface based cortical co-ordinates, and volume-based subcortical co-ordinates within the same file system (Glasser et al., 2013), should provide a useful practical push for more research to move in this direction. Thorny outstanding questions of node definition include how to achieve correspondence across subjects, whether common nodes should be used for structural and functional connectomes, and whether nodes should be fixed or dynamic (Fornito et al., 2013; Sporns, 2013; Varoquaux and Craddock, 2013). One key point made in this issue is that we perhaps should not be searching for the single best parcellation scheme but rather accept that different schemes may be appropriate for different questions (Fornito et al., 2013).

Similarly, multiple different approaches have been taken to defining network edges, the connections between nodes. In functional connectomes, edges usually reflect a measure of functional connectivity derived from fMRI, EEG, or MEG (Larson-Prior et al., 2013; Liu, 2013; Smith et al., 2013). For structural connectomes, they can reflect a tractography-derived connection (Mangin et al., 2013; Sotiropoulos et al., 2013), or inter-regional covariance of a local structural parameter such as cortical thickness (Evans, 2013). Typically, measures of (structural and functional) connectivity strength are thresholded and binarised to create unweighted graphs, but methods for dealing with weighted graphs are available and increasingly being applied to neuroimaging data (Fornito et al., 2013). Such methods are worth pursuing as they potentially allow for the full richness of the available data to be exploited. Further, empirical developments could allow for more detailed characterisation of, for example, polarity of edges. David et al., in this issue, describe a new 'functional tractography' atlas of human cortex which uses electrophysiological recordings of cortico-cortical connectivity to provide information on both latency and directionality of cortico-cortical connections (David et al., 2013). Such an atlas could complement existing connectome representations by providing information not available using conventional techniques such as tractography or resting fMRI

Some particularly exciting developments for building of connectomes concern integration between microstructural and macrostructural information. For edge definition, this might include incorporation of estimates of myelin content or axon calibre into this framework, potentially allowing for biologically meaningful parameters, such as conduction velocity, to be estimated and assigned as network weights (Assaf et al., 2013). Integration between microstructure and macro-scale connectomics could also be relevant to node definition and the creation of multi-scale connectomes. As we develop a richer idea of intrinsic microstructural properties within cortical or subcortical regions (Chung et al., 2013; da Costa and Martin, 2013; Livet et al., 2007), these micro-connectomic properties can be combined with macrostructural information on communication between regions to develop a multi-scale model of the connectome.

Once a network has been built, we are then faced with the challenge of how to analyse it. How do we infer differences in connectomes between clinical groups, through the lifespan, or in relation to behavioural variation? Addressing such questions raises statistical issues for which new and potentially powerful solutions are offered in this issue (Meskaldji et al., 2013; Varoquaux and Craddock, 2013).

Assuming that our methods for building and analysing connectomes are valid and robust, what progress has been made to demonstrate their utility in addressing questions in cognitive and clinical neuroscience? I would suggest that progress to date has been mixed, but that there is plenty of potential for these methods to have impact. One issue that plagues neuroscience applications of systems-level connectomics is that, in most cases, datasets for generating connectomes (such as resting fMRI or diffusion MRI) can be acquired in a hypothesis-free manner. This is both a blessing and curse. On the one hand, it allows for these rich datasets to be revisited time and time again to address novel questions, and for data to be combined across studies — both features that lend themselves to the type of data-sharing efforts that are proving so popular in this field. On the other hand, it can result in a 'fishing expedition' approach. This can be a useful way to progress science, and many of us will have benefited from the serendipitous discovery of an unpredicted finding. However, the ease with which resting FMRI or diffusion MRI can be added onto scanning sessions, just to see what happens, can make us all rather less rigorous in our hypothesis setting.

The majority of clinical neuroscience studies to date in this field have identified differences between patients and controls in local or global connectivity measures (Griffa et al., 2013). An advantage of approaches such as graph theory in this context is that they offer summary measures that could be sensitive to diffuse and non-localised pathology that could otherwise be difficult to detect. However, a challenge for such approaches is that few of us have an intuitive feel for what a difference in, say, betweenness centrality, between patients and controls, really means. If this field is to have any broader clinical impact then it is important for its practitioners to make efforts to bridge the gap between mathematical constructs and the pathological features that clinicians will be interested in. There is potential for detected differences in local or global connectivity measures between groups to be clinically useful in assisting with differential diagnoses, or with prognosis, though in practise their utility in these regards is

rarely directly tested. Some nice examples of studies that have followed through in this way are discussed by Castellanos and colleagues in this issue (Castellanos et al., 2013).

For the future, more formal modelling of brain networks, and their breakdown in disease is likely to greatly advance this field (Nakagawa et al., 2013; Woolrich and Stephan, 2013). Woolrich and Stephan (this issue) explain the benefits of a modelling framework for making formal, testable predictions. Using such models in a disease context allows for data describing the brain connections of a given individual to be compared to a number of different models to decide whether or not the individual has a particular disorder, or how well they are likely to respond to a specific treatment. Arguably, biophysical models of the sort proposed by Woolrich and Stephan will provide the most sensitive discrimination of relevant features. Importantly, having made a diagnosis, for example, it is then possible to return to model parameter space to figure out what feature of the model is driving the diagnoses. If the model features are biologically interpretable then such an approach offers the potential for gaining novel mechanistic insights into disease processes, as well as providing information to assist with clinical decision-making. However, although models have the advantage of testability, they are only as good as their underlying assumptions. If the connections of the model are not an accurate portrayal of the underlying biological reality then errors can arise.

This raises the challenge of validation. To what extent do our estimates of the human connectome reflect the biological reality (Passingham, 2013)? As discussed earlier, we know that our techniques are not perfect (Catani et al., 2013). Perhaps in some cases this does not matter too much. Let's say a graph theoretical measure allows us to accurately predict whether or not someone with mild cognitive impairment is going to convert to Alzheimer's disease. If this provides us with clinically useful information then arguably it does not matter if the graph from which the measure was derived is not an accurate reflection of the human connectome. However, in many cases we *do* need to be sure whether a connection that we have observed between two brain regions really does exist. For example, we may want to interpret our new finding about that connection in light of what we already know about the structure and function of the two brain regions. There have been some impressive recent attempts to directly compare tractography results with traditional tract tracing measures in the same species (Harsan et al., 2013; Jbabdi et al., 2013), but these studies are challenging and their conclusions cannot readily be generalised beyond the specific connections studied. Databases in which results from multiple tract tracing studies are collated, such as the cocomac database (Stephan, 2013), provide an invaluable resource in this regard, but there can be inconsistencies in reporting and methodology across laboratories and there are many areas of unchartered territory. In this issue, Kennedy and colleagues present a detailed analysis of the anatomical connections of 29 cortical regions from a parcellation of the macaque monkey cortex into 91 areas (Kennedy et al., 2013). The data have been painstakingly collected from 29 animals in a single laboratory over many years (Markov et al., in press). Kennedy et al. interrogate these data using graph theoretical approaches and report many novel features of the macaque connectome that were not apparent in previous analyses of collated data from multiple studies. This rich dataset will provide an outstanding resource for the human connectomics community, allowing for specific quantitative predictions to be generated and tested.

As our representations of the connectome begin to take more notice of the underlying biology, there are other features that should be taken into account. For example, glial cells (astrocytes, oligodendrocytes, microglia) are thought to outnumber neurons by around 6 to 1, and their roles are now known to extend far beyond passive support of neurons (Nedergaard and Verkhratsky, 2012). These non-neuronal cells form local connections, both with each other and with neurons (Araque and Navarrete, 2010; Fields and Stevens-Graham, 2002). Large scale patterning of these connections is very poorly understood. Could networks of astrocytes, for example, form another layer in the neuronal connectome that could play a modulatory role?

In addition to microstructural information, information on chemical neuromodulators could also be valuable to incorporate into models of the connectome (Sporns, 2013). This highlights that the connectome, even for a given individual, is not fixed. The issue of maps changing as methods develop was discussed earlier, but a more fundamental biological source of variability also exists. At a microstructural level, both functional and structural connections are strikingly dynamic (Sporns, 2013). Over a timescale of minutes to hours, synapses increase their efficacy, spines form and retract (Cooke and Bliss, 2006; Xu et al., 2009; Yang et al., 2009). Over slower timescales, activity dependent changes in myelin, axon calibre, or even neuron number may occur (Demerens et al., 1996; Fields, 2008; Gould et al., 1999; Hihara et al., 2006; Johansen-Berg, 2007). Such microstructural plasticity can potentially be captured at the macroscopic level using neuroimaging to study effects of learning or experience (Johansen-Berg et al., 2012; Sagi et al., 2012; Scholz et al., 2009; Zatorre et al., 2013). Reviews in this issue provide examples of how the connectome is susceptible to activity, learning or state dependent change (Evans, 2013; Picchione et al., 2013; Sadaghiani and Kleinschmidt, 2013; Sporns, 2013). In future, the multi-modal and context-dependent nature of the human connectome could perhaps best be captured through use of biophysical network models, allowing different sources of data to be integrated and mutually informative (Woolrich and Stephan, 2013).

In summary, human connectomics is a newly emerging field and as such it is rapidly developing. A limitation of the field is that we cannot claim to be able to produce definitive maps of the human connectome due to methodological limitations. However, with the rapid pace of technical development continued improvements should quickly be seen. More interestingly, we cannot claim to produce a definitive map of the human connectome as there is no such map. Each of our brains is wired up differently, and fascinating questions lie in trying to understand to what extent differences in our brain wiring can explain differences in our behaviour or clinical status. Even within an individual, the pattern of our structural and functional brain connections is not fixed but rather continually changes in response to experience. Studying such phenomena within the framework of connectomics opens up a powerful armoury of analysis and computational approaches that could provide important new insights into clinical and cognitive neuroscience.

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Conflict of interest

The author has no conflicts of interest to declare.

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