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Commentary: Developmental connectomics to advance our understanding of typical and atypical brain development – Commentary on Vertes & Bullmore (2015)

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Abstract

Vértes and Bullmore's article lays a framework for applying connectomics, the study of brain function from the perspective of underlying network organization, to advance understanding of healthy and maladaptive brain development. They elucidate the power of connectomics for bridging both different levels of analysis (e.g. from synapses to brain regions) and multiple academic fields. In this commentary, we highlight important themes and remaining questions stemming from Vértes and Bullmore's work, including: (1) the application of connectomics in the context of integrating analyses across multiple spatial and temporal dimensions, (2) the extent to which connectomics might be applied in translational and clinical studies of development, (3) growth connectomics and the Developmental Origins of Health and Disease (DOHaD) hypothesis, and (4) the importance and complexity of sound methodological practices in applying connectomics to developmental and clinical science. Ongoing work in these areas will be important for fulfilling the promise of connectomics as a bridge between neuroscience, developmental science, and translational and clinical research.

Keywords

Brain development; neuropsychiatric disorders; neuroimaging; connectome; DOHaD

Introduction

Human brain function is the result of a highly organized network of connections linking unique areas across the brain. While much research has been devoted to identifying the specialization of these distinct brain areas, recent work has argued that we may be able to significantly supplement our current understanding of brain function by characterizing it in

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terms of its underlying network organization. In this way, identifying large-scale network patterns of the “connectome” could prove pivotal for clarifying the mechanisms that lead to both healthy and disordered brain function. Vértés and Bullmore (2015; this issue) provide an excellent synthesis of the current state of the literature regarding connectomics in the typically developing and atypically developing brain. Here we reflect on their thoughts and highlight themes and remaining questions that are particularly pertinent to using connectomics to improve our understanding of brain function across development.

Theme 1: Bridging data in spatial and temporal dimensions

A prominent theme throughout the review by Vértés and Bullmore is how connectomics provides an integrated perspective on brain function that spans many spatial and temporal dimensions – one of the prominent challenges in the field. This challenge of integrating information across multiple levels of inquiry is nicely demonstrated by Churchland and Sejnowski's famous diagram showing the multiple levels of neuroanatomical organization of the human brain (Churchland & Sejnowski, 1992). From small molecules and synapses to the interconnections of multiple segregated systems or brain areas, understanding how these different levels of inquiry relate, is of the utmost importance, but of maximal difficulty. One source of this challenge is that the highly invasive measurements we use at the micro-scale, in both spatial and temporal dimensions, are often not possible to utilize in humans. On the other hand the non-invasive tools available for human use at the macro-scale are often indirect and non-specific measures of the underlying neurobiology. This state of affairs necessitates measurements and approaches that integrate information across multiple levels of analysis – a challenge well suited by connectomics.

Vértés and Bullmore nicely illustrate the power of connectomics in capturing structural and functional organization at the macro level of brain regions, as well as organization and interactions among individual neurons (both *in vivo* and in cell cultures). Applying connectomics and non-invasive imaging in conjunction with animal models may also facilitate the integration of macro and micro level levels of analysis in the study of human brain functioning. Leveraging information gained through animal models is complex because relating rodent and non-human primate behavior to complex human mental health conditions can be difficult and non-specific. Along the same lines, determining how specific human brain areas (particularly the evolutionary nascent cortical areas) map onto those of various animal models (particularly in rodents) is also a significant challenge. However, new advances in macroscopic techniques (e.g. MRI and fMRI) in animal models combined with analyses focused on connectomics, have provided examples of direct cross-species comparisons (Miranda-Dominguez et al., 2014; see also online supplementary material (Appendix S1) references² – Theme 1). Such work lays a foundation that allows for reassurance that the brain topology of a given animal model relates directly to the human condition being studied, while also allowing for a better understanding of how findings at the microscopic level from animals models are directly applicable to humans.

²Online supplementary material is available with the online version of this article: Appendix S1: Supplementary references by content area

Theme 2: Clinical relevance for psychiatric and neurological disorders

Another theme in the review by Vertes and Bull more relates to the extent to which connectomics provides clinically meaningful information about psychiatric and neurological disorders. Clinical relevance can be thought of in terms of increasing capacity for accurate diagnosis and prognosis, and effective therapeutics. Increasing capacity in these areas typically requires sensitivity to clinically meaningful differences in functioning, and specificity in identifying diagnostic categories and subcategories. Vértes and Bullmore correctly point out that many measures of overall brain organization frequently used in connectomics (e.g. global efficiency and small-worldness) may be sensitive to various psychopathologies, but are unlikely to be particularly specific to a given disorder. For example, atypical small worldness has now been documented for schizophrenia, Alzheimer's disease, autism, and attention-deficit/hyperactivity disorder (see Appendix S1 – Theme 2). However, the field of connectomics is vast, and thus, the question remains – will it be possible to use connectomics in a person centered, clinically relevant manner?

Three related lines of inquiry will likely be important in answering this question. First, as Vértes and Bullmore allude to, examining patterns of within subject development over time (“growth connectomics”) will likely provide valuable information for applying connectomic measures in translational, person-centered, studies. Identification of the best measurements for capturing developmental change in global brain topology has not received sufficient attention, and will be a central component in this work. Second, we need to understand the meaning of the variance of the connectome across individuals. While certainly a large portion of the variance observed in many studies related to the connectome can be attributed to measurement error, there is increasing evidence that understanding this variance is going to be of particular importance to characterizing and classifying the individual (i.e. in a clinical setting). At present, the utility of connectomics for developmental and clinical science is sorely limited by the lack of attention to characterizing heterogeneity across individuals, as has been done in other domains (Fair, Bathula, Nikolas, & Nigg, 2012; Karalunas et al., 2014; see also Appendix S1 – Theme 2). Finally, as noted by Vértes and Bullmore, while many global measurements may be sensitive to a given disorder, others may actually allow for specificity as well. The characterization and classification of atypical “hubs” at specified brain locations might provide this information. For example, Crossley and colleagues identified lesions in brain regions that serve as hubs as a common feature across multiple brain disorders, but the location of the lesioned hubs was specific to each disorder (Crossley et al., 2014).

When discussing clinical utility, it will also be worth considering whether specificity in these measurements is necessary to confer clinical relevance. For example, growth charts have very high clinical utility for indicating health problems, but are not disorder specific. Thus even if connectomics does not provide specificity in the context of the current diagnostic system, it may be important for pushing the system towards a more firm foundation in neuroscience.

Theme 3: The developmental origins of disease

While a large portion of knowledge regarding developmental connectomics begins in childhood, there is reason to believe the most clinically relevant work will come from investigations during the neonatal period and infancy – a time of marked change in brain size, synapse modulation, and network formation. Consistent with the Developmental Origins of Health and Disease (DOHaD) hypothesis (Barker, 1995), it has become increasingly clear that the origins of many childhood, adolescent and adult onset disorders have their roots in the prenatal and perinatal period. Vértes and Bullmore point out emerging evidence indicating that broad patterns of global topology are established during the prenatal period and first several years of life (see Appendix S1 – Theme 3). Aspects of global topology established during this early time period are presumably implicated in psychopathology in older children and adults. Indeed, altered trajectories seem to begin very early, as neonates at high genetic risk for schizophrenia already show lower global efficiency compared to neonates without this genetic loading (Shi et al., 2012).

Yet the questions remain, can we harness connectomics as a predictor of developmental trajectories of risk and resilience? Can it add to our capacity for early identification of individuals who may require additional support, or be particularly sensitive to environmental conditions? To answer these questions, new longitudinal work carefully documenting the environment (including maternal health during pregnancy, and family and socioeconomic factors), along with connectome measurements from pre- and early postnatal periods to later stages of development, is sorely needed.

Theme 4: Methodological issues

Finally, the promise of connectomics for advancing developmental and clinical science necessitates sound methodology. The authors allude to motion as an important methodological issue that has been most well studied in the field of resting state functional connectivity MRI (rs-fcMRI; Power, Schlaggar, & Petersen, 2015). While emerging work utilizing new standards of motion correction has confirmed some aspects of prior developmental work (Fair, Nigg, et al., 2012; Satterthwaite et al., 2013), it is important to note that motion is a significant source of artifact amongst all MR measures used to study the human connectome (see Appendix S1 – Theme 4). Thus, this confounder needs to be strongly considered in all aspects of this work. In addition, motion is only one of many methodological issues that can influence the results of research employing connectomics (see Appendix S1 – Theme 4). In order to move towards examining individual differences in connectomics as an indicator of health and disease, it will be critical to reduce variability attributable to multiple sources of error across all types and levels of analysis. However, we also note that different methodologies will confer different strengths and weaknesses in terms of susceptibility to specific types of artifacts. Therefore, convergent evidence across approaches can also contribute to confirming a given finding related to human brain function.

Conclusion

In his book, *Consilience, The Unity of Knowledge*, Edward O. Wilson (1999) described concentric rings moving towards the intersection between academic disciplines. He stated: “The ring closest to the intersection, where most real-world problems exist, is the one in which fundamental analysis is most needed. Yet virtually no maps exist” (p. 9). Vértes and Bullmore highlight the potential for connectomics to provide such a map through its focus on fundamental laws about the organization of systems. As they document, connectomics facilitates rigorous study of systems at multiple levels of analysis, and can be readily applied to characterizing both healthy and maladaptive development. Such a map holds promise for advancing our basic understanding of development, and the nature of many psychiatric and neurological disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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