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The mystery of developing connections

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Knowledge of brain development has advanced with detailed understanding about neuronal birth and specification, axonal extension and synapse formation, dendritic pruning, myelination, and regional brain specification. These events are characterized by both progressive and regressive processes, which occur in a temporally and spatially stereotyped pattern from "back to front" within the brain[1]. Beyond these structural relationships, functional connections exist between brain regions. Recent work has now raised questions about the biological basis and the development of these functional connections and how they can be altered by consciousness, drugs, and disease states.

Functional connectivity (FC) within the brain represents neuronal activity in spatially distinct regions and is characterized using resting state functional connectivity MRI (fc-rsMRI) [2]. This method measures resting, spontaneous, low frequency fluctuations in oxygen levels in blood within the brain, which correlates with regional changes in neuronal activation. Correlations of this signal across spatially distinct brain regions define resting state-networks (RSNs), whose characterization has attracted attention because the information can be acquired in a short time, there is no need for the subject to participate in any specific task, and the information obtained is robust across scans captured at different locations and with various states of consciousness[3].

How do these RSNs change during normal development, and how might they be altered in neurodevelopmental diseases (NDD) such as autism? Several studies indicate that a developmental pattern of FC continues throughout childhood and up to young adulthood[4]. In general, infants show developed local networks; however, longer range "front to back" connections important for more complicated networks, such as executive control and the default mode network, strengthen and local connections decrease as development proceeds.

Although the pattern of FC development can be defined, the ability to determine the developmental state of FC for a specific individual has been lacking. Recently, Dosenbach et al. [5] used a form of supervised computer learning to predict the FC 'maturity' of individual brains. Using these techniques, Dosenbach and colleagues were able to generate a "functional brain maturation curve", similar to a standard growth curve used to assess weight gain in children. This suggests the possibility that there is a simple way to assess the overall brain function and maturation and compare it in a meaningful fashion with known standardized growth curves, similar to what now is done for height, weight, and head size.

This study will have significant impact in translational research on neurodevelopmental disorders (NDDs), such as autism, as it may be used to characterize the FC development of affected individuals and to determine where they fall on the brain functional maturation curve. To date, characterization of the rs-fcMRI of a number of NDDs, including autism[6], attention deficit/hyperactivity disorder (ADHD)[7], and Tourette syndrome (TS)[8], have found

aberrant functional network structure in these disorders but the developmental trajectory of these disorders is currently unknown.

The early identification of affected individuals poses a challenge and one current approach aims to study 'at-risk' individuals, including siblings of identified affected individuals. But a promising approach would be studying the developmental trajectory of NDD with know genetic causes, such as Rett, Fragile X, and Angelman syndromes, which are increasingly identified through molecular testing at very young ages. Characterizing the network properties and development of FC in these forms of NDD may allow further identification of people with idiopathic forms of autism. Additionally, as animal models exist for these disorders, there may be opportunities to discover the cellular and molecular basis of the abnormal development of these functional networks. Finally, clustering those cases of idiopathic autism on the basis of their FC would create more homogeneous clinical populations to further discover the exact etiology of the specific NDD.

An open question exists as to the exact biological basis of the development of FC. Strictly anatomical developmental changes are clearly important in the ability for dispersed brain regions to form functional connections. But there is additional complexity that arises in neural circuits, as many functional pathways do not have direct monosynaptic structural connections but rather are generated across multiple synaptic connections. Additionally, FC can be reversibly altered by non-structural mechanisms. For example, altering neuromodulatory neurotransmitters such as dopamine[9] or serotonin[10] can modulate FC in disease states. Thus, although anatomical changes are clearly important in the formation of FC, additional non-anatomical features are also critical.

Although further understanding of the biological basis of the development of FC will be gained from human studies, ultimately more tractable systems will need to be used. rs-fcMRI has been developed in animal models including rats[11] and recently mice[12] and the first requirement for each will be to establish the developmental trajectory of FC. Thus, characterization and manipulation of specific cellular developmental processes and molecular changes that occur in discrete anatomical regions can be correlated with changes in FC. Alteration of neuronal properties at different time points and locations with currently available advanced techniques, such as optogenetics[13], while monitoring the functional connectivity of a specified network will help establish the formal relationship between specific cell populations and their firing patterns and the overall network properties[14]

Furthermore, characterizing functional connectivity in mouse models of NDD would allow correlation to network alterations in these diseases, providing a system to determine the structural and functional changes that underlie these disorders and to develop efficacious drugs.

A major challenge in neuroscience has been to develop methods to assay and bridge information between different levels of circuit organization. Although significant advances have furthered our understanding of how molecular, cellular, and electrical processes within a cell relate to the functioning of a local neural circuit, we are just now beginning to have tools capable of relating local to global changes in functional connectivity and, ultimately, to behavior. Perhaps combining these experimental techniques with rs-fcMRI in animal models and relating this to human rs-fcMRI may help to bridge these organizational levels to better understand brain development during both health and disease.

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