Title: fcMRI During Development: Exploration of the Functional Organization of the Developing Brain

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Introduction

Advanced neuroimaging techniques have been increasingly applied to the study of pediatric populations in an effort to further define the functional cerebral architecture of the developing brain. Despite improved understanding of the complex relationship between structure and function obtained through these investigations, significant questions remain regarding the nature, location, and timing of the maturational changes which occur during early development. Functional connectivity magnetic resonance imaging (fcMRI) utilizes spontaneous, low frequency (< 0.1 Hz), coherent fluctuations in blood oxygen level dependent (BOLD) signal to identify networks of functional cerebral connections [1]. In many regards, fcMRI is ideally suited to investigations of infants and children because of the intrinsic characteristics of its acquisition and analysis methods. To date, a limited number of investigations have applied fcMRI to the study of pediatric populations. Results of these inquiries have provided information regarding the earliest forms of cerebral connectivity in the developing brain, highlighting the intricacy of the relationship between cerebral structure and function throughout childhood and providing the foundation for further application of these methods to future neurodevelopmental investigations.

Biological Development of Neural Networks

The structure and function of the maturing brain change continuously throughout early development, beginning during the earliest stages of gestation. The structural foundation critical to neural network development is established early in gestation [2]. Formed upon this evolving cerebral architecture, neural networks arise and mature through coordination of a complex set of anatomical and functional interactions, shaped by the interplay of genetics, environmental exposure, and experience. Remodeling of synaptic connections in response to endogenous and sensory-driven neural input plays an important role in the early functional organization of cortical circuits [2, 3]. Progressive structural and functional development continues at a rapid pace throughout early postnatal life. The dramatic, ephemeral changes in structure and function produce characteristic physiological phenomena that are detectable *via* a variety of neurodiagnostic modalities, including EEG, DTI, fMRI, and PET. Application of fcMRI enables *in vivo* assessment of the earliest forms of functional connectivity, complementing these prior efforts and providing a more complete understanding of the interrelationship between structure and function.

Technical Aspects

The sensitivity of functional MRI is inherently limited by low signal-to-noise ratio and compromised by sources of spurious variance, both subject and equipment dependent. Application of functional MRI techniques to infants and children provides unique technical challenges, further confounded by the evolving milieu of developing neurophysiology. In an effort to obtain high quality images, institutions have applied new technology and modified acquisition practices when performing MRI investigations in these populations [4, 5]. Advanced analysis techniques have been developed and applied to improve anatomic registration, reduce signal change present due to non-neuronal causes, and identify resting state networks (RSNs) [6]. These measures have yielded significant improvement in the quality of results obtained in subsequent functional investigations of infants and children. Despite these advances, questions remain regarding optimal methods for fcMRI image acquisition and analysis in this population. This uncertainty encompasses variables including radiofrequency coil selection, acquisition parameters, level of arousal, image registration, movement analysis, frequency characteristics, data preprocessing, and analysis techniques.

Investigations of Resting State Network Development in Pediatric Populations using fcMRI

Results from the limited number of fcMRI studies investigating pediatric populations reflect the complex interplay of evolving structural and functional architecture during early development [6-11]. The majority of these studies have included healthy subjects of varied ages, beginning with prematurely-born infants and continuing through children in late childhood, seeking to define normal neural network development. A limited number have also explored longitudinal RSN development. Recognized networks across all developmental periods demonstrate a pattern of gradual maturation and dynamic configuration that correlates with subject age, with anatomic distance

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playing a critical role in RSN development. These studies have utilized varied acquisition and analysis techniques, at times demonstrating noted variability in results. As expanding numbers of fcMRI investigations of pediatric subjects serve to further define patterns of normative neural network development, findings can be increasingly correlated with those obtained from complementary modalities, providing greater understanding of the mechanisms of functional cerebral development.

Future Directions

Anatomical and functional connectivity are interrelated, but not identical [12]. Investigations combining structural and functional measures provide increased breadth to assessments of cerebral connectivity, allowing comprehensive characterization of heterogeneous development and maturation of the functional cerebral architecture. A growing number of studies have been performed examining the interrelationship of results obtained using fcMRI and diffusion tensor imaging (DTI) [12, 13]. Application of fcMRI in pediatric populations also has the potential to define the role of various risk factors in determining neurodevelopmental outcome and assist efforts targeting neuroprotection. Further, the clinical utility of fcMRI in pediatric populations remains unexplored. Early translation of fcMRI to pediatric practice will likely focus on two central issues – correlation of fcMRI results with neurodevelopmental outcomes and longitudinal investigation of the impact of specific forms of neuropathology on neural network development. Continued application of these methods in targeted clinical investigations of normal and aberrant neurodevelopment may ultimately serve to establish fcMRI as a technique for identifying neurodevelopmental biomarkers.

Conclusions

fcMRI offers great promise as an investigational tool of neurodevelopment, providing unique insight into maturation of the functional cerebral architecture of the developing brain. Its use in targeted investigations of pediatric populations has recently expanded, in parallel with the explosion in application of the technique in adults. While the field remains in its early stages, much has already been learned about the principles that guide early neural network development. Additional efforts are necessary to optimize methods for image acquisition, analysis, and interpretation of results. However, the groundwork has been laid for expanded investigations designed to further define normative findings within this population and identify and characterize factors which induce aberrant neural network development. The result will be a novel neuroimaging approach which ultimately affords greater understanding of the processes of typical functional cerebral development and enables identification of children at increased risk for disability, possibly allowing early neuroprotection and improving neurodevelopmental outcomes.

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