ENCYCLOPEDIA
on Early Childhood
Development

BRAIN

Brain Maturation of Newborns and Infants

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Introduction

Recently, imaging studies of early human development have received more attention, as improved modeling methods might lead to a clearer understanding of the origin, timing, and nature of differences in neurodevelopmental disorders. Non-invasive*magnetic resonance imaging (MRI)* can provide three-dimensional images of the infant brain in less than 20 minutes, with unprecedented anatomical details and contrast of brain anatomy *cortical and subcortical* structures and brain connectivity.[1,2,3] Repeating MRI at different stages of development, e.g., in yearly intervals starting after birth, gives scientists the opportunity to study the trajectory of brain growth and compare individual growth trajectories to normative models. These comparisons become highly relevant in personalized medicine, where early diagnosis is a critical juncture for timing and therapy types.

Subject

Clinical research questions related to pediatric neuroimaging focus on a better understanding of the variability and plasticity of early development, as well as differences between typical and atypical growth trajectories. Likewise, other questions are essential to patient care: maturation

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delays, accelerated growth, atypical development eventually rejoining typical trajectories, possible effects in different timing of brain maturation, a better understanding of developmental processes in view of risks for mental illness, and possibilities for early diagnosis. Ultimately, improved understanding of dynamic brain-development processes in the healthy and the sick will lead to better preventative care and more options for treatment.

Problems

Infant neuroimaging poses multiple challenges related to subject preparation for imaging and choice of optimal scanning parameters, given the strong constraints on shortest possible imaging time (preferably limited to 15 and 20 minutes). As a general rule in early brain development studies, infants are not sedated, so the optimal preparation of subjects and parents is essential to achieve high-quality images that are not corrupted by subject motion.

Image analysis is concerned with extracting quantitative information from image data, which include volume measurements of brain and cerebrospinal fluid, but also more detailed measurements on subcortical structures and localized cortical regions. Due to significantly different brain shapes, sizes and tissue contrast properties between infants, research laboratories have developed specialized analysis software[4,5,6] to account for regional contrast changes in the rapidly growing brains.

Research Context

Advanced imaging and image-processing capabilities have honed visualization studies in infant-brain analysis and advanced our understanding of early brain growth.[7] Getting detailed quantitative information about the individual growth of brain structures and connectivity via quick, non-invasive brain scans will benefit early diagnosis, decisions about early intervention and subject management, and improved comparison between groups of healthy infants and infants with psychiatric disorders or neurological disease. Neuroimaging is thus becoming a new tool to provide in vivo measurements of detailed anatomical and functional properties throughout the first few years of human brain development – information that has, so far, only been available during post-mortem brain studies. Most importantly, the ability to image individual subjects over time results in growth trajectories of clinically relevant brain measurements. This is also a radically new development, and it enables new clinical research to study the dynamic process of the path of early development.

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Key Research Questions

A key issue for advancing imaging science is the question of how to incorporate statistics with image data, which is the domain of computational anatomy. While we know how to analyze and compare standard measurements (e.g., height, weight, head circumference) and how to calculate longitudinal regression to predict the time-change of these features, extending similar statistics to image data requires significant future research efforts. Early success has been achieved by novel concepts that calculate the average 3D image based on a group of image data[8] and its extension to age regression,[9] resulting in a continuous model of brain images as a function of age. Similarly, longitudinal regression on shapes of brain structures has demonstrated how delayed or accelerated growth can be quantified.[10] This research is essential to answer questions about brain development in healthy infants and deviations thereof in the presence of illness. By examining changes of brain anatomy and white-matter connectivity, novel methodologies have examined the maturation of brain white-matter via longitudinal analysis of fibre tracts, structures that are closely correlated with the development of cognitive function.[11]

Recent Research Results

A study of 84 children at 2-4 weeks, 35 at 1 year, and 26 at 2 years of age[12] showed that total brain volume increased 101% in the first year, followed by a 15% increase in the second year. The major growth in the first year was attributed to gray matter (149%) and to a lesser extent, white matter (11%). The cerebellar volume increased 240% in the first year, whereas cerebral hemispheres increased by 90%. Such descriptive analysis of first- and second-year growth patterns will lead to significantly improved insight into the timing and growth rates of brain structures that are closely associated with cognitive brain function.

In a similar neuroimaging analysis of neonates, including *monozygotic* (MZ) and *dizygotic* (DZ) twins, researchers found significant group differences in intracranial volume on neonatal MRIs, with DZ twins showing significantly greater discordance than MZ twins.[13] Structural equation modeling was used to estimate additive genetic, common environmental, and unique environmental effects on brain structure.[14] Heritability of intracranial volume was found as 0.73, with a higher value in white matter (0.85) and lower heritability in gray matter (0.56). By comparing these studies with existing studies of older children, we can begin to answer questions about the influence of the environment on the growth trajectories of infant brains.

By including risk factors for mental illness, researchers found that prenatal mild *ventriculomegaly* might predict abnormal early brain development in neonates[15] and serve as a

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symptom for neuropsychiatric disorders associated with ventricle enlargement. A similar study was conducted to identity structural brain abnormalities in the prenatal and neonatal periods associated with the genetic risks for schizophrenia.[16] Results showed no large abnormalities of neonates at risk and concluded that structural brain abnormalities arise during postnatal brain development.

These studies demonstrate the importance of neuroimaging and image analysis to assess brain development differences between specific age groups, as well as the need to extend *cross-sectional studies to longitudinal data analysis*. This includes information on the early development of individual subjects.

Research Gaps

Whereas progress in advanced neuroimaging and image-analysis methodology is advancing rapidly, there are significant gaps in understanding the relationship between observed imaging data and the underlying neurobiology and function of the human brain. Researchers can measure and provide more data than we can currently understand, and new bioinformatics and statistical methodologies are required to better grasp what information is most relevant to patient care. Measurements include data as heterogeneous as image data, genetic information, behavioural scores, family history, blood tests, and much more. This flood of data creates a significant translational gap between technological advances in data collection and its subsequent interpretation and comprehension.

Conclusions

The scientific community sees significant progress in neuroimaging technology related to studies of the developing brain. Whereas initial efforts were directed towards improved imaging for the specific age range of the first few years of life, current research focuses on longitudinal aspects of early brain growth. Repeated imaging across the age window of interest only became possible with new scanner technologies, which provide non-invasive imaging with short scan times while increasing spatial resolution and contrast. Extracting trajectories of brain growth, in addition to regular cognitive assessments, will give clinicians a clearer insight into individual brain maturation. A comparison of individual growth trajectories is significantly different from cross-sectional evaluation at specific time points, as longitudinal data analysis naturally incorporates the correlation of repeated measure, thereby preserving subtle temporal changes versus cross-sectional variability.

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Implications for parents, services and policy

Progress in pediatric neuroimaging and associated image analysis will improve our understanding of healthy development and the eventual risk for mental illness and brain disorder. There is great hope that this additional information will lead to more accurate early diagnosis, so that optimal therapeutic intervention that can start as early as possible, with the aim to align an eventual atypical developmental path with a typical trajectory. Autism research, [17,18] for example, is one major clinical research area that has increased its effort to study early brain development. Following the practice of personalized medicine, individual treatment plans might be developed to optimally serve the patient. Non-invasive neuroimaging will therefore become an important instrument in gathering important information about the variability of human brain development, assessing individual growth patterns, and potentially defining structural correlates with critical periods of human cognitive development. Ultimately, early diagnosis and intervention might hopefully lead to improved patient management, successful prevention, and reduced health care costs.

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