Neurodevelopmental insights from fetal and infant imaging

Michelle Freund Co Organizer
National Institute on Drug Abuse
Rockville, MD
United States

Vani Pariyadath Organizer
National Institute on Drug Abuse
Rockville, MD
United States

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Symposium

Brain development during the fetal period and early infancy occurs at a dramatic pace. The implications of this rapid growth for healthy cognition and systemic vulnerabilities to pathology remain poorly understood. Recent advancements in fetal and infant imaging modalities, including transformative motion correction technology, have enabled deeper investigation of early brain development at a relatively high spatial resolution. This session seeks to discuss considerations involved in longitudinal imaging studies involving infants, such as imaging non-sedated neonates, children and fetuses in the presence of motion, and to highlight novel insights about neurocognitive development gleaned from recent studies.

The 4 speakers in this session will present recent advances in fetal imaging (Thomason), the connectome in late fetal and early neonatal life (Edwards), technical challenges to imaging infants and toddlers (Lin), and effects of early life adversity on the developing connectome (Rogers). Together, these presentations are expected to inform our understanding of 1) the state of the art in fetal and neonatal imaging, and 2) how these technologies can be utilized to advance studies of neurocognitive development.

Objective

1. Understanding challenges faced in pediatric imaging
2. Understanding recent advances in the cognitive neuroscience of early brain development

Target Audience

Cognitive neuroscientists and medical physicists with an interest in brain development, pediatric imaging, and longitudinal developmental studies.

Presentations

Novel insights into neurocognitive development gleaned from studies of the fetal brain in utero

Introduction: The critical role of healthy prenatal brain development is undisputed, and yet, we know very little about normative processes of human fetal systems level brain development. Much of what we have learned to date has been derived through evaluation of neonates born preterm, or study of the brain ex vivo. However, with advances in non-invasive prenatal MRI this picture has begun to change. Over recent years a number of studies using resting-state MRI and diffusion imaging in the fetal brain have generated foundational knowledge about the order and timing with which neural connectional systems emerge. With this technology it has become possible to tackle questions about how the brain is programmed before birth and also begin to address the relevance of variation in prenatal brain development to long-term neurodevelopmental outcomes. Here we will discuss new data that addresses these key objectives. Methods: We are testing models in which early psychosocial stress and concomitant chemical exposure influence development of neural systems in utero. We are also testing associations between prenatal brain development and behavioral attainment in infancy and in childhood. We perform functional MRI studies of the fetal brain in the late second and third trimester and follow children longitudinally with repeat assessments at birth, 7 months, 3 years and 5 years. Here, we will present data from >100 fetal MRI studies, summarizing normative processes of prenatal brain development and also addressing causes and consequences of neural programming events in utero. Results: Typical fetal development involves increase in signal efficiency, decreased modularity, and rapid expansion of long-range and cross-hemispheric connectivity. The fetal brain shows a high degree of overlap with organization of adult brain systems and is organized with a rich club structure comprised of hubs with enhanced connectivity degree. Maternal prenatal stress and chemical exposure can shift the specific ways in which networks are organized, and reflection of alterations in these prenatal networks can be seen in future child behavior. Further, sex-specific differences are apparent in the linkage between prenatal neural variation and child outcome data. Conclusions: Overall, we now have support for environmental programming of the human fetal brain and evidence that variations in prenatal brain networks relate to individual differences in neurodevelopment. Continued research in this area may help us to better understand the earliest origins of human neurodevelopmental problems and help us also to discover inroads for positive and resilience promoting prevention and intervention strategies.

Presenter

Moriah Thomason, New York University Langone Health New York, NY
United States

The Developing Human Connectome Project. An Open Science resource for fetal and neonatal neuroscience: early results

The Developing Human Connectome Project: The Developing Human Connectome Project (dHCP) is mapping the structural and functional connectivity of the human brain as it emerges in the third trimester of pregnancy and immediately after birth (20 to 44 weeks gestational age), making the data available for Open Access to the scientific community. The project has developed new MRI acquisition and analysis methods, including advanced motion correction approaches which support fetal and neonatal image aquisition, and is collecting a large dataset of fetal and neonatal brain images together with essential collateral information, including information on pregnancy and birth as well genetic, epigenetic and as neurocognitive follow-up data. The acquisition and analysis pipelines of the dHCP have been published, and to date around 1000 neonatal and 300 fetal high quality structural, diffusion and functional images sets have been acquired with follow-up completed on over 500 subjects. The first two tranches of data have been released: approximately 450 neonatal datasets are in the public domain together with minimal collateral datasets; further data releases of fetal, neonatal and collateral data will be made in 2020. To date there are several hundred registered users of the datasets, and the number of publications using these data is increasing rapidly. Developmental Connectomics: The connectome is likely to hold

a key to understanding aspects of both mental ability and behaviour, and the dHCP is part of a wider collaborative effort to understand connectivity across the lifecourse. While a complete read of the connectome must incorporate micro-, meso- and macro-scale data, the current state of the art requires that these be considered separately, although within an informatics structure that will facilitate large-scale, probabilistic, integration of data at a later stage. The millimeter scale macro-connectome can be studied non-invasively and directly in humans by neuroimaging, particularly diffusion Magnetic Resonance Imaging and functional connectivity Magnetic Resonance Imaging. Connectomics, like genomics, requires massive datasets that are comprehended computationally, and open-source neuroinformatic environments for large-scale integration of ever-increasing datasets are at the heart of this new science. Understanding normal cerebral connectivity in detail will provide insights into fundamental neural processes. By linking structural and functional connectivity to genetic, cognitive and environmental information it will be possible to answer specific neurobiological questions on the creation of mental functions, structure-function relationships, and the influences that shape them. Macro-connectomics also has potential for investigating many intractable neuropsychiatric diseases. Abnormal connectivity has been shown in disorders such as Autism, Schizophrenia and Alzheimer's disease, while environmental factors in late fetal or early neonatal life produce phenocopies of some of these conditions: the most important from a public health perspective is premature birth, which affects about 7% of all deliveries in Europe, and leads to a significantly increased risk of ASD (~5%) cognitive impairment (~35%) and Attention Deficit and Hyperactivity Disorder (ADHD, ~30%). These data argue that analysis of the connectome in late fetal and early neonatal life will provide significant insight into the normal brain and the abnormalities that lead to a number of major disabling neuropsychiatric diseases. Data from the dHCP is currently being used to study normal and abnormal development, for example the growth of multimodal similarity networks, the relation of gene expression and genetic polymorphisms to brain structure, the effect of preterm birth on connectivity, and the influence of antenatal adversity to brain growth. Researchers wishing to use the dHCP data can download the data from www.developingconnectome.org.

Presenter

David Edwards, King's College London London, London
United Kingdom

Imaging of Non-Sedated Pediatric Subjects 0 – 6 Years Old Using MRI: Logistics and Image Analysis

The first few years of life represent one of the most dynamic and critical phases of brain development. In addition to a rapid increase in brain volumes, complex functional maturation processes are the hallmarks of early brain development. This rapid developmental period also signifies a period of vulnerability. Adverse events during this period may lead to longstanding consequences and deviation from normal growth trajectories. Therefore, extensive efforts have been devoted to shedding new light on our understanding of the essential neural substrates underlying brain development during the first few years of life. Magnetic Resonance Imaging (MRI) provides superb soft-tissue contrast and high spatial resolution images along with brain functional information without radiation – a non-invasive imaging modality perfectly suited to uncover neural substrates of early brain development. However, MR is highly sensitive to motion, as slight subject motion during imaging could result in unusable images. Although sedation is typically used clinically to mitigate this difficulty, sedation is not applicable for research studies. In the past 15 years, teams at UNC have, and are conducting MR imaging studies focusing on early brain development, including the UNC/UMN Baby Connectome Project. Strategies and logistics of imaging non-sedated pediatric subjects and important factors leading to successful MR scans will be discussed. Furthermore, while obtaining high-quality MR images is undoubtedly critical for the investigation of early brain

development, equally important is the ability to extract anatomical attributes to quantitatively and rigorously characterize early brain development. Unlike adult MR images, several unique challenges associated with infant/toddler images have made it difficult to apply widely available adult image analysis tools for processing pediatric images. These factors include, but not limited to, the small size of the infant brain, the age-dependent gray/white contrast, motion artifacts, and the poor contrast-to-noise ratio, particularly during the first year of life. Therefore, novel image analysis approaches capable of handling these challenges will be needed. To this end, deep-learning based image analysis pipelines specifically tailored to analyze MR images during the first years of life will also be discussed. Finally, structural and functional developmental trajectories/features during the first 6 years of life will be presented.

Presenter

Weili Lin, University of North Carolina Chapel Hill, NC
United States

Early Life Adversity, Neonatal Brain Connectivity, and Early Childhood Psychopathology

Early life adversity including exposure to stressors during the perinatal period can alter early brain development. Brain regions underlying emotion regulation and reward processing are vulnerable to this early adversity. Prior work has demonstrated that alterations in functional and structural brain connectivity can be reliably detected in the neonatal brain. Further, variability in neonatal brain connectivity can predict early impairment in social-emotional domains that can place one on a trajectory for later psychopathology. This presentation will detail the pattern of connectivity at birth in ongoing longitudinal cohort studies enriched for early life adversity. Additionally, neonatal connectivity will be linked to later dimensional measures of childhood psychopathology and executive function. Methods: Preterm and full-term infants from these longitudinal studies underwent MRI on a 3T scanner at term-equivalent age (36-42 weeks post menstrual age) with diffusion MRI and resting state fMRI sequences acquired. Structural connectivity was measured using diffusion tractography and whole brain functional connectivity analyses were conducted with seeds placed in cortical and subcortical regions within a subset of neonates. A subgroup of n=45 neonates returned for a second visit and participated in a task-based fMRI task that assessed brain activity changes in response to an auditory 'oddball' white noise burst. In the first cohort, children returned at age 2 years, at age 5 years, and age 9-10 for assessment of their social-emotional development and symptoms of psychiatric disorders as well as behavioral assessments with repeat MRI at ages 9-10. In the second cohort, children are returning annually at ages 1, 2 and 3 years of age with repeat MRI at age 2. Measures of early life adversity including socioeconomic status and maternal psychosocial functioning were obtained during the perinatal period and during the follow-up periods. Results: Amygdala and striatal functional connectivity detected in neonates followed connectivity patterns similar to those in older children and adults including functional connections with the medial prefrontal cortex, anterior cingulate, and insula. Functional connections between the amygdala and striatum and these cortical regions as well as between network connectivity of cortical brain networks were related to variability in early life adversity. These neonatal functional connectivity relationships as well as structural connectivity of white matter tracts connecting these regions including the cingulum, uncinate, and anterior limb of the internal capsule were also related to variability in early childhood psychopathology particularly internalizing and externalizing symptoms. and executive function. Measures of early life adversity appeared to mediate some of these relationships Conclusions: Evidence form these longitudinal cohort studies support an impact of early life adversity on the functional and structural connectivity of the neonatal brain. Further, these results highlight that alterations in neonatal connectivity within key functional networks and white matter tracts are related to early childhood psychopathology with exposure to

early life adversity and related clinical and psychosocial risk factors modifying these relationships.

Presenter

Cynthia Rogers, Washington University St. Louis, MO
United States