NeuroImage 203 (2019) 116142

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Editorial

Imaging baby brain development

The most dynamic postnatal brain development takes place during human infancy. Brain size increases dramatically, reaching 80–90% of adult volume by age of year 2. Consistent with rapid elaboration of new synapses in the first 2 years, overall gray matter volumes increase to lifetime maximum around age of year 2. Elucidating the ontogeny of structure, function and physiology of early developing brain will not only greatly advance current understanding of the general principles of normal development, but also offer insights into neural disorders. Significant advances of neuroimaging techniques and findings on baby brain development have occured recently, along with improved infant health care. Cutting-edge imaging techniques including functional, diffusion, structural and perfusion MRI, electroencephalogram (EEG), magnetoencephalography (MEG), near-infrared spectroscopy (NIRS) and ultrasound, coupled with state-of-the-art analytic approaches for motion correction, baby brain atlas, computational neuroanatomy, morphology, connectivity and graph-theory-based networks have empowered recent investigations yielding new insights into baby brain structure and function, electrical and magnetic properties of current in brain circuits, and brain hemodynamics. These neuroimaging studies open up new avenues for understanding typical brain maturation and finding biomarkers of brain disorders. Even with such fascinating new approaches at hand, there are still traditional and new challenges in baby brain imaging particularly due to the babies' small physical size, immaturity and knowledge gaps in imaging high-risk and atypical early brain development. The steady advancement of imaging techniques and analysis methods continuously tackles these challenges.

Recognizing the vitality and diversity of the baby brain neuroimaging community, we have organized an issue focused on the research topic, "imaging baby brain development", collecting works at the forefront of studying healthy and diseased baby brain development based on neuroimaging. Among the 35 papers included in this issue, 17 are review articles contributed by invited internationally recognized experts on a variety of baby brain neuroimaging topics and 18 are unsolicited original research articles relevant to the special issue. All included papers went through regular peer review process of the Neuroimage journal. The topics covered diverse research directions of theoretical modeling, specific imaging techniques, atlases and anatomy, and brain development under normal, diseased, and high-risk conditions.

1. Reviews and perspectives

We were fortunate to collect excellent review and perspective articles from internationally recognized experts in the field. Two perspective articles and fifteen review articles are included in this special issue. In the first perspective article, Barkovich et al. (2019) thoroughly summarized the major challenges facing pediatric neuroimaging. The challenges include both general problems (e.g. motion and age) and condition-specific problems (e.g. imaging fetal brains and imaging children with autism spectrum disorder). Current methods to reduce artefacts at acquisition and post-processing stages and proposed improvements were also incorporated. In the second informative perspective article, Denisova et al. (2019) identified important knowledge gaps and suggested guidelines at the leading edge of baby neuroimaging science to transform our understanding of atypical brain development in humans. The article argued that precise identification of neurobiological underpinnings of atypical development in humans calls for approaches including quantitative MRI pulse sequences, multi-modal imaging (including diffusion tensor imaging (DTI), MR spectroscopy (MRS), and MEG), and infant-specific hemodynamic response function (HRF) shapes for modeling brain-oxygen-level-dependent (BOLD) signal. Among the fifteen review articles, Howell et al. (2019) discussed the overall study protocol used in the UNC/UMN Baby Connectome Project (BCP). The protocol included approaches for subject recruitment, strategies for imaging typically developing children 0–5 years of age without sedation, imaging protocol/optimization, battery of behavioral assessments, and quality assurance/quality control methods. Regarding **theoretical modeling**, Zhao et al., 2019b provided a detailed delineation of early changes (20 gestational weeks to 2 years old) of baby brains in a graph-theory modeling framework for understanding the developmental principles of the connectome. Six review articles focused on **specific imaging techniques** of baby brains. Ouyang et al. (2019) comprehensively summarized diffusion MRI findings that contribute to charting spatiotemporally heterogeneous gray and white matter structural development. These findings offer MRI-based landmarks of typical brain development, setting the stage for understanding aberrant brain development in neurodevelopmental disorders. Zhang et al. (2019) revisited previous findings and hypotheses using resting-state fMRI for pediatric brain imaging, highlighted existing issues and problems, and made a "to-do-list" for future studies. T. Liu et al., 2019 presented a novel non-invasive approach to study brain activations based on the brain's hemodynamic properties using functional NIRS. Demene et al. (2019) summarized the technical basis, added value and clinical perspectives provided by ultrafast Doppler, an imaging technique that could create a breakthrough in the fields of brain hemodynamics, brain injury, and neuroprotection. Chen et al. (2019) highlighted the use of MEG in exploring emerging brain function in 0–3 years of age in response to basic sensory stimuli in developing brains, as well as practices for incorporating MEG and advanced source analyses to study early cognitive processes. Vasung et al. (2019) gave an extensive overview of *ex vivo* MRI studies that characterize early brain development in humans, monkeys,

https://doi.org/10.1016/j.neuroimage.2019.116142

Available online 29 August 2019

cats, as well as rats/mice, and discussed current advantages and limitations of *ex vivo* fetal brain MRI. Four papers provided reviews of baby brain **atlases and anatomy**. Li et al. (2019) provided an illuminating overview of cutting-age computational methods for infant brain MRI processing and analysis. Kostovic et al. (2019) focused on early developmental periods (from 8 postconceptional weeks to the second postnatal year). They described the microstructural organization and neural circuitry of fetal and early postnatal human cerebrum in the perspective of neural histology and neurogenesis and their correlation with neuroimaging findings. In Oishi et al., 2019, the types and roles of currently available human baby brain MRI atlases were incisively described and discussed. Future directions in the field of developmental neuroscience and its clinical applications were proposed. The potential use of disease-based atlases to characterize clinically relevant information, such as clinical labels, in addition to conventional anatomical labels, was also discussed. Im and Grant (2019) summarized spatial distribution and specific geometric- and topological-pattern-based analysis of early sulcal folds. They suggested advancing the understanding of spatio-temporal dynamics of fetal cortical folding in a large longitudinal cohort to examine individual clinical fetal MRIs and to predict postnatal neurodevelopmental outcomes. Three review articles provided new insights on **development under diseased conditions.** Gao et al. (2019) reviewed studies of genetic and environmental risks. The article leveraged representative publications in the field to summarize the current state, point out potential limitations and discuss important future directions. Peyvandi et al. (2019) recapitulated on neuroimaging studies in congenial heart disease and their outcomes. They suggested an emerging focus on the impact of cardiovascular physiology on brain health and the complex heart-brain interplay that influences ultimate neurodevelopmental outcome in patients. Smyser et al. (2019) extensively reviewed the emerging body of literature detailing studies employing diffusion MRI, resting state-functional MRI and other complementary neuroimaging modalities to characterize structural and functional connectivity development in infants with brain injury. They also reviewed technical challenges associated with neonatal neuroimaging. Together, these review articles suggest continuous improvement in imaging techniques, theoretical modeling, atlases and anatomy, and applications in healthy and diseased conditions coherently push our understanding of early brain development forward.

2. Original research

We collected 18 original research articles, which can be roughly categorized into Methodologies and Tools, Normal Development and Prediction, Effects of Preterm Birth (compared to full-term birth) and Brain Disorders and High-Risk Development.

2.1. Methodologies and Tools

Focusing on early development of brain structural morphology, Duan et al. (2018) proposed a novel method for exploring the representative regional folding patterns of infant brains. Application to normal neonates and adults revealed that major cortical folding patterns of adults are largely established at birth. Three compelling studies contributed new tools to the diffusion MRI field. Two of them proposed new methods for creating atlases of the developing brain. Khan et al. (2018) presented the DTI atlas of fetal brain computed from in utero diffusion-weighted images, which could serve as a useful resource for detecting normal and abnormal fetal brain development in utero. In another study, Pietsch et al. (2018) described a framework for creating the DTI time-resolved template of developing brain using advanced multi-shell high angular resolution diffusion imaging (HARDI) data. Weekly multi-tissue atlases for neonates from 33 to 44 postmenstrual weeks were developed based on this technique. Lastly, Bastiani et al. (2019) developed an automated processing pipeline for neonatal diffusion MRI data in the developing Human Connectome Project (dHCP). The pipeline addresses specific issues related to neonates such as artefacts related to severe motion, small brain sizes, high brain water content and reduced anisotropy.

2.2. Normal Development and Prediction

Five papers described age-related brain alterations during early development. Taking advantage of high quality DTI data obtained from 84 healthy preterm and term-born neonates from 31 to 42 postmenstrual weeks (PMW), Feng et al. (2018) established age-specific brain templates and atlases at 33, 36 and 39 PMW. They further applied these atlases to delineate microstructural changes of major white matter tracts during the third trimester, and found significantly and heterogeneously age-related changes among tested white matter tracts. Utilizing DTI data of 77 preterm-born and full-term neonates scanned at 31–42 PMW, Zhao et al., 2019a investigated the topological properties of structural networks. They revealed rapid age-related increases of hubs and rich-club connections as well as higher developmental rates of edge strength in short-range and within-module connections, laying the foundation for efficient network communication around birth. Two studies focused on mapping the cortical maturation. Exploiting diffusion MRI data of preterm infants scanned between 25 and 47 PMW, Batalle et al. (2019) observed regional heterogeneity pattern of microstructural and macrostructural maturation during the third trimester. Labenberg et al. (2019) investigated the cortical microstructure in infants aged between 1 and 5 months. Taking advantage of the multi-parameter and clustering analysis, they characterized the temporal profiles and spatial patterns of maturation across cortical regions. P. Liu et al., 2019 applied phase-contrast MRI, a fast and reliable technique that measures cerebral blood flow (CBF), to infants aged 34 to 114 gestational weeks and found CBF rapidly increased during this period. The study also provided age-specific recommendations for parameter selection in a single PC-MRI scan for this population. Understanding the relationship between brain and future behavior outcomes is important in studying early brain development. Adeli et al. (2019) developed a multi-task machine learning framework to tackle this problem. The framework predicted multiple future cognitive scores with incomplete longitudinal imaging data. Their results affirmed that cognitive scores measured at the age of 4 years can be predicted by imaging data as early as 24 months of age. By training and testing 18-month-old infants, Monroy et al. (2019) provided evidence that the infant motor system can use knowledge from statistical learning to predict upcoming actions, extending our knowledge of learning mechanism in the developing brain.

2.3. Effects of Preterm Birth (compared to full term birth)

Preterm birth effects on brain structure and function were examined in five papers, among which four utilized T2-weighted MRI and one utilized fMRI. With T2-weighted MRI, Alexander et al. (2019) investigated the relationship between gestational age (GA) at birth and brain volumes at term-equivalent age. Interestingly, younger GA at birth was associated with smaller volumes at term-equivalent age in some regions such as bilateral cerebral white matter, middle temporal gyri, amygdalae, pallidum and brainstem, and larger volumes at term-equivalent age in other regions such as primary visual, motor and somatosensory cortices. In another study investigating brain volume change employing T2-weighted MRI data, Gui et al. (2019) presented intriguing findings. From birth to term-equivalent age, relative volumes of cortical gray matter, cerebellum, and cerebrospinal fluid (CBF) with respect to total intracranial volume increased, while relative volumes of unmyelinated white matter and subcortical gray matter decreased. Furthermore, brain tissue volumes at birth and term-equivalent age contributed to the prediction of motor outcomes at 18–24 months. Volumes at term-equivalent age and volume growth rates contributed to the prediction of cognitive scores at 5 years of age. In another insightful T2-weighted MRI study on brain volumes, Thompson et al. (2019) explored the effects of early life predictors on brain volume and microstructure for very preterm (<32

weeks GA), moderate preterm (32–33 weeks GA), late preterm (34–36 weeks GA) or full-term (≥37 weeks GA) infants at term-equivalent age. They found early life predictors including sex, birthweight standard deviation score, multiple birth and social risk for brain volumes and microstructure have different effects depending on the GA at birth. Employing the novel method of spectral analysis of gyrification, Dubois et al. (2019) aimed to characterize typical folding progression *ex utero* from the pre-to post-term period. They reported three successive waves which may correspond to primary, secondary and tertiary folding. Some deviations were detected in 10 premature infants without apparent neurological impairment and imaged at term equivalent age, suggesting that the approach was sensitive enough to detect subtle impacts of preterm birth and extra-uterine life on folding. Using fMRI, Lordier et al. (2019) explored cortico-subcortical music processing in newborns shortly after birth. They investigated whether early music exposure in the NICU modulates brain processing of music in preterm infants at term equivalent age and whether exposure modulates differences of music processing in preterm and full-term newborns. Their findings suggested that music exposure in NICUs can induce brain functional connectivity changes associated with music processing.

2.4. Brain disorders and high-risk development

Two studies focused on brain disorders and high risk development. Guo et al. (2019) proposed that white matter injury in term-born neonates with congenital heart disease had a characteristic volume and distribution pattern in the brain. Importantly, there was strong concordance in the spatial distribution and burden of white matter injury across three centers. Rasmussen et al. (2019) showed that maternal inflammation during pregnancy can alter the trajectory of baby brain development and increase the risk of offspring psychiatric disorders. The maternal inflammatory state during pregnancy was prospectively associated with offspring frontolimbic white matter microstructural properties. Further evidence suggested that maternal inflammatory-related maturational changes in frontolimbic white matter microstructural properties during the first 12 months of postnatal life were associated with early cognitive development.

Overall, the plentitude of novel study methods, imaging tools, and theoretical advances opens up new pathways deepening our understanding of infant brain development. The broadened range of ages and aberrant conditions, including populations under high-risk for developing neurological disorders, creates new opportunities for both unraveling the basic mechanisms underlying normal and atypical development and generating impactful clinical applications for early diagnosis of brain disorders. We would like to thank all of the authors, reviewers, and the NeuroImage editorial office for their important contributions to this issue.

Acknowledgment

The organization of this editorial and writing were assisted by Tianjia Zhu and Samantha Lam in Huang Lab, and Yuehua Xu and Miao Cao in He Lab.

References

Adeli, E., Meng, Y., Li, G., Lin, W., Shen, D., 2019. Multi-task prediction of infant cognitive scores from longitudinal incomplete neuroimaging data. Neuroimage 185, 783–792.

Alexander, B., Kelly, C.E., Adamson, C., Beare, R., Zannino, D., Chen, J., Murray, A.L., Loh, W.Y., Matthews, L.G., Warfield, S.K., Anderson, P.J., 2019. Changes in neonatal regional brain volume associated with preterm birth and perinatal factors. Neuroimage 185, 654–663.

Barkovich, M., Li, Y., Desikan, R., Barkovich, A., Xu, D., 2019. Challenges in pediatric neuroimaging. Neuroimage 185, 793–801.

Bastiani, M., Andersson, J.L., Cordero-Grande, L., Murgasova, M., Hutter, J., Price, A.N., Makropoulos, A., Fitzgibbon, S.P., Hughes, E., Rueckert, D., Victor, S., 2019. Automated processing pipeline for neonatal diffusion MRI in the developing human connectome project. Neuroimage 185, 750–763.

Batalle, D., O'muircheartaigh, J., Makropoulos, A., Kelly, C.J., Dimitrova, R., Hughes, E.J., Hajnal, J.V., Zhang, H., Alexander, D.C., Edwards, A.D., Counsell, S.J., 2019. Different patterns of cortical maturation before and after 38 weeks gestational age demonstrated by diffusion MRI in vivo. Neuroimage 185, 764–775.

Chen, Y., Saby, J., Gaetz, W., Edgar, J., Roberts, T., 2019. Magnetoencephalography (MEG) in infant brain development. Neuroimage 189, 445–458.

Demene, C., Mairesse, J., Baranger, J., Tanter, M., Baud, O., 2019. Ultrafast Doppler for neonatal brain imaging. Neuroimage 185, 851–856.

Denisova, K., 2019. Neurobiology, not artefacts: challenges and guidelines for imaging the high risk infant. Neuroimage 185, 624–640.

Duan, D., Xia, S., Rekik, I., Meng, Y., Wu, Z., Wang, L., Lin, W., Gilmore, J.H., Shen, D., Li, G., 2018. Exploring folding patterns of infant cerebral cortex based on multi-view curvature features: methods and applications. Neuroimage 185, 575–592.

Dubois, J., Lefèvre, J., Angleys, H., Leroy, F., Fischer, C., Lebenberg, J., Dehaene-Lambertz, G., Borradori-Tolsa, C., Lazeyras, F., Hertz-Pannier, L., Mangin, J.F., 2019. The dynamics of cortical folding waves and prematurity-related deviations revealed by spatial and spectral analysis of gyrification. Neuroimage 185, 934–946.

Feng, L., Li, H., Oishi, K., Mishra, V., Song, L., Peng, Q., Ouyang, M., Wang, J., Slinger, M., Jeon, T., Lee, L., 2018. Age-specific gray and white matter DTI atlas for human brain at 33, 36 and 39 postmenstrual weeks. Neuroimage 185, 685–698.

Gao, W., Grewen, K., Knickmeyer, R.C., Qiu, A., Salzwedel, A., Lin, W., Gilmore, J.H., 2019. A review on neuroimaging studies of genetic and environmental influences on early brain development. Neuroimage 185, 802–812.

Gui, L., Loukas, S., Lazeyras, F., Hüppi, P.S., Meskaldji, D.E., Tolsa, C.B., 2019. Longitudinal study of neonatal brain tissue volumes in preterm infants and their ability to predict neurodevelopmental outcome. Neuroimage 185, 728–741.

Guo, T., Chau, V., Peyvandi, S., Latal, B., McQuillen, P.S., Knirsch, W., Synnes, A., Feldmann, M., Naef, N., Chakravarty, M.M., De Petrillo, A., 2019. White matter injury in term neonates with congenital heart diseases: topology & comparison with preterm newborns. Neuroimage 185, 742–749.

Howell, B., Styner, M., Gao, W., Yap, P., Wang, L., Baluyot, K., Yacoub, E., Chen, Geng, Potts, T., Salzwedel, A., Li, G., Gilmore, J., Piven, J., Smith, K., Shen, D., Ugurbil, K., Zhu, H., Lin, W., Elison, J., 2019. The UNC/UMN Baby Connectome Project (BCP): an overview of the study design and protocol development. Neuroimage 185, 891–905.

Im, K., Grant, P.E., 2019. Sulcal pits and patterns in developing human brains. Neuroimage 185, 881–890.

Khan, S., Vasung, L., Marami, B., Rollins, C.K., Afacan, O., Ortinau, C.M., Yang, E., Warfield, S.K., Gholipour, A., 2018. Fetal brain growth portrayed by a spatiotemporal diffusion tensor MRI atlas computed from in utero images. Neuroimage 185, 593–608.

Kostović, I., Sedmak, G., Judaš, M., 2019. Neural histology and neurogenesis of the human fetal and infant brain. Neuroimage 188, 743–773.

Lebenberg, J., Mangin, J.F., Thirion, B., Poupon, C., Hertz-Pannier, L., Leroy, F., Adibpour, P., Dehaene-Lambertz, G., Dubois, J., 2019. Mapping the asynchrony of cortical maturation in the infant brain: a MRI multi-parametric clustering approach. Neuroimage 185, 641–653.

Li, G., Wang, L., Yap, P., Wang, F., Wu, Z., Meng, Y., Dong, P., Kim, J., Shi, F., Rekik, I., Lin, W., Shen, D., 2019. Computational neuroanatomy of baby brains: a review. Neuroimage 185, 906–925.

Liu, P., Qi, Y., Lin, Z., Guo, Q., Wang, X., Lu, H., 2019. Assessment of cerebral blood flow in neonates and infants: a phase-contrast MRI study. Neuroimage 185, 926–933.

Liu, T., Liu, X., Yi, L., Zhu, C., Markey, P., Pelowski, M., 2019. Assessing autism at its social and developmental roots: a review of Autism Spectrum Disorder studies using functional near-infrared spectroscopy. Neuroimage 185, 955–967.

Lordier, L., Loukas, S., Grouiller, F., Vollenweider, A., Vasung, L., Meskaldij, D.E., Lejeune, F., Pittet, M.P., Borradori-Tolsa, C., Lazeyras, F., Grandjean, D., 2019. Music processing in preterm and full-term newborns: a psychophysiological interaction (PPI) approach in neonatal fMRI. Neuroimage 185, 857–864.

Monroy, C.D., Meyer, M., Schröer, L., Gerson, S.A., Hunnius, S., 2019. The infant motor system predicts actions based on visual statistical learning. Neuroimage 185, 947–954.

Oishi, K., Chang, L., Huang, H., 2019. Baby brain atlases. Neuroimage 185, 865–880.

Ouyang, M., Dubois, J., Yu, Q., Mukherjee, P., Huang, H., 2019. Understanding early brain development from fetuses to infants with diffusion MRI and beyond. Neuroimage 185, 836–850.

Peyvandi, S., Latal, B., Miller, S.P., McQuillen, P.S., 2019. The neonatal brain in critical congenital heart disease: insights and future directions. Neuroimage 185, 776–782.

Pietsch, M., Christiaens, D., Hutter, J., Cordero-Grande, L., Price, A.N., Hughes, E., Edwards, A.D., Hajnal, J.V., Counsell, S.J., Tournier, J.D., 2018. A framework for multi-component analysis of diffusion MRI data over the neonatal period. Neuroimage 186, 321–337.

Rasmussen, J.M., Graham, A.M., Entringer, S., Gilmore, J.H., Styner, M., Fair, D.A., Wadhwa, P.D., Buss, C., 2019. Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. Neuroimage 185, 825–835.

Smyser, C.D., Wheelock, M.D., Limbrick Jr., D.D., Neil, J.J., 2018. Neonatal brain injury and aberrant connectivity. Neuroimage 185, 609–623.

Thompson, D.K., Kelly, C.E., Chen, J., Beare, R., Alexander, B., Seal, M.L., Lee, K., Matthews, L.G., Anderson, P.J., Doyle, L.W., Spittle, A.J., 2019. Early life predictors

of brain development at term-equivalent age in infants born across the gestational age spectrum. Neuroimage 185, 813–824.
Vasung, L., Charvet, C., Shiohama, T., Gagoski, Borjan, Levman, J., Takahashi, E., 2019. Ex vivo fetal brain MRI: recent advances, challenges, and future directions. Neuroimage 195, 23–37.
Zhang, H., Shen, D., Lin, W., 2019. Resting-state functional MRI studies on infant brains: a decade of gap-filling efforts. Neuroimage 185 (2019), 664–684.
Zhao, T., Mishra, V., Jeon, T., Ouyang, M., Peng, Q., Chalak, L., Wisnowski, J.L., Heyne, R., Rollins, N., Shu, N., Huang, H., 2019a. Structural network maturation of the preterm human brain. Neuroimage 185, 699–710.
Zhao, T., Xu, Y., He, Y., 2019b. Graph Theoretical Modeling of baby brain networks. Neuroimage 185, 711–727.

Hao Huang*, Petra S. Huppi, Yong He, Jason Lerch

E-mail address: hao.huang@pennmedicine.upenn.edu (H. Huang).