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Regional microstructural organization of the cerebral cortex is affected by preterm birth

Marine Bouyssi-Kobar[a,b], Marie Brossard-Racine[c], Marni Jacobs[d], Jonathan Murnick[a], Taeun Chang[e], Catherine Limperopoulos[a,*]

[a] The Developing Brain Research Laboratory, Department of Diagnostic Imaging and Radiology, Children's National Health System, Washington, DC 20010, USA
[b] Institute for Biomedical Sciences, George Washington University, Washington, DC 20037, USA
[c] Department of Pediatrics Neurology, McGill University Health Center, Montreal, QC H4A3J1, Canada
[d] Division of Biostatistics and Study Methodology, Children's Research Institute, Children's National Health System, Washington, DC 20010, USA
[e] Department of Neurology, Children's National Health System, Washington, DC 20010, USA

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ABSTRACT

Objectives: To compare regional cerebral cortical microstructural organization between preterm infants at term-equivalent age (TEA) and healthy full-term newborns, and to examine the impact of clinical risk factors on cerebral cortical micro-organization in the preterm cohort.

Study design: We prospectively enrolled very preterm infants (gestational age (GA) at birth < 32 weeks; birthweight < 1500 g) and healthy full-term controls. Using non-invasive 3T diffusion tensor imaging (DTI) metrics, we quantified regional micro-organization in ten cerebral cortical areas: medial/dorsolateral prefrontal cortex, anterior/posterior cingulate cortex, insula, posterior parietal cortex, motor/somatosensory/auditory/visual cortex. ANCOVA analyses were performed controlling for sex and postmenstrual age at MRI.

Results: We studied 91 preterm infants at TEA and 69 full-term controls. Preterm infants demonstrated significantly higher diffusivity in the prefrontal, parietal, motor, somatosensory, and visual cortices suggesting delayed maturation of these cortical areas. Additionally, postnatal hydrocortisone treatment was related to accelerated microstructural organization in the prefrontal and somatosensory cortices.

Conclusions: Preterm birth alters regional microstructural organization of the cerebral cortex in both neurocognitive brain regions and areas with primary sensory/motor functions. We also report for the first time a potential protective effect of postnatal hydrocortisone administration on cerebral cortical development in preterm infants.

1. Introduction

Infants born very preterm (before 32 weeks gestational age (GA)) are three times more likely than full-term born infants to develop psychiatric disorders (Johnson and Marlow, 2011), and are at higher risk for a wide range of socio-cognitive impairments (Blencowe et al., 2013). The neural substrates of socio-cognitive functioning are composed of cortical and subcortical interconnected neurons that co-activate for the purpose of mediating specific cognitive outputs and are organized in circuits called neurocognitive networks (Mesulam, 2012). The functional network foundations are already present during the third trimester of gestation (Doria et al., 2010). However, these neural networks are immature at birth, and can already exhibit early signs of impairment in infants born preterm (Ball et al., 2015; C. D. Smyser et al., 2015a). In adults who were born very preterm, alterations of these neurocognitive networks have recently been demonstrated (White et al., 2014). Interestingly, little is known about the early microstructural integrity of the cerebral cortical regions involved in socio-cognitive processing.

The cytoarchitecture of the cerebral cortex undergoes major transformations during the perinatal period as a result of critical developmental processes in neural migration, spinogenesis, synaptogenesis, and gyrification (Budday et al., 2015). Quantitative magnetic resonance imaging (MRI) techniques such as diffusion tensor imaging (DTI) allow for *in vivo* characterization of the microstructural cerebral organization (Mori and Zhang, 2006). Although DTI has been traditionally used to

* Corresponding author at: Developing Brain Research Laboratory, Departments of Diagnostic Imaging and Radiology, Children's National Health System, 111 Michigan Ave NW, Washington, DC 20010, USA.
E-mail addresses: marine@gwu.edu (M. Bouyssi-Kobar), marie.brossardracine@mcgill.ca (M. Brossard-Racine), MJacobs@childrensnational.org (M. Jacobs), JMurnick@childrensnational.org (J. Murnick), TChang@childrensnational.org (T. Chang), CLimpero@childrensnational.org (C. Limperopoulos).

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characterize white matter development in the neonatal population (Qiu et al., 2015), it also offers important insights into the maturation of the cerebral cortex (Hüppi and Dubois, 2006). Specifically, DTI probes the microstructural organization of brain tissue by measuring the three-dimensional spatial diffusion of water molecules (Basser et al., 1994). The properties of water diffusion are described through several DTI-based metrics; the most commonly used are mean diffusivity (MD), which provides the average water displacement, and fractional anisotropy (FA), which measures the directionality or anisotropy of the diffusion (Mori and Zhang, 2006). Using DTI metrics, it is possible to characterize the complex architectural changes of the cerebral cortex associated with maturational processes during critical periods of development. It has been shown that between 25 and 40 weeks GA, MD decreases as the water content of the cortex is reduced due to increasing cellular density and complexity (McKinstry et al., 2002). In contrast, FA increases during early GA (up to 28 weeks GA) reflecting the radial organization of the cortex (Gupta et al., 2005; Trivedi et al., 2009). Thereafter, FA decreases due to progressive differentiation of radial glia, arrival of axons, and dendritic arborization (Aeby et al., 2012; Gupta et al., 2005; McKinstry et al., 2002; Yu et al., 2015).

Longitudinal DTI studies in preterm infants have quantified *in vivo* the neurobiological processes occurring during the *ex-utero* third trimester (Ball et al., 2013; deIpolyi et al., 2005; Eaton-Rosen et al., 2017; Kersbergen et al., 2014; Schneider et al., 2016; T. A. Smyser et al., 2015b; Wu et al., 2017a). The cerebral cortex matures as a function of advancing GA with a central to peripheral and posterior to anterior regional gradient, and cortical areas with primary sensory and motor functions develop before association areas (Raybaud et al., 2013). This spatiotemporal gradient of maturity translates into a different rate of MD and/or FA decrease by brain region (Kersbergen et al., 2014; Wu et al., 2017b). Thus, DTI metrics have been used as markers of cerebral cortical maturation: slower postnatal growth in preterm infants has been associated with delayed maturation of the cerebral cortex characterized by higher FA values (Vinall et al., 2013). However, only two studies have compared cortical microstructural organization between preterm infants at term-equivalent age (TEA) and full-term controls (Ball et al., 2013; T. A. Smyser et al., 2015b). Although these studies have provided remarkable information about cerebral cortical micro-organization, none of the brain regions that play a crucial role in socio-cognitive processing have been assessed to date. These key neurocognitive regions are known to be impaired in neurodevelopmental disorders and remain to be examined in the premature infants. Consequently, we investigated the microstructural integrity of brain areas known to be involved in neurocognitive networks: the dorsolateral prefrontal cortex (dlPFC), the posterior parietal cortex (PPC), the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), the insula, and anterior cingulate cortex (ACC). Additionally, to further validate our findings, we sought to characterize the cortical areas linked to sensory and motor functions. Our primary objective was to compare the DTI metrics within these cerebral cortical regions of interest (ROIs) between very preterm infants at TEA and healthy full-term controls. As a secondary objective, we examined clinical risk factors that are associated with cerebral cortical development within the preterm cohort.

2. Materials and methods

2.1. Participants

Preterm infants born before 32 weeks GA and weighing < 1500 g admitted to the level IV NICU at Children's National Health System (Washington DC) from June 2012 to February 2016 were enrolled in a prospective observational study on brain development (Bouyssi-Kobar et al., 2017). Exclusion criteria for this preterm cohort included: chromosomal anomalies, dysmorphic features, congenital brain malformations, central nervous system infection, and metabolic disorders. In the context of another prospective research study on perinatal brain growth and development, healthy fetal/mother dyads with normal fetal sonography were enrolled as control participants (Bouyssi-Kobar et al., 2017). Exclusion criteria included evidence of dysmorphic features, chromosomal abnormalities, multiple gestations, congenital infections, maternal drug use, and maternal disease. All healthy newborns included in this study were born full-term (after 38 weeks GA) with uneventful deliveries and normal MRI brain scans. Both studies were approved by the Institutional Review Board of Children's National Health System and written informed consent was obtained from parents for all participants.

2.2. Clinical data collection

For all participants, demographic, prenatal, intrapartum, and neonatal information was collected including: maternal age at delivery, pregnancy complications, type of delivery, need for respiratory/cardiac resuscitation, birthweight, GA at birth, sex, ethnicity, and Apgar score at 1 and 5 min. In the preterm cohort, we also documented the presence of chorioamnionitis per placenta pathology records, and postnatal data reflecting infants' clinical status throughout their stay in the neonatal intensive care unit including: moderate to severe bronchopulmonary dysplasia (BPD) (Jobe and Bancalari, 2001), length of supplemental oxygen requirement, postnatal steroid treatment including length of treatment and type of steroid used (dexamethasone *versus* hydrocortisone), sepsis (confirmed by positive blood culture), necrotizing enterocolitis (NEC) diagnosis requiring bowel surgery, need for cardiac pressor support, and need for patent ductus arteriosus (PDA) surgical ligation.

2.3. MRI acquisitions

All participants underwent a brain MRI on a 3 T GE Healthcare Discovery MR750 scanner (Milwaukee, WI). Infants were scanned under natural sleep: after feeding, they were swaddled in warm blankets, provided with ear protection, and immobilized using a newborn vacuum pillow (Newmatic Medical, Caledonia, MI). A nurse was present for the duration of the MRI scan to monitor vital signs. Diffusion weighted images were obtained using a single shot echo-planar sequence: 27 non-collinear diffusion gradients with a b-value of 1000 s/mm^2, three non-diffusion weighted (b0) volumes, echo/repetition time = 80/8000 ms, voxel size = 1.56 × 1.56 × 3 mm, acquisition time = 4:08 min. An anatomical T2-weighted sequence (3D Cube) was also acquired: echo/repetition time = 65/2500 ms, voxel size = 0.63 × 1 × 0.63 mm, acquisition time = 3 min 20 s.

2.4. Brain assessment

Clinical readings of all brain MRI studies were carried out by an experienced pediatric neuroradiologist. For the preterm cohort, brain injury severity was also classified into normal, mild, moderate, and severe categories (Kidokoro et al., 2013), and intraventricular hemorrhage (IVH) severity was defined according to Papile et al. (1978). In order to avoid the known cofounding factor of severe brain injury on cerebral cortical development (Andiman et al., 2010; Sizonenko et al., 2007; T. A. Smyser et al., 2015b), we excluded infants with severe brain injury from further DTI analyses. Specifically, preterm infants with IVH grade III, periventricular hemorrhagic infarction, cystic periventricular leukomalacia, or those falling into the severe category classification on the Kidokoro et al. (2013) scoring system. Thus, our preterm cohort included only infants without evidence of structural brain lesions and infants with mild to moderate parenchymal brain injury on conventional MRI.

2.5. DTI processing

DTI data were preprocessed using a previously validated neonatal