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

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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

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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

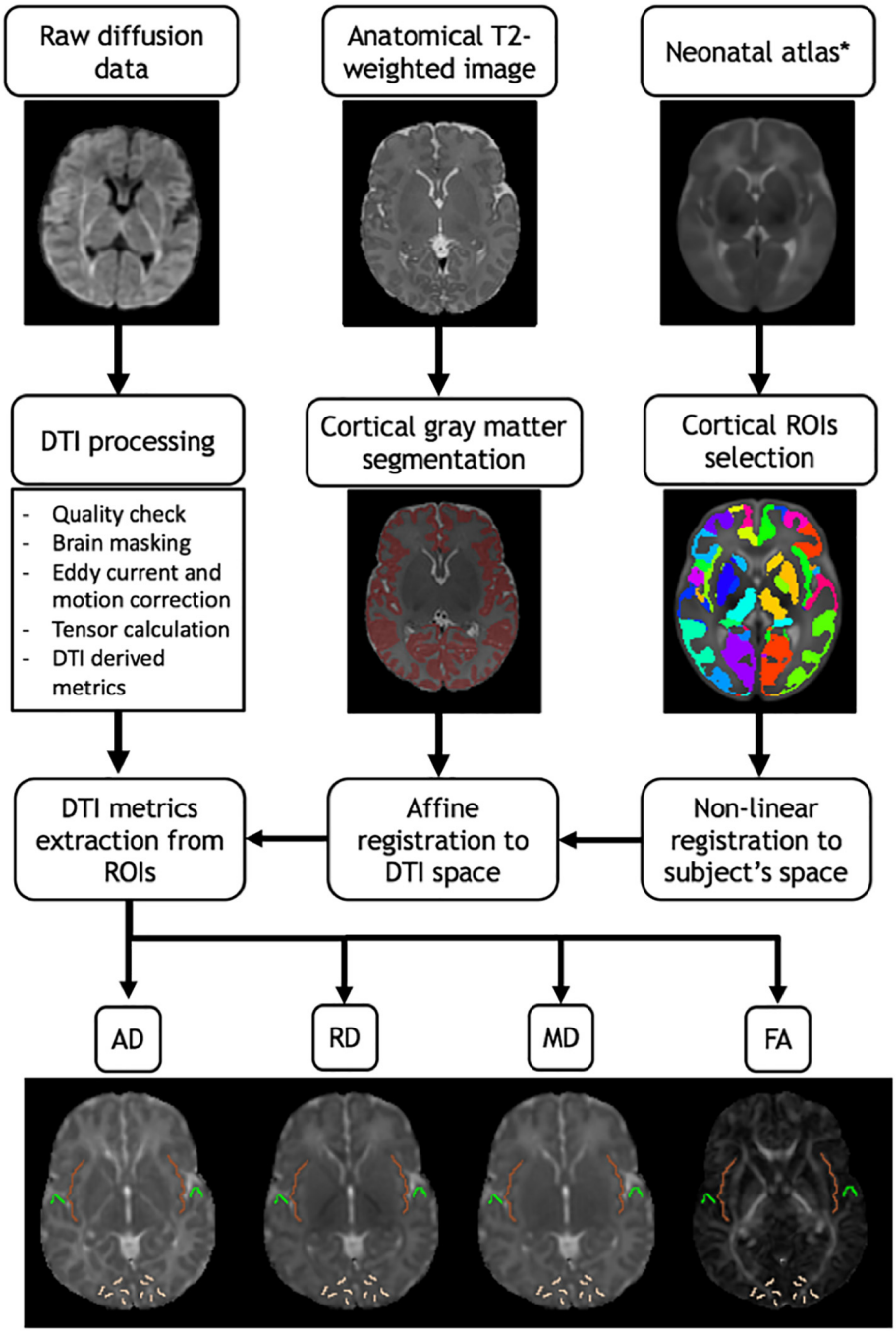

Fig. 1. Outline of the processing pipeline used for DTI data analysis.
*Neonatal Atlas from Shi et al. (2011).

pipeline (Brossard-Racine et al., 2016; Evangelou et al., 2014) (Fig. 1). We first visually inspected all 30 DTI volumes that were acquired and discarded individual diffusion weighted volumes if motion artifacts and/or signal dropout were encountered. We then selected the best b0 volume, *i.e.*, motion free with the highest signal-to-noise ratio. DTI acquisitions with more than two third of diffusion gradients corrupted were excluded from subsequent analysis resulting in an average of 24.7 ± 2.5 gradient directions (range: 18–27). Processing of the DTI datasets was performed using the FMRIB software (Jenkinson et al., 2012). First, non-brain tissue was removed (Smith, 2002); then, eddy current induced distortions and subject motion were corrected using *eddy_correct* from the FMRIB's diffusion toolbox, and gradient directions were rotated accordingly (Leemans and Jones, 2009). Finally, a diffusion tensor model was calculated for each voxel using *dtifit* from the FMRIB's diffusion toolbox. The tensor diffusion model fits diffusion measurements into a three-dimensional ellipsoid whose axes represent the average diffusivity in each direction (Mori and Zhang, 2006). The length of the longest, middle, and shortest axes are the eigenvalues λ_1, λ_2, and λ_3 respectively (units: mm^2/s), and the direction of the axes are the eigenvectors (Basser et al., 1994). Axial diffusivity (AD = λ_1) is the average diffusion along the principal direction of diffusion; radial diffusivity (RD) depicts the average diffusion in the plan orthogonal to the main diffusion direction and is the average of λ_2 and λ_3; MD is the overall amount of diffusion, which consists of the average of the three eigenvalues, and FA is an index related to the variance of the eigenvalues that reflects the overall directionality of diffusion which is scaled

between 0 (isotropic) and 1 (maximum anisotropy) (Pierpaoli and Basser, 1996).

2.6. Cerebral cortical regions of interest

We used the automatic anatomical labeling (AAL) parcellation (Tzourio-Mazoyer et al., 2002) mapped to neonatal MRI data by Shi et al. (2011) to retrieve our cerebral cortical regions of interest (ROIs) (Fig. 1). The ROIs examined included the dlPFC, the inferior parietal lobule as part of the PPC, the mPFC, the PCC, the insula, and the ACC, the precentral gyrus (motor cortex), postcentral gyrus (somatosensory cortex), calcarine cortex (visual cortex), and the superior transverse gyrus (auditory cortex). For these ten ROIs, we aimed to select only the central cerebral cortical voxels. Thus, within the template space we first selected the voxels with the highest probability of belonging to the cerebral cortex, *i.e.*, those voxels that were located centrally within the cerebral cortex, and then we transferred these cortical ROIs to the participant's native space. The neonatal atlas was non-linearly registered to each participants' anatomical T2-weighted image using AFNI non-linear warping program (Cox, 1996). The anatomical T2-weighted image was subsequently aligned using affine registration to its corresponding non-diffusion weighted (b0) of the DTI dataset (Studholme et al., 1999). In order to remove voxel contaminated by white matter and cerebrospinal fluid, we automatically segmented the anatomical T2-weighted image using the automatic segmentation software DrawEM (Makropoulos et al., 2014). Participant's cortical gray matter segmentation and cortical parcellation from the neonatal atlas were transferred to the DTI dataset and their intersection defined our ROIs. Additionally, all results were visually inspected, and misplaced voxels were removed if necessary before extraction of the DTI metrics from the native DTI participant's space.

2.7. Statistical analysis

Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). We first examined potential laterality differences using a paired *t*-test. No statistical differences between left/right sides were noted except for the calcarine cortex where the eigenvalues were significantly higher in the left side. Consequently, we analyzed left/right calcarine ROIs separately and we averaged the left/right DTI metrics for the remaining ROIs. The effect of group (preterm *versus* healthy full-term infants) on regional DTI metrics was assessed using ANCOVA analysis in which group, sex, and postmenstrual age (PMA) at MRI were the main effects. We also performed the same analysis adjusting for day of life at MRI, in order to measure the length of exposure to the extra-uterine environment. Similarly, the relationship between clinical risk factors on DTI metrics was investigated using ANCOVA analyses controlling for sex, PMA at MRI, and day of life at MRI. Significance level was set at $p < 0.05$.

3. Results

3.1. Participants studied

We acquired DTI datasets in 125 preterm infants and 95 healthy full-term infants, of which 18 (14%) preterm infants were excluded due to the presence of severe brain injury. An additional 16 (13%) preterm infants and 26 (27%) full-term controls were discarded because of motion artifacts or poor quality. The DTI metrics of the remaining 160 participants were analyzed and their clinical characteristics are summarized in Table 1. Preterm infants underwent brain MRI scans at a mean PMA of 40.10 weeks whereas healthy full-term infants were scanned at a mean PMA of 41.39 weeks.

3.2. Regional DTI metrics

Compared to healthy full-term controls, preterm infants had significantly higher AD, RD, and MD in the prefrontal cortex (dlPFC, mPFC), the PPC, the motor cortex, the somatosensory cortex, and the visual cortex (Fig. 2, Table 2). Fractional anisotropy was significantly higher in preterm infants in the motor cortex only; in all other nine areas studied, FA was not significantly different between the two groups. Our findings did not change when the variable day of life was accounted for in the statistical model. These results suggest altered regional microstructural organization in very preterm infants by TEA compared to healthy full-term controls.

3.3. Clinical risk factors: Influence on microstructural cerebral cortical organization

Forty-seven preterm infants (52%) had a normal MRI, 30 (33%) had mild brain injury and 14 (15%) had moderate brain injury (Table 1). Parenchymal brain injury was not associated with DTI metrics (Table 3), and the brain injury severity (moderate *versus* mild brain injury) was not related to microstructural organization. Among the other risk factors examined within the preterm cohort, only postnatal steroid treatment was associated with altered microstructural organization in the prefrontal and somatosensory cortices (Table 3). Surprisingly, steroid treatment was associated with decreased diffusivity ($\beta < 0$) in the prefrontal, motor, and somatosensory cortices, suggesting accelerated structural organization at the microscopic level following postnatal steroid administration. To further scrutinize this unexpected finding, for the preterm infants who received postnatal steroid treatment, we considered the length of steroid treatment, and the type of steroid administered. In our cohort, two pharmaceutical steroids were used: dexamethasone for chronic lung disease, and hydrocortisone for management of hypotension. We found that only hydrocortisone treatment was associated with increased microstructural organization (*i.e.*, reduced diffusivity) in the dlPFC, mPFC, and somatosensory cortex (Table 3).

4. Discussion

This study investigated the microstructural organization of the cerebral cortex in very preterm infants at TEA and healthy full-term neonates using DTI metrics. We demonstrated delayed regional microstructural organization in the prefrontal, parietal, somatosensory, and visual cortices of very preterm infants at TEA compared to full-term controls. Specifically, the main components of the central executive network (dlPFC and PPC) and the default mode network (mPFC), exhibited impaired microarchitecture at TEA. Interestingly, postnatal hydrocortisone treatment was associated with enhanced frontal and somatosensory microstructural organization in the preterm cohort at TEA.

The cytoarchitecture of the cerebral cortex undergoes dramatic changes during the third trimester of gestation which can be captured by DTI (Dean et al., 2013; Jespersen et al., 2013). DTI measures water diffusion properties which are strongly related to tissue micro-architectural organization (Mori and Zhang, 2006). In the cerebral cortex, several developmental processes influence water diffusion including arrival of afferent axons, dendritic arborization, decreased radial glial scaffolding, synaptic formation, and reduction in water content (Budday et al., 2015; McKinstry et al., 2002). During the third trimester of gestation, cerebral cortical diffusivity decreases due to an increase in cellular density and/or a reduction in water content; whereas, cerebral cortical anisotropy changes are related to loss of radial organization and dendritic arborization (Jespersen et al., 2013; McKinstry et al., 2002; Sizonenko et al., 2007). Given that our findings primarily showed a difference in diffusivity magnitude between preterm infants at TEA and full-term controls, we cannot exclude the possibility of diffusivity

Table 1
Clinical characteristics of the cohort (N = 160).

	Preterm infants, n = 91	Full-term control infants, n = 69	p-Value
Perinatal characteristics			
Birth gestational age, wk, mean ± SD	26.73 ± 2.62	39.64 ± 0.98	< 0.0001
Birthweight, g, mean ± SD	862 ± 298	3389 ± 367	< 0.0001
Small for gestational age, n (%)	14 (15)	5 (7)	0.12
Male, n (%)	35 (51)	44 (48)	0.76
Native American; Hispanic; White Asian; Black; Multiethnic, n (%)	0; 19 (21); 11 (12) 0; 55 (60); 6 (7)	2 (3); 7 (10); 24 (35) 6 (9); 28 (40); 2 (3)	< 0.0001
Vaginal delivery, n (%)	32 (35)	49 (71)	< 0.0001
Apgar score at 5 min, median [range]	7 [1–9]	9 [8–10]	< 0.001
Maternal age, y, mean ± SD	27.82 ± 6.19	29.78 ± 6.81	0.06
MRI characteristics			
Postmenstrual age at MRI, wk, mean ± SD	40.10 ± 1.35	41.39 ± 1.18	< 0.0001
Age at MRI, d, mean ± SD	93.68 ± 20.34	12.36 ± 5.52	< 0.0001
Head circumference at MRI, cm, mean ± SD	33.01 ± 1.92	35.65 ± 1.34	< 0.0001
Weight at MRI, g, mean ± SD	2740 ± 647	3596 ± 432	< 0.0001
Brain abnormalities classification[a]			
White matter signal abnormality, n (%)	18 (20)	na	na
Delayed myelination, n (%)	4 (4)	na	na
Thinning of the corpus callosum, n (%)	47 (52)	na	na
Dilation of the lateral ventricles, n (%)	37 (41)	na	na
Reduce white matter volume, n (%)	57 (63)	na	na
Increased extracerebral space, n (%)	26 (29)	na	na
Deep gray matter signal abnormality, n (%)	5 (5)	na	na
Reduce deep gray matter volume, n (%)	8 (9)	na	na
Cerebellar signal abnormality, n (%)	17 (19)	na	na
Reduce cerebellar volume, n (%)	40 (44)	na	na
Brain injury category, n (%) normal; mild; moderate	47 (52); 30 (33); 14 (15)	na	na

na: not applicable.
[a] The brain abnormalities were classified using the scoring system developed by Kidokoro et al. (2013).

parameters measuring only a reduction in cerebral cortical water. Nonetheless, higher diffusivity in preterm infants also reflects maturational delays since brain water content decreases with increasing gestational age during normal development (Dobbing and Sands, 1973; Kreis et al., 1993). We postulate that increased diffusivity in preterm infants at TEA reveals both a reduction in water content as well as decreased dendritic and synaptic density. Another hypothesis would be that DTI metrics differences between preterm and full-term infants result from acute injury to the developing cortex following preterm birth. Since we excluded severe brain injury by design, and mild to moderate parenchymal brain injury were not associated with DTI metrics, our findings likely reflect regional dysmaturation of the cerebral cortex in preterm infants at TEA.

Prior to the current investigation, only two studies with small sample size had compared cerebral cortical DTI metrics between very preterm infants at TEA and full-term neonates (Ball et al., 2013; T. A. Smyser et al., 2015b). In one study, mean diffusivity was increased in 22 preterm infants without brain injury compared to 12 full-term controls, however these results did not reach statistical significance (T. A. Smyser et al., 2015b). Another study, which included a slightly higher number of preterm infants (n = 37), reported significantly increased MD in the occipital, parietal, temporal, and frontal cortices of preterm infants compared to 10 full-term controls (Ball et al., 2013). In comparison, the present investigation provided information in a large cohort of preterm infants at TEA (n = 91) compared to a large sample of healthy full-term controls (n = 69). We found region-specific increased MD, AD, and RD in the dlPFC, mPFC, PPC, motor, somatosensory, and visual cortices in preterm infants at TEA suggesting delayed regional cerebral cortical maturation in preterm infants.

While MD was associated with cerebral cortical dysmaturation in preterm infants, FA was not found to be a good marker of regional cerebral cortical maturation at TEA. We found that FA was significantly elevated only in the primary motor cortex in very preterm infants. This finding is in keeping with the results of T. A. Smyser et al. (2015b), though, it differs from the findings of Ball et al. (2013), who reported significantly higher FA in preterm infants in the frontal, parietal, occipital, and temporal cortices. Mathematically, a proportional reduction or increase in diffusivity in all directions does not change FA. Thus, it is possible that alterations in microstructural organization affecting proportionally AD and RD result in MD differences between groups without FA differences. For instance, targeted apoptosis of the cerebral cortex in a rat model led to a progressive decrease in dendritic arbor of dying neurons and was characterized by an increase in AD and RD without FA changes during the apoptotic period (Petrenko et al., 2017). Additionally, since FA is a composite measure that expresses the directionality of diffusion, the relationship between FA and PMA is complex and varies depending on brain regions (Schneider et al., 2016; Wu et al., 2017a). Notably, at around TEA, the relationship between FA and PMA in the cerebral cortex is not linear. In fact, FA decreases up to 38/39 weeks PMA, and thereafter, either increases slightly or remains stationary (Aeby et al., 2012; Ball et al., 2013; Schneider et al., 2016). Lastly, cerebral cortical FA values were very low at TEA, ranging from 0.08 to 0.13 depending on the ROI. Thus, any subtle disruption of cortical FA developmental trajectory may be difficult to measure at TEA. As a result, FA may not be the most sensitive diffusion metric to characterize *in vivo* the developing cerebral cortex around TEA in preterm infants.

Our data also offer insights into the maturational status of different cortical regions in preterm infants at TEA. Specifically, the calcarine cortex followed by the paralimbic cortex (PCG, Insula) and the motor/somatosensory cortex were the brain areas with the lowest diffusivity (MD, AD, and RD), suggesting enhanced maturation compared to other brain areas. Conversely, the parietal, prefrontal, and temporal cortices showed higher diffusivity reflecting a less mature state. These findings

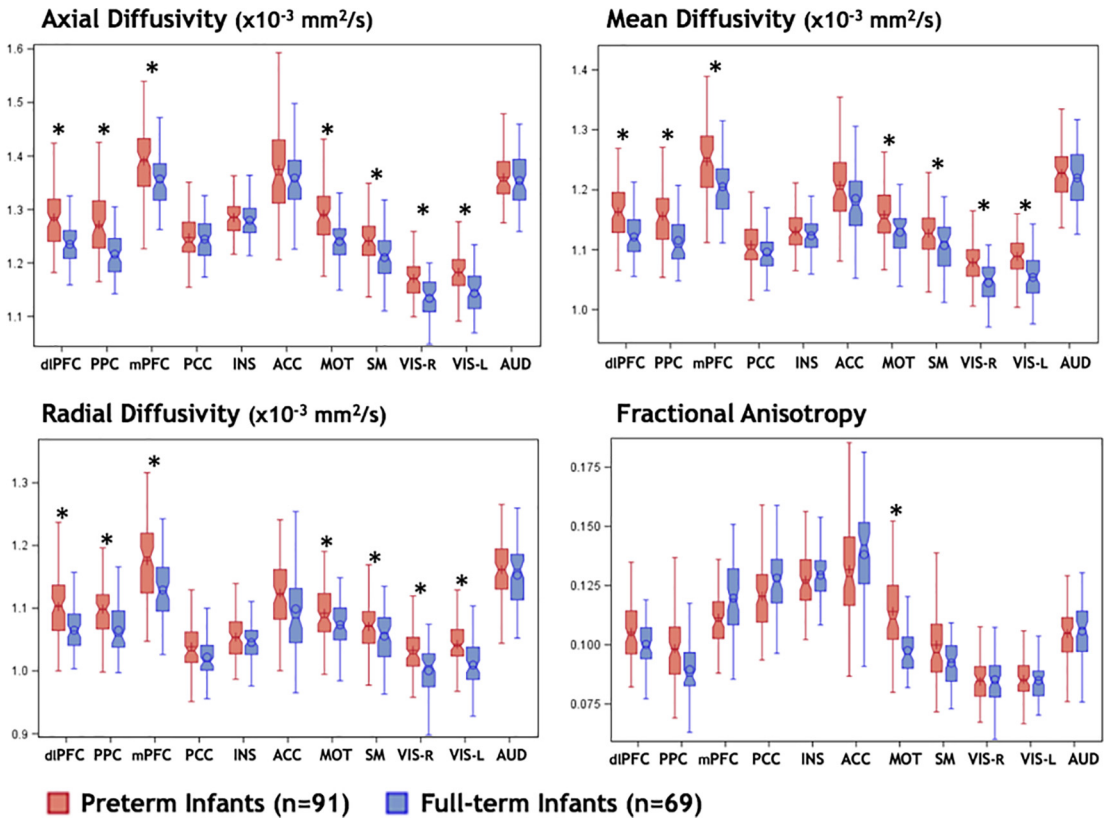

Fig. 2. Cerebral cortical microstructure in preterm infants (n = 91) and healthy full-term controls (n = 69) measured by DTI metrics.
** Indicates significant differences ($p < 0.05$) between preterm infants and healthy full-term controls controlling for sex and postmenstrual age at MRI.*
ACC: anterior cingulate cortex; AUD: auditory cortex; dlPFC: dorsolateral prefrontal cortex; INS: insula; MOT: motor cortex; mPFC: medial prefrontal cortex; PCC: posterior cingulate cortex; PPC: posterior parietal cortex; SM: somatosensory cortex; VIS: visual cortex (R: right; L: left).

Table 2
Comparison of DTI metrics by brain region in preterm and full-term infants.

Brain regions	Axial diffusivity β *p*-Value	Radial diffusivity β *p*-Value	Mean diffusivity β *p*-Value	Fractional anisotropy β *p*-Value
Dorsolateral prefrontal cortex	+0.099 0.0002	+0.083 0.0007	+0.088 0.0004	NS
Posterior parietal cortex	+0.08 0.0016	+0.074 0.001	+0.076 0.0008	NS
Medial prefrontal cortex	+0.07 0.019	+0.08 0.0063	+0.077 0.0079	NS
Posterior cingulate cortex	NS	NS	NS	NS
Insula	NS	NS	NS	NS
Anterior cingulate cortex	NS	NS	NS	NS
Motor cortex	+0.1 0.0002	+0.053 0.02	+0.068 0.0032	+0.024 0.0019
Somatosensory cortex	+0.052 0.02	+0.05 0.0156	+0.051 0.0137	NS
Right visual cortex	+0.064 0.0007	+0.047 0.013	+0.053 0.0045	NS
Left visual cortex	+0.067 0.0009	+0.048 0.0096	+0.055 0.0038	NS
Auditory cortex	NS	NS	NS	NS

β coefficient (preterm infants compared to full-term infants) and corresponding *p*-value were computed for each brain regions controlling for sex and postmenstrual age at MRI.
NS: Not significant.

are in agreement with Eaton-Rosen et al. (2017) who demonstrated the highest rate of change in cortical radiality in the occipital cortex followed by the parietal cortex, and a relatively low rate of change for the temporal and frontal cortices during the third trimester among preterm infants. Other DTI studies have also reported a gradient of cerebral cortical maturation during the third trimester (Ball et al., 2013; deIpolyi et al., 2005; T. A. Smyser et al., 2015b; Wu et al., 2017b; Yu et al., 2015). Taken together, diffusion imaging has enabled the *in vivo* quantification of known biological phenomena of spatiotemporal cerebral cortical maturation, which is characterized by a differential regional increase in dendritic spine density and synapse formation (Huttenlocher and Dabholkar, 1997; Travis et al., 2005).

Severe brain injury in preterm infants (grade III-IV IVH, cystic periventricular leukomalacia) has been associated with increased MD in the cerebral cortex (T. A. Smyser et al., 2015b), suggesting a negative trophic effect of brain injury on cortical development. In postmortem studies, periventricular leukomalacia in preterm infants has been linked with reduced neuronal density and/or neuronal gliosis (Andiman et al., 2010; Pierson et al., 2007). Additionally, in a fetal sheep model of prematurity, disruption in dendritic spine formation and remodeling following ischemic insult has been correlated with increased cortical FA (Dean et al., 2013). In contrast, we, and others (Aeby et al., 2012; Bonifacio et al., 2010; Vinall et al., 2013) found no association between mild/moderate brain injury and impaired cortical micro-organization assessed by DTI. The extent to which a cerebral insult in one region of the brain might affect the development of the cerebral cortex is likely related to the degree of brain injury severity and the topography of the injury. However, one cannot reject the hypothesis that current DTI metrics acquired on clinical scanners may not be sensitive enough to measure potential subtle microstructural changes following non-severe brain lesion. Noteworthy, in the fetal sheep model of prematurity, DTI data were acquired *ex vivo* using a high-field MRI scanner (11.7 T magnet), and demonstrates subtle microstructural changes following moderate white matter lesions (Dean et al., 2013). Thus, it may be

Table 3
Relationship between clinical risk factors and microstructural organization of the cerebral cortex in the preterm cohort.

Clinical risk factors	Preterm infants (n = 91)	Association with DTI metrics[a]
Parenchymal brain injury	44 (48%)	None
Chorioamnionitis	17 (19%)	None
Bronchopulmonary dysplasia (moderate to severe)	45 (50%)	None
Length of oxygen support (days)	91 ± 38 [0–172]	None
Postnatal steroid treatment	41 (45%)	Dorsolateral prefrontal cortex AD: β = −0.036 p = 0.009 RD: β = −0.029 p = 0.018 MD: β = −0.032 p = 0.012 Medial prefrontal cortex AD: β = −0.041 p = 0.006 RD: β = −0.038 p = 0.007 MD: β = −0.039 p = 0.005 Motor cortex AD: β = −0.022 p = 0.01 RD: β = −0.026 p = 0.023 MD: β = −0.025 p = 0.029 Somatosensory cortex AD: β = −0.028 p = 0.005 RD: β = −0.02 p = 0.026 MD: β = −0.022 p = 0.011
Length of steroid treatment[b] (days)	19 ± 13 [2–55]	None
Dexamethasone treatment	15 (17%)	None
Hydrocortisone treatment	26 (29%)	Dorsolateral prefrontal cortex *AD: β = −0.025 p = 0.05* MD: β = −0.02 p = 0.008 Medial prefrontal cortex AD: β = −0.036 p = 0.01 RD: β = −0.035 p = 0.008 MD: β = −0.036 p = 0.007 Somatosensory cortex AD: β = −0.025 p = 0.009 *MD: β = −0.016 p = 0.05*
Sepsis	15 (17%)	None
Necrotizing enterocolitis	11 (12%)	None
Pressor treatment	39 (43%)	None
Patent ductus arteriosus ligation	24 (26%)	None

[a] ANCOVA analysis included each individual clinical risk factor as well as sex, postmenstrual age at MRI, and day of life at MRI. β is the regression coefficient associated with the risk factor in the model.
[b] Length of steroid treatment for infants that received postnatal steroid treatment (n = 41).

possible to investigate the effect of mild to moderate brain injury on the developing cerebral cortex using high-resolution neuroimaging techniques (Dudink et al., 2014).

Another clinical risk factor we examined was the influence of postnatal steroid treatment. Steroids have been routinely used for their anti-inflammatory properties to prevent and treat chronic lung disease in preterm infants born with immature lungs (Kennedy et al., 2016). More recently, postnatal steroids have also been administered as an antihypertensive therapy (Higgins et al., 2009; Johnson, 2015). However, the administration of exogenous steroids may have beneficial and/or detrimental effects on the developing brain (Eventov-Friedman and Shinwell, 2008; Malaeb and Stonestreet, 2014). It has been reported that the effects of steroid administration on brain development varies according to the developmental stage at exposure (İşcan et al., 2017), the length and dose of exposure (Gray et al., 2013; Liston and Gan, 2011), and the pharmacodynamic properties of the steroid used (Malaeb and Stonestreet, 2014). Hydrocortisone is the closest and weakest pharmaceutical form of cortisol and has a high affinity for mineralocorticoid receptors, whereas dexamethasone is a synthetic steroid approximately 25 times more potent and is a glucocorticoid receptor agonist (Eventov-Friedman and Shinwell, 2008; Malaeb and Stonestreet, 2014; van der Heide-Jalving et al., 2003). These differences in pharmacological properties, specifically in receptor affinity, may be responsible for the complex and multifaceted relationship between steroids and the developing brain (Malaeb and Stonestreet, 2014).

On one hand, postnatal administration of dexamethasone has been linked with adverse neurodevelopmental outcome (Barrington, 2001; Yeh et al., 2004) and impaired cerebral growth from the early neonatal period to adolescence (Bouyssi-Kobar et al., 2016; Cheong et al., 2014; Murphy et al., 2001; Parikh et al., 2007), while on the other hand, postnatal hydrocortisone treatment has not been associated with adverse neurodevelopment during childhood (Baud et al., 2017; Lodygensky et al., 2005; Rademaker et al., 2008; Rademaker and de Vries, 2009; Renault et al., 2016; van der Heide-Jalving et al., 2003; Watterberg et al., 2007). Although we did not specifically test for the differential effect of steroid treatment on the cortex in our study, we independently investigated the effect of dexamethasone and hydrocortisone on cerebral cortical microstructural organization. We did not find an effect of dexamethasone on regional cerebral microstructural organization. Still, we demonstrated an association between hydrocortisone treatment and 'accelerated' microstructural organization in the prefrontal and somatosensory cortices. These results may be spurious, or may suggest a potentially protective effect on regional cerebral cortical maturation. As reported in mice models, this association might be due to enhancement in spine dynamics (elimination/remodeling) in brain regions undergoing active spinogenesis at the time of administration (Gray et al., 2013; Liston and Gan, 2011). Another hypothesis is that maintaining adequate blood pressure through hydrocortisone therapy improves hemodynamic support resulting in better cerebrovascular outcome (Fyfe et al., 2014; Johnson, 2015). Collectively, evidence suggest that hydrocortisone therapy might be a safer alternative to dexamethasone; though, large randomized clinical trials examining short- and long-term outcomes are necessary to confirm these results.

Our study has several limitations including the use of an anatomical neonatal atlas based on a different population (infants born after 33 weeks GA) than the one studied. The use of multi-contrast, PMA-appropriate, and population specific atlases would improve reliability of measurements (Deshpande et al., 2015; Oishi et al., 2011). Nonetheless, using an atlas facilitates the standardization of the ROIs placement across the cohort, reducing the bias introduced by manual drawing of ROIs. When dealing with the developing cerebral cortex, another concern is the risk of partial volume averaging of white matter or cerebrospinal fluid (Aeby et al., 2012). In order to minimize partial volume effect, we completed automatic segmentation of anatomical images using an age-appropriate atlas (Makropoulos et al., 2014) to select cortical gray matter voxels only. We also performed manual corrections of misplaced voxels from the automated ROIs placement. Nevertheless, we cannot exclude the possibility of partial volume effect influencing our data. Additionally, DTI metrics characterize multiple and heterogeneous tissue within a voxel and cannot decipher precisely the biological contribution from each tissue (Wu et al., 2017b). Thus, advanced diffusion acquisitions such as multi-shell high resolution techniques, which provide more detailed information about diffusion characteristic within each voxel, would allow for more precise *in vivo* characterization of the developing cerebral cortex (Dudink et al., 2014). Although the implementation of such advanced diffusion techniques might be more challenging in a clinical setting due to time constraints, its application to the preterm population has the potential to provide new detailed insights into cortical microstructural organization (Dudink et al., 2014; Eaton-Rosen et al., 2015; Shi et al., 2016). Finally, the relationship between altered cortical microstructural organization and neurodevelopmental outcome remains to be established once the follow-up data from this cohort are completed.

In conclusion, we demonstrated early alterations in cerebral cortical microstructural organization in a large cohort of preterm infants at TEA compared to healthy full-term newborns. Specifically, three brain regions involved in neurocognitive processing (dlPFC, mPFC, and PPC) as well as motor, somatosensory, and visual cortices, exhibited reduced microstructural organization suggesting delayed cortical maturation in very preterm infants at TEA. These findings highlight the vulnerability of cerebral cortical microstructural organization following preterm birth. Future work will examine the potential link between early alterations of the neurocognitive brain areas and later adverse socio-cognitive outcome. Interestingly, postnatal hydrocortisone treatment was associated with accelerated maturation in the prefrontal and somatosensory cortices suggesting a potential short-term protective effect of hydrocortisone administration on regional cortical development. Future studies are needed to examine the impact of postnatal hydrocortisone treatment on cortical development using more in-depth analysis that will incorporate length of treatment, cumulative dose, and timing of exposure.

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Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

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