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Neonatal inflammation and near-term white matter microstructure in infants born very preterm

Kathryn G. Anderson[a], **Molly F. Lazarus**[b,c], **Lisa Bruckert**[b], **Rocio V. Poblaciones**[b], **Melissa Scala**[d], **Virginia A. Marchman**[b,e], **Heidi M. Feldman**[b], **Katherine E. Travis**[b,c,*]

[a]Stanford University School of Medicine, Stanford, CA, USA

[b]Department of Pediatrics, Division of Developmental-Behavioral Pediatrics, Stanford University, Stanford, CA, USA

[c]Burke-Cornell Medical Research Institute at Weill Cornell Medicine and Department of Pediatrics, Weill Medical College, Cornell University, New York, NY, USA

[d]Department of Pediatrics, Division of Neonatology, Stanford University, Stanford, CA, USA

[e]Department of Psychology, Stanford University, Stanford, CA, USA

Abstract

Background: Severe neonatal inflammatory conditions in very preterm infants (VPT: <32 weeks gestational age, GA) are linked to adverse neurodevelopmental outcomes. Differences in white matter (WM) microstructure of the corpus callosum (CC) have been observed at age 6 in VPT children with a history of severe neonatal inflammation. The goal of this study was to determine whether these CC differences can be detected at term-equivalent age using diffusion MRI (dMRI), and whether neonatal inflammation is associated with altered WM in additional tracts implicated in the encephalopathy of prematurity.

Methods: We conducted a retrospective study of VPT infants (n = 152) born at 22–32 weeks GA, classified based on the presence (I+, n = 80) or absence (I−, n = 72) of severe

*Corresponding author. Burke-Cornell Medical Research Institute at Weill Cornell Medicine and Department of Pediatrics, Weill Medical College, Cornell University, New York, NY USA. ket4008@med.cornell.edu (K.E. Travis).

Declaration of competing interest

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CRediT authorship contribution statement

Kathryn G. Anderson: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Molly F. Lazarus:** Writing – review & editing, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lisa Bruckert:** Writing – review & editing, Validation, Software, Resources, Methodology, Investigation, Data curation. **Rocio V. Poblaciones:** Writing – review & editing, Software, Resources, Methodology, Investigation, Data curation, Conceptualization. **Melissa Scala:** Writing – review & editing, Resources, Methodology, Investigation. **Virginia A. Marchman:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Heidi M. Feldman:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Conceptualization. **Katherine E. Travis:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynirp.2024.100226.

neonatal inflammatory conditions (bronchopulmonary dysplasia, necrotizing enterocolitis, or culture-positive sepsis). Analysis of covariance (ANCOVA) assessed group differences in near-term dMRI mean fractional anisotropy (FA) and mean diffusivity (MD) across seven segments of the CC and the anterior thalamic radiation, arcuate fasciculus, cingulum, corticospinal tract, inferior longitudinal fasciculus, superior cerebellar peduncle, and uncinate fasciculus. Due to imbalance of GA in the full sample, secondary ANCOVA analyses were performed in a GA-matched subset ($n = 42$) to further isolate the effect of inflammation.

Results: FA was significantly lower in the I+ group compared to the I- group in the anterior frontal, posterior parietal, temporal, and occipital segments of the CC, and in the cingulum, inferior longitudinal fasciculus, and superior cerebellar peduncle. This general pattern persisted in the GA-matched subset, with significant differences in the anterior frontal and temporal CC segments.

Conclusions: VPT infants with severe neonatal inflammation had lower FA in multiple white matter tracts, suggesting that inflammation-related alterations in WM development begin in the neonatal period. The observed differences detected using dMRI at term-equivalent age corroborate prior findings and may provide a window of opportunity for early identification of VPT infants at increased risk of poor neurodevelopmental outcomes.

Keywords

Diffusion MRI; White matter; Tractography; Prematurity; Corpus callosum; Inflammation; Encephalopathy of prematurity

1. Introduction

Despite considerable advances in neonatal care, children born very or extremely preterm (VPT, gestational age <32 weeks) remain at high risk for long-term neurodevelopmental impairments in areas such as language, attention, and executive functioning (Foster-Cohen et al., 2007; Aarnoudse-Moens et al., 2009; Johnson and Marlow, 2017). These adverse consequences of VPT birth are thought to be mediated by early white matter injury and subsequent brain dysmaturation, a process termed encephalopathy of prematurity (Volpe, 2009). The variability in neurodevelopmental outcomes seen in VPT children may reflect the extent of early brain injury and/or dysmaturity. Infants who experience severe neonatal inflammatory conditions are at increased risk of adverse neurodevelopmental outcomes (Mitha et al., 2013; Schlapbach et al., 2012; Stoll et al., 2004; Leviton et al., 2019). In this study, we consider whether VPT infants who experience severe neonatal inflammation show evidence of changes in white matter connectivity, compared to VPT infants who do not experience inflammation.

Several important cellular events occur before 32 weeks' gestation as the immature brain develops. White matter injury in VPT infants is attributed to disruption of the differentiation and maturation of pre-oligodendrocyte cells, which are crucial for axonal myelination (Volpe, 2019; Back, 2017). These pre-oligodendrocyte cells are highly vulnerable to injury from oxidative stress, which occurs as a result of inflammation (Volpe, 2009; Back, 2017; Inder et al., 2023). Three severe inflammatory conditions – bronchopulmonary dysplasia,

necrotizing enterocolitis, and sepsis - commonly affect VPT infants during the neonatal period, triggering a diffuse inflammatory response and oxidative stress in the brain (Volpe, 2009; Inder et al., 2023). Infants who experience systemic inflammation during the critical period of pre-oligodendrocyte maturation may have increased disruption in white matter microstructure.

Diffusion magnetic resonance imaging (dMRI) is an effective, non-invasive tool for studying the microstructure of white matter pathways in VPT infants (Feldman et al., 2010, 2012). By measuring the diffusion of water molecules in brain tissue, this technique provides quantitative metrics such as fractional anisotropy (FA) and mean diffusivity (MD), which reflect the integrity and organization of white matter fiber tracts. Several studies performed at near-term age have observed lower FA and higher MD in VPT infants compared to their full-term counterparts in brain areas such as the corpus callosum (Pannek et al., 2014). Lower FA and higher MD in VPT compared to term infants is consistent with the histological data reporting reductions in myelin content and axonal loss following oxidative stress (Volpe, 2009, 2019; Back, 2006, 2017). However, there remains limited data in VPT infants linking variations in neonatal white matter to inflammatory conditions likely to induce oxidative-stress related injuries.

A study by Dubner et al. (2019) used dMRI to compare the white matter microstructure and cognitive outcomes among three groups of 6-year-old children: (1) VPT children with a history of bronchopulmonary dysplasia, necrotizing enterocolitis, and/or sepsis (PT+), (2) VPT children who did not experience a severe neonatal inflammatory condition (PT−), and (3) full-term children (FT) (Dubner et al., 2019). The findings revealed that PT + children had lower FA and higher MD in several segments of the corpus callosum, a large white matter tract essential for interhemispheric communication and cognitive functions such as attention, memory, and language. PT + children also exhibited significantly lower executive function compared to their PT− and FT counterparts. Notably, PT-children showed no difference in white matter microstructure or executive functioning compared to FT children. These findings highlight a potential link between neonatal inflammation and white matter dysmaturation, leading to lasting neurocognitive impairments in VPT children. Although near-term alterations in the corpus callosum white matter of VPT infants have been described (Volpe, 2009; Back, 2017), it remains to be determined whether white matter changes associated with inflammation can be detected in the corpus callosum of VPT infants as early as term-equivalent age.

Beyond the corpus callosum, alterations in the microstructure of several critical brain regions in VPT infants have been documented. Regions of increased vulnerability in VPT infants include the frontotemporal, periventricular, thalamic, and cerebellar areas of the brain (Inder et al., 2023). Using serial imaging of VPT infants during the neonatal period, Rogers et al. (2015) identified the anterior limb of the internal capsule, corpus callosum, and optic radiations as tracts most affected by gestational age, with higher FA slopes observed in infants born at later gestational ages (Rogers et al., 2016). Though not the primary focus of the study, Rodgers et al. also found that infants who had sepsis exhibited a significantly lower FA slope compared to those without sepsis, suggesting sepsis is associated with delayed white matter maturation. These insights support the notion that severe neonatal

inflammation may lead to dysmaturation in particularly vulnerable white matter tracts. However, the effects of severe neonatal inflammation on the cortical white matter tracts in these vulnerable brain regions in VPT infants have not been extensively studied.

To address these gaps in the literature, the objective of this investigation was to assess the relation between severe neonatal inflammatory conditions and near-term white matter microstructure in VPT infants. Specifically, this study sought to determine whether the white matter differences observed in the corpus callosum of 6-year-old VPT children with a history of neonatal inflammation can be detected early in development, at term-equivalent age. Further, this study investigated whether severe neonatal inflammation is associated with alterations in the following seven additional cerebral and cerebellar tracts implicated in the encephalopathy of prematurity.

i. The anterior thalamic radiation (ATR) connects the thalamus with the frontal cortex, facilitating executive functions and memory (Inder et al., 2023).

ii. The arcuate fasciculus is a major conduit between the temporal and frontal lobes and is implicated in language processing and speech production. FA of the arcuate has been directly linked to language outcomes in VPT children (Salvan et al., 2017; Mürner-Lavanchy et al., 2018).

iii. The cingulum contains fiber tracts that project over the corpus callosum, connecting the orbital frontal, parietal, and temporal cortices. Classified within the limbic system, the cingulum has been implicated in executive control, emotion, and pain (Bubb et al., 2018). Microstructural alterations of the cingulum are associated with attention functioning in VPT children (Murray et al., 2016).

iv. The corticospinal tract (CST) is the principal conduit for motor signals to the spinal cord, and is associated with motor development and the risk of cerebral palsy in VPT infants (Kelly et al., 2015; de Kieviet et al., 2014).

v. The inferior longitudinal fasciculus (ILF) connects occipital and occipital-temporal cortices to regions of the anterior temporal lobe. Functionally, the ILF is implicated in visual processes and language comprehension; disruptions in the ILF are associated with language development (Dubner et al., 2020; Herbet et al., 2018).

vi. The superior cerebellar peduncle (SCP) primarily comprises efferent projections from the cerebellum to midbrain structures, including the thalamus. Within the SCP, these efferent fibers extend to thalamic nuclei that connect to multiple cortical areas. Cerebellar injury is also associated with VPT infants, (Tam, 2018; Matthews et al., 2018) and has been associated with reading abilities and behavioral problems in VPT children.[28 29]

vii. The uncinate connects the frontal and temporal lobes and plays a key role in memory, language, and emotional processing (Travis et al., 2015; Lautarescu et al., 2020). Structural differences in the uncinate have been observed comparing VPT to full term children at school age (Travis et al., 2015; Dodson et al., 2017).

Following Dubner et al. (2019), we divided a sample of VPT children into those who experienced bronchopulmonary dysplasia, necrotizing enterocolitis, and/or sepsis (inflammation group, I+), and those who did not (no inflammation group, I−). Using dMRI, we compared the white matter microstructure of the eight tracts of interest between the two groups. We hypothesized that VPT infants with severe neonatal inflammation would have lower FA and higher MD in the corpus callosum and additional tracts in the frontotemporal, periventricular, cerebellar, and thalamic regions. Investigating the relationship between neonatal inflammation and near-term white matter microstructure in VPT infants is important for determining the early sensitivity of dMRI to conditions impacting preterm children. Furthermore, this study may enhance understanding of factors contributing to variability in neonatal brain development, potentially guiding early intervention strategies.

2. Methods

2.1. Participants

Infants born very preterm (VPT, gestational age <32 weeks) at Lucile Packard Children's Hospital (LPCH) Stanford Neonatal Intensive Care Unit (NICU) between March 1, 2016 and March 1, 2020 were eligible for this retrospective study. Infants were included in analyses if they underwent MRI imaging with diffusion (dMRI) scans prior to hospital discharge between 34 and 44 weeks postmenstrual age (PMA). These scans were acquired per LPCH NICU standard of care once an infant was stable in an open crib with no more than low-flow supplemental oxygen for respiratory support. Scanning was conducted during natural sleep without sedation while infants wore adhesive foam noise attenuators. A total of $n = 239$ very preterm infants had available MRI data. From these, $n = 87$ infants were excluded, leaving a final sample of $n = 152$ infants (Fig. 1).

Inflammation status was determined through medical chart review. Infants categorized to the inflammation group (I+, $n = 80$) experienced culture-positive sepsis, necrotizing enterocolitis (treated either medically or surgically), and/or bronchopulmonary dysplasia (BPD) grades 1–3. Based on the NICHD guidelines, BPD grades were calculated based on oxygen need for 28 consecutive days and respiratory support status at 36 weeks' PMA (Jensen et al., 2019). The I- group ($n = 72$) did not experience any of these neonatal inflammatory conditions. Medical chart review was also used to compare the groups on other complications of VPT birth: small for gestational age (≤3rd percentile birth weight for gestational age), retinopathy of prematurity, patent ductus arteriosus, and intraventricular hemorrhage grades ≤ III. This retrospective study was approved by the Stanford University Institutional Review Board #IRB-44480.

2.2. MRI acquisition

Neuroimaging data was collected during routine pre-discharge clinical imaging and included high-resolution T1-weighted anatomical MRI and dMRI. Scans were performed on a GE Discovery MR750 3.0 T scanner (General Electric Healthcare, Little Chalfont, UK) with either an 8-channel ($n = 93$) or a 32-channel ($n = 59$) HD head coil. The MRI protocol involved a 60-direction dMRI scan with b-values (b = 700 s/mm^2) collected with a multi-slice echoplanar imaging protocol for rapid image acquisition (~3 min) and with a spatial

resolution of 2.0 mm^3 isotropic voxels. Two six volumes were collected at b = 0 as a reference for baseline signal intensity. High-resolution T1-weighted scans collected at ~1 mm^3 spatial resolution served as an infant-specific anatomical reference.

2.3. Diffusion MRI analysis

The neuroinformatic platform Flywheel was used to manage and analyze MRI data. dMRI analysis followed established procedures as previously described in detail by Dubner et al., 2023) (Dubner et al., 2023). Briefly, dMRI data preprocessing and tractography were performed using procedures implemented in Reproducible Tract Profiles (RTP; https://github.com/vistalab/RTP-pipeline), which involves structural processing, region of interest (ROI) creation, dMRI preprocessing, whole-brain tractography, and tract-segmentation. Imaging parameters and procedures for data preprocessing steps are described in the Supplementary Material and in Dubner et al., 2023) (Dubner et al., 2023).

The Automated Fiber Quantification (AFQ; https://github.com/yeatmanlab/AFQ) (Yeatman et al., 2012) software package and MATLAB were used to segment and refine the whole-brain connectome for each infant into the tracts of interest. Tract mean FA and MD were calculated from the core region of each pathway, defined as the region between ROIs used to segment tracts from the whole brain connectome. The corpus callosum was divided into seven discrete, non-overlapping regions to create functionally relevant and anatomically specific segments: anterior frontal, superior frontal, motor, superior parietal, posterior parietal, temporal, and occipital (Fig. 2) using procedures first described by Huang et al. (2005) and modified by Doughtery et al. (2007) (Huang et al., 2005; Dougherty et al., 2007). We have used this approach in several studies involving children and neonates born preterm (Dubner et al., 2019, 2023; Travis et al., 2019). Seven additional bilateral white matter tracts were selected *a priori* based on clinical relevance to preterm birth: the anterior thalamic radiation, arcuate fasciculus, cingulum, corticospinaltract, inferior longitudinal fasciculus, superior cerebellar peduncle, and uncinate fasciculus.

2.4. Statistical approach

All statistical analyses were performed using SPSS (version 28.0.1.1, IBM Corporation, 2018). Statistical significance was set at $p < 0.05$, and the False Discovery Rate (FDR) correction was applied to control for multiple comparisons (Benjamini and Hochberg, 1995). Chi-square tests and independent samples t-tests were used to analyze differences in I+ and I- groups on the basis of demographic variables, clinical variables, and MRI head coil type (8 vs. 32-channel). Normality of distribution for each variable was assessed using the Shapiro-Wilk test. To compare mean fractional anisotropy (FA) or mean diffusivity (MD) values between the I+ and I- groups, analysis of covariance (ANCOVA) was used, controlling for postmenstrual age (PMA) at the time of scan and head coil type (8 vs. 32 channel). To reduce the number of comparisons, we averaged left and right tract metrics to generate a single tract metric for each of the seven bilateral cerebral and cerebellar pathways examined.

Infants born at a younger gestational age are at the greatest risk for altered white matter microstructure, and these infants born at a younger GA are also more susceptible to

inflammatory conditions. Given that inflammation may mediate the relationship between GA and white matter dysmaturation, GA was not considered as a covariate in this analysis. Instead, we constructed a subset of VPT infants matched on GA ($n = 42$) to determine whether inflammation is associated with FA and MD when matched on GA. Matching was performed using the case-control matching tool in SPSS, which employs a nearest-neighbor matching algorithm with a set tolerance of one. ANCOVA of FA and MD across the white matter tracts of interest were repeated using only participants in this matched cohort, controlling for PMA at scan and MRI head coil. A power analysis performed in G*Power for linear models (Faul et al., 2009) determined that we had sufficient power (beta = 0.8, alpha = 0.05) to detect small to medium effects ($\eta_p^2 = 0.01 - 0.06$) in the full sample and a large effects (ηp2 = 0.14) in the GA-matched sample.

3. Results

3.1. Sample characteristics

Table 1 presents a comparison of infant characteristics by inflammation status in the full cohort ($n = 152$) of VPT infants. Infants with neonatal inflammation (I+) had a significantly lower gestational age (GA) and birthweight compared to infants in the no inflammation (I−) group. I+ infants had a significantly older post-menstrual-age (PMA) at the time of dMRI scan compared to I− infants, likely because I+ infants required longer hospitalizations due to their severe inflammatory conditions. The proportion of Hispanic vs. non-Hispanic infants based on parent-reported ethnicity differed significantly between the two groups, with a lower proportion of Hispanic infants in the I+ group. The distribution of infants by assigned sex at birth, race, insurance type, and MRI head coils did not differ significantly across groups. GA and birth-weight were positively correlated in the full cohort ($r = 0.75$, $p < 0.001$) and in the I+ group alone ($r = 0.61$, $p < 0.001$).

Infant characteristics of the GA-matched cohort ($n = 42$) are shown in Supplementary Table 1. There were no significant group differences in GA, birth-weight or the proportion of infants by assigned sex at birth, ethnicity, insurance type, and head coil type. I+ infants had a significantly older PMA at dMRI scan and the proportion of White vs. non-White infants based on parent-reported race differed significantly between the two groups, with a lower proportion of White infants in the I-group.

Table 2 provides a comparison of additional medial risk factors for VPT infants. In both the full and GA-matched cohorts, we found no significant differences in the proportion of children born small for gestational age, those who did not receive antenatal steroids, or those with intraventricular hemorrhage grades I-II or grade III, between the I+ and I− groups. In the full cohort, a significantly higher proportion of I+ infants had a patent ductus arteriosus (PDA) and retinopathy of prematurity (ROP). Notably, PDA and ROP are strongly associated with GA, and the significant differences did not persist in the GA-matched cohort.

3.2. Group comparisons of FA and MD of the corpus callosum

Descriptive statistics and ANCOVA analyses for FA of the corpus callosum (CC) segments are shown in Table 3 for the full and matched cohorts. Analyses in the full cohort revealed group differences that were consistent with our hypothesis; the I+ group had lower FA across all seven CC segments compared to I−, with significantly lower FA in the anterior frontal, posterior parietal, temporal, and occipital CC segments. In the GA-matched cohort, group differences rose to statistical significance in the anterior frontal and temporal CC segments. Full cohort analysis of the average MD across white matter tracts showed the I+ group had higher MD of the posterior parietal segment of the corpus callosum ($F = 8.52$, $p = 0.004$; Supplementary Table 2). Secondary analyses confirmed that removal of the n = 2 participants with grade III IVH from the full cohort resulted in the same pattern of findings within callosal segments (data not shown).

After correcting for multiple comparisons using the FDR, significant differences in CC FA of the full cohort remain for the posterior parietal (adjusted $p = 0.03$), temporal (adjusted $p = 0.02$), and occipital (adjusted $p = 0.01$) segments. In the matched cohort, the temporal segment of the CC showed significant differences after FDR adjustment (adjusted $p = 0.04$).

3.3. Group comparisons of FA and MD of additional cortical white matter tracts

Table 4 presents descriptive statistics for FA of the seven bilateral cortical white matter tracts for infants in the full and matched cohorts. Results of the full cohort analysis shows the I+ group had significantly lower mean FA in the Cingulum, Inferior Longitudinal Fasciculus, and Superior Cerebellar Peduncle. After correcting for multiple comparisons, these differences did not rise to statistical significance. No significant group differences were seen in the GA-matched cohort analysis. Parallel analyses with MD of all cortical white matter tracts showed no significant differences between the I+ and I− groups (Supplementary Table 3). Secondary analyses confirmed that removal of the n = 2 participants with grade III IVH from the full cohort resulted in the same pattern of findings within the cerebral and cerebellar tracts examined (data not shown) (see Table 2).

4. Discussion

4.1. Summary and interpretation of results

Using dMRI, the present study investigated the relation between neonatal inflammation and the near-term white matter microstructure in infants born VPT, focusing on the corpus callosum and seven additional cerebral and cerebellar tracts implicated in the encephalopathy of prematurity. We found that VPT infants with major neonatal inflammatory conditions had lower FA in multiple segments of the corpus callosum and in the cingulum, inferior longitudinal fasciculus, and superior cerebellar peduncle. For analyses of groups matched on gestational age, group differences remained for the anterior frontal and temporal corpus callosum segments but were reduced in the additional cerebral and cerebellar tracts examined. This pattern of findings suggests that there may be regional differences in the sensitivity of white matter to inflammation and to developmental factors related to or altered by preterm birth.

Overall, the observed pattern for group differences in FA of the corpus callosum is aligned with our previous research in which we found similar group differences comparing 6-year-old VPT children with and without a history of neonatal inflammatory conditions (Dubner et al., 2019). We extend these findings to the neonatal period, when it may be important to monitor VPT infants at risk for adverse neurodevelopmental outcomes. Understanding how inflammation-related alterations in neonatal white matter contribute to neurodevelopmental outcomes requires further investigation. Moreover, our findings are consistent with previous work suggesting that preterm infants with sepsis experience a slower rate of white matter maturation during the neonatal period, particularly in vulnerable regions such as the corpus callosum (Rogers et al., 2016).

Previous neonatal studies report differences in white matter microstructure comparing preterm to term born neonates (Pannek et al., 2014). Our study adds to this body of work by relating variations in white matter microstructure to severe neonatal inflammatory conditions associated with preterm birth. Regions of vulnerability to white matter injury consistently described in the VPT population include the frontotemporal, periventricular, watershed parietal, thalamic, and cerebellar brain areas (Inder et al., 2023). Consistent with these observations, we found group differences to be most robust within callosal tracts as compared to the other cerebral and cerebellar tracts examined.

Being directly adjacent to the lateral ventricles, white matter tracts that traverse the corpus callosum may be more susceptible to oxidative-stress related injuries due to increased exposure to inflammatory cytokines and reactive oxygen species in the cerebrospinal fluid (Volpe, 2009). In particular, elevated levels of pro-inflammatory cytokines, such as interlukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), during the perinatal period have been associated with impaired neurodevelopment and conditions such as cerebral palsy (Jiang et al., 2018). These cytokines, along with oxidative stress from systemic inflammation, have been implicated in disrupting the differentiation and maturation of oligodendrocyte precursor cells, leading to impaired myelination (Back, 2017). Compared to frontal and temporal pathways, callosal and occipital white matter regions are also known to myelinate earlier compared to frontal and temporal pathways (Yeatman et al., 2012), as these areas may contain a higher proportion of pre-oligodendrocytes, contributing to the findings here.

In the subset of VPT infants matched on GA at birth, the inflammation group had significantly lower FA in the anterior frontal and temporal segments of the corpus callosum. This finding suggests inflammation may play a role in white matter independent of GA. It is also plausible that inflammation mediates the relationship between GA at birth and white matter dysmaturation. Infants born at a younger GA are more susceptible to severe neonatal inflammatory conditions, and the pre-oligodendrocyte cells are highly vulnerable to injury oxidative stress (Volpe, 2009). Therefore, infants born at a younger GA are not only more likely than infants born at an older GA to experience inflammatory conditions, but they also may be more susceptible to white matter dysmaturation as a result of systemic inflammation. Future studies using a more specific, quantitative biomarker of inflammation, such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), could provide a

more nuanced understanding of the relationship between GA, inflammation, and alterations in white matter microstructure.

We hypothesized that VPT infants with severe inflammatory conditions would have increased MD compared to VPT infants without these conditions. However, the differences based on inflammation seen in 6-year-old VPT children were not replicated. This finding may suggest that the magnitude of MD alterations is not as pronounced as those observed in FA at a term-equivalent age, or that our dMRI methods are less sensitive to changes in MD than FA in the neonatal brain. The relationship among FA, MD, and inflammation is likely to be complex and may differ across clinical populations and across different developmental periods. We speculate that the lack of significant differences in MD found here may reflect developmental differences in the sensitivity of MD to underlying tissue properties affected by inflammation. Exploring the use of other advanced imaging techniques, like quantitative T1 relaxometry, and other quantitative MRI metrics could enhance sensitivity to detect subtle changes in near-term white matter microstructure (Travis et al., 2019).

Additionally, effect sizes of the differences in FA in our analyses are smaller than those observed in 6-year-old children. While this difference is consistent with the theory that early white matter injury may alter subsequent brain development, future research is needed to determine whether these differences in FA seen at term age are clinically relevant. Longitudinal studies have demonstrated that white matter abnormalities in FA and MD detected on near-term dMRI scans are predictive of later cognitive and motor functioning (Woodward et al., 2006, 2012; Omizzolo et al., 2014), but such studies have not yet been done looking at differences based on inflammation status.

The observed differences in white matter microstructure detected at term-equivalent age not only corroborate findings in the prior literature, but also suggest a window of opportunity for early identification of VPT infants at increased risk of poor neurodevelopmental outcomes. Early identification can allow for targeted monitoring to assess developmental milestones and provide early, appropriate support. Additionally, identifying these infants at term-age may allow for early intervention, such as anti-inflammatory treatments, neuroprotective agents, and supportive care, which may mitigate risks of adverse outcomes. These insights reinforce the utility of dMRI as a valuable, non-invasive tool for assessing VPT infants in the neonatal period. Understanding the interaction between neonatal inflammatory conditions and other NICU factors is crucial for developing comprehensive care strategies that address both medical and environmental influences on preterm infants' brain development.

4.2. Limitations and future directions

This study has several limitations. First, the broad definition of severe neonatal inflammation relies on a clinical diagnosis without quantification. While this approach aligns with clinical practice and replicates methods used in previous studies with school-aged children (Dubner et al., 2019), it does not account for variations in severity or duration of illness. Future studies able to acquire continuous quantitative inflammatory biomarker data could achieve greater sensitivity for the impact of inflammation on brain development. The conditions used to group infants under the category of inflammation (BPD, sepsis, and NEC) may also elicit different inflammatory responses. Examining these conditions individually may

be important for understanding the distinct impact these conditions have on white matter development. A second limitation is the retrospective nature of our study, which precludes conclusions about causality to be drawn. Thirdly, the statistical analysis, though rigorous, does not account for all potential confounders inherent in clinical data. The GA-matched sample was also only powered to detect large effects. Factors such as nutritional status, the NICU environment, genetic predispositions, and extent of neonatal care may influence both the likelihood of neonatal inflammation and white matter development. Finally, the focus on specific white matter tracts may not capture the full extent of the impact of neonatal inflammation on the developing brain. Identifying additional areas of susceptibility to neonatal inflammation could be addressed in future work using exploratory whole-brain approaches (Yeh et al., 2016).

5. Conclusions

In conclusion, this study demonstrates that severe neonatal inflammatory conditions are associated with alterations in the white matter microstructure microstructure of VPT infants in several critical cerebral and cerebellar tracts implicated in the encephalopathy of preterm birth. These changes are detectable using clinical dMRI at a term-equivalent age. These findings enrich our understanding of the sequelae of preterm birth and emphasize the need for early identification and tailored intervention strategies to improve long-term outcomes in this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

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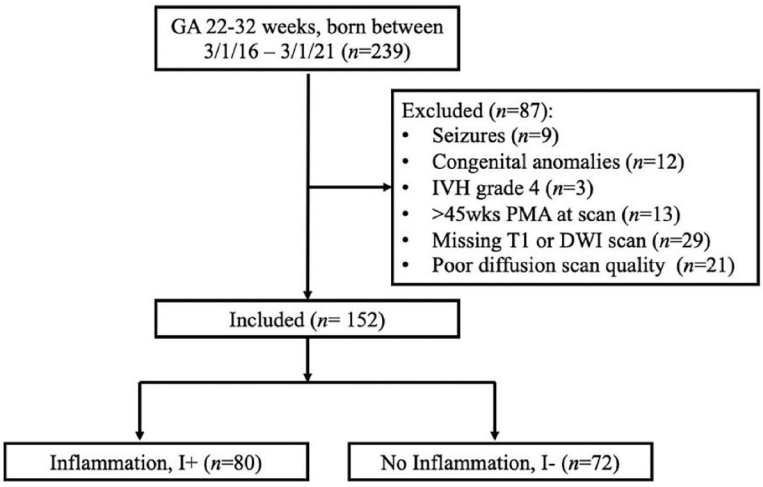

Fig. 1.
Consort diagram of eligible and included VPT infants.

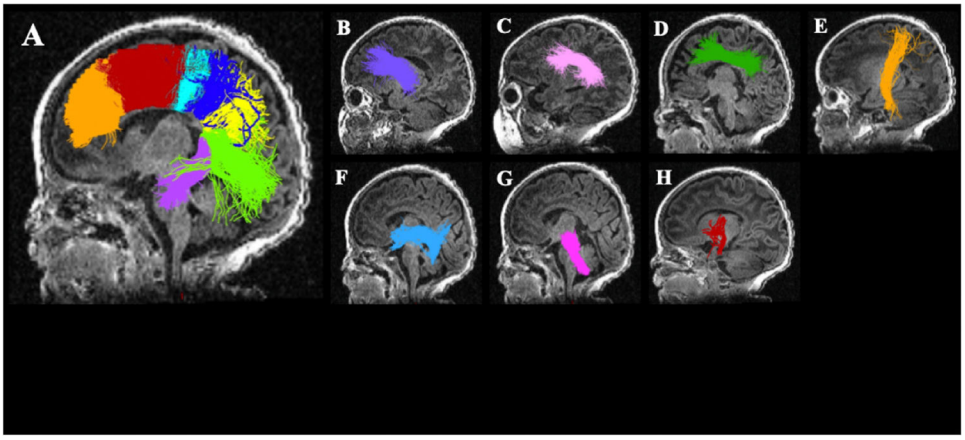

Fig. 2.

Tractography of white matter tracts displayed on a mid-sagittal T1-weighted image from a representative preterm subject. A) corpus callosal white matter segments: occipital = green, temporal = purple, posterior parietal yellow, superior = blue, motor aqua, superior frontal = red, anterior frontal = orange, B) anterior thalamic radiation, C) arcuate fasciculus, D) cingulum, E) corticospinal tract, F) inferior longitudinal fasciculus, G) superior cerebellar peduncle, H) uncinate. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1

Comparison of infant characteristics by inflammation status (n = 152).

	I- (n = 72)	I+ (n = 80)			
	Mean (SD) or *n* (%)	**Mean (SD) or *n* (%)**	**t(df) or χ (Aarnoudse-Moens et al., 2009) (df)**	**Cohen's *d***	***p***
Gestational Age, weeks	30.6 (1.0)	27.1 (1.9)	14.1 (150)	2.3	<0.01
Birthweight, grams	1414.6 (273.1)	956.0 (299.7)	9.8 (149)	1.6	<0.01
PMA[a] at Scan, week	35.9 (1.1)	37.3 (1.9)	− 5.6 (150)	− 0.9	<0.01
Male	38 (52.8)	42 (52.5)	0.001 (1)		0.97
Race[b]			0.74 (1)		0.39
Asian/Pacific Islander	15 (20.8)	10 (12.5)			
Black or African American	1 (1.4)	3 (3.8)			
Other	37 (5.1)	27 (33.8)			
Patient Refused/Unknown	6 (8.3)	21 (26.3)			
White	13 (18.1)	19 (23.8)			
Ethnicity[c]			2.18 (1)		0.03
Hispanic/Laitino	30 (41.7)	21 (26.3)			
Non-Hispanic/Non-Latino	37 (51.3)	40 (50.0)			
Patient Refused/Unknown	5 (6.9)	19 (23.8)			
Public Insurance[d]	34 (47.2)	31 (38.8)	1.11 (1)		0.29
MRI Head Coil			0.10 (1)		0.75
8 Channel	45 (62.5)	48 (60.0)			
32 Channel	27 (37.5)	32 (40.0)			

[a] PMA, postmenstrual age.

[b] Parent-reported race, chi-squared test for Non-White vs. White.

[c] Parent-reported ethnicity, chi-squared test for Hispanic vs. Non-Hispanic.

[d] Insurance type (public vs. private) was used as a proxy for socioeconomic status.

Table 2

Medical risk factors for infants in the full (n = 152) and GA-matched (n = 42) cohorts.

	Full Cohort		Matched Cohort	
	I− (n = 72)	**I+ (n = 80)**	**I− (n = 21)**	**I+ (n = 21)**
Small for Gestational Age	18 (25)	18 (23)	3 (14)	6 (29)
Patent Ductus Arteriosus	9 (13)	38 (48)[a]	4 (19)	9 (43)
Retinopathy of Prematurity	7 (10)	39 (49)[a]	4 (19)	6 (29)
No Antenatal Steroids	11 (15)	9 (11)	5 (24)	3 (14)
Intraventricular Hemorrhage, grades ≤ II	8 (11)	13 (16)	3 (14)	3 (14)
Intraventricular Hemorrhage, grade III	0 (0)	2 (3)	0 (0)	0 (0)

Note: Descriptive statistics reported as n (%).

[a] $p < 0.001$.

Table 3

Mean FA of cortical white matter tracts for the full (n = 152) and GA-matched (n = 42) cohorts.

	Full Cohort				Matched Cohort			
White Matter Tract	**I−**	**I+**	**F**	η_p^2	**I−**	**I+**	**F**	η_p^2
ATR	0.19 (0.03), 68	0.19 (0.03), 70	2.86	0.02	0.19 (0.03), 21	0.19 (0.03), 17	0.55	0.02
Arcuate	0.15 (0.02), 69	0.15 (0.02), 76	1.93	0.01	0.15 (0.03), 21	0.14 (0.02), 20	2.88	0.01
Cingulum	0.17 (0.02), 63	0.16 (0.02), 65	4.05[a]	0.03	0.17 (0.03), 20	0.17 (0.03), 17	0.50	0.02
CST	0.27 (0.04), 68	0.28 (0.05), 68	0.80	0.01	0.27 (0.04), 21	0.28 (0.05), 18	0.20	0.01
ILF	0.18 (0.02), 69	0.17 (0.02), 75	4.52[a]	0.03	0.18 (0.04), 21	0.17 (0.02), 18	1.35	0.03
SCP	0.20 (0.04), 63	0.19 (0.05), 67	5.37[a]	0.04	0.19 (0.04), 19	0.20 (0.05), 16	0.03	0.00
Uncinate	0.17 (0.03), 68	0.17 (0.03), 75	0.00	0.00	0.17 (0.03), 20	0.17 (0.03), 18	0.35	0.01

Descriptive statistics reported as mean (SD), n.

** p < 0.01; ATR, anterior thalamic radiation; ILF, inferior longitudinal fasciculus; CST, Corticospinal Tract; SCP, superior cerebellar peduncle.

[a] $p < 0.05$.

Table 4

Mean FA of corpus callosum (CC) segments for the full (n = 152) and GA-matched (n = 42) cohorts.

	Full Cohort				Matched Cohort			
CC Segment	**I−**	**I+**	**F**	η_p^2	**I−**	**I+**	**F**	η_p^2
Anterior Frontal	0.22 (0.04), 67	0.21 (0.04), 68	4.48[a]	0.03	0.24 (0.02), 19	0.20 (0.05), 17	9.06[a]	0.22
Superior Frontal	0.20 (0.03), 64	0.19 (0.03), 66	3.42	0.03	0.20 (0.02), 20	0.20 (0.03), 17	0.07	0.01
Motor	0.19 (0.03), 60	0.19 (0.03), 54	0.51	0.01	0.19 (0.03), 18	0.20 (0.03), 16	0.00	0.00
Superior Parietal	0.18 (0.03), 62	0.18 (0.03), 58	3.00	0.03	0.18 (0.02), 17	0.18 (0.03), 18	0.00	0.00
Posterior Parietal	0.22 (0.07), 65	0.20 (0.05), 63	6.63[a]	0.05	0.21 (0.06), 18	0.22 (0.06), 18	0.00	0.00
Temporal	0.24 (0.03), 50	0.22 (0.04), 46	7.67[b]	0.08	0.24 (0.03), 12	0.21 (0.03), 14	4.56[a]	0.17
Occipital	0.27 (0.06), 64	0.24 (0.07), 60	10.26[b]	0.08	0.29 (0.06), 19	0.26 (0.06), 18	2.20	0.07

Note: Descriptive statistics reported as mean (SD), n.

[a] $p < 0.05$.

[b] $p < 0.01$.