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Early breast milk exposure modifies brain connectivity in preterm infants

Manuel Blesa [a], Gemma Sullivan [a], Devasuda Anblagan [a,b], Emma J. Telford [a], Alan J. Quigley [c], Sarah A. Sparrow [a], Ahmed Serag [a], Scott I. Semple [d], Mark E. Bastin [b], James P. Boardman [a,b,*]

[a] MRC Centre for Reproductive Health, University of Edinburgh, EH16 4TJ, UK
[b] Centre for Clinical Brain Sciences, Chancellor's Building, 49 Little France Crescent, University of Edinburgh, Edinburgh EH16 4SB, UK
[c] Department of Radiology, Royal Hospital for Sick Children, 9 Sciennes Road, Edinburgh EH9 1LF, UK
[d] University / BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, EH16 4TJ, UK

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ABSTRACT

Preterm infants are at increased risk of alterations in brain structure and connectivity, and subsequent neurocognitive impairment. Breast milk may be more advantageous than formula feed for promoting brain development in infants born at term, but uncertainties remain about its effect on preterm brain development and the optimal nutritional regimen for preterm infants. We test the hypothesis that breast milk exposure is associated with improved markers of brain development and connectivity in preterm infants at term equivalent age.

We collected information about neonatal breast milk exposure and brain MRI at term equivalent age from 47 preterm infants (mean postmenstrual age [PMA] 29.43 weeks, range 23.28–33.0). Network-Based Statistics (NBS), Tract-based Spatial Statistics (TBSS) and volumetric analysis were used to investigate the effect of breast milk exposure on white matter water diffusion parameters, tissue volumes, and the structural connectome.

Twenty-seven infants received exclusive breast milk feeds for ≥75% of days of in-patient care and this was associated with higher connectivity in the fractional anisotropy (FA)-weighted connectome compared with the group who had < 75% of days receiving exclusive breast milk feeds (NBS, $p = 0.04$). Within the TBSS white matter skeleton, the group that received ≥75% exclusive breast milk days exhibited higher FA within the corpus callosum, cingulum cingulate gyri, centrum semiovale, corticospinal tracts, arcuate fasciculi and posterior limbs of the internal capsule compared with the low exposure group after adjustment for PMA at birth, PMA at image acquisition, bronchopulmonary dysplasia, and chorioamnionitis ($p < 0.05$). The effect on structural connectivity and tract water diffusion parameters was greater with ≥90% exposure, suggesting a dose effect. There were no significant groupwise differences in brain volumes.

Breast milk feeding in the weeks after preterm birth is associated with improved structural connectivity of developing networks and greater FA in major white matter fasciculi.

1. Introduction

Preterm birth is strongly associated with a magnetic resonance imaging (MRI) phenotype that includes altered structural connectivity of developing neural systems involving white matter, structural alteration in deep and cortical grey matter, and long term neurocognitive impairment (Batalle et al., 2017; Boardman et al., 2010; Counsell et al., 2008; van den Heuvel et al., 2015a; van Kooij et al., 2012). Co-morbidities of preterm birth, genetic factors, and environmental exposures contribute to white matter disease but they do not explain fully the risks for atypical brain development and adverse outcome (Anblagan et al., 2016; Ball et al., 2010, 2017; Boardman et al., 2014; Inder et al., 2005; Krishnan et al., 2017).

Nutritional factors may play an important role in preterm brain development. For example, optimal protein and energy intakes in the first days after preterm birth are associated with increased brain growth, improved white matter microstructure and neurodevelopmental performance (Beauport et al., 2017; Coviello et al., 2017; Morgan et al., 2014; Schneider et al., 2018).

Breastfeeding, when compared with formula feeding, is associated with increased performance in intelligence testing among the general population, and the effect may be enhanced in low birthweight infants (Anderson et al., 1999; Isaacs et al., 2010; Lucas et al., 1998; Vohr et al., 2006, 2007). In a recent meta-analysis of studies that controlled for

* Corresponding author. MRC Centre for Reproductive Health, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom.
E-mail address: james.boardman@ed.ac.uk (J.P. Boardman).

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maternal intelligence, which is a recognised confounder of childhood cognition, breast feeding remained associated with a gain in performance in IQ testing (Horta et al., 2015). Furthermore, breast milk appears to have lasting impact on cognition with improved performance at school, during adolescence and through to adulthood (Belfort et al., 2016; Horwood and Fergusson, 1998). MRI studies of children and adolescents report that breast milk feed in infancy is associated with increased white and grey matter volumes (Isaacs et al., 2010; Luby et al., 2016), increased cortical thickness (Kafouri et al., 2013) and improved white matter microstructure (Deoni et al., 2013) when compared with formula feeding. However, the extent to which observations from the general population can be extrapolated to preterm infants is unknown, and this leaves uncertainty about the effect of breast milk on preterm brain development, and the timing, dose and duration of breast milk that might confer benefit.

We combined nutritional data with brain MRI to test the hypothesis that exposure to breast milk enhances early brain development in preterm infants. We investigated the influence of breast milk intake during neonatal care on a comprehensive set of measures of brain development that are based on the MRI phenotype of preterm brain injury (Batalle et al., 2017; Counsell et al., 2008; Inder et al., 2005; van den Heuvel et al., 2015b). We combined structural and diffusion MRI (sMRI/dMRI) to perform anatomically-constrained tractography (ACT) (Smith et al., 2012) with spherical-deconvolution informed filtering of tractograms (SIFT) (Smith et al., 2013) to construct the structural connectome, and compared connectomes using global network measures and edge-wise values using Network-based Statistics (NBS). We used Tract-based Spatial Statistics (TBSS) to calculate voxel wise differences in fractional anisotropy (FA), mean (MD), axial (AD), and radial (RD) diffusivity across the white matter skeleton, and used optimized algorithms for brain extraction and tissue classification to measure global and local brain tissue volumes (Ball et al., 2010; Serag et al., 2017; Smith et al., 2006).

2. Subjects and methods

2.1. Participants

Participants were preterm infants delivered at $\leq$ 33.0 weeks who received care at the Royal Infirmary of Edinburgh and had brain MRI performed at term-equivalent age as part of a longitudinal study designed to investigate the effects of preterm birth on brain structure and outcome. The study was conducted according to the principles of the Declaration of Helsinki, and ethical approval was obtained from the UK National Research Ethics Service. Parents provided written informed consent.

Daily nutritional intake was collected from birth until discharge home from the neonatal unit using electronic patient records. Breast milk exposure was defined as the proportion of in-patient days receiving exclusive breast milk, categorized as $\geq$ 75% and $\geq$90% of days of in-patient care when exclusive breast milk was given.

The nutritional management of all participants conformed to following principles. Infants with birth weight <1500 g began parenteral nutrition upon admission to neonatal care. This was delivered using a standard solution (Scottish Neonatal Parenteral Nutrition 2.4 g protein/100 ml, ITH Pharma, London), commencing at 100 ml/kg/day if birth weight < 1000 g and 75 ml/kg/day if birthweight 1000–1500 g. This was increased to a maximum of 150 ml/kg/day in 25 ml/kg/day increments every 24 h. Fat and fat-soluble vitamins were provided using Intralipid 20% emulsion, which was commenced within 24 h of admission at 1 g/kg/day, increasing to 2 g/kg/day on day 2 and 3 g/kg/day on day 3.

Expression of breast milk was encouraged immediately after delivery and colostrum was given as soon as it became available. Enteral feeds were commenced at 12 ml/kg/day on day one and incremented by 30 ml/kg/day as standard. This increment was reduced to 18 ml/kg/day in babies identified as at high risk of developing necrotising enterocolitis (<1000 g, IUGR, absent or reversed umbilical artery end diastolic flow doppler). If there was insufficient maternal expressed breast milk by 48 h of age, donor expressed breast milk was given to supplement maternal milk. Once infants had reached 120 ml/kg/day of enteral feeds, parenteral nutrition was stopped. Feeds continued to increment to a maximum volume of 180–200 ml/kg/day. Human milk fortifier (Cow & Gate Nutriprem Human Milk Fortifier, Nutricia) was added to breast milk if weight gain remained sub-optimal despite 14 days of maximal volume breast milk (180–200 ml/kg/day). If mothers chose not to express milk or there was insufficient breast milk to meet the requirements of the infant beyond 34 weeks, donor expressed breast milk was replaced with preterm formula. All infants received multivitamins from day 7 of life and iron supplementation from day 42.

Bronchopulmonary dysplasia (BPD) was defined as the requirement for supplemental oxygen at 36 weeks corrected gestational age. All infants had placental histopathology performed and histological chorioamnionitis (HCA) was defined using an established system (Anblagan et al., 2016). Postnatal somatic growth was described as the difference between birthweight z-score and weight at scan z-score, calculated using INTERGROWTH-21st reference standards for preterm infants (Villar et al., 2016).

2.2. Image acquisition

Infants were scanned in natural sleep with pulse oximetry, electrocardiography and temperature monitoring. Flexible earplugs and neonatal earmuffs (MiniMuffs, Natus) were used for ear protection. All scans were supervised by a neonatal doctor.

A Siemens MAGNETOM Verio 3T MRI clinical scanner (Siemens Healthcare Gmbh, Erlangen, Germany) and 12-channel Siemens phased-array head matrix coil were used to acquire the following scans: 3D T1-weighted (T1w) MPRAGE (TR = 1650 ms, TE = 2.43 ms, inversion time = 160 ms, flip angle = 9°, acquisition plane = sagittal, voxel size = $1 \times 1 \times 1$ mm^3, FOV = 256 mm, acquired matrix = 256×256, acquisition time = 7 min 49 s and acceleration factor = 2); dMRI data consisting of 11 T2-and 64 diffusion-weighted (b = 750 s/mm^2) single-shot, spin-echo, echo planar imaging (EPI) volumes were acquired in the axial plane with 2 mm isotropic voxels (TR = 7300 ms, TE = 106 ms, FOV = 256 mm, acquired matrix = 128×128, 50 contiguous interleaved slices with 2 mm thickness, acquisition time = 9 min 29 s). To reduce eddy current induced artefacts and shimming errors to a minimum in the dMRI protocol, an optimized bipolar gradient pulse scheme was employed with a manually selected shim box covering a region extending from the top of the head to several centimetres below the chin.

Structural images were reported by an experienced paediatric radiologist (A.J.Q.) using the system described by Leuchter et al. (2014), and images with evidence of injury (post-haemorrhagic ventricular dilatation, porencephalic cyst or cystic periventricular leukomalacia), or central nervous system malformation were excluded.

2.3. Structural connectivity

The complete framework for the network construction can be seen in Fig. 1.

2.3.1. Preprocessing

The first step was to denoise the dMRI data (Veraart et al., 2016a, 2016b) followed by up-sampling by a factor of 2 to match the resolution of the T1w volumes using cubic b-spline interpolation (Raffelt et al., 2012). Then, the dMRI data were corrected for head motion and eddy current distortions (Smith et al., 2004) with the correspondent vector rotation, skull-stripped (Smith, 2002) (with manual editing) and corrected for bias field inhomogeneity (Tustison et al., 2010). The T1w volumes were skull-stripped (Serag et al., 2016) and corrected for bias field inhomogeneities (Tustison et al., 2010). Finally, the T1w volumes were co-registered to the first B0 EPI volumes for each subject and dMRI data were corrected for EPI distortions by non-rigidly registering the EPI

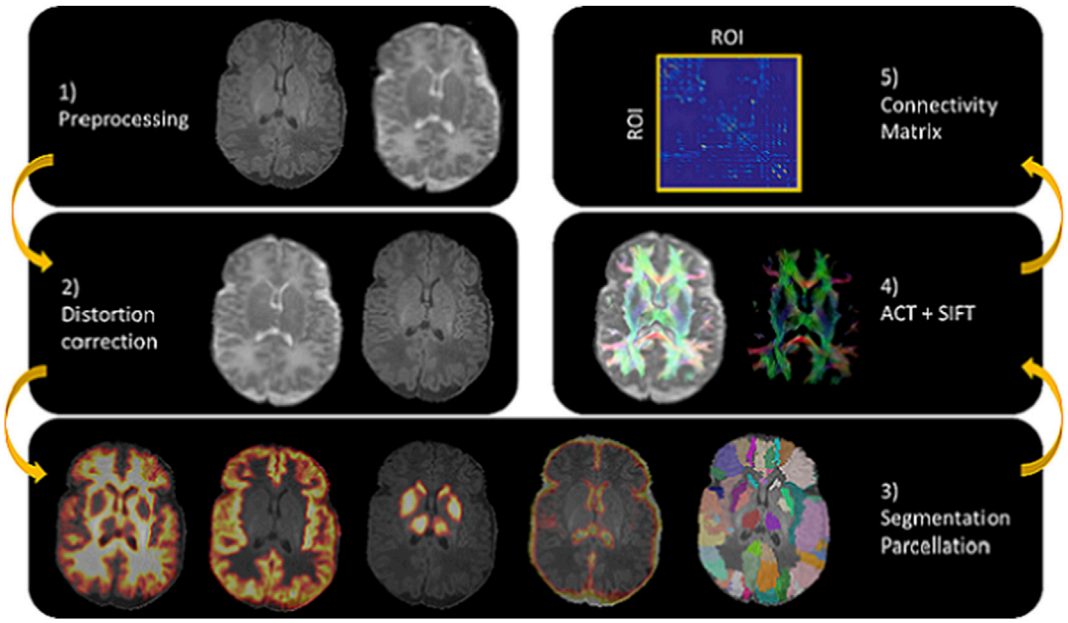

Fig. 1. Overview of the structural connectome creation framework.

volumes to the co-registered T1w volumes, restricting the registration to the phase encoding direction (Irfanoglu et al., 2012; Wu et al., 2008). This process was performed using Symmetric Normalization (SyN)(Avants et al., 2008) with mutual information as the registration metric.

For each voxel, the water diffusion tensor was estimated using the weighted least-squares method with DTIFIT (Smith et al., 2004). FA, MD, AD and RD maps were then generated for every subject.

2.3.2. Tissue segmentation and parcellation

The T1 template of Edinburgh Neonatal Atlas (ENA33) (Blesa et al., 2016) was used to parcellate the T1w volume of each participant using rigid, affine and SyN (Avants et al., 2008) registration with cross correlation as the registration metric. To generate the tissue segmentation we used SEGMA (Serag et al., 2017). This is an automatic SEGMentation Approach for human brain MRI using sliding window and random forests that provides accurate segmentations across the life course (including the neonatal period) to classify all T1w volumes into cortical grey matter, deep grey matter, white matter and cerebrospinal fluid (CSF).

2.3.3. Tractography

Tractography was generated using constrained spherical deconvolution (cSD) (Tournier et al., 2007, 2008). The fiber orientation distribution (FOD) was calculated with a maximum spherical harmonic degree (l_{max}) of 8 (Tournier et al., 2013). We used ACT (Smith et al., 2012) with the iFOD2 algorithm (Tournier et al., 2010). The ACT parameters were: seeding at the grey matter/white matter interface (GMWMI); minimum streamline length of 20 mm and maximum length of 200 mm (Keunen et al., 2017; Yap et al., 2011); the remainder of parameters were used as default (adjusted for upsampled data (Smith et al., 2012)). 10 million tracts were generated and spherical-deconvolution informed filtering of tractograms (SIFT) was applied to reduce the number of tracts to 2 million. This reduces the construction bias of the tractogram and improves the biological accuracy and interpretability of structural connectivity between regions (Smith et al., 2013).

2.3.4. Network construction

The connectome was constructed by assigning a weight to an edge based on the raw number of tracts between regions: $w(e_{i,j}) = c_{i,j}$. Where $e_{i,j}$ represents the connection between the nodes i and j; $w(e_{i,j})$ is the weight of the connection $e_{i,j}$; and $c_{i,j}$ is the number of tracts between i and j. Connections with less than five tracts and self-connections were set to 0 (Batalle et al., 2017) resulting in a network of size 98×98. Any implausible tracts traversing from one cortical hemisphere to any contralateral subcortical node were discarded (Funnell et al., 2000).

Note that the networks were not corrected for the inverse length of the paths, since this correction is not appropriate for tractograms calculated using a GMWMI seeding strategy (Yeh et al., 2016). We refer to those matrices as streamline-weighted matrices (M^{w-NOS}).

Next, FA-weighted connectomes were constructed using the mean FA computed over the $c_{i,j}$ streamlines as an edge weight: $w(e_{i,j}) = \frac{1}{c_{i,j}} \sum_{n=1}^{n=c_{i,j}} \overline{FA}_n$. Where i, j, $e_{i,j}$, $w(e_{i,j})$ and $c_{i,j}$ are defined as before; n is each streamline connecting i and j; and $\overline{FA}_n$ is the mean FA of the tract n. This weight represents the white matter tract "integrity" (Brown et al., 2014; van den Heuvel and Sporns, 2011). We refer to those matrices as FA-weighted matrices (M^{w-FA}).

Finally, each M^{w-NOS} was binarized and used to filter the correspondent M^{w-FA}. The resulting M^{w-FA} connectomes were not normalized because the FA values for a region-pair connection are averaged across all its $c_{i,j}$ streamlines, making it invariant to the number of tractography seeds used (Brown et al., 2014).

2.3.5. Edge-wise comparison

The M^{w-NOS} were thresholded keeping only the connections common to at least 2/3 of the subjects (de Reus and van den Heuvel, 2013), and the threshold was then applied to the M^{w-FA}. M^{w-FA} matrices were analysed using NBS.

2.3.6. Network metrics and analysis

We calculated 5 network parameters: Global efficiency (GE), local efficiency (LE), normalized cluster coefficient (CC), normalized characteristic path length (CPL) and small-worldness (SW). For a detailed explanation and the formulation of the metrics, see Rubinov and Sporns (2010). All the metrics were implemented in the Brain Connectivity Toolbox (brain-connectivity-toolbox.net) (Rubinov and Sporns, 2010). Note that for CPL the length matrix was generated using the inverse of each connection of the M^{w-FA}. The normalized CC and normalized CPL were calculated by dividing the CC and CPL, by the CC and CPL calculated from an average of 1000 random networks with the same degree and strength distributions.

The connectivity matrices do not have the same density (sparsity). To correct for this, each M^{w-NOS} was thresholded using its density in small steps from 0.02 to 0.5 in intervals of 0.02. After this the matrix was binarized and used as a threshold to filter the M^{w-FA}.

Connectomic data were visualised using Circos (Krzywinski et al., 2009) and BrainNet viewer (Xia et al., 2013).

2.4. Tract-based Spatial Statistics

TBSS analysis (Smith et al., 2006) was performed using a pipeline that was optimized for neonatal dMRI data (Ball et al., 2010). Using the most representative subject of the cohort as a target, an average FA map and mean FA skeleton (threshold FA > 0.15) were created from the aligned data representing the main white matter tracts common to all subject. RD, AD and MD were projected onto the FA skeleton for voxel wise comparisons.

2.5. Volumetric analysis

The brain tissue was separated from non-brain tissue using ALFA (Serag et al., 2016), and a brain mask was created. Volumes were corrected for field inhomogeneity using the N4 method (Tustison et al., 2010) and were segmented using SEGMA (Serag et al., 2017). Every brain volume was segmented into: brainstem, cerebellum, cortical grey matter, cerebrospinal fluid, deep grey matter and white matter (Fig. 2). Volumes were calculated for each individual tissue type, and total brain tissue volume was calculated as the sum of all compartments with the exception of CSF.

2.6. Analysis of dose effect

We explored the effect of breast milk dose by repeating group-wise analyses for infants with ≥90% exclusive breast milk days compared to infants with <90% of exclusive breast milk days.

2.7. Statistics

Edge-wise comparison of connectivity matrices was performed using NBS (Zalesky et al., 2010) with a t-statistic exceeding a threshold of 3 (Zalesky et al., 2012). Groupwise difference in breast milk exposure in the five network measures was investigated using ANOVA (in the original matrices and also at each level of density). For TBSS, group comparisons were performed with FSL's Randomise tool using a general linear univariate model (Winkler et al., 2014), with family-wise error correction for multiple testing using threshold-free cluster enhancement (TFCE) with a significance level of $p < 0.05$ (Smith and Nichols, 2009). For volumetric comparisons group-wise analyses were performed using ANOVA. In all analyses post-menstrual age (PMA) at birth, PMA at image acquisition, BPD and exposure to chorioamnionitis were entered as covariates. False discovery rate was used to control for multiple testing in analyses of volumes, network metrics and network metrics corrected for density.

3. Results

3.1. Baseline characteristics

Forty-seven participants were studied. 27 received exclusive breast milk feeds for ≥75% of days of neonatal in-patient care, and 20 received exclusive breast milk feeds for <75% of days (Table 1). The demographic and clinical features of the population with ≥90% exclusive breast milk days are shown in Supplementary Table 1.

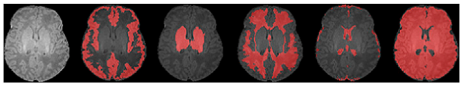

Fig. 2. From left to right: a single subject and the corresponding tissue segmentations for cortical grey matter, sub-cortical grey matter, white matter, CSF and whole brain.

3.2. Edge-wise connectome comparison

FA-weighted connectivity was increased in infants who received ≥75% of exclusive breast milk feeds compared to those who did not ($p = 0.0386$, NBS). The connections involved included intra- and inter-hemispheric fronto-parietal and limbic system structures; anatomical labels of altered structural connectivity are shown in Fig. 3a. The extent of anatomic connectivity was further increased in these neural systems in infants who received ≥90% of exclusive breast milk, as measured by incorporation of more nodes and edges, an in addition sub-cortical networks were involved at the higher breast milk intake threshold ($p = 0.0086$, NBS), Fig. 3b.

3.3. Network analysis

There were no statistically significant differences in global network metrics for M^{w-FA} at either milk intake threshold after FDR correction (Fig. 4), nor were there significant differences in network measures corrected for density (data not shown).

Table 1
Demographic and clinical features of study participants.

	<75% exclusive BM days (n = 20)	≥75% exclusive BM days (n = 27)	p value
Mean PMA at birth/weeks (range)	29.43 (23.28–33.0)	29.43 (26.14–32.86)	0.97
M:F ratio	8:12	12:15	0.76
Mean birthweight/g (range)	1121 (550–1450)	1160 (815–1465)	0.55
Mean birthweight z-score	−0.56	−0.37	0.55
Mean PMA at scan/weeks (range)	39.71 (38.0–42.28)	39.53 (38.0–42.0)	0.83
Mean weight at scan/g (range)	2838 (2160–3480)	2862 (2070–4870)	0.87
Mean weight at scan z-score	−1.06	−1.01	0.88
Difference in mean weight z-score from birth to scan	−0.43	−0.65	0.32
Proportion of infants with BPD (%)	4/20 (20)	9/27 (33)	0.31
Proportion of infants with HCA (%)	6/20 (30)	9/27 (33)	0.81
Proportion of infants with NEC (%)	1/20 (5)*	2/27 (7)	0.74
Mean number of days in neonatal unit (range)	62 (19–151)	59 (26–94)	0.68
Mean number of TPN days (range)	9 (0–30)	9 (0–30)	0.90
Mean plasma Urea concentration at 32 weeks PMA/mmol/L (range)	2.5 (1.4–3.9)	2.7 (1.4–7.3)	0.64
Median number of exclusive formula days (range)	12 (0–107)	0 (0–10)	<0.01
Median number of exclusive breast milk days (range)	19 (0–79)	57 (24–90)	<0.01
Median number of HMF days (range)	0 (0–58)	18 (0–62)	<0.01
Mean proportion of exclusive breast milk days with supplemental DEBM, % (range)	18 (0–100)	3 (0–30)	<0.01

BPD = Bronchopulmonary dysplasia, HCA = Histological chorioamnionitis, NEC = Necrotising enterocolitis, TPN = Total parenteral nutrition, HMF= Human Milk Fortifier, DEBM = Donor expressed breast milk. *One infant in the group who received exclusive breast milk feeds for <75% of neonatal inpatient required laparotomy for treatment of NEC; the two other cases of NEC were managed conservatively.

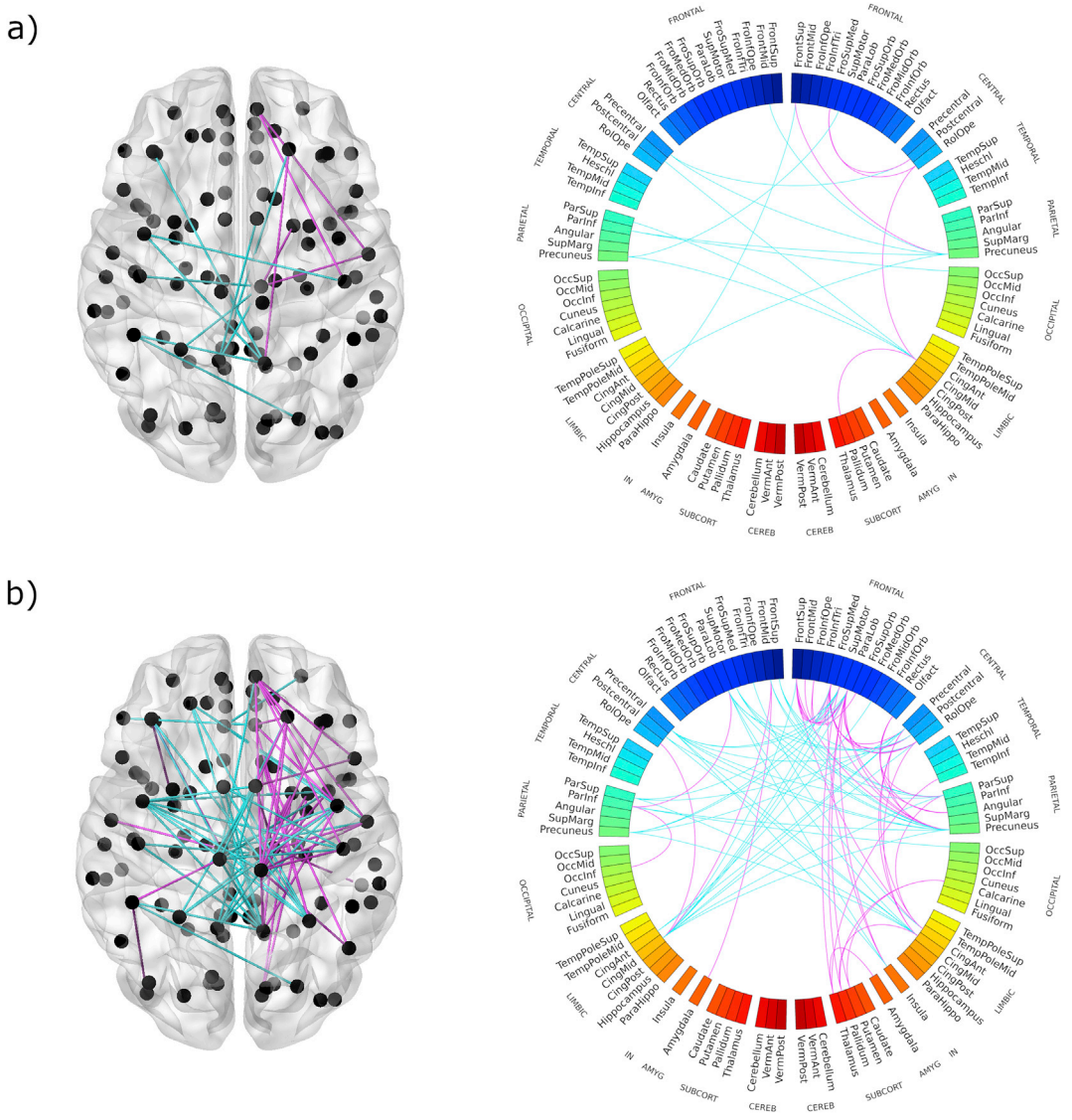

Fig. 3. Network differences in the FA-weighted connectome for the two thresholds: ≥ 75% (a) and ≥90% (b). Inter-hemispheric connections are shown in blue, and intra-hemispheric connections in magenta. For visualisation: anatomic left is on right side of image.

3.4. Tract-based spatial statistics

There were significant differences in water diffusion tensor parameters in major white matter tracts associated with breast milk exposure. Specifically, in the group with ≥75% days of exclusive breast milk feeds, FA was higher in the splenium of corpus callosum, cingulum cingulate gyri, centrum semiovale, corticospinal tracts, the arcuate fasciculi and the posterior limbs of internal capsule. These differences were more widespread and symmetrical at the ≥90% exclusive breast milk days threshold. Infants who received ≥90% days exclusive breast milk feeds had lower MD and RD than the other participants (Fig. 5).

3.5. Volumetric analysis

There were no significant differences in brain volumes between preterm infants who received ≥75% exclusive breast milk and those who received <75% breast milk feeds (FDR corrected). The mean (SD) for the total brain tissue volume of the group with ≥75% breast milk exposure was 359.34 ml (38.76 ml), while for the group with <75% breast milk exposure it was 361.56 ml (34.65 ml). Values for tissue compartments and CSF are shown in Table 2. There were no significant differences in brain volumes between preterm infants who received ≥90% exclusive breast milk and those who received <90% breast milk feeds (Supplementary Table 2).

4. Discussion

By combining nutritional data with brain MRI markers of preterm brain injury, we have shown that greater exposure to breast milk following preterm birth is associated with improved white matter microstructure at term-equivalent age. We found differences in the FA-weighted connectome and increased FA within white matter tracts of infants who received exclusive breast milk feeds for ≥75% days of neonatal in-patient care compared with infants who received exclusive breast milk for <75% of days. These effects showed a dose-dependent relationship with breast milk exposure and were independent of known predictors of preterm brain injury including gestational age at birth, chorioamnionitis, and BPD. The observed effects are unlikely to be attributable to parenteral nutrition because exposure to this did not differ significantly between the groups.

The TBSS results suggest that breast milk feeds had beneficial distributed effects throughout the white matter since voxels within corpus callosum, cingulum cingulate gyri, centrum semiovale, corticospinal tracts, arcuate fasciculi and posterior limbs of the internal capsule

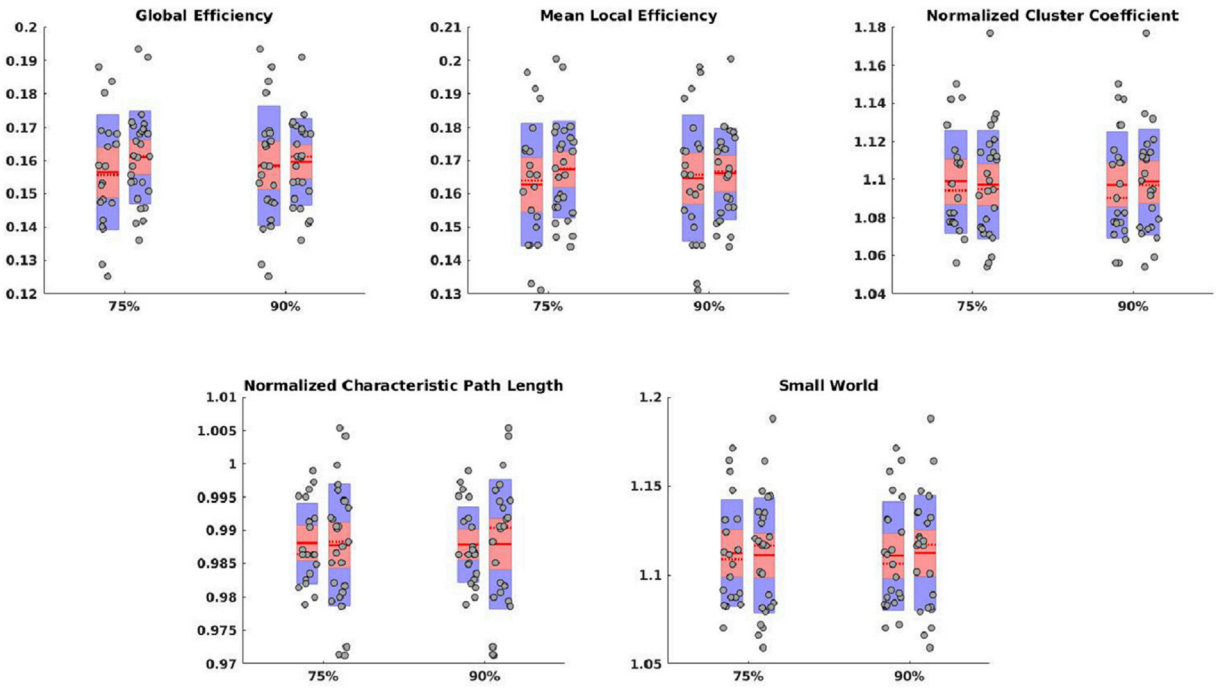

Fig. 4. Plot of the different network metrics for the M^{w-FA} connectivity matrices. In each metric both thresholds are represented, namely ≥75% and ≥90%. For each threshold the box on the left represents the subjects with the lower breast milk dose and the box on the right the higher dose. The red line represents the mean; the red dotted line represents the median; the red box the 95% interval confidence of the mean; and the blue box the interval between the mean ± 1 standard deviation.

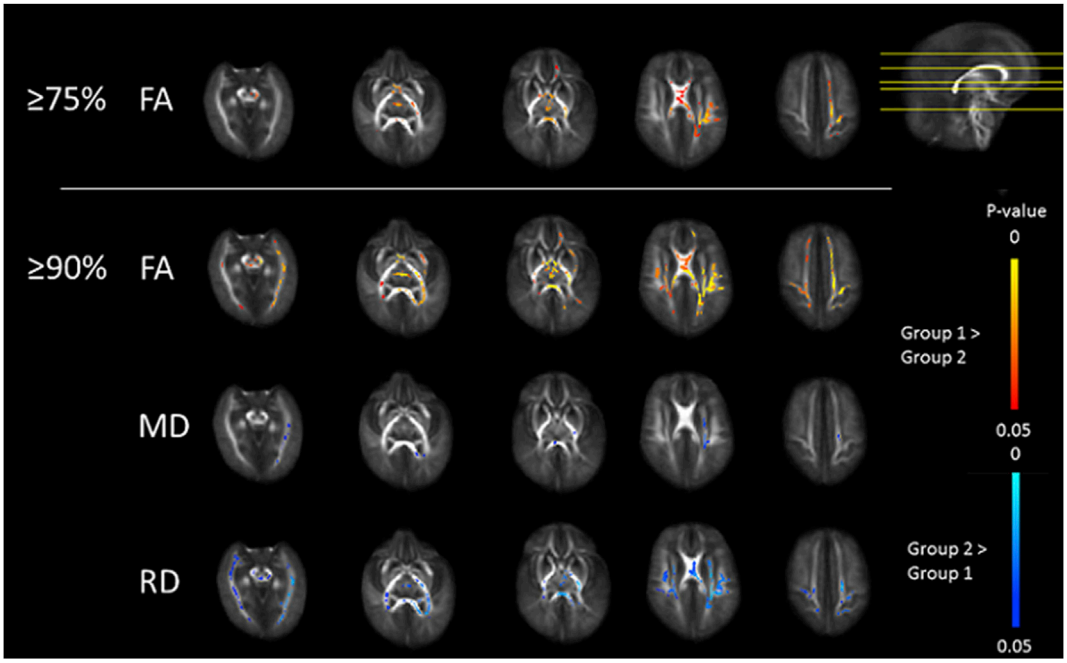

Fig. 5. TBSS results showing differences in FA for each of the breast milk thresholds: 75% and 90%. Differences in MD and RD are highlighted in infants who received <90% days exclusive breast milk. Group 1: higher than the specified threshold of exclusive breast milk and group 2: lower than the specified threshold of exclusive breast milk. For visualisation: anatomic left is on right side of image.

had higher FA in the higher breast milk group. Network alterations involved fronto-parietal and limbic systems, with increased sub-cortical connectivity apparent at the higher threshold of breast milk intake. Regional susceptibilities of fronto-parietal white matter to preterm birth have been reported, and regional cerebral vulnerability to nutritional deprivation is well described (e.g. fetal growth restriction and hypoglycaemia associated brain injury) (Burns et al., 2008; Inder et al., 2005; Lodygensky et al., 2008). Furthermore, fetal growth restriction is associated with tract-specific alterations in dMRI parameters in preterm infants (Barnett et al., 2018). Our data suggest that there are tract-specific effects of beneficial nutrient exposures in regions and networks; one explanation for this is that nutritional factors influence neurogenesis, neuronal differentiation, myelination and synaptogenesis at critical periods in development and these maturational processes take place at

Table 2
Mean (SD) brain tissue and cerebrospinal fluid volumes (ml) at term equivalent age.

	Mean volume (SD)/ml (≥75% exclusive breast milk)	Mean volume (SD)/ml (<75% exclusive breast milk)	p-value
Cortical grey matter	169.81 (23.39)	170.64 (19.10)	0.87
Sub-cortical grey matter	25.99 (3.67)	25.52 (3.21)	0.58
White matter	135.17 (14.01)	136.27 (12.95)	0.79
Cerebrospinal fluid	75.42 (16.51)	81.50 (16.26)	0.16
Brainstem	5.07 (0.87)	5.30 (0.62)	0.28
Cerebellum	23.29 (3.28)	23.82 (3.21)	0.47
Whole Brain	359.34 (38.76)	361.56 (34.66)	0.81

different times in different tracts over the course of development (Ramel and Georgieff, 2014), as evidenced by the systematic progression of MRI visible myelination in the developing brain (Counsell et al., 2002).

Our data are consistent with neurodevelopmental outcome studies of preterm infants that report improved neurodevelopmental outcomes in association with breast feeding (Isaacs et al., 2010; Lucas et al., 1998; Patra et al., 2017; Vohr et al., 2006, 2007). However, when outcomes are assessed in early childhood the effects of infant nutrition and other potential confounders limit inference about neonatal nutritional exposures. By parsing the complex behavioural trait of neurodevelopment to an intermediate phenotype (MRI markers of development at term equivalent age) we have shown that breast milk intake prior to discharge from hospital is critically important for optimal brain development after preterm birth. Previous studies have reported that cumulative lipid and caloric intake from all sources (parenteral and enteral) in the first weeks after preterm birth is associated with increased FA in the posterior limb of the internal capsule and different white matter tracts, that cumulative lipid is associated with cerebellar and grey matter volumes (Coviello et al., 2017; Schneider et al., 2018); and that higher energy and lipid intake during the first 2 weeks after birth is associated with a lower incidence of brain lesions and signs of dysmaturation on conventional MRI (Beauport et al., 2017). Our findings are consistent with the observation that early nutrition impacts brain tissue development, but they focus particular attention on the value of early breast milk for improving whole brain structural connectivity in preterm infants. Breast milk is a complex nutritional substrate that has theoretical nutritional advantages over formula milk for promoting brain development. These include favourable composition and absorption of fats and protein, improved bioavailability of trace elements, and the presence of non-nutrient factors (milk oligosaccharides, immunoglobulins, lactoferrin and lysozymes) that may confer direct or indirect benefit (Agostoni et al., 2010; Guesnet and Alessandri, 2011). Finally, the infant gut microbiome is affected by feeding practice (Pannaraj et al., 2017); modifications to the gut-brain axis via microbiome are known to influence brain development and behaviour in mice (Heijtz et al., 2011) and to predict cognitive performance in infants at 2 years of age (Carlson et al., 2018). Attachment, shared social determinants, and maternal education/IQ have been associated with breast feeding in healthy term infants (Britton et al., 2006; Der et al., 2006), although the role of these factors in influencing breast feeding in the NICU setting where the breast feeding rate is typically higher compared with the general population, is uncertain, as is their role in influencing structural connectivity in preterm infants. Further investigation of the role of these factors in influencing early brain development and their possible interaction with enteral nutrition is warranted.

The main strength of the study is the comprehensive assessment of brain development using three measures that describe the encephalopathy of prematurity: connectivity, tract microstructure, and local and global brain volumes. We were also able to explore dose effects. We evaluated infants at term equivalent age, so are able to rule out confounding by nutrition throughout infancy and socio-economic features of the home environment. Finally, we used a pragmatic measure of breast milk exposure that is available to healthcare providers and parents from routinely recorded data, and does not require additional measurements.

A limitation of our work is that we were not able to investigate the effect of common genetic variation in fatty acid metabolism, which may interact with breast milk exposure to influence childhood cognition (Caspi et al., 2007; Steer et al., 2010) and white matter development (Boardman et al., 2014; Krishnan et al., 2016); nor were we able to investigate genetic variants of the microglial inflammatory response linked to preterm white matter injury (Krishnan et al., 2017). Secondly, we performed a cross-sectional assessment at term equivalent age so could not investigate the putative benefits to the preterm brain of longer exposure to exclusive breast feeding through infancy. The sample size was not sufficient to study the effect of donor expressed breast milk or human milk fortifier on brain development. Finally, although the data indicate a dose effect, the difference in number of participants with 75% versus 90% exposure was low; larger sub-groups of infants with a range of breast milk exposures would be required to characterise fully the dose effect.

We used cSD with probabilistic tracking because it is beneficial over standard diffusion tensor reconstructions for tractography in paediatric brain, even with low b-values (Toselli et al., 2017). ACT and SIFT were used to reduce bias in the tractography reconstruction (Smith et al., 2012, 2013, 2015; Yeh et al., 2016), because recent studies have shown the benefit of this approach in the developing brain (Batalle et al., 2017; Salvan et al., 2017). M^{w-FA} were chosen because FA is established as a reliable marker of brain development (Ball et al., 2010; Brown et al., 2014; van den Heuvel et al., 2015b), but new models that rely on high b-value acquisitions to better characterise crossing fibres within WM may provide additional insights into the effect of breast milk on early brain development (Zhang et al., 2012), particularly in regions with a high density of crossing fibres such as the cerebellum (Pieterman et al., 2017).

5. Conclusion

In summary, these data show that the microstructural properties of white matter tracts and cerebral structural connectivity are improved in association with higher exposure to breast milk in preterm infants.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2018.09.045.

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