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Relationship between very early brain structure and neuromotor, neurological and neurobehavioral function in infants born < 31 weeks gestational age

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ABSTRACT

Aim: This study aimed to examine associations between structural MRI and concurrent motor, neurological and neurobehavioral measures at 30–32 weeks postmenstrual age (PMA; 'Early'), and at term equivalent age ('Term').

Method: In this prospective cohort study, infants underwent Early MRI (n = 119; 73 male; median 32 weeks 1 day PMA) and Term MRI (n = 102; 61 male; median 40 weeks 4 days PMA) at 3 T. Structural images were scored generating white matter (WM), cortical gray matter, deep gray matter, cerebellar and global brain abnormality scores. Clinical measures were General Movements Assessment (GMs), Hammersmith Neonatal Neurological Examination (HNNE) and NICU Neonatal Neurobehavioral Scale (NNNS). The Premie-Neuro was administered Early and the Test of Infant Motor Performance (TIMP) and a visual assessment at Term.

Results: Early MRI cerebellar scores were strongly associated with neurological components of HNNE (reflexes), NNNS (Hypertonicity), the Premie-Neuro neurological subscale (regression coefficient $\beta = -0.06$; 95% confidence interval CI = −0.09, −0.04; $p < .001$) and cramped-synchronized GMs ($\beta = 1.10$; 95%CI = 0.57, 1.63; $p < .001$). Term MRI WM and global scores were strongly associated with the TIMP (WM $\beta = -1.02$; 95%CI = −1.67, −0.36; $p = .002$; global $\beta = -1.59$; 95%CI = −2.62, −0.56; $p = .001$).

Interpretation: Brain structure on Early and Term MRI was associated with concurrent motor, neurological and neurobehavioral function in very preterm infants.

1. Introduction

Infants born very preterm are at high risk of impaired motor, cognitive, language and behavioral function which are the result of early brain injury and impaired brain development. Brain imaging such as magnetic resonance imaging (MRI) and clinical evaluation (motor, neurological or neurobehavioral function) are different techniques to identify structural and functional markers of brain injury and development. Both methods are used to predict outcomes, target interventions and counsel and support families [1–4]. Relationships between these brain structure and function methods have been demonstrated at term equivalent age (TEA) in very preterm infants [5–7]. Although MRI is now more frequently acquired earlier than TEA, there is little information yet on structure–function relationships at this earlier stage.

Abbreviations: GA, gestational age; GM, gray matter; MRI, magnetic resonance imaging; TEA, term equivalent age; PMA, postmenstrual age; WM, white matter

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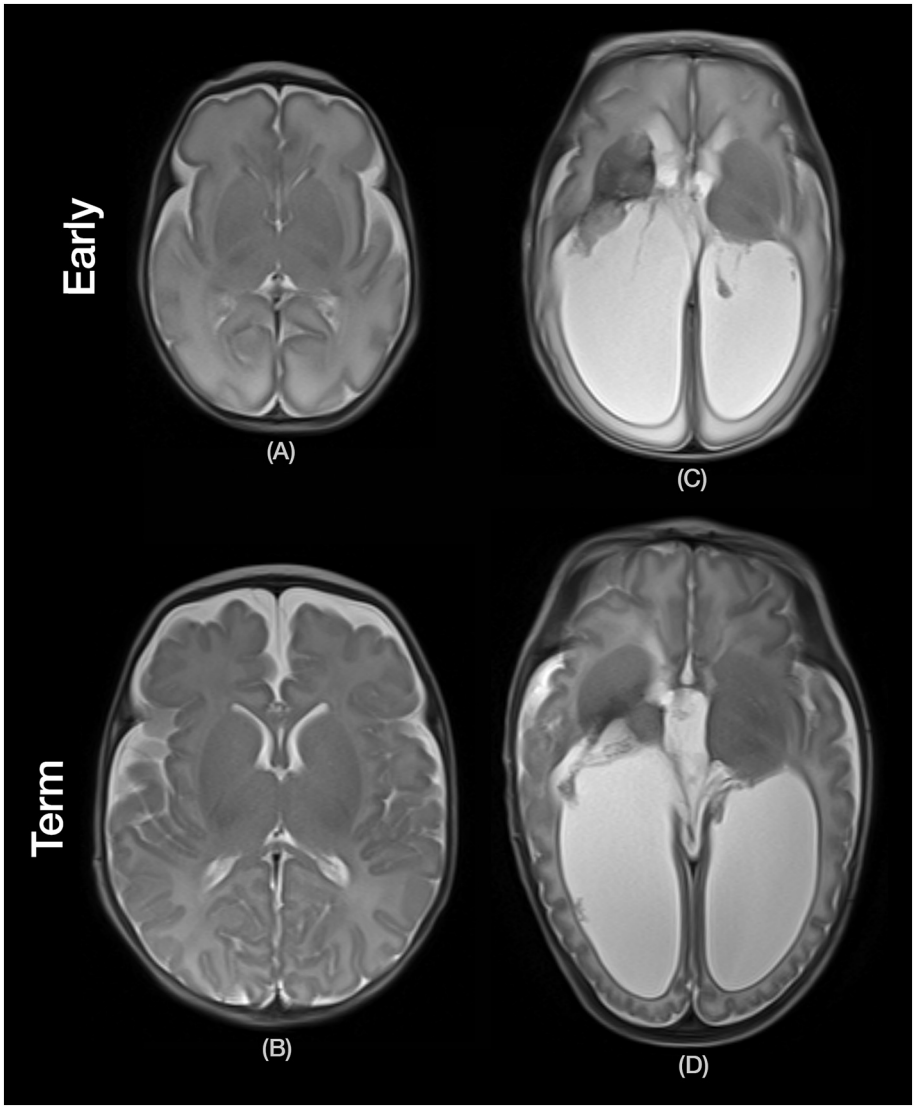

Fig. 1. T2 HASTE axial images. On the left: a subject with Early (31 weeks PMA; A) and Term (39 + 6 weeks PMA; B) MRI both scored as normal; and normal motor and cognitive outcomes at 12 months corrected age. On the right: a subject with post-hemorrhagic enlargement of lateral and III ventricles with capsular-thalamic right venous infarction. Early MRI (33 + 3 weeks PMA; C) and Term MRI (40 + 3 weeks PMA; D) for this infant scored in the severe brain abnormality range, and this infant has been diagnosed with cerebral palsy (left hemiplegia).

Availability of clinical correlates for this early structural MRI would support clinicians working without access to MRI, and guide selection of clinical measures to discriminate between infants with structural brain abnormalities and those without. It would assist our understanding of what clinical presentations are associated with structural brain abnormalities, so that in settings without MRI, the clinical assessments could be used to identify infants most likely to have structural brain abnormalities and therefore a greater risk of adverse outcomes. This would assist in planning of follow up care after discharge from the neonatal intensive care unit.

At TEA, structure–function relationships have been demonstrated between qualitative structural MRI scoring systems and clinical measures of motor (General Movements Assessment, GMs), neurological (Hammersmith Neonatal Neurological Examination, HNNE) and neurobehavioral function (NICU Network Neurobehavioral Scale, NNNS) [5–8]. The MRI scoring systems utilized in these studies evaluate white matter (WM) and cortical gray matter (GM) for evidence of injury. Cerebral WM abnormalities, the predominant pattern of brain injury in very preterm infants, are associated with poorer neurological and neurobehavioral scores at TEA [5–7]. Earlier MRI studies with qualitative scoring of structural images demonstrate associations with later neurodevelopmental outcomes [9–11]; however concurrent functional correlates have not yet been demonstrated.

Scoring systems of structural MRI at TEA have been further developed to include evaluation of deep GM structures and the cerebellum, and include regional measurements to capture the effect of impaired brain growth [12]. Validated for use from 36 to 42 weeks postmenstrual age (PMA), the scale demonstrates associations with gestational age (GA) at birth, birthweight, a number of clinical risk factors and neonatal infection [12, 13]. This scoring system, which includes evaluation of deep GM and the cerebellum as well as incorporating regional measurements, has recently been adapted and validated for use from 29 to 35 weeks PMA in very preterm infants [11]. These comprehensive scoring systems of structural MRI provide new biomarkers of brain injury and development in preterm infants.

The aim of this study was to examine the structure–function relationships between structural MRI brain abnormality scores and concurrent clinical measures of neuromotor, neurological and neurobehavioral performance at 30–32 weeks PMA ('Early' MRI) and again at 40–42 weeks PMA ('Term' MRI). A secondary aim was to evaluate which clinical measures demonstrated the strongest association with a) Early MRI and b) Term MRI.

2. Method

2.1. Study design and participants

This prospective cohort study enrolled infants born < 31 weeks GA

at the specialist tertiary neonatal center at the Royal Brisbane and Women's Hospital between February 2013 and February 2016. Infants were eligible if their parents/carers lived within a 200 km radius of the hospital and were English speaking. Infants with known congenital or chromosomal abnormalities likely to affect their neurodevelopmental outcome were excluded. Informed parental consent was obtained for all participants. This study is nested within a broader study, and sample size calculations are detailed in the study protocol [14]. Ethical approval was obtained from the RBWH Human Research Ethics Committee (HREC/12/QRBW/245), The University of Queensland (2012001060) and the trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000280707).

2.2. MRI acquisition

Brain MRI was performed between 30 and 32 weeks PMA or when the infant was medically stable ('Early'), and again at 40–42 weeks PMA ('Term'). Infants were scanned utilizing an MR compatible incubator equipped with a dedicated neonatal head coil (LMT Lammers Medical Technology, Lübeck, Germany). MRI was performed during natural sleep without sedation, and with ear protection to attenuate noise. A 3 T MRI Siemens Tim Trio (Erlangen, Germany) scanner was used. Coronal, axial, and sagittal T2-weighted HASTE (TR/TE 2000/90 ms, flip angle 150°, field of view 200 × 160 mm, matrix 320 × 256, slice thickness 4 mm) were acquired as they are more resilient to motion artefacts. Axial T1 TSE (TR/TE 1490/90 ms, flip angle 150°, field of view 200 × 160 mm, matrix 256 × 180, slice thickness 2 mm) and an axial multi-echo T2 TSE (TR/TE1/TE2/TE3 10,580/27/122/189 ms, flip angle 150°, field of view 144 × 180 mm, matrix 204 × 256, slice thickness 2 mm) were acquired. Fig. 1 presents some example images at each time point for one infant with no structural brain abnormality, and a second infant with marked structural brain abnormalities.

2.3. MRI scoring

A standardized MRI scoring system was used to score all MRIs by an independent neurologist with training in radiology (SF) [11, 12]. The scorer was blinded to birth and medical history, cranial ultrasound results and clinical assessment findings. Four subscale scores were generated; WM, cortical GM, deep GM, and the cerebellum, the total of which produced a global score [11, 12]. Each subscale included qualitative assessment for evidence of injury; and then 6 regional measurements evaluated evidence of growth impairment. Regional measurements were corrected for PMA at MRI to ensure that any differences found represented growth impairment and not PMA at MRI [11]. The cerebral WM subscale scoring evaluates cystic degeneration, focal signal abnormalities, delayed myelination, thinning of the corpus callosum, dilated lateral ventricles, and reduction of WM volume (scoring range 0–15). Cortical GM assesses signal abnormality, delayed gyration, and dilated extracerebral CSF space (scoring range 0–8). Signal abnormality and volume reduction of the deep GM and cerebellum are evaluated and scored (scoring range 0–6 for each). Higher scores indicate a greater degree of brain abnormality. Both T1 and T2 images were evaluated during scoring. T1 hyperintensities and T2 hypointensities were both recorded and considered as signal abnormalities. Sagittal T2 weighted images were used to score the corpus callosum as it is clearly visualized as low signal intensity prior to myelination. Inter- and intra-rater reproducibility of the scale have been demonstrated [11, 12].

2.4. Clinical measures

Clinical assessments were completed within a week of MRI. Tools were combined to reduce handling of the infant. At Early assessment the GMs, HNNE, NNNS and the Premie-Neuro were conducted and assessments were modified with items inappropriate for administration removed. At TEA, all assessments were completed in full (GMs, NNNS, HNNE, the Test of Infant Motor Performance TIMP, and a visual assessment). Clinical assessors were blinded to birth history and brain imaging findings.

The GMs evaluates neuromotor performance through observation of spontaneous movements and good predictive validity has been reported. Sensitivity in the preterm period and at TEA is 75–100%, with higher sensitivity for an outcome of cerebral palsy (CP) than general developmental outcomes; specificity ranges from 40 to 48% [15, 16]. Scoring was performed by advanced GMs raters JG and BS, with BS additionally blinded to other clinical assessment findings. Cases of non-agreement were reviewed until consensus was reached and advice sought from a third rater (blinded to all clinical and imaging information except PMA at assessment) where necessary.

The HNNE is a neurological assessment evaluating posture, tone, reflexes, spontaneous movements, orientation and behaviour [17]. All items except 'placing' were administered at the Early assessment. When performed in the preterm period, reported sensitivity and specificity for predicting an outcome of CP are 57–86% and 45–83% respectively, increasing to 68–96% and 52–97% respectively when administered at TEA [18]. Inter-rater reliability between the clinical assessor (JG) and an observer (PC) for the HNNE total optimality score was tested with the intra-class correlation coefficient calculated to be 0.94 Early, and 0.99 at Term.

The NNNS is a neurobehavioral assessment that evaluates an infant's response to stimuli and handling, state regulation, motor performance and neurological status [19]. For administration at Early assessment, a number of items were removed which resulted in availability of summary scores in 10 of the 13 domains of the test. The NNNS at TEA has been shown to predict motor and cognitive outcomes at 18 months corrected age (CA), motor outcomes at 24 months CA and cognitive outcomes at 4.5 years [20–22]. Cerebral abnormalities correlated with poorer NNNS scores at TEA [5]. The test administrators (JG and KM) are accredited on the NNNS.

The Premie-Neuro (PN) is a neurological examination designed for use from 23 to 37 weeks PMA in preterm infants [23]. It could be scored from the combination of the other Early assessments with the addition of only a single item. The PN consists of 3 categories; neurological, movement and responsiveness, and has scoring based on expected performance at each week of PMA [23].

At TEA, a visual assessment developed by Ricci et al. was used to examine visual function by testing ocular motility, acuity and the ability to fix and follow [24]. Visual function demonstrates predictive validity for neurodevelopmental outcomes in preterm cohorts [25]. The TIMP was introduced as a standardized assessment of gross motor development. Construct validity enabling discrimination between infants at high and low risk of adverse motor outcomes has been demonstrated [26]. Sensitivity for prediction of school age motor outcomes has been reported at 50%, and specificity of 100% [27].

2.5. Statistical analysis

Associations between each MRI subscale and global score and each concurrent clinical measure were evaluated using linear regression. This was performed separately for the Early and Term MRI data and the respective concurrent clinical data. Univariable analysis was performed, followed by multivariable analysis adjusting for GA at birth, sex and a measure of social risk [14, 28]. Results are presented as regression coefficients with 95% confidence intervals and the level of significance was set at 5%. There was no imputation for missing data and appropriateness of regression models was assessed using standard diagnostic tests. Analysis was performed using the Stata statistical software package, version 14 (StataCorp, College Station, TX, USA).

Table 1
Characteristics of the study sample.

	Sample with Early MRI n = 119	Sample with additional Term MRI n = 102
Birth and maternal data	n (%), median [25th–75th centiles] or mean (SD), range	
Gestational age at birth (weeks-w, days-d)	28w3d [26w6d-29w3d], range 23w1d–30w6d	28w5d [26w5d-29w4d], range 23w6d–30w6d
Birth weight (g)	1093 (321), range 494–1886	1079 (329), range 494–1886
Birth head circumference (cm)	25.77 (2.36), n = 114	25.68 (2.43), n = 98
Males	73 (61%)	61 (60%)
Multiple births	36 (30%)	29 (28%)
Premature rupture of membranes	27 (23%)	21 (21%)
Caesarian section	84 (71%)	75 (74%)
Chorioamnionitis	18 (15%)	16 (16%)
Antenatal steroids	83 (70%)	72 (71%)
Magnesium sulfate	63 (64%), n = 98	56 (66%), n = 85
Higher social risk	58 (49%), n = 117	46 (45%)
Acquired medical factors	**From birth to Early MRI**	**From birth to Term MRI**
Patent ductus arteriosus	59 (50%)	54 (53%)
Any intraventricular hemorrhage	30 (25%)	26 (25%)
Intraventricular hemorrhage grade III or IV	8 (7%)	8 (8%)
Periventricular leukomalacia	4 (3%)	4 (4%)
Hydrocephalus	4[b] (3%)	4 (4%)
Seizures treated with anticonvulsant therapy	1 (1%)	1 (1%)
NEC diagnosed or suspected	5 (4%)	4 (4%)
Confirmed sepsis	5 (4%)	4 (4%)
Total parenteral nutrition (days)	11 [7–14], range 0–36	11 [9–15], range 0–36
Postnatal corticosteroids	20 (17%)	19 (19%)
Ventilation (days)	2 [0–10], range 0–50	2 [0–15], range 0–50
CPAP (days)	14 [7–25], range 0–47	26 [7–47], range 0–81
Oxygen therapy (hours)	37 [2–210], Range 0–1515, n = 105	63 [3–543], range 0–3912, n = 92
Bronchopulmonary dysplasia[a]		32 (31%)
PMA at MRI (weeks-w, days-d)	32w1d (1w3d), range 29w3d–35w2d	40w4d (1w), range 38w3d–42w5d
Weight at MRI (g)	1500 (340), range 858–2715	3019 (510), range 1900–4300
PMA at clinical assessment (weeks-w, days-d)	32w3d (1w3d), range 29w4d–36w3d	40w6d (1w1d), range 38w4d–44w1d

Key: PMA postmenstrual age; NEC necrotizing enterocolitis; CPAP continuous positive airway pressure.
[a] Defined as oxygen requirement at 36 weeks.
[b] All 4 infants with hydrocephalus also had IVH grade III/IV.

Table 2
Summary of MRI and clinical scores.

	Preterm sample with Early MRI n = 119		Preterm sample with additional Term MRI N = 102
MRI scores median [25th–75th centiles]			
WM ↓	3 [2–5]		2 [1–3]
Cortical GM ↓	0 [0–1]		0 [0–1]
Deep GM ↓	0 [0–1]		0 [0–1]
Cerebellum ↓	0 [0–0]		0 [0–1]
Global ↓	4 [3–7]		3 [1–5]
GMs n (%)			n = 97
Normal	39 (33%)		31 (32%)
Poor repertoire	72 (61%)		57 (59%)
Cramped synchronized	8 (7%)		9 (9%)
HNNE n, mean (SD)			
Posture & tone ↓	n = 111	3.80 (1.90)	6.90 (1.64)
Tone patterns ↓	n = 111	3.91 (0.78)	3.65 (0.84)
Reflexes ↓	n = 113	2.43 (0.99)	4.18 (1.13)
Spontaneous movements ↓	n = 110	1.04 (0.84)	2.29 (0.79)
Abnormal signs ↓	n = 119	2.03 (0.60)	2.55 (0.53)
Orientation & behavior ↓	n = 118	2.96 (1.49)	5.19 (1.26)
HNNE total score ↓	n = 109	16.17 (3.73)	24.75 (3.76)
NNNS mean (SD)			n = 100
Quality of movement ↓	3.43 (0.61)		4.38 (0.57)
Regulation ↓	n = 118	4.14 (0.61)	4.95 (0.63)
Nonoptimal reflexes ↓	6.96 (1.50)		6.61 (2.80)
Stress/abstinence ↓	0.22 (0.07)		0.18 (0.07)
Arousal ↑↓	3.11 (0.57)		4.26 (0.56)
Hypertonicity ↓	0.12 (0.39)		0.19 (0.60)
Hypotonicity ↓	1.54 (1.15)		0.50 (0.72)
Asymmetric reflexes ↓	0.92 (0.95)		0.75 (0.98)
Excitability ↓	2.94 (1.71)		3.67 (1.84)
Lethargy ↓	8.48 (1.96)		5 (2.19)
Premie-Neuro n, mean (SD)			
Factor 1 neurological ↑		31.63 (4.28)	
Factor 2 movement ↑	n = 118	34.20 (4.57)	
Factor 3 responsiveness ↑	n = 111	31.33 (3.54)	
Total score ↑	n = 111	97.42 (7.79)	
TIMP mean (SD)			
z-Score ↑			−0.60 (0.66)
Visual score n, mean (SD)			
Total score ↑			15.95 (6.13)

Key: WM white matter; GM gray matter; GMs General Movements Assessment; HNNE Hammersmith Neonatal Neurological Examination; NNNS NICU Neonatal Neurobehavioral Scale; TIMP Test of Infant Motor Performance; SD standard deviation; IQR Interquartile range; ↑ higher scores better; ↓ lower scores better.

3. Results

Of 323 eligible preterm infants, 146 consented to the current study and 119 infants had Early MRI and clinical assessments completed and were included in this analysis (7 became medically unstable, 1 died, 7 canceled due to MRI equipment failures, 7 MRI slots unavailable, 1 withdrew, 2 had an MRI-incompatible surgical clip and 2 unsuccessful MRIs due to movement artefact). Of these, 102/119 infants also had MRI and clinical data available at Term (10 failed to attend, 4 had clinical assessment but no MRI - 2 MRI's canceled due to technical equipment difficulties, 1 declined Term MRI, 1 hospitalized remotely at Term; 3 excluded as PMA at MRI > 42 weeks). Statistical analysis of the birth and maternal characteristics of the 17 infants without a term MRI compared with the 102 with a term MRI, revealed no significant differences except for social risk. A higher social risk has been demonstrated to be associated with poorer neurodevelopmental outcomes and an increased risk of cerebral palsy [28, 29], and so all multivariable analyses included social risk as a covariate. Demographic and perinatal details of the included cohort are summarized in Table 1; MRI and clinical assessment scores are presented in Table 2. A summary of MRI brain abnormality category scores for subscales and the overall global total are included as Supplementary Table 1.

3.1. Early MRI structure–function relationships

Results of multivariable regression analyses between Early MRI and concurrent clinical measures are presented in Table 3; results of univariable analyses are presented in Supplementary Table 2. Strongest associations were between cerebellar scores and HNNE Reflexes ($\beta = -0.17$; 95%CI = −0.30, −0.05; $p = .006$), NNNS Hypertonicity

Table 3
Multivariable regression results of relationships between Early MRI scores and concurrent clinical data (model covariates: GA at birth, sex, social risk). N = 118 as 1 participant had no social risk data available.

	Early MRI scores													
	WM			**Cortical GM**			**Deep GM**			**Cerebellum**			**Global**		
	ß	95%CI	*p*	ß	95%CI	*p*	ß	95%CI	*p*	ß	95%CI	*p*	ß	95%CI	*p*
GMs (n = 118)															
Normal	ref			ref			ref			ref			ref		
Poor repertoire	−0.17	−0.93, 0.58	.65	0.04	−0.28, 0.36	.82	0.12	−0.31, 0.56	.58	0.12	−0.14, 0.38	.35	0.11	−1.13, 1.35	.86
Cramped synchronized	0.37	−1.17, 1.92	.63	−0.10	−0.76, 0.55	.75	0.07	−0.81, 0.96	.87	1.10	0.57, 1.63	**< .001**	1.45	−1.09, 3.98	.26
HNNE															
Posture & tone n = 110	0.08	−0.12, 0.28	.44	−0.11	−0.19, −0.03	**< .01**	0.03	−0.08, 0.14	.54	−0.01	−0.08, 0.06	.76	−0.01	−0.34, 0.32	.95
Tone patterns n = 110	0.09	−0.37, 0.54	.71	0.21	0.02, 0.40	**.03**	0.10	−0.16, 0.35	.46	0.15	−0.01, 0.30	.06	0.53	−0.20, 1.27	.15
Reflexes n = 112	−0.08	−0.43, 0.27	.64	−0.05	−0.20, 0.09	.47	−0.06	−0.24, 0.12	.49	−0.17	−0.30, −0.05	**< .01**	−0.37	−0.91, 0.17	.17
Spontaneous movements n = 109	−0.27	−0.70, 0.17	.23	−0.05	−0.23, 0.14	.62	0.02	−0.19, 0.24	.84	−0.05	−0.21, 0.11	.51	−0.34	−1.01, 0.33	.32
Abnormal signs	0.03	−0.53, 0.59	.92	0.04	−0.20, 0.28	.72	0.21	−0.11, 0.52	.20	−0.03	−0.24, 0.17	.77	0.25	−0.67, 1.17	.60
Orientation & behavior n = 117	0.07	−0.15, 0.30	.51	0	−0.09, 0.10	.99	0.10	−0.03, 0.22	.13	0.01	−0.07, 0.09	.81	0.18	−0.19, 0.55	.33
HNNE total n = 108	0.01	−0.09, 0.10	.91	−0.03	−0.07, 0.02	.21	0.01	−0.04, 0.06	.73	−0.02	−0.05, 0.01	.29	−0.03	−0.18, 0.12	.70
NNNS															
Quality of movement	−0.16	−0.72, 0.40	.57	0.07	−0.17, 0.30	.59	0.18	−0.14, 0.50	.27	−0.08	−0.28, 0.13	.46	0.01	−0.92, 0.93	.99
Regulation n = 117	−0.31	−0.86, 0.25	.28	−0.29	−0.52, −0.06	**.01**	−0.03	−0.35, 0.30	.85	−0.16	−0.36, 0.05	.13	−0.78	−1.69, 0.12	.09
Non-optimal reflexes	0.01	−0.21, 0.24	.90	0.06	−0.04, 0.16	.21	−0.04	−0.17, 0.09	.57	0.06	−0.02, 0.14	.13	0.10	−0.27, 0.47	.60
Stress	−1.82	−6.77, 3.14	.47	1.02	−1.09, 3.12	.34	−3.11	−5.89,-0.32	**.03**	1.73	−0.07, 3.53	.06	−2.18	−10.36, 5.99	.60
Arousal	0.00	−0.59, 0.59	.99	0.08	−0.17, 0.33	.54	−0.07	−0.41, 0.27	.67	−0.16	−0.37, 0.06	.15	−0.15	−1.12, 0.83	.76
Hypertonicity	0.26	−0.62, 1.14	.56	−0.06	−0.43, 0.32	.76	0.15	−0.36, 0.65	.56	0.49	0.18, 0.80	**< .01**	0.84	−0.60, 2.28	.25
Hypotonicity	−0.08	−0.37, 0.22	.60	0.13	0.01, 0.25	**.04**	−0.06	−0.23, 0.11	.49	0.01	−0.10, 0.12	.84	0.00	−0.48, 0.49	.99
Asymmetric reflexes	0.05	−0.30, 0.41	.76	0.05	−0.10, 0.20	.53	0.18	−0.02, 0.38	.08	−0.03	−0.16, 0.10	.64	0.25	−0.33, 0.83	.40
Excitability	−0.04	−0.24, 0.15	.68	0.02	−0.06, 0.11	.60	−0.06	−0.17, 0.05	.27	0.01	−0.06, 0.08	.74	−0.07	−0.39, 0.25	.67
Lethargy	−0.02	−0.19, 0.16	.85	0.01	−0.06, 0.09	.77	−0.03	−0.13, 0.07	.55	−0.03	−0.09, 0.04	.40	−0.07	−0.36, 0.22	.65
Premie-Neuro															
Neurological	−0.04	−0.12, 0.04	.36	−0.01	−0.05, 0.02	.42	−0.01	−0.06, 0.04	.65	−0.06	−0.09, −0.04	**< .001**	−0.13	−0.265, 0.01	.06
Movement n = 117	0.04	−0.04, 0.11	.31	0.01	−0.02, 0.04	.61	0.03	−0.02, 0.07	.21	0.01	−0.02, 0.03	.63	0.08	−0.04, 0.20	.20
Responsiveness n = 109	−0.04	−0.14, 0.06	.46	0.01	−0.03, 0.06	.49	0.01	−0.05, 0.07	.72	−0.01	−0.04, 0.03	.63	−0.02	−0.19, 0.15	.80
Total n = 109	−0.01	−0.05, 0.04	.81	0	−0.02, 0.02,	.95	0.01	−0.01, 0.04	.40	−0.01	−0.03, 0	.06	−0.01	−0.08, 0.06	.80

Bold text refers to p values < 0.05.

Table 4
Multivariable regression results of relationships between Term MRI scores and concurrent clinical data (model covariates: GA at birth, sex, social risk).

	Term MRI Scores														
	WM			**Cortical GM**			**Deep GM**			**Cerebellum**			**Global**		
	ß	95%CI	*p*	ß	95%CI	*p*	ß	95%CI	*p*	ß	95%CI	*p*	ß	95%CI	*p*
GMs (n = 97)															
Normal	ref			ref			ref			ref			ref		
Poor repertoire	−0.39	−1.45, 0.67	.47	−0.18	−0.57, 0.21	.37	−0.09	−0.54, 0.37	.71	0.10	−0.24, 0.44	.57	−0.56	−2.23, 1.12	.51
Cramped synchronized	−0.76	−2.56, 1.04	.41	0.15	−0.52, 0.82	.66	−0.32	−1.09, 0.46	.42	−0.02	−0.60, 0.57	.95	−0.95	−3.79, 1.90	.51
HNNE															
Posture & tone	−0.01	−0.28, 0.26	.93	−0.01	−0.11, 0.09	.79	−0.09	−0.20, 0.03	.14	−0.11	−0.19, −0.02	**.02**	−0.22	−0.64, 0.21	.31
Tone patterns	0.26	−0.27, 0.79	.33	−0.20	−0.39, −0.01	**.04**	0.10	−0.12, 0.33	.37	−0.05	−0.22, 0.12	.53	0.11	−0.72, 0.94	.79
Reflexes	0.03	−0.37, 0.43	.88	−0.05	−0.20, 0.09	.48	0.05	−0.13, 0.22	.59	−0.01	−0.14, 0.12	.86	0.01	−0.61, 0.64	.97
Spontaneous movements	−0.09	−0.72, 0.53	.77	−0.13	−0.36, 0.10	.26	−0.17	−0.44, 0.09	.20	−0.06	−0.26, 0.14	.58	−0.45	−1.43, 0.52	.36
Abnormal signs	−0.96	−1.80, −0.11	**.03**	−0.13	−0.45, 0.19	.43	−0.28	−0.65, 0.09	.14	−0.19	−0.47, 0.09	.18	−1.55	−2.87, −0.23	**.02**
Orientation & behavior	−0.18	−0.55, 0.19	.33	−0.14	−0.27, −0.01	**.04**	−0.18	−0.34, −0.03	**.02**	−0.02	−0.14, 0.10	.73	−0.52	−1.10, 0.05	.07
HNNE total	−0.03	−0.15, 0.09	.64	−0.04	−0.09, 0	.07	−0.04	−0.09, 0.01	.13	−0.03	−0.07, 0.01	.09	−0.14	−0.34, 0.05	.14
NNNS n = 100															
Quality of movement	−0.19	−0.99, 0.62	.65	−0.09	−0.39, 0.21	.54	−0.19	−0.53, 0.16	.28	−0.07	−0.33, 0.19	.58	−0.54	−1.80, 0.72	.40
Regulation	−0.33	−1.07, 0.40	.37	−0.21	−0.48, 0.06	.12	−0.22	−0.54, 0.09	.17	−0.07	−0.30, 0.17	.59	−0.83	−1.98, 0.31	.15
Nonoptimal reflexes	0	−0.17, 0.16	.98	0.03	−0.04, 0.09	.39	0	−0.07, 0.08	.91	0.05	0, 0.10	.07	0.08	−0.18, 0.34	.56
Stress	−3.16	−9.25, 2.94	.31	0.13	−2.14, 2.40	.91	0.31	−2.34, 2.95	.82	0.36	−1.62, 2.33	.72	−2.37	−11.97, 7.24	.63
Arousal	0.43	−0.43, 1.30	.32	0.21	−0.11, 0.53	.20	−0.02	−0.40, 0.35	.90	−0.10	−0.38, 0.18	.48	0.52	−0.84, 1.87	.45
Hypertonicity	0.85	0.08, 1.63	**.03**	0.16	−0.14, 0.45	.30	0.22	−0.12, 0.56	.21	0.26	0.01, 0.52	**.04**	1.50	0.28, 2.70	**.02**
Hypotonicity	0.11	−0.51, 0.74	.71	0.19	−0.04, 0.42	.10	0.23	−0.04, 0.50	.09	0.21	0.01, 0.40	**.04**	0.74	−0.23, 1.72	.13
Asymmetric reflexes	−0.13	−0.60, 0.33	.57	−0.09	−0.26, 0.08	.31	0.10	−0.10, 0.31	.31	0	−0.15, 0.15	1	−0.12	−0.86, 0.62	.75
Excitability	0.11	−0.15, −0.36	.42	0.08	−0.02, 0.17	.12	0.02	−0.09, 0.13	.69	−0.01	−0.10, 0.07	.76	0.19	−0.21, 0.60	.35
Lethargy	0.14	−0.07, 0.35	.20	0	−0.08, 0.08	.94	0.03	−0.06, 0.12	.49	−0.01	−0.08, 0.06	.84	0.16	−0.17, 0.49	.34
TIMP															
z-Score	−1.04	−1.71, −0.38	< **.01**	−0.04	−0.30, 0.21	.74	−0.34	−0.63, −0.05	**.02**	−0.20	−0.42, 0.02	.08	−1.62	−2.66, −0.58	< **.01**
Visual assessment n = 100															
Total	0.01	−0.07, 0.08	.85	0.01	−0.02, 0.03	.71	−0.02	−0.05, 0.01	.28	0.02	−0.01, 0.04	.14	0.01	−0.11, 0.13	.83

Key: Term MRI, 40–42 weeks postmenstrual age (range 38–42 weeks); WM, white matter; GM, gray matter; GMs, General Movements Assessment; HNNE, Hammersmith Neonatal Neurological Examination; NNNS, NICU Neonatal Neurobehavioral Scale; TIMP, Test of Infant Motor Performance; CI, confidence interval; ref, reference level.

(β = 0.49; 95%CI = 0.18, 0.80; p = .002), Premie-Neuro Neurological subscale (β = −0.06; 95%CI = −0.09, −0.04; $p < .001$) and cramped-synchronized GMs (β = 1.10; 95%CI = 0.57, 1.63; $p < .001$). Cortical GM scores were associated with the HNNE subscales of Posture and Tone (Regression coefficient β = −0.11; 95% confidence interval CI = −0.19, −0.03; $p = .008$) and Tone Patterns and the NNNS subscales of Regulation and Hypotonicity. Deep GM was associated with Stress on the NNNS.

3.2. Term MRI structure–function relationships

Results of multivariable regression analyses between Term MRI and concurrent clinical measures are presented in Table 4; results of univariable analyses are presented in Supplementary Table 3. White matter was associated with the TIMP (β = −1.04; 95%CI = −1.71, −0.38; $p = .002$), HNNE Abnormal Signs and NNNS Hypertonicity. Cortical GM was associated with HNNE Tone patterns and Orientation and Behavior. Deep GM was associated with the TIMP and HNNE Orientation and Behavior. Cerebellar scores were associated with HNNE Posture and Tone and NNNS Hyper- and Hypotonicity. Global scores were associated with the TIMP (β = −1.62; 95%CI = −2.66, −0.58; $p = .003$), HNNE abnormal signs and NNNS Hypertonicity. No associations were found between any MRI subscale scores and the GMs or visual scores.

4. Discussion

This study is, to our knowledge, the first to present structure–-function relationships between Early structural MRI and concurrent clinical measures of motor, neurological and neurobehavioral function in infants born very preterm. Of the Early MRI subscale scores, the cerebellar scores were most strongly associated with clinical measures. Neurological and motor items were the predominant functional correlates found for the Early cerebellar scores. These findings contribute to a growing body of evidence of the vital role of the cerebellum in early neurodevelopment [30]. The fact that cerebellar abnormality is associated with neurological test items demonstrates the likely important role of the cerebellum in mediating neurological function during this critical period of development. To our knowledge, these are the first direct functional correlates of Early cerebellar structural abnormality. It is pertinent to interpret these findings with caution; further follow up is necessary to determine if the structure–function relationships presented here are maintained as infants get older, and whether they represent clinically important differences related to longer term outcomes.

Cerebellar scores in the scoring system employed here consist of evaluation of signal abnormality as an indicator of brain injury and

measurement of transcerebellar diameter as a measure of volume reduction [11, 12]. Between Early and Term the incidence of signal abnormalities decreased from 7% to 5%, severity of signal abnormalities decreased possibly due to the likely hemorrhagic nature of the signal abnormalities seen, and volume reduction increased from 17% to 26%.The rate of cerebellar development surpasses most other structures between 24 and 40 weeks PMA and it is of interest that cerebellar volume reduction was already present at Early MRI in 17% of our cohort [31]. This rapid growth and maturation may possibly be a reason why Early cerebellar scores demonstrate a prominence of findings with clinical measures compared with the other Early MRI subscales and the global total. Injury and especially secondary growth impairment becomes more evident on neuroimaging over time, and this is likely the reason that a more distributed pattern of clinical findings with the Term MRI scores are seen.

In the absence of other published work with clinical correlates of early cerebellar findings, the data here suggest that Early neurological findings are indicative of early cerebellar injury and growth impairment. Studies of Early MRI have found that cerebellar hemorrhage alone is not associated with later adverse motor outcomes [9, 32, 33]. The Early MRI scoring system employed in the current study which combines cerebellar injury with evidence of volume reduction, previously also found Early cerebellar scores to be associated with motor outcomes at 12 months CA on the Neurosensory Motor Developmental Assessment [11, 34].

The lack of associations between Early WM scores and clinical measures is of particular interest. In contrast, the majority of Term MRI studies have found WM abnormalities to correlate with concurrent clinical presentations and predict later neurodevelopmental outcomes [5, 6, 35]. The present study confirms this with significant associations found between Term WM scores and motor function on the TIMP, as well as neurological features on the HNNE (Abnormal Signs) and NNNS (Hypertonicity). As research is moving from qualitative evaluation of structural MRI to more advanced diffusion and volumetric imaging, the focus has remained on WM injury, development and maturation. The data presented here supports inclusion of the cerebellum and deep gray matter in Early MRI studies [30].

Cortical GM scores at Early MRI demonstrate associations with the neurological elements of posture, tone and hypotonicity and the neurobehavioral feature of regulation. It must be noted that this subscale has the lowest reliability of the MRI subscales and so these relationships should be interpreted with caution [11].

At Term MRI, structure–function relationships were found for all MRI subscale scores. Of the subscales, WM and global scores demonstrated the strongest associations with clinical measures, predominantly with the TIMP which is a motor assessment tool. Term WM abnormality has been demonstrated to be significantly associated with motor performance on the TIMP at 10–15 weeks CA [36]. We have demonstrated that these associations are present concurrently at TEA. Term MRI cerebellar scores were associated with neurological test items (HNNE Posture and Tone; NNNS Hyper- and Hypotonicity).

The TIMP demonstrates both concurrent associations with MRI abnormalities (in the current study) and associations when performed 3–4 months after MRI [36]. The GMs can be conducted at both these time points, however GMs assessment at TEA is in the 'writhing period' while assessment at 3 months CA is in the 'fidgety period' [15]. The evidence to date reports very strong predictive and discriminative validity for GMs assessment in the fidgety period, but less so for the writhing period [16, 37]. This perhaps explains the lack of associations found in our study as GMs assessment was in the writhing, and not the fidgety period. One study of writhing GMs at 1 month CA did find associations with TEA WM abnormality scores [8]. As writhing movements evolve over time, and later assessment is more strongly related to outcomes, this could explain why they found significant associations and we did not. A study using the Kidokoro scoring method for MRI [12] which is more similar to our scoring method, reported that abnormal GMs were associated with the global MRI score and the subscale score of cortical GM [38]. This study grouped poor repertoire, cramped synchronized and chaotic GMs together as 'abnormal' GMs which may explain the differences in their findings compared with ours. They also had a higher incidence of cortical GM abnormalities than in the present cohort.

The secondary aim of this study was to evaluate which of the clinical measures demonstrated the strongest relationships with Early and Term MRI scores to aid selection of assessment measures in clinical practice. This study found that at the Early time point, measures of neurological function were most indicative of structural brain abnormality, whereas at Term, motor function on the TIMP was most indicative of structural brain abnormality. At Early MRI, no single clinical tool showed substantial associations with MRI scores. The Premie-Neuro neurological subscale did exhibit strong associations with cerebellar scores ($p < .001$), which may be of benefit clinically as it is a simple 8 item package that requires minimal infant handling. Cramped-synchronized GMs also demonstrated strong associations with cerebellar scores ($p < .001$). At Term, the TIMP demonstrated the strongest associations of the tools with MRI. The TIMP is readily available in clinical settings, requires minimal training for those already experienced in early infant assessment and handling, and is less time-intensive and more cost-effective than the NNNS or GMs. Follow up is required to determine if use of these clinical measures afford meaningful contributions to clinical practice.

A large number of statistical comparisons were undertaken in this study. All were based on robust hypotheses that clinical presentations of motor, neurological or neurobehavioral performance would be correlated with structural brain abnormalities measured by this comprehensive structural MRI scoring system. Analyses are exploratory in an area where very little published data exist, and so no correction for multiple comparisons was performed to ensure that all significant associations were identified. While it is appropriate to be cautious about these findings, biological plausibility is suggested by the consistency with which similar items from different clinical measures were found to demonstrate significant associations with the MRI scores, for example neurological items from different clinical tests with both Early and Term MRI cerebellar scores. We have been careful to emphasize only the strongest associations throughout the results and discussion of this paper ($p < .01$). Ultimately, replication of the study is required to determine if these findings are reproducible in other cohorts of preterm infants.

Strengths of the current study include the large sample of Early MRI data coupled with concurrent clinical data of infants born very preterm, in a contemporaneous study cohort with blinded clinical and MRI assessment. Limitations of the study include the relatively wide age range at Early MRI. The study protocol set the window for MRI at 30–32 weeks PMA, with sicker and more fragile infants undergoing MRI once they became medically stable and up to a maximum PMA of 36 weeks. This ensured that sicker infants were included in the sample, which was necessary for our results to be generalizable to other populations of very preterm infants. The MRI scoring system has been rigorously designed to account for brain changes in size and volume that are the result of variable PMA at MRI, thereby minimizing potential scoring bias due to PMA at MRI [11]. Another potential limitation is our use of an established scoring system for structural images rather than more complex volumetric or diffusion based systems. This is a clinically accessible MRI scoring system to examine associations that may be present with clinical bedside measures and is an important first step in understanding Early MRI data. It is less resource-intensive and more readily clinically available than advanced MRI measures. It also enables classification of all MRI's in a cohort whereas advanced diffusion imaging frequently excludes participant MRI's due to movement artefact, or the presence of structural brain lesions that interfere with or preclude automated quantitative analysis. Further evidence of clinical utility is required of both the early MRI scoring system employed in this

study, and the concurrent clinical measures, to determine the extent to which these findings may contribute to clinical patient care. Our MRI acquisition techniques used a slice thickness of 4 mm which may be a potential limitation, as some subtle abnormalities may have been missed. As this is a qualitative scoring system, we anticipate that the majority of injuries were detected and scored appropriately. Gradient echo techniques have been shown to be superior to conventional techniques in detection of cerebellar abnormalities. The T1 gradient echo sequence is very disruptive to the infant, often waking them up, although we did try to acquire the sequence at the end of the scan. The scorer (SF), in each case, selected the most appropriate image (whether T1 or T2) that best showed the underlying pathology for scoring. We recognize that an important future step is to report the longer term outcomes of this cohort. Cognitive and motor outcomes to 12 months CA for a subset of the present cohort are available and longer term follow up is underway [11]. Future work will investigate the relationship between volumetric, cortical thickness and cortical folding measures and the clinical assessments.

5. Conclusion

Structure–function relationships exist between structural MRI and concurrent clinical measures of motor, neurological and neurobehavioral function both Early and at Term in infants born preterm. At Early MRI, cerebellar subscale scores have the strongest associations with clinical measures. Early MRI cerebellar scores relate to neurological and motor rather than neurobehavioral items. At Term MRI, the strongest associations were with motor performance on the TIMP. White matter abnormality scores are related to motor and neurological performance at Term but not at Early MRI. These findings are an important contribution to the understanding of very early brain structure–function relationships in preterm infants.

Key: Early MRI, 30–32 weeks postmenstrual age (range 29–35 weeks); WM, white matter; GM, gray matter; GMs, General Movements Assessment; HNNE, Hammersmith Neonatal Neurological Examination; NNNS, NICU Neonatal Neurobehavioral Scale; CI, confidence interval; ref, reference level.

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Clinical trial registration

Australian New Zealand Clinical Trials Registry; Trial Registration Number: ACTRN12613000280707; web address of trial: http://www.ANZCTR.org.au/ACTRN12613000280707.aspx

Conflict of interest

The authors declare they have no conflicts of interest to disclose.

Appendix A. Supplementary tables

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2017.12.014.

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