



## Early general movements and brain magnetic resonance imaging at term-equivalent age in infants born <30 weeks' gestation

Joy E. Olsen<sup>a,b,\*</sup>, Nisha C. Brown<sup>a</sup>, Abbey L. Eeles<sup>a</sup>, Christa Einspieler<sup>c</sup>, Katherine J. Lee<sup>a,d</sup>,  
Deanne K. Thompson<sup>a,d</sup>, Peter J. Anderson<sup>a,d</sup>, Jeanie L.Y. Cheong<sup>a,b,e</sup>, Lex W. Doyle<sup>a,b,e</sup>, Alicia J. Spittle<sup>a,b,f</sup>

<sup>a</sup> Victorian Infant Brain Studies, Clinical Sciences, Murdoch Childrens Research Institute, The Royal Children's Hospital, Flemington Rd, Parkville, Victoria 3052, Australia

<sup>b</sup> Newborn Research, The Royal Women's Hospital, 20 Flemington Rd, Parkville, Victoria 3052, Australia

<sup>c</sup> Institute of Physiology, Center for Physiological Medicine, Medical University of Graz, Universitätsstrasse 15, 8010 Graz, Austria

<sup>d</sup> Department of Paediatrics, University of Melbourne, The Royal Children's Hospital, Flemington Rd, Parkville, Victoria 3052, Australia

<sup>e</sup> Department of Obstetrics and Gynaecology, University of Melbourne, The Royal Women's Hospital, 20 Flemington Rd, Parkville, Victoria 3052, Australia

<sup>f</sup> Physiotherapy Department, University of Melbourne, 7th Floor, Alan Gilbert Building, Grattan St, Parkville, Victoria 3052, Australia

### ARTICLE INFO

#### Article history:

Received 11 March 2016

Received in revised form 25 May 2016

Accepted 27 June 2016

#### Keywords:

General movements

Magnetic resonance imaging

Preterm infant

Neurodevelopmental assessment

### ABSTRACT

**Background:** Neurodevelopmental assessments and brain magnetic resonance imaging (MRI) at term-equivalent age (TEA) predict developmental outcomes in preterm infants. However, the relationship between neurodevelopment prior to term and cerebral structure is currently unknown.

**Aims:** To examine the relationships between General Movements (GMs) assessed from birth to TEA and brain MRI at TEA in infants born <30 weeks' gestation.

**Study design:** Prospective cohort study. GMs (categorised as 'normal' or 'abnormal') were recorded weekly from birth to 32 weeks, and at 34 and 36 weeks' postmenstrual age. At TEA, GMs were assessed concurrently with brain MRI (using a validated scoring system).

**Subjects:** 149 infants born <30 weeks' gestation were recruited from a tertiary hospital.

**Results:** 103 infants had MRI at TEA and GMs recorded. Abnormal GMs prior to term were associated with cortical grey matter abnormality ( $p < 0.03$ ), deep grey matter abnormality ( $p = 0.02$ ) and increased interhemispheric distance ( $p < 0.02$ ). Abnormal GMs at TEA ( $n = 55/90$ ) were associated with more global brain abnormality ( $p < 0.01$ ) and cortical grey matter abnormality ( $p = 0.01$ ), and decreased transcerebellar diameter ( $p = 0.04$ ) on concurrent brain MRI.

**Conclusions:** Abnormal GMs both prior to term and at TEA were associated with more marked brain abnormality, and smaller brains at TEA. Abnormal GMs are an early marker of brain abnormalities in very preterm infants.

© 2016 Elsevier Ireland Ltd. All rights reserved.

### 1. Introduction

The high prevalence of neurodevelopmental impairment in infants born very preterm (<32 weeks' gestation) is a challenging issue for clinicians working in neonatal care. Neurodevelopmental assessment in the neonatal period in conjunction with neuroimaging affords valuable information for counselling parents and targeting infants for early intervention [1]. There is increasing recognition that preterm birth may disrupt the growth and maturational process of neural

development and organisation [2]. As development occurs at variable rates within different cerebral regions and structures according to gestational age, preterm birth can result in diverse cerebral alterations depending on the region of insult, and the timing of disruption to maturational processes, particularly myelination [3]. Abnormal brain development can occur secondary to injury, or as a result of disruption of neuromaturational processes following preterm birth [4].

Cerebral magnetic resonance imaging (MRI) conducted at term-equivalent age (TEA) is a sensitive tool that can provide important information about preterm infant brain injury and structure, which is associated with long-term neurodevelopment, including motor and cognitive outcomes [5,6]. However, it is crucial to note, that MRI alone cannot predict the functional outcome for individual infants with 100% accuracy [7,8]. Neurodevelopmental assessments have an important role as they can identify infants at risk for later neurological impairment, and

Abbreviations: GMs, general movements; GMA, general movements assessment; MRI, magnetic resonance imaging; PMA, postmenstrual age; TEA, term-equivalent age.

\* Corresponding author at: 7th Floor, Newborn Research, The Royal Women's Hospital, 20 Flemington Road, Parkville, Victoria, 3052, Australia.

E-mail address: [joy.olsen@thewomens.org.au](mailto:joy.olsen@thewomens.org.au) (J.E. Olsen).

<http://dx.doi.org/10.1016/j.earlhumdev.2016.06.009>

0378-3782/© 2016 Elsevier Ireland Ltd. All rights reserved.

may enhance the prognostic utility of MRI if used in combination [9–11]. Prechtl's qualitative assessment of General Movements (GMA) [12] is an observational assessment of the infant's spontaneous movements with good predictive validity for neurodevelopmental outcomes, including cerebral palsy, motor impairment and cognitive outcomes [7,13,14]. Previous reports indicate that cerebral MRI and the GMA are reliable as complementary assessments to predict later neurodevelopmental outcome in very preterm infants [9–11]. Abnormal general movements (GMs) at one and three months' corrected age are associated with white matter abnormalities on MRI at TEA [15,16]; and combined GMA and white matter abnormality predict motor outcomes at 12 months' corrected age, with abnormal GMs and moderate-severe white matter abnormality demonstrating 100% sensitivity for predicting cerebral palsy in our previous study of very preterm infants [9].

While there is evidence of associations between brain structure [17] and injury on MRI at TEA and GMs assessed post-term [15,16,18,19], the relationships between GMs assessed prior to term and cerebral MRI remains largely unexplored, particularly in the early preterm phase. This is important information for two reasons. Firstly, to understand the relationships between cerebral structure, particularly size and maturation, and early neurodevelopment in very preterm infants, for whom critical brain development occurs in the neonatal intensive care environment. Secondly, to help clinicians identify optimal times for GMA so that infants with adverse neurodevelopment can be targeted for early intervention, including within the neonatal intensive care environment [20–22], and to ensure timely referrals and access to community-based early intervention services upon discharge from hospital. Only two studies have included GMs assessed prior to term and cerebral MRI [11,23] and neither study examined the relationship of GMs assessed prior to term, or at TEA, and MRI. The largest study [11] reported on the predictive accuracy for neurodevelopmental outcome of concurrent GMs and MRI assessed close to term at 36 weeks' postmenstrual age (PMA); MRI scoring included three measures of brain injury, but not brain size or maturation. MRI scoring systems that only measure brain injury may not be sensitive given that the prevalence of brain injury is low [6].

The aim of this study was to examine the relationships between GMs assessed from birth to TEA and brain MRI at TEA in infants born <30 weeks' gestation. It was hypothesised that abnormal GMs assessed soon after birth and at subsequent assessments would be associated with MRI-defined cerebral abnormalities at TEA.

## 2. Methods

### 2.1. Participants

Infants born <30 weeks' gestation were recruited from the Royal Women's Hospital, Melbourne, Australia, between January 2011 and December 2013 as part of a larger prospective longitudinal cohort study [24]. Infants with congenital abnormalities known to affect neurodevelopment, non-English speaking parents (as there was no funding for interpreters), and those unlikely to survive in the early neonatal period as assessed by clinical staff, were excluded from the study. Infants were enrolled within the first two postnatal weeks, once written parental consent was obtained. The study was approved by the Human Research Ethics Committee at the Royal Women's Hospital and the Royal Children's Hospital, Melbourne. Research nurses collected perinatal data from the medical histories, including gestational age at birth, birth weight, sex, multiple birth status, postnatal infections and oxygen requirements.

### 2.2. Procedure for general movements

Serial GMs were videoed weekly from enrolment until 32 weeks' PMA, and then fortnightly at 34 and 36 weeks' PMA, while infants

were inpatients at the Royal Women's Hospital. If infants were discharged home or transferred to another hospital prior to TEA, GMs were not recorded again until the time of the MRI as staff were unavailable to assess infants at other hospitals. For all assessments, infants were videoed wearing minimal clothing, in an active behavioural state, and assessors aimed to video at least three GMs. Recordings were between 5 and 20 min prior to term, and between 5 and 10 min at TEA. At TEA, GMs were videoed as an outpatient at the Royal Children's Hospital, Melbourne, at the time of the MRI scan, according to the larger study protocol [24].

### 2.3. General movements scoring

GMs were scored from video recordings according to Prechtl's GMA [12]. GMs were categorised as normal or abnormal, with consideration given to age-specific characteristics. GMs were classified as normal if they were fluent, and variable in speed, amplitude and force, and demonstrated a variety of movement patterns including flexion, extension and rotation. GMs were classified as abnormal if they were poor repertoire (monotonous, lacking in variety and complexity), cramped synchronised (stop-start GMs, lacking fluency and rotation) or chaotic (abrupt GMs with movements in all directions that lack fluency). GMs were classified unscorable if the infant was crying or hypokinetic. All GMs were scored by assessors with advanced GMA certification who were unaware of the infant's clinical history. Inter-rater and intra-rater reliability for GMs scoring in this cohort have previously been reported, with Cohen's kappa values of 0.75 and 0.94, respectively, indicating good to excellent agreement beyond that expected by chance [25].

### 2.4. Procedure for MRI

Brain MRI was conducted at the Royal Children's Hospital, Melbourne, between 38 and 44 weeks' PMA. Infants who were still inpatients during this period did not have a MRI due to inability to transport the infants to another hospital for the MRI scan. For the few participants who did not have a research MRI scan but had a brain MRI at TEA for clinical indications, the scans were obtained and scored according to the study protocol. Additionally, the MRI scan was an optional component of the larger research study [24], according to parent decision, and therefore some infants enrolled in the larger study had GMs assessed but no MRI. Infants were scanned during natural sleep, without sedation or anaesthesia, using the 3 Tesla Siemens Magnetom Tim Trio imager, with a 12-channel circular polarised volume extremity coil. Prior to the scan, infants were fed and swaddled, and earmuffs fitted to reduce noise. Infants were positioned in a vacuum fixation beanbag (MedVac; CFI solutions, Fenton, Mich) for stabilisation. Infants were closely monitored using pulse oximetry throughout the procedure.

Structural images were assessed using a standardised scoring system that has been validated with very preterm infants [4], using modified cut-off measurements based on normative data from local healthy term infants [26]. Scoring incorporated assessment of brain injury (including cysts and focal signal abnormalities), maturation (including gyral maturation and myelination of the posterior limb of the internal capsule) and size (two dimensional measurements including brain biparietal diameter, corpus callosum thickness and deep grey matter surface area). Four regional abnormality scores were calculated based on assessment of injury, growth and maturation: cerebral white matter abnormality, cortical grey matter abnormality, deep grey matter abnormality and cerebellar abnormality, and graded as none, mild, moderate or severe. The sum of the regional abnormality scores was used to calculate a global brain abnormality score that was categorised as normal (score 0–3), mild (score 4–7), moderate (score 8–11) or severe (score  $\geq 12$ ). In addition to the total scores, three regional measurements were selected a priori; brain biparietal diameter, as a measure

of total brain size [27], interhemispheric distance, as a measure of extracerebral space [2], and transcerebellar diameter due to previous reports of associations with GMs [17]. All scans were scored independently by experienced assessors (neonatologists and/or radiologists) who were unaware of the infant's perinatal history. Inter-rater and intra-rater reliability for this scoring system has previously been published, with good to excellent reliability reported for most of the measures [4,26].

2.5. Statistical analysis

Data were analysed using Stata 14. GMs were collapsed into four main timepoints according to when they were recorded: <32 weeks, 32–33 weeks, 34–36 weeks, and 38–44 weeks (TEA). The GMs recorded at the oldest PMA during each preterm timepoint were used for infants who had multiple assessments, given the influence of PMA on GMs quality [25]. Linear regression models were used to explore whether GMs at each timepoint (categorised as normal and abnormal) were associated with MRI findings at TEA, fitted using generalised estimating equations with robust (sandwich) estimation of standard errors to allow for multiple births given the high rate of multiple births in the very preterm population, both at the study site and in the larger study cohort [1,25]. Outcomes of interest were: regional abnormality scores (e.g. cerebral white matter abnormality, cortical grey matter abnormality), the global abnormality score, and three measures of brain growth (interhemispheric distance, brain biparietal diameter and transcerebellar diameter). A separate model was fitted for each GMs timepoint and all analyses were adjusted for age at MRI and sex, as these variables affect brain size and maturation [26].

3. Results

3.1. Participants

One hundred and forty nine infants born <30 weeks' gestation were recruited from the Royal Women's Hospital in Melbourne between January 2011 and Dec. 2013 (Fig. 1). Six infants died prior to term age. Of the remaining 143 infants, there were 32 infants who did not have a MRI, with the reasons outlined in Fig. 1. As the MRI scan was an optional component of the larger study, there were 14 infants who did not have a MRI due to parent preference and one scan was not usable due to movement artefacts. Of the 110 infants who had MRI scans suitable for assessment there were six infants scanned at >44 weeks' PMA excluded from

the analysis, and one infant did not have any GMs recorded, leaving a total of 103 infants with both GMs and MRI assessment. At TEA, 90 infants had both GMs and MRI assessed. Sample characteristics are presented in Table 1.

3.2. General movements

The majority of GMs were abnormal at all ages; 83% (n = 75/90) for those <32 weeks, 76% (n = 65/86) for those 32–33 weeks, 88% (n = 51/58) for those 34–36 weeks, and 61% (n = 55/90) at 38–44 weeks.

3.3. MRI findings

The majority of infants had global and regional abnormality categorised as normal or mild, with a higher proportion categorised as moderate for cortical grey matter and cerebellar abnormalities (Table 2). There were no infants with severe deep grey matter or cerebellar abnormality. The regional measurements that were assessed are summarised in Table 2.

3.4. Associations between general movements and MRI at term-equivalent age

The relationships between abnormal GMs assessed at different PMA and MRI are presented in Fig. 2. Prior to term, abnormal GMs assessed at <32 weeks and 32–33 weeks were associated with higher cortical grey matter abnormality, and at 34–36 weeks with higher deep grey matter abnormality scores. Abnormal GMs assessed at TEA were associated with higher global abnormality and cortical grey matter abnormality scores on concurrent MRI. There was little evidence for associations between abnormal GMs assessed at any time and cerebral white matter abnormality scores.

Abnormal GMs assessed at all timepoints were associated with larger interhemispheric distance on MRI at TEA. There was little evidence of associations between abnormal GMs assessed at any time and brain biparietal diameter. Abnormal GMs at TEA were associated with a smaller transcerebellar diameter, but not with GMs assessed prior to term.

4. Discussion

This study demonstrated that abnormal GMs in very preterm infants in both the preterm and term periods were associated with more brain

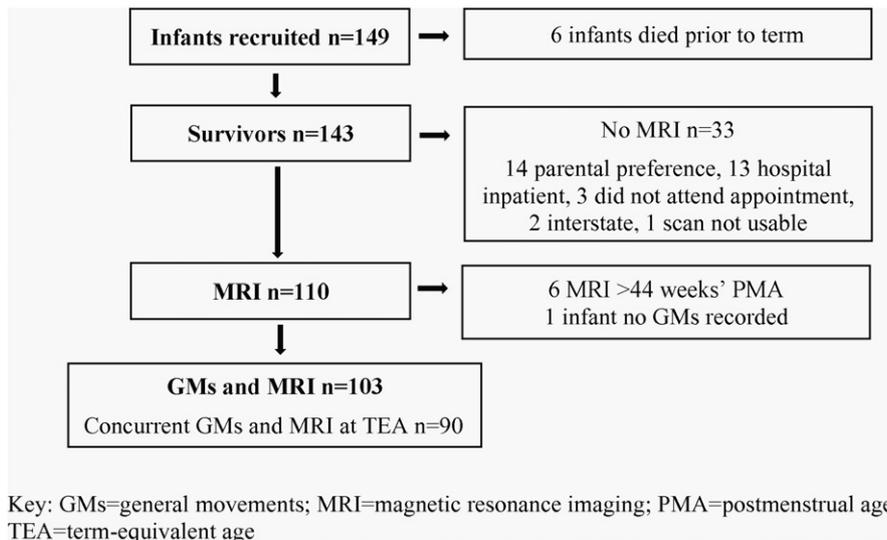


Fig. 1. Flowchart of GMs and MRI assessments in study. Key: GMs = general movements; MRI = magnetic resonance imaging; PMA = postmenstrual age; TEA = term-equivalent age.

**Table 1**  
Characteristics of the study sample with data for both GMs and MRI.

Characteristics (n = 103)	Mean (SD)/number (%)
Gestational age (weeks)-mean (SD)	28.0 (1.3)
Birth weight (g)-mean (SD)	1080 (247)
Birth weight z score-mean (SD)	-0.31 (1.01)
Male-n (%)	50 (49)
Multiple births-n (%)	46 (45)
Bronchopulmonary dysplasia-n (%)	24 (23)
NEC (proven) -n (%)	3 (3)
Sepsis (proven) -n (%)	13 (13)
IVH Grade III/IV -n (%)	3 (3)
Cystic periventricular leukomalacia -n (%)	1 (0.1) <sup>b</sup>
Surgery prior to hospital discharge -n (%)	4 (4)

Key: GMs = general movements; MRI = magnetic resonance imaging; SD = standard deviation; IVH = intraventricular haemorrhage; NEC = necrotising enterocolitis.

<sup>a</sup> Bronchopulmonary dysplasia = oxygen dependence at 36 weeks' postmenstrual age.

<sup>b</sup> Infant also had IVH grade III/IV.

abnormality and smaller brains on MRI at TEA. Our study provides further validation of the GMA as a measure of neurological function and that GMs quality reflects central nervous system integrity in very preterm infants. Unlike other studies that have assessed GMs prior to TEA [11,23], the MRI analysis in the current study included measures of brain size and maturation, as well as injury, in conjunction with serial GMA from soon after birth until TEA.

Our findings build on previous research that identified associations between brain size and GMs at one and three months' corrected age in very preterm infants [17]. Importantly, the current study demonstrated that regional alterations in brain size (i.e. increased interhemispheric distance) are associated with abnormal GMs assessed prior to term, even during the very preterm period (<32 weeks' PMA). A key finding was that early GMs predicted cortical grey matter abnormality at TEA, and a larger interhemispheric distance on MRI at TEA. Considering the cortical grey matter score comprises the measure of interhemispheric distance (as well as signal abnormality and gyral maturation measures), the association with cortical grey matter was likely primarily accounted for by the increased interhemispheric distance. Interhemispheric distance correlates with cerebrospinal fluid volumes, and a larger interhemispheric distance is thought to reflect a brain that has not grown to fill the extracerebral space [4]. Larger interhemispheric distance has been documented for infants born very preterm [4] as well as moderate and late preterm infants at TEA compared with healthy term infants [26], however, there is limited information on the implications of this measure for later motor outcome. An earlier brain metrics study did not find any associations with interhemispheric distance measurements and GMs assessed post-term [17]. Kidokoro and colleagues [2] examined brain injury and two measures of brain size in 325 very preterm

infants: biparietal width and interhemispheric distance. Only 7% (n = 22) of infants had smaller brain size on both measures, and increased interhemispheric distance was independently associated with higher grade brain injury and cognitive impairment at two years. Findings in the current study suggest that growth failure, as evidenced by a larger interhemispheric distance at TEA, may manifest as abnormal neurodevelopment (i.e. abnormal GMs), even prior to term, and suggest a link between preterm brain growth and GMs' quality.

Abnormal GMs were associated with higher cortical grey matter abnormality scores at all timepoints, except for 34–36 weeks' PMA, when they were associated with higher deep grey matter abnormality scores. This finding may reflect a systematic difference in the infants assessed during the late preterm period, when there were fewer GMA. This was due to stable infants being transferred to lower level hospitals (often by 32 weeks' PMA), while infants remaining at the Royal Women's Hospital were more likely to be sicker infants requiring respiratory support, with potentially different brain structure and neurodevelopment. Previous studies assessing MRI and GMs in very preterm infants did not identify any associations between abnormal GMs assessed post-term and grey matter abnormality; [10,15,16] these findings may be due to differences in the MRI scoring between studies, and timing of the GMA. In very preterm infants, decreased gyral maturation has been associated with tone and movement abnormalities at TEA, as well as lower total scores on the Hammersmith Neonatal Neurological Examination [1], and reductions in cortical and deep grey matter volumes with moderate-severe disability at one year corrected age [28].

In contrast to other studies of GMs and MRI in very preterm infants [9,10,16], we did not find any associations between cerebral white matter abnormality and abnormal GMs. However, the incidence of infants with moderate-severe white matter abnormality was relatively low in the current cohort (6%, n = 6) compared with the 10–12% reported in previous studies [9,10] and the GMA was conducted at later timepoints than the current study [9,10,16].

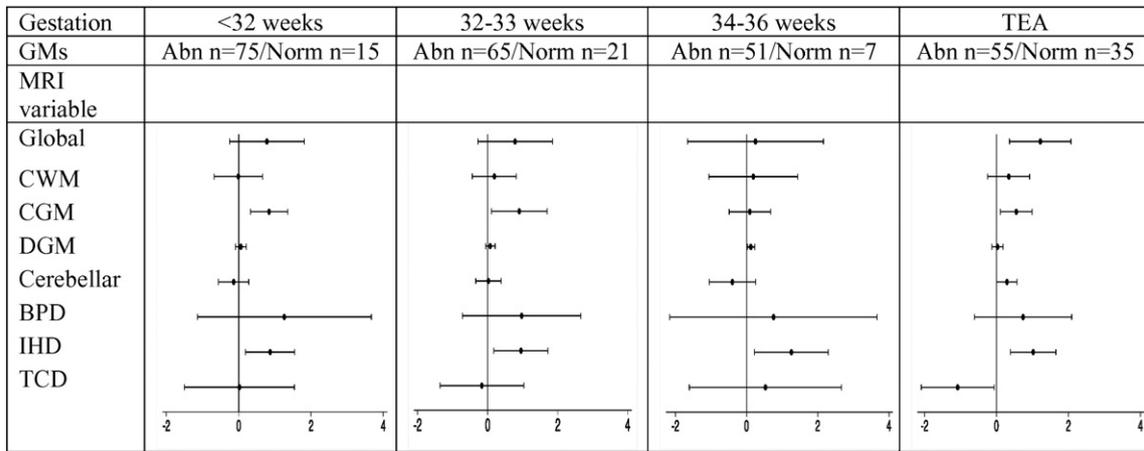
There is increasing recognition of the role of the cerebellum in neurodevelopmental outcomes for very preterm children [29–31], and associations of abnormal GMs with smaller transcerebellar diameter identified in the current study provide further evidence that cerebellar development is related to the quality of GMs in very preterm infants, even as early as TEA. These findings are in keeping with a previous study [17] which demonstrated that abnormal GMs at one and three months' corrected age were associated with reduced transcerebellar diameter at TEA, and support the hypothesis that the cerebellum plays an important role in early motor development. Smaller transcerebellar diameter on MRI at TEA correlates with motor and cognitive delay, and neurological disability at two years' corrected age for very preterm infants [29,30]; abnormal GMs assessed at TEA may therefore provide useful information for clinicians regarding infant's early neurodevelopment.

**Table 2**  
Total abnormality scores, grading of abnormality scores, and brain measurements on MRI at term-equivalent age.

MRI variable	n	Scores		Grading			
		Median	IQR	None n (%)	Mild n (%)	Mod n (%)	Severe n (%)
Global	102 <sup>a</sup>	4	3–5	33 (32)	63 (62)	5 (5)	1 (1)
Cerebral white matter	102 <sup>a</sup>	2	1–3	60 (59)	36 (35)	5 (5)	1 (1)
Cortical grey matter	103	1	1–2	24 (23)	47 (46)	12 (12)	20 (19)
Deep grey matter	103	0	0–0	92 (89)	10 (10)	1 (1)	0 (0)
Cerebellar	103	0	0–1	64 (62)	24 (23)	15 (15)	0 (0)
Brain measurements (mm)	n	Mean	SD				
Brain biparietal diameter	103	81.8	4.4				
Interhemispheric distance	103	3.3	1.7				
Transcerebellar diameter	103	55.0	3.1				

Key: IQR = interquartile range; mm = millimetres; SD = standard deviation.

<sup>a</sup> One infant with missing cerebral white matter abnormality and global abnormality scores.



Key: •=Regression coefficient |—|=95% Confidence interval; TEA=term-equivalent age; GMs=General Movements; Abn=abnormal; Norm=normal; Global=Global abnormality; CWM=cerebral white matter abnormality; CGM=cortical grey matter abnormality; DGM=deep grey matter abnormality; Cerebellar=cerebellar abnormality; BPD=brain biparietal diameter; IHD=interhemispheric distance; TCD=transcerebellar diameter

**Fig. 2.** Associations between abnormal GMs assessed at different postmenstrual ages and MRI findings at TEA. Key: • = regression coefficient |—| = 95% confidence interval; TEA = term-equivalent age; GMs = general movements; Abn = abnormal; Norm = normal; Global = global abnormality; CWM = cerebral white matter abnormality; CGM = cortical grey matter abnormality; DGM = deep grey matter abnormality; Cerebellar = cerebellar abnormality; BPD = brain biparietal diameter; IHD = interhemispheric distance; TCD = transcerebellar diameter.

Similarly, abnormal GMs assessed at, but not prior to, TEA were associated with higher global abnormality scores. Given that the global abnormality score incorporates measures of growth and maturation that occur until TEA, it is not surprising that it was most strongly associated with abnormal GMs assessed concurrently at TEA. While disruptions to brain development may occur prior to term, neurodevelopmental sequelae may not be evident until TEA, when brain abnormalities have had time to evolve.

There were a few limitations of this study. Of the 33 infants who did not have a MRI scan scored, 13 were still in hospital at TEA, and were therefore more likely to be sicker infants requiring respiratory support. Infants with greater illness severity, such as bronchopulmonary dysplasia, are at higher risk for both adverse MRI findings, such as white matter injury, and poor neurodevelopmental outcomes [32,33]. As MRI data were not collected for these infants who were likely to have more brain abnormalities, the power of the MRI component of the study to identify associations with abnormal GMs may have been reduced. Another limitation was that MRI was conducted at only one timepoint (TEA); consequently, there were no serial data to match GMs at each age of assessment to relate GMs to brain growth over time. Given the relationships between interhemispheric distance and GMs assessed prior to term in the current study, assessing GMs concurrently with measures of growth on cranial ultrasound, which is routinely used clinically, may provide further insight into the association of GMs and brain growth prior to term. Additionally, it is essential that infants in the current study are seen beyond term age in order to determine the predictive validity of preterm GMs, with or without MRI, for later neurodevelopment.

**5. Conclusion**

Abnormal GMs in very preterm infants were associated with more marked brain abnormality and smaller brains on MRI at TEA. Abnormal GMs assessed prior to term were associated with larger interhemispheric distance and higher cortical grey matter abnormality on MRI at TEA, indicating that abnormal GMs are an early marker for disrupted brain development in very preterm infants. Term-equivalent was highlighted as an important age for GMA given the associations of abnormal GMs with smaller brain size and higher abnormality scores on

concurrent MRI. The GMA is a useful tool to identify those infants most at risk for adverse neurodevelopment so that early intervention and developmental follow-up may be implemented during the key neonatal period when critical neural development and organisation is occurring. There is a need for additional studies that incorporate MRI and GMs in order to further examine links between brain growth and maturation for neurodevelopment, and to ascertain the clinical significance of the associations of MRI findings and GMs for long term developmental outcome.

**Acknowledgements**

This study was funded by grants from the National Health and Medical Research Council (Centre of Research Excellence in Newborn Medicine 1060733; Project Grants 1024516 and 1028822, Career Development Fellowship 1108714-AJS, 1085754-DKT and 1053609-KJL; Early Career Fellowship 1053787-JLYC, Senior Research Fellowship 1081288-PJA); Australian Postgraduate Association Scholarship, University of Melbourne (JEO), Murdoch Childrens Research Institute and the Victorian Government’s Operational Infrastructure Support Program.

**References**

- [1] N.C. Brown, T.E. Inder, M. Bear, R. Hunt, P.J. Anderson, L.W. Doyle, Neurobehavior at term and white and gray matter abnormalities in very preterm infants, *J. Pediatr.* 155 (2009) 32–38.
- [2] H. Kidokoro, P.J. Anderson, L.W. Doyle, L.J. Woodward, J.J. Neil, T.E. Inder, Brain injury and altered brain growth in preterm infants: predictors and prognosis, *Pediatrics* 134 (2014) e444–e453.
- [3] J.J. Volpe, Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances, *Lancet Neurol.* 8 (2009) 110–124.
- [4] H. Kidokoro, J.J. Neil, T.E. Inder, New MR imaging assessment tool to define brain abnormalities in very preterm infants at term, *Am. J. Neuroradiol.* 34 (2013) 2208–2214.
- [5] P.J. Anderson, J.L. Cheong, D.K. Thompson, The predictive validity of neonatal MRI for neurodevelopmental outcome in very preterm children, *Semin. Perinatol.* 39 (2015) 147–158.
- [6] L.J. Woodward, P.J. Anderson, N. Austin, K. Howard, T.E. Inder, Neonatal MRI to predict neurodevelopmental outcomes in preterm infants, *N. Engl. J. Med.* 355 (2006) 685–694.
- [7] M. Bosanquet, L. Copeland, R. Ware, R. Boyd, A systematic review of tests to predict cerebral palsy in young children, *Dev. Med. Child Neurol.* 55 (2013) 418–426.

- [8] S.J. Korzeniewski, G. Birbeck, M.C. DeLano, M.J. Potchen, N. Paneth, A systematic review of neuroimaging for cerebral palsy, *J. Child Neurol.* 23 (2008) 216–227.
- [9] A.J. Spittle, R.N. Boyd, T.E. Inder, L.W. Doyle, Predicting motor development in very preterm infants at 12 months' corrected age: the role of qualitative magnetic resonance imaging and general movements assessments, *Pediatrics* 123 (2009) 512–517.
- [10] B. Skiold, C. Eriksson, A.-C. Eliasson, U. Aden, B. Vollmer, General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm, *Early Hum. Dev.* 89 (2013) 467–472.
- [11] J.C. Constantinou, E.N. Adamson-Macedo, M. Mirmiran, B.E. Fleisher, Movement, imaging and neurobehavioral assessment as predictors of cerebral palsy in preterm infants, *J. Perinatol.* 27 (2007) 225–229.
- [12] C. Einspieler, H.F. Precht, A.F. Bos, F. Ferrari, G. Cioni, Precht's Method on the Qualitative Assessment of General Movements in Preterm, Term and Young Infants, MacKeith Press, London, 2004.
- [13] A.J. Spittle, M.M. Spencer-Smith, J.L.Y. Cheong, A.L. Eeles, K.J. Lee, P.J. Anderson, et al., General movements in very preterm children and neurodevelopment at 2 and 4 years, *Pediatrics* 132 (2013) (e452–e8).
- [14] V. Darsaklis, L.M. Snider, A. Majnemer, B. Mazer, Predictive validity of Precht's method on the qualitative assessment of general movements: a systematic review of the evidence, *Dev. Med. Child Neurol.* 53 (2011) 896–906.
- [15] A.J. Spittle, N.C. Brown, L.W. Doyle, R.N. Boyd, R.W. Hunt, M. Bear, et al., Quality of general movements is related to white matter pathology in very preterm infants, *Pediatrics* 121 (2008) e1184–e1189.
- [16] C. Peyton, E. Yang, M. Kocherginsky, L. Adde, T. Fjortoft, R. Stoen, et al., Relationship between white matter pathology and performance on the general movement assessment and the test of infant motor performance in very preterm infants, *Early Hum. Dev.* 95 (2016) 23–27.
- [17] A.J. Spittle, L.W. Doyle, P.J. Anderson, T.E. Inder, K.J. Lee, R.N. Boyd, et al., Reduced cerebellar diameter in very preterm infants with abnormal general movements, *Early Hum. Dev.* 86 (2010) 1–5.
- [18] F. Ferrari, A. Todeschini, I. Guidotti, M. Martinez-Biarge, M.F. Roversi, A. Berardi, et al., General movements in full-term infants with perinatal asphyxia are related to basal ganglia and thalamic lesions, *J. Pediatr.* 158 (2011) 904–911.
- [19] A. Guzzetta, E. Mercuri, G. Rapisardi, F. Ferrari, M.F. Roversi, F. Cowan, et al., General movements detect early signs of hemiplegia in term infants with neonatal cerebral infarction, *Neuropediatrics* 34 (2003) 61–66.
- [20] S. Ohgi, M. Fukuda, T. Akiyama, H. Gima, Effect of an early intervention programme on low birthweight infants with cerebral injuries, *J. Paediatr. Child Health* 40 (2004) 689–695.
- [21] H. Als, L. Gilkerson, F.H. Duffy, G.B. McAnulty, D.M. Buehler, K. Vandenberg, et al., A three-center, randomized, controlled trial of individualized developmental care for very low birth weight preterm infants: medical, neurodevelopmental, parenting, and caregiving effects, *J. Dev. Behav. Pediatr.* 24 (2003) 399–408.
- [22] S. Dusing, S. Brown, C. Van Drew, L.R. Thacker, K.D. Hendricks-Muñoz, Supporting play exploration and early development intervention from NICU to home: a feasibility study, *Pediatr. Phys. Ther.* 27 (2015) 267–274.
- [23] M. Zahed-Cheikh, V. Brevaut-Malaty, M. Busuttil, A.S. Monnier, M. Roussel, C. Gire, Comparative analysis of perinatal and postnatal factors, and general movement in extremely preterm infants, *Brain Dev.* 33 (2011) 656–665.
- [24] A.J. Spittle, D.K. Thompson, N.C. Brown, K. Treyvaud, J.L. Cheong, K.J. Lee, et al., Neurobehaviour between birth and 40 weeks gestation in infants born <30 weeks gestation and parental psychological wellbeing: predictors of brain development and child outcomes, *BMC Pediatr.* 14 (2014) 111.
- [25] J.E. Olsen, N.C. Brown, A.L. Eeles, K.J. Lee, P.J. Anderson, J.L. Cheong, et al., Trajectories of general movements from birth to term-equivalent age in infants born <30 weeks' gestation, *Early Hum. Dev.* 91 (2015) 683–688.
- [26] J.M. Walsh, L.W. Doyle, P.J. Anderson, K.J. Lee, J.L.Y. Cheong, Moderate and late preterm birth: effect on brain size and maturation at term-equivalent age, *Radiology* 273 (2014) 232–240.
- [27] S.N.T. Tich, P.J. Anderson, J.S. Shimony, R.W. Hunt, L.W. Doyle, T.E. Inder, A novel quantitative simple brain metric using MR imaging for preterm infants, *Am. J. Neuroradiol.* 30 (2009) 125–131.
- [28] T.E. Inder, S.K. Warfield, H. Wang, P.S. Huppi, J.J. Volpe, Abnormal cerebral structure is present at term in premature infants, *Pediatrics* 115 (2005) 286–294.
- [29] S.N.T. Tich, P.J. Anderson, R.W. Hunt, K.J. Lee, L.W. Doyle, T.E. Inder, Neurodevelopment and perinatal correlates of simple brain metrics in very preterm infants, *Arch. Pediatr. Adolesc. Med.* 165 (2011) 216–222.
- [30] H.W. Park, H.-K. Yoon, S.B. Han, B.S. Lee, I.Y. Sung, K.S. Kim, et al., Brain MRI measurements at a term-equivalent age and their relationship to neurodevelopmental outcomes, *Am. J. Neuroradiol.* 35 (2014) 599–603.
- [31] A. Messerschmidt, R. Fuiko, D. Prayer, P. Brugger, E. Boltshauser, G. Zoder, et al., Disrupted cerebellar development in preterm infants is associated with impaired neurodevelopmental outcome, *Eur. J. Pediatr.* 167 (2008) 1141–1147.
- [32] L.J. Van Marter, K.C. Kuban, E. Allred, C. Bose, O. Dammann, M. O'Shea, et al., Does bronchopulmonary dysplasia contribute to the occurrence of cerebral palsy among infants born before 28 weeks of gestation? *Arch. Dis. Child Fetal Neonatal Ed.* 96 (2011) 20–29.
- [33] L.W. Doyle, G. Roberts, P.J. Anderson, Outcomes at age 2 years of infants <28 weeks' gestational age born in Victoria in 2005, *J. Pediatr.* 156 (2010) 49–53.