



Article Early Motor Repertoire of Very Preterm Infants and Relationships with 2-Year Neurodevelopment

Amanda K.-L. Kwong ^{1,2,3}, Roslyn N. Boyd ^{1,4}, Mark D. Chatfield ^{1,4}, Robert S. Ware ⁵, Paul B. Colditz ^{6,7} and Joanne M. George ^{1,4,8,*}

- ¹ Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre, Faculty of Medicine, The University of Queensland, Brisbane, QLD 4101, Australia;
- amanda.kwong@mcri.edu.au (A.K.-L.K.); r.boyd@uq.edu.au (R.N.B.); m.chatfield@uq.edu.au (M.D.C.)
- ² Clinical Sciences, Murdoch Children's Research Institute, Melbourne, VIC 3052, Australia
- ³ Department of Physiotherapy, University of Melbourne, Parkville, VIC 3010, Australia
 ⁴ Australian Cerebral Palsy Clinical Trials Network CRE, The University of Queensland,
- Brisbane, QLD 4101, Australia
- ⁵ Menzies Health Institutes Queensland, Griffith University, Brisbane, QLD 4222, Australia; r.ware@griffith.edu.au
- ⁶ University of Queensland Centre for Clinical Research, The University of Queensland, Brisbane, QLD 4072, Australia; p.colditz@uq.edu.au
- ⁷ Perinatal Research Centre, Royal Brisbane and Women's Hospital, Brisbane, QLD 4029, Australia
- ⁸ Physiotherapy Department, Queensland Children's Hospital, Children's Health Queensland Hospital and Health Service, Brisbane, QLD 4101, Australia
- * Correspondence: j.george2@uq.edu.au; Tel.: +61-7-3068-4231

Abstract: The Motor Optimality Score, revised (MOS-R) is an extension of the Prechtl General Movements Assessment. This study aims to determine the relationship between MOS-R and 2-year neurodevelopmental outcomes in a cohort of 169 infants born very preterm (<31 weeks' gestational age), and to examine the predictive validity of the MOS-R at 3–4 months' corrected age (CA) above perinatal variables associated with poor outcomes, including Prechtl fidgety movements. Development at 2 years' CA was assessed using Bayley Scales of Infant and Toddler Development, Third edition (Bayley-III) (motor/cognitive impairment: Bayley-III \leq 85) and Neurological, Sensory, Motor, Developmental Assessment (NSMDA) (neurosensory motor impairment: NSMDA \geq 12). Cerebral palsy (CP) was classified at 2 years as definite or clinical. The MOS-R was related to 2-year outcomes: Bayley-III motor ($B_{MOS-R} = 1.24$ 95% confidence interval (0.78, 1.70)), cognitive ($B_{MOS-R} = 0.91$ (0.48, 1.35)), NSMDA scores ($B_{MOS-R} = -0.34$ (-0.42, -0.25)), definite CP (odds ratio [OR] 0.67 (0.53, 0.86)), clinical CP (OR 0.74 (0.66, 0.83)) for each 1-point increase in MOS-R. MOS-R \leq 23 predicted motor (sensitivity 78% (60–91%); specificity 63% (54–72%)) and neurosensory motor impairment (sensitivity 86% (64–97%); specificity 59% (51–68%)). The MOS-R is strongly related to CP and motor and cognitive delay at 2 years and is a good predictor of motor and neurosensory motor impairment.

Keywords: preterm infant; neurodevelopment; motor optimality score; general movements; motor impairment; cognitive impairment

1. Introduction

Preterm birth affects one in 11 births in Australia. Of those, approximately 20% are born very preterm (VPT, <32 weeks' gestation) and are more likely to experience developmental delay than infants who were born at term [1–3]. Potential delays in infants born VPT may be amenable to early intervention [4]. Early detection of developmental delay is a process of ongoing assessment and consideration of key perinatal events known to affect long-term outcomes [5,6]. In contrast, the prediction of cerebral palsy (CP) has been afforded much attention, with recent guidelines recommending the combination of brain neuroimaging, the Prechtl General Movements Assessment (GMA) [7], and neurological



Citation: Kwong, A.K.-L.; Boyd, R.N.; Chatfield, M.D.; Ware, R.S.; Colditz, P.B.; George, J.M. Early Motor Repertoire of Very Preterm Infants and Relationships with 2-Year Neurodevelopment. *J. Clin. Med.* 2022, *11*, 1833. https://doi.org/ 10.3390/jcm11071833

Academic Editor: Massimiliano Valeriani

Received: 14 February 2022 Accepted: 23 March 2022 Published: 25 March 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). examination (Hammersmith Infant Neurological Examination) [8] for a diagnosis of highrisk CP at less than 6 months' corrected age (CA) [9]. In order to direct early intervention resources to those most likely to experience developmental delay, it is paramount to accurately predict which infants born very preterm will go on to experience motor or cognitive delay.

The GMA is a widely used tool within Australian Neonatal Intensive Care Units (NICU) [10] but has lower predictive validity for cognitive and motor delays compared with CP [11–14]. This is particularly relevant for fidgety movements assessed according to Prechtl's method [7] which are a pattern of movements characterized by continuous, small amplitude movements of moderate velocity which can be typically recognized throughout the limbs and body of an alert infant between 9 and 20 weeks' corrected age. Fidgety movements are classified as normal, sporadic (observed only occasionally), absent (not seen at all), or abnormal (exaggerated with larger amplitude). A semi-quantitative measure that is an extension of the GMA, known as the Motor Optimality Score, revised 2019 (MOS-R) [15,16], provides an optimality score of an infant's motor movements and patterns between 9 and 20 weeks' CA. The MOS-R may provide a better association with later non-CP developmental outcomes [11,17–22] or indicate the severity of CP based on Gross Motor Function Classification System (GMFCS) grading [15], but while emerging evidence is encouraging, few studies have investigated the cut-off score to maximize predictive validity for motor, cognitive, or neurosensory impairment at 2 years' CA. The MOS-R is conducted without assessor handling, a key advantage where face-to-face assessments may be limited, but requires additional advanced training beyond a basic general movements course. The clinical utility of the MOS-R, therefore, needs to be explored in the very preterm population to justify the resources needed to acquire additional training.

Infants born preterm experience higher rates of cognitive, language, and motor delay, which can later affect academic performance [2]. As such, early detection of developmental delays not associated with disability should also be investigated. The classification of impairment at 2 years by commonly used tests may fail to classify all children who experience developmental delay at 8 years of age [23]. Other tests that evaluate more subtle differences in development, such as the Neurological, Sensory, Motor, Developmental Assessment (NSMDA) [24] may provide a better measure of impairment in children who otherwise appear to demonstrate typical development on standardized testing.

The current study aims to determine the relationships between the MOS-R and cognitive, motor, neurosensory motor, or CP outcomes at 2 years' CA. Additionally, the study aims to investigate whether the MOS-R is independently related to 2-year outcomes after adjustment for Prechtl fidgety movements or variables known to affect long-term outcome among infants born preterm <31 weeks' gestation. Third, the study aims to determine if the MOS-R, which is inclusive of fidgety movements assessment, provides better predictive ability with 2-year motor, cognitive, neurosensory motor, or CP outcomes than fidgety movements alone. Further to this, the predictive values of motor, cognitive, and neurosensory motor impairment will be described for the best cut-off point of the MOS-R.

2. Materials and Methods

2.1. Participants

Participants included infants born very preterm, between February 2016 and December 2018, who were free from congenital anomalies from the Prediction of Preterm Brain Outcomes (PREBO) [25]. Infants were recruited prospectively from the Royal Brisbane Women's Hospital (RBWH). Infants recruited to an earlier study cohort (Prediction of Preterm Motor Outcome (PPREMO)) [3] born January 2013–February 2016 at the RBWH were also invited to participate in the PREBO study. Families of the infants lived within 200 km of their recruiting hospital and needed to be able to communicate in English. Included infants were free from congenital or chromosomal abnormalities known to affect neurodevelopment. Infants with any contraindication to magnetic resonance imaging (MRI) were excluded due to the MRI component of the overarching study. Parents of

infants provided written informed consent to participate, and the study was approved by the Human Research Ethics Committees at the Royal Brisbane Women's Hospital (HREC/15/QRCH) and The University of Queensland (2015000290) and registered on the Australian New Zealand Clinical Trial Registry (ACTRN12615000591550). The studied cohort [3,25] presents those with completed 2-year data.

2.2. Acquisition and Scoring of General Movements and Motor Optimality Score, Revised

The MOS-R was applied to video recordings of infants by an advanced-certified assessor (AK), masked to infant clinical history. The GMA component of the MOS-R was scored by two advanced-certified raters and any disagreements were settled through review between three raters. Reliability for the MOS-R has previously been reported to be high with intraclass correlation coefficients of 0.86–0.98 [26–29]. The MOS-R consists of five subsections: (i) fidgety movements, which is assigned a score of 1, 4 or 12 for absent/sporadic, abnormal or normal movements respectively; (ii) observed movement patterns, that tallies the number of typical and atypical observed postures and assigns a score of 1 for more atypical movements, 2 for equal number of atypical and typical movements, and 4 for more typical movements/postures; (iii) the age-adequate movement repertoire scores 1 (absent), 2 (reduced), or 4 (present) which is determined by a checklist of movements that are expected to be observed depending on the age of assessments: at 9-11, 12-13, 14-15, and over 16 weeks' CA; (iv) observed postural patterns, which follows a similar scoring concept to subsection (ii), but observes postural patterns rather than movement patterns; (v) movement character, which describes an infant's movements as either smooth and fluent (score 4), not smooth and fluent, but not cramped-synchronized (score 2), or cramped-synchronized (score 1). Each subsection was scored and added to produce a final continuous score between 5 and 28 [15].

For this article (with the exception of Figure S1), GMA was classified as absent/abnormal (MOS-R, first subsection score 1 or 4, with sporadic movements classified as "absent") or as normal fidgety (MOS-R, first subsection score 12).

2.3. Assessment of 2-Year Outcomes

Motor and cognitive outcomes were assessed by a masked pediatric physiotherapist using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III) [30] and the NSMDA [24] described in a previously published protocol [3]. As the Bayley-III is known to underestimate the extent of delay in Australian children [31], a cut-off of Bayley composite score \leq 85 to indicate impairment for the motor and cognitive domains was used. The NSMDA was used as a continuous functional grade score (higher scores indicate worse impairment) and neuromotor-sensory impairment was defined as an NSMDA functional score of 12 or above.

CP was assessed at 2 years' CA by pediatricians who administered standardized neurological assessments and classified CP using the GMFCS [32] as well as CP motor distribution [33], and as described in previous protocols/study [3,25]. CP was classified as definite, possible (where children had neurological abnormalities, but could not be clearly classified as CP), or no CP. Infants were dichotomized as having definite CP (versus possible or no CP) or having a clinical CP diagnosis (definite or possible).

Social risk was determined through parent questionnaire which surveyed family structure, education level of primary caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home, and maternal age at birth with each category receiving 0–2 points depending on social risk, then tallied in accordance with Roberts et al. (2008) [34]. Families were considered to have a higher social risk if their score was 2 points or more and lower social risk if their score was 0–1 [34].

2.4. Statistical Analysis

Associations with Bayley-III motor and cognitive continuous standard scores and NSMDA functional scores were assessed using linear regression. Associations with CP

(definite and clinical classifications) were assessed using logistic regression. Infants with any missing data were not included in the analysis.

First, univariable associations between MOS-R and GMA (absent/abnormal fidgety movements) and 2-year outcomes were reported. The average change in the outcome per one-unit increase for the MOS-R (B_{MOS-R}) and for absent/abnormal and normal fidgety movements (B_{GMA}) was reported. Subsequent multivariable analyses using two different models were conducted (i) multivariable model 1: Predictors were MOS-R and absent/abnormal fidgety movements; (ii) multivariable model 2: Predictors were MOS-R and the following variables known to influence long-term outcomes: [5,6] brain injury (being the presence of major [grade 3 or 4] intraventricular hemorrhage or cystic periventricular leukomalacia), the administration of postnatal corticosteroids, male sex and higher social risk, or lower gestational age. For the analysis of CP, gestational age was the only variable within the model due to the low rate of CP.

Receiver operating characteristic (ROC) curves were plotted for MOS-R and absent/abnormal fidgety movements for each of the motor, cognitive, and neurosensory motor impairment and CP outcomes. Liu [35] and Youden's [36] statistics were used to determine the optimal cut-off point for the best combination of sensitivity and specificity values. The predictive validity of the MOS-R to detect motor, cognitive, and neurosensory motor impairment and CP was described by calculating the Area Under ROC Curve (AUC), sensitivity, specificity, positive and negative predictive values, and accuracy (percentage of correctly classified cases). Data were analyzed using Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA: StataCorp LLC.).

3. Results

3.1. Participants and Characteristics

Two-hundred and eighty-eight infants were recruited to the PREBO and PPREMO studies and 216 infants were assessed using the MOS-R. To date, 169 infants have been followed up at 2 years' CA for the Bayley-III motor domain (160 participants, 56%), Bayley-III cognitive domain (169 participants, 59%), and NSMDA (162 participants, 56%), and had a CP assessment (159 participants, 55%) (Figure 1). The characteristics of infants assessed are described in Table 1. There was a lower proportion of families with high social risk and a higher rate of postnatal corticosteroid use among those with complete data (Table S1). There were no other strong differences between groups who had complete and incomplete data. The distribution of the MOS-R across infants with absent, abnormal, and normal fidgety general movements is reported in Figure S1 and the proportion of scores across the MOS-R's five subsections is reported in Figure 2.

Table 1. Perinatal characteristics of infants assessed at 3–4 months and 2 years.

Perinatal Details	MOS-R and 2-Year Follow-Up Completed		
	<i>n</i> = 169		
Gestational age at birth weeks, mean (SD)	28.6 (1.9)		
Birth weight g, mean (SD)	1097 (310)		
Males	95 (56%)		
Multiple births	54 (32%)		
Higher social risk	81/168 (48%)		
IVH grade 3 or 4	16 (9%)		
Periventricular leukomalacia	8 (5%)		
Postnatal corticosteroids	30 (18%)		
Bronchopulmonary dysplasia	65 (38%)		
3–4 month assessment			
Corrected age of GMA/MOS-R assessment, weeks, mean (SD)	13.4 (1.3)		
MOS-R, median (IQR)	24.0 (21.0–26.0)		

Table 1. Cont.

Perinatal Details	MOS-R and 2-Year Follow-Up Completed		
GMA			
Normal	154 (91%)		
Abnormal	1 (0.6%)		
Absent	14 (8%)		
2-year details			
Age of assessment months, mean (SD)	24.2 (0.8)		
CP			
No CP	148/159 (94%)		
Possible CP	5/159 (3%)		
Definite CP	6/159 (4%)		
Bayley-III motor composite score, mean (SD) <i>n</i>	97.9 (16) 160		
Motor impairment	32/159 (20%)		
Bayley-III cognitive composite score, mean (SD) <i>n</i>	96.5 (15.1) 169		
Cognitive impairment	43 (25%)		
NSMDA functional grade, mean (SD) <i>n</i>	8.5 (2.9) 161		
Neurosensory motor impairment	21/161 (13%)		

Data are *n* (%) unless otherwise specified. Abbreviations: MOS-R: motor optimality score, revised; SD: standard deviation; IVH: intraventricular hemorrhage; GMA: General Movements Assessment; CP: cerebral palsy; NSMDA: Neurological, Sensory, Motor, Developmental Assessment.

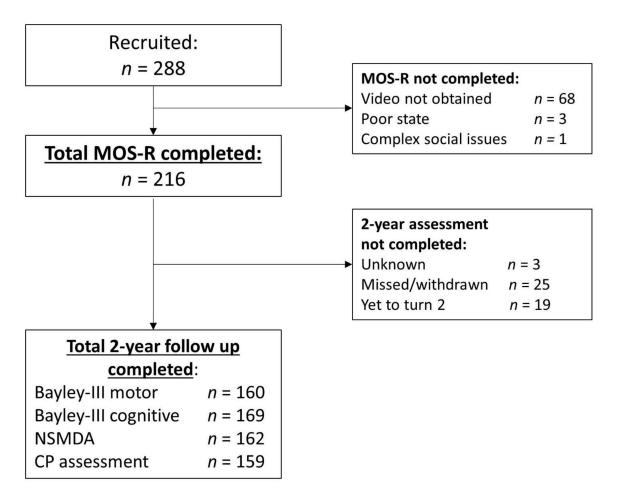


Figure 1. Flowchart of participants. Abbreviations: MOS-R: Motor Optimality Score, revised; Bayley-III: Bayley Scales of Infant and Toddler Development, 3rd edition; NSMDA: Neurological, Sensory, Motor Developmental Assessment; CP: cerebral palsy.

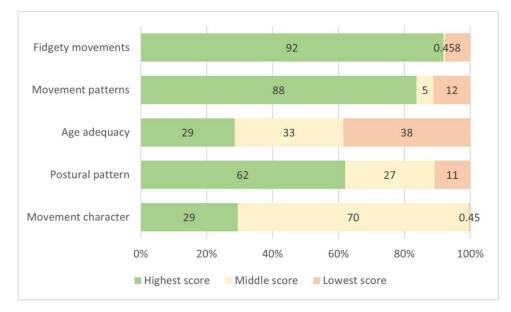


Figure 2. Proportion of infants represented within each subsection of MOS-R.

3.2. Relationships between MOS-R and 2-Year Outcomes

The univariable and multivariable relationships between MOS-R and 2-year outcomes are reported in Table 2. The MOS-R was strongly related to Bayley-III motor, cognitive, and NSMDA scores and CP outcome (both definite and possible/clinical diagnoses), and the MOS-R explained the highest proportion of variance for the NSMDA compared with motor or cognitive Bayley-III scores. The relationships remained strong for Bayley-III motor scores and NSMDA functional scores when corrected for absent/abnormal fidgety movements (model 1). The odds ratio for the likelihood of CP from GMA could not be calculated as all infants with CP had absent/abnormal fidgety movements and no infants with CP had normal fidgety movements. The MOS-R remained strongly related to motor, cognitive Bayley-III scores, NSMDA scores, and CP outcome (both definite and clinical CP) even when adjusted for perinatal variables (model 2). The univariable and multivariable relationships between absent/abnormal fidgety movements and 2-year outcomes are reported in Table 3.

Motor Optimality Score, Revised				
	Model	B _{MOS-R} (95% CI)	<i>p</i> -Value	R ²
Bayley-III motor scores	univariable	1.24 (0.78, 1.70)	<0.001	0.15
	multivariable 1	0.97 (0.12, 1.83)	0.03	0.15
	multivariable 2	1.22 (0.76, 1.69)	< 0.001	0.28
Bayley-III cognitive scores	univariable	0.91 (0.48, 1.35)	< 0.001	0.09
Ū.	multivariable 1	0.63 (-0.21, 1.47)	0.13	0.10
	multivariable 2	-0.34(-0.42, -0.25)	0.001	0.23
NSMDA				
functional scores *	univariable	-0.34 (-0.42, -0.25)	< 0.001	0.28
	multivariable 1	-0.28(-0.43, -0.12)	0.001	0.28
	multivariable 2	-0.30(-0.39, -0.21)	0.001	0.37

Table 2. Association between MOS-R with Bayley-III motor, cognitive scores, NSMDA functional grades and CP (definite and clinical classifications).

Table 2. Cont.

Motor Optimality Score, Revised					
	Model	B _{MOS-R} (95% CI)	<i>p</i> -Value	R ²	
		Odds Ratio (95% CI)			
Definite CP	univariable multivariable 1	0.67 (0.53, 0.86)	0.002 **		
	multivariable 2 ⁺	0.68 (0.53, 0.86)	0.001		
Clinical CP	univariable-MOS-R	0.74 (0.66, 0.83)	< 0.001	n/a	
	multivariable 1	0.68 (0.48, 0.96)	0.03		
	multivariable 2 ⁺	0.74 (0.66, 0.83)	0.001		

Abbreviations: MOS-R: Motor Optimality Score, revised 2019; Bayley-III: Bayley Scales of Infant and Toddler Development, 3rd edition; NSMDA: Neurological, Sensory, Motor Developmental Assessment; CP: cerebral palsy; Multivariable 1: MOS-R adjusted for fidgety movements, for given 2-year outcome; Multivariable 2: MOS-R adjusted for sex, postnatal corticosteroids, high social risk, brain injury (IVH $\frac{3}{4}$ or cystic PVL), gestational age; $B_{\text{MOS-R}}$: average change in Bayley-III/NSMDA score for every 1-point increase in MOS-R score; *: NSMDA, higher scores indicate poorer function; ** unable to calculate odds ratio due to diverging estimates; [†] adjusted for gestational age only.

Table 3. Association between absent/abnormal fidgety movements with Bayley-III motor, cognitive scores, NSMDA functional grades, and CP (definite and clinical classifications).

General Movemen	ts Assessment-Abso	ent/Abnormal Fidget	y Movements	
	B _{GMA}	(95% CI)	<i>p</i> -Value	R ²
Bayley-III motor scores	-20.55 (-28.99, -12.10)		< 0.001	0.13
Bayley-III cognitive scores	-15.43 (-23.22, -7.63)		< 0.001	0.08
NSMDA functional scores *	5.34 (3.79, 6.89)		< 0.001	0.23
	Odds rati	o (95% CI)		
Definite CP	n(CP)/n (ab- sent/abnormal fidgety) 6/14	n(CP)/n (normal fidgety) 0/145	<0.001‡	n/a
Clinical CP	63.1 (13.3, 299.8)		< 0.001	

Abbreviations: Bayley-III: Bayley Scales of Infants and Toddler Development, 3rd edition; NSMDA: Neurological, Sensory, Motor, Developmental Assessment; CP: cerebral palsy; *B*_{GMA}: average difference in Bayley-III composite score or NSMDA score for infants with absent/abnormal fidgety movements; *: NSMDA, higher scores indicate poorer function; [‡]: Fisher's exact test.

3.3. Predictive Validity of MOS-R and 2-Year Outcomes

The MOS-R had excellent prediction of CP outcome, with moderate–good results for motor and neurosensory motor impairment (Figure 3A–E). The ideal MOS-R cut-off for the prediction of motor, cognitive, and neurosensory motor impairment was scores \leq 23 and for CP, \leq 15 with predictive values listed in Table 4. The AUC was higher for MOS-R than GMA for the prediction of motor (difference in AUC, *p* = 0.002) and neurosensory motor impairment (difference in AUC, *p* = 0.005) (Figure 3A–E), however, the AUC values for motor and neurosensory motor impairment were moderate–good. Overall, sensitivity and positive predictive values of the MOS-R for motor, cognitive, and neurosensory motor impairment were higher than the sensitivity and positive predictive values of the GMA fidgety movement score to predict the same outcomes, but specificity and accuracy were lower for the MOS-R than the GMA in predicting motor, cognitive, and neurosensory motor impairment. Both MOS-R and GMA had good–excellent negative predictive values. Predictive values of the MOS-R and GMA did not differ for CP outcome.

A. Motor impairment

ROC area, MOS-R: 0.76 ROC area, GMA: 0.64 Difference ROC area: p=0.002

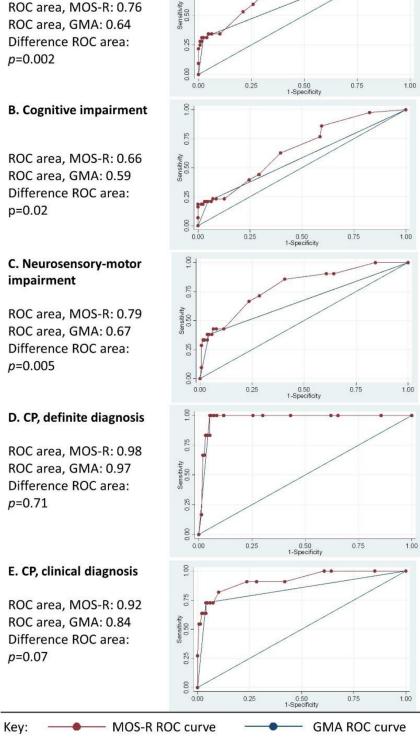
B. Cognitive impairment

ROC area, GMA: 0.59 Difference ROC area: p=0.02

C. Neurosensory-motor impairment

ROC area, MOS-R: 0.79 ROC area, GMA: 0.67 **Difference ROC area:** p=0.005

ROC area, MOS-R: 0.98 ROC area, GMA: 0.97 Difference ROC area: p=0.71



00.1

0.75

Figure 3. (A–E): ROC curves for several outcomes with GMA and MOS-R, testing hypothesis that AUC is not the same. MOS-R cut-off \leq 23 for Figure 3A–C, MOS-R cut-off \leq 15 for Figure 3D,E; Abbreviations: ROC: receiver operating characteristic; MOS-R: motor optimality score, revised; AUC: area under curve.

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy (Correctly Classified)
			MOS-R *		
Motor impairment	78% (60–91%)	63% (54–72%)	77% (46–95%)	85% (78–90%)	66% (58–74%)
Cognitive	63%	60%	60%	78%	61%
impairment	(47-77%)	(51–69%)	(32%, 84%)	(71-84%)	(53–68%)
Neurosensory	86%	59%	57%	91%	63%
motor impairment	(64–97%)	(51–68%)	(29-82%)	(85–95%)	(55–70%)
Cerebral palsy	100%	95%	43%	100%	95%
(definite only)	(54–100%)	(90–98%)	(18–71%)	(98–100%)	(90–98%)
Cerebral palsy (possible and definite)	73% (39–94%)	96% (91–99%)	57% (29–82%)	98% (94–100%)	94% (90–97%)
			GMA **		
Motor impairment	31% (16–50%)	98% (93–100%)	35% (24–47%)	92% (84–97%)	84% (78–90%)
Cognitive	21%	95%	35%	83%	76%
impairment	(10-36%)	(90–98%)	(25-47%)	(73–90%)	(69-83%)
Neurosensory	38%	96%	24%	97%	88%
motor impairment	(18–62%)	(91–98%)	(15-35%)	(90–99%)	(82–93%)
Cerebral palsy	100%	95%	43%	100%	95%
(definite only)	(54–100%)	(90–98%)	(18–71%)	(98–100%)	(90–98%)
Cerebral palsy (possible and definite)	73% (39–94%)	96% (91–99%)	57% (29–82%)	98% (94–100%)	94% (90–97%)

Table 4. Diagnostic statistics for MOS-R optimal cut-off and GMA with motor, cognitive, or neurosensory motor impairment.

All data are % (95% CI). Abbreviations: CI: confidence interval; MOS-R: motor optimality score, revised; GMA: General Movements Assessment; * Cut-off for MOS-R scores \leq 23 indicate poorer MOS-R for motor, cognitive, and neurosensory impairment; ** cut-off \leq 15 for cerebral palsy.

4. Discussion

A strong relationship was observed between the MOS-R and neurodevelopment as determined by motor and cognitive Bayley-III, NSMDA scores, and CP diagnosis in this prospective cohort of Australian infants born VPT. Furthermore, the MOS-R contributes independently to motor and neurosensory motor outcomes in addition to the assessment of fidgety movements alone, and independently from other perinatal variables known to be associated with poorer outcomes. While the MOS-R was strongly related to cognitive outcome on univariable analysis, the relationship weakened when corrected for absent/abnormal fidgety movements, indicating that the MOS-R was not independently related to cognitive outcomes when corrected for absent/abnormal fidgety movements. The relationship between the MOS-R and the NSMDA explained a higher proportion of variance than Bayley-III motor or cognitive scores. The MOS-R also had better predictive validity for non-CP developmental outcomes than absent/abnormal fidgety movements but the MOS-R was no better than absent/abnormal fidgety movements for predicting CP.

Infants born VPT who experience developmental delay are overwhelmingly represented by those with a spectrum of mild–severe delays in motor, cognitive, or language function, and less so with CP [2,37]. Furthermore, the rate of motor impairment appears to be increasing in other Australian cohorts of extremely preterm infants over time [38]. Therefore, the early detection of non-CP developmental delay is warranted and accordingly, this study's findings indicate that the MOS-R can provide additional insight into early neurodevelopmental delay. The MOS-R, having a better relationship with impairment outcomes than absent/abnormal fidgety movements, may be an early functional manifestation of injury or represent an early sign of the interplay between cognitive and motor development [39], and may be used as an early indicator of developmental delay. Similar studies have also found comparable results to the current study. A study based on infants born VPT in the US showed that the MOS-R was independently related to Bayley-III motor, cognitive, and language outcomes in a multivariable model with the GMA [18]. Within the current study, the relationship of the MOS-R represented a much higher proportion of variance with the NSMDA than Bayley-III scores, suggesting that the MOS-R is better related to the NSMDA at 2 years' CA. Consistent associations between the MOS-R and 2-year outcome have also been noted in extremely preterm (<28 weeks' gestational age) populations where lower MOS-R assessed at 14–16 weeks' corrected age has been related to motor and cognitive outcomes [29]. The MOS-R has also been found to have a strong relationship with other motor assessments, with one study finding a

strong relationship between the MOS-R and 1-year Peabody Developmental Motor Scales outcomes [19]. Additionally, another study which investigated predictive values for adverse outcomes (neurosensory disability, CP, or Movement Assessment Battery for Children score ≤5th percentile) noted a cut-off MOS-R of 21 among infants born extremely preterm [22]. Within the current study, absent/abnormal fidgety movements alone also had strong

relationships with motor, cognitive, and neurosensory motor outcomes, but the MOS-R had better prediction of impairment outcomes based on the set Bayley-III or NSMDA thresholds. MOS-R scores \leq 23 had a lower rate of false negatives than the GMA, reflected in the higher sensitivity of the MOS-R to detect developmental delay, but a much higher rate of false positives. In most instances, infants who do have fidgety movements but poorer MOS-R will eventually have a typical outcome, and given the high rate of false positives, using the MOS-R to detect non-CP developmental delay may result in over-surveillance of these infants with normal fidgety movements and has potential to cause unnecessary anxiety in parents and/or overuse of resources. Conversely, clearing infants with normal fidgety movements but poorer MOS-Rs from further surveillance may miss some infants who will later go on to have another non-CP neurodevelopmental delay which can have a significant impact on participation in daily life, and potentially lose opportunities to engage in timely early intervention. One solution to overcoming inaccurate early diagnoses of developmental delay would be to consider the MOS-R alongside other standardized neurological assessments. Indeed, future studies may need to contrast the relationships of the MOS-R with other assessments, for example, the Test of Infant Motor Performance [40] or the Hammersmith Infant Neurological Examination [8,41].

Other studies, including multiple systematic reviews [42,43], have agreed that the assessment of fidgety movements according to the Prechtl GMA has high predictive validity for CP, but a study in a clinical population has found lower predictive validity of the Prechtl GMA to detect CP [44]. Our current study defined CP in two ways: the first, which was aligned with previous research methods, where only infants with definite CP were included for prediction, and the second, a clinical CP diagnosis, where some infants may not show clear signs of CP, but had clinical markers that leaned towards a possibility of CP. Our findings reflect trends from both clinical and research settings, with the classification of CP from research settings producing a higher predictive value. CP will need to be confirmed with GMFCS classification at a later age (i.e., 5 years of age or older) according to Australian CP register guidelines [45], and further assessment at 6 years is planned for the current cohort [25]. This study supports the notion that the GMA has better prediction for CP than neurodevelopmental delay [12–14] and that the MOS-R may provide the extra information needed in addition to fidgety movements alone to detect motor, cognitive, or neurosensory motor impairment.

4.1. Strengths

A strength of the study is the relatively large sample size of infants born very preterm, recruited prospectively, representing one of the larger cohorts of infants studied using the MOS-R. Assessors were also masked to clinical history at all stages of assessment, and adjustment for key perinatal variables also strengthened the study. Additionally, our study used an a motor assessment (NSDMA) in addition to the Bayley-III to provide an

alternative and in-depth measure of neurosensory motor performance due to the Bayley-III having only moderate relationships with later motor outcomes [46].

4.2. Limitations

We were unable to compare the findings or measure impairment with a term-reference group. A conscious decision to recruit infants born VPT only was made due to resource limitations and available existing evidence [31,47] to determine appropriate cut-off scores for level of impairment within an Australian population. This study was also unable to ascertain the level of engagement with early intervention, which may have affected the rate of false positives of the MOS-R to predict motor, cognitive, and neurosensory motor impairment. Assessment at two years is also early within the trajectory of a child's development. As such, participants are currently being assessed at six years of age and repeated analysis may identify with better accuracy the predictive validity of the MOS-R for older childhood outcomes [48]. Finally, due to resource constraints, only one assessor was available to score the MOS-R, however, previous studies have indicated high inter-rater reliability [29].

4.3. Future Considerations

While the relationship between the MOS-R and neurodevelopmental outcomes is strong within the current population, further studies are needed in other high-risk populations and within other geographical settings to ensure that the findings can be applied to other infant risk groups. Additionally, larger studies focused on recruiting infants at high risk of developing CP are needed to ascertain prospectively the relationship between MOS-R and GMFCS level for infants who go on to develop CP. Finally, the relationships between MRI assessments and MOS-R should also be explored to guide early screening for developmental delay and to understand the structural/neurological correlates of MOS-R compared with the GMA.

5. Conclusions

The MOS-R is strongly related to neurodevelopmental outcomes, independent of fidgety movements alone and other perinatal variables associated with poor outcomes. The MOS-R has better prediction of developmental impairment than the assessment of fidgety movements, moderate prediction of motor and cognitive outcomes, and good prediction of neurosensory motor outcomes. Care should be taken to ensure that the MOS-R is still used alongside other assessments to guide clinical care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11071833/s1, Figure S1: Box and whisker plot of MOS-R scores by GM score category (Absent, Abnormal, Normal fidgety); Table S1: Perinatal characteristics of infants with incomplete data.

Author Contributions: Conceptualization, A.K.-L.K. and J.M.G.; methodology, data curation, writing original draft preparation, visualization, A.K.-L.K.; writing—review and editing, A.K.-L.K., R.N.B., M.D.C., R.S.W., P.B.C. and J.M.G.; formal analysis, A.K.-L.K. and M.D.C.; supervision, J.M.G.; funding acquisition, J.M.G. and P.B.C. All authors have read and agreed to the published version of the manuscript.

Funding: Grants from the Cerebral Palsy Alliance Research Foundation (IRG1413), the Financial Markets Foundation for Children (2014-074), NHMRC (NHMRC1084032), and the Queensland Government (Smart State; Health Practitioner Stimulus Grant, (AH000762)) supported the broader cohort study. NHMRC Senior Research Fellow (1105038) to RB. The 2020 Mary McConnel Career Boost Program for Women in Paediatric Research (WIS162020) provided funding for data collection and personnel support for this study.

Institutional Review Board Statement: The study was approved by the Human Research Ethics Committees at the Royal Brisbane Women's Hospital (HREC/12/QRBW/245) and The University

of Queensland (2012001060) and registered on the Australian New Zealand Clinical Trial Registry (ACTRN12613000280707); ACTRN12615000591550).

Informed Consent Statement: Parents of infants provided written informed consent to participate.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Acknowledgments: We would like to acknowledge the generosity of the families who participated in this study. We acknowledge the contributions of research nurses on the study, physiotherapists who conducted the clinical assessments, and paediatricians who completed the two-year assessments.

Conflicts of Interest: The authors declare no conflict of interest.

References

- 1. Australian Institute of Health and Welfare. *Australia's Mothers and Babies 2017-in Brief*; Perinatal Statistics no. 35; AIHW: Canberra, Australia, 2019.
- Saigal, S.; Doyle, L.W. Series: An Overview of Mortality and Sequelae of Preterm Birth from Infancy to Adulthood. *Lancet* 2008, 371, 261–269. [CrossRef]
- George, J.M.; Boyd, R.N.; Colditz, P.B.; Rose, S.E.; Pannek, K.; Fripp, J.; Lingwood, B.E.; Lai, M.M.; Kong, A.H.T.; Ware, R.S.; et al. PPREMO: A Prospective Cohort Study of Preterm Infant Brain Structure and Function to Predict Neurodevelopmental Outcome. BMC Pediatr. 2015, 15, 1–17. [CrossRef] [PubMed]
- Spittle, A.; Orton, J.; Anderson, P.J.; Boyd, R.; Doyle, L.W. Early Developmental Intervention Programmes Provided Post Hospital Discharge to Prevent Motor and Cognitive Impairment in Preterm Infants. *Cochrane Database Syst. Rev.* 2015, 2015, CD005495. [CrossRef]
- Cheong, J.L.Y.; Lee, K.J.; Boland, R.A.; Spittle, A.J.; Opie, G.F.; Burnett, A.C.; Hickey, L.M.; Roberts, G.; Anderson, P.; Doyle, L.W.; et al. Changes in Long-Term Prognosis with Increasing Postnatal Survival and the Occurrence of Postnatal Morbidities in Extremely Preterm Infants Offered Intensive Care: A Prospective Observational Study. *Lancet Child Adolesc. Health* 2018, 2, 872–879. [CrossRef]
- Burnett, A.C.; Cheong, J.L.; Doyle, L.W. Biological and Social Influences on the Neurodevelopmental Outcomes of Preterm Infants. *Clin. Perinatol.* 2018, 45, 485–500. [CrossRef]
- 7. Ferrari, F.; Einspieler, C.; Prechtl, H.; Bos, A.; Cioni, G. Prechtl's Method on the Qualitative Assessment of General Movements in Preterm, Term and Young Infants; Mac Keith Press: London, UK, 2004.
- 8. Haataja, L.; Mercuri, E.; Regev, R.; Cowan, F.; Rutherford, M.; Dubowitz, V.; Dubowitz, L. Optimality Score for the Neurologic Examination of the Infant at 12 and 18 Months of Age. *J. Pediatr.* **1999**, *135*, 153–161. [CrossRef]
- Novak, I.; Morgan, C.; Adde, L.; Blackman, J.; Boyd, R.N.; Brunstrom-Hernandez, J.; Cioni, G.; Damiano, D.; Darrah, J.; Eliasson, A.-C.; et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. *JAMA Pediatr.* 2017, 171, 897–907. [CrossRef]
- Allinson, L.G.; Doyle, L.; Denehy, L.; Spittle, A.J. Survey of Neurodevelopmental Allied Health Teams in Australian and New Zealand Neonatal Nurseries: Staff Profile and Standardised Neurobehavioural/Neurological Assessment. J. Paediatr. Child Health 2017, 53, 578–584. [CrossRef]
- 11. Einspieler, C.; Bos, A.F.; Libertus, M.E.; Marschik, P.B. The General Movement Assessment Helps Us to Identify Preterm Infants at Risk for Cognitive Dysfunction. *Front. Psychol.* **2016**, *7*, 406. [CrossRef]
- 12. Darsaklis, V.; Snider, L.M.; Majnemer, A.; Mazer, B. Predictive Validity of Prechtl's Method on the Qualitative Assessment of General Movements: A Systematic Review of the Evidence. *Dev. Med. Child Neurol.* **2011**, *53*, 896–906. [CrossRef]
- 13. Spittle, A.J.; Spencer-Smith, M.M.; Cheong, J.L.; Eeles, A.L.; Lee, K.J.; Anderson, P.J.; Doyle, L.W. General Movements in Very Preterm Children and Neurodevelopment at 2 and 4 Years. *Pediatrics* **2013**, *132*, e452–e458. [CrossRef] [PubMed]
- 14. Caesar, R.; Colditz, P.B.; Cioni, G.; Boyd, R.N. Clinical Tools Used in Young Infants Born Very Preterm to Predict Motor and Cognitive Delay (Not Cerebral Palsy): A Systematic Review. *Dev. Med. Child Neurol.* **2020**, *63*, 387–395. [CrossRef] [PubMed]
- Einspieler, C.; Bos, A.F.; Krieber-Tomantschger, M.; Alvarado, E.; Barbosa, V.M.; Bertoncelli, N.; Burger, M.; Chorna, O.; Del Secco, S.; Deregnier, R.-A.; et al. Cerebral Palsy: Early Markers of Clinical Phenotype and Functional Outcome. *J. Clin. Med.* 2019, *8*, 1616. [CrossRef] [PubMed]
- 16. Örtqvist, M.; Einspieler, C.; Marschik, P.B.; Ådén, U. Movements and Posture in Infants Born Extremely Preterm in Comparison to Term-Born Controls. *Early Hum. Dev.* **2020**, *154*, 105304. [CrossRef]
- Butcher, P.R.; Van Braeckel, K.; Bouma, A.; Einspieler, C.; Stremmelaar, E.F.; Bos, A.F. The Quality of Preterm Infants' Spontaneous Movements: An Early Indicator of Intelligence and Behaviour at School Age. J. Child Psychol. Psychiatr. 2009, 50, 920–930. [CrossRef]
- Peyton, C.; Einspieler, C.; Fjørtoft, T.; Adde, L.; Schreiber, M.D.; Drobyshevsky, A.; Marks, J.D. Correlates of Normal and Abnormal General Movements in Infancy and Long-Term Neurodevelopment of Preterm Infants: Insights from Functional Connectivity Studies at Term Equivalence. J. Clin. Med. 2020, 9, 834. [CrossRef]

- 19. Zang, F.-F.; Yang, H.; Han, Q.; Cao, J.-Y.; Tomantschger, I.; Krieber, M.; Shi, W.; Luo, D.-D.; Zhu, M.; Einspieler, C. Very Low Birth Weight Infants in China: The Predictive Value of the Motor Repertoire at 3 to 5 Months for the Motor Performance at 12 Months. *Early Hum. Dev.* **2016**, *100*, 27–32. [CrossRef]
- Yuge, M.; Marschik, P.B.; Nakajima, Y.; Yamori, Y.; Kanda, T.; Hirota, H.; Yoshida, N.; Einspieler, C. Movements and Postures of Infants Aged 3 to 5 Months: To What Extent Is Their Optimality Related to Perinatal Events and to the Neurological Outcome? *Early Hum. Dev.* 2011, 87, 231–237. [CrossRef]
- Salavati, S.; Einspieler, C.; Vagelli, G.; Zhang, D.; Pansy, J.; Burgerhof, J.G.; Marschik, P.B.; Bos, A.F. The Association between the Early Motor Repertoire and Language Development in Term Children Born after Normal Pregnancy. *Early Hum. Dev.* 2017, 111, 30–35. [CrossRef]
- 22. Örtqvist, M.; Einspieler, C.; Ådén, U. Early Prediction of Neurodevelopmental Outcomes at 12 Years in Children Born Extremely Preterm. *Pediatr. Res.* 2021, 1–8. [CrossRef]
- Roberts, G.; Anderson, P.J.; Davis, N.; De Luca, C.; Cheong, J.; Doyle, L.W.; The Victorian Infant Collaborative Study Group. Developmental Coordination Disorder in Geographic Cohorts of 8-Year-Old Children Born Extremely Preterm or Extremely Low Birthweight in the 1990s. *Dev. Med. Child Neurol.* 2010, 53, 55–60. [CrossRef] [PubMed]
- 24. Burns, Y.R.; Ensbey, R.M.; Norrie, M.A. The Neuro-Sensory Motor Developmental Assessment Part 1: Development and Administration of the Test. *Aust. J. Physiother.* **1989**, *35*, 141–149. [CrossRef]
- George, J.M.; Colditz, P.B.; Chatfield, M.D.; Fiori, S.; Pannek, K.; Fripp, J.; Guzzetta, A.; Rose, S.E.; Ware, R.S.; Boyd, R.N. Early Clinical and MRI Biomarkers of Cognitive and Motor Outcomes in Very Preterm Born Infants. *Pediatr. Res.* 2021, *90*, 1243–1250. [CrossRef] [PubMed]
- Rodijk, L.H.; Bos, A.F.; Verkade, H.J.; De Kleine, R.H.; Hulscher, J.B.; Bruggink, J.L. Early Motor Repertoire in Infants with Biliary Atresia: A Nationwide Prospective Cohort Study. J. Pediatr. Gastroenterol. Nutr. 2020, 72, 592–596. [CrossRef] [PubMed]
- 27. Alkan, H.; Kahraman, A.; Mutlu, A. Early Spontaneous Movements of Infants with Hypoxic-Ischemic Encephalopathy. *Pediatr. Phys. Ther.* **2021**, *33*, 18–22. [CrossRef]
- Kahraman, A.; Alkan, H.; Çelik, H.T.; Mutlu, A. The Effect of Hyperbilirubinemia on Motor Repertoire of Infants between 3 and 5 Months of Age. *Eur. J. Pediatr.* 2021, 181, 99–105. [CrossRef]
- Kwong, A.K.L.; Doyle, L.W.; Olsen, J.E.; Eeles, A.L.; Lee, K.J.; Cheong, J.L.Y.; Spittle, A.J. Early Motor Repertoire and Neurodevelopment at 2 Years in Infants Born Extremely Preterm or Extremely-Low-Birthweight. *Dev. Med. Child Neurol.* 2022. [CrossRef]
- 30. Bayley, N. *Bayley Scales of Infant and Toddler Development*, 3rd ed.; Administration Manual; Harcourt Assessment: San Antonio, TX, USA, 2005.
- Anderson, P.J.; De Luca, C.R.; Hutchinson, E.; Roberts, G.; Doyle, L. Underestimation of Developmental Delay by the New Bayley-III Scale. Arch. Pediatr. Adolesc. Med. 2010, 164, 352–356. [CrossRef]
- 32. Palisano, R.J.; Rosenbaum, P.; Bartlett, D.; Livingston, M.H. Content Validity of the Expanded and Revised Gross Motor Function Classification System. *Dev. Med. Child Neurol.* **2008**, *50*, 744–750. [CrossRef]
- Cans, C. Surveillance of Cerebral Palsy in Europe. Surveillance of Cerebral Palsy in Europe: A Collaboration of Cerebral Palsy Surveys and Registers. Surveillance of Cerebral Palsy in Europe (SCPE). Dev. Med. Child Neurol. 2000, 42, 816–824. [CrossRef]
- 34. Roberts, G.; Howard, K.; Spittle, A.; Brown, N.; Anderson, P.; Doyle, L. Rates of Early Intervention Services in Very Preterm Children with Developmental Disabilities at Age 2 Years. *J. Paediatr. Child Health* **2008**, 44, 276–280. [CrossRef] [PubMed]
- 35. Liu, X. Classification Accuracy and Cut Point Selection. Stat. Med. 2012, 31, 2676–2686. [CrossRef] [PubMed]
- 36. Youden, W.J. Index for Rating Diagnostic Tests. Cancer 1950, 3, 32–35. [CrossRef]
- 37. Marlow, N. Neurocognitive Outcome after Very Preterm Birth. Arch. Dis. Child.-Fetal Neonatal Ed. 2004, 89, F224–F228. [CrossRef]
- Spittle, A.J.; Cameron, K.; Doyle, L.W.; Cheong, J.L.; for the Victorian Infant Collaborative Study Group. Motor Impairment Trends in Extremely Preterm Children: 1991–2005. *Pediatrics* 2018, 141, e20173410. [CrossRef]
- Bos, A.F. Early Neuromotor Performance and Later Cognition in Children Born Preterm. Dev. Med. Child Neurol. 2021, 63, 891. [CrossRef]
- 40. Campbell, S.K.; Kolobe, T.H.A.; Osten, E.T.; Lenke, M.; Girolami, G.L. *Test User's Manual for the Test of Infant Motor Performance V.3 for the TIMP Version 5*; Infant Motor Performance Scales, LLC.: Chicago, IL, USA, 2012.
- 41. Dubowitz, L.; Dubowitz, V.; Mercuri, E. *The Neurological Assessment of the Preterm & Full-Term Newborn Infant*; Mac Keith: London, UK, 1999.
- 42. Bosanquet, M.; Copeland, L.; Ware, R.; Boyd, R. A Systematic Review of Tests to Predict Cerebral Palsy in Young Children. *Dev. Med. Child Neurol.* **2013**, *55*, 418–426. [CrossRef]
- 43. Kwong, A.K.L.; Fitzgerald, T.L.; Doyle, L.W.; Cheong, J.L.Y.; Spittle, A.J. Predictive Validity of Spontaneous Early Infant Movement for Later Cerebral Palsy: A Systematic Review. *Dev. Med. Child Neurol.* **2018**, *60*, 480–489. [CrossRef]
- Datta, A.N.; Furrer, M.A.; Bernhardt, I.; Borradori-Tolsa, C.; Bucher, H.U.; Latal, B.; Grunt, S.; Natalucci, G.; Hüppi, P.S. Fidgety Movements in Infants Born Very Preterm: Predictive Value for Cerebral Palsy in a Clinical Multicentre Setting. *Dev. Med. Child Neurol.* 2017, 59, 618–624. [CrossRef]
- 45. Australian Cerebral Palsy Register Group. Australian Cerebral Palsy Register: Report 2013; Cerebral Palsy Alliance: Sydney, Australia, 2013.

- Dos Santos, E.S.L.; De Kieviet, J.F.; Königs, M.; Van Elburg, R.M.; Oosterlaan, J. Predictive Value of the Bayley Scales of Infant Development on Development of Very Preterm/Very Low Birth Weight Children: A Meta-Analysis. *Early Hum. Dev.* 2013, *89*, 487–496. [CrossRef]
- Chinta, S.; Walker, K.; Halliday, R.; Loughran-Fowlds, A.; Badawi, N. A Comparison of the Performance of Healthy Australian 3-Year-Olds with the Standardised Norms of the Bayley Scales of Infant and Toddler Development (version-III). *Arch. Dis. Child.* 2014, 99, 621–624. [CrossRef] [PubMed]
- George, J.M.; Pagnozzi, A.M.; Bora, S.; Boyd, R.N.; Colditz, P.B.; Rose, S.E.; Ware, R.; Pannek, K.; Bursle, J.E.; Fripp, J.; et al. Prediction of Childhood Brain Outcomes in Infants Born Preterm Using Neonatal MRI and Concurrent Clinical Biomarkers (PREBO-6): Study Protocol for a Prospective Cohort Study. *BMJ Open* 2020, *10*, e036480. [CrossRef] [PubMed]