European Journal of Paediatric Neurology 32 (2021) 56–65

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

Prognostic value of brain abnormalities for cognitive functioning in cerebral palsy: A prospective cohort study

Irene Moll [a, i], Jeanine M. Voorman [b], Marjolijn Ketelaar [c], Petra E. van Schie [d], Jan Willem Gorter [e], Maarten H. Lequin [f], Linda S. de Vries [g], R. Jeroen Vermeulen [h, *]

[a] Department of Neurology, Maastricht University Medical Center, the Netherlands
[b] Department of Rehabilitation, Physical Therapy Science and Sports and Center of Excellence for Rehabilitation Medicine, UMC Utrecht Brain Center, University Medical Center Utrecht and De Hoogstraat Rehabilitation, Utrecht, the Netherlands
[c] Center of Excellence for Rehabilitation Medicine; UMC Utrecht Brain Center, University Medical Center Utrecht, and De Hoogstraat Rehabilitation, Utrecht, the Netherlands
[d] Department of Rehabilitation Medicine, Amsterdam University Medical Centers, Amsterdam, the Netherlands
[e] CanChild, Department of Pediatrics, School of Rehabilitation Science, McMaster University, Hamilton, Canada
[f] Department of Radiology, UMC Utrecht, the Netherlands
[g] Department of Neonatology, UMC Utrecht, the Netherlands
[h] Department of Neurology, Child Neurology, Maastricht University Medical Center and School of Mental Health and Neuroscience, Maastricht University, the Netherlands
[i] Department of Nutrition and Movement Sciences and School of Mental Health and Neuroscience, Maastricht University, the Netherlands

ARTICLE INFO

Article history:
Received 3 November 2020
Received in revised form
1 March 2021
Accepted 7 March 2021

Keywords:
Cerebral palsy
Cognitive function
Cognitive impairment
Neuroimaging
MRI

ABSTRACT

Introduction: Brain abnormalities in cerebral palsy (CP) are known to relate to motor outcome; however, their association with cognitive functioning is less clear.
Aim of the study: 1) To investigate the prognostic value of brain abnormalities for cognitive functioning; 2) To explore the added value of prognostic variables across ICF domains: motor function, epilepsy, gestational age, birthweight and educational level of the parents.
Methods: We retrospectively analyzed brain MRI scans of 75 children with CP (GMFCS level I–V, 36% born preterm), as part of a longitudinal study. MRI classification: qualitative classification of brain abnormality pattern and semi-quantitative grading of the extent of damage. Cognitive functioning, measured as non-verbal intelligent quotient (IQ), was dichotomized into 'impaired cognition' (IQ $\leq$ 70) and 'normal' (IQ > 70). Multivariable logistic regression produced odds ratios (OR) with 95% confidence interval (C.I.) of risk factors for impaired cognition.
Results: Overall, 27% of the tested participants had a non-verbal IQ below 70 and 36% of the participants was classified as 'having impaired cognition'. At a young age, a higher degree of white matter damage (OR 1.6, 95% C.I. 0.97–2.67) and a more severe GMFCS level (OR 3.2, 95% C.I. 1.70–5.98) are risk factors for impaired cognition at school-age (4–7 years of age). This model correctly predicts 89% of the cases. Brain damage alone predicts the presence of impaired cognition in 71% of the cases.
Interpretation: Brain MRI characteristics and GMFCS level at a young age can each help identify children with CP at risk for impaired cognition at school age and together have a strong predictive value.

1. Introduction

Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitations, attributed to non-progressive disturbances in the developing fetal or infant brain. CP is the most frequent diagnosis in cases of motor disability in childhood [1] and often leads to impairments in cognition, communication and behavior, thereby negatively influencing daily life [2]. Previous studies report intellectual disability (ID) in 24–45% of the children [3,4].

Motor and non-motor symptoms are clearly related: children

* Corresponding author. Department of Neurology, Debyelaan 25, 6227, HX, Maastricht, the Netherlands.
E-mail addresses: irene.moll@maastrichtuniversity.nl (I. Moll), Jeroen.vermeulen@mumc.nl (R.J. Vermeulen).

https://doi.org/10.1016/j.ejpn.2021.03.010

with more restricted mobility (gross motor function classification system [GMFCS] level IV and V) also have more non-motor impairments like cognitive deficits or seizures [5]. The GMFCS level is based on motor performance and a poor motor function can be associated with poor cognitive function [3,6]. Epilepsy is also associated with cognitive deficits [7]. Other known factors are educational level of the parents and low birth weight, although the negative association of the latter is reported to have declined over the years [8,9].

Patterns of brain damage vary with their time of onset. Brain malformations arise in the first trimester of pregnancy and are associated with spasticity and specific cognitive disabilities (e.g. decreased comprehension of spoken language) [10]. Brain damage in spastic CP, namely white matter damage, is associated with the second trimester. In the more severe cases (GMFCS IV and V), this brain damage is associated with very poor cognitive functioning [11,12].

Grey matter damage, including bilateral basal ganglia and thalami (BGT) damage and middle cerebral artery infarction, is due to an intra-uterine event in the third trimester [13]. BGT injuries are associated with dyskinetic CP and in severe cases also with spasticity [14]. Comprehension of spoken language can be preserved in these patients, depending on the white matter involvement, despite severe motor disability [10]. It is reported that dyskinetic CP patients have higher intellectual and executive functioning than spastic CP patients when correcting for GMFCS level and prematurity [15].

Unilateral CP is associated with disturbances in executive functions, which can be caused by lesions at any location in the frontal-subcortical network [16].

However, prediction of cognitive functioning of an individual patient is still difficult, while early identification of CP patients at risk for intellectual disability is useful. Few studies report individual testing in a representative sample [17]. Little is known about the prognostic value of both qualitative and quantitative MRI brain assessments at a young age, especially when combined with other clinical features.

The aim of the study is to analyze the relation between cognitive functioning at school age in CP patients with 1) brain abnormalities and 2) a set of variables across the International Classification of Functioning, Disability and Health (ICF) domains, based on previous knowledge and available data: motor function (GMFCS level), epilepsy, gestational age, birthweight and educational level of parents. The ICF domains include 1) Body structures 2) Body functions 3) Activities and participation 4) Contextual factors (including environmental - and personal factors) [18].

2. Methods

2.1. Participants

PERRIN, Pediatric Rehabilitation Research in the Netherlands Cerebral Palsy, is a prospective longitudinal cohort study on the course and determinants of daily function in children with CP. The current study uses data of the PERRIN 0–5 and 5–9 cohorts. For the 0–5 cohort (n = 100), children at ages 1.5 or 2.5 were included with follow-up to age 4.5. For the 5–9 cohort (n = 115), children at ages 5 or 7 were included with follow-up for 3 consecutive years [19]. Recruitment took place between 2002 and 2007. Informed consent was obtained from all parents. Ethical approval for the study was given by the committees for medical ethics at University Medical Centre Utrecht, VU University Medical Centre (Amsterdam) and the four participating rehabilitation centers (For details see Ref. [19].).

In 77 out of 215 children in this study, neuroimaging was clinically available. For two children, only computed tomography (CT) scans were available and only the qualitative part of the MRI assessment could be retrieved. Two children were excluded because of another diagnosis. In total, the 'PERRIN 0–9 neuroimaging cohort' consists of 75 children (n = 27 from the 0–5 group and n = 48 from the 5–9 group).

Distributions of gender, CP type and GMFCS level were very similar in the PERRIN MRI group versus the PERRIN no MRI group (Pearson Chi-square 2-sided p-values 0.108, 0.604 and 0.959), assuring that the current PERRIN MRI group is representative for the whole PERRIN cohort. The following information was derived from medical history obtained from the parents: gestational age; birthweight; diagnosis of epilepsy. Table 1 displays the characteristics of the population: more than one third was born preterm (<37 weeks: n = 26, 36.1%), 13 participants (17.3%) had a birthweight <1500 g and 12 participants (16%) were diagnosed with epilepsy.

2.2. Neuroimaging: assessment of brain abnormalities – ICF domain of body structures

Technical details of the scanners used, varied between hospitals and years (2000–2006). Median age at the time of neuro-imaging was 17 months (IQR 6.25–25). In total, 52 participants (69.3%) were scanned <2 years of age: 16 of them (21.6%) were scanned in the neonatal period (≤1 month of age) and 12 (16.2%) between 18 and 23 months. The remaining 24 participants (32%) were 2–17 months old at the time of neuroimaging. We applied both a qualitative and a semi-quantitative MRI evaluation system. Qualitative: we used the MRI based classification 'pattern of brain damage' by Himmelmann et al. [13]. See Table 2 for an overview of the applied classification. Semi-quantitative: grading of neuroimaging was done according to a scale adapted from Cioni et al. [20] regardless of the qualitative pattern. The semi-quantitative scale of Cioni consists of 7 items, ranging from grade 1 ((almost) normal) to grade 3 (most abnormal). The items on the scale were expanded: the item 'white matter reduction' was split into 'frontal -' and 'occipital white matter reduction'. Furthermore, the following items were added on the scale: cerebellum, thalamus, putamen and globus pallidus. These last four items can be scored normal (grade 1) or abnormal (grade 2). The 12 semi-quantitative scales were summed up to subscores for 'extent of white matter damage' (grades of white matter signal abnormality, white matter reduction frontal and occipital, cysts and corpus callosum, ranging from 5 to 15) and 'extent of grey matter damage' (grades of thalamus, putamen, cortical grey matter and globus pallidus, ranging from 4 to 9).

A neonatologist (LSdV, with >30 years of experience) graded the neuroimaging of all participants. A second physician, a child neurologist (RJV, with >15 years of experience), also graded the neuroimaging of 46 participants, independently. To test the reliability of the applied rating scale, the intraclass correlation coefficient (ICC) was calculated (see Table 3).

2.3. Functional assessment

2.3.1. Cognitive functioning assessment – ICF domain of Body functions

Impaired cognition was defined as a non-verbal intelligence quotient (IQ) of 70 and below. The IQ of the 0–5 cohort was based on IQ scores from the Snijders–Oomen Nonverbal Intelligence (SON) Test at age 4.5 [21]. The IQ of the 5–9 cohort was based on scores from the Raven's Colored Progressive Matrices for children at first measurement (ages 5 or 7) [22]. Participants were excluded from this outcome if they could not perform the IQ test because of motor disabilities.

2.3.2. Motor function classification – ICF domain of activities

Children were classified according to GMFCS level (I–V), type of

Table 1
Baseline characteristics, n = 75.

Characteristic	Value
Gender: male, n (%)	41 (54.7%)
Completed weeks of gestation	Mean 36.4 weeks, SD 5.1 (range 24.9–42.0 weeks)
	≤32 weeks: n = 21 (26.4%)
	<37 weeks: n = 26 (36.1%)
Birth weight	Mean 2725 g, SD 1047.8 (range 850–4750 g)
	<1500 g: n = 13 (17.3%)
Intelligent quotient, n (%)	
- missing	9 (12%)
- not testable	10 (13.3%)
- <70	15 (20%)
- ≥70	41 (54.7%)
Epilepsy	
- Yes	12 (16%)
- No	52 (69.3%)
- Missing	11 (14.7%)
GMFCS level, n (%)	
- I	32 (42.7%)
- II	12 (16%)
- III	13 (17.3%)
- IV	10 (13.3%)
- V	8 (10.7%)
CP type, n (%)	
- Bilateral spastic	41 (54.7%)
- Unilateral spastic	25 (33.3%)
- Dyskinetic	4 (5.3%)
- Ataxic	2 (2.7%)
- Non-classifiable	3 (4%)
Patterns of brain damage	
- Normal	3 (4%)
- Predominant white matter injury	45 (60%)
o *multicystic encephalomalacia*	*1*
o *periventricular leukomalacia*	*26*
o *porencephaly following PVHI*	*18*
- Predominant grey matter injury	17 (22.7%)
o *basal ganglia-thalamic injuries (BGT)*	*9*
o *full term watershed infarction*	*2*
o *middle cerebral artery infarction*	*6*
- Brain malformation	6 (8%)
- Miscellaneous	4 (5.3%)

Abbreviations used: BGT, basal ganglia-thalamic injuries; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; n, number; PVHI, periventricular hemorrhagic infarction; SD, standard deviation.

motor impairment and limb distribution by a trained researcher [19,23]. To allow for a reliable assessment, data from measurements at age 30 months were used for the 0–5 cohort, and baseline measurements at ages 5 or 7 for the 5–9 cohort [24]. Fig. 1 shows the timeline of inclusion and functional assessments for the two cohorts.

2.3.3. Educational level of the parents – ICF domain of Environmental factors

Data on educational level of both parents was collected using questionnaires and divided into eight levels; from primary school (level 1) to university (level 8). The highest level was used.

2.4. Statistics

All statistical analyses were performed using IBM SPSS Statistics version 24. Exploratory univariate logistic regression analysis was performed for all variables with impaired cognition (dichotomous variable) as dependent outcome: white matter subscore (ranging from 5 to 15), grey matter subscore (ranging from 4 to 9), GMFCS level (level I–V), birth weight (in grams) and highest educational level of the parents (level 1–8). Fisher's exact test was performed to assess possible relations with impaired cognition for categorical data: the five different brain damage patterns and epilepsy.

Multivariable logistic regression analysis was used to produce a model for risk factors for impaired cognition, including those variables showing a significant univariate relation with impaired cognition, and to calculate the odds ratios (OR; including 95% confidence intervals; C.I.). This analysis included the white matter subscore and GMFCS level. Six participants with a brain malformation (BM) were excluded from this analysis, because the MRI assessment scale for the white and grey matter damage was not intended for this patient group.

Stochastic regression imputation was applied for some missing neuroimaging data, in order to limit the risk of bias by deleting incomplete cases. The analyses with and without imputation were compared.

3. Results

3.1. Patterns of brain abnormality – ICF domain of body structures

'Predominant white matter injury' (60%) and 'predominant grey matter injury' (23%) were the most common brain damage patterns. In only 4% of the cases, the brain MRI was classified as 'normal'. See Table 1 for details. The ICC of the grading ranged from 0.44 (fair) to 1 (excellent) [mean 0.73: good] (See Table 3.).

3.2. Cognitive functioning – ICF domain of body functions

The non-verbal IQ could be tested in 56 participants: 17

Table 2
MRI assessment items.

Qualitative assessment	
Pattern of brain damage	A. Developmental brain malformations - Agyria-pachygyria-band-spectrum, polymicrogyria - Schizencephaly - Unilateral megalencephaly - Unclassifiable brain malformations B. Predominant white matter injury - Periventricular leukomalacia - Multicystic encephalomalacia - Posthaemorrhagic porencephaly C. Predominant grey matter injury - Basal ganglia and/or Thalamic lesions - Watershed infarction - Arterial ischemic infarction D. Miscellaneous - Ventriculomegaly - Atrophy - Combination of these abnormalities not consistent with one pattern of pre-/perinatally acquired lesions E. Normal

Semi-quantitative assessment[a]

	Grade 1	**Grade 2**	**Grade 3**
1. Size of lateral ventricles	Normal size of both ventricles	Bilateral mild enlargement	Bilateral enlargement of severe grade at least of one ventricle frontal and occipital
2. Size of subarachnoid space	No enlargement or limited to one lobe	Diffuse but mild enlargement	Diffuse and severe enlargement
3. White matter abnormal signal intensity	Normal or bilateral involvement only peritrigonal	Diffuse bilateral involvement of PV WM, no U fibers involvement	Bilateral involvement of SC WM
4. White matter reduction frontal	Not reduced	Reduction of PV WM in both hemispheres or of SC WM diffusely in one hemisphere	Reduction of SC WM diffusely in both hemispheres (absent white matter)
5. White matter reduction occipital	Not reduced	Reduction of PV WM in both hemispheres or of SC WM diffusely in one hemisphere	Reduction of SC WM diffusely in both hemispheres (absent white matter)
6. Cysts	No cysts	Few cysts (<3) unilateral or bilateral involving PV regions or only one large cyst involving SC WM	Bilateral multiple cysts (>3) involving PV regions and/or SC WM
7. Corpus callosum	Normal or thinning involving the posterior body	Thinning involving the total body	Diffuse thinning
8. Cerebellum	Normal	Abnormal	N/A
9. Thalamus	Normal	Abnormal	N/A
10. Putamen	Normal	Abnormal	N/A
11. Cortical grey matter (ulegyria and cortical dysplasia)	No cortical abnormalities	Unilateral cortical abnormalities	Bilateral cortical abnormalities
12. Globus Pallidus	Normal	Abnormal	
Total Score:			

[a] Item 1 and 2: reflect the amount of atrophy. Items 3 up to 7 are summed to get a 'degree of white matter damage subscore' (ranging from 5 to 15). Items 9 up to 12 are summed to get a 'degree of grey matter damage subscore' (ranging from 4 to 9).

Table 3
Reliability of MRI assessment depicted as intraclass correlation (ICC).

Variable	ICC	n
Pattern	0.874	46
Ventricle size	0.777	43
WM abnormality	0.459	42
WM reduction frontal	0.440	41
WM reduction occipital	0.750	41
Cysts	0.607	41
Size of subarachnoid space	0.6	40
Corpus callosum	0.599	40
Cerebellum	0.796	41
Thalamus	0.738	41
Putamen	0.813	41
Globus pallidus	1	43
Cortical grey	0.878	41

Abbreviations used: ICC, intraclass correlation; WM, white matter.

participants performed the SON test (age 4.5) and 39 participants performed the Raven's Colored Progressive Matrices (ages 5 or 7). Of these participants, 41 (73%) were classified as having normal cognition (i.e. IQ > 70) and 15 (27%) as having impaired cognition (i.e. IQ $\leq$ 70). Eight additional participants (mostly in GMFCS level IV-V) tried to perform the tests but appeared to be unable because of their cognitive impairments, and were therefore classified as having impaired cognition. Thus, in total, 23 out of 64 (36%) of the participants with available information was classified as having impaired cognition. For two participants, the IQ was missing because of motor impairments. For nine other participants, the IQ was missing because of other reasons that were not related to cognitive functioning. See Fig. 2A for the distribution of cognitive functioning across the patterns of brain damage (additional information is shown in Table A.1 and Fig. A.1 in the appendix).

3.3. CP type and motor function classification – ICF domains of body functions & activities

The majority of the 75 participants had spastic CP; 41 (55%) had bilateral spastic CP; 25 (33%) unilateral spastic CP; four dyskinetic

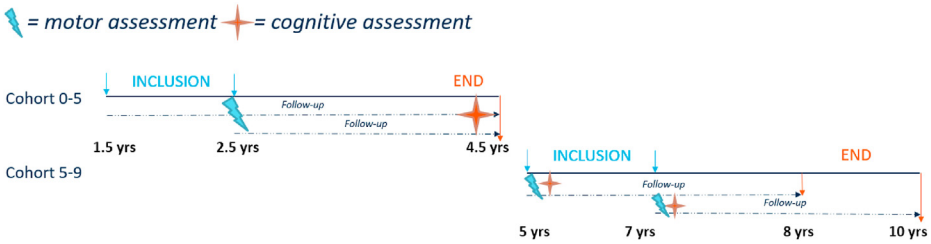

Fig. 1. Timeline of inclusion and functional assessments.

CP; 2 ataxic CP and 3 non-classifiable CP. The most common GMFCS level was level I (n = 32, 43%) and the distribution over the remaining four levels was relatively even. See Table 1, Fig. 2B and C for details (and Tables A.2, A.3 and Fig. A.2 in the appendix for more detailed information).

3.4. Prognostic factors for cognitive functioning

Univariate analysis did not show a statistically significant relation between impaired cognition and any pattern of brain damage, grey matter subscore, epilepsy, gestational age, birth weight or educational level of the parents. However, for white matter subscore and GMFCS level, there was a significant relation with impaired cognition. See Table A.4 in the appendix for details. Multivariable logistic regression showed that a higher degree of white matter damage, assessed at MRI obtained at a young age (median 17 months), is a prognostic factor for later impaired cognition (OR 1.63 for the extent of white matter subscore, 95% C.I. 1.13–2.36). This MRI based model can correctly distinguish between presence and absence of ID in 71% of the cases. When adding functional information, a model containing GMFCS level (OR 3.18, 95% C.I. 1.69–5.98) and the degree of white matter damage (OR 1.61, 95% C.I. 0.97–2.67) can explain impaired cognition correctly in 89% of the cases. See Tables 4 and 5 for details. The conclusions did not change after stochastic regression imputation of some missing neuroimaging values, nor after exclusion of the eight patients who were not able to perform the test for cognitive functioning. (see Tables A.5-A.7 in the appendix for details).

4. Discussion

4.1. Patterns of brain abnormality – ICF domain of body structures

The prevalences of brain abnormality patterns we found are quite similar to previously reported numbers in CP ('predominant white matter injury' 60%, 'predominant grey matter injury' 23%, normal imaging 4% and brain malformation 8%) [3,13,25]. In a large review on 2076 patients, Arnfield et al. found brain malformations in 9.3%, white matter lesions in 46.2%, grey matter lesions in 25.4% (excluding post-natal strokes) and normal MRI in 12% of the patients. It cannot be completely ruled out that hereditary spastic paraplegia (HSP) was present in any of the three (4%) patients who had a normal MRI, as advanced genetic analysis was not part of the common diagnostic work-up in the time of PERRIN inclusions (2002–2007). However, there were no clinical clues for HSP, nor for progressive encephalopathy during the longitudinal follow-up.

4.2. Cognitive functioning – ICF domain of body functions

In our cohort, 23 out of 64 (36%) participants were classified as having impaired cognition (including eight patients who were not able to perform tests because of cognitive impairments) and 27% of the tested patients had a non-verbal IQ $\leq$ 70. Previous literature reports numbers ranging from 24 to 51% for intellectual disability [1,3,4,11].

It should be noted that our numbers are solely based on the non-verbal IQ, and we therefore call it 'impaired cognition' instead of 'intellectual disability'. According to the definition of the American Association on Intellectual and Developmental Disabilities (AAIDD) adaptive behavior should also be taken into account for a diagnosis of ID (i.e. conceptual, social and practical skills), besides cognitive functioning [26]. Stadskleiv et al. applies this broader definition: the proportion of patients with ID was 24%, while the proportion with IQ < 70 was 33% [3]. Stadskleiv et al. also reports an uneven cognitive profile in about 20% of the patients. Our data only partly distinguishes cognitive profiles: the SON test reports a 'performal' and 'reasoning' IQ, but the Raven's Colored Progressive Matrices only reports a total IQ. In nine children (out of 21), the SON test reported a significant difference between the two types of intelligence, of whom two were classified as 'intellectually disabled'. This means that for the 21 children in our cohort tested with the SON test, most children classified as 'intellectually disabled' do not have a significant difference between performal and reasoning IQ. Our data does not, however, reveal which patients have limited *verbal* cognitive capacities, nor which patients experience problems in daily life due to a disharmonic cognitive profile.

4.3. Motor classifications – ICF domain of activities

Our numbers for CP distribution are in line with the literature, describing ranges from 39 to 55% for bilateral spastic CP (55%) and 29–50% for unilateral CP (33%) [3,4]. In our cohort, 43% of the participants were classified in GMFCS level I and 76% in GMFCS level I-III. In the literature, GMFCS level I is the most common, ranging from 32 to 51%, and 65–70% of CP patients who can walk independently [3,4,11,25].

4.4. Prognostic factors for cognitive functioning

The multivariable analysis showed that the extent of white matter damage and GMFCS level are prognostic factors for cognitive functioning at school age. The five qualitative patterns of brain damage did not show an association with cognitive functioning. However, it is possible to compare the prevalence of impaired cognition in these subgroups to the literature. In addition to brain damage patterns, impaired visual function is associated with worse neurodevelopmental outcomes [27]. Information on visual function was unfortunately not systematically collected in the PERRIN study.

In our cohort, the nine participants with BGT injury performed quite well, compared to the literature: eight of them are classified in GMFCS level I-III and only one out of seven tested had impaired cognition. BGT lesions are more often associated with GMFCS level IV and V (67% according to Himmelmann [4]) and impaired cognitive outcome [28]. However, other literature reports that the

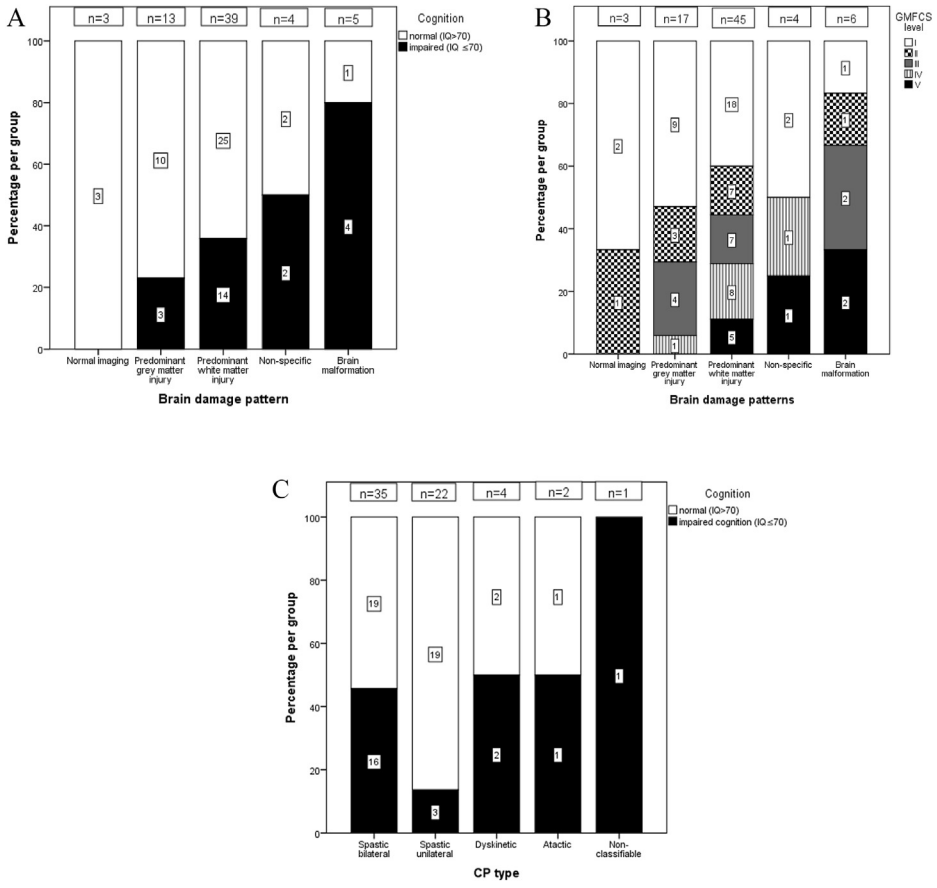

Fig. 2. Distributions of brain damage patterns, GMFCS level, impaired cognition and CP type.

Table 4
Multivariable logistic regression model for presence of impaired cognitive functioning, based on MRI characteristics. N = 54, 15 missing (6 participants with BM excluded).

	B (S.E.)	OR	p-value	95% C.I.
Extent of white matter damage	0.491 (0.188)	1.633	0.009	1.130–2.362
Constant	−4.541 (1.524)	0.011	0.003	

R^2 (Nagelkerke) = 0.212; Abbreviations used: S.E. standard error; C.I. confidence interval; OR, odds ratio.
Area under the ROC curve: 0.710 (S.E. 0.071, 95% C.I. 0.571–0.849).

Table 5
Multivariable logistic regression model for presence of impaired cognitive functioning, based on MRI characteristics and GMFCS level. N = 54, 15 missing (6 participants with BM excluded).

	B (S.E.)	OR	p-value	95% C.I.
GMFCS level	1.157 (0.322)	3.180	0.000	1.692–5.975
Extent of white matter damage	0.473 (0.259)	1.605	0.068	0.966–2.667
Constant	−7.288(2.349)	0.002	0.001	

R^2 (Nagelkerke) = 0.568; Abbreviations used: S.E. standard error; C.I. confidence interval; OR, odds ratio.
Area under the ROC curve: 0.890 (S.E. 0.050, 95% C.I. 0.793–0.988).

outcome of patients with BGT injury is variable and depends on the degree of additional damage, especially in the white matter [14,29]. Additional damage to the pericentral cortex increases the risk of cognitive impairment [14]. More detailed grading in the applied MRI assessment might be needed to explain the good results in our participants. However, since seven of the nine participants are classified as spastic CP, it is unlikely that their MRI scans did not show additional damage.

Weeke et al. found, in contrast to most reported studies, that IQ at school age is associated with the extent of grey matter damage, instead of white matter damage [30]. However, this study by Weeke et al. specifically used MRIs performed in the first week after birth of patients treated with hypothermia after hypoxic-ischemic encephalopathy. Due to the application of cooling, less severe damage of the white matter might be expected, with subsequent consequences for cognition [30]. In our cohort, the prevalence of impaired cognition is higher in the group with predominantly white matter damage (31%, 13% missing) than in the group with predominantly grey matter damage (18%, 24% missing). Also, 71% of our participants with predominantly white matter damage is

ambulant (GMFCS level I-III). White matter lesions are correspondingly reported in the literature to relate to mild motor disabilities (GMFCS I-II) in about 75% of cases, and to impaired language comprehension [4,10,25].

Besides the association of cognitive functioning with the degree of white matter damage and GMFCS level, our data did not show associations of cognitive functioning with educational level of the parents, gestational age, birth weight and epilepsy. The literature reports that parental schooling is related to child cognitive functioning and prevalence of ID, especially in preterm born children [9,31]. As not only maternal level of education is of importance, we chose to include the highest parental level of education [31]. In our cohort, 36.1% of the participants was born preterm (<37 weeks of gestation). Our study seems to provide evidence that in a population with mixed gestational age, brain damage and CP, brain damage is a stronger prognostic factor for cognition than educational level of the parents.

Furthermore, birth weight and epilepsy were not identified as prognostic factors for cognitive functioning in our population. The prevalence of epilepsy in our population (16%) is lower than reported in the literature (around 30%) [32]. It could be that epilepsy has a later onset in part of the patients. There was no collinearity between the extent of white matter damage and birth weight. Although it is known that low birth weight and epilepsy can have negative impact on cognitive functioning, it could be that MRI characteristics are related more directly to cognitive functioning.

4.5. Limitations of the study

The number of available MRIs was limited (77/215 = 36%) because neuroimaging was not part of the original PERRIN studies. We took advantage of clinically available MRI brain scans in the time period 2000–2007. Although it is recommended that every child suspected of having CP, will have a brain MRI as an infant [33], this did (and does) not always happen due to personal or age related reasons, or limited resources. Additionally, this study is based on conventional MR images (made between 2000 and 2006). Newer studies have the opportunity to apply more sophisticated MR sequences like DTI and 3D volumetry which may reveal more subtle abnormalities.

For reliable MRI classification, a patient's age at time of imaging is important, as mentioned by Himmelmann et al.: because of incomplete myelination, mild lesions can be missed before the age of 2 years [13]. The median age of neuroimaging was 17 months (IQR (IQR 6.25–25) and only 22 participants (29.3%) were 2 years or older at the time of neuroimaging. However, neonatal scanning (≤1 month) is also reliable and was applied in 16 patients (21%). Twenty-four participants (32%) were scanned at ages 2–17 months, which is the least reliable period. Of these 24 participants, 10 were classified as 'periventricular leukomalacia', the most difficult pattern to assess reliably prior to 24 months. The other patterns in this group were porencephaly (n = 5), brain malformation (n = 5), middle cerebral artery infarction (n = 2), BGT injury (n = 1) and normal (n = 1). Nine of these 10 participants classified as PVL, had enlarged ventricles, which can be assessed reliably at all ages. In total, normal imaging was only found in 4% which is quite low compared to the literature. This makes it unlikely that a substantial part was incorrectly classified as 'normal'. Furthermore, an extra (exploratory) analysis including only the patients with MRI at age >17 months (28 complete cases) showed the same trends, although it was no longer statistically significant due to small numbers.

The reliability of the MRI classification was generally good. However, the interrater agreement for the frontal white matter reduction was relatively low. This item was not analyzed separately, but only together with the other white matter items, and therefore the influence of this lower reliability is limited. Moreover, it is unfortunate that only limited information on epilepsy was available – information on treatment would have been useful, as well as information on visual function.

As mentioned before, a limitation of this study is that only non-verbal intelligence was measured, while intellectual disability depends on total cognitive functioning and adaptive behavior [26]. Therefore, our results comprise impaired cognitive functioning, but not intellectual disability. Furthermore, there were no adaptations made for children with severe motor impairments to allow them to respond to the cognitive tests. As described, 8 patients (mostly GMFCS level IV-V) tried to perform tests but appeared to be incapable because of their cognitive functioning. However, since no adaptations for motor impairment were made, it is hard to assure that it was merely cognitive impairment hindering the children from answering. Therefore, we also performed the regression analyses after excluding these 8 patients (Table A.7 in the appendix). The conclusion based on these extra analyses remains unchanged.

5. Conclusion

The amount of cerebral white matter damage, assessed with MRI at a young age, is a risk factor for later cognitive functioning. The GMFCS level can also help to distinguish children at risk of impaired cognition. Brain damage on MRI and GMFCS together have a strong predictive value for impaired cognition. Birth weight, gestational age, epilepsy and educational level of the parents were not related to impaired cognition in our cohort. Our findings provide valuable prognostic information for clinicians, which could create opportunities to adjust care, support and expectations in an early phase of life of children with CP and their families.

Declaration of competing interest

None of the authors has any competing interest to declare.

Acknowledgement

This research has been performed as part of the PERRIN (Pediatric Rehabilitation Research in the Netherlands) research program and has been supported by the Netherlands Organization for Health Research and Development (grant numbers 1435.0011 and 1435.0028). The Hague, The Netherlands. The authors would like to thank the children and parents for their participation, and thank the university medical centers and rehabilitation centers for their collaboration in data collection. We thank D.W. Smits (De Hoogstraat Rehabilitation and University Medical Center Utrecht) for preparing the data, and the PERRIN consortium for their contribution to the program; A.J. Dallmeijer (Amsterdam UMC, Vrije Universiteit Amsterdam); M.E. Roebroeck (Erasmus MC, University Medical Center and Rijndam Rehabilitation, Rotterdam); M. Ketelaar, J.M. Voorman (University Medical Center Utrecht and Rehabilitation Center De Hoogstraat, Utrecht); H.A. Reinders-Messelink (Revalidatie Friesland and University Medical Center Groningen); J.W. Gorter (McMaster University, Hamilton, Canada), and J. Verheijden, BOSK (Association of Physically Disabled Persons and their Parents).

Appendix. additional tables and graphs (online only)

Table A.1
Distribution of patterns of brain damage and impaired cognition

Cognition Pattern	Normal (IQ > 70)	Impaired (IQ ≤ 70)	Missing	Total
Normal	3	0		3
Predominant grey matter	10	3	4	17
- Basal ganglia	6	1		7
- Watershed	1	1		2
- MCA infarction	3	1		4
Predominant white matter	25	14	6	45
- PVL	11	10		21
- Porencephaly	14	3		17
- MCE	0	1		1
Brain malformation	1	4	1	6
Non-specific	2	2		4
Total	41	25		66

Abbreviations used: CP: cerebral palsy; Dev. Developmental; GMFCS, gross motor classification system; IQ, intelligence quotient; MCE multicystic encephalomalacia; PVL, periventricular leukomalacia.

Table A.2
Distribution of patterns of brain damage and type of cerebral palsy (CP)

CP type Pattern	BSCP	USCP	DCP	ACP	NC	Total
Normal	2	0	0	1	0	3
Predominant grey matter injury	8	7	2	0	0	17
- Basal ganglia-thalamic injuries	5	2	2	0	0	9
- Watershed	0	2	0	0	0	2
- MCA infarction	3	3	0	0	0	6
Predominant white matter injury	26	14	1	1	3	45
- PVL	20	1	1	1	3	26
- Porencephaly	5	13	0	0	0	18
- MCE	1	0	0	0	0	1
Brain malformation	4	2	0	0	0	6
Miscellaneous	1	2	1	0	0	4
Total	41	25	4	2	3	75

Abbreviations used: CP, cerebral palsy, BSCP, bilateral spastic CP; USCP, unilateral spastic cerebral palsy; DCP, dyskinetic cerebral palsy; ACP, ataxic cerebral palsy; MCA, Middle cerebral artery infarction; MCE, multicystic encephalomalacia; NC, non-classifiable; PVL, periventricular leukomalacia.

Table A.3
Distribution of patterns of brain damage and GMFCS level

GMFCS Pattern	I	II	III	IV	V	Total
Normal	2	1	0	0	0	3
Predominant grey matter	9	3	4	1	0	17
- Basal ganglia thalamic	3	1	4	1	0	9
- Watershed	2	0	0	0	0	2
- MCA infarction	4	2	0	0	0	6
Predominant white matter	18	7	7	8	5	45
- PVL	7	4	5	6	4	26
- Porencephaly	11	3	2	2	0	18
- MCE	0	0	0	0	1	1
Brain malformation	1	1	2	0	2	6
Miscellaneous	2	0	0	1	1	4
Total	32	12	13	10	8	75

Abbreviations used: GMFCS, gross motor classification system; MCA, Middle cerebral artery; MCE, multicystic encephalomalacia; PVL, periventricular leukomalacia.

Table A.4
p-values based on univariate analysis for possible relation with impaired cognition

Variable	p-value	Test
Brain damage patterns	0.134	Fisher's Exact Test
Epilepsy (dichotomous)	0.743	
Grey matter subscore	0.164	Univariate logistic regression
White matter subscore	0.005	
GMFCS level	<0.001	
Birth weight	0.534	
Highest educational level parents	0.908	

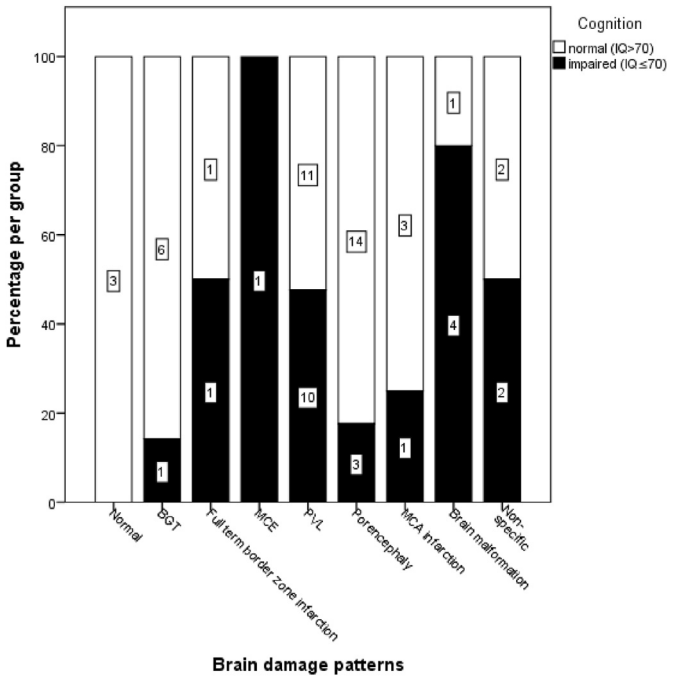

Fig. A.1. Brain damage patterns and the percentage of intellectual disability.

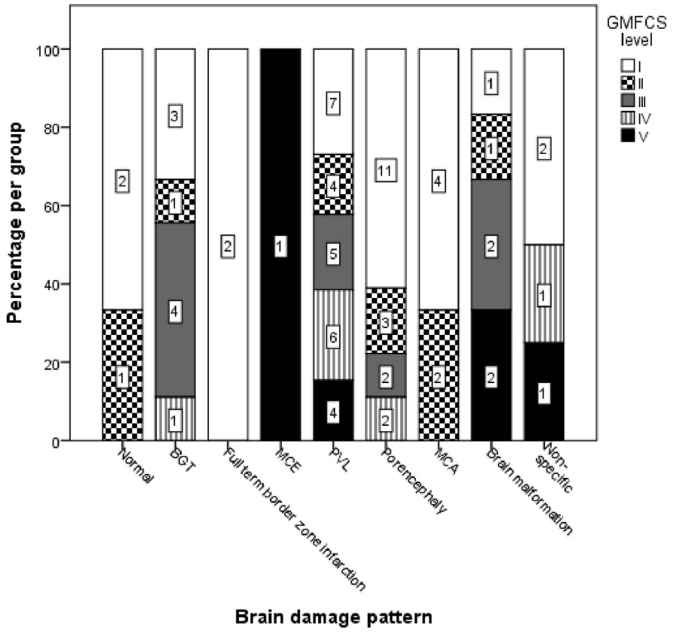

Fig. A.2. Distribution of brain damage patterns and GMFCS level.
Abbreviations used in Fig. A.1 and A.2: GMFCS, gross motor classification system; IQ, intelligence quotient; BGT, basal ganglia-thalamic lesion, MCE multicystic encephalomalacia; PVL, periventricular leukomalacia; MCA, middle cerebral artery ischemia.

Table A.5
Additional multivariable logistic regression model for presence of impaired cognitive functioning, based on MRI characteristics with imputation for the white matter subscore. N = 59, 10 missing (6 participants with BM excluded).

	B (S.E.)	OR	p-value	95% C.I.
Extent of white matter damage	.421 (.171)	1.524	0.014	1.091–2.130
Constant	−4.013 (1.373)	0.018	0.003	

R^2 (Nagelkerke) = 0.167; Abbreviations used: S.E. standard error; C.I. confidence interval; OR, odds ratio.
Area under the ROC curve: 0.685 (S.E. 0.073, 95% C.I. 0.542–0.827).

Table A.6
Additional multivariable logistic regression model for presence of impaired cognitive functioning, based on MRI characteristics with imputation for the white matter subscore and GMFCS level. N = 59, 10 missing (6 participants with BM excluded).

	B (S.E.)	OR	p-value	95% C.I.
GMFCS level	1.138 (0.303)	3.119	0.000	1.721–5.653
Extent of white matter damage	0.405 (0.230)	1.499	0.078	0.956–2.353
Constant	−6.714 (2.070)	0.001	0.001	

R^2 (Nagelkerke) = 0.534; Abbreviations used: S.E. standard error; C.I. confidence interval; OR, odds ratio.
Area under the ROC curve: 0.875 (S.E. 0.050, 95% C.I. 0.776–0.974).

Table A.7
Additional multivariable logistic regression model for presence of impaired cognitive functioning, based on MRI characteristics and GMFCS level, after exclusion of 8 patients who were not able to perform tests. N = 48, 14 missing (5 participants with BM excluded).

	B (S.E.)	OR	p-value	95% C.I.
GMFCS level	0.933 (0.340)	2.542	0.006	1.306–4.947
Extent of white matter damage	0.498 (0.258)	1.646	0.053	0.993–2.728
Constant	−7.114 (2.328)	0.001	0.002	

R^2 (Nagelkerke) = 0.427; Abbreviations used: S.E. standard error; C.I. confidence interval; OR, odds ratio.
Area under the ROC curve: 0.722 (S.E. 0.078, 95% C.I. 0.569–0.876).

References

[1] C. Cans, 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. 42 (12) (2000) 816–824.
[2] P. Rosenbaum, N. Paneth, A. Leviton, M. Goldstein, M. Bax, D. Damiano, et al., A report: the definition and classification of cerebral palsy April 2006, Dev. Med. Child Neurol. Suppl. 109 (suppl 109) (2007) 8–14.
[3] K. Stadskleiv, R. Jahnsen, G.L. Andersen, S. von Tetzchner, Neuropsychological profiles of children with cerebral palsy, Dev. Neurorehabil. 21 (2) (2018) 108–120.
[4] K. Himmelmann, P. Uvebrant, Function and neuroimaging in cerebral palsy: a population-based study, Dev. Med. Child Neurol. 53 (6) (2011) 516–521.
[5] L. Enkelaar, M. Ketelaar, J.W. Gorter, Association between motor and mental functioning in toddlers with cerebral palsy, Dev. Neurorehabil. 11 (4) (2008) 276–282.
[6] Y.C. Wu, K.R. Heineman, S. La Bastide-Van Gemert, D. Kuiper, M. Drenth Olivares, M. Hadders-Algra, Motor behaviour in infancy is associated with neurological, cognitive, and behavioural function of children born to parents with reduced fertility, Dev. Med. Child Neurol. 62 (9) (2020) 1089–1095, https://doi.org/10.1111/dmcn.14520.
[7] L.V. Gabis, N.M. Tsubary, O. Leon, A. Ashkenasi, S. Shefer, Assessment of abilities and comorbidities in children with cerebral palsy, J. Child Neurol. 30 (12) (2015) 1640–1645.
[8] A. Goisis, B. Ozcan, M. Myrskyla, Decline in the negative association between low birth weight and cognitive ability, Proc. Natl. Acad. Sci. U. S. A. 114 (1) (2017) 84–88.
[9] H.S. Wong, P. Edwards, Nature or nurture: a systematic review of the effect of socio-economic status on the developmental and cognitive outcomes of children born preterm, Matern. Child Health J. 17 (9) (2013) 1689–1700.
[10] J.J. Geytenbeek, K.J. Oostrom, L. Harlaar, J.G. Becher, D.L. Knol, F. Barkhof, et al., Language comprehension in nonspeaking children with severe cerebral palsy: neuroanatomical substrate? Eur. J. Paediatr. Neurol. : EJPN : Off. J. Eur. Paediatr. Neurol. Soc. 19 (5) (2015) 510–520.
[11] K. Himmelmann, E. Beckung, G. Hagberg, P. Uvebrant, Gross and fine motor function and accompanying impairments in cerebral palsy, Dev. Med. Child Neurol. 48 (6) (2006) 417–423.
[12] S.M. Reid, E.M. Meehan, S.J. Arnup, D.S. Reddihough, Intellectual disability in cerebral palsy: a population-based retrospective study, Dev. Med. Child Neurol. 60 (7) (2018) 687–694.
[13] K. Himmelmann, V. Horber, J. De La Cruz, K. Horridge, V. Mejaski-Bosnjak, K. Hollody, et al., MRI classification system (MRICS) for children with cerebral palsy: development, reliability, and recommendations, Dev. Med. Child Neurol. 59 (1) (2017) 57–64.
[14] I. Krägeloh-Mann, A. Helber, I. Mader, M. Staudt, M. Wolff, F. Groenendaal, et al., Bilateral lesions of thalamus and basal ganglia: origin and outcome, Dev. Med. Child Neurol. 44 (7) (2002) 477–484.
[15] O. Laporta-Hoyos, J. Ballester-Plane, D. Leiva, T. Ribas, J. Miralbell, C. Torroja-Nualart, et al., Executive function and general intellectual functioning in dyskinetic cerebral palsy: comparison with spastic cerebral palsy and typically developing controls, Eur. J. Paediatr. Neurol. : EJPN : Off. J. Eur. Paediatr. Neurol. Soc. 23 (4) (2019) 546–559.
[16] A. Crichton, M. Ditchfield, S. Gwini, M. Wallen, M. Thorley, J. Bracken, et al., Brain magnetic resonance imaging is a predictor of bimanual performance and executive function in children with unilateral cerebral palsy, Dev. Med. Child Neurol. 62 (5) (2020) 615–624. https://onlinelibrary.wiley.com/doi/10.1111/dmcn.14462.
[17] K. Stadskleiv, Cognitive functioning in children with cerebral palsy, Dev. Med. Child Neurol. 62 (3) (2020) 283–289.
[18] W.H. Organisation, International Classification of Functioning, Disability and Health, 2001. Geneva.
[19] D.W. Smits, J.W. Gorter, M. Ketelaar, P.E. Van Schie, A.J. Dallmeijer, E. Lindeman, et al., Relationship between gross motor capacity and daily-life mobility in children with cerebral palsy, Dev. Med. Child Neurol. 52 (3) (2010).
[20] G. Cioni, M.C. Di Paoo, B. Bertuccelli, P.B. Paolicelli, R. Canapicchi, MRI findings and sensorimotor development in infants with bilateral spastic cerebral palsy, Brain Dev. 19 (4) (1997) 245–253.
[21] P. Tellegen, M. Winkel, B. Wijnberg-Williams, J. Laros, Snijders-Oomen Nietverbale Intelligentietest, SON-R 21/2-7: Verantwoording en handleiding [Snijders-Oomen Nonverbal Intelligence Test, SON-R 21/2-7: Manual], Swets &Zeitlinger, Lisse, Netherlands, 1998.
[22] J.C. Raven, J.H. Court, Raven's Progressive Matrices and Vocabulary Scales, Oxford pyschologists Press, 1998.
[23] R. Palisano, P. Rosenbaum, S. Walter, D. Russell, E. Wood, B. Galuppi, Development and reliability of a system to classify gross motor function in children with cerebral palsy, Dev. Med. Child Neurol. 39 (4) (1997) 214–223.
[24] D.-W. Smits, J.W. Gorter, P.E. van Schie, A.J. Dallmeijer, M. Ketelaar, P.S. Group, How do changes in motor capacity, motor capability, and motor performance relate in children and adolescents with cerebral palsy? Arch. Phys. Med. Rehabil. 95 (8) (2014) 1577–1584.
[25] E. Arnfield, A. Guzzetta, R. Boyd, Relationship between brain structure on magnetic resonance imaging and motor outcomes in children with cerebral palsy: a systematic review, Res. Dev. Disabil. 34 (7) (2013) 2234–2250.

[26] R.L. Schalock, S.A. Borthwick-Duffy, V.J. Bradley, W.H. Buntinx, D.L. Coulter, E.M. Craig, et al., Intellectual Disability: Definition, Classification, and Systems of Supports, ERIC, 2010.
[27] G. Cioni, B. Bertuccelli, A. Boldrini, R. Canapicchi, B. Fazzi, A. Guzzetta, et al., Correlation between visual function, neurodevelopmental outcome, and magnetic resonance imaging findings in infants with periventricular leucomalacia, Arch. Dis. Child. Fetal Neonatal Ed. 82 (2) (2000) F134–F140.
[28] S.P. Miller, V. Ramaswamy, D. Michelson, A.J. Barkovich, B. Holshouser, N. Wycliffe, et al., Patterns of brain injury in term neonatal encephalopathy, J. Pediatr. 146 (4) (2005) 453–460.
[29] O. Laporta-Hoyos, K. Pannek, J. Ballester-Plane, L.B. Reid, E. Vazquez, I. Delgado, et al., White matter integrity in dyskinetic cerebral palsy: relationship with intelligence quotient and executive function, NeuroImag. Clinic. 15 (2017) 789–800.
[30] L.C. Weeke, F. Groenendaal, K. Mudigonda, M. Blennow, M.H. Lequin, L.C. Meiners, et al., A novel magnetic resonance imaging score predicts neurodevelopmental outcome after perinatal asphyxia and therapeutic hypothermia, J. Pediatr. 192 (2018) 33–40.e2.
[31] C.A. van Houdt, A.G. van Wassenaer-Leemhuis, J. Oosterlaan, A.H. van Kaam, C.S.H. Aarnoudse-Moens, Developmental outcomes of very preterm children with high parental education level, Early Hum. Dev. 133 (2019) 11–17.
[32] M. van Gorp, S.R. Hilberink, S. Noten, J.L. Benner, H.J. Stam, W.M.A. van der Slot, et al., Epidemiology of cerebral palsy in adulthood: a systematic review and meta-analysis of the most frequently studied outcomes, Arch. Phys. Med. Rehabil. 101 (6) (2020) 1041–1052, https://doi.org/10.1016/j.apmr.2020.01.009.
[33] I. Novak, C. Morgan, L. Adde, J. Blackman, R.N. Boyd, J. Brunstrom-Hernandez, et al., Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment, JAMA Pediatr. 171 (9) (2017) 897–907.