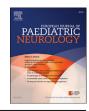
ELSEVIER

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology



Bimanual performance in children with unilateral perinatal arterial ischaemic stroke or periventricular haemorrhagic infarction

Check for updates

Cornelia H. Verhage ^{a, *}, Floris Groenendaal ^b, Janjaap van der Net ^a, Monique MJ. van Schooneveld ^c, Linda S. de Vries ^b, Niek E. van der Aa ^b

^a Center for Child Development, Exercise and Physical Literacy, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

^b Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

^c Sector of Neuropsychology, Department of Pediatric Psychology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht University,

Utrecht, the Netherlands

ARTICLE INFO

Article history: Received 22 March 2021 Received in revised form 13 August 2021 Accepted 11 January 2022

Keywords:

Perinatal arterial ischaemic stroke Periventricular haemorrhagic infarction Unilateral cerebral palsy Bimanual performance Hand function Cognitive outcome

ABSTRACT

Background: Long term outcome data on bimanual performance in children with perinatal arterial ischaemic stroke (PAIS) and periventricular haemorrhagic infarction (PVHI) with and without unilateral spastic cerebral palsy (USCP) is sparse.

Aims: To assess bimanual performance in children with PAIS or PVHI with and without USCP and to explore the relationship with unilateral hand function and full-scale IQ (FSIQ) in a cross-sectional study. *Methods:* Fifty-two children with PAIS (n = 27) or PVHI (n = 25) participated at a median age of 12 years and 1 month (range 6–20 years). The Bruininks Oseretsky Test of Motor Proficiency-2 (bimanual precision and dexterity subtest), Assisting Hand Assessment, Purdue Pegboard Test and Wechsler Intelligence scale were administered.

Results: Bimanual dexterity was worse in children with USCP (p < 0.02) without a difference for the pathology groups. In children without USCP (n = 21), those with PAIS showed a better bimanual precision compared to children with PVHI (p < 0.04). The AHA score and the Purdue Pegboard score of the dominant hand explained 51% of the variance in bimanual precision and dexterity in children with USCP. In absence of USCP, FSIQ together with AHA scores explained 66% of the variance in bimanual precision and FSIQ together with the Purdue Pegboard Test score of the dominant hand, 71% of the variance in bimanual dexterity.

Conclusions: Children with PAIS without USCP have a more favourable bimanual hand function compared to children with PVHI. This difference appears to be associated with a preserved FSIQ.

© 2022 The Authors. Published by Elsevier Ltd on behalf of European Paediatric Neurology Society. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Unilateral spastic cerebral palsy (USCP) is a neurological condition that is characterized by motor impairments mainly lateralized to one side of the body, often accompanied by disturbances of sensation, cognition, behaviour and epilepsy [1]. Perinatal arterial ischaemic stroke (PAIS) and periventricular haemorrhagic infarction (PVHI) are two different types of unilateral perinatal brain injury which together are responsible for the majority of children with USCP [2]. PAIS results in USCP in 20–40% of the cases and 50–85% of the preterm born infants with PVHI will develop USCP. Children with PAIS or PVHI but without subsequent development of USCP often have mild neurological signs [3–6].

Research in USCP tends to focus on function of the affected upper limb and its impact on daily activities [7–11]. Motor impairments of the affected (contralesional) arm and hand include decreased grip strength and lack of selective (finger) movements. In addition, the ipsilesional hand can show a decrease in fine finger dexterity [12,13]. Bimanual performance in daily activities in

https://doi.org/10.1016/j.ejpn.2022.01.009

1090-3798/© 2022 The Authors. Published by Elsevier Ltd on behalf of European Paediatric Neurology Society. This is an open access article under the CC BY license (http:// creativecommons.org/licenses/by/4.0/).

Abbreviations: PAIS, perinatal arterial ischemic stroke; PVHI, periventricular haemorrhagic infarction; USCP, unilateral spastic cerebral palsy; FSIQ, full scale intelligent quotient; MACS, Manual Ability Classification System; TMS, Transcranial magnetic stimulation; BOT-2, Bruininks Oseretsky Test of Motor Proficiency; AHA, Assisting Hand Assessment; FFD, Fine finger dexterity.

^{*} Corresponding author. Wilhelmina Children's Hospital, University Medical Center Utrecht, P.O. Box 85090, 3508 AB Utrecht, the Netherlands.

E-mail addresses: c.h.verhage@umcutrecht.nl (C.H. Verhage), n.vanderaa@ umcutrecht.nl (N.E. van der Aa).

children with USCP is generally measured by proxy-report and rates the perception of parents of the capacity of their children to manage daily activities requiring the use of the upper limbs [14,15]. Subjective measures are important for therapeutic purposes, but they do not provide sufficient detail about the domains of bimanual performance the child is most impaired in and do not allow comparison between individual subjects.

Data of performance based assessments of bimanual activities in children with PAIS and PVHI, taking the type of brain lesion into account, is limited. It is to be expected that children perform differently on bimanual tasks as both groups have a different time of lesion onset. PAIS most often occurs in term born infants, with involvement of the cortex, white matter and sometimes deep grey matter, while PVHI generally affects preterm infants, with mainly white matter involvement and with an onset at a gestational age below 33 weeks [16]. Prematurity itself is associated with motor, cognitive and behavioural disabilities which might also affect bimanual performance [17]. Additionally, several studies in children with USCP showed that children with PAIS have a worse upper limb function compared to PVHI [18,19].

Impaired performance of bimanual activities can be a result of unilateral upper limb impairment but as motor skills are part of a learning process it is understandable that there is a relationship between learning motor skills and cognition as well [20,21]. A follow-up study in children with USCP from the age of nine years onwards showed that the bimanual performance improved as children got older, as reported by their proxy. In contrast the effectiveness and use of the affected hand deteriorated over time [14]. The authors assumed that with maturation, children improve motor learning and planning and adopt compensation strategies to perform activities of daily living. Previously, we have shown that children with PAIS and PVHI have a below average cognitive ability and we hypothesize that besides capacity of unilateral hand function this could also affect bimanual performance [22].

The primary aim of this study was to explore differences in outcome of bimanual performance in children with PAIS and PVHI with and without subsequent development of USCP. The second aim was to explore relationships between unimanual capacity and cognitive performance in bimanual performance.

2. Materials and methods

2.1. Participants

This cross-sectional study recruited children who were previously admitted to the neonatal intensive care unit of the University Medical Center Utrecht between 1991 and 2006. Participants were recruited for a follow-up study following unilateral perinatal brain injury and underwent a neuropsychological evaluation and an extensive examination of hand function. Inclusion criteria were (1) PAIS or PVHI diagnosed with a neonatal MRI or sequential cranial ultrasound in the neonatal period, currently at an age between 6 and 21 years. Exclusion criteria were: (1) insufficient cooperation to perform assessments, (2) Botulinum toxin-A injections during the last six months prior to testing and (3) Seizures that were not controlled by medication. The children were part of a larger study, investigating cortical reorganisation following perinatal brain injury. Children enrolled in this study had to be able to lie still for the MRI and were also undergoing transcranial magnetic stimulation (TMS) [23].

The institutional review board of University Medical Center Utrecht approved the study protocol and informed consent was acquired from all participants and their parents when applicable.

2.2. Procedure

Hand function of all children was tested using the same test battery, which was independent of whether they had developed USCP or not. Assessments were conducted during a single day at the University Medical Center Utrecht and were video recorded. The assessments were scored by a trained occupational therapist blinded for lesion location, lesion type and results of the neuropsychological assessment. Parents of children with USCP classified the Manual Ability Classification System (MACS) [24].

Passive range of motion of wrist and elbow of the affected hand in children with USCP was measured prior to the hand assessments.

2.3. Assessments

Clinical characteristics (such as gestational age, sex, birthweight, pathology, affected side, treatment and diagnosis of USCP) were obtained from their medical records. Presence of USCP was determined by a neurologist or neonatologist together with a paediatric physiotherapist during routine follow-up, using the criteria of Rosenbaum et al. [1].

Two subtests of the American version of the Bruininks Oseretsky Test of Motor Proficiency (BOT-2), second version were used to examine bimanual performance [25]. The BOT-2 is a standardized battery using goal-directed activities to measure a wide array of motor skills and is reliable to use in children with USCP [26]. Bimanual precision was measured with the *Fine Motor Precision* subtest which consists of bimanual activities that require precise control of finger and hand movements, e.g. tasks include: coloring shapes, drawing within lines, cutting out a circle, filling in shapes and folding a piece of paper. The items in this subtest are untimed and performance is evaluated based on precision, e.g. how well the child remains within a boundary.

The *Manual Dexterity* subtest involves bimanual coordination in manipulating small objects. Items include stringing small blocks, sorting cards, picking up pennies and transferring them to the other hand. By including speed, as these items are timed, this subtest evaluates bimanual dexterity. For both subtests normative data accounting for age and sex were used to calculate z-scores.

2.4. Unilateral hand function assessment

Hand preference was determined using the Dutch Handedness Questionnaire, which assesses the hand preference in everyday activities using a 10-item questionnaire derived from the Edinburgh Handedness Inventory [27,28]. The laterality of hand dominance ranges from -10 to 10. A laterality over 8 indicates righthandedness and a laterality less than -8 indicated lefthandedness. Other scores were considered as ambidexterity.

The Assisting Hand Assessment (AHA, version 4.4) was used to describe how effectively the non-dominant hand is used in bimanual performance. The AHA is a valid and reliable measure of the function of the affected hand for children with USCP from the age of 18 months to 12 years [29]. A preliminary version of the AHA for older children was kindly provided by the developers and was used for children aged 12 up to 21 years. AHA raw-scores were converted to Logit-scores (0–100).

Fine finger dexterity (FFD) of each hand separately was assessed using the Purdue Pegboard test. Normative data accounting for age, sex and handedness were used to convert scores to z-scores [30,31]. Z-scores below -2.0 are defined as an impaired fine finger dexterity.

2.5. Full scale intelligence score

Intelligence was tested with either the Wechsler Intelligence Scale for Children-III or the Wechsler Adult Intelligence Scale-III depending on child's age [32,33]. A full-scale IQ (FSIQ) score was derived with a mean score of 100 and an SD of 15.

2.6. Statistical analysis

Differences in clinical characteristics and test results between groups or dominant and non-dominant hand were compared using a *t*-test or chi [2]-test where appropriate. A two-way ANOVA was conducted to explore the impact of pathology and presence of USCP on bimanual precision and dexterity, FFD of the dominant hand and FSIQ. Additional post-hoc analyses were performed when significant differences were demonstrated. Interaction effects were examined using multivariable regression analysis. To compare subgroup means with the normative sample a one-sample *t*-test or the non-parametric equivalent was used. A paired sample T-test or Wilcoxon signed rank test was used to compare means of the FFD of the contralesional and ipsilesional hand in children without USCP and separately for both pathology groups in children without USCP.

Multivariable regression analysis was used to assess the association of unilateral hand function of both hands and cognition with bimanual precision and dexterity for children with USCP and without USCP. Multivariable regression analyses of bimanual precision and dexterity were performed twice, once using unilateral hand function scores and FSIQ as independent variables and once using the unilateral hand functions scores only. Any change in the coefficients of more than 20% was considered relevant and multicollinearity was explored. Missing data were pairwise deleted from the model.

All data were analysed using IBM SPSS Statistics version 25.0 (IBM SPSS statistics, IBM Corp., NY, USA).

3. Results

3.1. Patient characteristics

The study included 52 children aged 6–20 years of whom 28 were male and 31 children were diagnosed with USCP. According to the MACS, 11 children with USCP were classified as level I, 15 as level II and 5 as level III. Twenty-seven children were diagnosed with PAIS and 25 children with PVHI (Table 1). In children with PVHI no difference in gestational age was found between children with and without USCP. The diagnosis of PAIS or PVHI was based on magnetic resonance imaging (MRI) performed in the neonatal period. Two children did not have a neonatal MRI but sequential cranial ultrasounds which allowed making the diagnosis, which was

Table 1 Patient characteristics.

	$\text{PAIS}\ (n=27)$	$PVHI \ (n=25)$	р
Male/female	12/15	16/9	0.26
Age (years)	11.2 [6]	11.6 [6]	0.38
Location injury (left/right)	14/13	13/12	0.99
Hand preference (left/right)	10/17	13/12	0.40
Gestational age (weeks)	39.0 [7.6]	30.0 [4.0]	< 0.001
Birthweight (gram)	3225 [1537]	1407 [649]	< 0.001
Birthweight z-score	0.27 [1.3]	0.33 [1.3]	0.45
USCP (%)	13 (48)	18 (72)	0.14
MACS (I/II/III)	5/5/3	6/10/2	0.55

Data are given as numbers (percentage) or as median [interquartile range]. PAIS, perinatal arterial ischaemic stroke; PVHI, periventricular haemorrhagic infarction; USCP, unilateral spastic cerebral palsy; MACS, manual ability classification system.

subsequently confirmed by a childhood MRI. PAIS was most frequently noted in the middle cerebral artery territory (n = 25; in the main branch in 7 children in the anterior branch in 3 children in the posterior branch in 1 child, in the lenticulostriate branches in 6 children, in the cortical branch in 7 children, and in the distal middle cerebral artery branch in 1 child). The two remaining children showed a PAIS in the posterior (n = 1) and anterior (n = 1) cerebral artery territory. PVHI was located in the frontal region of the brain in six children, in the frontoparietal region in 18 children and in the parietal region in one child. Eight children developed postneonatal epilepsy and seizures were more often observed in children with PAIS (n = 6) than in children with PVHI. Most children suffered simple partial seizures (n = 6), which extended into secondary generalized seizures in two children. Of the remaining two children, one child suffered symptomatic multifocal seizures and one child's EEG showed electric status epilepticus in slow-wave sleep.

In all 31 children with USCP the non-dominant hand corresponded to the contralesional side. In seventeen out of 21 children without USCP the contralesional hand was the non-dominant hand. Eight out of twelve children with a lesion in the left hemisphere were left-handed and all nine children with a right-sided brain injury were right-handed.

All children had access to regular rehabilitation services. Two children with USCP received botulinum toxin-A injections more than two years prior to the assessments. Twelve out of the 31 children with USCP showed more than 10° limitation in passive range of motion in one or two joints. Nine children showed limitations in supination and five children showed limitations in dorsal flexion of the wrist of the affected side.

FSIQ was not available in two children with PVHI and USCP. One child chose to withdraw early from the study and one child had a disharmonic IQ profile which made the use of FSIQ not reliable. Both children attended main stream school.

3.2. Bimanual performance and unilateral hand function

Children with USCP showed a poorer bimanual dexterity compared to children without USCP (p < 0.02). Bimanual precision did not differ between children with and without USCP. Bimanual precision and dexterity did not differ between the two pathology groups. When children did not develop USCP, children with PAIS performed better on bimanual precision (p < 0.04). Multivariable regression analysis demonstrated that children with USCP (p < 0.02) and children with PHVI showed poorer bimanual dexterity (p < 0.02), demonstrating that children with PAIS without USCP had a significantly better bimanual precision than the 3 other groups (Fig. 1).

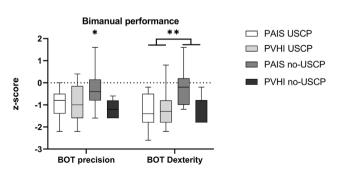


Fig. 1. Bimanual performance. Bimanual performance in children with USCP (n = 31) and children without USCP (n = 21). Data are given as medians (±interquartile range). PAIS, perinatal arterial ischaemic stroke; PVHI, periventricular haemorrhagic infarction; USCP, unilateral spastic cerebral palsy. *, interaction effect (p < 0.05); **, main effect (p < 0.05).

Table 2 Test results.

USCP ($n = 31$)	PAIS $(n = 13)$	PVHI (n = 18)	Norm	p value PAIS vs norm	p value PVHI vs norm
BOT-2 Precision	-0.80 [0.9]	-0.90 [1.6]	0(1)	<0.001	<0.001
BOT-2 Dexterity	-1.40 [1.3]	-1.30 [1.0]	0(1)	<0.001	< 0.001
AHA	59 [40]	68 [37]	n/a	n/a	n/a
PPT DH	-0.40 [2.2]	-1.45 [2.5]	0(1)	0.008	0.06
FSIQ	86 [21]	90 [23]	100 (15)	<0.001	0.010
No-USCP ($n = 21$)	PAIS (n = 14)	PVHI (n = 7)			
BOT-2 Precision	-0.40 [1.0]	-1.20 [0.8]	0(1)	0.33	<0.001
BOT-2 Dexterity	-0.20 [1.2]	-0.80 [1.0]	0(1)	0.15	0.003
AHA	100 [2]	100 [7]	n/a	n/a	n/a
PPT DH	-1.15 [1.8]	-1.80 [2.5]	0(1)	0.002	0.09
PPT non-DH	-1.25 [3.3]	-1.90 [1.4]	0(1)	<0.001	0.021
FSIQ	94 [24]	83 [24]	100 (15)	0.52	0.030

Data are given as median [interquartile range] and test mean (standard deviation); PAIS, perinatal arterial ischaemic stroke; PVHI, periventricular haemorrhagic infarction; USCP, unilateral spastic cerebral palsy; BOT, Bruininks-Oseretsky Test of Motor Proficiency; AHA, Assisting Hand Assessment; PPT, Purdue pegboard test; DH, Dominant hand; non-DH, non-dominant hand; FSIQ, Full scale IQ.

In children with USCP no significant difference was found in AHA scores between children with PAIS and children with PVHI (Table 2). Children with USCP had difficulties to execute the Purdue pegboard test with the affected hand. Two out of 31 children scored within the normal range, 16 had a FFD z-score below -2 SD, and 13 out of 31 children were not able to pick up a single peg.

Children without USCP showed a ceiling effect of their AHA scores of their non-dominant hand. No significant difference was found in FFD of the non-dominant hand between children with PAIS and PVHI in children without USCP. FFD of the dominant hand did not differ between children with and without USCP and between pathology groups. When both pathology groups were combined, the contralesional hand showed a lower FFD (mean -2.34; SD 2.03) compared to the ipsilesional hand (mean -1.06; SD 1.03) (p < 0.01). No difference was found in FFD between contra- and ipsilesional hand when analyses were done separately for both pathology groups. FFD of the contralesional and ipsilesional hand in children without USCP is presented in Fig. 2.

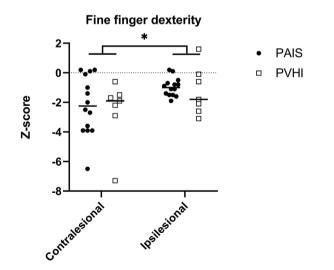


Fig. 2. Fine finger dexterity of the contra- and ipsilesional hand of children without development of USCP.

Medians of fine finger dexterity of the contra- and ipsilesional hand of children without USCP (n = 21) are indicated with a horizontal line. * PAIS and PVHI groups combined, contralesional versus ipsilesional hand (p < 0.05). PAIS, perinatal arterial ischaemic stroke; PVHI, periventricular haemorrhagic infarction; USCP, unilateral spastic cerebral palsy.

In children with PAIS, bimanual precision and dexterity of children were only below the normative sample for those with USCP, whereas children with PVHI both with and without USCP scored below the normative sample. In all children without USCP, FFD of the non-dominant hand, as measured with the Purdue Pegboard test, was significantly lower compared to the normative sample for both groups. FFD of the dominant hand was poorer compared to the normative sample only in children with PAIS (Table 2).

3.3. Cognitive outcome

Multivariable regression analysis demonstrated that children with USCP had a significantly lower FSIQ (p < 0.01), and that children with PHVI showed a trend for lower FSIQ (p < 0.06), while an interaction effect could be demonstrated.

FSIQ of children with PAIS without USCP did not differ from the normative sample, whereas the other three subgroups scored significant lower compared to the normative sample (Table 2).

3.4. Factors associated with bimanual performance

No multicollinearity between FSIQ and the other independent variables was observed. In children with USCP, FFD of the dominant hand and effectiveness of the affected hand (as measured with the AHA) explained 51% of the variance in both bimanual precision and dexterity (Table 3). Adding FSIQ to the model did not improve this model. FFD-scores of the affected hand were not normally distributed and therefore not added to the model.

In children without USCP, AHA-scores were not normally distributed due to a ceiling effect. Therefore AHA-scores were dichotomised (maximum AHA score being 100 versus non maximum AHA score being <100). Four out of 21 children (two with PAIS) did not score the maximum score on the AHA. FSIQ together with effectiveness of the non-dominant hand (dichotomised AHA score) was associated with bimanual precision, accounting for 66% of the variance. For bimanual dexterity 72% of the variance could be explained by FSIQ and FFD of the dominant hand (Table 3).

4. Discussion

4.1. Bimanual performance

A more favourable bimanual performance was found in children with PAIS without subsequent development of USCP and this

Factors associated with bimanual performance in children with and without subsequent development of USCP.	Table 3	
	actors associated with bimanual performance in children with and without subsequent development of USCP	

Children with USCP	ith USCP		FFD DH		АНА		FSIQ	
	R ²	β	CI	β	CI	β	CI	
Bimanual precision Bimanual dexterity	0.51 (<i>p</i> < 0.001) 0.51 (<i>p</i> < 0.001)	$\begin{array}{c} 0.21 \; (p < 0.001) \\ 0.18 \; (p = 0.004) \end{array}$	0.087-0.323 0.051-0.307	$0.01 \ (p = 0.027) \ 0.02 \ (p = 0.008)$	0.001-0.022 0.006-0.028	_	_	
Children without USCP		FFD DH		AHA dichotomized		FSIQ		
	R ²	β	CI	β	CI	β	CI	
Bimanual precision Bimanual dexterity	0.66 (<i>p</i> < 0.001) 0.72 (<i>p</i> < 0.001)	 0.21 (p = 0.018)		-0.96 (p = 0.004) _	-1.580.34 -	0.04 (<i>p</i> < 0.001) 0.03 (<i>p</i> < 0.001)	0.021-0.049 0.018-0.042	

USCP, unilateral spastic cerebral palsy. Dependent variables were: Bimanual Precision; Bimanual Dexterity. Independent variables were: FFD DH, fine finger dexterity dominant hand; AHA, Assisting Hand Assessment; FSIQ, Full scale IQ; R^2 , Cumulative adjusted R^2 ; β , coefficient in the model; CI, 95%- confidence interval β value.

advantageous outcome seems to be related to preserved cognitive functions. To the best of our knowledge an association between FSIQ and bimanual performance in children with unilateral brain injury has not yet been described. In addition, we observed that, even in the absence of USCP, children showed a poorer FFD of their contralesional hand compared to their ipsilesional hand, independent of the underlying aetiology. FFD was corrected for age and handedness.

Data on bimanual performance in children with PAIS and PVHI is limited and in most studies motor outcome is described as presence or absence of USCP, or studies include children in a younger age range [4,34,35]. Mercuri et al. [3] measured motor outcome with the M-ABC-1, with one bimanual item, in a group of children with PAIS aged 4 till 6 years. Two out of 16 children without USCP and 3 out of 6 children with USCP showed scores below the 5th percentile. Their results are in agreement with our findings where 2 out of 14 children without USCP and 3 out of 13 children with USCP scored well below average (<-2 standard deviations) for bimanual dexterity. Roze et al. [5] explored long term motor and cognitive outcome in children with PVHI. Sixteen out of 21 children developed USCP and gross motor and fine motor function were described using the Gross Motor Function Classification System, Manual Ability Classification System and Touwen's neurological examination. Overall abnormal unilateral fine manipulation abilities were found but separate results for children with and without USCP were not reported.

A few studies on unilateral hand function in children with USCP showed that children with PVHI have a better outcome of the affected hand compared to children with PAIS [18,19]. These results were not confirmed by our data. Scores of the AHA in our sample ranged from 35 till 100 which is in the upper range of the AHA scale. This is in contrast with the study by Holmefur et al. [18] which included more children in the lower range of the AHA scale.

Studies on motor function and in particular fine motor function of children with PVHI and PAIS without USCP are scarce. In this study children with PVHI without USCP showed a poorer bimanual precision and FSIQ compared to children with PAIS without USCP. Prematurity itself associated with motor, cognitive and behavioural disabilities and extensive research has been done on long term motor outcome in very preterm infants, but infants with PVHI are often excluded from these studies [17]. In a systematic review the effect size of prematurity on motor skills was found to be -0.62 for manual dexterity (measured with the M-ABC) and -0.86 for fine motor skills (measured with the BOT-2). In our cohort, children with PVHI without USCP performed worse for bimanual precision and dexterity. Although they did not develop USCP, this would suggest that their hand function is affected by the PVHI.

Additionally, we hypothesize that cognitive and behavioural disabilities inherent to prematurity itself could affect bimanual performance as well. Children with PAIS and PVHI without USCP showed equivalent impairments of fine finger dexterity of the dominant and non-dominant hand compared to the normative sample. No differences were found between both pathology groups. Despite a comparable unimanual capacity in FFD of both hands, children with PAIS showed a better bimanual precision. Preterm birth and its inherent neonatal complications are well known to affect neurodevelopmental outcome. Underlying non-overt brain injury related to prematurity in children with PVHI could affect FSIQ which in turn affects bimanual performance.

4.2. Factors associated with bimanual performance

In children with USCP we found that FFD of the dominant hand and effectiveness of the affected hand were associated with bimanual precision and dexterity.

Arnould et al. described that gross manual dexterity of the dominant hand and grip strength of the affected hand explained 58% of the variance in bimanual ability which was measured by proxi report. This is in line with our study in which 51% of bimanual precision and bimanual dexterity was associated with FFD of the dominant hand and effectiveness of the non-dominant hand. This suggests that other factors contribute to bimanual precision and dexterity too. Children with USCP may compensate their loss of function of the non-dominant and dominant hand with learned adapted strategies which could depend on children's motivation, cognitive skills, sustained attention or executive functioning. In our study FSIQ didn't significantly contribute to bimanual performance and dexterity in children with USCP, although there was a trend for FSIQ in bimanual precision.

In children without USCP the contralesional hand was the nondominant hand in 17 out of 21 children. Eight out of 12 children with a left-sided brain injury were left-handed, suggesting that the side of brain lesion affects lateralisation as the proportion of left handers in a healthy population is approximately 10% [36]. Although children were not diagnosed with USCP, the contralesional hand was less dexterous compared to the ipsilesional hand according to FFD zscores which were corrected for age and handedness. As far as we know, this has not previously been reported. In other studies in adults and children with USCP it has been reported that the integrity of the corticospinal tract plays a major role for control of independent finger movements [12,13]. FFD was measured with the Purdue pegboard test, which addresses interdigital movements. In our study children with USCP had difficulties in execution of the Purdue pegboard test and 13 out of 31 children were not able to execute the test with their affected hand. It is likely that children with PAIS and PVHI but without USCP could have discrete involvement of the corticospinal tract and present a mild motor impairment, but not enough to have a diagnosis of USCP. As 17 out of 21 children use their contralesional hand as their non-dominant hand, affected fine finger dexterity can remain undetected.

FSIQ seems to play an important role in bimanual performance in children without development of USCP. FSIQ and FFD of the dominant hand were significantly associated with bimanual dexterity and FSIQ together with effectiveness of the non-dominant hand was significantly associated with bimanual precision. We hypothesize that a better FSIQ contributes to adapted strategies in both bimanual precision and dexterity. On the contrary, a low AHA score of the non-dominant hand could affect precision of bimanual performance and a poor FFD of the dominant hand could affect bimanual dexterity.

In children with PAIS and PVHI cognitive impairments and executive problems have been described [4,5,21,34]. In contrast to our study these studies did not distinguish between cognitive results of children with and without USCP and impact of cognitive impairments on bimanual performance in both pathology groups is still an understudied area. Guillery et al. [37] studied dexterous manipulation in a dual task in healthy adults and showed that dexterous manipulation involves higher-order cognitive functions to be planned and executed. FSIQ in children with PAIS without USCP was significantly better compared to children with USCP. In children with PVHI this preserved FSIQ was not observed, most likely as a consequence of prematurity, which is a known risk factor for cognitive impairment [38].

4.3. Limitations

This study has some limitations. The children included in this study had a wide age range between 6 and 20 years. Younger children in our study were still developing their fine motor skills whereas the older children might have reached their maximum capacity in hand function and children with USCP could even show deterioration. Age referenced norms were used for all assessments, to minimize the effect of age.

Another limitation is the small number of children with PVHI without development of USCP. However, the underlying pathology and subsequent development of USCP is in agreement with other studies and can be considered a representation of the population of children with PAIS and PVHI [5,34]. As prematurity itself is associated with motor, cognitive and behavioural disabilities, it would be of interest to compare bimanual performance in children with PVHI without USCP with preterm born children without PVHI. However, no such control group was available.

Bimanual performance was measured using two subtests of BOT-2 which included two out of 12 unilateral items (sorting cards and placing pegs). All other items of the BOT-2 were bimanual with role differentiation. In these tasks each hand had a different role and carried out a different action. This role differentiation reflects the nature of everyday activities in which the nondominant hand has a stabilizing role and the dominant hand carries out the object manipulation role (e.g. colouring shapes while holding a paper). In everyday activities the dominant hand is used more frequently compared to the non-dominant hand. A study of hand use in everyday activities in healthy adults showed that most every day activities are bimanual and about 40% is unimanual [39]. As far as we know the BOT-2 is the only performance based assessment of bimanual activities which is validated for children with USCP. The items of both subtests reflect the nature of everyday activities with role differentiation and as norm referenced values could not be calculated if we removed the unimanual items from the subtests of the BOT-2, we chose to retain the items in the data set.

Our study sample comprised a group of children with USCP with relatively mild limitations in hand use and consequently the results may not be generalizable to severely affected children with USCP. As this study was part of a larger study, only children who were able to sufficiently cooperate to perform the assessments, including MRI and TMS were included. It is plausible that more severely affected children with USCP have more problems in execution of hand function and cognitive assessment.

5. Conclusion

In this cross-sectional study we demonstrated a better bimanual performance in children with PAIS without subsequent development of USCP and demonstrated that bimanual function also depends on the function of the dominant hand and FSIQ. In children without subsequent development of USCP, the contralesional hand was less dexterous compared to the ipsilesional hand and the side of brain injury seems to affect lateralisation.

For future research we recommend examining the relationship between executive functions and bimanual performance in children with PAIS and PVHI.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study received financial support from the Dutch Phelps Foundation and from the Wilhelmina Children's Hospital Research Fund.

References

- P. Rosenbaum, N. Paneth, A. Leviton, et al., A report: the definition and classification of cerebral palsy April 2006, Dev Med Child Neurol 49 (SUPPL109) (2007) 8–14, https://doi.org/10.1111/j.1469-8749.2007.tb12610.x.
- [2] G. Cioni, B. Sales, P. Paolicelli, E. Petacchi, M. Scusa, R. Canapicchi, MRI and clinical characteristics of children with hemiplegic cerebral palsy, Neuropediatrics 30 (1999) 249–255, https://doi.org/10.1055/s-2007-973499, 05.
- [3] E. Mercuri, A. Barnett, M. Rutherford, et al., Neonatal Cerebral Infarction and Neuromotor Outcome at School Age Eugenio Mercuri, Anna Barnett, Mary Rutherford, Andrea Guzzetta, Leena Haataja, Giovanni Cioni, Frances Cowan and Lilly Dubowitz, 2011. Published online.
- [4] S. Chabrier, E. Peyric, L. Drutel, et al., Multimodal outcome at 7 years of age after neonatal arterial ischemic stroke, J Pediatr 172 (2016) 156–161, https:// doi.org/10.1016/j.jpeds.2016.01.069, e3.
- [5] E. Roze, K.N.J.A. Van Braeckel, C.N. van der Veere, C.G.B. Maathuis, A. Martijn, A.F. Bos, Functional outcome at school age of preterm infants with periventricular hemorrhagic infarction, Pediatrics 123 (6) (2009) 1493–1500, https:// doi.org/10.1542/peds.2008-1919.
- [6] L.S. De Vries, J. Van der Grond, I.C. Van Haastert, F. Groenendaal, Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusionweighted magnetic resonance imaging, Neuropediatrics 36 (1) (2005) 12–20, https://doi.org/10.1055/s-2005-837544.
- [7] K. Klingels, I. Demeyere, E. Jaspers, et al., Upper limb impairments and their impact on activity measures in children with unilateral cerebral palsy, Eur J Paediatr Neurol 16 (5) (2012) 475–484, https://doi.org/10.1016/ j.ejpn.2011.12.008.
- [8] A.M. Öhrvall, A.C. Eliasson, K. Löwing, P. Ödman, L. Krumlinde-Sundholm, Selfcare and mobility skills in children with cerebral palsy, related to their manual ability and gross motor function classifications, Dev Med Child Neurol 52 (11) (2010) 1048–1055, https://doi.org/10.1111/j.1469-8749.2010.03764.x.
- [9] L. Sakzewski, J. Ziviani, R. Boyd, The relationship between unimanual capacity and bimanual performance in children with congenital hemiplegia, Dev Med Child Neurol 52 (9) (2010) 811–816, https://doi.org/10.1111/j.1469-8749.2009.03588.x.
- [10] S.M. Brændvik, A.K.G. Elvrum, B. Vereijken, K. Roeleveld, Relationship between neuromuscular body functions and upper extremity activity in children with cerebral palsy, *Dev Med Child Neurol*. Published online (2010), https:// doi.org/10.1111/j.1469-8749.2009.03490.x.
- [11] E. Fedrizzi, E. Pagliano, E. Andreucci, G. Oleari, Hand function in children with hemiplegic cerebral palsy: prospective follow-up and functional outcome in adolescence, Dev Med Child Neurol 45 (2) (2003) 85–91, https://doi.org/ 10.1111/j.1469-8749.2003.tb00910.x.
- [12] Y. Bleyenheuft, C.B. Grandin, G. Cosnard, E. Olivier, J.L. Thonnard, Corticospinal dysgenesis and upper-limb deficits in congenital hemiplegia: a diffusion

tensor imaging study, Pediatrics 120 (6) (2007) e1502-e1511, https://doi.org/10.1542/peds.2007-0394.

- [13] J. Duque, Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia, Brain 126 (3) (2003) 732–747, https:// doi.org/10.1093/brain/awg069.
- [14] K. Klingels, S. Meyer, L. Mailleux, et al., Time course of upper limb function in children with unilateral cerebral palsy: a five-year follow-up study, Neural Plast 2018 (2018), https://doi.org/10.1155/2018/2831342.
- [15] C. Arnould, M. Penta, J.L. Thonnard, Hand impairments and their relationship with manual ability in children with cerebral palsy, J Rehabil Med 39 (9) (2007) 708-714, https://doi.org/10.2340/16501977-0111.
- [16] C.M. Novak, M. Ozen, I. Burd, Perinatal brain injury: mechanisms, prevention, and outcomes, Clin Perinatol 45 (2) (2018) 357–375, https://doi.org/10.1016/ J.CLP.2018.01.015.
- [17] J.F. de Kieviet, J.P. Piek, C.S. Aarnoudse-Moens, J. Oosterlaan, Motor development in very preterm and very low-birth-weight children from birth to adolescence, JAMA 302 (20) (2009) 2235, https://doi.org/10.1001/jama.2009.1708.
- [18] M. Holmefur, A. Kits, J. Bergström, et al., Neuroradiology can predict the development of hand function in children with unilateral cerebral palsy, Neurorehabil Neural Repair 27 (1) (2013) 72–78, https://doi.org/10.1177/ 1545968312446950.
- [19] L. Holmström, B. Vollmer, K. Tedroff, et al., Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy, Dev Med Child Neurol 52 (2) (2010) 145–152, https://doi.org/ 10.1111/j.1469-8749.2009.03496.x.
- [20] B. Hoare, M. Ditchfield, M. Thorley, et al., Cognition and bimanual performance in children with unilateral cerebral palsy: protocol for a multicentre, cross-sectional study, BMC Neurol 18 (1) (2018) 63, https://doi.org/10.1186/ s12883-018-1070-z.
- [21] A.S. Gosling, Recent advances in the neuroimaging and neuropsychology of cerebral palsy, Appl Neuropsychol Child 6 (1) (2017) 55–63, https://doi.org/ 10.1080/21622965.2015.1074914.
- [22] L.M. van Buuren, N.E. van der Aa, H.C. Dekker, et al., Cognitive outcome in childhood after unilateral perinatal brain injury, Dev Med Child Neurol 55 (10) (2013) 934–940, https://doi.org/10.1111/dmcn.12187.
- [23] N.E. van der Aa, C.H. Verhage, F. Groenendaal, et al., Neonatal neuroimaging predicts recruitment of contralesional corticospinal tracts following perinatal brain injury, Dev Med Child Neurol 55 (8) (2013), https://doi.org/10.1111/ dmcn.12160 n/a-n/a.
- [24] A.C. Eliasson, L. Krumlinde-Sundholm, B. Rösblad, et al., The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability, Dev Med Child Neurol 48 (2006) 549, https://doi.org/10.1017/S0012162206001162, 07.

- [25] R.H. Bruininks, B.D. Bruininks, Bruininks–Oseretsky Test of Motor Proficiency, second ed., 2005.
- [26] C. Selves, Reliability and concurrent validity of the bruininks-oseretsky test in children with cerebral palsy, Biomed J Sci Tech Res 18 (5) (2019), https:// doi.org/10.26717/bjstr.2019.18.003226.
- [27] J.W. Van Strien, Vragenlijst voor Handvoorkeur. Ned Tijdschr Psychol. 47 (2) (2002) 88–92.
- [28] R.C. Oldfield, The assessment and analysis of handedness: the Edinburgh inventory, Neuropsychologia 9 (1) (1971) 97–113, https://doi.org/10.1016/ 0028-3932(71)90067-4.
- [29] L. Krumlinde-Sundholm, M. Holmefur, A. Kottorp, A.C. Eliasson, The Assisting Hand Assessment: current evidence of validity, reliability, and responsiveness to change, Dev Med Child Neurol 49 (4) (2007) 259–264, https://doi.org/ 10.1111/j.1469-8749.2007.00259.x.
- [30] V. Mathiowetz, S.L. Rogers, M. Dowe-Keval, L. Donahoe, C. Rennells, The Purdue pegboard: norms for 14- to 19-year-olds, Am J Occup Ther Off Publ Am Occup Ther Assoc 40 (3) (1986) 174–179, https://doi.org/10.5014/ ajot.40.3.174.
- [31] C. Arnould, Hand Functioning in Children with Cerebral Palsy, 2006, p. 128, https://doi.org/10.3389/fneur.2014.00048, Published online.
- [32] D.W. Wechsler, Wechsler Intelligence Scale for Children, third ed., Hartcourt Assessment. Dutch Adaptation. 2005.
- [33] D.W. Wechsler, Wechsler Adult Intelligence Scale, third ed., Swets & Zeitlinger, Dutch Adaptation, 2005.
- [34] M. Dunbar, A. Kirton, Perinatal stroke: mechanisms, management, and outcomes of early cerebrovascular brain injury, Lancet Child Adolesc Heal 2 (9) (2018) 666–676, https://doi.org/10.1016/S2352-4642(18)30173-1.
- [35] S. Lõo, P. Ilves, M. Männamaa, et al., Long-term neurodevelopmental outcome after perinatal arterial ischemic stroke and periventricular venous infarction, Ec 22 (6) (2018) 1006–1015, https://doi.org/10.1016/j.ejpn.2018.07.005.
- [36] S.M. Scharoun, P.J. Bryden, Hand preference, performance abilities, and hand selection in children, Front Psychol 5 (FEB) (2014) 1–15, https://doi.org/ 10.3389/fpsyg.2014.00082.
- [37] E. Guillery, A. Mouraux, J.-L. Thonnard, V. Legrain, Mind your grip: even usual dexterous manipulation requires high level cognition, Front Behav Neurosci 11 (2017), https://doi.org/10.3389/fnbeh.2017.00220.
- [38] D. Wolke, V.Y.C. Strauss, S. Johnson, C. Gilmore, N. Marlow, J. Jaekel, Universal gestational age effects on cognitive and basic mathematic processing: 2 cohorts in 2 countries, J Pediatr 166 (6) (2015) 1410–1416, https://doi.org/ 10.1016/j.jpeds.2015.02.065, e2.
- [39] S.L. Kilbreath, R.C. Heard, Frequency of hand use in healthy older persons, Aust J Physiother 51 (2) (2005) 119–122, https://doi.org/10.1016/S0004-9514(05) 70040-4.