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Manual dexterity, but not cerebral palsy, predicts cognitive functioning after neonatal stroke

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ABBREVIATIONS

BBT	Box and Blocks Test
BFMF	Bimanual Fine Motor Function
FSIQ	Full-scale IQ
MDI	Manual Dexterity Index
NAIS	Neonatal arterial ischaemic stroke
NHPT	Nine-Hole Peg Test
PSI	Processing Speed Index
SES	Socio-economic status
WISC-IV	Wechsler Intelligence Scale for Children, Fourth Edition
WMI	Working Memory Index

AIM To disentangle the respective impacts of manual dexterity and cerebral palsy (CP) in cognitive functioning after neonatal arterial ischaemic stroke.

METHOD The population included 60 children (21 females, 39 males) with neonatal arterial ischaemic stroke but not epilepsy. The presence of CP was assessed clinically at the age of 7 years and 2 months (range 6y 11mo–7y 8mo) using the definition of the Surveillance of CP in Europe network. Standardized tests (Nine-Hole Peg Test and Box and Blocks Test) were used to quantify manual (finger and hand respectively) dexterity. General cognitive functioning was evaluated with the Wechsler Intelligence Scale for Children, Fourth Edition. Simple and multiple linear regression models were performed while controlling for socio-economic status, lesion side, and sex.

RESULTS Fifteen children were diagnosed with CP. In simple regression models, both manual dexterity and CP were associated with cognitive functioning ($\beta=0.41$ [$p=0.002$] and $\beta=0.31$ [$p=0.019$] respectively). However, in multiple regression models, manual dexterity was the only associated variable of cognitive functioning, whether or not a child had CP ($\beta=0.35$; $p=0.007$). This result was reproduced in models with other covariables ($\beta=0.31$; $p=0.017$).

INTERPRETATION As observed in typically developing children, manual dexterity is related to cognitive functioning in children having suffered a focal brain insult during the neonatal period.

Studies on cognitive and motor development after perinatal stroke provide interesting insights not only into the capacity, but also into the limits of brain plasticity.¹ However, debate still persists on the impact of early brain focal insult on later cognitive outcome. Some studies have reported a decrease of cognitive functioning, emphasizing brain vulnerability.² Other studies have shown stability in cognitive scores, suggesting that the developing brain can buffer the effect of an early focal insult.³

In most studies, the determinants of outcome have been primarily focused on presumably deleterious factors (lesion size or diagnosis of epilepsy, or a disorder of motor function like cerebral palsy [CP]),^{1,4,5} but potentially protective factors have not been addressed. In addition, several studies have included various perinatal stroke syndromes where the timing, localization, and type of insults are diverse. Neonatal arterial ischaemic stroke (NAIS) represents a unique model to study the impact of an early brain insult

on development, as the lesion and its timing are well circumscribed.^{6,7}

In typically developing children, cognitive development is related to early sensorimotor abilities and experiences.⁸ At 3 months, the motor repertoire is correlated with global intelligence, attention, and visual–motor integration at school age.⁹ In children with early brain insult, CP and epilepsy segregate with lower cognitive functioning,^{1,10} while high socio-economic status (SES) is protective.¹¹ Yet despite this generally accepted overview, the intimate relation between motor and cognitive functioning deserves further exploration.

In summary, studying children with NAIS may allow disentanglement of the respective contributions of CP on its own and manual dexterity to childhood cognitive functioning. We hypothesized (1) that a diagnosis of CP and manual dexterity are both associated with cognitive functioning; (2) that these associations are mutually

independent; and (3) that they are also independent of sex, SES, and lesion side.

METHOD

Ethical

The study was conducted in accordance with international ethical standards and the Declaration of Helsinki. This specific research project was approved by the regional ethics committee in May 2010. Informed consent was obtained from each family.

Participants

Put together between November 2003 and October 2006 in 39 French neonatology and paediatric neurology units, the AVCnn cohort provides a unique opportunity to follow a population of 100 children born at term (36 females, 64 males) having suffered an NAIS.¹² The stroke, as well as its location and side, were confirmed by brain imaging performed before day 28 of life. This cohort has enabled us to study distinct developmental areas, particularly motor outcome and handedness, quality of life, functional autonomy, multimodal assessment at school age, and epilepsy. The current study is part of the assessment at 7 years of age.¹²

Two children died in the neonatal period and 13 families were lost to follow-up. Of the 85 families contacted, 73 accepted the face-to-face encounter at 7 years that was required for this work. The current sample of 60 children excludes those with incomplete data ($n=2$) and epilepsy ($n=11$), with the aim of reducing this confounding factor (see Fig. 1).

Epilepsy was defined as the occurrence of two or more febrile unprovoked seizures after the neonatal period or, in the case of a single seizure, if it was decided to introduce antiepileptic treatment. Seizure-free children (i.e. included

What this paper adds

- Manual dexterity predicts cognitive functioning after neonatal arterial ischaemic stroke.
- Correlations between manual dexterity and cognitive functioning occur irrespective of sex, lesion side, presence of cerebral palsy, and socio-economic status.
- Residual motor ability may support cognitive functioning.

in the current study) at 7 years were those without seizure and without treatment for over 1 year.¹²

All parents were asked to complete a questionnaire about their personal school achievements and current occupation. The Four-Factor Index of Social Status was adapted for French schooling and used as a surrogate of SES.¹³ This so-called Hollingshead score was obtained by calculating the average of the scores of both parents (or the unique score for an isolated parent) for the Education Schooling Score and the Occupation Score. When only one parent worked, only her/his score was kept. A high score indicates a high SES.

Motor functioning

All children were examined during the 7-year assessment by an experienced clinician: either a paediatric neurologist or a paediatric rehabilitation specialist.

The definition provided by the Surveillance of CP in Europe network was used: (1) permanent but not unchanging disorder of movement and/or posture; and (2) of motor function; (3) caused by a non-progressive interference/lesion/abnormality of the developing/immature brain; and (4) in a child 4-years-old or older when assessed.¹⁴ Criteria (3) and (4) were, by definition, present in our population. This also means that a child with minimal neurological abnormality (e.g. tendon reflex asymmetry) but without limitation of motor function (criterion 2) was not diagnosed with CP.

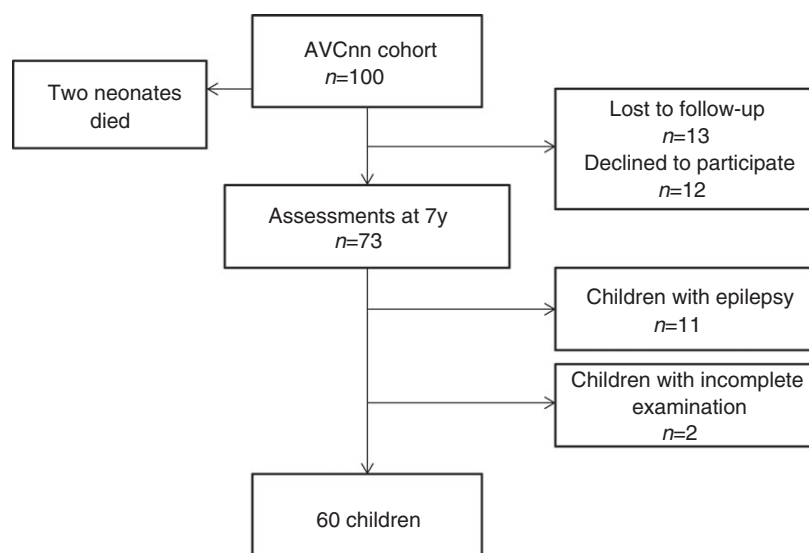


Figure 1: Follow-up until 7 years of age and exclusion of children.

The assessment of children with CP was completed by the Gross Motor Function Classification System (GMFCS) and the Bimanual Fine Motor Function (BFMF). The GMFCS provides a measure of gross mobility capacities. According to the scale, individuals at level I walk without limitations, individuals at level II have limitations walking outdoors, individuals at level III need assistive mobility device, individuals at level IV are transported or use power mobility outdoors, and a manual wheelchair is needed by individuals at level V. The BFMF scale indicates ability to grasp, manipulate, and hold objects for each hand separately. As the other hand manipulates without restrictions, scores range in children with unilateral CP from level I (the affected hand manipulates without restrictions or has limitations in more advanced fine motor skills) to level II (the affected hand has only ability to grasp or hold) and level III (the affected hand has no functional ability).¹⁵

Manual dexterity was evaluated with the Nine-Hole Peg Test (NHPT)¹⁶ and the Box and Blocks Test (BBT),¹⁷ which are commonly used in clinical studies and experimental research to measure finger dexterity and hand dexterity respectively.¹⁸ The NHPT consists of inserting nine small pegs on a board and then taking them off, as quickly as possible. The time to finish the NHPT was reported. The BBT consists of a box with two compartments separated in the middle. At the beginning, 100 small blocks are located in one of the compartments, on the same side of the tested hand. Children move as many cubes as they can from one compartment to the other. The result is the number of cubes moved into the second compartment in 1 minute. Both hands were evaluated and, for each test, the score of the best hand was considered.

Cognitive functioning

The Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), provides a global assessment of intelligence from 15 subtests, including five optional subtests.¹⁹ The 10 main subtests and the arithmetic subtest were administered during the 7-year assessment by an experienced child neuropsychologist. Based on the results, the four WISC-IV indexes were calculated: Verbal Comprehension Index, Perceptual Reasoning Index, Processing Speed Index (PSI), and Working Memory Index (WMI). The Full-scale IQ (FSIQ) was then computed. The WISC-IV has good psychometric properties. Furthermore, this scale was used in previous studies on cognitive functioning in children with NAIS. Only PSI needs unilateral manual dexterity to write.

Statistical analysis

Descriptive statistics were performed using a univariate test to estimate differences between the sample and the norm of WISC-IV on FSIQ and the four indexes.

To test the first association, the FSIQ and the four indexes of the WISC-IV were the dependent variables. Explanatory variables were manual dexterity and CP. For overall manual dexterity, a score averaging the BBT and

the NHPT scores was calculated and called the Manual Dexterity Index (MDI). To define it, we converted each individual raw score obtained from NHPT and BBT into z-scores. The NHPT score is a time delay to accomplish the required task; a negative z-score means a good performance. Conversely, the BBT score is the number of cubes translated during a specified period; a positive z-score means a good performance. To average the z-scores of BBT and NHPT of an individual child, the NHPT positive z-scores were converted to negative z-scores and vice versa. A high MDI therefore indicates a good performance. The advantage of the z-score transformation is to retain the position of each child in the sample.²⁰

Linear models were used to establish the respective importance of motor variables (i.e. MDI and CP) on WISC-IV scores. We performed linear regressions for both motor variables on WISC-IV indexes to test the first association (models 1 and 2). From the results of this first analysis, multiple linear regressions were used to test the second and third associations, specifically to measure the effect of CP independently of the effect of the MDI on FSIQ and other indexes (second association; model 3). The variables kept in the modelling had a level of significance of $p < 0.15$.²¹ The same design was used by integrating sex, lesion side, and SES (third association; model 4).

To appreciate the results of linear regressions, we used adjusted R^2 . Established from R^2 , adjusted R^2 takes into account the number of variables introduced in the analysis. The adjusted R^2 corresponds to the variance of dependent variable explained by regression model. Moreover, the β designs the standardized regression coefficient. It means, for instance, that with every increase of one SD in FSIQ, the MDI rises by 0.41 SD. We expected to observe an adjusted R^2 explaining about 20% of variance as in previous results.²²

All statistics were performed using R software environment (R Development Core Team, Vienna, Austria). The significant threshold was $p < 0.05$.

RESULTS

Population, sex, lesion side, and socioeconomic status

Twenty-one females and 39 males with NAIS but not epilepsy were examined at a median age of 7 years and 2 months (range 6y 11mo–7y 8mo). The infarct was located in the following territories: middle cerebral artery ($n=53$), anterior cerebral artery ($n=3$), posterior cerebral artery ($n=2$), multiple territories ($n=2$). It was superficial in 44 cases, deep in six, and involved both regions in 10. Unilateral infarct was more common on the left ($n=37$) than on the right ($n=19$). Four children had bilateral infarction. The Hollingshead score ranged from 13.5 to 66, with a normal distribution (Tables I and II).

Motor and intelligence variables

During the 7-year assessment, 15 of the 60 children (25%) were diagnosed with CP by clinical examination, unilateral in all. BBT and NHPT scores of the best hand, cognitive

Table I: Individual children information and lesion/neurological characteristics of the population (n=60)

Participant/sex	Age at assessment y:mo	Holligshead score	Territory and side of infarct	CP	GMFCS	BFMF	BBT ^a	NHPT ^a	FSIQ	
1/M	7:0	14.5	MCA	R	Superficial	No	27	33	94	
2/M	7:2	53	PCA	R	Deep	No	35	29	94	
3/F	7:1	31.5	MCA	R	Superficial	No	23	23	105	
4/M	7:3	22.5	MCA	R	Superficial	No	31	30	71	
5/M	7:4	27.5	ACA	L	Superficial	No	31	30	68	
6/M	7:1	57	MCA	L	Superficial	No	38	30	136	
7/M	7:2	48	MCA	R	Deep	No	31	26	99	
8/F	7:1	28.5	MCA	R	Superficial	No	37	20	108	
9/M	7:0	28.5	ACA	L	Superficial	Yes II	I	24	32	101
10/M	7:5	28	MCA	L	Superficial	Yes II	I	34	27	74
11/M	7:2	37.5	ACA	L	Mixed	Yes II	I	45	20	101
12/M	7:3	36.5	MCA	R	Deep	No	25	33	93	
13/M	7:2	13.5	MCA	B	Superficial	No	31	34	–	
14/F	7:1	35	MCA	L	Superficial	No	39	26	104	
15/M	7:1	38.5	MCA	L	Superficial	No	31	27	98	
16/M	6:11	25	MCA	L	Superficial	No	26	32	81	
17/F	7:4	29	MCA	R	Superficial	No	32	24	112	
18/F	7:3	25.5	MCA	L	Mixed	No	30	25	117	
19/M	7:1	23	MCA	R	Superficial	Yes I	II	28	30	82
20/F	7:1	50.5	MCA	L	Superficial	No	32	22	111	
21/M	6:11	18	MCA	L	Superficial	No	33	25	84	
22/F	7:3	32.5	MCA	L	Superficial	No	33	27	107	
23/M	7:2	55.5	MCA	L	Mixed	Yes I	I	42	29	103
24/M	7:0	46	MCA	L	Mixed	Yes II	II	22	29	69
25/M	7:0	62	MCA	L	Mixed	No	42	27	107	
26/M	7:0	32.5	MCA	R	Superficial	No	44	22	108	
27/F	7:0	44	MCA	R	Superficial	Yes I	I	34	24	89
28/F	7:3	26	MCA	L	Superficial	No	34	30	115	
29/F	7:1	19.5	MCA	L	Superficial	No	25	30	71	
30/M	7:1	31	MCA	R	Superficial	No	39	29	115	
31/M	7:2	34	MCA	L	Superficial	No	31	23	110	
32/M	7:2	52	MCA	L	Superficial	No	28	32	92	
33/M	6:11	66	MCA	L	Superficial	Yes I	II	36	29	92
34/M	7:3	46	ACA+MCA	L	Superficial	No	45	29	101	
35/M	7:2	58	MCA	L	Superficial	No	39	33	104	
36/F	7:2	37.5	MCA	L	Superficial	No	41	20	100	
37/F	7:4	27	MCA	R	Superficial	No	39	32	90	
38/M	7:0	21.5	ACA+MCA+PCA	L	Superficial	No	33	26	117	
39/M	7:0	23.5	MCA	L	Superficial	No	44	27	94	
40/F	7:3	42.5	MCA	L	Superficial	No	34	30	94	
41/M	7:2	38	MCA	L	Mixed	Yes II	II	28	26	107
42/M	7:0	23	MCA	L	Superficial	No	37	25	79	
43/F	7:7	29	MCA	R	Mixed	Yes II	I	31	23	91
44/F	7:2	25.5	MCA	L	Deep	No	43	22	93	
45/M	7:8	58	MCA	R	Superficial	No	33	25	116	
46/F	7:2	58	MCA	R	Superficial	No	31	30	111	
47/F	7:2	44	PCA	B	Superficial	No	44	26	109	
48/M	7:4	33.5	MCA	L	Deep	Yes II	II	30	25	–
49/M	7:3	26.5	MCA	B	Superficial	No	26	28	84	
50/F	7:2	54.5	MCA	L	Superficial	No	40	29	111	
51/F	6:11	20.5	MCA	L	Mixed	Yes II	I	17	28	102
52/F	9:2	26	MCA	L	Mixed	Yes I	II	27	30	93
53/M	7:1	31	MCA	L	Superficial	No	35	23	105	
54/M	7:2	31	MCA	R	Superficial	No	31	28	126	
55/M	6:11	21.5	MCA	R	Superficial	No	34	25	94	
56/F	7:1	36.5	MCA	L	Superficial	No	35	25	106	
57/M	6:11	47	MCA	R	Mixed	Yes I	III	23	46	69
58/M	7:4	21	MCA	B	Superficial	No	42	31	101	
59/M	7:3	16	MCA	L	Deep	No	32	24	–	
60/M	7:3	21.5	MCA	L	Superficial	Yes I	I	34	24	93

^aResults of the best hand. CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; BFMF, Bimanual Fine Motor Function; BBT, Box and Blocks Test; NHPT, Nine-Hole Peg Test; FSIQ, Full-scale IQ (assessed by the Wechsler Intelligence Scale for Children); M, male; MCA, middle cerebral artery; R, right; PCA, posterior cerebral artery; F, female; ACA, anterior cerebral artery; L, left; B, bilateral.

assessment in the whole population, and GMFCS and BFMF scores in children with CP are reported in Table I. FSIQ score was not calculable in three children and one

child had no PSI score. These missing data did not allow us to take into account these participants in corresponding analyses (regression concerning FSIQ and PSI). The

Table II: Statistical analysis of motor, cognitive, and socio-economic variables

	Mean (SD)	Median	95% CI
BBT ^a	33.51 (6.47)	33	29.82–37.21
NHPT ^a	27.4 (4.34)	27	23.71–31.09
CP (yes/no)	15/45		
FSIQ	98.26 (14.59)	101	94.57–101.95
Verbal Comprehension Index	99.63 (13.91)	101	95.93–103.33
Perceptual Reasoning Index	96.27 (15.72)	102	92.57–99.96
Processing Speed Index	101.43 (16.39)	100	97.74–105.12
Working Memory Index	92.07 (16.91)	92.5	88.37–95.76
Hollingshead score	34.83 (13.3)	31.25	31.14–38.53

^aResults of best hand. CI, confidence interval; BBT, Box and Blocks Test; NHPT, Nine-Hole Peg Test; CP, cerebral palsy; FSIQ, Full-scale IQ.

results of the WISC-IV subtests are specified in Table SI (online supporting information).

Three children had an FSIQ score below 1.96 SD and one above 1.96 SD. When comparing FSIQ averages and each index to WISC-IV, FSIQ, Verbal Comprehension Index, Perceptual Reasoning Index, and PSI, they were not different from norms, but WMI was significantly lower ($t[59]=-3.63$, $p=0.001$).

Motor and cognitive variables had normal distributions.

Relationship between motor and intelligence variables

The results of simple linear regression models showed a strong relationship between FSIQ and both motor variables (CP and MDI; see models 1 and 2 in Table III). A relationship was found between CP and Verbal Comprehension Index but not with other indexes. MDI was significant on all indexes except for WMI.

In the first step of multiple regressions, motor variables were introduced and WMI removed ($p>0.15$). Whether a child had CP or not, MDI was associated with intelligence scores (see model 3 in Table IV). A second step integrated Hollingshead score, sex, and lesion side (see model 4 in Table IV). MDI was still significant on all indexes except for WMI. The Hollingshead score effect was significant on FSIQ, Verbal Comprehension Index, and Perceptual

Reasoning Index. The sex effect was significant on PSI, with females having better scores. The lesion side effect was not significant.

In order to further investigate the lack of significant data observed for the CP effect, we performed a post hoc analysis. In this analysis, the binary CP variable was substituted by the GMFCS and BFMF scores to test the severity of clinical symptoms of CP as an associated variable of FSIQ scores. In this analysis, GMFCS and BFMF scores were defined at 0 for children without CP. We ran multiple regression models using MDI and severity of CP as the explanatory variables and FSIQ score as the dependent variable. This analysis showed no significant effect of CP severity, but MDI did (data not shown).

DISCUSSION

Our results establish a strong relationship between motor and cognitive functioning in children having suffered an NAIS. While significant links were found simultaneously for CP and manual dexterity with IQ scores, manual dexterity acts on its own as an independent variable to explain higher cognitive functioning. Whatever the CP status, manual dexterity associates with IQ. In accordance with previous studies, SES was also correlated with IQ. However, putting the SES as an independent covariable in the statistical model, our main result remains valid.

This is in line with studies on children with typical development, in which motor ability is also closely linked to IQ.^{23,24} Furthermore, our results show that this relationship is independent of sex, lesion side, SES, and, finally, CP. This highlights the strength of the relationship between manual dexterity and IQ in comparison with other variables. It also supports the fact that in early brain-damaged children, some developmental processes are comparable to those of typically developing children.^{25,26}

Two main hypotheses can be formulated to explain these findings. Firstly, it might be that some subtle limitations in manual dexterity in children not categorized as CP are not detectable through clinical examination. The second hypothesis considers the role of motor ability in development.²⁷ In our cohort, the preservation of fine motor function could contribute to the development of cognitive

Table III: Regression analyses from Manual Dexterity Index (MDI), cerebral palsy (CP), and other covariables on Wechsler Intelligence Scale for Children, Fourth Edition

Variables and models	FSIQ		VCI		PRI		PSI		WMI	
	β	p	β	p	β	p	β	p	β	p
Model 1										
MDI	0.41	0.002	0.39	0.002	0.36	0.005	0.42	0.001	-0.02	0.872
Adjusted R^2		0.152		0.136		0.116		0.164		-0.017
Model 2										
Absence of CP	0.31	0.019	-0.33	0.009	-0.09	0.488	-0.25	0.06	-0.05	0.702
Adjusted R^2		0.079		0.096		-0.009		0.045		-0.015

FSIQ, Full-scale IQ; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; WMI, Working Memory Index.

Table IV: Results of multiple linear regressions associating covariables

Variables and models	FSIQ		VCI		PRI		PSI	
	β	p	β	p	β	p	β	p
Model 3								
MDI	0.35	0.007	0.33	0.009	0.36	0.006	0.39	0.003
Absence of CP	0.22	0.083	-0.26	0.038	-0.01	0.951	-0.02	0.232
Adjusted R^2		0.183		0.185		0.100		0.171
Model 4								
MDI	0.31	0.017	0.29	0.013	0.33	0.013	0.34	0.006
Absence of CP	0.23	0.067	-0.27	0.021	-0.04	0.774	-0.15	0.194
Sex ^a	-0.06	0.229	0.08	0.468	0	0.994	0.35	0.004
Hollingshead score	0.27	0.026	0.4	0.0003	0.3	0.01	0.005	0.966
Lesion side ^b								
Bilateral	-0.03	0.789	0.12	0.287	0.002	0.989	-0.19	0.097
Right	-0.06	0.637	0.11	0.627	-0.001	0.993	-0.08	0.489
Adjusted R^2		0.221		0.324		0.152		0.283

^aMale was designated as the reference category. ^bLeft lesion was designated as the reference category. FSIQ, Full-scale IQ; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; MDI, Manual Dexterity Index; CP, cerebral palsy.

functioning. One can eventually speculate that in some situations the negative effects of unilateral CP on development can be blurred by the motor ability of the non-affected hand.

Our results show an association between cognitive functioning and manual dexterity. However, as stated by Fjørtoft et al.,²⁸ a causal relationship can neither be established nor the direction of this relationship. In other words: is the cognitive impairment a direct consequence of the poor movement quality or does the quality of movements reflect global brain dysfunctioning? More likely both are coextensive, with the necessary implication of motor activity in cognitive or executive tasks, such as visuo-constructional processes. And, conversely, the execution of any ecological motor tasks involves a complex interplay between motor planning, motor control, visual perception, and intention. Although cognitive and motor domains can be considered distinct, they are necessarily overlapping during initial development and also for later cognitive skills.²⁷ For instance, fine motor function and arithmetical ability are intimately intricated.²⁹

Besides these developmental issues, the perspectives are therapeutic and methodological. Regarding the latter, examining the relationships between motor and cognitive processes requires the inclusion of motor performance values more complex than CP as a binary variable. Our results also suggest that a quantitative evaluation of manual dexterity can be valuable when assessing cognitive functioning in children with early brain lesion. Furthermore, our study is consistent with data that efficient motor interactions with the environment are important for cognitive development.^{30,31} Future therapeutic trials should take into account the potential positive value of favouring such interactions with the valid hand or through bimanual tasks, as well as providing an enriched environment, notably at home.^{28,29} According to this

hypothesis, favouring residual motor ability may support cognitive functioning and help to counterbalance the negative effect of CP.

Having included only part (60/73 children) of the AVCnn cohort assessed at 7 years of age is a limitation. Nevertheless, our primary goal was to analyse a population without confounding deleterious factors, such as epilepsy. Furthermore, although the original cohort is longitudinal in nature, this assessment is cross-sectional. This means that we have not been able to study developmental trajectories and the potential crucial role of fine motor skills in the first months of life as an early determinant of further cognitive functioning after early brain insult.

In conclusion, having taken into consideration well-studied factors contributing to development, we have shown that manual dexterity of children with NAIS is closely linked to cognitive functioning.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: AVCnn Study Group.

Table S1: Results of IQ including scores of subtests

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