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Lesion size and long-term cognitive outcome after pediatric stroke: A comparison between two techniques to assess lesion size

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ABSTRACT

Background: There is little consensus on how lesion size impacts long-term cognitive outcome after pediatric arterial ischemic stroke (AIS). This study, therefore, compared two techniques to assessed lesion size in the chronic phase after AIS and determined their measurement agreement in relation to cognitive functions in patients after pediatric stroke.

Methods: Twenty-five patients after pediatric AIS were examined in the chronic phase (>2 years after stroke) in respect to intelligence, memory, executive functions, visuo-motor functions, motor abilities, and disease-specific outcome. Lesion size was measured using the ABC/2 formula and segmentation technique (3D Slicer). Correlation analysis determined the association between volumetry techniques and outcome measures in respect to long-term cognitive outcome.

Results: The measurements from the ABC/2 and segmentation technique were strongly correlated ($r = 0.878$, $p < .001$) and displayed agreement in particular for small lesions. Lesion size from both techniques was significantly correlated with disease-specific outcome ($p < .001$) and processing speed ($p < .005$) after controlling for age at stroke and multiple comparison.

Conclusion: The two techniques showed convergent validity and were both significantly correlated with long-term outcome after pediatric AIS. Compared to the time-consuming segmentation technique, ABC/2 facilitates clinical and research work as it requires relatively little time and is easy to apply.

1. Introduction

Pediatric arterial ischemic stroke (AIS) is an acute cerebrovascular injury that occurs when blood supply to the brain is interrupted by a blockage in a cerebral artery. Neonatal stroke (birth – 28 days) occurs with an incidence of 1 in 4000 live births and is more common than childhood stroke (after 28 days of life) reported in 1.3–13 cases per 100,000 [1].

Pediatric AIS may lead to delayed cognitive development or reduced cognitive functions within the lower normal range [2–10]. The extent to which cognitive long-term sequelae manifest is suggested to depend on risk factors such as age at stroke [9], lesion location, presence of epilepsy or the size of the lesion [2,11–18] but also on environmental factors, such as socio-economic status [19,20]. However, compared to motor outcome studies, there is little consensus on the influence of the above risk factors on long-term cognitive outcome. In respect to lesion size, some studies did not find a significant association between lesion size and cognitive outcome [21–23]. Earlier studies have indicated that solely lesions greater than 25% of the intracranial volume, or those with a diameter of at least 6 cm at the point of maximum expansion, were associated with significant cognitive impairment [2,14]. By contrast, others reported that small lesions covering only 3% of affected intracranial volume can already have an impact on cognitive outcome [11]. Further, the development of cerebral palsy was associated with a lesion size above 3% of intracranial volume in children after neonatal stroke [17].

Several neuroimaging methods have been used to determine the lesion size such as for example the ABC/2 technique first described by

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Kwak et al. [24] and validated by Kothari et al. [25] for predicting mortality according to intracerebral hemorrhage volume. With the ABC/2 technique, the length, width, and depth of damaged brain tissue in magnetic resonance images (MRI) is measured in an ellipsoid manner. For any imaging slice, the dimensions are measured where the length or width are greatest, and their product is then multiplied by the height (depth) through which the lesion extends. An ABC/2 assessment is rapidly performed but can be inaccurate for calculating the volume of relatively large or irregularly shaped lesions [26]. However, the ABC/2 technique is suggested to be the most reliable geometric formula to calculate lesion size after stroke despite some tendency for subjectivity [27].

Another technique to determine lesion size is the manual segmentation of the lesion, which has long been the standard method. Manual segmentation involves manually drawing in areas of reduced water diffusion on diffusion weighted images (DWI) or of regions of scarred brain tissue on T1-weighted images in MRI, layer by layer. This technique requires considerable time, depending on the size and extent of the lesion and is prone to some degree of subjectivity. However, the meticulous procedure used in segmentation means that lesions are measured accurately, regardless of their shape or size. This point argues for a higher measurement precision of the segmentation technique compared to the ABC/2 method. The question thus arises whether or not ABC/2 is a preferable method compared to manual segmentation.

Therefore the aim of this study was to investigate whether there is a difference in the results of the ABC/2 and segmentation method used to assess lesion size and whether lesion size measured in the chronic phase after AIS (>2 years after stroke) is associated with long-term cognitive outcome in patients. We hypothesized that (1) the ABC/2 and segmentation method assessed in the chronic phase after pediatric AIS are correlated and that (2) lesion size measured in the chronic phase after pediatric AIS is significantly correlated with disease-specific outcome and long-term cognitive performance such as intelligence, verbal memory, verbal fluency, processing speed, executive functioning, and visuo-motor functions. Further, we hypothesize that (3) the association of ABC/2 in respect to cognitive outcome would be neither inferior nor superior to the segmentation method.

2. Methods

Demographic, cognitive and neuroimaging data of patients in the chronic phase after pediatric AIS were collected from 2014 through 2017 mono-centrically within the framework of the Hemispheric Reorganization (HERO) study [28], a clinical trial that investigated functional organization of patients after pediatric AIS at the Children's University Hospital, Inselspital, Bern [9,10,28,30,54]. The HERO study was approved by the local ethics committee of the Canton of Berne (KEK 212/13) and the ethics committee of the Children's University Hospital. Participants older than 18 years, or the parents or guardians of younger children, gave their written informed consent. This was done according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.1. Study population

For the HERO study, patients in the chronic stage after AIS (>2 years after stroke) were selected from the Swiss Neuropediatric Stroke Registry (SNPSR). The SNPSR is a multicenter, prospective population-based registry that registers patients who are diagnosed with stroke before 16 years of age [16]. Inclusion criteria of the HERO study were a confirmed diagnosis of stroke (according to the initial MRI and/or computed tomography in the acute stage of stroke), diagnosis of AIS at least 2 years prior to the assessment, and aged between 5 and 16 years (in order to participate in the neuropsychological assessment and the MRI). Exclusion criteria for the HERO study were active epilepsy, iron implants, claustrophobia and behavioral problems that make a study MRI scan impossible.

Twenty-nine patients in the chronic phase after AIS were assessed in the framework of the HERO study. Four of these patients were excluded from the present study due to missing data of motor and cognitive assessment or insufficient image quality (motion artifacts) on T1 -weighted images. The final sample size for this study thus comprised 25 patients. Detailed clinical characteristics of the study participants are provided in Supplementary Tables S1 and S2.

2.2. Outcome assessment

All participants underwent a standardized neurological examination performed by a research physician. All tests were conducted by a trained neuropsychologist. To obtain a reliable and valid assessment of different cognitive domains, an extended and standardized test battery was adopted. Details on the tests have been previously published [9,10,17,23,29,30]). Raw scores for all tests were transformed into age-dependent standard scores (M = 100, SD = 15) according to the relevant test manual.

2.3. Disease-specific and motor outcome

The Pediatric Stroke Outcome Measure (PSOM) assesses neurological impairment after pediatric AIS and is currently the most strongly validated and standardized disease-specific neurological examination for pediatric stroke [31,32]. The PSOM consists of the following five subscales (1): right and (2) left sensorimotor functioning (3), language production and (4) comprehension, and (5) cognition and behavior (scores range from 0: no deficit to 10: strong deficit).

2.4. Cognitive outcome

The Test of Nonverbal Intelligence – Fourth Edition (TONI-4) was applied to assess fluid intelligence [33] as well as general intelligence [34] by means of abstract reasoning and problem solving [35,36]. The verbal learning and memory test (VLMT) was performed to assess verbal learning (word list), verbal recall (half-hour delay) and recognition [37]. Verbal fluency was assessed using the verbal fluency test from the Delis Kaplan Executive Functioning System (D-KEFS, [40]). To determine patients' processing speed abilities, two of the three processing speed subtests from the short version of the Wechsler Intelligence Scale for Children – Fourth Edition (WISC– IV) were applied. The results were summarized as a short-form index [38]. We used the fifth edition of the Beery-Buktenica Developmental Test of Visual-Motor Integration to evaluate patients' visuo-motor functions [55].

Executive functioning was examined according to the model of executive functions by Myiake et al. [39], which includes inhibition, cognitive flexibility, and working memory. Both inhibition and cognitive flexibility were assessed using the Color–Word Interference Test (CWI) from the D-KEFS [40]. The CWI measures suppressed automatic responses, also called inhibition, in accordance with the Stroop effect [41]. It also measures the person's ability to switch back and forth between conditions, which is referred to as cognitive flexibility. Furthermore, we measured the patient's working memory using the subtest Letter–Number Sequencing (LNS) from the WISC-IV [38], by asking participants to repeat a random sequence of letters and numbers, in both alphabetical and numerical order.

2.5. Neuroimaging

Neuroimaging was performed in the framework of the HERO study and thus in the chronic phase after pediatric AIS (> 2 years after stroke), using magnetic resonance imaging. A 3T scanner (Magnetom Verio, Siemens, Erlangen, Germany) with a 32-channel phased-array head coil at the Inselspital, Bern University Hospital, Switzerland. High-resolution anatomical three dimensional T1-weighted images were obtained from a

magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) sequence. The following parameters were configured for the sequences: repetition time (TR) = 2530 ms; echo time (TE) = 2.92 ms; inversion time (Ti) = 1100 ms; flip angle (FA) = 9°; field-of-view (FOV) = 256 mm × 256 mm; matrix dimension = 256 × 256; and isotropic voxel resolution = 1 mm^3.

For each T1-weighted brain scan, a board-certified neuroradiologist determined the lesion's characteristics, such as exact location (anatomical structures: cortical, subcortical or both) and affected side (right hemisphere, left hemisphere or bilateral). Lesion size is typically determined using diffusion-weighted images (DWI). When it comes to research on long-term outcome in the developing child using functional imaging, lesion size must be measured on chronic T1-weighted MRI. The lesion size determination on the chronic T1-weighted MRI was performed by a neuroradiologist (N.S.) while inspecting the initial lesion localization using the initial DWI from the acute phase of stroke as a baseline measurement. This was done in order to get information on the exact lesion localization in case of uncertainty.

2.5.1. Lesion size quantified with ABC/2 method

The ABC/2 method to determine the lesion size was performed by the neuroradiologist N.S. in accordance with Sims et al. (2009). The images were measured on the local Picture Archiving and Communication System (PACS) of the Inselspital, Bern. In the sagittal plane, the length (A) was measured in the slice where the lesion appeared largest. Perpendicular to the length, a second line was drawn at the widest dimension (B). To calculate the height (C), the number of slices over which the lesion extended was multiplied by the thickness of these slices (1 mm). The three measurements were computed according to the ellipsoid formula for volumetry: 4/3πrArBrC. The π term was estimated as 3, which simplifies the formula in 4/3*3*(A/2)*(B/2)*(C/2) = ABC/2, and the calculated final volumes were converted into cm^3. Hence, the measured lesion sizes were presented as ellipsoids.

2.5.2. Lesion size quantified with segmentation method

Lesion sizes were segmented on the T1-weighted MRI in the chronic stage of stroke using the open-source software, 3D Slicer (Version 4, https://www.download.slicer.org). The volumetry by segmentation was performed by S.B., who was closely supervised by the neuroradiologist N.S. (every patient's data was reviewed separately) by using the 3D Slicer editor program, lesions were manually segmented in each layer in the axial plane. The traced tissue resulted in individual lesion shapes (in contrast to the ABC/2 method). The calculated infarct volumes by 3D Slicer in mm^3 were converted into cm^3. Lesion size quantification on the chronic T1-weighted MRI using segmentation was performed while inspecting the initial diffusion-weighted images.

Because of significant variations in whole-brain volumes that depend on the age of a child [42], working with absolute lesion size would not be meaningful. Therefore, a relative lesion size (in %) was calculated for both techniques (ABC/2 and segmentation) with the following formula: lesion size (in cm^3) divided by total brain volume (in cm^3) multiplied by 100, whereas total brain volume includes everything within the skull, including the ventricular system.

2.6. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 27.0 for Windows (IBM Corp., Armonk, NY), with the significance level (α) set to 5%. Lesion sizes and cognitive data were tested for normal distribution with the Kolmogorov-Smirnov test. Lesion size, disease-specific outcome, motor outcome, as well as most of the cognitive variables were not normally distributed. Hence, non-parametric tests were used where suitable. Absolute lesion size was used only for the investigation of the first hypothesis, whereas relative lesion size was employed for all further analyses.

Our first hypothesis assumes that the results from the two volumetry techniques are correlated. To test this hypothesis, we estimated the relationship between the absolute lesion size assessed with the two techniques for evidence of convergent validity and calculated the Spearman rank correlation coefficients. Agreement between the results of the two techniques was illustrated with Bland & Altmann [43] plots.

To test for our second hypothesis, namely the association between relative lesion size and cognitive outcome, we conducted Spearman rank correlation coefficients with Bonferroni correction. If necessary, non-parametric partial correlations were performed to reduce the influence of a third confounding variable on significant correlations between relative lesion size as measured by segmentation and/or ABC/2 and any cognitive variable.

Additionally, we conducted the same correlational analyses to check for a possible relationship between relative lesion size and other lesion-related variables. Because of the small sample, inferential statistical analyses were not performed for some of the lesion-related variables (e.g. lesion location and laterality; these two variables were presented graphically). A correction for multiple testing was not performed, since the four variables considered were generally confirmed in the literature as being influencing variables in pediatric AIS and therefore, pre-existing assumptions were given [44].

3. Results

3.1. Participants

Demographic data are summarized in Table 1. 25 patients were included in the data analysis (6 neonatal stroke, 19 childhood stroke, 11 females). Clinical data regarding localization, laterality and etiology of stroke, are presented in Tables S1 and S2. Given the small sample size, analysis were not perfomed for subgroups, i.e. location, laterality or etiology of stroke or age at stroke.

3.2. Cognitive outcome

Overall, the cognitive performance was within the normal range, however, group means were slightly below the mean scores expected in a healthy population (see Table 2). Participants with neonatal stroke (n = 6) did not differ in their cognitive performance from participants with stroke during childhood (all $t < 1.78$, all $p > .09$). There was no significant association between cognitive outcome and time between stroke and chronic MRI (all $r < 0.14$, all $p > .32$).

3.3. Measurement of absolute and relative lesion sizes

The ABC/2 method identified lesions of less than 1% of the intracranial volume in 16 participants, whereas segmentation identified 19 participants with lesions less than 1% of the intracranial volume. Two patients had a large lesion (>3% of the intracranial volume), regardless of the measurement technique applied. The segmentation method resulted in larger absolute lesion sizes for all patients than the ABC/2 method (see Table 3). This was also evident when the lesion size was set

Table 1
Demographic and Clinical Data of Study Participants.

Patients after pediatric AIS (n = 25)		
	N, Mean (SD)	Range
Neonatal stroke/childhood stroke (n)	6/25	
Age at stroke (in years)	6.31 (5.4)	0.1–15.58
Age at examination (in years)	14.81 (5.09)	6.08–23.08
Time between stroke and chronic MRI (in years)	8.49 (3.56)	2.08–15.5
Disease specific outcome (PSOM)	0.66 (0.93)	0.00–3.5
Sensorimotor functioning, left (PSOM)	0.14 (0.34)	0–1
Sensorimotor functioning, right (PSOM)	0.34 (0.59)	0–2

Note. Values are rounded to two decimal places. *SD*: standard deviation.

Table 2
Cognitive Outcome after Pediatric AIS.

	n	Mean (SD)	Range
Intelligence[a]	25	97.28 (8.33)	84–118
Verbal memory			
Verbal learning[b]	25	51.8 (33.16)	3–98
Verbal recall[b]	24	47.38 (28.34)	3–98
Verbal fluency	23	9.39 (3.53)	2–16
Processing speed (Index)[a]	25	99.6 (15.14)	65–125
Executive functions			
Working memory[c]	25	8.88 (3.87)	2–16
Inhibition[c]	23	9.39 (3.01)	1–13
Cognitive Flexibility[c]	22	9.73 (3.44)	1–13
Visuo-motor functions			
Visuo-motor integration[c]	24	8.33 (3.23)	2–14
Visuo-motor coordination[c]	24	8.33 (2.58)	4–12

[a] Intelligence scale: mean (*SD*) 100 (+/-15).
[b] Percentile: mean (*SD*) 50 (+/-34).
[c] Scaled scores: mean (*SD*) 10 (+/-3); *SD*: standard deviation. Values are rounded to two decimal places.

in relation to the total volume of the brain (relative lesion size). Participants with neonatal stroke did not differ in respect to lesion size from patients with childhood stroke (all $t < -4.36$, all $p > .48$). There was no significant association between lesion size and time passed since stroke (all $r < 0.08$, all $p > .68$). Detailed results of volumetric analysis are shown in Table 3.

3.4. Relationship between ABC/2 and segmentation method

There was a significant association between the two lesion techniques (df (25), $r = 0.878$, $p < .001$) (Fig. 1). When excluding the two outliers (two participants with lesions >3% of the intracranial volume) the correlation remained strong (df (23),) $r = 0.845$, $p < .001$) The degree of agreement between the two techniques is illustrated in a Bland-Altman plot while differentiating participants with neonatal and childhood stroke (Fig. 1).

3.5. Association between lesion size and cognitive and disease-specific outcome

Disease-specific outcome (PSOM) and processing speed were significantly correlated with the relative lesion size (after Bonferroni correction, see Table 4). Correlation coefficients were higher for the ABC/2 method than for segmentation method. As analyses showed that age at stroke was significantly correlated with lesion size ($r = -0.441$, $p = .027$), this variable was integrated as a covariate. The correlations between lesion size, PSOM and processing speed remained significant after controlling for age at stroke (for both techniques, see Table 5), with no differences between participants with neonatal versus childhood stroke when it comes to the association between lesion size and outcome.

4. Discussion

The present study examined whether there is a difference in the results of two volumetry techniques used to measure the lesion size (ABC/2 and segmentation) and whether lesion size in the chronic phase was

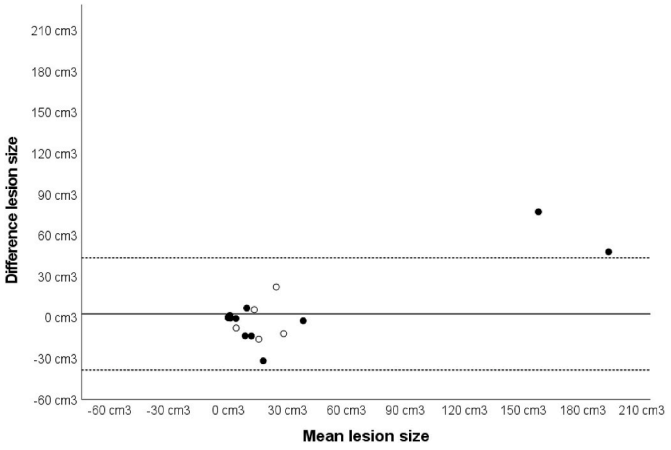

Fig. 1. Measurement Agreement Between the ABC/2 Method and Segmentation *(*white dots indicate lesion size of participants after neonatal stroke, black dots represent participants after childhood stroke).
Note. X-axis: The average of value pairs of absolute lesion size resulting from the ABC/2 method and segmentation. Y-axis: the difference of value pairs of absolute lesion size between the two volumetry techniques.
The bold line represents the mean value of the measurement difference. The dashed lines mark two standard deviations of the mean and are referred to as limits of agreement.

Table 4
Association Between Cognitive Variables and Relative Lesion size measured with Segmentation and ABC/2.

	N	Segmentation	p-value (1-sided)	ABC/2	p-value (1-sided)
PSOM	25	0.633	<.001**	0.667	0.000**
Intelligence	25	−0.286	0.083	−0.404	0.023*
Verbal memory					
Verbal learning	25	−0.241	0.123	−0.161	0.222
Verbal recall	24	−0.504	0.006**	−0.478	0.009**
Verbal fluency	23	−0.429	0.020*	−0.539	0.004**
Processing speed (Index)	25	−0.559	0.002**	−0.603	0.001**
Executive functions					
Working memory	25	−0.303	0.071	−0.345	0.046*
Inhibition	23	−0.360	0.046*	−0.425	0.022*
Cognitive Flexibility	22	−0.232	0.149	−0.337	0.063
Visuo-motor functions					
Visuo-motor integration	24	−0.152	0.240	−0.225	0.115
Visuo-motor coordination	24	−0.363	0.040*	−0.440	0.016*

Note. Relative volume was calculated for both, ABC/2 and segmentation (%) as follows: absolute lesion size divided by total intracranial volume * 100. PSOM = Disease-specific outcome, higher scores indicate more problems. Values are rounded to three decimal places.
*The correlation is significant if $p < .05$; **The correlation is significant if $p < .01$; **Correlations remained significant after Bonferroni correction if $p < .0038$.

Table 3
Lesion size Measurements for the ABC/2 and Segmentation method.

	Absolute lesion size (cm^3)			Relative lesion size (%)		
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range
Segmentation	22.55 (56.51)	1.65 (0.25–12.92)	0.043–217.2	1.55 (3.81)	0.09 (0.02–0.89)	0.003–15.2
ABC/2	19.94 (39.9)	4.36 (0.2–18.6)	0.036–169.2	1.39 (2.72)	0.35 (0.01–1.08)	0.003–11.7

Note. Relative lesion size (in %) was calculated for both ABC/2 and segmentation as follows: absolute lesion size divided by total intracranial volume * 100. SD: standard deviation; IQR: interquartile range. Values are rounded to two decimal places.

Table 5
Controlling for the Influence of Age at Stroke on the Relationship between cognitive Variables and Relative Lesion size.

	N	Segmentation	p-value (1-sided)	ABC/2	p-value (1-sided)
PSOM	25	0.634	<.001⁂	0.656	0.000⁂
Processing speed (Index)	25	−0.551	0.005**	−0.572	0.002⁂

Note. Nonparametric partial correlation coefficients on a selection of variables based on previous analyses. Relative volume was calculated for both ABC/2 and segmentation (%) as follows: absolute lesion size divided by total intracranial volume * 100. PSOM = Disease-specific outcome, higher scores indicate more problems. Values are rounded to three decimal places.
**The correlation is significant if $p < .01$; ⁂Correlations remained significant after Bonferroni correction if $p < .0038$.

associated with cognitive and disease-specific outcome in patients after pediatric stroke. The two techniques showed a strong association and reached agreement in particular for small lesions, whereas measurement agreement was reduced for larger lesions. Correlation coefficients between lesion size and cognitive functions were comparable for the ABC/2 technique and for the segmentation technique. After correcting for multiple comparisons and controlling for the influence of age at stroke on lesion size, the correlation between lesion size and disease-specific outcome (PSOM), as well as processing speed remained significant.

4.1. Relationship between volumetry techniques

The strong correlation between the lesion size resulting from the ABC/2 and the segmentation technique supports the convergent validity of the two methods [45]. The extent to which these methods were consistent in absolute lesion size measurement was evident in the Bland-Altman plot. However, two patients with lesions bigger than 3% of the intracranial volume, exceeded the upper limit of agreement (see Fig. 1). The question arises why the agreement differed considerably in larger lesions. An explanation may be found in previous studies which suggested that the ABC/2 method tends to overestimate volumes that are irregularly shaped, large [26] or in a non-ellipsoid shape [56]. These previous results therefore propose that the ellipsoid formula does not adequately measure certain lesion characteristics, a notion that is supported by our data.

Another study included 109 adult patients in the acute phase after AIS and presents similar results with strong positive correlations between the ABC/2 method and manual segmentation [57]. As in our pediatric study, adult data showed that larger lesion sizes entailed stronger discrepancy between the assessment techniques [57]. In a study with 38 patients after stroke, investigators compared the reproducibility of five different methods to measure lesions size on CT scans. Manual tracing of the lesion perimenter was the most reproducible methods [58].

4.2. Impact of lesion size on cognitive outcome

Without correction for multiple comparison, lesion size was associated with lower cognitive functions, including verbal recall, verbal fluency, inhibition, visuo-motor coordination, processing speed, and disease-specific outcome (PSOM). These results held true regardless of the implemented volumetry technique and are largely consistent with the literature [1,2,4,5,9,10,46–49].

After controlling for age at stroke and correcting for multiple comparison, only disease-specific outcome (PSOM) and processing speed were significantly correlated with lesion size (for both techniques). Slightly higher effect sizes were found for the ABC/2 method than the segmentation technique (Table 5). The question arises why in particular disease-specific outcome and processing speed were strongly related to lesion size. A possible explanation regarding disease-specific outcome might be that performance was measured in different functional domains, including sensorimotor functions, language production, comprehension, cognition and behavior. For processing speed, its broad influence on many cognitive subdomains may explain its strong association with lesion size. Processing speed is based upon efficient communication between widespread regions of the brain, forming a large-scale network [50]. The remaining cognitive domains which were measured in this study only showed low to moderate correlations with lesion size.

There is no clear pattern in the literature regarding the influence of lesion size on cognitive functions, with some domains suggested to relate more closely to lesion size than others [2,9–12,14,15,17]. This inconsistency might be due to the fact that a cognitive function may be impaired when the structure or the functional network is affected, regardless of the exact lesion size [2,10,23,52,53]. Hence, our results add further insight into the impact of lesion size on long-term outcome after pediatric AIS while showing a relationship between lesion size and the pediatric stroke outcome measure (PSOM) and processing speed.

4.3. Limitations

The present study has certain limitations to report. First of all, the sample size was relatively small and patients were clinically heterogeneous, with non-normally distributed clinical data for i.e. lesion size, lesion location and age at stroke. Therefore, subgroup analysis were impossible. Second, a selection bias has to be taken into account when interpreting the data since patients who were unable to follow the study procedure were excluded. Third, we were unable to perform a statistically appropriate comparison of the differences between correlation coefficients or the predictive validity of relative lesion size in respect to the two volumetry techniques, because lesion sizes resulting from either volumetry technique stemmed from the same patients. Fourth, post-stroke treatment, the rehabilitation setting or family ressources may be associated with lesion size and long-term outcome and should ideally be included in future research. Finally, considering prognosis and decision-making about interventions and preventive strategies after pediatric AIS, the volumes measured in the present study are relevant only to the chronic and not the acute phase after stroke. To draw valid conclusions about the predictive value of lesion size in the acute phase on long-term outcome, further studies are needed.

5. Conclusion

Our work provides insight into the association of the presumably rapidly implemented ABC/2 method and the time-consuming but more detailed segmentation technique, both frequently used to measure lesion size in clinical work and research. The results of the two volumetric techniques showed convergent validity, especially for measurements of relatively small lesions. Both the ABC/2 method and segmentation method were closely related to disease-specific outcome and processing speed with comparable correlation coefficients. However, the ABC/2 technique may be preferable because of its rapid measurement of the lesion size. Compared to the time-consuming segmentation technique, ABC/2 facilitates clinical and research work as it requires relatively little time and is easy to apply.

Our research contributes to a better understanding of the relationship between lesion size and long-term outcome in young patients after pediatric AIS. To better understand the implications of our results, future investigations could include a larger sample with patients in the acute phase after pediatric stroke and implement other volumetry techniques, such as i.e. computer-assisted approaches. Given the rise of artificial intelligence algorithms, semi-automated and fully automated programs likely present the future approach to measure lesion size. Samples with greater variability in lesion size and the inclusion of additional outcome measures could shed even clearer light on the predictive power of different lesion size techniques on post stroke outcome.

Data availability statement

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

Declaration of competing interest

There are no conflicts of interest reported for any of the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2023.01.001.

References

[1] A.A. Mallick, V. Ganesan, F.J. Kirkham, P. Fallon, T. Hedderly, T. McShane, et al., Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective populationbased study, Lancet Neurol. 13 (1) (2014) 35–43.
[2] R. Everts, J. Pavlovic, F. Kaufmann, B. Uhlenberg, U. Seidel, K. Nedeltchev, et al., Cognitive functioning, behavior, and quality of life after stroke in childhood [cited 2014 Sep 28], Child Neuropsychol [Internet] 14 (4) (2008 Jul), 323–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18568780.
[3] K. Murias, B. Brooks, A. Kirton, G. Iaria, A review of cognitive outcomes in children following perinatal stroke, Dev. Neuropsychol. 39 (2) (2014) 131–157.
[4] F. O'Keeffe, F. Liégeois, M. Eve, V. Ganesan, J. King, T. Murphy, Neuropsychological and neurobehavioral outcome following childhood arterial ischemic stroke: attention deficits, emotional dysregulation, and executive dysfunction, Child Neuropsychol. 20 (5) (2014) 557–582.
[5] M. Studer, E. Boltshauser, A.C. Mori, A. Datta, J. Fluss, D. Mercati, et al., Factors affecting cognitive outcome in early pediatric stroke, Neurology 82 (9) (2014) 784–792.
[6] C. Amlie-Lefond, G. Sébire, H.J. Fullerton, Recent developments in childhood arterial ischaemic stroke, Lancet Neurol. 7 (5) (2008) 425–435.
[7] S. Christerson, B. Strömberg, Stroke in Swedish children II: long-term outcome, Acta Paediatr Int J Paediatr 99 (11) (2010) 1650–1656.
[8] J.E. Max, K. Mathews, A.E. Lansing, B.A.M. Robertson, P.T. Fox, J.L. Lancaster, et al., Psychiatric disorders after childhood stroke, J. Am. Acad. Child Adolesc. Psychiatry 41 (5) (2002) 555–562.
[9] S. Abgottspon, L. Steiner, N. Slavova, M. Steinlin, S. Grunt, R. Everts, Applied Neuropsychology : child Relationship between motor abilities and executive functions in patients after pediatric stroke, 0(0, Appl Neuropsychol Child [Internet (2021) 1–10, https://doi.org/10.1080/21622965.2021.1919111. Available from:.
[10] L. Steiner, A. Federspiel, J. Jaros, N. Slavova, R. Wiest, M. Steinlin, et al., Cerebral blood flow and cognitive outcome after pediatric stroke in the middle cerebral artery, Sci. Rep. 11 (1) (2021).
[11] C.G. Filippi, A.M. El-Ali, V.Z. Miloushev, D.S. Chow, X. Guo, B. Zhao, Computer-assisted volumetric measurement of core infarct volume in pediatric patients: feasibility for clinical use and development of quantitative metrics for outcome prediction, Am. J. Neuroradiol. 36 (4) (2015) 789–794.
[12] J. Lee, L.A. Croen, C. Lindan, K.B. Nash, C.K. Yoshida, D.M. Ferriero, et al., Predictors of outcome in perinatal arterial stroke: a population-based study, Ann. Neurol. 58 (2) (2005) 303–308.
[13] K. Lidzba, R. Everts, G. Reuner, Neuropsychologie bei Kindern und Jugendlichen. Neuropsychologie bei Kindern und Jugendlichen, 2019, p. 114.
[14] B. Long, V. Anderson, R. Jacobs, M. Mackay, R. Leventer, C. Barnes, et al., Executive function following child stroke: the impact of lesion size, Dev. Neuropsychol. 36 (8) (2011) 971–987.
[15] J.K. Lynch, D.G. Hirtz, G. DeVeber, K.B. Nelson, Report of the national institute of neurological disorders and stroke workshop on perinatal and childhood stroke, Pediatrics 109 (1) (2002) 116–123.
[16] M. Steinlin, I. Pfister, J. Pavlovic, R. Everts, E. Boltshauser, A.C. Mori, et al., The first three years of the Swiss Neuropaediatric Stroke Registry (SNPSR): a population-based study of incidence, symptoms and risk factors, Neuropediatrics 36 (2) (2005) 90–97.
[17] A. Wiedemann, M. Pastore-Wapp, N. Slavova, L. Steiner, C. Weisstanner, M. Regényi, et al., Impact of stroke volume on motor outcome in neonatal arterial ischemic stroke, Eur. J. Paediatr. Neurol. 25 (2020) 97–105.
[18] C.J. Wusthoff, S.K. Kessler, A. Vossough, R. Ichord, S. Zelonis, A. Halperin, et al., Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study, Pediatrics 127 (6) (2011) e1550–e1557.
[19] L.C. Jordan, N.K. Hills, C.K. Fox, R.N. Ichord, P. Pergami, G.A. Deveber, et al., Socioeconomic determinants of outcome after childhood arterial ischemic stroke, Neurology 91 (6) (2018) e509–e516.
[20] L. Bartha-Doering, A. Gleiss, S. Knaus, M.T. Schmook, R. Seidl, Influence of socioeconomic status on cognitive outcome after childhood arterial ischemic stroke, Dev. Med. Child Neurol. 63 (4) (2021) 465–471.
[21] A.M. Chilosi, P. Cipriani, B. Bertuccelli, L. Pfanner, G. Cioni, Early cognitive and communication development in children with focal brain lesions, J. Child Neurol. 16 (5) (2001 May) 309–316.
[22] C.A. Hajek, K.O. Yeates, V. Anderson, M. Mackay, M. Greenham, A. Gomes, et al., Cognitive outcomes following arterial ischemic stroke in infants and children, J. Child Neurol. 29 (7) (2013 Jun) 887–894.
[23] S.KornfeldR. Yuan, B.B. Biswal, S. Grunt, S. Kamal, J.A. Delgado Rodríguez, et al., Resting-state connectivity and executive functions after pediatric arterial ischemic stroke, NeuroImage Clin [Internet 17 (2018) October 2017) 359–67. Available from: doi:10.1016/j.nicl.2017.10.016.
[24] R. Kwak, S. Kadoya, T. Suzuki, Factors affecting the prognosis in thalamic hemorrage, Stroke 14 (4) (1983) 493–500.
[25] R.U. Kothari, T. Brott, J.P. Broderick, W.G. Barsan, L.R. Sauerbeck, M. Zuccarello, et al., The ABCs of measuring intracerebral hemorrhage volumes, Stroke 27 (8) (1996 Aug) 1304–1305.
[26] B. Zhao, W.B. Jia, L.Y. Zhang, T.Z. Wang, 1/2SH: a simple, accurate, and reliable method of calculating the hematoma volume of spontaneous intracerebral hemorrhage, Stroke 51 (1) (2020) 193–201.
[27] J.R. Sims, L.R. Gharai, P.W. Schaefer, M. Vangel, E.S. Rosenthal, M.H. Lev, et al., ABC/2 for rapid clinical estimate of infarct, perfusion, and mismatch volumes, Neurology 72 (24) (2009) 2104–2110.
[28] S. Kornfeld, J.A.D. Rodríguez, R. Everts, A. Kaelin-Lang, R. Wiest, C. Weisstanner, et al., Cortical reorganisation of cerebral networks after childhood stroke: impact on outcome, BMC Neurol. 15 (90) (2015).
[29] C. Simon-martinez, S. Kamal, F. Frickmann, L. Steiner, Participation after Childhood Stroke : Is There a Relationship with Lesion Size , Motor Function and Manual Ability, 2021, pp. 1–21.
[30] S. Kornfeld, J.A.D. Rodríguez, R. Everts, A. Kaelin-Lang, R. Wiest, C. Weisstanner, et al., Cortical reorganisation of cerebral networks after childhood stroke: impact on outcome [Internet], BMC Neurol. 15 (1) (2015) 1–7. Available from: 10.1186/s12883-015-0309-1.
[31] K.A. Engelmann, L.C. Jordan, Outcome measures used in pediatric stroke studies: a systematic review, Arch. Neurol. 69 (1) (2012) 23–27.
[32] L. Kitchen, R. Westmacott, S. Friefeld, D. MacGregor, R. Curtis, A. Allen, et al., The pediatric stroke outcome measure: a validation and reliability study, Stroke 43 (6) (2012) 1602–1608.
[33] J.L. Horn, R.B. Cattell, Refinement and test of the theory of fluid and crystallized general intelligences, J. Educ. Psychol. 57 (1966) 253–270. US: American Psychological Association.
[34] C. Spearman, General intelligence, objectively determined and measured. Am J Psychol 15 (2) (1904) 201–292.
[35] Test Review N. Ritter, E. Kilinc, B. Navruz, Y. Bae, L. Brown, R.J. Sherbenou, S. K. Johnsen, Test of nonverbal intelligence-4 (TONI-4). Austin, TX: PRO-ED, J. Psychoeduc. Assess. 29 (5) (2011 Oct) 484–488, 2010.
[36] J. Fopiano, Test of nonverbal intelligence (TONI-4), in: Encyclopedia of Autism Spectrum Disorders, 2013, pp. 3089–3092. New York.
[37] C. Helmstaedter, H.F. Durwen, VLMT: Verbaler Lern- und Merkfähigkeitstest: Ein praktikables und differenziertes Instrumentarium zur Prüfung der verbalen Gedächtnisleistungen. = VLMT: a useful tool to assess and differentiate verbal memory performance, Schweiz. Arch. Neurol. Neurochir. Psychiatr. 141 (1990) 21–30. Switzerland: Schwabe & Co.
[38] F. Petermann, U. Petermann, Hamburg-Wechsler-Intelligenztest für Kinder - IV (HAWIK-IV), Bern, 2012.
[39] A. Miyake, N.P. Friedman, M.J. Emerson, A.H. Witzki, A. Howerter, T.D. Wager, The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis, Cognit. Psychol. 41 (1) (2000) 49–100.
[40] E.M. Fine, D.C. Delis, Delis–Kaplan executive functioning system, in: Encyclopedia of Clinical Neuropsychology, 2011, pp. 796–801.
[41] J.R. Stroop, Studies of interference in serial verbal reactions, J. Exp. Psychol. 18 (6) (1935) 643–662.
[42] L.C. Jordan, J.T. Kleinman, A.E. Hillis, Intracerebral hemorrhage volume predicts poor neurologic outcome in children, Stroke 40 (5) (2009) 1666–1671.
[43] J.M. Bland, D.G. Altmann, Statistical methods for assessing agreement between two methods of clinical measurement, Int. J. Nurs. Stud. 47 (8) (2010) 931–936.
[44] R.A. Armstrong, When to use the Bonferroni correction, Ophthalmic Physiol. Opt. 34 (5) (2014) 502–508.
[45] M.J. Sirgy, D. Grewal, T.F. Mangleburg, J.-O. Park, K.-S. Chon, C.B. Claiborne, et al., Assessing the predictive validity of two methods of measuring self-image congruence, J. Acad. Market. Sci. 25 (3) (1997) 229–241.
[46] E.L.L.M. De Schryver, L.J. Kappelle, A. Jennekens-Schinkel, A.C.B. Peters, Prognosis of ischemic stroke in childhood: a long-term follow-up study, Dev. Med. Child Neurol. 42 (5) (2000) 313–318.
[47] A. Eikelmann, F. Petermann, M. Daseking, Aufmerksamkeitsstörungen nach Schlaganfällen im Kindesalter, Z. Kinder JugenPsychiatr. Psychother. 36 (6) (2008) 419–426.

[48] T.L. Talib, S.J. Pongonis, L.S. Williams, B.P. Garg, D.K. Sokol, C. Saha, et al., Neuropsychological outcomes in a case series of twins discordant for perinatal stroke, Pediatr. Neurol. 38 (2) (2008) 118–125.
[49] R. Westmacott, R. Askalan, D. MacGregor, P. Anderson, G. Deveber, Cognitive outcome following unilateral arterial ischaemic stroke in childhood: effects of age at stroke and lesion location [cited 2014 Oct 10], Dev Med Child Neurol [Internet] 52 (4) (2010 Apr), 386–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19694778.
[50] P. Imms, D.J.F. Domínguez, A. Burmester, C. Seguin, A. Clemente, T. Dhollander, et al., Navigating the link between processing speed and network communication in the human brain, Brain Struct. Funct. 226 (4) (2021) 1281–1302.
[52] A.O. Ballantyne, A.M. Spilkin, J. Hesselink, D.A. Trauner, Plasticity in the developing brain: intellectual, language and academic functions in children with ischaemic perinatal stroke, Brain 131 (11) (2008) 2975–2985.
[53] M. Daseking, D. Heubrock, A. Hetzel, F. Petermann, Schlaganfälle bei Kindern und Jugendlichen: Epidemiologie - Ätiologie - neurologische Defizite - neuropsychologische Beeinträchtigungen, Nervenarzt 74 (12) (2003) 1088–1097.
[54] L. Steiner, A. Federspiel, N. Slavova, R. Wiest, S. Grunt, M. Steinlin, R. Everts, Cognitive outcome is related to functional thalamo-cortical connectivity after paediatric stroke, Brain Commun 4 (3) (2022 Apr 28) fcac110.
[55] Keith E. Beery, The Beery-Buktenica Developmental Test of Visual-Motor Integration, Administration scoring and teaching manual, 1997.
[56] A.K. Maeda, L.R. Aguiar, C. Martins, G.L. Bichinho, M.A. Gariba, Hematoma volumes of spontaneous intracerebral hemorrhage: the ellipse (ABC/2) method yielded volumes smaller than those measured using the planimetric method, Arquivos de neuro-psiquiatria 71 (2013) 540–544.
[57] T. Sananmuang, T. Dejsiripongsa, J. Keandoungchun, M. Apirakkan, Reliability of ABC/2 method in measuring of infarct volume in magnetic resonance diffusion-weighted image, Asian Journal of Neurosurgery 14 (3) (2019) 801.
[58] H.B. van der Worp, S.P. Claus, P.R. Bär, L.M. Ramos, A. Algra, J. van Gijn, L. J. Kappelle, Reproducibility of measurements of cerebral infarct volume on CT scans, Stroke 32 (2) (2001 Feb) 424–430.