Effect of Age at Pediatric Stroke on Long-term Cognitive Outcome

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Abstract

Background and Objectives
To investigate the effect of age at pediatric arterial ischemic stroke on long-term cognitive outcome in order to identify patients particularly at risk for the development of long-term cognitive sequelae.

Methods
This cross-sectional study included patients in the chronic phase of stroke (>2 years after stroke) previously diagnosed with neonatal or childhood arterial ischemic stroke and a control group. Participants with active epilepsy, severe learning difficulties, or behavioral problems hindering the cognitive assessment were excluded. Several cognitive domains, including intelligence, executive functions (working memory, inhibition, and cognitive flexibility), processing speed, memory, letter fluency, and visual-motor skills were assessed with neuropsychological tests. Cognitive long-term outcome was compared across patients after neonatal stroke (stroke between 0 and 28 days of life), early childhood stroke (stroke between 29 days and <6 years), and late childhood stroke (stroke between ≥6 and <16 years).

Results
Fifty-two patients after neonatal or childhood arterial ischemic stroke (median age 15.3 years, interquartile range [IQR] 10.6–18.7) and 49 healthy controls (median age 13.6 years, IQR 9.8–17.2) met the inclusion criteria. Cognitive outcome was significantly worse in the pediatric stroke group compared to the control group. A nonlinear effect of age at stroke (irrespective of lesion size and lesion location) was found for cognitive flexibility, processing speed, and verbal learning with early childhood stroke (29 days to <6 years), showing significantly worse cognitive outcome compared to neonatal or late childhood stroke ($p < 0.05$, false discovery rate–corrected).

Discussion
Age at stroke is an important factor for poststroke recovery and modulates long-term cognitive outcome irrespective of lesion size and lesion location. Children after early childhood stroke are at particular risk for long-term alterations in cognitive functions.

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Pediatric arterial ischemic stroke is a rare event accompanied by an increased risk for cognitive and neurologic sequelae.[1-3] Identification of factors associated with poor outcome has been the focus of research for several years, but knowledge about outcome prediction remains insufficient.[4-6]

An inherent property of the developing brain is increased plasticity.[7-9] Due to rapid synaptogenesis as well as increased myelination and reorganization processes of neuronal networks during this period, the developing brain is suggested to be more flexible with better recovery capacity after early brain insult.[2,7,9] On the other hand, the developing brain is particularly vulnerable to early brain insult, leading to disrupted brain development.[7,9] In light of the 2 contradictory perspectives—plasticity vs vulnerability—findings about the effect of age at pediatric stroke remain unclear, with some studies showing that younger age at stroke is associated with worse[6,10-13] or better cognitive outcome.[14,15]

Whereas several studies examined cognitive outcome in the acute phase of the stroke up until 2 years poststroke,[6,10,12] studies investigating the outcome of patients in the late chronic stage (>2 years after stroke) are limited. Focusing on patients in the late chronic stage is essential as deficits may emerge and increase over time[5,11,16] and recovery processes can extend far beyond the first months poststroke.[17] Furthermore, the developmental stage at the time of the brain insult can modulate cognitive outcome.[18,19] Brain insults during a critical period of cognitive development likely entail poorer cognitive outcome compared to brain injuries occurring before, during, or after the emergence of cognitive function.[19] Moreover, cognitive functions, in particular executive functions, are strongly associated with quality of life,[20] scholastic achievement,[21] and social competence,[22] which highlights the importance to monitor poststroke cognitive outcome.

In the present study, we aimed to examine long-term cognitive outcome following pediatric stroke in the chronic stage (>2 years after stroke) and to investigate whether age at stroke affects cognition in order to identify patients at risk for poor cognitive outcome.

Methods

Study Design and Study Population

This cross-sectional study includes data from 2 research projects that were carried out at the Division of Neuropediatrics, Development, and Rehabilitation at the University Hospital in Berne, Switzerland (Hemispheric Reorganization[3] [HERO] study,[3] 2014–2016, and Onset study, 2019–2020). In both research projects, participants diagnosed with pediatric arterial ischemic stroke were recruited from the population-based Swiss Neuropediatric Stroke Registry (SNPSR).[6,23] The control group was recruited within the HERO study through advertisement in the hospital intranet and flyers.

Inclusion criteria for the stroke group were a diagnosis of pediatric arterial ischemic stroke (neonatal or childhood stroke, confirmed by MRI or CT) at least 2 years prior to study participation, age at stroke ≤16 years, and age at examination ≥6 years. Exclusion criteria were active epilepsy (defined as seizures or treatment with antiseizure medication during the 12 months prior to study participation), additional neurologic disorders not attributable to stroke, severe learning difficulties, or pronounced behavioral problems that would make assessments impossible. Patients with active epilepsy were excluded because transcranial magnetic stimulation was performed as part of the HERO study. Inclusion criteria for the control group were age at examination ≥6 years and no impairments influencing cognitive and neurologic development. Exclusion criteria were the same as for the stroke sample.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocols of both research projects were approved by the Research Ethics Committee of Berne, Switzerland (HERO study: 212/13,[3] Onset study: 2019–00546). Depending on the age of the participants, written informed consent was obtained from the participant (if >16 years of age) or parent/legal guardian (if <16 years of age). Examinations were performed at the University Hospital, Inselspital Bern, or, in individual cases, home visits were performed. Both studies were conducted according to the Declaration of Helsinki.

Clinical Data and Lesion Characteristics

Clinical data, including sex, age at stroke, and stroke risk factors, were obtained from medical records and the SNPSR database. Stroke risk factors were categorized according to Steinlin and Wehrli.[24] Lesion volume was estimated using the pediatric modification of the Alberta Stroke Program Early Computed Tomography Score (pedASPECTS),[25-27] a score that was validated in a previous study in 71 individuals with neonatal or childhood arterial ischemic stroke.[25] The procedure is described elsewhere.[28,29] Maximum score of the pedASPECTS is 30, indicating uttermost severity. Scores were determined based on diffusion-weighted imaging sequences from the acute MRI, or—if not available—on

Table 1 Overview of the Cognitive Assessment

Cognitive domain	Test	Task description	Outcome measure	Scores	Missing data
Intelligence	TONI[45]	Pattern completion task	Number of correct answers	IS	
Executive functions					
Working memory	Letter-number sequencing[46,47]	Repetition of an auditory presented sequence of numbers and letters	Number of correct answers	SS	
Inhibition	CWI[48]	Naming the color of color words, printed in incongruent color ink	Completion time	SS	C: n = 7[a] P: n = 3
Cognitive flexibility	TMT[48]	Connecting numbers and letters in alternating order	Completion time	SS	C: n = 6[a] P: n = 5
Processing speed	Coding and symbol search[46,47]	Coding: matching numbers to symbols using a number-symbol key; symbol search: finding a target symbol in a group of symbols	Number of correct answers	IS	
Memory					
Verbal learning	VLMT[49]	Immediate recall of 15-item word list after auditory presentation ($\sum$ DG1–5)	Sum of correct answers in 5 trials	PR	
Verbal recall	VLMT[49]	Delayed recall (30 minutes) of the 15-item word list (DG 7)	Number of correctly retrieved words	PR	P: n = 2
Letter fluency	Verbal fluency[48]	Generating as many words as possible beginning with a specific letter within 60 s	Number of correct answers	SS	C: n = 6[a] P: n = 3
Visual-motor skills	Visual-motor integration[50]	Copying geometric designs	Number of correct imitated designs	IS	C: n = 17[b] P: n = 9

Abbreviations: C = controls; CWI = Color-Word Interference Test; IS = index score (mean 100, SD 15); P = patients; PR = percentile rank (mean 50, SD 34.1); SS = standard score (mean 10, SD 3); TMT = Trail-Making Test; TONI = Test of Nonverbal Intelligence; VLMT = Verbal Learning and Memory Test.
[a] According to the manual, normative data are only available from the age of 8 years.
[b] According to the manual, normative data are only available for individuals aged 8–18 years; we therefore excluded the late childhood stroke group as 66.6% of the participants were older than 18 years at the time of the assessment and normative data were not available.

morphologic magnetic resonance sequences of the first-available poststroke brain MRI (T2-weighted imaging or fluid-attenuated inversion recovery imaging). For 7 patients, the acute MRI was not available and hence the pedASPECTS was determined using the first available poststroke MRI. Ped-ASPECTS of patients with poststroke MRI did not differ from pedASPECTS determined on the acute MRI ($p = 0.282$). Information about lesion laterality (left, right, or bilateral) and lesion location (cortical, subcortical, or combined cortical and subcortical) were derived from the pedASPECTS.[30] Neurologic outcome at the time of the study assessment was assessed via the Pediatric Stroke Outcome Measure (PSOM).[31] The PSOM consists of 5 subscales (right sensorimotor, left sensorimotor, language production, language comprehension, and cognitive/behavior) and yields a total score ranging from 0 (no deficits) to 10 (maximum deficits).

Cognitive Assessments

Several cognitive domains, such as nonverbal intelligence, executive functions, processing speed, memory, letter fluency, and visual-motor skills, were evaluated during the neuropsychological assessment by an experienced neuropsychologist. A description of the cognitive tests and the outcomes is provided in Table 1. For all tests, age-corrected standard scores, index scores, or percentile ranks were used according to the test manual.

Data Analysis

To assess the effect of stroke on long-term cognitive outcome, the stroke sample was divided into 3 age at stroke groups: neonatal stroke (stroke between 0 and 28 days of life), early childhood stroke (stroke between 29 days and <6 years), and late childhood stroke (stroke between ≥6 and <16 years) such as described in a previous study.[11] We performed locally weighted regression and scatterplot smoothing (LOESS) to display possible associations between cognitive outcome and age at stroke and to verify the cutoff points of the age at stroke groups.[32]

Demographic and clinical data were presented for the control group and the 3 age at stroke groups. Continuous variables were reported as mean and SD for normally distributed variables and median and interquartile range for non-normally distributed variables. Categorical variables were presented as frequencies and percentages. Descriptive and baseline variables in the 3 age at stroke groups were compared using analyses of variance (ANOVAs) with Bonferroni post hoc tests (or Kruskal-Wallis tests for nonparametric data) and Pearson χ^2 tests followed by post hoc pairwise comparisons. Group differences in cognitive performance between the total stroke sample and the control sample were computed using 2-sided independent t tests. To identify possible confounders, associations between lesion size, lesion location, lesion

Table 2 Demographic and Clinical Data for the Total Stroke Sample, the 3 Age at Stroke Groups, and the Control Sample

| | | Age at stroke groups | | | | | |
	Total stroke	Neonatal (0–28 days)	Early childhood (29 days to <6 years)	Late childhood (≥6 years to <16 years)	Controls	U/χ^{2a}	$F/\chi^{2b,c}$
Sample size	52	16	21	15	49	—	—
Male	29 (55.8)	8 (50.0)	13 (61.9)	8 (53.3)	22 (44.9)	1.193	0.572
Age at examination, y	15.3 (10.6–18.7)	12.5 (9.3–16.5)	13.2 (10.3–16.2)	18.8 (15.5–22.3)	13.6 (9.8–17.2)	1185.00	11.14***
Age at stroke, y	3.5 (0.0–6.7)	2.0 (1.0–2.8)[d]	3.6 (1.4–4.9)	11.8 (7.9–14.4)	—	—	45.030***[e]
PSOM total	0.5 (0.0–1.0)	0.3 (0.0–1.0)	0.3 (0.0–0.9)[f]	0.5 (0.0–1.0)	—	—	0.058[e]
pedASPECTS	4 (2–6.5)	3 (2–8)[f]	4 (3–5)[f]	4 (1–8)	—	—	0.801[e]
Lesion laterality					—	—	5.652[g]
Left	27 (54.0)	11 (73.3)	8 (40.0)	8 (53.3)			
Right	15 (30.0)	3 (20.0)	9 (45.0)	3 (20.0)			
Bilateral	8 (16.0)	1 (6.7)	3 (15.0)	4 (26.7)			
Lesion location					—	—	9.520*[a,g]
Subcortical	8 (16.0)	0	3 (15.0)	5 (33.3)			
Cortical	14 (28.0)	7 (46.7)	6 (30.0)	1 (6.7)			
Both	28 (56.0)	8 (53.3)	11 (55.0)	9 (60.0)			
Stroke risk factors					—	—	—
Infections	9 (17.3)	1 (6.2)	5 (23.8)	3 (20.0)			
Vasculopathy	2 (3.8)	0	0	2 (13.3)			
Cardiac disorders	7 (13.5)	3 (18.8)	4 (19.0)	0			
Hematologic disorders	3 (5.8)	1 (6.2)	1 (4.8)	1 (6.7)			
Multiple risk factors	13 (25.0)	0	8 (38.1)	5 (33.3)			
No identifiable risk factor	18 (34.6)	11 (68.8)	3 (14.3)	4 (26.7)			

Abbreviations: F = analysis of variance; pedASPECTS = pediatric modification of the Alberta Stroke Program Early Computed Tomography Score; PSOM = Pediatric Stroke Outcome Measure; U = Mann-Whitney U test (2-sided); χ2 = Pearson's chi-square.
Data are presented as frequencies (%) for categorical variables or median (interquartile range) for continuous variables.
[a] Comparisons between the total stroke group and the control group.
[b] Comparisons within the 3 age at stroke groups.
[c] *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[d] In days.
[e] Kruskal-Wallis test was performed as data were non-normally distributed.
[f] Missing data for one participant.
[g] Fisher exact test was performed.

laterality, and cognitive outcome (within the total stroke group) were examined with 2-sided Spearman correlations or ANOVAs, respectively. We did not investigate associations between stroke risk factors and cognitive outcome because of the limited number of patients in each stroke risk factor category.

To investigate the effect of age at stroke on long-term cognitive outcome, a series of one-way analyses of covariance (ANCOVAs) using the 3 age at stroke groups as independent variables and the respective cognitive domain as dependent variable (controlling for the effect of lesion size and lesion location) were conducted followed by Bonferroni post hoc tests. Results of the ANCOVA analyses were reported as estimated marginal means with associated 95% confidence intervals. Cohen d effect sizes were calculated for independent t test and partial eta squared (η_p^2) for ANCOVAs.[33] Statistical significance was set at $p < 0.05$. We report alpha values adjusted according to the Benjamini-Hochberg procedure (false discovery rate [FDR]) to correct for multiple testing.[34] All statistical analyses were performed with SPSS, version 25. Data visualization was generated using the R package ggplot2.[35]

Data Availability
All anonymized data are available on request from any qualified investigator.

Table 3 Mean Cognitive Performance for the Total Stroke Sample, the 3 Age at Stroke Groups, and the Control Sample

Cognitive outcome	Total stroke	Neonatal (0–28 days)	Early childhood (29 days to <6 years)	Late childhood (≥6 years to <16 years)	Controls	$t^{a,b}$	d
Intelligence	97.8 (10.3)	101.4 (10.5)	93.9 (9.9)	99.2 (9.5)	103.7 (9.8)	2.976**	0.59
Executive functions							
Working memory	8.7 (3.5)	10.1 (2.4)	7.2 (3.9)	9.2 (3.3)	10.5 (2.1)	3.109**	0.62
Inhibition	9.1 (3.4)	10.0 (3.1)	8.4 (3.4)	9.1 (3.7)	11.0 (2.2)	3.188**	0.66
Cognitive flexibility	9.5 (3.3)	11.0 (2.3)	7.7 (3.5)	9.9 (3.1)	11.0 (2.5)	2.445*	0.51
Processing speed	95.2 (17.6)	102.9 (14.2)	85.9 (18.2)	100.0 (14.4)	109.0 (13.6)	4.394***	0.88
Memory							
Verbal learning	48.0 (35.6)	58.9 (34.9)	30.1 (34.3)	61.5 (28.6)	64.8 (29.40)	2.589*	0.51
Verbal recall	46.8 (29.2)	51.8 (30.3)	37.9 (28.6)	52.7 (27.8)	60.9 (27.5)	2.486*	0.50
Letter fluency	8.9 (3.8)	10.6 (4.20)	8.0 (3.4)	8.4 (3.6)	11.9 (3.7)	3.375***	0.78
Visual-motor skills	95.0 (17.4)	102.8 (13.6)	89.1 (18.0)	—	108.5 (11.2)	3.632**	0.93

The header row above "Neonatal", "Early childhood", and "Late childhood" reads: **Age at stroke groups**

Abbreviations: d = Cohen d effect size (d = 0.2 small effect, d = 0.5 medium effect, and d = 0.8 large effect); t = 2-sample t test (2-sided).
Data are presented as mean (SD).
[a] Comparisons between the total stroke group and the control group.
[b] *p < 0.05, **p < 0.01; ***p < .001.

Results

Baseline Characteristics

Fifty-four participants diagnosed with pediatric stroke and 50 healthy controls were identified from the HERO or Onset study, of whom 52 patients and 49 healthy controls were included in the present study. One patient and one control did not meet the inclusion criteria for the present study because they were younger than 6 years and one patient was excluded due to missing data. The study flow chart is presented in eFigure 1, links.lww.com/WNL/B701. Demographic and clinical data are described in Table 2. Both groups were comparable in terms of age at examination (p = 0.587) and sex (p = 0.275). As an inherent characteristic of our subgroups, the 3 age at stroke groups differed significantly in their age at stroke (p < 0.000) and age at examination (p < 0.000). We did not adjust for the effect of age at examination in the following analysis, as we used age-corrected scores for all cognitive tests.

The 3 age at stroke groups were comparable in regard to sex, lesion size, and lesion laterality (Table 2). Neurologic outcome (PSOM) did not differ in the 3 age at stroke groups. A significant group effect was found for lesion location (p = 0.016), revealing that cortical lesions occurred significantly more often in the neonatal group (46.7%) compared to the late childhood stroke group (6.7%). Across the total stroke sample, lesion size correlated negatively with intelligence (r = −0.338, p = 0.016), working memory (r = −0.335, p = 0.017), inhibition (r = −0.381, p = 0.008), processing speed (r = −0.319, p = 0.024), letter fluency (r = −0.444, p = 0.002), and visual motor skills (r = −0.381, p = 0.050). Lesion location was not associated with cognitive outcome. Lesion laterality did not affect cognitive performance, except for cognitive flexibility (F = 4.198, p = 0.022, η_p^2 = 0.167), where right hemispheric lesions entailed worse performance than left hemispheric lesions (p = 0.018). As a consequence of these findings, all following ANCOVA analyses were adjusted for the effect of lesion size and lesion location.

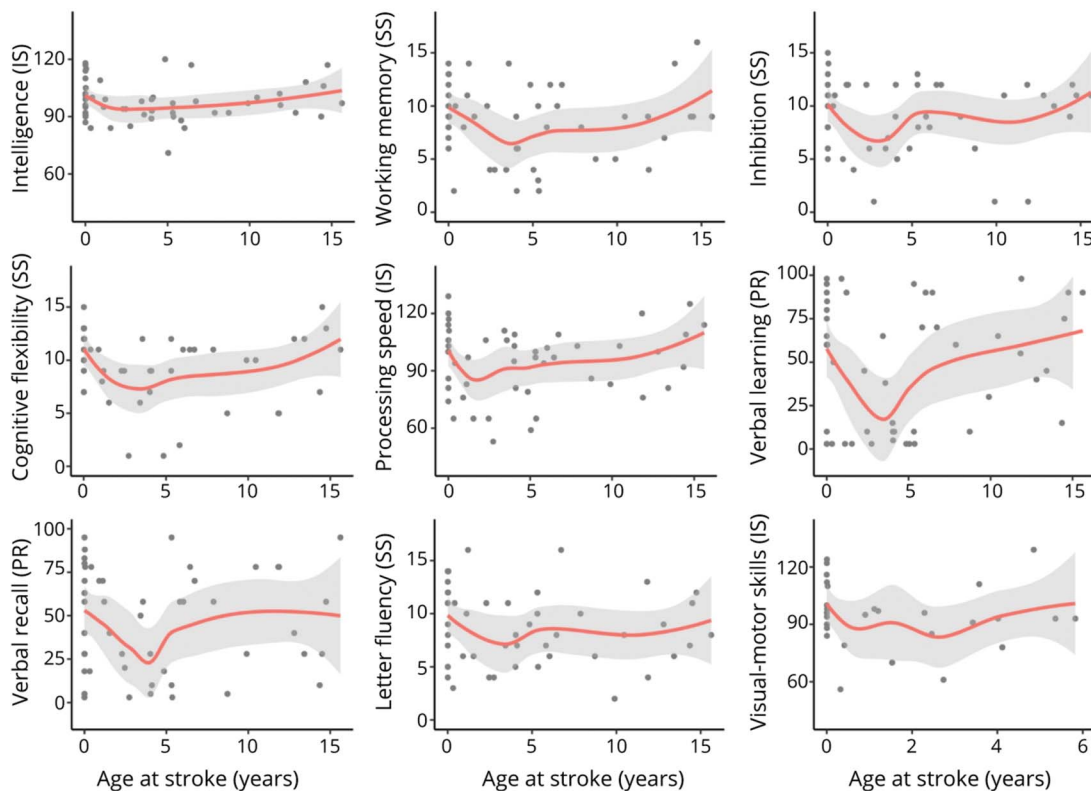## Long-term Cognitive Outcome in Patients and Controls

Cognitive outcome in patients after pediatric stroke and healthy controls is displayed in Table 3. Although mean group performance was within the normative reference range for both groups, significantly lower cognitive performance occurred in all cognitive domains in patients vs controls (medium to large effect sizes). All group differences remained significant after adjusting for multiple comparisons (FDR correction).

Effect of Age at Stroke on Long-term Cognitive Outcome

LOESS plots are displayed in Figure 1. A nonlinear relationship was observed between age at stroke and cognitive outcome. Next, we investigated the effect of age at stroke on long-term cognitive outcome using a series of ANCOVAs controlling for the effect of lesion size and lesion location. Results are presented in Figure 2. A significant effect for age at stroke was found for performance in working memory (F = 4.131, p = 0.023, η_p^2 = 0.155), cognitive flexibility (F = 5.368, p = 0.009, η_p^2 = 0.212), processing speed (F = 6.537, p = 0.003, η_p^2 = 0.225), and verbal learning (F = 5.099, p = 0.010, η_p^2 = 0.185) with early childhood stroke displaying the worst outcome. All effect sizes were interpreted as large. The

LOESS plots of cognitive outcome as a function of age at stroke. X-axis represents age at stroke (in years). 95% confidence interval in gray. IS = index score; PR = percentile range; SS = standard score.

significant effect of age at stroke on cognitive flexibility ($p = 0.040$), processing speed ($p = 0.027$), and verbal learning ($p = 0.030$) persisted after FDR correction, except for working memory ($p = 0.052$). Although not significant, intelligence ($F = 2.793$, $p = 0.072$, $\eta_p^2 = 0.110$), inhibition ($F = 1.137$, $p = 0.331$, $\eta_p^2 = 0.051$), verbal recall ($F = 1.678$, $p = 0.199$, $\eta_p^2 = 0.072$), letter fluency ($F = 1.748$, $p = 0.186$, $\eta_p^2 = 0.077$), and visual-motor skills ($F = 3.141$, $p = 0.090$, $\eta_p^2 = 0.120$) were slightly lower in the early childhood stroke group compared to the neonatal and late childhood stroke group.

Discussion

In this cross-sectional study, we demonstrated that patients after pediatric stroke displayed worse cognitive performance compared to a control group and that age at stroke affects cognitive outcome. Neonatal stroke and late childhood stroke were associated with better outcome whereas early childhood stroke led to significantly worse outcome in cognitive flexibility, processing speed, and verbal learning, irrespective of lesion size and lesion location.

Our results suggest that age at stroke is an important factor for poststroke recovery and modulates long-term cognitive outcome even when controlling for lesion size and lesion location. In contrast to previous studies indicating that younger age at stroke relates to worse[6,10-13] or better cognitive outcome,[14,15] our data revealed a U-shaped association between age at stroke and long-term cognitive outcome, with children after early childhood stroke showing the worst outcome. Only a limited number of studies have shown a non-linear effect of age at stroke on cognitive outcome.[5,30,36] A study of 21 Swiss children after pediatric stroke found better cognitive performance in children who had a stroke at the ages between 5 and 10 years compared to earlier (0–5 years) or later (10–18 years).[30] Similarly, Allman and Scott[36] found in a sample of 44 participants that stroke occurring between the ages of 1 and 6 years entailed better cognitive outcome than earlier stroke (before the age of 1) and later stroke (6–16 years). Both studies demonstrated an inverted U-shaped association between age at stroke and cognitive outcome, which is exactly the opposite pattern compared to our data. In terms of neurologic outcome, a recent study with 587 patients after pediatric stroke concluded that younger children (28 days and 1 year at the time of the stroke) are particularly vulnerable for poor neurologic outcome (PSOM total score) 2 years after stroke when compared to children after neonatal stroke or stroke >1 year of age.[5] This U-shaped relationship between age and outcome is in line with our results, but the PSOM assesses neurologic (i.e., sensorimotor, language, and cognitive functions) and not purely cognitive performance.

Figure 2 Effect of Age at Stroke on Long-term Cognitive Outcome
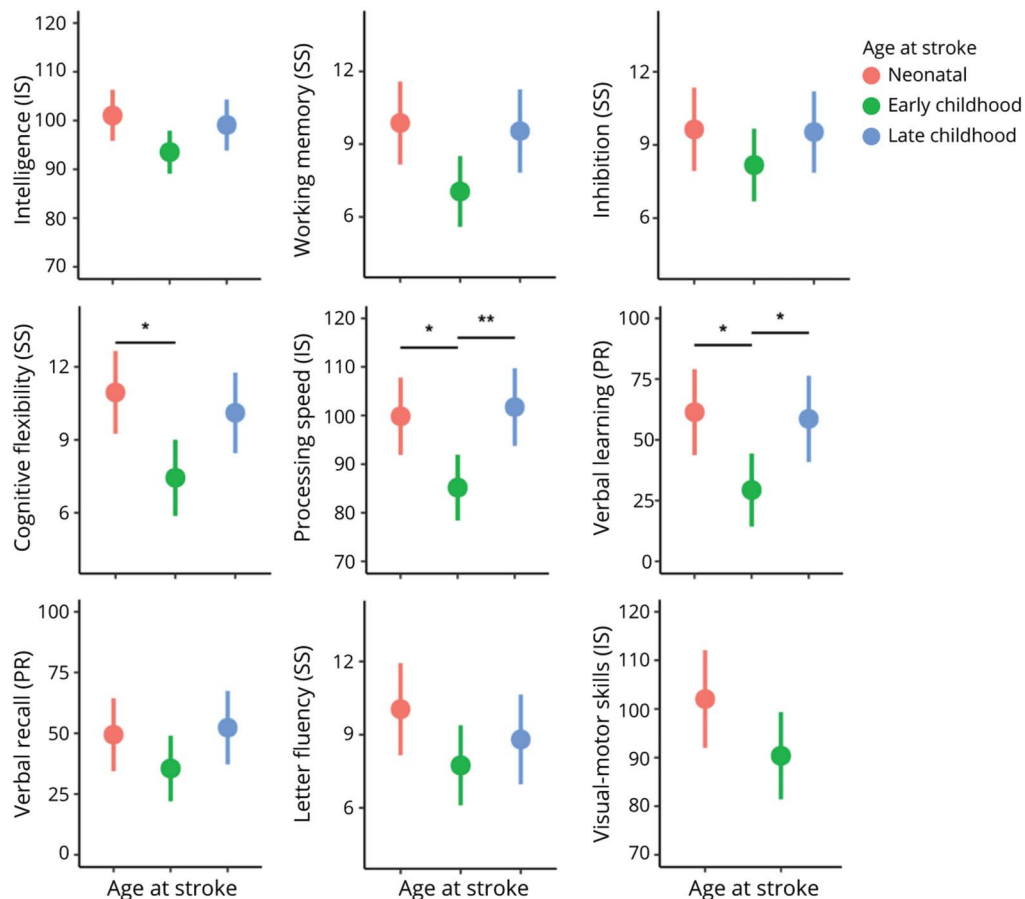
A significant effect of age at stroke on cognitive flexibility, processing speed, and verbal learning was found ($p < 0.05$, false discovery rate–corrected). Estimated marginal means (adjusted for the mean of covariates) with associated 95% confidence interval are displayed on the X-axis for the 3 age at stroke groups: neonatal stroke (red), early childhood (green), and late childhood (blue). Due to missing normative data, data about visual-motor skills were not available for the late childhood stroke group. IS = index score; PR = percentile range; SS = standard score. Significant Bonferroni post hoc results: *$p < 0.05$, ** $p < 0.01$.

The current study included only patients in the chronic phase of the stroke (>2 years after stroke), whereas previous studies included patients with shorter follow-up periods as well.[30,36] In fact, cognitive alterations may emerge and increase over time[16] and the full extent of cognitive sequelae may only appear several years poststroke.[7] Also, developmental processes and recovery trajectories may be different depending on the cognitive function measured.[7] For instance, executive functions are not fully developed until early adulthood and rely on intact frontal and prefrontal cortices.[37] This highlights the importance of long-term follow-ups in patients after pediatric stroke in order to identify patients particularly at risk for alterations in long-term cognitive outcome.[7]

There is an ongoing debate around plasticity and vulnerability of the developing brain following early brain injury.[7-9] The early plasticity approach supports the idea of maximum plasticity in the developing brain with better recovery of cognitive functions after brain lesion in childhood compared to adulthood.[7,8] In contrast, the vulnerability perspective argues that the developing brain is particularly vulnerable to

stroke, which leads to disrupted brain and cognitive development.[7,30,38] Our results did not favor one or the other perspective but support a recent idea combining these to concepts to a "recovery continuum," suggesting that cognitive outcome after stroke is determined by several factors such as age at stroke, lesion-related characteristics, and sociodemographic factors.[7] Hence, our results may be inconsistent with previous studies,[30,36] because several factors affect cognitive outcome and, for instance, patient or lesion characteristics vary across studies.

Findings from the current study propose that early childhood is a particularly vulnerable developmental period in terms of poststroke cognitive outcome. Between the age of 29 days to <6 years, cognitive functions measured in our study are about to emerge and continuously develop; however, none of the cognitive domains we have measured is fully established yet. Hence, in line with previous findings from epilepsy research, we suggest that stroke during a critical period of cognitive development has a particularly detrimental effect on outcome.[18,19] This is further supported by neuroimaging

studies, revealing that functional and structural brain development is a nonlinear process with critical periods for plasticity as well as maturational processes (i.e., myelination and synaptogenesis).[39-41]

In addition, we examined our total stroke sample with regard to the effect of lesion size, lesion location, and lesion laterality on cognitive outcome. Larger lesion size was related to poorer performance in intelligence, working memory, inhibition, processing speed, letter fluency, and visual-motor skills in the present study, which is consistent with previous findings.[30,42] Also in line with previous findings,[11] we found that cortical lesions occurred more often in the neonatal group compared to the late childhood stroke group. In terms of the effect of lesion location on cognitive outcome, previous findings are inconsistent. Whereas Westmacott et al.[11] suggest that combined lesions (cortical and subcortical) were associated with worse cognitive performance, other studies[12,30] as well as our data did not reveal an effect of lesion location on cognitive outcome. However, different approaches to classify lesion location hinders comparability between studies. Furthermore, except for cognitive flexibility, lesion laterality did not affect cognitive performance. Our data support the functional network approach, claiming that even remote lesion locations can affect functional brain networks and thus affect cognitive performance.[43]

A strength of our study is the large sample size of 52 patients after pediatric stroke, a rare neurologic disease in childhood (incidence of neonatal ischemic stroke in Switzerland is 13 per 100,000 live births,[44] incidence of childhood stroke in Switzerland is 2.1:100,000 children per year[23]). The inclusion of a control group further strengthens our study. We only included patients in the chronic phase of the stroke (>2 years after stroke), allowing us to draw conclusions about long-term cognitive outcome. Other strengths include the broad spectrum of cognitive functions assessed in this study. Furthermore, we estimated lesion size using a relatively new method in pediatric and pediatric neuroimaging, the pedASPECTS, which has fair to good accuracy for predicting cerebral palsy as well as neurologic impairment and was shown to correlate with lesion size.[28] The findings remain robust after adjusting for multiple testing (FDR correction).

Some limitations have to be acknowledged. First, the cross-sectional design of this study does not allow us to draw conclusions about developmental trajectories of cognitive functions. Second, our age at stroke groups were defined according to a prior study.[11] Other studies adopted different classification approaches.[6,30,36] However, when defining the cutoffs differently, the effect of our results remained similar. Third, pediatric stroke is a heterogeneous disease with diverse clinical presentation and etiology, hindering comparability across studies. Fourth, for a small number of patients, acute neuroimaging was not available. Determining pedASPECTS on postacute imaging may have led to underestimation of the score because punctate lesions may become unrecognizable due to so-called pseudonormalization of diffusion restriction, or—in the chronic stage—may shrink over time and remain hardly visible. Yet pedASPECTS of patients with poststroke MRI did not differ from pedASPECTS determined on the acute MRI. Fifth, the patient group may be biased as it does not account for patients who were lost to follow-up or died during the poststroke phase. Likewise, a large number of potential participants were too young (n = 112) or unwilling to participate in the study (n = 191), increasing the risk of a potential selection bias.

We have shown that long-term cognitive outcome varied according to age at stroke in a population of pediatric stroke survivors without severe learning difficulties. Our findings suggest a nonlinear relationship between age at stroke and cognitive outcome with patients after early childhood stroke (29 days to <6 years) performing worse than patients after neonatal or late childhood stroke. These results propose that early childhood is a particularly vulnerable developmental period for negative long-term cognitive outcome in survivors of pediatric stroke, irrespective of lesion size and lesion location. Children with early childhood stroke should be monitored closely and provided with adequate treatment and rehabilitation options tailored on their age at stroke and current developmental period in order to prevent cognitive sequelae and improve cognitive outcome.

Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
Stephanie Abgottspon, MSc	University of Bern, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
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Leonie Steiner, PhD	University of Bern, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content
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