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Resting-state connectivity and executive functions after pediatric arterial ischemic stroke

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ABSTRACT

Background: The aim of this study was to compare the relationship between core executive functions and frontoparietal network connections at rest between children who had suffered an arterial ischemic stroke and typically developing peers.

Methods: Children diagnosed with arterial ischemic stroke more than two years previously and typically developing controls were included. Executive function (EF) measures comprised inhibition (Go-NoGo task), fluency (category fluency task), processing speed (processing speed tasks), divided attention, working memory (letter-number sequencing), conceptual reasoning (matrices) and EF in everyday life (questionnaire). High-resolution T1-weighted magnetic resonance (MR) structural images and resting-state functional MR imaging were acquired. Independent component analysis was used to identify the frontoparietal network. Functional connections were obtained through correlation matrices; associations between cognitive measures and functional connections through Pearson's correlations.

Results: Twenty participants after stroke (7 females; mean age 16.0 years) and 22 controls (13 females; mean age 14.8 years) were examined. Patients and controls performed within the normal range in all executive tasks. Patients who had had a stroke performed significantly less well in tests of fluency, processing speed and conceptual reasoning than controls. Resting-state functional connectivity between the left and right inferior parietal lobe was significantly reduced in patients after pediatric stroke. Fluency, processing speed and perceptual reasoning correlated positively with the interhemispheric inferior parietal lobe connection in patients and controls.

Conclusion: Decreased interhemispheric connections after stroke in childhood may indicate a disruption of typical interhemispheric interactions relating to executive functions. The present results emphasize the relationship between functional organization of the brain at rest and cognitive processes.

1. Introduction

Pediatric arterial ischemic stroke (AIS) has an incidence of 2.1:100,000 children per year (Steinlin et al., 2005) and impacts on the lives of affected children (Christerson and Strömberg, 2010; Kornfeld et al., 2017). As two-thirds of affected children suffer from lifelong cognitive or neurological problems (Christerson and Strömberg, 2010; Everts et al., 2008; Hajek et al., 2014; Kolk et al., 2011; Kornfeld et al., 2017; Studer et al., 2014), prediction of recovery and adaptation of interventions are important. This requires knowledge about both structural and functional recovery mechanisms after stroke.

After AIS, children often exhibit problems in executive domains, e.g. working memory and processing speed (Studer et al., 2014). Executive functions (EF) encompass diverse higher-order cognitive skills (Alvarez and Emory, 2006). According to Anderson (2002), EF comprise attention, information processing, cognitive flexibility and goal setting. These core processing skills are important for planning, problem solving and decision-making (Alvarez and Emory, 2006), and develop

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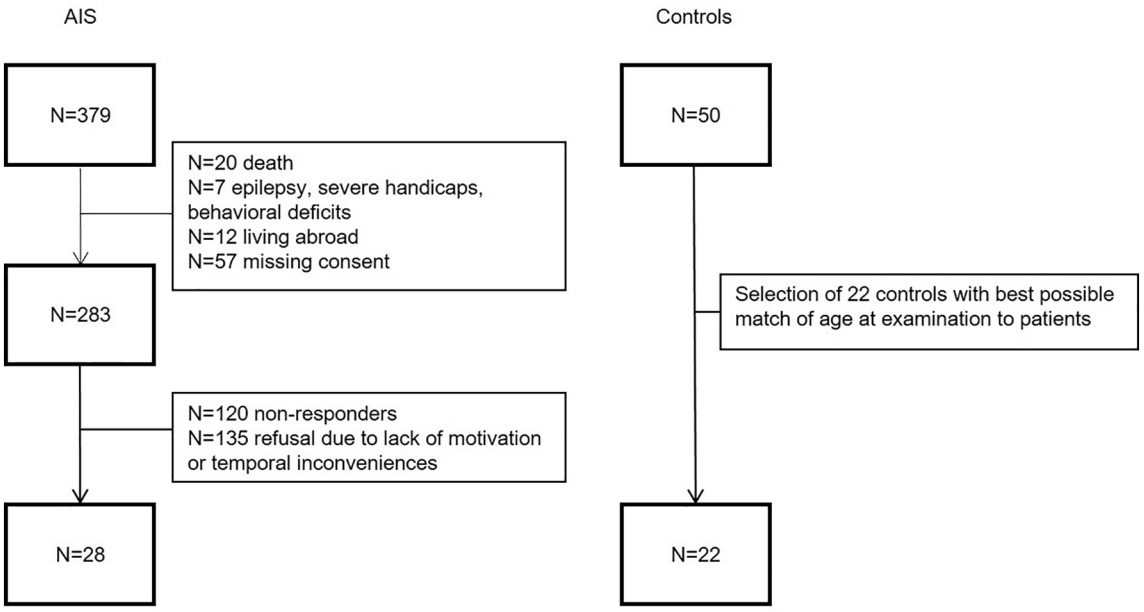

Fig. 1. Study population flowchart.
AIS = patients with arterial ischemic stroke; N = number of participants.

throughout childhood in parallel with maturation of prefrontal and parietal brain structures (Anderson, 2002).

AIS causes structural brain damage in circumscribed cerebral regions within the supply area of a specific artery. A brain lesion may affect functions that are not directly related to the damaged brain structure. This points to a complex system underlying functional brain organization, consisting of broader functional networks rather than simple structure–function relationships (Corbetta, 2012; Fornito et al., 2015; McIntosh, 2000).

Resting-state functional MRI (rsfMRI) is used to investigate functional networks based on synchronous oscillations in the blood-oxygen level dependent (BOLD) signal between structurally separated brain regions (Biswal et al., 1995; Fair et al., 2007) and has the advantage of independence from the compliance and performance level (Dinomais et al., 2012). Resting-state fMRI measures BOLD signals in the frequency range below 0.1 Hz, and allows the correlation between the BOLD-response and various cognitive functions, as no specific task is performed during MRI acquisition. It is particularly well-suited for detecting subtle alterations in the hemodynamic response to brain lesions (Biswal et al., 1995; Dinomais et al., 2012; Fair et al., 2007; Stevens and Spreng, 2014).

Findings in adults reveal associations between resting-state fluctuations and individual differences in language, memory and conceptual knowledge (Stevens and Spreng, 2014). In adult patients after acute stroke, a reduction in interhemispheric resting-state connectivity was found to be associated with reduced attention (Carter et al., 2010; He et al., 2007). These findings suggest that cognitive performance after stroke is related to the strength of corresponding functional resting-state network connections. Function-specific processes in the resting brain also exist in children (Thomason et al., 2011). Thomason et al. (2011) defined an “executive network” in healthy children, consisting of frontoparietal brain regions. Based on the network perspective, it is assumed that a lesion at any level of the neural systems within the executive network might lead to cognitive problems (Anderson, 2002). Very little is known about resting-state network properties and their influence on cognitive outcome after pediatric stroke although in a study on a mixed sample of 17 patients after perinatal AIS and periventricular venous infarction, an increase in default mode network connectivity and lower cognitive functions was reported (Ilves et al., 2016).

Based on this finding and previous literature reporting of executive post-stroke deficits, the present study investigated the frontoparietal network (FPN) in children who had experienced AIS more than two years previously and in typically developing controls. It was hypothesized that children who have experienced AIS would show lower EF than controls, and that resting-state FPN properties would differ between patients after pediatric AIS and controls. Finally, it was assumed that FPN connections at rest would correlate with EF in both groups. The findings of the present study aim to contribute to the knowledge about EF characteristics and executive resting-state networks after a focal brain lesion in childhood, and provide new insights into the underlying mechanisms of recovery following pediatric stroke.

2. Materials and methods

2.1. Participants

All participants were part of a clinical study investigating cortical reorganization after pediatric stroke, the HERO (Hemispheric Reorganization)-Study (Kornfeld et al., 2015). Children and adolescents who had an AIS before the age of 16 years were recruited from the population-based Swiss Neuropaediatric Stroke Registry (SNPSR) (Steinlin et al., 2005; Studer et al., 2014). The criteria for inclusion of patients in this study were: (1) diagnosis of AIS (confirmed by MRI or computed tomography), defined as a focal or generalized neurological deficit with acute onset showing infarction in a localization consistent with neurological symptoms (Steinlin et al., 2005), (2) AIS at chronic stage, namely that the acute stroke event had happened at least two years prior to the study, (3) age $\leq$ 16 years at the time of AIS, and (4) at least five years old at the time of assessment due to the MR-compatibility. Exclusion criteria were ferrous implants, active epilepsy, claustrophobia, additional neurological disorder not attributable to stroke (e.g. trisomy 21) and behavioral problems that would make assessments impossible. Details of the patient and control recruitment process are presented in Fig. 1. Of 379 patients from the SNPSR who met the criteria, 96 were not contacted due to the following reasons: death (n = 20), trisomy 21, epilepsy, other severe handicaps or heavy behavioral problems (n = 7), living abroad (n = 12), missing consent for SNPSR or follow-up studies (n = 57). All 283 remaining patients were contacted by letter post and additionally by phone two weeks later if no

answer was received. Of the 283 patients contacted, 120 were non-responders and 135 reported a lack of motivation or that the duration and type of assessment (MRI, TMS) would be inconvenient. A final sample of 28 patients agreed to participate and was examined. Controls were recruited through advertisement in the hospital intranet and self-created flyers. Inclusion criteria for controls were no impairment influencing development. Exclusion criteria were the same as in patients. The flyer, an information brochure and an informed consent document were sent to eligible participants by letter post. Of the 50 examined controls, 22 were selected as the comparative sample in the present study. They were chosen only according to their age and matched as accurately as possible to the age of the patients in the study.

Neuropsychological assessments were performed by a psychologist (S.K.) between autumn 2014 and summer 2016 in the Division of Neuropediatrics, Development and Rehabilitation at the University Hospital Inselspital in Berne, Switzerland. The neuropsychological assessment took approximately 2 h, including a five-minute break after 1 h. All MRI assessments were performed in a 3 T Magnetom Verio Siemens scanner at the Institute of Diagnostic and Interventional Neuroradiology at the University Hospital Inselspital, Berne, Switzerland. The MRI assessment lasted 20 min. Both assessments for each participant were performed within one week to ensure comparability of outcomes.

Demographic and other basic data, such as sex, age at assessment, age at stroke and time since stroke, were gathered from the SNPSR and at the time of the first assessment. Handedness was determined at the time of the study, so after the AIS, by means of the Edinburgh Handedness Inventory (Oldfield, 1971). Information on localization and the side of the acute lesion was obtained from the original medical reports, the SNPSR database and the present anatomical images. Lesions were classified according to their localization: (1) cortical, (2) subcortical, (3) infratentorial, and (4) combined cortical and subcortical. Lesion laterality was divided into: (1) left, (2) right, and (3) bilateral. To define the lesion size at the time of assessment, volumetric analyses were performed where the volume of the lesion was divided by the total intracranial volume in mm^3.

The Research Ethics Committee of Berne, Switzerland approved the SNPSR and the present study. All parents and legal guardians of participants who were minors and all participants who had reached the age of majority provided written consent, in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Study sample

Of the 28 participants examined after chronic AIS, eight were excluded from the present analyses for the following reasons: uncooperative behavior of a very young patient during the neuropsychological assessment ($n = 1$), whole hemisphere lesions ($n = 2$), imaging distortion caused by a non-removable retainer ($n = 1$), motion distortion > 3 mm ($n = 3$). In order to avoid direct effects of structural damage to the FPN connectivity and consequently to EFs, one patient with a lesion inside one of the seed regions of the FPN (n = 1) was excluded from the present analysis. The final patient sample consisted of 20 participants who had had chronic AIS (7 females; mean age at assessment: 16.0 years, range: 9.5–23.1 years) and 22 typically developing controls (13 females; mean age at assessment: 14.8 years, range: 7.9–24.5 years). Information on the 20 study patients, such as lesion characteristics, is presented in Table 1.

2.3. Cognitive assessment

Comprehensive neuropsychological tests were used to assess cognitive performance. Details of cognitive assessment have been described in the study protocol (Kornfeld et al., 2015). All participants were assessed according to the methods described in the study protocol. As the present study focused on EF according to the model of Anderson (2002), the four main EF were assessed: 1.) attention control (selective attention, self-regulation, self-monitoring, inhibition); 2.) information processing (efficiency, fluency, speed of processing); 3.) cognitive flexibility (divided attention, working memory, conceptual transfer, feedback utilization); and 4.) goal setting (initiative, conceptual reasoning, planning, strategic organization). These EF domains were measured as follows: 1.) *inhibition*: errors in a Go-NoGo task (TAP; Zimmermann and Fimm, 2012); 2.) *fluency*: correct answers in the Delis–Kaplan Executive Function System category fluency task (D-KEFS; Delis et al., 2012); *processing speed*: total score of the Wechsler Intelligence Scale for Children (WISC-IV processing speed index (coding and symbol search subtest scores of the WISC-IV; Petermann and Petermann, 2012), and time taken for D-KEFS' Stroop word reading task; 3.) *divided attention*: errors in a divided attention task (TAP); *working memory*: correct answers in the WISC letter-number sequencing; and 4.) *conceptual reasoning*: correct answers in the Test of Non-Verbal Intelligence (TONI-4; Brown et al., 2010). EF in everyday life was measured with the German version of the Behavior Rating Inventory of Executive Function (BRIEF; Drechsler and Steinhausen, 2013). In contrast to the cognitive scores, higher scores in the BRIEF mean more dysfunction.

2.4. Imaging acquisition

MRI was performed using a 3 T Magnetom Verio Siemens scanner (Siemens, Erlangen, Germany). High-resolution T1-weighted MR structural images were recorded with a 3D magnetization-prepared rapid gradient-echo (MP RAGE) sequence using the following parameters: repetition time = 2530 ms, inversion time = 1100 ms, echo time = 2.92 ms, 160 sagittal slices, field of view 256 × 256 mm^2, matrix size 256 × 256 mm^2, resulting in an isovoxel resolution of 1 mm^3 and the use of generalized autocalibrating partially parallel acquisition parallel imaging with an acceleration factor of 2 (acquisition time = 5.05 min). Functional imaging was performed using a multiband echo-planar imaging (EPI) sequence (Release 014, VB17A) from the University of Minnesota (Center for Magnetic Resonance Research), distance factor 0% (gap 0 mm), excitation pulse duration 5120 us, flip angle 30° (avoiding rf-clipping; is in the order of the Ernst angle for repetition time TR = 300 ms and T1 of gray matter), multiband factor S = 8, $N = 32$ slices, TA = 5:06 min. Each scan consisted of 1000 image volumes. To minimize head motion, a head support system consisting of two pillows positioned on either side of the head was used. Earplugs reduced the scanner noise. All participants were instructed to stay awake and relax with their eyes closed during scanning, and also to remain as motionless as possible. Younger children were shown a short instructive video beforehand.

2.5. Pre-processing of functional images

All images were preprocessed using the SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and Analysis of Functional NeuroImages (AFNI) (http://afni.nimh.nih.gov/afni/). The functional MRI datasets were realigned to the first image to correct for head motion and linearly co-registered to the individual T1-weighted image. Six motion parameters, derivatives of each motion parameter, forward derivatives of each motion parameter, and squared forward derivatives of those total 24 motion parameters were regressed out from all time series. The anatomical images were partitioned into gray matter, white matter and cerebrospinal fluid. Each participant's deformation map, obtained from the anatomical image, was applied to the functional images for normalization into the Montreal Neurological Institute space with the voxel size of isotropic 3 mm^3. The first five principal components from both cerebrospinal fluid and white matter were regressed out. A bandpass filter ranging from 0.01 Hz to 0.1 Hz was applied to all the time series. Finally, the functional images were spatially smoothed by a 6 mm full-width-at-half-maximum Gaussian

Table 1
Patient and lesion characteristics.

ID	Sex	Age at stroke (y)	Age at assessment (y)	Time since stroke (y)	IQ	Handedness	Acute stroke localization	Side of stroke	Lesion size ratio (mm^3)
3	M	14.6	22.8	8.2	106	Right	Thal	Left	6.024
4	F	10.5	20.1	10.5	100	Right	Thal	Left	4.624
5	F	11.9	15.6	3.8	102	Right	Thal + CI	Right	Not visible
7	M	6.3	18.5	12.1	84	Left	BG + CI	Left	0.002
9	F	3.5	13.11	10.6	98	Right	Striatum	Right	0.001
10	M	15.7	23.1	7.6	97	Right	Striatum	Left	0.001
11	F	7.1	15.4	7.5	92	Right	BG	Left	4.578
12	M	3.6	11.5	7.1	91	Left	CI	Left	3.864
13	M	5.9	13.2	7.4	88	Right	Not visible	Left	Not visible
14	M	8.8	14.6	5.9	92	Right	Thal + Ceb	Bilateral	0.001
17	M	14.4	18.9	4.5	90	Right	BG + centrum semiovale	Left	Not visible
19	M	1.6	9.5	7.11	84	Left	BG	Left	0.001
23	M	6.8	11.8	4.11	98	Right	BG	Left	Not visible
32	F	14.8	18.6	3.9	117	Right	Thal + mes-encephalon	Left	Not visible
34	F	12.9	22.3	9.5	92	Right	Not visible	Bilateral	Not visible
35	M	0.1	9.6	9.6	118	Right	Gyrus precentralis	Left	Not visible
37	F	0.1	13.5	13.5	91	Left	BG	Left	0.006
54	M	0.1	10.9	10.11	101	Right	Gyrus precentralis	Left	Not visible
60	M	1.2	16.9	15.6	99	Left	CI + nucleus lenticularis	Left	0.001
65	M	5.3	19.8	14.4	97	Right	Ceb + Thal + temporal/occipital lobe	Bilateral	0.006
Mean (SD)		7.26 (5.41)	15.99 (4.36)	8.65 (3.47)	96.85 (9.16)				

BG = basal ganglia; Ceb = cerebellum; CI = capsula interna; ID = patient identification number; IQ = intelligence quotient (mean = 100, SD = 15); F = female; M = male; Not visible = no visible damage; SD = standard deviation; Thal = thalamus; y = years.
Calculation of lesion size ratio: volume of lesion/total intracranial volume * 1000.

kernel.

2.6. Defining frontoparietal network

To identify the FPN across participants, independent component analysis, a data-driven multivariate method, was applied to the processed fMRI images. First, resting scans from all participants were concatenated along the time axis into a single 4D dataset. FSL's MELODIC (Smith et al., 2004) was used to decompose the 4D dataset into 20 spatio-temporal independent components, which are statistically independent sources of the resting-state signal. Based on visual comparison with previously identified major networks in adults (Biswal et al., 2010; Smith et al., 2009), a left and right frontoparietal, ventral attention, salience, posterior default mode, default mode, medial and lateral visual, auditory, sensorimotor and cerebellum network was detected. Because of the focus of this study on EF, the left and right FPN were selected for further analysis.

2.7. Functional connectivity analysis within the frontoparietal network

Peak coordinates from the left and right FPN were extracted (Fig. 2A). Based on these coordinates, 9 spherical regions of interest (ROIs) with a 6 mm radius on the Montreal Neurological Institute template were created. For each participant, the average time series from each of the 9 ROIs comprising the FPN were extracted. Pairwise correlation was performed between the ROIs. To compare differences in correlation between the FPN ROI pairs between the AIS group and the control group, two-sample *t*-tests were performed with age at assessment and sex as covariates. The results were thresholded at $p < 0.05$ (false discovery rate (FDR) corrected).

2.8. Functional connectivity differences associated with FPN

To examine the effect of FPN ROIs, we computed the whole brain connectivity map for each ROI as a seed. The averaged time series of each seed were correlated with all the voxels in the brain. For each participant, correlation maps were obtained and fisher-z transformed. A permutation test was performed using FSL's RANDOMISE[27] function to conduct two-sample *t*-tests comparing the AIS patients and controls with age and sex as covariates. The results were thresholded at $p < 0.05$ (family wise error (FWE) corrected).

Due to the uneven group sizes concerning the lesion characteristics, non-parametric Kruskal-Wallis tests were used to compare the connectivity between the lesion localization and laterality groups.

2.9. Statistical analysis of cognitive data

Cognitive data were analyzed using the Statistical Package for Social Sciences (SPSS), version 21. Data were tested for normal distribution using the Kolmogorov–Smirnov test. In order to check if a bias towards especially low (≤ 1 SD from the mean of cognitive scores) or high (≥ 1 SD from the mean of cognitive scores) performers in cognitive tests existed differences in the number of low and high performers between the two groups were analyzed using x^2-tests. Differences between the AIS and control group in the cognitive measures were analyzed with two-sample *t*-tests or Mann-Whitney *U* tests respectively. Pearson's correlation was performed to examine the association between cognitive measures and functional connections. The significance level was set at $p = 0.05$.

3. Results

Cognitive measures and the inferior parietal lobe (IPL) connectivity strength were normally distributed across the whole study sample, except for processing speed (Stroop word reading, Kolmogorov-Smirnov-$Z = 1.556, p = 0.016$). The number of low and high performers did not differ between the study group and the control group.

3.1. Cognitive measures

Group mean values of patients and controls were within the normal range, of controls even above the normal range in the fluency task. Details on the outcomes are shown in Table 2.

A trend towards lower everyday EF in patients than in controls was

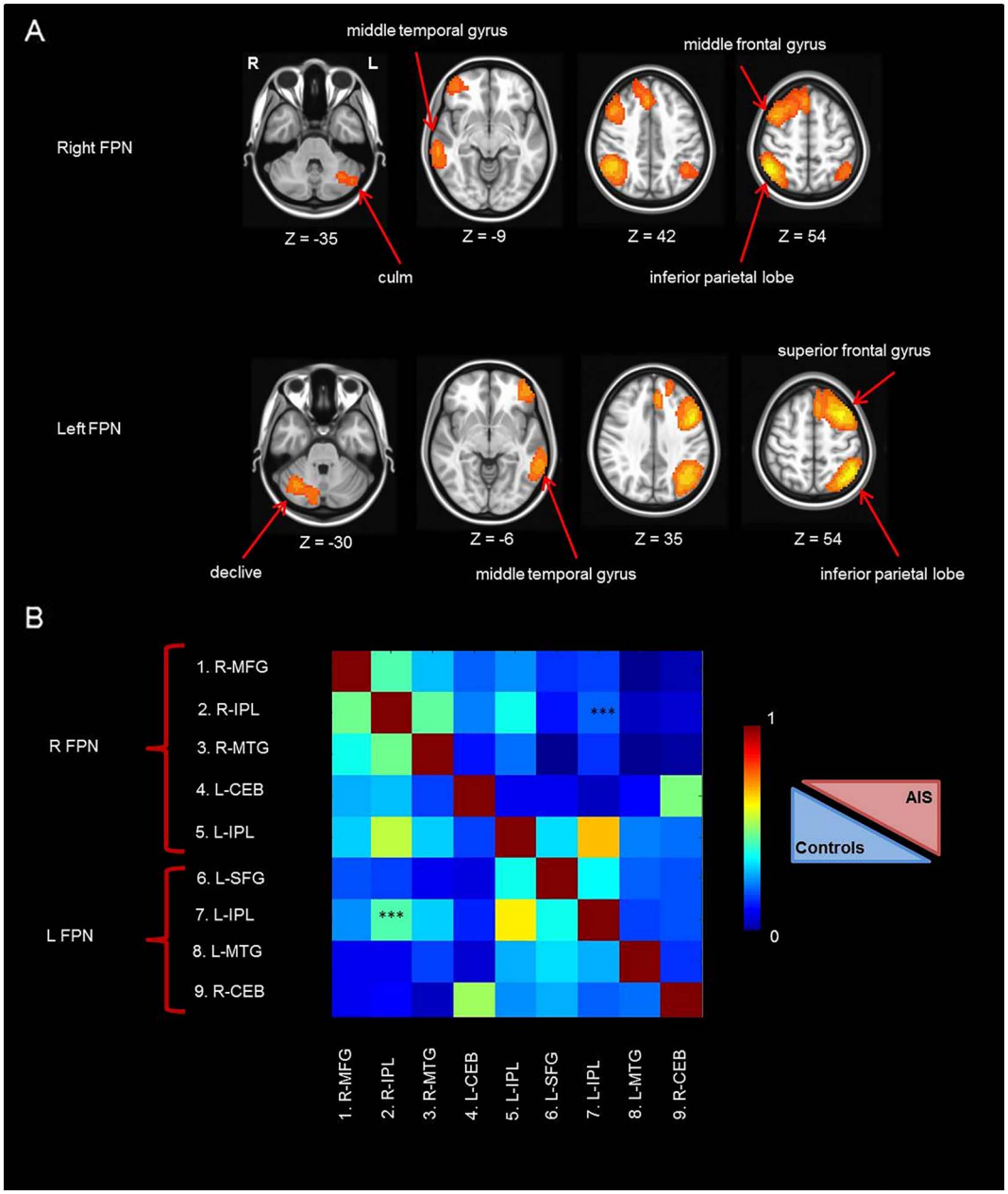

Fig. 2. A. Right and left FPN. B. Averaged functional connectivity between each spherical ROI within FPN. The upper triangular part of the matrix indicates the average connections of AIS, the lower triangular part the averaged connections across controls. The significant differences between AIS and controls were marked with stars (***FDR corrected $p \leq 0.001$). AIS = patients with arterial ischemic stroke; CEB = cerebellum; FPN = frontoparietal network; IPL = inferior parietal lobe; L = left; MFG = middle frontal gyrus; MTG = middle temporal gyrus; R = right; ROI = region of interest; SFG = superior frontal gyrus.

observed (parents' BRIEF ratings: $t(15.24) = 1.389$, $p = 0.185$, $d = -0.539$; self-ratings: $t(25) = 1.277$, $p = 0.213$, $d = 0.487$). Comparison of mean parents' and self ratings of BRIEF scores indicated worse parental than children's ratings of EF in everyday life ($t(53) = 1.816$, $p = 0.075$, $d = 0.491$). Self-ratings of everyday EF were the only to be positively correlated with lesion size ($r = 0.605$, $p = 0.029$). None of the other cognitive measures were related to sex, age at stroke, time since stroke, lesion localization, lesion side or lesion size. Details of the cognitive measures of patients and controls are shown in Table 2.

3.2. Frontoparietal network connections

When comparing all connections within the FPN, a significantly lower connectivity between right IPL and the left IPL at rest was found in AIS patients than in controls (FDR correction $p < 0.05$; mean connectivity strength AIS: 0.25 (SD = 0.23), mean connectivity strength controls: 0.47 (SD = 0.25); $t(40) = -3.637$, $p = 0.000$; Fig. 2B). Based on the seed-based correlation analysis, voxel-wise correlation maps were compared between AIS patients and controls. In children who had had AIS, the left IPL was significantly lower connected only to the right IPL and not to any other brain region (FDR correction $p < 0.05$; mean connectivity strength AIS: 0.26 (SD = 0.16), mean connectivity strength controls: 0.61 (SD = 0.21); $t(38) = 4.747$, $p = 0.000$; Fig. 3A–B). For all other FPN ROIs, no significant differences of voxel-wise resting-state connection were noted between the two groups.

3.3. Correlation between resting-state connection and cognitive measures

To explore the relationship between resting-state functional

Table 2
Characteristics of study sample.

	Patients	Controls	Patients vs. controls t(df)/U(df), p
N	20	22	
Age at assessment in years, mean (SD), range	16.0(4.4), 9.5–23.1	14.8 (5.1), 7.9–24.5	0.810(40), 0.422
Sex (female/male)	7/13	13/9	− 1.570(40), 0.124
Inhibition, median (25./75. PR), range	50.0 (22.5/80.5), 1.0–96.0	36.0 (18.0/62.0), 2.0–98.0	1.001(40), 0.323
Fluency, mean (SD), range	12.1 (3.5), 7.0–19.0	14.2 (3.3), 8.0–19.0	310.00(40), 0.019*
Processing speed 1, mean (SD), range	101.8 (12.7), 65.0–125.0	111.4 (13.4), 86.0–134.0	− 2.370(40), 0.023*
Processing speed 2, mean (SD), range	10.4 (2.8), 1.0–13.0	12.1 (1.2), 10.0–14.0	− 2.639(40), 0.012*
Divided attention, median (25./75. PR), range	62.0 (46.0/79.0), 4.0–91.0	62.0 (27.0/79.0), 2.0–91.0	− 0.508(40), 0.699
Working memory, mean (SD), range	9.4 (3.4), 3.0–16.0	10.9 (1.6), 7.0–14.0	− 1.875(40),0.068
Conceptual reasoning, mean (SD), range	96.9 (9.2), 84.0–118.0	105.7 (9.3), 91.0–127.0	− 3.095(40), 0.004**
BRIEF parents' rating, mean (SD), range	51.69 (14.0), 34.0–80.0	45.93 (5.6) 36.0–56.0	1.389(15.24), 0.185
BRIEF self-rating, mean (SD), range	46.0 (9.5), 29.0–61.0	42.3 (5.1), 32.0–51.0	1.277(25), 0.213
IPL connection z-scores, mean (SD), range	0.3 (0.2), 0.03–0.6	0.6(0.2), 0.2–1.1	− 5.798(40), 0.000***

ID = patient identification number; IQ = intelligence quotient; PR = percentage rank; SD = standard deviation; SS = scaled score; TAP = Test of Attentional Performance; WISC = Wechsler Intelligence Scale for Children.
Inhibition: TAP Go NoGo errors (PR).
Fluency: D-KEFS category fluency (SS).
Processing speed 1: WISC processing speed (Index Score).
Processing speed 2: Stroop word reading time (SS).
Divided attention: TAP divided attention errors (PR).
Working memory: WISC letter-number sequencing (SS).
Conceptual reasoning: TONI-4 (IQ Score).
Executive functions in everyday life: BRIEF (T-values).
Index Score mean = 100, SD = 15; IQ Score mean = 100, SD = 15; PR = 25., 50., 75. Percentile; SS mean = 10, SD = 3: T-values mean = 50, SD = 10.
* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.

connectivity and cognitive performance, the connection between the left and right IPL was correlated with several cognitive measures for all study participants. The left-right IPL connection was significantly correlated with fluency, processing speed and conceptual reasoning (Fig. 3C–E). When the data for the patient and control groups were analyzed separately, the correlation between the IPL connection and cognitive measures was not significant. The IPL connection was not related to sex, age at stroke, time since stroke, lesion localization, lesion side or lesion size.

4. Discussion

The present study investigated the FPN at rest and its relation to EF in patients after pediatric AIS and in typically developing controls. It was hypothesized that patients who have experienced AIS would show lower EF than controls. Patients and controls in the present study performed within the normal range both in EF and in everyday EF as assessed by parental and self-ratings. However, 5 of the 20 AIS patients (25%) showed working memory performance below the normal range (scaled score ≤ 7), whereas only 1 of 22 controls (4.5%) had below average working memory. Lower everyday EF ratings were significantly correlated with lower working memory, fluency and processing speed scores in the study sample. Although patients after pediatric AIS performed well on a group level in all EF, individual EF problems after stroke occurred that influenced EF in everyday life. The findings of mild EF problems after stroke in this study contradict the findings of Studer et al. (2014), who conducted an analysis of the same patient cohort. This is most likely related to the exclusion criteria of the present study, as children with behavioral problems or severe disabilities were excluded due to ineligibility for MRI.

Since the patient with a lesion within the FPN was excluded, none of the patients had a lesion of frontoparietal regions, despite lower performance in some EF (fluency, processing speed, conceptual reasoning) compared to controls. Hence, even after distant lesions, complex frontal lobe functions are affected by stroke, which is in line with theories supporting a network organization of the brain (Corbetta, 2012; Fornito et al., 2015; McIntosh, 2000).

The second hypothesis was that FPN connections at rest would differ between patients after pediatric AIS and children in the control group. Consistent with this hypothesis, the interhemispheric IPL connectivity was found to be significantly reduced in patients after childhood AIS. This points towards a reduced interaction between homologous brain regions at rest after stroke. Interhemispheric interactions are mediated by the corpus callosum which typically matures in a “front-to-back” manner between the ages of 3 and 15 years (Toga et al., 2006). Early brain damage might alter the maturation of the corpus callosum and thereby influence the structural and functional interhemispheric interactions necessary for higher level cognition. Functional brain organization is assumed to take place by means of Hebbian learning. Frequent simultaneous activation of specific regions leads to efficient coupling of these regions and a strengthening of cognitive performance (Stevens and Spreng, 2014). In our patients, the repetitive co-activation of specific brain regions might have become disrupted after stroke, resulting in the altered FPN connectivity. Structural and functional development of the parietal regions is known to take place at a relatively late stage, with prominent cortical thinning throughout childhood in normally developing children (Toga et al., 2006). The IPL comprises multimodal neurons which process auditory, sensory, visual and motor information (Zeller et al., 2015). Even though the exact function of the IPL is unclear (Singh-Curry and Husain, 2009), it is assumed that it plays a crucial role in diverse cognitive functions, such as language and semantic processing, memory and working memory (Zhang and Li, 2014). The protracted development and multimodal nature of the IPL might render this brain region particularly vulnerable to lesions during brain maturation. Additional analysis within the framework of the HERO-Study revealed that patients after childhood AIS show deficits in sensory inputs (e.g. in a 2-point-discrimination task). Interestingly, the sensory performance is positively related to IPL-connectivity, highlighting the multi-modal consolidation characteristics of the IPLs and their interhemispheric connection.

The left and right IPLs are known to differ in their functional properties (Zhang and Li, 2014; Koch et al., 2011). The left parietal cortex is suggested to be particularly important for cognitive performance (Toga et al., 2006). A right parietal dominance has been reported from a transcranial magnetic stimulation study where right parietal regions inhibited the activation state of the left parietofrontal connection more strongly than vice versa (Koch et al., 2011). For the present patient group we propose that, as a consequence of more left-sided lesions, the right hemisphere might compensate by means of an over-inhibition of the right onto the left IPL.

Surprisingly, frontal connections within the FPN were neither affected from stroke nor associated to EF. The age of stroke onset may serve as one explanation: peaks in frontal gray matter volumes occur around 11 to 12 years of age and are accompanied by changes in synaptic pruning and functional connectivity in the frontal lobes up into adolescence (Johnson et al., 2009; Lenroot and Giedd, 2006). In the present study, 76.2% of the children suffered from stroke before the age of 12 years. Brain lesions before major maturational changes may

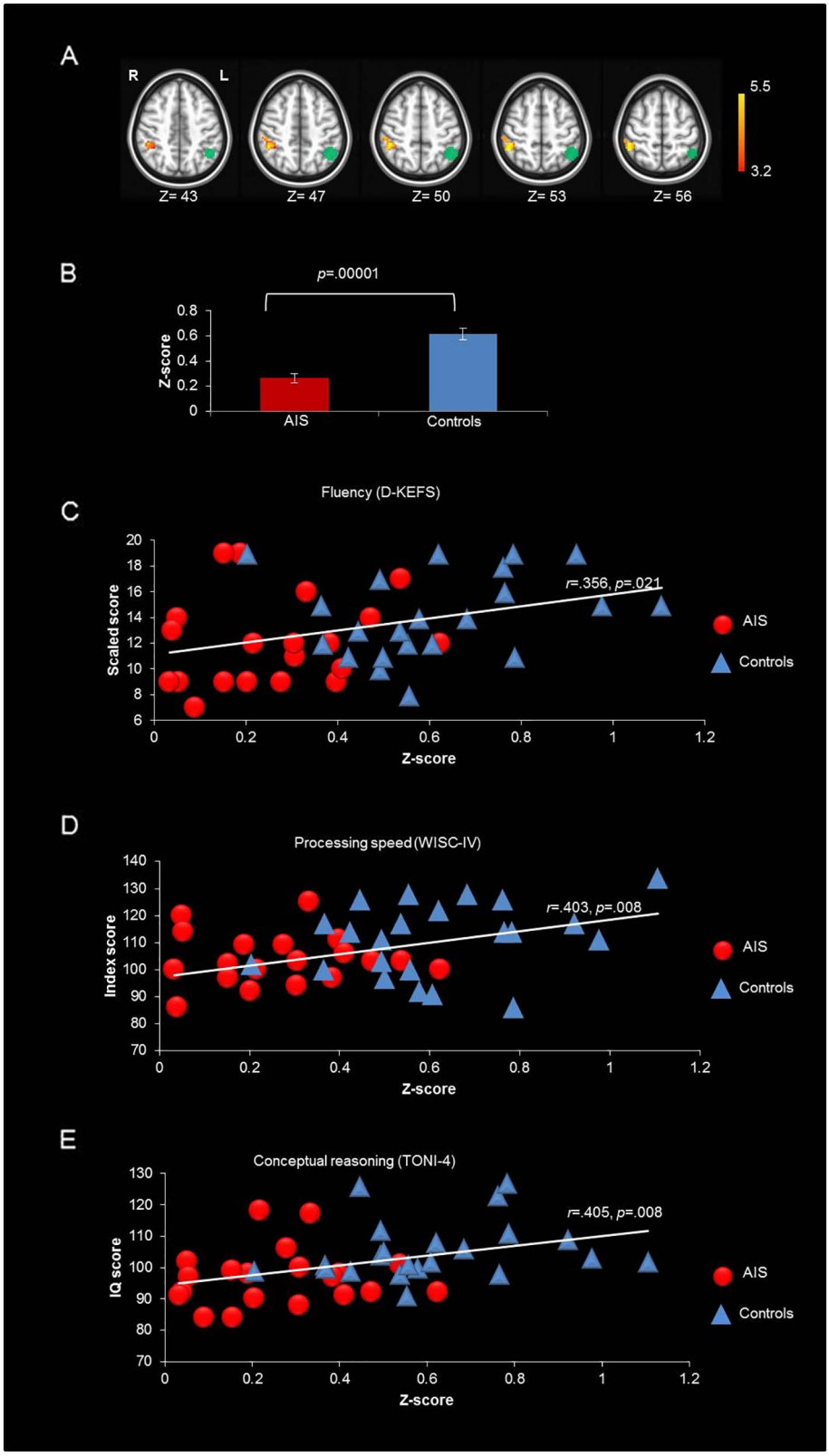

Fig. 3. A. Whole brain voxel-wise functional connectivity from each FPN seed. The seed left IPL (green) shows decreased connection to right IPL in AIS compared to controls (FDR corrected $p < 0.05$). B. Difference of IPL connection in AIS and controls. C–E. Significant correlations between the connectivity strength and fluency (C), processing speed (D) and conceptual reasoning (E).
AIS = patients with arterial ischemic stroke; D-KEFS = Delis–Kaplan Executive Function System; FPN = frontoparietal network; IPL = inferior parietal lobe; L = left; R = right; WISC = Wechsler Intelligence Scale for Children.

impact on corresponding brain connections differentially than lesions occurring during a critical developmental phase.

Our third hypothesis was that FPN connections at rest correlate with EF. This hypothesis was confirmed in regard to the interhemispheric IPL connection and some executive sub-functions: the IPL connection significantly correlated with fluency, processing speed and conceptual reasoning across all study participants. The IPL is part of various functional networks, such as the default mode network (Buckner and Vincent, 2007), the FPN (Vincent et al., 2008) and the attention network (Cabeza, 2008). The IPL is suggested to enable the switch between maintaining attention and responding to new stimuli (Singh-Curry and Husain, 2009). If the switching process is affected by a stroke, this

might influence processing speed and consequently problem solving. Processing speed was lower in the patients after pediatric AIS than in the controls. Slower processing speed was associated with lower interhemispheric IPL connectivity, pointing towards a particular importance of the IPL in the speed of processing information. When the patient and control groups were analyzed separately, the IPL connection was not significantly correlated to any of the EF measures, which might be an effect of the more homogeneous performance within the groups than across all subjects or an effect of sample size. Nevertheless, the results clearly reveal a linear relationship between IPL connection strength and performance in EF across the whole study sample, indicating that the IPL connection is related to cognitive performance. EF of the patients after AIS were not related to sex, age at stroke, time since stroke, lesion localization, lesion side or lesion size. It can therefore be assumed that it is the altered connectivity within the FPN that plays the major role in the final executive performance. The question arises why EF were not related to the localization, side or size of the lesion. As the lesions were generally small, the lesion characteristics themselves may not have been the critical factor for the EF outcome. Rather, it was the disruption of existing functional connections which became influenced by the lesion and affected EF outcomes. This assumption is underpinned by the finding that functional connectivity in the present sample was not explained by gray matter volume itself such as previously reported in children after AIS (Dinomais et al., 2012). Instead, group differences of functional network connectivity and corresponding functions occurred in remote regions which were not directly affected by the stroke. Thus, neither lesion localization, side, size nor gray matter volume loss were the decisive factors for the final EF outcome.

One exception was that BRIEF self ratings were positively correlated with lesion size, indicating that children with larger lesions reported worse EF in everyday life. This finding underpins the importance of detailed assessment of cognitive function not only with cognitive tests but also through the ratings of patients and parents.

Recent findings in adults suggest that therapeutic interventions impact on functional resting-state connectivity. In adult patients after stroke, enhanced connectivity between the ipsi- and contralesional M1 area and associated improvement of motor functions were observed following robot-assisted bilateral arm therapy (Fan et al., 2015). In the cognitive domain, post-interventional changes in resting-state connectivity were observed in adults with schizophrenia (Eack et al., 2016). Cognitive enhancement therapy, a psychosocial cognitive remediation approach, enhanced resting-state connections between frontal and temporal regions that are important for problem solving and emotion processing. It is not yet known if and how therapeutic interventions in children impact on resting-state connections after brain lesions. Future studies should focus on the effect of interventions in children after brain lesions and their impact on functional connectivity in the brain at rest and on cognition.

Over the past two decades, methods used for resting-state analyses have become more sophisticated and resting-state research has grown rapidly. This renders navigation through this complex field and the choice of an appropriate technique within a given setting a complicated task (Preti et al., 2016). Associating resting-state BOLD activity with cognitive processes and not only with functional-anatomic networks is a promising new avenue of resting-state research (Stevens and Spreng, 2014). Normative data on resting-state fMRI and cognition is scarce, making the interpretation of results difficult.

Some study limitations have to be acknowledged. First, the patient sample was heterogeneous, including children of different age at assessment, age at stroke, time since stroke and infarct localizations and sizes. Due to the rarity of pediatric AIS and the diverse lesion characteristics, recruitment of a homogeneous sample is not possible. Secondly, the high-performing control group may not be representative of the normal population; hence between-group differences need to be interpreted with caution. However, the fact that statistically significant differences were noted only in certain EF points to specific problem areas for children after stroke. Also, because children with behavioral problems were excluded, the patient sample might show an upward-shift further enhancing the comparability of the groups. Furthermore, the results are inevitably influenced by the method used to perform resting-state functional connectivity analyses and by the choice of the parameters, such as motion limit or voxel size limit for ICA-seeds. Lastly, the IPL is a relatively large brain area with many functions and processes. Other authors suggest a functional clustering of the IPL with functional sub-regions within the IPL (Zhang and Li, 2014), likely entailing more differentiated results.

In conclusion, the present study is among the first to show that in the maturing brain at rest, dynamic post-stroke changes in the BOLD signal occur that are closely related to EF problems. Even though children who have experienced AIS have lesions distant from the network examined, deviations in the FPN at rest were found in the patient group. In a nutshell, patients after pediatric AIS show a decreased connection between the IPLs at rest when compared to controls, pointing to altered interhemispheric interactions. It remains to be seen whether therapeutic interventions can foster the reorganization of functional network connections in the developing brain after lesion. The present results deepen our understanding of the association between higher-order EF and corresponding networks at rest after a stroke in childhood and provide new insights into functional organization mechanisms after damage to the developing brain.

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Author contributions

M.S., S.G., and R.E. were responsible for the conception and design of the study. Data acquisition was carried out by Sa.Ko., Sa.Ka., J.D.R., M.R., and C.W. and data analysis was performed by Sa.Ko., R.Y., B.B., C.W., C.K., and R.W. The manuscript was written by Sa.Ko., R.E., R.Y., B.B., M.S., S.G., and C.K.

Potential conflicts of interest

Nothing to report.

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