Received: 25 November 2022 | Accepted: 9 August 2023

DOI: 10.1111/dmcn.15751

ORIGINAL ARTICLE

Atypical language organization following perinatal infarctions of the left hemisphere is associated with structural changes in right-hemispheric grey matter

Lukas Schnaufer[1,2] | **Alisa Gschaidmeier**[1,3] | **Magdalena Heimgärtner**[1] | **Pablo Hernáiz Driever**[4] | **Till-Karsten Hauser**[5] | **Marko Wilke**[1,2] | **Karen Lidzba**[1,6] | **Martin Staudt**[1,7]

[1]Department of Paediatric Neurology and Developmental Medicine, University Children's Hospital, Tübingen, Germany

[2]Experimental Paediatric Neuroimaging, Children's Hospital and Department of Neuroradiology, University Hospital, Tübingen, Germany

[3]Centre for Paediatric Neurology, Neurorehabilitation and Epileptology, Schön Klinik, Vogtareuth, Germany

[4]Department of Paediatric Oncology and Haematology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany

[5]Department of Diagnostic and Interventional Neuroradiology, University Hospital, Tübingen, Germany

[6]Division of Neuropaediatrics, Development and Rehabilitation, University Children's Hospital Inselspital, Bern University Hospital, University of Bern, Switzerland

[7]Centre for Paediatric Palliative Care, University Children's Hospital, Ludwig-Maximilians-University Munich, Munich, Germany

Correspondence
Lukas Schnaufer, University Children's Hospital, Hoppe-Seyler-Str. 1, D – 72076 Tübingen, Germany.
Email: lukas.schnaufer@med.uni-tuebingen.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: DFG LI1925/4-1

Abstract

Aim: To assess how atypical language organization after early left-hemispheric brain lesions affects grey matter in the contralesional hemisphere.

Method: This was a cross-sectional study with between-group comparisons of 14 patients (six female, 8–26 years) with perinatal left-hemispheric brain lesions (two arterial ischemic strokes, 11 periventricular haemorrhagic infarctions, one without classification) and 14 typically developing age-matched controls (TDC) with functional magnetic resonance imaging (fMRI) documented left-hemispheric language organization (six female, 8–28 years). MRI data were analysed with SPM12, CAT12, and custom scripts. Language lateralization indices were determined by fMRI within a prefrontal mask and right-hemispheric grey matter group differences by voxel-based morphometry (VBM).

Results: FMRI revealed left-dominance in seven patients with typical language organization (TYP) and right-dominance in seven patients with atypical language organization (ATYP) of 14 patients. VBM analysis of all patients versus controls showed grey matter reductions in the middle temporal gyrus of patients. A comparison between the two patient subgroups revealed an increase of grey matter in the middle frontal gyrus in the ATYP group. Voxel-based regression analysis confirmed that grey matter increases in the middle frontal gyrus were correlated with atypical language organization.

Interpretation: Compatible with a non-specific lesion effect, we found areas of grey matter reduction in patients as compared to TDC. The grey matter increase in the middle frontal gyrus seems to reflect a specific compensatory effect in patients with atypical language organization.

Abbreviations: ATYP, patients with atypical language organization; DARTEL, diffeomorphic anatomical registration using exponentiated lie algebra; fMRI, functional magnetic resonance imaging; TDC, typically developing controls; TYP, patients with typical language organization; VBM, voxel-based morphometry.

Language has a long developmental trajectory as well as a performance/age-linked increase[1,2] in lateralization, with the majority of population norm adults being left-hemispheric dominant for language.[3] Both factors seem to underlie the astounding compensatory potential of language abilities in the case of early left-hemispheric lesions. Older children usually have more persistent language deficits after extensive left-hemispheric brain damage[4] while children with prenatally/perinatally acquired lesions (hitherto referred to as 'early lesions') develop normal language,[5] with only subtle deficits.[6] A striking feature in this is the reliance on language reorganization in topographically homologous areas of the right hemisphere.[4,7,8] However, interhemispheric reorganization is not the only compensatory mechanism in this population, as left-hemispheric perilesional activation has also been observed.[7,8] This is similar to aphasia recovery in adults and was even linked to better performance in language tasks.[7] Irrespective of the mechanism, however, high-level functional compensation seems to be limited to congenital and unilateral focal lesions, providing an ideal model to study brain reorganization and developmental plasticity.[9]

Similar to the functionally observed asymmetries, there is also evidence for distinct structural asymmetries between both hemispheres in population norm adults[10] and children[11] as well as adult[12,13] and underage patients with epilepsy,[11] including typical language areas like the planum temporale/Wernicke's area and the inferior frontal gyrus/Broca's area. Advanced analysis approaches such as voxel-based morphometry (VBM) have demonstrated an overall leftward asymmetry of these areas in typically developing participants.[10,11] While there is mixed evidence concerning the relationship between these structural asymmetries and language lateralization in typically developing participants,[10,11] patients with (lesional) epilepsy and atypical language organization showed a positive correlation between atypical language lateralization and rightward asymmetry of the planum temporale and inferior frontal gyrus.[11,12] However, little is known about structural correlates of functional language reorganization in children after early left-hemispheric brain lesions without epilepsy.

In this observational cross-sectional study, we assessed how early left-hemispheric lesions affect contralesional grey matter using VBM. This approach allows for a mass-univariate voxel by voxel analysis across the entire brain without relying on a priori defined regions of interest or manual parcellation.[14] We performed an exploratory voxel-wise grey matter comparison restricted to the right hemisphere of patients with typical/atypical language organization after early left hemispheric stroke, and TDC with left-hemispheric language organization. Similar to adults,[15] we expected unilateral early lesions to induce a general, non-specific decrease of grey matter not only in the lesional but also in the contralesional hemisphere when compared to controls (Hypothesis 1). Further, considering that language reorganization after early left-hemispheric lesions occurs in topographically homologous areas of the right hemisphere, we hypothesized that patients with left-hemispheric lesions inducing right-hemispheric language would exhibit grey matter increases within language-associated regions when compared to patients with typical left-sided language representation (Hypothesis 2).

What this paper adds

- Perinatal stroke leads to decreased grey matter in the contralesional hemisphere.
- Atypical language organization is associated with grey matter increases in contralesional language areas.

METHOD

Participants

Patients were recruited either from the study databases in Tübingen and Vogtareuth or via the regular clinical service in the latter. TDC were recruited from the community; participants were excluded because of an IQ below 70 and, for TDC, because of subsequently detected right-hemispheric language representation. Since participants needed to be able to comply with the scanning procedure, only participants aged 8 years and older were included, and all were required to be native German speakers. General magnetic resonance contraindications were applied for all participants (ferromagnetic metal implants, claustrophobia, and pregnancy).

We included 14 patients (median age 14 years, range 8–26 years, six female) with a diagnosis of a prenatally, perinatally, or neonatally acquired unilateral arterial ischaemic stroke or unilateral periventricular haemorrhagic infarction. For every patient, we age-matched (median age 14 years, range 8–28 years, six female) a person from our cohort of 38 controls.

All adult participants and the parents of minors gave written informed consent, and all children gave oral assent. Volunteers were compensated for their participation according to the time dedicated. This study was part of a larger project examining reorganization of functions after unilateral stroke occurring at different time-points. The study was approved by the ethics committee of the Medical Faculty of the University of Tübingen (Nr. 693/2014B01) in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964 in its latest applicable version).

Data acquisition

Depending on the recruitment site, participants were either scanned on a Siemens 1.5 T Avanto (Tübingen) or Symphony (Vogtareuth) scanner (both: Siemens Medizintechnik, Erlangen, Germany), using the same sequences and a standard quadrature head coil. An echo-planar

imaging sequence was used to acquire functional series (repetition time = 3000 ms, echo time = 40 ms, 40 axial slices, no gap, in plane matrix = 64 x 64, covering the whole brain with a voxel size = 3 x 3 x 3mm^3) as well as a gradient-echo B0-field-map with the same voxel size and slice prescription as in the functional series. Anatomical images were acquired in the form of a T1-weighted 3D data set (repetition time = 1300 ms, echo time = 2.92 ms, 176 contiguous sagittal slices, in plane matrix 265 x 265, resulting in a voxel size of 1 x 1 x 1mm^3). All participants performed the Vowel Identification task,[16] in which pictures of objects were presented and participants had to decide if the name of the object contained the vowel [i]. Since word generation is a crucial part of the task, it reflects the language production process. These active (language associated) blocks were alternated with control blocks consisting of a task where participants were presented two fractal images and should determine if the smaller one was part of the larger picture. The Vowel Identification task is easily doable from about 6 years of age and was shown to focally activate inferior frontal language regions in the dominant hemisphere.[16]

All participants completed neuropsychological tests of verbal (Potsdam-Illinois Test for Psycholinguistic Abilities) and nonverbal abilities (Test of Nonverbal Intelligence, Fourth Edition). The Potsdam-Illinois Test for Psycholinguistic Abilities is a standardized test for psycholinguistic abilities focusing on language development.[17] The Test of Nonverbal Intelligence, Fourth Edition measures the ability for abstract reasoning and problem-solving capability.[18] Since the test for nonverbal abilities does not require bimanual manipulation it is suitable for children with hand motor impairment. Information about hand preference was obtained by asking 'what hand do you write with?', which correlates very strongly (r = 0.91) with more extensive hand preference questionnaires.[19]

Data analysis

Functional and anatomical data was preprocessed and analysed with SPM12 (Wellcome Department of Imaging Neurosciences, UCL, London, UK), the Computational Anatomy Toolbox CAT12 (Christian Gaser and Robert Dahnke, Departments of Psychiatry and Neurology, Jena University Hospital, Jena, Germany), as well as custom scripts and functions running within MATLAB (MathWorks, Natrick, MA, USA) and MRIcron[20] for additional steps. All subsequent statistical analyses were performed using SPSS 28 (IBM Corp., Armonk, NY, USA).

fMRI and lateralization index

Using a custom script, the first 10 volumes of the functional images were removed to allow for stabilization of longitudinal magnetization. The remaining 100 echo-planar imaging volumes were subjected to a wavelet-based denoising step,[21] followed by the removal of echo-planar imaging distortions and B0*movement interaction effects using the individual field map.[22] After realignment and extraction of a motion fingerprint to discard series with total displacement exceeding the voxel size of 3 mm,[23] normalization was achieved by segmenting the anatomical images.[24] After coregistration and application of the corresponding parameters to the functional series, normalized images were smoothed with an isotropic Gaussian filter of 9 mm (full width at half maximum). Single-subject statistical analyses were performed, employing the framework of the general linear model. Lateralization was assessed on a single-subject level by calculating a laterality index on the statistical parametric mapping t-maps using the laterality index toolbox,[25] with a prefrontal mask as the region of interest referred from the Hammersmith population-based atlas.[26] We used a bootstrapping approach[27] assessing lateralization independently of statistical thresholds. With laterality indices ranging from −1 (exclusively right-hemispheric) to +1 (exclusively left-hemispheric), values below −0.2 were categorized as 'atypical', values between −0.2 and + 0.2 as 'bilateral', and above +0.2 as 'typical' language representation.[4]

Lesion masking

Individual lesion masks were manually delineated in native space on the anatomical T1-weighted image using MRIcron[20] under the instruction of an experienced examiner (MW), using standardized written instructions. To compensate for asymmetric ventricular enlargement (i.e. indirect lesion effects), the mirrored ventricles of the contralesional hemisphere were excluded from the lesion masks for all participants. Lesion volumes were calculated in native space using a custom script. To ensure consistency across several slices not only in the axial dimension (in which the lesion masks were manually defined) a 3D dilation-erosion step (achieved by application of an isotropic Gaussian filter of 2 mm [full width at half maximum] with a 0.5 threshold) was conducted. After warping the masks into the mean template space by means of deformations fields resulting from CAT12 segmentation (see below), individual lesion masks were summarized for visualization.

Voxel-based morphometry

Using CAT12, the individual high-resolution structural images were first segmented into white matter, grey matter, and cerebrospinal fluid, whereby the individual lesions were set to zero (cost function masking). The segmentation outputs were visually assessed to exclude overt segmentation failure and total intracranial volume was calculated for each participant. The segmentation algorithm implemented in CAT12 is based on an adaptive maximum a posteriori technique[28]

and accounts for partial volume effects allowing for more precise segmentation. In addition, two denoising methods are used to make data processing more robust against noise, a spatial-adaptive non-local means filter[29] implemented as preprocessing step and a classical Markov random field as part of the adaptive maximum a posteriori segmentation.[30] The subsequent high dimensional diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL)[14] locally changes the volume of the tissue segments whilst coding the anatomical differences in the resulting deformation fields.[31] These deformations are then used to generate modulated versions of the original images in the mean template space.[32]

In order to create an optimized, study-specific reference atlas, the normalized grey and white matter tissue segments of all participants were used to iteratively generate a custom DARTEL template.[31] Given the gross anatomical anomalies, the individual lesions were excluded during DARTEL template creation. Subsequently, the original grey matter maps were then warped to the custom DARTEL template and then modulated.[32] The grey matter tissue segments were then convolved with an isotropic Gaussian kernel of 8 mm, increasing the signal-to-noise ratio, compensating for misregistration, and ensuring a normal distribution.[31] These spatially normalized and smoothed grey matter segments were then entered into the VBM analyses.

VBM of the right hemisphere was performed using the general linear model; because of age and sex dependent maturational processes in grey matter[33] and the acquisition at two different study sites, these factors were included as nuisance regressors. To test our first hypothesis, controls were compared with all patients. In a second step, patients were split with respect to lateralization of language production and the two groups were separately compared with controls, as well as with each other, to test our second hypothesis. All findings from the group comparisons were corrected for multiple comparisons at the cluster level using a cluster forming-height threshold of a p-value of 0.001 and controlling the false discovery rate at a family-wise error corrected p-value of 0.05. To further quantify the right-brain results, we performed region of interest analyses. First, we used a modified script (Supplementary Software 1 in Kurth et al.[31]) to extract the voxel-wise grey matter volumes from the resulting significant clusters, which were subsequently z-transformed for reasons of comparability taking the nuisance regressors into account. The cluster volumes between the three subgroups and the z-transformed cluster volumes within the subgroups were compared by means of analyses of covariance (ANCOVA) with age at scan, sex, study site, and total intracranial volume as nuisance regressors, post hoc significance level was adjusted according to Bonferroni. A voxel-wise regression analysis in the right hemisphere of the patient subgroup was performed with the individual prefrontal language laterality index as the covariate of interest and age, sex, and study site as nuisance regressors. The findings were corrected for multiple comparisons as stated above.

Statistical analyses

The Shapiro–Wilk test was used to assess data distribution. Comparisons of clinical and demographic characteristics between study groups were performed with the χ^2, Kruskal–Wallis test/Mann–Whitney U test, or ANCOVA/t-test depending on data distribution and type. Lesion size was compared between the patient subgroups by means of ANCOVA with correction for total intracranial volume. The relationships between language lateralization indices and age as well as laterality index and lesion size were investigated using bivariate correlations and the relationship between laterality index and verbal ability using partial correlation controlling for sex and age. Kendall's Tau correlation coefficients were calculated because of small subgroup sizes. Two-sided significance level at a p-value less than 0.05 was assumed, unless otherwise specified.

RESULTS

Clinical and demographic characteristics of each diagnostic group are summarized in Table 1 and individual characteristics of all 14 patients in Table 2, who were split into subgroups according to their language lateralization indices (see below). According to the Shapiro–Wilk test, the parameters Test of Nonverbal Intelligence, Fourth Edition, Potsdam-Illinois Test for Psycholinguistic Abilities, total intracranial volume, and lesion size were normally distributed in all clinical subgroups, whereas age and laterality index were normally distributed only in the patient subgroups. Lesion size could be calculated in 13 out of 14 patients, an implanted shunt system prevented the reliable determination of lesion size and type in one patient (#9). Figure 1a (top) shows the summarized lesion masks of all patients. There was a significant difference in lesion size between the ATYP and TYP groups ($F(1, 10) = 8.65$, $p = 0.015$) with higher estimated marginal means in patients with atypical language organization (mean = 102.75 vs mean = 29.37). However, the patient subgroups did not differ significantly in verbal ($t(14) = 0.43$, $p = 0.68$) and non-verbal ($t(12) = 0.03$, $p = 0.97$) abilities.

Language lateralization

In the TDC sample, mean laterality index in the Vowel Identification task was 0.76 (SD = 0.26, range = 0.33–0.95). In the patient sample, 7 of 14 participants showed right-hemispheric language organization (mean laterality index = −0.53; range = −0.87 to −0.25) and were considered as atypical, whereas the other seven patients had left-dominance (mean laterality index = 0.70; range = 0.61–0.85), that is, typical

TABLE 1 Statistical comparison of demographic and clinical subgroup details.

	ATYP		TYP		TDC		Statistic	Statistic
	n = 7		*n* = 7		*n* = 14		all groups	patients
Age, months	232.3	(76.3)	143.1	(53.3)	199.3	(90.25)	H = 4.59 *p* = 0.10	*U* = 7.0 *p* = 0.026
Females, *n* (%)	4	(57.1)	2	(28.6)	6	(42.9)	$\chi^2 = 1.17$ *p* = 0.56	$\chi^2 = 1.17$ *p* = 0.28
Study site TUE, *n* (%)	6	(85.7)	3	(42.9)	14	(100)	$\chi^2 = 10.47$ *p* = 0.005	$\chi^2 = 2.80$ *p* = 0.09
Handedness, left, *n* (%)	7	(100)	7	(100)	3	(21.4)	$\chi^2 = 18.12$ *p* < 0.001	N/A
Laterality index prefrontal	−0.53	(0.26)	0.70	(0.09)	0.76	(0.17)	H = 16.38 *p* < 0.001	*U* < 0.001 *p* < 0.001
TONI	94.7	(10.5)	94.6	(4.12)	106.5	(10.1)	F = 5.9 *p* = 0.008	T = 0.03 *p* = 0.97
P-ITPA	52	(7.8)	50.3	(7.3)	67.2	(11.3)	F = 9.62 *p* < 0.001	T = 0.43 *p* = 0.68
TIV, ml	1453	(57.9)	1435.3	(41.3)	1479.6	(37.9)	F = 0.26 *p* = 0.77	T = 0.25 *p* = 0.38
Lesion size, ml	101.7	(56.0)	27.2	(20.3)			N/A	F = 8.65 *p* = 0.015

Note: Patients were split into subgroups according to their prefrontal language laterality index. Data are presented as mean (SD) unless otherwise stated. Reported *p*-values from Kruskall–Wallis/Mann–Whitney *U* test for age and laterality index, χ^2 test for sex and study site, ANOVA/t-test for TONI and P-ITPA, ANCOVA for lesion size (adjusted for TIV).

Abbreviations: ATYP, atypical language organization; N/A, not applicable; P-ITPA, Potsdam-Illinois Test for Psycholinguistic Abilities; TDC, typically developing controls; TIV, total intracranial volume; TONI, Test of Nonverbal Intelligence, Fourth Edition; TUE, Tübingen; TYP, typical language organization.

TABLE 2 Patient characteristics.

#	Site	Age (months)	Sex	Lesion type	Lesion location	Lesion size (ml)	Laterality index (prefrontal)	Language organization
01	TUE	150	F	PVI[a]	Left PWM	97.30	−0.32	Atypical
02	TUE	193	M	AIS	Left MCA	133.93	−0.50	Atypical
03	TUE	283	F	PVI	Left PWM	36.05	−0.83	Atypical
04	TUE	283	F	PVI	Left PWM	29.57	−0.25	Atypical
05	TUE	283	M	PVI	Left PWM	161.77	−0.66	Atypical
06	TUE	313	M	AIS	Left MCA	197.79	−0.87	Atypical
07	VOG	121	F	PVI	Left PWM	85.36	−0.31	Atypical
08	TUE	106	M	PVI[a]	Left PWM	22.82	+0.85	Typical
09	TUE	201	M	Not classified[a]	Not classified[a]	N/A	+0.69	Typical
10	TUE	233	F	PVI	Left PWM	1.16	+0.64	Typical
11	VOG	105	M	PVI	Left PWM	24.80	+0.61	Typical
12	VOG	141	F	PVI	Left PWM	55.82	+0.67	Typical
13	VOG	96	M	PVI	Left PWM	28.33	+0.78	Typical
14	VOG	120	M	PVI	Left PWM	50.29	+0.63	Typical

Note: Patients sorted by patient code.

[a]#1, #8, and #9: presence of magnetic resonance imaging (MRI) compatible ventriculoperitoneal shunt. The lesion in #9 could not unequivocally be classified as AIS or PVI because only MRI after implantation of a ventriculoperitoneal shunt was available.

Abbreviations: AIS, arterial ischemic stroke; F, female; MCA, middle cerebral artery; M, male; N/A, no data available because of technical failure; PVI, periventricular venous infarction; PWM, periventricular white matter; TUE, Tübingen; VOG, Vogtareuth.

language organization. Language laterality was increasingly right-sided in patients with larger left-sided lesions ($r_T = -0.61$, $p = 0.003$, $n = 14$), the other correlations (age, verbal ability) did not reach significance. None of the participants had to be excluded because of motion fingerprint exceeding.

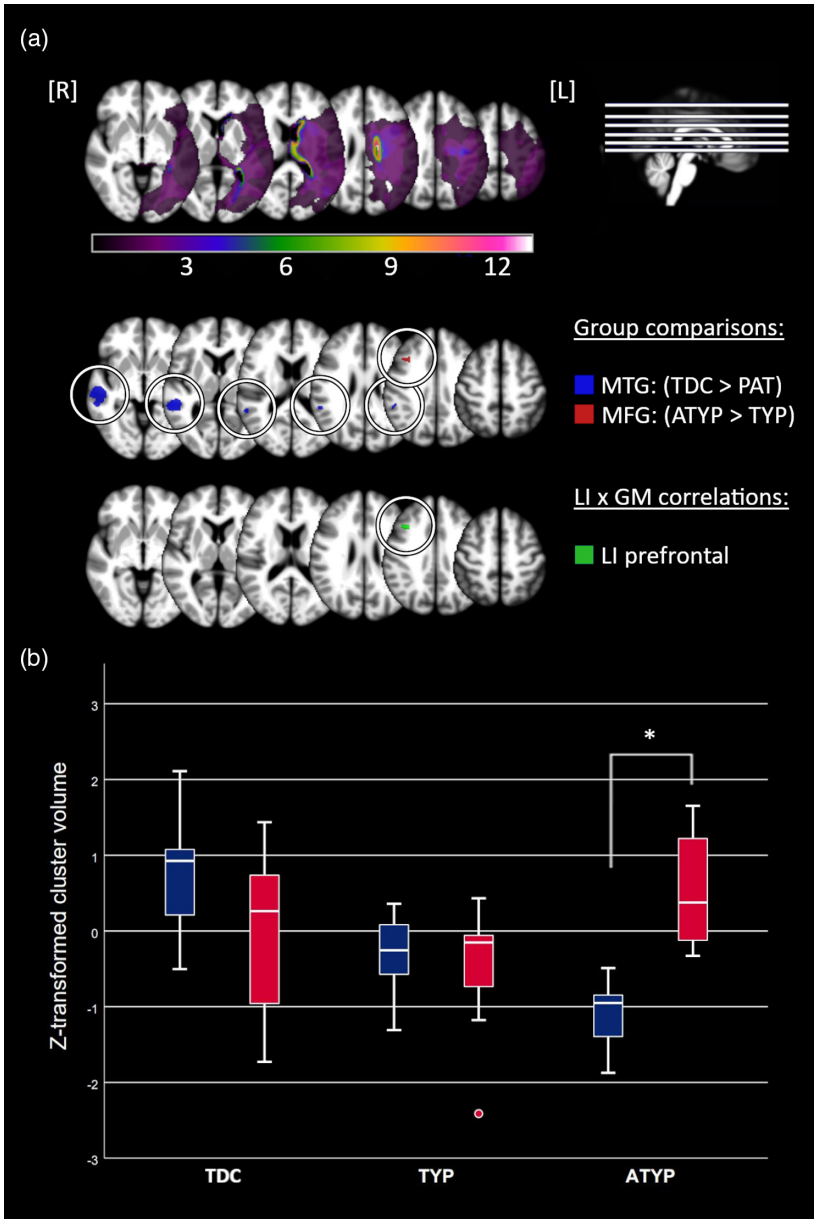

FIGURE 1 (a) Top: Summarized lesion masks of 13 patients. Middle: Significant group difference clusters of the VBM analysis (TDC > PAT and ATYP > TYP). Bottom: Significant clusters of VBM regression analysis between grey matter density and atypical language lateralization in the patient sample. Threshold for displaying VBM results: Cluster forming-height threshold of $p = 0.001$ and family-wise error correction at $p = 0.05$. All overlaid on axial slices of custom diffeomorphic anatomical registration using exponentiated lie algebra template (white matter and grey matter only) in radiological convention. The analyses were restricted to the right hemisphere only. (b) Grouped boxplot of the z-transformed cluster volumes.
* MTG and MFG clusters differed significantly within the ATYP group ($p = 0.011$). Abbreviations: ATYP, patients with atypical language organization; GM, grey matter; LI, laterality index; MFG, middle frontal gyrus; MTG, middle temporal gyrus; PAT, patients; TDC, typically developing controls; TYP, patients with typical language organization; VBM, voxel-based morphometry.

Voxel-based morphometry

Exploratory analyses revealed two significant clusters of group differences in right-hemispheric grey matter, as demonstrated in Figure 1a (middle). The first analysis showed an area with grey matter reductions in the patient sample (comprising all patients) compared to the TDC in the middle temporal gyrus, extending into the supramarginal gyrus ($k = 2120$, $T = 4.93$, family-wise error corrected $p = 0.001$). A comparison between the two patient groups revealed middle frontal grey matter increases in the ATYP group ($k = 126$, $T = 8.04$, family-wise error corrected $p = 0.004$). There were no clusters where patients showed more grey matter volume than controls.

Region of interest analyses

The middle temporal gyrus ($F(2, 21) = 11.11$, $p < 0.001$) and the middle frontal gyrus cluster volume ($F(2, 21) = 5.49$, $p = 0.012$)

differed significantly between the three subgroups. Bonferroni corrected post hoc analyses revealed a significantly lower mean middle temporal gyrus cluster volume in the ATYP group compared to the TDC group ($p<0.001$) and a significantly higher mean middle frontal gyrus cluster volume compared to the TYP group ($p=0.01$). Following z-transformation, these volumes were then compared as a function of group as shown in Figure 1b. ANCOVA yielded a significant difference between the two clusters for the ATYP group ($F(1, 8) = 10.96$, $p=0.011$) but not within the other groups.

Correlation analyses

When correlating prefrontal laterality indices with grey matter density in the right hemisphere of all patients using a VBM regression analysis, we found increases of grey matter associated with negative laterality indices in the medial frontal gyrus ($k=142$, $T=7.51$, family-wise error corrected $p=0.014$): the stronger the right-sided language dominance, the higher the grey matter density. This correlation cluster coincided with the cluster of the VBM group analysis between the patient subgroups. Results are displayed in Figure 1a (bottom).

DISCUSSION

In the present study, we assessed how unilateral early left-hemispheric brain lesions affect grey matter volume in the contralesional hemisphere depending on the language organization pattern. Language lateralization indices were determined by fMRI and right-hemispheric grey matter group differences by voxel-based morphometry. Regarding our hypotheses the major findings of this study were that: (1) such patients have areas of lower grey matter volumes in the contralesional hemisphere (i.e. the middle temporal extending to the supramarginal gyrus) as compared to TDC and (2) there are areas of increased grey matter volume in the middle frontal gyrus in patients with right-hemispheric language as a consequence of early left-sided stroke. These increases were also correlated with the individual strength of atypical language activation in fMRI, suggesting a structural correlate of language reorganization in the right hemisphere.

Our results of contralesional lower grey matter volume are in line with recent findings in adult stroke patients, showing cortical volume loss (brought about by cortical thinning) in contralesional homologue regions 1 year after stroke in adults.[15] The authors hypothesized these secondary changes to be caused by secondary apoptosis due to loss of synaptic input (i.e. transcollosal diaschisis).[15] It seems plausible that a similar mechanism is responsible for our findings, although developmental processes have to be taken into account in children.[9] Here, progressive mechanisms like myelination and regressive processes, such as synaptic pruning, often occur simultaneously.

We could not identify other studies linking frontal language lateralization and grey matter volume changes in patients with early left-hemispheric stroke. However, there are some studies examining speech-related grey matter asymmetries in other patient groups. Comparing adult patients with epilepsy showing atypical and typical language representation, Labudda et al.[12] not only demonstrated a relative grey matter volume increase of contralesional frontal areas but correlated these increases with the individual strength of fMRI activation.[12] Specifically, the authors described grey matter increases in the right superior/middle temporal and right superior/middle/medial frontal gyrus in patients with atypical language representation.[12] In agreement, Pahs et al.[11] reported a relationship between rightward asymmetry of the planum temporale and atypical language in children with left-sided focal epilepsy as well as the extension of a VBM correlation cluster between grey matter density and fMRI lateralization into the right Heschl's gyrus. However, the authors could not confirm Labudda's findings of correlations within the medial frontal gyrus.[11]

Although there is an evident lack of comparability between ours and the aforementioned studies (see 'Limitations'), using similar methodological approaches the authors provide a framework to interpret our results: While patients with left-hemispheric lesions inducing right-hemispheric language did not show grey matter increases within primary language regions using a right-hemispheric search volume, in concordance with Labudda et al.[12] exploratory analyses revealed significant volume differences in the middle frontal gyrus, a secondary language area. Agreement is also seen with the correlation of this right-hemispheric volume increase and the individual strength of atypical language activation in fMRI. Previous studies showed an involvement of this region in semantic[34] and syntactic processing,[35] in verbal fluency[36] and verbal working memory.[37] Further, it was shown to be similarly effective in determining language lateralization compared to Wada testing[38] and Broca's area activation when using a verbal fluency task.[39]

Limitations

There are a number of limitations to our study. First, the sample size seems small, which is an inherent and recurrent problem in studying rare diseases such as perinatal stroke. Considering our stringent inclusion criteria, we were able to recruit a rather large and homogenous group. Second, the wide age range of our sample might be considered a confounding factor because of the long developmental trajectory and age-dependent increasing of language lateralization,[1,40] which is why age was always used as a covariate in statistical analyses. Third, we used only one task (the Vowel Identification task)[16] to determine language lateralization. While this approach may misclassify patients with reorganized language comprehension,[4] it still strongly argues in favour of our approach in a setting

where a more complete task battery is not feasible. Fourth, another possible confound could be the presence of neurovascular uncoupling near the stroke lesions. As we did not collect multimodal MRI data as would be necessary to assess the presence and magnitude of this effect,[41] there is no way to rule in or out in how far this is relevant in our sample. Fifth, although VBM is sensitive to morphological differences, it is not possible to distinctly attribute these differences in volume to shape, cortical surface, or thickness, since VBM does not distinguish between causes at the micro-level.[42] In future studies, VBM should be combined with alternative morphological methods like the measurement of surface area, cortical volume, and gyrification. Lastly, because of differences in age at onset (early vs late) and in underlying pathologies (acute vs chronic damage), there is an evident lack of comparability between ours and the studies used as a framework to interpret our results.

Conclusion

Our study provides new insights into the structure–function relationship of language in patients with perinatal stroke. We showed morphological correlates as a function of language reorganization in the contralesional hemisphere. We assume that these grey matter differences between the two patient groups reflect compensatory morphological changes in patients with language reorganization, counteracting the lesion-driven effect of grey matter decreases in the contralesional hemisphere.

ACKNOWLEDGMENTS

We would like to acknowledge the volunteers and their families participating in this study as well as the department of Diagnostic and Interventional Neuroradiology. Open Access funding enabled and organized by Projekt DEAL.

This work was supported by the German research council (DFG LI1925/4-1). PHD was supported through a BIH Clinical Fellowship by 'Stiftung Charité'.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The raw and processed data required to reproduce all of the above findings cannot be shared at this time due to legal and ethical reasons.

ORCID

Lukas Schnaufer https://orcid.org/0000-0002-9247-8575
Marko Wilke https://orcid.org/0000-0001-5655-027X

REFERENCES

1. Holland SK, Plante E, Weber Byars A, Strawsburg RH, Schmithorst VJ, Ball WS, Jr. Normal fMRI brain activation patterns in children performing a verb generation task. Neuroimage 2001; 14: 837–43.
2. Weiss-Croft LJ, Baldeweg T. Maturation of language networks in children: A systematic review of 22years of functional MRI. Neuroimage 2015; 123: 269–81.
3. Knecht S, Drager B, Deppe M, Bobe L, Lohmann H, Floel A, et al. Handedness and hemispheric language dominance in healthy humans. Brain 2000; 123: 2512–8.
4. Lidzba K, Küpper H, Kluger G, Staudt M. The time window for successful right-hemispheric language reorganization in children. Eur J Paediatr Neurol 2017; 21: 715–21.
5. Ballantyne AO, Spilkin AM, Hesselink J, Trauner DA. Plasticity in the developing brain: intellectual, language and academic functions in children with ischaemic perinatal stroke. Brain 2008; 131: 2975–85.
6. Knecht M, Lidzba K. Processing verbal morphology in patients with congenital left-hemispheric brain lesions. Brain Lang 2016; 157-158: 25–34.
7. Raja Beharelle A, Dick AS, Josse G, Solodkin A, Huttenlocher PR, Levine SC, et al. Left hemisphere regions are critical for language in the face of early left focal brain injury. Brain 2010; 133: 1707–16.
8. Liegeois F, Connelly A, Cross JH, Boyd SG, Gadian DG, Vargha-Khadem F, et al. Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. Brain 2004; 127: 1229–36.
9. Kirton A, Deveber G. Life after perinatal stroke. Stroke 2013; 44: 3265–71.
10. James JS, Kumari SR, Sreedharan RM, Thomas B, Radhkrishnan A, Kesavadas C. Analyzing functional, structural, and anatomical correlation of hemispheric language lateralization in healthy subjects using functional MRI, diffusion tensor imaging, and voxel-based morphometry. Neurol India 2015; 63: 49–57.
11. Pahs G, Rankin P, Helen Cross J, Croft L, Northam GB, Liegeois F, et al. Asymmetry of planum temporale constrains interhemispheric language plasticity in children with focal epilepsy. Brain 2013; 136: 3163–75.
12. Labudda K, Mertens M, Janszky J, Bien CG, Woermann FG. Atypical language lateralisation associated with right fronto-temporal grey matter increases--a combined fMRI and VBM study in left-sided mesial temporal lobe epilepsy patients. Neuroimage 2012; 59: 728–37.
13. Dorsaint-Pierre R, Penhune VB, Watkins KE, Neelin P, Lerch JP, Bouffard M, et al. Asymmetries of the planum temporale and Heschl's gyrus: relationship to language lateralization. Brain 2006; 129: 1164–76.
14. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007; 38: 95–113.
15. Cheng B, Dietzmann P, Schulz R, Boenstrup M, Krawinkel L, Fiehler J, et al. Cortical atrophy and transcallosal diaschisis following isolated subcortical stroke. J Cereb Blood Flow Metab 2020; 40: 611–21.
16. Wilke M, Lidzba K, Staudt M, Buchenau K, Grodd W, Krägeloh-Mann I. An fMRI task battery for assessing hemispheric language dominance in children. Neuroimage 2006; 32: 400–10.
17. Esser G, Wyschkon A. P-ITPA Potsdam-Illinois Test für psycholinguistische Fähigkeiten (deutsche Fassung des Illinois Test of Psycholinguistic Abilities, third Edition (ITPA-3) von D. D. Hammill, N. Mather & R. Roberts). Göttingen: Hogrefe, 2010.
18. Brown L, Sherbenou RJ, Johnsen SK. Test of nonverbal intelligence: TONI-4. Austin: Pro-ed, 2010.
19. Wilke M, Holland SK, Altaye M, Gaser C. Template-O-Matic: A toolbox for creating customized pediatric templates. Neuroimage 2008; 41: 903–13.
20. Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. J Cogn Neurosci 2007; 19: 1081–8.
21. Wink AM, Roerdink JBTM. Denoising functional MR images: a comparison of wavelet denoising and Gaussian smoothing. IEEE Trans Med Imaging 2004; 23: 374–87.
22. Andersson JL, Hutton C, Ashburner J, Turner R, Friston K. Modeling geometric deformations in EPI time series. Neuroimage 2001; 13: 903–19.

23. Wilke M. An alternative approach towards assessing and accounting for individual motion in fMRI timeseries. Neuroimage 2012; 59: 2062–72.
24. Ashburner J, Friston KJ. Unified segmentation. Neuroimage 2005; 26: 839–51.
25. Wilke M, Lidzba K. LI-tool: a new toolbox to assess lateralization in functional MR-data. J Neurosci Methods 2007; 163: 128–36.
26. Hammers A, Allom R, Koepp MJ, Free SL, Myers R, Lemieux L, et al. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. Hum Brain Mapp 2003; 19: 224–47.
27. Wilke M, Schmithorst VJ. A combined bootstrap/histogram analysis approach for computing a lateralization index from neuroimaging data. Neuroimage 2006; 33: 522–30.
28. Rajapakse JC, Giedd JN, Rapoport JL. Statistical approach to segmentation of single-channel cerebral MR images. IEEE Trans Med Imaging 1997; 16: 176–86.
29. Manjon JV, Coupe P, Marti-Bonmati L, Collins DL, Robles M. Adaptive non-local means denoising of MR images with spatially varying noise levels. J Magn Reson Imaging 2010; 31: 192–203.
30. Bach Cuadra M, Cammoun L, Butz T, Cuisenaire O, Thiran J-P. Cuadra MB, Cammoun L, Butz T, Cuisenaire O, Thiran JP. Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. IEEE Trans Med Imaging 24: 1548-1565. IEEE Trans Med Imaging 2006; 24: 1548–65.
31. Kurth F, Gaser C, Luders E. A 12-step user guide for analyzing voxel-wise gray matter asymmetries in statistical parametric mapping (SPM). Nat Protoc 2015; 10: 293–304.
32. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001; 14: 21–36.
33. Gennatas ED, Avants BB, Wolf DH, Satterthwaite TD, Ruparel K, Ciric R, et al. Age-Related Effects and Sex Differences in Gray Matter Density, Volume, Mass, and Cortical Thickness from Childhood to Young Adulthood. The Journal of neuroscience: the official journal of the Society for Neuroscience 2017; 37: 5065–73.
34. Wang S, Zhu Z, Zhang JX, Wang Z, Xiao Z, Xiang H, et al. Broca's area plays a role in syntactic processing during Chinese reading comprehension. Neuropsychologia 2008; 46: 1371–8.
35. Luke K-K, Liu H-L, Wai Y-Y, Wan Y-L, Tan LH. Functional anatomy of syntactic and semantic processing in language comprehension. Hum Brain Mapp 2002; 16: 133–45.
36. Abrahams S, Goldstein LH, Simmons A, Brammer MJ, Williams SC, Giampietro VP, et al. Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. Hum Brain Mapp 2003; 20: 29–40.
37. Emch M, von Bastian CC, Koch K. Neural Correlates of Verbal Working Memory: An fMRI Meta-Analysis. Front Hum Neurosci 2019; 13: 180-.
38. Lehéricy S, Cohen L, Bazin B, Samson S, Giacomini E, Rougetet R, et al. Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. Neurology 2000; 54: 1625–33.
39. Dong JW, Brennan NM, Izzo G, Peck KK, Holodny AI. fMRI activation in the middle frontal gyrus as an indicator of hemispheric dominance for language in brain tumor patients: a comparison with Broca's area. Neuroradiology 2016; 58: 513–20.
40. Brauer J, Friederici AD. Functional Neural Networks of Semantic and Syntactic Processes in the Developing Brain. J Cogn Neurosci 2007; 19: 1609–23.
41. Blicher JU, Stagg CJ, O'Shea J, Østergaard L, MacIntosh BJ, Johansen-Berg H, et al. Visualization of altered neurovascular coupling in chronic stroke patients using multimodal functional MRI. J Cereb Blood Flow Metab 2012; 32: 2044–54.
42. Richardson FM, Price CJ. Structural MRI studies of language function in the undamaged brain. Brain Struct Funct 2009; 213: 511–23.

How to cite this article: Schnaufer L, Gschaidmeier A, Heimgärtner M, Driever PH, Hauser T-K, Wilke M, et al. Atypical language organization following perinatal infarctions of the left hemisphere is associated with structural changes in right-hemispheric grey matter. Dev Med Child Neurol. 2023;00:1–9. https://doi.org/10.1111/dmcn.15751