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Karen Lidzba[1,2], Bianca de Haan[3], Marko Wilke[1,2], Ingeborg Krägeloh-Mann[1], Martin Staudt[1,4]

[1]University Children's Hospital, Department of Pediatric Neurology and Developmental Medicine, University of Tübingen, Hoppe-Seyler-Str. 1, 72076 Tübingen, Germany

[2]Experimental Pediatric Neuroimaging group, Department of Pediatric Neurology and Developmental Medicine & Department of Neuroradiology, University Hospital Tübingen, Hoppe-Seyler-Str. 1, 72076 Tübingen, Germany

[3]Center of Neurology, Division of Neuropsychology, Hertie-Institute of Clinical Brain Research, Hoppe-Seyler-Str. 3, 72076 Tübingen, University of Tübingen, Germany

[4]Clinic for Neuropediatrics and Neurorehabilitation, Epilepsy Center for Children and Adolescents, Schön Klinik Vogtareuth, Krankenhausstr. 20, 83569 Vogtareuth, Germany

Running Title: Reorganization of Language Comprehension

Corresponding Author:

Karen Lidzba, PhD; University Children's Hospital; Department of Pediatric Neurology and Developmental Medicine; Hoppe-Seyler-Str. 1; 72076 Tübingen;

Tel.: +49-7071-2980881; Fax: +49-7071-295236; e-mail: Karen.lidzba@med.uni-tuebingen.de

Abstract

Pre- or perinatally acquired (“congenital”) left-hemispheric brain lesions can be compensated for by reorganizing language into homotopic brain regions in the right hemisphere. Language comprehension may be hemispherically dissociated from language production. We investigated the lesion characteristics driving inter-hemispheric reorganization of language comprehension and language production in 19 patients (7 - 32 years; eight females) with congenital left-hemispheric brain lesions (periventricular lesions [n=11] and middle cerebral artery infarctions [n=8]) by fMRI. 16 / 17 patients demonstrated reorganized language production, while 7 / 19 patients had reorganized language comprehension. Lesions to the insular cortex and the temporo-parietal junction (predominantly supramarginal gyrus) were significantly more common in patients in whom both, language production and comprehension were reorganized. These areas belong to the dorsal stream of the language network, participating in the auditory-motor integration of language. Our data suggest that the integrity of this stream might be crucial for a normal left-lateralized language development.

Key words: congenital brain lesion; language reorganisation; language comprehension; lesion-symptom mapping

1. Introduction

1.1 Language reorganization in adults and children

In adults, damage to the left cerebral hemisphere commonly results in specific aphasic symptoms associated with the lesion site (Gottesman & Hillis, 2010; Kreisler et al., 2000). Satisfying recovery from aphasia is often associated with left-hemispheric perilesional activation (Lidzba, Staudt, Zieske, Schwilling, & Ackermann, 2012; Saur et al., 2006; Szaflarski, Allendorfer, Banks, Vannest, & Holland, 2013), with right-hemispheric language activation more commonly seen in the more impaired patients, i.e., those with large lesions (Sims et al., 2016) or incomplete recovery (Saur et al., 2006; Szaflarski et al., 2013). In contrast to this pattern, children with left hemispheric brain damage (i.e., acquired pre- or perinatally) do not usually show persisting and substantial language deficits. Language development after congenital brain lesions may be delayed (Chilosi et al., 2005), but by school-age, such patients are perceived as competent speakers of their native language (Bates & Roe, 2001; Ilves et al., 2014). Only when confronted with linguistically complex tasks do children and adolescents with early left-hemispheric brain lesions show deficits in grammar processing (Knecht & Lidzba, 2016; Lidzba, Konietzko, Schwilling, Krägeloh-Mann, & Winkler, 2013; Schwilling, Krägeloh-Mann, Konietzko, Winkler, & Lidzba, 2012) and discourse (Reilly, Bates, & Marchman, 1998; Reilly, Wasserman, & Appelbaum, 2013). The neural mechanisms underlying language recovery in adult aphasics and language acquisition in patients with perinatal stroke seem to differ with respect to the brain tissue involved: Directly comparing children with perinatal left-hemispheric stroke with recovered adult aphasics, Szaflarski and colleagues demonstrated that the pediatric group recruited a bilateral network for language production, while the adult group was indistinguishable from healthy controls regarding lateralization (Szaflarski et al., 2014). That many (but not all) patients with left-hemispheric pre-/perinatal pathology may rely on a right-hemispheric language network has repeatedly been demonstrated for patients with and without epilepsy (Liegeois et al.,

2004; Rasmussen & Milner, 1977; Tillema et al., 2008). The reorganized, right-hemispheric activation pattern encompasses areas homotopic to those involved in left-hemispheric language organisation, as investigated in patients with congenital white-matter lesions (Staudt et al., 2002), and in patients with left-hemispheric brain damage after epilepsy surgery (Tivarus, Starling, Newport, & Langfitt, 2012). Interhemispheric reorganization seems to affect networks connecting various regions of the brain, including the cerebellum (Lidzba, Wilke, Staudt, Krägeloh-Mann, & Grodd, 2008). This mirrored topography in cortical representation is also reflected in a corresponding reorganization of the subcortical fibre tracts in the right as compared to the left hemisphere (Duffau, Peggy Gatignol, Mandonnet, Capelle, & Taillandier, 2008).

1.2 Factors related to language reorganization

The driving force of typical or atypical language lateralization both in healthy subjects and patients with early left-hemispheric brain lesions has been a relevant research topic since Rasmussen's and Milner's (1977) seminal report on a large series of Wada tests. Not all patients with early left-hemispheric lesions have right-sided language dominance (Liegeois et al., 2004; Rasmussen & Milner, 1977), and thus, more specific factors must be expected to play a role. Perinatal infarctions of the left middle cerebral artery (predominantly affecting perisylvian cortex including the temporal lobe) seem to be more often associated with reorganization of language comprehension (Jacola et al., 2006) than pre- or perinatally acquired periventricular lesions affecting fronto-parietal white matter only (Brizzolara et al., 2002; Staudt et al., 2001). Small developmental lesions (like vascular malformations) or slowly evolving pathologies (like tumours) are not commonly associated with atypical language (Gaillard et al., 2007; Pataraia et al., 2004). In children with intractable epilepsy due to early lesions, lesion location at or near the typical language areas were not commonly associated with language reorganization in one study (Liegeois et al., 2004), but the

likelyhood for atypical language organization was increased with left frontal malformations of cortical development in another sample (Wilke et al., 2011). Epileptic seizures and even interictal epileptic activity have the potential to interfere with the representation of language function, presumably even independently of a structural lesion (Janszky, Mertens, Janszky, Ebner, & Woermann, 2006). In the absence of epileptic activity, strategically-located lesions affecting the articulatory motor tract may be sufficient for the reorganization of language production in patients with periventricular brain damage and intact cortex (Staudt et al., 2001; Staudt, Ticini, Grodd, Krageloh-Mann, & Karnath, 2008). Thus, the specific topography, extent and timing of a lesion, but also accompanying factors such as epilepsy seem to be important factors driving language (re-)organisation.

1.3 Language networks

When studying language reorganization, it is important to consider that numerous functional imaging studies have shown that language comprehension and language production recruit overlapping, but dissociable neural networks in the brain (for a review see (Price, 2012)). Language production and language comprehension can be hemispherically dissociated not only in children with epilepsy (Wilke et al., 2010; Kurthen, Helmstaedter, Linke, Solymosi, Elger, & Schramm, 1992) and patients with prenatally acquired periventricular lesions (Staudt et al., 2001), but also in healthy children and adolescents (Lidzba, Schwilling, Grodd, Krageloh-Mann, & Wilke, 2011). Current neuroanatomical models propose that language processing is organized in a dorsal and a ventral language stream (‘dual-route model’), where both streams participate both in language comprehension and production (Dick & Tremblay, 2012; Friederici, 2015; Hickok & Poeppel, 2015). In the domain of language comprehension, however, the bilaterally represented ventral stream seems more important. This pathway of temporal and frontal language regions, connected by the extreme capsule fibre system and the uncinate fascicle, is involved in bottom-up language processing, such as phonological word

form detection, morphosyntactic and lexical-semantic categorization, and lexical access (Friederici, 2015; Hickok & Poeppel, 2015; Skeide & Friederici, 2016). Consequently, in adult aphasics, comprehension deficits are associated with damage to the ventral extreme capsule fibre system (Kummerer et al., 2013). In the course of typical language acquisition in healthy children, the first two or three years are dominated by bottom-up language processing, relying mainly on the ventral stream (Skeide & Friederici, 2016). In contrast, the strongly left-lateralized dorsal stream is engaged in functions seemingly more crucial for language production. It encompasses the posterior frontal lobe, anterior insula, and the temporo-parietal junction, and it is relevant for the integration of sensory-motor information and the processing of complex syntax (Friederici, 2015; Hickok & Poeppel, 2015). Analogously, impairments in speech repetition are associated with lesions to the dorsal superior longitudinal and arcuate fascicle pathway in aphasic patients (Kummerer et al., 2013).

The usually small and often heterogeneous samples in which language reorganization after congenital brain lesions can be studied pose a methodological challenge. Nevertheless, it is of both clinical and neuroscientific interest to investigate in more detail 1) the gross lesion characteristics forcing the right hemisphere into language processing, and 2) specific brain regions that are crucial for typical language representation. In order to address these issues, we studied a homogeneous sample of patients with pre- and perinatally acquired left-hemispheric brain lesions. As done previously (Staudt et al., 2001; Staudt et al., 2002), we included only patients with clearly defined lesions involving only the left hemisphere, i.e., strictly unilateral periventricular white matter lesions or middle cerebral artery infarctions. We here employed functional MRI tasks for language production and comprehension in combination with the voxel-lesion symptom mapping (VLSM) approach to identify brain regions that induce reorganization of language comprehension or language production when damaged. Since infarctions of the middle cerebral artery typically affect the frontal and/or

temporal grey and white matter, we expected a higher probability of reorganization of language comprehension in patients with middle cerebral artery infarctions than in those with periventricular lesions (Hypothesis 1a). More specifically, we expected that regions within the ventral stream of language processing, namely the middle temporal gyrus and inferior temporal sulcus, and underlying white-matter structures (i.e., the extreme capsule fibre system and the uncinate fascicle) would be the most relevant in driving reorganization of language comprehension (Hypothesis 1b). For language production, we expected that lesions within the dorsal stream of language processing, namely the temporo-parietal junction, premotor cortex, inferior frontal gyrus and anterior insula, and underlying white matter structures would be predictive for reorganization (Hypothesis 1c). Since language production and language comprehension usually recruit overlapping networks of the same hemisphere, we also expected a significant correlation between lateralization of language production and language perception (Hypothesis 2).

Since our sample also contained patients with epilepsy, we were able to test also an alternative hypotheses, namely that language reorganization will be more frequent in patients with epilepsy as compared to patients without epilepsy, irrespective of lesion location or lesion type (Alternative hypothesis 1a*).

2. Materials and Methods

2.1 Subjects

Nineteen patients with pre- and perinatally acquired focal lesions to the left hemisphere participated in the study (age range 7 - 32 years; eight females). Eight patients had infarctions of the middle cerebral artery (MCA), while 11 had unilateral periventricular lesions (PL). Four out of 8 patients with MCA infarction (patients 02, 16, 18, 19) and 2 out of 10 patients with PL (patients 15 and 17) had epilepsy (medicated in all but patient 02; age at manifestation of epilepsy between 0 and 20 years). 14 patients were scanned in the framework of a larger fMRI study, 5 patients received standardized language fMRI (with the same parameters as in the study) in a clinical setting. Representative MR images are shown in Figure1; detailed patient characterization is provided in Table 1.

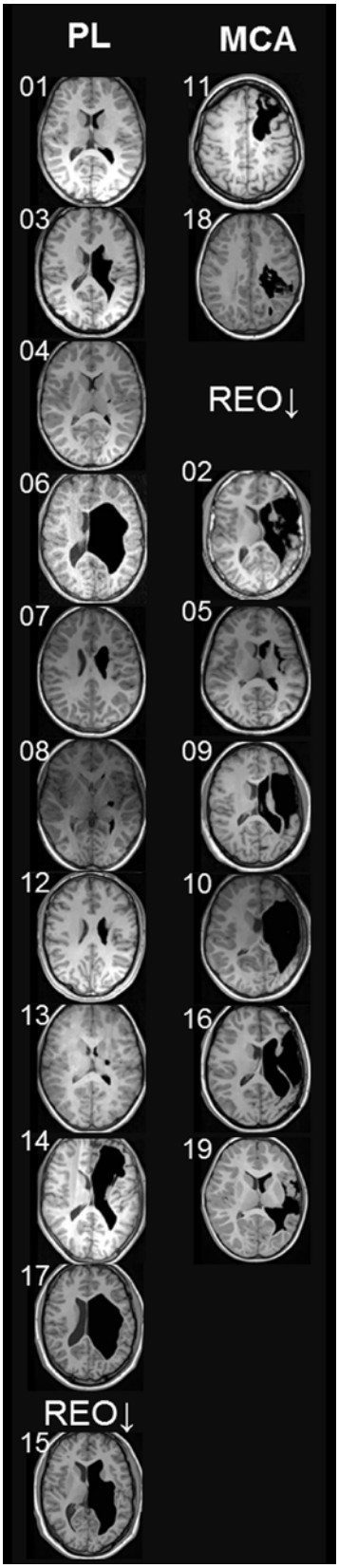

Figure 1. Axial slices of T1 images in radiological convention, illustrating the individual brain lesions, sorted by lesion type (columns) and lateralization of language comprehension (top images: typical lateralization, bottom images: reorganization).

Table 1: Patient characteristics, sorted by lesion type and lateralization of language comprehension.

Patient code	age at scan (years)	sex	lesion type	LI (comp)	Laterality (comp)	LI (prod)	Laterality (prod)
01	9	f	PL	+0.72	TYP	-0.10	REO
03	17	f	PL	+0.24	TYP	-0.66	REO
04	9	m	PL	+0.55	TYP	+0.86	TYP
06	11	m	PL	+0.33	TYP	-0.14	REO
07	10	m	PL	-0.45	TYP	-0.80	REO
08	13	m	PL	+0.13	TYP	+0.15	REO
12	17	m	PL	+0.69	TYP	-0.42	REO
13	9	f	PL	+0.02	TYP	-0.51	REO
14	14	m	PL	-0.39	TYP	+0.12	REO
17	18	m	PL	-0.05	TYP	-0.07	REO
15	15	f	PL	-0.87	REO	-0.56	REO
11	32	f	MCA	+0.35	TYP	-0.49	REO
18	7	f	MCA	-0.56	TYP	N/A	N/A
02	19	m	MCA	-0.79	REO	-0.66	REO
05	18	f	MCA	-0.64	REO	-0.67	REO
09	21	f	MCA	-0.62	REO	-0.69	REO
10	9	m	MCA	-0.88	REO	+0.24	REO
16	20	f	MCA	-0.90	REO	N/A	N/A
19	7	f	MCA	-0.92	REO	-0.05	REO

LI = laterality index (negative: right; positive: left); comp = language comprehension; prod = language production; f = female; m = male; PL = periventricular white-matter lesion; MCA = infarction of middle cerebral artery; TYP = typical lateralization (Comp: LI > -.62; Prod: LI > .35); REO = language reorganization (Comp: LI ≤ -.62; Prod: LI ≤ .35). N/A: no data available no data available due to incompliance (18) or technical failure (16). *Note*: Age at scan equals time since lesion. Patients are sorted as in Figure 1.

For comparison, data from 28 healthy controls (age 6 to 30 years; 16 females) was retrieved from a previous study exploring the effects of age and performance on the fMRI activation during language perception and production (Lidzba et al., 2011), using the same tasks and fMRI protocols as employed here.

All participants and the parents of minors gave written informed consent, and all children assented. Study subjects were compensated for participation according to their time dedicated. The study was approved by the ethical committee of the Medical Faculty of the University of Tübingen (Nr. 420/2010BO2) and complied with the Code of Ethics set forth by the World Medical Association (Declaration of Helsinki).

2.2 Functional MRI tasks

All patients performed the *Beep Stories* task (Wilke et al., 2005) and the *Vowel Identification* task (Wilke et al., 2006). In the *Beep Stories* task, they were presented with short stories in which some of the nouns are replaced by a "beep" sound (story condition). This manipulation increases the difficulty to understand the story content and, thus, allows to capture a broad range of functions needed for **language comprehension**, when contrasted with the control condition. Subjects were asked to follow the story without a specific task, but they knew they would be quizzed after the scanning session to ensure that they had understood it properly. If subjects failed to answer the questions regarding more than half of the stories correctly (i.e., 3/5 questions), they were excluded from the study. Story blocks were alternated with control blocks of sinus tones within the frequency range of human speech. This task mainly induces activation in receptive (temporal lobe) language regions. In the *Vowel Identification* task, subjects were presented with pictures of objects and asked to decide if the generated name of the object contained the phoneme /i/. Since this decision requires, in the first place, a silent generation of the name of the presented object, this task can be considered a word generation task, reflecting **language production.** Word blocks were alternated with control blocks of fractal images where subjects were asked to decide if a small picture fitted into a larger picture "like a piece in a puzzle". Performance (correct button presses) in the control condition was required to be above chance level as this condition is less ambiguous than the language task, in which the same image can be named with or without an /i/ (e.g., "ship" vs. "boat"; Dorn et al., 2014; Ebner, Lidzba, Hauser, & Wilke, 2011).

2.3 Data acquisition

We used a Siemens 1.5T Sonata scanner to acquire whole brain functional echoplanar images (repetition time = 3,000 ms, echo time = 40 ms, 40 axial slices, 64 x 64 in-plane resolution, 3 x 3 x 3.5 mm^3 voxel size; 110 volumes per task). Anatomical images were acquired in the

form of a T1-weighed three-dimensional dataset (repetition time = 1,300 ms, echo time = 2.92 ms, 176 sagittal slices, 256 x 256 in-plane resolution, 1 x 1 x 1 mm^3 voxel size).

2.4 Data analysis

Functional and anatomical data was preprocessed and analyzed with SPM8 and SPM12 (Statistical parametric mapping; Wellcome Department of Imaging Neurosciences, UCL, UK), and custom scripts and functions running within Matlab (Mathworks, Natick, MA, USA), as well as MRIcron and NPM (Rorden, Karnath, & Bonilha, 2007); www.mricro.com) for additional steps of analysis.

Individual lesion masks were semi-manually delineated in native space on the anatomical T1-weighted image using the Clusterize toolbox (Clas, Groeschel, & Wilke, 2012), and manually refined in MRIcron (Rorden et al., 2007). Since many of the subjects had periventricular lesions, leading to asymmetric ventricular enlargement, the ventricles were included in the lesion mask for all subjects. To make sure that our comparisons were not unduly influenced by simply comparing larger with smaller lesions, lesion sizes were compared between comparison groups by non-parametrical Mann-Whitney U-tests.

All functional images were first subjected to a wavelet-based denoising step (Wink & Roerdink, 2004), then realigned to correct movement in SPM8. After realignment, a motion fingerprint was extracted for each subject (Wilke, 2012). For normalisation, the area of the individual lesion masks were set to zero (cost function masking; (Andersen, Rapcsak, & Beeson, 2010)). Following the suggestion of Crinion for lesioned brains (Crinion et al., 2007) the functional and anatomical images, including the lesion masks, were subjected to affine normalization to standard MNI (Montreal Neurological Institute) space in SPM12. This version was used here as the affine normalization is more robust in this later implementation.

After that, functional volumes were smoothed with a Gaussian filter of FWHM (full width at half maximum) = 9 mm and entered into the statistical single subject analysis in SPM8. For statistical analyses, the framework of the general linear model (Friston, Frith, Frackowiak, & Turner, 1995) was employed, using a box-car reference function convolved with the hemodynamic response function. To account for technical or physiological noise, we subjected the functional data to a high-pass filter of 128 sec. To minimize movement-correlated artefacts, the individual motion fingerprints (3 original and 3 shifted traces) were introduced as covariates into the statistical model.

Lateralization effects were estimated on a single-subject level by use of the LI-toolbox (Wilke & Lidzba, 2007), with the temporal lobe (referred from the Hammersmith population-based atlas; (Hammers et al., 2003)) as the ROI for the *Beep Stories* task and the frontal lobe (Hammersmith atlas; (Hammers et al., 2003)) as the ROI for the *Vowel Identification* task. We employed a bootstrap-analysis approach which assesses lateralization independently of statistical thresholds (Wilke & Schmithorst, 2006). LIs can assume values between -1 and +1, with positive values implying predominantly left-hemispheric activation, and values between - .2 and + .2 indicating bilateral activation. To classify the patients' LIs, we first determined the arithmetic means and standard deviations for the healthy sample. LIs falling more than two standard deviations below the healthy sample's mean of the given modality (production or comprehension) were classified as "reorganized" (REO), while all others were considered "typical" (TYP).

To test our first hypothesis (H1a), the two groups with MCA and PL were compared with respect to reorganization (TYP vs. REO). We expected a higher frequency of REO in the MCA group. To test the alternative hypothesis (H1a*), we first compared all patients with

epilepsy to all patients without epilepsy. H1a* would predict a higher frequency of REO in the epilepsy group. To separate the effects of lesion type and epilepsy, we repeated this analysis for the patients with MCA only, albeit in an exploratory fashion due to the smaller sample size.

To safeguard against false-positives in the presence of small groups, a non-parametrical, one-tailed Fisher's exact test was used for all planned comparisons.

Lesion-symptom analysis was then employed to test our anatomically more specific hypotheses H1b and H1c. We performed VLSM with the nonparametrical Liebermeister statistic in NPM (Rorden *et al.*, 2007), excluding voxels lesioned in less than three patients in order to further increase robustness. Statistical significance was assumed at $p < .05$, corrected for multiple comparisons by permutation tests (4000 permutations).

To finally investigate whether lateralization of language comprehension is significantly related to the lateralization of language production (H2), the two groups (TYP_{comp} vs. REO_{comp}) were then compared with respect to lateralization of language production (TYP_{prod} vs. REO_{prod}) by a one-tailed Fisher's exact test. We expected a higher number of patients with reorganization of language production in the REO_{comp} group.

3. Results:

3.1 Lateralization analyses

In the healthy control sample, mean LI in the *Beep Stories* task was .12 (SD .37; range -.67 to .81), indicating, on average across the group, a bilateral activation pattern in the temporal lobe. The lower limit for typical lateralization (mean – 2 SD) was -.62. Typical lateralization is therefore LI > -.62 (TYP_{comp}) and atypical lateralization is LI ≤ -.62 (REO_{comp}). Mean LI in the *Vowel Identification* task in the healthy control sample was .69 (SD .17; range .23 to .91), indicating, on average across the group, a left-dominant pattern of activation in the frontal lobe. The lower limit for typical lateralization was .35. Typical lateralization is therefore LI > .35 (TYP_{prod}) and atypical lateralization is LI ≤ .35 (REO_{prod}).

In the patient sample, for the *Beep Stories* task, 12/19 patients were classified as having typical lateralization, 7/19 as having atypical right-hemispheric lateralization. For the *Vowel Identification* task, 1/17 patients was classified as having typical left-lateralization, 16/17 as having atypical lateralization (Table 1). Thus, in our sample, only one patient demonstrated typical lateralization of language production. Therefore, hypotheses 1b, regarding the lesion factors driving reorganization of language production, and hypothesis 2, regarding the correlation between language production and comprehension, could not be investigated.

*3.2 Lesion types and lateralization of language **comprehension***

The two groups of patients (PL and MCA) differed significantly with respect to lesion sizes (PL: median mask volume 19.37 cm^3 vs. MCA: median mask volume 181.29 cm^3; exact p = .005, Mann-Whitney U-test). The two groups also differed with respect to the proportions of reorganized and typical lateralization of language comprehension: Reorganized language comprehension was found in 6 / 7 patients with MCA infarctions, but only in 1 / 11 patients with periventricular lesions (p= .0017; Fisher's exact test). Lesion sizes between patients with

reorganized vs. typical language did not differ significantly (mean lesion size TYP_{comp} 36.94 cm^3vs. REO_{comp} 101.21 cm^3; exact p = .482, Mann-Whitney U-test).

The alternative hypothesis, namely an effect of epilepsy on reorganization, either directly or mediated by lesion type, could not be substantiated in our sample: a) Reorganized language comprehension was not significantly more frequent in patients with epilepsy (4 / 6) as compared to patients without epilepsy (3 / 13; p = .09; Fisher's exact test). b) Epilepsy was not significantly more frequent in MCA (4 / 8) as compared to PL (2 / 11; p = .17; Fisher's exact test). c) Finally, when restricting the analysis to patients with MCA, there is no effect of epilepsy: Reorganized language was equally frequent in patients with epilepsy (3 / 4) as in patients without epilepsy (3 / 4). Since only 2 patients with PL had epilepsy, the same analysis could not be performed for the PL group.

*3.3 Lesion location and lateralization of language **comprehension**: VLSM*

Figure 2 shows the lesion overlap images of the two lateralization groups. Figure 3 illustrates the statistical comparison between the groups; the Liebermeister statistics (permutation-FWE [familywise error]-corrected significance threshold $z \geq 3.51$ for $p < .05$) revealed two areas which were affected significantly more frequently in the REO_{comp} than in the TYP_{comp} group. Specifically, these were the posterior insular cortex (z = 3.81; MNI coordinates: -43 / -13 / 10) and the supramarginal gyrus, extending dorsally into the inferior parietal lobule (z = 3.81; MNI coordinates of largest cluster: -51 / -33 / 27 extending to -51 / -36 / 42).

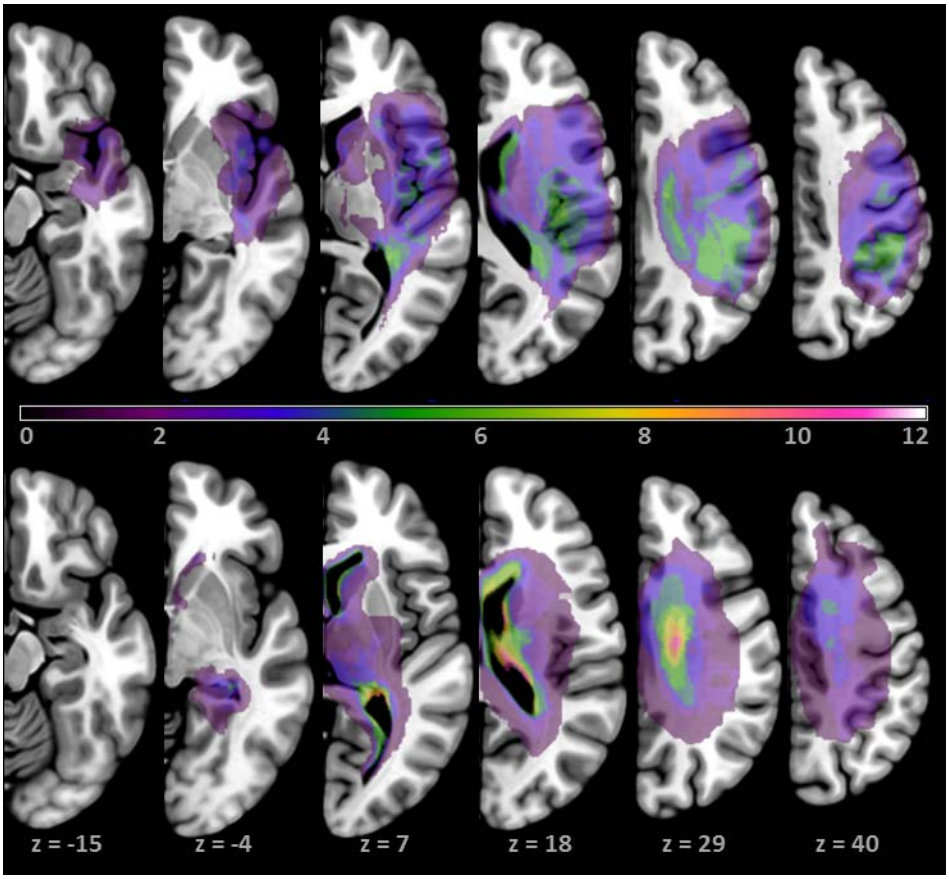

Figure 2. Summarized lesion masks overlaid on axial slices of MNI standard T1 template in radiological convention. Top: n = 7 patients with reorganization of language comprehension (REO_{comp}); Bottom: n= 12 patients with typical representation of language comprehension (TYP_{comp}).

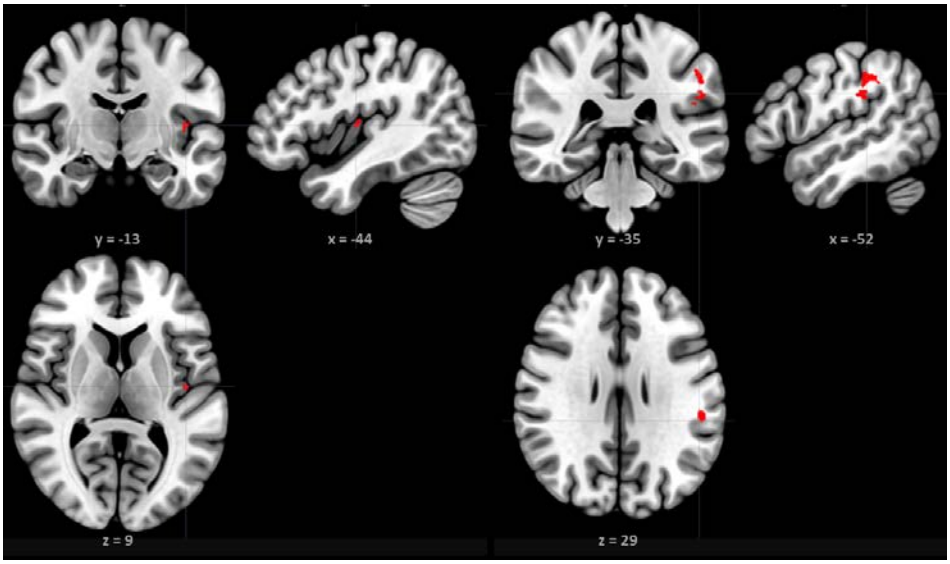

Figure 3. VLSM-results of statistical group comparison (REO_{comp} > TYP_{comp}), overlaid on axial, coronar and sagittal slices of MNI standard T1 template in radiological convention. Liebermeister statistics: $p < .05$, permutation-FWE-corrected for multiple comparisons. Left panel: posterior insula; right panel: supramarginal gyrus.

4. Discussion:

In a homogeneous sample of patients with pre-/perinatally acquired, exclusively left-hemispheric lesions, we could identify two predictors, namely lesion type and topography, for the reorganization of language comprehension.

Lesions caused by infarction of the left middle cerebral artery have a higher potential to drive atypical representation of language comprehension than lesions in the left periventricular white matter. The VLSM analysis further specified that this relation is topographical in nature, since lesions of the left temporo-parietal junction and the posterior insular cortex were significantly associated with the reorganization of language comprehension.

4.1 Lesion type and reorganization

Literature on patients with early lesions is surprisingly scarce on the matter of factors leading to right-hemispheric reorganization of language comprehension. The middle cerebral artery provides arterial blood supply for the whole perisylvian region, which is the centre of the language network (Price, 2012). Using dichotic listening, reorganized language (comprehension) was associated more with cortico-subcortical lesions involving the temporal lobe than with periventricular lesions (Brizzolara et al., 2002). To our knowledge, ours is the first study directly contrasting periventricular lesions with MCA infarctions with respect to reorganization of language comprehension in fMRI. Our analysis of lesion sizes revealed that patients with MCA infarctions had significantly more tissue loss in the left hemisphere than patients with periventricular lesions. Thus, in our sample, the effect of lesion type cannot be completely differentiated from lesion size. An important point with respect to networks is the fact that the (often large) MCA infarctions of our cohort have a higher potential to disturb or even destroy long-range association pathways than do the (often smaller) periventricular lesions in our cohort affecting mainly the cortico-spinal tracts. It seems, thus, very plausible that such larger lesions, directly and indirectly affecting both cortex and white matter, will

also affect a larger part of the language network. Such lesions will, as a consequence, very probably also be more likely to induce language reorganization than are smaller lesions. The non-significant difference of lesion sizes between patients with and patients without language reorganization, however, suggests that there must be more factors than just lesion size alone.

4.2 Lesion location and language reorganization: The dorsal language stream

The fine-grained result of our VLSM approach offers further insights into the process of language reorganization. Interestingly, and contrary to our initial hypothesis, both regions being more likely affected in patients with reorganized language can be attributed to the *dorsal* stream of language processing. The temporo-parietal junction has been considered as the sensorimotor interface of the dorsal stream, while the insular cortex is part of the articulatory network (Hickok & Poeppel, 2015). These regions are in close proximity to a subset of fibres of the superior longitudinal fascicle, linking the inferior parietal to the inferior frontal cortex (Catani & Bambini, 2014). Of note, insular involvement in language processing, namely articulation, usually concerns the anterior part of insular cortex (Ackermann & Riecker, 2010; Hickok & Poeppel, 2015), while we have identified a region in *posterior* insular cortex as trigger for reorganization. We will come back to this issue later in the discussion. Data on the maturation of the dorsal and the ventral language pathways in healthy children provides an intriguing framework for our results. While, generally, the dorsal stream seems to mature later than the ventral stream, the part terminating in premotor cortex (the superior longitudinal fascicle) is present already at birth (Brauer, Anwander, Perani, & Friederici, 2013) and is myelinated very early (Catani & Bambini, 2014). Above all, the auditory-to-motor mapping function provided by the superior longitudinal fascicle probably lies at the very beginning of speech and language acquisition, where the child aims at matching her babbling output to the environmental verbal input (Brauer et al., 2013; Hickok & Poeppel, 2015). Recently, the subset of fibres linking inferior parietal cortex to Broca's

area has even been associated with the precommunicative stage of language development, where children learn to identify a person as a relevant source of information (Catani & Bambini, 2014). It is therefore highly plausible that, in the scenario of a congenital lesion destroying an integral part of this pathway, the language system is forced into compensation right from the start – probably leading to a more comprehensive reorganization than in situations where language acquisition starts in the predetermined left-hemispheric networks, as it does in patients with periventricular lesions affecting only speech motor parts of the language system. This assumption is corroborated by a study on a sample of non-speaking children with cerebral palsy. Here, bilateral parieto-occipital white matter reduction associated with periventricular leucomalacia entailed the worst outcome regarding language comprehension (Geytenbeek et al., 2015). Thus, without compensatory potential in the contralesional dorsal language stream, language comprehension can be expected to be severely impaired, even in perinatally acquired brain lesions.

The posterior insula is usually associated with somatosensory or vestibular functions (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Shura, Hurley, & Taber, 2014), but rarely with language. The posterior insula is situated in close anatomical vicinity of the anterior insula and the primary auditory cortex (Heschl's gyri). Thus, it is possible that our posterior insula result may be owed to mislocation due to normalization and smoothing of the lesion masks. On the other hand, great care was taken to achieve an optimal overlap given these severely lesioned brains (cf. Fig. 1). Additionally, a blinded rater (MS) manually analysed all scans individually for intactness or lesion of posterior insula, planum temporale, and Heschl's gyri. The result of this post-hoc analysis reveals that in all seven patients with reorganized language, the lesion affected both the posterior insula and the planum temporale, while Heschl's gyrus was clearly lesioned in only 4 / 7 patients. On the contrary, only 1 / 12 patients with typical language had potential damage to planum temporale and posterior insula. The

literature does provide case reports of aphasic or dysarthric symptoms after lesions restricted to posterior insular cortex (Lemieux et al., 2012), and lesion analyses of aphasic symptoms mapped repetition disorders to lesions in the region of posterior insula and the internal capsule (Kreisler et al., 2000; Kummerer et al., 2013). Furthermore, the posterior insula plays an important role in respiratory activity during speech (Ackermann & Riecker, 2010). Thus, we will assume that the posterior insula location in our VLSM results is anatomically correctly located, and may be accompanied by lesions to the planum temporale (which is an integral part of primary auditory cortex) in the patients with language reorganization. Both results would indicate the lesion-induced impairment of a language precursor function as trigger for reorganization.

4.3 Language comprehension and language production: tightly linked in development

Having elaborated on the functions of the regions involved in the reorganization of language comprehension, it is, at first sight, irritating that these functions seem to be related to articulation more than to language comprehension. In the framework of the motor theory of speech perception (Liberman & Mattingly, 1985), however, this finding is not only not surprising anymore, it is, actually, to be expected. There is evidence that passive listening to speech sounds automatically and differentially activates the speech motor system (Fadiga, Craighero, Buccino, & Rizzolatti, 2002; Wilson, Saygin, Sereno, & Iacoboni, 2004) and, even more importantly, that perception of speech sounds can be disturbed and even altered by stimulation of the articulatory motor cortex (Bartoli et al., 2013; D'Ausilio et al., 2009). There is only sparse data on the role of the motor system in the development of speech perception, but a recent study using magnetoencephalography in infants demonstrated that infants as young as 7 months activated motor brain areas in response to speech sounds (Kuhl, Ramirez, Bosseler, Lin, & Imada, 2014). Cerebral palsy, which is associated with speech disability in many, but not all cases (Pennington et al., 2013), poses a good model to investigate language

development with normal vs. abnormal speech motor function: Children with cerebral palsy and associated articulatory problems seem to have a smaller receptive vocabulary than those without speech disability (Bishop, Brown, & Robson, 1990).

Another observation likely to contribute to the interpretation of our result is the fact that all patients with reorganized language comprehension had also reorganized language production. Typical representation of language production can co-occur with atypical representation of language comprehension in children and adolescents without brain lesion (Lidzba et al., 2011), and in patients with intractable epilepsy (Wilke et al., 2010; Kurthen et al., 1996). In our sample of patients with pre-/perinatal ischemic lesions, however, isolated reorganization of language comprehension just did not occur. Thus, our hypothesis that language production and language comprehension would typically be mediated by the same hemisphere was to be rejected. In fact, in our sample, lesions triggering the reorganization of language comprehension were always also associated with reorganization of language production, while language production could be reorganized independently of language comprehension. In contrast to this scenario, left-hemispheric frontal language production is often accompanied by bilateral or right-hemispheric language comprehension in patients with epilepsy (Korman et al., 2010; Wilke et al., 2010; Thivard et al., 2005). For these cases, we suggest the hypothesis that language was able to develop within largely intact networks for a significant period of time, until epilepsy started to disturb the aspects of language comprehension located in the left temporal lobe. The result of this scenario would be a predominantly right-hemispheric representation of language comprehension in the temporal lobes.

4.4 Limitations

Although our results, in conjunction with previous studies, fit well in a sound and plausible theoretical framework, there are some limiting factors in our study which warrant verification in future research. First of all, our sample size is small, which is a problem inherent in the

study of rare diseases such as pre-/perinatal stroke. On the other hand, we were able to investigate a well characterized and homogeneous sample of patients. Second, we did not assess language function on a behavioural level, so we are not able to contribute to the still cloudy picture of the quality of interhemispheric vs. perilesionally reorganized language (Francois et al., 2016; Ilves et al., 2014; Raja Beharelle et al., 2010). However, our aim was to identify, in a patient group which has repeatedly been reported to have largely preserved language function (Bates & Roe, 2001; Ilves et al., 2014), lesion characteristics forcing the brain into language reorganization. Third, epilepsy can influence brain plasticity and language reorganization. We explicitly tested the hypothesis that language reorganization is associated with epilepsy and did not find significant relations in our sample: Reorganization was not significantly more frequent in patients with epilepsy – neither in the whole sample, nor within the group with MCA infarctions. Epilepsy was, in our sample, also not significantly associated with lesion type, thus, our finding that MCA infarctions lead to language reorganization cannot be (solely) attributed to a higher probability of epileptic activity. As a last double-check, we repeated the VLSM analysis for the epileptic vs. non-epileptic patients post-hoc, revealing "epileptogenic" lesion sites. Supplementary figure S1 illustrates that, in our sample, lesions associated with epilepsy were topographically distinct from lesions associated with language reorganization, even at a low statistical threshold. Thus, while a certain influence of epilepsy cannot entirely be ruled out, lesion topography seems to play the decisive role in language reorganization. Next, the somewhat surprising finding that 16 / 17 patients were reorganized for language production can probably be explained by a sampling bias: We recruited patients who mostly came to medical attention because of a unilateral spastic cerebral palsy (18 / 19 cases). In children with cerebral palsy, damage to the motor system (i.e., motor cortex and / or cortico-spinal pathway) often affects also the facial motor tract, which, in turn, is highly associated with reorganization of language production (Staudt et al, 2001). Thus, we do not claim that the proportion of patients with reorganized language

production can be generalized to the whole population of patients with congenital left-hemispheric brain lesions. Fourth, the role of network damage for language reorganization would have, potentially, better been captured by the direct study of white matter tracts via diffusion MRI tractography. Unfortunately, diffusion MRI was not part of our initial protocol, but a confirmation of our findings by means of a diffusion study is warranted. Lastly, the age of our patients ranged from school-age to adulthood at the time of study. This could be a confounding factor, since there is evidence for a dynamic development of language lateralization during childhood and adolescence (Everts et al., 2009; Holland et al., 2007). In the domain of language perception, the effects of age on language lateralization are, however, much weaker (Karunanayaka et al., 2007) if not non-existent (Lidzba et al., 2011).

4.5 Conclusion

In our sample, reorganization of language comprehension was related to lesions at the temporo-parietal junction, particularly the supramarginal gyrus, and the posterior insular cortex. In the framework of modern theories of language acquisition, it is tempting to speculate that the integrity of the dorsal language pathway, especially the parts responsible for basal functions like sound-to-motor mapping, might be crucial for the beginnings of language acquisition. As a consequence, a congenital lesion of these structures in the left hemisphere may induce interhemispheric reorganization of the entire language network, including language comprehension.

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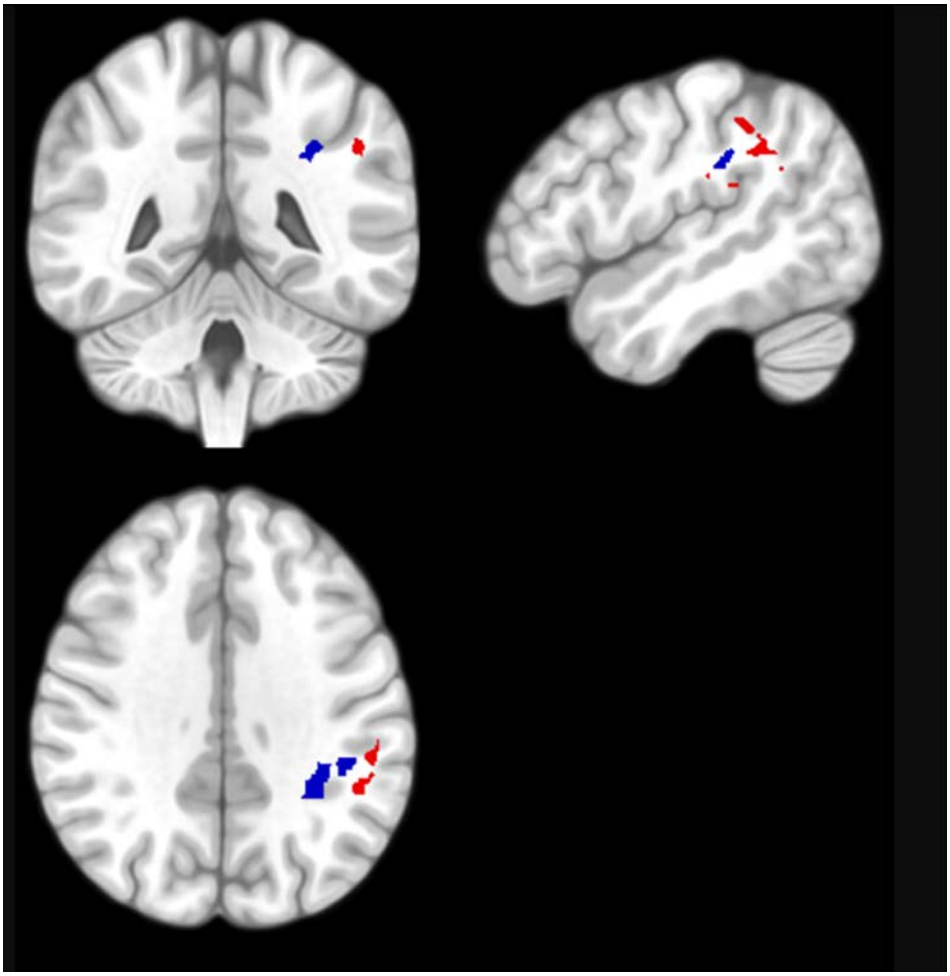

Supplementary Figure 1. Results of statistical group comparison epileptic vs. non-epileptic patients (in blue), in relation to the statistical group comparison REO_{comp} vs. TYP_{comp} (in red). Liebermeister statistics: $p < .05$, permutation-FWE-corrected for multiple comparisons.