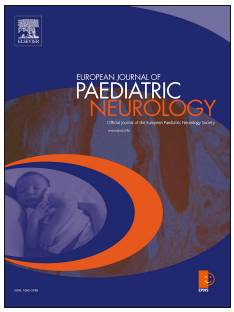
Journal Pre-proof



Cognitive development after perinatal unilateral infarctions: No evidence for preferential sparing of verbal functions

Alisa Gschaidmeier, Magdalena Heimgärtner, Lukas Schnaufer, Pablo Hernáiz Driever, Marko Wilke, Karen Lidzba, Martin Staudt

PII: S1090-3798(21)00227-0

DOI: https://doi.org/10.1016/j.ejpn.2021.12.007

Reference: YEJPN 2897

To appear in: *European Journal of Paediatric Neurology*

Received Date: 22 July 2021

Revised Date: 26 November 2021

Accepted Date: 9 December 2021

Please cite this article as: Gschaidmeier A, Heimgärtner M, Schnaufer L, Driever PabloHerná, Wilke M, Lidzba K, Staudt M, Cognitive development after perinatal unilateral infarctions: No evidence for preferential sparing of verbal functions, *European Journal of Paediatric Neurology* (2022), doi: https://doi.org/10.1016/j.ejpn.2021.12.007.

Cognitive development after perinatal unilateral infarctions:

No evidence for preferential sparing of verbal functions

Alisa Gschaidmeier[1,2*], Magdalena Heimgärtner[1], Lukas Schnaufer[1,3], Pablo Hernáiz Driever[4], Marko Wilke[1,3], Karen Lidzba[1,5], Martin Staudt[1,2]

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

[2]Center for Pediatric Neurology, Neurorehabilitation and Epileptology, Schön Klinik Vogtareuth, Germany;

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

[4] Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Department of Pediatric Oncology and Hematology, Germany;

[5]Division of Neuropediatrics, Development and Rehabilitation, University Children's Hospital Inselspital, Bern University Hospital, University of Bern, Switzerland.

*** Correspondence:**

Alisa Gschaidmeier, Center for Pediatric Neurology, Neurorehabilitation and Epileptology, Schön Klinik Vogtareuth, Krankenhausstraße 20, 83569 Vogtareuth, Germany;

agschaidmeier@schoen-klinik.de

Highlights:

- Prospective study on the cognitive development of verbal and nonverbal functions after perinatal strokes.
- In our cohort, we found no evidence for a differential effect of perinatal strokes on the development of verbal versus nonverbal functions, and, specifically, no evidence for a preferential sparing of verbal functions.
- Epilepsy, even when well-controlled, is a key risk factor for impaired language functions.

Abstract

Background:

Even children with extensive perinatal left-sided lesions have been reported to show normal language functions based on right-hemispheric language reorganization. This reorganization can lead to deficits in originary right hemispheric functions ("crowding hypothesis"). In a previous study, however, we identified epilepsy (even when well-controlled), and not language reorganization, as the major risk factor for impaired nonverbal functions. Here, we asked whether verbal and nonverbal functions develop differently, and whether they share the same risk factors.

Methods:

We investigated 23 patients (11f, Md=12.56years) with perinatal strokes (16 left-sided, 8 with epilepsy), and 23 healthy age-matched controls (8 f, Md=12.42years). Language functions were assessed using the Potsdam Illinois Test of Psycholinguistic Abilities, nonverbal intelligence with the Test of Nonverbal Intelligence, language lateralization with functional MRI, and lesion size with MRI-based volumetry.

Results:

We found no systematic difference between verbal and nonverbal skills in our patients or controls [median difference Z(PITPA)-Z(TONI): patients=-0.03, controls=-.06]. Accordingly, verbal and nonverbal functions were strongly correlated in patients (r=.80) and in controls (r=.74).
Language ability correlated significantly with epilepsy. Furthermore, in patients with epilepsies, verbal skills were significantly lower than in controls.

Conclusion:

In our cohort, we found no evidence for a differential effect of perinatal strokes on the development of verbal versus nonverbal functions, and, specifically, no evidence for a preferential sparing of verbal functions. Epilepsy, even when well-controlled, was confirmed as a single key risk factor for verbal functions.

Keywords:

Early brain lesion, functional magnetic resonance imaging, crowding hypothesis, language lateralization, cognitive performance

1 Introduction

Patients with perinatal left-sided infarctions have often been reported to show preserved language skills in most of its components, even in the case of extensive lesions destroying typical language areas in the left hemisphere (Teuber 1974, Rasmussen and Milner 1977, Strauss, Satz et al. 1990, Staudt, Grodd et al. 2001, Staudt, Lidzba et al. 2002, Lidzba, Staudt et al. 2006, Lidzba, Staudt et al. 2006, Lidzba and Staudt 2008, Lidzba, de Haan et al. 2017).
This remarkable resilience of language is achieved by a shift in language dominance to the contra-lesional right hemisphere (Rasmussen & Milner 1977). This shift of language to the right hemisphere has been hypothesized to impair originary right hemispheric cognitive functions such as nonverbal intelligence - the "crowding hypothesis" (Teuber 1974), assuming an interference effect due to limited capacity of the right hemisphere for its originary tasks *plus* language (Strauss, Satz et al. 1990).
If this hypothesis is correct, patients with right-sided lesions should also show deficits in nonverbal cognitive functions, assuming that these will not be reorganized to the left in order to preferentially spare left-hemispheric language. Hence, one would expect superior verbal versus nonverbal cognitive abilities irrespective of the side of the lesion.
Contrary to this hypothesis, however, we found no evidence for impaired nonverbal functions as a consequence of language reorganization in a previous study in survivors of perinatal stroke (Gschaidmeier, Heimgärtner et al. 2021). Instead, we identified epilepsy, even when well-controlled, as the major risk factor for impaired development of nonverbal functions. In the current study, we now compared verbal and nonverbal functions following perinatal unilateral infarctions and asked whether they share the same risk factors.

2 Methods

We investigated the same cohort as in our previous study (Gschaidmeier, Heimgärtner et al. 2021): 23 patients (11 females; age range 8 – 26 years; median age 12.56 years, 16 left-sided) with unilateral perinatally acquired unilateral arterial ischemic stroke (AIS) or unilateral periventricular hemorrhagic infarction (PVI) and 23 age-matched controls. Patients were defined as epileptic (n =8), when at least two afebrile, unprovoked seizures had occurred in the post-neonatal period (definition as suggested in (Raju, Nelson et al. 2007).)
Inclusion criteria were native German-speaking and a minimum age of 8 years. Patients with a previous diagnosis of intellectual disability (defined as IQ below 70) or with seizures during the last 6 months were excluded, as were subjects with contraindications for an MRI exam.
The study was approved by the local ethics committee (Nr. 693/2014B01). All adult participants and the parents of underage participants gave their written, informed consent. The study was in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964 in its latest version).

2.1 Neuropsychological protocol

The participants completed neuropsychological tests of verbal (P-ITPA) and nonverbal abilities(TONI-4). The Potsdam-Illinois Test for Psycholinguistic Abilities (P-ITPA) is a standardized test for psycholinguistic abilities, which focuses on language development and contains nine tasks for different language-relevant subscales. The participants completed the German edition (Esser and Wyschkon 2010). The Test of Nonverbal Intelligence, Fourth Edition (TONI-4) measures the ability for abstract reasoning and the problem-solving capability (Brown, Sherbenou et al. 2010). This test is especially suited for children with hand motor impairment, since none of the subtests requires bimanual manipulation.

2.2 Structural and functional magnetic resonance imaging (MRI)

Details were described in our previous study, briefly summarized: Lesion size was determined from structural 3D-MPRAGE datasets using a semi-automated approach (Rorden, Karnath et al. 2007). Language lateralization was determined for all patients with left-sided lesions by fMRI using the Vowel Identification Task (Wilke, Lidzba et al. 2006, Máté, Lidzba et al. 2016, Meinhold, Hofer et al. 2020). After calculating a bootstrapped lateralization index (LI) within the frontal lobe from the individual fMRI activation, patients were classified as "left-dominant" (LI > + 0.2), as "right-dominant" (LI < -0.2) or as "bilateral" (-0.2 ≤ LI ≤ + 0.2) (Lidzba, de Haan et al. 2017).

2.3 Statistics

The statistical analyzes were performed using SPSS 25. For correlation analyses, we used Spearman rank correlations and partial correlations (when controlling for age was appropriate). Significance was assumed at $p \leq 0.05$, two-tailed. The Shapiro-Wilk test was used to determine distribution normality (nonverbal intelligence p = .056; verbal abilities p = .331, difference (verbal-nonverbal intelligence) p = .771). We used the non-parametric Kruskal-Wallis test for group comparisons between three groups, corrected for multiple comparisons by Bonferroni correction, and the non-parametric Mann Whitney *U* Test for comparisons between two groups.
Since age-adjusted norms for the P-ITPA are not available for all tested age groups and to make the two tests comparable within our sample, we standardized the raw scores of both tests by building percentile ranks with the total of our study sample and converting them into z-scores afterwards (z standard scale: mean = 0, SD = 1). Correlations were controlled for age, since, as expected, age was significantly correlated with P-ITPA (Spearman Rank, r =.57, p < .001) and TONI-4 z-scores (Spearman Rank, r =.51, p < .001).

3 Results

Language skills differed between the three groups - patients with epilepsies (n = 8), patients without epilepsies (n = 15), and controls (n = 23) (Kruskal Wallis, H (2) = 10.66, n = 46, p = .005, d = 1.01). Pairwise comparisons demonstrated only one significant group comparison: patients with epilepsies showed significantly lower language skills than controls (p = .004, r = 0.58) (Figure 1A).
As reported in our previous article nonverbal intelligence also differed between the three groups (Kruskal Wallis, (H (2) = 8.36, n = 46, p = .015, d = .833), with patients with epilepsies scoring significantly lower than controls (p = .013, r = .51).
In patients, verbal functions correlated significantly with epilepsy (partial correlation, r = .53, p = .012), but not with lesion size (r=.18) or lesion side (partial correlation, r=.12). Furthermore, in patients with left-sided lesions, language lateralization did not correlate with verbal performances (partial correlation r =.15).
Verbal and nonverbal performances did not differ between the right- and left sided stroke group (verbal skills Mann Whitney, *U* = 44.000, exact p = .452, d = .339, nonverbal skills: Mann Whitney, *U* = 49.500, exact p = .671, d = .018).

To test our second hypothesis, we compared the z-scores of verbal (converted from P-ITPA raw scores) and the z-scores of nonverbal abilities (converted from TONI-4 raw scores). Verbal and nonverbal parameters were strongly and similarly correlated in patients without epilepsies (Spearman rank, r = .70, p = .004), in patients with epilepsies (Spearman rank, r = .78, p = .022), and in controls (Spearman rank, r = .74, p = .000), see Fig. 1B.
The difference between verbal and nonverbal performances [calculated as Z(verbal) – Z(nonverbal)] did not differ within the three groups (median difference in patients without epilepsies Md = -.11, SD

= .68; median difference in patients with epilepsies Md = .08, SD = .28; median difference in controls Md = -.06, SD =.62; Kruskal Wallis test: H (2) = .587, p = .75, d = .369), indicating a comparable relationship between verbal and nonverbal performances in all three groups (Fig. 2).

Figure 1:

A Comparison of verbal skills between the three groups: patients without epilepsies (n = 15, median z = -.04, SD = 0.54; blue), patients with epilepsies (n = 8, median z = -.70, SD = .50; red), and controls (n = 23, median z = .043, SD =.88; green). Patients with epilepsies differed significantly from controls (marked with *).

B Correlation between verbal and nonverbal skills, visualized as scatterplots of the three groups. The dashed line represents a perfect positive correlation (r =1.0).

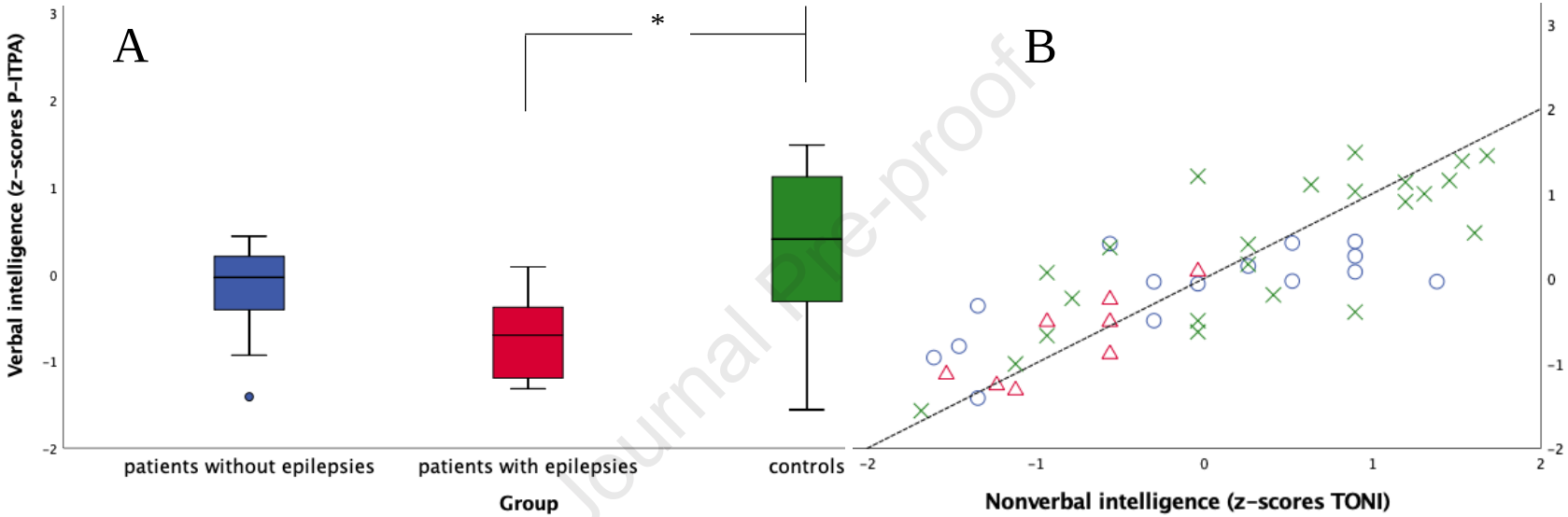
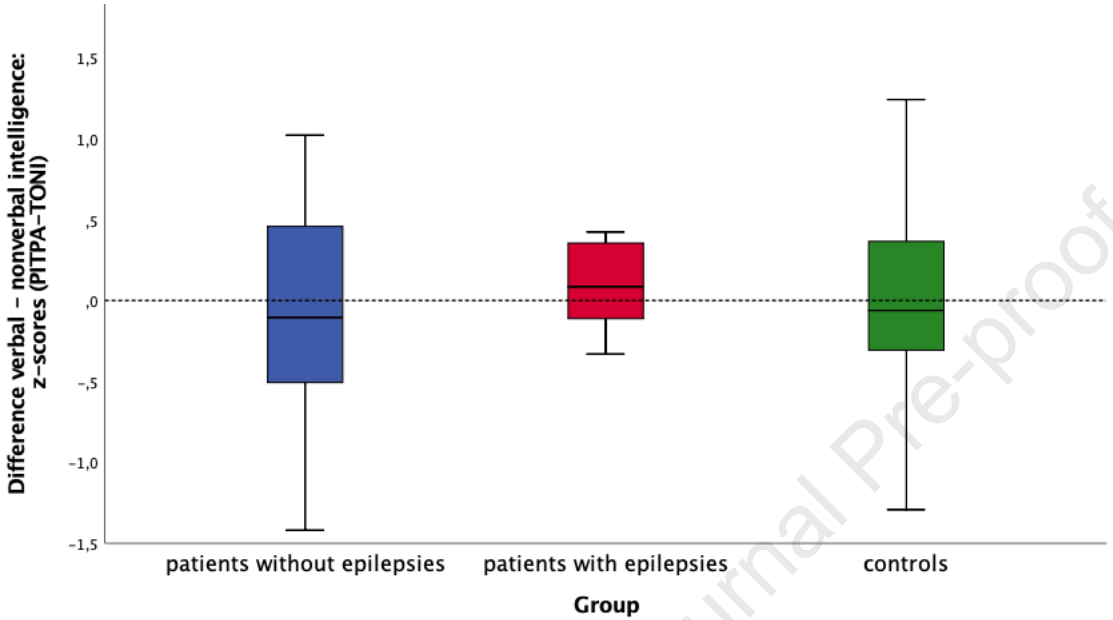


Figure 2:
Visualization of the difference between verbal and nonverbal functions, as measured with the z-Scores of P-ITPA (verbal functions) and TONI (nonverbal functions). A difference term > 0 indicates better verbal, a difference term < 0 indicates better non-verbal functions.



4 Discussion:

Our study had two major findings. First, in our cohort, we found no evidence for a differential effect of perinatal strokes on the development of verbal versus nonverbal functions, and, specifically, no evidence for a preferential sparing of verbal functions.
Second, in line with this finding, we confirmed epilepsy, even when well-controlled, as a key risk factor for impaired verbal skills. This had already been demonstrated for nonverbal cognitive abilities in the same sample of patients (Gschaidmeier, Heimgärtner et al. 2021).
In our cohort, verbal and nonverbal functions were strongly correlated, in the patient groups as well as in our group of typically developing controls (Fig. 1B). In healthy children, it is well known that verbal and nonverbal performances are correlated (Schneider and Bullock 2010). Our data demonstrate this correlation also in patients with perinatally acquired unilateral infarctions, indicating that, in these patients, neither verbal nor nonverbal functions are preferentially spared during cognitive development. This somewhat contradicts older studies proposing a relative sparing of verbal over nonverbal functions, especially studies supporting the crowding hypothesis (Teuber 1974, Rasmussen and Milner 1977, Strauss, Satz et al. 1990). This discrepancy may be explained by the fact that some of these studies used hand motor-dependent tests for measuring nonverbal functions, so that low scores in nonverbal cognition of hemiparetic children were possibly due to motor impairment rather than limitation of intelligence (Ballantyne, Spilkin et al. 2008, Westmacott, Askalan et al. 2010, van Buuren, van der Aa et al. 2013, Bajer, Hofer et al. 2020). Furthermore, many of these studies included patients with severely impaired cognitive functions and pharmaco-refractory epilepsies (Ballantyne, Spilkin et al. 2008, van Buuren, van der Aa et al. 2013, Bajer, Hofer et al. 2020). In contrast, the sample used in the present study only included participants with well-controlled epilepsies and patients without intellectual disability. Another reason may be that language reorganization to the right side does not compromise all nonverbal functions at the same extent, but affects specifically visuospatial functions (Lidzba, Staudt et al. 2006) as discussed earlier (Gschaidmeier, Heimgärtner et al. 2021).
Almost all previous studies reported a clinically surprisingly normal language development in most of its components after perinatal stroke (Staudt, Lidzba et al. 2002, Ilves, Tomberg et al. 2014). Our data are in line with these findings, especially in the absence of epilepsy. Age-adjusted norms for the P-ITPA were only available for 10 of our 23 patients (3 with, 7 without epilepsies). All were within the age range of the P-ITPA norms, with their T-scores for the spoken language composite ranging from 41-59 (corresponding IQ scores according to the test manual 85-100). Hence, at least all these 10 participants for whom formal reference data was available showed language skills in the normal range.
One of the most feared complications after perinatal stroke is the development of epilepsy. We previously showed that epilepsy is a key risk factor for impaired nonverbal intelligence in perinatal stroke patients and that even well-controlled epilepsies lead to impaired performances in nonverbal intelligence (Gschaidmeier, Heimgärtner et al. 2021). In line with the finding that verbal and nonverbal parameters are highly correlated, we confirmed well-controlled epilepsy as a key risk factor for impaired verbal performances as well. This supports the finding of other studies reporting impaired language development in case of (mostly refractory) epilepsies (Ballantyne, Spilkin et al. 2007, Ballantyne, Spilkin et al. 2008, van Buuren, van der Aa et al. 2013).
Limitations of our study include the following: We did not include patients with IQ < 70. Therefore, we have certainly underestimated the extent of the impairment of language functions caused by epilepsies. Furthermore, we could not provide population-based age-adjusted norms for all participants. Since the majority of the probands (13/23 patients, 13/23 controls) are over the age of the P-ITPA norm population of 11.5 years, we could not use the given norms. We accounted for this problem by calculating a z-standardization within our sample. We counterbalanced the age effect by

using the same test, notably its z-score, in age-matched controls. A ceiling effect, however, cannot be excluded in neither population.
Furthermore, some of the more elaborate language functions such as subtle grammar, narration, fine comprehension of nuances, use of the right word, however, have previously been reported to be more impaired than components allowing an appropriate exchange in everday life (Reilly, Wasserman et al. 2013, Lai and Reilly 2015, Dunbar and Kirton 2019). In this study, we did not perform analyses of such sub-categories.
Third, we have not collected data on the socioeconomic level (or some of its determinants, especially maternal education). Hence, we cannot exclude that our participants differ in the socioeconomic level, and we cannot add the socioeconomic level as a covariate in the multivariate model."
Fourth, our conclusions were based on a relatively small sample size (23 patients with perinatal strokes, 16 left sided). With the strict inclusion criteria, however, we were able to investigate a homogenous sample of patients.

5 Conclusion

In conclusion, we found no evidence for a preferential sparing of verbal over nonverbal functions - indicating that during cognitive development, neither function is preferred. Nonverbal and verbal cognitive functions share the same risk factors. Epilepsy, even when well-controlled, could be confirmed as a key risk factor not only for impaired nonverbal, but also for impaired verbal functions in our patient sample with perinatal stroke.

Conflict of Interest

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.

Funding

This research study was supported by the German Research Foundation (DFG LI1925/4-1).

Acknowledgments

PHD was supported through a BIH Clinical Fellowship by “Stiftung Charité”.

References

Bajer, C., W. Hofer, T. Pieper, M. Kudernatsch, H. Holthausen and M. Staudt (2020). "Correlates of intellectual development before and after hemispherotomy: an analysis of 75 children and adolescents." Epileptic Disord **22**(5): 571-581.

Ballantyne, A. O., A. M. Spilkin, J. Hesselink and D. A. Trauner (2008). "Plasticity in the developing brain: intellectual, language and academic functions in children with ischaemic perinatal stroke." Brain **131**(Pt 11): 2975-2985.

Ballantyne, A. O., A. M. Spilkin and D. A. Trauner (2007). "Language Outcome After Perinatal Stroke: Does Side Matter?" Child Neuropsychology **13**(6): 494-509.

Brown, L., R. J. Sherbenou and S. K. Johnsen (2010). Test of nonverbal intelligence: TONI-4, Pro-ed Austin, TX.

Dunbar, M. and A. Kirton (2019). "Perinatal Stroke." Semin Pediatr Neurol **32**: 100767.

Esser, G. n. and A. Wyschkon (2010). P-IPTA deutsche Fassung des Illinois test of psycholinguistic abilities, third edition (ITPA-3) von D.D. Hammill, N. Mather & R. Roberts : Manual.

Gschaidmeier, A., M. Heimgärtner, L. Schnaufer, P. Hernáiz Driever, M. Wilke, K. Lidzba and M. Staudt (2021). "Non-verbal Intelligence in Unilateral Perinatal Stroke Patients With and Without Epilepsies." Frontiers in Pediatrics **9**(515).

Ilves, P., T. Tomberg, J. Kepler, R. Laugesaar, M. L. Kaldoja, K. Kepler and A. Kolk (2014). "Different plasticity patterns of language function in children with perinatal and childhood stroke." J Child Neurol **29**(6): 756-764.

Lai, P. T. and J. S. Reilly (2015). "Language and affective facial expression in children with perinatal stroke." Brain and Language **147**: 85-95.

Lidzba, K., B. de Haan, M. Wilke, I. Krageloh-Mann and M. Staudt (2017). "Lesion characteristics driving right-hemispheric language reorganization in congenital left-hemispheric brain damage." Brain Lang **173**: 1-9.

Lidzba, K. and M. Staudt (2008). "Development and (re)organization of language after early brain lesions: capacities and limitation of early brain plasticity." Brain Lang **106**(3): 165-166.

Lidzba, K., M. Staudt, M. Wilke, W. Grodd and I. Krageloh-Mann (2006). "Lesion-induced right-hemispheric language and organization of nonverbal functions." Neuroreport **17**(9): 929-933.

Lidzba, K., M. Staudt, M. Wilke and I. Krageloh-Mann (2006). "Visuospatial deficits in patients with early left-hemispheric lesions and functional reorganization of language: consequence of lesion or reorganization?" Neuropsychologia **44**(7): 1088-1094.

Máté, A., K. Lidzba, T. K. Hauser, M. Staudt and M. Wilke (2016). "A "one size fits all" approach to language fMRI: increasing specificity and applicability by adding a self-paced component." Exp Brain Res **234**(3): 673-684.

Meinhold, T., W. Hofer, T. Pieper, M. Kudernatsch and M. Staudt (2020). "Presurgical Language fMRI in Children, Adolescents and Young Adults." Clinical Neuroradiology **30**(4): 691-704.

Raju, T. N., K. B. Nelson, D. Ferriero and J. K. Lynch (2007). "Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke." Pediatrics **120**(3): 609-616.

Rasmussen, T. and B. Milner (1977). "The role of early left-brain injury in determining lateralization of cerebral speech functions." Ann N Y Acad Sci **299**: 355-369.

Reilly, J. S., S. Wasserman and M. Appelbaum (2013). "Later language development in narratives in children with perinatal stroke." Dev Sci **16**(1): 67-83.

Rorden, C., H. O. Karnath and L. Bonilha (2007). "Improving lesion-symptom mapping." J Cogn Neurosci **19**(7): 1081-1088.

Schneider, W. and M. Bullock (2010). Human development from early childhood to early adulthood: Findings from a 20 year longitudinal study, Psychology Press.

Staudt, M., W. Grodd, G. Niemann, D. Wildgruber, M. Erb and I. Krägeloh-Mann (2001). "Early left periventricular brain lesions induce right hemispheric organization of speech." Neurology **57**(1): 122-125.

Staudt, M., K. Lidzba, W. Grodd, D. Wildgruber, M. Erb and I. Krageloh-Mann (2002). "Right-hemispheric organization of language following early left-sided brain lesions: functional MRI topography." Neuroimage **16**(4): 954-967.

Strauss, E., P. Satz and J. Wada (1990). "An examination of the crowding hypothesis in epileptic patients who have undergone the carotid amytal test." Neuropsychologia **28**(11): 1221-1227.

Teuber, H. (1974). Why two brains? in fo schmitt & fg worden (eds.), Neurosciences: Third study program (pp. 71-74), boston: mit press.

van Buuren, L. M., N. E. van der Aa, H. C. Dekker, R. J. Vermeulen, O. van Nieuwenhuizen, M. M. van Schooneveld and L. S. de Vries (2013). "Cognitive outcome in childhood after unilateral perinatal brain injury." Dev Med Child Neurol **55**(10): 934-940.

Westmacott, R., R. Askalan, D. MacGregor, P. Anderson and G. Deveber (2010). "Cognitive outcome following unilateral arterial ischaemic stroke in childhood: effects of age at stroke and lesion location." Developmental Medicine & Child Neurology **52**(4): 386-393.

Wilke, M., K. Lidzba, M. Staudt, K. Buchenau, W. Grodd and I. Krageloh-Mann (2006). "An fMRI task battery for assessing hemispheric language dominance in children." Neuroimage **32**(1): 400-410.

Cognitive development after perinatal unilateral infarctions: No evidence for preferential sparing of verbal functions

Alisa Gschaidmeier[1,2*], Magdalena Heimgärtner[1], Lukas Schnaufer[1,3], Pablo Hernáiz Driever[4], Marko Wilke[1,3], Karen Lidzba[1,5], Martin Staudt[1,2]

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

[2]Center for Pediatric Neurology, Neurorehabilitation and Epileptology, Schön Klinik Vogtareuth, Germany;

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

[4] Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Department of Pediatric Oncology and Hematology, Germany;

[5]Division of Neuropediatrics, Development and Rehabilitation, University Children's Hospital Inselspital, Bern University Hospital, University of Bern, Switzerland.

Highlights:

- Prospective study on the cognitive development of verbal and nonverbal functions after perinatal strokes.
- In our cohort, we found no evidence for a differential effect of perinatal strokes on the development of verbal versus nonverbal functions, and, specifically, no evidence for a preferential sparing of verbal functions.
- Epilepsy, even when well-controlled, is a key risk factor for impaired language functions.

-

Cognitive development after perinatal unilateral infarctions: No evidence for preferential sparing of verbal functions

Alisa Gschaidmeier[1,2*], Magdalena Heimgärtner[1], Lukas Schnaufer[1,3], Pablo Hernáiz Driever[4], Marko Wilke[1,3], Karen Lidzba[1,5], Martin Staudt[1,2]

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

[2]Center for Pediatric Neurology, Neurorehabilitation and Epileptology, Schön Klinik Vogtareuth, Germany;

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

[4] Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Department of Pediatric Oncology and Hematology, Germany;

[5]Division of Neuropediatrics, Development and Rehabilitation, University Children's Hospital Inselspital, Bern University Hospital, University of Bern, Switzerland.

*** Correspondence:**
Alisa Gschaidmeier, Center for Pediatric Neurology, Neurorehabilitation and Epileptology, Schön Klinik Vogtareuth, Krankenhausstraße 20, 83569 Vogtareuth, Germany;

agschaidmeier@schoen-klinik.de

Conflict of Interest

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.