



## Single Case Report

# Language development and brain reorganization in a child born without the left hemisphere



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## ABSTRACT

We present a case of a 14-year-old girl born without the left hemisphere due to prenatal left internal carotid occlusion. We combined longitudinal language and cognitive assessments with functional and structural neuroimaging data to situate the case within age-matched, typically developing children. Despite having had a delay in getting language off the ground during the preschool years, our case performed within the normal range on a variety of standardized language tests, and exceptionally well on phonology and word reading, during the elementary and middle school years. Moreover, her spatial, number, and reasoning skills also fell in the average to above-average range based on assessments during these time periods. Functional MRI data revealed activation in right fronto-temporal areas when listening to short stories, resembling the bilateral activation patterns in age-matched typically developing children. Diffusion MRI data showed significantly larger dorsal white matter association tracts (the direct and anterior segments of the arcuate fasciculus) connecting areas active during language processing in her remaining right hemisphere, compared to either hemisphere in control children. We hypothesize that these changes in functional and structural brain organization are the result of compensatory brain plasticity, manifesting in unusually large right dorsal tracts, and exceptional performance in phonology, speech repetition, and decoding. More specifically, we posit that our case's large white matter connections might have played a compensatory role by providing fast and reliable transfer of information between cortical areas for language in the right hemisphere.

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## 1. Introduction

The developing brain has a remarkable ability to reorganize and recover from injuries that would cause long-lasting impairments to the mature adult brain. This phenomenon has been experimentally established in animal studies showing that neuronal network reorganization after injury, in the form of synaptogenesis and pruning, is related to positive behavioral change in the neonate, but not in a similarly injured adult animal (for reviews see [Kolb & Gibb, 2014](#); [Sebastianelli et al., 2017](#); [Villablanca & Hovda, 1999](#)). The study of early effects of injury in the human brain *in vivo* was not possible until the advent of neuroimaging. Using functional and structural MRI, the reorganization of sensorimotor ([Graveline, Mikulis, Crawley, & Hwang, 1998](#); [Holloway et al., 2000](#); [Küpper et al., 2016](#); [Wakamoto, Eluvathingal, Makki, Juhasz, & Chugani, 2006](#); [Wilke et al., 2009](#)) and visual ([Mikellidou et al., 2017](#); [Muckli, Naumer, & Singer, 2009](#); [Werth, 2006](#)) systems has been well described in individuals who have suffered substantial focal injury early in life. Importantly, neuroimaging has enabled the study of brain reorganization after early injury for a uniquely human behavior, language. Unlike the adult brain, in which an insult to left perisylvian areas usually results in significant language impairment and moderate recovery, the developing brain is much more plastic such that the same insult results in low-normal to normal language performance ([Bates et al., 1997](#); [Levine, Raja Beharelle, Demir, & Small, 2016](#); [Stiles, Reilly, Levine, Trauner, & Nass, 2012](#)).

Here, we examine a case of a girl we have followed from 14 months to 14 years of age (Child 1; C1). She was born without a left hemisphere but nevertheless developed age-appropriate language skills. Her lesion is characteristic of hemispherectomy (HHE), a rare neurological condition characterized by the absence of a cerebral hemisphere due to presumed occlusion of a single carotid artery very early in gestation. In HHE, the cerebellum, pons, medulla, meninges, falx, basal ganglia, and thalamus are usually intact and the missing hemisphere is replaced by cerebrospinal fluid ([Pavone et al., 2013](#)). HHE is extremely rare, with only 9 cases reported in the literature to date (for a review see [Pavone et al., 2013](#)). Although contralesional motor dysfunction has been found in all reported HHE cases (including ours), cognitive and language functions are often spared, with 3 of the 7 cases who had cognitive assessment and 2 of the 6 cases who had language assessment showing no delays. Our case is unique in that we were able to gather detailed longitudinal data on her language and cognitive development.

The purpose of the current study was four-fold. First, we aimed to describe C1's language, literacy, and other cognitive skills across time, from 14 months to 14 years of age, using observational data and a large battery of standardized tests. These data allowed us to examine her strengths and weaknesses across many different aspects of language/cognitive functioning. None of the previous reports on HHE cases had included such an in-depth assessment of language skills.

Second, we aimed to describe structural brain reorganization in C1's single cortical hemisphere that developed in the absence of the entire contralateral hemisphere. To this end, we used diffusion weighted imaging (DWI), a technique that

enables the characterization of structural white matter connectivity in the brain. Using a graph theoretical approach, we investigated the topological properties of brain networks that developed in the right hemisphere without the presence of the left hemisphere. A great advantage of a graph theoretical approach is that it permits examination of global properties of the whole network, as well as local properties of specific network nodes of interest. By situating network properties within those of age-matched controls, and comparing their network properties to those in C1's right hemisphere, we explore for the first time how the human brain network reorganizes developmentally in the absence of one entire cerebral hemisphere.

Third, we aimed to describe how language is accommodated in a solitary right hemisphere. To do so, we used fMRI to examine functional activation during language processing in C1, and compared this activation to age-matched controls. The linguistic potential of the right hemisphere has been tested previously in individuals who have undergone hemispherectomy, the complete surgical removal and/or functional disconnection of a cerebral hemisphere typically during childhood to alleviate medically refractory epilepsy ([Griessenauer et al., 2015](#)). Left hemispherectomy patients occasionally demonstrate a shift in activation for language from left to right frontal areas ([Hertz-Pannier et al., 2002](#)), but these right homolog areas are not necessarily co-localized with the left areas seen either pre-surgically ([Voets et al., 2006](#)) or in controls ([Liégeois, Connelly, Baldeweg, & Vargha-Khadem, 2008](#); [Voets et al., 2006](#)). fMRI data, gathered while C1 listened to short spoken stories, allowed us to test whether she shows activation in the right homolog areas of the left inferior frontal gyrus and temporal lobe areas (areas activated bilaterally in normal controls), as do the previously studied hemispherectomy cases, or whether she shows a different pattern of reorganization.

Fourth, using DWI data from C1, we aimed to identify and characterize the major dorsal and ventral tracts associated with her language processing, and to compare her data to a group of age-matched, typically developing children. The importance of white matter tracts connecting frontal, temporal, and parietal areas for language has been demonstrated in adults ([Catani et al., 2007](#); [López-Barroso et al., 2013](#); [Teubner-Rhodes et al., 2016](#)) and highlighted in many neurobiological accounts for language ([Bornkessel-Schlesewsky, Schlesewsky, Small, & Rauschecker, 2015](#); [Catani & Bambini, 2014](#); [Friederici, 2012](#); [Hagoort, 2014](#); [Poeppl, 2014](#)). The integrity of these fiber pathways has been found to be associated with variation in performance on standardized language tests in children with perinatal stroke ([François et al., 2016](#); [Northam et al., 2018](#); [Yeatman & Feldman, 2013](#)). Given C1's normal range and, in some tasks, above normal range language performance, we hypothesized that the anatomical characteristics of these pathways would constitute candidate compensatory mechanisms for language in the right hemisphere.

In addition to situating our case within a group of demographically matched, typically developing children, we also compared her to her younger sibling and to three children with large left perinatal stroke lesions (L1, L2, L3). The comparison to her younger sibling (Sibling 1; S1) allowed us to

consider genetic and environmental factors shared between them that could have influenced C1's behavioral and brain development. The comparison to demographically matched cases with large left perinatal lesions allowed us to make inferences about the potential roles of very early lesion timing and very large lesion size. The maturational stage of the nervous system at the time of insult differs in these two conditions, with HHE occurring before the last trimester, and middle cerebral artery infarcts occurring late in the last trimester of gestation (Staudt et al., 2004).

To the best of our knowledge, this is the first time that longitudinal behavioral data, along with neuroimaging data on brain reorganization, has been described in an individual missing the entire left hemisphere from birth. This case thus provides a unique window on functional and neural plasticity and how it unfolds over time after an early brain injury that affects the entire left hemisphere.

## 2. Methods

### 2.1. Participants

The child who is the focus of this paper, C1, was enrolled in a longitudinal study on language development in typically developing children (TD) and children with perinatal brain injury (BI). Here we compare C1's performance to TD children, C1's younger sibling S1, who also participated in the longitudinal study, as well as three children with large left perinatal lesions (L1, L2, L3) from the same longitudinal cohort. Below we first describe the TD and BI children to provide the broader study context, and then present the case history for C1.

#### 2.1.1. Typically developing children

The control group consisted of sixty-four typically developing children, monolingual speakers of English without any physical, developmental, psychiatric or neurological impairment, and were selected to be representative of the greater Chicago area in terms of ethnicity and income. These children were followed longitudinally, as were the children with brain injury. Their data, along with normative data from standardized tests, provided us with a frame within which we could situate and interpret the case findings.

The study followed language development in children from child age 14 months to 13 years (for an overview see Goldin-Meadow et al., 2014). During middle school, the children were invited to participate in a brain imaging session. Twenty-two TD children, from the longitudinal cohort completed the imaging study. In order to increase the TD sample size for the imaging study, eight more children with no longitudinal data were recruited, making the total 30 for the TD imaging data. C1's sibling, S1, right-handed, male, 12 y; 5mo of age, also completed the imaging study. It should be noted here that sample size was set to the maximum possible given available resources and was not determined a priori.

All participants in the current study reported normal hearing and normal or corrected-to-normal vision. Parents gave written informed consent following the guidelines of the Institutional Review Boards for the Division of Biological Sciences at The University of Chicago, and the Office of Research

at the University of California, Irvine, which approved the study. Children gave verbal assent.

#### 2.1.2. Children with brain injury

The study followed a group of 40 children (21 girls) who suffered a brain injury resulting from hemorrhagic or ischemic perinatal stroke, as diagnosed by two pediatric neurologists with the support of MRI and/or CT scans. The children were recruited through pediatric neurologists and parent support groups in the greater Chicago area (Childhood Stroke and Hemiplegia Connections of Illinois, CSHC; Pediatric Stroke Network, PSN; and Children's Hemiplegia and Stroke Association, CHASA). Inclusion criteria were: (1) the presence of unilateral perinatal brain injury and (2) being raised as a monolingual speaker of English.

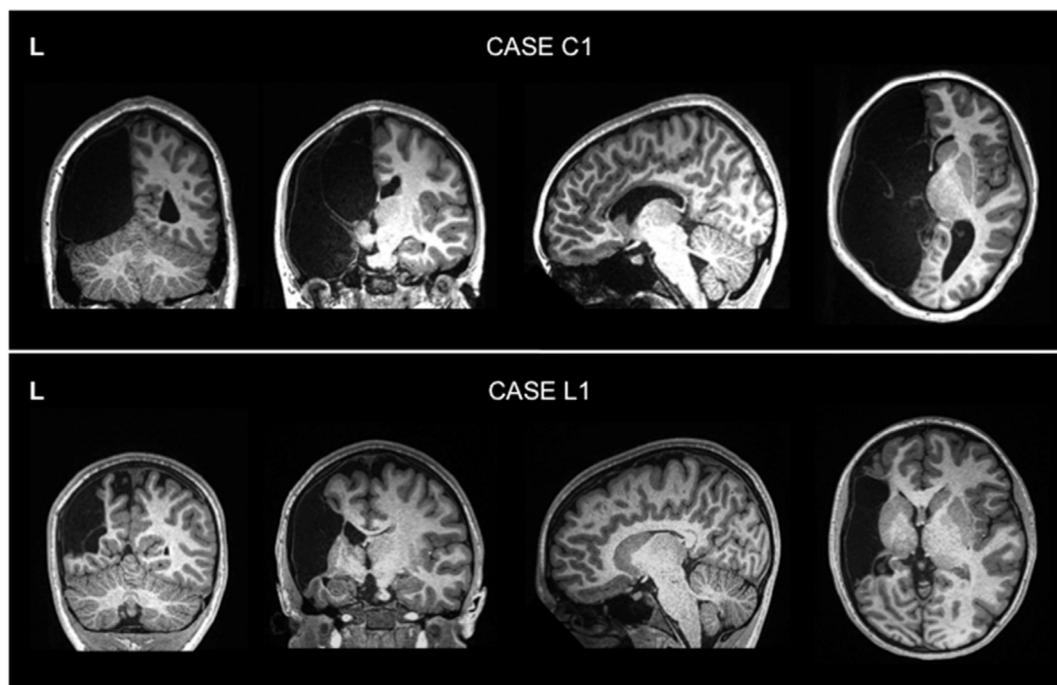
To test the effect of large left hemisphere lesions on language development, we compared C1 to the three other cases with large left perinatal lesions (L1, L2, L3) from the same longitudinal cohort. We defined lesions as large when they affected three or more lobes; a total of 20 BI children's lesion matched this definition. Out of these 20, three cases were selected that best matched C1's characteristics. Their lesions affected the left perisylvian areas, the left inferior frontal gyrus and inferior parietal lobule, most likely the result of middle cerebral artery infarction. This type of infarction is assumed to occur during the last trimester of gestation. All were left-handed, most likely due to their right hemiparesis, and were female. Importantly, like C1, the three comparison cases with large left lesions did not have a history of seizures and did not differ from C1 in socioeconomic status (SES).

Eight children with brain injury, including C1 (Fig. 1, top) and one of the comparison children, L1 (Fig. 1, bottom), took part in the imaging study. C1's language development trajectory, in combination with the extent of her lesion, which included the whole left hemisphere, led us to study her more closely. Results from previous studies have found that children with large perinatal lesions tend to have poor cognitive outcomes, compared to children with medium and small lesions (Brizzolara et al., 2002; Demir, Levine, & Goldin-Meadow, 2010; Levine, Kraus, Alexander, Suriyakham, & Huttenlocher, 2005; Rowe, Levine, Fisher, & Goldin-Meadow, 2009) which makes C1 an important case to examine.

### 2.2. Case history

C1 is a white non-Hispanic female, raised as a monolingual speaker of American English in a high SES background family (maternal years of education: 18 corresponding to a graduate degree). She is left handed, likely due to right hemiparesis. She was born at full-term (41 weeks of gestation) without any complications during pregnancy, labor, or delivery (Apgar score of 9). During her first seven months, she had had pneumonia, ear infections, and reflux, but no surgeries or seizures. She was first referred to physical therapy at seven months because of a persistent infolding of the right thumb (cortical thumb), decreased range of motion in the right arm, leg and foot, and delayed developmental milestones.

MRI of the brain at 10 months demonstrated an absent left cerebral hemisphere secondary to a large infarction (Fig. 1, top). The corpus callosum was thinned and almost absent; a



**Fig. 1 – Coronal, axial and sagittal views of C1 and L1 from the T1-weighted imaging scan.**

small portion of the left thalamus was identified while the left basal ganglia were not; the cerebellum was normal; the left side of the brainstem was small; the right cerebral hemisphere was within normal limits. There was no evidence of cerebral parenchyma, or flow voids representing vessels supplying the infarcted left cerebral hemisphere.

MR Angiography (MRA) of the brain at 10 months demonstrated absence of the intracranial vessels supplying the left cerebral hemisphere. MRA of the neck revealed normal vertebral arteries, right common carotid artery and its branches, normal left common carotid artery, normal left external carotid artery, and a left internal carotid artery ending in the A1 segment of the left anterior cerebral artery. MR Venography of the brain showed no evidence of venous thrombosis. Neurological examination at 10 months revealed severe right hand paresis, right hemineglect, right homianopsia, and minimal right leg paresis with tight heel cord. Cardiological examination results (physical examination, electrocardiogram, and echocardiogram) were normal.

Based on the extent of the lesion and the fact that the infarct involved the left internal carotid artery rather than the middle cerebral artery, we identified C1 as a case of hemihydranencephaly. Hemihydranencephaly (HHE) is a rare neurological condition in which one brain hemisphere is missing, presumably due to unilateral vascular anomaly, most likely occlusion of the ipsilateral carotid artery occurring early in gestation. This type of damage is assumed to occur after neural migration has started and before the onset of synaptogenesis (Ulmer et al., 2005).

C1 has received extensive support throughout her development. She started receiving weekly physiotherapy (PT) at 7 months, occupational therapy (OT) sessions at 8 months, and speech therapy (ST) at 30 months of age and continued until

4th grade. After that, she consulted for PT and OT as needed (about 4 times/year for PT and OT), and did not receive ST anymore by the time of MRI testing. With respect to her educational course, at age 3 she began attending a public preschool and then school for children with and without special needs, while from 6th grade she started having an Individualized Education Plan (IEP) which provided her with any needed accommodations in classroom (e.g., extra time on tests). Although we did not perform a clinical assessment of C1's gait, visual and motor functions, at 13 years of age we assessed her manual dexterity and visuo-motor coordination using the Purdue Pegboard task. C1 completed the task with her dominant hand in 70 sec, well within the TD group mean [TD mean ( $\pm$ SD) = 72.49 ( $\pm$ 10.75), range = 53–102, with dominant hand].

### 2.3. Procedure

#### 2.3.1. Behavioral measures

As described earlier, case C1 and the other children were participating in a longitudinal study of language development (for a detailed description, see Goldin-Meadow et al., 2014). The longitudinal study includes data collected between child ages 14 months to 13 years of age. The data collected included naturalistic data from videotaped natural child–parent interactions as well as data from a wide range of standardized tests, questionnaires and unstandardized measures of language, reading, math, spatial, working memory and IQ. For the purposes of the current paper we focused on a subset of the language measures collected between ages 14 months and 13 years. These measures are described below in detail (see Table 1 for a summary). Note that not all TD children completed all of the measures at all time points. Missing data were due to

**Table 1 – Language and non-language cognitive tasks administered between 14 months and 13 years of age.**

Skill Area	Measure	Description	TD ages when assessed
Vocabulary	Naturalistic Data: Word Types	Number of different word types produced based on the transcripts of each home visit	14, 18, 22, 26, 30, 42, 54 months
	MacArthur Communicative Development Inventory (CDI) Words and Sentences	Parents asked to identify the words the child has understood or used	18, 22, 26, 30 months
	Peabody Picture Vocabulary Test – Third Edition (PPVT-III)	Multiple-choice task, children asked point to one of four pictures that matches an orally-presented word	30, 42, 54 months, 8 years, 12 years
Syntax	MacArthur Communicative Development Inventory (CDI) Words and Sentences	Parents asked to provide written examples of the child's three longest sentences	18, 22, 26, 30 months
	Syntax Comprehension (Huttenlocher, Vasilyeva, Cymerman, & Levine, 2002)	Multiple-choice task, children asked point to one of three pictures that depicts the relation in the orally presented sentence	14, 18, 22, 26, 30, 42, 54 months
	Clinical Evaluation of Language Fundamentals – Fifth Edition (CELF-5) Formulated Sentences subtest	Children asked to formulate complete, semantically and grammatically correct spoken sentences of increasing length and complexity, using given words and contextual constraints imposed by illustrations	9, 10, 12 years
Discourse	Clinical Evaluation of Language Fundamentals - Fifth Edition (CELF-5) Recalling Sentences subtest	Children listen and repeat sentences of increasing length and complexity without changing meaning, content or structure	9, 10, 12 years
	Narrative production	Children watch a wordless cartoon and retell what they have seen	6 years
Phonology	Woodcock-Johnson IV Test of Achievement (WJ-IV) Verbal Comprehension subtest	Children name pictures, give antonyms or synonyms for spoken words, and complete oral analogies	12 years
	Comprehensive Test of Phonological Processing – Second Edition (CTOPP-2) Ellision subtest	Children remove phonological segments from spoken words to form other words	6, 7 years
Reading decoding	Woodcock-Johnson IV Test of Achievement (WJ-IV) Word Attack subtest	Children read nonsense words (e.g., plurp, fronkett) aloud to test phonetic word attack skills	8 measurements between 7 and 10 years
	Woodcock-Johnson IV Test of Achievement (WJ-IV) Letter-Word Identification subtest	Children name letters and read words aloud from a list to test decoding skills	8 measurements between 7 and 10 years
Reading comprehension	Woodcock-Johnson IV Test of Achievement (WJ-IV) Passage Comprehension subtest	Children read sentences and decide on a word that is needed to fill in the blank to make the sentence complete.	7, 8 years
	Gates–MacGinitie Reading Test Comprehension subtest	Children read written passages related to various content areas and asked multiple-choice comprehension questions about each passage	9, 10 years
Mathematics	Woodcock-Johnson IV Test of Achievement Calculation subtest	Children complete a worksheet of calculations of increasing difficulty	9, 10 years
	Woodcock-Johnson IV Test of Achievement Applied Problems subtest	Children solve math word problems that were read to the child	9, 10 years
Short-term Memory	Digit Span	Children presented with an oral sequence of numerical digits and asked to repeat the sequence in the correct order	8, 9 years
Spatial skill	Kaufman Assessment Battery for Children (KABC) Triangles subtest	Children assemble foam triangles to match a picture	8, 9 years
Nonverbal Reasoning	Raven's Progressive Matrices	Children presented with visual geometric patterns and asked to select missing piece that completes the pattern	12 years

families missing a visit, to a task not being administered in a given visit due to child fatigue or experimenter error, and in later years to attrition. The number of TD children contributing to each measure is noted in [Supplementary Material Table S1](#). We also included behavioral data from S1, L1, L2, and L3 when available (these children did not complete all of the tasks).

### 2.3.2. Imaging

In addition to the home visits, during middle school, children were invited to participate in a brain imaging session designed to study the effects of early input and other factors on brain structure and function for language. Eight children with BI, including C1 and L1, participated in the imaging study. C1 was 14 y; 2 m old when she participated in the imaging study. L1, the only comparison case in the imaging part of the study, participated at age 13 y; 0 m. Only twenty-three TD children from the longitudinal cohort for whom we had behavioral data completed the imaging study, along with the 8 additional TD children recruited to increase sample size. In total 30 TD children (age range: 11–15 years; mean  $\pm$  SD: 13 y; 7mo  $\pm$  9.6mo; 5 left-handed; 17 males) participated in the imaging study. The children came primarily from high SES background families (years of maternal education range: 10–18 years, mean  $\pm$  SD: 16 y  $\pm$  2 y). Although we acquired imaging data from S1, the sibling of C1, we did not include him in the TD group to avoid biasing case – control comparisons.

Imaging data were collected during a single session. Participants provided verbal assent, went through the MRI safety screening, and completed the short training and handedness questionnaire before going into the scanner. The DWI data were acquired last as part of a longer scanning session in which resting-state fMRI and an audio-visual task were also performed.

### 2.3.3. fMRI task

The fMRI stimuli consisted of 40 pairs of two-sentence “stories”. The pairs of stories were identical apart from 1 to 3 words in the second sentence (target), which rendered half of stories less coherent given the preceding sentence (context) (e.g., “Lindsey loved warm weather. Summer was her favorite season” vs “Lindsey loved warm weather. Winter was her favorite season.”). Since we were interested primarily in regular sentence comprehension, we excluded all target sentences that did not match the context sentences from the current analysis. The stories were recorded by a native speaker of Standard American English. Participants were presented with audio stories in an event-related fMRI design. In each trial, the context sentence was presented followed by a jittered inter-stimulus interval and then the target sentence. Trials were separated by a jittered inter-trial interval. In some cases the target would be followed by a catch trial, in which participants would hear a statement regarding the story that they had just heard (e.g., “The story mentioned a math problem.”: “TRUE” or FALSE ?”). Participants responded by pressing a button with their dominant hand. The purpose of the catch trials was to keep participants engaged in the task. Participants received a short training session outside the scanner to familiarize them with the task. Inside the scanner, they were instructed to

listen carefully to the stories – no explicit semantic judgment task was required. The fMRI task was split into two runs of ~10 min each.

### 2.3.4. Image acquisition

MRI data were acquired on a 3 T Siemens Prisma scanner with a 32-channel head-coil on the medical campus of Northwestern University. A T1-weighted structural scan was acquired for each participant with TR = 2300 msec, TE = 1.91 msec, flip angle = 7°, Inversion Time = 1100 msec, and 208 contiguous sagittal slices (slice thickness = .8 mm, voxel size = .8  $\times$  .8  $\times$  .8 mm<sup>3</sup>, matrix size = 256  $\times$  256). The functional T2\*-weighted images were acquired using an echo-planar sequence with TR = 2000 msec, TE = 25 msec, flip angle = 80°, and 64 axial slices in ascending order (slice thickness = 2 mm, voxel size = 2  $\times$  2  $\times$  2 mm<sup>3</sup>, matrix size = 832  $\times$  784). We also acquired diffusion weighted imaging (DWI) data using a single-shot pulsed gradient spin-echo sequence (TR = 4000 msec, TE = 68 msec, flip angle = 90°). The diffusion weighting orientations were isotropically distributed along 60 directions with two b-values of 1,000 sec/mm<sup>2</sup> and 2,000 sec/mm<sup>2</sup>. Seventeen volumes without diffusion weighting (b-value of zero) were acquired, interspersed into the sequence. A total of 137 slices covering the whole brain were acquired (voxel size = 1.5  $\times$  1.5  $\times$  1.5 mm<sup>3</sup>).

## 2.4. Analysis

### 2.4.1. Behavioral analysis

As a first pass comparison of C1 to the TD children in our sample, we determined whether she performed below the 25th percentile (1st quartile), within the interquartile range, or above the 75th percentile (3rd quartile) of our TD sample. To compare C1’s performance to test norms, we follow a standardized psychometric conversion table ([Psychometric conversion table, 2011](#)). We examined C1’s performance on standardized language tasks using percentiles and her performance on experimental language tasks using z-scores.

To examine whether case C1’s performance on the language and cognitive tests was significantly below the average score for the TD children in the sample, we followed the reporting standards for case studies suggested by [Crawford, Garthwaite, and Porter \(2010\)](#). We performed two-tailed t-tests for case–control comparisons ([Crawford & Howell, 1998](#)); we estimated effect sizes using the ratio of the difference between the case score and the average TD control score divided by the standard deviation in the control group (denoted as Zcc); we used Bayesian interval estimates with Monte Carlo simulations to obtain point estimates of the percentage of the TD control group that would obtain less extreme (higher or lower) scores than the case ([Crawford & Garthwaite, 2007](#)), and estimated their respective 95% confidence intervals (Singlims\_ES.exe and SingleBayes.exe from <http://www.abdn.ac.uk/~psy086/dept/Programs/>). While Bayesian point estimates are very informative, we base our conclusions on significance testing in order to keep inference making consistent across the different analyses.

### 2.4.2. fMRI analysis

Additional steps were taken before preprocessing the data from C1 and L1, including: (1) drawing a lesion mask on the T1-weighted structural scan and (2) performing “Virtual Brain Transplantation” (Solodkin et al., 2010) to replace the lesion with anatomically realistic “transplant” tissue and to adjust for post-stroke gross morphological changes. The virtual transplant provided missing anatomical landmarks necessary for applying alignment, segmentation, cortical reconstruction, and parcellation algorithms.

The MRI data were preprocessed using AFNI (Analysis of Functional Neuroimages, Version AFNI\_17.3.07; <http://afni.nimh.nih.gov>; Cox, 1996). The individual time series were despiked (3dDespike), slice-time corrected (3dTshift) and aligned to standard space by computing: (1) the T1 to EPI transforms (3dAllineate); (2) the T1 to a pediatric MNI transforms (average of ages 10–14 years; Fonov et al., 2011) (@auto\_t1rc); and (3) the EPI functional volumes to an EPI base image transforms (3dVolreg). We concatenated the transformation matrix (2) and the inverse of matrices (1) and (3) and applied the resulting transformation to all the functional volumes. Functional data were then iteratively smoothed until they reached smoothness of 8 mm full width at half maximum in each x, y, z direction (3dBlurtoFWHM). Lastly, the smoothed functional data were scaled to a mean of 100 (3dCalc).

Since pediatric populations are more prone to motion artifacts during language tasks (Yuan et al., 2009), we implemented strict motion controls by censoring (i) time points with Euclidean norm of the motion derivatives exceeding .2 mm (1d\_tool.py) and (ii) time points with intensity outlier fraction exceeding .1 (3dToutcount). Four TD control participants were excluded due to 30% or more of their time points being censored.

**2.4.2.1. FIRST LEVEL fMRI ANALYSIS.** The percent signal change at each voxel was modeled using ordinary least squares linear regression (3dDeconvolve) with the three sentence types (context, predictable, unpredictable) as predictors, six motion parameters, trials of no interest (instructions, ISI, catch trials and button presses), average white matter and ventricle signal as nuisance regressors, and three polynomial terms (constant, linear, quadratic) for modeling the baseline. The hemodynamic response for the sentence types and trials of no interest was modeled from the event onset convolved with a duration modulated block function with fixed peak response amplitude of one. Outliers and time points that did not meet our motion criteria (see above) were censored at this step.

In order to examine individual variation in the activation patterns of TD control participants and to visually compare them to C1 and L1 activation patterns, we also estimated the first level statistics in each participant’s native space. This was done by not transforming the functional volumes to MNI space before running the linear regression. The estimated t-statistics for the story > baseline condition were transformed into z-statistics and thresholded individually at voxelwise  $p = .001$ , FWE = .05 (3dClustSim). We used the Connectome Workbench platform (version 1.3.1) (Marcus et al., 2011) to project the thresholded z-stat data from volume space to the individual’s cortical surface space, reconstructed with

Freesurfer (v5.3.0) using the T1-weighted image. The surface-based z-maps were then registered onto a standard surface mesh (with 163 k vertices), binarized and overlaid on the Freesurfer average inflated cortical surface to create activation conjunction maps. These conjunction maps allowed us to visualize the number of TD control participants that showed activation in a cortical area for our contrast of interest, providing complementary information on individual variation not captured in average group activation maps.

**2.4.2.2. SECOND LEVEL fMRI ANALYSIS.** The estimated beta weights for the sentence/story condition from the first level analysis (percent signal change in context and target sentences relative to baseline) were entered in a one-sample t-test on the sentence versus baseline beta weights for control participants. In this case, thresholding was performed using AFNI’s 3dttest++’s -Clustsim option (voxel-wise  $p = .001$ , FWE = .05,  $k = 78$ ).

We performed two singleton independent t-tests (3dttest++) to assess the difference between activation in case C1 and TD controls, between case L1 and TD controls and between sibling S1 and TD controls; this is done by normalizing the difference by the standard deviation in TD controls and a scale factor making Student’s t the distribution of the null hypothesis. The resulting t-maps were thresholded using a Monte Carlo simulation (3dClustSim with 10,000 permutations) to estimate the minimum cluster size ( $k = 70$ ) needed for a voxel-wise threshold of .001 and a family-wise error (FWE) p-value of .05 (estimated using 3dFWHMx; Cox, Chen, Glen, Reynolds, & Taylor, 2017).

### 2.4.3. DWI analysis

The diffusion data were preprocessed using FSL’s eddy current correction (mean relative displacement = .8, SD = .16, range = .51 – 1.32; C1 = .95; L1 = .92; S1 = 1.09); the tensors were fitted using linear least-squares and the apparent diffusion coefficient, fractional anisotropy (FA), and radial diffusivity were estimated with the Diffusion Toolkit (Wang, Benner, Sorensen, & Wedeen, 2007). The high resolution T1 was segmented and parcellated into 83 cortical and subcortical areas with Freesurfer (v5.3.0) using the Lausanne 2008 atlas scheme (Hagmann et al., 2008). Tractography was performed using the FACT (Fiber Assignment by Continuous Tracking) method (Mori, Crain, Chacko, & Van Zijl, 1999), seeding randomly from 16 different voxels in each area. Tracking was terminated when a streamline had an angle larger than  $\pm 60^\circ$  degrees or if FA value was lower than .2. Lastly, streamlines were spline filtered to smooth and clean them up.

The structural connectomes were computed with Connectome Mapper (Daducci et al., 2012) to construct  $83 \times 83$  connectivity matrices in which matrix entries consisted of the number of streamlines connecting pairs of areas. The connectomes were analyzed using a graph theoretical approach with each brain area representing a network node, and density of streamlines connecting pairs of nodes representing the edge. To maintain the same number of edges across each subject, the adjacency matrices were thresholded keeping only the upper 30% of total possible connections. We used the Brain Connectivity Toolbox (Rubinov & Sporns, 2010) to estimate

global and nodal graph theoretical network measures in our weighted, undirected connectivity matrices. With respect to global measures, we focused on network density (a ratio of existing edges to all possible edges in a network), efficiency (the average inverse shortest path length in the network), and modularity (the number of within-module connections to all connections, a measure of subdivision of a network to modules/sub-networks) of C1's solitary right hemisphere and compared it to our TD controls' right and left brain scores. Regarding nodal measures, we focused on degree centrality (the sum of edges connected to a node), betweenness centrality (the number of shortest paths that pass through a node) and nodal efficiency (how well neighboring nodes are connected once a node is removed from the network) in the right homolog areas of the key language network regions defined in Chai, Mattar, Blank, Fedorenko, and Bassett (2016) and Fedorenko and Thompson-Schill (2014), which included the three parts of the left inferior frontal gyrus (IFG) [pars opercularis (IFGop), pars triangularis (IFGtri), pars orbitalis (IFGorb)], as well as the left superior temporal gyrus (STG), and the left middle temporal gyrus (MTG).

Lastly, we used the tractography output to virtually dissect the direct arcuate fasciculus (AF), the anterior part of the arcuate fasciculus (aAF), the inferior fronto-occipital fasciculus (IFOF), the inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UF) in the right hemisphere for C1 and L1, and bilaterally in controls. We followed Wakana et al.'s (2007) two ROI approach, as well as the three ROI approach by Kamali, Flanders, Brody, Hunter, and Hasan (2014) for the aAF, by drawing each ROI by hand in each participant's native space using TrackVis. Once dissected, the average tract volume was extracted and normalized as a percentage of hemispheric volume (white and grey matter). This was performed to avoid biasing tract volume measures especially since C1's right hemisphere was very large (546775 mm<sup>3</sup>) compared to the TD average [LH mean ( $\pm$ SD) = 499951 mm<sup>3</sup> ( $\pm$ 43,831); RH mean ( $\pm$ SD) = 500394 mm<sup>3</sup> ( $\pm$ 44,467)]. The normalized tract volume was therefore used for statistical comparisons. We also estimated each tract's lateralization index using the following formula:  $LI = \text{Volume}_{\text{LEFT}} - \text{Volume}_{\text{RIGHT}} / \text{Volume}_{\text{LEFT}} + \text{Volume}_{\text{RIGHT}}$  in the TD control group and tested its significance with One Sample t-tests.

Case-control comparisons were performed following the same procedure (Crawford et al., 2010) described in the behavioral analysis (2.4.1).

## 3. Results

### 3.1. Behavioral results

The purpose of the behavioral analysis was to describe C1's longitudinal performance on different aspects of language, as well as other cognitive domains, such as short-term memory, mathematics, and nonverbal reasoning. We first report C1's performance (in terms of percentile) in comparison to the performance of our TD control group, and (whenever available) to test norms. We next compare C1's performance to her sibling, S1, and to the three other children with large left hemisphere lesions, L1, L2, and L3.

#### 3.1.1. C1 compared to TD controls and normed test performance

Fig. 2 presents scores for a subset of the tests that are most representative of C1's overall performance, and situates her in relation to a box plot established on the basis of the quartile data for the TD sample; C1's scores are represented by the green dot on the box plots.

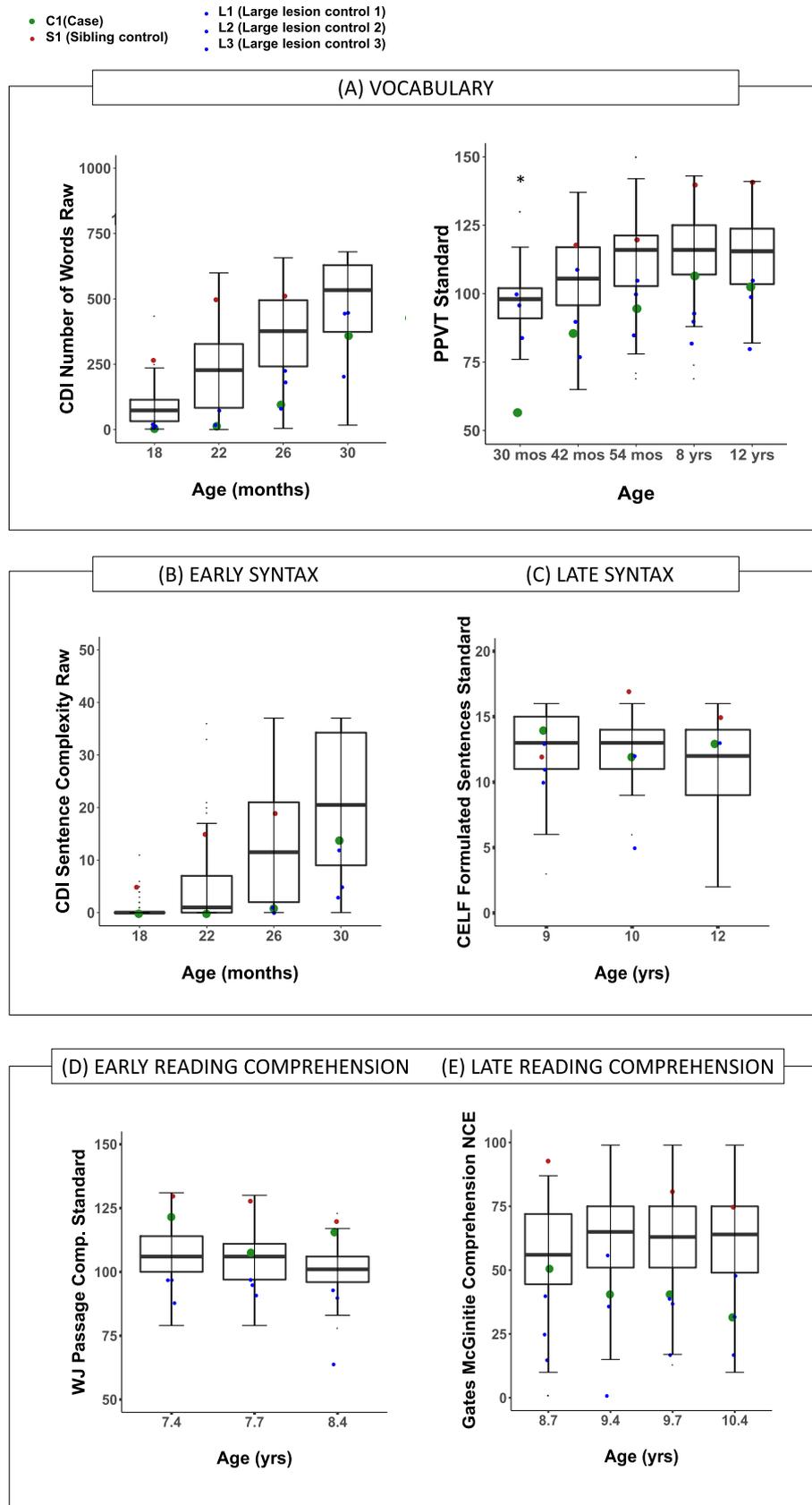
3.1.1.1. LANGUAGE TASKS. On vocabulary, as measured by the CDI and PPVT, standardized tests of vocabulary, as well as naturalistic measures of vocabulary production, C1's performance was below the 25th percentile of the TD controls at 13 out of 16 time points (see Fig. 2, Supplementary Material Tables S1 and S2). Compared to PPVT norms, C1's performance was profoundly low early in development, but improved to average at 54 months. Bayesian single-case tests showed that C1's performance on the PPVT was significantly below the TD controls at 30 months of age, [ $t(58) = -2.165$ , 95% CI = (-2.778, -1.540),  $p < .05$ ].

On syntax, as measured by CDI and CELF, standardized measures of syntax and, as well as an experimental measure of syntax comprehension, C1's performance, when compared to TD children, was within the interquartile range at the majority of time points (14 out of 17). Compared to norms on standardized tests of syntax, C1's performance ranged from borderline/low to high average (see Fig. 2, Tables S1 and S2). Notably, on the standardized syntax tasks, her lowest scores are from the earliest time points.

On discourse tasks, C1's performance was below the 25th percentile on a narrative production task given in Kindergarten and on the WJ Verbal Comprehension test, a standardized verbal comprehension task given at 12 years of age. However, compared to norms of the WJ Verbal Comprehension subtest, C1's performance was within the average range (see Tables S1 and S2).

On reading comprehension tests, C1 was below the 25th percentile on 3 of the 7 measures, within the interquartile range on 2 measures, and above the 75th percentile on 2 measures. When compared to test norms, C1 ranged from low average to superior, but for the most part performed in the average range on the WJ Passage Comprehension subtest. On a more challenging reading comprehension test, the Gates-MacGinitie, which involves silent reading of longer passages, she had more difficulty, performing below the IQR on three of four test points, and in the low average range according to the norms at 10.4 years of age. The difference in WJ Passage Comprehension and Gates-MacGinitie scores is likely due to the former relying on comprehension of single sentences, whereas the latter requiring comprehension of longer passages. In addition, Gates-MacGinitie was administered at a later age, but on many measures C1 tends to be stronger at later ages (See Fig. 2, Table S1).

In contrast to her level of performance on language and reading comprehension and production tasks, on phonological tasks, as measured by CTOPP, C1's performance was above the 75th percentile at all time points (this difference was statistically significant at 3 of 4 time points, Table S1). Compared to test norms, her performance also ranged from high-average to superior. Bayesian single-case tests showed that C1's performance on the CTOPP Ellison was significantly above the TD



**Fig. 2 – Scores of case C1 (green dot), S1 (red dot), L1, L2, and L3 (blue dots) overlaid on a boxplot of TD controls’ scores on standardized language measures: (A) Vocabulary (CDI, PPVT), (B) Early syntax (Syntax comprehension), (C) Late syntax (CELF-Formulated Sentences) (D) Early reading comprehension (WJ Passage Comprehension), (E) Later reading comprehension (Gates–MacGinitie Comprehension), (F) Decoding words (WJ Letter-Word Identification), (G) Decoding**

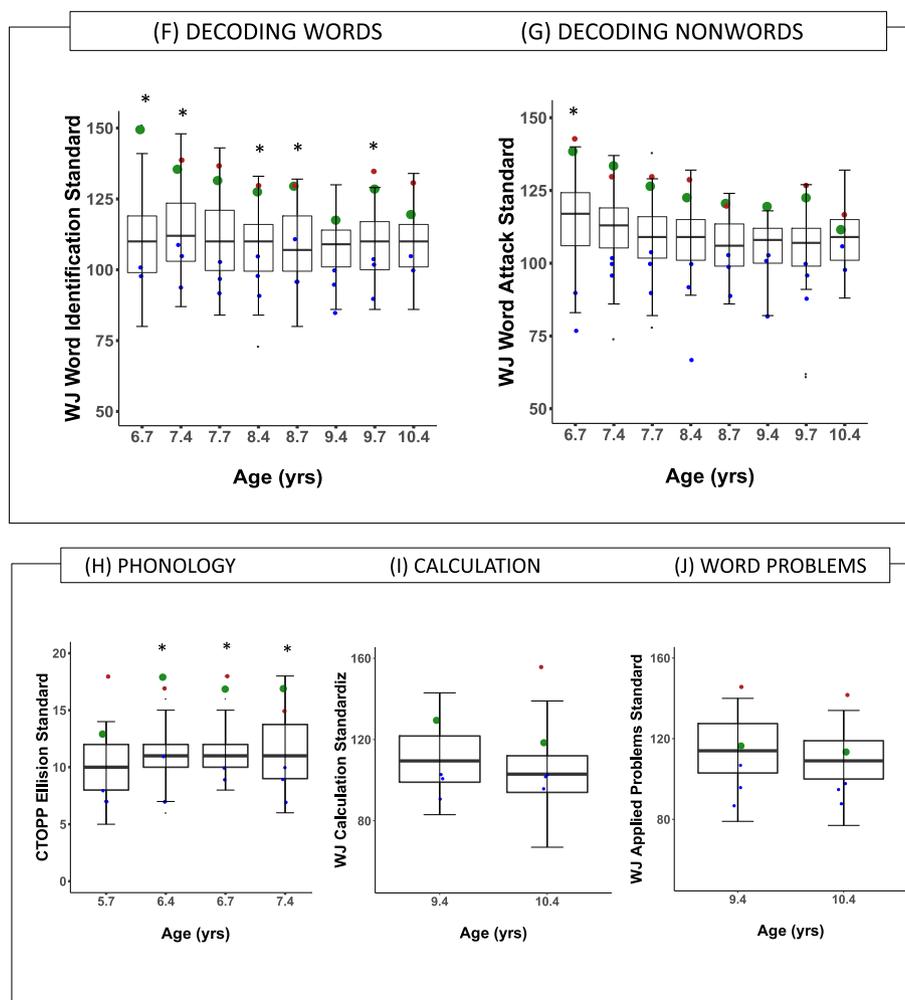


Fig. 2 – (continued).

controls on three of the four measurement occasions; at 6.4 years of age [ $t(56) = 2.958$ , 95% CI = [2.350, 3.559],  $p < .01$ ], at 6.7 years of age [ $t(51) = 2.437$ , 95% CI = [1.888, 2.978],  $p = .01$ ], and at 7.4 years of age [ $t(53) = 2.074$ , 95% CI = [1.594, 2.545],  $p = .04$ ] (See Fig. 2, Table S1).

On reading decoding tasks, C1 was again above the 75 h percentile on 6 of 16 time points, (Table S1), and tended to fall in the superior (or very superior) range based on test norms. Bayesian single-case tests showed that C1's performance on the WJ Word Identification subtest was marginally to significantly above the TD controls on five of the eight measurement occasions; at 6.7 years of age [ $t(52) = 2.583$ , 95% CI = [2.015, 3.142],  $p = .01$ ], at 7.4 years of age [ $t(54) = 1.752$ , 95% CI = [1.325, 2.170],  $p = .08$ ], 8.4 years of age [ $t(54) = 1.709$ , 95% CI = [1.289, 2.121],  $p = .09$ ], 8.7 years of age [ $t(54) = 1.844$ , 95% CI = [1.404, 2.276],  $p = .07$ ], and 9.7 years of age [ $t(52) = 1.743$ , 95%

CI = [1.310 to 2.168],  $p = .09$ ]. Similarly, C1's performance on the WJ Word Attack subtest was marginally above the TD controls at 6.7 years of age [ $t(52) = 1.746$ , 95% CI = [1.311, 2.171],  $p = .09$ ] (See Fig. 2, Table S1).

To summarize, in terms of C1's developmental trajectory, early in development (during preschool), C1 tended to perform lower than expected on receptive and expressive vocabulary and syntax tasks. Her language skills improved across the board during the school years and her performance typically fell into the average or above average range. Taken together, after some initial delays, C1 tended to perform *within the typical range* on a variety of vocabulary, syntax, discourse, and reading comprehension measures. In contrast, C1 exhibited exceptionally *high* performance on phonological and reading decoding tasks, consistently exceeding the TD scores.

**nonwords (WJ Word Attack), (H) Phonology (CTOPP Elision), (I) Calculation (WJ Calculation), (J) Word Problems (WJ Applied Problems).** Note that C1 exhibited below normal to normal range performance relative to controls on measures (A)–(E), but consistently performed higher than controls on measures (F)–(H). C1 – TD comparisons with significantly different performance are indicated with an asterisk.

**Table 2 – Clusters showing significantly different activation to Normal Stories versus Baseline in TD control participants (voxel-wise  $p = .001$ , cluster-wise FWE = .05,  $t = 3.291$ ,  $k = 78$ ), in C1 (voxel-wise  $p = .001$ , cluster-wise FWE = .05,  $t = 3.32$ ,  $k = 78$ ) and in L1 (voxel-wise  $p = .001$ , cluster-wise FWE = .5,  $k = 75$ ).**

	No of Voxels	Z stat	Talairach Coordinates			Atlas Region(s)
			x	y	z	
<b>TD Group</b>						
Story > Baseline	9417	4.34	-52	-18	-2	Left STG, STS, MTG
	6717	4.14	54	-12	-1	Right STG, STS, MTG
	465	3.69	-18	-78	-38	Left Cerebellum
	415	4.03	20	-83	-41	Right Cerebellum
	263	3.85	-42	-21	-25	Left ITG, Fusiform Gyrus
	249	3.51	-50	17	24	Left IFGop
	245	3.76	-1	53	-17	Left Cerebellum
	245	3.65	-40	-60	-35	Left mPFC
	147	3.67	1	47	46	Right SFG
	126	3.73	44	-61	28	Right MTG, AG
	123	3.62	-16	-58	4	Left Calcarine Sulcus
	Baseline > Story	472	3.72	-10	-73.3	48
111		3.68	-64	-26.6	41	Left postCG
<b>C1</b>						
Story > Baseline	6308	5.46	57	-16	3	Right Heschl's Gyrus, STG, STS, subC Sulcus/Gyrus, IFG
	475	4.33	6	38	50	Right SFG
	457	4.01	-21	-84	-27	Left Cerebellum
	392	4.80	41	10	36	Right preCS, MFG
	245	4.07	45	-35	-19	Right ITG, Fusiform Gyrus
	138	4.14	25	-83	-36	Right Cerebellum
Baseline > Story	559	3.90	40	-53	48	Right AG
	444	3.64	3	-66	54	Right Precuneus
	418	4.06	60	-29	46	Right SMG, postCG
	132	3.95	24	48	36	Right MFG, SFG, SFS
	107	4.11	9	48	-5	Right ACC, SFG
	89	3.84	55	-1	46	Right preCG
<b>L1</b>						
Story > Baseline	5615	5.90	61	-18	2	Right STG, STS, MTG
	382	4.05	10	-67	13	Right Precuneus, Cuneus, PCG
	113	3.80	-34	-63	-57	Left Cerebellum
	91	3.83	-14	-76	-53	Left Cerebellum
Baseline > Story	n.s.	n.s.	-	-	-	-

ACC: anterior cingulate gyrus, AG: angular gyrus, ITG: inferior temporal gyrus, mPFC: medial prefrontal cortex, MFG: middle frontal gyrus, preCS: precentral sulcus, postCG: postcentral gyrus, PCG: posterior cingulate gyrus, SFG: superior frontal gyrus, subC: subcentral, SFS: superior frontal sulcus, SMG: supramarginal gyrus, SPG: superior parietal gyrus, STS: superior temporal sulcus.

3.1.1.2. **MATH, SPATIAL, REASONING AND MEMORY TASKS.** On math word problems (WJ Applied Problems), tests of spatial cognition (KABC Triangles), and nonverbal reasoning tests (Ravens), C1 tended to perform within the interquartile range of TD controls (Fig. 2). However, she did perform in the High Average range on the Applied Problems test according to test norms, with her performances on the other two tests falling in the Average Range (see Table S1).

On two other tasks, WJ Calculation and Digit Span, C1 consistently performed better than TD controls (Fig. 2), and tended to perform in the superior to very superior range when compared to norms (Table S1).

3.1.2. **C1 compared to sibling control S1 and controls with lesions, L1, L2, L3**

Fig. 2 also presents TD's sibling control (red dot) and the three controls with lesions (blue dots) in relation to C1 (green dot); all dots are situated within the boxplots for the TD controls.

Compared to S1, C1 performed lower on vocabulary, syntax, and reading comprehension (particularly later reading comprehension, measured by the Gates–MacGinitie test), but performed at his (high) level on decoding words and non-words and on phonology.

L1, L2, and L3 patterned like C1 on vocabulary, syntax, and later reading comprehension (C1 outperformed L1, L2, and L3 on early reading comprehension). However, C1 performed well above L1, L2, and L3 on decoding words and nonwords, and on phonology.

## 3.2. Imaging

### 3.2.1. fMRI

The purpose of the fMRI task was to describe how language is processed in C1's sole right hemisphere, with TD control participants providing a reference for the expected patterns of activity in typical development. We therefore recorded brain

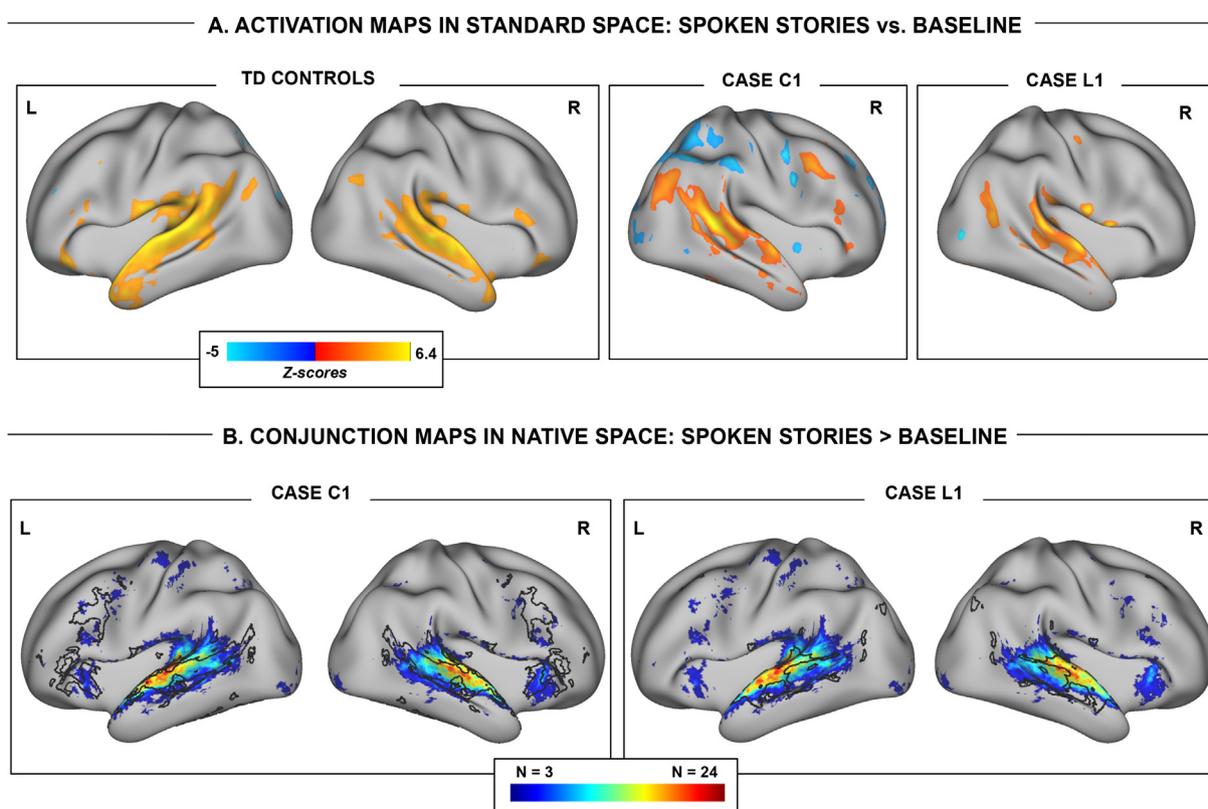
activity while C1, L1, S1 and TD control participants listened to short stories.

Children's responses to the intermittent questions posed during the task-dependent fMRI task were at ceiling with a median of 6 out of 6 correct responses and a mean of 5.5 [SD = .64, range = 4–6; C1 score = 6; L1 score = 3 out of 3 (due to technical difficulties only half of her responses were recorded)], indicating that they were paying attention to the stories in the scanner.

Table 2 presents the regions that were active during listening to story versus baseline in TD children (see also Fig. 3A); the superior temporal gyri and sulci and middle temporal gyri bilaterally, the left inferior frontal gyrus (IFGop), and the cerebellum bilaterally showed higher activation for the stories than for baseline in our TD control group. The story versus baseline comparison in C1 revealed higher activation in the right primary auditory cortex, the right superior temporal gyrus and sulcus, the right inferior frontal gyrus, the right superior frontal gyrus, the right fusiform gyrus, the right precentral gyrus and the cerebellum bilaterally for spoken stories (see Fig. 3A and Table 2 for the activated regions and their coordinates). L1, the only one of our comparison cases with brain lesions who had imaging data, showed higher activation to stories versus baseline in the right superior temporal gyrus

and sulcus, the precuneus, and the left cerebellum (see Table 2). Unlike C1 who displayed significant activation in the right IFG and TD controls who displayed significant activation in the left IFG, L1 did not have a significant cluster that included the IFG. The results remained the same when considering only the context sentences in the analysis.

Another way to look at the data, one that takes into account how many control participants displayed a particular pattern, is to create a conjunction map for the TD controls and overlay data for C1 and L1 onto that map (see Fig. 3B). Warm colors in Fig. 3B indicate that a relatively large number of TD controls displayed activation in a particular area; cold colors indicate that a relatively small number of TD controls displayed activations. C1's right hemisphere z-score map is outlined in black and overlaid on top of the TD right and left hemisphere conjunction maps in the left panel of Fig. 3B; L1's right hemisphere z-score map is overlaid on top of the TD controls in the right panel of the figure. Patterns of activation to language in the right hemisphere seem to be within normal variation in both C1 and L1. This finding suggests that reorganization did not introduce radical changes, but rather followed the organization shown in both hemispheres in TD children in the remaining right hemisphere.



**Fig. 3 – (A) Group activation maps of the Spoken Story versus Baseline fMRI comparison in TD controls, C1, and L1 as estimated in standard MNI space; in this figure, warm colors indicate higher activation for Spoken Stories > Baseline and cold colors higher activation for Baseline > Spoken Stories. (B) Conjunction z-score maps of Spoken Story > Baseline comparisons in TD controls as estimated in each individual's native space; in this figure, warm colors indicate a higher count number of TD control participants who showed activation when listening to stories and cold colors indicate a lower count number. C1's and L1's z-score maps in the right hemisphere are outlined in black and overlaid on the TD right and left hemisphere conjunction maps, respectively. All contrast maps in this figure are displayed on a standard inflated cortical surface (164 k mesh) and thresholded individually at voxel-wise  $p = .001$ , cluster-wise FWE = .05.**

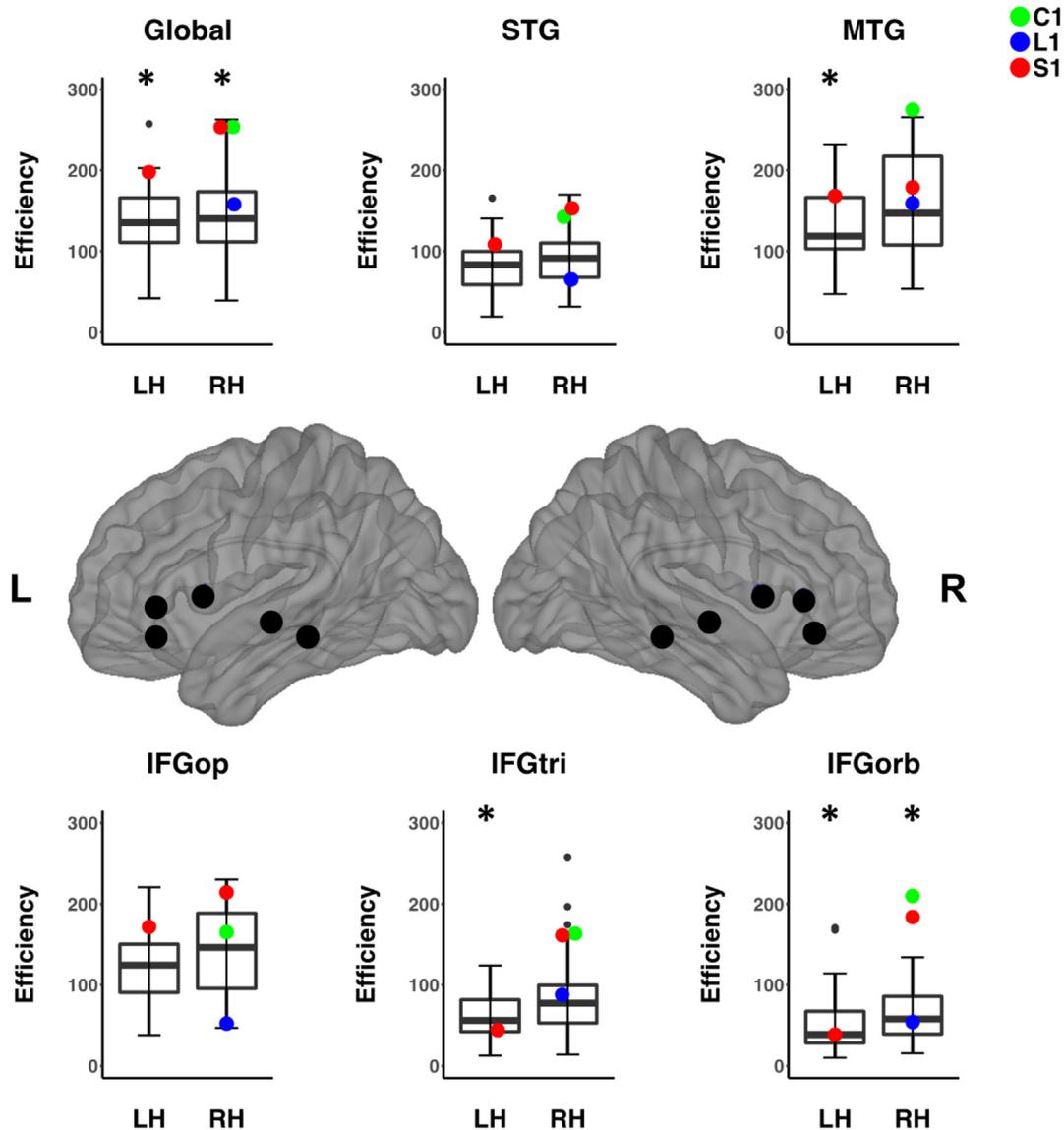


Fig. 4 – Boxplots representing the mean and distribution of Global Efficiency as well as Efficiency in language network nodes in the TD group with C1 (green dot), L1 (blue dot) and S1 (red dot) overlaid. Significant differences between C1’s right and either hemisphere in TD controls are indicated with an asterisk. Error bars represent Standard Error of the Mean.

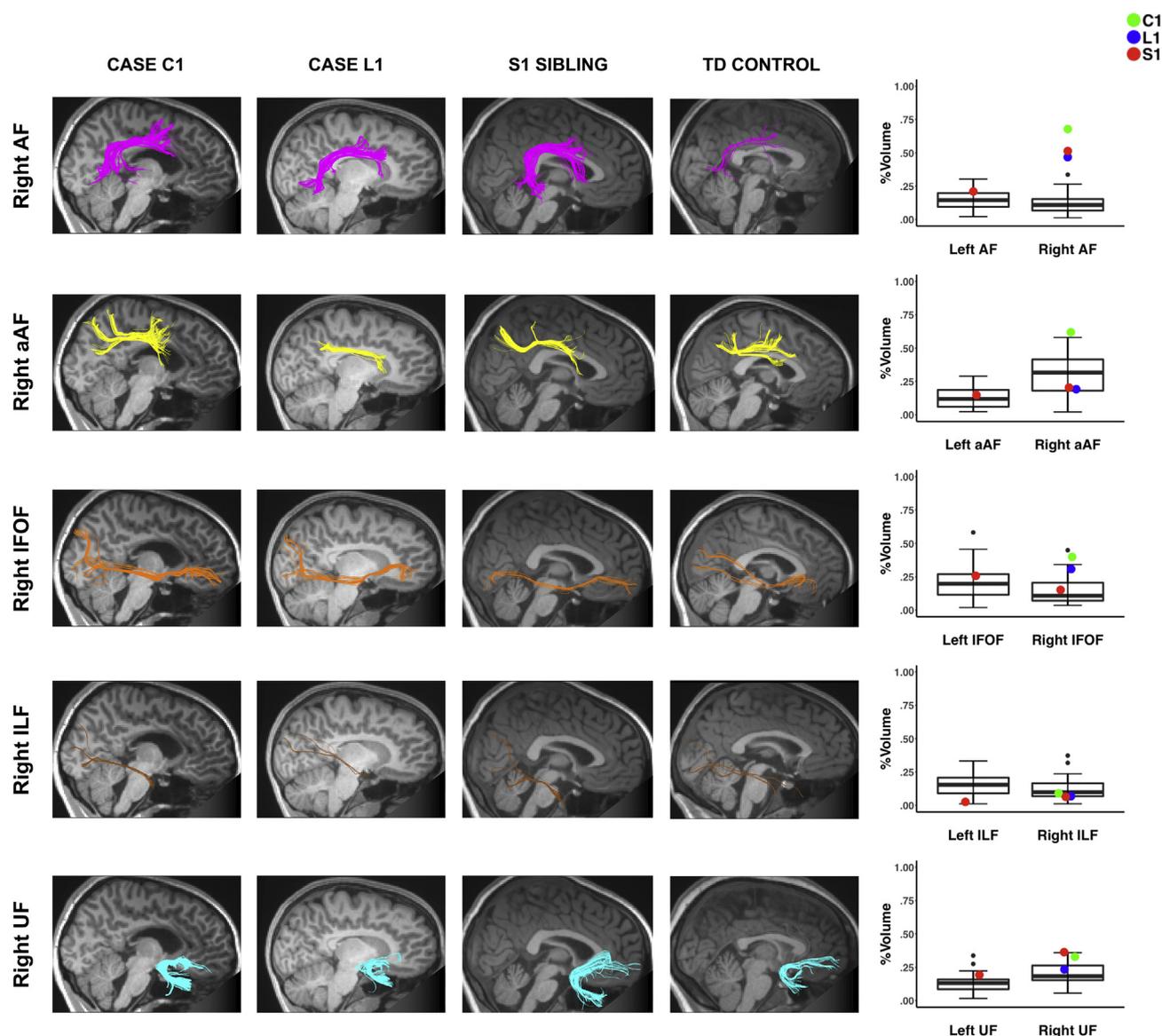
Singleton t-tests comparing C1 to TD controls and comparing L1 to TD controls showed significantly more activation to spoken sentences versus baseline in a cluster encompassing the right angular gyrus (AG) and the posterior

part of the superior temporal sulcus (STS) and in the right inferior temporal gyrus (ITG) in both C1 and L1 than in the controls. L1 showed higher activation in the left superior frontal gyrus than the TD controls [see [Supplementary](#)

Table 3 – Summary of white matter tract volume characteristics (percent of total hemispheric volume in voxels, SD in parenthesis) in C1 and TD controls, and Bayesian Point Estimates, t-statistics (highlighted in bold when significant) and Effect size (Z-CC) for comparisons between case and controls (plus 95% CI).

	TD		C1	C1 RH vs TD Controls LH			C1 RH vs TD Controls RH		
	LH	RH	RH	Bayesian PE	T stat	Zcc [CI]	Bayesian PE	T stat	Zcc [CI]
Direct AF	.15 (.08)	.12 (.09)	.68	100%	<b>6.517</b>	6.625 [4.887, 8.351]	99.99%	<b>6.079</b>	6.222 [4.258, 8.174]
Anterior AF	.13 (.08)	.3 (.15)	.62	99.99%	<b>6.022</b>	6.125 [4.483, 7.754]	97.76%	2.099	2.133 [1.473, 2.778]
IFOB	.22 (.13)	.15 (.11)	.4	90.81%	1.362	1.385 [.874, 1.881]	98.25%	2.230	2.273 [1.530, 2.998]
ILF	.16 (.08)	.13 (.09)	.09	19.85%	-.860	-.875 [-1.298, -.440]	33.27%	-.437	-.444 [-.822, -.059]
UF	.13 (.07)	.2 (.09)	.33	99.56%	<b>2.811</b>	2.857 [2.036, 3.664]	91.69%	1.421	1.444 [.923, 1.952]

AF: Arcuate Fasciculus, IFOB: Inferior Fronto-Occipital Fasciculus, ILF: Inferior Longitudinal Fasciculus, UF: Uncinate Fasciculus.



**Fig. 5** – Sagittal views of the right direct AF (magenta), right anterior AF (yellow), right IFOF (orange), right ILF (brown), and right UF (cyan) traced in C1, L1, S1, and a typical TD control participant (the participant closest to the group average) overlaid on their anatomical images in native space (panels on the left). Tract volume (percent of total hemispheric volume in voxels) in C1 (green dot), L1 (blue dot) and S1 (red dot), overlaid on a boxplot representing the mean and distribution of the tracts in each hemisphere in control participants (graphs on the right). Error bars represent Standard Error of the Mean.

material Table S3], whereas C1 showed higher activation in the right superior frontal gyrus and a cluster in the inferior part of the right precentral sulcus (PreCS) than the TD controls [see Supplementary material Table S3]. The singleton t-test comparing the sibling S1 to TD controls was performed to ensure that S1 did not demonstrate a substantially different pattern of activation to spoken stories. The comparison revealed increased activation in the left AG and decreased activation in the cerebellum bilaterally for S1 compared to the TD control group [see Supplementary material Table S3].

### 3.2.2. DWI

3.2.2.1. GRAPH THEORETICAL STRUCTURAL ANALYSIS. The purpose of the graph theoretical analysis was to describe white matter

structure reorganization in C1 by using global measures that characterize the properties of the brain network as a whole, as well as nodal measures that characterize the properties of specific brain areas (nodes) and their connections (white matter fibers) that are important for language processing.

*Global Measures.* The graph theoretical structural analysis revealed differences in network integration (global efficiency) between C1 and the TD controls (see Fig. 4 as well as Supplementary Material Table S4 for descriptive statistics and Bayesian Point estimates for the case–control comparisons on global and nodal measures). When comparing C1's right hemisphere *global efficiency* to either left or right hemispheres in the TD control group, we find that C1 has higher global efficiency [Right Hemisphere:  $t = 2.212$ ,  $p = .035$ ,  $Z_{cc} = 2.248$

(1.563–2.918), Bayesian Point Estimate = 98.24%; Left Hemisphere:  $t = 2.347$ ,  $p = .025$ ,  $Z_{cc} = 2.386$  (1.671–3.086), Bayesian Point Estimate = 98.70%. There was no difference in *network density and modularity* between the right hemisphere of C1 and either hemisphere of TD controls.

**Nodal Measures.** We compared degree centrality, nodal efficiency, and betweenness centrality in C1's right IFGop, IFGtri, IFGorb, STG, and MTG to those areas bilaterally in TD controls. We used the Benjamini–Hochberg procedure (FDR-BH) to control the false discovery rate due to the large number of comparisons. We found no differences between C1 and the TD control group in *degree and betweenness centrality* of these nodes. However, nodal efficiency, a measure of how important a node is within a network, was significantly higher in the right IFGtri in C1, compared to the left IFGtri in TD controls [ $t = 3.624$ ,  $p = .011$ ,  $Z_{cc} = 3.762$  (2.728–4.782), Bayesian Point Estimate = 99.94%]; in the right IFGorb in C1, compared to both the left IFGorb [ $t = 3.974$ ,  $p = .011$ ,  $Z_{cc} = 4.012$  (2.919–5.092), Bayesian Point Estimate = 99.95%] and right IFGorb in TD controls [ $t = 3.350$ ,  $p = .01$ ,  $Z_{cc} = 4.012$  (2.919–5.092), Bayesian Point Estimate = 99.97%]; and in the right MTG in C1, compared to the left MTG in TD controls [ $t = 3.292$ ,  $p = .019$ ,  $Z_{cc} = 3.347$  (2.412–4.267), Bayesian Point Estimate = 99.86%].

A summary of the global and nodal measures for L1 and S1, as well as the comparisons to the TD controls and the Bayesian Point Estimates, is available in Supplementary Material (Tables S5 and S6). Graph theoretical measures in L1's right hemisphere did not differ significantly from either hemisphere in TD controls. Like C1, S1 showed significantly higher efficiency in the right IFGtri and right IFGorb when compared to the left IFGtri in TD controls and to both, left and right, IFGorb in TD controls. In addition to that, he showed significantly higher degree centrality in the right IFGop and right MTG compared to the same right hemisphere areas in TD controls.

C1's nodal degree centrality, efficiency, and betweenness centrality was highly correlated with the average scores for each of these measures in the TD control group [Pearson correlation with right hemisphere nodes in controls: degree centrality  $r(32) = .88$ ,  $p = 4 \times 10^{-11}$ ; efficiency  $r(32) = .73$ ,  $p = 12 \times 10^{-7}$ ; betweenness  $r(32) = .58$ ,  $p = .0003$ ; correlation with left hemisphere: degree centrality  $r(32) = .87$ ,  $p = 5 \times 10^{-11}$ ; efficiency  $r(32) = .67$ ,  $p = 15 \times 10^{-6}$ ; betweenness  $r(32) = .44$ ,  $p = .0088$ ; FDR-BH corrected]. We estimated the deviation of C1's nodal metrics from those in TD controls by subtracting the average score in controls in each node from C1's score for that node [average case node(i) – control node(i)]. We then looked at the correlation between the increase in nodal degree centrality, efficiency, and betweenness in C1 and the average scores in the TD control group for each measure; no correlation survived correction for multiple comparisons.

### 3.2.3. White matter pathways for language in the right hemisphere

We used tractography to identify white matter pathways implicated in language processing in our TD group. These pathways included the AF, aAF, IFOF, ILF, and UF bilaterally (see Supplementary Material Table S7 for a summary of all the fiber tract characteristics, including number of streamlines,

FA, and Lateralization Index). The direct AF and the IFOF were significantly left lateralized in TD controls [AF:  $M = .20$ ,  $SD = .37$ ,  $t(20) = 2.42$ ,  $p = .024$ ; IFOF:  $M = .21$ ,  $SD = .40$ ,  $t(25) = 2.63$ ,  $p = .014$ ] (the right direct AF could not be identified in nine participants and the right IFOF in four). The aAF and UF were significantly right lateralized [aAF:  $M = -.40$ ,  $SD = .34$ ,  $t(28) = -6.39$ ,  $p = 7 \times 10^{-7}$ ; UF:  $M = -.19$ ,  $SD = .27$ ,  $t(29) = -3.96$ ,  $p = .0004$ ] whereas lateralization was marginally left for the ILF [ $M = .13$ ,  $SD = .34$ ,  $t(28) = 2.02$ ,  $p = .05$ ].

We performed case–control comparisons to test for significant differences in white matter tract volume characteristics (results summarized in Table 3; see Fig. 5). The results were FDR-BH corrected to control for the number of comparisons. The most striking finding in terms of macrostructure was that the direct segment of the AF in C1 was significantly larger in volume, compared to either left or right segments in TD controls [Left AF:  $t = 6.517$ ,  $p = 4 \times 10^{-6}$ ,  $Z_{cc} = 6.625$  (4.887–8.351), Bayesian Point Estimate = 100.00%; Right AF:  $t = 6.079$ ,  $p = 21 \times 10^{-6}$ ,  $Z_{cc} = 6.222$  (4.258–8.174), Bayesian Point Estimate = 99.99%]. The anterior segment of the AF was significantly larger than the left anterior segment in TD controls [ $t = 6.022$ ,  $p = 9 \times 10^{-6}$ ,  $Z_{cc} = 6.987$  (5.190–8.777), Bayesian Point Estimate = 99.99%]. C1's UF volume also was significantly larger than the left UF in TD controls [ $t = 2.811$ ,  $p = .021$ ,  $Z_{cc} = 2.857$  (2.036–3.664), Bayesian Point Estimate = 99.56%]. Case L1 differed significantly from TD controls in the volume of the direct segment of the AF [Left AF:  $t = 3.935$ ,  $p = .005$ ,  $Z_{cc} = 4.000$  (2.910–5.077), Bayesian Point Estimate = 99.97%; Right AF:  $t = 3.799$ ,  $p = .006$ ,  $Z_{cc} = 3.889$  (2.612–5.149), Bayesian Point Estimate = 99.94%]. Similar to his sibling, S1 had a significantly larger right direct AF than TD controls [ $t = 4.234$ ,  $p = .004$ ,  $Z_{cc} = 4.333$  (2.928–5.723), Bayesian Point Estimate = 99.97%].

Lastly, we performed a *post hoc* correlation analysis to test whether tract volume was related to behavioral performance in our TD control sample. We focused exclusively on the tracts that were significantly larger in C1 than TD controls (the direct AF bilaterally, the left aAF, and the left UF), and compared them to behavioral measures in which C1 performed in the superior or very superior range (CTOPP Elision, WJ Word Attack, WJ Word ID, WJ Calculation and Digit Span). Pearson correlation coefficients were estimated and  $p$ -values were corrected using FDR-BH. We found a significant positive correlation between the volume in the left aAF and Word Attack performance [ $r(21) = .661$ ,  $p = .015$ ] (see Supplementary Table S8 for a full list of the correlation coefficients).

## 4. Discussion

We described language performance and brain reorganization in a rare case of a child (C1) with hemihydranencephaly (HHE) who was born without the left hemisphere. Despite difficulty getting language off the ground during preschool, by the time C1 was 14 years old, her language performance was average for children her age on many standardized language tests, and exceptional in phonology (word repetition, elision) and word reading. These behavioral outcomes were accompanied by: (i) structural MRI data showing significantly stronger white

matter connectivity in her remaining (right) hemisphere than age-matched TD controls, and (ii) functional MRI data revealing right fronto-temporal activation when listening to speech that was comparable in its pattern to bilateral activation in TD controls. We propose that these changes in functional and structural brain organization reflect brain plasticity in a child with a rarely observed lesion that occurred in a very early period of fetal development. To the best of our knowledge, this case represents only the tenth instance of HHE reported in the literature, and the only study with longitudinal data that combines detailed language and cognitive assessment with functional and structural neuroimaging data to situate the case within age-matched, typically developing children.

#### 4.1. Language performance across time and tasks

The first goal of our study was to describe C1's language performance across time and across different language domains tapping a wide range of language functions. We were interested in the developmental consequences of being born without a left hemisphere with respect to these language functions. When examining performance across time, we found that early in development (during preschool), C1 tended to perform relatively poorly, with lower than expected receptive and expressive vocabulary and syntax ability. However, her language skills improved across the board and typically fell into the average or above average range during the school years. Thus, although her language development began slowly, she eventually caught up with her peers. Longitudinal studies of children with perinatal lesions due to stroke have documented a similar trajectory, one that is characterized by early delays in babbling, expressive and receptive vocabulary, and syntax, followed by a "catch-up" period during school years (Bates et al., 1997; Levine et al., 2016; Stiles et al., 2012).

C1's within – age average language skills are consistent with those of two previously described children with HHE (Balpande, Pathak, Agrawal, & Singh, 2009; Ulmer et al., 2005) but different from four others, who had delayed language development. One of these four children had seizures (Dias, Shivashankara, & Vivek, 2011), and children with seizures are known to have relatively bad language outcomes (Ballantyne, Spilkin, Hesselink, & Trauner, 2008; Levine et al., 2005). Two others were assessed early, at 30 and 27 months (Greco, Finocchiaro, Pavone, Trifiletti, & Parano, 2001; Hassanein, Abbas, Monib, & El Alfy, 2011), and showed delay at those time points. One of these two was assessed subsequently (at 12 years of age) and showed some improvement although still in the borderline range (Pavone et al., 2013) potentially due to premature birth.

The pattern that emerged when looking across tasks is that C1's performance was uneven: superior in several areas, including phonology and word reading (words and nonwords), and average in others, including vocabulary, reading comprehension, and syntax during the school years. With respect to other cognitive abilities, C1 again excelled in several areas – matrix reasoning, spatial processing, calculation and short-term and working memory. On cognitive assessments taken at the time of imaging (middle school), C1 performed

well within the average range for her age in a wide variety of domains, including language and spatial, numerical, and general reasoning. Thus, we found no evidence of a "crowding effect" (Teuber, 1975) in the solitary right hemisphere; in other words, accommodating her remaining hemisphere to handle language did not come at the cost of other functions, such as visual or spatial abilities.

The fact that C1's performance on certain tasks was superior to typically developing children is extraordinary given the extent of her lesion. Cognitive performance is usually negatively related to lesion size in children with perinatal injury, with larger lesions leading to poorer outcomes (Brizzolara et al., 2002; Levine et al., 2005; Rowe et al., 2009; Sauer, Levine, & Goldin-Meadow, 2010). For comparison purposes, we examined cognitive performance in three children with large left hemisphere lesions from our longitudinal study. As in the case of C1, these three children showed reduced early language performance. However, unlike C1, these three children did not catch up during school years, performing in the borderline to low-average range. We believe that the uniqueness of C1's performance stems from a combination of factors, including (but not limited to) genetic factors, experience-independent developmental processes related to lesion timing (and perhaps extent), and experience-dependent processes related to environmental input. We discuss these factors at length in the following sections.

#### 4.2. Processing language without the left hemisphere

Functional activation to spoken language in C1 revealed that reorganization for language in the spared right hemisphere resembled the activation seen bilaterally in the typically developing brain with more engagement of prefrontal regions. While listening to short stories, C1 engaged many right hemisphere regions including the ventral inferior frontal gyrus as well as the cerebellar hemispheres bilaterally. L1 showed activation in right temporo-parietal and left cerebellar areas, but no activation in the right inferior frontal areas or the right cerebellum.

Assuming functional homology between the right IFG of C1 and the left IFG of the TD control participants, C1's right IFG activation during language processing makes sense in terms of the task performed in the scanner, which tapped semantic processing (typically engaging the ventral IFG), and is in alignment with findings on left perinatal stroke patients (Ilves et al., 2014) and left hemispherectomy patients (Hertz-Pannier et al., 2002; Liégeois et al., 2008; Voets et al., 2006). In hemispherectomy patients, activation in the "Broca homologue", specifically right ventral IFG, has been shown to correlate with language performance (Liégeois et al., 2008), highlighting the right hemisphere's potential to compensate for the absence of the left hemisphere. Unlike hemispherectomy cases, C1 was born full-term, had no history of seizures, and we can be fairly certain that no inter-hemispheric transfer ever occurred during her language development. Interestingly, there seems to be no clear pattern with respect to laterality and language outcomes in the HHE cases reported thus far in the literature, perhaps due to the timing of the lesions. Three of the four HHE patients with language delays were missing the right rather than the left hemisphere. The absence of laterality effects in

HHE is in agreement with hemispherectomy studies, where laterality was a significant predictor of language outcomes only for pathologies acquired *postnatally* (in these cases, right hemispherectomy had better outcomes than left with respect to language; Curtiss, de Bode, & Mathern, 2001).

Although our analysis focused primarily on cerebral structures, it is noteworthy that C1 had an intact cerebellum, which was active during speech processing. TD control participants activated the cerebellum bilaterally during this task; by contrast, C1 had a larger cluster of activation in the left, compared to the right, cerebellum (457 vs 138 voxels, respectively), whereas L1 only activated the left cerebellum (see also [Supplementary Material Figure S1](#)). This pattern may reflect the absence of input projections from the missing left cerebral cortex to the contralateral cerebellar cortex leading to reduced (as in C1) or no significant activation (as in L1) in the right cerebellum. A similar reorganization of the cerebro-cerebellar network has been reported before in patients with perinatal left-hemispheric brain lesions (Lidzba, Wilke, Staudt, Krägeloh-Mann, & Grodd, 2008; Northam et al., 2018). In these patients, preserved speech repetition was associated with atypical lateralization in Broca's area (right lateralized) and concomitant lateralization in the cerebellum (left lateralized) (Northam et al., 2018). L1's performance in speech repetition tasks was average, whereas C1's was exceptional. This discrepancy in performance could be related to the discrepancy between L1's left and C1's bilateral pattern of cerebellar activation to language. Given the role of the cerebellum in motor control during speech production (Hickok, 2012; Lametti, Smith, Freidin, & Watkins, 2018) and verbal working memory (Ben-Yehudah, Guediche, & Fiez, 2007; Durisko & Fiez, 2010), and C1's superior performance in speech repetition, we speculate that the engagement and contribution of the cerebellum bilaterally in a network missing an entire cerebral hemisphere may be important.

#### 4.3. White matter reorganization

The picture that emerges from our graph theoretical analysis of the structural connectome in C1 is one of a highly interconnected right hemisphere network, more efficiently connected than the right hemisphere of age-matched controls. The right hemisphere network organization of C1 follows the pattern of organization in the left and right hemisphere in TD controls: nodes with high functional integration in TD controls also showed high functional integration in C1. Importantly, key areas in C1's language network such as the ventral IFG and MTG were significantly more efficiently connected to the rest of her network, compared to their connectivity in TD control network, which was not the case for L1.

Evidence from early lesions in animal studies support our hypothesis that these changes in white matter connectivity are compensatory. Reactive synaptogenesis, large-scale sprouting in white matter tracts, and novel innervation have been documented in animals with good behavioral recovery after hemidecortication (Kolb & Tomie, 1988; Villablanca, Carlson-Kuhta, Schmanke, & Hovda, 1998; Villablanca & Hovda, 1999). Importantly, these changes are only observed when a lesion is performed early in life, during particular developmental stages, and correlate positively with

behavioral outcomes. Thus, in animals, reduced vulnerability to a lesion involving a whole cerebral hemisphere can be attributed to specific morphological processes taking place during specific developmental periods.

Looking specifically into language-related white matter tracts connecting temporo-parietal and frontal areas, our tractography analysis revealed that the volume of these tracts in C1's right hemisphere was at least a standard deviation higher than the average volume in either hemisphere in TD controls (except for ILF). Given C1's largely normal language performance, the large white matter connections might have played a compensatory role by providing fast and reliable transfer of information between cortical areas for language in the right hemisphere. When we focused solely on associations between the tracts that were significantly larger in C1 and the behavioral measures on which she excelled, we found a significant positive correlation between the volume of the left anterior AF and non-word reading scores in the TD children. L1 also had a large direct AF, but only C1 had a significantly larger anterior AF, compared to TD controls. While this tract is often overlooked, in their anatomical model for language development, Catani and Bambini (2014) suggest that the anterior AF supports the recognition of informative actions and plays an important role during language acquisition.

With a sample of only 23 TD children who had both imaging data and behavioral language assessment, we did not have the statistical power to test for associations between all the tract characteristics and all language performance measures. However, studies with larger samples have demonstrated the importance of the dorsal language tracts, which connect posterior superior temporal and inferior parietal areas to dorsal inferior frontal and premotor areas, and enable the mapping of speech sounds to motor representations. Fractional anisotropy (FA) and/or volume of the left AF have been associated with the rate of vocabulary growth (Su et al., 2018), phonological skills (Yeatman et al., 2011), word reading development (Wang et al., 2016), phonological awareness (Saygin et al., 2013; Travis, Adams, Kovachy, Ben-Shachar, & Feldman, 2017), vocabulary size (Teubner-Rhodes et al., 2016) and phonological vocabulary learning (López-Barroso et al., 2013). At the same time, perinatal lesions in the left AF cause long-lasting speech repetition impairments (François et al., 2016; Northam et al., 2018) unless an intact ventral pathway is in place (Yeatman & Feldman, 2013). The fact that L1 and C1 have unusually large right dorsal tracts and either average (L1) or exceptional (C1) performance in phonology, speech repetition, and decoding tasks, speaks in favor of compensatory structural reorganization. In line with this view, the volume of the right direct AF has been found to be the best predictor of language recovery in adults with left perisylvian damage due to stroke (Forkel et al., 2014).

Ventral white matter tracts, which connect occipital, posterior, and anterior temporal areas to ventral inferior frontal areas, and enable the mapping of visual and auditory inputs to semantic representations, were also identified in C1. Her right IFOF and UF were significantly larger than the right IFOF and left UF in TD controls. FA and radial diffusivity in these tracts have been associated with higher phonological skills (Travis et al., 2017; Vandermosten et al., 2015; Walton, Dewey, & Lebel, 2018) and better word learning

from semantic context (Ripollés et al., 2017). More complex linguistic behaviors, such as narrative comprehension and production, in which C1 as well as L1 showed low preschool and average school performance, may depend heavily on cross-hemispheric interactions and children with large unilateral lesions simply may not have enough tissue to master these skills.

#### 4.4. Lesion timing and limits to plasticity

Bearing in mind the critical role of time at insult for plasticity and behavioral outcomes in animals (Kolb & Gibb, 2014; Villablanca & Hovda, 1999) and humans (Anderson, Spencer-Smith, & Wood, 2011; Staudt, 2010), the timing of C1's lesion might have contributed uniquely to her behavioral and brain reorganization outcomes. The underlying pathogenesis of HHE is a vascular disruption thought to occur before the onset of synaptogenesis (Pavone et al., 2013), that is, before the onset of myelination and before synaptic density in the cortical plate starts exhibiting rapid growth (Tau & Peterson, 2010). Specific developmental, experience-independent processes that occur after the injury, along with experience-dependent processes, enable the brain to adapt and reorganize in an optimal manner. This flexible reorganization is not only evident in higher cortical functions, such as language, but also in more basic cortical functions, such as early vision (Muckli et al., 2009). Borderline, low, and average behavioral outcomes in L1, L2, and L3, matched for gender, SES, and absence of seizures, are consistent with the importance of lesion timing. While HHE is thought to occur during the first trimester of gestation, middle cerebral artery infarctions occur during the late third trimester, when the potential for brain reorganization is decreased (Staudt et al., 2002).

There are also limits to cerebral reorganization and plasticity, as manifested by C1's less successful motor recovery. C1 did not recover from congenital hemiparesis, nor did any of the other HHE cases reported in the literature (Pavone et al., 2013). In addition to the absence of a left cerebral cortex, C1 was also missing two structures important for motor control: the left basal ganglia and a large part of the left thalamus. The basal ganglia play an important role in the regulation of voluntary movement initiation and execution in the contralateral extremities (Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo, 2014), and perinatal lesion in the basal ganglia has been associated with poor motor outcome and spasticity (Kirton, DeVeber, Pontigon, Macgregor, & Shroff, 2008). The thalamus contributes to motor control by relaying sensorimotor information from the basal ganglia and cerebellum to the cortex, and vice versa (Sommer, 2003). Lesions to subcortical structures are more deleterious for behavioral outcomes when sustained during the pre- or perinatal period, compared to childhood or adolescence (Westmacott, Askalan, Macgregor, Anderson, & Deveber, 2010). These findings suggest that the discrepancy between language and motor recovery in C1 might stem from differences in the developmental trajectories of motor versus language networks (Anderson et al., 2011; Staudt, 2010). As a result, early brain injury might have a greater impact on motor function than on language.

Despite reaching within and above average cognitive performance at school age, C1 struggled during the first years of language acquisition, which leads to the following question: what caused this initial delay? We can exclude the absence of environmental input as a reason for this trajectory: C1 grew up in a family with high income and education, and was exposed to high quality and quantity linguistic input during those early years. The data from our longitudinal language project show that her primary caregiver provided early language input that was well within the normal range (number of word tokens produced by parent during our observations: C1 mean = 4005, TD mean  $\pm$  SD = 3735.01  $\pm$  2096.29; number of word types produced by parent during our observations: C1 mean = 500.58, TD mean  $\pm$  SD = 451.12  $\pm$  172.45). This is important given our prior findings showing that early language input is even more correlated with language outcomes in children with early lesions than in typical children (Demir, Rowe, Heller, Goldin-Meadow, & Levine, 2015; Levine et al., 2016; Rowe et al., 2009). We can only speculate that the reasons underlying her slow start must be related to the fact that she had to rely on suboptimal systems; half of the cortical structures available to healthy infants were not available to her. The two hemispheres are not interchangeable and structural asymmetries due to differential gene expression are already present at birth (Kasprian et al., 2011), including differences in myelin content (O'Muircheartaigh et al., 2013), cytoarchitecture (Amunts, Schmidt-Passos, Schleicher, & Zilles, 1997), cortical (Hill et al., 2010) and white matter structure (Liu et al., 2010). Further, newborn infants show more inter-hemispheric than intra-hemispheric resting state connectivity (Perani et al., 2011), reflecting, among other things, the asynchrony in myelination, as commissural and projection fibers mature earlier than association fibers (Dubois et al., 2014). Lastly, hemispheric differentiation for speech processing is present even before the completion of neuronal migration, as evident in preterm infants (Mahmoudzadeh et al., 2013).

Several processes that underlie the massive growth in brain volume during the first postnatal years, astrogliogenesis, oligodendrogenesis, synaptogenesis, and myelination, are taking place in the first postnatal years and are completed in childhood (Silbereis, Pochareddy, Zhu, Li, & Sestan, 2016); they could have contributed to the "catching up" observed in C1 during school years. The myelination of axons, which ensures the fast transfer of information between neurons, may have played a central role in C1's improvement in performance, transforming the suboptimal networks in the remaining hemisphere by providing more efficient neuronal communication pathways.

Finally, C1's language development trajectory highlights the importance of experience-dependent plasticity (Greenough, Black, & Wallace, 1987; Kolb & Gibb, 2014): Growing up in a highly educated and supportive family that provided rich stimulation and input is likely to have played an important role in her brain development and behavioral outcomes. Early language input quality has been shown to predict later language development in children with perinatal lesions, over and above SES and lesion characteristics (Demir et al., 2015; Rowe et al., 2009). In addition, C1 received speech and occupational therapy beginning in the first year of her life.

Finally, the fact that her younger sibling (S1) was outstanding in all the standardized language tasks also suggests the presence of genetic predisposition for high levels of cognitive skill as well as an environment that supports this kind of development. All of these factors are likely to have influenced C1's synaptic organization, brain plasticity, and behavioral performance (cf. Anderson et al., 2011).

The comparison of C1's performance to S1 (as well as to the group of TD control children) suggests that there are limits to plasticity, even given highly supportive environmental conditions. Specifically, although her performance is comparable to her sibling's in some areas (phonological processing, word and nonword reading), it is significantly below his level in other areas (vocabulary, reading comprehension). This suggests that C1 would have had high academic potential had it not been for her lesion, and that performing within the average range is not equivalent to performing within the expected range for her family.

#### 4.5. Limitations

A limitation in our study was that data from this case were acquired as part of a larger longitudinal study with a specific focus on language development. Consequently, we acquired rich language data, but did not assess other important functions in detail, such as motor or visual functions. Similarly, the fMRI task only tested language comprehension and not language production resulting in only partial assessment of our case's functional language network. Another limitation was that we used diffusion weighted imaging tractography to describe white matter architecture in our participants, which offers an indirect and not always accurate measure of white matter connectivity (Thomas et al., 2014). Furthermore, we used deterministic tractography to trace the language fiber tracts, which has good sensitivity but poor specificity as it cannot model crossing fibers and can result in false positive fibers that may be difficult to detect and remove (Thomas et al., 2014). Deterministic tractography can also reduce the robustness of the graph theoretical measures and their comparisons (Bonilha et al., 2015). Finally, although we chose to focus on the dorsal and ventral association pathways connecting frontal and temporo-parietal areas, we cannot rule out that other tracts might have been important for language reorganization.

#### 4.6. Conclusions

Here we provide the first report of functional and structural brain reorganization in a child missing the entire left hemisphere from birth. Her language development was slow in the first years of life, but reached age-appropriate levels during the school years in many aspects of language as well as other domains of cognitive functioning. This developmental pattern suggests that, when the typical brain infrastructure for cognitive development is not available, it takes time for reorganization and plasticity to take place. Even though C1's cognitive skills at school age were average for her age, her performance was not uniform across domains. She was exceptional in single word reading, phonology, and speech repetition, but average in vocabulary, syntax, and reading comprehension.

Her white matter development and organization reflected this unevenness: C1's dorsal white matter tracts, which are thought to support the mapping of sound to articulation, were significantly larger in C1 than in the TD group. These findings show that it is possible to achieve normal or near normal language abilities when a lesion is sustained early in neural development, even when that lesion is large enough to include the whole left hemisphere. Although we do not yet understand the conditions that allow for this remarkable plasticity, we hypothesize that they include lesion timing as well as genetic and environmental factors.

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### Research data and code for this article

The data used in this manuscript are currently confidential due to ethical restrictions and cannot be publicly archived. In their assent and consent forms, participants and their guardians were assured that their imaging and behavioral data would remain confidential and would not be shared. For this reason, no data supporting the conclusions of this study can be shared with any individual outside the author team. Consent to release all the data collected during this longitudinal study will be sought upon participants' 18th birthday. Please contact the study coordinator, Kristi Schonwald ([kschoend@uchicago.edu](mailto:kschoend@uchicago.edu)), who is overseeing the consenting process for future data access requests. The experiment code to reproduce the MRI data analysis is publicly available at the following website: <https://github.com/savvatia/CaseStudyScripts>.

No part of the study procedures or analyses was pre-registered prior to the research being conducted. We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

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### Credit author statement

**Salomi S. Asaridou:** Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft, Visualization, Project Administration.

**Özlem Ece Demir-Lira:** Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft, Visualization.

**Susan Goldin-Meadow:** Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding Acquisition.

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### Open practices

The study in this article earned an Open Materials badge for transparent practices. Materials for the study are available at

[https://github.com/savvatia/CaseStudyScripts/fMRI\\_Presentation\\_material](https://github.com/savvatia/CaseStudyScripts/fMRI_Presentation_material).

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## Supplementary data

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## REFERENCES

- Amunts, K., Schmidt-Passos, F., Schleicher, A., & Zilles, K. (1997). Postnatal development of interhemispheric asymmetry in the cytoarchitecture of human area 4. *Anatomy and Embryology*, 196(5), 393–402. <https://doi.org/10.1007/s004290050107>.
- Anderson, V., Spencer-Smith, M., & Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*, 134(8), 2197–2221. <https://doi.org/10.1093/brain/awr103>.
- Ballantyne, A. O., Spilkin, A. M., Hesselink, J., & Trauner, D. A. (2008). Plasticity in the developing brain: Intellectual, language and academic functions in children with ischaemic perinatal stroke. *Brain*, 131(11), 2975–2985. <https://doi.org/10.1093/brain/awn176>.
- Balpande, D., Pathak, C., Agrawal, A., & Singh, B. (2009). Hemihydranencephaly; a case report. *Iranian Journal of Pediatrics*, 19(2), 180–184. Retrieved from <http://ijp.tums.ac.ir/index.php/ijp/article/view/849>.
- Bates, E., Thal, D., Trauner, D., Fenson, J., Aram, D., Eisele, J., et al. (1997). From first words to grammar in children with focal brain injury. *Developmental Neuropsychology*, 13(3), 275–343. <https://doi.org/10.1080/87565649709540682>.
- Ben-Yehudah, G., Guediche, S., & Fiez, J. A. (2007). Cerebellar contributions to verbal working memory: Beyond cognitive theory. *The Cerebellum*, 6(3), 193–201. <https://doi.org/10.1080/14734220701286195>.
- Bonilha, L., Gleichgerrcht, E., Fridriksson, J., Rorden, C., Breedlove, J. L., Nesland, T., et al. (2015). Reproducibility of the structural brain connectome derived from diffusion tensor imaging. *Plos One*, 10(8), e0135247. <https://doi.org/10.1371/journal.pone.0135247>.
- Bornkessel-Schlesewsky, I., Schlesewsky, M., Small, S. L., & Rauschecker, J. P. (2015). Neurobiological roots of language in primate audition: Common computational properties. *Trends in Cognitive Sciences*, 19(3), 142–150. <https://doi.org/10.1016/J.TICS.2014.12.008>.
- Brizzolaro, D., Pecini, C., Brovedani, P., Ferretti, G., Cipriani, P., & Cioni, G. (2002). Timing and type of congenital brain lesion determine different patterns of language lateralization in hemiplegic children. *Neuropsychologia*, 40(6), 620–632. [https://doi.org/10.1016/S0028-3932\(01\)00158-0](https://doi.org/10.1016/S0028-3932(01)00158-0).
- Calabresi, P., Picconi, B., Tozzi, A., Chiglieri, V., & Di Filippo, M. (2014). Direct and indirect pathways of basal ganglia: A critical reappraisal. *Nature Neuroscience*, 17(8), 1022–1030. <https://doi.org/10.1038/nn.3743>.
- Catani, M., Allin, M. P. G., Husain, M., Pugliese, L., Mesulam, M. M., Murray, R. M., et al. (2007). Symmetries in human brain language pathways correlate with verbal recall. *Proceedings of the National Academy of Sciences of the United States of America*, 104(43), 17163–17168. <https://doi.org/10.1073/pnas.0702116104>.
- Catani, M., & Bambini, V. (2014). A model for social communication and language evolution and development (SCALED). *Current Opinion in Neurobiology*, 28, 165–171. <https://doi.org/10.1016/j.conb.2014.07.018>.
- Chai, L. R., Mattar, M. G., Blank, I. A., Fedorenko, E., & Bassett, D. S. (2016). Functional network dynamics of the language system. *Cerebral Cortex*, 26(11), 4148–4159. <https://doi.org/10.1093/cercor/bhw238>.
- Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance Neuroimages. *Computers and Biomedical Research*, 29(3), 162–173. <https://doi.org/10.1006/CBMR.1996.0014>.
- Cox, R. W., Chen, G., Glen, D. R., Reynolds, R. C., & Taylor, P. A. (2017). FMRI clustering in AFNI: False-positive rates redux. *Brain Connectivity*, 7(3), 152–171. <https://doi.org/10.1089/brain.2016.0475>.
- Crawford, J. R., & Garthwaite, P. H. (2007). Comparison of a single case to a control or normative sample in neuropsychology: Development of a Bayesian approach. *Cognitive Neuropsychology*, 24(4), 343–372. <https://doi.org/10.1080/02643290701290146>.
- Crawford, J. R., Garthwaite, P. H., & Porter, S. (2010). Point and interval estimates of effect sizes for the case-controls design in neuropsychology: Rationale, methods, implementations, and proposed reporting standards. *Cognitive Neuropsychology*, 27(3), 245–260. <https://doi.org/10.1080/02643294.2010.513967>.
- Crawford, J. R., & Howell, D. C. (1998). Comparing an individual's test score against norms derived from small samples. *The Clinical Neuropsychologist*, 12(4), 482–486. <https://doi.org/10.1076/clin.12.4.482.7241>.
- Curtiss, S., de Bode, S., & Mathern, G. W. (2001). Spoken language outcomes after hemispherectomy: Factoring in etiology. *Brain and Language*, 79(3), 379–396. <https://doi.org/10.1006/brln.2001.2487>.
- Daducci, A., Gerhard, S., Griffa, A., Lemkaddem, A., Cammoun, L., Gigandet, X., et al. (2012). The connectome mapper: An open-source processing pipeline to map connectomes with MRI. *Plos One*, 7(12), e48121. <https://doi.org/10.1371/journal.pone.0048121>.
- Demir, Ö. E., Levine, S. C., & Goldin-Meadow, S. (2010). Narrative skill in children with early unilateral brain injury: A possible limit to functional plasticity. *Developmental Science*, 13(4), 636–647. <https://doi.org/10.1111/j.1467-7687.2009.00920.x>.
- Demir, Ö. E., Rowe, M. L., Heller, G., Goldin-Meadow, S., & Levine, S. C. (2015). Vocabulary, syntax, and narrative development in typically developing children and children with early unilateral brain injury: Early parental talk about the “there-and-then” matters. *Developmental Psychology*, 51(2), 161–175. <https://doi.org/10.1037/a0038476>.
- Dias, L. S., Shivashankara, K. N., & Vivek, G. (2011). Hemihydranencephaly: Rare disease with key to secrets of the brain. *BMJ Case Reports*, 2011. <https://doi.org/10.1136/bcr.12.2010.3658>.
- Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., Hüppi, P. S., & Hertz-Pannier, L. (2014). The early development of brain white matter: A review of imaging studies in fetuses,

- newborns and infants. *Neuroscience*, 276, 48–71. <https://doi.org/10.1016/J.NEUROSCIENCE.2013.12.044>.
- Durisko, C., & Fiez, J. A. (2010). Functional activation in the cerebellum during working memory and simple speech tasks. *Cortex*, 46(7), 896–906. <https://doi.org/10.1016/j.cortex.2009.09.009>.
- Fedorenko, E., & Thompson-Schill, S. L. (2014). Reworking the language network. *Trends in Cognitive Sciences*, 18(3), 120–126. <https://doi.org/10.1016/J.TICS.2013.12.006>.
- Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *Neuroimage*, 54(1), 313–327. <https://doi.org/10.1016/J.NEUROIMAGE.2010.07.033>.
- Forkel, S. J., Thiebaut de Schotten, M., Dell'Acqua, F., Kalra, L., Murphy, D. G. M., Williams, S. C. R., et al. (2014). Anatomical predictors of aphasia recovery: A tractography study of bilateral perisylvian language networks. *Brain*, 137(7), 2027–2039. <https://doi.org/10.1093/brain/awu113>.
- François, C., Ripollés, P., Bosch, L., Garcia-Alix, A., Muchart, J., Sierpowska, J., et al. (2016). Language learning and brain reorganization in a 3.5-year-old child with left perinatal stroke revealed using structural and functional connectivity. *Cortex*, 77, 95–118. <https://doi.org/10.1016/J.CORTEX.2016.01.010>.
- Friederici, A. D. (2012). The cortical language circuit: From auditory perception to sentence comprehension. *Trends in Cognitive Sciences*, 16(5), 262–268. <https://doi.org/10.1016/J.TICS.2012.04.001>.
- Goldin-Meadow, S., Levine, S. C., Hedges, L. V., Huttenlocher, J., Raudenbush, S. W., & Small, S. L. (2014). New evidence about language and cognitive development based on a longitudinal study: Hypotheses for intervention. *American Psychologist*, 69(6), 588–599. <https://doi.org/10.1037/a0036886>.
- Graveline, C. J., Mikulis, D. J., Crawley, A. P., & Hwang, P. A. (1998). Regionalized sensorimotor plasticity after hemispherectomy fMRI evaluation. *Pediatric Neurology*, 19(5), 337–342. [https://doi.org/10.1016/S0887-8994\(98\)00082-4](https://doi.org/10.1016/S0887-8994(98)00082-4).
- Greco, F., Finocchiaro, M., Pavone, P., Trifiletti, R. R., & Parano, E. (2001). Hemihydranencephaly: Case report and literature review. *Journal of Child Neurology*, 16(3), 218–221. <https://doi.org/10.1177/088307380101600311>.
- Greenough, W. T., Black, J. E., & Wallace, C. S. (1987). Experience and brain development. *Child Development*, 58(3), 539. <https://doi.org/10.2307/1130197>.
- Griessenauer, C. J., Salam, S., Hendrix, P., Patel, D. M., Tubbs, R. S., Blount, J. P., et al. (2015). Hemispherectomy for treatment of refractory epilepsy in the pediatric age group: A systematic review. *Journal of Neurosurgery: Pediatrics*, 15(1), 34–44. <https://doi.org/10.3171/2014.10.PEDS14155>.
- Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., et al. (2008). Mapping the structural core of human cerebral cortex. *Plos Biology*, 6(7), e159. <https://doi.org/10.1371/journal.pbio.0060159>.
- Hagoort, P. (2014). Nodes and networks in the neural architecture for language: Broca's region and beyond. *Current Opinion in Neurobiology*, 28, 136–141. <https://doi.org/10.1016/j.conb.2014.07.013>.
- Hassanein, S. M. A., Abbas, Y. A., Monib, A. M., & El Alfy, M. S. (2011). Hemihydranencephaly syndrome: Case report and review. *Developmental Neurorehabilitation*, 14(5), 323–329. <https://doi.org/10.3109/17518423.2011.593574>.
- Hertz-Pannier, L., Chiron, C., Jambaqué, I., Renaux-Kieffer, V., Van de Moortele, P., Delalande, O., et al. (2002). Late plasticity for language in a child's non-dominant hemisphere. *Brain*, 125(2), 361–372. <https://doi.org/10.1093/brain/awf020>.
- Hickok, G. (2012). Computational neuroanatomy of speech production. *Nature Reviews Neuroscience*, 13(2), 135–145. <https://doi.org/10.1038/nrn3158>.
- Hill, J., Dierker, D., Neil, J., Inder, T., Knutsen, A., Harwell, J., et al. (2010). A surface-based analysis of hemispheric asymmetries and folding of cerebral cortex in term-born human infants. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 30(6), 2268–2276. <https://doi.org/10.1523/JNEUROSCI.4682-09.2010>.
- Holloway, V., Gadian, D. G., Vargha-Khadem, F., Porter, D. A., Boyd, S. G., & Connelly, A. (2000). The reorganization of sensorimotor function in children after hemispherectomy: A functional MRI and somatosensory evoked potential study. *Brain*, 123(12), 2432–2444. <https://doi.org/10.1093/brain/123.12.2432>.
- Huttenlocher, J., Vasilyeva, M., Cymerman, E., & Levine, S. (2002). Language input and child syntax. *Cognitive Psychology*, 45(3), 337–374. [https://doi.org/10.1016/S0010-0285\(02\)00500-5](https://doi.org/10.1016/S0010-0285(02)00500-5).
- Ivles, P., Tomberg, T., Kepler, J., Laugesaar, R., Kaldoja, M.-L., Kepler, K., et al. (2014). Different plasticity patterns of language function in children with perinatal and childhood stroke. *Journal of Child Neurology*, 29(6), 756–764. <https://doi.org/10.1177/0883073813489350>.
- Kamali, A., Flanders, A. E., Brody, J., Hunter, J. V., & Hasan, K. M. (2014). Tracing superior longitudinal fasciculus connectivity in the human brain using high resolution diffusion tensor tractography. *Brain Structure & Function*, 219(1), 269–281. <https://doi.org/10.1007/s00429-012-0498-y>.
- Kasprian, G., Langs, G., Brugger, P. C., Bittner, M., Weber, M., Arantes, M., et al. (2011). The prenatal origin of hemispheric asymmetry: An in utero neuroimaging study. *Cerebral Cortex*, 21(5), 1076–1083. <https://doi.org/10.1093/cercor/bhq179>.
- Kirton, A., DeVeber, G., Pontigon, A.-M., Macgregor, D., & Shroff, M. (2008). Presumed perinatal ischemic stroke: Vascular classification predicts outcomes. *Annals of Neurology*, 63(4), 436–443. <https://doi.org/10.1002/ana.21334>.
- Kolb, B., & Gibb, R. (2014). Searching for the principles of brain plasticity and behavior. *Cortex*, 58, 251–260. <https://doi.org/10.1016/J.CORTEX.2013.11.012>.
- Kolb, B., & Tomie, J.-A. (1988). Recovery from early cortical damage in rats: IV. Effects of hemidecortication at 1, 5 or 10 days of age on cerebral anatomy and behavior. *Behavioural Brain Research*, 28(3), 259–274. [https://doi.org/10.1016/0166-4328\(88\)90129-5](https://doi.org/10.1016/0166-4328(88)90129-5).
- Küpper, H., Kudernatsch, M., Pieper, T., Groeschel, S., Tournier, J.-D., Raffelt, D., et al. (2016). Predicting hand function after hemidisconnection. *Brain*, 139(9), 2456–2468. <https://doi.org/10.1093/brain/aww170>.
- Lametti, D. R., Smith, H. J., Freidin, P. F., & Watkins, K. E. (2018). Cortico-cerebellar networks drive sensorimotor learning in speech. *Journal of Cognitive Neuroscience*, 30(4), 540–551. [https://doi.org/10.1162/jocn\\_a\\_01216](https://doi.org/10.1162/jocn_a_01216).
- Levine, S. C., Kraus, R., Alexander, E., Suriyakham, L. W., & Huttenlocher, P. R. (2005). IQ decline following early unilateral brain injury: A longitudinal study. *Brain and Cognition*, 59(2), 114–123. <https://doi.org/10.1016/J.BANDC.2005.05.008>.
- Levine, S. C., Raja Beharelle, A., Demir, Ö. E., & Small, S. L. (2016). Perinatal focal brain injury: Scope and limits of plasticity of language learning, knowledge and use. In G. Hickok, & S. L. Small (Eds.), *Neurobiology of language* (pp. 969–979). Amsterdam: Elsevier.
- Lidzba, K., Wilke, M., Staudt, M., Krägeloh-Mann, I., & Grodd, W. (2008). Reorganization of the cerebro-cerebellar network of language production in patients with congenital left-hemispheric brain lesions. *Brain and Language*, 106(3), 204–210. <https://doi.org/10.1016/J.BANDL.2007.11.003>.
- Liégeois, F., Connelly, A., Baldeweg, T., & Vargha-Khadem, F. (2008). Speaking with a single cerebral hemisphere: fMRI language organization after hemispherectomy in childhood.

- Brain and Language*, 106(3), 195–203. <https://doi.org/10.1016/J.BANDL.2008.01.010>.
- Liu, Y., Balériaux, D., Kavec, M., Metens, T., Absil, J., Denolin, V., et al. (2010). Structural asymmetries in motor and language networks in a population of healthy preterm neonates at term equivalent age: A diffusion tensor imaging and probabilistic tractography study. <https://doi.org/10.1016/j.neuroimage.2010.02.066>.
- López-Barroso, D., Catani, M., Ripollés, P., Dell'acqua, F., Rodríguez-Fornells, A., & de Diego-Balaguer, R. (2013). Word learning is mediated by the left arcuate fasciculus. In *Proceedings of the national academy of Sciences of the United States of America*. <https://doi.org/10.1073/pnas.1301696110>.
- Mahmoudzadeh, M., Dehaene-Lambertz, G., Fournier, M., Kongolo, G., Goudjil, S., Dubois, J., et al. (2013). Syllabic discrimination in premature human infants prior to complete formation of cortical layers. *Proceedings of the National Academy of Sciences*, 110, 4846–4851.
- Marcus, D. S., Harwell, J., Olsen, T., Hodge, M., Glasser, M. F., Prior, F., et al. (2011). Informatics and data mining tools and strategies for the human connectome project. *Frontiers in Neuroinformatics*, 5, 4. <https://doi.org/10.3389/fninf.2011.00004>.
- Mikellidou, K., Arrighi, R., Aghakhanyan, G., Tinelli, F., Frijia, F., Crespi, S., et al. (2017). Plasticity of the human visual brain after an early cortical lesion. *Neuropsychologia*. <https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2017.10.033>.
- Mori, S., Crain, B. J., Chacko, V. P., & Van Zijl, P. C. M. (1999). Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Annals of Neurology*, 45(2), 265–269. [https://doi.org/10.1002/1531-8249\(199902\)45:2<265::AID-ANA21>3.0.CO;2-3](https://doi.org/10.1002/1531-8249(199902)45:2<265::AID-ANA21>3.0.CO;2-3).
- Muckli, L., Naumer, M. J., & Singer, W. (2009). Bilateral visual field maps in a patient with only one hemisphere. *Proceedings of the National Academy of Sciences of the United States of America*, 106(31), 13034–13039. <https://doi.org/10.1073/pnas.0809688106>.
- Northam, G. B., Adler, S., Eschmann, K. C. J., Chong, W. K., Cowan, F. M., & Baldeweg, T. (2018). Developmental conduction aphasia after neonatal stroke. *Annals of Neurology*, 83(4), 664–675. <https://doi.org/10.1002/ana.25218>.
- O'Muircheartaigh, J., Dean, D. C., Dirks, H., Waskiewicz, N., Lehman, K., Jerskey, B. A., et al. (2013). Interactions between white matter asymmetry and language during neurodevelopment. *Journal of Neuroscience*, 33(41), 16170–16177. <https://doi.org/10.1523/JNEUROSCI.1463-13.2013>.
- Pavone, P., Nigro, F., Falsaperla, R., Greco, F., Ruggieri, M., Rizzo, R., et al. (2013). Hemihydranencephaly: Living with half brain dysfunction. *Italian Journal of Pediatrics*, 39(1), 3. <https://doi.org/10.1186/1824-7288-39-3>.
- Perani, D., Saccuman, M. C., Scifo, P., Anwander, A., Anwander, A., Spada, D., et al. (2011). Neural language networks at birth. *Proceedings of the National Academy of Sciences of the United States of America*, 108(38), 16056–16061. <https://doi.org/10.1073/pnas.1102991108>.
- Poeppl, D. (2014). The neuroanatomic and neurophysiological infrastructure for speech and language. *Current Opinion in Neurobiology*, 28, 142–149. <https://doi.org/10.1016/J.CONB.2014.07.005>.
- Psychometric conversion table. (2011). Retrieved from [http://www.ritenour.k12.mo.us/cms/lib011/MO01910124/Centricity/Domain/69/Psychometric\\_Conversion\\_Table.pdf](http://www.ritenour.k12.mo.us/cms/lib011/MO01910124/Centricity/Domain/69/Psychometric_Conversion_Table.pdf).
- Ripollés, P., Biel, D., Peñaloz, C., Kaufmann, J., Marco-Pallarés, J., Noesselt, T., et al. (2017). Strength of temporal white matter pathways predicts semantic learning. *The Journal of Neuroscience*, 37(46), 11101–11113. <https://doi.org/10.1523/JNEUROSCI.1720-17.2017>.
- Rowe, M. L., Levine, S. C., Fisher, J. A., & Goldin-Meadow, S. (2009). Does linguistic input play the same role in language learning for children with and without early brain injury? *Developmental Psychology*, 45(1), 90–102. <https://doi.org/10.1037/a0012848>.
- Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage*, 52(3), 1059–1069. <https://doi.org/10.1016/J.NEUROIMAGE.2009.10.003>.
- Sauer, E., Levine, S. C., & Goldin-Meadow, S. (2010). Early gesture predicts language delay in children with pre- or perinatal brain lesions. *Child Development*, 81(2), 528–539. <https://doi.org/10.1111/j.1467-8624.2009.01413.x>.
- Saygin, Z. M., Norton, E. S., Osher, D. E., Beach, S. D., Cyr, A. B., Ozernov-Palchik, O., et al. (2013). Tracking the roots of reading ability: White matter volume and integrity correlate with phonological awareness in prereading and early-reading kindergarten children. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 33(33), 13251–13258. <https://doi.org/10.1523/JNEUROSCI.4383-12.2013>.
- Sebastianelli, L., Versace, V., Taylor, A., Brigo, F., Nothdurfter, W., Saltuari, L., et al. (2017). Functional reorganization after hemispherectomy in humans and animal models: What can we learn about the brain's resilience to extensive unilateral lesions? *Brain Research Bulletin*, 131, 156–167. <https://doi.org/10.1016/J.BRAINRESBULL.2017.04.005>.
- Silbereis, J. C., Pochareddy, S., Zhu, Y., Li, M., & Sestan, N. (2016). The cellular and molecular landscapes of the developing human central nervous system. *Neuron*, 89(2), 248–268. <https://doi.org/10.1016/J.NEURON.2015.12.008>.
- Solodkin, A., Hasson, U., Siugzdaite, R., Schiel, M., Chen, E. E., Rolf, K., et al. (2010). Virtual brain transplantation (VBT): A method for accurate image registration and parcellation in large cortical stroke. *Archives Italiennes de Biologie*, 148(3), 219–241. <https://doi.org/10.4449/AIB.V148I3.1221>.
- Sommer, M. A. (2003). The role of the thalamus in motor control. *Current Opinion in Neurobiology*, 13(6), 663–670. <https://doi.org/10.1016/J.CONB.2003.10.014>.
- Staudt, M. (2010). Reorganization after pre- and perinatal brain lesions. *Journal of Anatomy*, 217(4), 469–474. <https://doi.org/10.1111/j.1469-7580.2010.01262.x>.
- Staudt, M., Gerloff, C., Grodd, W., Holthausen, H., Niemann, G., & Krägeloh-Mann, I. (2004). Reorganization in congenital hemiparesis acquired at different gestational ages. *Annals of Neurology*, 56(6), 854–863. <https://doi.org/10.1002/ana.20297>.
- Staudt, M., Grodd, W., Gerloff, C., Erb, M., Stitz, J., & Krägeloh-Mann, I. (2002). Two types of ipsilateral reorganization in congenital hemiparesis: A TMS and fMRI study. *Brain*, 125(10), 2222–2237. <https://doi.org/10.1093/brain/awf227>.
- Stiles, J., Reilly, J. S., Levine, S. C., Trauner, D. A., & Nass, R. (2012). *Neural plasticity and cognitive development: Insights from children with perinatal brain injury*. New York, NY: Oxford University Press.
- Su, M., Thiebaut de Schotten, M., Zhao, J., Song, S., Zhou, W., Gong, G., et al. (2018). Vocabulary growth rate from preschool to school-age years is reflected in the connectivity of the arcuate fasciculus in 14-year-old children. *Developmental Science*, e12647. <https://doi.org/10.1111/desc.12647>.
- Tau, G. Z., & Peterson, B. S. (2010). Normal development of brain circuits. *Neuropsychopharmacology*, 35(1), 147–168. <https://doi.org/10.1038/npp.2009.115>.
- Teuber, H. L. (1975). Effects of focal brain injury on human behavior. In Donald Tower (Ed.), Vol. 2. *The Nervous System* (pp. 182–201). New York: Raven Press.
- Teubner-Rhodes, S., Vaden, K. I., Cute, S. L., Yeatman, J. D., Dougherty, R. F., & Eckert, M. A. (2016). Aging-resilient associations between the arcuate fasciculus and vocabulary knowledge: Microstructure or morphology? *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*,

- 36(27), 7210–7222. <https://doi.org/10.1523/JNEUROSCI.4342-15.2016>.
- Thomas, C., Ye, F. Q., Irfanoglu, M. O., Modi, P., Saleem, K. S., Leopold, D. A., et al. (2014). Anatomical accuracy of brain connections derived from diffusion MRI tractography is inherently limited. *Proceedings of the National Academy of Sciences*, 111(46), 16574–16579. <https://doi.org/10.1073/pnas.1405672111>.
- Travis, K. E., Adams, J. N., Kovachy, V. N., Ben-Shachar, M., & Feldman, H. M. (2017). White matter properties differ in 6-year old Readers and Pre-readers. *Brain Structure & Function*, 222(4), 1685–1703. <https://doi.org/10.1007/s00429-016-1302-1>.
- Ulmer, S., Moeller, F., Brockmann, M. A., Kuhtz-Buschbeck, J. P., Stephani, U., & Jansen, O. (2005). Living a normal life with the nondominant hemisphere: Magnetic resonance imaging findings and clinical outcome for a patient with left-hemispheric hydranencephaly. *Pediatrics*, 116(1), 242–245. <https://doi.org/10.1542/peds.2004-0425>.
- Vandermosten, M., Vanderauwera, J., Theys, C., De Vos, A., Vanvooren, S., Sunaert, S., et al. (2015). A DTI tractography study in pre-readers at risk for dyslexia. *Developmental Cognitive Neuroscience*, 14, 8–15. <https://doi.org/10.1016/j.dcn.2015.05.006>.
- Villablanca, J. R., Carlson-Kuhta, P., Schmanke, T. D., & Hovda, D. A. (1998). A critical maturational period of reduced brain vulnerability to developmental injury. *Developmental Brain Research*, 105(2), 309–324. [https://doi.org/10.1016/S0165-3806\(97\)00187-9](https://doi.org/10.1016/S0165-3806(97)00187-9).
- Villablanca, J., & Hovda, D. (1999). Developmental neuroplasticity in a model of cerebral hemispherectomy and stroke. *Neuroscience*, 95(3), 625–637. [https://doi.org/10.1016/S0306-4522\(99\)00482-0](https://doi.org/10.1016/S0306-4522(99)00482-0).
- Voets, N. L., Adcock, J. E., Flitney, D. E., Behrens, T. E. J., Hart, Y., Stacey, R., et al. (2006). Distinct right frontal lobe activation in language processing following left hemisphere injury. *Brain*, 129(3), 754–766. <https://doi.org/10.1093/brain/awh679>.
- Wakamoto, H., Eluvathingal, T. J., Makki, M., Juhasz, C., & Chugani, H. T. (2006). Diffusion tensor imaging of the corticospinal tract following cerebral hemispherectomy. *Journal of Child Neurology*, 21(7), 566–571. <https://doi.org/10.1177/08830738060210071401>.
- Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., et al. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *Neuroimage*, 36(3), 630–644. <https://doi.org/10.1016/J.NEUROIMAGE.2007.02.049>.
- Walton, M., Dewey, D., & Lebel, C. (2018). Brain white matter structure and language ability in preschool-aged children. *Brain and Language*, 176, 19–25. <https://doi.org/10.1016/j.bandl.2017.10.008>.
- Wang, R., Benner, T., Sorensen, A. G., & Wedeen, V. J. (2007). Diffusion Toolkit : A software package for diffusion imaging data processing and tractography. In *Proc. Intl. Soc. Mag. Reson. Med.* (Vol. 15, p. 3720). <https://doi.org/10.1128/MCB.25.11.4371>.
- Wang, Y., Mauer, M. V., Raney, T., Peysakhovich, B., Becker, B. L. C., Sliva, D. D., et al. (2016). Development of tract-specific white matter pathways during early reading development in at-risk children and typical controls. *Cerebral Cortex*, 27(4), bhw095. <https://doi.org/10.1093/cercor/bhw095>.
- Werth, R. (2006). Visual functions without the occipital lobe or after cerebral hemispherectomy in infancy. *European Journal of Neuroscience*, 24(10), 2932–2944. <https://doi.org/10.1111/j.1460-9568.2006.05171.x>.
- Westmacott, R., Askalan, R., Macgregor, D., Anderson, P., & Deveber, G. (2010). Cognitive outcome following unilateral arterial ischaemic stroke in childhood: Effects of age at stroke and lesion location. *Developmental Medicine and Child Neurology*, 52(4), 386–393. <https://doi.org/10.1111/j.1469-8749.2009.03403.x>.
- Wilke, M., Staudt, M., Juenger, H., Grodd, W., Braun, C., & Krägeloh-Mann, I. (2009). Somatosensory system in two types of motor reorganization in congenital hemiparesis: Topography and function. *Human Brain Mapping*, 30(3), 776–788. <https://doi.org/10.1002/hbm.20545>.
- Yeatman, J. D., Dougherty, R. F., Rykhlevskaia, E., Sherbondy, A. J., Deutsch, G. K., Wandell, B. A., et al. (2011). Anatomical properties of the arcuate fasciculus predict phonological and reading skills in children. *Journal of Cognitive Neuroscience*, 23(11), 3304–3317. [https://doi.org/10.1162/jocn\\_a\\_00061](https://doi.org/10.1162/jocn_a_00061).
- Yeatman, J. D., & Feldman, H. M. (2013). Neural plasticity after pre-linguistic injury to the arcuate and superior longitudinal fasciculi. *Cortex*, 49(1), 301–311. <https://doi.org/10.1016/J.CORTEX.2011.08.006>.
- Yuan, W., Altaye, M., Ret, J., Schmithorst, V., Byars, A. W., Plante, E., et al. (2009). Quantification of head motion in children during various fMRI language tasks. *Human Brain Mapping*, 30(5), 1481–1489. <https://doi.org/10.1002/hbm.20616>.