Language and developmental plasticity after perinatal stroke

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The mature human brain is lateralized for language, with the left hemisphere (LH) primarily responsible for sentence processing and the right hemisphere (RH) primarily responsible for processing suprasegmental aspects of language such as vocal emotion. However, it has long been hypothesized that in early life there is plasticity for language, allowing young children to acquire language in other cortical regions when LH areas are damaged. If true, what are the constraints on functional reorganization? Which areas of the brain can acquire language, and what happens to the functions these regions ordinarily perform? We address these questions by examining long-term outcomes in adolescents and young adults who, as infants, had a perinatal arterial ischemic stroke to the LH areas ordinarily subserving sentence processing. We compared them with their healthy age-matched siblings. All participants were tested on a battery of behavioral and functional imaging tasks. While stroke participants were impaired in some nonlinguistic cognitive abilities, their processing of sentences and of vocal emotion was normal and equal to that of their healthy siblings. In almost all, these abilities have both developed in the healthy RH. Our results provide insights into the remarkable ability of the young brain to reorganize language. Reorganization is highly constrained, with sentence processing almost always in the RH frontotemporal regions homotopic to their location in the healthy brain. This activation is somewhat segregated from RH emotion processing, suggesting that the two functions perform best when each has its own neural territory.

language | pediatric stroke | developmental plasticity | brain reorganization

While the human brain shows many localized functions, recent research has shown that it is also capable of striking reorganization, particularly in the face of early sensory or motor loss or acute injury. In some of the most dramatic findings, the visual cortex of congenitally blind individuals is activated by tactile braille reading (1), and the hand area of the motor cortex in individuals born without arms is activated by reaching with the feet (2). There are equally striking findings for language reorganization in children with early damage to the left hemisphere (LH): while language in healthy adults is virtually always lateralized to the LH, many researchers have claimed that children with severe damage to the LH during infancy can acquire language in the right hemisphere (RH) (3–12). What is not clear from these various findings, however, is what principles underlie neural plasticity and what constraints there may be on neural reorganization during early development.

In the present paper, we focus on the organization of language after acute perinatal injury as a potential model for understanding developmental plasticity more broadly. Our focus is on adolescents and young adults who had a LH stroke at birth, damaging the territory that would ordinarily subserve word and sentence production and comprehension. We recruited individuals who had a perinatal arterial ischemic stroke to the LH middle cerebral artery (MCA) territory and, as much as possible, had had no other medical problems, and we tested them many years later to observe the long-term outcome of their language abilities and their organization in the brain.

Views of Plasticity and the Reorganization of Language

The suggestion that there is heightened plasticity in early development after injury or altered input (13, 14) has been a particular focus in work on language. As noted above, language in healthy adults is virtually always lateralized to the LH (15–17). However, Basser (3) and Lenneberg [(4); see also (18)] suggested that after early damage to the LH, language could recover in the RH. This is not the case for adults, who do not show this pattern of recovery and do not ordinarily recover full language abilities after severe LH injuries (19).

However, recent research on LH damage in infants and young children has found more varied patterns of recovery and reorganization. Some studies have found good

Significance

It has long been claimed that the young brain is capable of recovery and reorganization that does not occur in adults. However, evidence has been mixed, and the principles and constraints of developmental plasticity are not well understood. Here, we study long-term language outcomes in adolescents and young adults who suffered a major stroke at birth to the classic left-hemisphere (LH) language areas. Our participants have developed normal sentence processing abilities in right-hemisphere (RH) areas homotopic to typical LH regions, near the RH regions responsible for processing vocal emotion. There is indeed a dramatic capacity for early brain reorganization. However, the systematic pattern of reorganization across individuals suggests that only certain brain areas are capable of taking on language functions.

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language abilities after focal brain injury in children (5, 20, 21), but others have not (22–24). Studies of neural organization underlying these outcomes in children, using functional MRI (fMRI), find three different types of patterns. Many investigators (7–12, 25–34) have found recovery of LH language skills in the RH frontotemporal cortex, in accord with Basser and Lenneberg. Others (35–37) have suggested that the LH is uniquely suited for language and that successful recovery of language is limited to LH language areas or their surrounding margins [cf. (37), which argued that remaining LH voxels correlate best with language proficiency]. A third view is that the young brain is highly plastic and that language skills can develop in other, nonlanguage brain regions (38), even including V1 and occipital-parietal regions (39). In the present work, we seek to reexamine what brain areas can support language under atypical circumstances and ultimately to understand why some areas but not others are suitable for developing language.

The Present Studies

There are several reasons why previous work might have produced inconsistent results. First, while many studies have included children with focal lesions of various types and etiologies—often including those with prenatal, perinatal, or later infant stroke, as well as periventricular venous stroke and other injuries—here we chose to focus on a more well-defined participant group: adolescents and young adults who, many years earlier, suffered a *perinatal arterial ischemic stroke* (that is, an arterial ischemic stroke at or near birth) to the LH MCA and, as a result, had a large infarct to the LH regions ordinarily subserving language [(40) for perinatal stroke subtypes]. We have recruited participants who, like many with perinatal stroke, were born after a full-term pregnancy with no other disorders and since that time have experienced few medical complications (see *Participants*). Second, while most studies have focused on infants or young children, we are studying older children and young adults in order to observe the long-term outcome of such injuries. Third, we have chosen language tasks for our assessments that, as much as possible, evaluate language skills per se and avoid confounding them with executive function demands that are often impaired after brain injuries (41).

We also take an expanded view of the language system. While language is often described as lateralized to the LH in healthy adults, this refers to the most well-studied linguistic functions: phonology, word recognition and retrieval, and sentence processing. There are also linguistic functions that are typically lateralized to the RH: suprasegmental language functions, such as processing vocal emotion (42). Here we present findings on both of these types of functions, allowing us to ask how both types of functions develop when only one hemisphere is healthy.

Our first question concerns sentence processing, which in healthy adults is lateralized to the perisylvian areas of the LH (43). By 'sentence processing,' we mean here the many lexical, syntactic, and semantic processes that occur when we understand and make decisions about a sentence. What happens to sentence processing when those regions are partially or wholly damaged by a stroke at birth? What areas of the remaining cortex are capable of acquiring and supporting this central feature of language, and how well do they do? To ask this question, we used a functional imaging task that has been well studied in healthy and neurologically impaired children and adults: the Auditory Description Decision Task (ADDT) (25). We selected this task because it typically produces strong activation throughout the LH language network, in both the frontal and temporal cortices, in healthy individuals and would allow us to ask whether there is a language network after perinatal injury and where it might be localized. We also administered a variety of behavioral language tasks. As we show, virtually all of our LH stroke participants activate the perisylvian regions of the RH during the ADDT, as has been found in some of the previous literature on children with perinatal stroke (7–11, 32, 34) and in about 20% of children with early LH epilepsy (25–29). Surprisingly, our behavioral testing shows that their language abilities are quite normal and no different from those of their healthy siblings.

We then turn to assessing the processing of vocal emotion, which in healthy adults is ordinarily lateralized to the same RH perisylvian regions that in LH perinatal stroke participants support sentence processing (42, 44–46). Here we find, also surprising, that those RH perisylvian regions support the processing of vocal emotion too—though in somewhat distinct subregions from those that support sentence processing.

Finally, we return to a discussion of what these results tell us about the flexibility and the limits of developmental plasticity.

Results

Sentence Processing after LH Perinatal Stroke.

Imaging: ADDT (sentence processing) activation. We tested 15 adolescents and young adults (ages 9.7 to 26.5 y) who had had an arterial ischemic stroke to the LH MCA territory during the perinatal period, around the time of birth (henceforth LHPS participants). Our focus is on the long-term outcome for language, in terms of its proficiency and its organization in the brain, after LH perinatal stroke. While this age range is somewhat large, all are old enough to be at an asymptotic level for language processing, and as we show, all show very consistent results in both language abilities and their representation in the brain. We selected participants who had medium to large strokes, affecting the anterior portion, posterior portion, or all of the LH perisylvian territory ordinarily controlling sentence processing and other linguistic abilities in the healthy brain. An MRI of each participant is shown in *SI Appendix*, Fig. S1, with infarct sizes and locations listed in *SI Appendix*, Table S1. For comparison, we also tested 12 healthy controls who were the siblings of these participants (ages 9.75 to 29.5 y) and who therefore grew up with the same families and socioeconomic circumstances as the stroke participants. There were no significant differences between the groups in age [healthy controls mean (SD) = 15.44 y (5.09), LHPS participants mean (SD) = 17.33 y (5.17); t (25) = 0.96, P = 0.35] or in proportion of females (healthy siblings = 3/12, LHPS participants = 6/15; P = 0.40 on Fisher's exact probability).

Each participant was tested in a 3-tesla (3T) scanner on the ADDT (25, 47). In the target condition, participants heard sentences like "A big gray animal is an elephant" and were asked to push a button if the sentence was correct; in the control condition, they heard the same sentences backward, as a control for auditory stimulation (but without comprehensible language) and were asked to push a button if they heard a beep at the end, as a control for motor responding. Comparing activation for forward > backward conditions should thus reveal brain areas involved in speech and sentence comprehension. As noted above, this task typically produces strong activation throughout the LH language network, in the frontal and temporal cortices, in healthy participants.

In-scanner behavior. All participants performed well above chance in the scanner. Healthy controls averaged 97.22% correct

(SD 2.56), and the LHPS group averaged 95.14% correct (SD 5.66), with no significant differences between groups in accuracy [$t(25) = 1.27$, $P = 0.22$] or reaction time [healthy controls mean 3,010 ms (SD 125); LHPS participants mean 3,068 ms (SD 176); $t(25) = 0.99$, $P = 0.33$].

Individual and group-level activations. Fig. 1 shows example individual activation maps for three healthy controls and six LHPS participants in the forward > backward speech contrast. The healthy controls show activation predominantly in the typical LH language areas (LH inferior frontal and temporal cortices), as is the case for many language tasks. In contrast, the LHPS participants show activation in the RH frontal and/or temporal regions, homotopic to those of the healthy controls. *SI Appendix*, *Fig. S2* shows the individual activation maps for all of the participants in both groups, and *SI Appendix*, *Fig. S3A* shows the laterality indices (LIs) for all participants. The LIs show that while all of the healthy control participants were left-lateralized for sentence processing, all but one of the LHPS participants were right-lateralized for sentence processing. Only the two stroke participants with the smallest lesions showed a somewhat different pattern than the others: L15 showed bilateral but still right-dominant language activation. L14 showed left-dominant activation. The group difference in the ADDT LIs is highly significant [$t(25) = 11.01$, $P < 0.0001$].
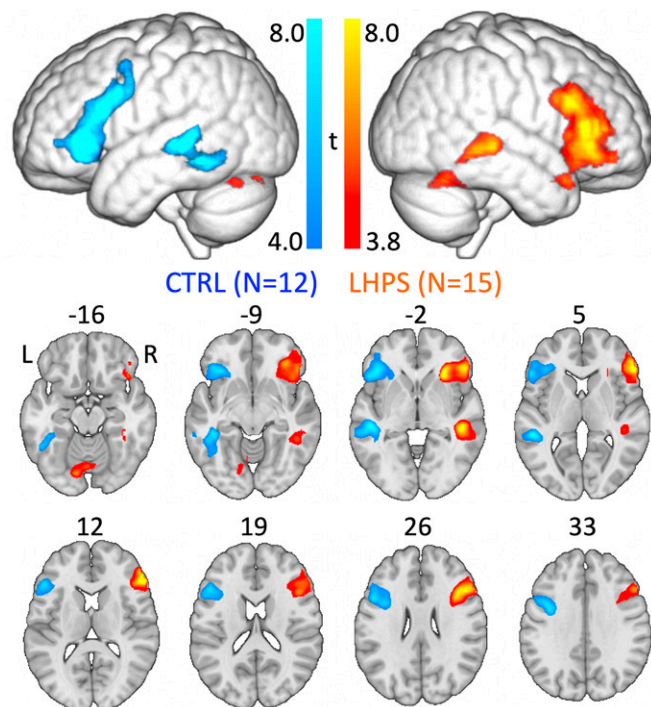

Fig. 2. Group-level activation maps for the sentence processing task (forward > reverse speech contrast) for the CTRL (blue) and LHPS (red/orange) groups, overlaid on the same MNI-space template brain. Both group maps are thresholded at a single-voxel threshold of $P < 0.001$ and a cluster-size threshold corresponding to $P < 0.05$ (1,377 mm³ for the CTRL group and 1,485 mm³ for the LHPS group).

Fig. 2 shows the group-level activation maps for the healthy controls and LHPS groups. As seen in the individual examples, the healthy control group shows activations in the left inferior frontal and temporal cortices (in classic Broca's and Wernicke's areas). In contrast, the LHPS group shows RH inferior frontal and temporal activations, roughly homotopic to those of the healthy control group. Activation details are listed in Table 1.

Consistency of RH Activation and Possible Relation to Lesion Size and Location. This result of RH activation after LH perinatal stroke is in accord with the findings of several other investigators [(7–11, 18, 32–34); see related findings on children with epilepsy (26–28)] but has been questioned by some (30, 37). Importantly, the studies of early brain injuries that have argued for the importance of retaining LH language dominance for best language outcomes (30, 37) have included many children with prenatal or perinatal periventricular venous injuries, along with children with perinatal arterial stroke. However, periventricular injuries do not typically include extensive cortical damage to MCA territory. This type of injury may therefore present a different developmental picture for language and should be evaluated separately. In the present data, to address the inconsistent findings of previous studies, our participants have been carefully selected: they all have had a perinatal or presumed perinatal arterial ischemic stroke (no children are included with other types of neurological injuries), they all have fairly large MCA cortical lesions, and they have few or no other medical complications (especially no complex or recent seizure history).

Of particular interest is the high degree of consistency in the activation of RH regions homotopic to the typical LH language areas. While our participants are a more uniform group than those in previous studies, they did vary quite a bit in the
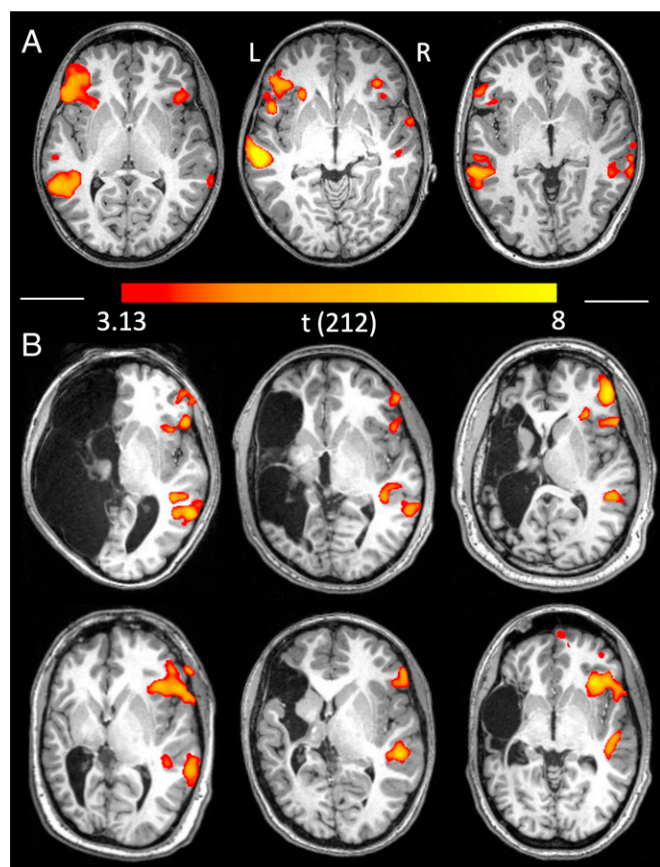
Fig. 1. Individual-level activations for sentence processing (forward > reverse speech contrast) in (*A*) three healthy controls (CTRLs) and (*B*) six LHPS participants, overlaid on horizontal slices of their anatomical scans in native space. Slices were selected to best show the activation, with the constraint that they are within 5 mm above or below the horizontal slice showing the anterior and posterior commissure. Maps are thresholded at a single-voxel threshold of $P < 0.001$ paired with a cluster-size threshold of 108 mm³. Slice views for all participants are shown in *SI Appendix*, *Fig. S2*.

Table 1. Activation peaks for the sentence processing task (forward > reverse speech contrast)

	Peak MNI coordinates	Peak *t* value	Description	Cluster size (mm³)
CTRL (*n* = 12)	−51, −28, −1	9.22	Left temporal cortex, overlapping with BAs 22, 21, and 37	8,424
	−54, −37, 2	8.53		
	−39, −37, −10	8.25		
	−39, 29, −7	8.15	Left inferior frontal cortex, overlapping with BAs 44, 45, 47, 8, and 6	18,630
	−48, 26, 14	7.94		
	−39, 5, 32	7.88		
LHPS (*n* = 15)	45, −31, −1	9.00	Right temporal cortex, overlapping with BAs 22, 21, 37, and 38	8,073
	33, −31, −22	6.35		
	39, −61, −25	5.56		
	57, 32, 11	14.57	Right inferior frontal cortex, overlapping with BAs 44, 45, and 47	25,785
	27, 23, −1	9.45		
	45, 20, 23	9.06		
	−9, −76, −22	7.56	Left cerebellum (extending into the right cerebellum)	10,395
	−21, −70, −46	6.18		
	9, −76, −28	5.73		
	−12, −70, 8	5.19	Left cerebellum	2,430
	−15, −79, 5	4.71		
	−3, −79, 17	3.88		

Reporting local maxima more than 8 mm apart, following SPM12 conventions. BAs, Brodmann areas.

location and sizes of their LH infarcts (*SI Appendix*, Fig. S1 and Table S1). However, in contrast to stroke in adults (48, 49), these infarct variables do not predict the specific language activations in our sentence processing task (or in their language abilities; see *Can the RH Fully Support Language after LH Perinatal Stroke?*). All of them activate the RH frontotemporal cortex for sentence processing, with no discernable relationship between their patterns of activation and the details of their infarcts, except at the very smallest size infarcts (L14 and perhaps L15) [(34) for a similar finding in a verb generation task]. *SI Appendix*, Fig. S4 shows a penetrance map illustrating the consistency of the activation patterns in the LH frontotemporal cortex for the healthy controls and in the RH frontotemporal cortex for the LHPS participants. This is particularly notable since many of our participants have infarcts that would appear to leave adequate healthy tissue to have developed some aspects of language in the LH. However, our results suggest that the classic language network more frequently develops as a whole in the opposite hemisphere, rather than developing, for example, a frontal component in one hemisphere and a temporal component in the other.

Can the RH Fully Support Language after LH Perinatal Stroke? How well does the RH support language in the LHPS participants? It is well known that children with early stroke may have executive function impairments (usually mild), including slower processing speed and slightly reduced short-term memory capacities (24), which we found in our participants as well. Therefore, to assess language abilities without confounding language with executive function, we selected tasks that involved language comprehension or production, ranging from simple to complex linguistic structures, but did not require memorizing or problem solving (as is often the case in standardized language tasks, which may, for example, ask children to assemble words or phrases printed on cards into sentences).

Fig. 3 shows scores for the LHPS participants, compared with their healthy sibling controls, on a number of language tasks: the Clinical Evaluation of Language Fundamentals (CELF) sentence comprehension and word structure subtests (50), the

Active-Passive Test (51), and the Test for Reception of Grammar (TROG-2) (52). All of the language tasks show fully normal language abilities in perinatal stroke participants. There was a significant difference between groups only on the CELF sentence comprehension subtest (U = 55, P = 0.039), where scores on this very simple task were mostly at ceiling (98% correct for LHPS participants versus 99.7% for healthy controls). All of the other language tasks show no significant differences between the LHPS group and their healthy controls [for the word structure subtest, $t(25) = 1.30$, $P = 0.21$; for the Active-Passive Test, $t(25) = 0.96$, $P = 0.35$; for the TROG-2, $t(25) = 1.07$, $P = 0.30$]. This is true even for the most complex items on the Active-Passive Test (passive affirmatives and negatives) and the TROG-2 (center embedded sentences), which are off the ceiling for healthy controls and still show no difference between LHPS participants and healthy controls [for passive sentences, $t(25) = 0.74$, $P = 0.47$; for center embedded items on the TROG-2, $t(25) = 0.04$, $P = 0.97$].

In short, then, the RH frontotemporal cortex does appear to be fully capable of supporting basic, as well as complex, sentence processing in individuals with LH perinatal stroke. This is not ordinarily the case in adults who have had a stroke later in life (53), nor is it the typical ability of the RH in healthy controls (16, 17).

Emotional Prosody Processing after LH Perinatal Stroke. In the healthy adult brain, the broader processing of language is laterally segregated. As already noted, sentence/syntax processing is ordinarily controlled by the LH. In contrast, the RH frontotemporal cortex ordinarily supports suprasegmental aspects of language: for example, the expression and recognition of vocal emotion and individual voice recognition—aspects of language carried through the prosody of the sentence (42, 44, 45). What happens to these suprasegmental processes if, after a LH perinatal stroke, sentence processing develops in the RH areas ordinarily devoted to the processing of emotion? To address this question, we administered a task we have developed for activating the RH regions for processing emotional prosody (EP) in the healthy brain.
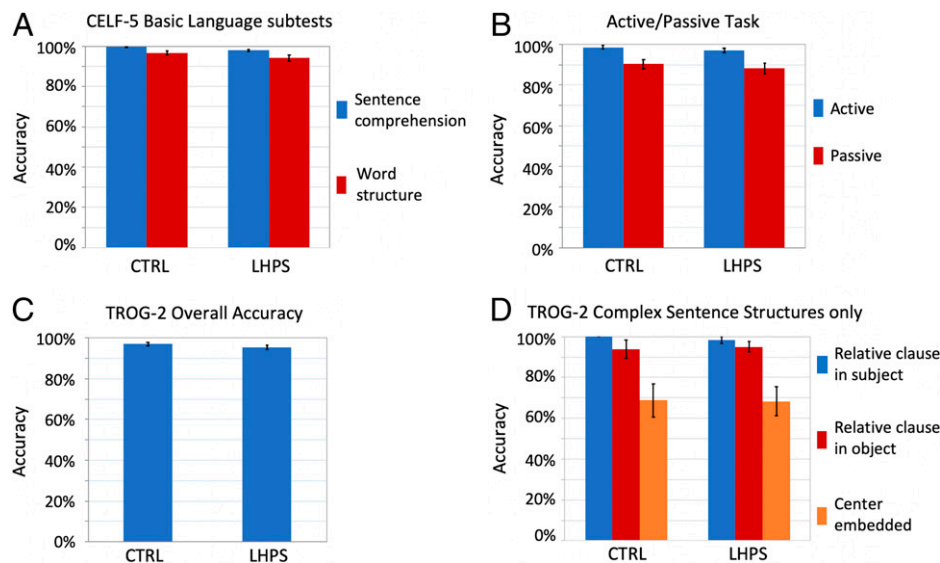
Fig. 3. Scores on several language tasks (*A-D*) for CTRL and LHPS participants.

Imaging: EP activation. We tested the same 15 LHPS participants and their 12 healthy sibling controls* in the same 3T scanner on a modified version of the EP task developed by Seydell-Greenwald et al.. In the target condition, participants heard sentences with neutral semantic content (e.g., "Dad made pot roast for dinner") but spoken with one of three vocal emotions—happy, sad, or angry—and were asked to push a button if the emotion matched a visual icon for an emotion presented at the end of the utterance (a sun for happy, teardrops for sad, or a boxing glove for angry). In the control condition, they heard the same sentences expressed with neutral prosody and were asked to push a button if the semantic content matched a visual icon for one of the content categories (a plate with fork and knife for food, a wrapped package for gift, or a van with suitcases on the roof for trip). Comparing activation for the emotion condition > neutral condition should reveal brain areas involved in processing EP. As noted, this task in healthy participants typically produces RH-dominant activation in the frontal and temporal cortices, roughly mirroring the LH-dominant language network (and also some bilateral activation in the auditory cortex due to the stronger auditory features of the emotional stimuli).

In-scanner behavior. All participants performed well above chance in the scanner. Healthy controls averaged 92.53% correct (SD 6.43), and the LHPS group averaged 90.69% correct (SD 7.79), with no significant differences between groups in accuracy [$t(25) = 0.67$, $P = 0.51$] or reaction time [healthy controls mean 502 ms (SD 73 ms); LHPS participants mean 534 ms (SD 91 ms); $t(25) = 1.02$, $P = 0.32$].

Individual and group-level activations. Fig. 4 shows example individual activation maps for three healthy controls and six LHPS participants in the emotional > neutral speech contrast. The LHPS participants all show activation in the RH frontal and temporal regions, in the same areas that are active in the healthy controls' RH, and in approximately the same areas that

we found (above) to be activated for LHPS participants' sentence processing. *SI Appendix*, Fig. S5 shows the individual activation maps for all of the participants in both groups. *SI Appendix*, Fig. S3B shows the LIs for all participants, almost all of whom show right lateralization for EP, with no significant differences between the groups [$t(25) = 0.87$, $P = 0.39$].
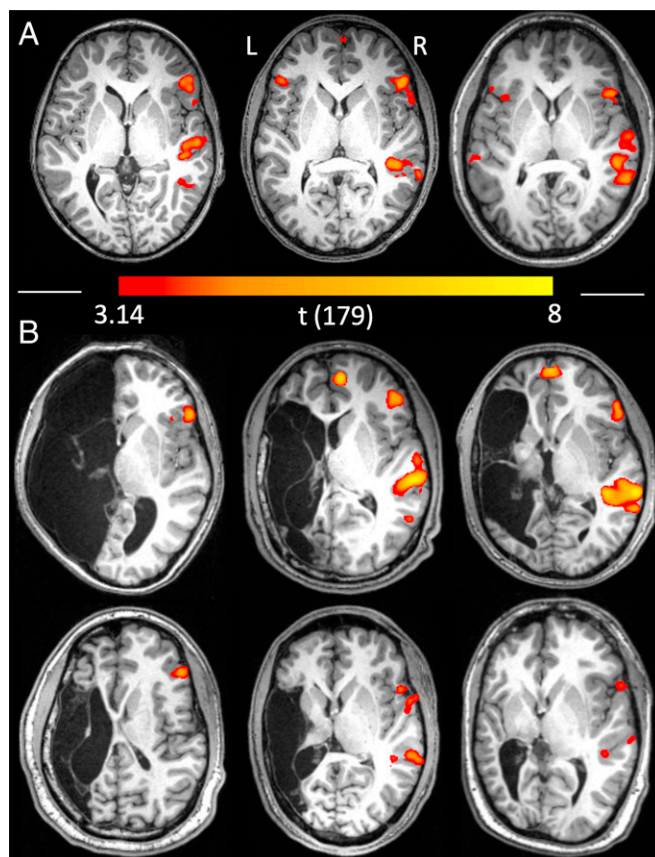

Fig. 4. Individual-level activations for EP (emotion condition > neutral speech) in (*A*) three healthy CTRLs and (*B*) six LHPS participants. Conventions as in Fig. 1. Slice views for all participants are shown in *SI Appendix*, Fig. S5.

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*Most of the participants were tested on this task at the same test sessions as for the ADDT and the language behavioral tasks. However, five LHPS participants and three healthy controls were tested 2 y later on this task because the task was developed later in our research. The age ranges for the groups were the same as for the ADDT, and there were still no age differences between the groups [healthy controls mean (SD) = 16.04 y (4.86), LHPS participants mean (SD) = 18.14 y (8.92); t (25) = 1.11, p = 0.28].
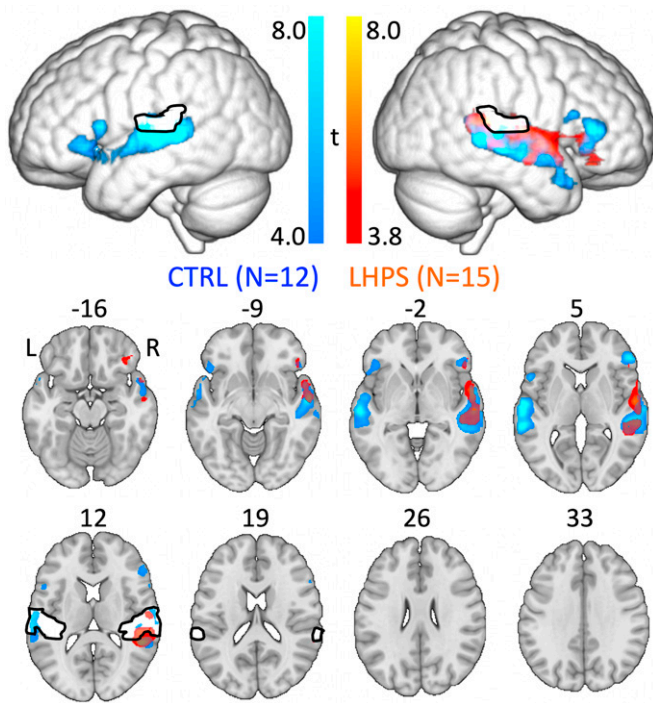
Fig. 5. Group-level activation maps for the EP task (emotional > neutral speech contrast) for the CTRL (blue) and LHPS (orange) groups, overlaid on the same MNI-space template brain. Both group maps are thresholded at a single-voxel threshold of $P < 0.001$ and a cluster-size threshold corresponding to $P < 0.05$ (1,539 mm³ for the CTRL group and 1,323 mm³ for the LHPS group). Highlighted in white with a black outline is the primary auditory cortex (Brodmann areas 41 and 42 from the Wake Forest Pickatlas, exported at a dilation of 2). While there is some overlap with this anatomical region of interest, activations extend far beyond primary auditory areas, suggesting that they are not driven purely by acoustic differences between the emotional and neutral speech stimuli.

Fig. 5 shows the group-level activation maps for emotional > neutral speech contrast for the healthy controls and LHPS groups. As expected, the healthy control group displayed somewhat bilateral but right-dominant temporal and inferior frontal activations; activation in the LHPS group was constrained to

the RH in the same regions. Activation details are listed in Table 2. For the LHPS group, these RH frontotemporal areas of activation are in roughly the same regions as those activated for sentence processing in the ADDT.

Spatial Separation of Sentence Processing and EP Processing

Taken together, these analyses show that in the healthy control group, the LH was dominant for sentence processing and the RH was dominant for EP processing; in contrast, for the vast majority of our LHPS participants, the RH was dominant for both sentence processing and EP. This raises the question of how these two functions share the available RH cortical territory in the LHPS participants. For this purpose, we examined individual activation patterns, whose precise spatial layout may be somewhat different from one individual to another, and we used a top-voxel analysis to roughly equate the activation levels of the two tasks for each individual (see *Materials and Methods* for details).

Fig. 6A shows, for three healthy control individuals, that the LH activation for sentence processing and the RH activation for EP are roughly symmetric. Given this symmetry, one would expect considerable overlap in the activations for these tasks if the LH activation for sentence processing were flipped across the midline to the RH and combined with the RH activation for EP. Indeed, this is what we see in Fig. 6B for these individuals.

But this is not what we see when we examine the overlap in the RH for the two tasks in LHPS participants. Fig. 6C shows individual activation maps for these tasks in six LHPS participants. There is surprisingly little overlap between the activations for sentence processing and EP processing, even though they both activate the RH frontotemporal cortex. *SI Appendix,* *Fig. S6* shows activation maps for all the LHPS participants and all the healthy control participants. Martin (54) compares these two groups quantitatively, using a Dice coefficient and shows that there is significantly less overlap between the activation maps of the two tasks in the LHPS group than in the

Table 2. Activation peaks for the EP task (emotional > neutral speech contrast)

	Peak MNI coordinates	Peak *t* value	Description	Cluster size (mm³)
CTRL (*n* = 12)	−60, −13, 5	12.42	Left temporal cortex, overlapping with BAs 42, 22, 21, and 38; *extending anteriorly into BAs 47 and 45	12,150
	−60, −37, 5	9.35		
	−60, −1, −7	6.75		
	−51, 17, 8*	6.83*		
	−48, 23, −7*	5.35*		
	−42, 29, −1*	4.89*		
	69, −19, 8	8.78	Right temporal cortex, overlapping with BAs 41, 42, 22, 21, and 38	19,278
	57, −10, −7	8.31		
	48, −37, 2	8.26		
	51, 35, 5	7.78	Right inferior frontal cortex, overlapping with BAs 47 and 45	3,105
	45, 29, −4	5.45		
	60, 17, 14	4.44		
LHPS (*n* = 15)	51, −43, 11	6.04	Right temporal cortex, overlapping with BAs 41, 42, 22, 21, and 38; *extending into the inferior frontal cortex (BAs 47 and 45)	16,173
	57, −10, 5	5.88		
	51, −34, 14	5.65		
	39, 32, −16*	5.13*		
	54, 29, −1*	4.97*		

Reporting, for each cluster, the top three local maxima more than 8 mm apart, following SPM12 conventions.
*Peaks of the inferior frontal portion of the activation clusters in cases where the temporal and frontal activations are joined (the LH activation of the CTRL group and the RH activation of the LHPS group). These inferior frontal activations emerge as a separate clusters when the single-voxel threshold is tightened to $P < 0.0005$.
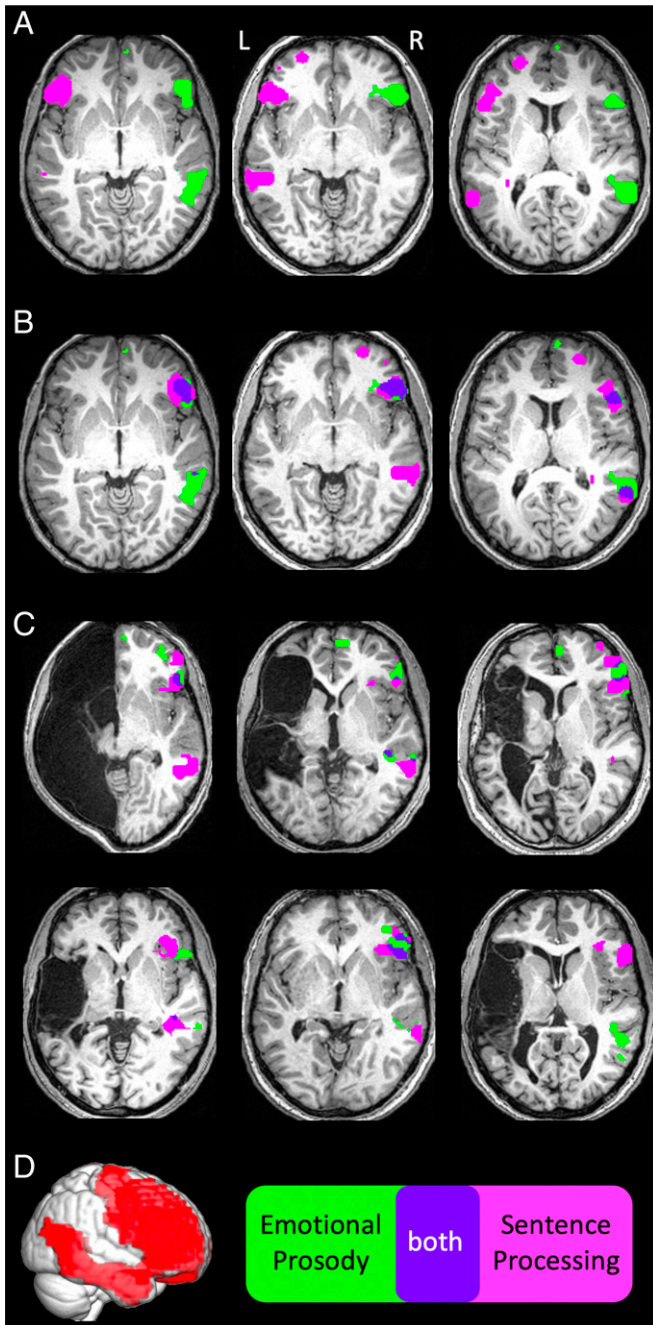
Fig. 6. Overlap of individual-level activations for sentence processing (magenta) and EP (green). (*A*) Activation maps for sentence processing in the LH and EP in the RH in three healthy CTRLs, illustrating that the activations for the two tasks are roughly homotopic. (*B*) Sentence processing activation is flipped into the RH to illustrate how much overlap (violet) there would be if both tasks activated the RH in these CTRLs. (*C*) Activation maps in six LHPS participants. As can be seen, there is surprisingly little overlap between the two tasks when they develop in the same hemisphere. To optimize conditions for comparing the spatial layout of the activation maps, the same number of active voxels is shown for all maps. This number was determined by averaging the number of active voxels inside the frontotemporal ROI (*D*) at *P* < 0.005 across participants and tasks. Note that we excluded the early auditory cortex from this ROI by removing voxels showing a significantly stronger response to reverse speech than to silence in a group-level analysis. Thus, activations shown here are not likely driven purely by low-level acoustic differences between emotional and neutral speech. Maps for all participants, along with the associated p thresholds, are shown in *SI Appendix*, Fig. S6.

healthy control group. This outcome suggests that when the two functions reside in the same hemisphere, they develop in a somewhat segregated way. It has been argued that the language processes ordinarily performed by the LH and RH—here

sentence processing and EP—involve different types of computations (55, 56). This may be an efficient way to achieve high performance on quite different types of neural computations: in the healthy brain by establishing these functions in distinct hemispheres and in the injured brain by establishing these functions in distinct regions of the same hemisphere (57).

Discussion

In this study, we have focused on a carefully selected group of participants with early LH injury, with the aim of asking about the long-term outcomes for language in terms of behavioral performance, as well as the organization of these functions in the brain. There are several important differences between our participants and previous studies of perinatal injuries. First, in many studies, the participants have experienced various types of perinatal or prenatal injuries, often including both perinatal arterial ischemic stroke and periventricular venous injuries and sometimes including other types of early focal injuries as well. In contrast, we have focused only on perinatal or presumed perinatal arterial ischemic stroke to MCA cortical territory and on children who have had as few other medical complications as possible (especially those with very limited seizure histories). Second, we have tested our participants at older ages than tested in other studies in order to observe final outcomes in language acquisition, and we have used carefully selected imaging and behavioral tasks as our assessments. In light of these differences, we have reported several new and important findings.

In accord with previous research (7–9, 34) but contrary to the claims of some (30, 37), we find that virtually every LH stroke participant shows their activation for language (here sentence processing) in the RH frontotemporal cortex, homotopic to the typical LH language network. All of the earlier studies that do not find consistent RH outcomes include many children with smaller cortical infarcts (31) or a large portion of the participant group with periventricular venous injuries (30, 37), which do not typically involve cortical damage. Importantly, our own inclusion criteria focused on children with medium to large infarcts to MCA cortical territory. For these participants, there was a highly consistent pattern of activation in the RH, regardless of whether their LH infarcts were complete MCA infarcts or were restricted to only the anterior or only the posterior portion of the MCA territory. Only the two participants with the smallest lesions (just barely one-third of the LH MCA territory) did not show clearly RH-dominant activation, with one showing bilateral and the other showing LH-dominant activation. Within a striking range, then, neither the size nor the location of perinatal MCA infarcts to the LH had differential effects (34). However, at the lower edge of the range we have studied, we may be beginning to see the retention of LH dominance with smaller infarcts; this will require future analyses of participants with smaller infarcts.

We also asked how well the RH can support language abilities. In contrast to earlier studies that have noted some language delay or impairment in young children after perinatal stroke (5, 23), we found that the behavioral performance of LH stroke participants on both simple and complex language processing tasks was no different from that of healthy controls. There are two differences between our assessments and earlier studies: first, we selected language tasks that tapped complex sentence processing without unnecessary executive function demands, and second, we tested our participants at much older ages than in almost any other study in the literature. Apparently, when one reduces demands on executive function (which is somewhat limited in

most of our participants), their processing of complex syntax is excellent. This result shows that the RH is capable of developing language (though perhaps a bit more slowly) if the left is damaged—as suggested years ago by Lenneberg and others (3, 4).

Finally, we asked what part of the brain supports the processing of EP, since sentence processing has developed in the regions that ordinarily process EP in the RH. What we have found is that both sentence processing and EP activate the RH frontotemporal cortex. However, in contrast to what might be expected from simply flipping sentence processing from LH to RH, these two functions are not entirely overlapping but rather have established somewhat distinct and separate subparts of the RH. This pattern of activation suggests that even when they are both in the same hemisphere, different computational functions may be instantiated in distinct cortical regions [(57) for a relevant neural network model].

Conclusions and Future Directions

We began with a number of larger questions about the regularities or principles underlying developmental plasticity for language. We asked, first, if there is heightened plasticity for language in early development, what areas of the brain are capable of supporting language? We alluded to three views in prior literature on this question. Some investigators have suggested that the LH is always privileged for language, even after injury early in life (30, 35–37). Others, including many who have studied perinatal stroke, have suggested that early injury to the frontotemporal cortex of the LH can lead to successful recovery and reorganization of language in frontotemporal regions of the RH [(3, 4, 7–12, 32, 34); see (25–29, 33) in epilepsy]. Still others have suggested that the young brain is even more plastic and that language can develop in other nonlanguage regions under certain circumstances (38, 39).

From our own work, our most important conclusion is that plasticity and reorganization are principled and constrained, even quite early in life. In our very well-defined participant group, almost everyone in our LHPS group showed the same outcome: RH-dominant activation for both sentence processing and emotional processing. An even broader view of the early developmental plasticity literature, including healthy controls and a variety of children with focal injuries, shows that the patterns of language organization are also constrained, with language functions developing in either the LH or the RH frontotemporal cortex again and again. Developmental plasticity for language thus appears to be restricted to these two sets of regions and not available for more drastic reorganization.

The consistency of reorganization to RH language that we find after perinatal stroke suggests that whatever differences exist in the architecture of the two hemispheres that produce strong left lateralization in the healthy adult brain must be rather small at the beginning of life (58–60) and that early cortical injuries to the LH may tip the balance in the opposite direction, making the RH better for supporting language. Some investigators have suggested that there are nonlinguistic processing biases that differentiate, probabilistically, the two hemispheres—for example, a temporal versus spectral bias (54) or a fast versus slow processing window (56) for the LH versus the RH. However, almost all the research on these biases has been conducted in adults (54, 56). In future studies it will be important to investigate whether these nonlinguistic processing biases thought to favor phonology and syntax in the LH are present, and to what degree, in young infants. This will help us to understand why the LH routinely becomes dominant for these functions in the healthy brain but consistently loses out to the RH when there are significant LH perinatal infarcts.

An additional question of great theoretical interest, and also clinical importance, is what permits homotopic reorganization of LH language to the RH very early in life and not later. We have suggested elsewhere that the distribution of language in the healthy brain—much more bilateral for sentence processing in young healthy children than in older children and adults (47, 61)—is what underlies the successful development of language in the RH of LHPS participants. We have called this the Developmental Origins Hypothesis (12, 61). Our hypothesis is that as long as language is somewhat bilaterally distributed, children can recover from LH injury and maintain or develop linguistic abilities in the healthy RH. It is unclear how long this bilaterality lasts, but current evidence suggests it may only be for the first few years of life (47, 61). However, as originally suggested by Lenneberg (4), recovery will be much more difficult if injury occurs to the LH once language is more completely lateralized away from the RH [(12, 47); see also (62)]. The literature on stroke recovery and aphasia in adults suggests that plasticity narrows even further with age, limiting sentence processing to the LH and EP to the RH, with stroke to these regions producing long-lasting impairments. While some homotopic reorganization may occur in adults with aphasia due to LH stroke, such changes are very modest compared with the reorganization shown here and cannot fully compensate for loss of the LH language network (63–65).

Finally, our results raise questions regarding what is special about the frontotemporal cortex in the two hemispheres that makes them capable of language processing and differentiates them from other cortical regions. Since signed languages are localized to the same brain areas (66–68), explanations focused on auditory and vocal-motor control regions will not be adequate. As noted above, prominent accounts in the literature focus on temporal and spectral processing explanations for why the LH is best suited for sentence processing and the RH is best suited for prosody (54, 56). We believe that our results on perinatal stroke contribute to our understanding of these issues and suggest that these differences must be small in early life and not immutable since they are readily overcome in the face of perinatal cortical injury.

Materials and Methods

Participants. Our participants are 15 adolescents and young adults, tested at ages 9.7 to 26.5 y, who had a significant perinatal or presumed perinatal arterial ischemic stroke involving the LH MCA territory many years earlier and who, as much as possible, have had no or few additional medical complications that would independently affect their cognitive and language abilities. Our inclusion/exclusion criteria were as follows: 1) Arterial ischemic infarct involving at least one-third of the MCA cortical territory, documented or presumed perinatal onset. The occurrence of stroke symptoms in the nursery and/or examination of their scans (excluding CVA before 28 wk by observing no gliosis) excluded those with prenatal rather than perinatal injuries. 2) Born after full-term healthy pregnancy. 3) No health condition that causes complicating additional brain injury (e.g., congenital heart defect, sickle cell anemia, infection, vasculitis, or other systemic inflammatory condition). 4) No history of traumatic brain injury or concussion. 5) No medically refractory seizure disorder. 6) No history of other medical condition affecting brain or cognitive development. 7) Native English speakers (English exposure from birth and spoken fluently in the home). *SI Appendix*, Table S2 lists the time of stroke diagnosis and the seizure history, if any, for all participants. They are compared with a group of 12 healthy controls who are the siblings of the perinatal stroke participants and of approximately the same age (ages 9.75 to 29.5 y), with no known medical history affecting cognitive or language. The study was approved by the Institutional Review Board at Georgetown University Medical Center; all participants provided consent (adults) or parental consent and child assent (children).

Behavioral Testing. All participants and their families visited our laboratory for 3 days of testing, including the behavioral tests and imaging tasks described in the present paper, several nonlanguage tasks assessing general intelligence and executive function, and a battery of visual-spatial perception tasks that will be described in other papers.

To assess their language abilities, participants were given the CELF sentence comprehension and word structure subtests (50), an Active-Passive Test modeled after Dennis and Kohn (51), and the TROG-2 (52). The CELF tasks were intended to test basic language abilities. They are normed for children ages 5 to 8 y; for our older participants, we used accuracy rather than a scaled score.[†] The Active-Passive Test and the TROG-2 were designed to test more complex sentence comprehension. The Active-Passive Test presents four types of sentences (active affirmative and negative and passive affirmative and negative) and asks the participant to point at one of two pictures (e.g., the boy pushing the girl versus the girl pushing the boy) corresponding to the meaning. The TROG-2 presents a series of sentences in blocks that increase in complexity, from simple sentences to sentences with relative clauses and center embedding, and asks the participant to point at one of four pictures corresponding to the meaning.

MRI. Imaging data were acquired on a research-dedicated 3T MRI scanner at Georgetown University Medical Center, with participants lying in supine position and responding to stimuli using a Cedrus fiber-optic button box held in their dominant hand. For all but three participants in the LHPS group, the scanner was a Siemens Trio TIM model with a 12-channel head coil. The remaining three participants' data were acquired after the MRI scanner was upgraded to a Prisma model with a 20-channel head coil, but otherwise the scanning parameters were held constant. The functional scans used echo-planar T2*-weighted imaging covering the whole brain in 50 horizontal slices (64×64 matrix) and an effective voxel size of $3 \times 3 \times 3$ mm^3, repetition time (TR) of 3 s, echo time (TE) of 30 ms, flip angle of 90 degrees. High-resolution anatomical (T1 weighted) images (MPRAGE) covered the whole brain in 176 sagittal slices (256×256 matrix) with an effective voxel size of $1 \times 1 \times 1$ mm^3, TR of 2,530 ms, TE of 3.5 ms, inversion time (TI) of 1100 ms, flip angle of 7 degrees. A pilot study in which we compared fMRI activations for the tasks reported here within the same participants (neurologically healthy members from the Georgetown University community) before and after the scanner upgrade did not reveal any systematic differences, so we do not believe that including these three participants altered our results, but they did helpfully enlarge our participant sample.

In-Scanner Tasks.

Sentence processing task (ADDT). The ADDT, developed by Berl et al. (47), presents participants with auditory sentences one at a time and instructs them to press a button if the sentence is correct. Correct comprehension of the sentences involves many aspects of sentence processing: recognizing human speech, understanding the particular lexical items, and grasping the syntactic and semantic structure of the sentence. It was used in the present study because it activates most or all of the classic language network and evokes robust activation at the single-subject level (25, 47). The present version is slightly modified from the version used by Berl et al. (47). The task contrasts periods of silence (baseline) with periods of forward speech (experimental condition) and backward speech (control condition) in a block design. During the forward speech blocks, participants hear sentences like "A big gray animal is an elephant" and push a button if it is correct or "A big gray animal is a banana" and do not push the button if it is incorrect. Sentences are relatively simple so that all participants will perform the task with high accuracy, avoiding differences across participants and groups in activation arising from errors, confusion, or uncertainty. As described in *Results*, LHPS participants scored 95.14% correct and healthy controls scored 97.22% correct, with no reaction time differences between the groups. During backward speech, the same recordings are played in reverse, controlling for basic auditory stimulation, but they could not be produced by a human vocal tract, are not comprehensible, and do not activate the classic language network. To control for motor responses, a soft beep is inserted at the end of some of the reverse speech utterances, and participants are asked to push a button when they hear a beep. Correct statements or beeps are presented on 50% of the trials. Each trial lasts 5 s, leaving ample time for the response. There are six trials per block, for a

block duration of 30 s, and each functional run contains four forward and four reverse speech blocks interleaved with 12-s periods of silent rest, for a total run duration of 5 min and 48 s (116 volume acquisitions). Each participant's dataset includes two runs, with block order counterbalanced across runs.

EP task. The EP task (46) contrasts periods of silence (baseline) with periods of emotional speech (experimental condition) and neutral speech (control condition). During the emotional speech blocks, participants hear content-neutral English sentences like "Dad made pot roast for dinner" spoken with happy, sad, or angry prosody. Following each sentence, an icon representing one of the emotions (a sun for happy, teardrops for sad, and a boxing glove for angry) is presented at screen center, and participants are asked to push a button if the icon matches the emotion they just heard. During the neutral speech blocks, the same sentences are spoken in a neutral tone and are followed by an icon representing one of three content categories (a dinner plate with fork and knife for food, a wrapped gift box for gift, and a van with suitcases on the roof for trip). Participants are asked to push the button if the icon fits the sentence content. In both conditions, 50% of the trials require a button push as the correct response. Each trial lasts 4 s, and trials are presented in 24-s blocks of six trials each, with each task block preceded by a 3-s instruction screen indicating whether the participant is to pay attention to the speaker's emotional tone or the sentence content. Each functional run contains four emotional and four neutral speech blocks interleaved with 12-s periods of silent rest, for a total run duration of 5 min (100 volume acquisitions). Each participant's dataset includes two runs, with block order counterbalanced across runs.

For both tasks, runs were redone if motion exceeded 3 mm in any direction according to the scanner's real-time motion estimation algorithm or if there was any indication that the participant fell asleep.

MRI Data Analysis.

Preprocessing. MRI data were analyzed with SPM12 using default settings except where specifically mentioned, with statistical analyses in Excel and SPSS (v.27.0.1.0). Functional images of each run were realigned to the run's mean functional image in a two-pass procedure to reduce the effect of motion between volume acquisitions and to obtain motion estimates for later use as nuisance regressors. The functional images were then coregistered with the native-space anatomical image. For native-space analyses, functional data were smoothed with a Gaussian kernel of 6 mm full-width at half-maximum (FWHM).

For standard-space analyses, the high-resolution anatomical (T1 weighted) images were warped to SPM's built-in MNI template using the unified segmentation and normalization approach with enantiomorphic lesion healing based on manually segmented lesions (69, 70). Unified segmentation sometimes mistook expanded subarachnoid spaces for gray or white matter. In these cases, the warping was repeated after applying a mask with voxel values of 1 to these areas in order to make unified segmentation classify them as cerebrospinal fluid. Even with this method, in some perinatal stroke participants with large lesions and significant midline shifts, the standard warp failed to align the individual's brain with the template brain, instead pulling part of the occipital RH tissue further across the midline. In those cases, we performed two different warps: one optimizing the alignment of the participant's lesioned LH to the template's LH and one optimizing the alignment of the RH. The former warp was used for determining lesion size and location, whereas the latter warp was used for the standard-space functional analyses.

Functional data were then warped into MNI space using the deformation field determined for the anatomical image and smoothed with a Gaussian kernel of 8 mm FWHM.

Modeling of fMRI Data. Individual subject (first level) analyses combined the two runs of each task into a single model whose design matrix included predictors for the experimental and control condition (each convolved with a standard hemodynamic response function), the six motion regressors (translation in and rotation around the x, y, and z axes) estimated during realignment for each run, and two run-specific predictors to capture global differences between the two runs. A high-pass filter cutoff of 400 s was applied to capture linear trends.

Group (second level) analyses combined the individual contrast images of interest (forward > reverse speech for the sentence comprehension task and emotional > neutral speech for the EP task) across all participants in a group ($n = 12$ for the control group and $n = 15$ for the LHPS group).

[†]While both CELF subtests are normed for younger children, older children with language impairments do have difficulties on these tasks and make errors.

Thresholding of Activation Maps.

P and cluster thresholding. Unless otherwise specified, all activation maps were thresholded at a single-voxel threshold of $P < 0.001$, combined with a cluster threshold of $P < 0.05$ as determined by AFNI's 3dClustSim function (71, 72). Specifically, we estimated autocorrelation parameters from the SPM residuals using the mixed-model approach implemented in AFNI's 3dFWHMx function, fed them into 3dClustSim, and applied the second-nearest-neighbor cluster-size threshold determined with two-sided thresholding.

Top-voxel thresholding. To optimize conditions for showing similarities in the spatial layout of activation maps across participants and tasks (Fig. 6 and *SI Appendix*, Figs. S4 and S6), we equated the number of voxels shown in all maps using a top-voxel approach. First, we thresholded each map at $P < 0.005$ and determined the number of voxels showing significant activation at that threshold. We then averaged that number of voxels across participants and tasks to arrive at the number of voxels N to be displayed in all maps. Lastly, each map was thresholded such that only the N most activated voxels were shown as part of the activation pattern.

For Fig. 6 and *SI Appendix*, Fig. S6, this top-voxel analysis was constrained to an anatomically defined frontotemporal region of interest (ROI) from which all auditory voxels (voxels showing a significant reverse speech > silence effect at the group level) were removed. This ROI was chosen because it encompasses the areas in which we expect our sentence processing and EP contrasts to show the strongest activation but excludes those voxels whose response to the contrast might be driven solely by low-level acoustic differences.

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