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## Right-lateralization of the visual word form area after left-hemisphere perinatal stroke

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2 hemisphere perinatal stroke  
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4 **Abbreviated title:** Right-lateralized VWFA after left perinatal stroke  
5

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## 35 Abstract

36 In literate adults, an area along the left posterior fusiform gyrus that is often referred to as the  
37 “visual word form area” (VWFA) responds particularly strongly to written characters compared to  
38 other visually similar stimuli. Theoretical accounts differ in whether they attribute the strong left-  
39 lateralization of the VWFA to a left-hemisphere bias towards visual features used in script, to  
40 competition of visual word form processing with that of other visual stimuli processed in the  
41 same general cortical territory (especially faces), or to the well-established left-lateralization of  
42 the language system.

43 Here we used functional magnetic resonance imaging to test the last hypothesis by investigating  
44 lateralization of the VWFA in participants (male and female) who have right-hemisphere  
45 language due to a large left-hemisphere perinatal stroke. Demographically matched Controls  
46 were included for comparison. All participants had intact language skills and were proficient  
47 readers; age at testing ranged from 9.75 years to early adulthood.

48 Individual whole-brain activation maps contrasting activation during rapid presentation of  
49 pseudowords and pictures of places, and analyses comparing activations during these  
50 conditions in independently defined VWFA regions of interest in left and right ventral  
51 occipitotemporal cortex, both demonstrated that while visual word form processing was left-  
52 lateralized in Controls, it was right-lateralized in participants with left-hemisphere stroke. This  
53 was despite the fact that the tissue normally occupied by the VWFA was not damaged by the  
54 stroke. This provides compelling evidence that the lateralization of the VWFA indeed follows  
55 that of the frontotemporal language system.

56

## 57 Significance Statement

58 The visual word form area (VWFA) in healthy adults is almost always lateralized to the left  
59 hemisphere. One hypothesis is that this is due to co-localization with the LH language network.  
60 This study provides support for this hypothesis from a rare participant group with RH language;  
61 we find that their VWFA is also right-lateralized. Our findings also support the notion that the  
62 hemispheres are equipotential early in life, with a fully functional language system – including  
63 the VWFA – able to develop in the RH if the LH is damaged. These findings contribute to our  
64 understanding of functional brain organization and plasticity, with potential implications for  
65 rehabilitation approaches for adults with reading impairments due to acquired brain injury.

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## 68 Introduction

69 The notion that a portion of the left ventral occipitotemporal cortex (vOTC) along the fusiform  
70 gyrus responds strongly to familiar script and may constitute a “Visual Word Form Area”  
71 (VWFA) was introduced by Cohen and colleagues (Cohen et al., 2000). Since then, the nature  
72 and selectivity of this area has been debated, with several studies casting doubt on its visual  
73 nature ((Yoncheva et al., 2010), (Reich et al., 2011), (Planton et al., 2019)), and others  
74 questioning how specific its activation is to word forms versus other visual stimuli ((Song et al.,  
75 2012), (Neudorf et al., 2022)). Theoretical accounts differ in whether they consider the VWFA to  
76 be a part of the visual object recognition system that becomes particularly tuned to visual word  
77 forms due to the acquisition of literacy ((McCandliss et al., 2003), (Dehaene et al., 2015),  
78 (Dehaene-Lambertz et al., 2018)) in a mostly bottom-up, hierarchical manner, or rather as part  
79 of the speech processing system whose activation during reading is at least partly driven by its  
80 involvement in phonological processing ((Dębska et al., 2016), (Conant et al., 2020)) and/or  
81 reflects integration of bottom-up visual information with top-down linguistic information ((Price &  
82 Devlin, 2003), (Twomey et al., 2011)).

83 One key argument in favor of the latter account is the VWFA’s lateralization to the left  
84 hemisphere (LH), which is the language-dominant hemisphere in most adults ((Broca, 1861),  
85 (Wernicke, 1874), (Branch et al., 1964)), as well as its connectivity with areas of the left  
86 frontotemporal language cortex ((Bouhali et al., 2014), (Chen et al., 2019)). This connectivity  
87 precedes the acquisition of literacy ((Saygin et al., 2016), (Li et al., 2020)) and is correlated with  
88 reading skill especially in early reading ((Morken et al., 2017), (Vanderauwera et al., 2018)).

89 This raises the question of what happens to the lateralization of the VWFA when the language  
90 network is not left-lateralized. Right hemisphere (RH) language dominance happens  
91 spontaneously in a small proportion of the healthy population and is more common among left  
92 handers (Knecht, 2000). Several studies have shown that, in cases of spontaneous RH

93 language dominance, the VWFA develops in right rather than left vOTC ((Cai et al., 2010), (Van  
94 der Haegen et al., 2012), (Gerrits et al., 2019)). However, it is possible that in these cases the  
95 lateralization of the brain is reversed more generally (e.g., due to genetic influences; (Pinel et  
96 al., 2015)) rather than only with respect to language dominance. If so, this finding need not  
97 imply a causal connection between the two; the lateralization of both could be determined by  
98 other factors.

99 The present investigation uses functional magnetic resonance imaging (fMRI) to probe  
100 lateralization of the VWFA in another population with atypical RH language dominance: people  
101 who had a large perinatal arterial ischemic stroke affecting the left perisylvian cortex and  
102 therefore developed RH dominance for spoken language processing. In the absence of a strong  
103 familial history of left-handedness, these individuals would presumably have been left-dominant  
104 for language if not for their early LH damage. Crucially, perinatal strokes affecting the middle  
105 cerebral artery (and therefore the perisylvian cortex) usually spare the portion of vOTC in which  
106 the VWFA develops, since the vOTC is fed by the posterior rather than the middle cerebral  
107 artery. Thus our participants could have developed a left-lateralized VWFA despite being right-  
108 dominant for spoken language processing. They therefore are an excellent population for testing  
109 whether the VWFA develops in the same hemisphere where spoken language processing has  
110 already developed, or whether differential hemispheric biases for visual object processing (e.g.,  
111 a LH preference for visual stimuli with high spatial frequency (Woodhead et al., 2011) or for  
112 abstract stimuli (Dien, 2009)) lead the VWFA to consistently develop in left vOTC, regardless of  
113 language lateralization.

## 114 **Materials and Methods**

115 Study procedures followed the ethical guidelines for human subjects research laid out in the  
116 Declaration of Helsinki and were approved by the Georgetown University Medical Center's

117 Institutional Review Board. All participants provided informed consent or, in the case of minors,  
118 parental consent in conjunction with written consent (ages 12+) or assent (for children younger  
119 than 12) from the participating minor.

120 [Insert Figure 1 about here]

## 121 Participants

122 Data presented here are from 15 adolescents and young adults (9 male, 6 female) with a history  
123 of perinatal or presumed perinatal arterial ischemic stroke to the left hemisphere (left-  
124 hemisphere perinatal stroke; LHPS) whose lesions encompassed at least 1/3 of the middle  
125 cerebral artery (MCA) territory (**Figure 1**) and whose fMRI response to an auditory sentence  
126 comprehension task was strongly right-lateralized. Neurologically healthy siblings served as  
127 controls (n=14, 8 male). Most of these participants were part of a previously reported study on  
128 language lateralization after perinatal stroke (Newport et al., 2022); we here use the same  
129 participant labels as in this previous publication. The present sample includes five additional  
130 participants (C13, C14, C15, L16, L17) whose data were collected more recently. The present  
131 sample excludes participant C9, who did not complete the fMRI task reported on here,  
132 participant L1, whose lesion directly affected left vOTC, and participant L14, who did not have  
133 right-lateralized language activation (see supplementary Figures S2 and S3 in (Newport et al.,  
134 2022)). Thus, by design, in the sample reported here, all participants with LHPS showed right-  
135 lateralized activation during auditory sentence comprehension, whereas all control participants  
136 showed the typical left-lateralized activation pattern. Language lateralization for the sentence  
137 comprehension task was quantified by computing a Lateralization Index across supratentorial  
138 cortex using the LI toolbox ((Wilke & Schmithorst, 2006), (Wilke & Lidzba, 2007)), which  
139 compares activation between the left and right hemisphere such that values near 1 indicate left-  
140 lateralization, values near -1 indicate right-lateralization, and values near 0 indicate roughly

141 equal activation in both hemispheres. These LIs are illustrated in Figure 2 along with axial views  
142 of activation maps for all participants included here.

143

144 [Insert Figure 2 about here]

145 All participants were native speakers of English and fluent readers. As reported previously for a  
146 mostly overlapping sample (Newport et al., 2022), the CTRL and LHPS groups performed  
147 comparably well on various assessments of language skills, including tasks in which both  
148 groups' performance was far from ceiling (see Figure 3 for details). The groups also did not  
149 differ significantly in age (CTRL: mean = 16.20 years, std = 4.93 years, range = 9.75 to 29.50  
150 years; LHPS: mean = 19.42 years, std = 4.69 years, range = 10.00 to 26.67 years) or in gender  
151 distribution.

152 [Insert Figure 3 about here]

### 153 **Magnetic Resonance Imaging Setup and Parameters**

154 Participants underwent functional magnetic resonance imaging at Georgetown University's  
155 research-dedicated neuroimaging facility on a 3-Tesla Siemens MRI scanner. This scanner was  
156 upgraded from a Trio to a Prisma model towards the end of the data collection period. Five  
157 participants in the LHPS group and two in the CTRL group were scanned after the upgrade  
158 using a 20-channel head coil; all other participants were scanned before the upgrade using a  
159 12-channel head coil. Scanning parameters were held as constant as possible across pre- and  
160 post-upgrade scans. Several neurologically healthy participants were scanned before and after  
161 the scanner upgrade to determine whether the upgrade altered the activation maps. No  
162 systematic differences were found between pre- and post-upgrade results in this control study.

163 Functional imaging data were acquired using an echo-planar (EPI) T2\*-weighted sequence that  
164 covered the entire brain in 50 horizontal slices, with a 64x64 matrix and an effective voxel size



165 of 3x3x3 mm<sup>3</sup> (in-plane resolution 3x3, slice thickness 2.8 mm, distance factor 7%, slice  
166 acquisition in descending order). Repetition time (TR) was 3 seconds, Echo Time (TE) was 30  
167 ms, and the flip angle was set to 90 degrees. Each participant contributed 2 functional runs of  
168 80 volumes each.

169 For assessment of lesions and as a reference to co-register the functional data with, a high-  
170 resolution T1-weighted MPRAGE scan was also obtained from each participant. It covered the  
171 brain in 176 sagittal slices with an effective voxel size of 1x1x1 mm<sup>3</sup> (256x256 matrix), a TR of  
172 2530 ms, TE of 3.5 ms, inversion time of 1100 ms, and flip angle of 7 degrees.

## 173 In-scanner Tasks

### 174 Auditory Sentence Comprehension Task

175 Lateralization of the frontotemporal language network was determined using an auditory  
176 sentence comprehension task first introduced by Berl and colleagues (Berl et al., 2014) and  
177 administered to the participants of this study as described previously (Newport et al., 2022).  
178 Briefly, this task contrasts blocks of forward speech, during which participants listen to short  
179 English sentences, with blocks of reverse speech, during which the same sentences are played  
180 in reverse and thus rendered incomprehensible while retaining their basic auditory  
181 characteristics. The resulting activation maps reliably identify the inferior frontal and superior  
182 temporal brain areas commonly referred to as the frontotemporal language network, which in  
183 our neurologically healthy control participants is in the LH and in our participants with large  
184 perinatal LH strokes is in the RH homotopic regions, including the RH correlate to Broca's and  
185 Wernicke's areas (Newport et al., 2022).

### 186 Word Form/Place/Face Localizer Task

187 Lateralization of the VWFA was determined using a visual localizer paradigm that contrasts  
188 activation evoked by rapid sequential presentation of word forms (W), places (P), and faces (F).

189 Each participant contributed two runs of the Localizer task. Each run was four minutes long and  
190 consisted of three 18-second blocks of each of the three experimental conditions during which  
191 participants performed a one-back repetition detection task, interleaved with 18-second Rest (R)  
192 periods during which participants rested their eyes on a black fixation cross at screen center.  
193 Runs were repeated if motion (as estimated by the scanner in real time) exceeded 3 mm in  
194 either direction, or if participants failed to detect several repetitions in a row (indicating that they  
195 were no longer paying attention to the stimuli).

196 During Word Form blocks, participants viewed pseudowords generated by MCWord (Medler &  
197 Binder, 2005). Pseudowords varied in length from 5 to 7 letters and were generated based on  
198 constrained trigram-based strings. We chose pseudowords rather than English words to prevent  
199 evoking semantic processing and visual imagery, and because pseudowords have been shown  
200 to lead to stronger VWFA activation than words ((Kronbichler et al., 2004), (Ludersdorfer et al.,  
201 2013)). To reduce differences in low-level visual stimulation between the Word Form condition  
202 and the Face and Place conditions, the pseudowords were presented on a background of  
203 phase-scrambled versions of the Place stimuli (see (Sadr & Sinha, 2004) for the use of phase-  
204 scrambling as a visual control) and located at the same height as the eyes in the Face  
205 condition. During Place blocks, participants viewed grayscale images of scenes containing one  
206 or multiple buildings seen from the outside. During Face blocks, participants viewed grayscale  
207 images of young adult faces (50% male, 50% female) smiling frontally at the camera. Each  
208 image was a close-up of the face and cut into a square shape such that little was visible of hair,  
209 clothing, and ears. None of the pictures included glasses or jewelry. Face and Place stimuli  
210 were subsets of those used by (Marois et al., 2004) that excluded highly recognizable place  
211 stimuli (such as the Twin Towers). All stimuli were squares subtending roughly 5 degrees of  
212 visual angle as viewed via a slanted mirror inside the scanner bore and presented at screen  
213 center in front of a gray (RGB 128, 128, 128) background. Example stimuli are shown in **Figure**

214 4. Stimuli were drawn randomly without replacement from sets of 144 for each experimental  
215 condition; no stimulus was shown twice except as a one-back repetition, to which participants  
216 responded with a button press. Which stimuli repeated was determined randomly, with the  
217 constraint that repetitions occurred at least 4 and at most 12 stimuli apart, for a total of 2 or 3  
218 repetitions in an 18-second block.

219 Each 18-second block contained 24 stimulus presentations lasting 500 ms each, followed by a  
220 250 ms inter-stimulus interval, during which the fixation cross was shown. For two LHPS  
221 participants, we reduced the rate of stimulus presentation to half, i.e., to 12 per block, showing  
222 each stimulus for 1 s followed by a 500 ms inter-stimulus interval, because practice outside the  
223 scanner revealed that the fast rate of stimulus presentation generated more stress than would  
224 have been conducive to a successful scanning session. These participants' activation maps  
225 were not systematically different from those of the other participants, and removing them from  
226 the analysis did not change the inferences derived from the statistical tests. We thus decided to  
227 include them.

228 [Insert Figure 4 about here]

229  
230 For this investigation of VWFA lateralization, we contrasted activation during the Word Form  
231 condition with activation during the Places condition to control for visual stimulation because  
232 unlike the visual processing of Faces ((Dehaene et al., 2010), (Behrmann & Plaut, 2020)),  
233 processing of Places has not been hypothesized to be in direct competition for vOTC territory  
234 with that of Word Forms (Rosenke et al., 2021). (Activation in response to Face stimuli will be  
235 the focus of a separate publication.)

## 236 Data Analysis

### 237 Software

238 Imaging data were preprocessed and modeled at the whole-brain level using SPM12 (v. 7771),  
239 and statistical comparisons of data extracted from the resulting activation maps were performed  
240 in Matlab (v. R2023b) and Excel (v. 16.16.27.) Activation maps were visualized using Mango (v.  
241 4.1.)

### 242 Preprocessing

243 Preprocessing steps included dicom-to-nifti conversion, re-alignment of each functional run's  
244 individual images to the run's mean functional image to reduce motion-related displacements  
245 between volumes, and co-registration of functional to anatomical data in native space, all using  
246 SPM's default parameters. The native-space MPRAGE was then warped to SPM's built-in MNI  
247 template using the unified segmentation and normalization approach with standard parameters  
248 except for re-scaling regularization by a factor of 0.1 (as recommended by John Ashburner, one  
249 of the developers of this approach.) The resulting warps were inspected for alignment with the  
250 MNI template and distortions relative to the native-space brain. Where necessary due to poor  
251 warping results, the procedure was repeated using a manually drawn lesion mask and  
252 enantiomorphic lesion healing (Nachev et al., 2008), as well as additional masks to prevent  
253 SPM from mistaking expanded subarachnoid spaces for gray or white matter. Once acceptable  
254 warps were achieved for the MPRAGE, the same warp field was used to bring the co-registered  
255 functional data into MNI space. Lastly, the functional data were smoothed with a 6 mm full-  
256 width-at-half-maximum Gaussian kernel.

### 257 Modeling of individual whole-brain activations

258 Voxel time-courses were modeled at the individual subject level using a general linear model  
259 that included, for each of the two functional runs, three predictors of interest modeling the  
260 presence of the three stimulation conditions (Faces, Places, and Word Forms) convolved with  
261 SPM's default hemodynamic response function, six predictors to capture signal changes

262 associated with translational movement along and rotational movement around the x, y, and z  
263 axis, respectively, and a constant to capture global differences between the two runs. A high-  
264 pass filter with a 400 s cutoff was applied to remove linear trends. After modeling, we contrasted  
265 the beta map for the Word Form predictor and the beta map for the Places predictor (W>P) to  
266 identify voxels with a significant preference for Word Forms over pictures of Places. We also  
267 looked at activation for the Word Form and Place stimuli relative to the resting baseline  
268 condition without visual stimulation.

### 269 Regions of interest

270 Our analysis focuses on activation in the ventral occipitotemporal cortex (vOTC), which we  
271 defined liberally as including Brodmann areas 37, 36, and 20 using the Wake Forest Pickatlas  
272 included with SPM (dilation: 6). In addition to inspecting this large anatomical region for clusters  
273 with W>P preference, we also performed an analysis of activation changes averaged across an  
274 independently defined functional region of interest (ROI). To achieve an ROI that would be as  
275 spatially specific as possible to the putative location of the VWFA while also accounting for the  
276 well-known inter-individual variability in the exact location of the VWFA and for the fact that its  
277 location can vary depending on which contrast is used to identify it, we based this ROI on a  
278 meta-analysis. We downloaded the meta-analytic “association test” map for the term “Word  
279 Form” from the Neurosynth website (<https://neurosynth.org/analyses/terms/word%20form/>),  
280 increased the threshold (to 11) until only voxels in left vOTC remained, and then binarized the  
281 map. The resulting ROI had a volume of 3712 mm<sup>3</sup> and almost exclusively included voxels  
282 labeled as “Fusiform Gyrus, Brodmann Area 37” on the MNI Atlas included with Mango. This  
283 ROI thus contains only voxels for which (nearby) activation is reported more often in  
284 neuroimaging studies frequently mentioning the term “Word Form” than in neuroimaging studies  
285 that do not mention this term (Yarkoni et al., 2011). A corresponding RH ROI was generated by  
286 inverting the sign on the x-coordinates, mirroring the LH ROI across the midline.

## 287 Statistical analyses

288 Statistical analyses were conducted using Students T-tests in Excel. We used one-tailed tests  
289 for comparing the left and right-hemisphere ROI response to the W>P contrast, which we  
290 expected to be left-lateralized in the CTRL group and right-lateralized in the LHPS group. Two-  
291 tailed tests were used for all other comparisons. Results are reported in terms of uncorrected p-  
292 values, along with associated t-values and their degrees of freedom.

## 293 Results

### 294 Behavioral performance in the scanner

295 Accuracy and reaction time data from the in-scanner task were available for all participants  
296 except one participant in the LHPS group, during whose session the response buttons did not  
297 work. We scored accuracy for our one-back task as the percentage of correctly detected  
298 repetitions, and computed the average reaction time for all correct button pushes. There were  
299 no significant differences between the groups in accuracy or reaction time in any of the  
300 conditions, with detection performance around 80% and reaction times around 480 ms (see  
301 Table 1).

302 [Insert Table 1 about here]

### 304 Inspection of individual whole-brain activation maps for word-selective clusters in 305 vOTC

306 Individual whole-brain activation maps for the W>P contrast at a single-voxel threshold of  
307  $p < 0.001$  revealed clusters of voxels that showed a significantly stronger response to Word Form  
308 than to Place stimuli in the left vOTC for 13 of the 14 participants in the CTRL group, and in the  
309 right vOTC for 9 of the 15 participants in the LHPS group. Three of the CTRL participants also  
310 had a significant cluster in the right vOTC, and two of the LHPS participants had a significant

311 cluster in the left vOTC in addition to a larger one in right vOTC. Activation maps for the  
312 remaining participants (1 CTRL, 6 LHPS) did not reveal significant vOTC activation for the W>P  
313 contrast on either side at this relatively stringent threshold. With a more lenient threshold of  
314  $p < 0.01$ , LH activation was observed in 13 of 14 participants in the CTRL group, and RH  
315 activation in 11 of 15 participants in the LHPS group. While the exact location of these putative  
316 VWFAs varied across participants, the right-hemisphere activation clusters of the LHPS  
317 participants roughly mirrored the left-hemisphere activation clusters of the CTRL participants.  
318 Example activation maps are shown in **Figure 5**.

319 [Insert Figure 5 about here]

## 320 Statistical evaluation of average W>P effects in an independently defined VWFA 321 ROI

322 To quantitatively test whether lateralization of visual word form processing was indeed reversed  
323 in the LHPS group, and to overcome the problem that conventionally thresholded activation  
324 maps did not reveal significant vOTC activation in every participant, we averaged, for each  
325 participant, the t-values for the W>P contrast across a left fusiform VWFA ROI and a right-  
326 hemisphere mirror version of that ROI (**Figure 6A**). These ROIs were defined independently of  
327 the current dataset using the meta-analytic results of other studies as aggregated using  
328 Neurosynth (see Regions of interest). At the individual level, 13 of 14 CTRL participants showed  
329 stronger activation in the left than in the right ROI (negative sloping blue lines in Figure 6A), and  
330 11 of 14 LHPS participants showed stronger activation in the right than in the left ROI (positive  
331 sloping orange lines in Figure 6A). There were no reversals of this pattern in either group; the  
332 participants (1 CTRL, 3 LHPS) whose lateralization did not follow this pattern had similar  
333 activation in both hemispheres, likely because the ROIs were much larger than any participant's  
334 individual VWFA and thus contained a large number of voxels without a preference for visual  
335 word forms in either hemisphere. At the group level, the CTRL group showed the expected left-

336 lateralization (CTRL LH>RH,  $t(13)=6.03$ ,  $p<0.0001$  one-tailed) and the LHPS group showed  
337 right-lateralization (LHPS RH>LH,  $t(14)=3.35$ ,  $p=0.002$  one-tailed). This reversal of VWFA  
338 lateralization in the LHPS group was not solely driven by a decrease in LH activation, as one  
339 might expect due to the proximity of a lesion (CTRL\_LH vs. LHPS\_LH,  $t(27)=2.54$ ,  $p=0.017$  two-  
340 tailed), but also by an increase in RH activation in the LHPS group relative to the CTRL group  
341 (LHPS\_RH vs. CTRL\_RH,  $t(27)=2.45$ ,  $p=0.021$  two-tailed). There were no significant group  
342 differences between activations in the language dominant hemispheres (CTRL\_LH vs.  
343 LHPS\_RH,  $t(27)=0.72$ ,  $p=0.480$  two-tailed) or in the non-dominant hemispheres (LHPS\_LH vs.  
344 CTRL\_RH,  $t(27)=0.81$ ,  $p=0.423$  two-tailed.) Taken together, these findings confirm a reversal of  
345 the typical lateralization pattern in the LHPS group.

346 [Insert Figure 6 about here]

#### 347 Statistical evaluation of average ROI effects for Word Forms and Places relative 348 to Rest

349 To further reduce concerns about whether the lesioned left hemisphere was not able to activate  
350 normally in the LHPS group, we also looked at LH ROI activation relative to the resting baseline,  
351 reasoning that if activation evoked by visual stimulation in general were suppressed due to the  
352 ipsilateral lesion, we should see weaker Place activation in the LHPS group relative to the CTRL  
353 group. As can be seen in **Figure 6B**, this was not the case. At the individual level, 12 of the 14  
354 CTRL participants and 13 of the 15 LHPS participants showed a positive response to Place  
355 stimuli. Across participants, average LH ROI activation to Place stimuli was comparable in both  
356 groups (CTRL\_LH vs. LHPS\_LH for  $P>R$ ,  $t(27)=-0.42$ ,  $p=0.679$  two-tailed.)

357 We did not necessarily expect a significant group difference in the RH ROI response to Word  
358 Form stimuli relative to baseline (fixation) because both groups should show strong activation  
359 for any visual stimulation, and this large general visual effect might overpower a small group



360 difference driven by right-lateralization of visual word form processing in the LHPS group.  
361 Nonetheless, a group difference in RH Word Form activation was clearly evident and nearly  
362 reached significance even relative to baseline (LHPS\_RH vs. CTRL\_RH for W>R,  $t(27)=2.00$ ,  
363  $p=0.056$  two-tailed, see **Figure 6C**.)

### 364 365 **Statistical comparison of the strongest individual Word Form responses between** 366 **groups and hemispheres**

367 Because the Neurosynth ROI is bigger than we would expect any individual VWFA to be,  
368 averaging responses across the entire ROI has the disadvantage of including voxels that are  
369 not responsive to the stimulus of interest at the individual level. Thus, our final analysis was a  
370 top-voxel analysis focused on the 8 voxels with the strongest Word Form response inside the  
371 Neurosynth “Word Form” ROI and its right-hemisphere mirror version. The constraint to the  
372 Neurosynth ROI excludes voxels from early visual areas whose strong responses are  
373 predominantly driven by visual stimulation in general and not specific to Word Forms.

374 As can be seen in Figure 7, the results of this W>Rest top-voxel analysis support the same  
375 conclusions as the ROI-wide W>P analysis: Activation was left-lateralized in the CTRL group  
376 (CTRL LH>RH,  $t(13)=3.90$ ,  $p<0.001$  one-tailed) and right-lateralized in the LHPS group (LHPS  
377 RH>LH,  $t(14)=4.67$ ,  $p<0.001$  one-tailed. Compared to the CTRL group, the LHPS group had  
378 significantly weaker activation on the left side (CTRL\_LH vs. LHPS\_LH,  $t(27)=2.30$ ,  $p=0.030$   
379 two-tailed) and significantly stronger activation on the right side (LHPS\_RH vs. CTRL\_RH,  
380  $t(27)=3.02$ ,  $p=0.005$  two-tailed). Also as in the previous analyses, there were no significant  
381 group differences regarding activation in each group’s language-dominant hemisphere  
382 (CTRL\_LH vs. LHPS\_RH,  $t(27)=-0.95$ ,  $p=0.352$  two-tailed) or in each group’s non-dominant  
383 hemisphere (CTRL\_RH vs. LHPS\_LH,  $t(27)=0.30$ ,  $p=0.764$  two-tailed).

384

[Insert Figure 7 about here]

385 In summary, we have converging evidence across whole-brain, independent ROI, and top-voxel  
386 analyses investigating activation to visual word forms relative to a visual control stimulus  
387 (places) and relative to baseline that in our participants with right-hemisphere language due to  
388 perinatal left-hemisphere stroke, the visual word form area is right-lateralized.

## 389 Discussion

390 This fMRI study investigated the lateralization of visual word form processing in a sample of 15  
391 adolescents and young adults with right-hemisphere dominance for spoken language  
392 processing due to a large perinatal arterial ischemic stroke to the left perisylvian cortex. Their  
393 blood-oxygen-level-dependent (BOLD) response to rapid visual presentation of pseudowords  
394 (relative to rapid visual presentation of pictures of places, and relative to a fixation-only  
395 baseline) was compared to that of neurologically healthy controls (n=14), all of whom showed  
396 the typical left-hemisphere dominant response to spoken language. The control group showed  
397 the expected left-lateralized response for visual word form processing in a region of ventral  
398 occipitotemporal cortex that has been dubbed the Visual Word Form Area. In contrast, the  
399 participants with right-hemisphere language dominance subsequent to left-hemisphere perinatal  
400 stroke showed a stronger response (both compared to their own left vOTC and compared to the  
401 control group) in the corresponding region of right vOTC. This difference was not driven by a  
402 general depression of left vOTC activation in response to visual stimuli, but rather by an  
403 atypically strong visual word form response in right vOTC. The strong visual word form  
404 response in the RH was similar to the atypically strong right-hemisphere response to  
405 comprehension of spoken sentences already reported for this participant group (Newport et al.,  
406 2022).

407 This finding makes an important contribution to the debate on whether lateralization of the  
408 VWFA is influenced by lateralization of the language system. Right-lateralization of the VWFA  
409 has already been reported for neurologically healthy adults with atypical language dominance  
410 ((Cai et al., 2010), (Van der Haegen et al., 2012), (Gerrits et al., 2019)) as well as for cases of  
411 direct early damage to the usual (left midfusiform) location of the VWFA ((Cohen et al., 2004),  
412 (Liu et al., 2019)). However, the participants at the center of our study are unlike these other two  
413 groups in that their atypical RH language dominance was not genetically driven (and thus not  
414 potentially part of a more general reversal of cerebral lateralization), but rather was secondary  
415 to their perinatal stroke, with no direct damage to the canonical location of the VWFA in left  
416 vOTC or to the posterior occipitotemporal pathways connecting this location with lower stations  
417 along the ventral visual stream. If the VWFA were simply a station at the higher end of the visual  
418 object processing hierarchy and independent of the language system, then our participants'  
419 VWFA should have developed in left vOTC as it does in the vast majority of neurologically  
420 healthy adults. The fact that it instead developed in the right hemisphere is in line with the  
421 hypothesis that the VWFA typically co-lateralizes with the language system ((Dehaene et al.,  
422 2015), (Behrmann & Plaut, 2020)).

423 One limitation of the present study is that we did not formally assess reading skill. However, we  
424 have the educational levels for each participant and know that participants were either at the  
425 expected grade level in school or had already graduated from high school. We also have parent  
426 reports of grade-level appropriate reading performance and informal observations during  
427 consenting and testing to confirm that all participants were fluent and competent readers. Some  
428 studies have shown correlations between task performance and language lateralization  
429 ((Donnelly et al., 2011),(Bartha-Doering et al., 2018)). Thus, if participants in the LHPS group  
430 had greater difficulty with reading the pseudowords than participants in the CTRL group, this  
431 would pose a potential confound and could be an alternative explanation for the stronger right-

432 hemisphere activation in the LHPS group. However, there were no differences between the two  
433 groups in accuracy or reaction times (even when accuracy was not at ceiling) on the in-scanner  
434 task, nor any differences regarding language skills as assessed outside the scanner. We  
435 therefore feel confident that we can rule out this alternative explanation and instead interpret the  
436 findings as a reversal in lateralization of the visual word form area in association with the  
437 lateralization of the rest of the language network.

438 Another limitation is that our study did not include participants who remained left-hemisphere  
439 dominant for language after a large perinatal stroke to the left hemisphere. Such cases are rare  
440 (or perhaps nonexistent) because large perinatal strokes almost always affect the  
441 frontotemporal language network. One future direction for our research is to recruit participants  
442 with small strokes to determine which lesion locations are compatible with developing typical LH  
443 language dominance and to ask whether the VWFA consistently develops in the left vOTC in  
444 those cases. There is evidence of left-lateralization for the VWFA in a group of patients with  
445 resections of parts of the posterior vOTC due to epilepsy (Lopes et al., 2015). These resections  
446 spared the midfusiform location of the VWFA, as well as its connections to portions of the  
447 temporal lobe that are involved in language processing, but damaged connections to the  
448 occipital lobe. Taken together, these studies suggest that lateralization of the VWFA is linked  
449 closely to lateralization of the frontotemporal language system.

450 This conclusion is in agreement with other studies using non-lesion approaches. For example,  
451 Moore and colleagues demonstrated in an fMRI study that an area in left vOTC whose  
452 coordinates correspond well with those published for the VWFA showed an increased response  
453 to face stimuli in a group of participants who had been trained to associate different faces with  
454 different letter sounds relative to control groups who had not learned this “face alphabet” (Moore  
455 et al., 2014). As the authors argue, this provides strong support that the VWFA serves as an  
456 interaction point for spoken language processing and processing of complex visual stimuli (even

457 visual stimuli that, in the absence of learned association with speech sounds, do not drive this  
458 area strongly) and thus co-lateralizes with the spoken language processing for maximum  
459 efficiency (Dehaene et al., 2015). The emergence of a preference for visual word form  
460 processing (as opposed to face processing) in the language-dominant hemisphere has also  
461 been demonstrated in computational simulations using an artificial neural network (Plaut &  
462 Behrmann, 2011). Further, top-down effective connectivity from left inferior frontal cortex was  
463 found in neurologically healthy literate adults for a functionally defined VWFA in left vOTC, but  
464 not for the corresponding right VWFA or for left vOTC voxels with a significant preference for  
465 faces rather than word forms (Canário et al., 2020), demonstrating that connectivity between the  
466 VWFA and frontal and temporal language areas is lateralized to the left hemisphere ((Bouhali et  
467 al., 2014), (Chen et al., 2019)).

468 In summary, our study demonstrates that major perinatal strokes to the left hemisphere that  
469 result in right-hemisphere dominance for spoken language processing also typically lead to  
470 development of the visual word form area in the right hemisphere, even if the lesion does not  
471 damage the left-hemisphere tissue in which the VWFA normally develops or its connections to  
472 earlier stations in the visual object processing hierarchy. This accords with the hypothesis that  
473 development and lateralization of the VWFA are determined by connectivity with the language  
474 system. It also supports the notion that the two hemispheres are equipotential early in life such  
475 that either of them can develop a functional language system, including the ability to respond to  
476 print.

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## 685 Figure Captions

686

687 **Figure 1. Lesion overview.** Horizontal and sagittal views of native-space MPRAGEs for all  
688 participants in the LHPS group. The horizontal slice was chosen to best show the lesion; the  
689 sagittal view was chosen to illustrate that in all participants it spared the posterior left vOTC.

690

691 **Figure 2. Lateralization of auditory sentence comprehension.** Axial views of individual  
692 activation maps contrasting activation during auditory sentence comprehension with activation  
693 during listening to (incomprehensible) reverse speech, overlaid on an MNI template brain. In all  
694 CTRL participants (blue, top), these activations showed the expected left-lateralization, whereas  
695 all LHPS participants showed a roughly mirror-symmetric right-lateralized activation pattern. The  
696 insert on the right quantifies this using a lateralization index. Adapted from (Newport et al.,  
697 2022), Figures S2 and S3, with inclusion of new participants C13, C14, C14, L16, and L17, and  
698 removal of participants C9, L1, and L14.

699

700 **Figure 3. Language skills.** All participants completed the sentence comprehension and word  
701 structure subtests of the Clinical Evaluation of Language Fundamentals (CELF, (Wiig et al.,  
702 2013)), and all participants except for one CTRL participant completed the Active-Passive Test  
703 (developed based on (Dennis & Kohn, 1975)) and the Test for Reception of Grammar (TROG-2;  
704 (Bishop, 2003)). As is evident, performance levels for the two groups were quite similar across  
705 all measures and did not reveal the large impact on language skills that one would expect  
706 following a large stroke to the left hemisphere if it occurred in adulthood. The only measure that  
707 showed a significant group difference in a Student's t-test was the CELF Sentence  
708 Comprehension subtest (CTRL mean: 99.7%, LHPS mean: 97.7%,  $t(27)=2.89$ ,  $p=0.007$ );



709 however, due to the large number of participants performing at ceiling in this test, this statistical  
710 comparison should be interpreted with caution (Q. Liu & Wang, 2021). Importantly, there were  
711 no significant group differences on measures without ceiling effects, such as the TROG-2  
712 center-embedded items (CTRL mean: 71.1%, LHPS mean: 71.7%,  $t(26)=-0.05$ ,  $p=0.960$ ) or the  
713 Passive items from the Active-Passive test (CTRL mean: 92.8%, LHPS mean: 88.5%,  $t(26)=-$   
714 1.33,  $p=0.196$ .) Taken together, these results indicate that the participants in the LHPS group  
715 had language skills within the normal range despite their large LH lesions. Adapted from  
716 (Newport et al., 2022), Figure 3, with inclusion of new participants C13, C14, C14, L16, and L17,  
717 and removal of participants C9, L1, and L14.

718

719 **Figure 4. Experimental design. (A)** Example stimuli illustrating the three experimental  
720 conditions, arranged as excerpts of an experimental block. The first two stimuli of “Places”  
721 illustrate a repetition. **(B)** Time course of one of the two functional runs, with gray, blue, green,  
722 and orange indicating Rest, Face, Place, and Word Form stimulation, respectively. The other  
723 run presented the experimental conditions in the remaining three possible orders: PFW, FWP,  
724 and WPF. Rest periods occurred at the same times in both runs.

725

726 **Figure 5. Examples of individual activation maps. (A)** In the CTRL group, clusters of voxels  
727 with a significant preference for visual word forms over pictures of places (contrast  $W>P$ ) were  
728 identified in the left fusiform gyrus (BA 37), at locations consistent with published coordinates for  
729 the VWFA. **(B)** In the LHPS group, clusters with this preference were located in the right  
730 fusiform gyrus, roughly mirroring the usual location. Unthresholded activation maps for all  
731 participants, an overview figure showing slice views of all participants, and a table summarizing  
732 peak coordinates and sizes of the VWFA activation clusters can be found at [osf.io/8x49a](https://osf.io/8x49a).

733

734 **Figure 6. Region-of-interest analysis.** Each data point represents a participant's activation  
735 averaged across all voxels inside independently defined VWFA ROIs in the left and right  
736 hemisphere (shown in red on the brain insert); short horizontal lines represent the group mean,  
737 vertical lines the standard error of the mean. **(A)** Contrasting the response to Word Form stimuli  
738 with that to Place stimuli (contrast  $W>P$ ). The slope of the lines connecting each participant's LH  
739 and RH activation shows the lateralization of ROI activation. As expected, most CTRL  
740 participants showed a stronger  $W>P$  effect in the left compared to the right fusiform ROI (blue,  
741 left panel). The opposite was true for the LHPS participants (orange, right panel.) The LHPS  
742 group's activation in the right hemisphere ROI was significantly stronger than that of the CTRL  
743 group and not significantly different from the CTRL group's activation in the left hemisphere  
744 ROI. **(B)** Relative to baseline (fixation only), activation of the left ROI in response to Place  
745 stimuli was no weaker in the LHPS group than in the CTRL group, showing that right-  
746 lateralization of Word Form processing in the LHPS group was not driven by overall depressed  
747 activation in the lesioned hemisphere. **(C)** Activation in the right hemisphere ROI in response to  
748 Word Form stimuli was stronger in the LHPS group than in the CTRL group even relative to  
749 baseline (i.e., without controlling for the effect of visual stimulation).

750

751 **Figure 7. Comparison of individual activation peaks between groups and hemispheres.**  
752 Each data point represents the average t-value of a participants 8 voxels with the strongest  
753 activation for Word Forms relative to Rest (contrast  $W>Rest$ ) inside an independently defined  
754 VWFA ROI (shown in red on the brain insert). As in Figure 6, short horizontal lines represent the  
755 group mean of these individual top activations, vertical lines the standard error of the mean. The  
756 pattern of results is identical to that shown in Figure 6 for the ROI-wide analysis of the  $W>P$   
757 contrast, with reversed lateralization in the LHPS group relative to the CTRL group.

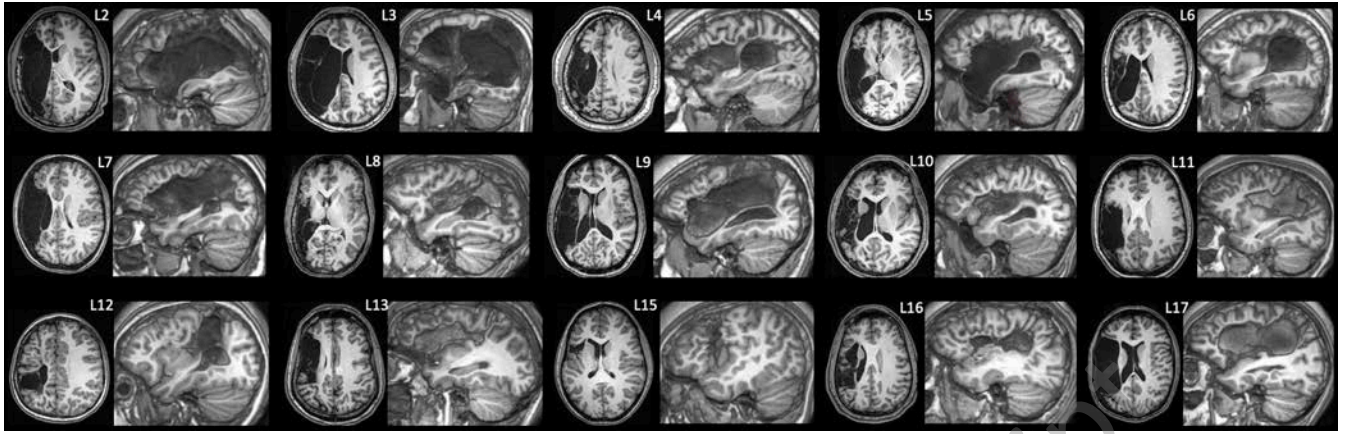
759

760 **Table 1. Accuracy and reaction time on the in-scanner one-back tasks**

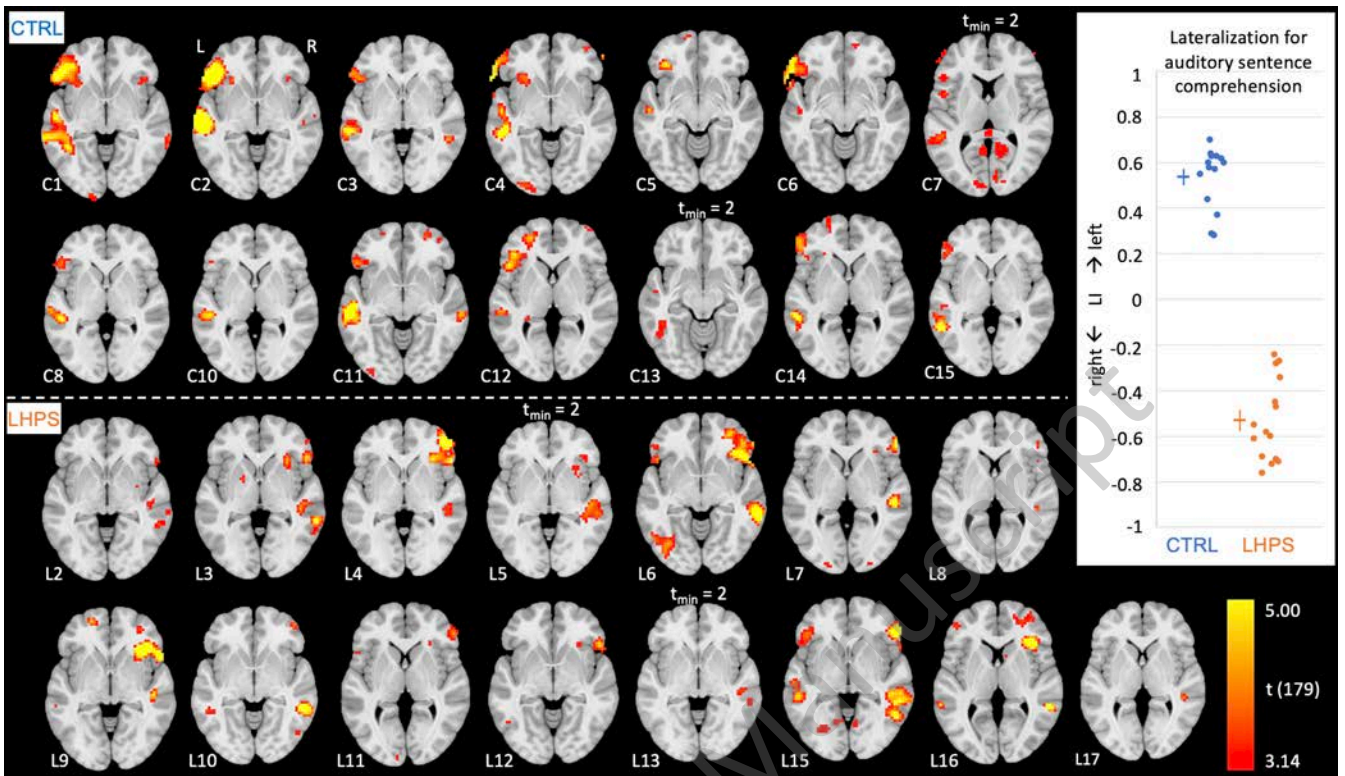
	Percentage of detected repeats			Average reaction time (ms)		
	Words	Places	Faces	Words	Places	Faces
CTRL mean (SD)	82 (14)	84 (18)	83 (15)	492 (88)	464 (72)	467 (75)
LHPS mean (SD)	82 (14)	77 (7)	85 (11)	504 (61)	485 (46)	482 (59)
CTRL vs. LHPS						
t(28)	0	1.42	-0.40	-0.41	-0.93	-0.57
CTRL vs. LHPS p	1	0.174	0.696	0.687	0.361	0.575

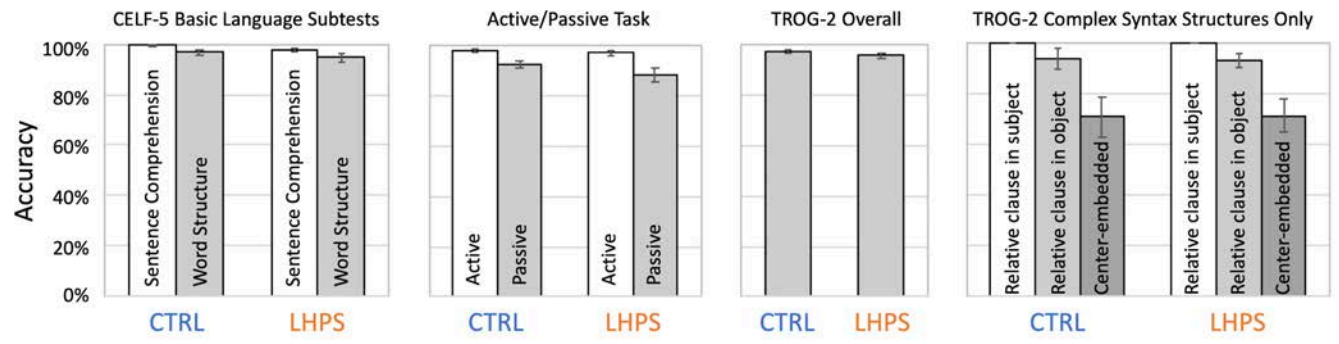
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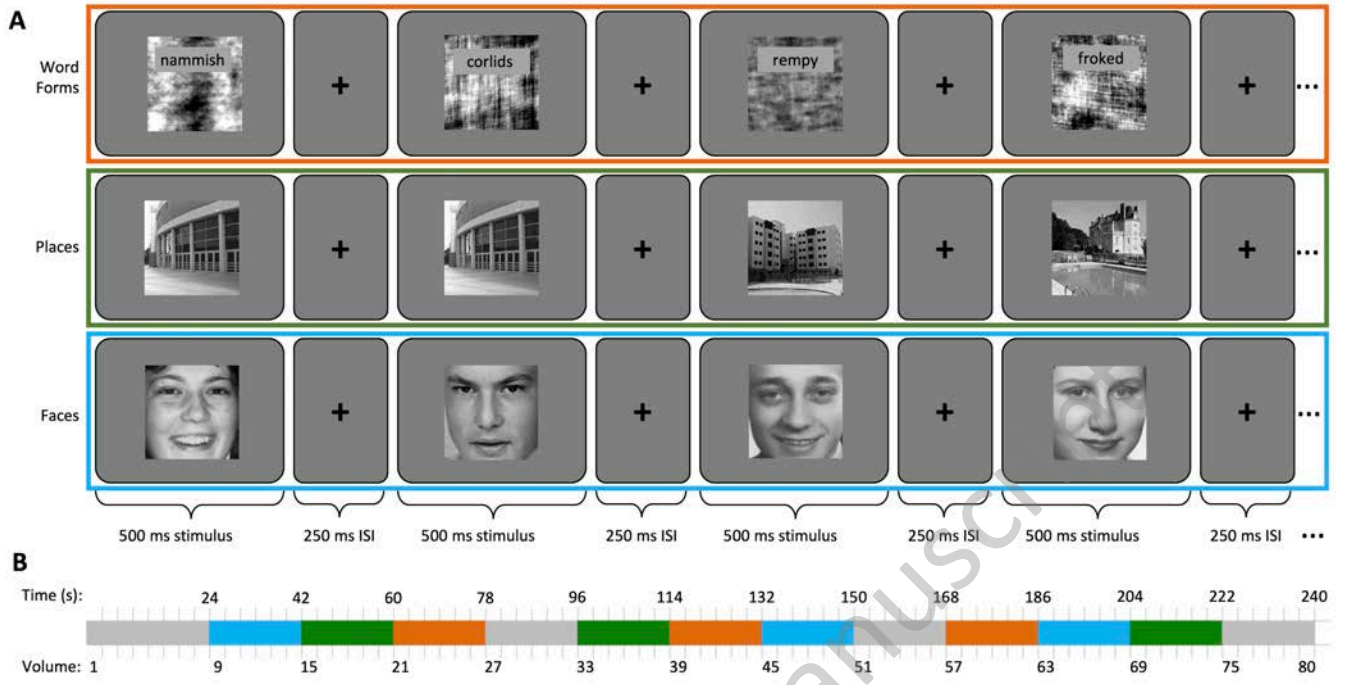


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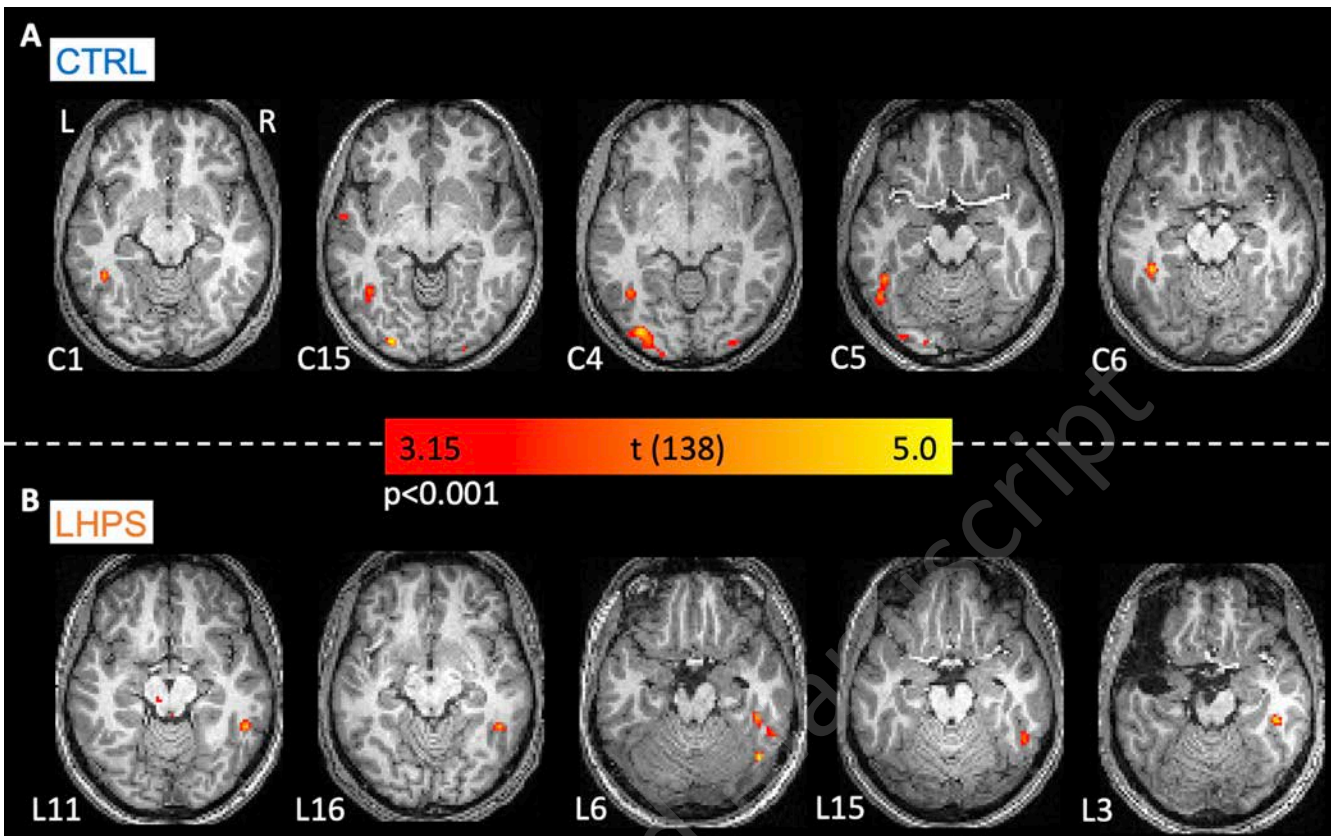




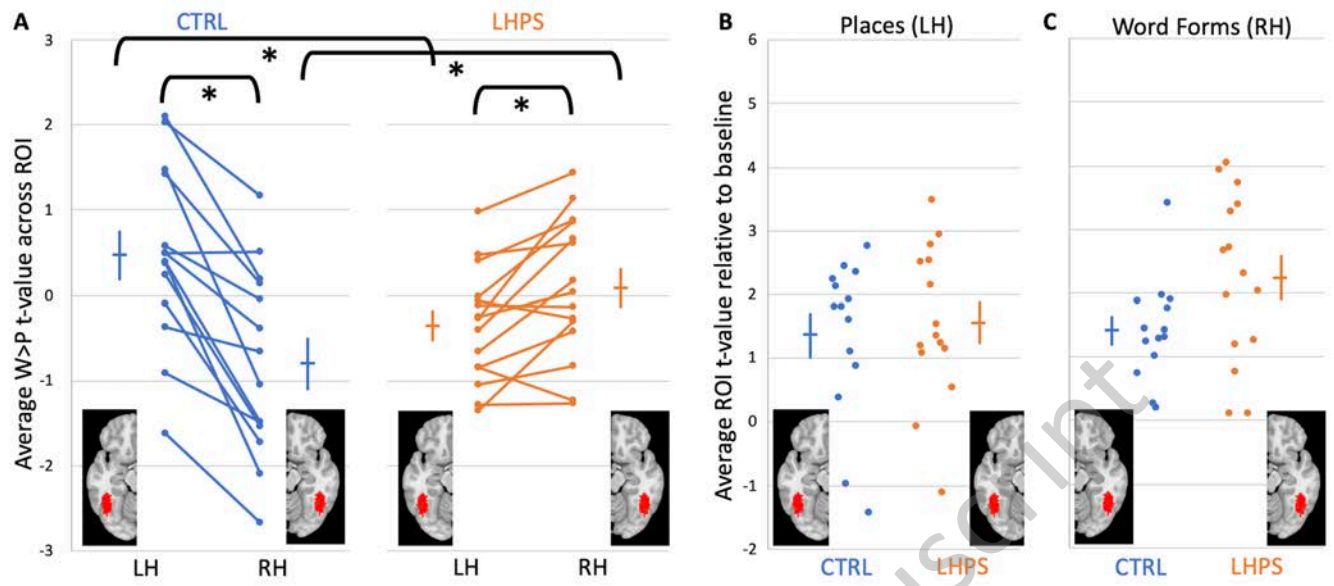
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