# The typical and atypical development of the visual word form area: the role of innate connectivity and experience

Thesis

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# Abstract

What determines the functional organization of cortex? One hypothesis is that innate connectivity patterns set up a scaffold upon which functional specialization can later take place. In the present work, we tested this hypothesis by asking whether the visual word form area (VWFA), an experience-driven region, was already connected to proto language networks in neonates scanned within one week of birth (Study 1); and further we asked what happens if the site of putative VWFA doesn't have access to temporal language regions (Study 2). In Study 1, with resting-state fMRI, we found that neonates showed adult-like functional connectivity, and observed that i) language regions connected more strongly with the putative VWFA than other adjacent ventral visual regions that also show foveal bias, and ii) the VWFA connected more strongly with frontotemporal language regions than with regions adjacent to these language regions. In Study 2, with task-based fMRI, we examined the functional response from an individual born without the left temporal lobe (EG), and compared it to typical adults and school-age kids. We first replicated the functional connectivity results from Study 1 in an independent group of adults and in school-age kids. Next, we found that i) before becoming selective to words, the site of future VWFA responds to objects in typically developed young kids; ii) in the individual with the dorso-temporal lesion, we failed to identify any word selective response in the canonical VWFA location; and iii) with multivariate pattern analysis, we found that there was a reliable response pattern in the ventral occipitotemporal cortex that can distinguish words from other categories in EG. Altogether, these findings suggest that the location of the VWFA is earmarked at birth due to its connectivity with the language network and the failure of connection to temporal language regions might lead to displacement of the word-selective region.

# Vita

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# Publications

Li, J., Osher, D. E., Hansen, H. A., & Saygin, Z. M. (revision under review). Cortical selectivity driven by connectivity: Innate connectivity patterns of the visual word form area. *Nature Human Behaviour.*

Li, J., Song, Y., & Liu, J. (2019). Functional connectivity pattern in the core face network reflects different mechanisms of holistic face processing measured by the whole-part effect and composite-face effect. *Neuroscience*, *408*, 248-258.

Li, J., Huang, L., Song, Y., & Liu, J. (2017). Dissociated neural basis of two behavioral hallmarks of holistic face processing: the whole-part effect and composite-face effect. *Neuropsychologia*, *102*, 52.

# Fields of Study

Major Field: Psychology

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# Chapter 1. Introduction

Decades of research suggest that the adult brain is composed of patches of cortex that are specialized for unique mental functions. To what extent is the functional organization of the human brain innate? Recent advances in developmental neuroimaging have made it possible to start to answer this question. For example, a previous study showed category-selective responses in high-level visual cortex for faces and scenes in infants (Deen et al., 2017). Further, research in congenitally blind individuals suggests that cortical selectivity for high-level visual categories may not require visual experience (van den Hurk, Van Baelen, & de Beeck, 2017). In addition to the early emergence of visual processing, a previous study also found a neural precursor of language processing in infants (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002). Specifically, they found brain activity in left superior temporal and angular gyri to human speech in 3-month-old infants. These studies support the protomap hypothesis, which suggests that early genetic instructions give rise to the mature functional areas of cortex. However, the mechanisms that drive this early functional specialization remains ambiguous.

One possibility is that the specialization of a given brain region is largely shaped by how it connects and communicates with the rest of the brain (the Connectivity Hypothesis). Consistent with this hypothesis, previous work showed that structural connectivity (via diffusion imaging) as well as functional connectivity (via resting-state scans) can predict task-based selectivity across the brain (Osher et al., 2015; Saygin et al., 2012). Further, Barttfeld et al. (2018) found a lateral-to-mesial organization in ventral visual cortex in newborns, suggesting that functional connectivity present at birth may constrain the subsequent functional specialization of visual areas (Barttfeld et al., 2018). This work suggests that connectivity is tightly intertwined with functional selectivity, and that perhaps early connectivity patterns may earmark the location of functionally selective cortices.

However, very few studies directly looked at the innateness of the connectivity patterns for the putative functional regions in newborns. A very recent study looking at the putative face- and scene-selective regions in 27 day neonates found that domain-specific patterns of functional connectivity (Kamps, Hendrix, Brennan, & Dilks, 2020). Nevertheless, given the evolutionary importance of face and scene recognition as well as evidence of early existence of faces and scenes responses in infants (Deen et al., 2017), it remains unknown whether the functional connectivity already set up a scaffold for developing a highly experience-dependent region even at birth. The visual word form area (VWFA) is a region in the lateral portion of left fusiform gyrus that particularly responsive to visual words (McCandliss et al., 2003). Visual words is a very recent invention, and the VWFA only exists in literate individuals (Baker et al., 2007; Dehaene et al., 2010). Therefore, the VWFA serves as a good subject to study the innateness of its functional connectivity pattern that might later instruct the development of word selectivity. Can the VWFA be differentiated from the adjacent fusiform face area (FFA) by its connections to the high-level cortex like the frontotemporal language network?

In adults, the VWFA connects with perisylvian language cortex, differentiating it from adjacent visual cortex (Bouhali et al., 2014); other studies also found that white matter fibers that originated from the VWFA pass through fascicles that may be critical for language processing (Epelbaum et al., 2008; Yeatman, Rauschecker, & Wandell, 2013). In children, a longitudinal study found that connectivity patterns in pre-literate 5-year-olds predicted the location of the VWFA in each child at age 8 after they learned to read, and differentiated it from the adjacent FFA (Saygin et al., 2016). The connectivity patterns that predicted the VWFA included putative language areas, suggesting that connectivity to these regions may earmark the future location of the VWFA, and also set up a scaffold upon which future functional specialization can take place. However, while the 5-year-olds could not read (and at that age, lacked neural selectivity to letters or letter-like stimuli), they still would have had years of visual experience with letters and words. Is the putative VWFA already connected differently and set up to be differentiated from adjacent visual regions, even at birth with no visual experience with words and little visual experience at all?  Moreover, what happens if the site that would later develop as the VWFA does not have access to language regions?

Previous studies have investigated the impact of temporal lobe lesion in patients with temporal lobe epilepsy or post-stroke aphasia and these studies were mostly focused on language reorganization. Studies show that undamaged left hemisphere language networks primarily contribute to language recovery while recruitment of right hemisphere lesion-homologues and bilateral domain-general areas also observed in some cases (Stockert et al., 2020). Stockert et al. (2020) also reported that the dynamics of language reorganization in patients varies with different lesion sites. Moreover, a study looked at children with perinatal left middle cerebral artery (MCA) and found their language areas were displaced to right hemisphere and they also showed more bilateral activation in superior temporal and anterior cingulate gyri and increased activation in primary visual cortex when compared to healthy controls (Tillema et al., 2008). Altogether it suggested the role of experience along with plasticity of the brain. However, it remains unknown how the lesion would affect the development of a functional region it connects to: specifically, does the lesion in the left temporal lobe lead to atypical development of word selectivity in the brain?

The present work aims to answer these questions based on a diverse group of subjects in two studies. In study 1, we tested the proto-organization of the VWFA in the newborn brain. Based on the Connectivity Hypothesis, we hypothesized that although the VWFA is highly experience-dependent, it is already ‘prewired’ to be selective for visual words by communicating with proto language regions at birth. By examining neonates who were scanned within one week of birth, we asked i) Do language regions show stronger functional connectivity (FC) with the putative VWFA than with other high-level visual areas like face, scene, and object areas? and ii) Does the VWFA show stronger FC with language regions than with adjacent frontotemporal regions like the multiple-demand (MD) network, speech regions, and primary auditory cortex (A1)? In Study 2, we explored the role of experience in developing the word selectivity by comparing response profiles of the canonical VWFA between independent groups of adults, school-age kids and an adult who has left temporal lesion but with normal reading and language ability.

Since the lesion disrupts the connection between the VWFA and temporal language regions, we asked i) Without access to language regions, is there any word selectivity left in the canonical location of the VWFA or does it remap to right homogeneous region? and ii) does the remained left ventral temporal cortex has a distinct response pattern for words, just as typical adults?

# Chapter 2. Study 1

## Method

### Participants

*Neonates.* We used the initial release of the Developing Human Connectome Project (dHCP) neonatal data (http://www.developingconnectome.org) (Makropoulos et al., 2018). Neonates were recruited and imaged at the Evelina Neonatal Imaging Centre, London. Informed parental consent was obtained for imaging and data release, and the study was approved by the UK Health Research Authority. All 40 neonates of the initial release were included in functional connectivity analysis and were born and imaged at term age (15 female, mean gestational age at birth = 38.99 weeks, gestational age range at scan = 37-44 weeks).

*Adults*. Adult data were obtained from the Human Connectome Project (HCP), WU-Minn HCP 1200 Subjects Data Release (https://www.humanconnectome.org/study/hcp-young-adult) (Van Essen et al., 2013). All participants were scanned at Washington University in St. Louis (WashU). 40 adults were included in functional connectivity analysis (15 female, age range = 22-36 years old). These adult participants were motion and sex matched to the neonates. Specifically, for each neonatal participant we matched with an adult from the HCP dataset with the same sex who showed the most similar motion parameter (i.e., framewise displacement, FD) with the k-nearest neighbors' approach. By doing this, we are able to match the sex ratio and no evidence for a statistically difference was found for head motion between groups (t(78) = 0.77, p = 0.45, Cohen's d = 0.17, 95% CI = [-0.02, 0.01]).

## Data acquisition

### *Neonates.*

Imaging was carried out on 3T Philips Achieva (running modified R3.2.2 software) using a dedicated neonatal imaging system which included a neonatal 32 channel phased array head coil (Hughes et al., 2017). All neonates were scanned in natural sleep; previous studies have shown that the resting-state FC remains consistent while awake and asleep, as well as while under anesthesia (Larson-Prior et al., 2009; Liu, Yanagawa, Leopold, Fujii, & Duyn, 2015).

*Resting-state fMRI.* High temporal resolution fMRI developed for neonates using multiband (MB) 9x accelerated echo-planar imaging was collected (TE/TR = 38/392ms, voxel size = $2.15 \times 2.15 \times 2.15 mm^3$). The duration of resting-state fMRI scanning was approximately 15 minutes and consisted of 2300 volumes for each run. No in-plane acceleration or partial Fourier was used. Single-band reference scans were also acquired with bandwidth matched readout, along with additional spin-echo acquisitions with both AP/PA fold-over encoding directions.

*Anatomical MRI.* High-resolution T2-weighted and inversion recovery T1-weighted multi-slice fast spin-echo images were acquired with in-plane resolution 0.8 × 0.8mm$_2$ and 1.6mm slices overlapped by 0.8mm (T2-weighted: TE/TR = 156/12000ms; T1 weighted: TE/TR/TI = 8.7/4795/1740ms).

*Adults.*

All the scans of WU-Minn HCP 1200 Subjects Data Release was carried out using a customized 3T Connectome Scanner adapted from a Siemens Skyra (Siemens AG, Erlanger, Germany) with 32-channel Siemens receive head coil and a “body” transmission coil designed by Siemens specifically for the smaller space available using the special gradients for the WU-Minn and MGH-UCLA Connectome scanners.

*Resting-state fMRI.* Participants were scanned using the Gradient-echo EPI sequence (TE/TR = 33.1/720ms, flip angle = 52°, number of slices = 72, voxel size = 2 × 2 × 2 mm$^3$). The duration of resting-state fMRI scanning was approximately 15 minutes and consisted of 1200 volumes for each run. All participants accomplished two resting-state fMRI sessions. Within each session, there were two phases encoding in a right-to-left (RL) direction in one run and phase encoding in a left-to-right (LR) direction in the other run. In current analysis, we used the LR phase encoding from the first session. Participants were instructed to open their eyes with relaxed fixation on a projected bright cross-hair on a dark background.

*Anatomical MRI.* High-resolution T2-weighted and T1-weighted images were acquired with isotropic voxel resolution of 0.7mm$^3$ (T2-weighted 3D T2-SPACE scan: TE/TR = 565/3200ms; T1-weighted 3D MPRAGE: TE/TR/TI = 2.14/2400/1000ms).

**Preprocessing.**

*Structural data Preprocessing.* The dHCP data were released as preprocessed data; they used the dHCP structural minimal preprocessing pipeline (Makropoulos et al., 2018), briefly: bias correction, brain extraction using BET from FSL, and segmentation of the T2w volume using DRAW-EM algorithm (Makropoulos et al., 2014) which were developed for neonatal brain segmentation. Gray and white matter masks were obtained from segmentations using DRAW-EM algorithm provided by dHCP. The HCP data were released as preprocessed data; they used the HCP structural preprocessing pipeline (Glasser et al., 2013), briefly: gradient distortion correction, brain extraction, a bias field correction, and registration between the T2-weighted scan and T1-weighted scan. Each individual brain was also aligned to common MNI152 template (with 0.7mm isotropic resolution). Then, the FreeSurfer pipeline (based on FreeSurfer 5.3.0-HCP) was performed to segment the volume into predefined structures and surface reconstruction.

*Functional data Preprocessing.* The pre-processed functional data released by the dHCP had already undergone basic pre-processing steps (for details see Fitzgibbon et al., 2019): distortion-correction, motion correction, 2-stage registration of the MB-EPI functional image to T2 structural image and also generated a combined transform from MB-EPI to 40-week T2 template, and ICA denoising using ICA-FIX (Salimi-Khorshidi et al., 2014). The data released by the HCP had already undergone basic pre-processing steps (for details see Glasser et al., 2013): removed spatial distortions, corrected for motion, registered the fMRI data to both structural and MNI152 template, reduced the bias field, and ICA denoising using ICA-FIX (Salimi-Khorshidi et al., 2014). The HCP data were registered to each individual's native space using the transformation supplied by the HCP and the following steps were performed on both the HCP and dHCP data: applied smoothing (Gaussian filter with the FWHM = 3 mm) within the all gray matter, and band-pass filter at 0.009-0.08 Hz. As a further denoising step, we used aCompCor44 to regress out signals from white matter and cerebrospinal fluid (CSF) to control physiological noise like respiration and heartbeat as well as non-neuronal contributions to the resting state signal. All the FC analyses were performed in native functional space.

### Defining the functional parcels.

The parcels used here were originally created from probabilistic maps of functional activation across independent groups of participants, and are generated such that they encapsulate most individuals’ functional regions, via the group-constrained subject-specific method (GSS) (Fedorenko, Hsieh, Nieto-Castañón, Whitfield-Gabrieli, & Kanwisher, 2010). Contrary to traditional group-based methods (e.g., random-effects analyses) or using anatomical approximations or Talairach coordinates based on meta analyses, the GSS approach takes individual variability of functional responses (size, shape, and location) into account, providing the anchor space for functionally specialized regions that activate systematically across individuals. The present study especially benefits from this approach due to the study of nonverbal neonates. Additionally, these GSS studies were chosen particularly because the tasks and fMRI contrasts that were used to define the functional regions of interest offer better controls for the domains of interest. All parcels are available online or via contacting the corresponding author of the cited publications.

All parcels were mapped to the FreeSurfer CVS average-35 MNI152 brain (if they were not already publicly provided in that space) and were subsequently registered to each individual's brain (see below). Language regions were released by Fedorenko et al. and were defined by Sentences vs. pronounceable non-word sentences (Fedorenko et al., 2010) thus controlling for prosody, low-level auditory features, and speaker identify, and are found to respond similarly to auditory and visual versions of the stimuli (Fedorenko, 2014; Scott, Gallée, & Fedorenko, 2017). Temporal regions included: AntTemp, anterior temporal lobe; MidAntTemp, middle-anterior temporal lobe; MidPostTemp, middle-posterior temporal lobe; PostTemp, posterior temporal lobe; and AngG, angular gyrus. Frontal regions included: IFG, interior frontal gyrus; and IFGorb, orbital IFG. To get a narrower definition of language regions, we selected the IFG language parcel for Broca's area and the MidAntTemp language parcel for Wernike's area. The speech region was from Basilakos et al. (2018) and the region we used was in superior temporal gyrus, which was shown to be sensitive to the phonemic structure of human speech rather than low-level auditory properties or task-difficulty. A1 was anatomically defined as Heschl's gyrus (superior and transverse temporal cortex from the FreeSurfer Desikan-Killiany parcellation (Desikan et al., 2006) in CVS average-35

MNI152 space). Multiple-demand (MD) parcels located in left frontal cortex were obtained from Fedorenko et al. (2013), showing activation to hard vs. easy conditions of working memory tasks (Blank, Kanwisher, & Fedorenko, 2014; Fedorenko, 2014; Fedorenko et al., 2013). These parcels were in MFGorb, orbital part of the middle frontal gyrus; Insula; IFGop, opercular part of the inferior frontal gyrus; SMA, supplementary motor area; and ACC, anterior/mid cingulate cortex. The VWFA, located in left occipitotemporal cortex, was created from Words vs. line drawings of Objects, from Saygin et al. (2016). The other high-level visual parcels were derived from Julian et al.(2012), and were based on responses to dynamic movie clips (Pitcher, Dilks, Saxe, Triantafyllou, & Kanwisher, 2011) and activation for the contrast of interest. FFA and OFA located in the fusiform and occipital cortex respectively were identified with faces > objects contrasts (Gauthier et al., 2000; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997) ; scene selective PPA was identified with scenes > objects contrast (Epstein & Kanwisher, 1998) and was located in the parahippocampus; object selective LO and PFS were defined with objects > scrambled objects contrasts (Grill-Spector et al., 1999) and located in the lateral occipital and posterior fusiform sulcus respectively.  Because both VWFA and language are largely left lateralized (Dundas, Plaut, & Behrmann, 2013; Frost et al., 1999) , our study includes left hemisphere seeds and targets only, as was the case with previous studies of these regions (Bouhali et al., 2014; Stevens, Kravitz, Peng, Tessler, & Martin, 2017) as well as a recent study which also looked at VWFA connectivity using the adult HCP dataset (Chen et al., 2019).

All functional parcels were placed in the template CVS average-35 MNI152 space, and were overlaid onto each individual's native anatomical brain using Advanced Normalization Tools (ANTs version 2.1.0; http://stnava.github.io/ANTs) (Avants et al., 2014; Menze et al., 2014; Wang & Yushkevich, 2013) for both adults and neonates. For registration between modalities (i.e., anatomical to native functional image for neonates), we used nearest neighbor interpolation with Freesurfer's mri_vol2vol function (https://surfer.nmr.mgh.harvard.edu/fswiki/mri_vol2vol). To ensure no voxel belonged to more than one functional parcel, we assigned any intersecting voxels of two functional parcels to the one with smaller size as a way to compensate size differences (e.g., Brissenden, Levin, Osher, Halko, & Somers, 2016). Additionally, voxels within white matter and cerebellum were also removed. In total, we used 20 non-overlapping functional parcels from eight categories in the present study.

### Calculating functional connectivity.

The mean timecourse of each functional parcel was computed from the preprocessed resting state images, and FC was calculated with Pearson's correlation between the mean timecourse of each seed parcel and each target parcel. To generate normally distributed values, each FC value was Fisher z-transformed.

### FC fingerprint plots

First, we calculated the average FC from the seed to each of the target categories. Then we subtracted the mean FC across all categories from each of the averaged FC.

Thus, the value in the fingerprint plots indicates how the seed connects to the targets compared to the mean connectivity of the seed to all categories (mean-centering) across subjects in each group. We further quantified the similarity of FC patterns between adults and neonates. Specifically, for each participant, the Euclidean distance was calculated between the 4-dimensional FC pattern of the seed (i.e., VWFA or language regions) and the average FC pattern of others either from the same group or the different group. This measured how similar each participant was to others.

### Voxel-wise FC analysis in the ventral temporal cortex (VTC) and frontotemporal cortex.

We performed a voxel-wise analysis across VTC to get a finer characterization of the connectivity pattern with language regions. We defined the VTC from the Desikan-Killiany parcellation (Desikan et al., 2006), including the fusiform and inferior temporal labels, in FreeSurfer CVS average-35 MNI152 space, which were registered to each individual's anatomy and masked with the gray matter image for each individual subject (as provided by the HCP and dHCP datasets).  FC was computed between the mean timecourse of the language regions and the timecourse of each VTC voxel. Without predefining any functional parcels within the VTC, this analysis allowed us to characterize where the voxels with highest connectivity were located within the VTC. To quantify this, we performed a parametric analysis where we increased the threshold of FCs across all VTC voxels from the 50th percentile (median) to the 95th and calculated the overlap of these voxels with each of VTC regions with Dice coefficient.  Specifically, each percentile determines the threshold for binarizing the connectivity data and overlap is calculated using Dice coefficient for each subject. For example, for the 50th percentile threshold, Dice coefficient was calculated by 2 * (A AND B) / A OR B, where set A are the voxels in VTC that are connected to language regions above the 50th percentile and set B are the voxels within the VWFA. We used Matlab to calculate percentiles and Dice coefficient. The same analysis was performed for frontal cortex and temporal cortex separately, and frontal and temporal cortex were again defined with Desikan-Killiany parcellation in the CVS average-35 MNI152 space and masked to only include gray matter within each subject's individual space). Temporal cortex analyses were restricted to the more superior regions to prevent overlap with the VTC analysis. Individual subject results were projected to the surface of each subject using the surfaces provided by the dHCP and HCP with trilinear interpolation, which takes the average across the surface normal.

### Statistics.

2-way mixed design ANOVA were used to test our main focus. Age group (adults, neonates) was the between-subject variable and target (i.e., different target categories) was our within-subject variable (i.e., repeated-measures), and thus there was no experimental group randomization or blinding in the present study. Paired t-tests were conducted for within group comparisons and two-tailed t-tests for across-group comparisons. The 95% confidence interval of the mean FC true population difference was also reported for each post hoc t-test. Benjamini & Hochberg/Yekutieli false discovery rate control (FDR) (Benjamini & Yekutieli, 2005) was used for multiple comparisons correction. Each post hoc t-test was corrected for the total number of paired-wise comparisons for each analysis. Data distribution was assumed to be normal, but this was not formally tested.

## Results

We examined whether the putative VWFA showed privileged connections with language regions even at birth. Because neonates cannot participate in task-based fMRI experiments, and because they do not yet have a VWFA, we overlaid functional parcels from previous studies and atlases (Fedorenko et al., 2013; Fedorenko et al., 2010; Julian et al., 2012; Saygin et al., 2016) to the neonates and adults in this study (see Method for details).

### The selectivity of VWFA-language connections compared with other visual areas

First, we asked: do language regions selectively connect to the expected site of the VWFA, compared with other adjacent high-level visual regions? We compared the functional connectivity (FC) of language regions to the VWFA vs. to other high-level visual areas in the ventral stream, specifically in regions in the vicinity of the VWFA, including face selective regions (Fusiform Face Area, FFA; Occipital Face Area, OFA), scene selective region (Parahippocampal Place Area; PPA), and object selective regions (Lateral Occipital, LO; Posterior Fusiform Sulcus, PFS) (Figure 1).

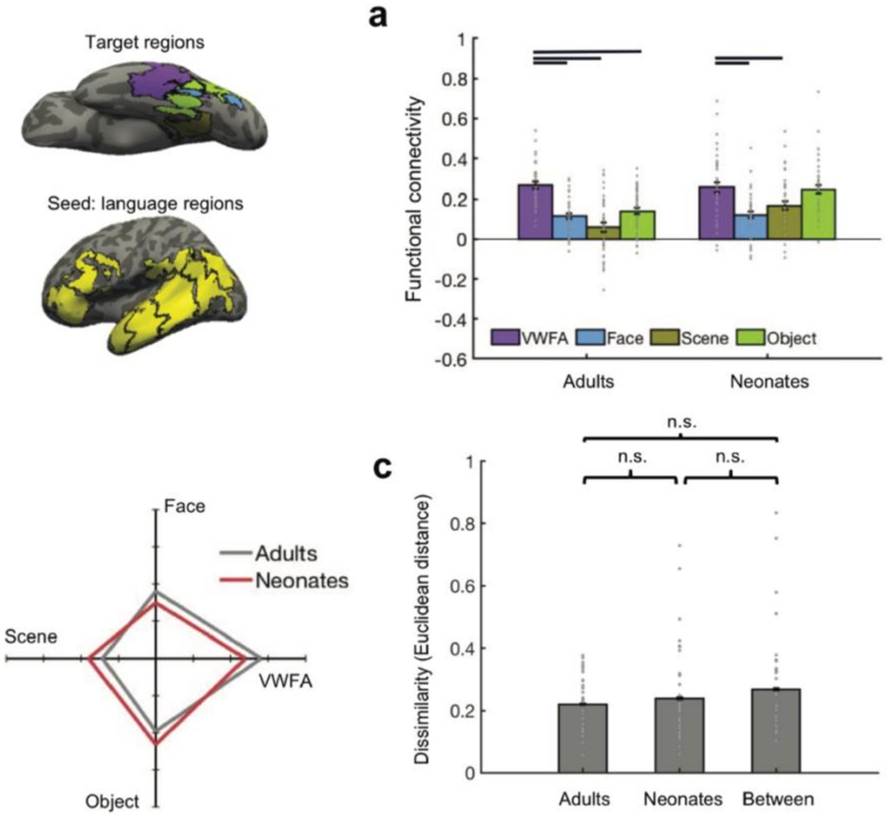

Figure 1 | FC between language regions (seed) and high-level visual regions (targets).

Seed, language (yellow); targets, VWFA (purple), faces (blue), scenes (olive), objects (light green). **(a)** Mean FC between language regions and high-level visual regions in ventral visual stream. Connectivity values were Fisher z transformed. Individual data points (n = 40 for each age group) were shown for each category. Error bars denote s.e.m. Horizontal bars reflect significant *post hoc* paired *t*-tests $p < 0.05$, corrected. **(b)** FC fingerprint of language regions. Connectivity values were mean-centered and averaged within each of the four categories to plot the relative patterns for the adult (n = 40) and neonate groups (n = 40). **(c)** FC pattern dissimilarity for within and between groups (n = 40 for each age group). Euclidean distance between each individual and others either from the same group or different group. n.s., non-significant.

We first performed a complete 2-way mixed design ANOVA with age group (neonate, adult) as the between-group variable and target (VWFA, faces, scenes, objects) as the within-group variable. We found significant main effects for both target and age group (target, (F(3,312) = 24.47, p < 0.001, partial $\eta_2$ = 0.19, 95% CI of partial $\eta_2$ =

[0.11, 0.26]; age group, F(1,312) = 14.07, p = 0.002, partial $\eta_2$ = 0.04, 95% CI of partial $\eta_2$ = [0.01, 0.09]; and a significant interaction (F(3,312) = 4.92, p = 0.002, partial $\eta_2$ = 0.05, 95% CI of partial $\eta_2$ = [0.01, 0.09]). *Post-hoc t*-tests revealed that in adults, language regions showed significantly higher FC with the VWFA than they did with faces (t(39) = 7.58, p<0.001), Cohen's d = 1.20, corrected; 95% CI = [0.11, 0.19]), scenes (t(39) = 9.39, p < 0.001, Cohen's d = 1.49, corrected; 95% CI = [0.16, 0.25]) and objects (t(39) = 7.84, p < 0.001, Cohen's d = 1.24, correct; 95% CI = [0.09, 0.16]) (Figure 1b). The neonates showed a similar pattern, where connectivity between language regions and the VWFA was significantly higher than connectivity of language regions to face (t(39) = 6.28,p < 0.001, Cohen's d = 0.99, corrected; 95% CI = [0.09, 0.18]) and scene (t(78) = 3.90, p < 0.001, Cohen's d = 0.62, corrected, 95% CI = [0.04, 0.14]) regions, but we found no statistically significant evidence for a difference between language regions' connectivity to the VWFA vs. object regions in neonates (t(39) = 0.55, p = 0.59, Cohen's d = 0.09; 95% CI = [-0.03, 0.06]) (Figure 1a).

An exploratory analysis revealed that the VWFA was more connected than object regions to the more canonical aspects of the language network, the language parcel that likely encompasses Broca's and the language parcel that like encompasses Wernicke's areas (Method) in neonates as well as in adults (neonates: Broca: t(39) = 3.06, p = 0.004, Cohen's d = 0.48, corrected; 95% CI = [0.03, 0.15]; Wernicke: t(39) = 3.23, p = 0.003, Cohen's d = 0.51, corrected; 95% CI = [0.04, 0.16]; adults: Broca: t(39) = 7.21, p < 0.001, Cohen's d = 1.14, corrected; 95% CI = [0.21, 0.38]; Wernicke: t(39) = 3.13, p = 0.003, Cohen's d = 0.50, corrected; 95% CI = [0.03, 0.15]).

To further compare connectivity patterns between groups, we next looked at the connectivity fingerprints of language regions to visual cortex in neonates and adults (Figure 1b). Here we plot the relative connectivity of language regions to each of the four target categories (VWFA, face, scene, object regions) as compared to the mean of all four categories. We found that neonates had a very similar shape of the connectivity fingerprints as adults, suggesting similar FC patterns between groups. We statistically quantify the similarity of FC patterns between adults and neonates using Euclidean distance (as a measure of similarity) of the 4-dimensional FC pattern between participants.  No statistically significant evidence for a difference between the within-group similarity and between-group similarity was found (within-adults vs. within neonates: t(78) = -0.72, p = 0.47, Cohen's d = 0.16; 95% CI = [-0.07, 0.03]; within-adults vs. neonates-adults: t(78) = -1.68, p = 0.10, Cohen's d = 0.38; 95% CI = [-0.11, 0.01]; within-neonates vs. neonates-adults: t(78) = -0.85, p = 0.40, Cohen's d = 0.19; 95% CI = [-0.10, 0.04]) (Figure 1c; see Method for more details).

These results indicate that neonates show an overall similar FC pattern as adults, with the highest connectivity between language regions and the VWFA. Interestingly, neonates show similar connectivity between language-VWFA and language-object regions for the language network as a whole, but show dissociations in VWFA vs. object connectivity to the more canonical aspects of the language network, suggesting that further developmental refinement of connectivity does occur, especially to specific aspects of the language circuit.

## Functional connectivity at a voxelwise level in ventral temporal cortex

Next, we applied a voxelwise approach to analyze the functional connectivity profiles of language regions at a more fine-grain level. This analysis allowed us to examine spatial specificity of language-VWFA connectivity, which would serve as a complement to the parcel-wise analyses.  We used language regions as the seed and we looked within ventral temporal cortex (VTC) for voxels that connected most with these language regions. Figure 2a shows the connectivity of VTC voxels to language regions in representative neonates and adults. Consistent with the previous parcel-wise analysis, the voxels that have highest connectivity to language regions were mostly located in the lateral portion of VTC, which is within the putative VWFA location. To quantitatively identify which functional regions these voxels belonged to, we parametrically increased the connectivity threshold from the median to the top 95th percentile of FC across VTC, and calculated the number of voxels within the VTC that were connected to language regions; we then quantified how many of these voxels belonged in each functional region using Dice coefficient (Method). We found that voxels that were connected to language regions were always located in the expected VWFA, vs. all other functional regions in the vicinity; this result was significant for all thresholds (Figure 2b).

Overall, the parcel-based and voxelwise results indicate that the cortical tissue that may later develop sensitivity to visual words has connectivity patterns that are relatively adult-like in the neonatal brain, suggesting that it may be earmarked for function due to its preferential connectivity with language regions at birth. However, we also found differences between neonates and adults, especially with respect to object cortex, suggesting that there exist changes in this connectivity scaffold that likely result due to experience with literacy.

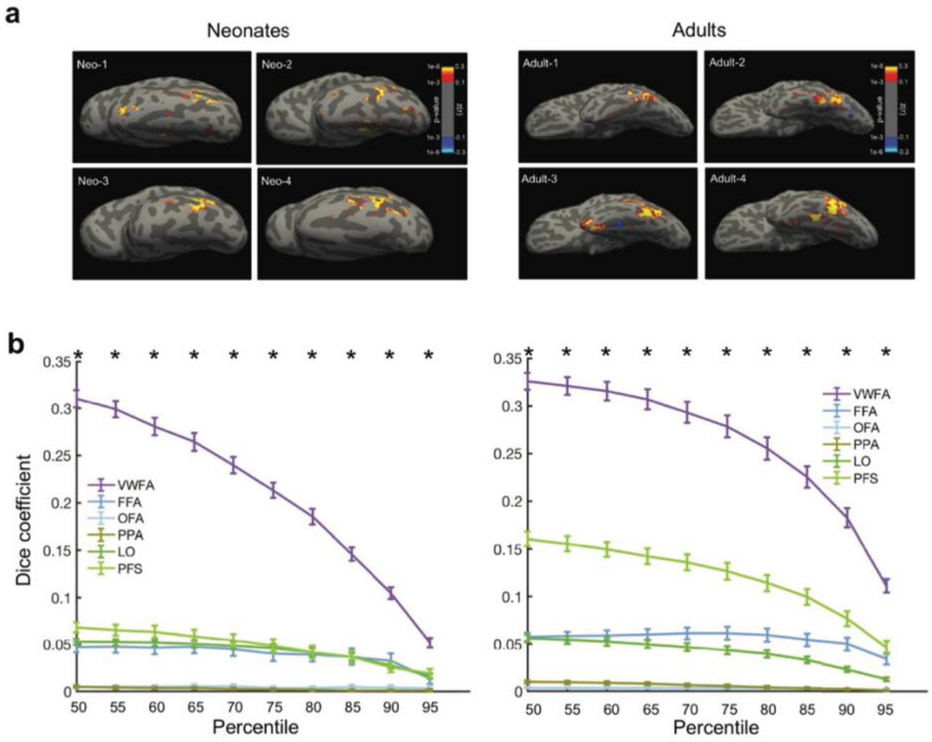

Figure 2 | Voxel-wise analyses within the ventral temporal cortex (VTC) using language regions as the seed.

**(a)** Heatmaps for voxels with connectivity to language regions in representative neonates and adults, thresholded at z(r) greater than 0.1 ($p < 0.001$). **(b)** Parametrically increasing the threshold of FC from the median to the 95th percentile within VTC, we quantified how many of these voxels belonged in each functional region using *Dice coefficient*. Averaged FC (Fisher's z transformed) across neonates (n = 40; 50th: z(r) = 0.25, $p < 0.001$; 95th: z(r) = 0.52, $p < 0.001$; Average FC across adults (n = 40; 50th: z(r) = 0.22, $p < 0.001$; 95th: z(r) = 0.45, $p < 0.001$). Error bars denote s.e.m across participants. * denotes significant paired *t*-test (VWFA vs. average of other functional regions, $p < 0.05$, corrected).

## Functional connectivity between the putative VWFA and language regions

Next, we asked, does the VWFA connect more to language regions vs. regions in the vicinity of language areas? We calculated FC between the VWFA (seed region) and the language, MD, speech, and A1 regions (target regions) (Figure 3). We first performed a complete 2-way mixed design ANOVA with age group (neonate, adult) as the between-group variable and target (language, MD, speech, A1) as the within-group variable to examine VWFA's connectivity. We found both that main effect of age and target were significant (age, F(1,312) = 9.29, p = 0.002, partial $\eta_2$ = 0.03, 95% CI of partial $\eta_2$ = [0, 0,07]; target, F(3,312) = 24.45, p < 0.001, partial $\eta_2$ = 0.19, 95% CI of partial $\eta_2$ = [0.11, 0.26]), and the interaction was also significant (F(3,312) = 3.90, p = 0.009, partial $\eta_2$ = 0.04, 95% CI of partial $\eta_2$ = [0, 0.08]). Post-hoc t-tests revealed that in both adults and neonates the putative VWFA was more connected with language regions than with the other regions (Adults, MD: t(39) = 5.72, p < 0.001, Cohen's d = 0.90, corrected; 95% CI = [0.10, 0.21]; Speech: t(39) = 6.48, p < 0.001, Cohen's d = 1.02, corrected; 95% CI = [0.14, 0.26]; A1: t(39) = 9.32, p < 0.001, Cohen's d = 1.47, corrected; 95% CI = [0.23, 0.36]; Neonates, MD: t(39) = 8.47, p < 0.001, Cohen's d = 1.34, corrected; 95% CI = [0.11, 0.18]; Speech: t(39) = 4.79, p = 0.028, Cohen's d = 0.76, corrected; 95% CI = [0.06, 0.14]; A1: t(78) = 5.63, p < 0.001, Cohen's d = 0.89, corrected; 95% CI = [0.09, 0.19]) (Figure 3a).

To further compare FC patterns between groups, we next plotted the connectivity fingerprint of the VWFA in neonates and adults, and observed similar fingerprint shapes between the two groups (Figure 3b). Quantitative analyses of the similarity of FC profiles also confirmed this observation: no statistically significant evidence for a difference between the within-group similarity and between-group similarity was found (within-adults vs. within neonates: t(78)=-0.55, p=0.58, Cohen's d = 0.12; 95% CI = [-0.08, 0.05]; within-adults vs. neonates-adults: t(78)=-1.29, p=0.20, Cohen's d = 0.29; 95% CI = [-0.11, 0.02]; within-neonates vs. neonates-adults: t(78)=-0.66, p=0.51, Cohen's d = 0.15; 95% CI = [-0.11, 0.05]) (Figure 3c; see Method for details).

Altogether, these results are consistent with previous adult studies by showing that the VWFA has higher FC to language related regions than to adjacent regions; here we also find that the neonatal VWFA has similar patterns of FC to language regions as the adult VWFA.

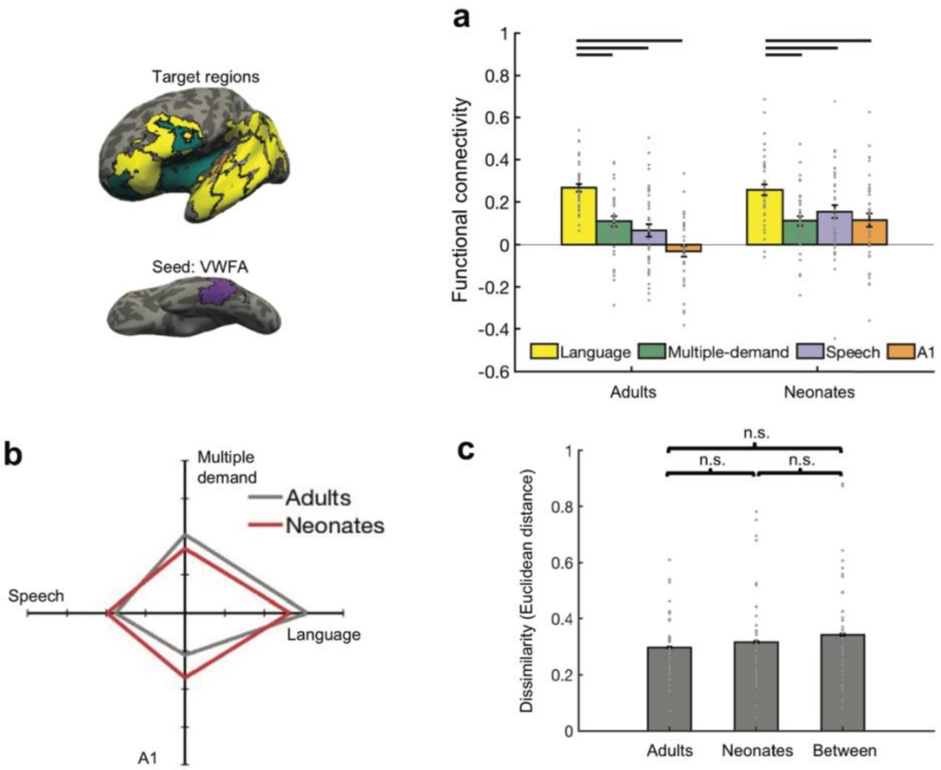

Figure 3 | FC between VWFA (seed) and non-visual regions (targets).

Seed, VWFA (purple); targets, language (yellow), speech (light purple), A1 (orange), MD (green). **(a)** Mean FC between VWFA and regions in temporal and frontal cortices. Connectivity values were Fisher z transformed. Error bars denote s.e.m. Individual data points (n = 40 for each age group) were shown for each category. Horizontal bars reflect significant *post hoc* paired *t*-tests $p < 0.05$, corrected. (**b**) FC fingerprint of VWFA. Connectivity values were mean-centered and averaged within each of the four categories to plot the relative patterns for the adult (n = 40) and neonate (n = 40) groups. **(c)** FC pattern dissimilarity for within and between groups (n = 40 for each age group). Euclidean distance between each individual and others either from the same group or different group. n.s., non-significant.

## Functional connectivity at a voxelwise level in frontal and temporal cortices

We also performed voxelwise parametric analyses for the frontal and temporal cortex using the VWFA as the seed. Consistent with the parcel-based analysis, we found that the voxels connected to the VWFA were most likely located in the expected language regions in temporal and frontal cortex in both neonates and adults (Figure 4a and 4b). Heatmaps that illustrate the connectivity of frontotemporal voxels to the VWFA in representative neonates and adults are provided in Figure 4c. These results indicate that voxels connected to the VWFA are located within putative frontal and temporal language regions in neonates and adults alike.

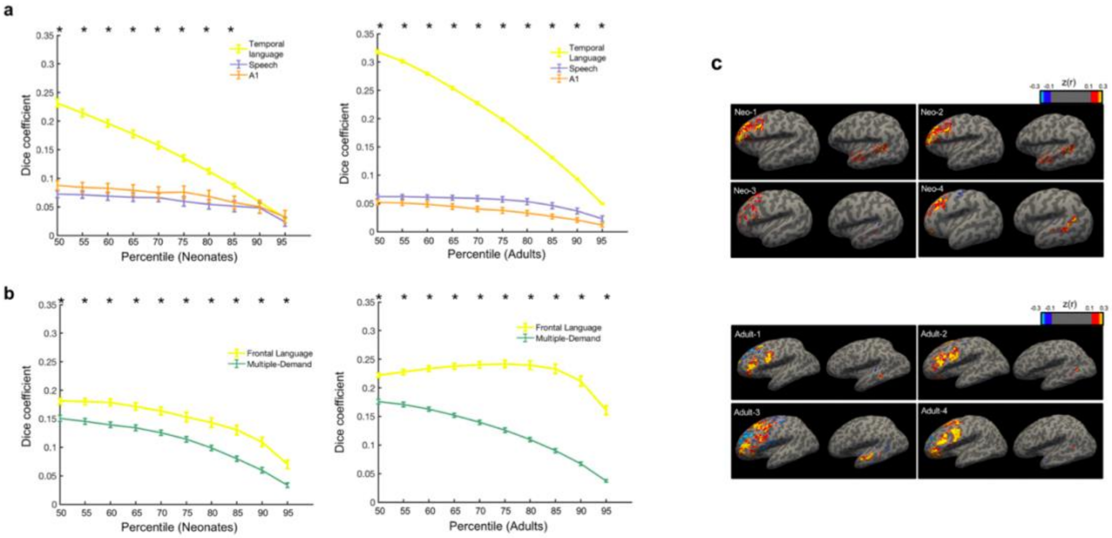

Figure 4 | Voxel-wise analyses from VWFA to frontotemporal cortices.

**(a)** As we parametrically increasing the threshold of FC within temporal cortex, we quantified how many of these voxels belonged in each functional category using *Dice coefficient*. Averaged FC (Fisher's z transformed) across neonates ($n = 40$; 50th: $z(r) = 0.19$, $p < 0.001$; 95th: $z(r) = 0.39$, $p < 0.001$); Average FC across adults ($n = 40$; 50th: $z(r) = 0.17$, $p < 0.001$; 95th: $z(r) = 0.42$, $p < 0.001$). **(b)** As we parametrically increasing the threshold of FC within frontal cortex, we quantified how many of these voxels belonged in each functional category using Dice coefficient. Averaged FC across neonates ($n = 40$; 50th: $z(r) = 0.22$, $p < 0.001$; 95th: $z(r) = 0.40$, $p < 0.001$); Average FC across adults ($n = 40$; 50th: $z(r) = 0.16$, $p < 0.001$; 95th: $z(r) = 0.39$, $p < 0.001$). * denotes significant paired t-test (temporal/frontal language vs. averaged of other adjacent functional regions, $p < 0.05$, corrected). **(c)** Heatmaps for VWFA's connectivity within frontotemporal in representative neonates and adults, thresholded at $z(r)$ greater than 0.1 ($p < 0.001$).

## Discussion

The Connectivity Hypothesis proposes that the future function of a given brain area is largely shaped by how this region connects with the rest of the brain. Classic studies of ‘rewired’ ferrets showed that the cortical region that would have developed into A1 took on many of the properties of V1 after retinal input was rerouted to that location, showing in animal models that connectivity precedes function (Horng et al., 2009; Roe, Pallas, Hahm, & Sur, 1990; Roe, Pallas, Kwon, & Sur, 1992; Sharma, Angelucci, & Sur, 2000; Sur, Garraghty, & Roe, 1988). Here, we tested the Connectivity Hypothesis in human neonates and specifically for a high-level visual function that is uniquely human. In the study 1 we asked: is the putative VWFA already pre-wired at birth to develop differential functional specialization from its neighbors?

The VWFA serves as a good model to study the emergence of functionally selective regions since this region is highly experience-dependent. We first found higher connectivity of language regions with the VWFA than with adjacent regions in visual cortex, and we further replicated previous FC findings in adults (Stevens et al., 2017), showing higher connectivity of the VWFA with language regions that might be involved in different aspects of language processing (i.e., lexico-semantic processing, syntactic processing, structural processing) than with adjacent regions in frontotemporal cortex. Importantly, we also found that this region already shows adult-like connectivity patterns in neonates, suggesting that it may be earmarked to become selective to visual words by showing preferential connectivity with language regions. This research provides the earliest possible evidence in humans that the cortical tissue that will likely later develop sensitivity to visual words has a connectivity pattern at birth that makes it a fertile ground for such development – even before any exposure to words.

The organization of visual cortex, including high-level cortex, is largely biased by retinotopy (Gomez, Barnett, & Grill-Spector, 2019; Hasson, Levy, Behrmann, Hendler, & Malach, 2002; Malach, Levy, & Hasson, 2002). This retinotopic organization is present very early in development, as evidenced by previous work, a recent study found that infant macaques, much like adults, showed a proto-organization for retinotopy throughout the visual system (Arcaro & Livingstone, 2017). It is possible that early genetic instructions and underlying molecular/cytoarchitectonic determine the retinotopic preferences of neurons within these visual regions, including in high-level regions. Indeed, it has been posited that the VWFA starts out as part of the face network, and becomes increasingly selective to words and less selective to faces in the left hemisphere as literacy is acquired (Dehaene et al., 2010; Dundas et al., 2013). This hypothesis is attractive because the perception of both faces and words require high-spatial frequency information that is represented foveally. Thus, with a retinotopic bias/connectivity from lower-level visual regions, it may be possible to first differentiate face regions from scene regions (foveal vs. peripheral bias) early in development (if not at birth), and then face from word regions after literacy is gained, perhaps through differential connections with fronto-temporal language regions. However, retinotopic organization or connectivity to early retinotopic cortex alone cannot explain the early differentiation of the VWFA from face regions, as we found here. We propose that in addition to its predisposition to foveal stimuli, the location of the future VWFA also depends on its innate connectivity with language regions even at birth.

Another question that remains unanswered is how the connectivity patterns themselves arose prenatally and evolutionarily. It is likely that a complex mechanism of intrinsic properties of cortical regions and early signaling mechanisms set up these large-scale connections. The VWFA may simply be in a privileged location, due to a myriad of mechanisms including cellular properties and intrinsic circuitry, in addition to large-scale connectivity that facilitates its later selectivity. Future studies combining animal models with studies in other human populations, e.g. premature human infants, may help further elucidate the evolution of these mechanisms. Moreover, the present study focused on functional connectivity, which raises another interesting question about whether there exists innate structural connectivity between the putative VWFA and language regions at birth and what its developmental trajectory looks like. A recent study observed white matter (i.e., arcuate fasciculus) alterations in 18 months infants with familiar risk of developmental dyslexia (Langer et al., 2017). A potential future direction in this line of research is to explore the role of white matter maturation properties (e.g., fiber density and myelination) in prolonged language development, and examine how their interplay with functional connectivity and experience. Other open avenues of future research include looking at effective connectivity to try to tease apart the directionality of connectivity (which would need to be verified with animal models) as well as graph theoretical approaches (Arslan, Parisot, & Rueckert, 2015) to show similarities or differences in network structure between neonates and adults.

There exist certain limitations in the current study. We found evidence in favor of the Connectivity Hypothesis; stronger causal evidence would involve experimental manipulations of connectivity patterns to test if functional specialization changes as a consequence of these connectivity changes. However, this type of study would be invasive in newborn humans; here we attempt to leverage experience-dependent domains and a study of neonates to test the Connectivity Hypothesis but acknowledge the limitations of causal inferences that can be drawn from noninvasive studies. Further, a challenge of studying the functional organization of the neonatal brain is that there is no adequate way to localize functional responses using fMRI in neonates. Here we used functional parcels from previous studies and overlaid these parcels onto both adult and neonate brains. These parcels likely encompass the functional regions in individual subjects which offer better functional relevance than anatomical landmarks, but as a consequence, also likely overestimate the size of the functional regions. To further explore spatial specificity, we chose adjacent functional parcels as comparisons, explored smaller subsets of the language parcels, and performed voxelwise analyses on individual subject data without predefined functional regions. However, the present results are still limited by the functional parcels as well as current registration and image processing methods in neonates; better registration methods such as surface-based registration to an adult template are currently unavailable in neonates but will likely improve the results and inferences drawn from these studies. Additionally, future studies may consider new approaches to localize functional responses in young infants or longitudinal studies, e.g., Saygin et al. (2016), to define each of these functional regions in individual subjects and further test the specificity of the current findings.  Finally, we tested the Connectivity Hypothesis for the VWFA specifically. The findings suggest that connectivity-based scaffolding may be a general driving mechanism for the functional organization of human cortex, but the generality of this hypothesis for other mental domains remains to be tested.

# Chapter 3. Study 2

Study 1 answers many questions but also opens up new questions. For example, what are the changes that occur with reading? And although the connectivity is adult-like, the VWFA is likely not selective to words in neonates; so what is it selective to? Further, Study 1 provided evidence for the Connectivity Hypothesis; but what happens if the canonical location of the VWFA doesn’t have access to temporal language regions? Study 2 aimed to provide answers to these questions.

## Method

### Participants

*Adults.* Twenty-two adults (10 female, mean age = 23.77 years) from The Ohio State University were used as a part of an ongoing fMRI study exploring the relationship between brain function and connectivity.

*Kids.* Fifteen kids (13 female, mean age = 5.80 years) from the local community were recruited as part of an ongoing project exploring developmental changes of brain connectivity. To explore the effect of age and literacy, we further divided the 15 kids into two subgroups with the cut-off at 5.5 years, resulting 9 kids in younger group and 6 kids in older group.

All adults and kids had normal or corrected-to-normal vision, and report no neurological, neuropsychological, or developmental diagnoses. The study was approved by the Internal Review Board at The Ohio State University.

*EG.* As part of an ongoing collaborative project with Dr. Fedorenko at MIT, we are scanning a family of three sisters (age 50-60). The present study used data from sister EG who was born without her temporal lobe (Figure 5). Of the other two sisters, one was born without her right temporal lobe and one has a typical brain. EG did not exhibit any deficits in reading or other domains.

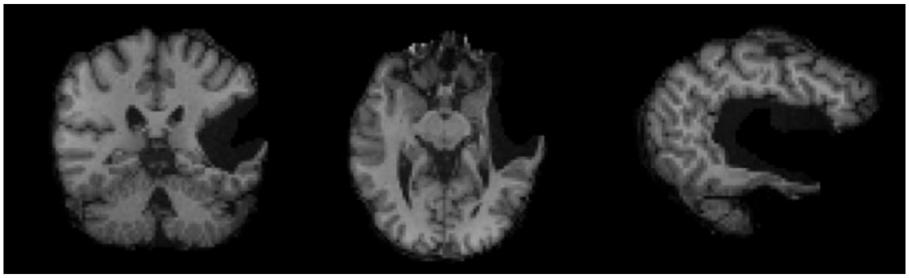

Figure 5 | The brain anatomy of EG

**Data acquisition**

Data of adults and kids were acquired on a Siemens Prisma 3 Tesla MRI scanner with integrated Total Imaging Matrix (TIM) system at OSU's CCBBI imaging center. EG's data was collected on a 3T Siemens Trio Tim MRI scanner at MIT. A whole-head, high resolution T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) scan was acquired on all participants (acquisition parameters: adults, TR = 1390 ms, TE = 4.62 ms, TI = 477 ms, flip angle = 12°, voxel resolution = 1.0 mm3; kids, TR = 1900 ms, TE = 4.44 ms, TI = 950 ms, flip angle = 12°, voxel resolution = 1.0 mm3; EG, TR = 2530 ms, TE = 3.48 ms; TI = 900 ms; flip angle = 9°, voxel resolution = 1.0

mm$^3$). All structural MRI data were processed in FreeSurfer v.6.0.0 (http://surfer.nmr.mgh.harvard.edu/) using a semiautomated processing stream with default parameters (recon-all function).

All functional data were collected with 2-mm$^3$ resolution, 2-s TR, 30-ms TE, 80° flip, 172 TRs, 100 × 100 base resolution, 25 slices approximately parallel to the base of the temporal lobe to cover the entire inferior temporal cortex. For adults and kids, we also collected a field map for distortion correction every two runs with the same slice prescription as the fMRI sequence (25 slices, 2-mm$^3$ resolution, 500-ms TR, 55° flip, 100 × 100 base resolution).

**fMRI task and analysis**

All adults and kids viewed 2 runs of 18-s blocks (26 stimuli + 2 repetitions per block) of black and white line-drawings of faces, objects, words, scrambled words and a fixation condition (see Saygin et al., 2016 for details). EG viewed 5 runs of the same tasks in two separate sessions, and data from the first session (3 runs) were used in the present analyses.

Data were analyzed with Freesurfer (http://surfer.nmr.mgh. harvard.edu/), FsFast (https://surfer.nmr.mgh.harvard.edu/fswiki/FsFast/), and custom Matlab code. Images were motion corrected (time points where the difference in total vector motion from the previous time point exceeded 1mm were excluded, and orthogonalized motion measures were used as nuisance regressors for the GLM), detrended, and fit using a standard gamma function (d = 2.25 and t = 1.25). Adults and kids data were also distortion-corrected using the field maps.

### Define subject-specific fROI and extract activation

The same VWFA parcel used in Study 1 was registered to each individual's native anatomy, this time using Freesurfer's bbregister function, and was used as the functional constraint to identify subject-specific functional regions (fROIs) using the same GSS approach. Individual fROIs were defined using the top 10% most active voxels within the VWFA parcel for the contrast of interest: words > line-drawings of objects. As a comparison, we also defined subject-specific FFA using the contrast of line-drawings of faces > objects. Similar to Study 1, our main analyses focused on the left hemisphere only. To further examine if word selectivity reorganized to right-homologue regions of the VWFA, a rVWFA parcel was created by flipping the VWFA to the right hemisphere and was then registered to each individual to identify subject-specific rVWFA fROIs. We then extracted percent signal change (PSC) for each of the conditions within these fROIs using independent fMRI runs than those used to define the fROIs. fROI PSCs were averaged for each category of interest and nonparametric Wilcoxon sign-rank tests were performed to see if the conditions of interest for each fROI were higher than other conditions (right-tailed).

### Compare EG results to adults: the bootstrap

To quantitively compare EG's results to the other groups, we used a bootstrap approach to examine the possibility that EG's responses fall into the normal range of typical adults, older, or younger kids. Specifically, we created bootstrapped means by resampling with replacement, and then generating distributions for each age group based on 2000 bootstrapping. Next, we calculated p-value by counting of bootstrapped cases that smaller (or larger) than EG's result and then dividing by 2000.

## Results

### The VWFA's functional response in typical developmental scenario

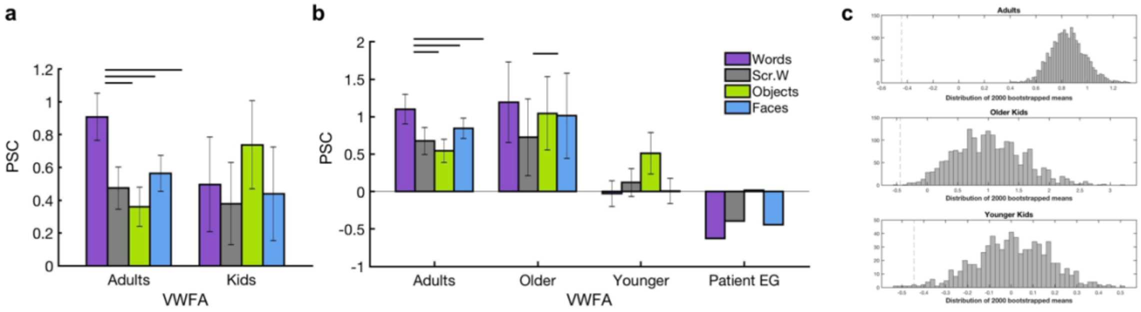

Figure 6 | Functional response profiles of VWFA in different groups

Percent signal change (PSC) was extracted from the subject-specific VWFA from an independent run (separate from those used to define each region. **(a)** Functional responses in the VWFA for each of four functional categories for all adults (N = 22) and kids (N = 15). **(b)** Functional responses in the VWFA for a subset of adults (N = 10), older kids (N = 6), younger kids (N = 9) and EG. **(c)** Comparisons of EG's VWFA response (dashed line) to words in adults and kids using bootstrapping. Note that EG had 3 runs of data, so we did the analyses iteratively and averaged results from all iterations. Error bars denote s.e.m for adult and kid groups. Horizontal bars reflect significant Wilcoxon sign-rank tests, $p < 0.05$, corrected. Src.W, Scrambled Words.

We first examined the functional response profiles of the VWFA in adults and kids. We defined the subject-specific VWFA from one run and extracted PSC for each condition from the left out run (see Methods for details).

Consistent with previous studies, we found that adults' VWFA showed highest responses to words compared to other visual categories (Figure 6a; Words > Scr.W, p < 0.001, Wilcoxon signed-rank (W) = 252; Words > Objects, p < 0.001, W = 249; Words > Faces, p = 0.001, Bonferroni-Holm corrected). On the other hand, VWFA in kids didn't show preferred responses to words; instead, the region defined within the canonical VWFA showed higher activity to objects, though none of the effects passed multiple-correction (Figure 6b; Objects > Words, p = 0.33, W = 60; Objects > Scr.W, p = 0.02, W = 84; Objects > Faces, p = 0.16, W = 69, uncorrected). This observation in line with a previous finding showing that VWFA also respond to objects in 7 years old children (Centanni et al., 2017) but also likely reflects the large variance in age and reading ability in the kid group.

To explore the effect of age and literacy, and the potential role of experience in typically developing kids, we divided the kids into older (N = 6) and younger groups (N = 9). To match the sample size of the kid groups, a subset of 10 adults were used. Again, this subset of adults showed significantly higher responses to words compared to other categories (Words > Src.W, p = 0.003, W = 55; Words > Objects, p = 0.004, W = 54; Words > Faces, p = 0.024, W = 47; corrected). As expected, whereas younger kids' VWFA showed higher responses to objects, older kids already showed adult-like response patterns and started to exhibited preference to words, although none of the effects pass the multiple-comparison (younger: Objects > Words, p = 0.10, W = 28; Objects > Scr.W, p = 0.16, W = 26; Objects > Faces, p = 0.19, W = 25; older: Words > Objects, p = 0.22, W = 15; Words > Faces, p = 0.08, W = 18; uncorrected) except for Words vs. Scr.W in older kids (p = 0.05, W = 21; corrected) (Figure 6b).

## Abnormal functional response in the VWFA in an individual with temporal lobe lesion

Next, we looked at the functional response profile of the VWFA location in the EG, who was born without the left temporal lobe. Does any word selectivity remain in the canonical VWFA location even if its access to left temporal language regions is disrupted due to the lesion? Similar steps were used to define the fROI from one run and PSC was extracted in the left out run. Note that since EG had 3 runs of data, we did the analyses iteratively and the average from all iterations were presented.

We found that overall, EG's VWFA showed small responses to all four categories, and more importantly, no word-selective response was observed. We further implemented a bootstrap approach to quantitively examined the possibility that EG's VWFA response to words fall into the normal range of typical adults, older kids, and younger kids. Figure 6c shows that EG's VWFA response to words was significantly smaller than normal adults ($p = 0$), older ($p < 0.001$) and younger kids ($p = 0.002$).

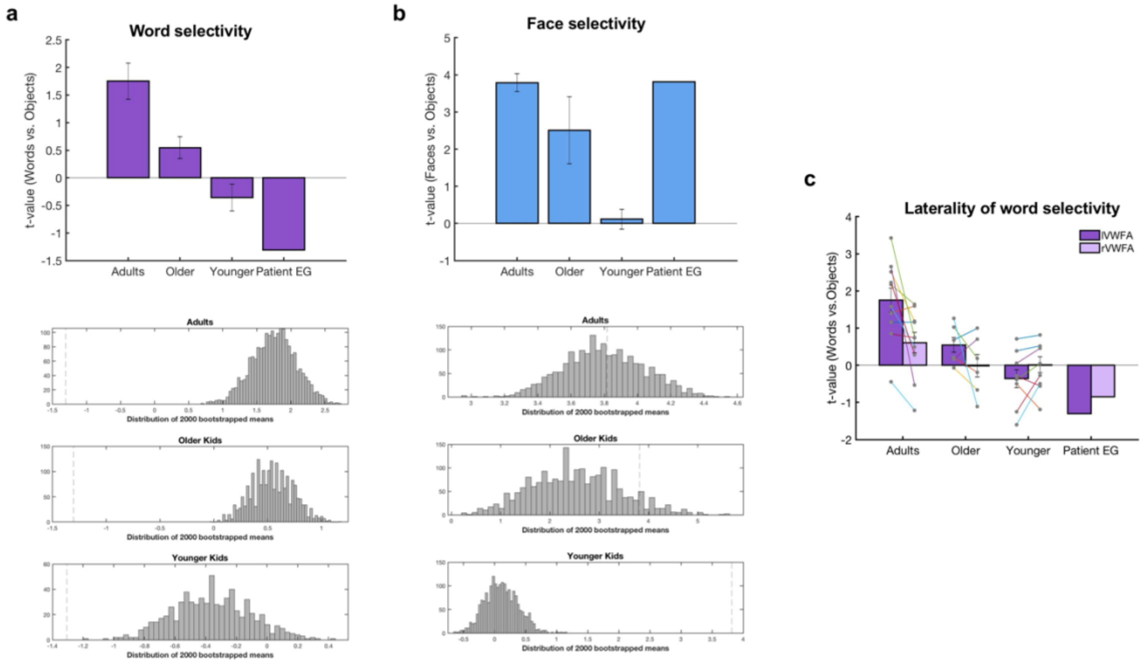

Figure 7 | Compare EG’s VWFA response to other groups

**(a)** Top, word selectivity within the subject-specific VWFA was calculated and averaged across each group and EG using the words vs. objects contrast; bottom, comparing EG’s word selectivity to adults and kids using bootstrapping. **(b)** Top, face selectivity within the subject-specific left FFA was calculated and averaged across each group and EG using faces vs. object contrast; bottom, comparing EG’s face selectivity to adults and kids using bootstrapping. **(c)** Comparison of word selectivity in left and right VWFA, where each line represents data for one subject.

## Typical and atypical development of word selectivity and laterality

Previous studies define word selectivity as the effect where a voxel showed significantly higher response to words vs. objects. Here we examined the change of word selectivity in adults, older kids, younger kids and EG. For normal developmental group, we observed a clear decrease of word selectivity with age (Figure 7a). Consistent with PSC results, word selectivity in EG’s VWFA significantly smaller than adults ($p = 0$), older ($p = 0$) and younger kids ($p = 0$) (Figure 7a).

Next, we looked at the laterality of the VWFA. We examined word selectivity in the right-homologue regions of the VWFA (rVWFA), and we found that left laterality also developed with age. Specifically, adults showed some degree of word selectivity in the left hemisphere (defined as significantly higher than 0 activation for words > objects; left: $p = 0.004$, $W= 54$; right: $p = 0.11$, $W = 44$; two-tailed, uncorrected) with 9 out of 10 adults showing higher word selectivity in the lVWFA than rVWFA; older kids showed a trend of word selectivity only in the lVWFA (left: $p = 0.063$, $W = 20$; right: $p = 1$, $W = 10$), with 4 out of 6 showing significantly greater selectivity in lVWFA > rVWFA; younger kids showed no to negative word selectivity in both hemispheres (left: $p = 0.38$, $W = 11$; right: $p = 0.91$, $W = 24$) and only 2 of the 9 kids showed lVWFA > rVWFA pattern where they had less negative word selectivity in the lVWFA than rVWFA. Because left temporal lesion cases show a remapping of language activations to right-homologue regions, we expected EG's orthographic activations to also remap to the right VWFA. However, as shown in Figure 7c, no word selectivity was observed in rVWFA.

So far, the results indicate that EG's word selective responses in the canonical VWFA location were impaired. This leads us to ask, does the lesion selectively affect the VWFA or does it also affect nearby cortex? As a comparison, we also used the same approach and defined the left FFA, which is a face-selective region next to the VWFA. We found EG's FFA showed similar face selectivity as that found in normal adults ($p = 0.45$) and older kids ($p = 0.09$), and significantly higher face selectivity than younger kids ($p = 0$) (Figure 7b).

### Distinct representation patterns of word in the left ventral temporal cortex

Previous studies have found distinct response patterns in the ventral temporal cortex for different visual categories (e.g., Haxby et al., 2000). Here, we applied multivariate pattern analysis (MVPA) to explore whether there exists a voxelwise pattern that reliably distinguishes words from other categories in EG and in the adult and kid groups. Specifically, we calculated between-category distance within a run and within-category distance between two runs based on response patterns in the entire left ventral occipitotemporal cortex. If the within-category distance between runs for words is smaller than the distance between words and other categories from the same run, we counted as 1 (or hit), otherwise is 0 (or miss). We averaged the number of hits in each group to get an accuracy score. We found the adult group has very high accuracy (0.9; chance level: 0.25). Surprisingly, although univariate analyses found no word-selective responses in younger and some selectivity in older kids, multivariate analyses showed that there is a distinct response pattern for words in both age groups that can be differentiated from other categories above chance (Figure 8a).

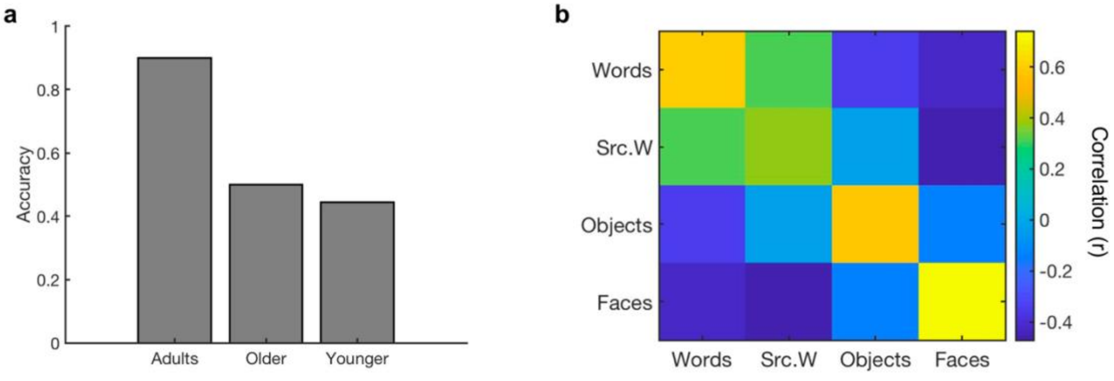

Figure 8 | Results of multivariate pattern analysis

**(a)** We compared the within-category distance between runs for words vs. the distance between words and other categories from the same run to find whether there is a distinct pattern between runs for words that different from other categories. We averaged the number of hits in each group to get an accuracy score (chance level: 0.25). **(b)** For EG, we calculated response pattern similarity between categories between two different runs. Note that EG has three runs of data, so we did the same procedure iteratively and average result was present.

We did the same analysis for EG where we randomly selected 2 runs of data and compared response distances. We found that EG also had high accuracy for words, i.e. the distance of words responses between runs is closer than distance between words and other categories from the same run. To further examine if there is any reliable pattern that distinguished words from any other category in the VTC for EG, we used all three runs of data, and calculated the similarity of response patterns between different conditions from different runs. Figure 8b showed a cleared differentiation between within-category correlations and between-category correlations (i.e., warmest color at the diagonal). These results suggest that there is a distinct response pattern for words in the lVTC for EG and for children regardless of age or experience with words.

### Replication of functional connectivity results in adults and school-age kids

Lastly, we replicated the functional connectivity results in Study 1 in this group of adults (N = 22) used in Study 2. Consistent with results in Study 1, the adult group showed a privileged connection between the VWFA and language regions. Specifically, language regions connected significantly more with the VWFA compared to other visual categories (Faces: $p < 0.001$, W = 204; Scenes: $p < 0.001$, W = 208; objects: $p < 0.001$, W = 201; corrected) (Figure 9a). Meanwhile, the VWFA also connected more to language regions compared to adjacent regions (multiple-demand (MD): $p < 0.001$, W = 204; Speech: p = 0.007, W = 171; A1: $p < 0.001$, W = 209; corrected) (Figure 9b).

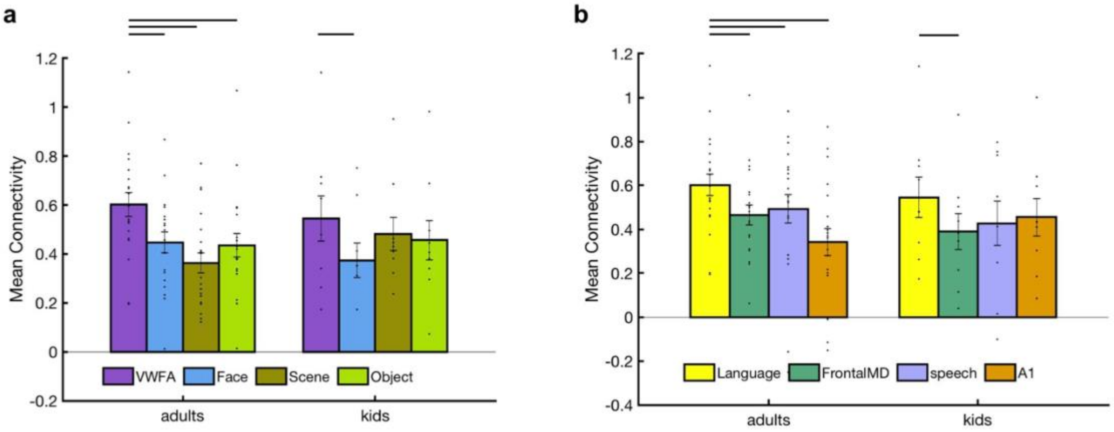

Figure 9 | Replication of functional connectivity results in an independent adults and school-age kids.

**(a)** Mean FC between language regions (seed) and high-level visual regions in ventral visual stream. **(b)** Mean FC between VWFA (seed) and regions in temporal and frontal cortices. Connectivity values were Fisher z transformed. Error bars denote s.e.m. Individual data points (22 adults and 9 kids) were shown for each category. Error bars denote s.e.m. Horizontal bars reflect significant *post hoc* paired *t*-tests $p < 0.05$, corrected. (b)

Next, we tested whether similar connectivity patterns were observed in school-age kids. Note that this is still ongoing work and only 9 kids in Study 2 have resting-state data at this point. Nevertheless, we also observed adult-like FC patterns in this group of kids. Specifically, language regions connected more with the VWFA as compared to other visual regions, although only the difference between the VWFA and face regions passed multiple-comparison correction (Faces: p = 0.014, W = 41; Scenes: p = 0.18, W = 31; Objects: p = 0.08, W = 35; uncorrected); the VWFA also had highest connections to language regions compared to adjacent regions, although again only the comparison of language vs. MD regions passed multiple-comparison corrections (MD, $p = 0.01$, $W = 42$; Speech, $p = 0.21$, $W = 30$; A1, $p = 0.20$, $W = 34$; uncorrected).

These results suggest that connectivity between the VWFA and language regions can be reliably observed and that the neonate connectivity patterns found in Study 1 are observed in school-age kids. Our future work will involve data collection from more kids of different ages and literacy, as well as an analysis of EG's resting-state data, to have a better understanding of the developmental trajectory of connectivity and its role in developing word selectivity.

## Discussion

In Study 2, we aimed to examine the role of experience in developing word selectivity in typical and atypical participants. Specifically, what happens if the canonical VWFA location doesn't have access to language regions? We looked at data from an adult who was born without the temporal lobe but successfully developed reading and language abilities. By comparing EG's neural activity to typically developed adults and school-age kids, we asked: is there any word selective response in the VWFA even without connections to temporal language regions due to the lesion? Does the lesion selectively affect VWFA within the VTC? Lastly, we explored whether there was any reliable pattern that distinguished words from any other categories in the VTC using multivariate pattern analysis. Note that Study 2 is still an ongoing project and preliminary results are presented here.

Firstly, based on results from our typical developed adults and kids, we found that before developing word selectivity, the canonical location of the VWFA responds to objects, and as a child gains literacy, the VWFA's response to words increase and ultimately differentiate it from other categories. Surprisingly, this in line with our observation in Study 1, where we show that object regions also have high FC to language regions in neonates whereas in adults they do not; on a finer grain, our parametric analyses show that the putative VWFA is in fact differentiated from object regions in their connectivity to language cortex. These findings suggest that there is likely further refinement to fully differentiate orthographic representations from other objects in visual cortex, in line with e.g. Augustin et al. (2015), Kubota et al. (2018) and Centanni et al. (2017). In normal developmental situations, experience with spoken and written language will likely strengthen connections with specific aspects of the language circuit and further differentiate this region's function from its neighbors as an individual gains literacy.

The major goal of Study 2 was to explore neural activity in an individual who was born without her left temporal lobe, given the role of FC between the VWFA and temporal language regions established in Study 1. Our first attempt was to look at the functional response in the classic VWFA location. However, we were unable to find any word selectivity in the VWFA. Although previous studies found recruitment of the right hemisphere for language responses, we failed to find word-selective responses in the right-homologue region of the VWFA. We plan to look at more extended regions to search for any potential word-selective regions in our future work. Note that the current

VWFA localizer only covered a part of the brain that includes ventral temporal cortex to achieve high spatial resolution in a manageable amount of time.

Interestingly, even though we failed to identify any voxels in the VWFA that consistently respond more to word across runs using the traditional univariate analysis, MVPA looking at the response patterns suggests that there's a reliable representation of words in different runs that can distinguish words responses from other categories. On the one hand, univariate and multivariate analyses characterize different ways our brain used to process information; our exploratory results in EG suggest that EG failed to develop the word-selective region in the canonical VWFA due to the disrupted connection to language regions could potentially rely on multivariate information. On the other hand, however, we noticed that in younger kids, who showed no word selectivity, their MVPA results still had above chance accuracy; this suggest that the successful decoding of words in EG may solely reflect the reliable signal to low-level visual features of words, rather than the word recognition supported by the VWFA.

The current preliminary findings exist certain limitations and further raise several future directions. First, we used an arbitrary cut-off to divide our kids into the older and younger groups, and the number of subjects in each subgroup is very small; so we will continue to collect more adults and kids data. Ideally, with more data and behavioral measures available, we can divide kids by their actual reading ability, and can thoroughly characterize the developing trajectories of functional response profiles as well as changes of connectivity patterns of the VWFA. Second, given our comparison between these diverse groups, the different acquisition parameters and sites may be a potential problem.

For example, for both adults and kids data, we collected a field map for distortion correction, which was not collected for the patient. Therefore, the effect of these differences should be examined by i) looking at adults and kids collected at the same site as EG and ii) acquiring more data from the patient including a field map that used to correct distortion. Third, the group that we are collaborated with has found that EG's language regions are remapped to the right hemisphere. Based on Study 1, we can use the resting state data from EG to guide us to find the candidate word-selective region. For example, where are the patient language regions mostly connected to?  We will then use those connected voxels to guide our functional activation analyses.

# Chapter 5. Conclusions

A mosaic-like functional organization is consistently found in the adult brain. However, the driving factor of this functional organization and its variation across individuals remains unclear. With a diverse sample including newborns, adults, school-age kids, and an individual born without the left temporal lobe (EG), the present work looked at the role of innate functional connectivity in developing the visual word form area, and further explored what happens with word selectivity if an individual lacks of these innate connections. In Study 1 we found that neonates showed adult-like functional connectivity, and observed that i) language regions connected more strongly with the putative VWFA than other adjacent ventral visual regions that also show foveal bias, and ii) the VWFA connected more strongly with frontotemporal language regions than with regions adjacent to these language regions. The preliminary results in Study 2 found that: i) before becoming selective to words, the VWFA site responds to objects in typical developed young kids; ii) we failed to find any word selective response in the canonical VWFA location in EG who has the dorso-temporal lesion; iii) lastly, with multivariate pattern analysis, we found that there is a reliable response patterns in the ventral temporal cortex that can distinguish words from other categories in EG.

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