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Occipital Cortex of Blind Individuals Is Functionally Coupled with Executive Control Areas of Frontal Cortex

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Occipital Cortex of Blind Individuals Is Functionally Coupled with Executive Control Areas of Frontal Cortex

Ben Deen, Rebecca Saxe, and Marina Bedny

Abstract

■ In congenital blindness, the occipital cortex responds to a range of nonvisual inputs, including tactile, auditory, and linguistic stimuli. Are these changes in functional responses to stimuli accompanied by altered interactions with nonvisual functional networks? To answer this question, we introduce a data-driven method that searches across cortex for functional connectivity differences across groups. Replicating prior work, we find increased fronto-occipital functional connectivity in congenitally blind relative to blindfolded sighted participants. We demonstrate that this heightened connectivity extends over most of occipital cortex but is specific to a sub- set of regions in the inferior, dorsal, and medial frontal lobe. To assess the functional profile of these frontal areas, we used an *n*-back working memory task and a sentence comprehen- sion task. We find that, among prefrontal areas with overcon- nectivity to occipital cortex, one left inferior frontal region responds to language over music. By contrast, the majority of these regions responded to working memory load but not language. These results suggest that in blindness occipital cor- tex interacts more with working memory systems and raise new questions about the function and mechanism of occipital plasticity. ■

INTRODUCTION

The human brain has a remarkable capacity for reorgani- zation. Studies of occipital cortex function in congenitally blind individuals provide a key example of such cortical plasticity: Cortex normally recruited for vision instead responds to nonvisual input. The occipital cortex of con- genitally blind individuals responds to tactile (Weaver & Stevens, 2007; Ptito, Moesgaard, Gjedde, & Kupers, 2005; Sadato, Okada, Kubota, & Yonekura, 2004; Sadato et al., 1996) and auditory stimuli (Collignon et al., 2011; Weaver & Stevens, 2007; Gougoux, Zatorre, Lassonde, Voss, & Lepore, 2005; Kujala et al., 2005). In addition, occipital cortex is active during high-level cognitive tasks, such as reading Braille, listening to sentences, and generating verbs to heard nouns, and during verbal recall (Bedny, Pascual-Leone, Dodell-Feder, Fedorenko, & Saxe, 2011; Amedi, Raz, Pianka, Malach, & Zohary, 2003; Burton, Snyder, Conturo, et al., 2002; Burton, Snyder, Diamond, & Raichle, 2002; Röder, Stock, Bien, Neville, & Rösler, 2002; Sadato et al., 1996). These studies suggest that, in the absence of visual input, occipital areas acquire novel, nonvisual cognitive functions.

Early blindness also alters the interactions of occipital cortex with other cortical areas. Evidence for this comes from studies of resting state functional connectivity MRI

(fcMRI), which measures temporal correlations between hemodynamic signals from different brain regions, in the absence of a task (Biswal, Yetkin, Haughton, & Hyde, 1995). Previous fcMRI studies of blind individuals con- verge on a surprising finding: Rather than increased functional connectivity to nonvisual sensory areas, the occipital cortex of early blind adults shows increased func- tional connectivity to regions of pFC (Watkins et al., 2012; Bedny et al., 2011; Liu et al., 2007).

A key open question concerns *which* regions within prefrontal and occipital cortices have increased connec- tivity in the blind. pFC contains regions associated with multiple distinct functional networks. For example, in- ferior frontal regions respond specifically to language (Fedorenko, Behr, & Kanwisher, 2011) and are function- ally connected to temporal language regions; other pre- frontal regions are active during working memory and cognitive control tasks (Fedorenko, Duncan, & Kanwisher, 2013; Duncan & Owen, 2000) and are functionally con- nected to parietal regions. Blindness could affect con- nectivity of occipital areas with frontal components of one or more specific functional networks, or it could nonspecifically increase connectivity between occipital cortex and frontal cortex. Characterizing these connectivity changes could provide insight into the mechanisms of blindness-related plasticity.

One challenge in addressing this question is the need to characterize the anatomical layout of fronto-occipital

connections in an unbiased manner. Most investigations of functional connectivity in blindness use predefined "seed" regions and thus depend on prior assumptions about which regions are altered (Bedny et al., 2011; Bedny, Konkle, Pelphrey, Saxe, & Pascual-Leone, 2010). Such approaches might miss other regions with altered functional connectivity. Independent component analysis has also been used to assess group differences in functional connectivity. Unlike seed-based methods, this approach is data driven and does not require a predefined seed region. However, this method also has limitations. Typical methods for group comparison using independent component analysis involve assessing correlations between individual voxels' time series and a network-wide time course. This does not directly assess pairwise connections between specific regions and thus could miss differences in specific connections.

Here we introduce a data-driven approach for discovering regions with group differences in functional connectivity: the group difference count (GDC) method. We first compute correlations between all fronto-occipital voxel pairs and then search for voxels with a significantly large number of group differences. This approach allows us to discover regions with group differences in functional connectivity without predefined seeds. Next, we asked whether prefrontal regions with increased functional connectivity belong to the language or executive control network by measuring their responses in a language comprehension task and an *n*-back working memory task.

METHODS

Participants

Participants were 13 congenitally blind adults (mean age = 43.6 years, SD = 15.8, range = 24–62 years, 6 women) and 23 sighted adults (mean age = 39.5 years, SD = 11.9, range = 18–59 years, 12 women; further demographic data in Table 1). Blind participants had vision loss from birth, caused by abnormality at or anterior to the optic chiasm (i.e., not due to brain damage). All blind participants reported, at most, faint light perception, with 10/13 participants having no light perception at the time of the study. Detailed demographic information about blind participants is provided in Table 2. Sighted participants had normal or corrected vision. None of the participants had any history of neurological or psychiatric impairment, and all were fluent English speakers. All participants gave written, informed consent, in accordance with the Committee on the Use of Humans as Experimental Subjects at MIT.

Resting state data were collected from 12 blind participants and 21 sighted participants, and task data were collected from 13 blind participants and 16 sighted participants. No significant group differences were found in age, mean frame-to-frame translation or rotation, number

Table 1. Participant Demographics

	Blind	Sighted
Rest		
Age (years)	44.7 (15.9)	39.0 (12.4)
Gender	6/12 F	10/21 F
Handedness	10/12 R	21/21 R
Mean translation (mm)	0.26 (0.21)	0.16 (0.10)
Mean rotation (mm)	0.16 (0.14)	0.12 (0.13)
Volumes removed	3.1 (9.2)	1.1 (3.9)
Task		
Age (years)	43.6 (15.8)	43.8 (12.1)
Gender	6/13 F	7/16 F
Handedness	10/13 R	16/16 R
Mean translation (mm)	0.21 (0.08)	0.19 (0.05)
Mean rotation (mm)	0.09 (0.08)	0.06 (0.05)
Volumes removed	5.2 (8.1)	4.9 (8.7)

of volumes removed from the data set (p > .05, two-sample t test), gender, or handedness (p > .05, Fisher's exact test).

Paradigm

Sighted adults wore total light exclusion blindfolds to eliminate external visual stimulation. Blind participants did not wear blindfolds; however, lights in the scanner room were turned off during this scan. During resting state scans, participants were instructed to relax and stay as still as possible without falling asleep; additionally, sighted participants were asked to keep their eyes closed. Resting state scans lasted 6.2 min.

For the language task, during each trial, participants listened to a 20-sec-long clip from one of three conditions: a story in English (language), a story in a foreign language (foreign), or instrumental music (music). They then heard the question, "Does this come next?" (1.5 sec), followed by a probe clip (3 sec). For the language condition, the probe either fit or did not fit with the plot of the preceding story. For the foreign condition, the probe was either in the same or a different language as the preceding story. For the music condition, the probe either contained the same melody and instrument as the preceding clip or a different melody and instrument. During the response period (6.5 sec), yes/no responses were provided by right/left button presses, followed by 5-sec intertrial interval. The language condition comprised three subconditions (stories with mental, social, or physical content), which are collapsed in the present analyses. Foreign languages included

Hebrew, Russian, and Korean; no participant had any proficiency in any of these languages. Each run consisted of 10 trials (6 language, 2 foreign, and 2 music) in counterbalanced order and three resting periods (12 sec each), for a total of 6.6 min. Participants received three to four runs of the task. Further details on this task can be found in Gweon, Dodell-Feder, Bedny, and Saxe (2012).

The auditory n-back task consisted of three conditions: $n = 1, 2,$ and 3. Each 24-sec-long block included a pause (0.5 sec), an instruction phase specifying the value of n (3.5 sec), and then 10 trials (an individual English letter [0.5 sec] followed by an intertrial interval [1.5 sec]). Participants were instructed to press a button when the letter matched the letter presented in trials earlier; targets occurred three times per block. Conditions were counterbalanced across runs and participants. Each run consisted of 18 blocks, separated by rest periods (12 sec), for a total of 10.8 min. Participants received two runs of this task.

Data Acquisition

Images were acquired on a Siemens 3T Magnetom Trio scanner, using a 12-channel head coil. High-resolution T1-weighted anatomical images were acquired using a MPRAGE pulse sequence (repetition time [TR] = 2 sec, echo time [TE] = 3.39 msec, flip angle $\alpha = 9°$, field of view [FOV] = 256 mm, matrix = 256 × 192, slice thickness =

1.33 mm, 128 near-axial slices, acceleration factor = 2, 48 reference lines). Task functional data were acquired using a T2*-weighted EPI pulse sequence sensitive to BOLD contrast (TR = 2 sec, TE = 30 msec, $\alpha = 90°$, FOV = 200 mm, matrix = 64 × 64, slice thickness = 4 mm, 30 near-axial slices). Resting state functional data were acquired using a T2*-weighted EPI pulse sequence (TR = 6 sec, TE = 30 msec, $\alpha = 90°$, FOV = 256 mm, matrix = 128 × 128, slice thickness = 2 mm, 67 near-axial slices). Resting data were acquired at higher resolution (2 mm isotropic) to reduce the relative influence of physiological noise (Triantafyllou, Hoge, & Wald, 2006; Triantafyllou et al., 2005). This necessitated a somewhat high TR, which is justified by the observation that most of the power in resting state fluctuations is in frequencies lower than our sampling rate.

Data Preprocessing

Data were processed using the FMRIB Software Library (FSL), version 4.1.8, along with custom MATLAB scripts. Functional data were motion-corrected using rigid body transformations to the middle image in each 4-D data set, corrected for interleaved slice timing using sinc interpolation, spatially smoothed with a 5-mm FWHM Gaussian kernel, and high-pass filtered (Gaussian-weighted least squares fit straight line subtraction, with $\sigma = 50$ sec; Marchini & Ripley, 2000). Functional images were linearly

Table 2. Blind Participant Information

Participant	Age	Gender	Onset of Vision Loss	Cause of Blindness	Residual Light Perception	Age Started to Learn Braille	T/R
B1	58	M	Birth	ROP	None. Had LP until age 20.	6	T + R
B2	41	M	Birth	Unknown, nerve disconnect between eyes and brain	None	5	T + R
B3	41	M	Birth	Retinoblastoma	None	5.5	T + R
B4	25	F	Birth	Unattached optic nerve	None	4	T + R
B5	64	F	Birth	Malformation of optic nerve	Tiny LP in corner of one eye. Had slightly more LP as a toddler.	4	T + R
B6	30	M	Birth	Optic nerve hypoplasia	Some LP in both eyes	7	T
B7	32	M	Birth	ROP	None	5	T + R
B8	62	F	Birth	ROP	Minimal LP, previously had more.	6	T + R
B9	57	F	Birth	ROP	None	6	T + R
B10	62	F	Birth	ROP	None	6 or before	T + R
B11	25	F	Birth	ROP	None	3	T + R
B12	24	M	Birth	Anopthalmia	None	4	T + R
B13	38	M	Birth	Leber's congenital amaurosis	None	5	T + R

M = male; F = female; ROP = retinopathy of prematurity; LP = light perception; T = task; R = rest.

registered to anatomical images using FMRIB's linear image registration tool followed by Freesurfer's bbregister (Greve & Fischl, 2009). Anatomical images were normalized to the Montreal Neurological Institute (MNI)-152 template brain using FMRIB's nonlinear registration tool.

We used three procedures to reduce the influence of physiological and motion-related noise. First, six motion parameters estimated during motion correction were removed from the data via linear regression. Second, signals from white matter and cerebrospinal fluid were removed using the CompCorr procedure (Chai, Castañón, Ongür, & Whitfield-Gabrieli, 2012; Behzadi, Restom, Liau, & Liu, 2007). The first four principal components, as well as the mean signal, were extracted for individually defined white matter and cerebrospinal fluid masks and removed from the data via linear regression. Third, pairs of volumes with more than 1.2 mm of translation or 1.2° of rotation between them were removed from subsequent analysis (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012).

Resting State Data Analysis

We introduce a data-driven method for identifying group differences in functional connectivity. We focus on correlations between ipsilateral frontal and occipital cortices, which are thought to be altered in blindness (Watkins et al., 2012). Specifically, we search for occipital voxels that have group differences in connectivity with a large number of frontal voxels and frontal voxels that have group differences with a large number of occipital voxels. This approach will be referred to as the GDC method.

Left and right frontal and occipital gray matter masks were defined using regions provided in the MNI structural atlas, thresholded at a probability of .5. For each participant and hemisphere, a matrix of functional connectivity strengths between all frontal voxels and all occipital voxels was computed by regressing time series from frontal voxels on time series from occipital voxels. Group differences (blind > sighted) were computed using a two-sample t test on beta values for each pair of voxels, thresholded at $p < .01$, one-tailed. For each frontal voxel, the total number of ipsilateral occipital voxels for which it had a group difference in functional connectivity (the GDC statistic) was computed; likewise, for each occipital voxel, the total number of ipsilateral frontal voxels with group differences was computed.

We then used a permutation test to build a null distribution for GDC values. In each of 500 iterations (separately for each hemisphere), group assignment was randomized. For each voxel, the GDC statistic was computed and contributed to a null histogram for either frontal or occipital voxels. The resulting null distributions were then thresholded at $p < .01$.

Lastly, we used a cluster size threshold to correct for multiple comparisons across voxels (Forman et al., 1995). To determine this threshold, another permutation test was performed in the same way, but as an additional step, the computed GDC threshold was applied to define clusters. The resulting null distributions for cluster size were thresholded at $p < .01$ to determine a cluster size cutoff. This procedure was analogous to standard nonparametric approaches to generating a cluster size threshold (Winkler, Ridgway, Webster, Smith, & Nichols, 2014; Nichols & Holmes, 2002). The resulting cluster size cutoffs were 22 (left hemisphere) and 21 (right hemisphere) for occipital cortex and 42 (left hemisphere) and 35 (right hemisphere) for frontal cortex.

The GDC analysis produced a map of voxels showing increased fronto-occipital correlations in blind individuals as compared to the sighted control group. On the basis of these results, we defined frontal and occipital ROIs termed group difference (GD) ROIs. Each ROI consisted of all suprathreshold voxels within a 7.5-mm-radius sphere around a local peak statistic. In addition, to determine whether null effects would replicate in independent data, we defined non-group difference (NGD) ROIs: 7.5-mm-radius spheres surrounding local minima of the GD statistic from the resting analysis, intersected with the gray matter mask.

Additionally, to look at group differences in functional connectivity between occipital cortex and other parts of the brain and to test whether our results in frontal cortex would replicate in a bilateral analysis, we applied the GDC analysis to bilateral occipito-temporal, parieto-occipital, and fronto-occipital connections. Specifically, we applied the GDC method described above using three new pairs of masks: bilateral temporal and bilateral occipital cortex, bilateral parietal and bilateral occipital cortex, and bilateral frontal and bilateral occipital cortex. Data analysis and thresholding were the same as described above. This approach identifies voxels in temporal, parietal, and frontal cortex with significantly many group differences in functional connections with the occipital lobe. Using these results, GD ROIs for parietal and temporal cortex were defined in the manner described above.

Task Residual Data Analysis

To replicate and evaluate functional connectivity between occipital and frontal ROIs, we measured correlations between the ROIs in two independent data sets (the language and n-back task data, after removing task-evoked responses via linear regression). Whole-brain general linear model (GLM)-based analyses were used to model task-evoked responses (see Task Data Analysis section below), and subsequent functional connectivity analyses were performed on the residuals from this model. For residual extraction, the models differed in two ways: temporal derivatives were not included, and autocorrelation correction was not performed. Additionally, nuisance removal was performed in the same way as for resting state data.

We extracted mean time series in each ROI and computed a matrix of correlations between each pair of ROIs for each participant. To assess group differences in correlation strengths, a multiple regression was performed for each pair of ROIs, with Fisher-transformed correlation values as the response, group as the predictor of interest, and age, mean translation, and mean rotation as nuisance covariates. Group differences were assessed using a t test. We focused on group differences that were consistent across the two data sets (both $p < .05$), because any effects observed in only one of data sets may result from imperfectly modeled evoked responses and/or differences in "background connectivity" induced by each task (Al-Aidroos, Said, & Turk-Browne, 2012).

Hemispheric Differences in Functional Connectivity

We next investigated how fronto-occipital correlations in blind individuals varied by hemisphere, using correlations computed from task residual data. We thus used a linear mixed model to compare correlations in four categories: left frontal to left occipital (LF-LO), right frontal to right occipital (RF-RO), right frontal to left occipital (RF-LO), and left frontal to right occipital (LF-RO). The dependent variable for this model consisted of Fisher-transformed correlation values for all 70 frontal-occipital GD ROI pairs and all 13 blind participants, averaged across the two data sets (language and n-back tasks). A one-way ANOVA with four levels was used, parameterized with the following regressors: (1) an intercept term, (2) a regressor comparing ipsilateral with contralateral correlations, (3) a regressor comparing LF-LO with RF-RO correlations, and (4) a regressor comparing RF-LO with LF-RO correlations. Random effect terms for all regressors were included, because this minimized Aikake and Bayesian information criteria among models with random effect terms for different subsets of regressors. Individual comparisons were tested using a Wald test, with the normal approximation justified by the large number of degrees of freedom in the model.

Task Data Analysis

To functionally characterize regions with increased connectivity to occipital cortex, we used task responses and resting data. For the task data, whole-brain GLM-based analyses were performed for each participant and each run of the language and n-back tasks. Regressors were defined as boxcar functions, convolved with a canonical double-gamma hemodynamic response function. For the language task, there were regressors for the five conditions (3 language, 1 foreign, and 1 music) peaking during the 20-sec story period, as well as a response regressor, collapsed across conditions, peaking during the remaining 16 sec of each trial. For the n-back task, there were regressors for 1-, 2-, and 3-back conditions, each peaking

during the 20-sec task blocks (excluding the instruction phase). Additionally, temporal derivatives of each regressor were included, and all regressors were high-pass filtered. FMRIB's improved linear model was used to correct for temporal autocorrelation (Woolrich, Ripley, Brady, & Smith, 2001).

Fitted beta values were extracted from each frontal, parietal, and temporal ROI identified by the GDC method. In each ROI, we performed paired one-tailed t tests comparing responses to language versus music and 2-back versus 1-back. Qualitatively identical results for the one-tailed comparison were obtained using language versus foreign and language versus foreign + music contrasts, as well as 3-back versus 1-back and 3-back + 2-back versus 1-back contrasts. Additionally, to test the hypothesis that task responses differ across frontal regions and to test for possible effects of group, we performed a repeated-measures ANOVA on the contrast values from frontal ROIs. Contrast (language or working memory) and ROI were included as within-participant factors, and group was included as a between-participant factor.

Functional Connectivity of Left Frontal Regions

Finally, we used resting data to assess the typical functional connectivity patterns of left frontal regions identified by the GDC analysis in typical individuals. Resting state data were preprocessed as described above. Time series from left frontal ROIs were extracted for each sighted participant and used as regressors in whole-brain GLM-based analyses, along with their temporal derivatives. Within-participant results were combined across participants with a mixed effects model, using FSL's Local Analysis of Mixed Effects Stage 1 (Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Results were thresholded with an initial voxelwise cutoff of $p < .01$. Subsequently, correction for multiple comparisons was performed using a cluster size cutoff based on Gaussian random field theory (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 2004) with a cluster-wise threshold of $p < .05$.

RESULTS

Which Occipital and Frontal Areas Show Connectivity Changes?

Results from the GDC analysis are shown in Figure 1. In the left occipital lobe, a large area of cortex was found to have stronger connectivity with left frontal cortex in blind as compared to sighted participants. Increased correlations were observed in nearly all of the lingual gyrus (termed left medial occipital cortex, LMOC), along the ventral surface in the fusiform gyrus (LFus) and along the lateral occipital surface in the lateral occipital sulcus and surrounding gyri (left lateral occipital cortex, LLOC),
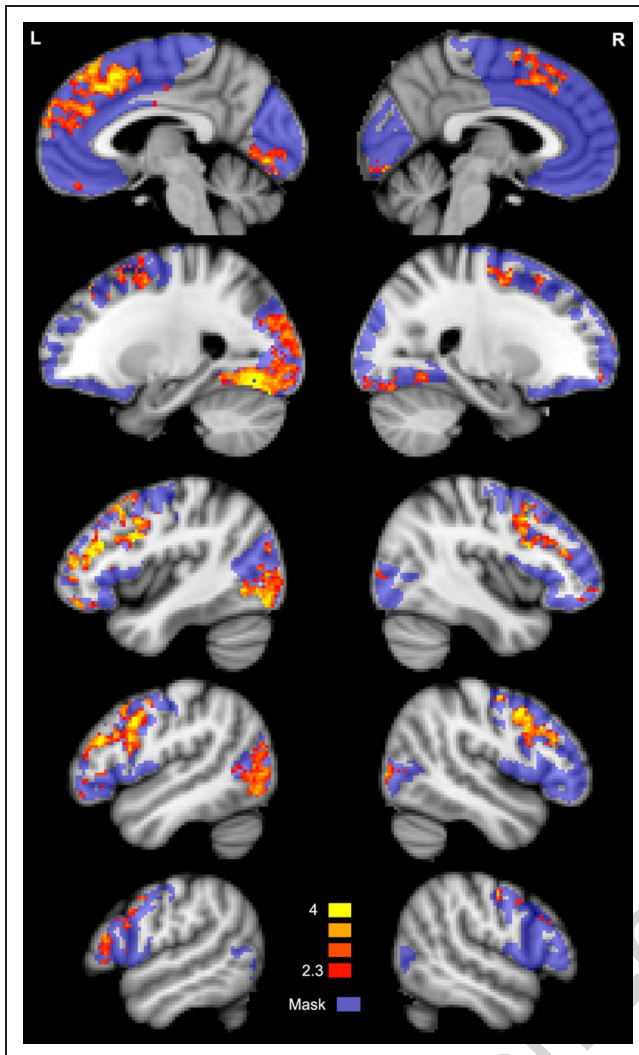
Figure 1. Z-statistic map for resting state GDC analysis, corrected for multiple comparisons using a permutation test to threshold cluster size. GDC statistics were transformed to z-statistics based on their *p* value. The voxels shown in frontal cortex have a significant number of group differences (blind > sighted) in functional connectivity with voxels in ipsilateral occipital cortex; likewise, voxels shown in occipital cortex have a significant number of group differences with voxels in ipsilateral frontal cortex. Occipital and frontal masks are shown in a semitransparent blue color. Slices shown are ±4, ±24, ±42, ±48, and ±54 (MNI *x*-coordinates).

and superiorly to the inferior aspect of the intraparietal sulcus (left superior occipital cortex, LSOC).

In the left pFC, we observed increased correlations medially in the pre-SMA (LMSFC) and medial pFC (LMPFC). Laterally, effects were observed along much of the precentral sulcus (LPCS), the posterior part of the inferior frontal sulcus (IFS), as well as smaller areas within the superior frontal sulcus (LSFS) and inferior frontal gyrus (LIFG). A similar but weaker pattern of group differences was observed in the right hemisphere, with no effect in RIFG.

As a proportion of voxels in the corresponding gray matter mask, we found higher fronto-occipital correla-

tions in blind individuals for 36% of voxels in left occipital cortex (3026/8420), 19% of voxels in left frontal cortex (2435/12563), 14% of voxels in right occipital cortex (747/5518), and 8% of voxels in right frontal cortex (1092/13867), demonstrating clear left-lateralization of the effects.

To assess group differences functional connections between occipital lobe and other parts of the brain, we next performed GDC analyses for bilateral occipito-temporal, parieto-occipital, and fronto-occipital connections. Frontal regions with altered connectivity were virtually identical to those observed in the prior analysis, indicating these findings are robust to the choice of whether to consider bilateral or just ipsilateral fronto-occipital connections. Additionally, in the parietal lobe, regions in the bilateral intraparietal sulcus and inferior parietal lobe (IPS) and left posterior-to-middle cingulate cortex were found to have increased functional connectivity with occipital cortex in blindness. In the temporal lobe, a region of bilateral posterior inferior temporal sulcus and gyrus was also found to have increased functional connectivity (Figure 2).

Replicating and Characterizing the Altered Connectivity in Independent Data

The GDC approach enabled us to identify two sets of ROIs in occipital and frontal cortex: those with increased resting state correlations in blind individuals (GD ROIs) and those with no difference across groups (NGD ROIs; Figure 3). We next asked whether these profiles would replicate in two independent data sets. This analysis also allowed us to test whether connectivity is increased between specific pairs of regions (i.e., relatively sparse, one-to-one connections) or is widespread across occipital and prefrontal cortices (i.e., relatively distributed, many-to-many connections).

The results of the task residual analysis confirmed that all of the GD ROIs identified by the GDC method do have increased fronto-occipital correlations in blind compared to sighted individuals (Figure 4). All frontal ROIs showed consistent group differences in functional connectivity with at least one ipsilateral occipital ROI, and the majority had group differences with all ipsilateral occipital ROIs. Likewise, all occipital ROIs had group differences with at least one ipsilateral frontal ROI, and the majority had group differences with all ipsilateral frontal ROIs. Among left frontal to left occipital (LF-LO) correlations, 21/24 pairs of ROI had significantly stronger correlations in blind than sighted participants in both tasks. Among right frontal to right occipital (RF-RO) correlations, 10/12 pairs were significantly stronger in blind participants in both tasks. Differences between the blind and sighted groups were due to near-zero correlations between occipital and frontal regions in sighted individuals and positive correlations between occipital and frontal regions in blind individuals. These results provide strong evidence that our initial resting state analysis identified regions of frontal and occipital

Figure 2. Z-statistic map for temporal/parietal/frontal resting state GDC analyses, corrected for multiple comparisons using a permutation test to threshold cluster size. GDC statistics were transformed to z-statistics based on their *p* value. The voxels shown in frontal, parietal, and temporal cortex have a significant number of group differences (blind > sighted) in functional connectivity with voxels in occipital cortex. Gray matter masks are shown in a semitransparent blue color. Slices shown are −10, +42 (MNI z-coordinates).
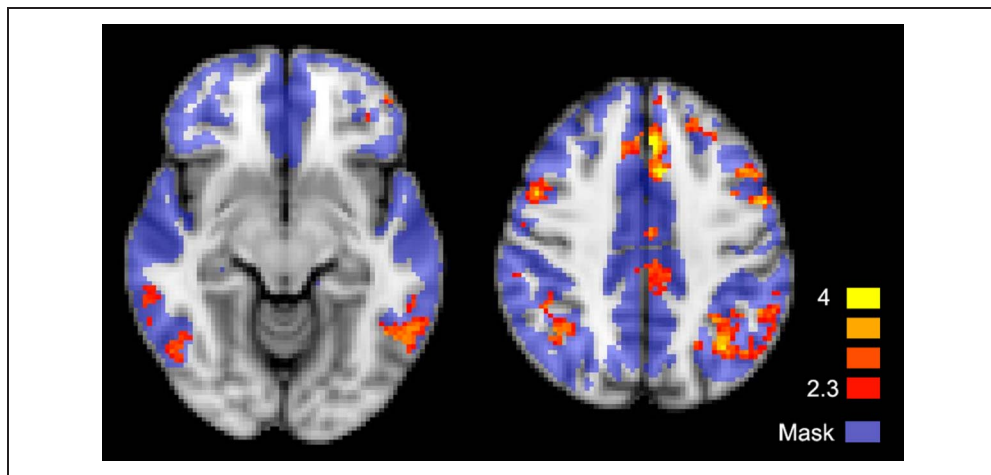
cortex with systematically altered functional connectivity in blind individuals and suggest that in blindness each occipital area has increased connectivity with multiple prefrontal areas.

Are increased correlations in blindness specific to subregions of frontal and occipital cortex or widespread across these lobes? The regions of frontal and occipital cortex not identified by the GDC analysis might truly lack group differences, or they may have subtle differences that were too weak to be detected. To address this, we used task residual data to assess group differences in functional connectivity of NGD ROIs, which lacked group differences in resting data (Figure 5). Among frontal NGD regions, 6/8 regions had no consistent increases in functional connectivity with occipital regions in blind individuals. Among the remaining two frontal regions, RMFG had consistent increases in functional connectivity with one occipital region, whereas RIFG had consistent in-

creases with 5/9 occipital regions. This analysis demonstrates that there are frontal regions where functional connectivity to the occipital lobe is not increased in blindness, across three data sets.

For the two occipital NGD ROIs, some increased functional connectivity with frontal regions was observed in task residual data. LCuneus had consistent increases in functional connectivity with 9/18 frontal regions, and RCuneus had increases with 3/18 frontal regions. Thus, we cannot rule out the possibility that all of occipital cortex has altered functional connectivity with parts of frontal cortex in blindness.

Hemispheric Differences in Functional Connectivity

Do frontal-occipital correlations in blind individuals differ across hemispheres? A linear mixed model demonstrated
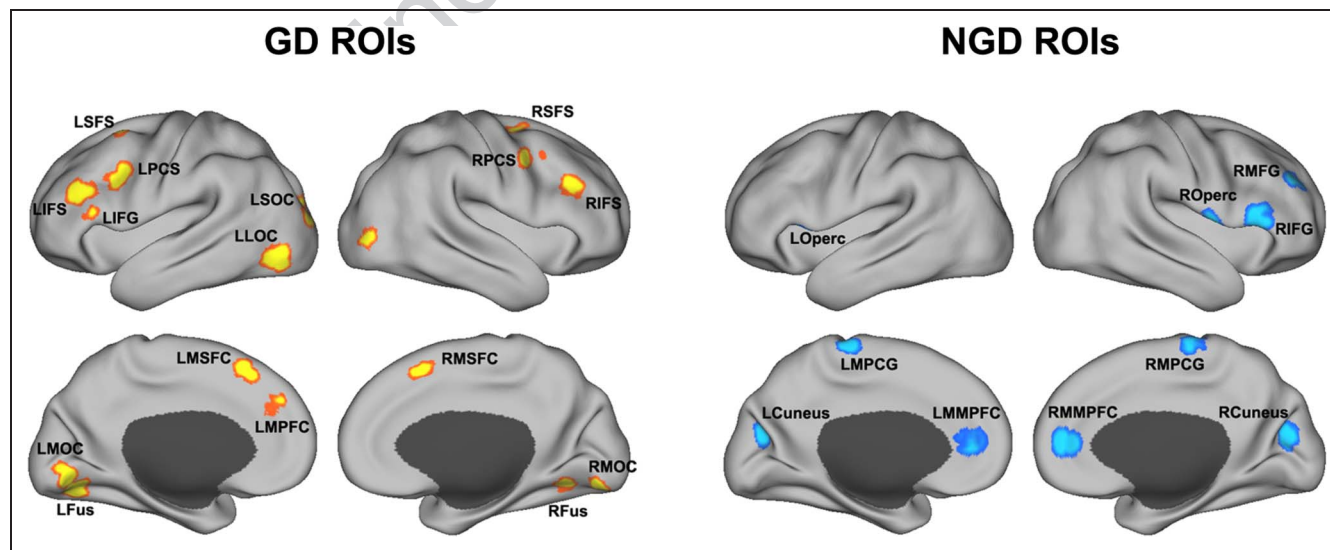

Figure 3. Surface rendering showing ROIs defined from resting state analyses. GD ROIs had group differences in resting state data, whereas NGD ROIs did not. Abbreviations: L = left; R = right; IFS = inferior frontal sulcus; PCS = precentral sulcus; SFS = superior frontal sulcus; MSFC = medial superior frontal cortex; IFG = inferior frontal gyrus; MPFC = medial pFC; MOC = medial occipital cortex; Fus = fusiform gyrus; LOC = ateral occipital cortex; SOC = superior occipital cortex; MMPFC = middle medial pFC; MPCG = medial precentral gyrus; Operc = operculum.

Figure 4. Top and middle rows: correlation matrices in blind and sighted groups, from language and *n*-back task residual data and GD ROIs defined from the resting state analysis. Each cell in the matrix shows the correlation between two ROIs. Matrix indices 1–17 correspond to the following ROIs: LMOC, LFus, LLOC, LSOC, RMOC, RFus, RMOC, LIFS, LPCS, LSFS, LMSFC, LIFG, LMPFC, RIFS, RPCS, RSFS, RMSFC. Bottom row: matrices showing group differences in correlation strengths. Cells with no significant group difference are in green, whereas cells with a significant group difference show the magnitude of the difference (blind minus sighted).
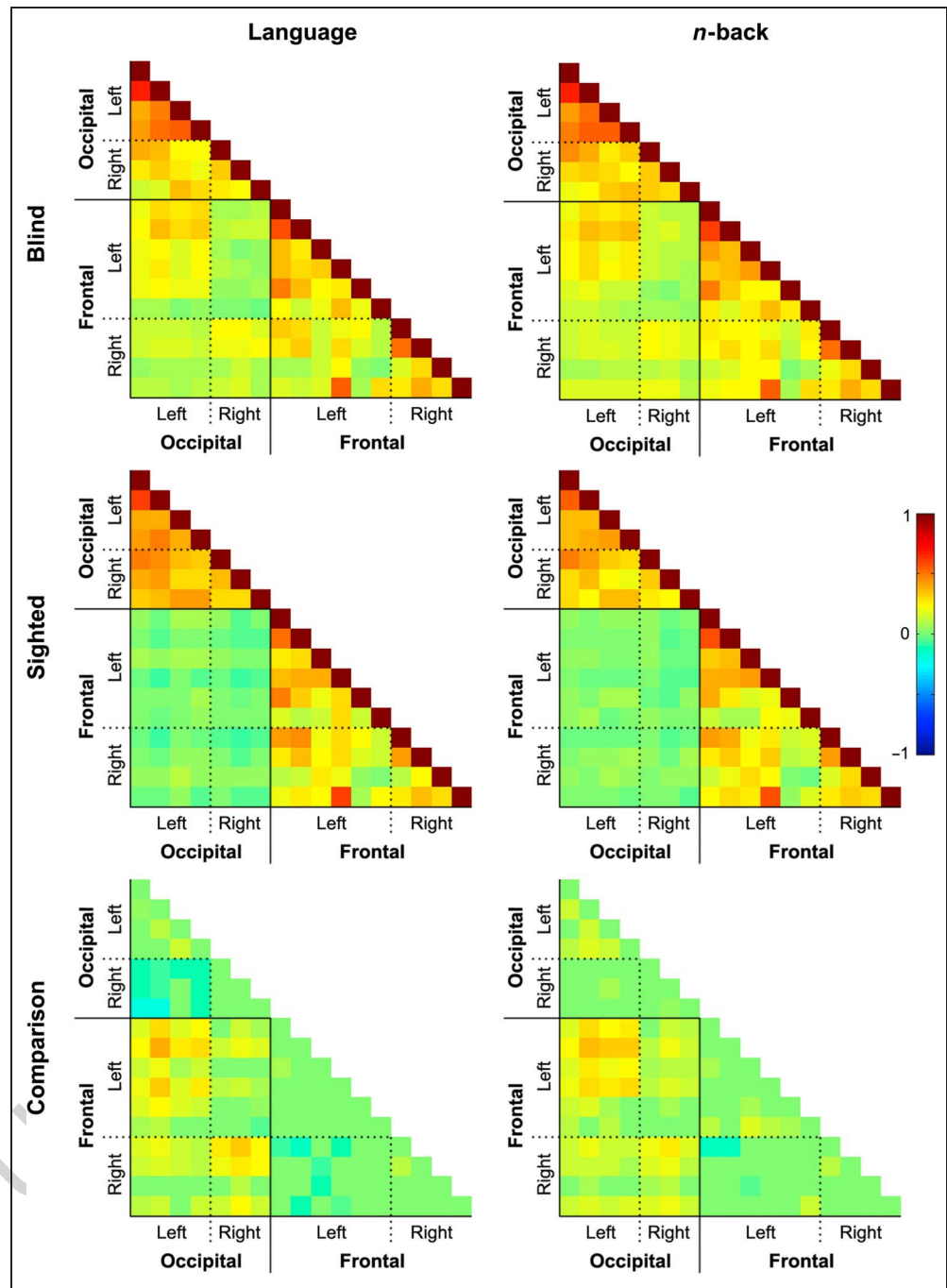
a number of differences based on hemispheric associa-tion. Ipsilateral correlations were stronger than contralat-eral correlations (mean difference = 0.1, $z = 3.62$, $p <$ .0005). Among ipsilateral correlations, correlations in the left hemisphere were stronger than those in the right hemisphere (LF-LO vs. RF-RO, mean difference = 0.05, $z = 3.37$, $p < 10^{-3}$). This is consistent with the finding of stronger effects in the left hemisphere in the resting state analysis. Among contralateral correlations, correlations with left occipital cortex were stronger than those with right occipital cortex (RF-LO vs. LF-RO, mean difference = 0.04, $z = 2.01$, $p < .05$). The last

two effects indicate that frontal-occipital correlations are stronger for left than right occipital cortex, whether ipsi- or contralateral.

Functional Profile of Frontal Regions with Altered Connectivity

A key question for the current analysis was, what are the functional properties of frontal regions overcon-nectivity to occipital cortex in blindness? We addressed this question by characterizing the frontal GD ROIs in two analyses. First, we investigated the functional response

Figure 5. Correlations between frontal and occipital regions identified from the resting state analysis as having group differences in functional connectivity (GD) or not having group differences (NGD). The top two rows show correlation values in blind and sighted participants, as well as a comparison matrix. In the comparison matrix, cells with no significant differences are in green, whereas cells with a significant group difference show the magnitude of the difference (blind minus sighted). The frontal ROIs are ordered as follows from top to bottom: LIFS, LPCS, LSFS, LMSFC, LIFG, LMPFC, RIFS, RPCS, RSFS, RMSFC, LMMPFC, LMPCG, LOperc, RMMPFC, RMPCG, ROperc, RIFG, RMFG. The occipital ROIs are ordered as follows from left to right: LMOC, LFus, LLOC, LSOC, RMOC, RFus, RLOC, LCuneus, RCuneus. The bottom row shows the locations of GD and NGD ROIs.
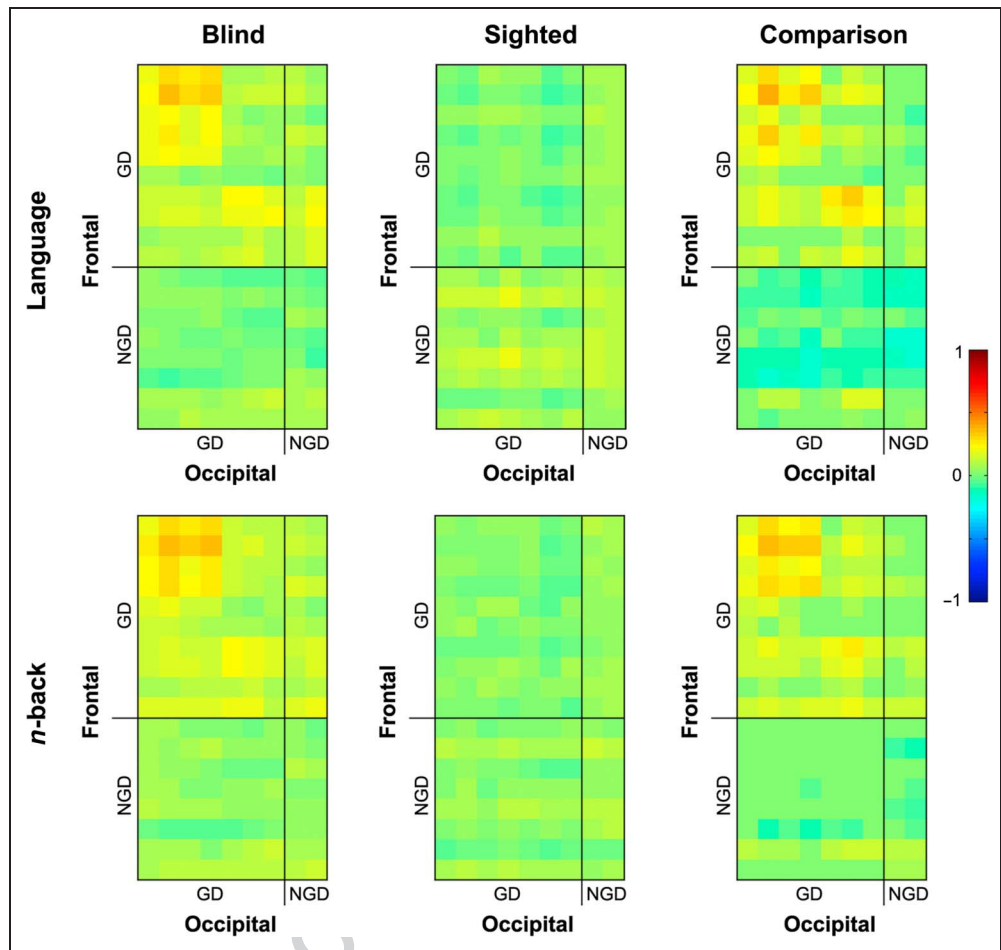
of these regions in language and executive function tasks. Task responses to the language and *n*-back tasks in frontal ROIs are shown in Figure 6. Only one ROI, the LIFG, had a significantly greater response to language over music ($t(28) = 4.55, p < 10^{-5}$). This region did not respond to working memory load ($p > .05$). By contrast, eight regions showed a significantly greater response to 2-back versus 1-back: LIFS ($t(27) = 3.21, p < .005$), LPCS ($t(27) = 4.43, p < 10^{-5}$), LSFS ($t(27) = 2.96, p < .005$), LMSFC ($t(27) = 4.07, p < .0005$), RIFS ($t(27) = 2.56, p < .01$),
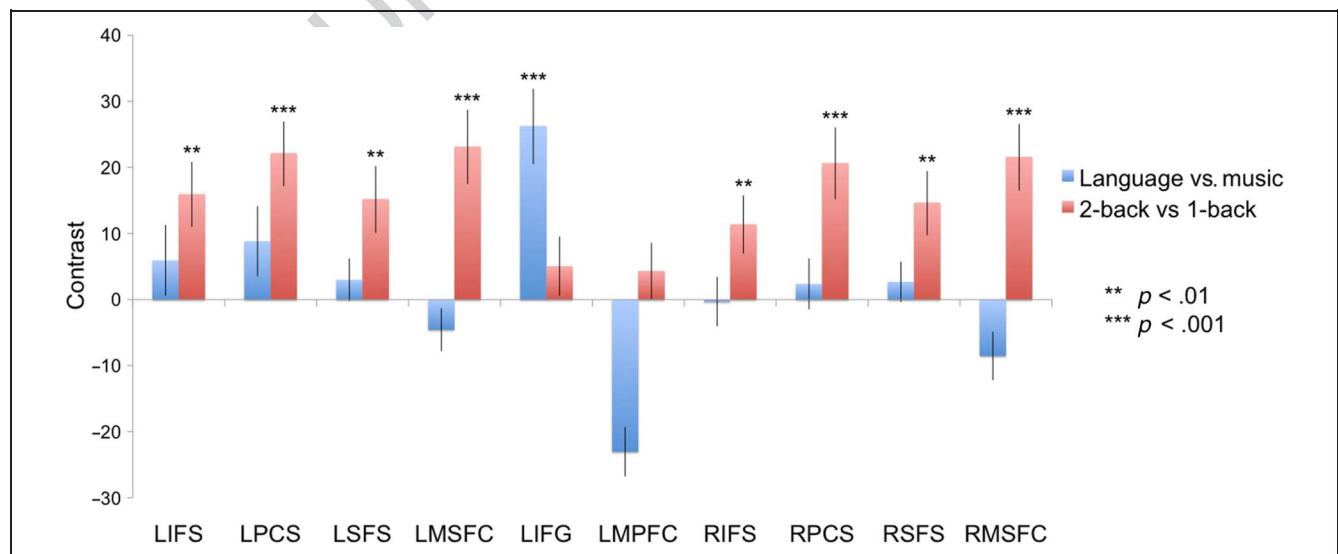

Figure 6. Responses to the language task (language vs. music contrast, blue) and working memory task (2-back vs. 1-back contrast, red) in the 10 frontal ROIs defined by the resting state analysis. The stars show contrasts that are significantly greater than zero; error bars reflect *SEM*.

RPCS ($t(27) = 3.78, p < .0005$), RSFS ($t(27) = 2.97, p < .005$), and RMSFC ($t(27) = 4.23, p < .0005$). None of these ROIs responded to linguistic content ($p > .05$). A three-way repeated-measures ANOVA with contrast (n-back, language), ROI, and group as factors revealed significant differences in functional profile among frontal ROIs (contrast-by-ROI interaction $F(9, 503) = 6.19, p < 10^{-8}$). Main effects of task and ROI were also observed (task $F(1, 503) = 58.68, p < 10^{-14}$, ROI ($F(9, 503) = 5.79, p < 10^{-7}$). Neither the main effect of group nor any interaction term involving the group factor was significant, indicating that these frontal regions have similar functions in language and n-back tasks, across blind and sighted individuals. That is, dramatically increased connectivity with occipital cortex does not appear to alter the function of these frontal regions.

In summary, the majority of frontal areas with altered connectivity in blindness are sensitive to working memory load and not to linguistic information. However, two regions break from this pattern: The LIFG shows a response to linguistic content, whereas LMPFC shows neither a language nor working memory response.

## Functional Profile of Parietal and Temporal Regions with Altered Connectivity

Do parietal and temporal regions with increased connectivity to the occipital lobes share similar functional profiles with frontal regions? To answer this, we assessed functional responses to language and executive function tasks in parietal and temporal regions (Figure 7). Three of these five regions showed a significantly greater response to 2-back versus 1-back conditions: LIPS ($t(27) = 3.29, p < .005$), LITS ($t(27) = 1.81, p < .05$), and RIPS ($t(27) = 4.19, p < 10^{-4}$). No region showed a significant response to linguistic input. This demonstrates that at least three of the parietal/temporal regions identified in

the resting state analysis belong to the executive control network, consistent with the predominance of executive responses among identified frontal regions.

Functional Connectivity of Left Frontal Regions

We identified three distinct functional profiles among prefrontal areas with increased occipital connectivity in blindness: (1) working memory responsive areas, (2) one language responsive area (LIFG), and (3) one region with neither a language nor working memory response (LMPFC). We next asked whether these distinct functional profiles align with distinct patterns of functional connectivity to the rest of the brain. Resting state functional connectivity maps for left frontal ROIs (GD) are shown in Figure 8. Consistent with prior evidence, we find that language-sensitive and the working memory-sensitive regions of pFC have different profiles of functional connectivity with temporal and parietal cortices, as well as contralateral frontal cortex. In contrast to working memory-responsive regions, the language-responsive LIFG region was functionally connected with the superior temporal and inferior parietal areas typically associated with linguistic processing. Working memory-responsive regions were functionally connected with the intraparietal sulcus and superior part of the IPS, as well as a lateral inferior temporal region. Very similar parietal and temporal regions were also observed to have increased functional connectivity with occipital cortex in blindness (Figure 2), indicating temporal and parietal areas associated with the executive control network are also characterized by occipital overconnectivity. The LMPFC region showed a distinct pattern altogether, with functional connectivity to medial and lateral parietal regions associated with the default mode network. Together with the task-based responses, these findings support the hypothesis that occipital cortex is coupled with regions from at least three distinct

Figure 7. Responses to the language task (language vs. music contrast, blue) and working memory task (2-back vs. 1-back contrast, red) in the five parietal and temporal ROIs defined by the whole-brain resting state analysis. The stars show contrasts that are significantly greater than zero; error bars reflect *SEM*.
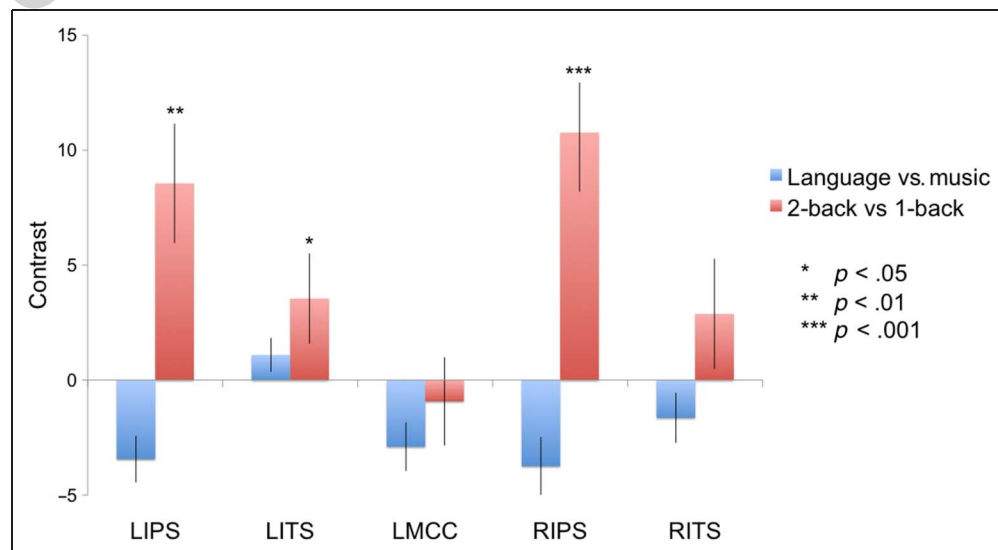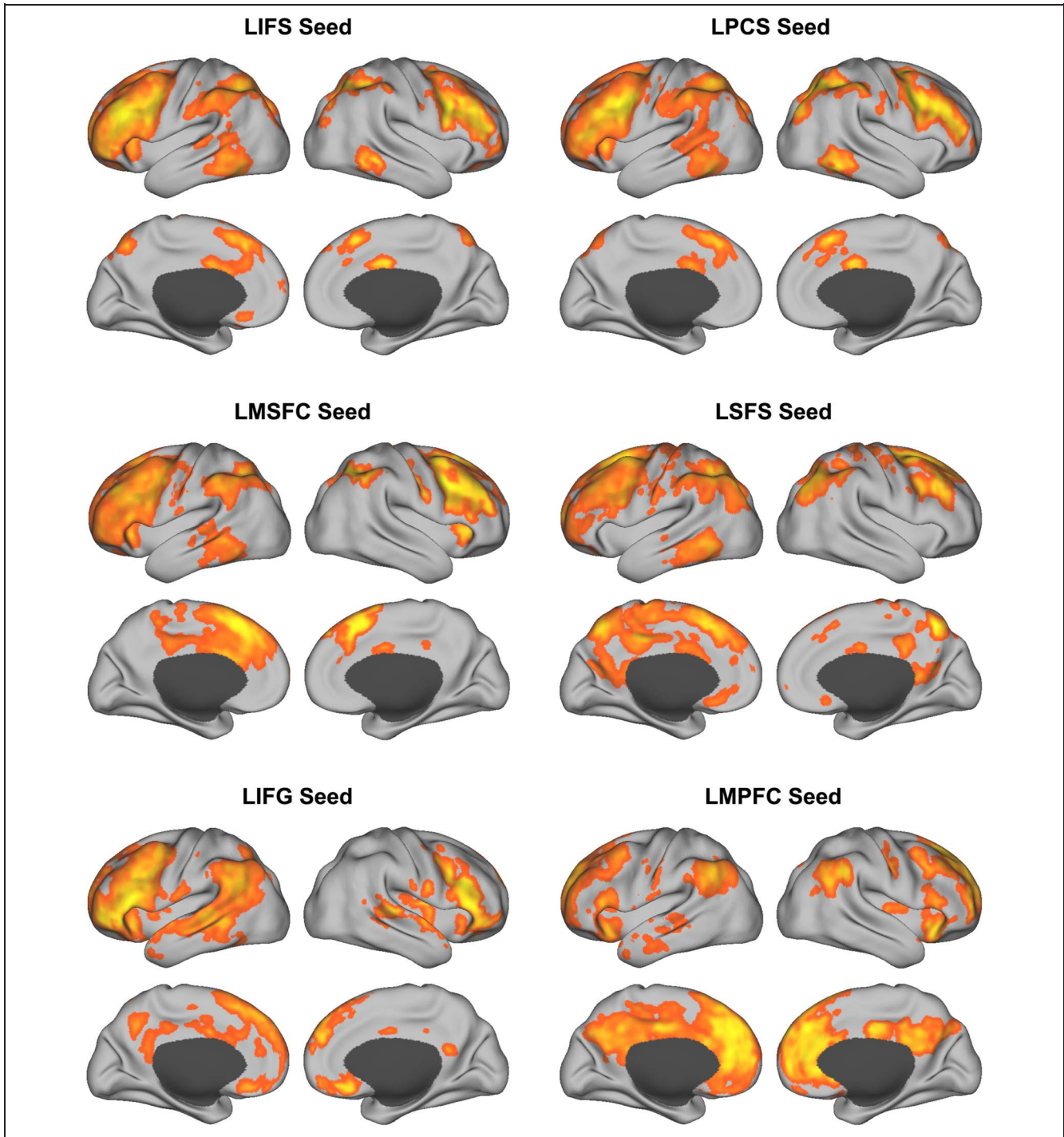
Figure 8. Group level maps of resting state functional connectivity of left frontal seed regions, in sighted participants ($N = 21$).

functional networks. Most increases in occipital connectivity are with the executive control network. The remainders correspond to the language network and a third network whose function remains to be characterized but which resembles the default mode network.

DISCUSSION

We use a data-driven GDC approach to identify a group of prefrontal areas that has increased connectivity with occipital cortex in congenitally blind individuals (Watkins et al., 2012; Bedny et al., 2011; Liu et al., 2007). The GDC approach provides a more comprehensive picture of occipital functional connectivity in blindness than previously possible. We find that one of the identified prefrontal regions, in the LIFG, responds to linguistic content (larger response to speech than nonlinguistic sounds; Bedny et al., 2011). Crucially, we show for the first time that the majority of prefrontal areas with altered connectivity respond to working memory load in an *n*-back

task, but not to linguistic content. These findings indicate that, in blindness, the occipital lobe has altered interactions with frontal regions belonging to multiple networks, with a predominance of regions associated with the executive control network.

Implications of Resting State Group Differences for Anatomy and Function

One straightforward interpretation of increased functional connectivity between occipital and prefrontal cortices would be to infer a strengthened anatomical pathway. However, prior diffusion tensor imaging studies with blind individuals argue against this possibility. The frontal and occipital lobes are connected by the inferior fronto-occipital fasciculus and by a portion of the superior longitudinal fasciculus extending into the occipital lobe (Forkel et al., in press). Contrary to the hypothesis of increased anatomical connectivity, inferior fronto-occipital fasciculus shows reduced white matter integrity in blindness (Shu, Liu, et al., 2009). In general, white matter tracts connecting occipital cortex to the rest of the brain are diminished in blind individuals, showing reduced fractional anisotropy or increased mean or radial diffusivity (Bridge, Cowey, Ragge, & Watkins, 2009; Shu, Li, Li, Yu, & Jiang, 2009; Shu, Liu, et al., 2009; Park et al., 2007; Shimony et al., 2006). Thus, all extant data suggest that the functional changes observed here occur in the absence of increased long-range anatomical connections.

At the opposite extreme, an alternative hypothesis is that increased "functional connectivity" does not reflect changes in fronto-occipital connectivity per se, but only in coactivation. fcMRI measures correlations in hemodynamic responses; two regions could appear to be connected when in fact they are both independently driven by external stimuli or ongoing cognitive activity. In the current context, for example, left occipital cortex of blind individuals might coactivate with LIFG because both regions (independently) play a role in linguistic processing. However, we consider this interpretation unlikely. Our study, like prior reports, did not observe increased functional connectivity between occipital cortex and other regions involved in language processing, such as left temporal regions (Watkins et al., 2012; Bedny et al., 2011), suggesting that a role in language processing is not sufficient to increase functional connectivity with occipital areas. Second, we find that increased functional correlations were stable across rest and two different task contexts, suggesting that the observed group differences are robust to substantial variations in ongoing cognitive activity.

Therefore, we hypothesize that increased resting state correlations in blind individuals reflect increased interaction or information flow between occipital cortex and language as well as executive function regions of the frontal lobe. In sighted adults, occipital and frontal cortices in-

teract during visual attention and visual working memory tasks (Zanto, Rubens, Thangavel, & Gazzaley, 2011; Moore & Armstrong, 2003; Kastner & Ungerleider, 2000; Miller, Erickson, & Desimone, 1996). There is also some evidence that in the absence of a task, fronto-occipital correlations are higher in sighted individuals during visually attentive states (Liu, Dong, Zuo, Wang, & Zang, in press; McAvoy et al., 2012), although these correlations are substantially more restricted in spatial extent than those observed here. Increased fronto-occipital connectivity in blind individuals could reflect an expansion and repurposing of this functional connection for nonvisual processing.

A key open question, regarding this interpretation, concerns the direction of information flow between prefrontal and occipital regions. Prefrontal regions might transmit information to occipital cortex, providing a means for the occipital lobe to receive nonvisual information. On the other hand, prefrontal regions may receive information processed by occipital cortex for further processing or maintenance. This directionality could potentially be tested using techniques with relatively high temporal and spatial resolution, such as magnetoencephalography.

Implications for the Function of Occipital Cortices in Blindness

How do the present resting state results inform hypotheses about the functional role of occipital cortex in blind individuals? Like prior studies, we find that occipital cortex is functionally connected with an area of the frontal lobe that is specifically involved in language processing (Watkins et al., 2012; Bedny et al., 2011). This observation is consistent with the hypotheses that a subset of left occipital cortex contributes to language processing in blindness (Bedny et al., 2011, 2012; Burton et al., 2003; Röder et al., 2002). We also find that the majority of identified prefrontal areas respond to working memory load and not to linguistic content. Additionally, occipital cortex has increased functional connectivity with temporal and parietal regions associated with the executive control network. These results raise the possibility that, in addition to language-related plasticity, parts of occipital cortex contribute to executive and working memory functions in blind individuals. Although this hypothesis remains to be tested directly, it is consistent with several lines of evidence. First, during sensory tasks, occipital cortices of blind individuals are sensitive to attention and task demands. For example, two studies reported responses only for target and/or distractor stimuli, but not for nontarget stimuli during auditory and tactile change detection tasks (Weaver & Stevens, 2007; Kujala et al., 2005). Occipital cortex responds more during an auditory and tactile discrimination tasks than control tasks with matching sensory input and motor output (Voss, Gougoux, Zatorre, Lassonde, & Lepore, 2008; Gougoux et al., 2005; Sadato et al., 1996). These data point to a functional role beyond sensory analysis.

Further support for the hypothesis that occipital areas contribute to executive processes comes from studies of verbal memory in blind individuals. Occipital areas are active when blind individuals recall words from memory or generate verbs to heard nouns (Raz, Amedi, & Zohary, 2005; Amedi et al., 2003). TMS to the occipital cortex impairs verb generation in blind individuals (Amedi, Floel, Knecht, Zohary, & Cohen, 2004). As a group, blind individuals are better than sighted at remembering lists of words, and those blind individuals with better long-term memory have higher occipital responses during verbal memory tasks (Raz, Striem, Pundak, Orlov, & Zohary, 2007; Amedi et al., 2003). An intriguing possibility is that these behavioral gains result because blind individuals use visual cortex as a secondary working memory resource.

An alternative possibility is that executive function regions in prefrontal and parietal cortex are correlated with language-responsive areas in occipital cortex, perhaps because many online language tasks require executive and working memory functions (Thompson-Schill, Bedny, & Goldberg, 2005). Although the majority of frontal regions with increased connectivity in blindness did not respond selectively to linguistic input versus music, this does not preclude the possibility that these regions play a role in linguistic processing. Intriguingly, fronto-occipital functional connectivity in blindness was stronger in the left than in the right hemisphere, including in regions with a working memory response and no selective response to language. Although any interpretation of the cause or relevance of this lateralization is highly speculative, one possibility is that these functional connections are lateralized because they do relate to linguistic processing and to occipital responses to linguistic stimuli.

Developmental Mechanisms of Plasticity

Another set of questions for future research concerns the developmental mechanism and timing of connectivity changes. Are fronto-occipital correlations present in infants but suppressed by visual input during development in sighted children? Or are these correlations acquired by occipital cortex only in the absence of visual input? Relatedly, what is the causal relationship between occipital functional plasticity and changes in fronto-occipital correlations in blindness? Are occipital and frontal areas functionally connected because of frequent coactivation during development (Dosenbach et al., 2007; Fair et al., 2007)? Alternatively, the opposite causal mechanism is also possible: Increased connectivity to prefrontal regions might enable functional plasticity of occipital cortex.

Differentiating between these developmental accounts will require characterizing both functional plasticity and functional connectivity to pFC in the occipital cortex of blind infants and children or of adults who became blind at different ages. For example, one previous study found that functional connectivity between prefrontal and occipital regions was increased in adults who were blind throughout childhood but not those who became blind after age 9, despite decades of subsequent blindness (Bedny et al., 2010).

Finally, a key question about these results concerns their implications for efforts to restore sight to blind individuals. Individuals who grow up without vision and then recover sight in adulthood have lasting impairments in visual perception (Lewis & Maurer, 2005; Maurer, Lewis, & Mondloch, 2005; Le Grand, Mondloch, Maurer, & Brent, 2004; Fine et al., 2003; but see Ostrovsky, Andalman, & Sinha, 2006). Such impairments are believed to result from local microcircuitry changes within occipital cortex in the absence of vision (Espinosa & Stryker, 2012; Hensch, 2005). However, altered connectivity of occipital cortex with more remote regions like pFC may also interfere with sight recovery. For example, the frontal lobe is believed to modulate occipital responses to stimuli based on current task demands and attention. Changes in frontal-occipital connectivity could alter these functions. Future research should therefore test whether increased connectivity to prefrontal regions affects visual functions in occipital cortex after sight recovery.

Conclusion and Future Directions

Using a data-driven approach for assessing whole-brain group differences in functional connectivity, we mapped regions of frontal and occipital cortex with increased synchronization in blind adults. Although much of occipital cortex had increased correlations, functional connectivity was increased only with a specific set of prefrontal regions, belonging to several functional networks. The majority of the overconnected prefrontal areas respond to working memory load, whereas one responded to linguistic content. Our findings open a range of questions for future research: How exactly does increased functional connectivity relate to altered functional responses in occipital cortex? And what is the developmental trajectory of increased fronto-occipital functional connectivity? Addressing these questions will further our understanding of the mechanisms underlying cortical plasticity.

REFERENCES

Al-Aidroos, N., Said, C. P., & Turk-Browne, N. B. (2012). Top–down attention switches coupling between low-level and high-level areas of human visual cortex. *Proceedings of the National Academy of Sciences, 109,* 14675–14680.

Amedi, A., Floel, A., Knecht, S., Zohary, E., & Cohen, L. G. (2004). Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. *Nature Neuroscience, 7,* 1266–1270.

Amedi, A., Raz, N., Pianka, P., Malach, R., & Zohary, E. (2003). Early 'visual' cortex activation correlates with superior verbal memory performance in the blind. *Nature Neuroscience, 6,* 758–766.

Bedny, M., Konkle, T., Pelphrey, K., Saxe, R., & Pascual-Leone, A. (2010). Sensitive period for a multimodal response in human visual motion area MT/MST. *Current Biology, 20,* 1900–1906.

Bedny, M., Pascual-Leone, A., Dodell-Feder, D., Fedorenko, E., & Saxe, R. (2011). Language processing in the occipital cortex of congenitally blind adults. *Proceedings of the National Academy of Sciences, 108,* 4429–4434.

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage, 37,* 90.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine, 34,* 537–541.

Bridge, H., Cowey, A., Ragge, N., & Watkins, K. (2009). Imaging studies in congenital anophthalmia reveal preservation of brain architecture in 'visual' cortex. *Brain, 132,* 3467–3480.

Burton, H., Snyder, A., Conturo, T., Akbudak, E., Ollinger, J., & Raichle, M. (2002). Adaptive changes in early and late blind: A fMRI study of Braille reading. *Journal of Neurophysiology, 87,* 589–607.

Burton, H., Snyder, A., Diamond, J., & Raichle, M. (2002). Adaptive changes in early and late blind: A fMRI study of verb generation to heard nouns. *Journal of Neurophysiology, 88,* 3359–3371.

Chai, X. J., Castañón, A. N., Ongür, D., & Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. *Neuroimage, 59,* 1420–1428.

Collignon, O., Vandewalle, G., Voss, P., Albouy, G., Charbonneau, G., Lassonde, M., et al. (2011). Functional specialization for auditory-spatial processing in the occipital cortex of congenitally blind humans. *Proceedings of the National Academy of Sciences, 108,* 4435–4440.

Dosenbach, N. U. F., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A. T., et al. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proceedings of the National Academy of Sciences, 104,* 11073–11078.

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences.*

Espinosa, J. S., & Stryker, M. P. (2012). Development and plasticity of the primary visual cortex. *Neuron, 75,* 230–249.

Fair, D. A., Dosenbach, N. U., Church, J. A., Cohen, A. L., Brahmbhatt, S., Miezin, F. M., et al. (2007). Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences, 104,* 13507–13512.

Fedorenko, E., Behr, M. K., & Kanwisher, N. (2011). Functional specificity for high-level linguistic processing in the human brain. *Proceedings of the National Academy of Sciences, 108,* 16428–16433.

Fedorenko, E., Duncan, J., & Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. *Proceedings of the National Academy of Sciences, 110,* 16616–16621.

Fine, I., Wade, A. R., Brewer, A. A., May, M. G., Goodman, D. F., Boynton, G. M., et al. (2003). Long-term deprivation affects visual perception and cortex. *Nature Neuroscience, 6,* 915–916.

Forkel, S. J., Thiebaut de Schotten, M., Kawadler, J. M., Dell'Acqua, F., Danek, A., & Catani, M. (in press). The anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography. *Cortex.*

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster size threshold. *Magnetic Resonance in Medicine, 33,* 636–647.

Friston, K. J., Worsley, K. J., Frackowiak, R., Mazziotta, J. C., & Evans, A. C. (2004). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping, 1,* 210–220.

Gougoux, F., Zatorre, R. J., Lassonde, M., Voss, P., & Lepore, F. (2005). A functional neuroimaging study of sound localization: Visual cortex activity predicts performance in early-blind individuals. *PLoS Biology, 3,* e27.

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *Neuroimage, 48,* 63.

Gweon, H., Dodell-Feder, D., Bedny, M., & Saxe, R. (2012). Theory of mind performance in children correlates with functional specialization of a brain region for thinking about thoughts. *Child Development, 83,* 1853–1868.

Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience, 6,* 877–888.

Kastner, S., & Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annual Review of Neuroscience, 23,* 315–341.

Kujala, T., Palva, M. J., Salonen, O., Alku, P., Huotilainen, M., Järvinen, A., et al. (2005). The role of blind humans' visual cortex in auditory change detection. *Neuroscience Letters, 379,* 127–131.

Le Grand, R., Mondloch, C. J., Maurer, D., & Brent, H. P. (2004). Impairment in holistic face processing following early visual deprivation. *Psychological Science, 15,* 762–768.

Lewis, T. L., & Maurer, D. (2005). Multiple sensitive periods in human visual development: Evidence from visually deprived children. *Developmental Psychobiology, 46,* 163–183.

Liu, D., Dong, Z., Zuo, X., Wang, J., & Zang, Y. (in press). Eyes-open/eyes-closed dataset sharing for reproducibility evaluation of resting state fMRI data analysis methods. *Neuroinformatics.*

Liu, Y., Yu, C., Liang, M., Li, J., Tian, L., Zhou, Y., et al. (2007). Whole brain functional connectivity in the early blind. *Brain, 130,* 2085–2096.

Marchini, J. L., & Ripley, B. D. (2000). A new statistical approach to detecting significant activation in functional MRI. *Neuroimage, 12,* 366–380.

Maurer, D., Lewis, T. L., & Mondloch, C. J. (2005). Missing sights: Consequences for visual cognitive development. *Trends in Cognitive Sciences, 9,* 144–151.

McAvoy, M., Larson-Prior, L., Ludwikow, M., Zhang, D., Snyder, A. Z., Gusnard, D. L., et al. (2012). Dissociated mean and functional connectivity BOLD signals in visual cortex during eyes closed and fixation. *Journal of Neurophysiology, 108,* 2363–2372.

Miller, E. K., Erickson, C. A., & Desimone, R. (1996). Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *The Journal of Neuroscience, 16,* 5154–5167.

Moore, T., & Armstrong, K. M. (2003). Selective gating of visual signals by microstimulation of frontal cortex. *Nature, 421,* 370–373.

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping, 15,* 1–25.

Ostrovsky, Y., Andalman, A., & Sinha, P. (2006). Vision following extended congenital blindness. *Psychological Science, 17,* 1009–1014.

Park, H.-J., Jeong, S.-O., Kim, E. Y., Kim, J. I., Park, H., Oh, M.-K., et al. (2007). Reorganization of neural circuits in the blind on diffusion direction analysis. *NeuroReport, 18,* 1757–1760.

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage, 59,* 2142–2154.

Ptito, M., Moesgaard, S. M., Gjedde, A., & Kupers, R. (2005). Cross-modal plasticity revealed by electrotactile stimulation of the tongue in the congenitally blind. *Brain, 128,* 606–614.

Raz, N., Amedi, A., & Zohary, E. (2005). V1 activation in congenitally blind humans is associated with episodic retrieval. *Cerebral Cortex, 15,* 1459–1468.

Raz, N., Striem, E., Pundak, G., Orlov, T., & Zohary, E. (2007). Superior serial memory in the blind: A case of cognitive compensatory adjustment. *Current Biology, 17,* 1129–1133.

Röder, B., Stock, O., Bien, S., Neville, H., & Rösler, F. (2002). Speech processing activates visual cortex in congenitally blind humans. *European Journal of Neuroscience, 16,* 930–936.

Sadato, N., Okada, T., Kubota, K., & Yonekura, Y. (2004). Tactile discrimination activates the visual cortex of the recently blind naive to Braille: A functional magnetic resonance imaging study in humans. *Neuroscience Letters, 359,* 49–52.

Sadato, N., Pascual-Leone, A., Grafman, J., Ibanez, V., Deiber, M.-P., Dold, G., et al. (1996). Activation of the primary visual cortex by Braille reading in blind subjects. *Nature, 380,* 526–528.

Shimony, J., Burton, H., Epstein, A., McLaren, D., Sun, S., & Snyder, A. (2006). Diffusion tensor imaging reveals white matter reorganization in early blind humans. *Cerebral Cortex, 16,* 1653–1661.

Shu, N., Li, J., Li, K., Yu, C., & Jiang, T. (2009). Abnormal diffusion of cerebral white matter in early blindness. *Human Brain Mapping, 30,* 220–227.

Shu, N., Liu, Y., Li, J., Li, Y., Yu, C., & Jiang, T. (2009). Altered anatomical network in early blindness revealed by diffusion tensor tractography. *PLoS ONE, 4,* e7228.

Thompson-Schill, S. L., Bedny, M., & Goldberg, R. F. (2005). The frontal lobes and the regulation of mental activity. *Current Opinion in Neurobiology, 15,* 219–224.

Triantafyllou, C., Hoge, R. D., Krueger, G., Wiggins, C. J., Potthast, A., Wiggins, G. C., et al. (2005). Comparison of physiological noise at 1.5 T, 3 T and 7 T and optimization of fMRI acquisition parameters. *Neuroimage, 26,* 243–250.

Triantafyllou, C., Hoge, R. D., & Wald, L. L. (2006). Effect of spatial smoothing on physiological noise in high-resolution fMRI. *Neuroimage, 32,* 551–557.

Voss, P., Gougoux, F., Zatorre, R. J., Lassonde, M., & Lepore, F. (2008). Differential occipital responses in early- and late-blind individuals during a sound-source discrimination task. *Neuroimage, 40,* 746–758.

Watkins, K. E., Cowey, A., Alexander, I., Filippini, N., Kennedy, J. M., Smith, S. M., et al. (2012). Language networks in anophthalmia: Maintained hierarchy of processing in 'visual' cortex. *Brain, 135,* 1566–1577.

Weaver, K. E., & Stevens, A. A. (2007). Attention and sensory interactions within the occipital cortex in the early blind: An fMRI study. *Journal of Cognitive Neuroscience, 19,* 315–330.

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *Neuroimage, 92,* 381–397.

Woolrich, M. W., Behrens, T. E. J., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for fMRI group analysis using Bayesian inference. *Neuroimage, 21,* 1732–1747.

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of fMRI data. *Neuroimage, 14,* 1370–1386.

Zanto, T. P., Rubens, M. T., Thangavel, A., & Gazzaley, A. (2011). Causal role of the prefrontal cortex in top–down modulation of visual processing and working memory. *Nature Neuroscience, 14,* 656–661.