Functional Connectivity Density in Congenitally and Late Blind Subjects

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Visual deprivation during different developmental periods leads to different structural and functional alterations in the brain; however, the effects of visual deprivation on the spontaneous functional organization of the brain remain largely unknown. In this study, we used voxel-based functional connectivity density (FCD) analyses to investigate the effects of visual deprivation during different developmental periods on the spontaneous functional organization of the brain. Compared with the sighted controls (SC), both the congenitally blind (CB) and the late blind (LB) exhibited decreased short- and long-range FCDs in the primary visual cortex (V1) and decreased long-range FCDs in the primary somatosensory and auditory cortices. Although both the CB and LB exhibited increased short-range FCD in the dorsal visual stream, the CB exhibited greater increases in the short- and long-range FCDs in the ventral visual stream and hippocampal complex compared with the LB. Moreover, the short-range FCD of the left V1 exhibited a significant positive correlation with the duration of blindness in the LB. Our findings suggest that visual deprivation before the developmental sensitive period can induce more extensive brain functional reorganization than does visual deprivation after the sensitive period, which may underlie an enhanced capacity for processing nonvisual information in the CB.

Keywords: functional connectivity density, functional magnetic resonance imaging, occipital cortex, sensitive period, visual deprivation

Introduction

Visual deprivation during different developmental periods provides a unique model for understanding the complex interactions among developmental, plastic, and degenerative mechanisms of brain organization. The visual cortex develops during a limited time window in which the visual experience exerts unusually strong effects on the formation of the structural and functional organization of the visual cortex (Wiesel and Hubel 1965; Lewis and Maurer 2009). This time period is called the sensitive period, which ranges from several months to 10 years after birth for different occipital areas (Lewis and Maurer 2009; Wattam-Bell et al. 2010). In congenitally (CB) or early blind (EB) subjects who lost their sight before or within the sensitive period, the occipital cortex, which normally processes visual information, shifts to respond to nonvisual stimuli; however, this response pattern is weak or absent in late blind (LB) individuals who lost their sight after the sensitive period (Burton et al. 2004; Stilla et al. 2008; Bedny et al. 2010, 2012; Collignon et al. 2013). Structural and metabolic differences between the CB/EB and the LB are also present. The resting-state glucose metabolism in the occipital cortex is abnormally elevated in the EB compared with sighted controls (SC) (Veraart et al. 1990; De Volder et al. 1997, 1999; Kupers et al. 2011b) but is decreases in the LB (Veraart et al. 1990). The CB/EB but not the LB exhibit greater thickness (Jiang et al. 2009; Park et al. 2009; Kupers et al. 2011b) and reduced anatomical connectivity and network efficiency in the occipital cortex compared with the SC (Li et al. 2013). Additionally, the age of onset of blindness is significantly correlated with the topological properties of the anatomical network of the blind (Li et al. 2013). These findings suggest that visual deprivation before and after the sensitive period can result in different structural and functional alterations of the brain. However, the effects of visual deprivation on spontaneous functional organization remain largely unknown.

The spontaneous functional organization can be investigated via functional connectivity (FC), which measures the temporal correlation between time series of the blood oxygen level–dependent (BOLD) signals of 2 brain regions. Prior studies have reported decreased FC between the occipital cortex and the nonvisual sensory cortices (Liu et al. 2007; Yu et al. 2008; Bedny et al. 2010; Qin et al. 2013) and increased FC between the occipital cortex and the prefrontal cortex in the CB/EB (Liu et al. 2007; Bedny et al. 2010, 2011). One study found only decreased FC between middle temporal/medial superior temporal and nonvisual sensory areas in the LB (Bedny et al. 2010); however, this finding requires validation because of the relatively small sample size (5 LB subjects) of the study. Moreover, these studies have all adopted region of interest (ROI)-based FC analyses, which may miss important unpredictable findings. Whole-brain FC analyses with relatively larger samples are needed to reveal the complete picture of spontaneous functional reorganization in blind subjects.

Functional connectivity density (FCD) mapping is an ultrafast voxel-wise method that measures the number of functional connections of a given voxel with others (Tomasi and Volkow 2010). Greater FCD values for particular voxels indicate that those voxels are functionally connected to a greater number of other brain voxels and suggest that those voxels play more important roles in the information processing. Based on the neighboring relationships between brain voxels, the global FCD can be further divided into short- and long-range FCDs (Tomasi and Volkow 2011a). In this study, we recruited 19 CB and 34 LB subjects to identify the effects of visual deprivation before and after the sensitive period on spontaneous functional organization using whole-brain FCD analyses. We predicted that the CB would exhibit more extensive increases in FCDs because the CB subjects have greater capacities for cross-modal plasticity than do the LB.

Materials and Methods

Subjects

Nineteen CB (12 males, range: 20–39 years old), 34 LB (age of onset of blindness >12 years old; 22 males, range: 20–38 years old), and 42 SC (30 males, range: 19–37 years old) subjects were recruited for this study (Table 1). All subjects were right-handed. None of the CB subjects had histories of pattern vision (i.e., any ability to see shape, contour, and orientation) or any memory of visual experience, and none of the LB had experienced pattern vision after visual deprivation. The protocol was approved by the Medical Research Ethics Committee of Tianjin Medical University, and written informed consent was obtained from all participants prior to the experiment.

MRI Image Acquisition

MRI images were acquired using a 3.0-Tesla MR scanner (Trio Tim system; Siemens, Erlangen, Germany) equipped with a 12-channel head coil. Tight but comfortable foam padding was used to minimize head movement, and earplugs were used to reduce scanner noise. Structural images were acquired using a 3D magnetization-prepared rapid-acquisition gradient-echo (MP-RAGE) sequence with the following parameters: repetition time (TR)/echo time (TE)/inversion time (TI) = 2000/2.6/900 ms, flip angle = 9°, matrix = 256 × 224, field of view (FOV) = 256 × 224 mm, thickness = 1 mm, and 176 continuous sagittal slices. Resting-state fMRI data were obtained using a gradient-echo echo-planar imaging (GRE-EPI) sequence with the following parameters: TR/TE = 2000/30 ms, matrix = 64 × 64, flip angle = 90°, FOV = 220 × 220 mm, 32 interleaved axial slices, thickness = 3 mm, slice gap = 1 mm, and 180 time points. During the fMRI scan, all subjects were instructed to remain as still as possible, to think of nothing in particular, and to not fall asleep. As even minimal visual stimuli can alter the activity of the visual cortex, all subjects were also instructed to keep their eyes closed during the fMRI examinations. We also turned off the room light to establish a dark environment that was similar for all subjects. After the scan, we asked each subject whether they kept their eyes closed during the scan. If a subject opened his/her eyes during the scan, the fMRI scan was repeated with the eyes closed. Thus, all resting-state fMRI scans were obtained in the same dark environment and with the subjects' eyes closed.

Data Preprocessing

The resting-state fMRI data were preprocessed using the Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes for each subject were discarded to allow the signal to reach equilibrium and the participants to adapt to the scanning noise. The remaining 170 volumes were then corrected for the acquisition time delays between slices. The 3 translational and 3 rotational motion parameters were computed during the realignment step. The frame-wise displacement (FD), which represents the scalar quantity of instantaneous head motion of each volume relative to its earlier neighboring volume, was also calculated based on the head motion parameters (Power et al. 2012). Because several recent studies have shown that high levels of head motion can significantly influence the estimation of resting-state FC (Power et al. 2012; Satterthwaite et al. 2012; van Dijk et al. 2012), the following steps were adopted to reduce these motion effects: 1) the fMRI data were excluded from further analysis if the maximum displacement in one or more of the orthogonal directions was >1 mm or a maximum rotation >1.0°; 2) the data were also excluded if the average FD of the subject exceeded 0.3; and 3) the average FDs were considered as nuisance covariates in the statistical analyses described below. After realignment, the individual structural images were linearly registered to the mean functional images. Next, the structural images were segmented into gray matter (GM), white matter, and cerebrospinal fluid and were normalized to Montreal Neurological Institute (MNI) space using a high-level nonlinear warping algorithm, that is, the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) technique (Ashburner 2007). The motion-corrected functional volumes were spatially normalized to the MNI space and resampled to $3 × 3 × 3$ mm^3 voxels using the normalization parameters for their respective structural images. After normalization, the nuisance variables, including 6 head motion parameters and the average BOLD signals of the ventricular and white matter, were linearly regressed out from the data. Finally, the fMRI data were band-pass filtered from 0.01 to 0.08 Hz.

FCD Calculation

We calculated the FCD of each voxel using an in-house script written on Linux platform that was based on the method described by Tomasi and Volkow (Tomasi and Volkow 2010, 2011a). FCD calculations were restricted to voxels within the GM regions with signals >50% of the mean of the whole brain to minimize unwanted effects from susceptibility-related signal loss. Pearson correlation was used to calculate the FC, and pair of 2 voxels with a correlation coefficient $r > 0.6$ was considered functionally connected. The global FCD of a given voxel (x_0) was defined as the number of voxels that were functionally connected with voxel x_0 (Tomasi and Volkow 2011b).

The short-range FCD of voxel x_0 was defined as the total number of directly and indirectly neighboring voxels that were functionally connected with x_0. Specifically, we first calculated the FC between x_0 and each voxel (x_i) that directly neighbors with x_0. For each x_i, if the FC was significant ($r > 0.6$), it was counted as a neighboring voxel that was functionally connected to x_0. Then, we calculated the FC between x_0 and each voxel (x_j) that directly neighbors with x_i but not with x_0. For each x_j, if the FC was significant ($r > 0.6$), it was also counted as a neighboring voxel that was functionally connected with x_0. This search strategy was continued until no further voxels could be included. Long-range FCD was calculated as the global FCD minus the short-range FCD and thus reflected the number of non-neighboring voxels of x_0 that were functionally connected to x_0. Thus, the short- and long-range FCDs provide information about the relative rather than the absolute spatial distance between voxels. A schematic diagram of the FCD calculations is shown in Supplementary Figure 1.

The generated FCDs did not conform to a normal probability distribution (see Supplementary Figs 2 and 3 and Table 1) and thus was not suitable for parametric statistical inference. To increase the normality, grand mean scaling was applied to the short- and long-ranged FCD maps, this scaling was performed by dividing the FCD of each voxel by the mean value for the whole brain of each subject. After grand mean scaling, both the whole-brain mean FCDs (Supplementary Fig. 2) and the FCDs within each major rest-state functional network (Supplementary Fig. 3 and Table 1) were normally distributed, which indicates that parametric group comparisons using the normalized FCDs were more reliable than comparisons using the non-normalized FCDs. Consequently, the normalized FCD data were used in the following analyses. Finally, the normalized FCDs were spatially smoothed with a $6 × 6 × 6$ mm^3 Gaussian kernel.

Statistical Analysis

One-sample Kolmogorov–Smirnov tests were used to evaluate the normalities of both the short- and long-range FCDs ($P > 0.05$). Next, a voxel-wise one-way analysis of variance (ANOVA) was performed on the normalized FCD data to test the group differences among the CB, LB, and SC groups with age, gender, and the motion scalars as nuisance covariates. To investigate the effect of the duration of blindness

Table 1

Demographic information of the recruited subjects

	CB	LB	SC	Statistics	P value
Gender (males/females)	12/7	22/12	30/12	$\chi^2 = 0.58$	0.75
Age (years)	26.7 ± 5.1	27.5 ± 4.2	25.9 ± 4.4	$F = 1.20$	0.31
Age of onset of blindness (years)	0	17.6 ± 4.3	–	–	–
Duration of blindness (years)	26.7 ± 5.1	9.9 ± 4.0	–	–	–

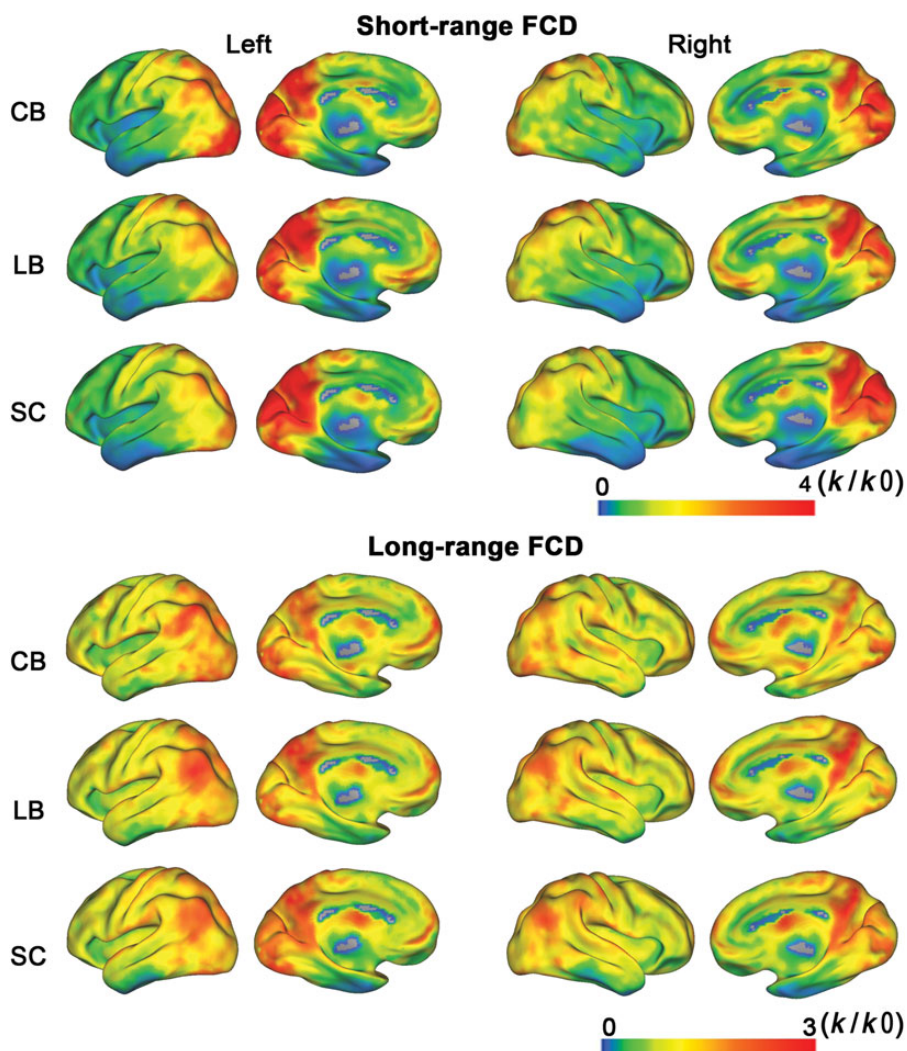Note: CB, congenitally blind; LB, late blind; SC, sighted control.

Figure 1. Spatial distributions of the averaged short- and long-range FCDs. The color bar represents the normalized FCD value; that is, the average number of functional connections per voxel (k) divided by the grand mean of the whole brain of each subjects (k_0).

on the FCDs, a voxel-wise multiple regression analysis was performed on the data from the LB within a binary mask constructed from the group differences between the LB and SC. Gender, age, and motion effects were controlled for in this regression analysis. A correction for multiple comparisons was performed using a Monte Carlo simulation, resulting in a corrected threshold of $P < 0.05$ (AlphaSim program, parameters including: single voxel $P = 0.01$, 5000 simulations, full width at half maximum = 6 mm, cluster connection radius $r = 5$ mm; with a GM mask and a resolution of $3 \times 3 \times 3$ mm^3).

ROI-based partial correlation analyses were performed to investigate the separate contributions of the duration of blindness and the age of onset of blindness to the FCD because chronological age, the age of onset and duration of blindness are highly correlated with each other in the LB. First, we performed a partial correlation analysis that controlled for gender and head motion to clarify whether the FCD in the ROI was correlated with the chronological age. Second, we investigated the correlation between duration of blindness and FCD while controlling for gender, head motion, and age of onset of blindness to evaluate the independent contribution of the duration of blindness to the changes in FCD. Third, we investigated the correlation between age of onset of blindness and FCD while controlling for gender, head motion, and duration of the blindness to evaluate the independent contribution of age of onset of blindness to the changes in FCD. The level of statistical significance was set at $P < 0.05$.

Results

Demographic Information of the Blind Subjects

As shown in Table 1, the mean age of onset of blindness for the LB was 17.6 ± 4.3 years, and the mean durations of blindness were 26.7 ± 5.1 and 9.9 ± 4.0 years for the CB and the LB, respectively. There were no significant differences between the 3 groups in terms of age (one-way ANOVA, $F_{2,92} = 1.20$, $P = 0.31$) or gender (χ^2 test, $\chi^2_1 = 0.58$, $P = 0.75$). The major causes of visual deprivation in the CB included congenital eyeball dysplasia, congenital cataract, congenital microphthalmus, and congenital glaucoma. For the LB, these causes included retinal detachment, cataract, retinal pigmentosa, glaucoma, optic atrophy, and fundus hemorrhage.

Spatial Distribution of the FCDs in Blind and Sighted Subjects

The 3 groups exhibited similar FCD spatial distributions (Fig. 1). Specifically, the short-range FCDs were greatest in the posterior cingulate cortex (PCC), precuneus, and medial

occipital cortex. Relatively greater short-range FCDs were also observed in the superior lateral occipital cortex (SPL), inferior parietal lobe (IPL), medial prefrontal cortex (MPFC), thalamus, and postcentral gyrus (PostCG). In contrast, the short-range FCDs were weaker in the basal ganglia regions, the ventral anterior part of the temporal cortex, and the insula. The long-range FCDs were greatest in the PCC, precuneus, SPL, IPL, and occipital cortex. Relatively greater long-range FCDs were also observed in the thalamus, superior temporal cortex, MPFC, and dorsolateral prefrontal cortex. Weaker long-range FCDs were observed in the basal ganglia regions and the ventral anterior part of the temporal cortex.

Differences in the Short-range FCD Between the Blind and Sighted Subjects

A one-way ANOVA was performed to explore group differences in FCDs after controlling for the nuisance effects of age, gender, and motion scalars. As shown in Figure 2, Compared with sighted subjects, the CB exhibited significantly decreased short-range FCDs in the left primary visual cortex (V1). The LB also exhibited decreased short-range FCDs in the V1 that had broader spatial distribution than that of the CB. The posterior thalamus, which is the subcortical relay of visual input, also exhibited decreased short-range FCD in the LB.

Compared with the SC, both of the blind groups exhibited increased short-range FCDs in the dorsal visual stream, including the middle (MOG) and superior occipital gyri (SOG), SPL, IPL, and middle frontal cortex (MFG). Additionally, the CB subjects also exhibited significantly increased short-range FCD in the ventral visual stream and the medial temporal cortex, including the left inferior occipital gyrus (IOG), and the bilateral inferior temporal gyri (ITG), fusiform gyri (FG), parahippocampal gyri (PHG), and hippocampi. In contrast, the LB also exhibited increased short-range FCD in the dorsal anterior

cingulate cortex (dACC) and MPFC (Fig. 2, Supplementary Tables 2 and 3).

Differences in the Long-Range FCDs Between the Blind and Sighted Subjects

Compared with the SC, both the CB and LB exhibited significantly decreased long-range FCDs in the bilateral V1 and primary sensorimotor cortices (SM1). Additionally, the CB exhibited decreased long-range FCD in the right primary auditory cortex (A1), whereas the LB exhibited reduced long-range FCDs in the bilateral posterior thalami.

In the CB subjects, the increased long-range FCDs were mainly located in the ventral visual stream and the medial temporal cortex, including the IOG, ITG, FG, orbital frontal cortex (OFC), PHG, and hippocampi. In contrast, the LB also exhibited increased long-range FCDs in the ventral visual stream, but the spatial extent was smaller compared with that of the CB. Additionally, the LB exhibited increased long-range FCDs in the dACC and MPFC (Fig. 3, Supplementary Tables 4 and 5).

Differences in the FCD Between the CB and LB

Compared with the LB, the CB exhibited greater short-range FCDs in the ITG, FG, PHG and hippocampi bilaterally, and greater long-range FCD in the right ITG, FG, lateral OFC, PHG, and left MOG (Fig. 4, Supplementary Tables 6 and 7).

Associations Between FCD and the Duration and age of Onset of Blindness in the LB

After controlling for gender, age, and head motion effects, a significant positive correlation between the short-range FCD of the left V1 and the duration of blindness was found in the LB [partial correlation coefficient $(pr) = 0.581$, $P < 0.001$] (Fig. 5). No brain regions exhibited a statistical correlation between the long-range FCD and the duration of blindness. Because chronological age, age of onset, and duration of blindness
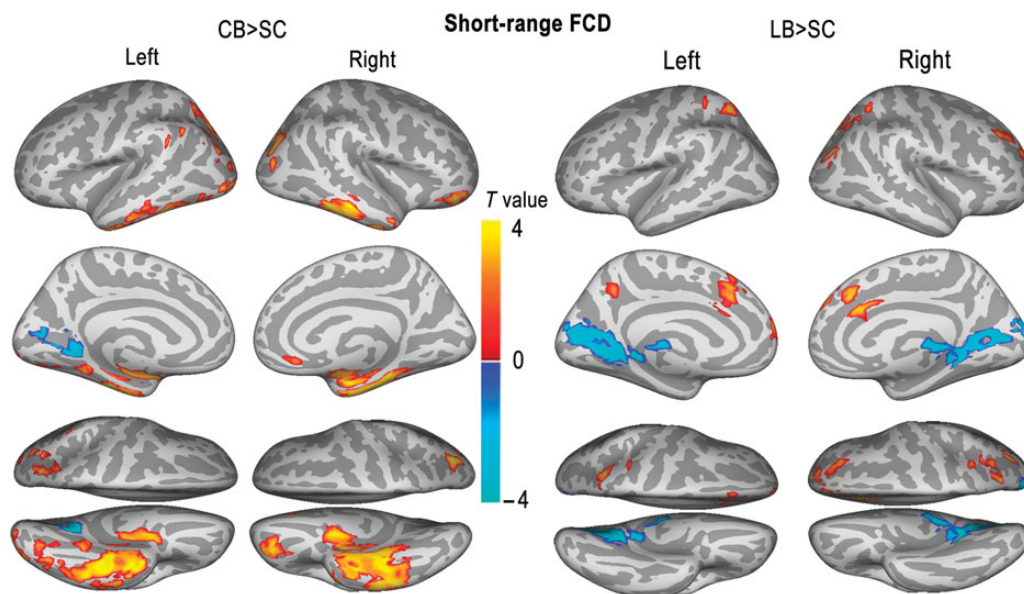

Figure 2. Group differences in short-range FCDs between the blind subjects and the SC. The main effects of blindness are shown on the surface of the PALS12 human atlas using CARET software. The color bar indicates the t values. Compared with the SC, both the CB and LB exhibit significantly decreased short-range FCD in the primary visual cortex. Although both the CB and LB exhibit increased short-range FCDs in the dorsal visual pathway, the CB also exhibit increased short-range FCD in the ventral visual pathway and hippocampal regions.
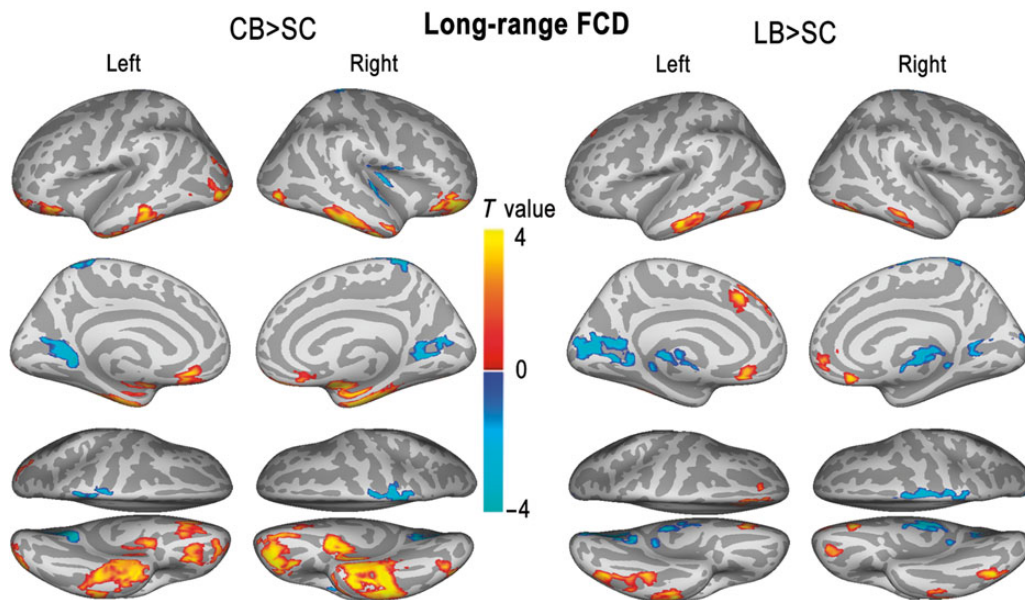
Figure 3. Group differences in long-range FCDs between the blind subjects and the SC. The main effects of blindness are shown on the surface of the PALS12 human atlas using CARET software. The color bar indicates the *t* values. Compared with the SC, both the CB and LB exhibit significantly decreased long-range FCDs in the primary sensory cortices. Both the CB and LB exhibit increased long-range FCD in the ventral visual pathway; however, the spatial extent of these increases is much larger in the CB than in the LB.
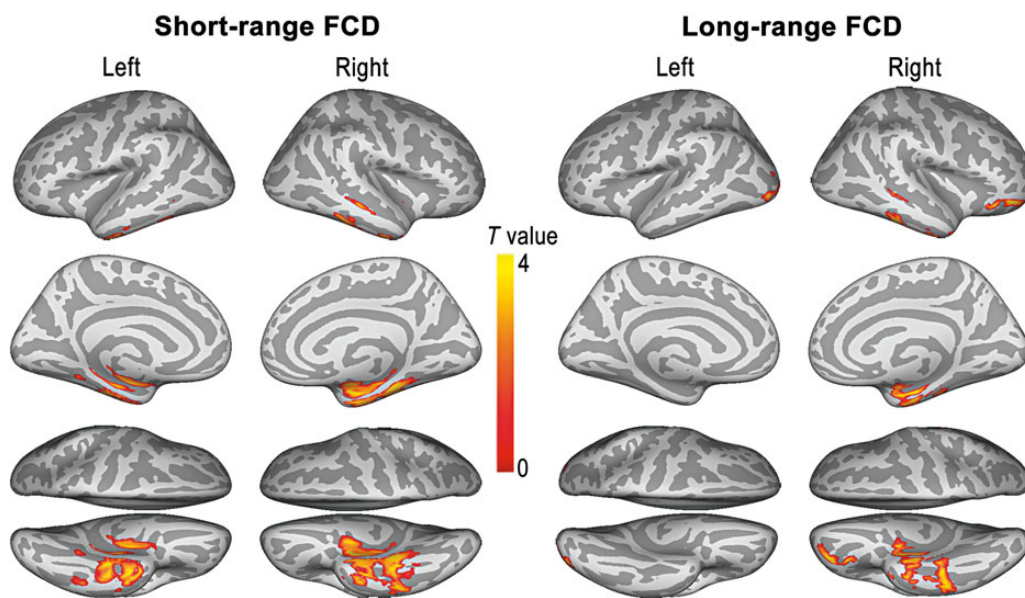

Figure 4. Differences in FCDs between the CB and LB. Compared with the LB, the CB exhibit increased short- and long-range FCDs in the ventral visual pathways and hippocampal/parahippocampal regions.

were highly correlated with each other, when controlling for age, we found that the positive correlation between FCD and the duration of blindness ($pr = 0.581$, $P < 0.001$) was the same as the negative correlation between FCD and age of onset of blindness ($pr = -0.581$, $P < 0.001$).

Thus, ROI-based analyses were performed to investigate the separate contributions of the duration and age of onset of blindness to the FCDs. We first performed ROI-based partial correlations between FCD and chronological age after controlling for gender and motion parameters. We did not find any significant correlations between FCD and chronological age

($pr = 0.21$, $P = 0.25$), which suggests that chronological age might not affect the short-range FCD in this ROI. Second, we performed partial correlations between FCD and the duration of blindness after controlling for gender and motion parameters. We found a positive correlation between the short-range FCD of this ROI and the duration of blindness ($pr = 0.602$, $P < 0.001$), and this positive correlation survived a further control for the age of onset of blindness ($pr = 0.510$, $P = 0.003$). Third, we performed partial correlations between FCD and age of onset of blindness after controlling for gender and motion parameters. We found a negative correlation
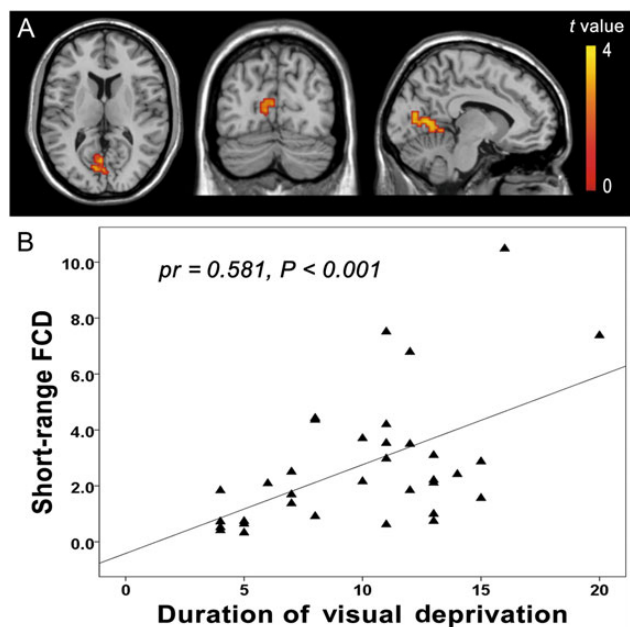
Figure 5. Correlation between short-range FCD and the duration of blindness in the LB. A partial correlation is performed using gender, age and motion scalars as nuisance covariates. The color bar represents the statistical *t* values. The upper panel exhibits the positive correlation between the short-range FCD and the duration of blindness in the left primary visual cortex; the lower panel exhibits the scatter plot of the correlation in this region.

between the short-range FCD of the ROI and the age of onset of blindness ($pr = -0.378$, $P = 0.033$); however, after further controlling for the duration of blindness, this correlation was not significant ($pr = -0.082$, $P = 0.660$). These findings indicate that the duration rather than the age of onset of blindness was the primary factor affecting the short-range FCD in the left V1 of the LB.

Discussion

Neural Mechanisms Underlying Changes in FCD in the Blind

The FC is closely associated with monosynaptic or polysynaptic structural connectivity (Fox and Raichle 2007). As an index derived from the FC, the FCD measures the number of FCs of a given voxel with others. Thus, any structural connectivity changes after visual deprivation may result in FCD changes. In the CB, the FCD of the occipital cortex may have been modulated by developmental, plastic, and degenerative mechanisms. Degenerative mechanisms result in damage to the structural connectivity of the occipital cortex (Shimony et al. 2006; Pan et al. 2007; Ptito et al. 2008; Bridge et al. 2009; Shu, Li et al. 2009; Shu, Liu et al. 2009), which may contribute to the decreases in FCD. The effects of developmental mechanisms on the FCD of the occipital cortex are rather complex in the CB. The immaturity of the occipital cortex and its fibers could potentially lead to decreased FCD in the CB, whereas the redundant synapses (Jiang et al. 2009) that results from pruning failure may induce increases in FCD. Plastic mechanisms may be related to the establishment of new connections and the unmasking of existing connections (Karlen et al. 2006; Beer et al. 2011), resulting in increases in FCD. Although the FCD of the

occipital cortex is mainly modulated by plastic and degenerative mechanisms in the LB, the capacity for cross-modal plasticity in this group is much weaker than that in the CB (Voss 2013), and degenerative mechanisms affect the mature visual system of the LB but the immature visual system of the CB. Thus, the observation that the changes in FCD were similar between the CB and LB does not mean that the neural mechanisms underlying these changes were similar. Moreover, changes in the FCDs in the brains of blind cannot be explained by a single mechanism, rather, these changes likely resulted from the combined actions of these mechanisms operating with different weights.

Decreased FCDs in the Primary Sensory Cortices of the Blind

The CB exhibited a decreased FCD in the V1, and this finding is consistent with decreases in FC (Liu et al. 2007; Yu et al. 2008; Qin et al. 2013), volumetric atrophy (Pan et al. 2007; Ptito et al. 2008; Lepore et al. 2010), and impaired anatomical connections (Shimony et al. 2006; Pan et al. 2007; Ptito et al. 2008; Bridge et al. 2009; Shu, Li et al. 2009; Shu, Liu et al. 2009) that have been observed in the V1 of the CB. More importantly, we also found that both the short- and long-range FCDs of the V1 were reduced in the LB compared with those of the SC, which was indirectly supported by previous findings of structural atrophy (Lepore et al. 2010) and impaired anatomical connections (Li et al. 2013; Wang et al. 2013) in the V1 of the LB. Degenerative mechanisms may account for the structural and functional impairments in the V1 after visual deprivation. However, the degenerative mechanisms alone cannot explain previous findings of the recruitment of V1 in the cross-modal processing of perception and cognitive tasks (Sadato et al. 1998; Amedi et al. 2003; Buchel 2003; Lambert et al. 2004; Garg et al. 2007; Collignon et al. 2013), the formation of new projections that convey nonvisual signals to the visual cortex (Karlen et al. 2006; Chabot et al. 2008), and the enhanced effective connectivity from the primary somatosensory cortex (S1) or A1 to the V1 in the CB (Wittenberg et al. 2004; Klinge et al. 2010) in the CB. Thus, these findings indicate that developmental and plastic mechanisms may also play important roles in reshaping the spontaneous functional organization of the V1 after visual deprivation. The connectivity of V1 with the nonvisual sensory areas may be strengthened or even rewired by developmental and plastic mechanisms after visual deprivation, which can partly compensate for the functional disconnections that result from the degenerative mechanism. Thus, the decreased FCDs in V1 observed in the CB reflect the combined action of these mechanisms.

We found a greater reduction in FCD in the occipital cortex in the LB than in the CB. This finding can also be understood from the perspective of the combined action of multiple neural mechanisms. Developmental mechanisms that operate in the CB are unique, the capacity for cross-modal plasticity is much stronger in the CB than in the LB, and degenerative mechanisms exert their effects on the mature visual systems of the LB and on the immature visual system of the CB. We also found that the short-range FCD of the left V1 was positively correlated with the duration of blindness in the LB, and this correlation still survived when the age of onset of blindness was further controlled. This finding indicates that, even when visual deprivation occurs after the sensitive period of development, plastic

mechanisms may also play a role in the functional reorganization of the V1. Although the neural mechanisms underlying this correlation in the LB remain unclear, they may be related to the slow, long-lasting cross-modal plasticity in the LB.

We also found decreased long-range FCDs in the primary somatosensory and auditory cortices of the blind. These findings are consistent with those of ROI-based FC studies that have found reduced FCs between the visual cortex and the other sensory cortices in both the CB (Liu et al. 2007; Yu et al. 2008; Qin et al. 2013) and the LB (Bedny et al. 2010). However, these reduced FCDs do not indicate the presence of impairments in the perceptual abilities of the nonvisual sensory cortices. Indeed, the CB and LB exhibit superior auditory and tactile abilities than those of the SC (Roder et al. 1999; Gougoux et al. 2005; Fieger et al. 2006). Moreover, the CB exhibit increased effective connectivities from the primary somatosensory area (Wittenberg et al. 2004) and primary auditory area (Klinge et al. 2010) to the V1. Thus, our findings only reflect the decoupling of spontaneous brain activity between nonvisual sensory cortices and visual cortex, and the functional significance of this decoupling requires further elucidation.

Increased FCDs in the Dorsal Visual Stream in the Blind

The dorsal visual stream serves to analyze visual spatial information (Haxby et al. 1991; Goodale and Milner 1992; Konen and Kastner 2008) and is involved in the multisensory integration (Kitada et al. 2006; Makin et al. 2007; Pasalar et al. 2010; Serino et al. 2011) and spatial attention (Anderson et al. 2010; Corbetta and Shulman 2011) in sighted subjects. Many studies have reported that the dorsal visual areas of the CB are also involved in the processing of auditory/tactile spatial information (Ricciardi et al. 2007; Bedny et al. 2010; Fiehler and Rosler 2010; Collignon et al. 2011), which suggest that nonvisual signals are sufficient to drive the functional differentiation of the dorsal visual stream in the CB. The increased short-range FCD in the dorsal visual stream of the CB may reflect cross-modal plasticity. We also observed increased FCDs in the dorsal visual stream of the LB, which is consistent with several studies that have shown increased activation elicited by nonvisual stimuli in these regions (Mahon et al. 2010; Collignon et al. 2013); however, the underling neural mechanisms may not be similar to those operating in the CB. Nonvisual information prefers to flow through the "A1 → V1→dorsal visual stream" pathway in the CB, whereas this information flows via an "A1 → dorsal visual stream → V1" pathway in the LB (Collignon et al. 2013). Thus, the increased FCD in the dorsal stream for the CB may be better explained by enhanced transmission of bottom-up nonvisual signals, and the increased FCDs in the dorsal stream of the LB may represent an enhancement of the relay through which top-down nonvisual signals reach the V1. Notably, this top-down mechanism may also play a role in the increased FCDs in the dorsal stream that occur after early visual deprivation because several studies have shown enhanced nonvisual involvement of dorsal attention networks in the CB (Burton et al. 2004, 2010; Garg et al. 2007; Stevens et al. 2007).

Increased FCD in the Ventral Visual Stream in the Blind

The ventral visual stream is associated with the processing of category-related visual information in the SC (Hadjikhani et al. 1998; Janssen et al. 1999; Mahon et al. 2009). The ventral visual stream is also involved in the processing of nonvisual stimuli in the CB; for example, the ITG and FG process tactile/auditory object recognition information (Pietrini et al. 2004; Mahon et al. 2009), the lateral occipital cortex processes tactile/auditory shape recognition information (Amedi et al. 2002, 2007; Kim and Zatorre 2011; Ptito et al. 2012), the PHG processes tongue virtual route recognition information (Kupers et al. 2010), and the PHG and OFC participate in olfactory processing (Kupers et al. 2011a). Thus, the increased FCDs in the ventral stream of the CB may reflect enhanced transmission efficiency of nonvisual signals, which may underlie the enhanced capacity of the ventral stream to process nonvisual information. Although the functional relevance of the increased FCDs in the LB remains unclear, the stronger FCD in the ventral stream of the CB relative to the LB may be attributable to the greater capacity for cross-modal plasticity in the CB relative to the LB (Bedny et al. 2012).

The sensitive period for the development of the perceptual abilities related to contour and form (the abilities are mediated by the ventral stream, and the sensitive period lasts several years) is much longer than that for the perceptual abilities related to the action and motion (mediated by the dorsal stream, lasting several months) (Kovacs et al. 1999; Kovacs 2000; Wattam-Bell et al. 2010), which suggests that the ventral visual stream matures more slowly than the dorsal one. Consequently, on the one hand, the ventral visual stream may experience greater cross-modal plasticity compared with the dorsal visual stream in the CB. This greater plasticity may partially explain the greater increased FCD in the ventral visual stream than in the dorsal one in the CB. On the other hand, the ventral visual stream may suffer more serious structural damage compared with the dorsal visual stream, which was supported by previous structural studies (Shimony et al. 2006; Shu, Li et al. 2009; Qin et al. 2013; Wang et al. 2013). Thus, the prominently increased FCDs in the ventral stream may also reflect functional compensations for structural impairment to maintain the normal functioning of these brain regions.

The hippocampal complex is associated with navigation, particularly navigation based on visual signals. The volume of the anterior hippocampus has been found to be increased in blind subjects (Fortin et al. 2008; Lepore et al. 2009), and decreased posterior hippocampal volumes have also been reported (Chebat et al. 2007; Lepore et al. 2009). The tactile maze navigation task activates this area in the CB but not in the SC (Gagnon et al. 2012). The hippocampal complex exhibits increased nodal importance within the anatomical network only in the CB (Li et al. 2013). These findings suggest that the organization of the hippocampus is affected by early visual deprivation, which may underlie the more dramatic changes in the FCD of the hippocampal complex observed in the CB relative to the LB. Visual signals reach the hippocampal complex via the ventral visual pathway, suggesting that the functional organization of the hippocampal complex may depend on the organization of the ventral visual stream. Thus, the abovementioned mechanisms may also explain the increased hippocampal FCDs in the CB.

In the CB, we found increased FCD in the OFC, which serves to process olfactory information, reward, facial expression, and social emotion information (Tsao et al. 2008). In the CB, the higher order olfactory areas such as the lateral OFC and hippocampus exhibit greater activations than those

of the SC during an odor detection task, which provides a neurobiological substrate for the increased odor awareness of the CB (Kupers et al. 2011a). The increased FCD indicates that the OFC in the CB has much more connectivity than in SC, which may be associated with the improved olfactory abilities of the CB. Additionally, given that the OFC is an important node of the ventral visual stream, the increased FCD in the OFC in the CB may also be explained by the mechanisms responsible for the reorganization of ventral visual stream.

How Nonvisual Information is Processed and Flows in the Occipital Cortex in the Blind

Two major pathways have been hypothesized to carry nonvisual signals to the occipital cortex: the thalamo-occipital pathway and cortical-occipital pathway (Qin and Yu 2013). The thalamo-occipital pathway hypothesis states that the auditory/tactile signals reach the occipital cortex via rewired subcortical connections. This hypothesis is supported by findings that the lateral geniculate nucleus (LGN) receives rewired auditory projections from the inferior colliculus (Chabot et al. 2008) and medial geniculate nucleus (Karlen et al. 2006), and rewired somatosensory projections from the ventral posterior nuclei of the thalamus (Karlen et al. 2006). Moreover, the LGN sends efferent fibers to the occipital areas in enucleated animals. The cortico-occipital pathway can be further subdivided into direct and indirect pathways. The direct pathway has been found between A1 and the occipital cortex in sighted adult Mongolian gerbils (Budinger et al. 2006), cats (Clemo et al. 2008), primates (Falchier et al. 2010), humans (Beer et al. 2011), and CB opossums (Karlen et al. 2006) and between S1 and V1 in enucleated opossums (Karlen et al. 2006). The indirect pathway has been indicated by studies that have shown indirect connections between A1/S1 and V1 via multisensory areas such as the superior temporal sulcus, ventral lateral prefrontal cortex, and extrastriate areas (Driver and Noesselt 2008; Smiley and Falchier 2009; Romanski 2012).

In this study, we found that the FCDs of both the dorsal and ventral pathways were strengthened in the CB, which supports the notion of a reinforced (or rewired) cortico-cortical pathway. This hypothesis is also supported by the observations of enhanced effective connectivities between S1/A1 and V1 (Wittenberg et al. 2004; Klinge et al. 2010) and strengthened frontal-occipital functional connectivities in the CB (Liu et al. 2007; Bedny et al. 2010, 2011). In the present study, increased FCD was also found in the LB; however, this finding does not indicate that the pathways and processing of nonvisual information in the occipital cortices of the LB and CB are similar. Although both the CB and LB recruited the occipital cortex for nonvisual processing, the functional relevance of the occipital cortex is different between the CB and LB. For example, the dorsal stream seems to maintain its functional tuning for "space" only in the CB (Bedny et al. 2010; Collignon et al. 2013), and the left occipital cortex is specifically involved in the processing of language information only in the CB (Bedny et al. 2012). Moreover, the neural pathways through which nonvisual signals reach the visual cortex differ between the CB and LB. For example, CB subjects directly convey "feed-forward" auditory signals from A1 to V1 (Klinge et al. 2010; Collignon et al. 2013) and to higher tier visual areas, whereas LB subjects indirectly convey "feed-back" auditory signals from A1 to V1 via the parietal region (Collignon et al. 2013).

Thus, the increased FCD in the CB may suggest a rewired (or strengthened) cortico-cortical pathway through which auditory/tactile stimulus-driven signals reach the ventral and dorsal streams via relay of V1, and may represent increased cross-modal reorganization for the processing of nonvisual information (Kupers et al. 2010; Bedny et al. 2012; Collignon et al. 2013). In contrast, the LB subjects have formed their normal visual connections prior to visual deprivation, and the increased short-range FCD might reflect strengthening of the cortico-cortical pathways that transfer top-down nonvisual signals to the early visual areas. However, the functional relevance of this increased FCD in the LB remains unclear and requires further investigation.

Lateralization of Changes in FCD in the Blind

We found that the increases in short- and long-range FCD in the occipital cortex occurred predominately in the left hemisphere of the CB but not the LB (Figs 2 and 3). These findings are consistent with previous findings that have shown that the left occipital cortex is more involved in language processing only in the CB (Amedi et al. 2004; Bedny et al. 2011, 2012). Although short-range FCD was decreased in V1 of the LB, we also found a positive correlation between short-range FCD in the left V1 and the duration of blindness in these subjects (Fig. 5). This finding suggests that longer duration of blindness predicts greater short-range FCDs in the left V1 of the LB. Although the mechanisms underlying the left-dominant association remains unclear, it may be related to reorganizations of the left-lateralized functional networks, such as the language network, but this hypothesis requires validation in the future. Compared with the LB, the CB exhibited a right-dominant increase in long-range FCDs in the ventral stream that included the critical node (i.e., the ventrolateral prefrontal cortex) of the ventral attention network (VAN), which is a right-dominant functional network (Corbetta et al. 2008). Thus, the increased FCDs in the right ventral stream in the CB compared with those of the LB may reflect greater functional reorganization of the VAN in the CB.

Conclusions

Here, we used whole-brain FCD analyses to obtain complete maps of the spontaneous functional reorganizations of blind subjects who lost their sight before and after the sensitive period. We found that, although both the CB and LB exhibited decreased FCDs in the occipital cortex, the CB were less affected than the LB. Furthermore, although both the CB and the LB exhibited increased FCDs in both the dorsal and ventral visual streams, the CB exhibited more predominantly functional reorganization in the ventral visual stream compared with the LB. Our findings suggest that visual deprivation before the developmentally sensitive period can induce more extensive functional brain reorganization than that after the sensitive period, which may underlie the enhanced capacity for the processing nonvisual information in the CB.

Supplementary Material

Supplementary can be found at: http://www.cercor.oxfordjournals.org/.

Notes

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